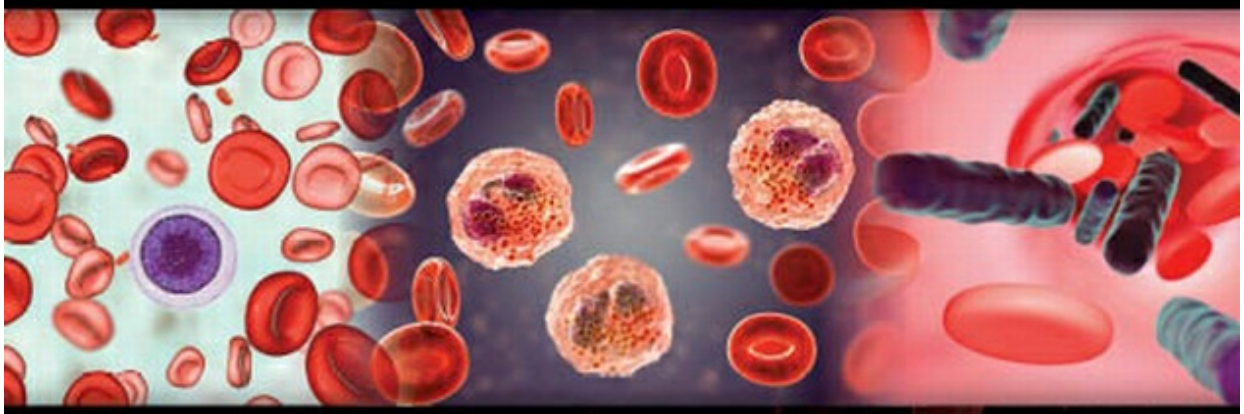
ANDERSON'S Atlas of Hematology

THIRD EDITION



Shauna C. Anderson Young
Keila B. Poulsen

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Atlas of Hematology

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Preface

After many years of interacting with students, Shauna Anderson Young and Keila Poulsen have produced this atlas with high-quality images, which are combined with in-depth descriptive text to create an ideal bench-top tool for the student and practitioner.

ORGANIZATION

The text has two units: Cell Descriptions (or normal hematology) and Hematologic Disorders. The first unit is organized into three parts:

- Hematopoietic cells, including a comparison of some of the commonly confused cells
- Bone marrow cellularity, cells of the reticuloendothelial system, and nonhematopoietic cells
- Cytochemical stains

Each cell description includes the cell size, a description of the nucleus and cytoplasm, and a list of associated clinical conditions. A drawing of the maturation series for each cell type accompanies the high-quality photographs.

The second unit describes hematologic disorders. Each description includes a brief summary of the clinical features, pathology, laboratory features, and a diagnostic scheme. The diagnostic scheme summarizes the relevant laboratory findings that lead to the features of a particular disorder. This unit is also organized into three parts:

- Red blood cell disorders
- White cell disorders

- Miscellaneous disorders

The WHO classification of hematopoietic and lymphoid tissue has been incorporated into this atlas.

IS THIS TEXT FOR YOU?

Yes! The atlas can be used to teach any level of hematology. Whether it is used for teaching cell identification or for the diagnosis of disease, it is a valuable learning tool for students in medical laboratory technician or medical laboratory science/technology programs. It is also a great reference for students in nursing and nurse practitioner programs, as well as medical students or residents. Finally, this spiral-bound atlas is an ideal, user-friendly, convenient companion at the microscope and can be used as a retraining resource or as a laboratory reference.

ADDITIONAL RESOURCES

Additional resources are available in the Navigate 2 Advantage platform to help you learn the material and prepare for assessments. Simply redeem the access code found on the card at the front of the book at **www.jblearning.com**.

Instructor Resources

Approved adopting instructors will be given access to the following additional resources:

- Image Banks
- Answers to Case Studies

Student Resources

Students who have purchased Anderson's Atlas of Hematology, third edition, have access to the following additional resources:

- Atlas of Hematology Image Bank
- Atlas of Hematologic Disorders Image Bank
- Book Image Bank
- Case Studies
- Self-study sheets divided by the category of the disorderPrintable Hematology Tri-folds

Acknowledgments

We would like to thank our families for their continued support. Our students have always been a source of stimulus and enjoyment. We would like to thank them for their suggestions and our colleagues for their contributions.

Special thanks to Brigham Young University for allowing us the opportunity to teach such wonderful students.

Eastern Idaho Regional Medical Center has provided the chance for Keila to work and learn at that institution for 50 years, thank you so much.

Shauna C. Anderson Young
Keila B. Poulsen

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With Microorganisms
Chapter 3: Reticuloendothelial System Storage Disorders

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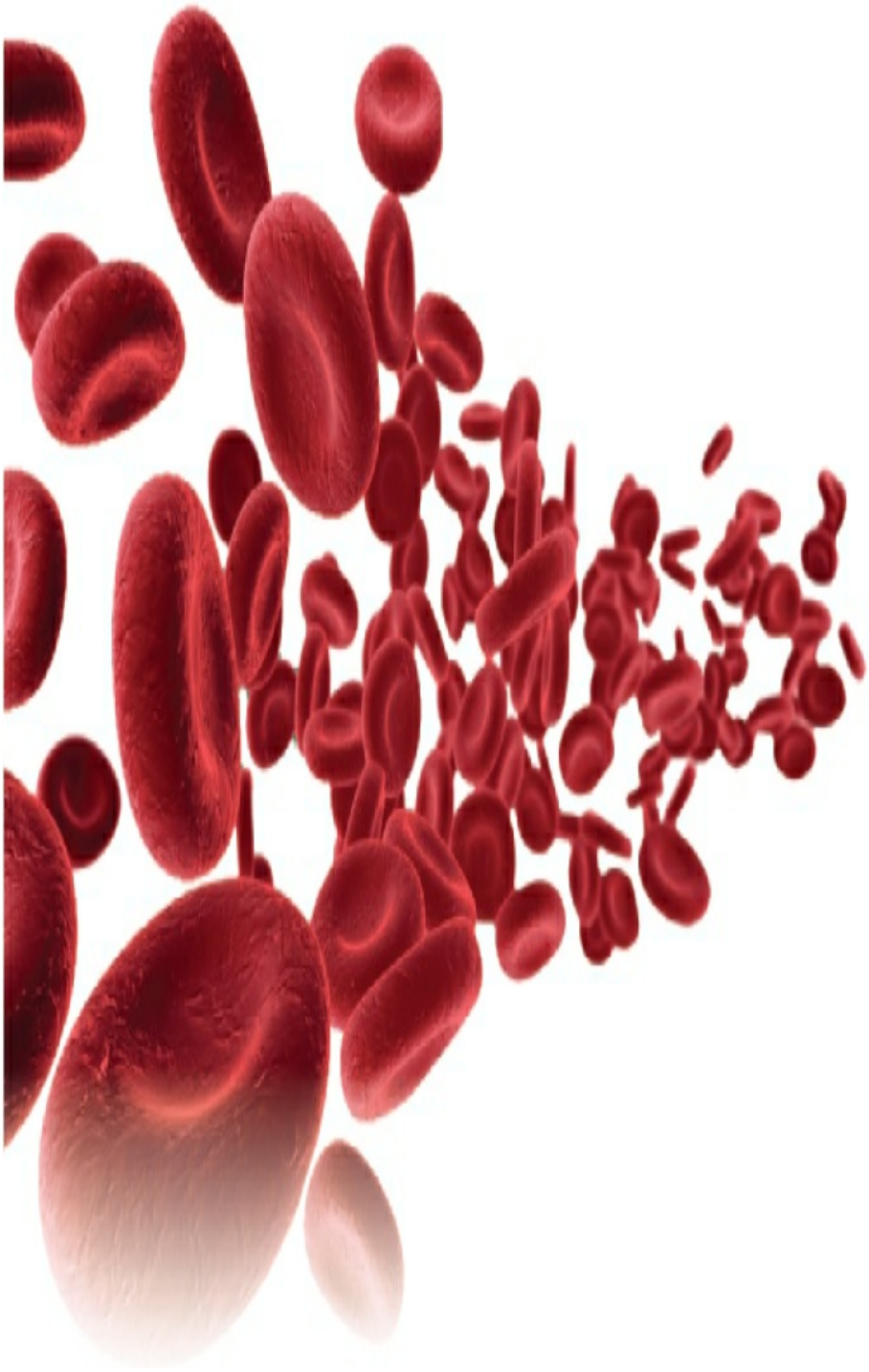
Cell Descriptions



- Section A Blood Cells
- Section B Bone Marrow
- Section C Cytochemistry

Section A
Blood Cells

CHAPTER 1

Red Blood Cells

NORMAL MATURATION SERIES

Erythrocyte Series

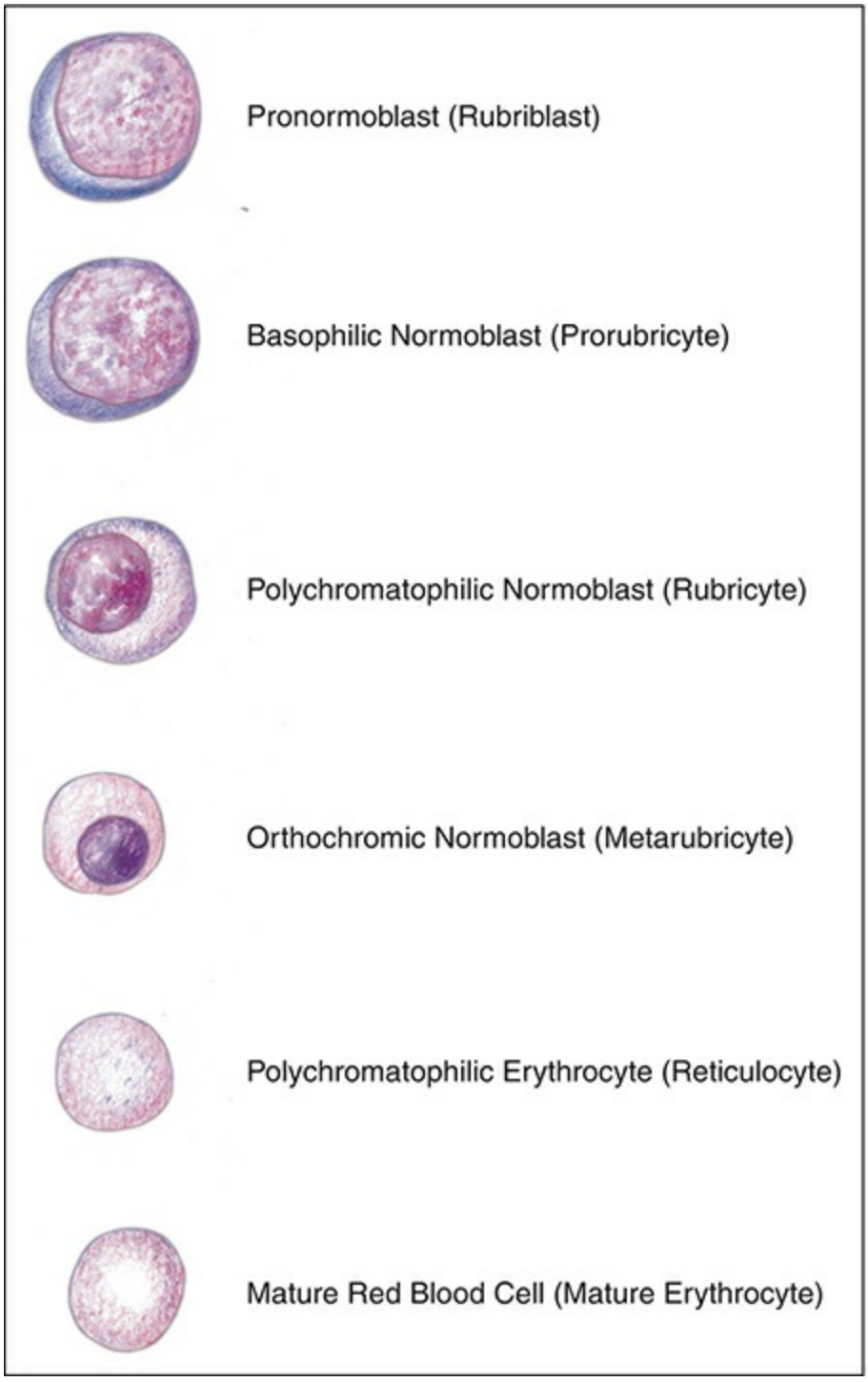


Figure IA1-1

Pronormoblast (Rubriblast)

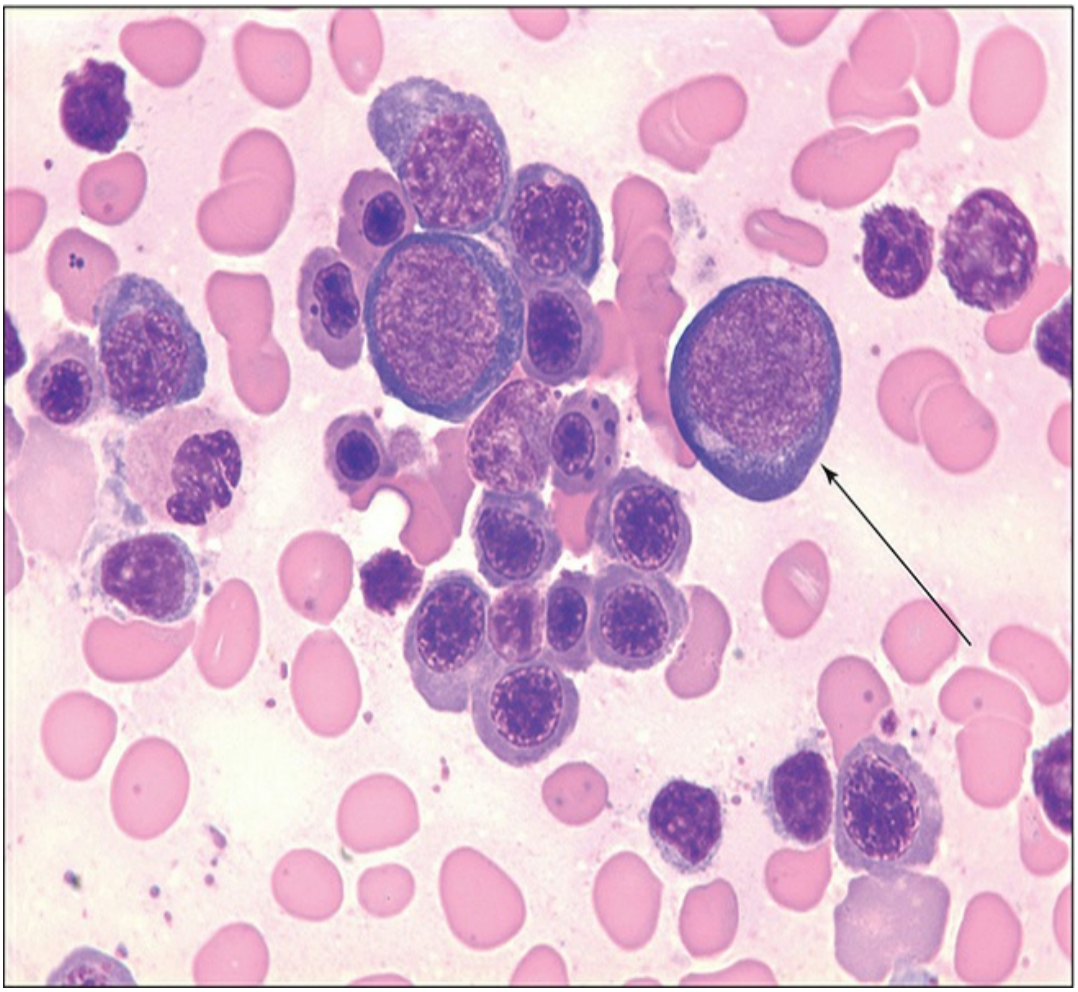


Figure **IA1-2**

Size: 14–22 μ

Nucleus

Shape: Round to slightly oval

N/C Ratio: 5:1–8:1

Color: Purple-red

Chromatin: Fine, but granular; parachromatin sparse

Nucleoli: 1–2 prominent; have a bluish tint

Cytoplasm

Color: Deep blue

Contents: Golgi, mitochondria, which produce a lighter blue color (perinuclear halo)

Clinical Conditions

- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Hemolytic disease of the newborn
- Myelodysplastic syndromes

Basophilic Normoblast (Prorubricyte)

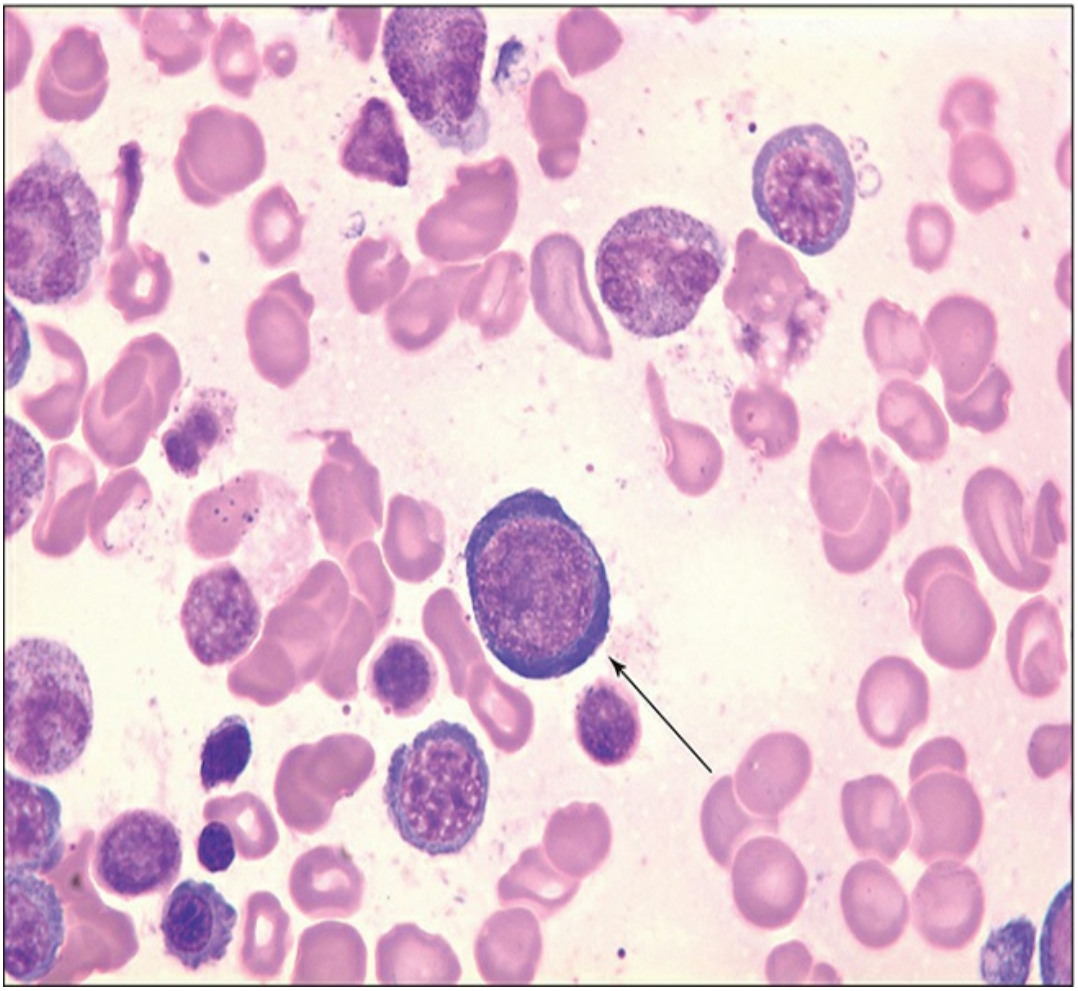


Figure IA1-3

Size: 12–17 µ

Nucleus

Shape: Round, centered

N/C Ratio: 4:1–6:1

Color: Purple interspersed with light areas

Chromatin: Coarse and somewhat condensed

Nucleoli: Usually not visible

Cytoplasm

Color: Deep blue

Contents: Golgi may produce a light blue area near the nucleus, many mitochondria

Clinical Conditions

- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Hemolytic disease of the newborn
- Myelodysplastic syndromes

Polychromatophilic Normoblast (Rubricyte)

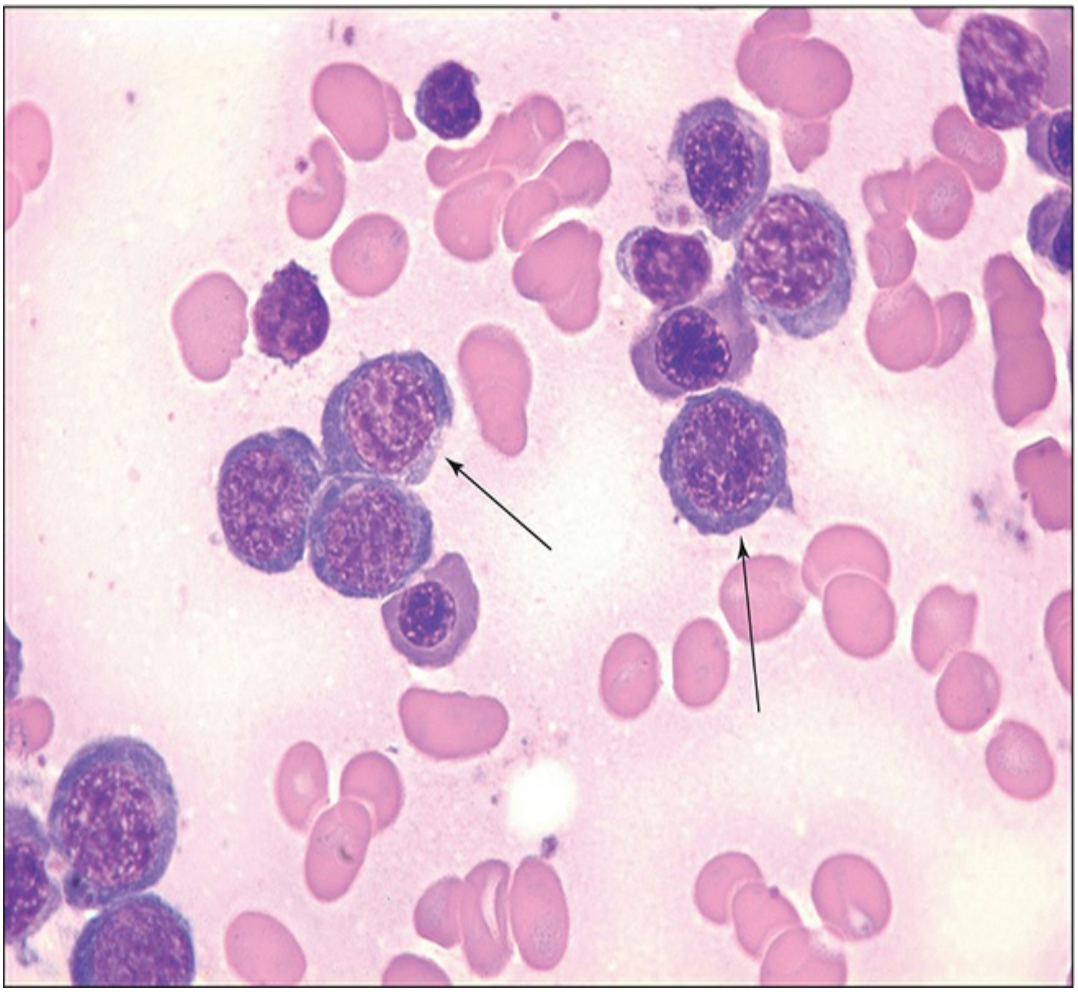


Figure **IA1-4**

Size: 11–14 µ

Nucleus

Shape: Round, centered to eccentric

N/C Ratio: 1:1–4:1

Color: Red-purple

Chromatin: Coarse and condensed; parachromatin distinct, producing a "checkerboard" appearance

Nucleoli: None

Cytoplasm

Color: Bluish-pink to gray-blue

Contents: Perinuclear halo visible; increased hemoglobin

causing the pink-gray color; decreased RNA causing the lighter blue color

Clinical Conditions

- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Hemolytic disease of the newborn
- Primary myelofibrosis (PMF)
- Chronic myelocytic leukemia (CML)
- Myelodysplastic syndromes
- Hemolytic anemias
- Thalassemia major
- Sickle cell disease

Orthochromic Normoblast (Metarubricyte)

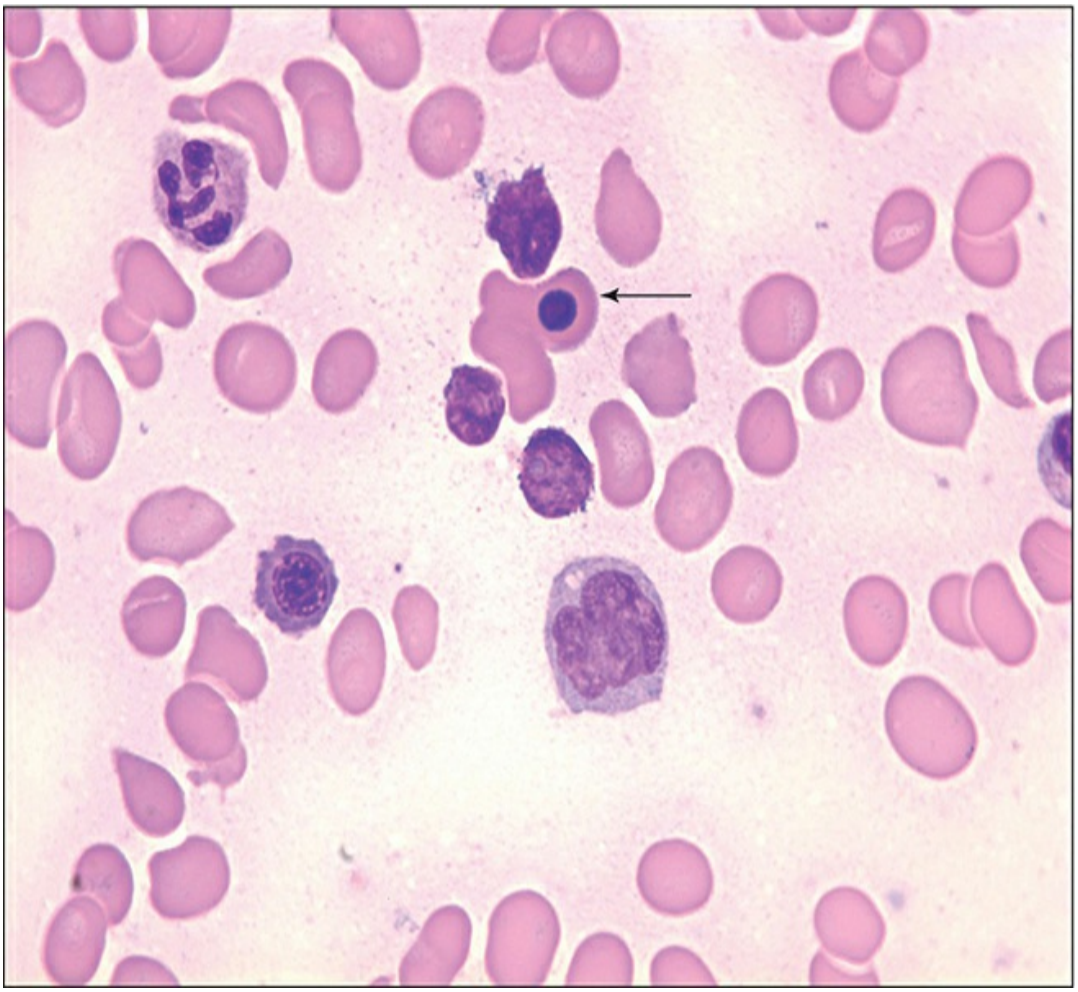


Figure **IA1-5**

Size: 8–12 μ

Nucleus

Shape: Round, centered to eccentric; may be fragmented or extruding

N/C Ratio: 1:4–1:2

Color: Blue-purple

Chromatin: Condensed and homogeneous (pyknotic)

Nucleoli: None

Cytoplasm

Color: Pink to orange-pink with a hint of blue

Contents: Hemoglobin production increased

Clinical Conditions

- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Hemolytic disease of the newborn
- Myeloproliferative neoplasms—PMF, CML
- Myelodysplastic syndromes
- Thalassemia major
- Sickle cell disease

Polychromatophilic Erythrocyte (Reticulocyte)

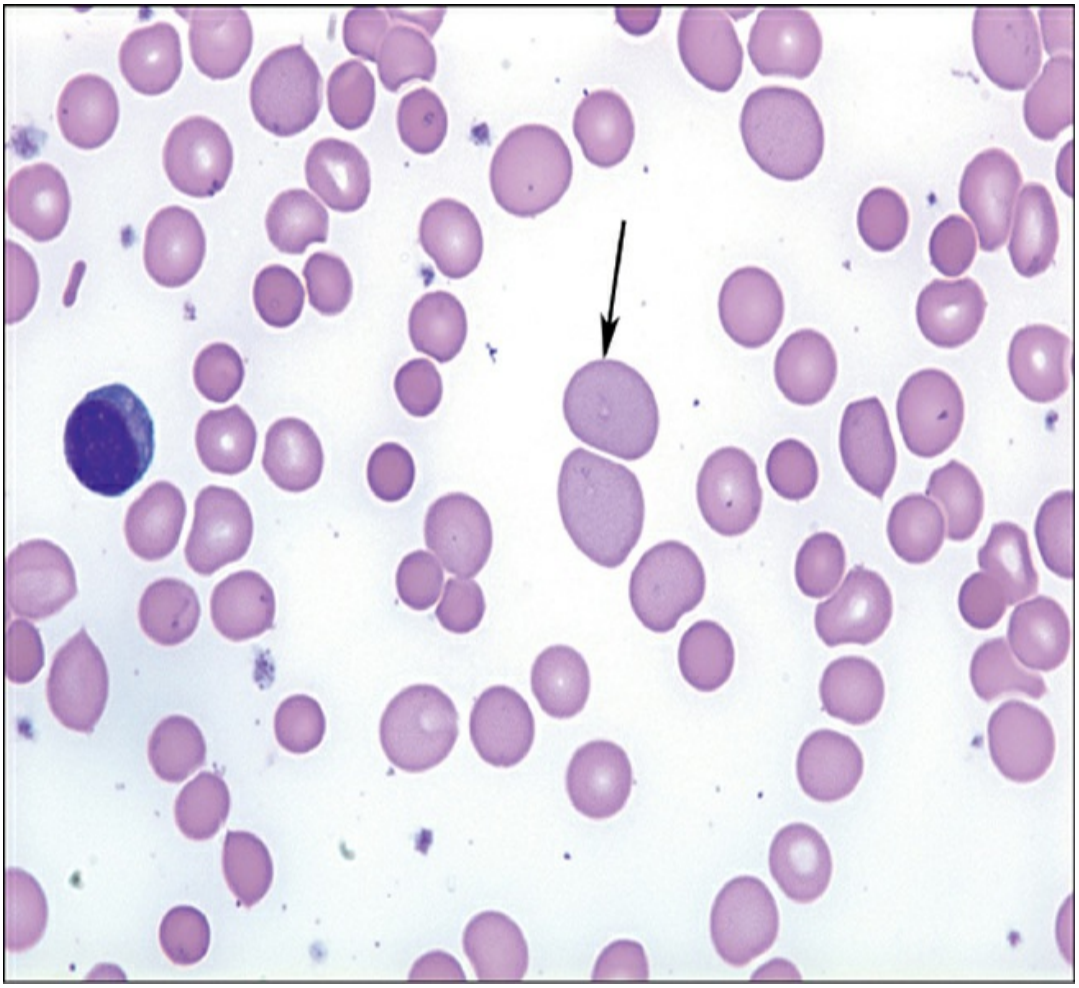


Figure IA1-6

Size: 8–11 µ

Nucleus

None

Cytoplasm

Color: Pink with a tint of blue

Contents: Remnants of Golgi and mitochondria, residual RNA (reticulum)

Clinical Conditions

- Increased erythrocyte production
- Hemolytic anemias
- Membrane disorders
- Hemolytic disease of the newborn

Mature Red Blood Cell (Mature Erythrocyte)

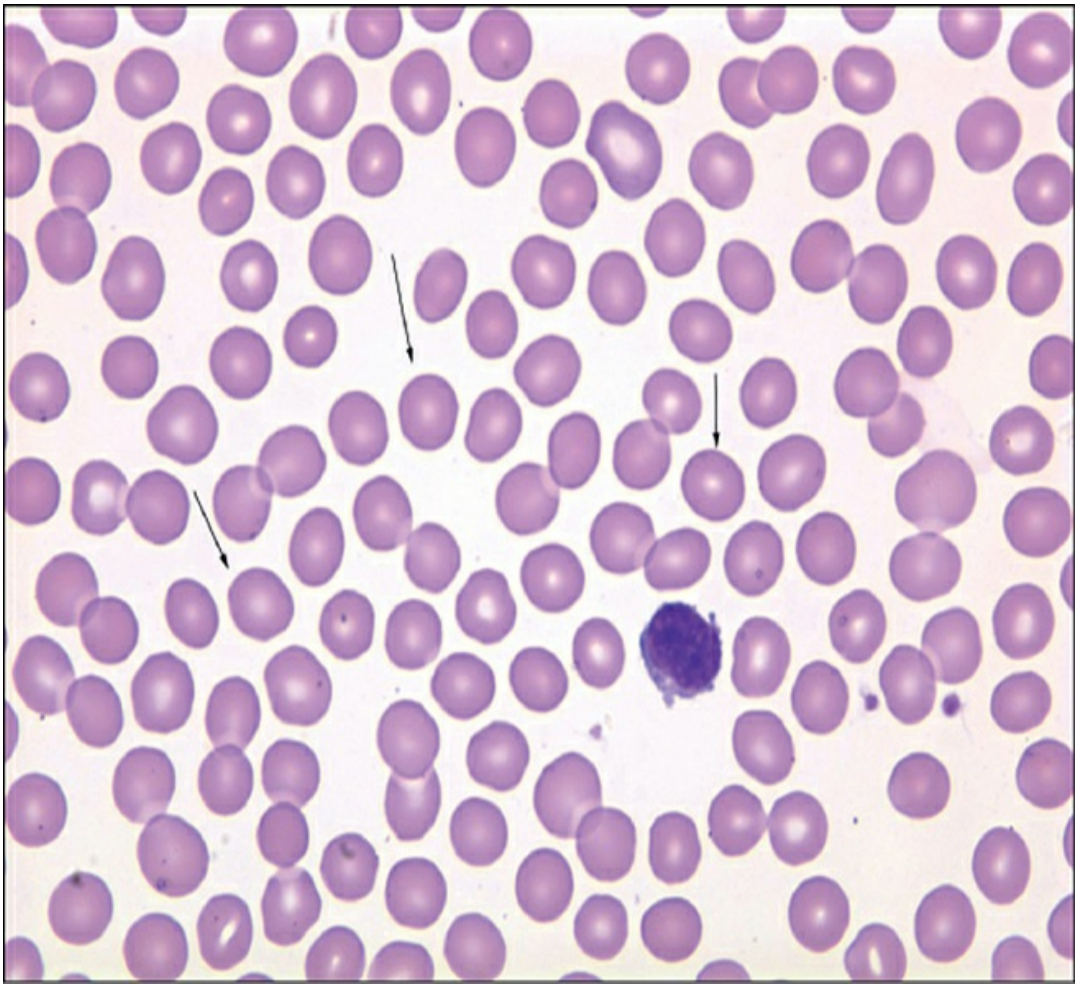


Figure **IA1-7**

Nucleus

None

Cytoplasm

Color: Pink, central pallor about 1/3 of the cell

Contents: No mitochondria

MEGALOBLASTIC MATURATION SERIES

Megaloblastic Series

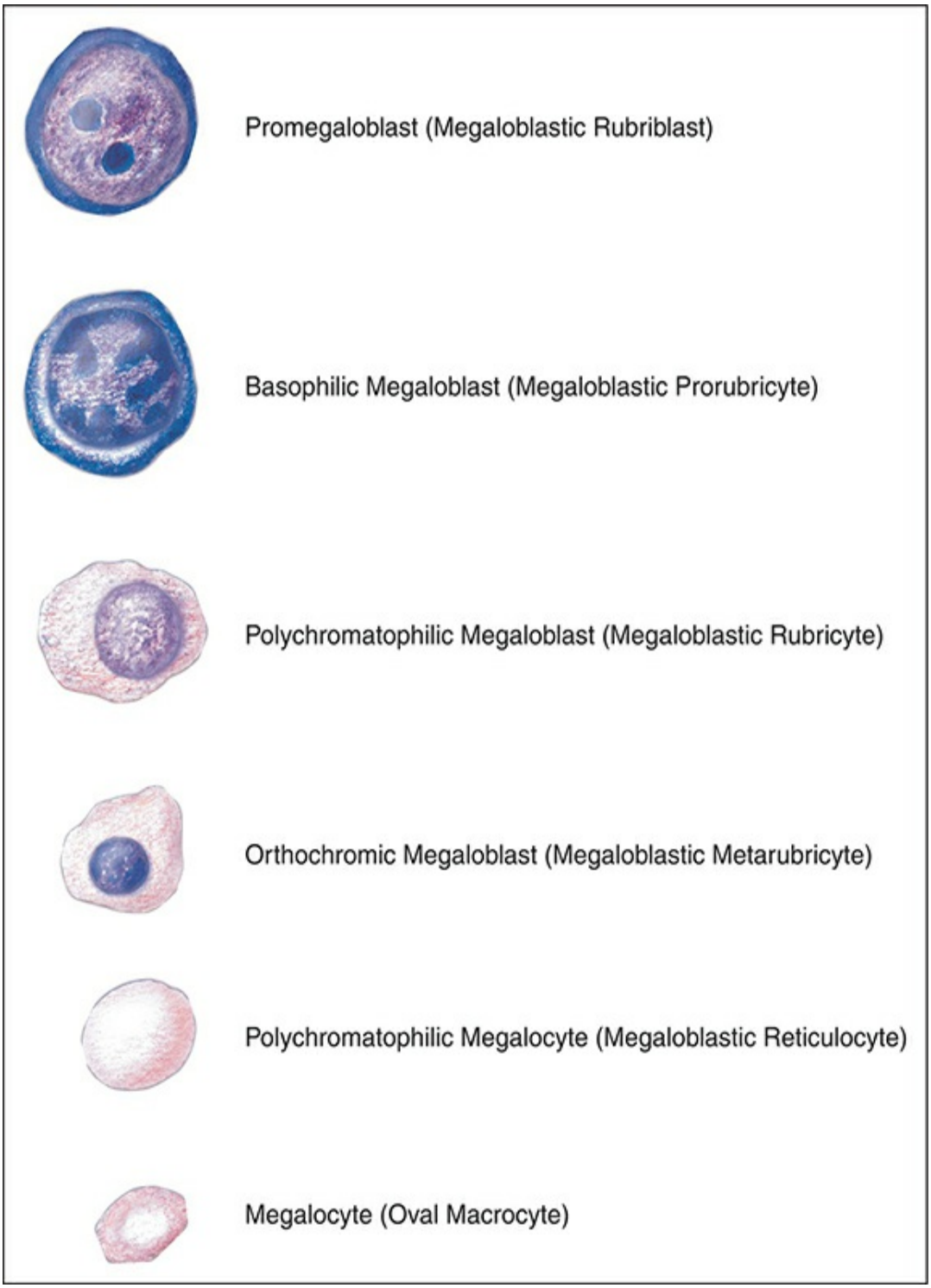


Figure IA1-8

Promegaloblast (Megaloblastic Rubriblast)

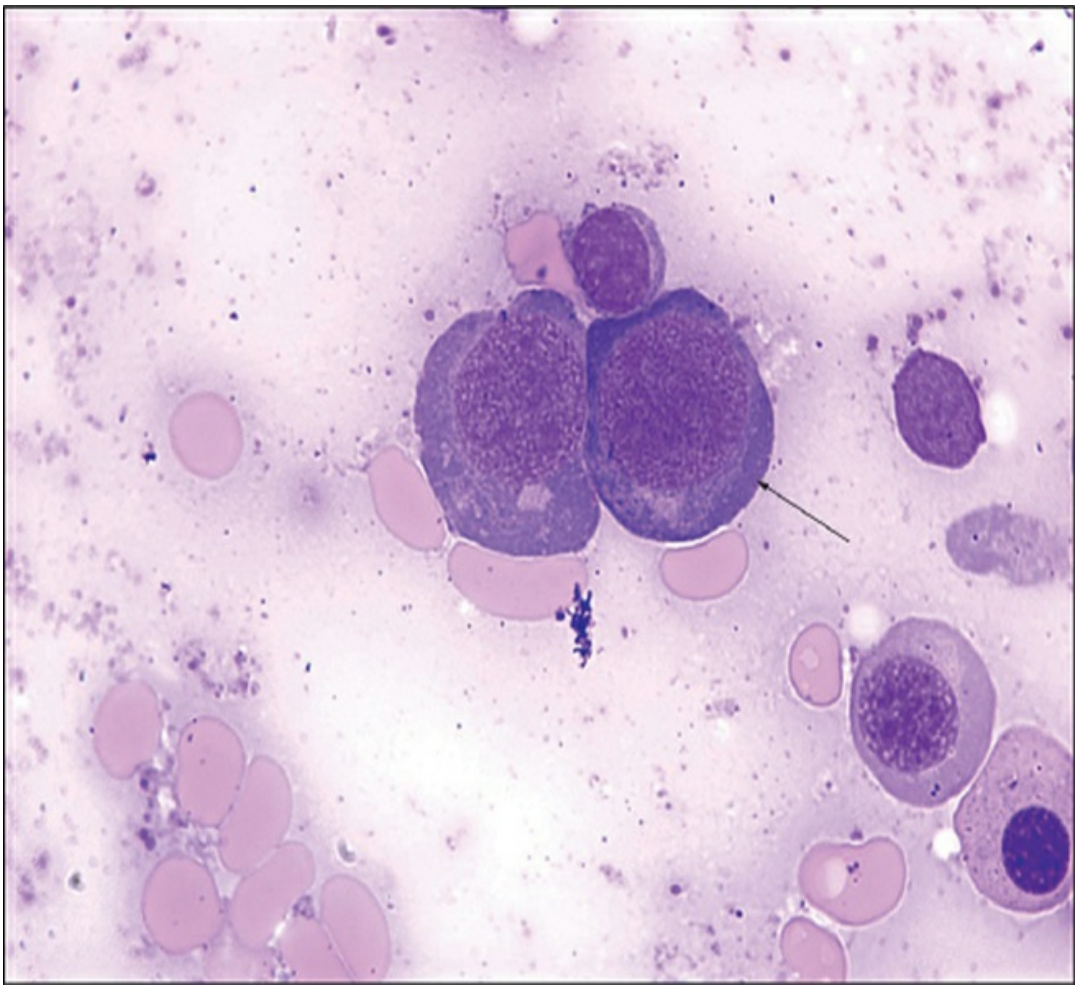


Figure IA1-9

Size: 19–27 µ

Nucleus

Shape: Round or irregular

N/C Ratio: 5:1

Color: Purple

Chromatin: Fine and closely meshed

Nucleoli: Multiple

Cytoplasm

Color: Deep blue

Contents: Nongranular with perinuclear halo

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic syndrome
- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Myelodysplastic syndromes

Basophilic Megaloblast (Megaloblastic Prorubricyte)

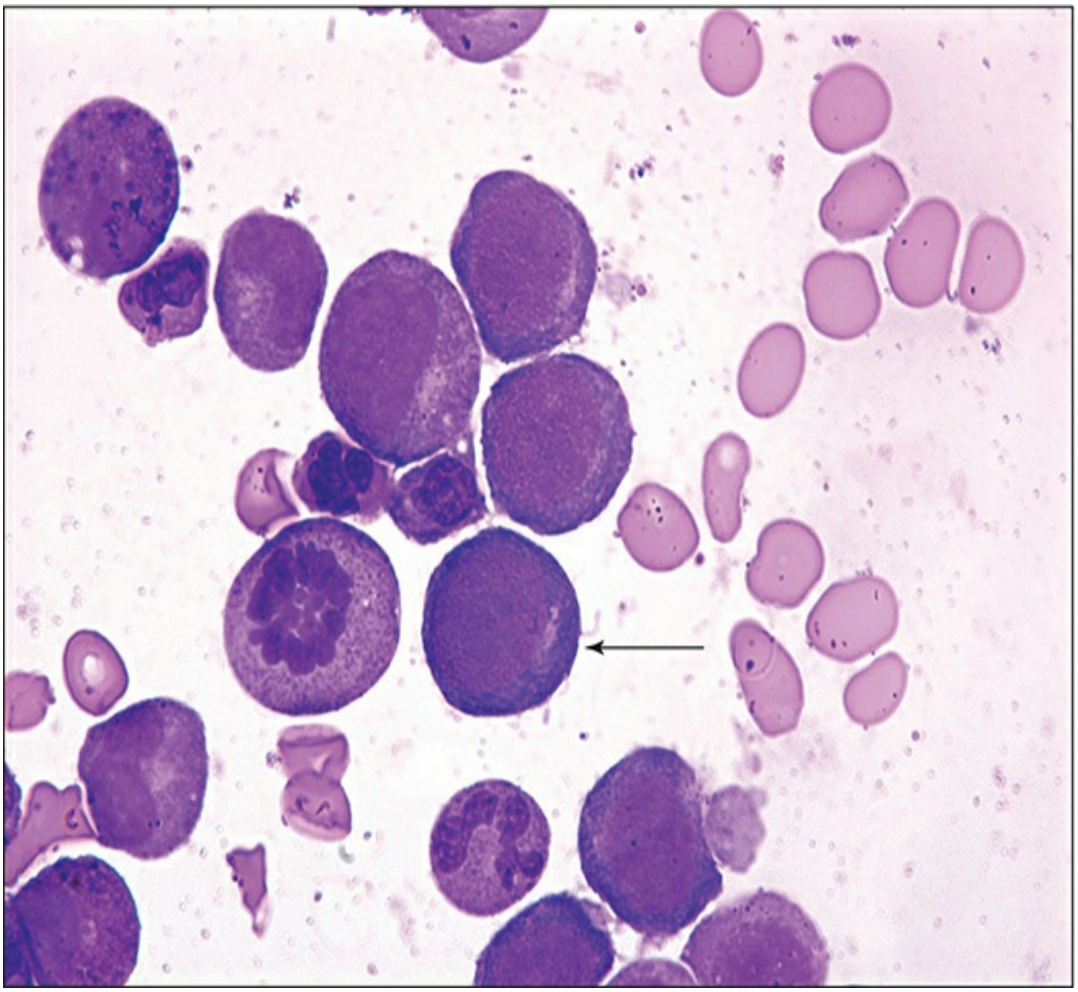


Figure IA1-10

Size: 17–24 μ

Nucleus

Shape: Round

N/C Ratio: 4:1

Color: Purple

Chromatin: Coarser than previous cell but still fine and open

Nucleoli: Not visible

Cytoplasm

Color: Deep blue

Contents: Faint perinuclear halo

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic syndrome
- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Myelodysplastic syndromes

Polychromatophilic Megaloblast (Megaloblastic Rubricyte)

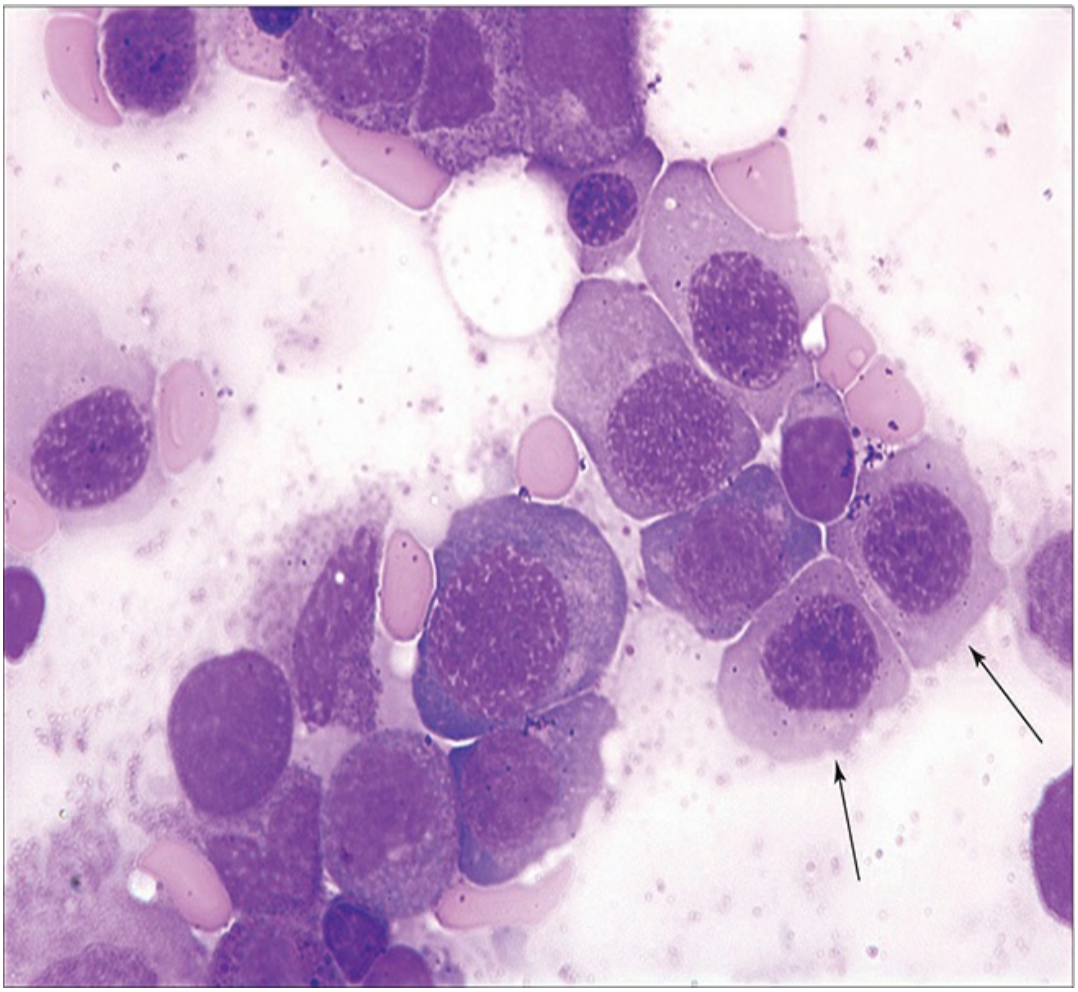


Figure **IA1-11**

Size: 15–20 μ

Nucleus

Shape: Round and central

N/C Ratio: 2:1

Color: Purple

Chromatin: Minimal clumping, loosely defined

Nucleoli: Not visible

Cytoplasm

Color: Blue-gray to pink-gray

Contents: More cytoplasm than in normoblastic cell

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic syndrome
- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Myelodysplastic syndromes

Orthochromic Megaloblast (Megaloblastic Metarubricyte)

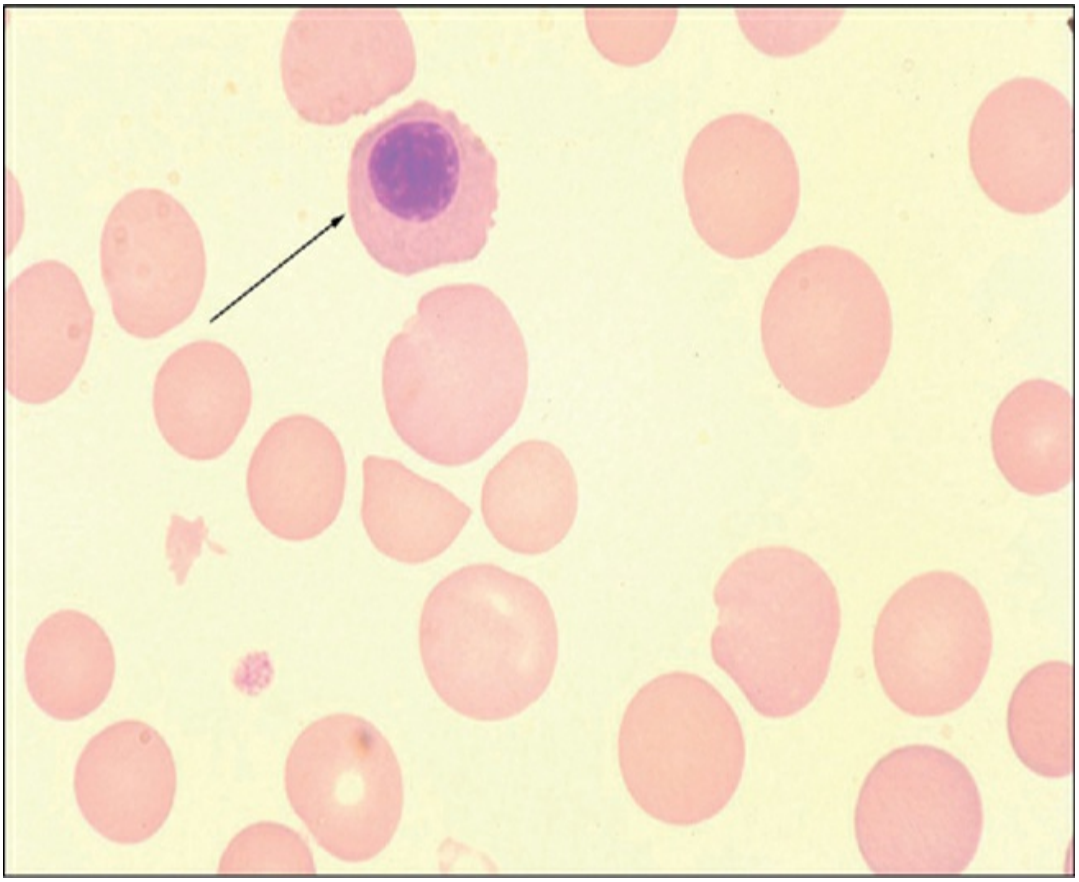


Figure IA1-12

Size: 10–15 µ

Nucleus

Shape: Round to slightly irregular, central or slightly eccentric

N/C Ratio: 1:1

Color: Deep purple but still some chromatin structure

Chromatin: Clumped, but less than in normoblastic cell

Nucleoli: Not visible

Cytoplasm

Color: Pink with hint of blue

Contents: More cytoplasm than in normoblastic cell

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic syndrome
- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Myelodysplastic syndromes

Polychromatophilic Megalocyte (Megaloblastic Reticulocyte)

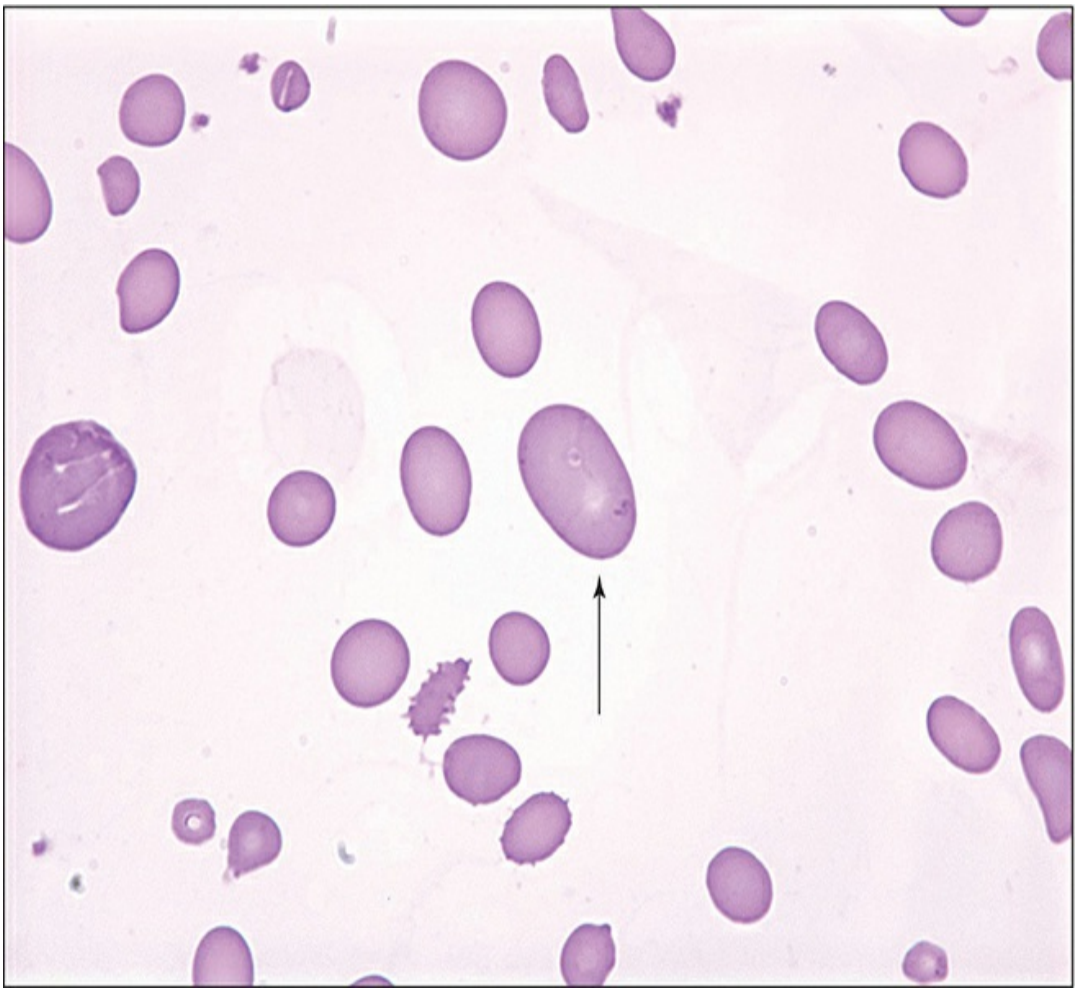


Figure **IA1-13**

Size: 9–15 µ

Nucleus

None

Cytoplasm

Color: Pink, with a hint of blue

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Congenital dyserythropoietic syndrome
- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)

- Myelodysplastic syndromes

Megalocyte (Oval Macrocyte)

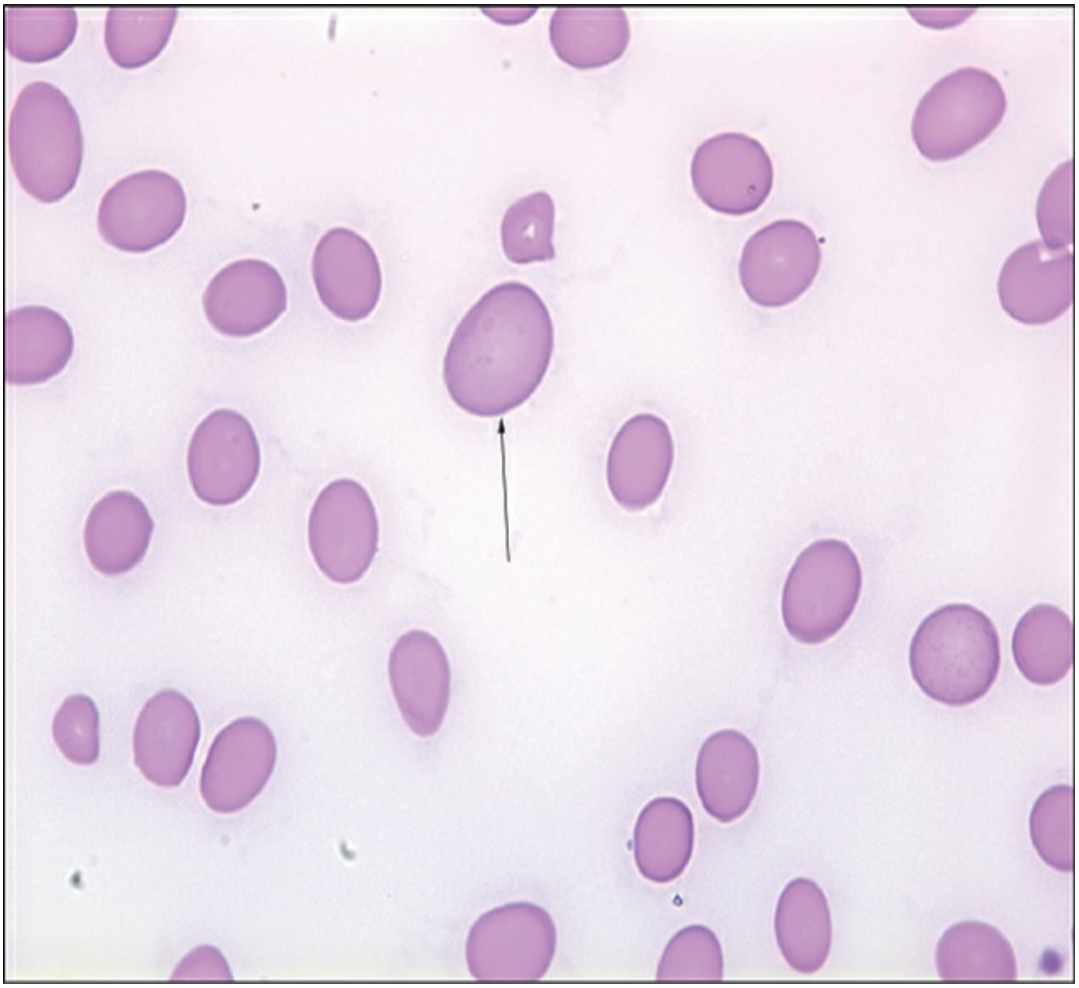


Figure IA1-14

Size: 9–12 µ

Nucleus

None

Cytoplasm

Color: Pink, central pallor less distinct

Contents: Increased hemoglobin content

Clinical Conditions

- Vitamin B_{12} deficiency

- Folic acid deficiency
- Congenital dyserythropoietic syndrome
- Myelodysplastic syndromes
- Newborn
- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)

IRON-DEFICIENT MATURATION SERIES

Iron-deficient Series

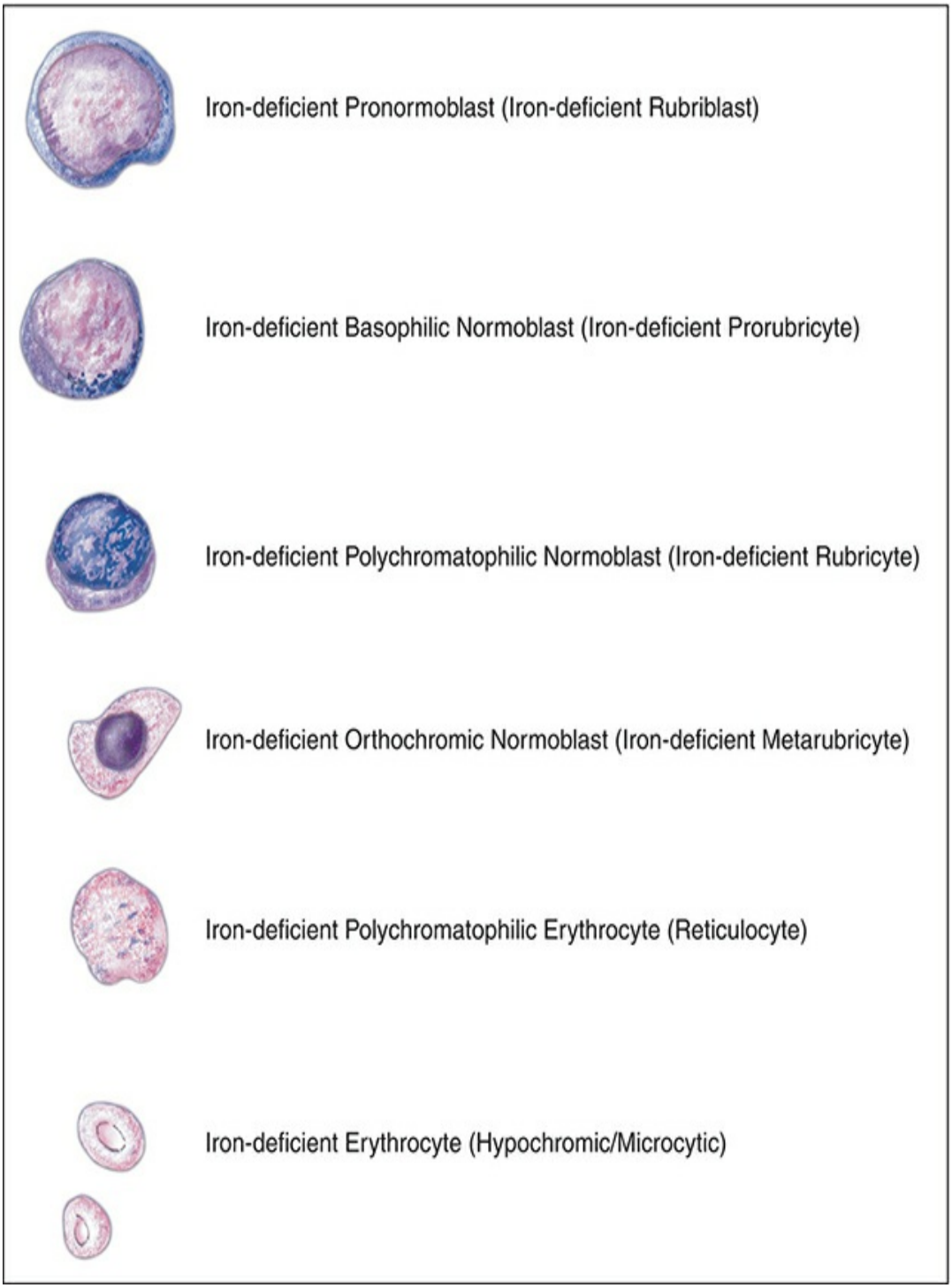


Figure IA1-15

Iron-deficient Pronormoblast (Iron-deficient Rubriblast)

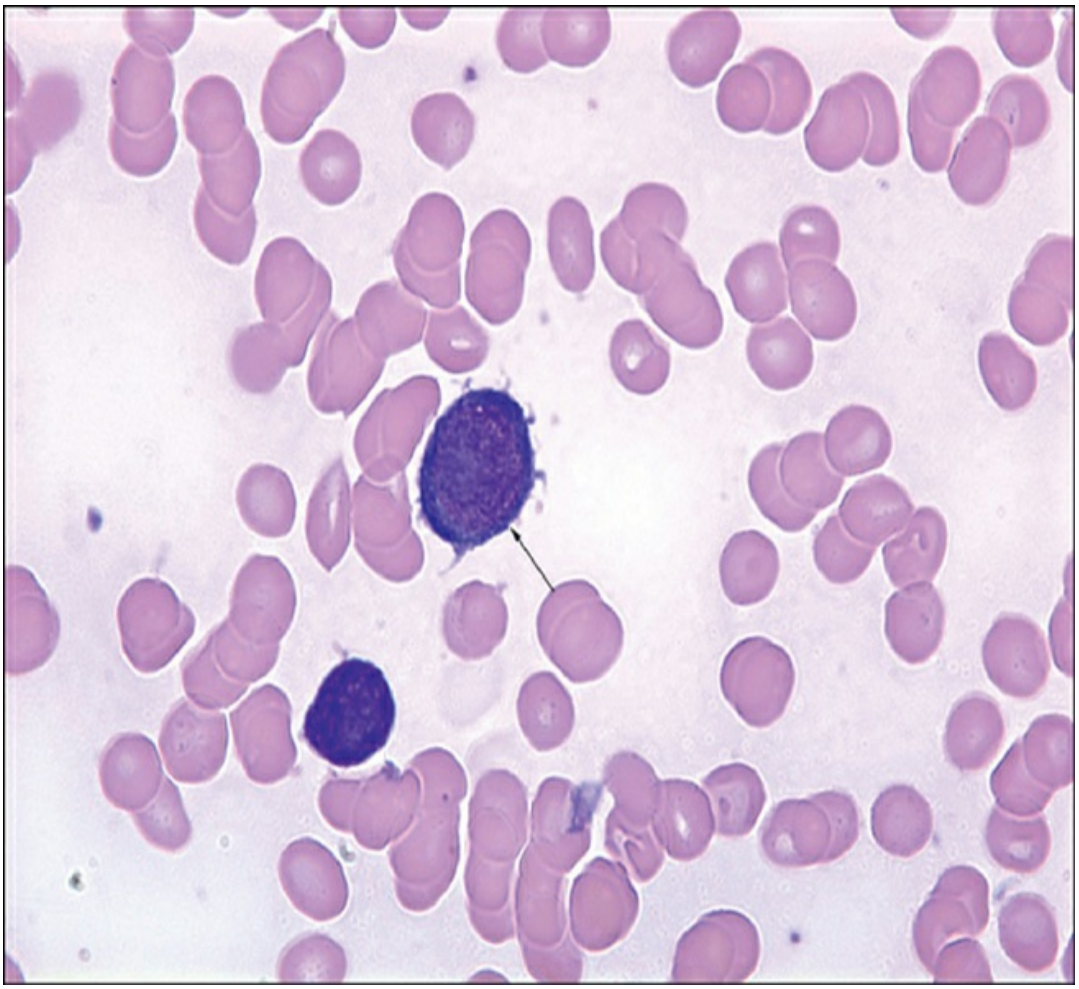


Figure IA1-16

Size: 14–20 µ

Nucleus

Shape: Irregularly round to slightly oval

N/C Ratio: 5:1

Color: Purple-red

Chromatin: Fine, but granular

Nucleoli: Present, but not distinct

Cytoplasm

Shape: Irregular

Color: Deep blue

Contents: Golgi; mitochondria, which produce a lighter blue perinuclear halo

Clinical Condition

- Iron deficiency

Iron-deficient Basophilic Normoblast (Iron-deficient Prorubricyte)

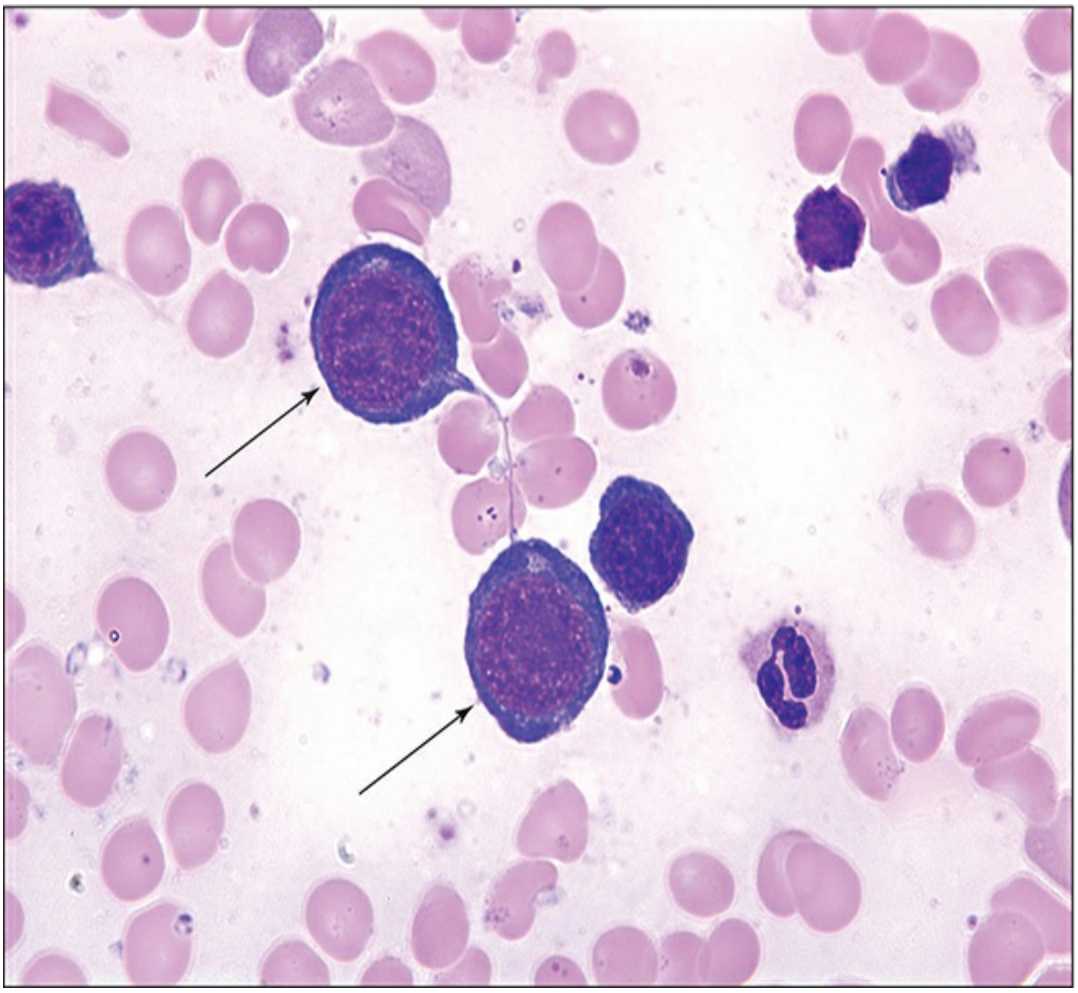


Figure IA1-17

Size: 10–15 µ

Nucleus

Shape: Round, centered

N/C Ratio: 5:1

Color: Purple, interspersed with light areas

Chromatin: Granular to slightly lumpy

Nucleoli: Usually not visible

Cytoplasm

Shape: Irregular

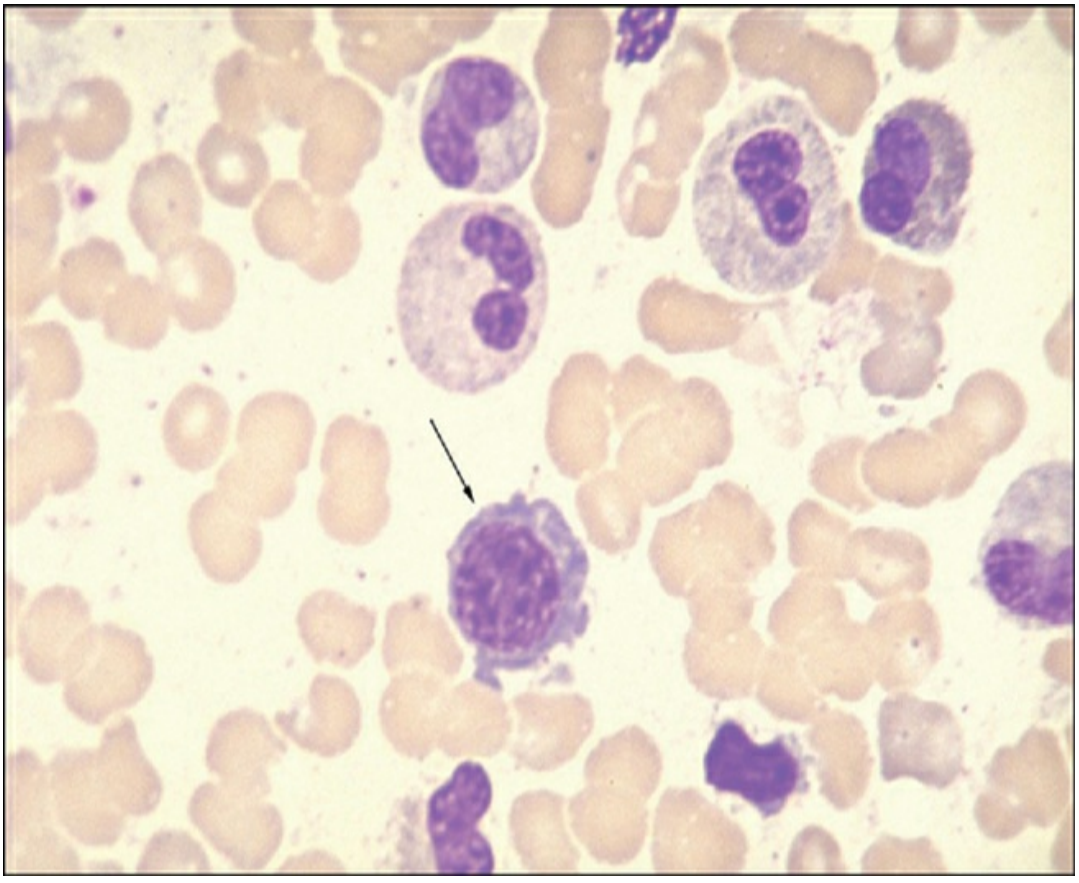
Color: Deep blue

Contents: Golgi may produce a light blue area near the nucleus; many mitochondria

Clinical Condition

- Iron deficiency

Iron-deficient Polychromatophilic Normoblast (Iron-deficient Rubricyte)



Size: 9–12 μ

Nucleus

Shape: Round

N/C Ratio: 2:1

Color: Purple-red

Chromatin: Lumpy with lighter parachromatin

Nucleoli: None

Cytoplasm

Color: Bluer than when found in normoblastic maturation

Contents: Less amount with shaggy blunt extensions

Clinical Condition

- Iron deficiency

Iron-deficient Orthochromic Normoblast (Iron-deficient Metarubricyte)

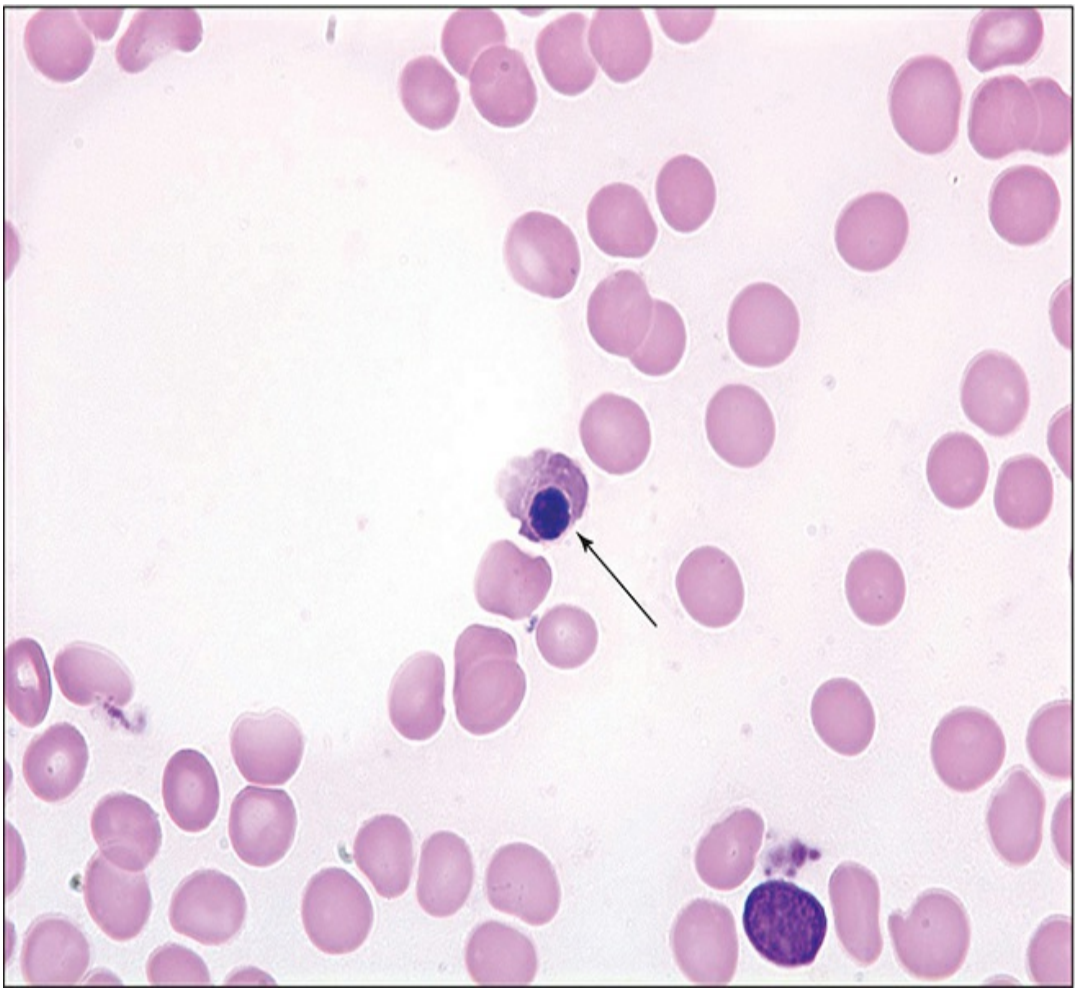


Figure **IA1-19**

Size: 7–11 µ

Nucleus

Shape: Round

N/C Ratio: 1:2

Color: Blue-purple

Chromatin: Condensed and homogeneous

Nucleoli: None

Cytoplasm

Shape: Irregular

Color: Pink with residual blueness of RNA

Clinical Condition

- Iron deficiency

Iron-deficient Polychromatophilic Erythrocyte (Reticulocyte)

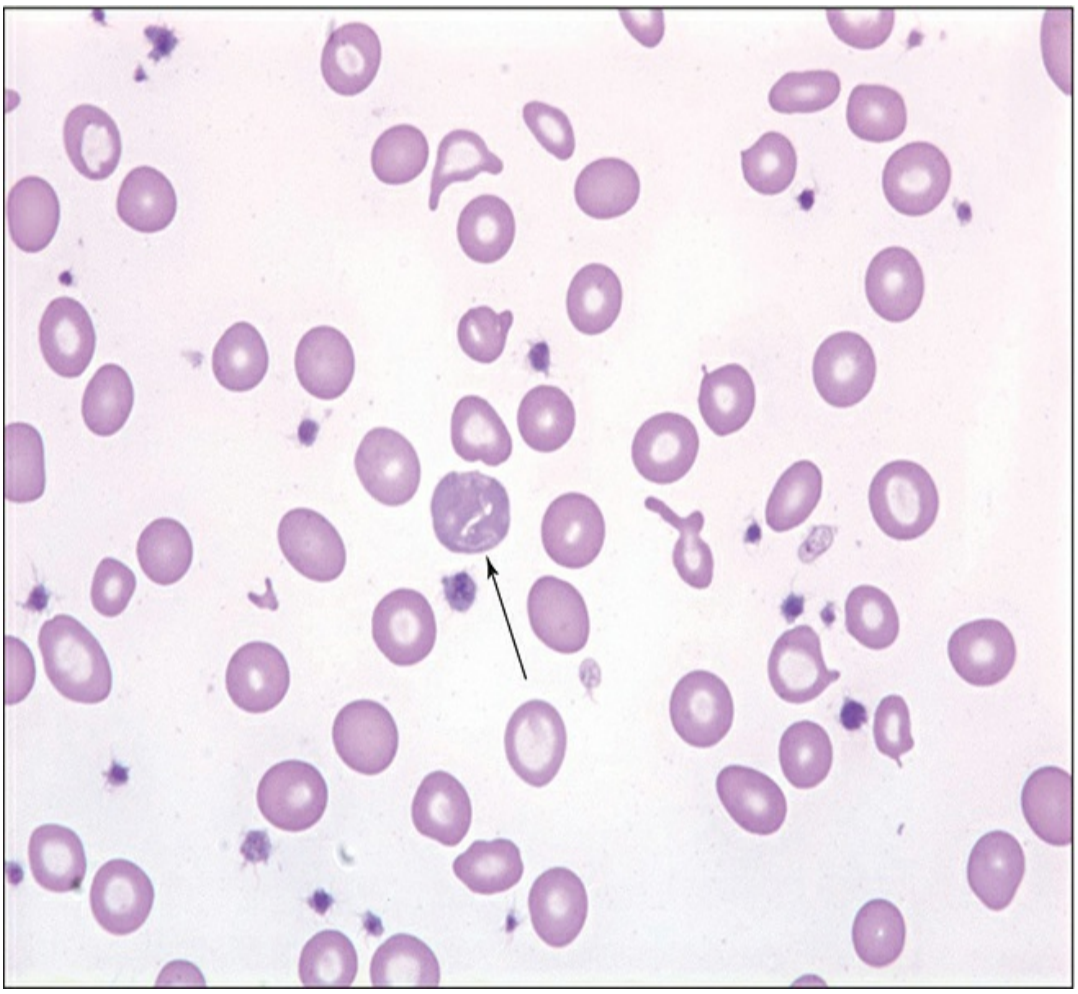


Figure IA1-20

Size: <6.5–10 µ

Nucleus

None

Cytoplasm

Color: Pink, with a hint of blue

Clinical Condition

- Iron deficiency

Iron-deficient Erythrocyte (Hypochromic/Microcytic)

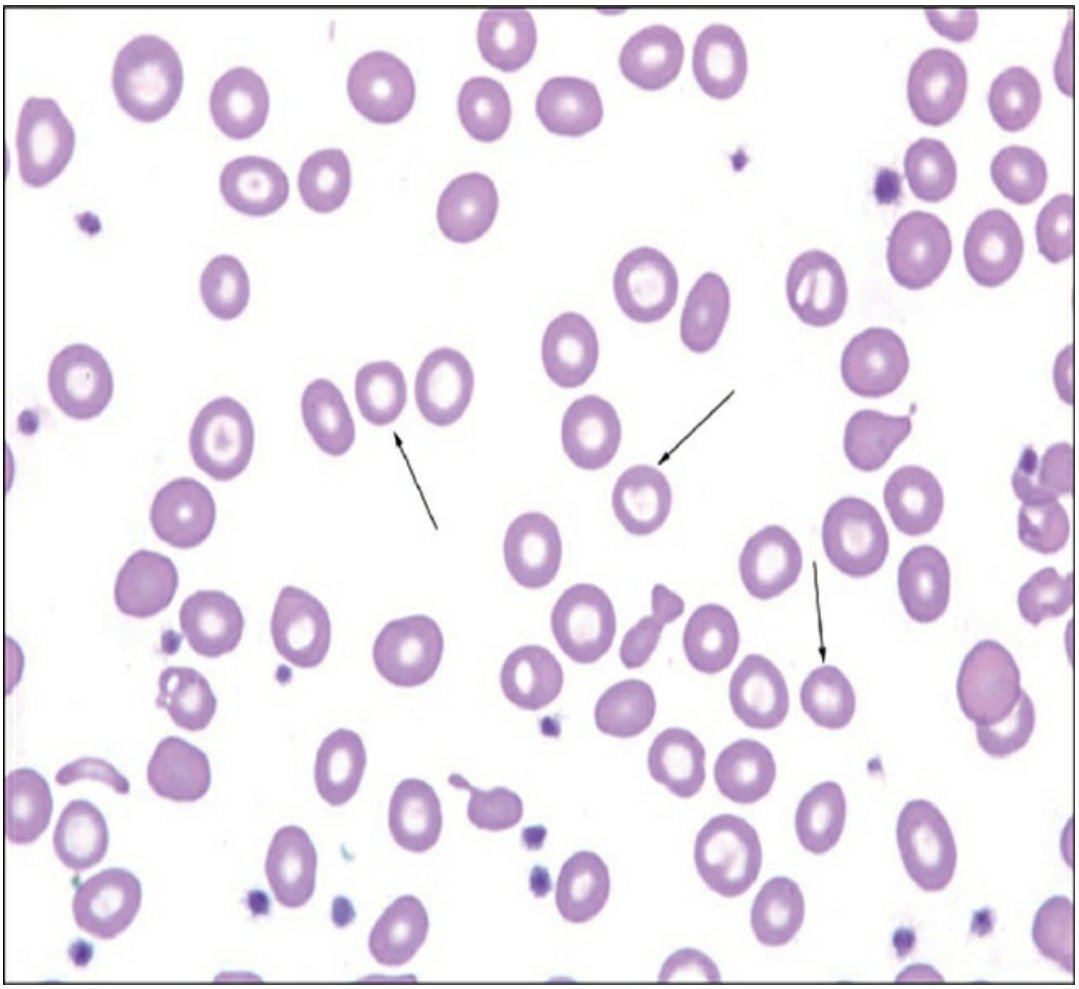


Figure IA1-21

Size: <6.5 µ

Nucleus

None

Cytoplasm

Color: Pink, central pallor greater than one-third of cell

Contents: Hemoglobin decreased

Clinical Condition

- Iron deficiency

DISTRIBUTION

Agglutination

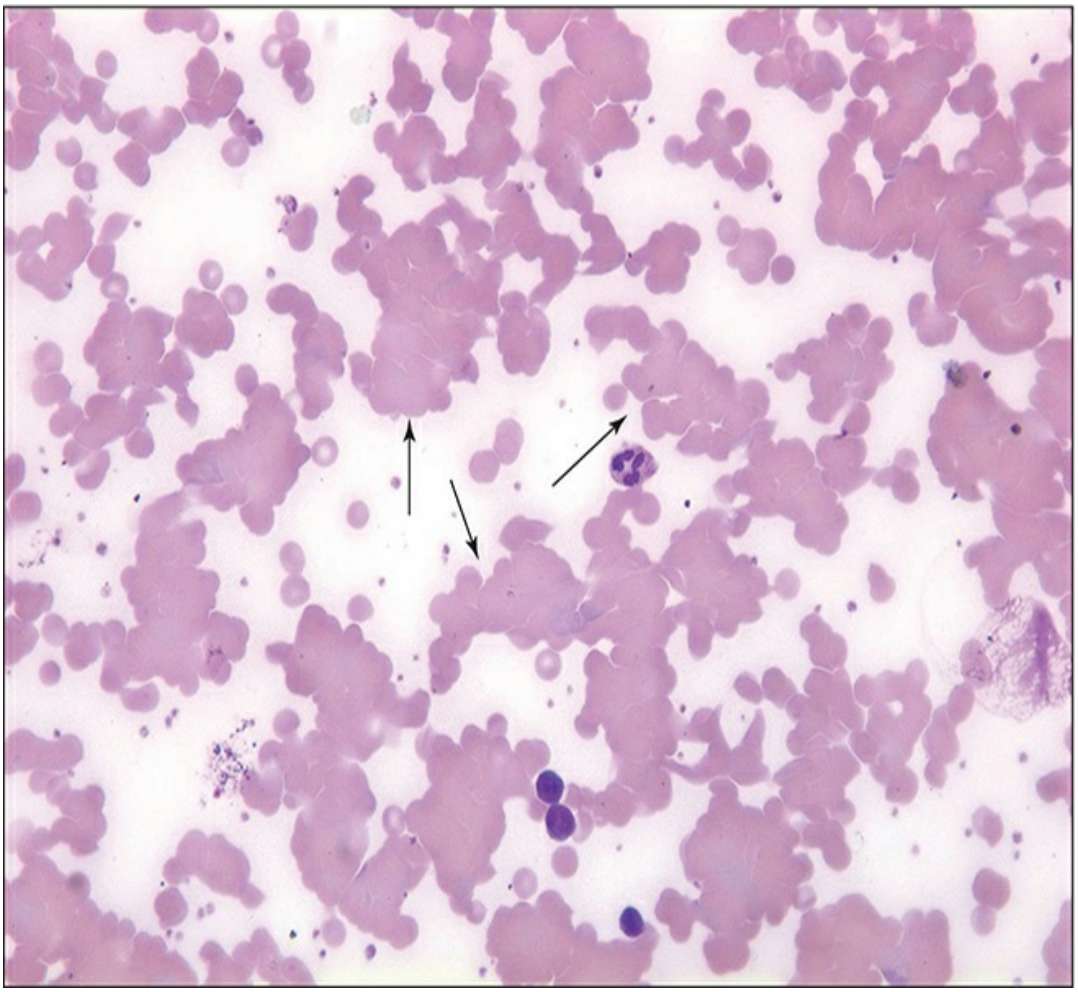


Figure IA1-22

Cell Type

Mature red blood cells

Description

Random masses or clusters of cells

Clinical Conditions

- Exposure to a variety of antibodies
- Hemolytic anemia (autoimmune)
- Atypical pneumonia

- Staphylococcal infections
- Trypanosomiasis
- Cold agglutinin disease

Rouleaux

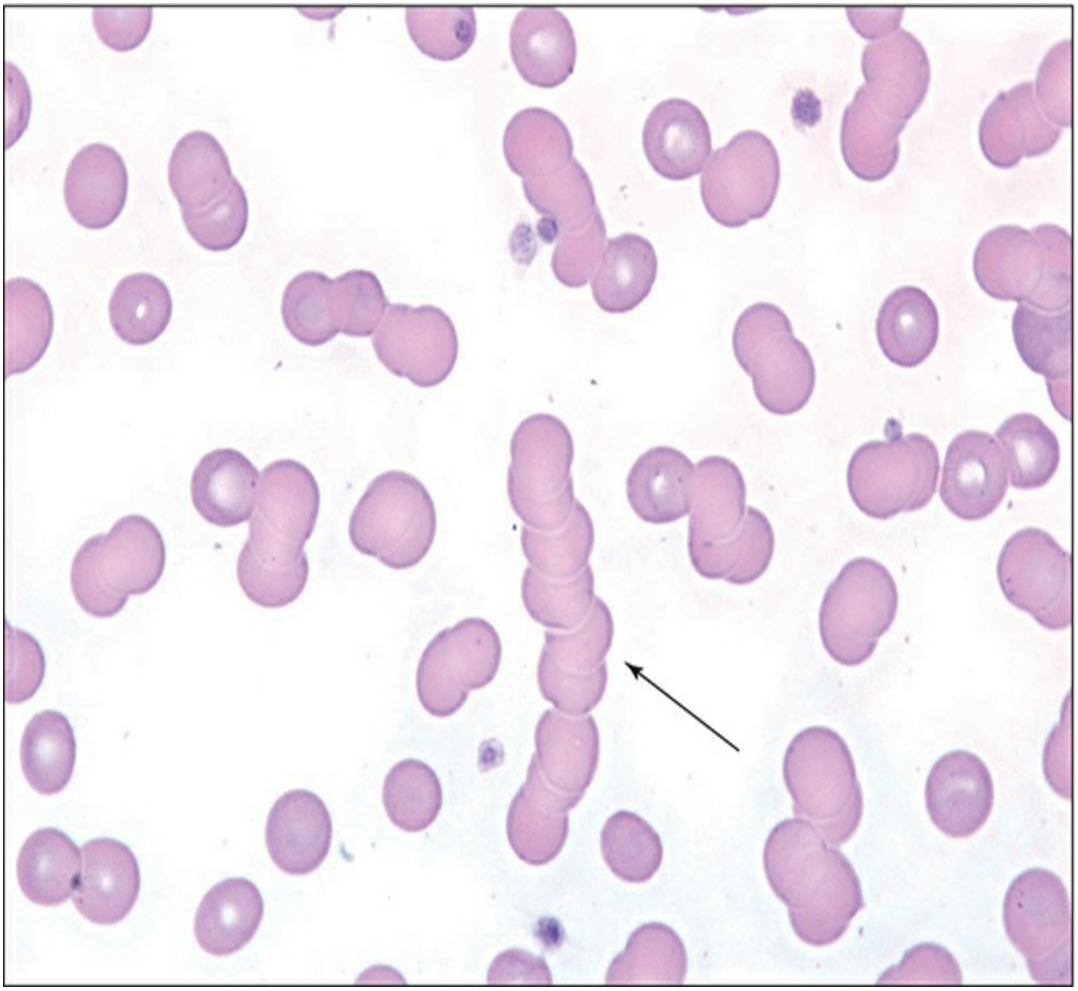


Figure IA1-23

Cell Type

Mature red blood cell

Description

Short or long stacks of cells (3 or 4 or more) resembling coins; often a blue-staining background is also present

Clinical Conditions

- Hyperproteinemia
- Multiple myeloma
- Macroglobulinemia
- Increased fibrinogen (infection, pregnancy)

SHAPES

Acanthocyte

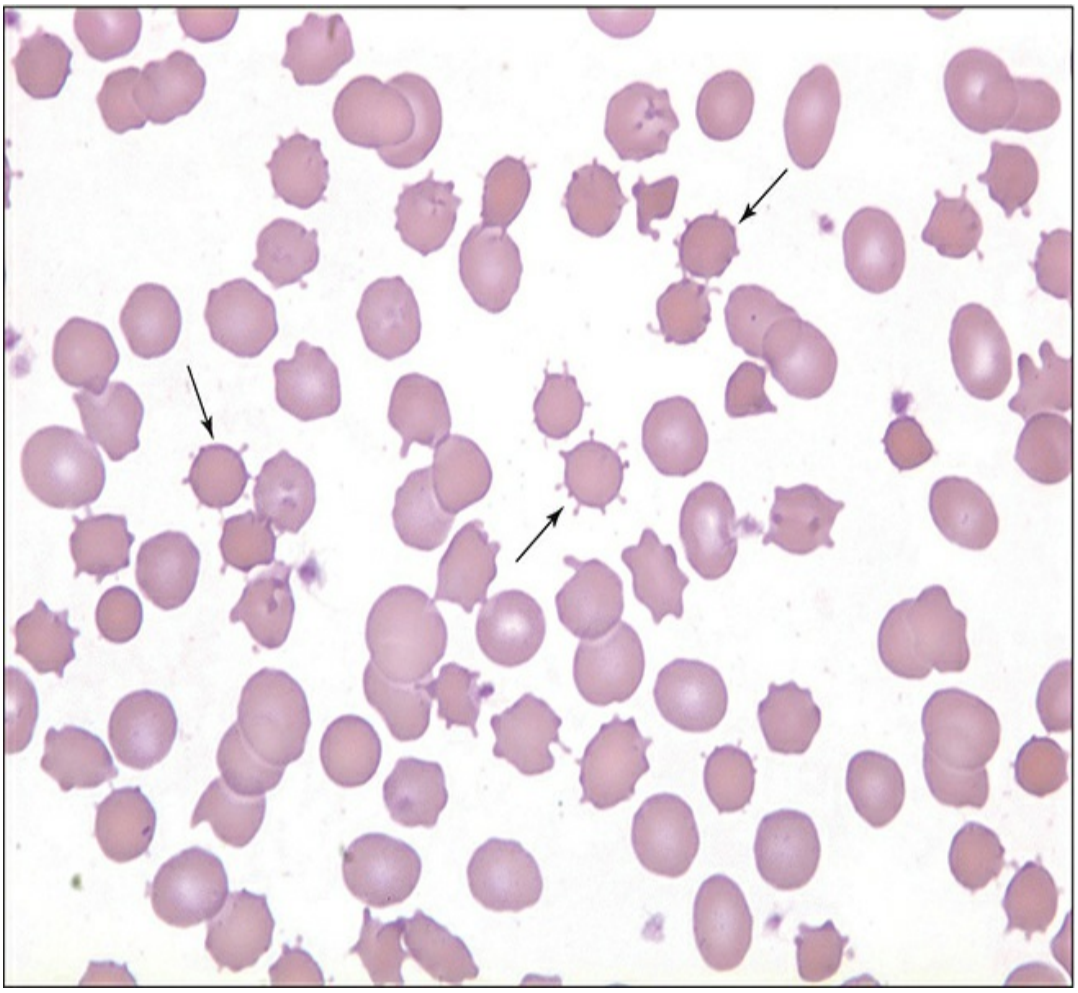


Figure IA1-24

Cell Type

Mature red blood cell

Description

Spherical and densely stained cell with 3–12 spicules of uneven length and width around the surface

Clinical Conditions

- Inherited lipid disorder (abetalipoproteinemia)
- Alcoholic cirrhosis

- Malabsorption states
- Neonatal hepatitis
- Pyruvate kinase deficiency

Codocyte (Target Cell)

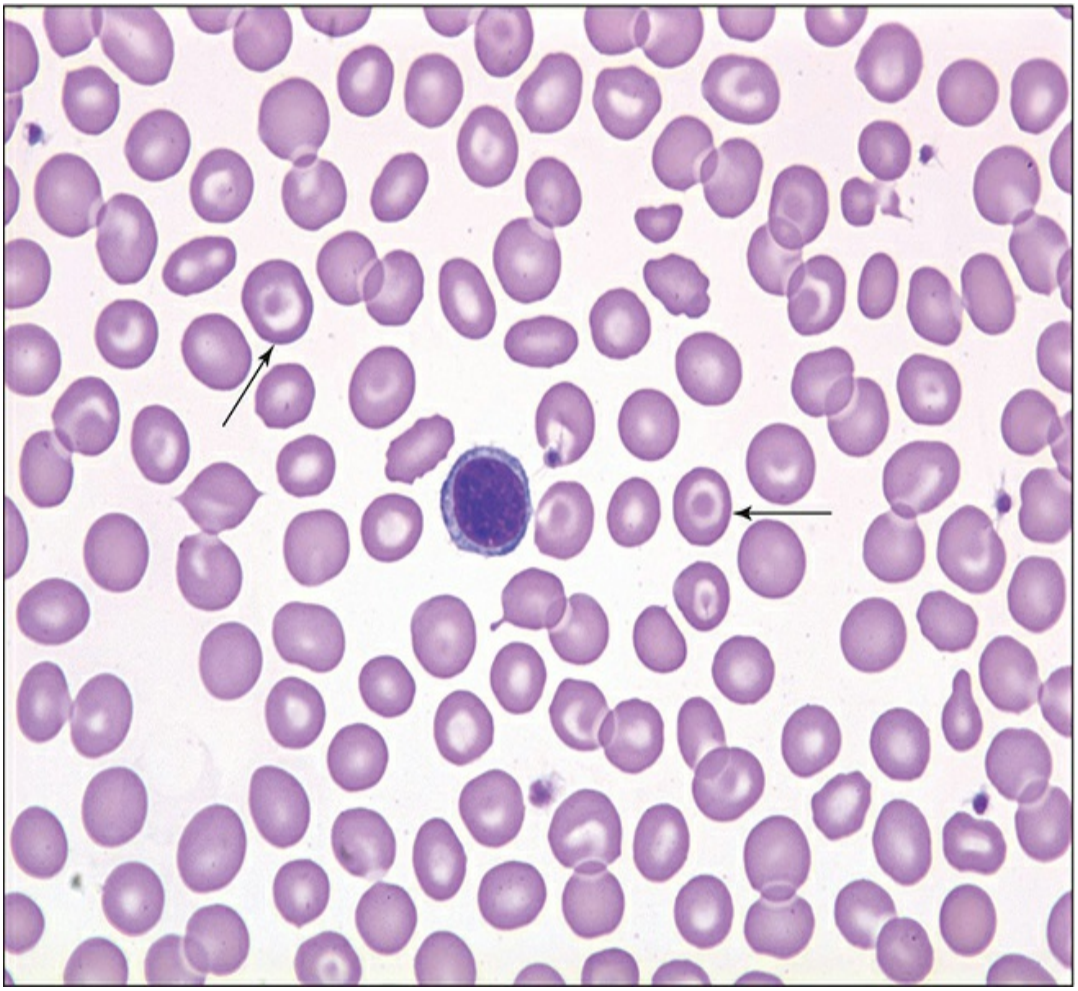


Figure IA1-25

Cell Type

Mature red blood cell

Description

Bell shaped with thin wall having a greater than normal surface membrane to volume ratio; central area of

hemoglobin, a clear ring, and a peripheral ring of hemoglobin giving an appearance of a bull's eye

Clinical Conditions

- Hemoglobinopathies
- Thalassemia
- Obstructive liver disease
- Iron deficiency anemia

Dacryocyte (Teardrop Cell)

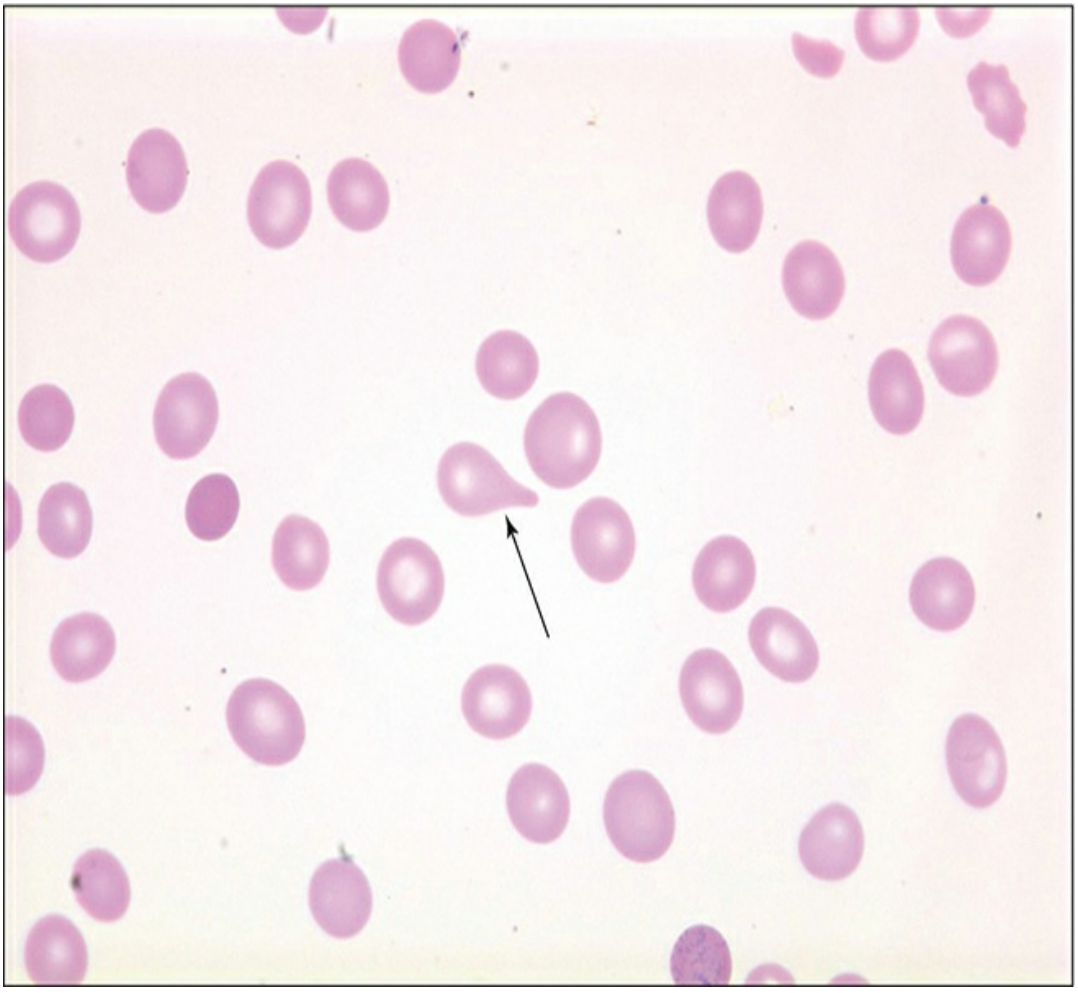


Figure IA1-26

Cell Type

Mature red blood cell

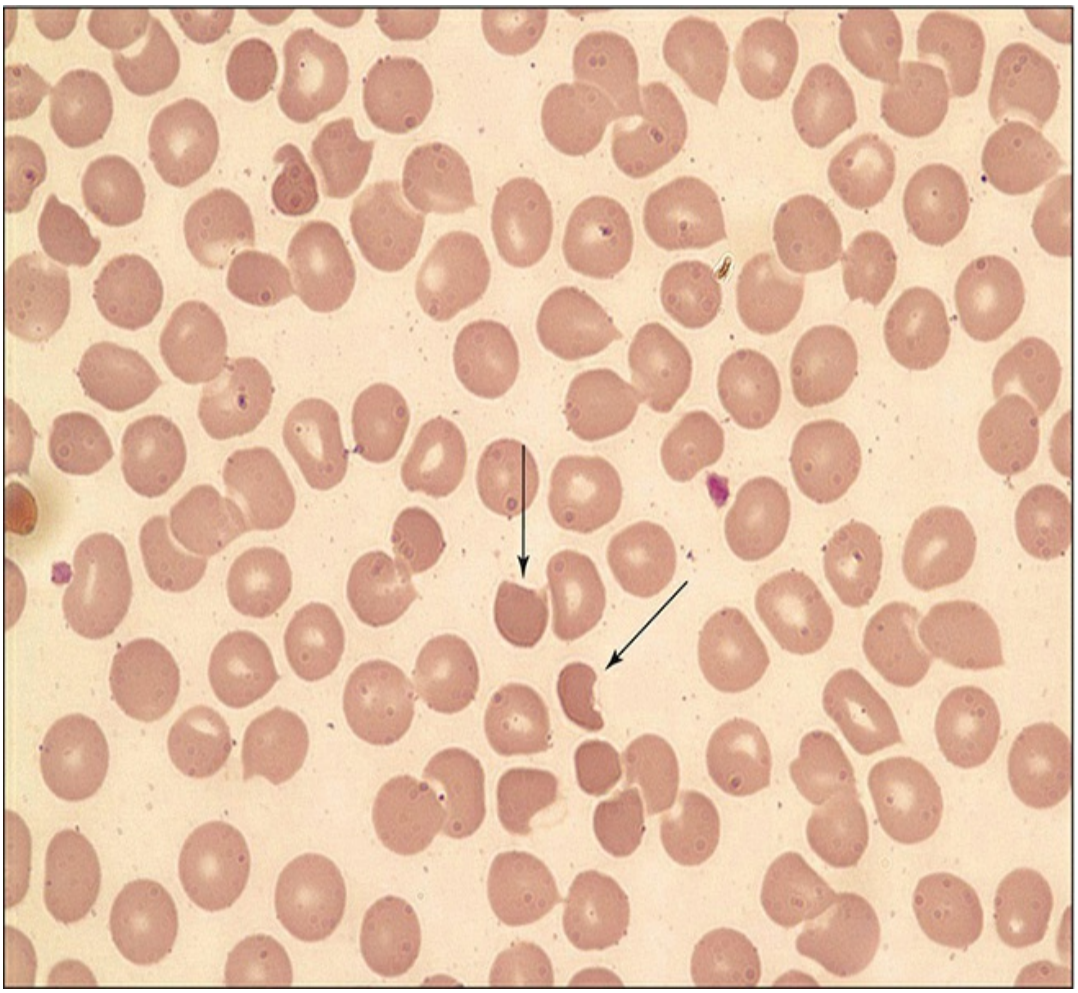
Description

Pear-shaped cell with blunt pointed projection

Clinical Conditions

- Extramedullary hematopoiesis (myelofibrosis, myelophthisic anemia)
- Megaloblastic anemia
- Thalassemia
- Hypersplenism

Degmacyte (Bite Cell)



Cell Type

Mature red blood cells

Description

Semicircular area (denatured and precipitated masses of hemoglobin) of cell removed by spleen; these cells may show multiple peripheral defects

Clinical Conditions

- Drug-induced anemias
- Glucose-6-phosphate dehydrogenase deficiency
- Thalassemia
- Unstable hemoglobinopathies

Drepanocyte (Sickle Cell)

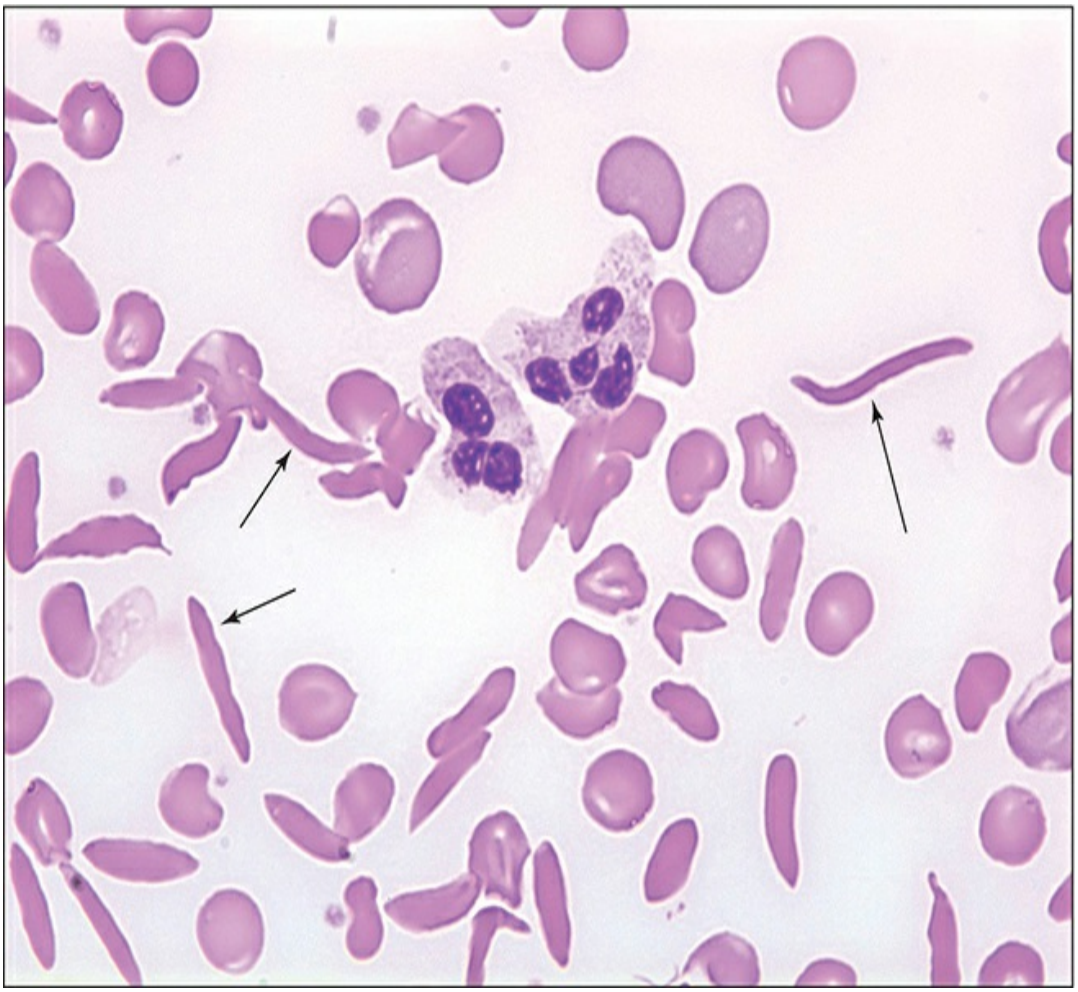


Figure IA1-28

Cell Type

Mature red blood cells

Description

Elongated cell due to polymers of abnormal hemoglobin; terminal projections causing the cell to take on an irregular shape; usually lack a central pallor

Clinical Condition

- Hemoglobinopathies (SS, SC, SD, S-β thalassemia)

Echinocyte (Burr Cell)

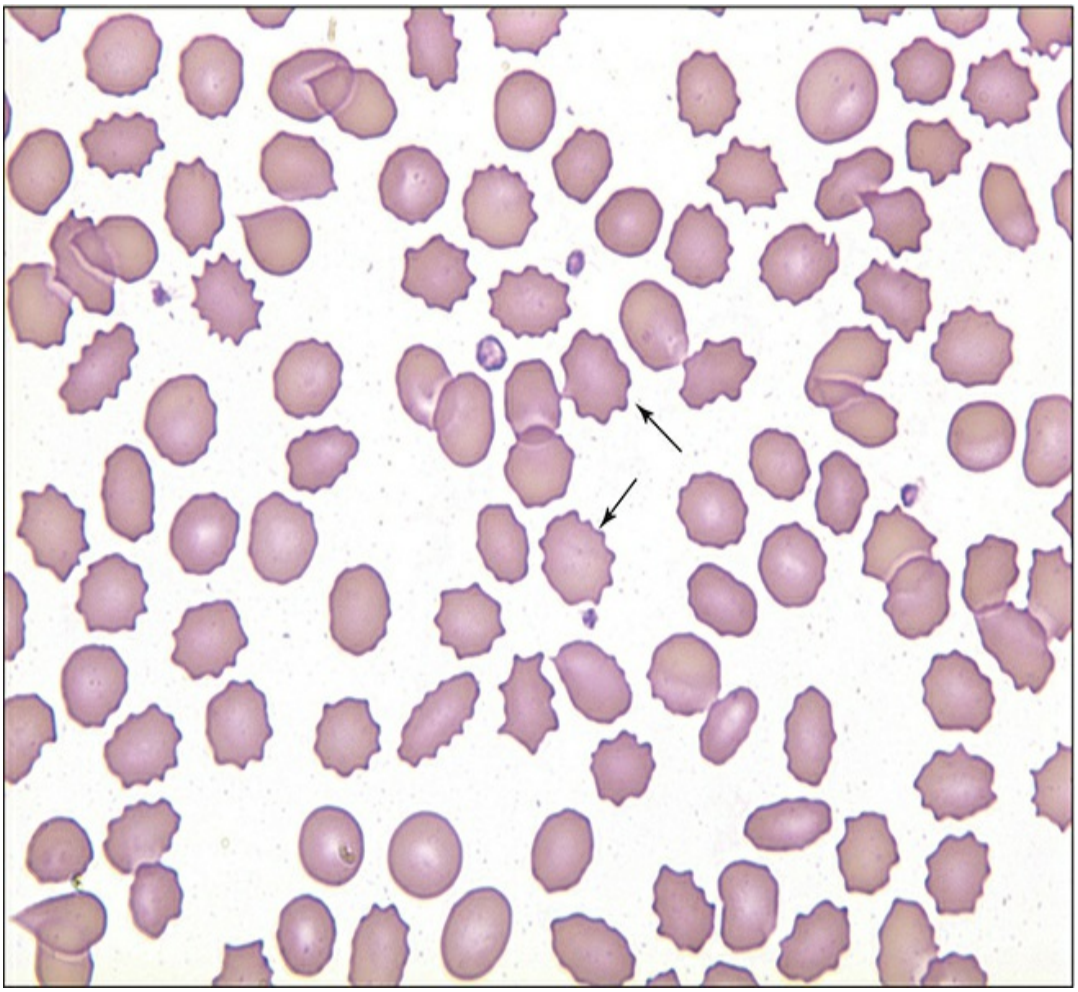


Figure **IA1-29**

Cell Type

Mature red blood cells

Description

Cell with evenly distributed, short spicules; the spicules have a blunt end; retains central pallor

Clinical Conditions

- Slow drying in high humidity
- Renal insufficiency
- Pyruvate kinase deficiency
- Stored blood
- Severe dehydration

- Burns

Keratocyte (Horn Cell)

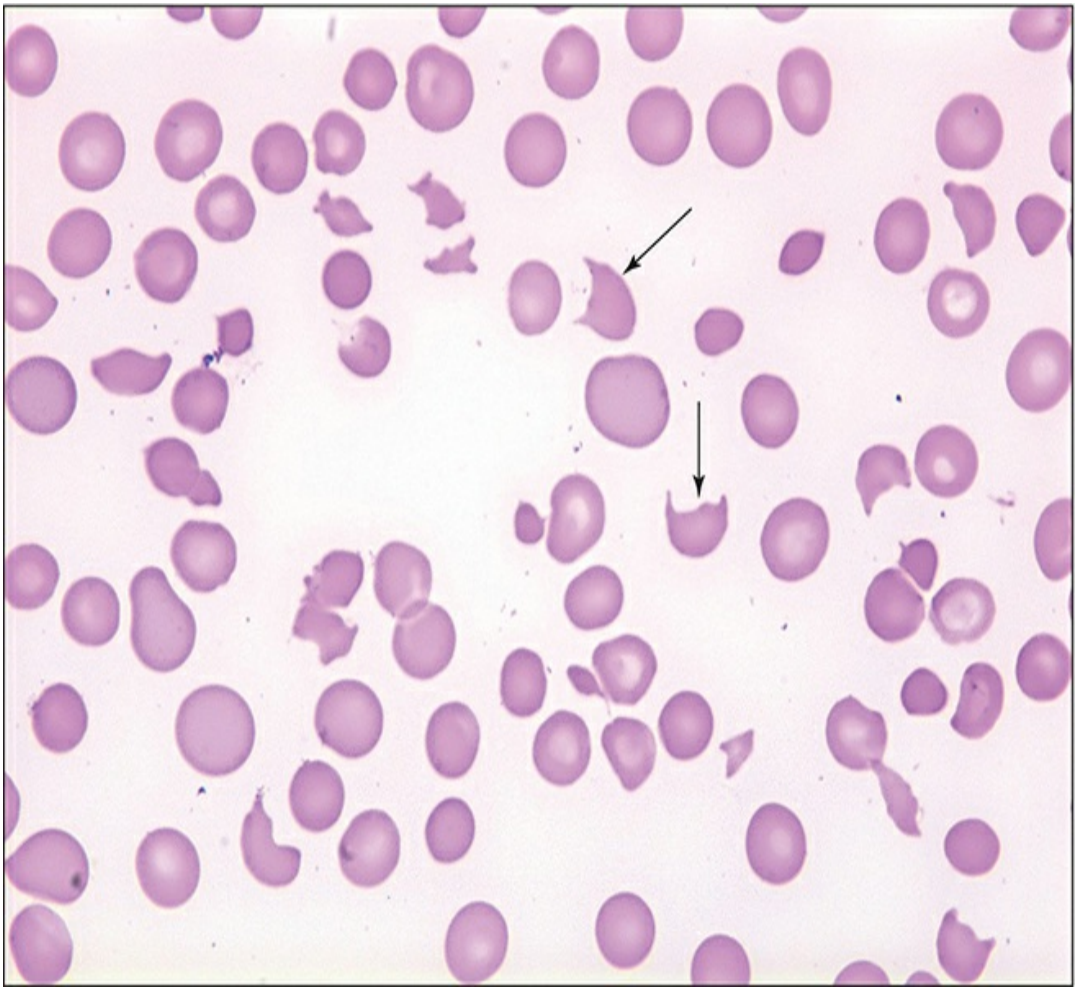


Figure IA1-30

Cell Type

Mature red blood cells

Description

Cell with projections (usually two) that resemble horns

Clinical Conditions

- Microangiopathic hemolytic anemia

- Glomerulonephritis
- Waring blender syndrome
- Pyruvate kinase deficiency

Knizocyte (Pinch Cell)

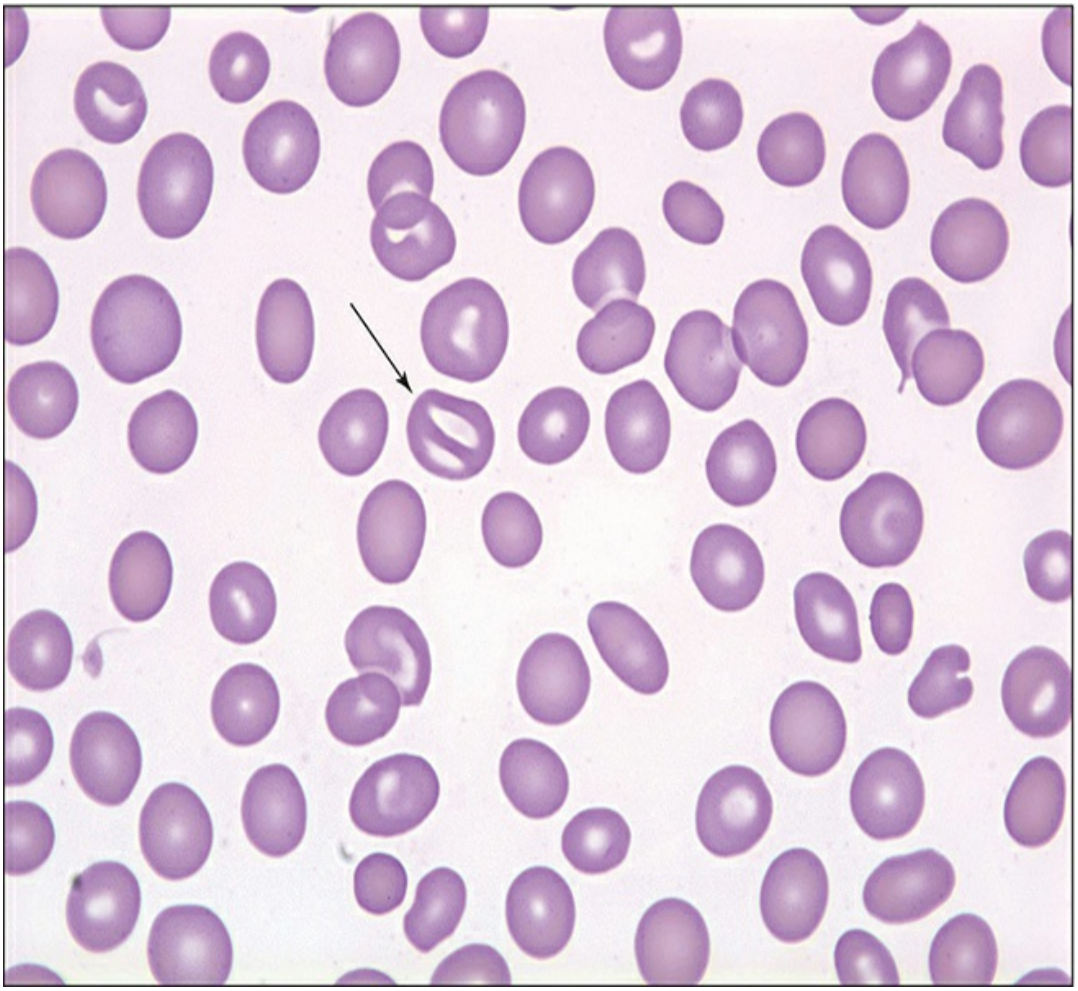


Figure IA1-31

Cell Type

Mature red blood cells

Description

Cell with triconcave shape having two central pallors

Clinical Conditions

- Hemolytic anemia
- Hemoglobinopathies
- Pancreatitis

Ovalocyte (Elliptocyte)

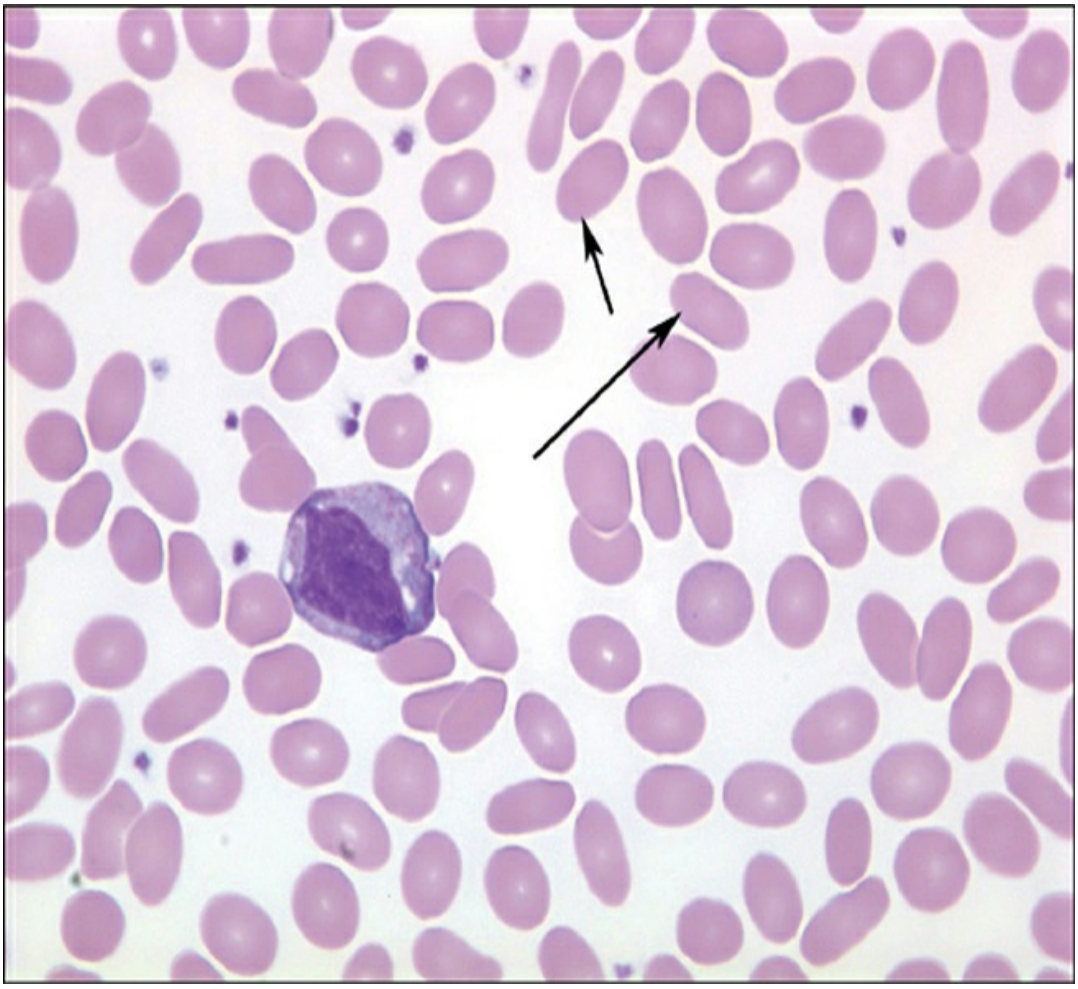


Figure IA1-32

Cell Type

Mature red blood cells

Description

Oval-shaped cell (may be slightly egg shaped, rod shaped, or pencil shaped); hemoglobin is concentrated at two

ends; normal central pallor

Clinical Conditions

- Hereditary elliptocytosis
- Iron deficiency anemia
- Myelophthisic anemia
- Megaloblastic anemia
- Thalassemia
- Sideroblastic anemia
- Congenital dyserythropoietic anemia

Pyknocyte (Blister Cell)

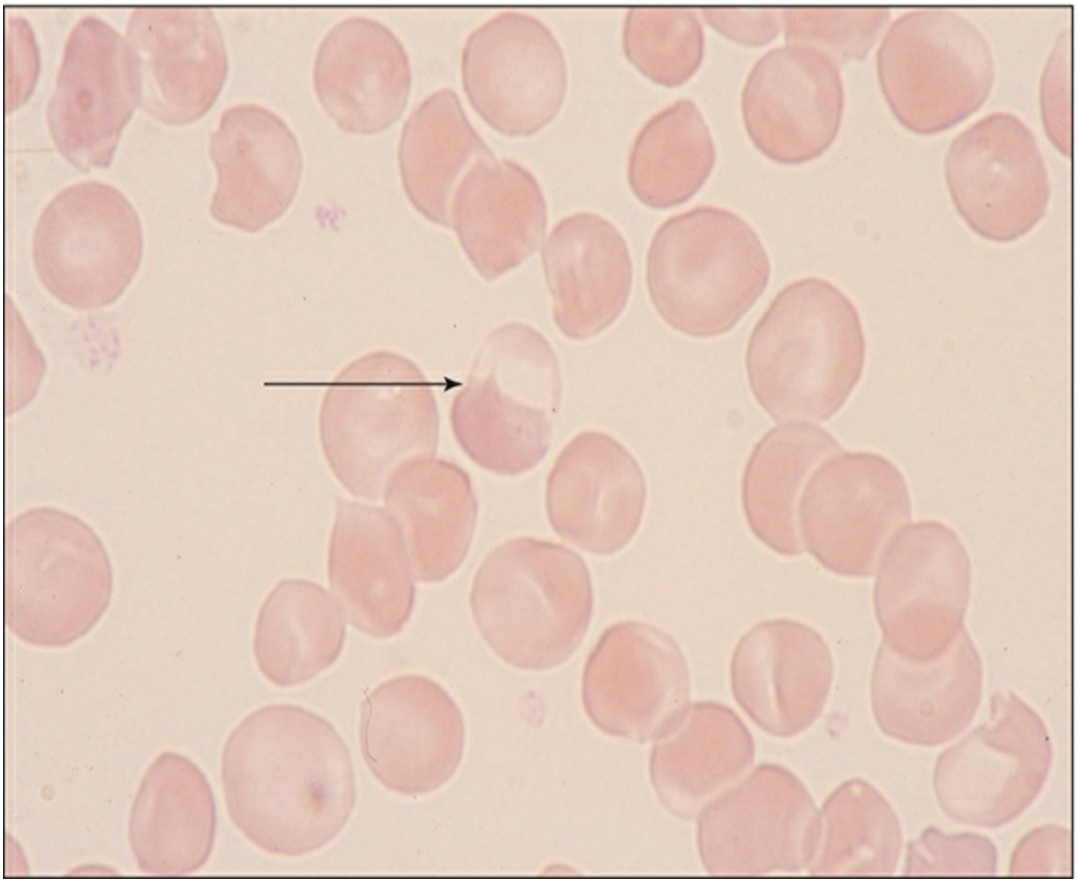


Figure IA1-33

Cell Type

Mature red blood cells

Description

Cell with clearing on one side and concentrated area of hemoglobin on the other

Clinical Conditions

- Infantile pyknocytosis
- Infantile viremia

Schistocyte (Schizocyte)

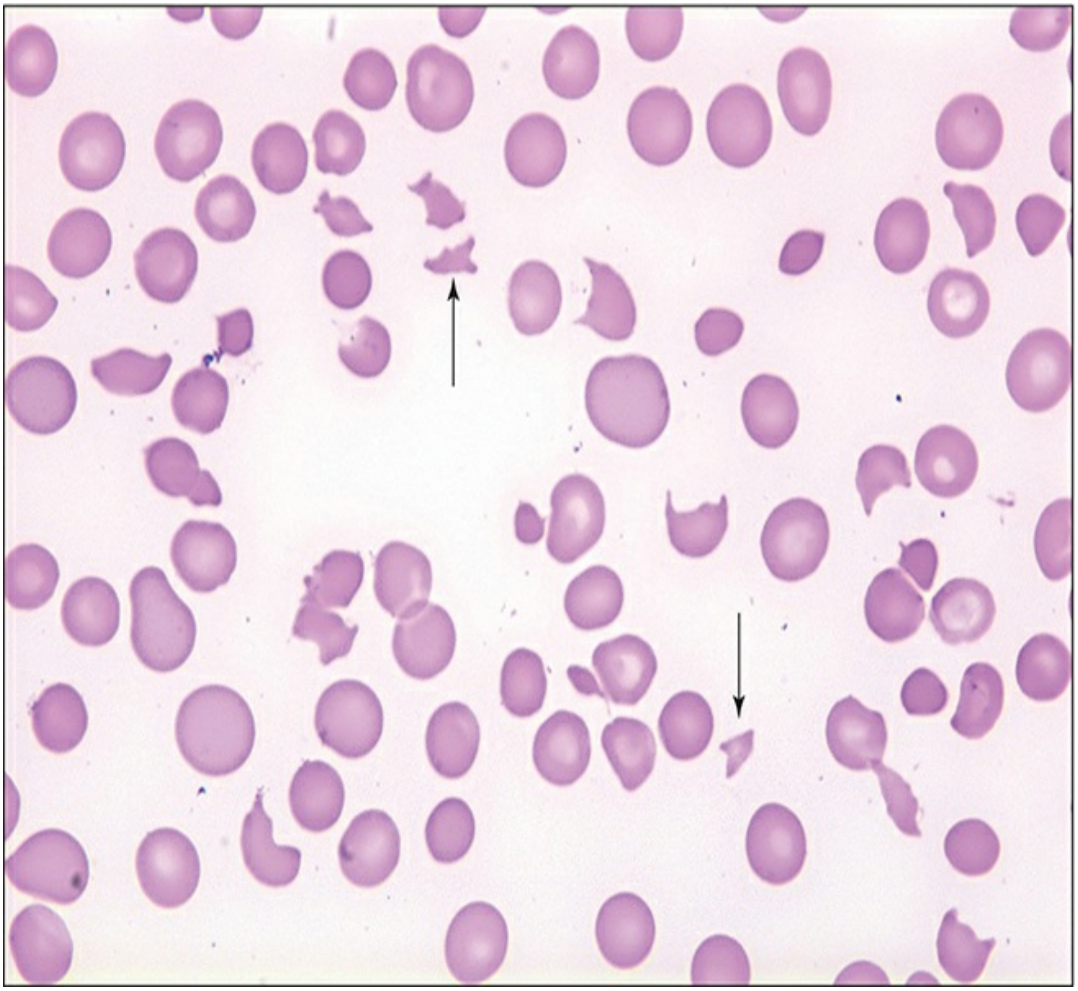


Figure IA1-34

Cell Type

Mature red blood cells

Description

Irregular shape or fragment of cell; results from damaged membrane

Clinical Conditions

- Microangiopathic hemolytic anemias
- Traumatic hemolytic anemias
- Waring blender syndrome

Spherocyte

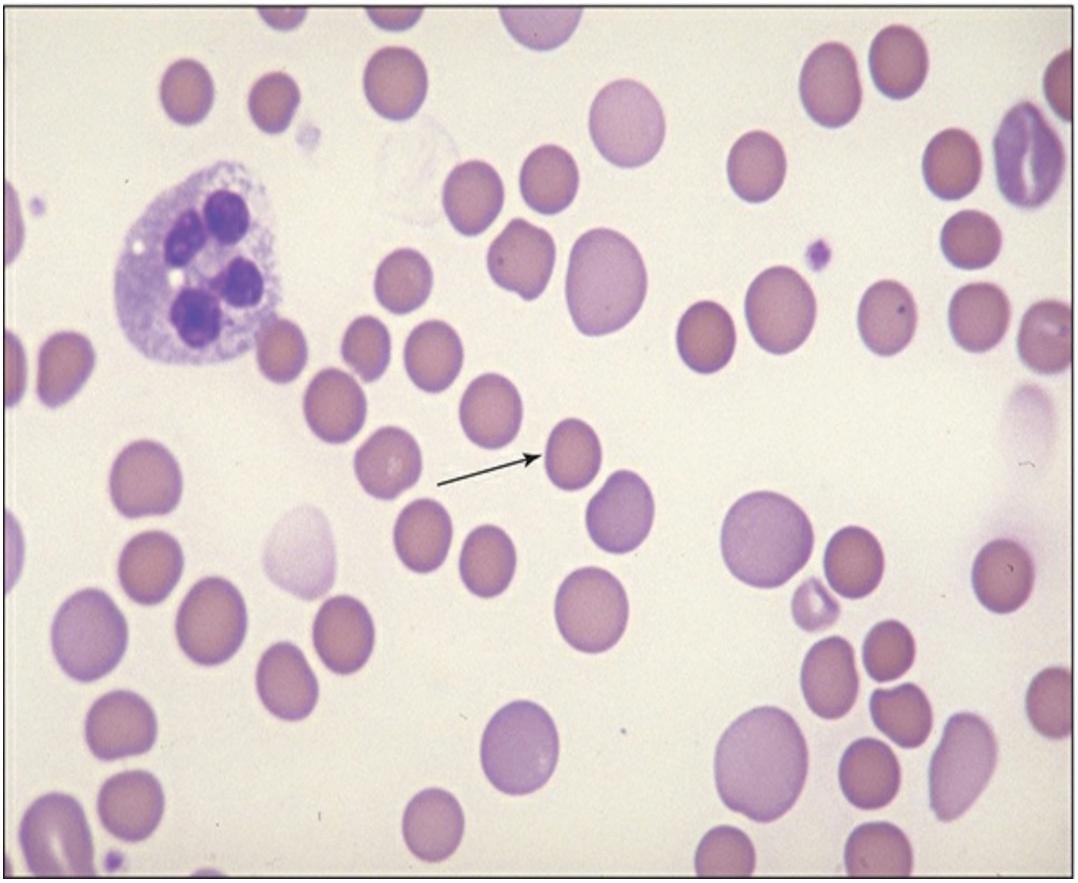


Figure IA1-35

Cell Type

Mature red blood cells

Size: 6.1–7.0 µ

Description

Round cells; increased staining intensity with no central pallor; smaller volume than a normal cell (decreased surface to volume ratio)

Clinical Conditions

- Hereditary spherocytosis
- Immunohemolytic anemias
- Heinz body hemolytic anemia
- Severe burns (microspherocytes seen); microspherocytes are <4.0 µ
- Hypersplenism

Stomatocyte

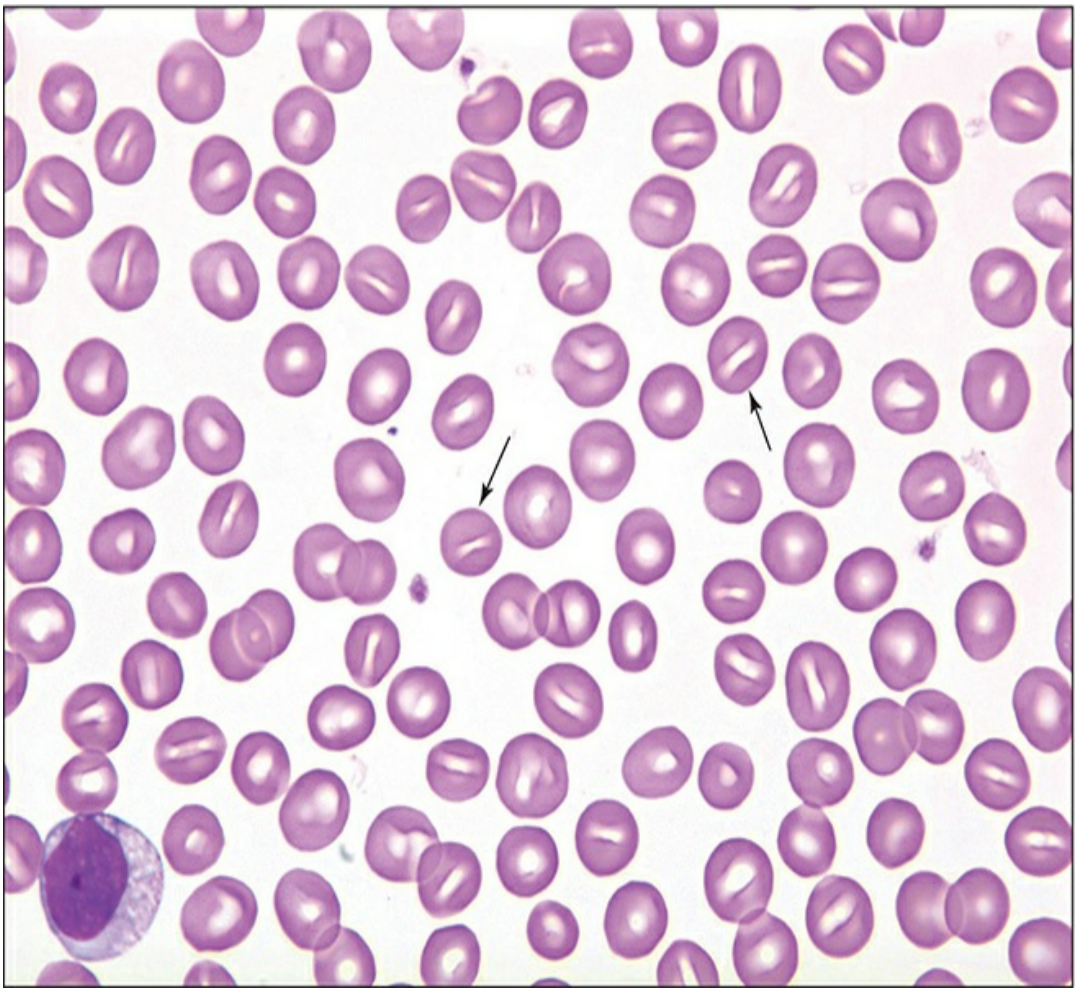


Figure **IA1-36**

Cell Type

Mature red blood cells

Description

Cell having a slit-like area of central pallor

Clinical Conditions

- Hereditary stomatocytosis
- Alcoholism
- Obstructive liver disease
- Cirrhosis
- Rh-null disease

SIZE

Macrocyte

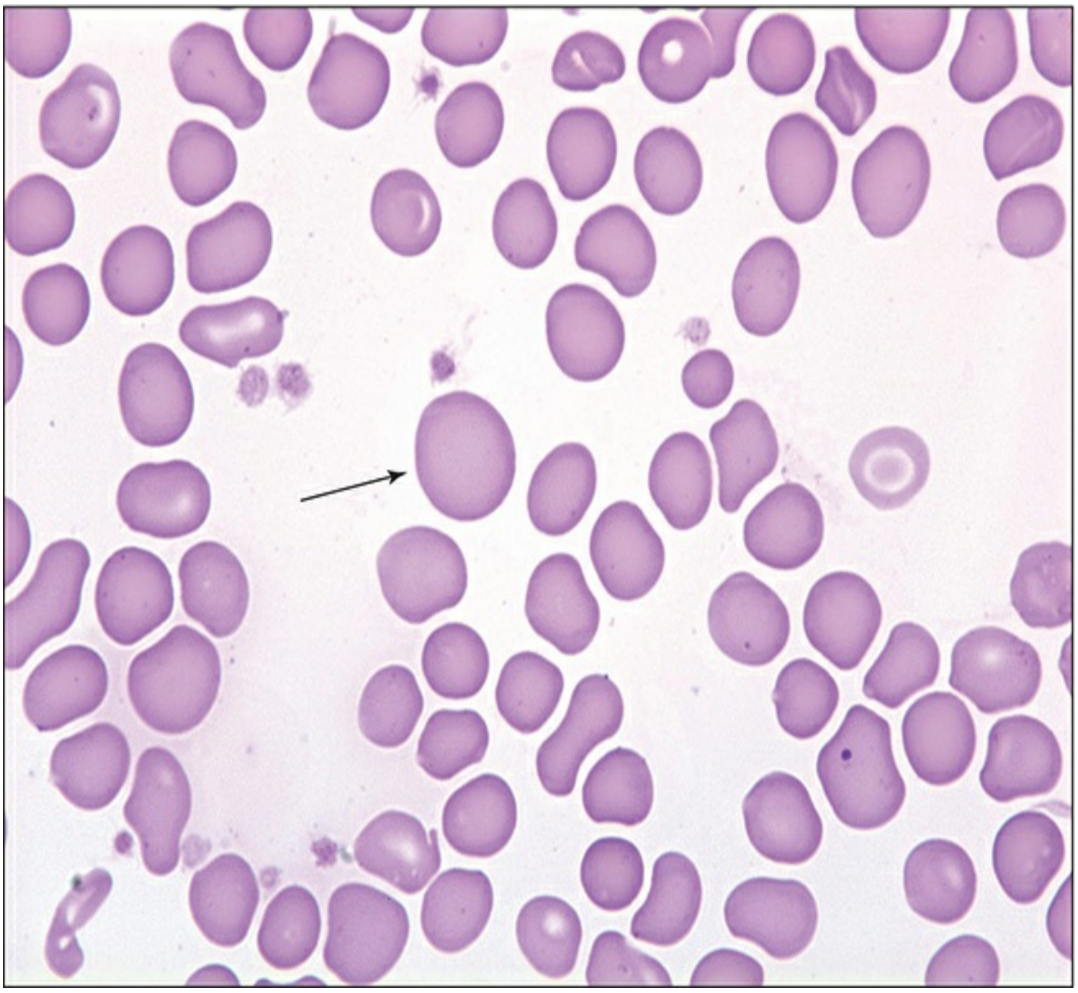


Figure IA1-37

Size: >7.8 µ

Cell Type

Mature red blood cells

Description

Large cell, MCV usually >100 fL; usually normochromic; may be round or oval; cytoplasm is pink-red

Clinical Conditions

- Liver disease (round macrocytes seen)

- Megaloblastic anemias (oval macrocytes seen)
- Myelodysplastic syndromes
- Acute blood loss
- Chemotherapy

Microcyte

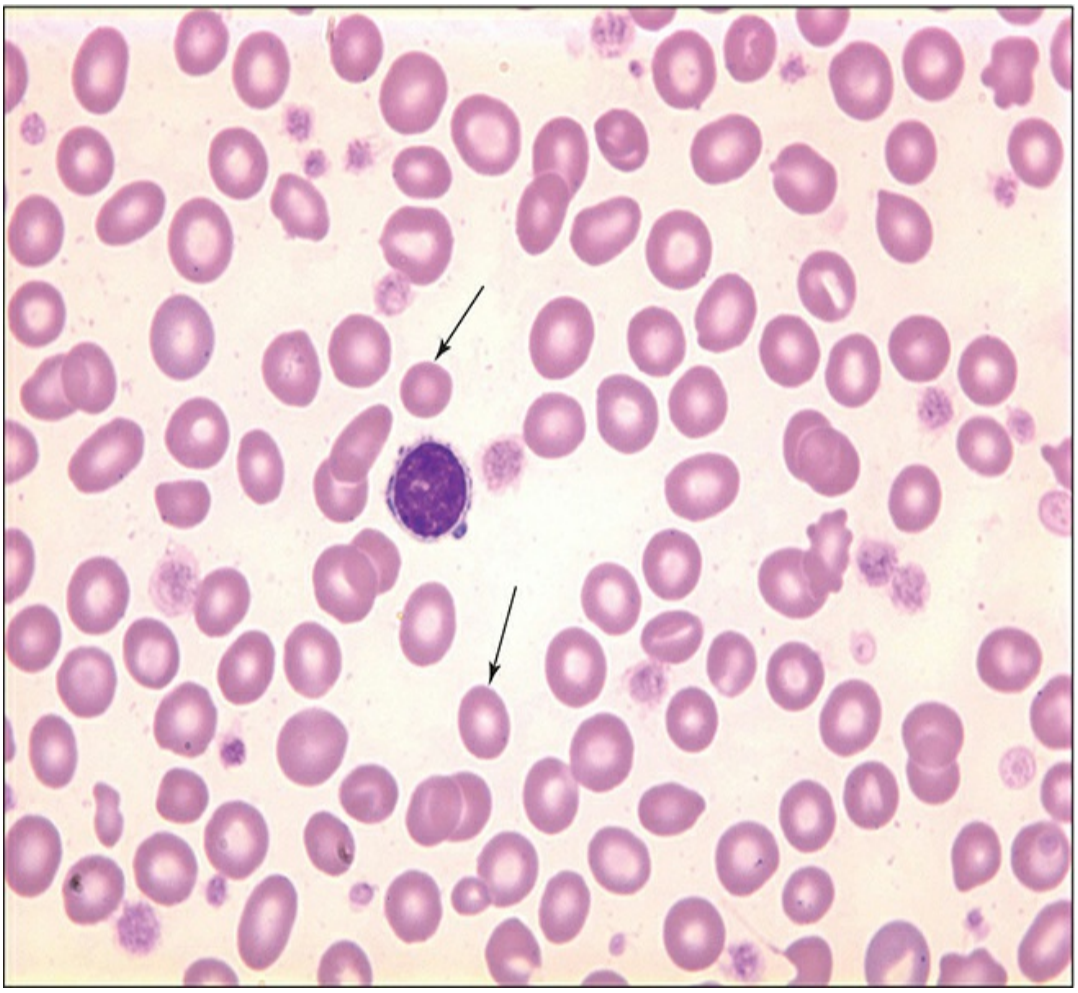


Figure IA1-38

Size: <6.5 µ

Cell Type

Mature red blood cells

Description

Smaller than normal cell; MCV usually <80 fL; has a

central pallor; normochromic or hypochromic

Clinical Conditions

- Iron deficiency anemia
- Thalassemias
- Lead poisoning
- Anemia of chronic disease
- Sideroblastic anemia

COLORING

Dimorphic

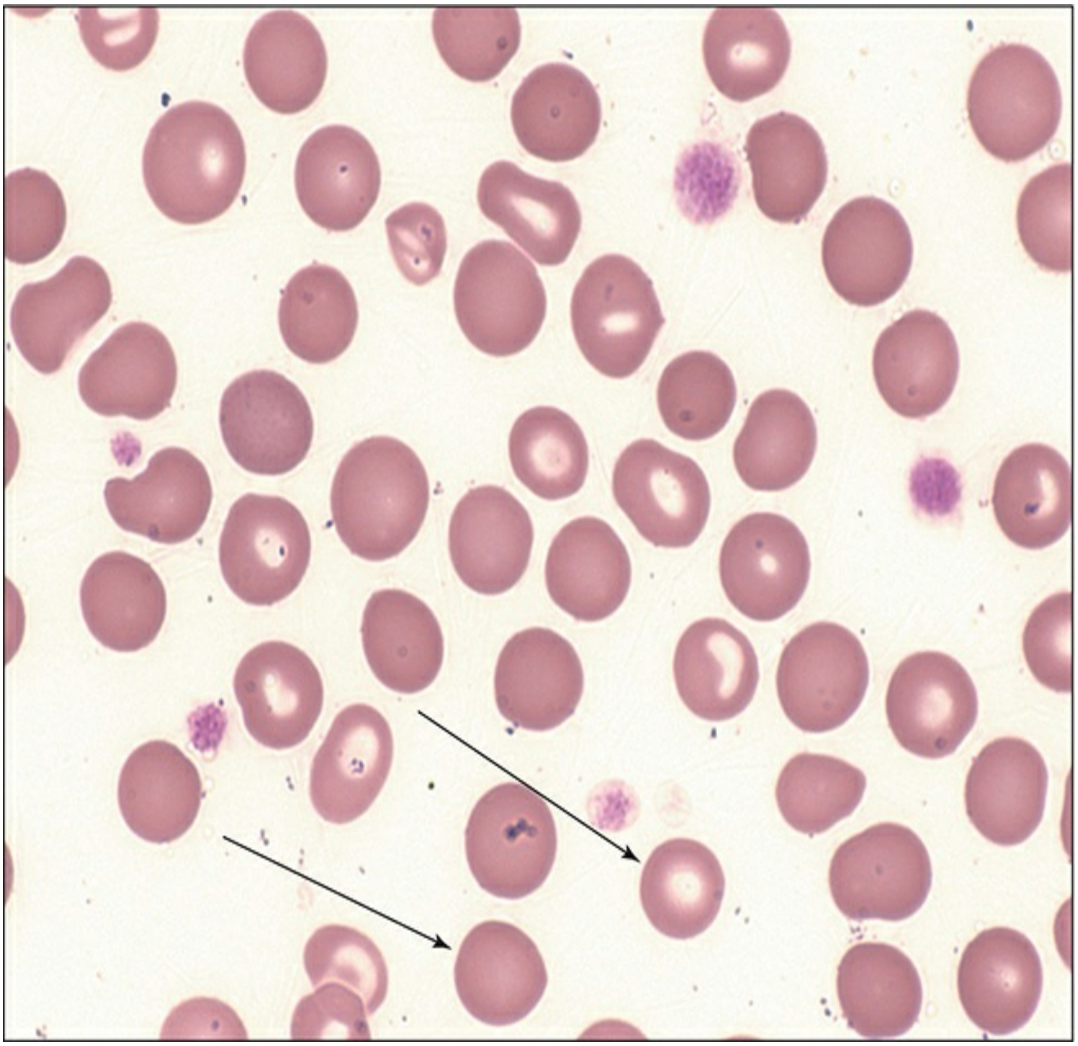


Figure IA1-39

Cell Type

Mature erythrocytes

Size: 6–11 µ

Description

Dual population of cells, normocytic and microcytic; normocytic and macrocytic; may also exhibit normochromia and hypochromia

Clinical Conditions

Clinical Conditions

- Sideroblastic anemia
- Myelodysplastic syndromes

Hypochromic

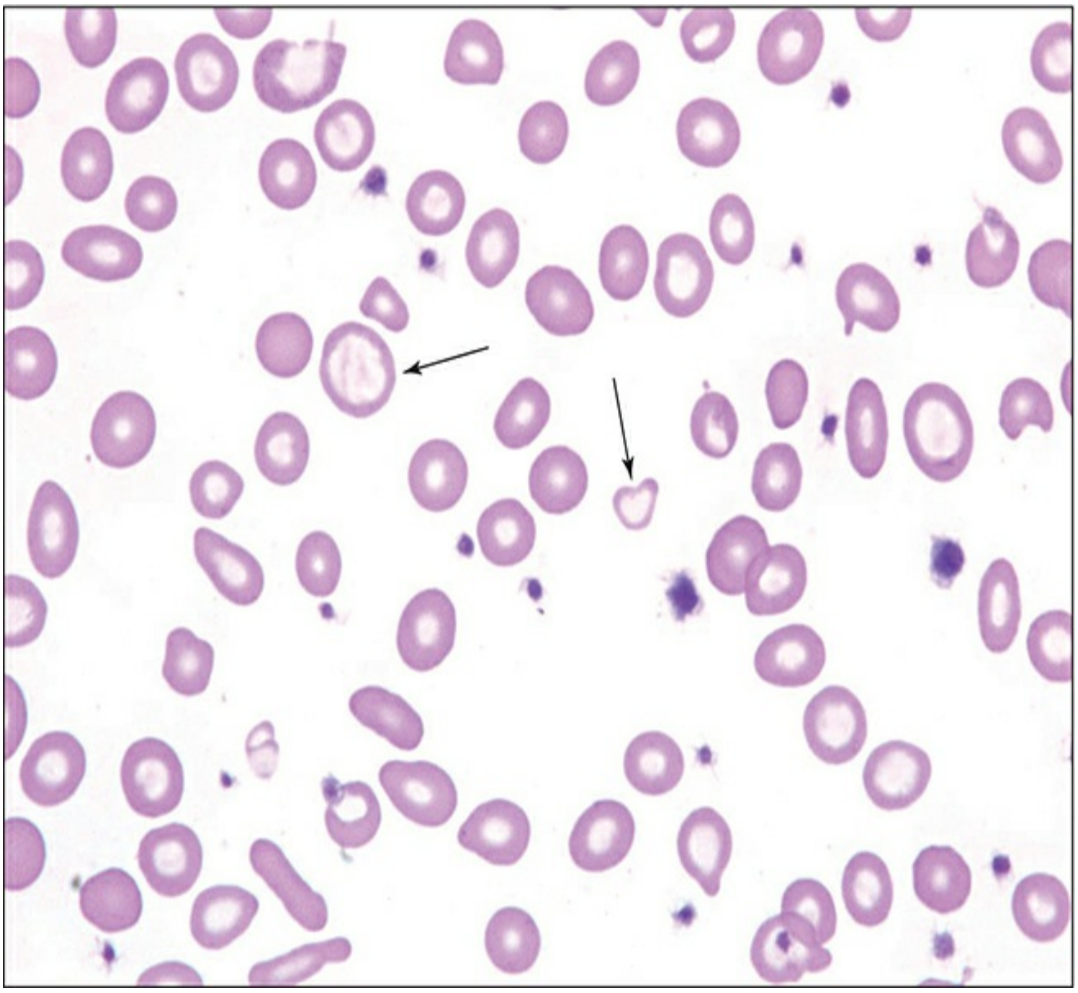


Figure IA1-40

Cell Type

Mature red blood cell

Description

Cells possess a greater central pallor than normal (greater than one-third); may lack hemoglobin and have a decreased MCHC or may be abnormally thin

Clinical Conditions

- Iron deficiency anemia
- Thalassemia
- Anemia of chronic disease
- Sideroblastic anemia
- Myelodysplastic syndromes

Polychromatophilic

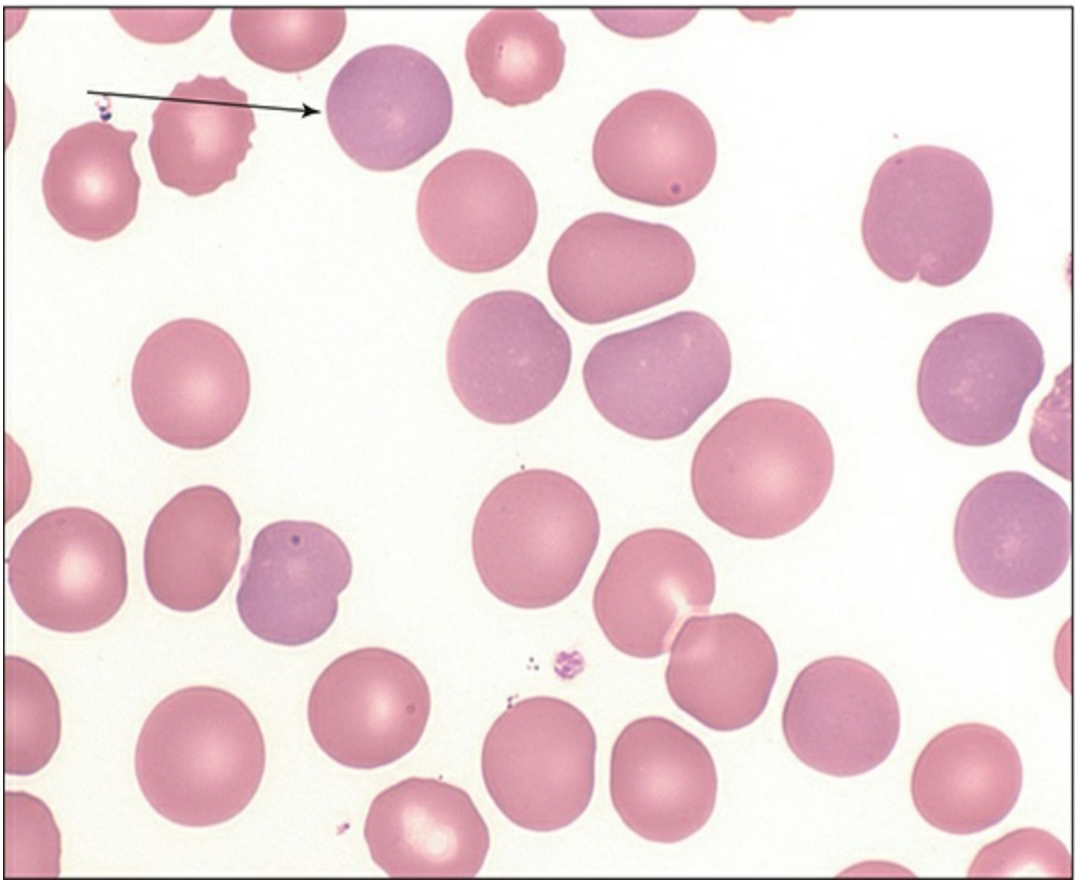


Figure IA1-41

Cell Type

Young red blood cell with no nucleus

Size: 8–11 µ

Description

Contains residual RNA, which stains diffusely blue;

identified as reticulocyte when stained with a supravital dye

Clinical Conditions

- Increased erythrocyte production
- Hemolytic anemias
- Membrane disorders
- Hemolytic disease of the newborn

INCLUSIONS

Basophilic Stippling (Punctuate Basophilia)

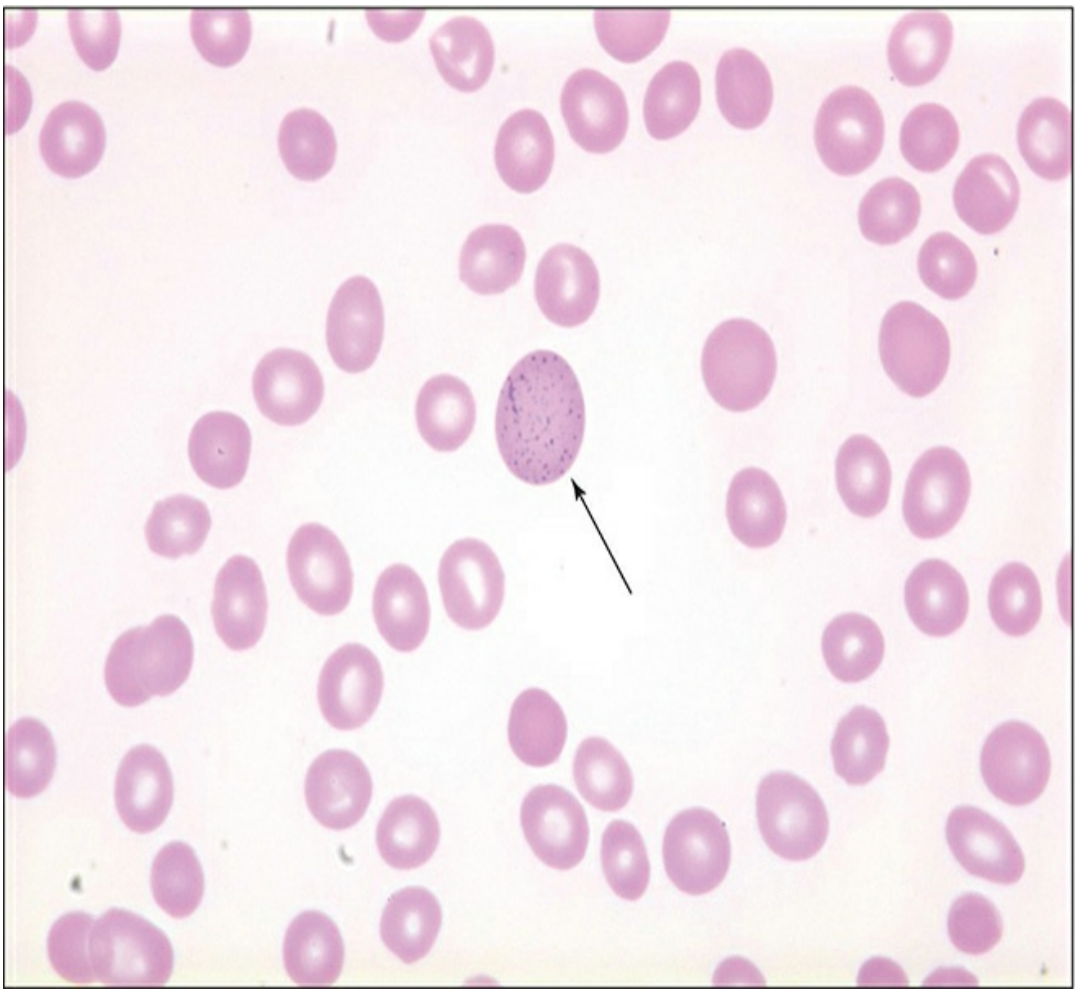


Figure IA1-42

Cell Type

Mature red blood cell

Description

Coarse, deep blue inclusions; irregularly aggregated or clumped ribosomes throughout the cell; mitochondria and siderosomes may also aggregate

Clinical Conditions

- Altered hemoglobin biosynthesis
- Lead intoxication
- Thalassemia
- Megaloblastic anemia
- Alcoholism
- Sideroblastic anemia
- Pyrimidine-5′-nucleotidase deficiency

Cabot Ring

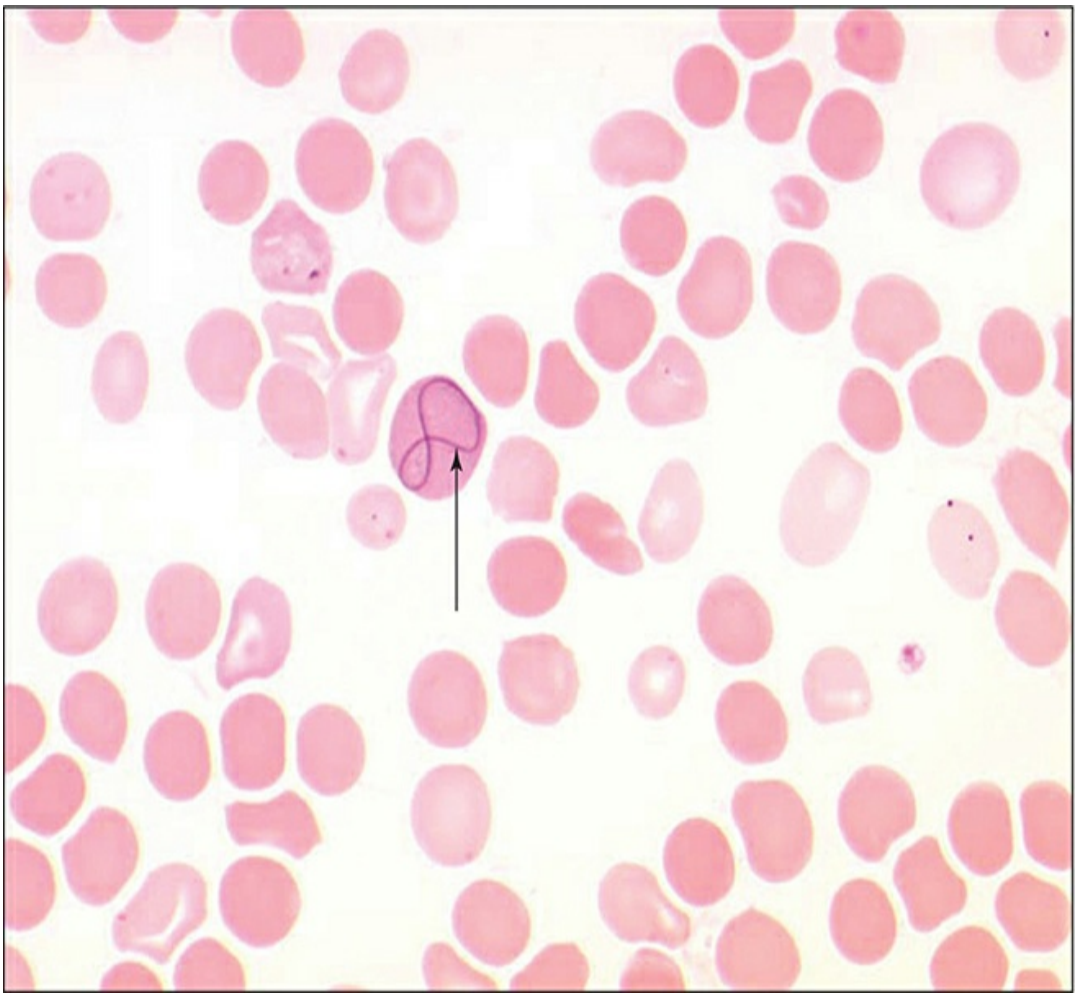


Figure IA1-43

Cell Type

Mature red blood cell

Description

Oval or figure-of-8–shaped inclusion; red-violet in color; usually one per cell; consists of nuclear remnants or part of the mitotic spindle

Clinical Conditions

- Severe anemias
- Dyserythropoiesis

Heinz Bodies

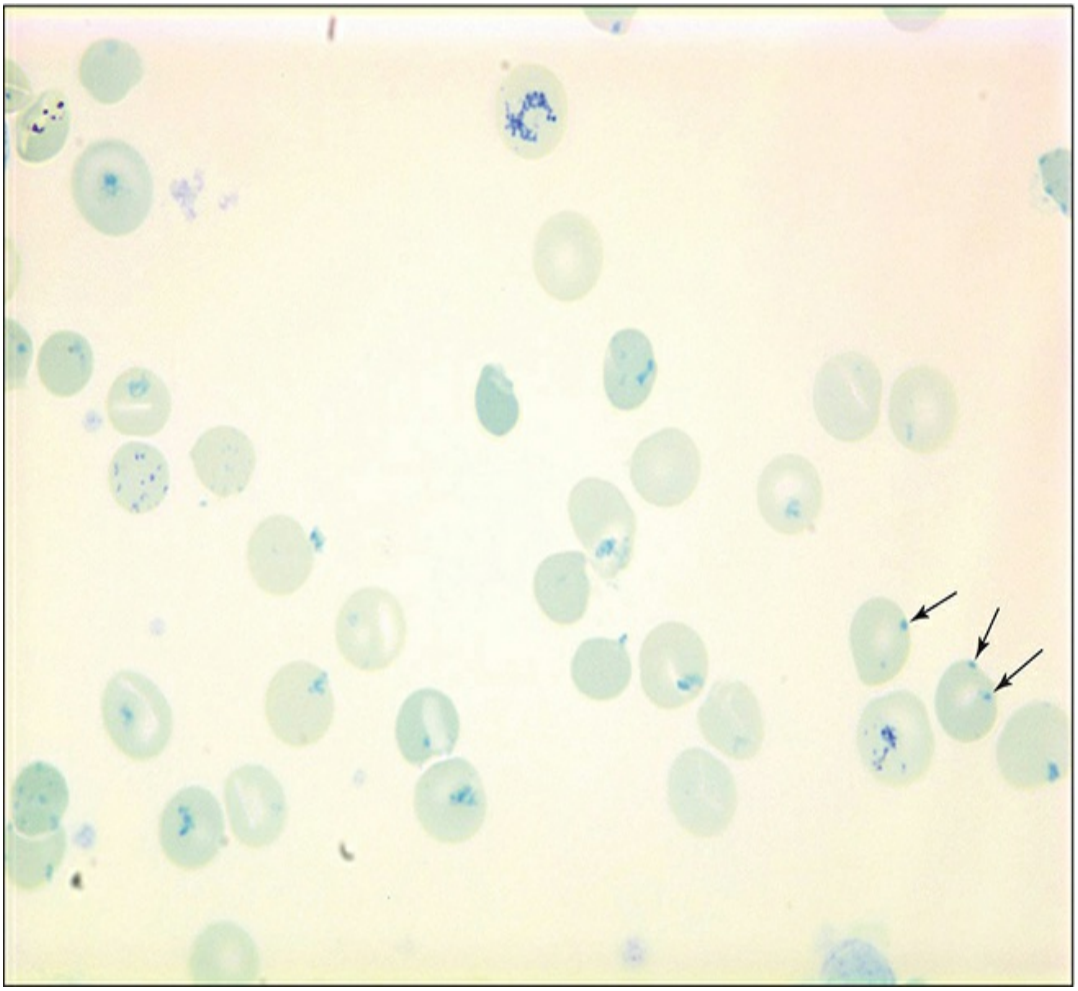


Figure IA1-44

Cell Type

Young and mature red blood cells

Size: 1–2 µ

Description

Round, refractile inclusions found on the periphery of the cell when stained with a supravital dye; consists of denatured globin produced by the destruction of hemoglobin; they may occur in multiple numbers

Clinical Conditions

- Drug-induced anemias
- Thalassemia
- Glucose-6-phophate dehydrogenase deficiency and other red blood cell enzymopathies
- Unstable hemoglobinopathies

Hemoglobin C Crystals

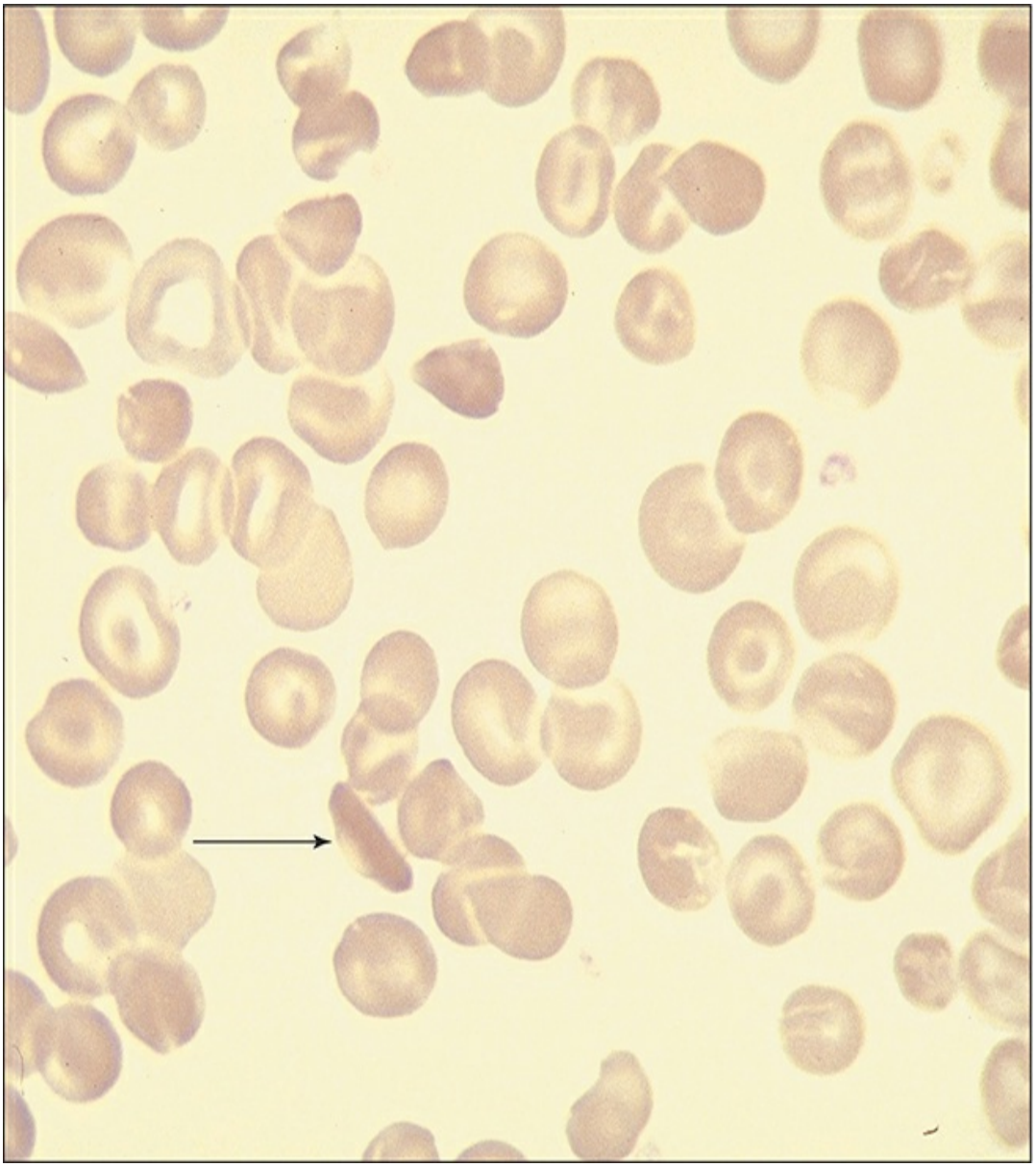


Figure **IA1-45**

Cell Type

Mature red blood cells

Description

Hexagonal, rod-shaped inclusions with blunt ends that stain very dark; formed within the cell membrane; remainder of cell has a clear area

Clinical Condition

- Hemoglobin CC disease

Hemoglobin H Inclusions

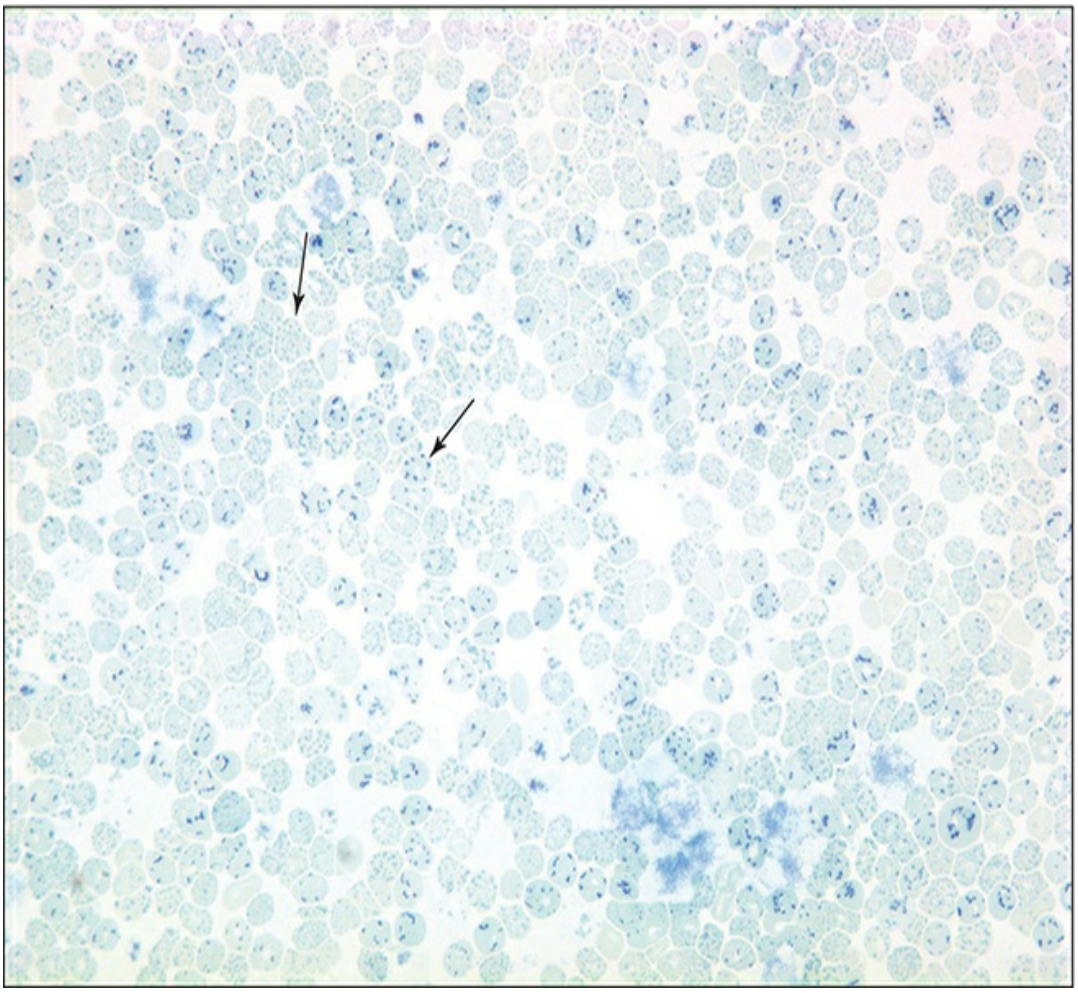


Figure IA1-46

Cell Type

Nucleated and nonnucleated red blood cells

Description

Unpaired beta-chains form small, greenish-blue inclusions when stained with brilliant cresyl blue; uniformly dispersed throughout cell; when present in multiple numbers, they give the cell a "golf ball" appearance

Clinical Condition

- Hemoglobin H disease

Hemoglobin SC Crystals

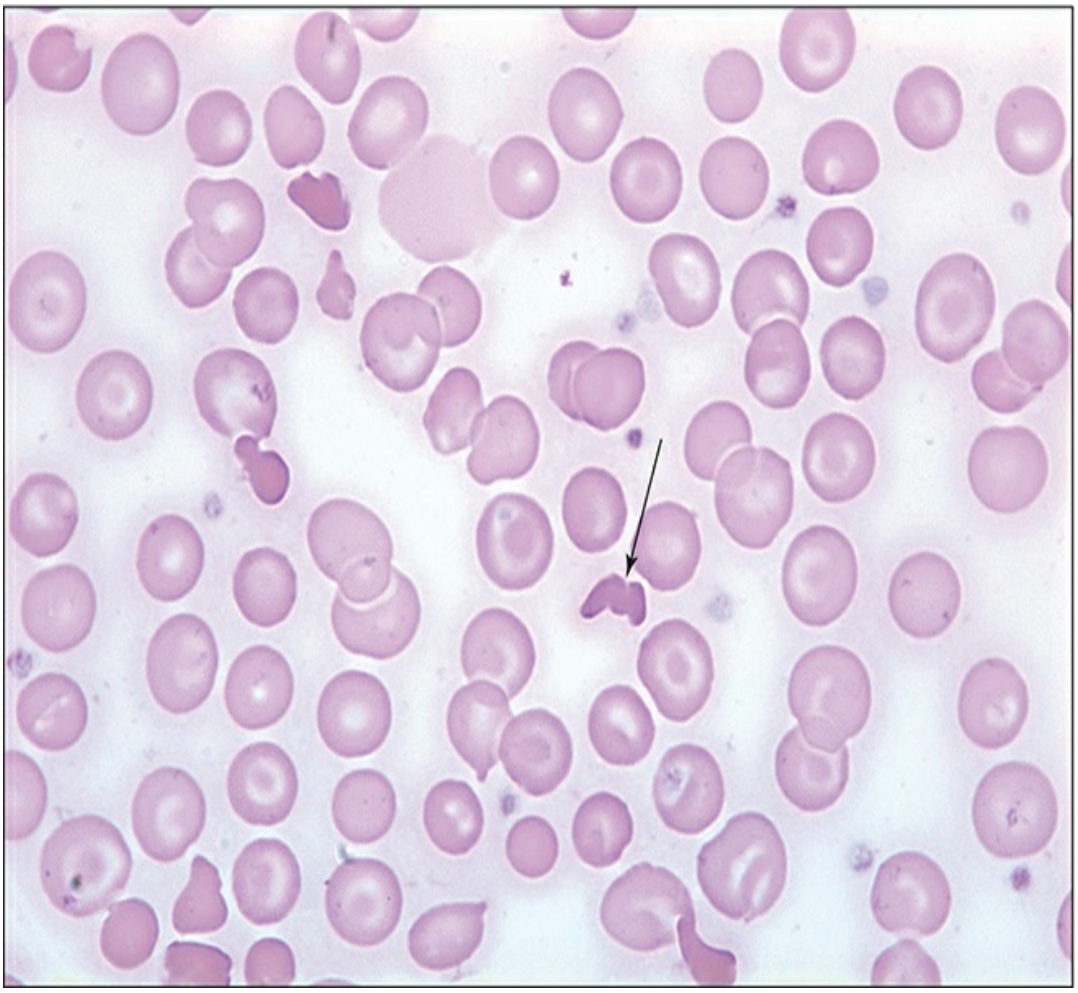


Figure IA1-47

Cell Type

Mature red blood cell

Description

Darkly stained condensed hemoglobin; crystals may be straight with parallel sides and a blunt protruding end or have several finger-like projections from the center; crystals may protrude from cell membrane; remainder of cell has pallor or distorted membrane

Clinical Condition

Clinical Condition

- Hemoglobin SC disease

Howell-Jolly Body

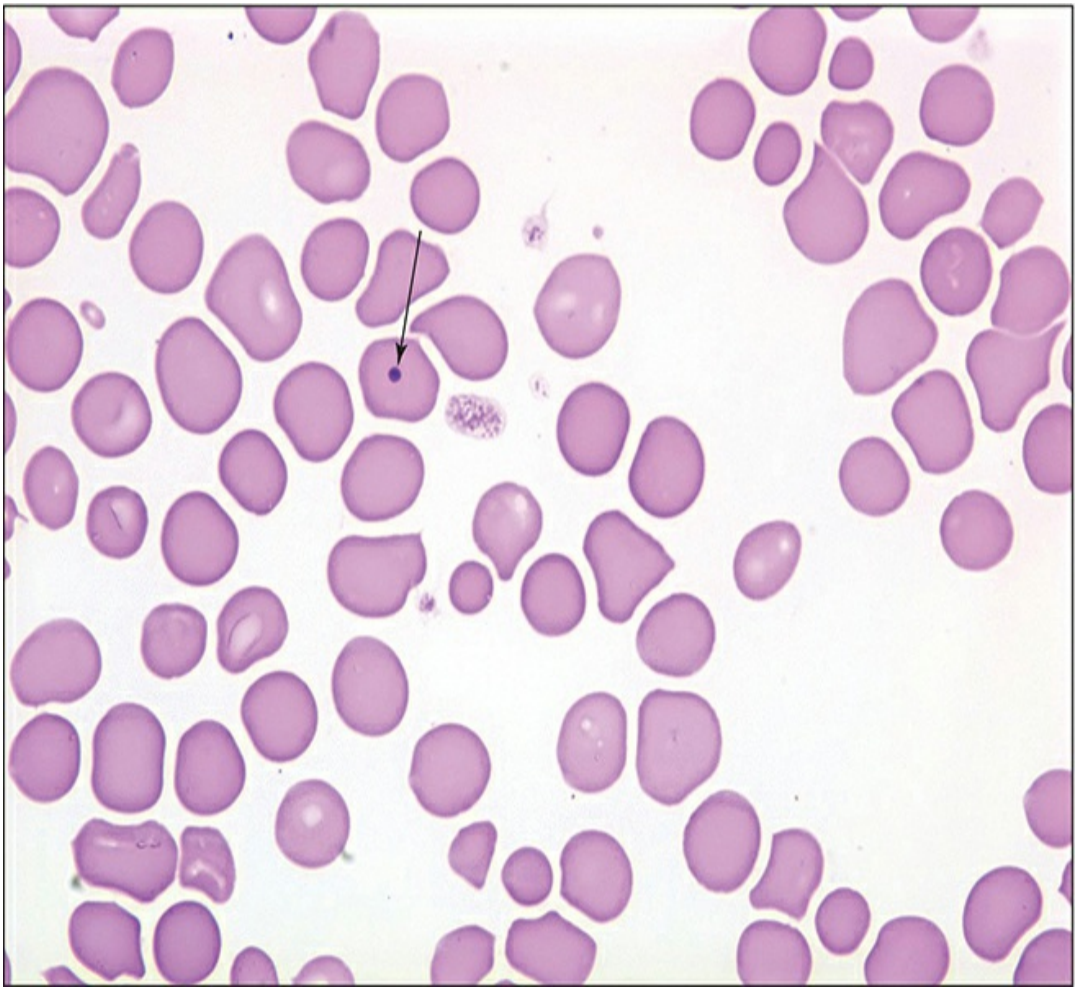


Figure IA1-48

Size: 0.5–1.0 μ

Cell Type

Nucleated and nonnucleated red blood cells

Description

Round fragments of nucleus (DNA); reddish-blue to deep purple in color; usually one per cell but occasionally may be two or more; represents chromosomes that have been separated from the mitotic spindle during

abnormal mitosis; may also appear to arise from nuclear fragmentation or abnormal expulsion of the nucleus

Clinical Conditions

- Megaloblastic anemia
- Hemolytic anemias
- Hyposplenism
- Splenectomized persons
- Alcoholism
- Sickle cell anemia

Malaria

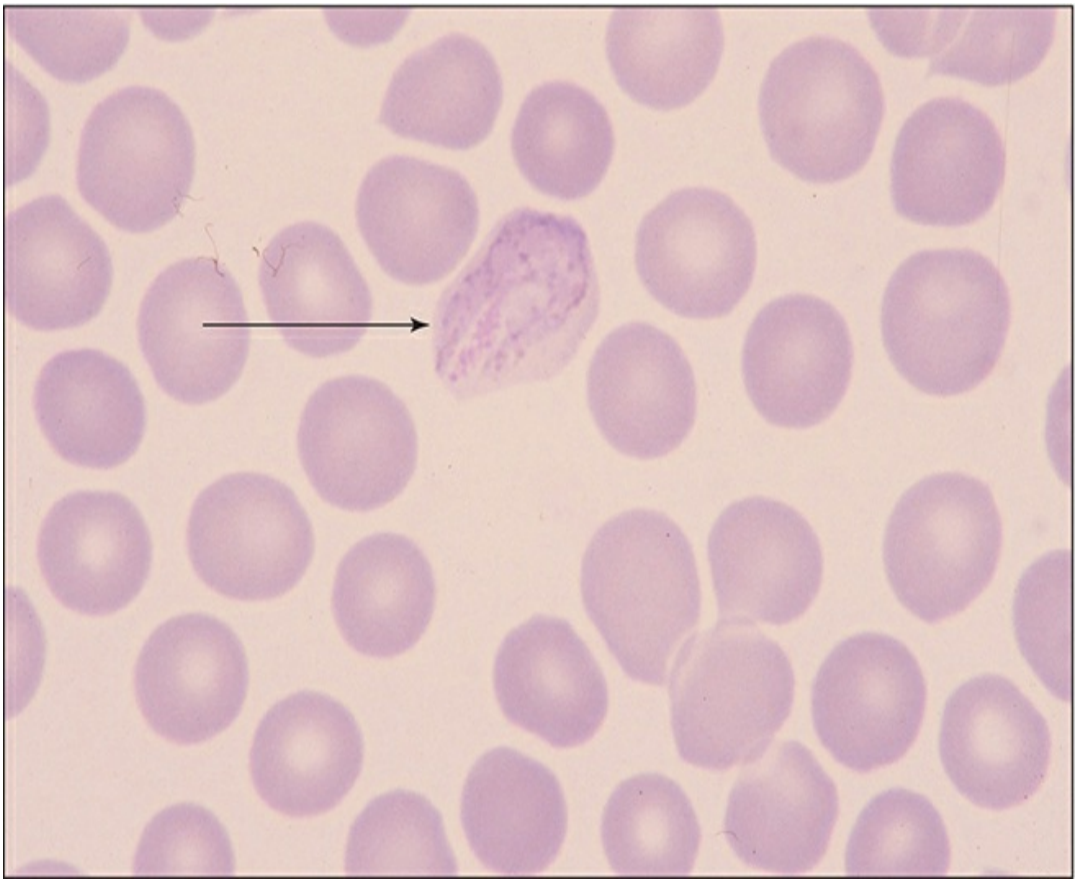


Figure IA1-49

Cell Type

Red blood cell

Description

Depends on species of Plasmodium that infects the cells

- Plasmodium vivax infection enlarges the cell; Schüffner granules may be present
- Plasmodium malariae infection does not enlarge the cell
- Plasmodium falciparum infection produces delicate ring forms; cells are not enlarged; Schüffner granules are not present
- Plasmodium ovale infection produces large, oval cells; Schüffner granules are present

Clinical Condition

- Plasmodium infections

Pappenheimer Body

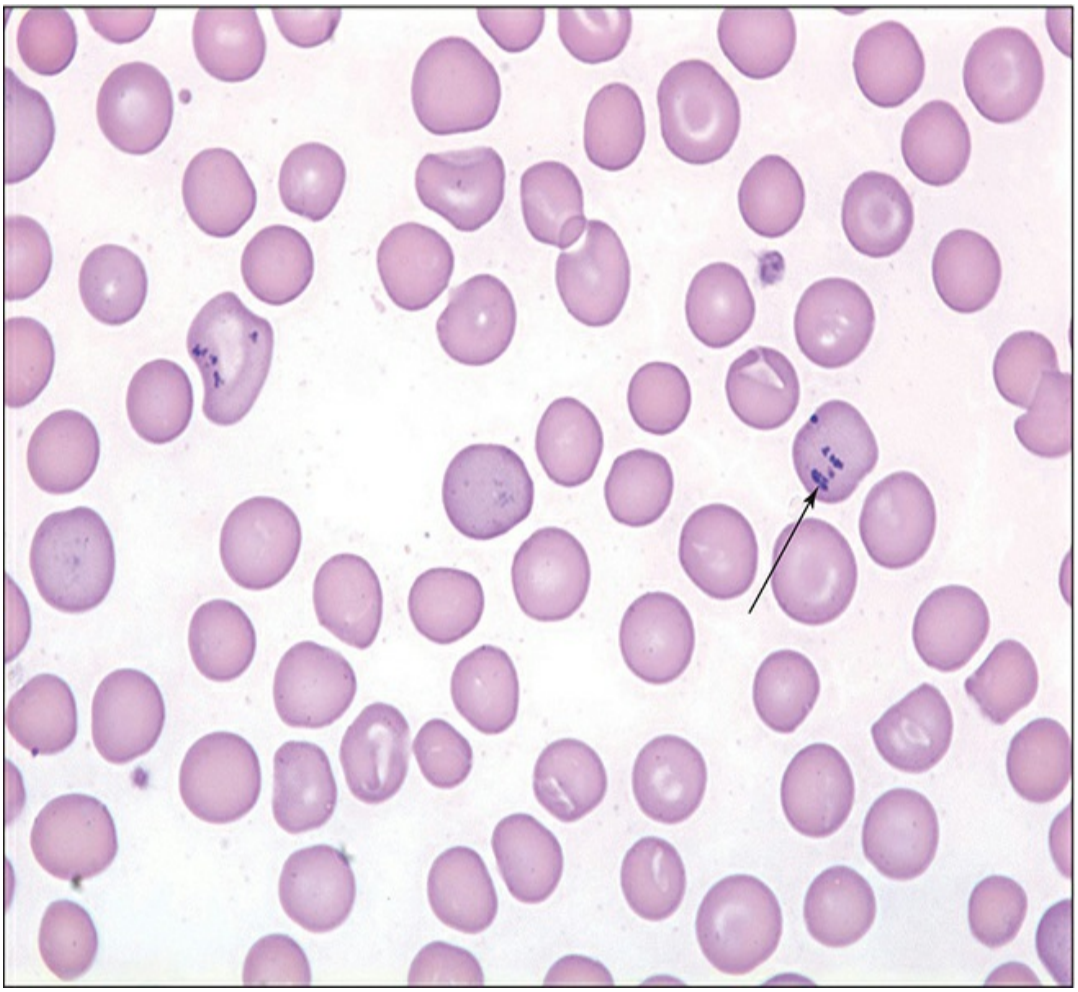


Figure **IA1-50**

Cell Type

Mature red blood cells, reticulocytes, metarubricytes

Description

Small, irregular, pale blue to dark-staining granules; usually found on the periphery of cell and in groups; smaller than Howell-Jolly bodies; represent siderosomes, which stain positive with Perls Prussian blue stain and indicate iron content

Clinical Conditions

- Disturbed hemoglobin synthesis
- Sideroblastic anemia

- Dyserythropoietic anemias
- Thalassemia
- Myelodysplastic syndromes

ABNORMAL MATURATION

Dyserythropoiesis

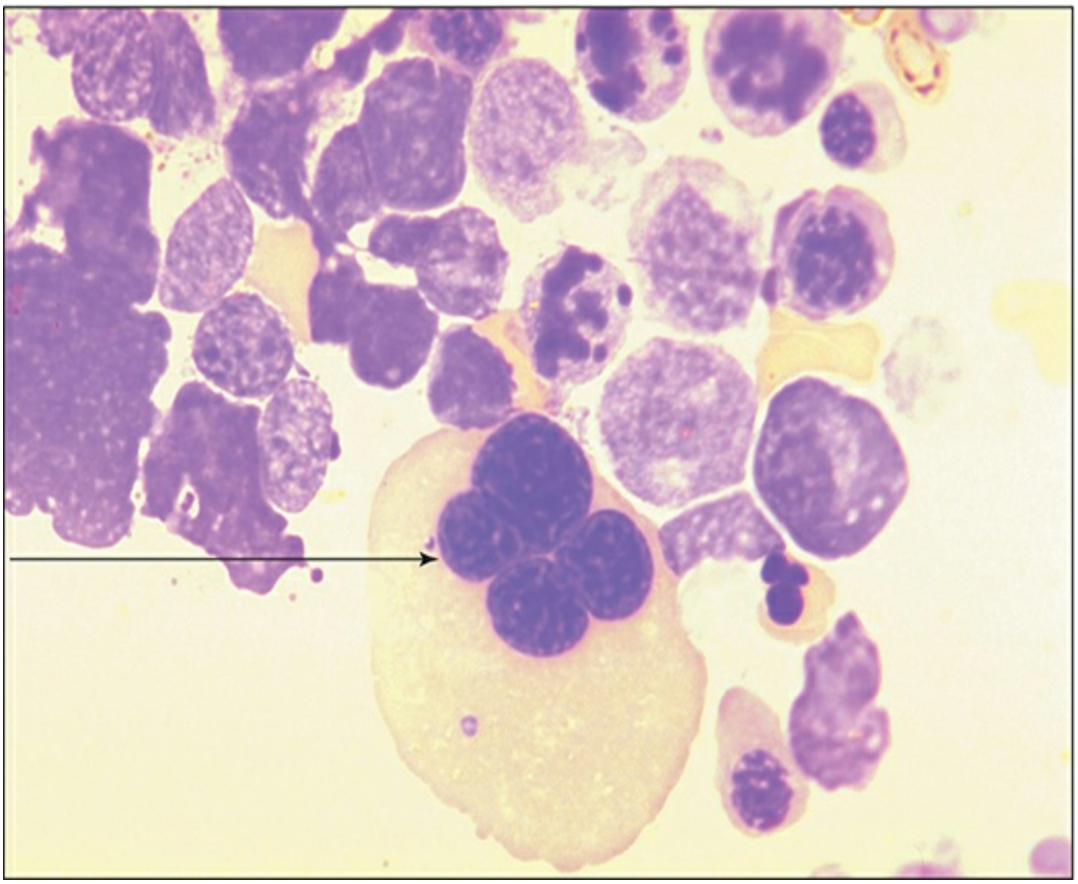


Figure IA1-51

Cell Type

Red blood cell precursors

Description

Abnormal findings in red blood cell precursors including abnormal nuclear shapes, more than one nucleus, nuclear fragments, megaloblastoid and/or megaloblastic maturation, and vacuolated cytoplasm

Clinical Conditions

- Myelodysplastic syndromes
- Megaloblastic anemias

- Arsenic poisoning
- Erythroleukemia (M6a) (FAB)
- Pure erythroid leukemia (M6b) (FAB) (WHO)
- Myelodysplastic syndromes

CHAPTER 2

White Blood Cells

NORMAL GRANULOCYTIC MATURATION SERIES

Neutrophilic Series

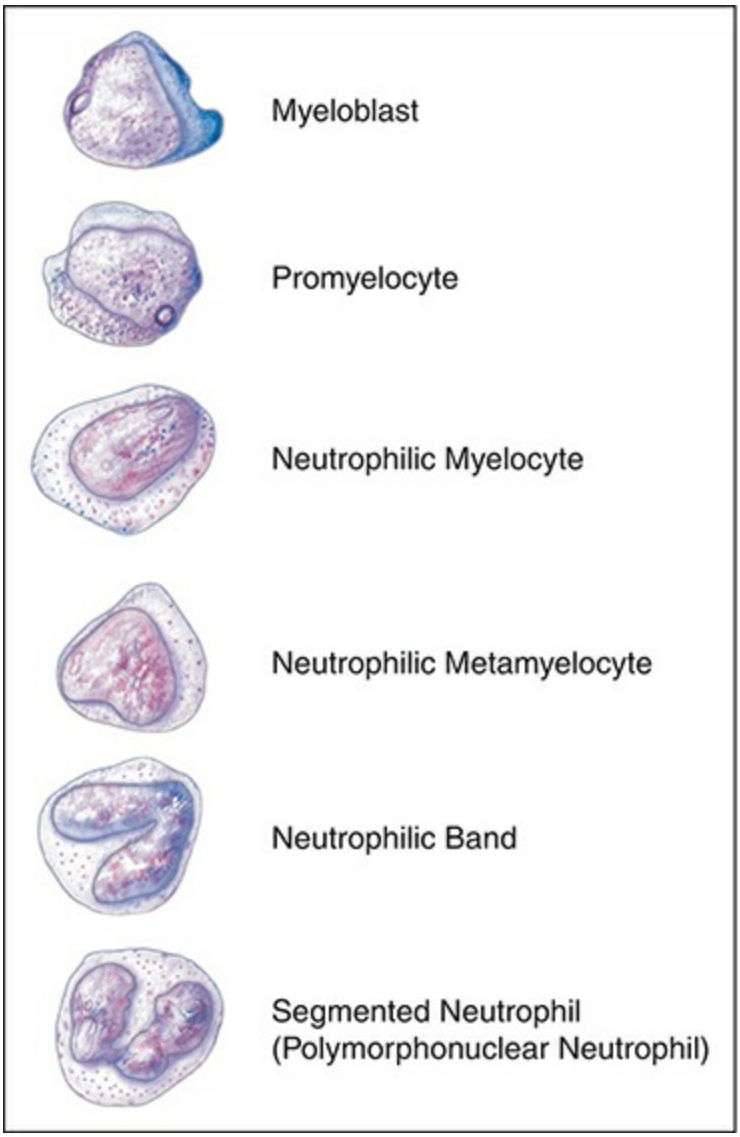


Figure IA2-1

Eosinophilic Series

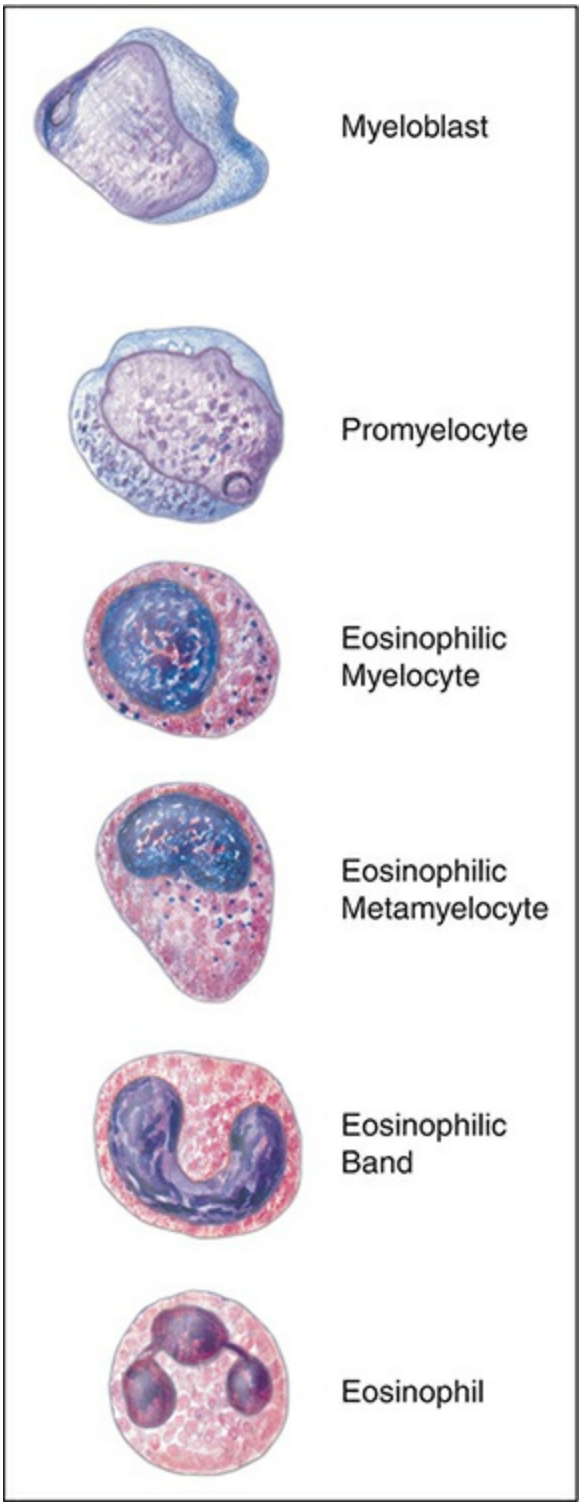


Figure IA2-2

Basophilic Series

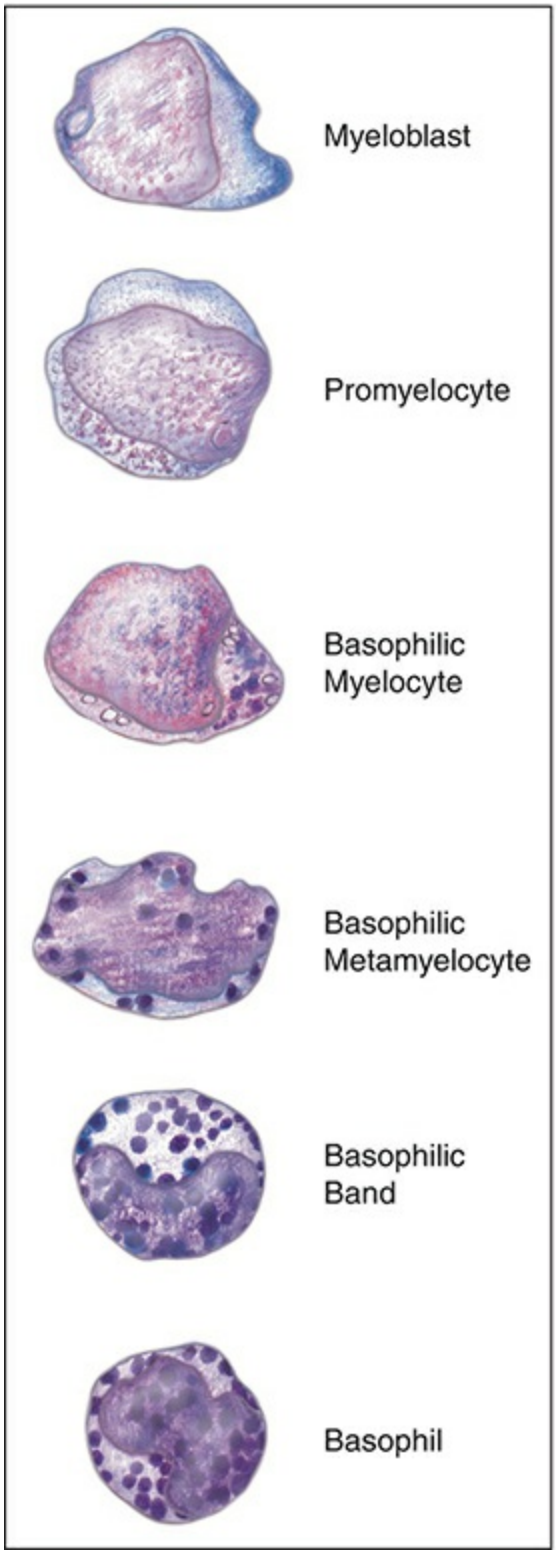


Figure IA2-3

Myeloblast

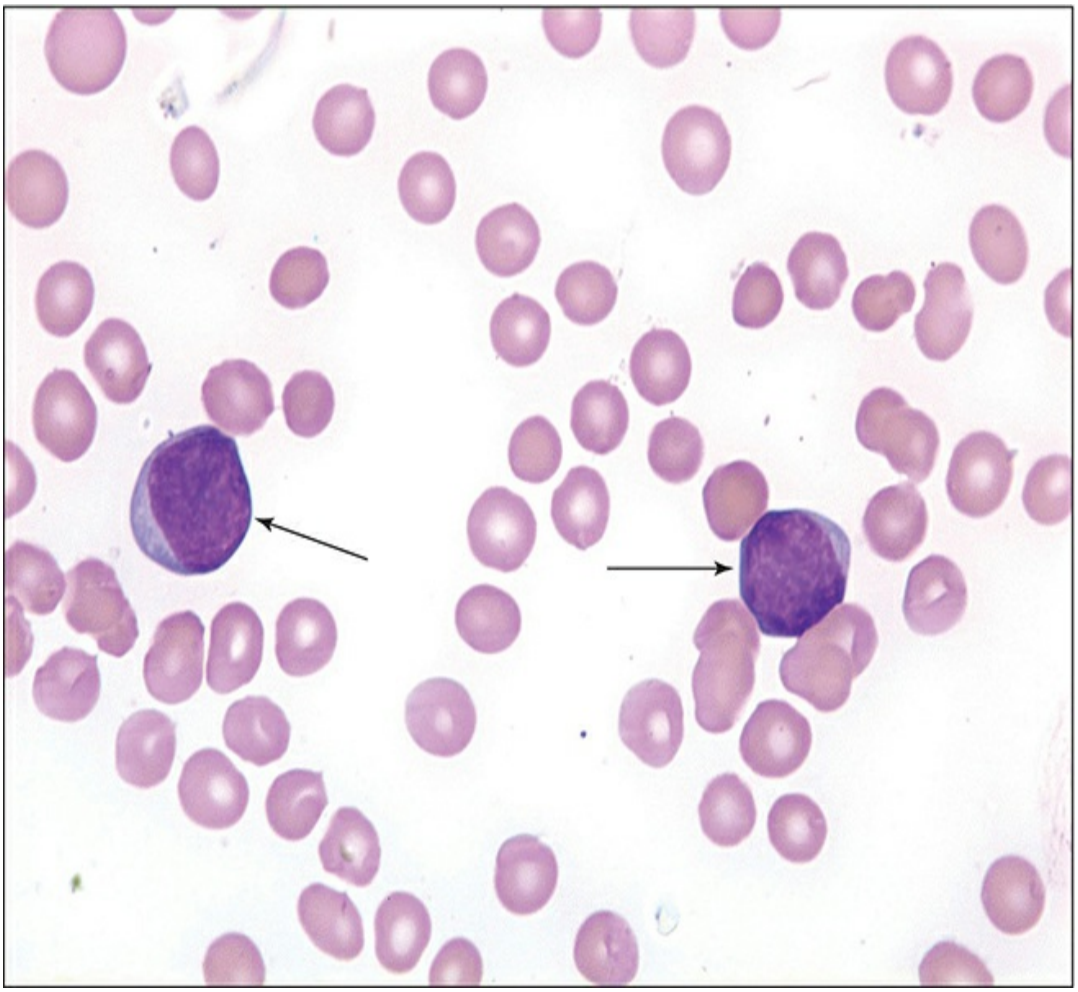


Figure **IA2-4**

Size: 15–20 µ

Nucleus

Shape: Round

N/C Ratio: 7:1–4:1

Color: Reddish-purple

Chromatin: Delicate and dispersed

Nucleoli: 2–3

Cytoplasm

Color: Pale to deep blue; lighter staining adjacent to nucleus

Contents: Varying amounts of granules depending on

whether the blast is classified as a type I, II, or III (FAB)

Clinical Conditions

- Myelodysplastic syndromes—refractory anemia with excess blasts (RAEB) 1, 2
- Myeloproliferative neoplasms—CML, PMF
- Acute myelocytic leukemia minimally differentiated (M0) (FAB) (WHO)
- Acute myelocytic leukemia without maturation (M1) (FAB) (WHO)
- Acute myelocytic leukemia with maturation (M2) (FAB) (WHO)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Acute myelocytic leukemia with myelodysplasia-related changes (WHO)
- Acute monoblastic leukemia (M5a)—<20% myeloblasts (FAB) (WHO)
- Acute monocytic leukemia (M5b)—<20% myeloblasts (FAB) (WHO)
- AML with t(8;21) (WHO)
- AML with t(15;17) (WHO)
- AML with inv(16) or t(16;16) (WHO)

Promyelocyte

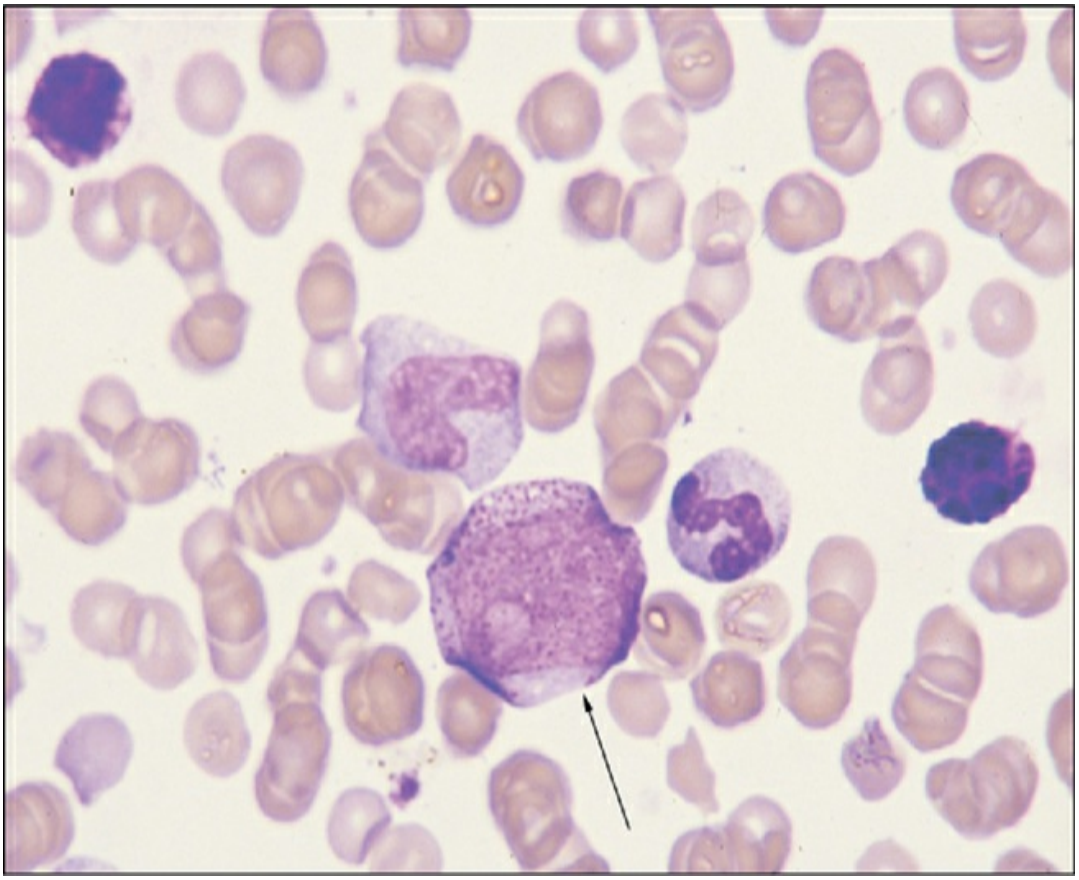


Figure **IA2-5**

Size: 18–25 µ

Nucleus

Shape: Round or oval; central or eccentric

N/C Ratio: 2:1–5:1

Color: Purple

Chromatin: Relatively fine becoming coarser

Nucleoli: 2–3, varying from visible to indistinct

Cytoplasm

Color: Blue; lighter staining adjacent to nucleus

Contents: Few to many dark blue or reddish-blue primary granules

Clinical Conditions

- Acute myelocytic leukemia with maturation (M2) (FAB)

(WHO)

- Acute promyelocytic leukemia (M3) (FAB)
- Myeloproliferative neoplasms—CML, PMF
- Growth factor therapy
- Severe infections
- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Acute myelocytic leukemia with myelodysplasia-related changes (WHO)
- AML with t(8;21) (WHO)
- AML with t(15;17) (WHO)
- AML with inv(16) or t(16;16) (WHO)

Neutrophilic Myelocyte

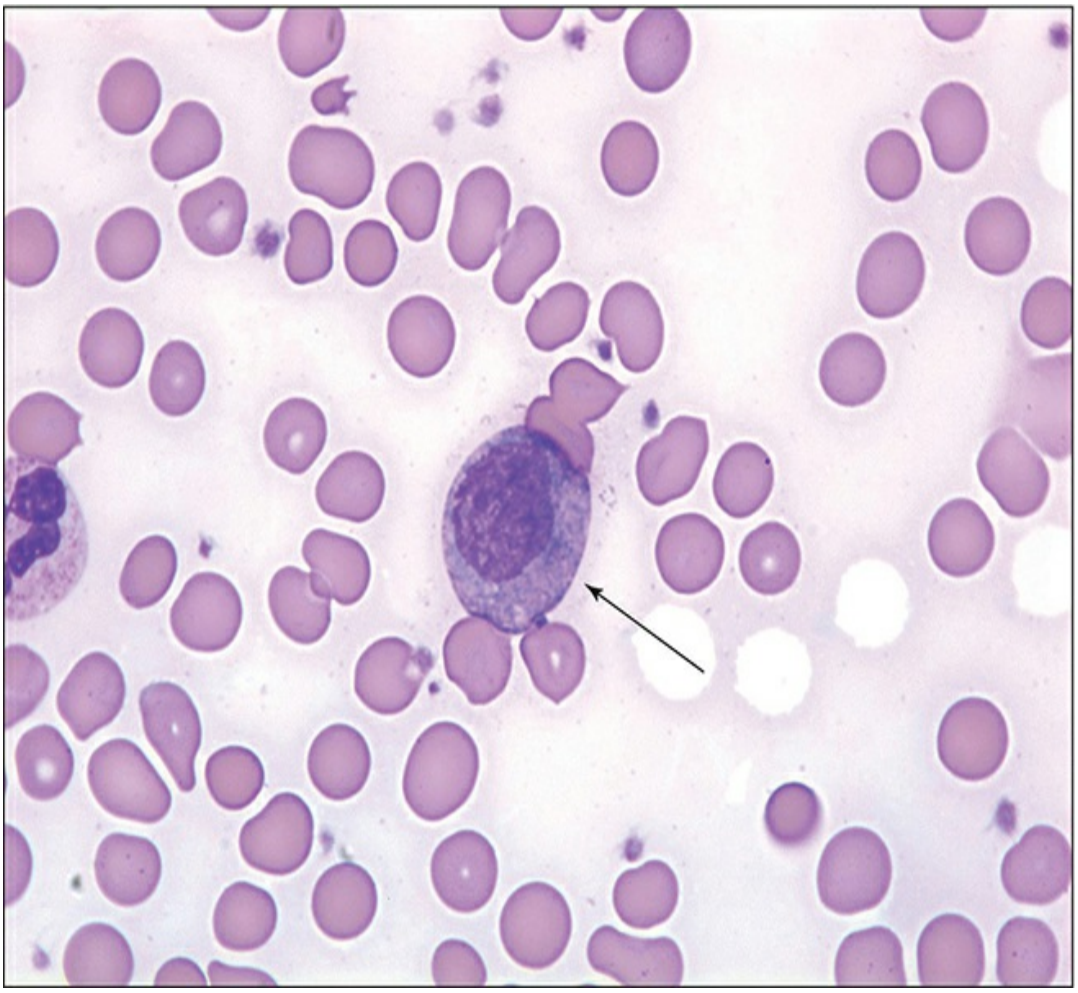


Figure IA2-6

Size: 12–18 µ

Nucleus

Shape: Round, oval, or flattened on one side

N/C Ratio: 3:1–3:2

Color: Dark purple

Chromatin: Coarser chromatin pattern

Nucleoli: Early myelocytes may have visible nucleoli

Cytoplasm

Color: Pinkish-blue

Contents: Variable numbers of secondary granules; small, pinkish to reddish specific granules first appearing next to nucleus and then throughout cytoplasm

Clinical Conditions

- Acute myelocytic leukemia with maturation (M2) (FAB) (WHO)
- Growth factor therapy
- Myeloproliferative neoplasms—CML, PMF
- Stress
- Severe infections
- AML with t(8;21) (WHO)

Eosinophilic Myelocyte

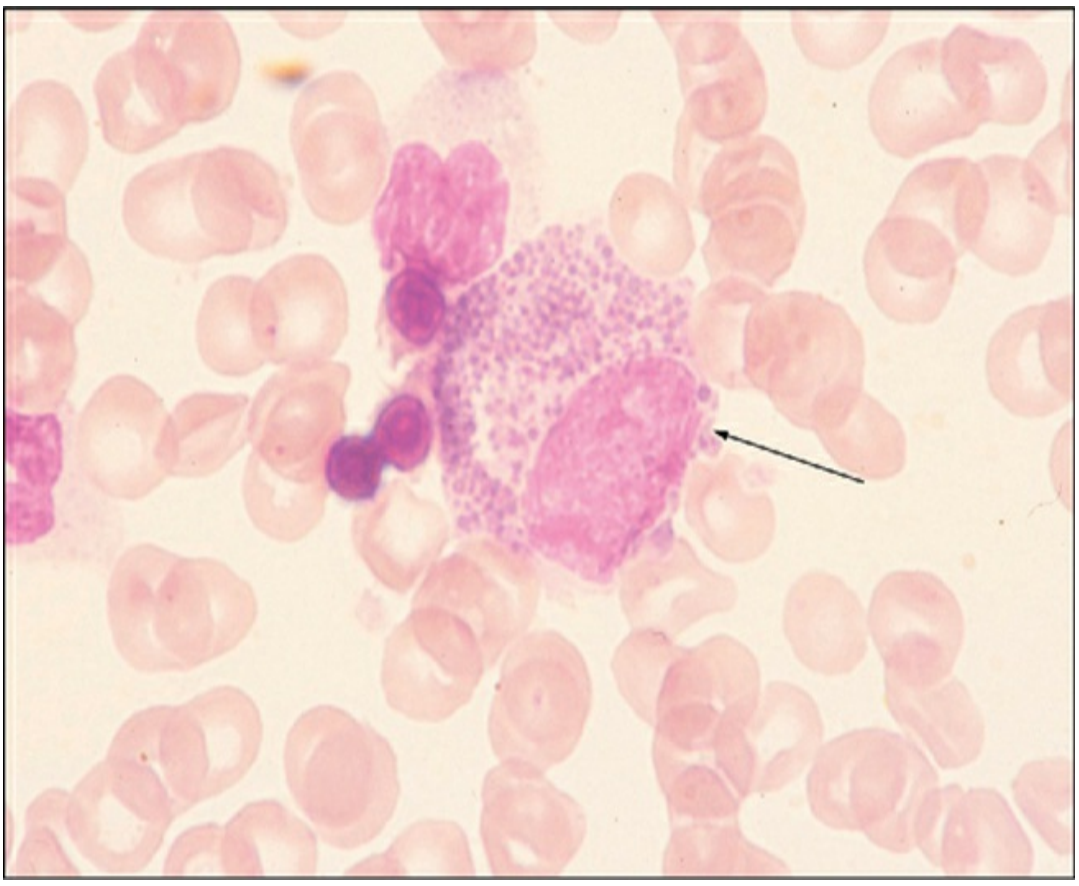


Figure IA2-7

Size: 12–18 µ

Nucleus

Shape: Round, oval, or flattened on one side

N/C Ratio: 3:1–3:2

Color: Dark purple

Chromatin: Coarser chromatin pattern

Nucleoli: Early myelocytes may have visible nucleoli

Cytoplasm

Color: Pinkish-blue

Contents: Numerous large, round eosinophilic granules staining orange-brown to orange-blue; variable numbers of nonspecific granules

Clinical Conditions

- Chronic eosinophilic leukemia (NOS) (WHO)
- Hypereosinophilic syndrome
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)
- PCM1-JAK2 (WHO)

Basophilic Myelocyte

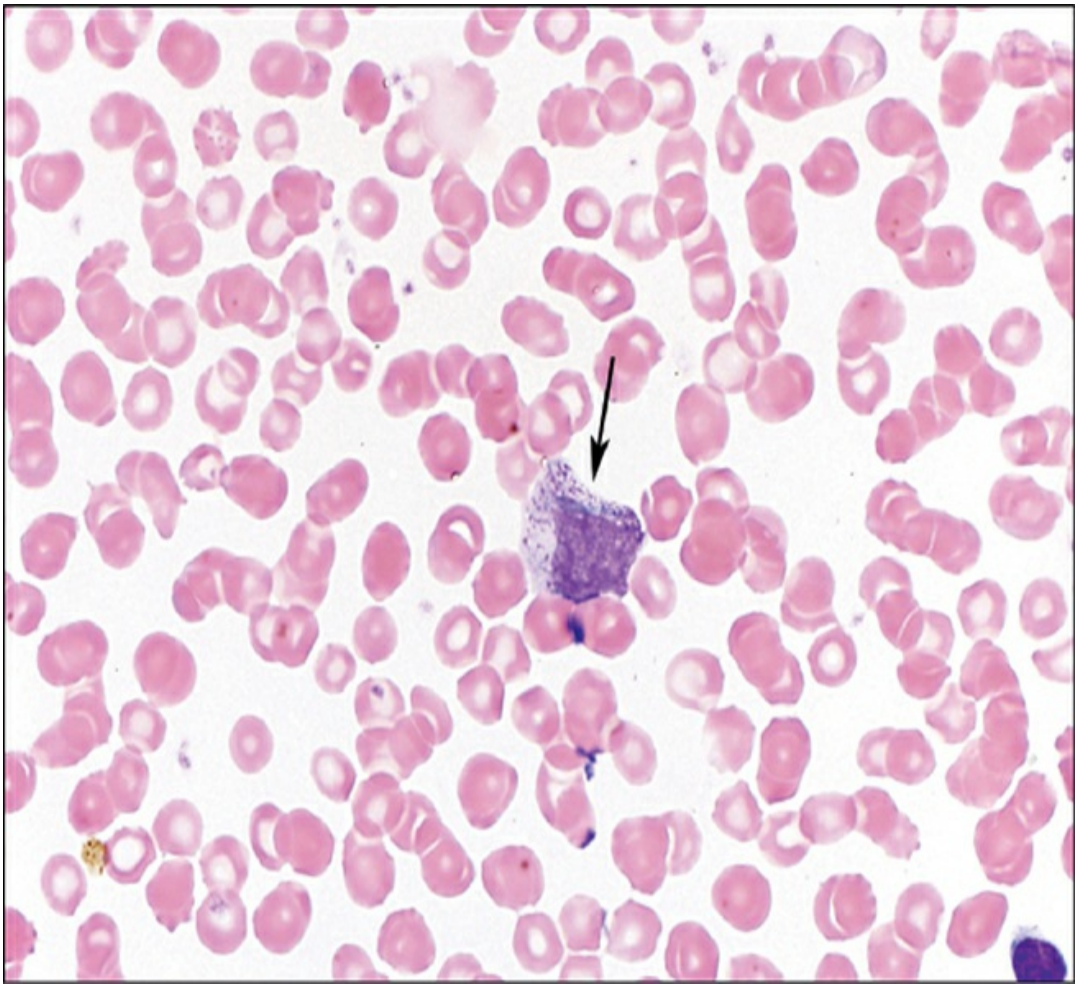


Figure IA2-8

Size: 12–18 µ

Nucleus

Shape: Round, oval, or flattened on one side

N/C Ratio: 3:1–3:2

Color: Dark purple

Chromatin: Coarser chromatin pattern

Nucleoli: Early myelocytes may have visible nucleoli

Cytoplasm

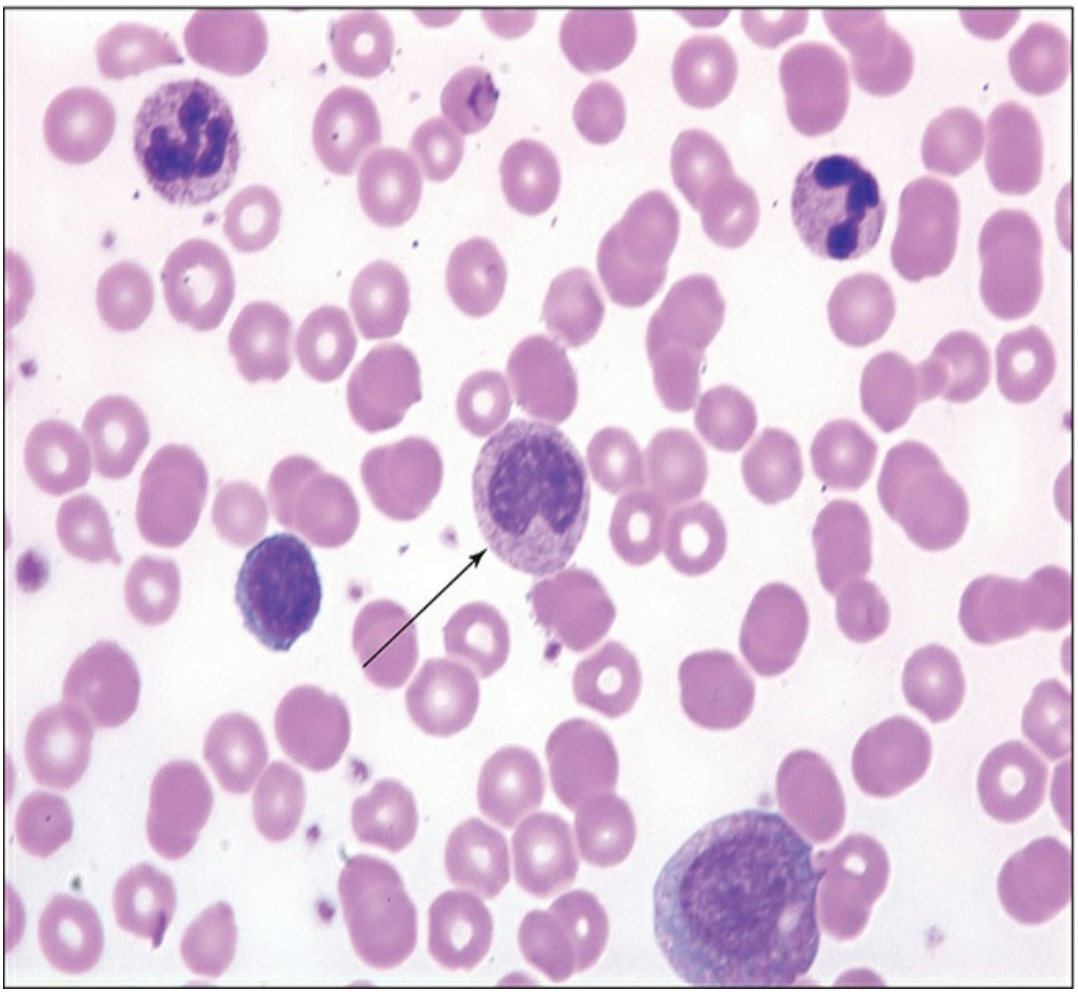
Color: Pinkish-blue

Contents: Few large basophilic granules staining dark bluish purple to bluish black

Clinical Conditions

- Acute basophilic leukemia
- Chronic myelogenous leukemia
- AML with t(6;9) (WHO)

Neutrophilic Metamyelocyte



Size: 10–15 µ

Nucleus

Shape: Typical kidney shape or slightly indented

N/C Ratio: 7:3–1:1

Color: Dark purple

Chromatin: Coarse, purple chromatin

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Pinkish to reddish-blue granules

Clinical Conditions

- Growth factor therapy
- Stress
- Severe infections
- Myeloproliferative neoplasms—CML, PMF
- AML with maturation (M2) (FAB) (WHO)
- AML with t(8;21) (WHO)

Eosinophilic Metamyelocyte

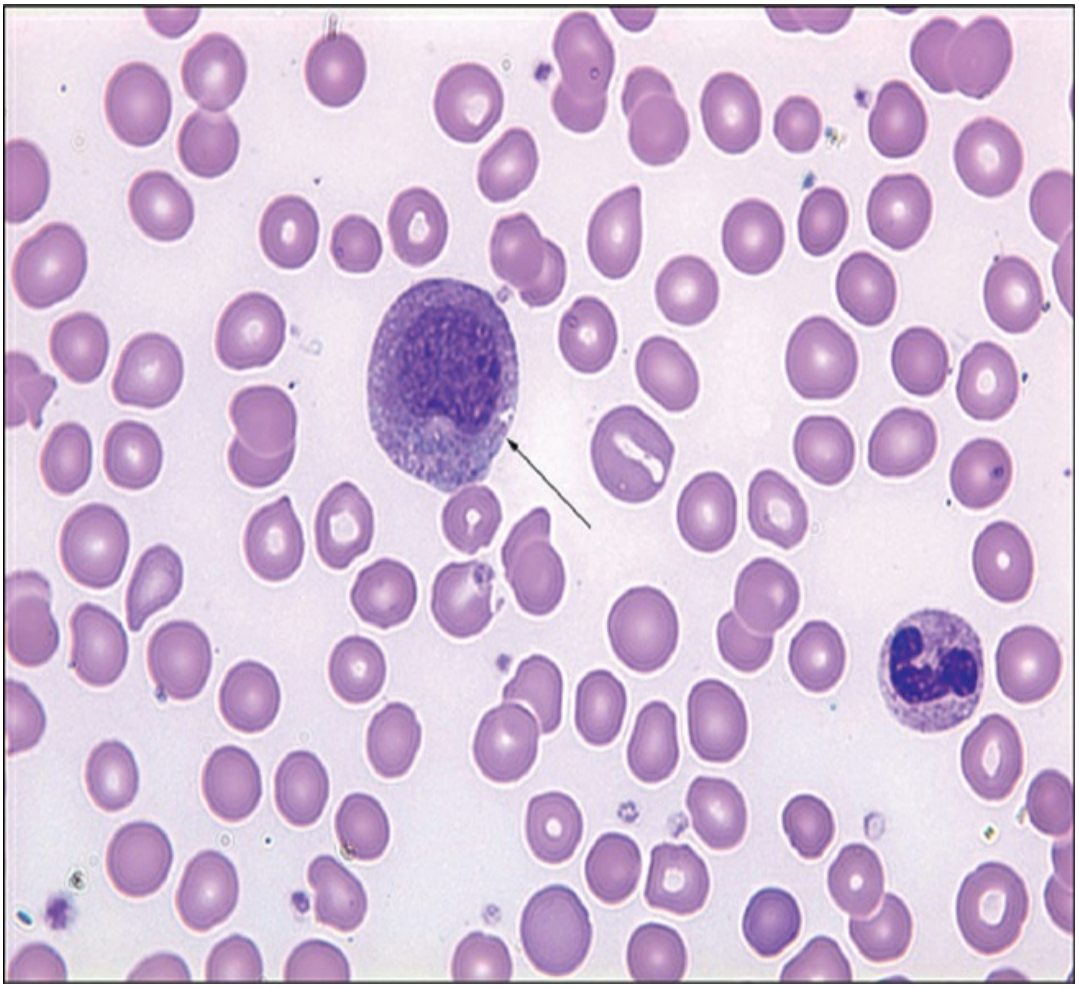


Figure **IA2-10**

Size: 10–15 μ

Nucleus

Shape: Typical kidney shape or slightly indented

N/C Ratio: 7:3–1:1

Color: Dark purple

Chromatin: Coarse blue-black

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Numerous medium bright orange to reddish granules

Clinical Conditions

- Parasitic infections
- Chronic eosinophilic leukemia (NOS) (WHO)
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)
- PCM1-JAK2 (WHO)

Basophilic Metamyelocyte

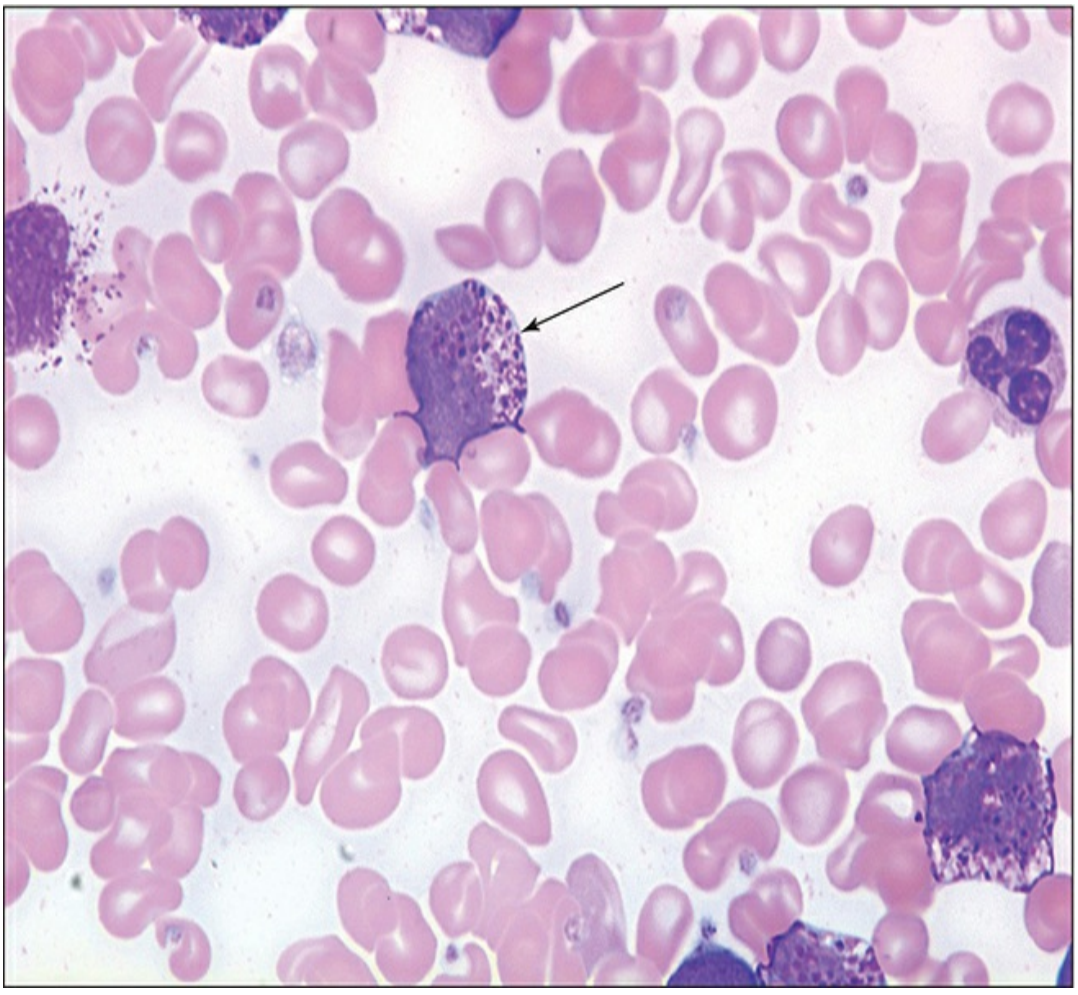


Figure IA2-11

Size: 10–15 µ

Nucleus

Shape: Typical kidney shape or slightly indented

N/C Ratio: 7:3–1:1

Color: Dark purple

Chromatin: Coarse, blue-black

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Few large dark blue-black granules

Clinical Conditions

- Chronic myelogenous leukemia
- Basophilic leukemia (WHO)
- AML with t(6;9) (WHO)

Neutrophilic Band

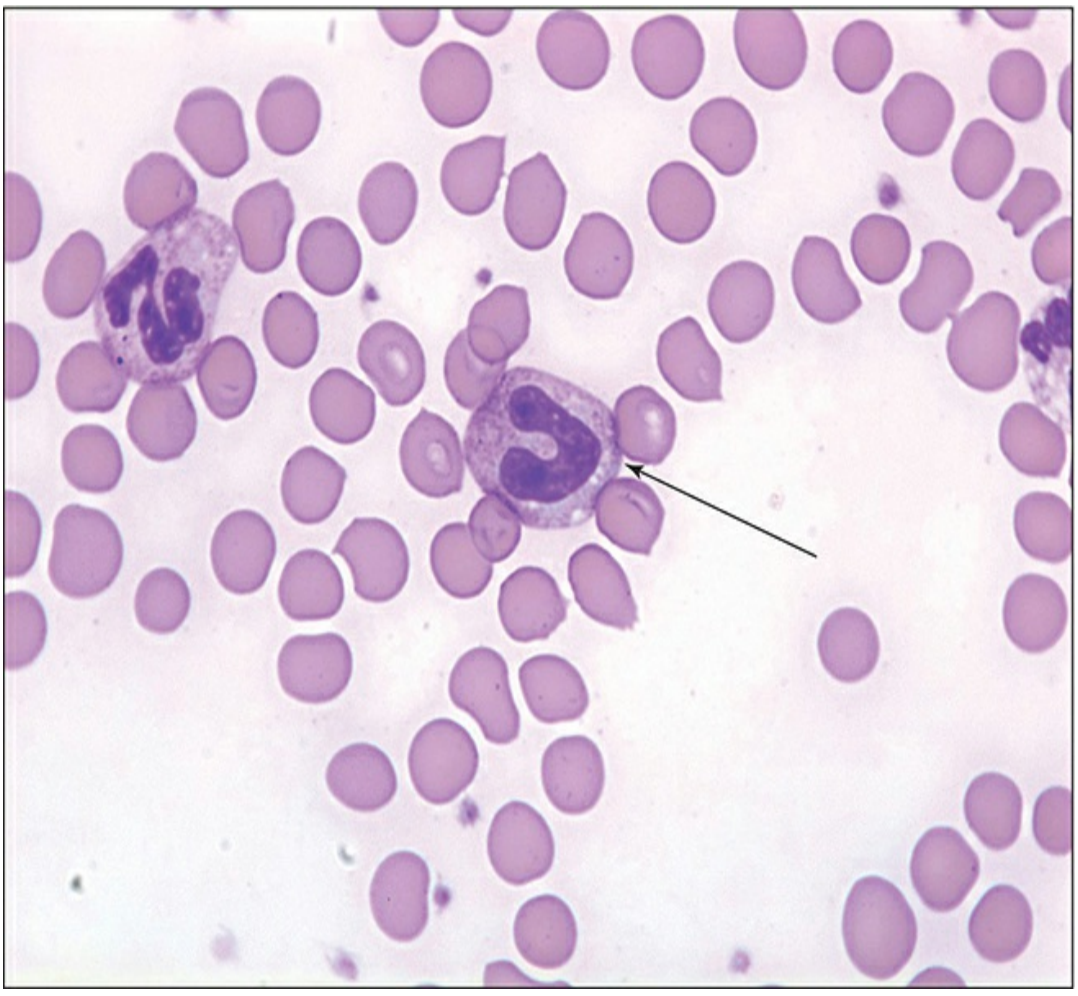


Figure IA2-12

Size: 10–16 μ

Nucleus

Shape: Band shape or markedly indented; indentation is greater than one-half the width of the hypothetical round nucleus

N/C Ratio: 1:1–1:2

Color: Dark purple

Chromatin: Coarse, blue-black

Cytoplasm

Color: Pinkish-blue

Contents: Pinkish-blue granules

Clinical Conditions

- Growth factor therapy
- Stress
- Infections
- Myeloproliferative neoplasms—CML, PMF
- AML with maturation (M2) (FAB) (WHO)
- AML with t(8;21) (WHO)

Eosinophilic Band

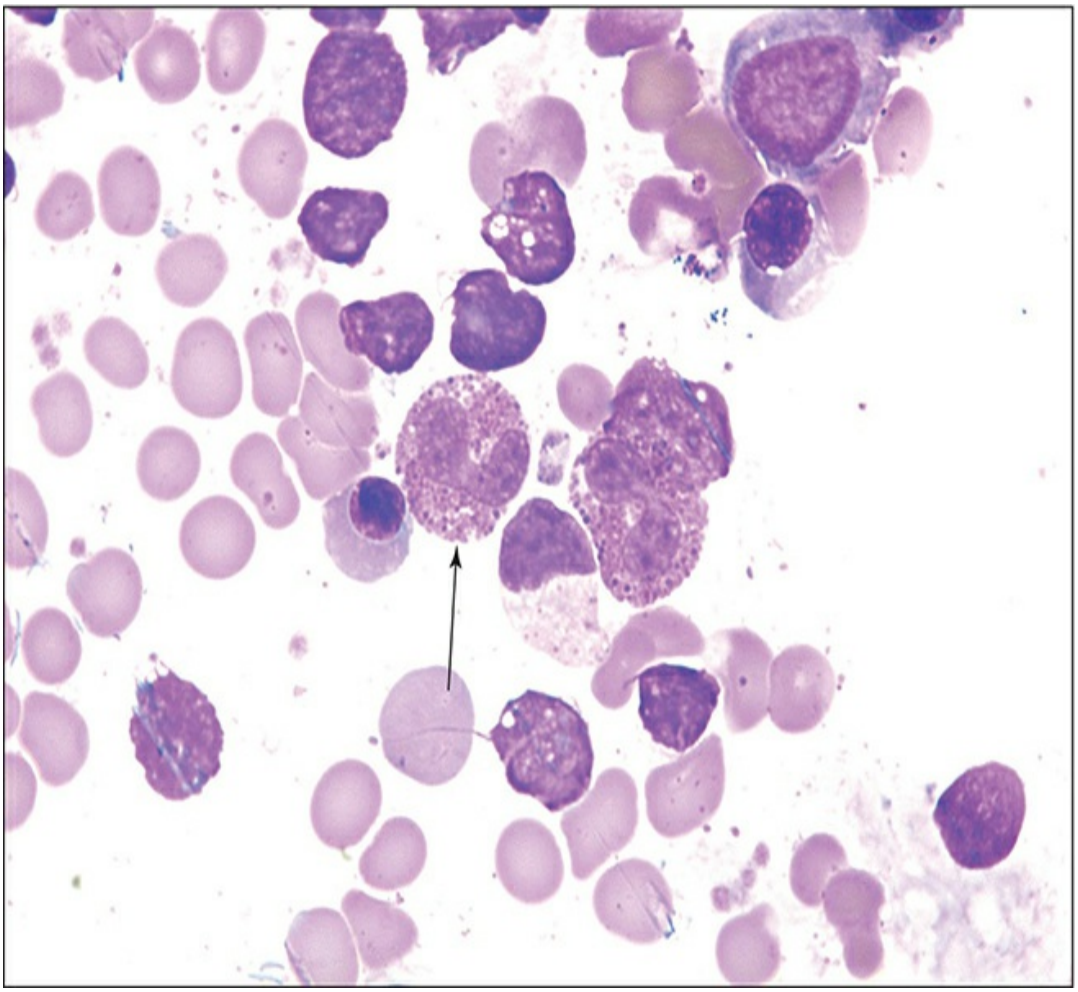


Figure **IA2-13**

Size: 10–16 µ

Nucleus

Shape: Band shape or markedly indented

N/C Ratio: 1:1–1:2

Color: Dark purple

Chromatin: Coarse, blue-black

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Numerous orange-red granules

Clinical Conditions

- Parasitic infections
- Chronic eosinophilic leukemia (NOS) (WHO)
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)
- PCM1-JAK2 (WHO)

Basophilic Band

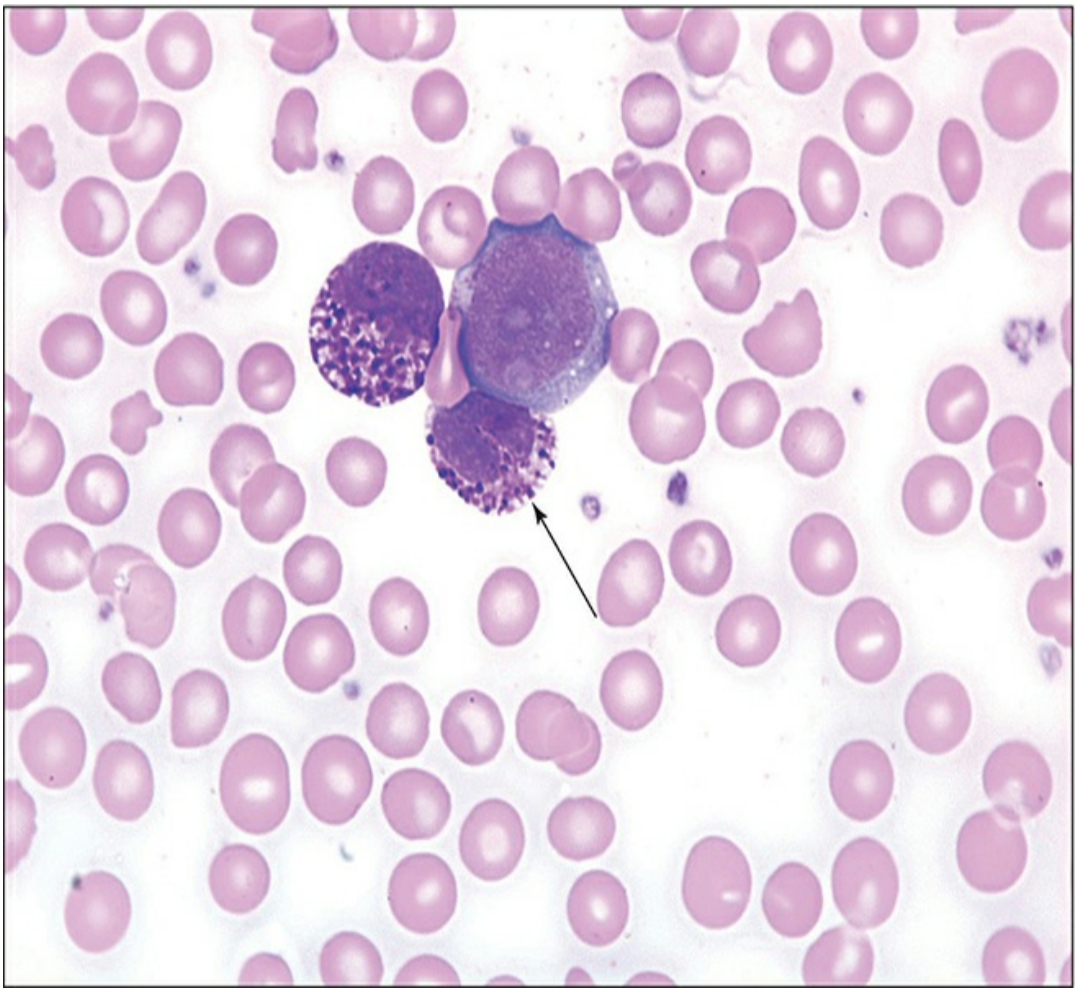


Figure IA2-14

Size: 10–16 µ

Nucleus

Shape: Band shape or markedly indented

N/C Ratio: 1:1–1:2

Color: Dark purple

Chromatin: Coarse, blue-black

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Few large dark bluish-purple to bluish-black granules

Clinical Conditions

- Myeloproliferative neoplasms—CML, PMF
- Basophilic leukemia (WHO)
- AML with t(6;9) (WHO)

Segmented Neutrophil (Polymorphonuclear Neutrophil)

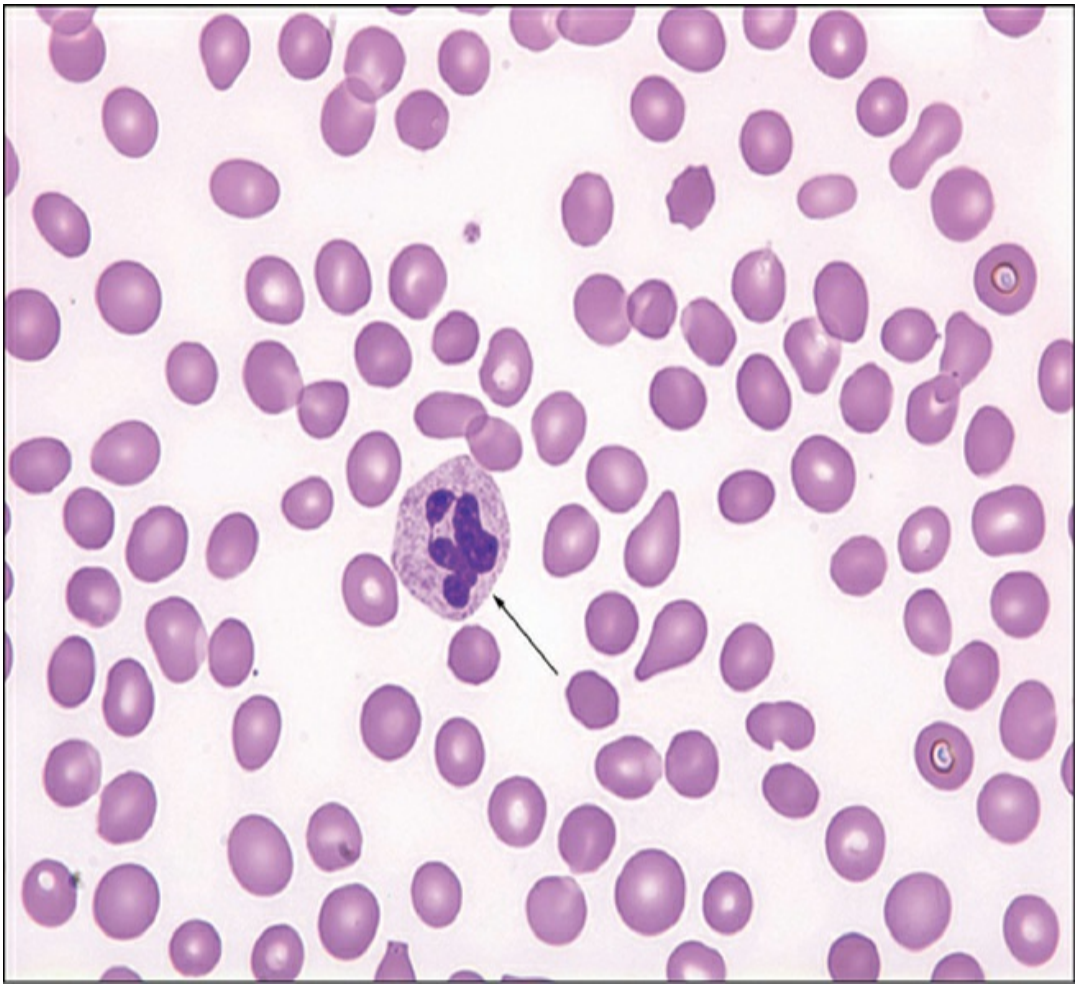


Figure IA2-15

Size: 10–16 μ

Nucleus

Shape: 2–5 lobes connected by a very narrow filament; nuclear indentation is greater than one-half its diameter

N/C Ratio: 1:3–1:5

Color: Dark purple

Chromatin: Heavily clumped

Nucleoli: None

Cytoplasm

Color: Light pink to bluish

Contents: Many small, evenly distributed pink to rose-violet granules

Clinical Conditions

- Infections
- Chronic neutrophilic leukemia
- Growth factor therapy
- Stress

Eosinophil

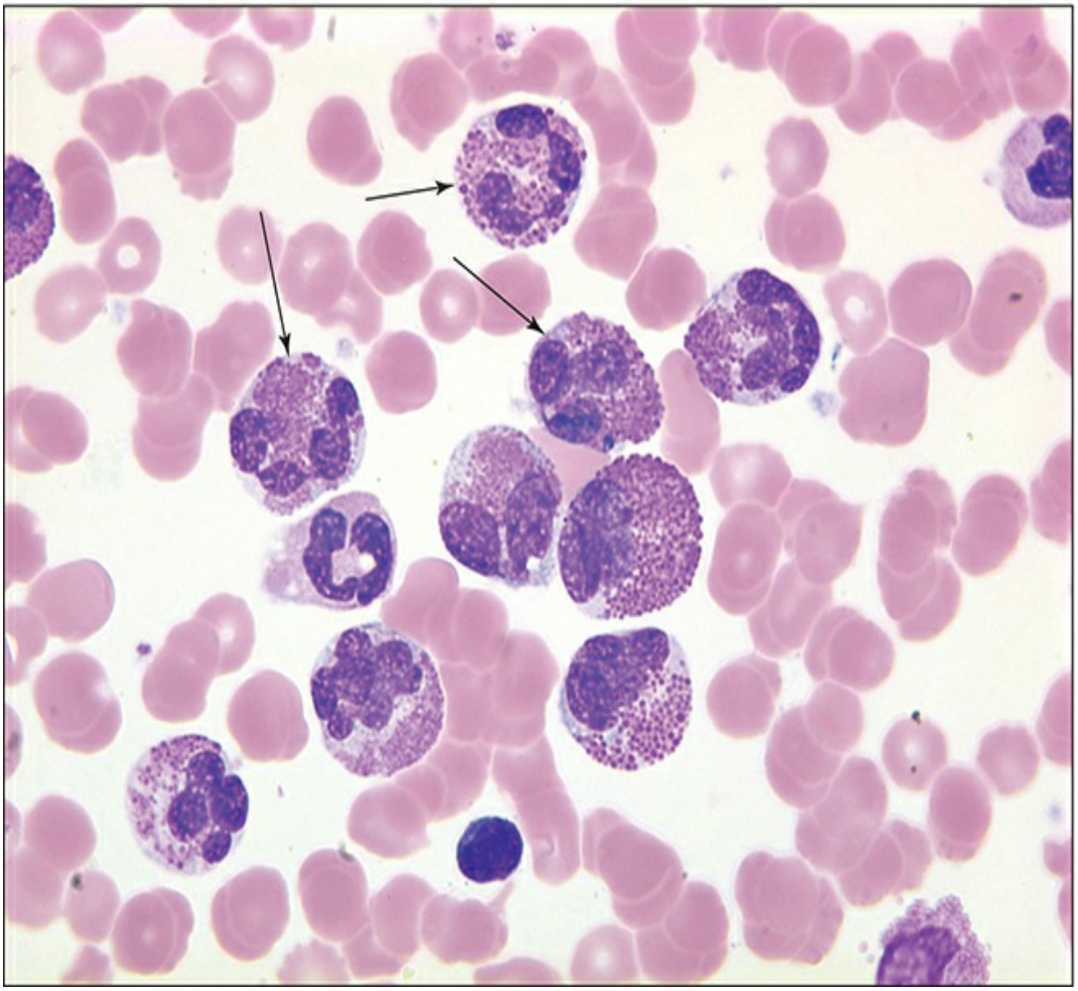


Figure IA2-16

Size: 10–16 µ

Nucleus

Shape: 2–3 lobes

N/C Ratio: 1:3–1:5

Color: Dark purple

Chromatin: Heavily clumped

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Many large, round, uniform reddish-orange granules

Clinical Conditions

- Protozoan infections
- Allergic disorders
- Chronic myelocytic leukemia
- Dermatitis
- Hodgkin lymphoma
- Chronic eosinophilic leukemia (NOS) (WHO)
- PDGFRA rearrangement (WHO)
- PDGFRB rearrangement (WHO)
- FGFR1 rearrangement (WHO)
- PCM1-JAK2 (WHO)

Basophil

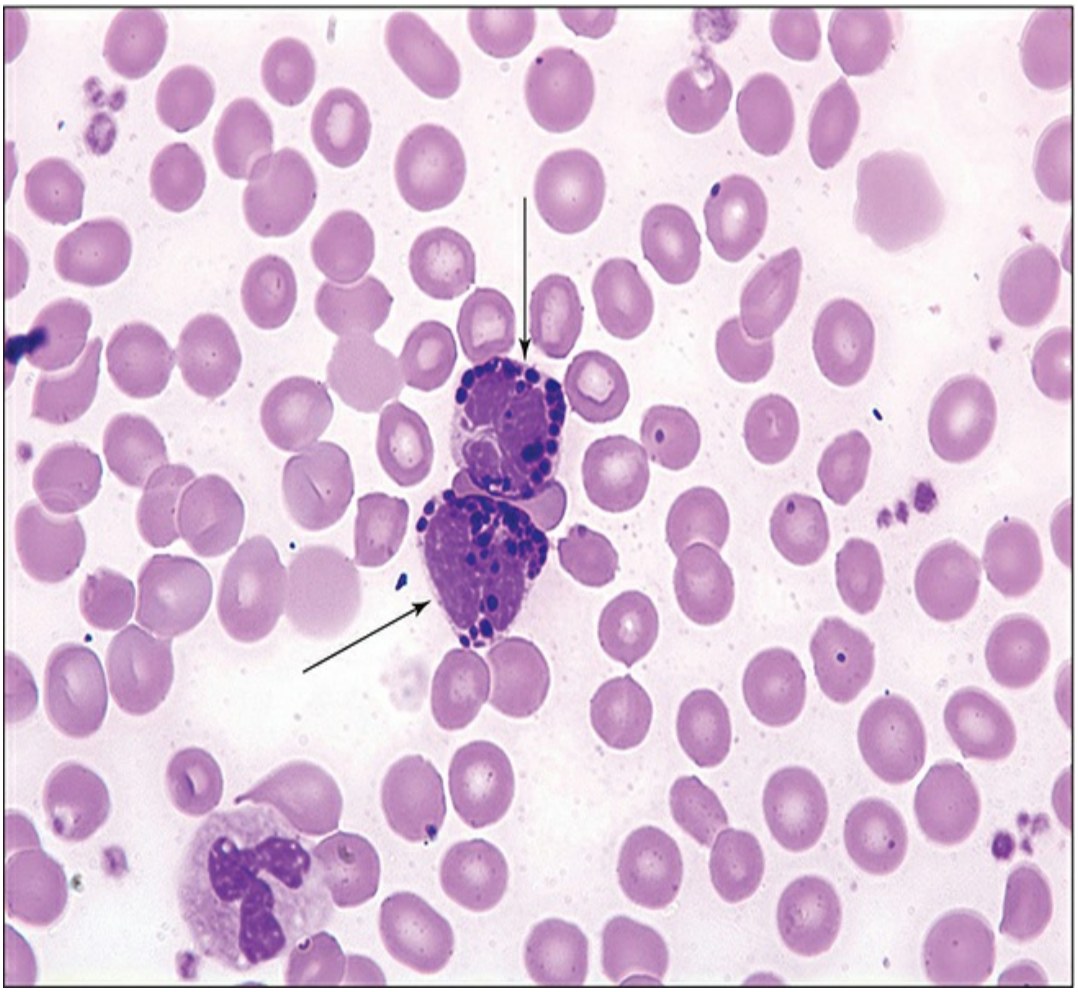


Figure **IA2-17**

Size: 10–16 μ

Nucleus

Shape: 2 lobes usually obscured by granules

N/C Ratio: 1:3–1:5

Color: Dark purple

Chromatin: Heavily clumped

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Few dark blue-black granules

Clinical Conditions

- Acute basophilic leukemia
- Myeloproliferative neoplasms
- Allergy and inflammation
- AML with t(6;9) (WHO)

Mast Cell

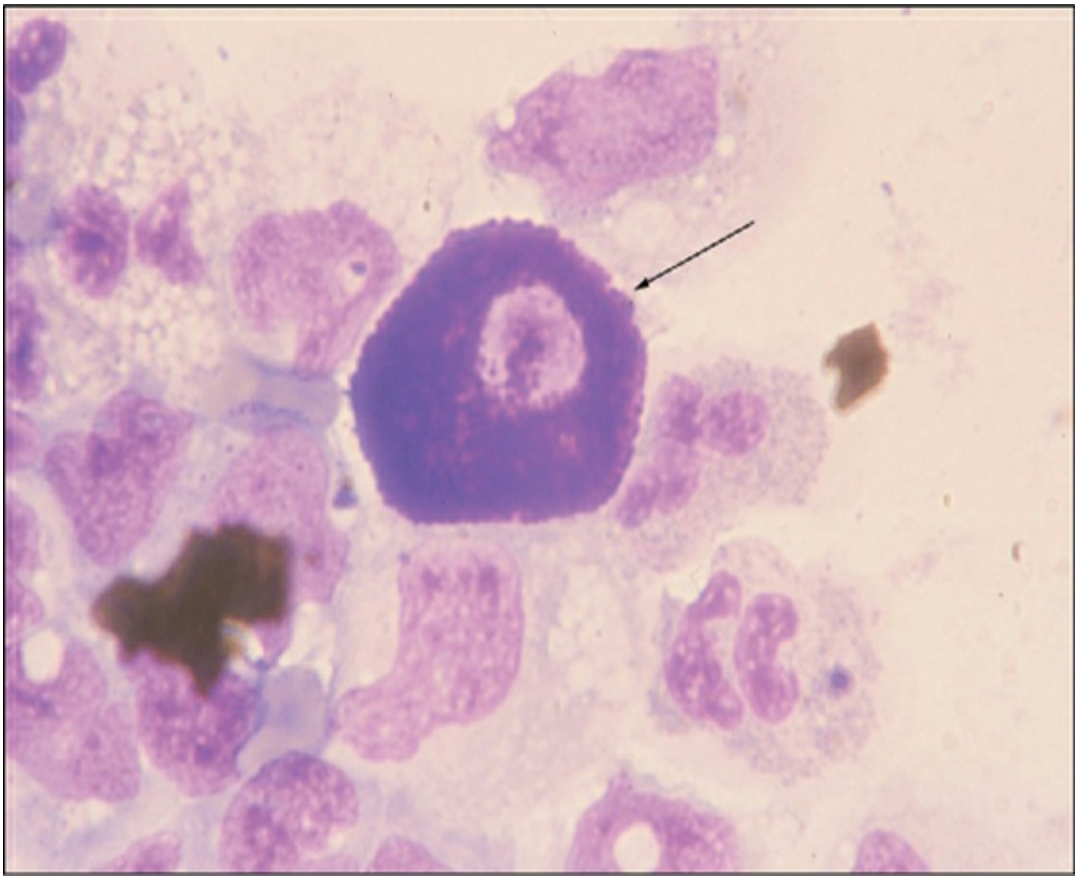


Figure **IA2-18**

Size: 9–12 µ

Nucleus

Shape: Round

N/C Ratio: 1:1

Color: Dark purple

Chromatin: Heavily clumped

Nucleoli: None

Cytoplasm

Cytoplasm

Color: Dark blue

Contents: Many dark blue granules

Clinical Condition

- Mast cell disease

NUCLEAR SEGMENTATION

Hypersegmentation

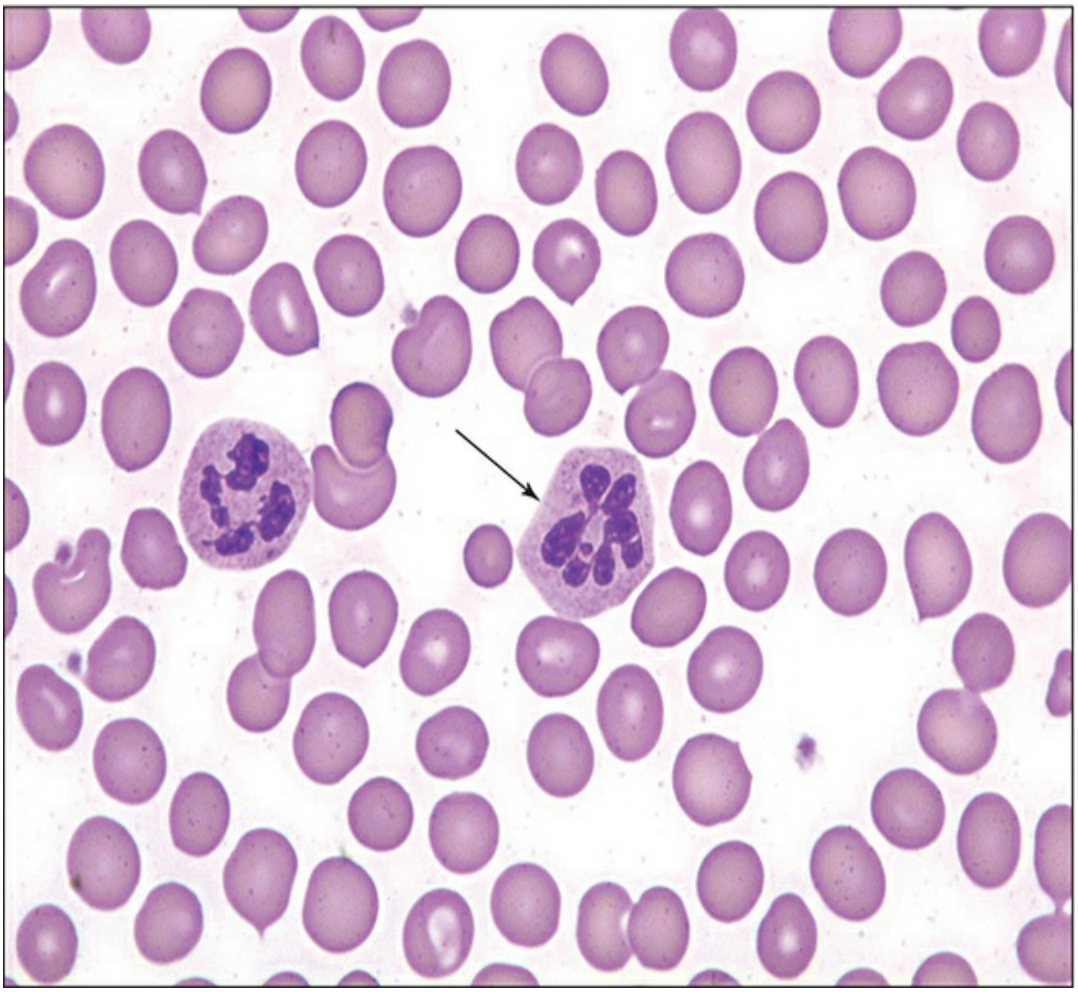


Figure IA2-19

Cell Type

Neutrophil, eosinophil

Description

Neutrophil has 6 or more nuclear lobes; eosinophil has >4 lobes

Clinical Conditions

- Chronic infections
- B_{12} deficiency

- Folic acid deficiency
- Myelodysplastic syndromes
- Hereditary hypersegmentation
- Long-term infections

Pelger-Huët

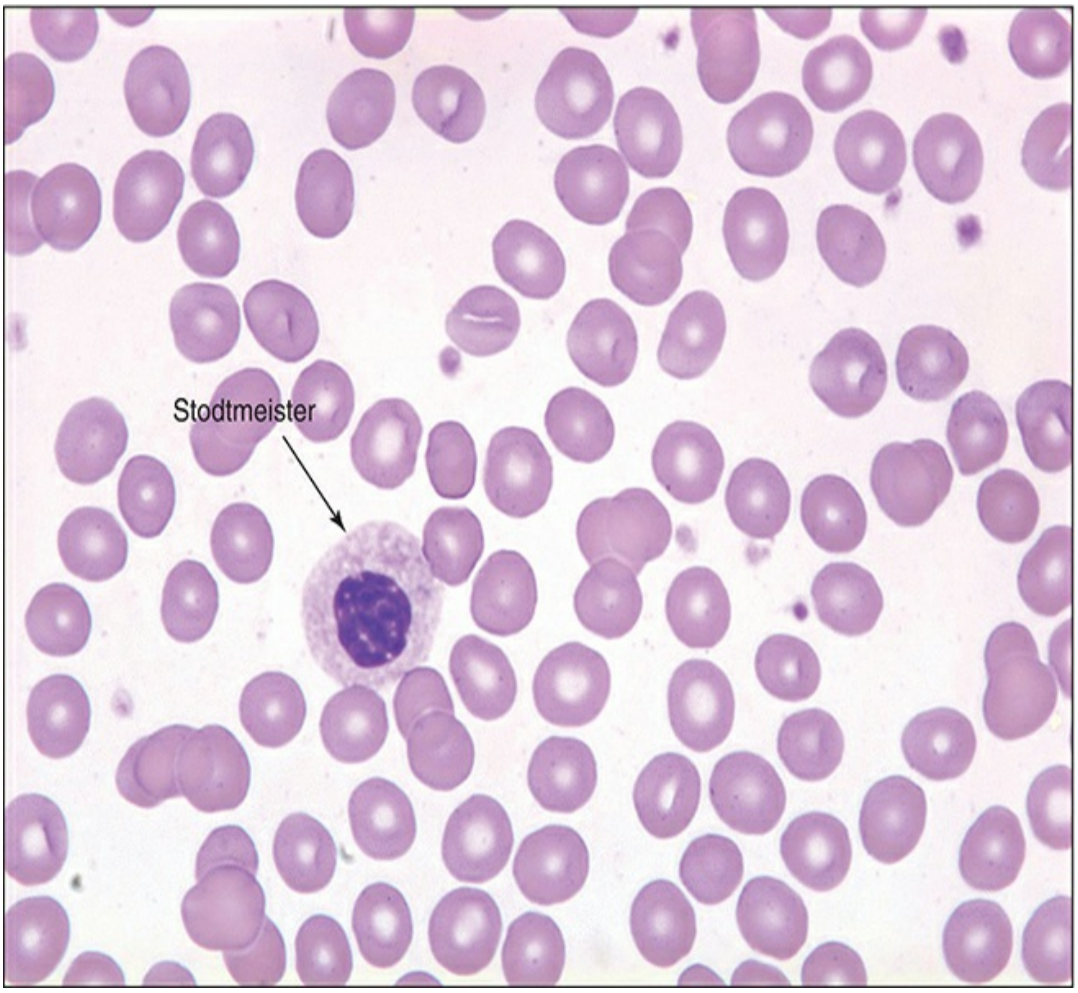


Figure IA2-20A

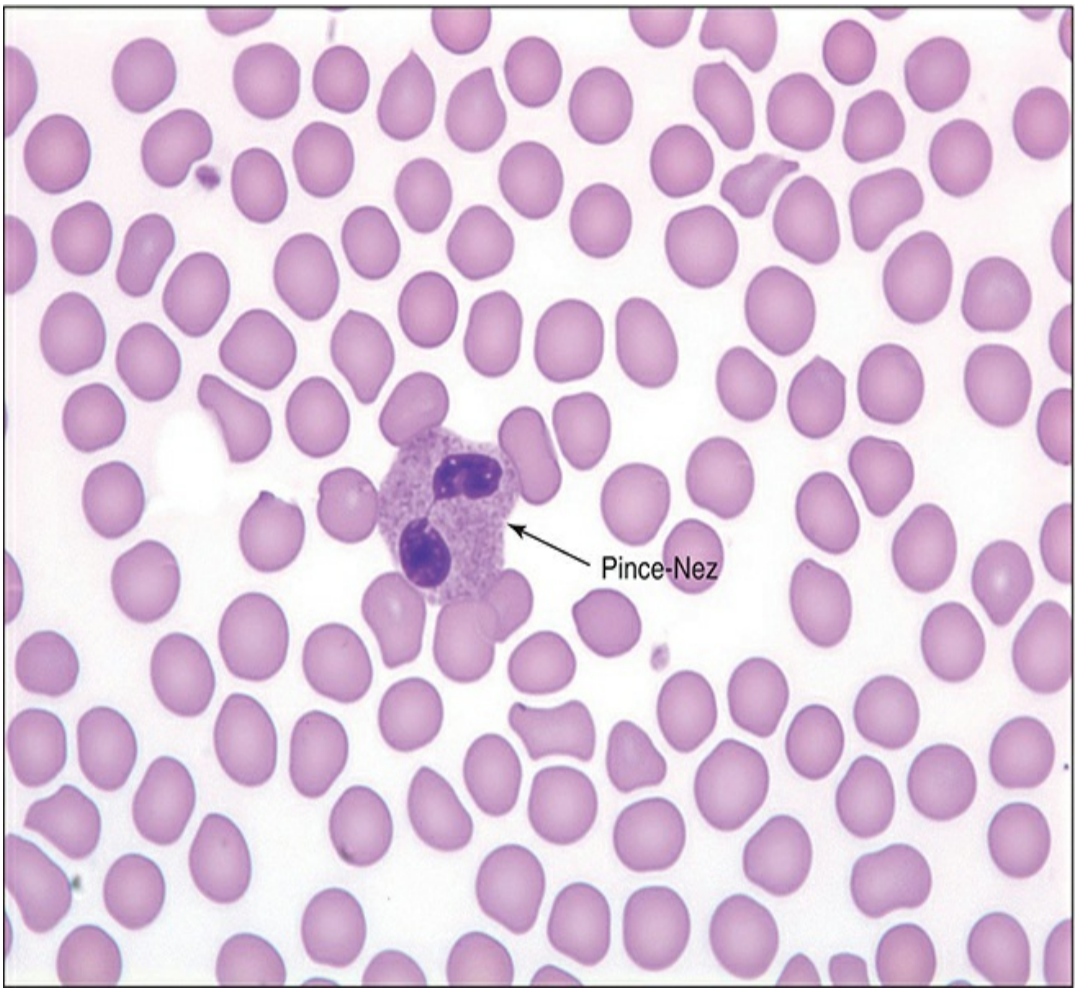


Figure **IA2-20B**

Cell Type

Neutrophil

Description

Heterozygous inherited disorder (Pince-Nez)

Bilobed or dumbbell-shaped nucleus; clumped, coarse chromatin; normal cytoplasmic granules

Homozygous inherited disorder (Stodtmeister)

Round or oval nuclei; dense clumped coarse chromatin; normal cytoplasmic granules

Clinical Condition

- Pelger-Huët—inherited disorder (autosomal dominant)

Pelgeroid Cells

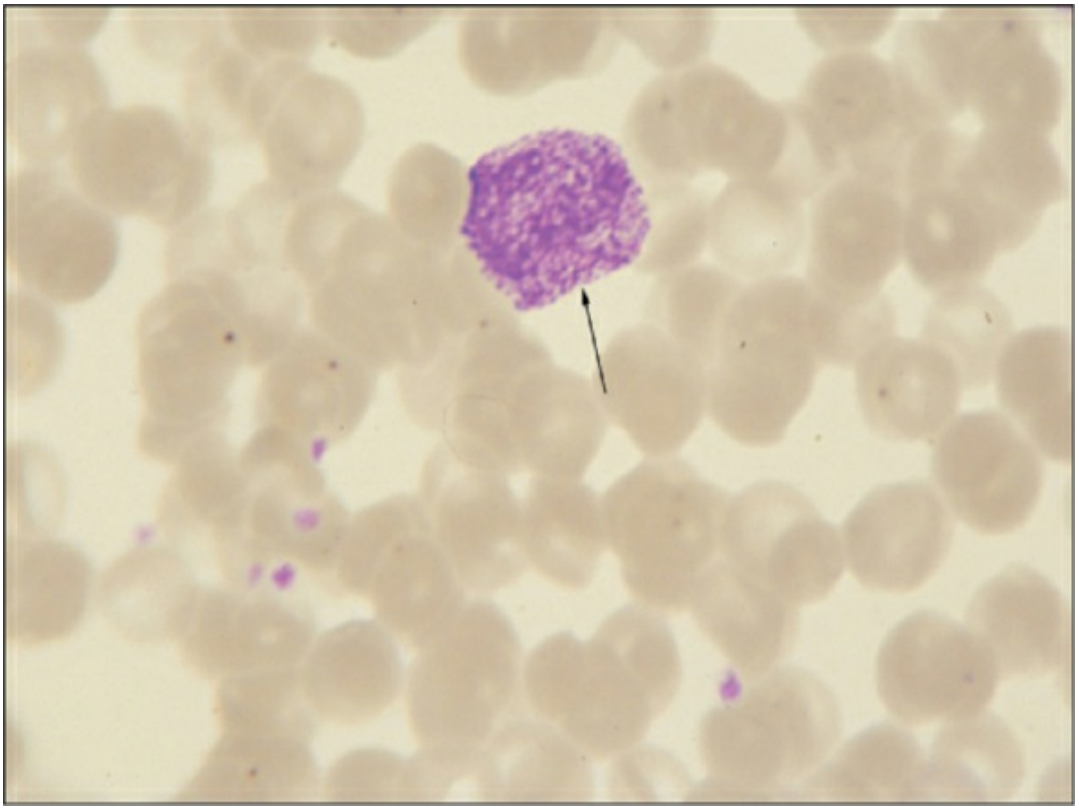


Figure IA2-21

Cell Type

Neutrophils

Description

Nucleus resembles Pelger-Huët (round or bilobed); few or no cytoplasmic granules

Clinical Conditions

- Myelodysplastic syndromes
- Acute myelogenous leukemias—dysplastic finding
- Myelodysplastic/myeloproliferative neoplasms (WHO)
- AML with myelodysplasia-related changes (WHO)

CYTOPLASMIC INCLUSIONS

Alder-Reilly Bodies

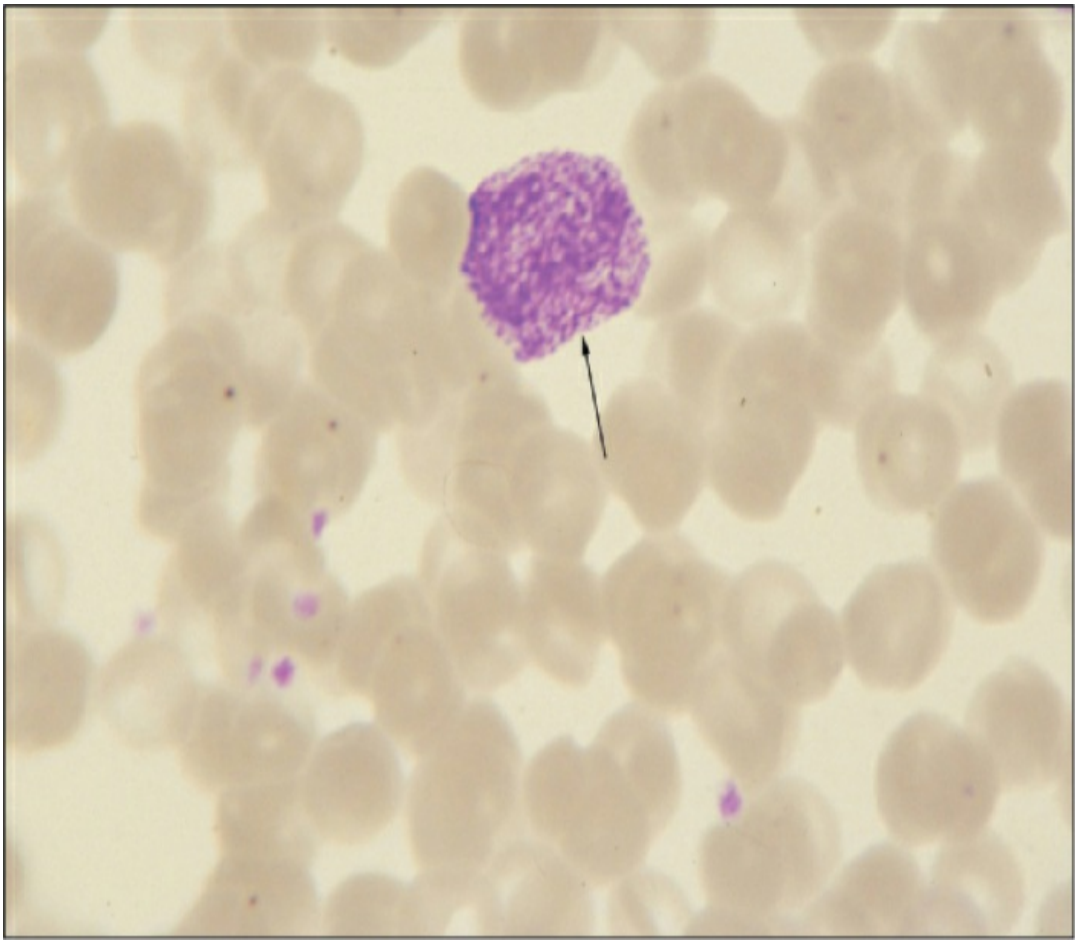


Figure IA2-22

Cell Type

Neutrophil, eosinophil, basophil; occasionally lymphocyte and monocyte

Description

Inherited condition (autosomal recessive)

Dense blue cytoplasmic granules consisting of stored mucopolysaccharides and sphingomyelin

Normal nuclear maturation

Clinical Condition

- Mucopolysaccharidoses (e.g., Hurler syndrome, Hunter syndrome)

Auer Rods

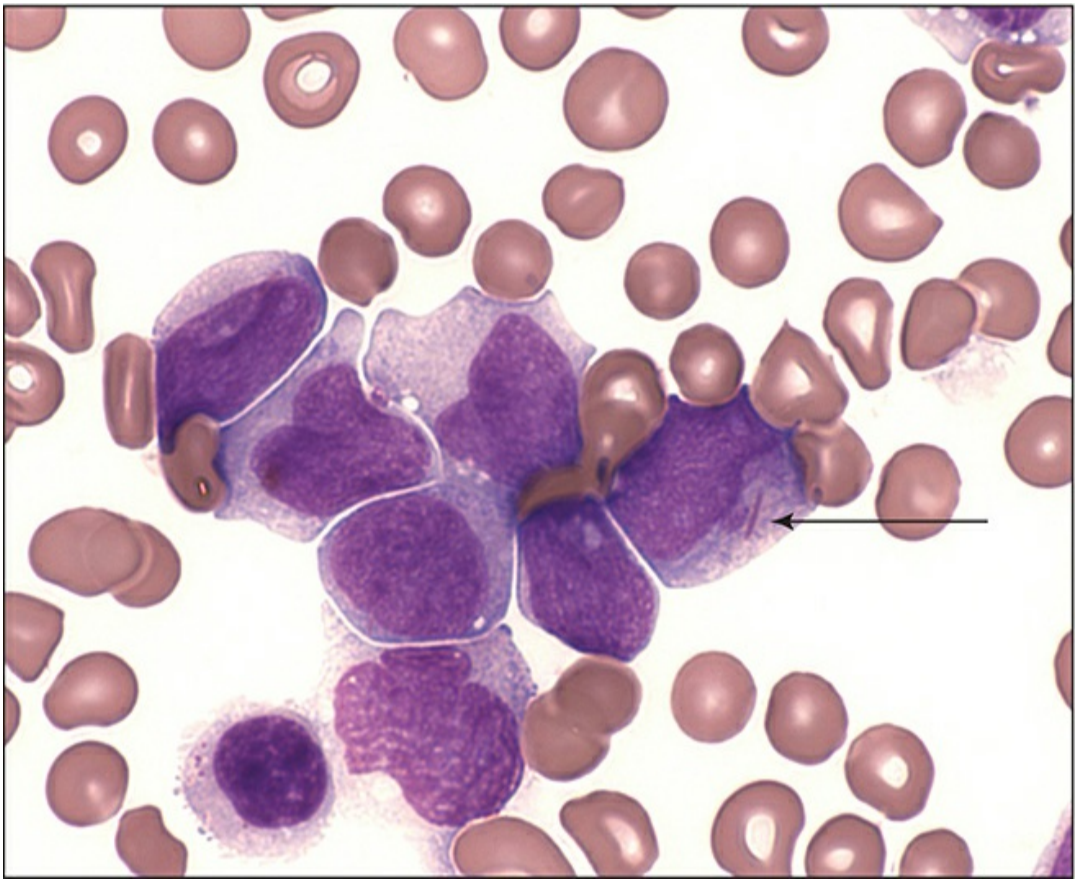


Figure IA2-23

Cell Type

Myeloblast and promyelocyte

Description

Reddish-purple rod-shaped cytoplasmic inclusions

Alignment of primary granules

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1) (FAB) (WHO)
- Acute myelocytic leukemia with maturation (M2) (FAB)

(WHO)

- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Acute myelocytic leukemia with myelodysplasia-related changes (WHO)
- Chronic myelocytic leukemia in blastic transformation
- AML with t(8;21) (WHO)
- AML with t(15;17) (WHO)
- AML with inv(16) or t(16;16) (WHO)

Chédiak-Higashi Granules

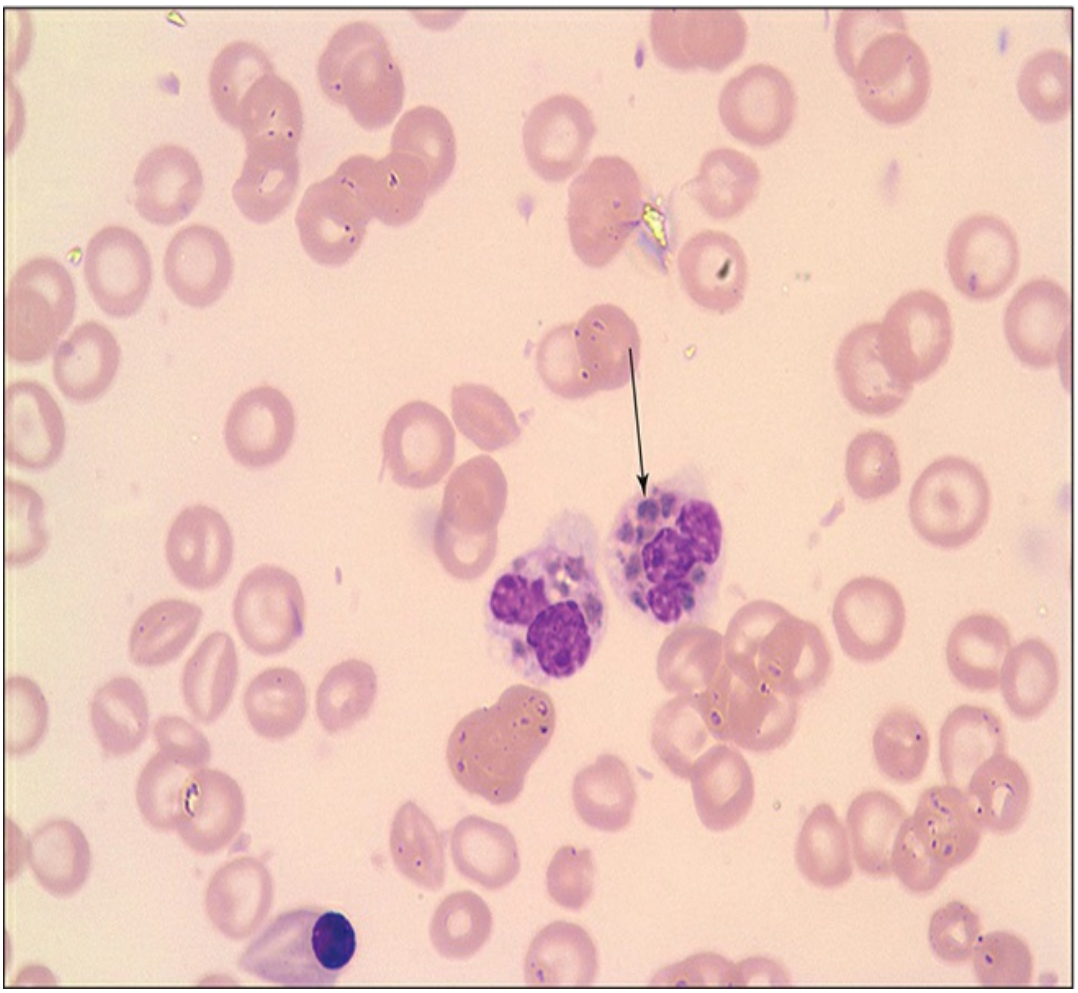


Figure IA2-24

Cell Type

Granulocyte, lymphocyte, monocyte

Description

Inherited (autosomal recessive)

Many large, greenish primary cytoplasmic granules or many large, reddish-purple secondary cytoplasmic granules

Clinical Condition

- Chédiak-Higashi syndrome—severe and often fatal infections in children; complete or partial albinism

LE Cell

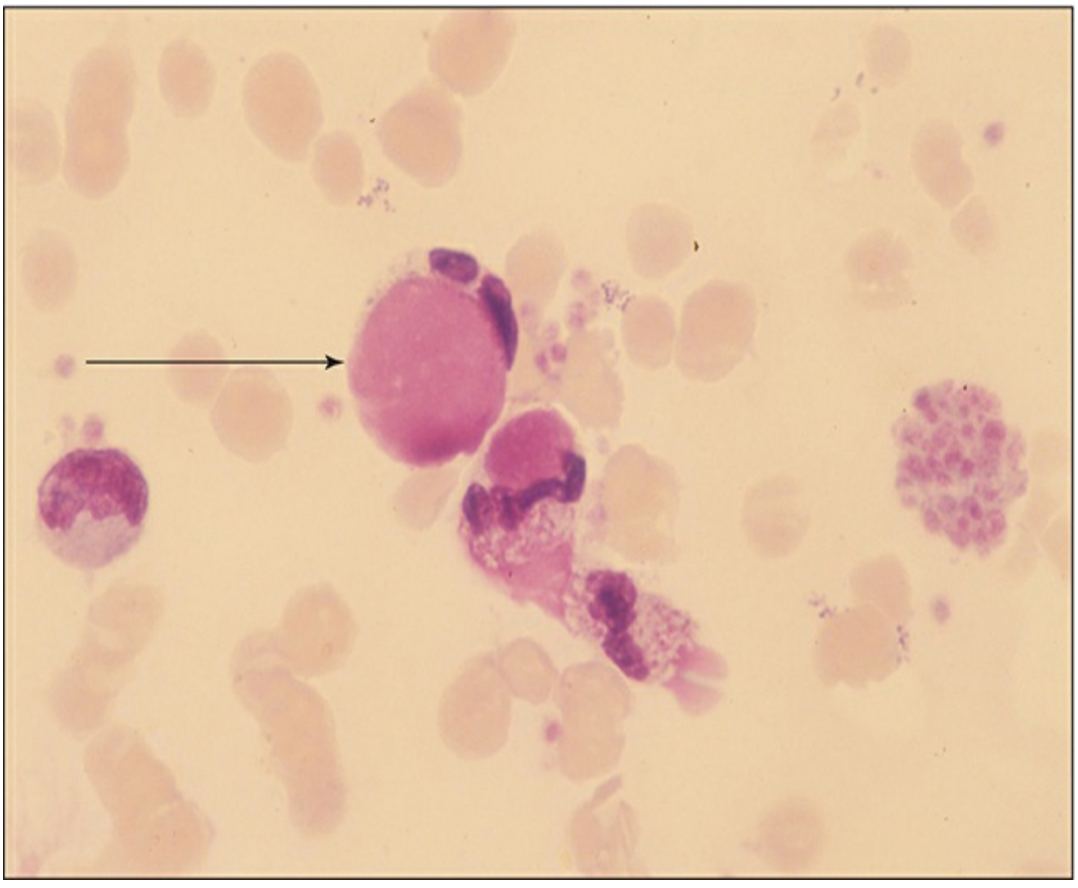


Figure IA2-25

Cell Type

Neutrophil

Description

Large, spherical body in cytoplasm is homogeneous, has no nuclear structure, and stains pale purple; nucleus of cell is pushed to periphery and appears to wrap around cytoplasmic inclusion

Clinical Condition

- Systemic lupus erythematosus

May-Hegglin Inclusion

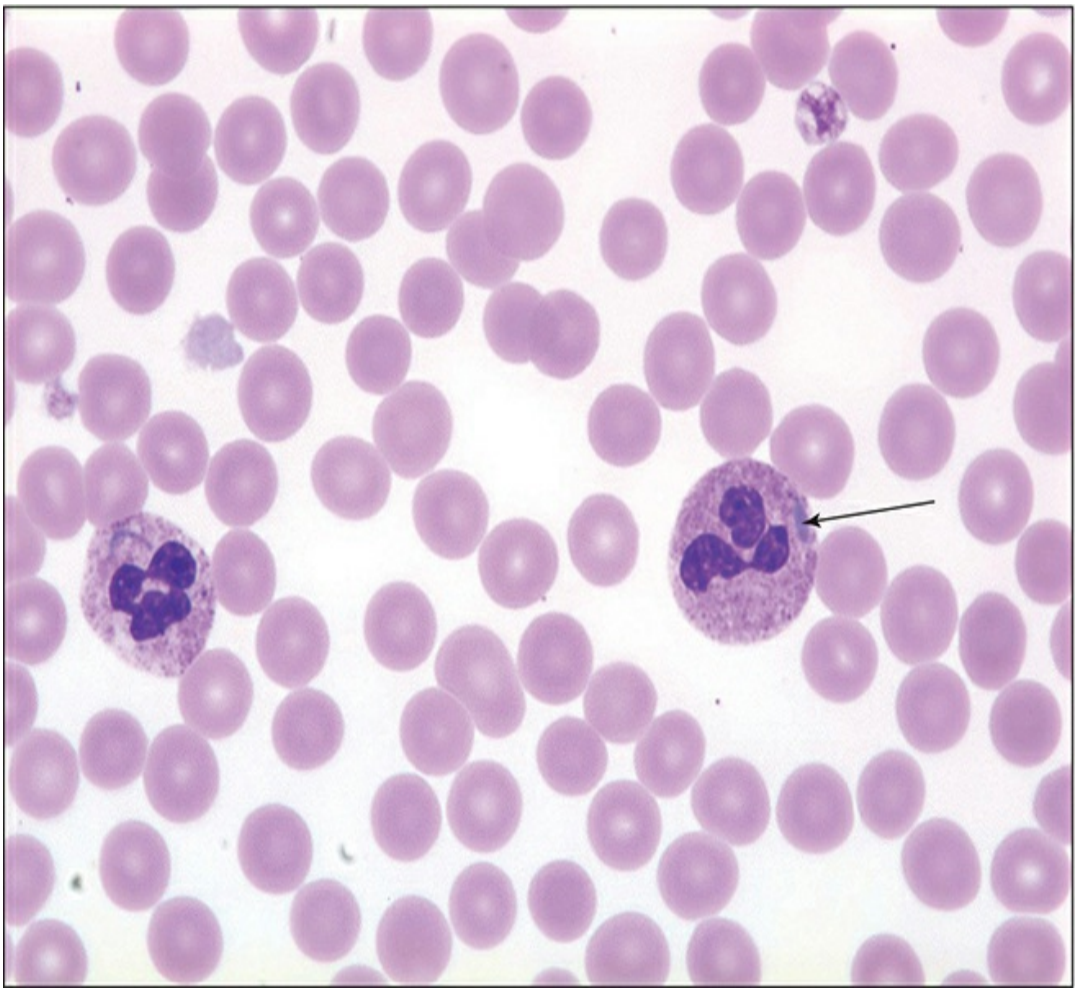


Figure IA2-26

Cell Type

Neutrophil, eosinophil, basophil, monocyte

Description

Inherited (autosomal dominant)

Large, blue, crescent-shaped cytoplasmic inclusions consisting of RNA

Resemble large Döhle bodies

Presence of enlarged and decreased platelets

Clinical Condition

- May-Hegglin anomaly

Microorganisms

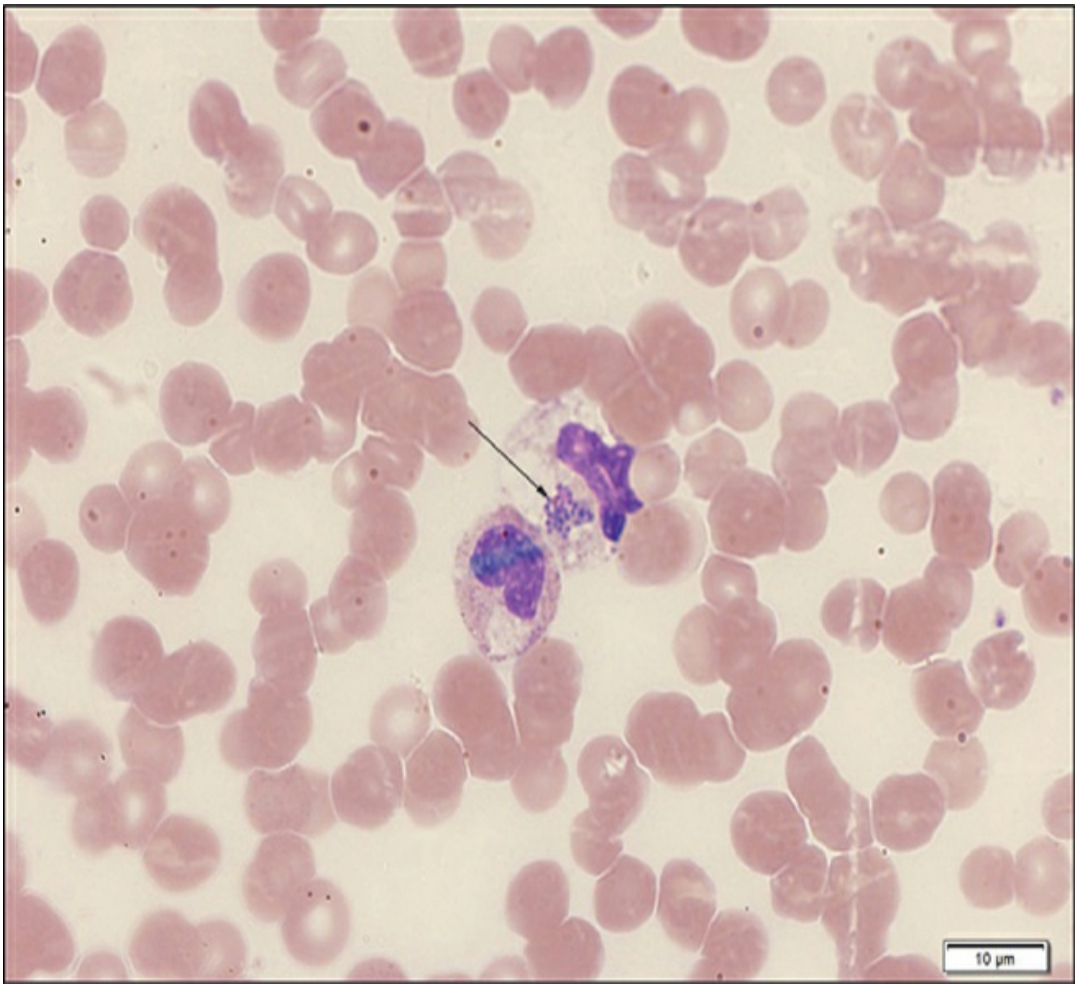


Figure IA2-27

Cell Type

Neutrophil, monocyte (macrophage)

Description

Microorganisms in cytoplasm

Clinical Condition

- Microbial infections

Döhle Body

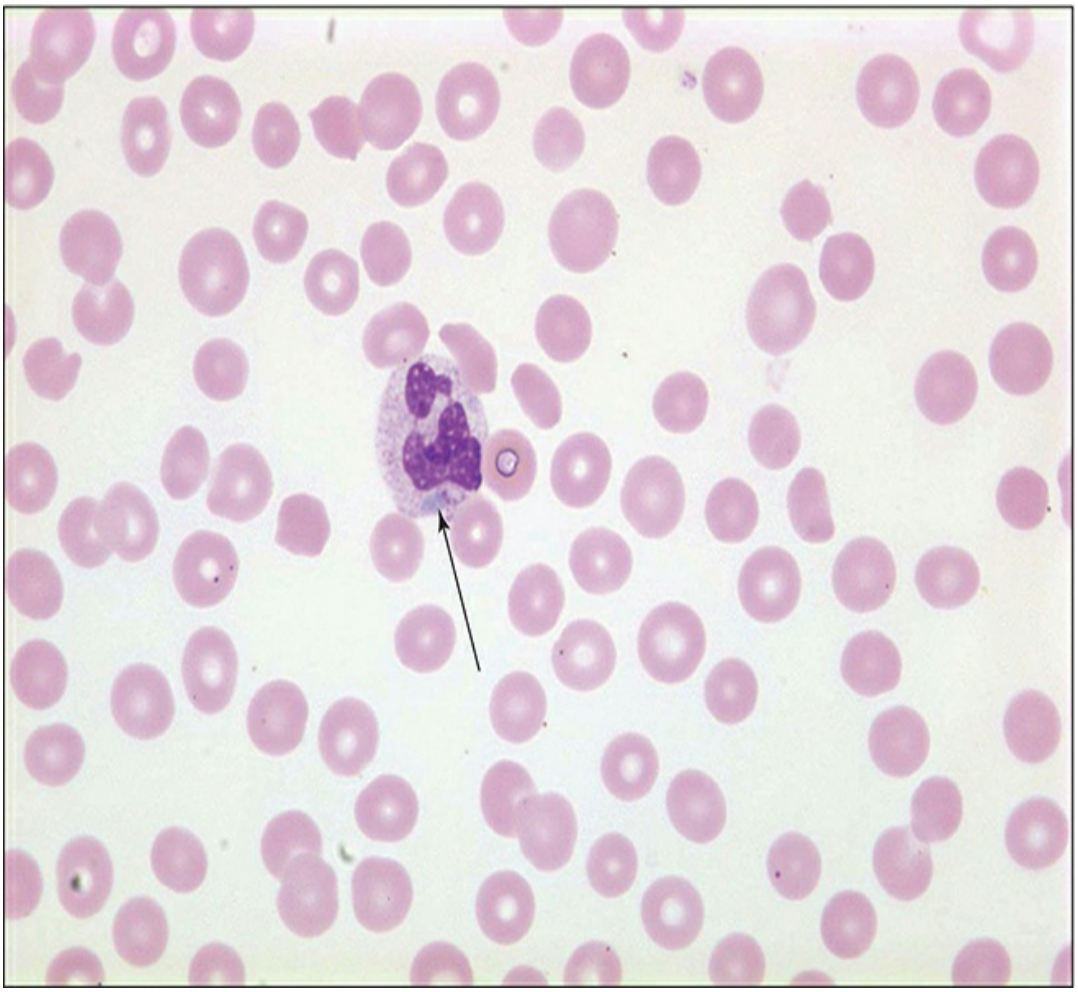


Figure IA2-28

Cell Type

Neutrophils

Description

Round or rod-shaped, light-blue cytoplasmic inclusions, often located near cell membrane

Inclusions represent ribosomes or rough endoplasmic reticulum

Clinical Conditions

- Infections
- Drug intoxication
- Burns
- Myelodysplastic syndromes—often seen in the degranulated segmented cells
- May-Hegglin anomaly
- Pregnancy
- Growth factor therapy

Toxic Granulation

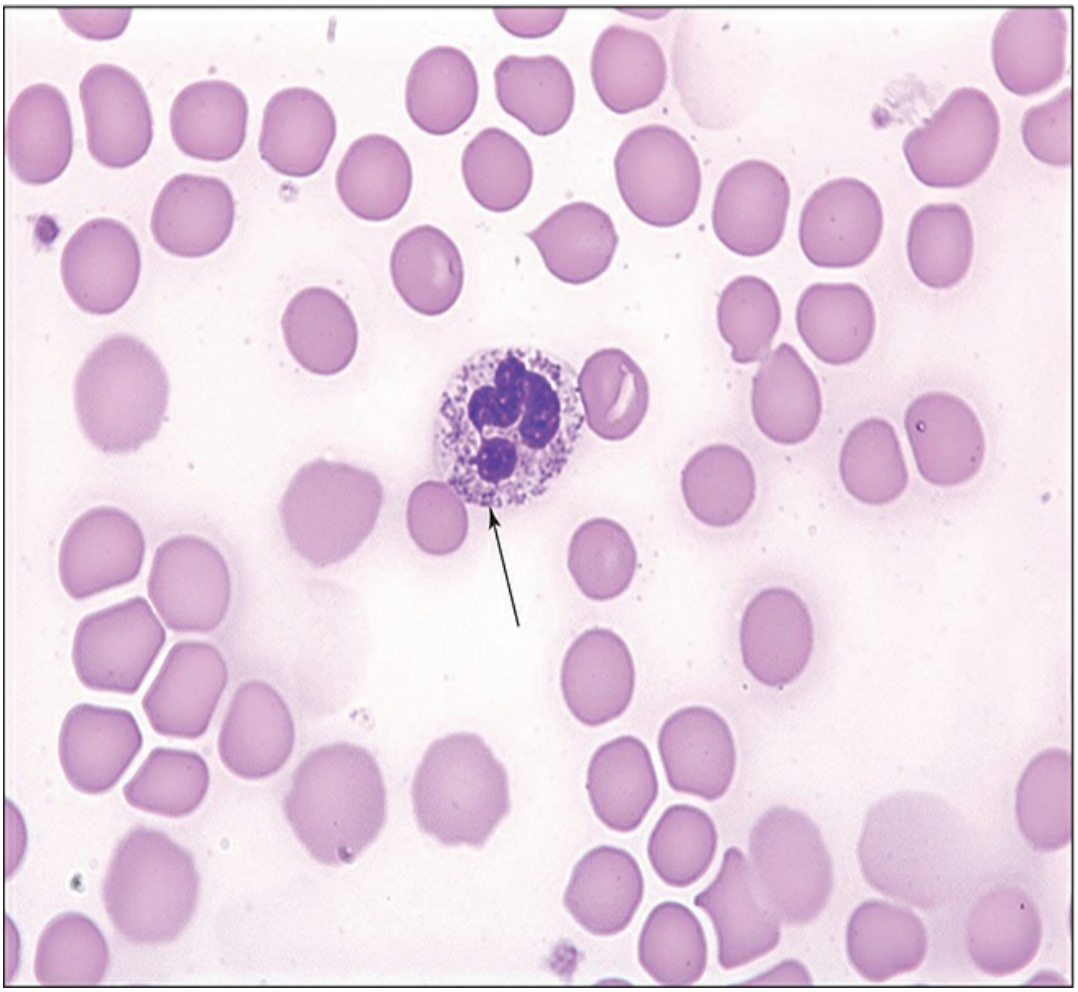


Figure **IA2-29**

Cell Type

Neutrophil

Description

Heavy, coarse, dark-blue primary cytoplasmic granules

Strong peroxidase reactivity

Clinical Conditions

- Infections
- Burns
- Drug intoxication
- Inflammation
- Growth factor therapy

Vacuolization

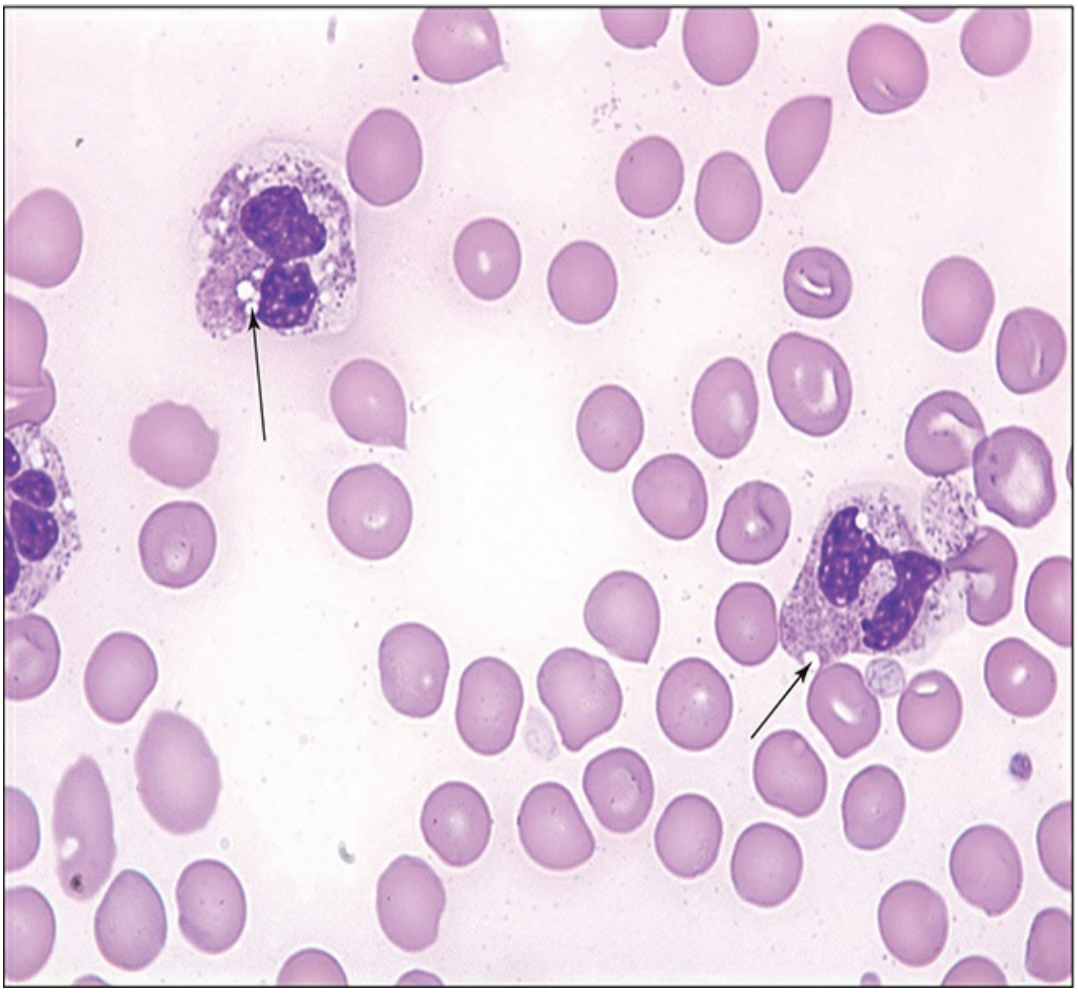


Figure IA2-30

Cell Type

Neutrophil, monocyte

Description

Vacuoles (holes) in cytoplasm

Clinical Conditions

- Severe infection
- Cell degeneration
- Phagocytosis
- Burns

- Toxins

ABNORMAL MATURATION

Dysgranulopoiesis

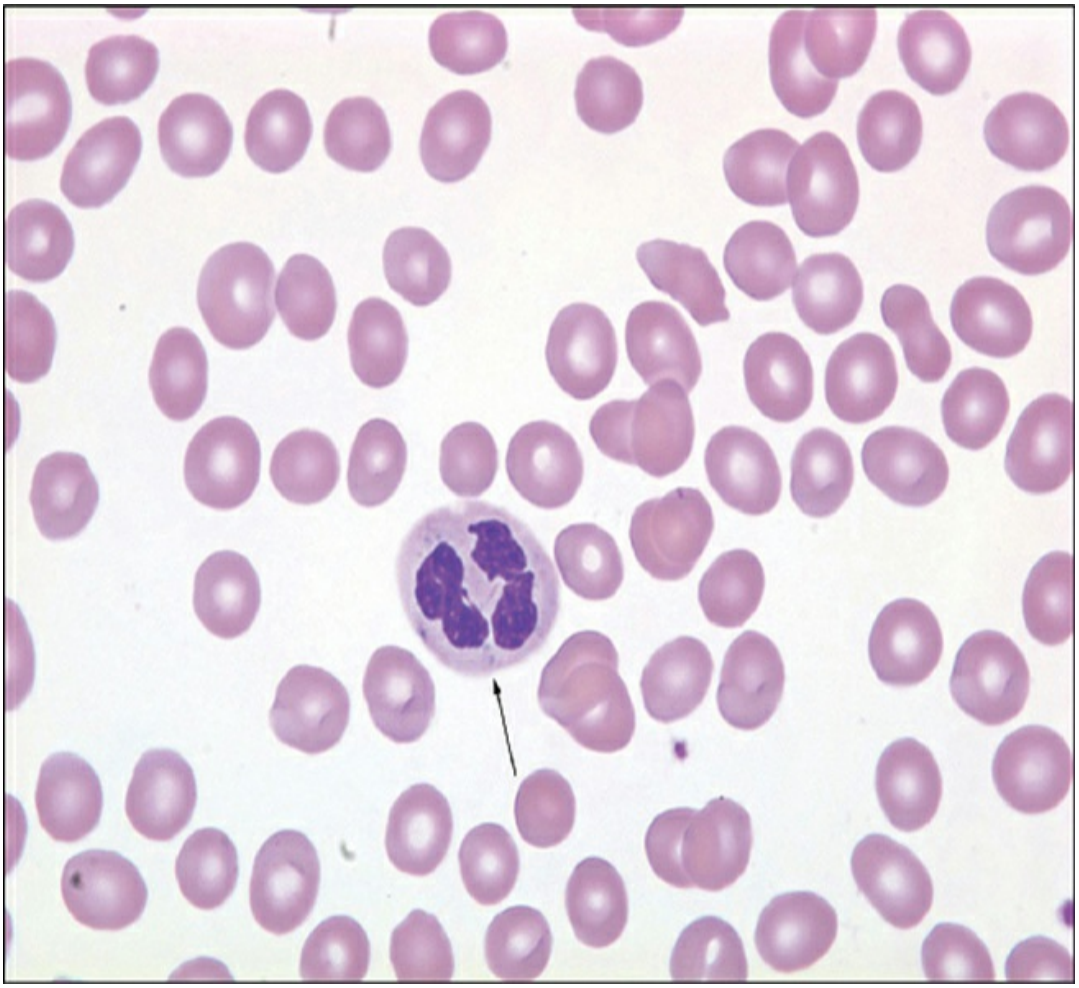


Figure IA2-31

Cell Type

Granulocyte cell line

Description

Nuclear/cytoplasmic asynchrony

Cytoplasm shows persistence of basophilia and may exhibit enlarged granules, hypogranulation, or agranularity

Nuclear asynchrony includes hypersegmentation or

hyposegmentation

Clinical Conditions

- Myelodysplastic syndromes
- Some acute myeloid leukemias

Giant Myelocytes, Metamyelocytes, and Bands

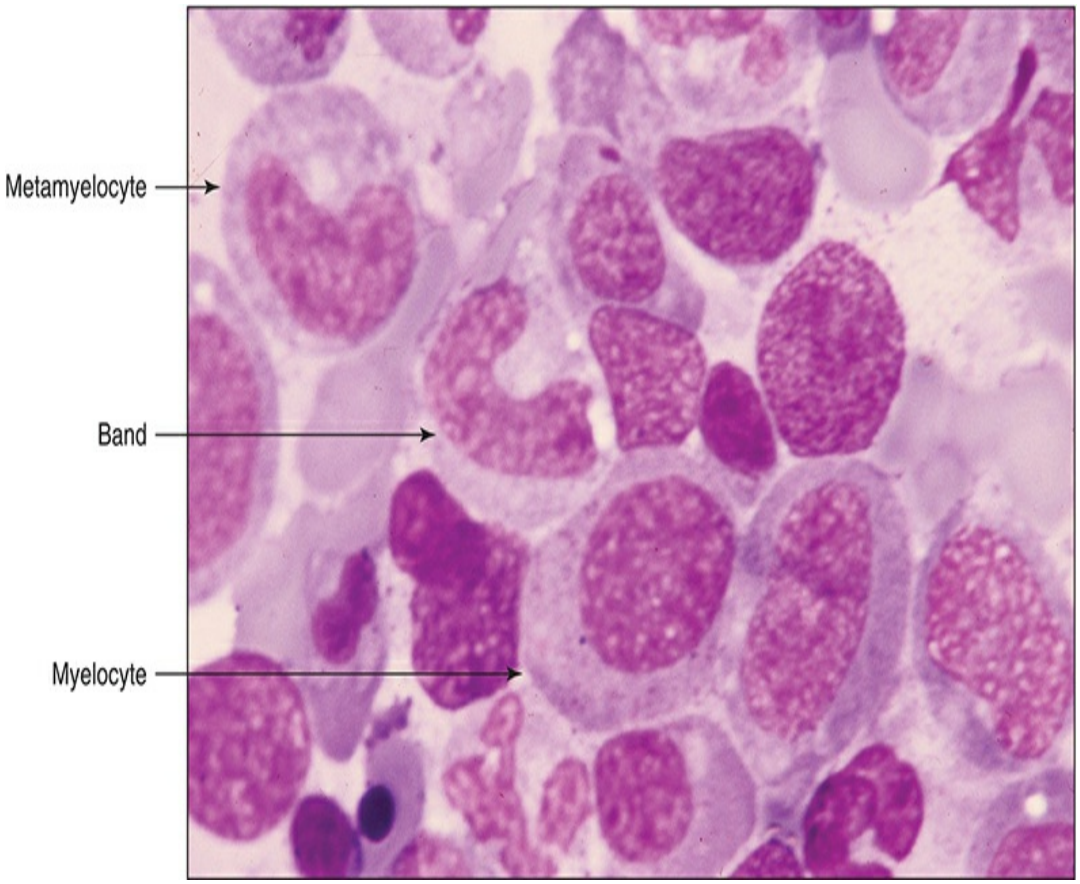


Figure IA2-32

Cell Type

Myelocyte, metamyelocyte, band

Description

Giant myelocytes are 17–26 µ ; nucleus is round, oval, or flattened on one side, dark purple, coarse chromatin, and no visible nucleoli; cytoplasm is pinkish-blue with

variable numbers of granules

Giant metamyelocytes are 15–22 μ ; typical dark purple, kidney-shaped nucleus; cytoplasm is pink-blue with pinkish to reddish-blue granules

Giant bands are 14–20 μ ; dark purple nucleus is band shaped; cytoplasm is pink-blue with pinkish-blue granules

Clinical Conditions

- Folate deficiency
- Vitamin B_{12} deficiency
- Chemotherapy (folate antagonists)

NORMAL MONOCYTE MATURATION SERIES

Monocyte Series

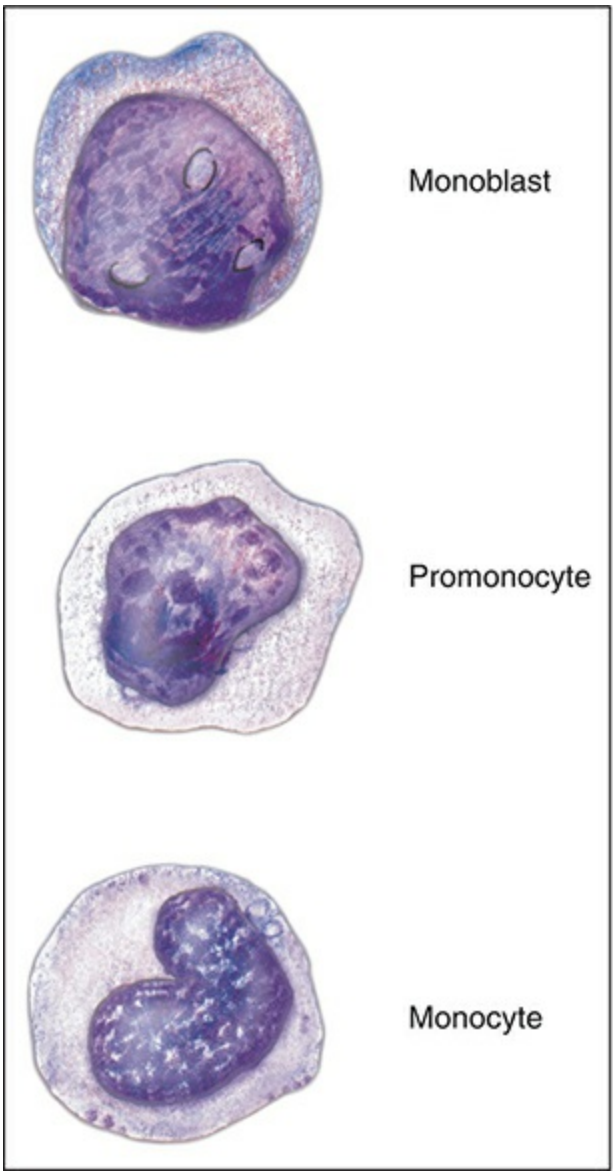


Figure IA2-33

Monoblast

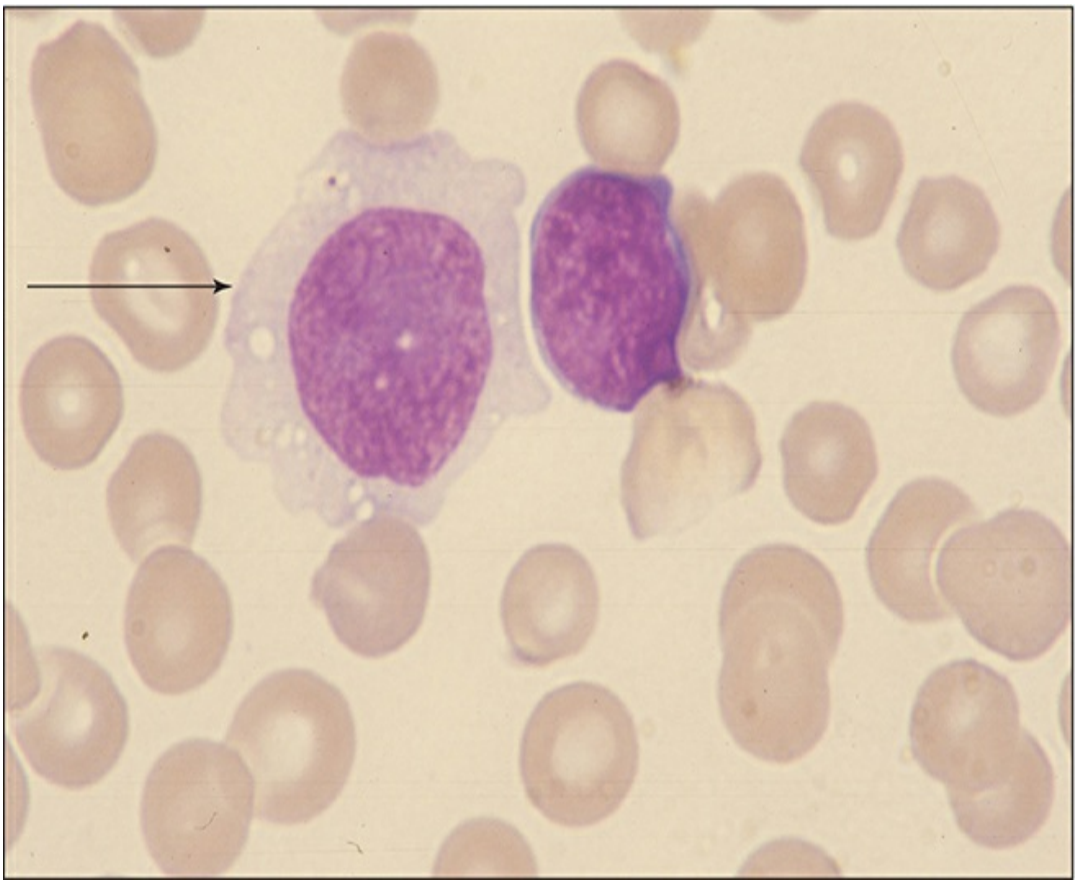


Figure IA2-34

Size: 14–20 µ

Nucleus

Shape: Round or oval

N/C Ratio: 3:1–1:1

Color: Light bluish-purple

Chromatin: Fine and distinct

Nucleoli: 1–5

Cytoplasm

Color: Blue-gray

Contents: No granules

Clinical Conditions

- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Acute monoblastic leukemia (M5a) (FAB) (WHO)

- Acute monocytic leukemia (M5b) (FAB) (WHO)
- AML with inv(16) or t(16;16) (WHO)

Promonocyte

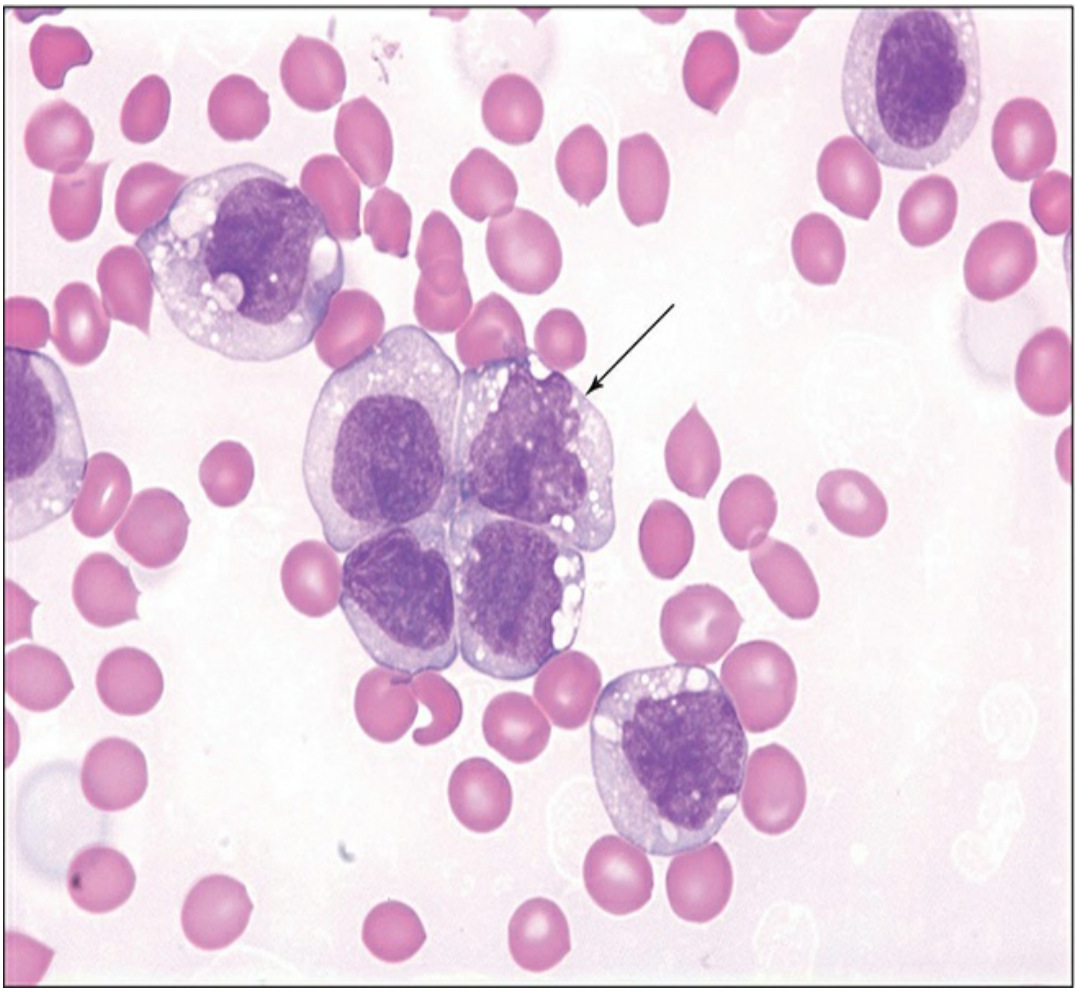


Figure **IA2-35**

Size: 14–20 µ

Nucleus

Shape: Oval or indented

N/C Ratio: 2:1–1:1

Color: Light bluish-purple

Chromatin: Fine reticular pattern

Nucleoli: 1–5

Cytoplasm

Cytoplasm

Color: Blue-gray finely granular (ground glass) appearance

Contents: Many fine dust-like bluish granules; occasional vacuole

Clinical Conditions

- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Acute monoblastic leukemia (M5a) (FAB) (WHO)
- Acute monocytic leukemia (M5b) (FAB) (WHO)
- AML with inv(16) or t(16;16) (WHO)

Monocyte

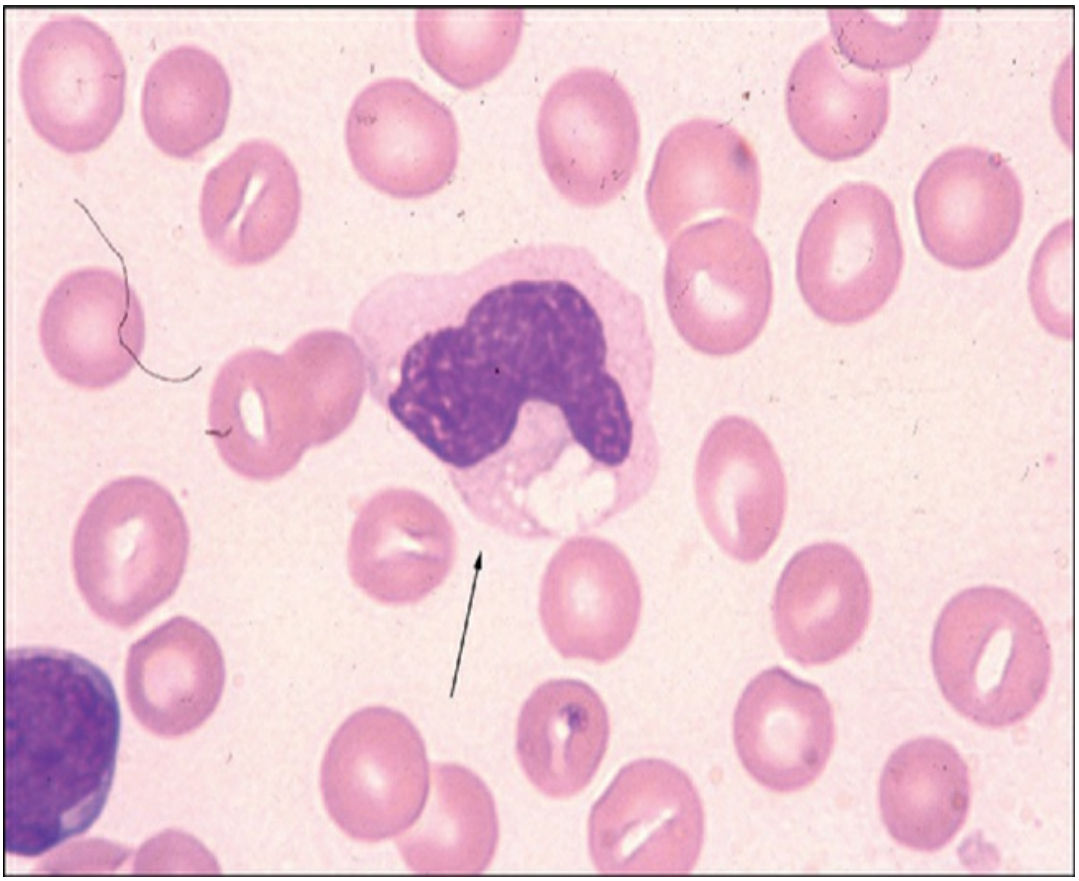


Figure IA2-36

Size: 14–21 µ

Nucleus

Shape: Horseshoe shaped or indented; nuclear folding may give the appearance of brain-like convolutions

N/C Ratio: 1:1

Color: Dark purple

Chromatin: Fine, delicate strands in linear arrangement with light spaces between strands

Nucleoli: None

Cytoplasm

Color: Blue-gray, finely granular (ground glass) appearance

Contents: Many fine dust-like bluish granules, occasional vacuole and blunt pseudopods

Clinical Conditions

- Myelodysplastic/myeloproliferative neoplasms—CMML, juvenile myelomonocytic leukemia (JMML)
- Myeloproliferative neoplasms—CML (few cases)
- Severe infections

NORMAL LYMPHOCYTE MATURATION SERIES

Lymphocyte Series

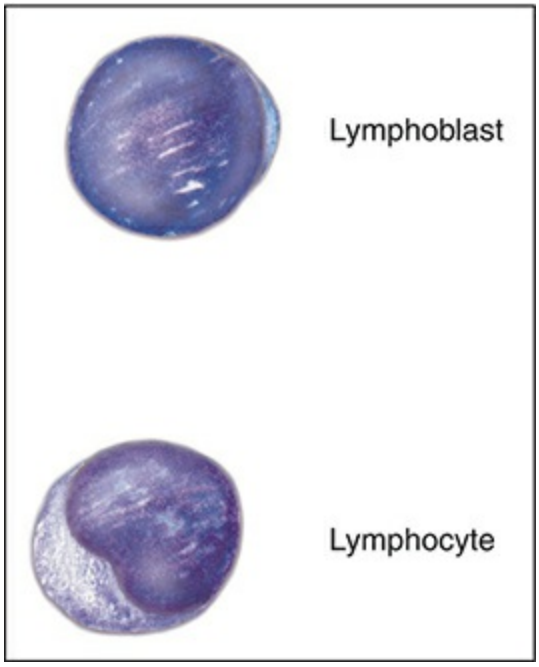


Figure IA2-37

Lymphoblast

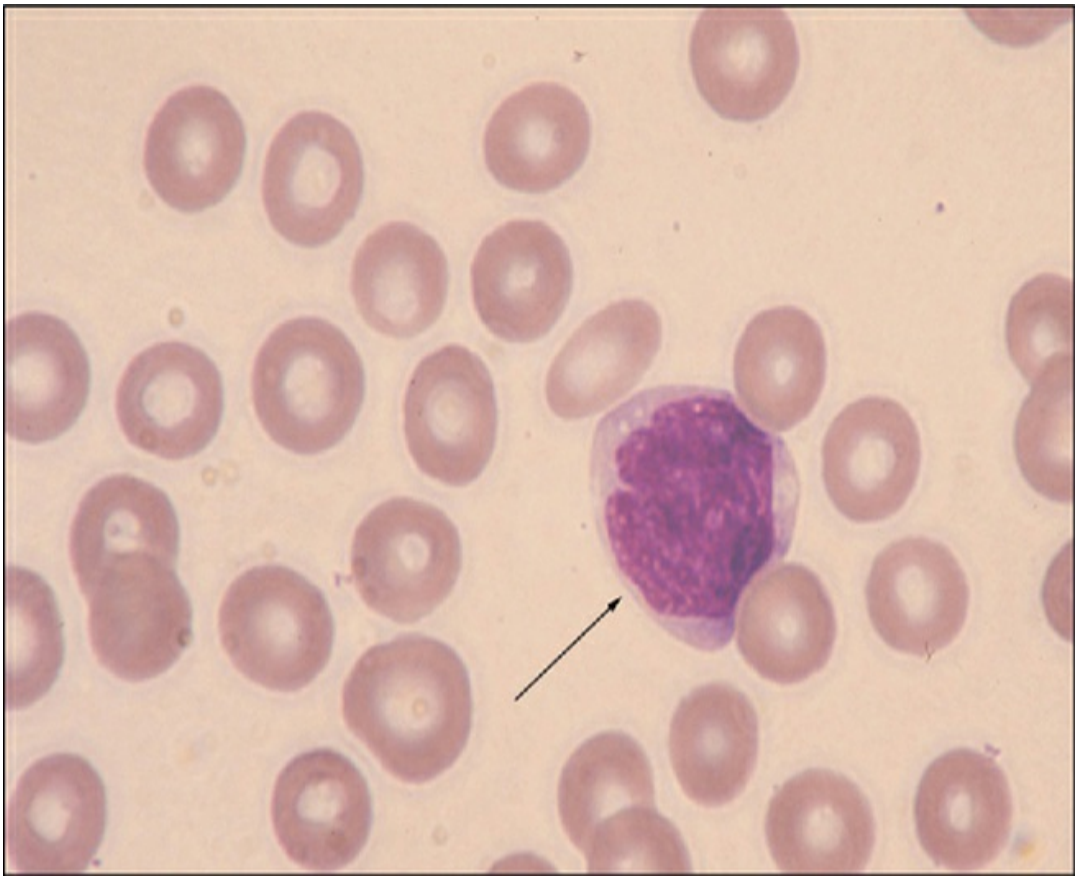


Figure **IA2-38**

Size: 10–22 µ

Nucleus

Shape: Round or oval, centrally or eccentrically placed

N/C Ratio: 7:1–4:1

Color: Reddish-purple

Chromatin: Fine, lacy pattern to moderately coarse

Nucleoli: 1–2 prominent

Cytoplasm

Color: Moderate to dark blue

Contents: Smooth, no granules, occasional vacuoles

Clinical Conditions

- Precursor lymphoblastic leukemia (L_1, L_2) (FAB) (WHO)
- Burkitt lymphoma (L_3) (FAB)

- Lymphoblastic lymphoma

Mature Lymphocyte

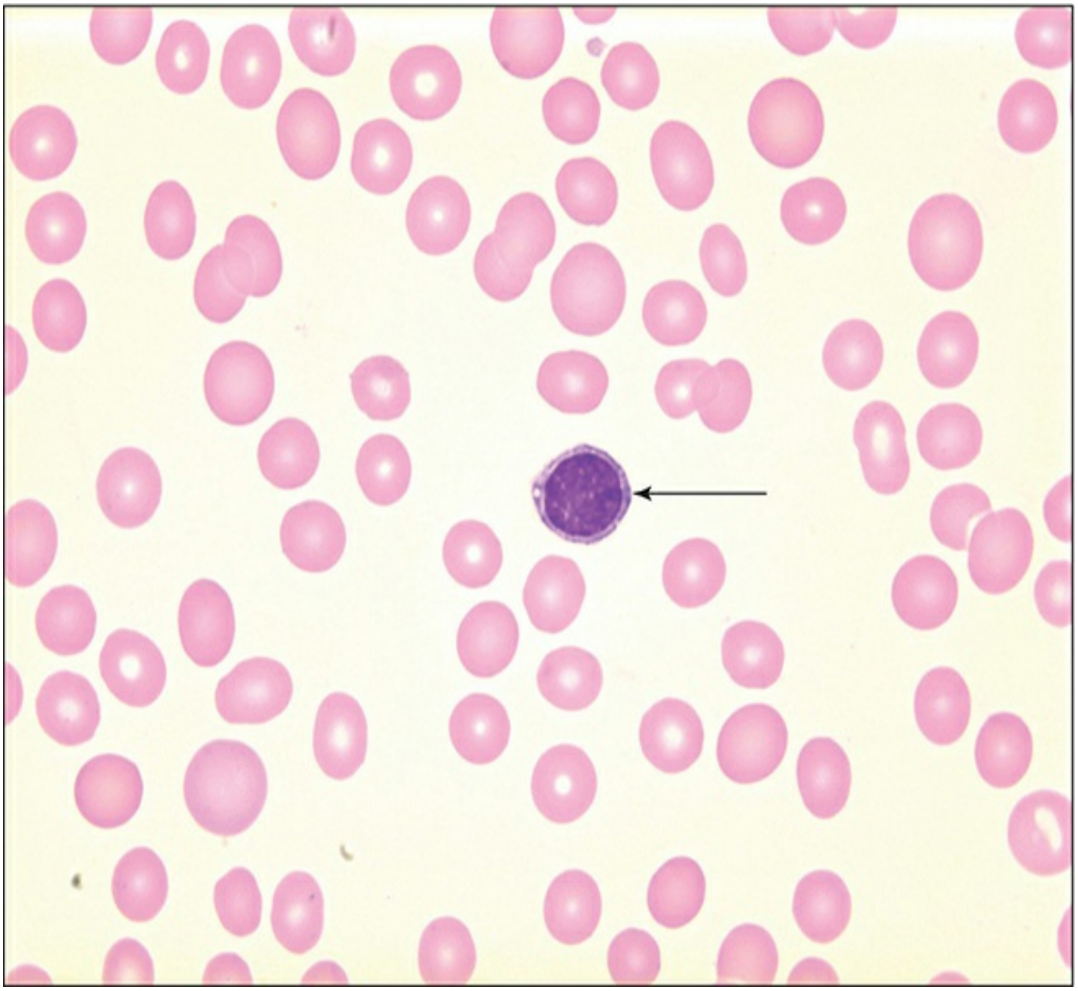


Figure IA2-39

Size: 7–15 µ

Nucleus

Shape: Round or slightly indented, eccentric

N/C Ratio: 3:1

Color: Deep purple-blue

Chromatin: Course and clumped

Nucleoli: None visible

Cytoplasm

Color: Sky blue to deep blue

Contents: Scant and usually nongranular; few azurophilic granules may be seen

REACTIVE LYMPHOCYTES

Reactive Lymphocytes (Atypical Lymphocytes)

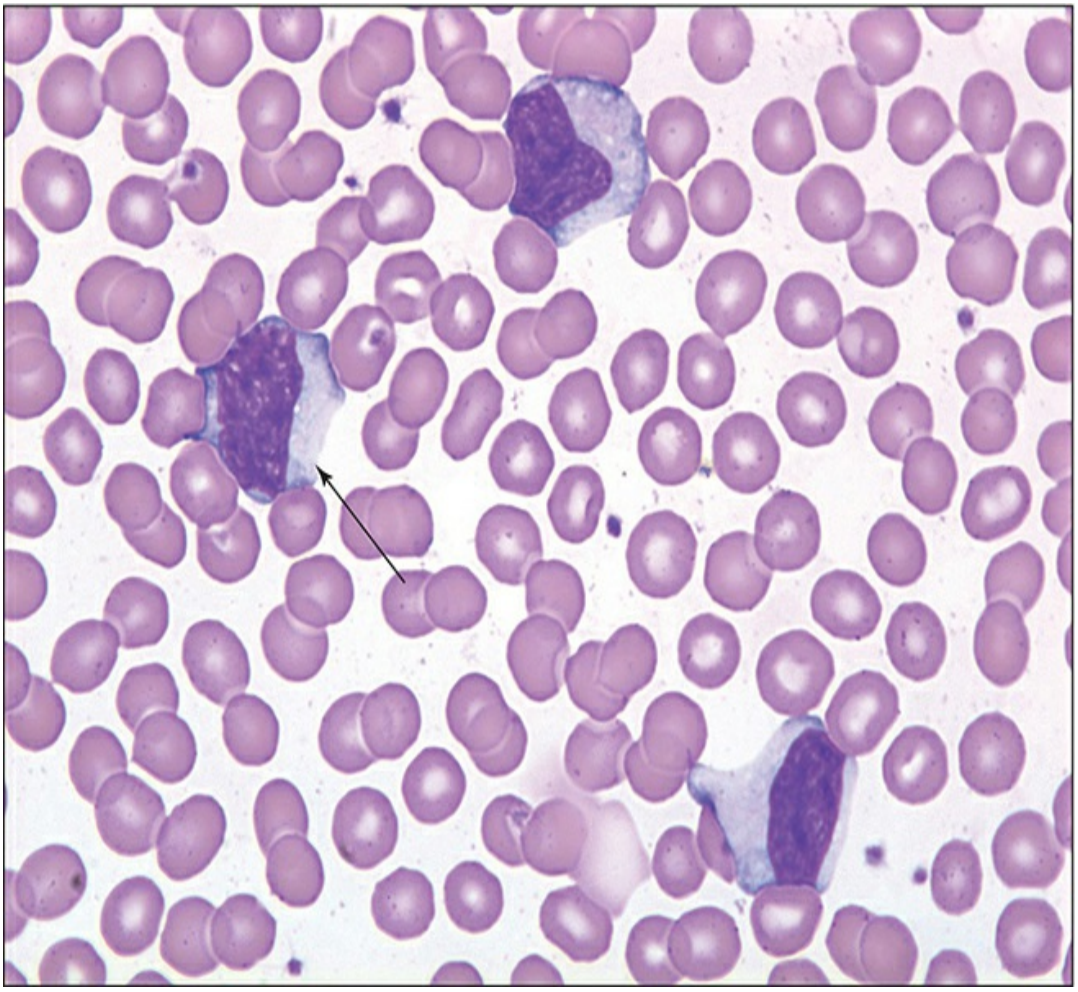


Figure **IA2-40**

Cell Type

Lymphocyte

Description

Cell size ranges from 10 to 25 µ

Nucleus can be oval, notched, indented, or elongated

One or more large nucleoli may be visible

Cytoplasm is often abundant and stains pale to deep blue

and darker at periphery; may be partially indented by adjacent red cells; few lavender granules and/or vacuoles

Clinical Conditions

- Infectious mononucleosis
- Other viral diseases including cytomegalovirus, toxoplasmosis, hepatitis, and catscratch fever

Cleaved Cell (Butt Cell)

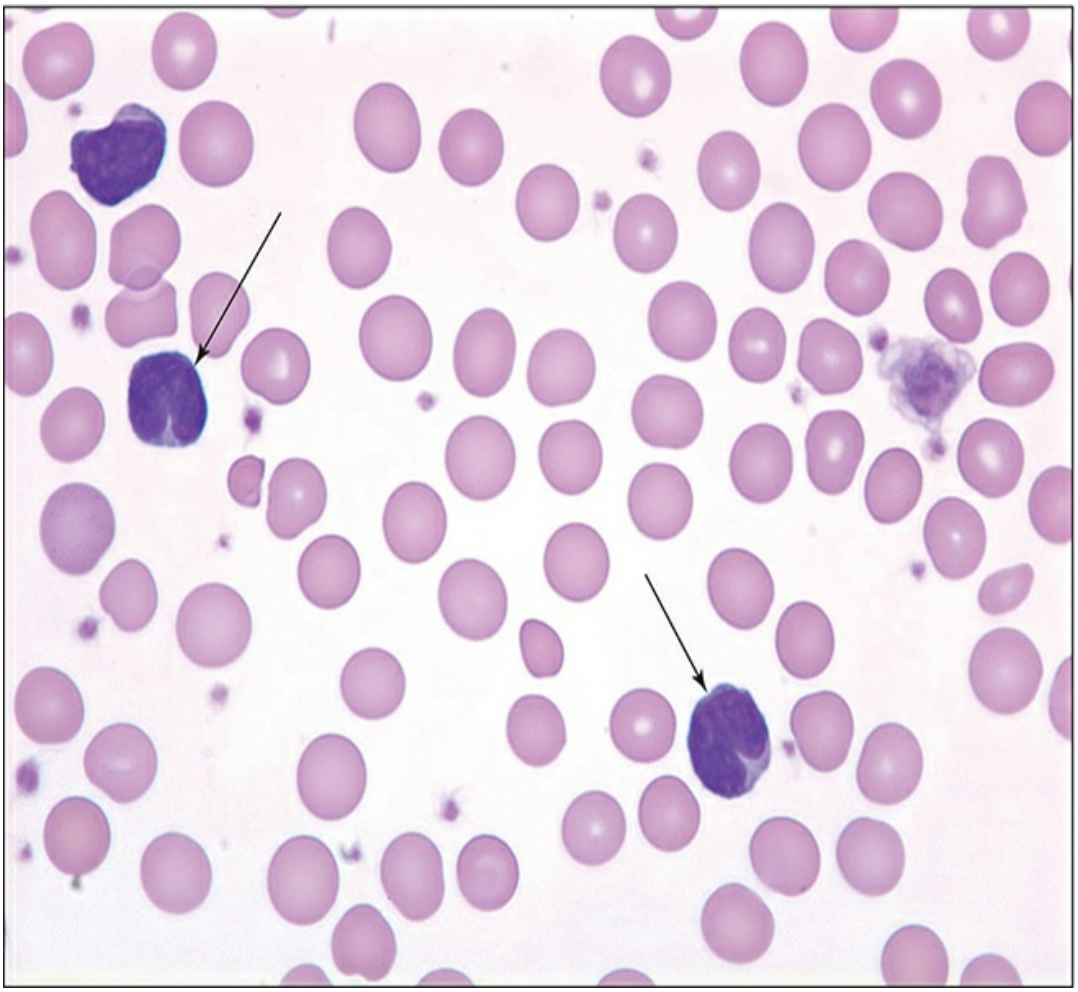


Figure IA2-41

Cell Type

Lymphocyte

Description

Description

Small, mature lymphocyte with cleaved nucleus

Clinical Conditions

- Pertussis (whooping cough)
- Lymphoma
- Chronic lymphocytic leukemia

Immunoblast

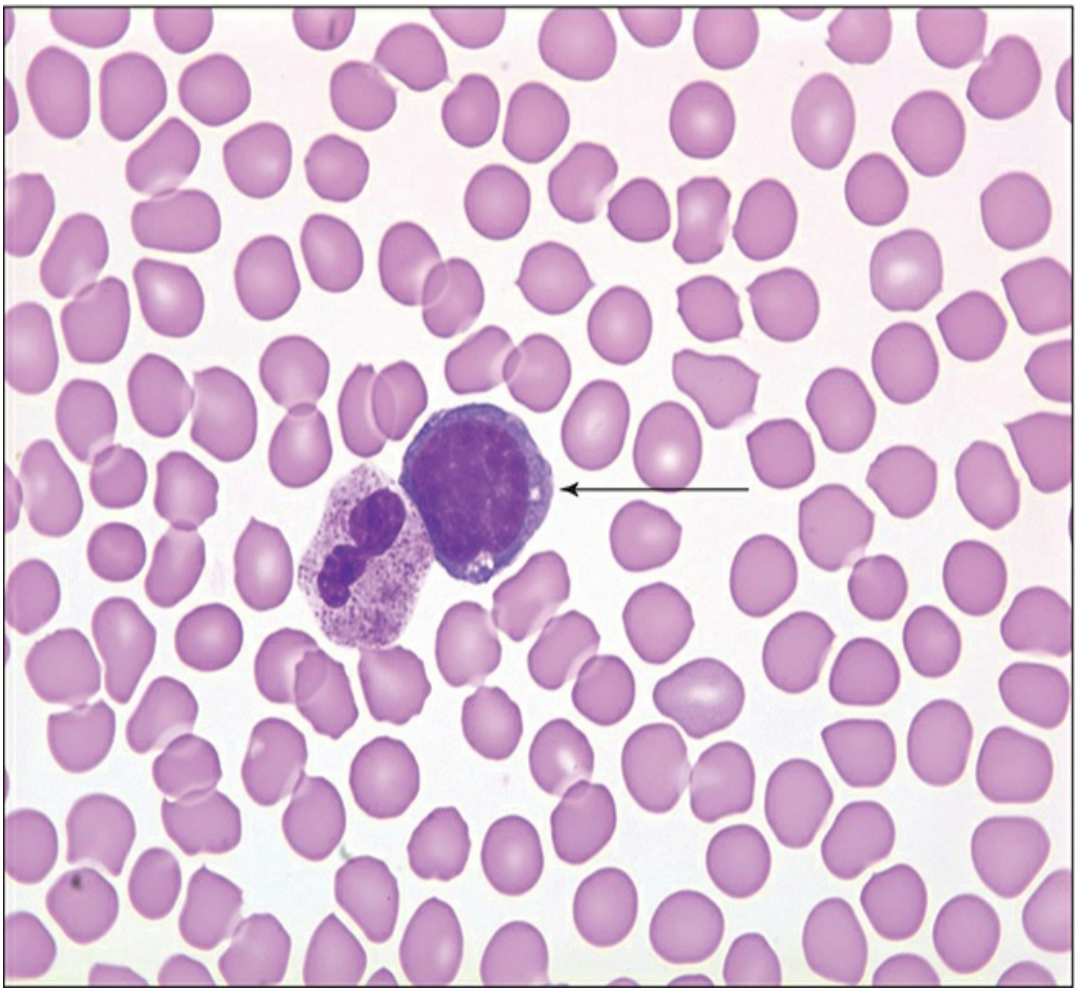


Figure IA2-42

Cell Type

Lymphocyte

Description

Large cell (12–25 μ) with bluish-purple nucleus and fine chromatin pattern with several prominent nucleoli

Cytoplasm is deep blue

Clinical Conditions

- Viral and nonviral infections
- Immune disorders

Large Granular Lymphocyte

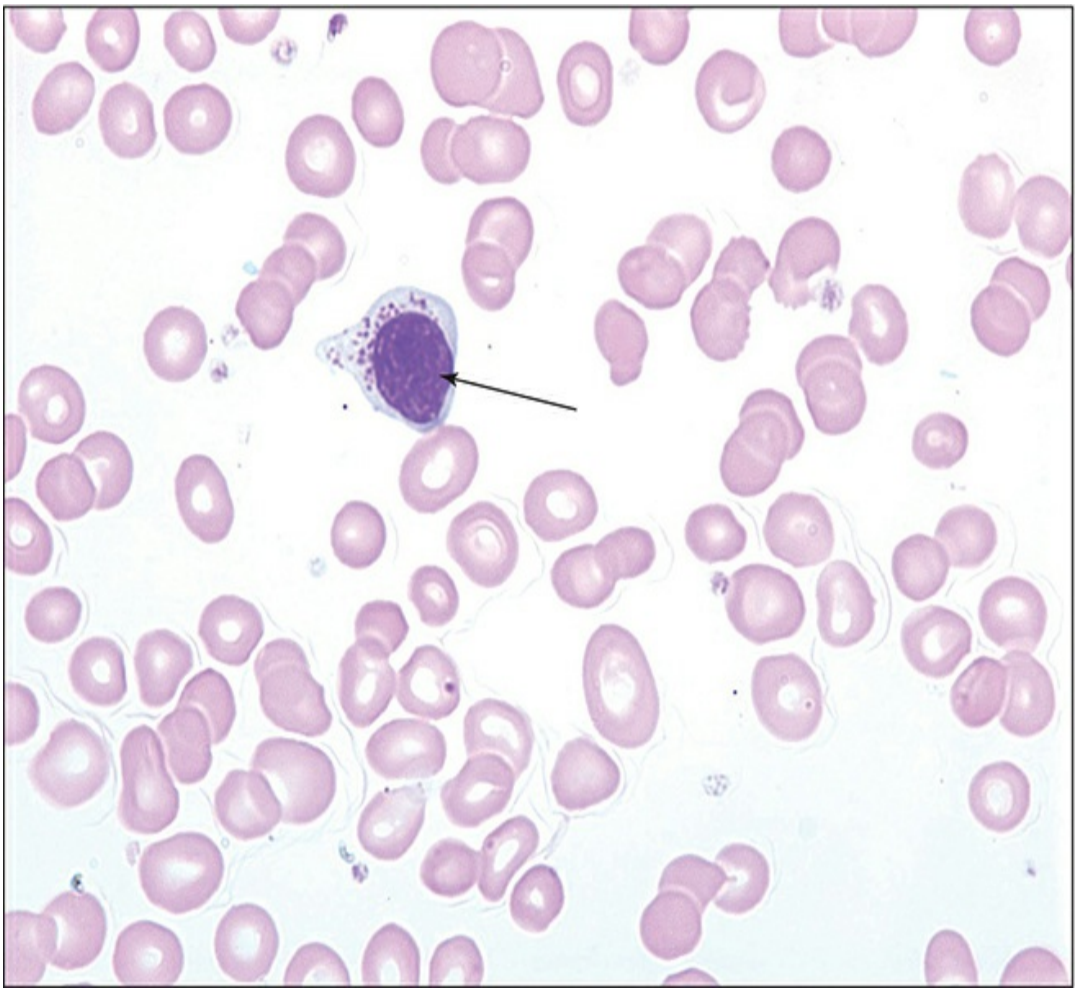


Figure IA2-43

Cell Type

Lymphocyte

Description

Large cells (14–16 μ) with moderate to abundant pale-blue cytoplasm

Prominent azurophilic granules

Clinical Conditions

- Large granular lymphocytic leukemia
- NK-cell leukemia

Large Lymphocyte

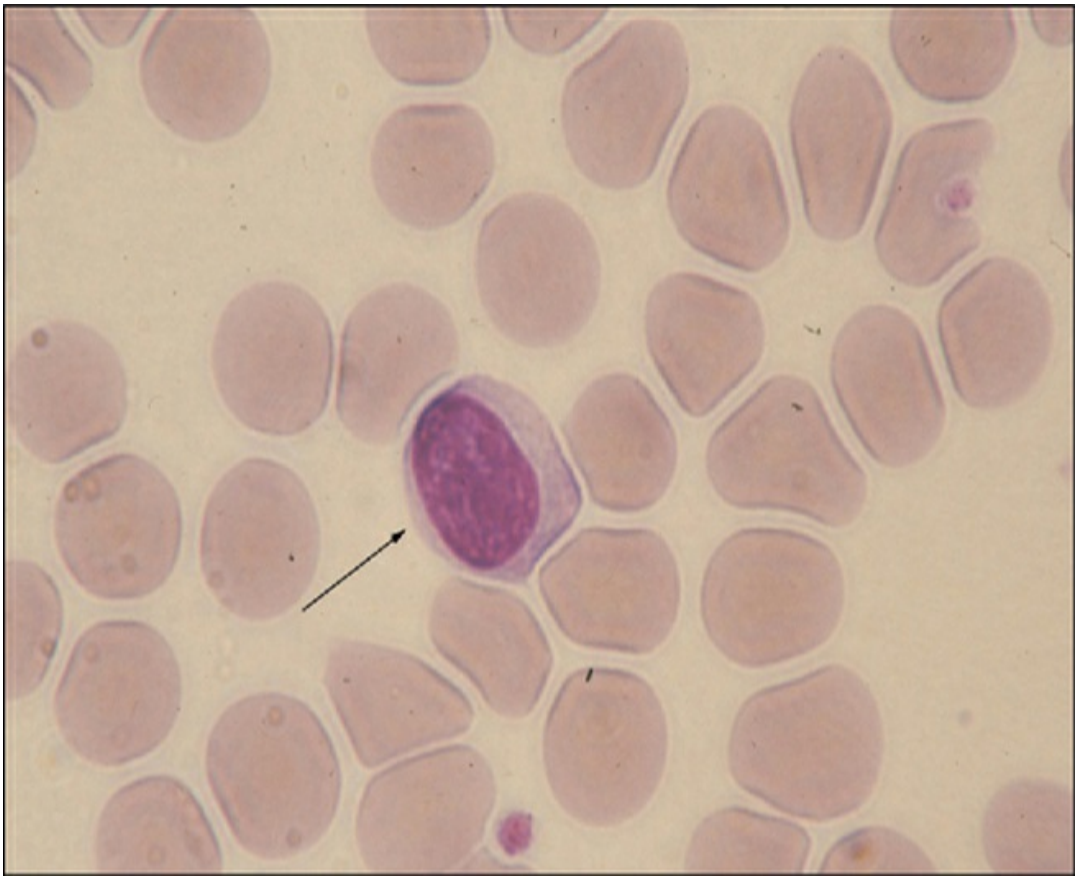


Figure IA2-44

Cell Type

Lymphocyte

Description

Nucleus is round or oval, may be slightly indented with coarse chromatin pattern and no visible nucleoli;

moderate, pale-blue cytoplasm with rare purplish-red granules

Clinical Condition

- 10–12% of lymphocytes is normal

Plasmacytoid Lymphocyte

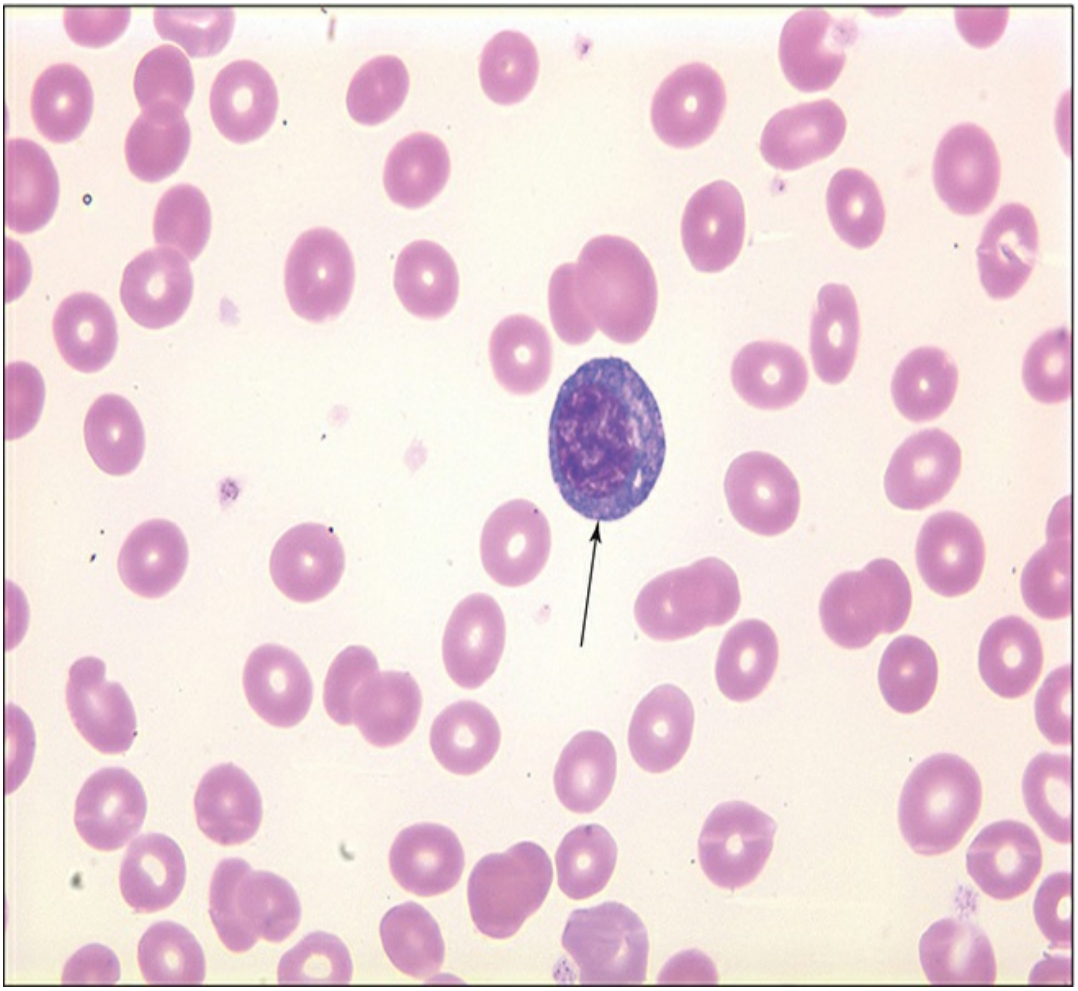


Figure IA2-45

Cell Type

Lymphocyte

Description

Cell is intermediated between small lymphocyte and plasma cell (9–20 μ); nucleus is centrally to slightly

eccentrically located, indented or oval, with a developing perinuclear halo; chromatin strands are heavy or in dense blocks; cytoplasm is intensely basophilic and may contain few vacuoles

Clinical Conditions

- Viral and nonviral infections
- Immune disorders
- Plasma cell neoplasms
- Waldenström macroglobulinemia

LYMPHOMA CELLS

Lymphoblastic Lymphoma Cell

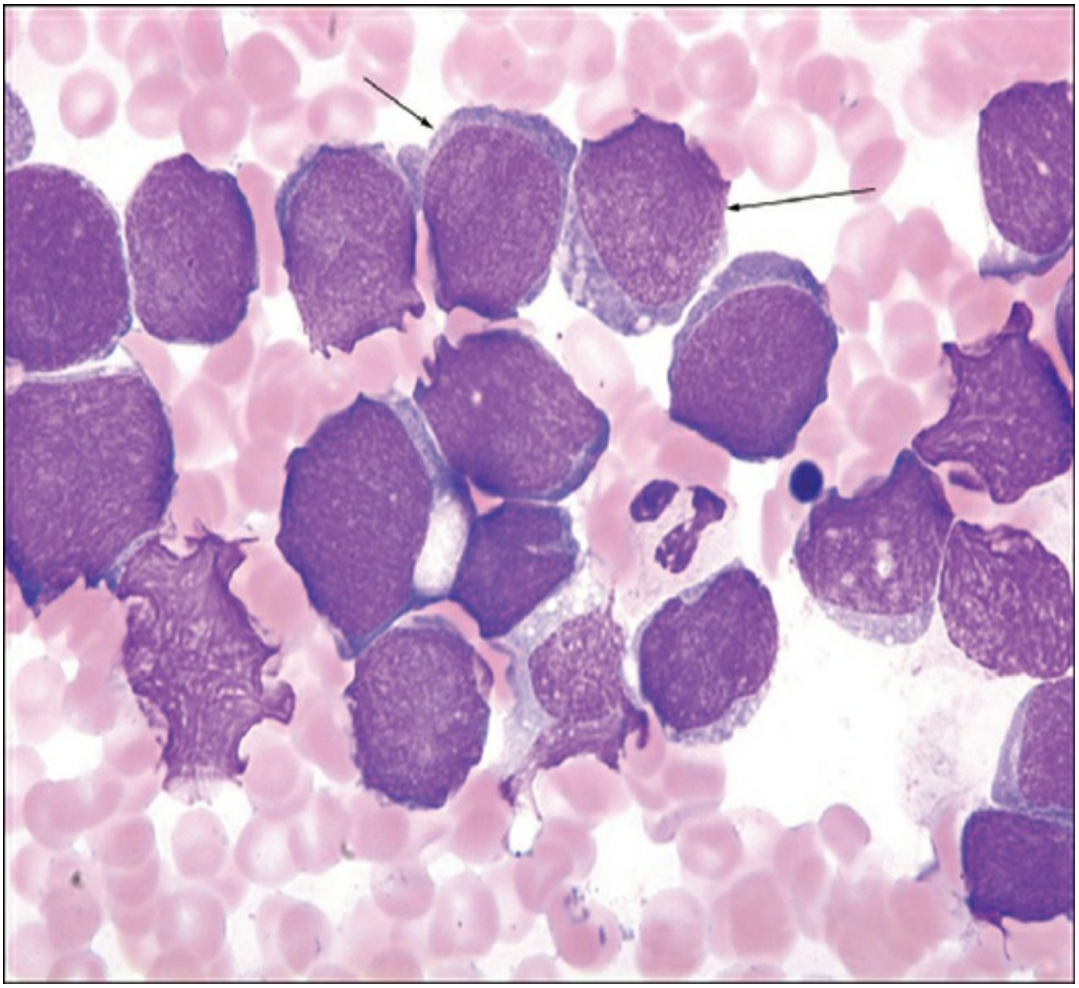


Figure IA2-46

Cell Type

Lymphoblast

Description

Cell size is variable

Nucleus is indented or convoluted with fine chromatin pattern and small, inconspicuous nucleoli

Cytoplasm is scant

Clinical Condition

- Lymphoblastic lymphoma

Reed-Sternberg Cell

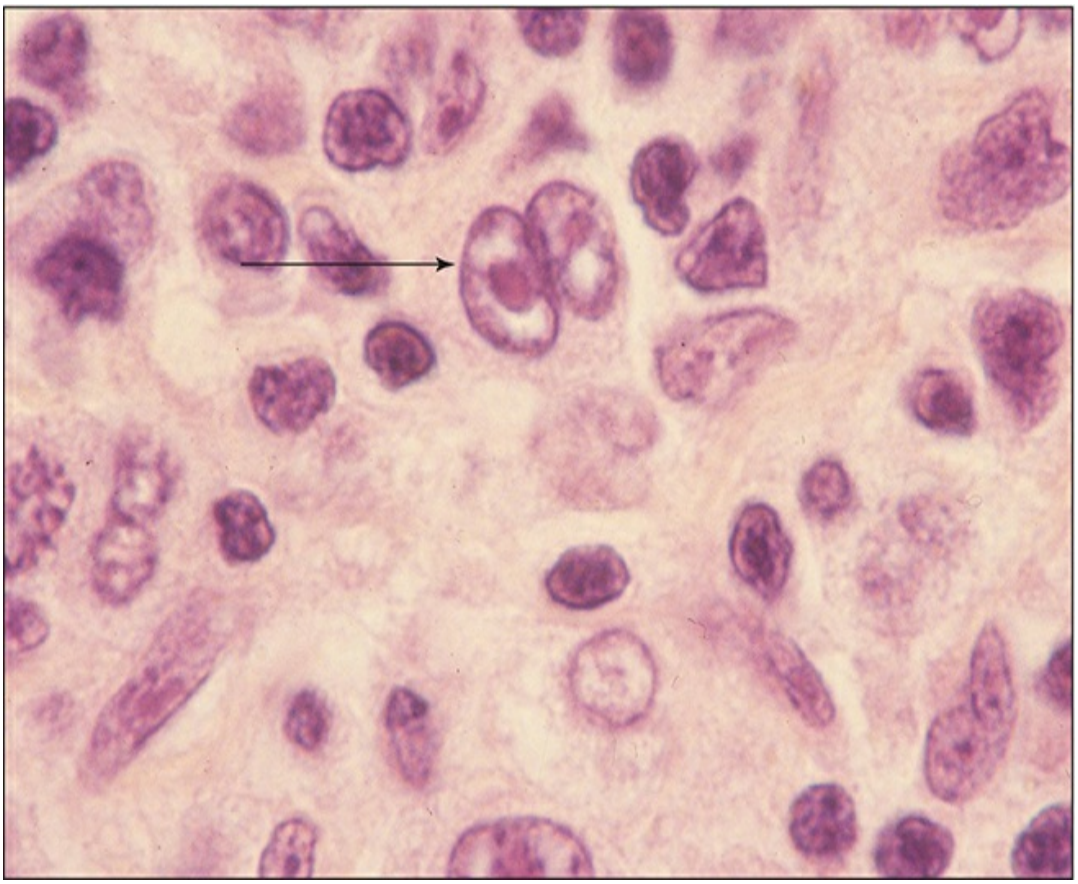


Figure IA2-47

Cell Type

Lymphocytic lineage

Description

A large cell (50–100 μ) with an abundance of cytoplasm

Nucleus is often bilobed or binucleated with prominent large nucleoli resembling owl eyes; the two halves of a binucleated cell often appear as mirror images

Not found in peripheral blood; found in lymph nodes

Clinical Condition

- Hodgkin lymphoma

Sézary Cell

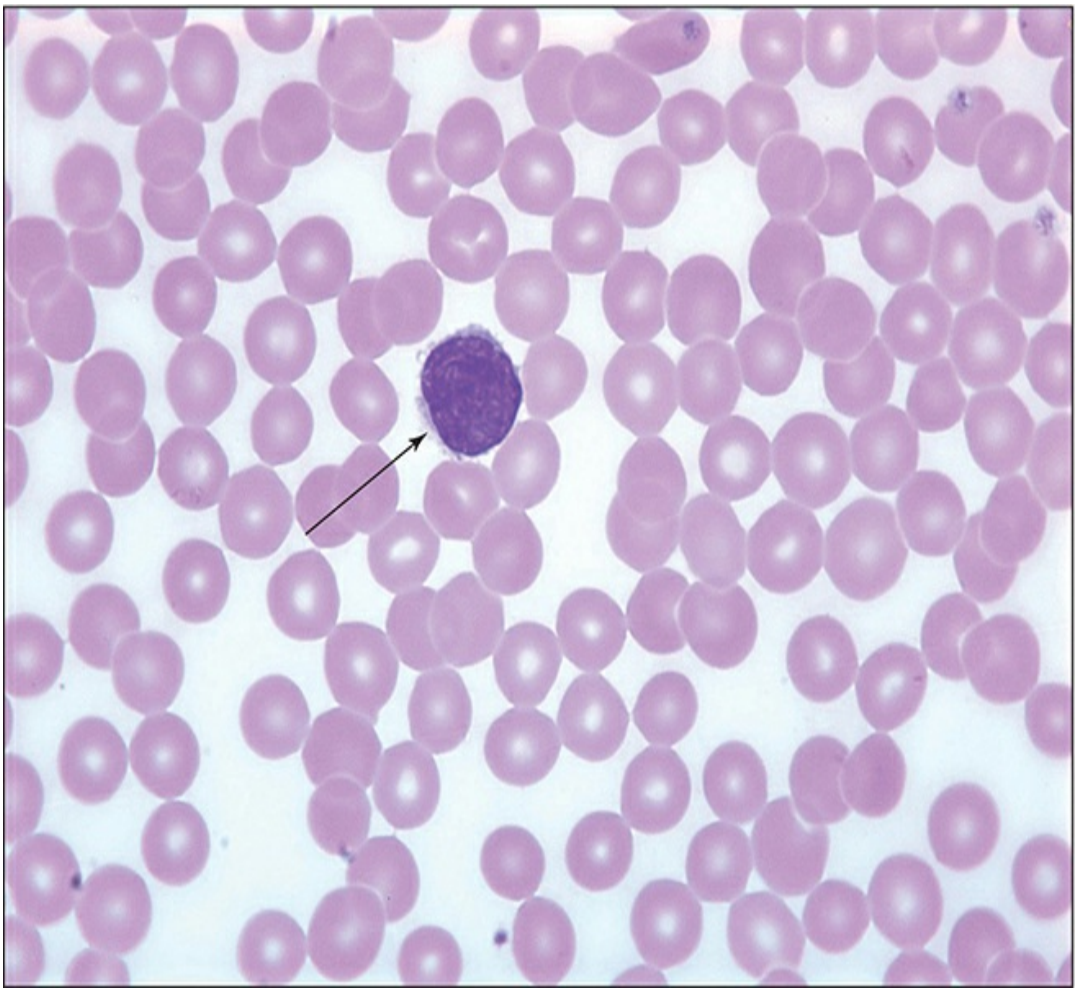


Figure IA2-48

Cell Type

Lymphocyte

Description

Small and large cell ranging from 8 to 30 µ

Nucleus has brain-like convolutions and is dark purple, with moderately coarse chromatin; nucleoli are not visible

Cytoplasm is scanty and pale to deep blue with occasional vacuoles

Clinical Condition

- Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)

Small Cleaved Lymphoma Cell

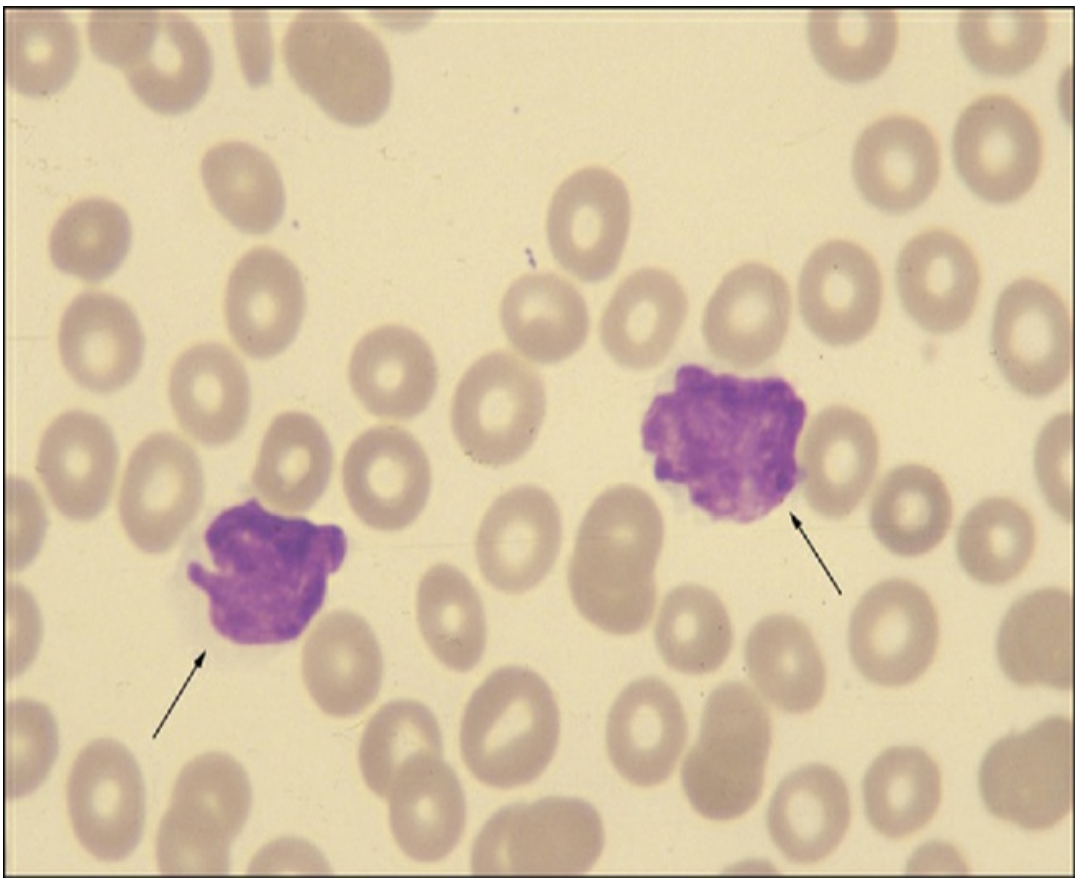


Figure IA2-49

Cell Type

Lymphoma cell

Description

Cell size is 6–12 μ ; nucleus is twisted, angulated, and indented with clumped chromatin and no nucleoli

Cytoplasm is scant to imperceptible

Clinical Condition

- Small cleaved cell lymphoma

Chronic Lymphocytic Leukemia/Small B Lymphoma Cell

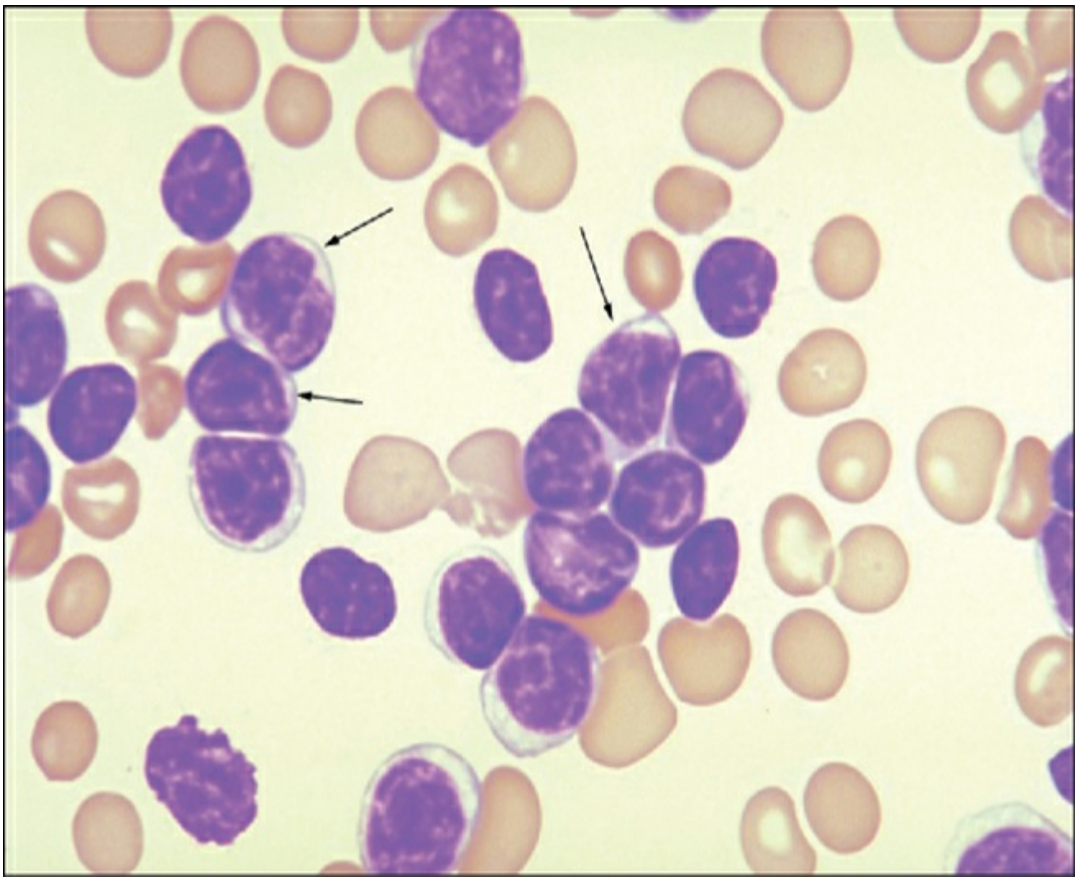


Figure IA2-50

Cell Type

Lymphocyte

Description

Cell is 10–25 µ ; round nucleus has clumped chromatin and may show a compartmentalization phenomenon

Nucleoli are inconspicuous or not visible

Cytoplasm is sparse to abundant and clear and lightly basophilic

Clinical Condition

- CLL/SLL

NORMAL PLASMACYTE MATURATION SERIES

Plasma Cell Series

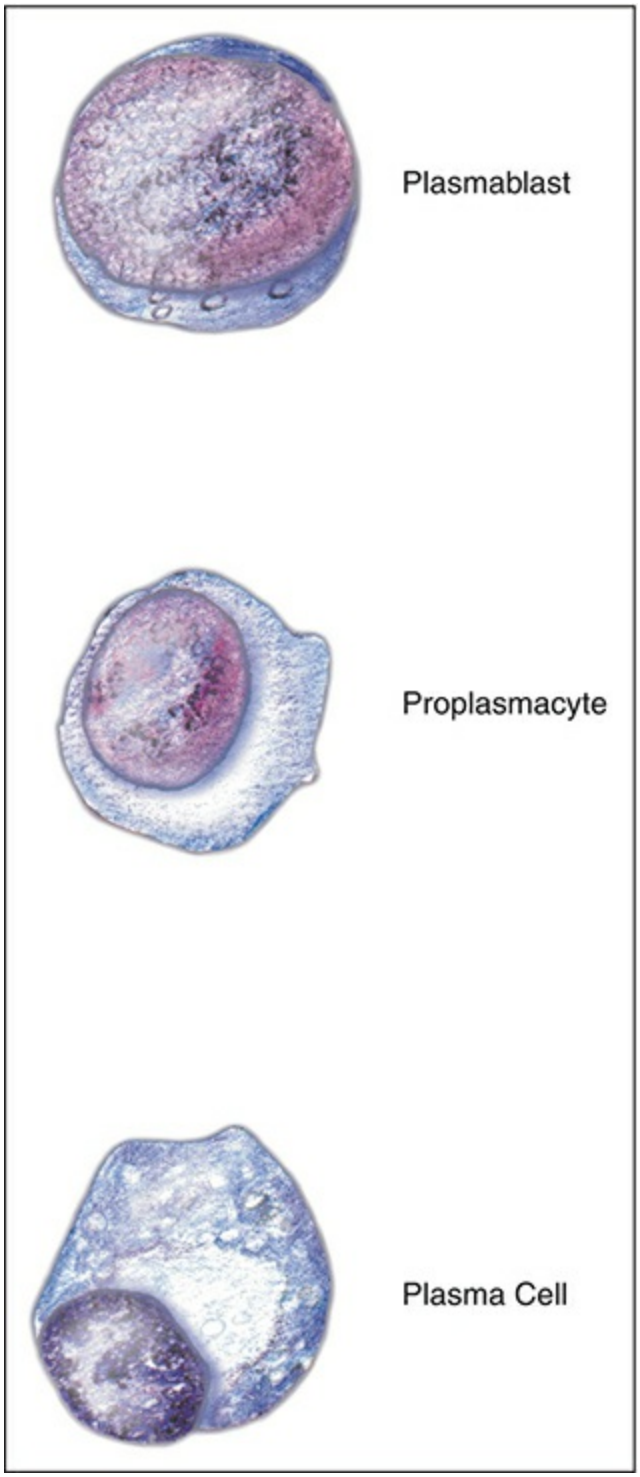


Figure IA2-51

Plasmablast

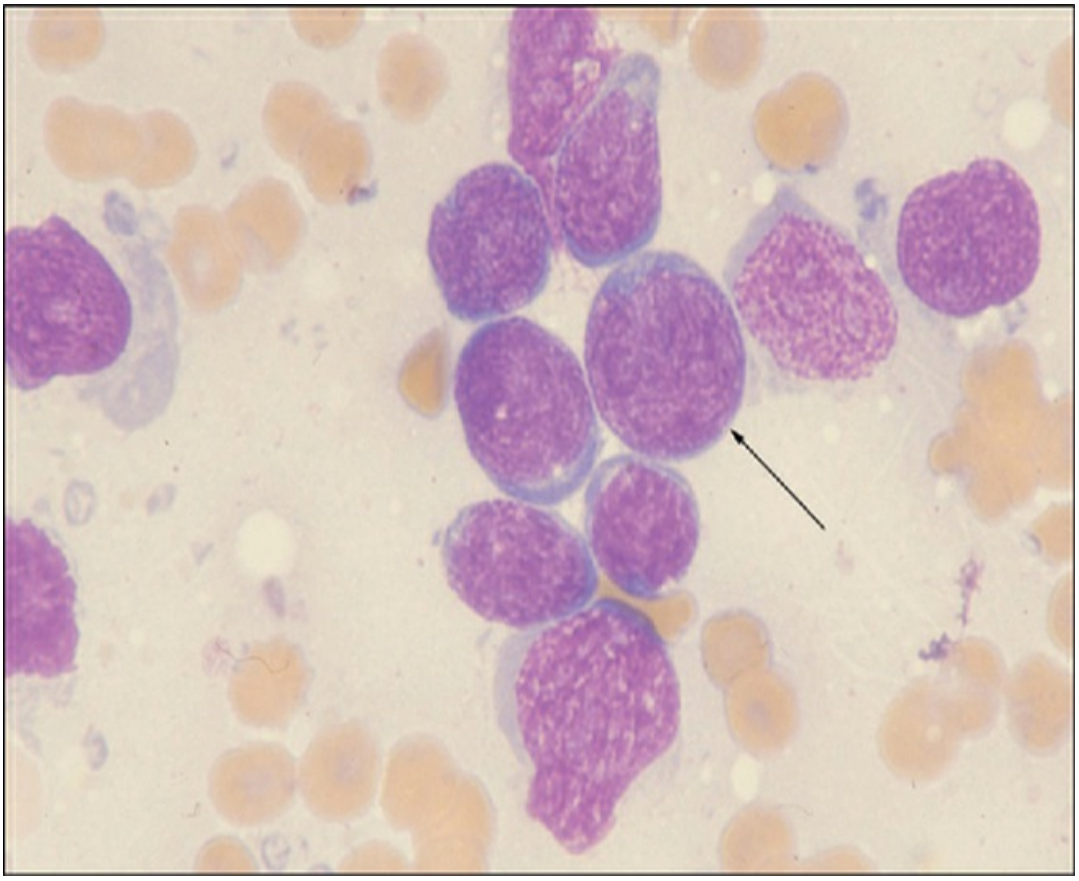


Figure IA2-52

Size: 12–15 µ

Nucleus

Shape: Round

N/C Ratio: 5:1–4:1

Color: Purplish red

Chromatin: Fine and linear strands

Nucleoli: One or more

Cytoplasm

Color: Blue

Contents: Nongranular

Clinical Condition

- Plasma cell neoplasms

Proplasmacyte

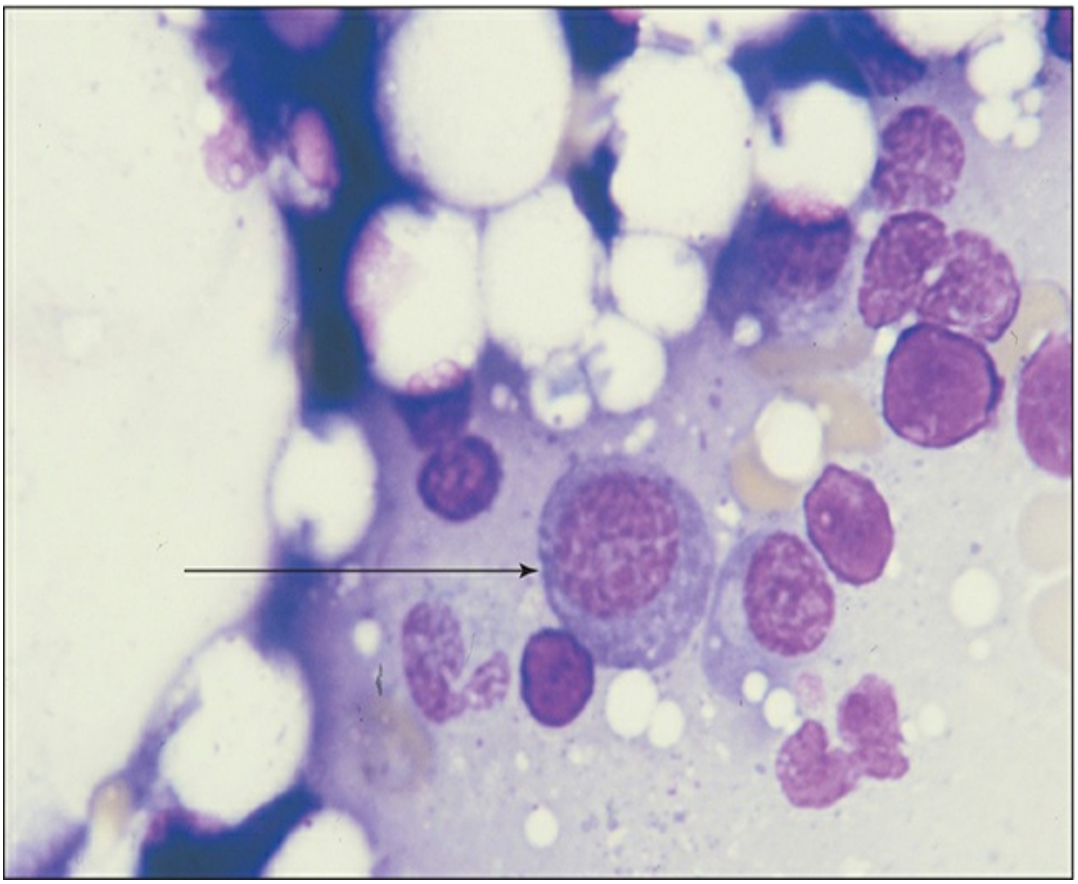


Figure IA2-53

Size: 12–15 μ

Nucleus

Shape: Round, eccentrically placed

N/C Ratio: 5:1–4:1

Color: Purplish-red

Chromatin: Moderately clumped

Nucleoli: 0–2

Cytoplasm

Color: Medium to dark blue

Contents: Nongranular

Clinical Conditions

- Plasma cell neoplasms
- Waldenström macroglobulinemia
- Response to infection

Plasma Cell

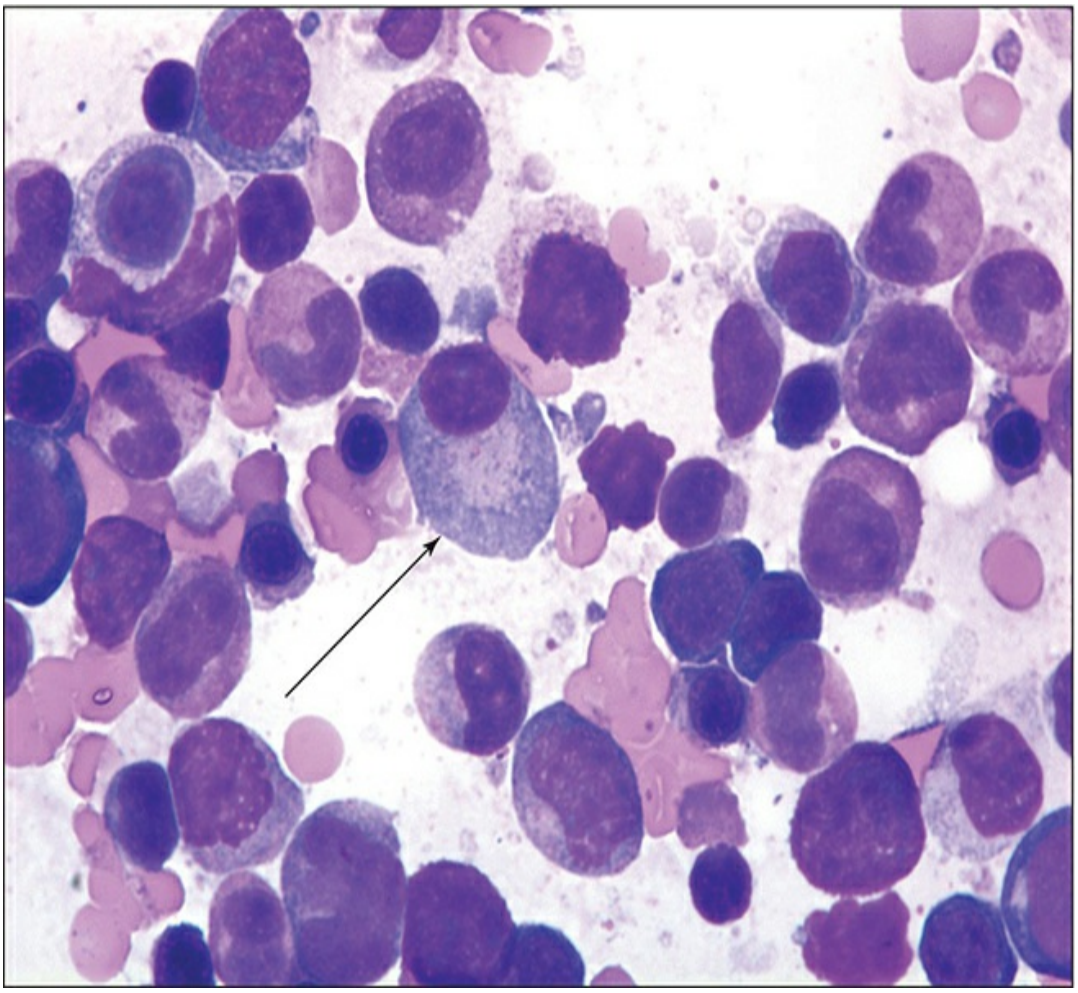


Figure IA2-54

Cell Type

Plasma cell

Description

Size ranges from 9 to 20 µ

Dark purple nucleus is ovoid and eccentrically placed with

a wheel-spoke pattern

No nucleoli

Cytoplasm is abundant and deep blue with a clear area next to the nucleus

Clinical Conditions

- Plasma cell neoplasms
- Response to infection

ABNORMAL PLASMA CELLS AND INCLUSIONS

Bilobed Plasma Cell

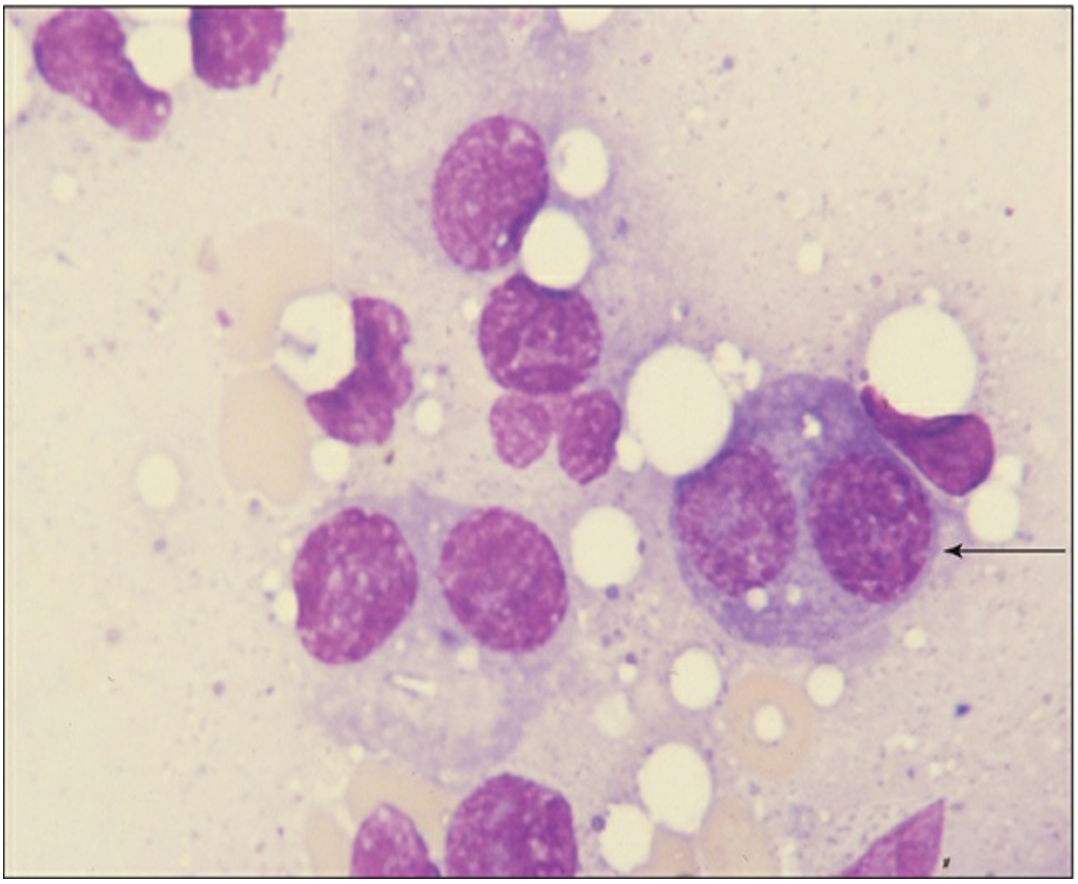


Figure IA2-55

Cell Type

Plasma cell

Description

Dark purple nucleus is bilobed rather than ovoid

Cytoplasm is pale to deeply basophilic

Clinical Conditions

- Plasma cell neoplasms
- Response to infection

Dutcher Body

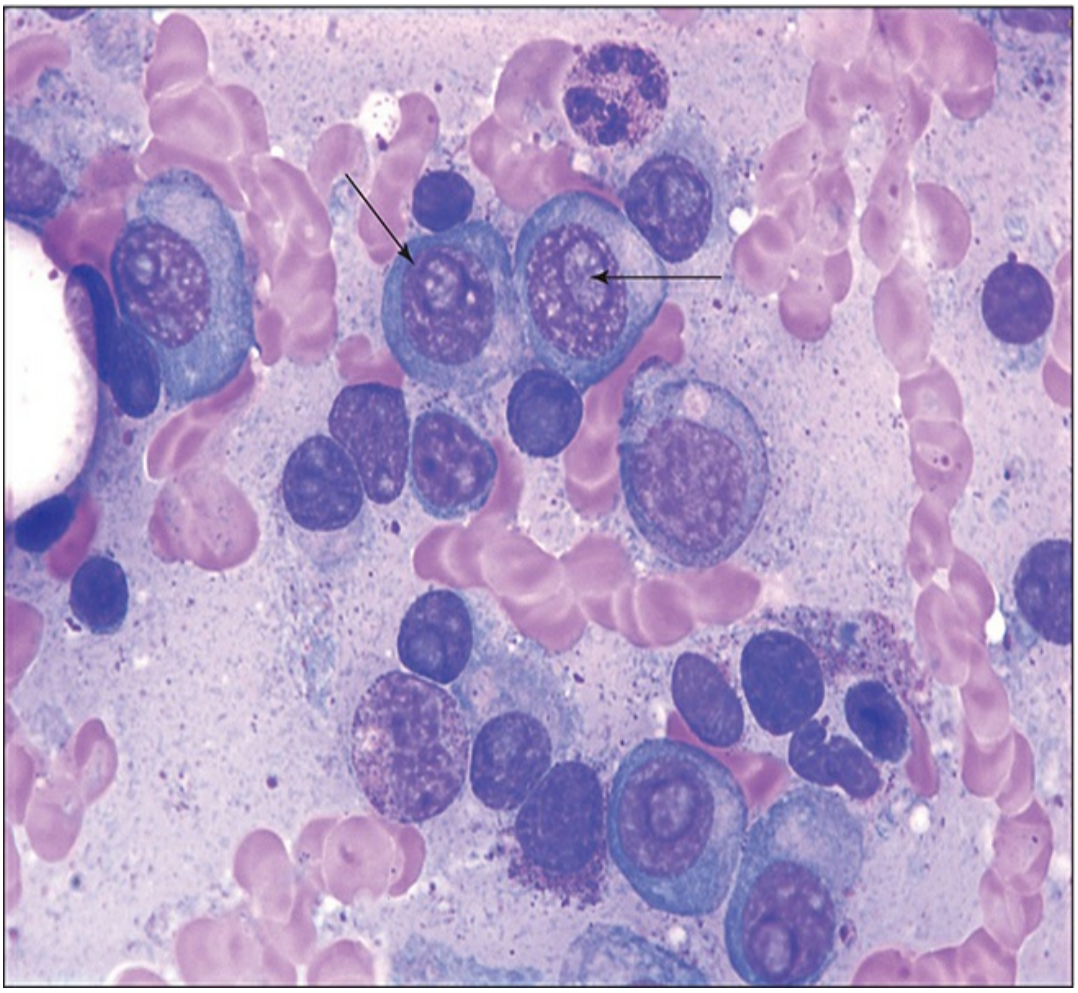


Figure IA2-56

Cell Type

Plasma cell

Description

Intranuclear protein inclusions resulting from membrane-bound cytoplasm in the nucleus

Clinical Conditions

- Plasma cell neoplasms
- Response to infection

Flaming Plasma Cell

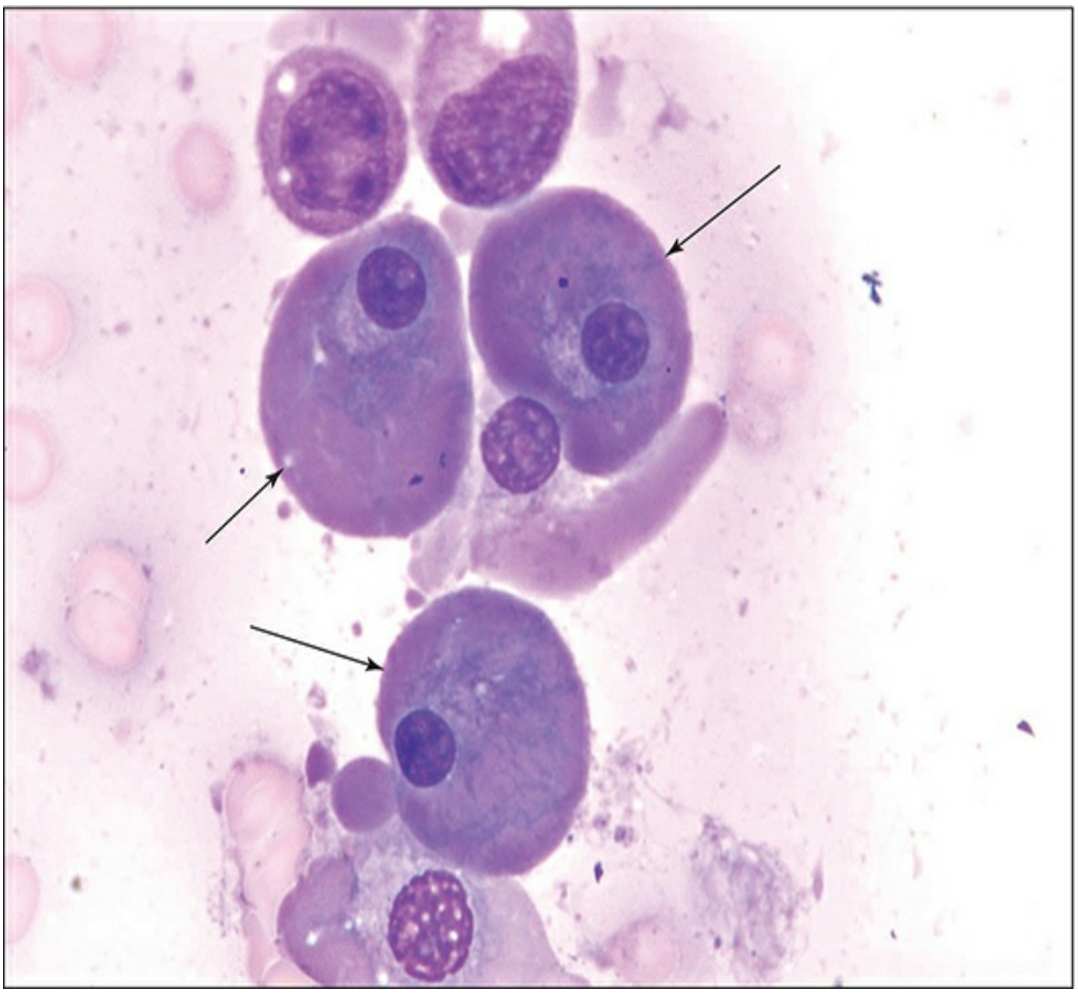


Figure IA2-57

Cell Type

Plasma cell

Description

Cytoplasmic immunoglobulin (often IgA) accumulating in the peripheral cytoplasm; stains reddish purple

Clinical Conditions

- Plasma cell neoplasms
- Response to infection

Mott Cell (Grape Cell)

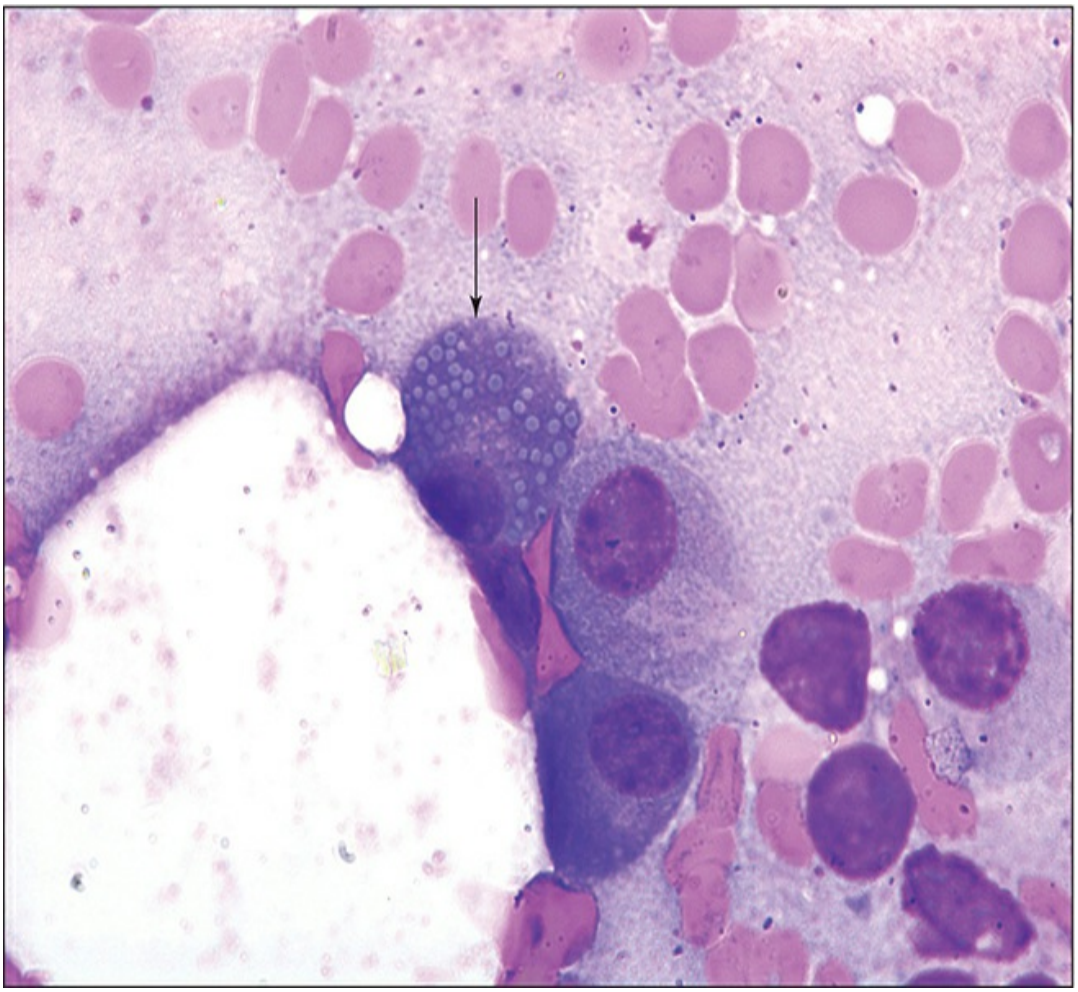


Figure **IA2-58**

Cell Type

Plasma cell

Description

Cytoplasm filled with Russell bodies resembling clusters of grapes

Clinical Conditions

- Plasma cell neoplasms
- Response to infection

Russell Bodies

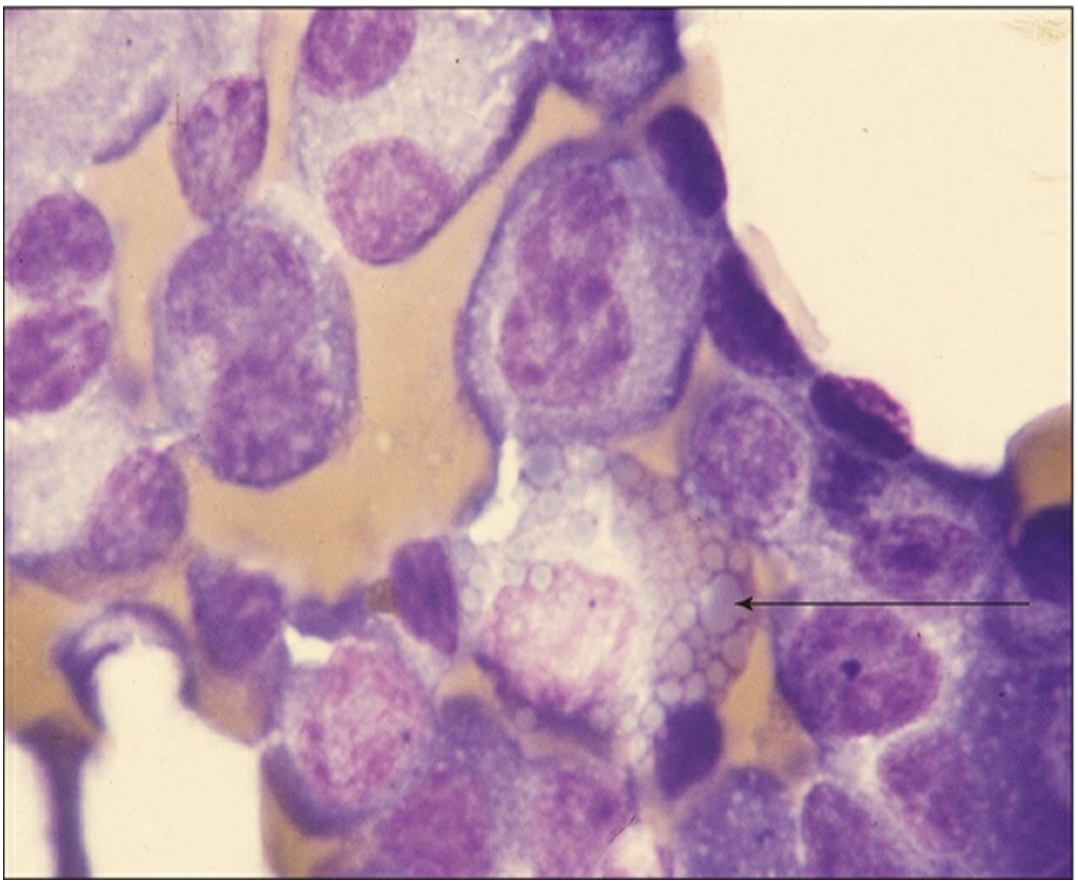


Figure **IA2-59**

Cell Type

Plasma cell

Description

Individual globules of immunoglobulin in cytoplasm, which represent rough endoplasmic reticulum, smooth endoplasmic reticulum, and Golgi filled with immunoglobulin due to secretory obstruction; globules stain pink or blue depending on pH; if immunoglobulin disappears, colorless vacuoles result

Clinical Conditions

- Plasma cell neoplasms
- Response to infection

CHAPTER 3

Megakaryocytes

NORMAL MEGAKARYOCYTIC MATURATION SERIES

Megakaryocytic Series

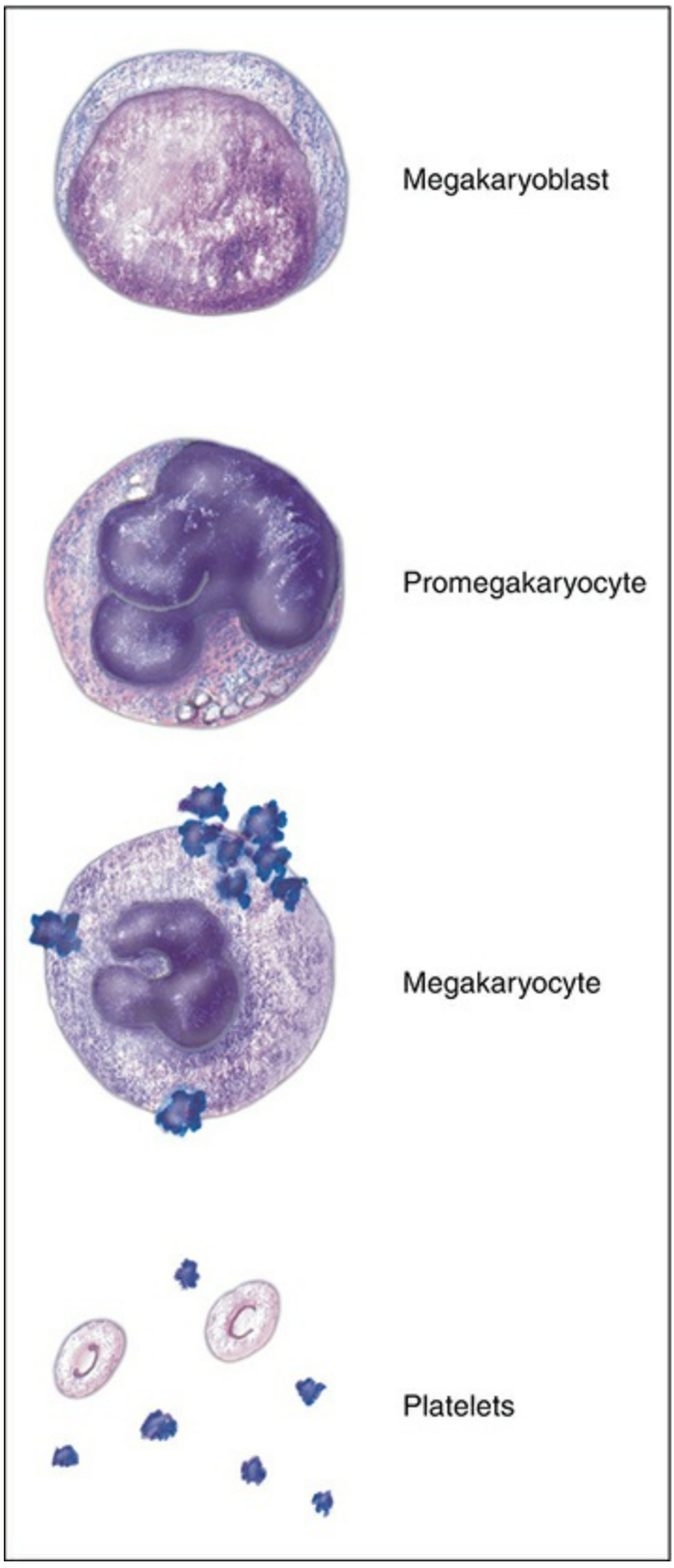


Figure IA3-1

Megakaryoblast (Stage I)

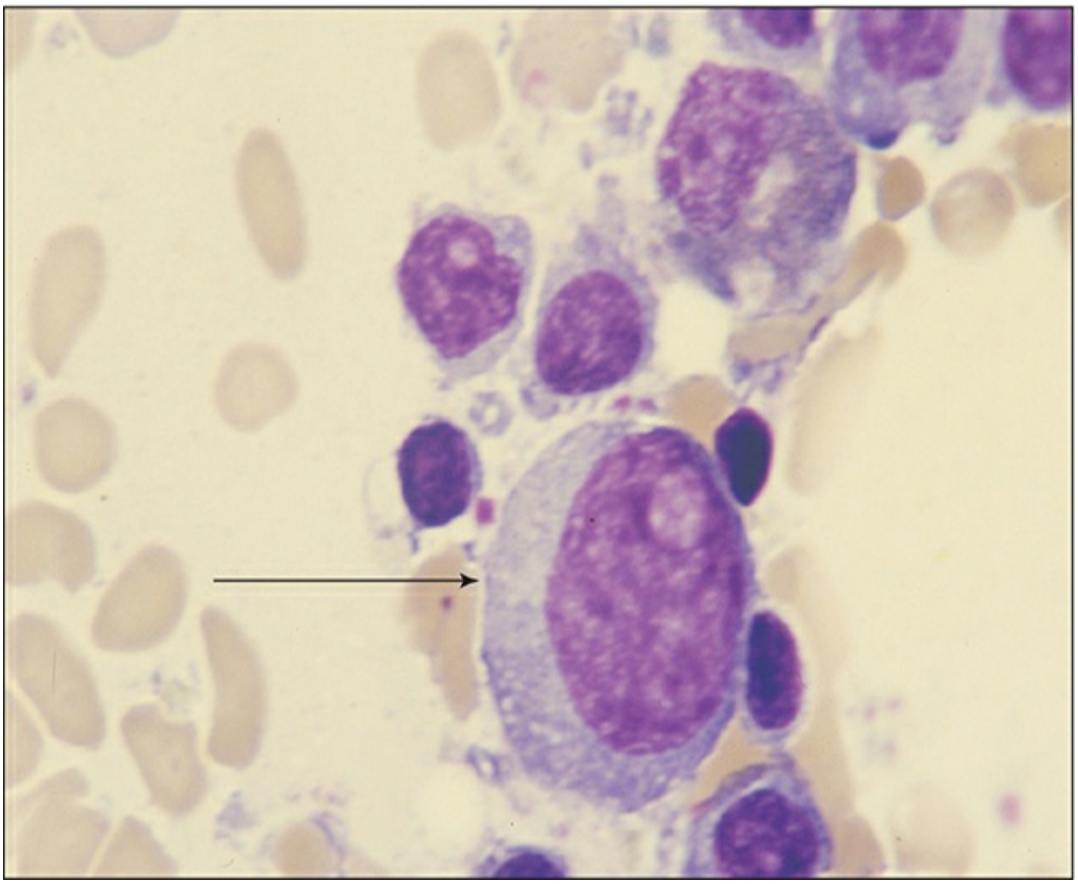


Figure IA3-2

Size: 6–24 μ in Diameter

Nucleus

Shape: Round, oval

N/C Ratio: 5:1–3:1

Color: Reddish purple to purple

Chromatin: Loosely organized

Nucleoli: Several, often indistinct or may be more distinct in larger blasts

Cytoplasm

Color: Moderate to dark blue (basophilic)

Contents: Blunt cytoplasmic extensions; no granules to fine azurophilic granules in the larger blasts

Clinical Conditions

- Acute megakaryoblastic leukemia (M7) (FAB) (WHO)
- Myeloproliferative neoplasms—CML, PMF
- Myelodysplastic syndromes

Promegakaryocyte (Stage II)

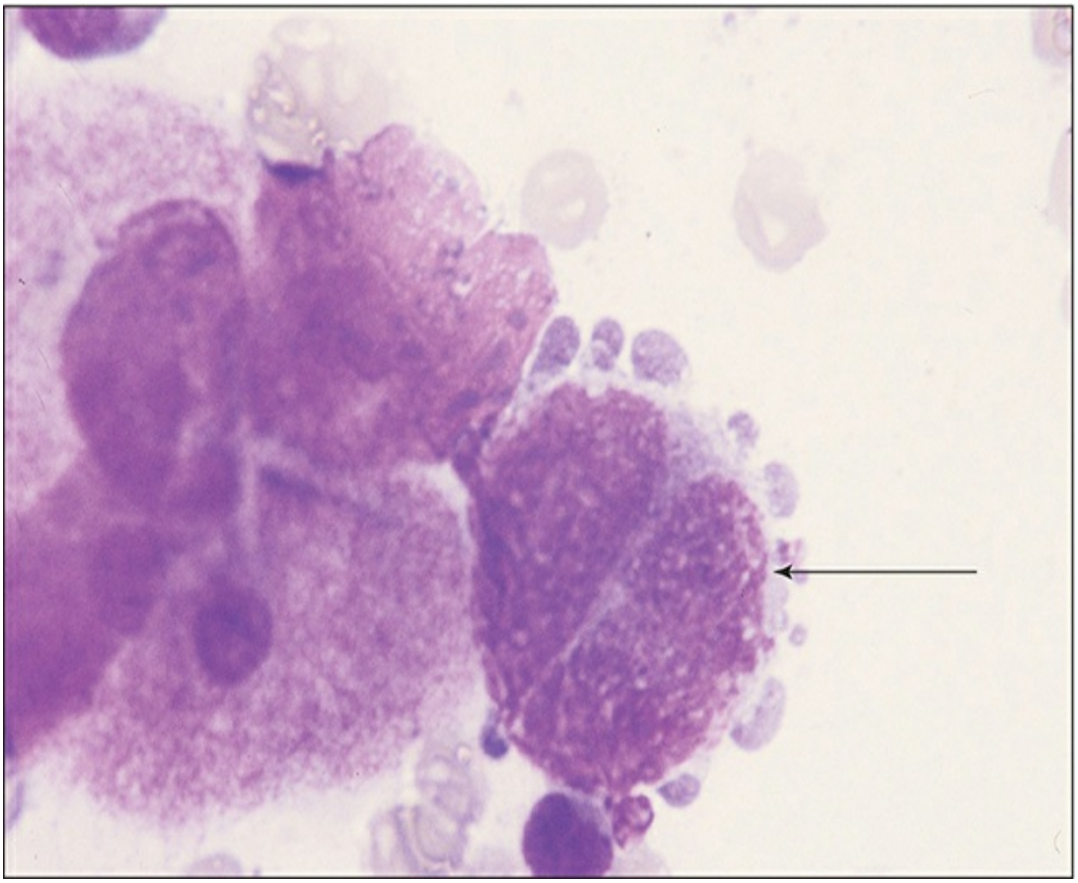


Figure IA3-3

Size: 14–30 μ in Diameter

Nucleus

Shape: Irregularly indented with 2–4 lobes

N/C Ratio: 1:1

Color: Dark purple

Chromatin: Fine; condensed near periphery

Nucleoli: Several

Cytoplasm

Color: Moderate blue to pinkish-blue

Contents: Few bluish granules; development of demarcation membrane system forming small cytoplasmic extensions

Clinical Conditions

- Acute megakaryoblastic leukemia (M7) (FAB) (WHO)
- Myeloproliferative neoplasms—CML, PMF, essential thrombocytosis (ET)
- Myelodysplastic syndromes
- Acute myelocytic leukemia with multilineage dysplasia

Megakaryocyte (Stage III)

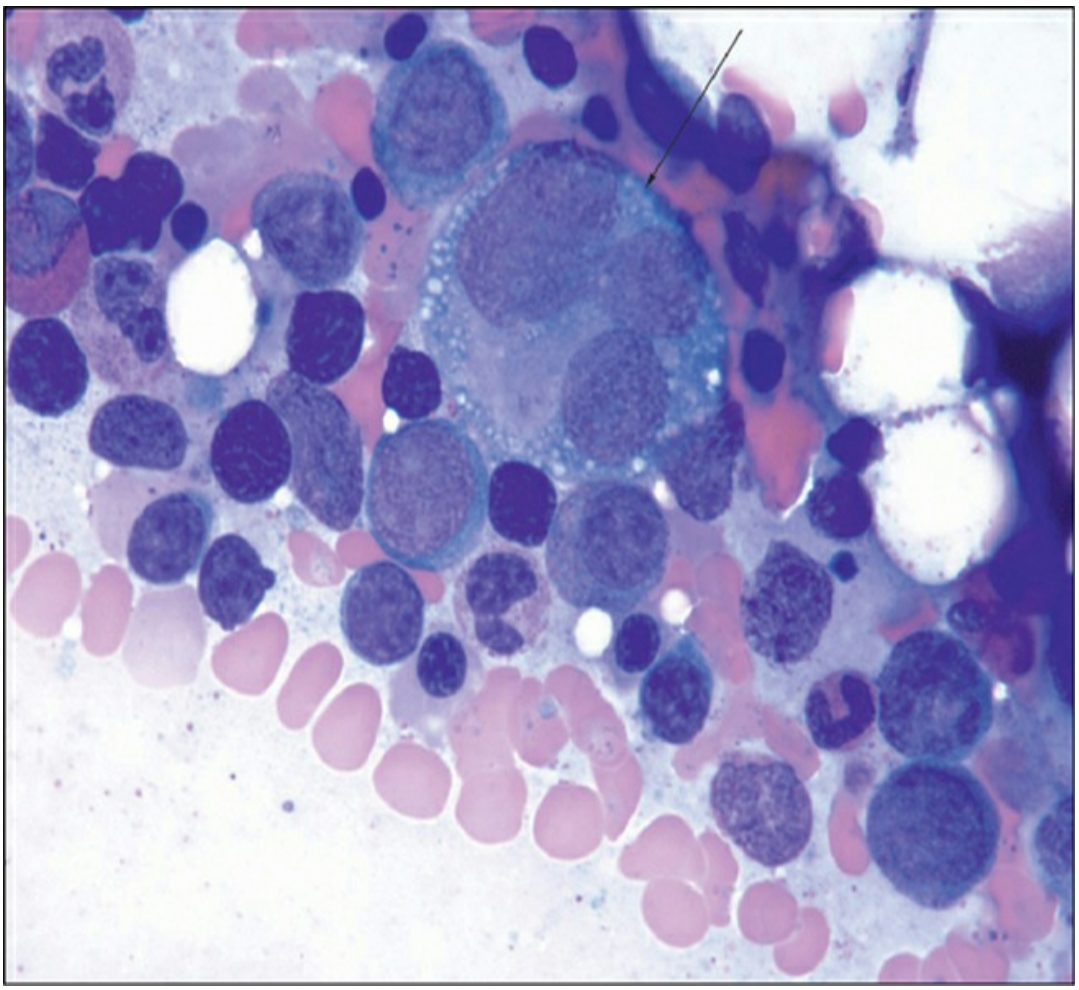


Figure IA3-4

Size: 40–60 μ in Diameter

Nucleus

Shape: Multilobular

N/C Ratio: 1:1–1:12

Color: Dark purple

Chromatin: Coarse, linear

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Numerous reddish-blue granules

Clinical Conditions

- Myeloproliferative neoplasms—CML, PMF, ET
- Myelodysplastic syndromes
- Acute myelocytic leukemia with multilineage dysplasia

Megakaryocyte (Stage IV)

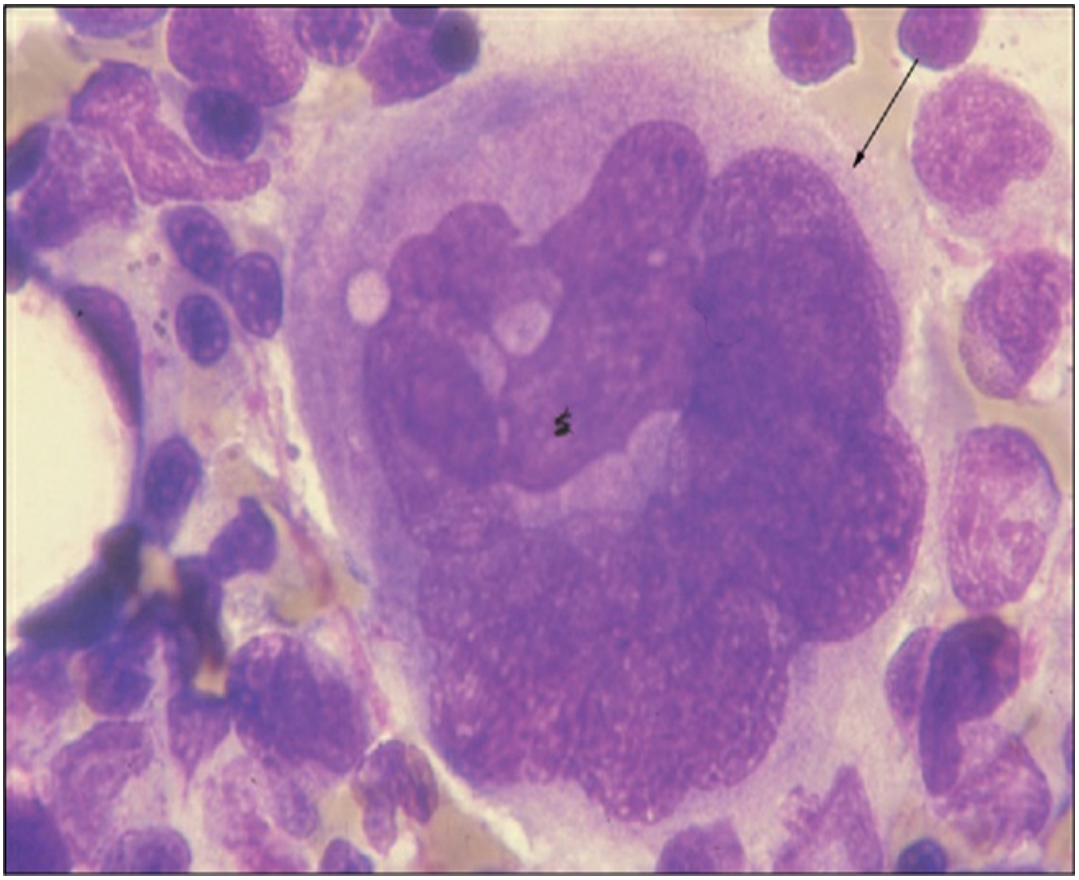


Figure **IA3-5**

Size: 40–60 μ in Diameter

Nucleus (8–64 N)

Shape: Pyknotic

N/C Ratio: 1:1–1:12

Color: Dark purple

Chromatin: Coarse, linear

Nucleoli: None

Cytoplasm

Color: Pinkish-blue

Contents: Numerous reddish-blue granules

Clinical Conditions

- Myeloproliferative neoplasms—CML, PMF, ET
- Myelodysplastic syndromes

- Acute myelocytic leukemia with multilineage dysplasia

Platelets

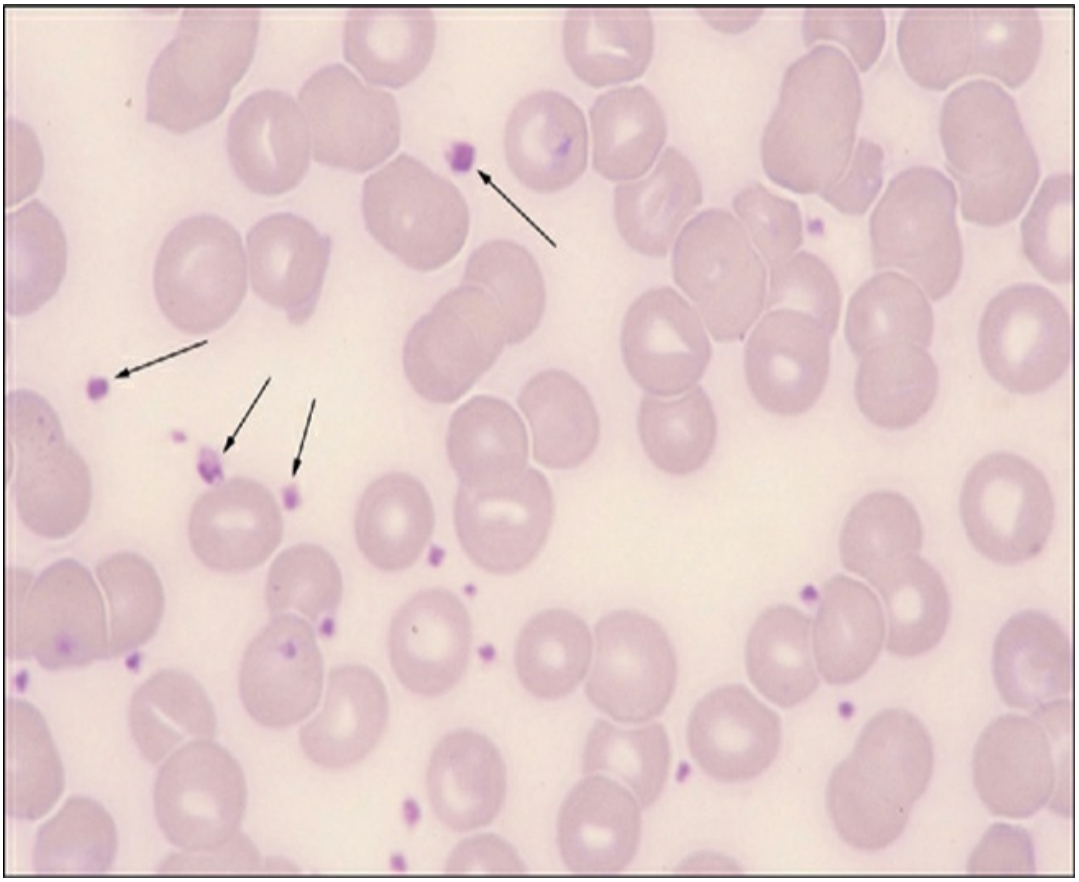


Figure IA3-6

Size: 1–4 μ

Nucleus

None

Cytoplasm

Color: Light blue

Contents: Small reddish-blue granules

ABNORMAL MEGAKARYOCYTIC CELLS

Giant Platelet

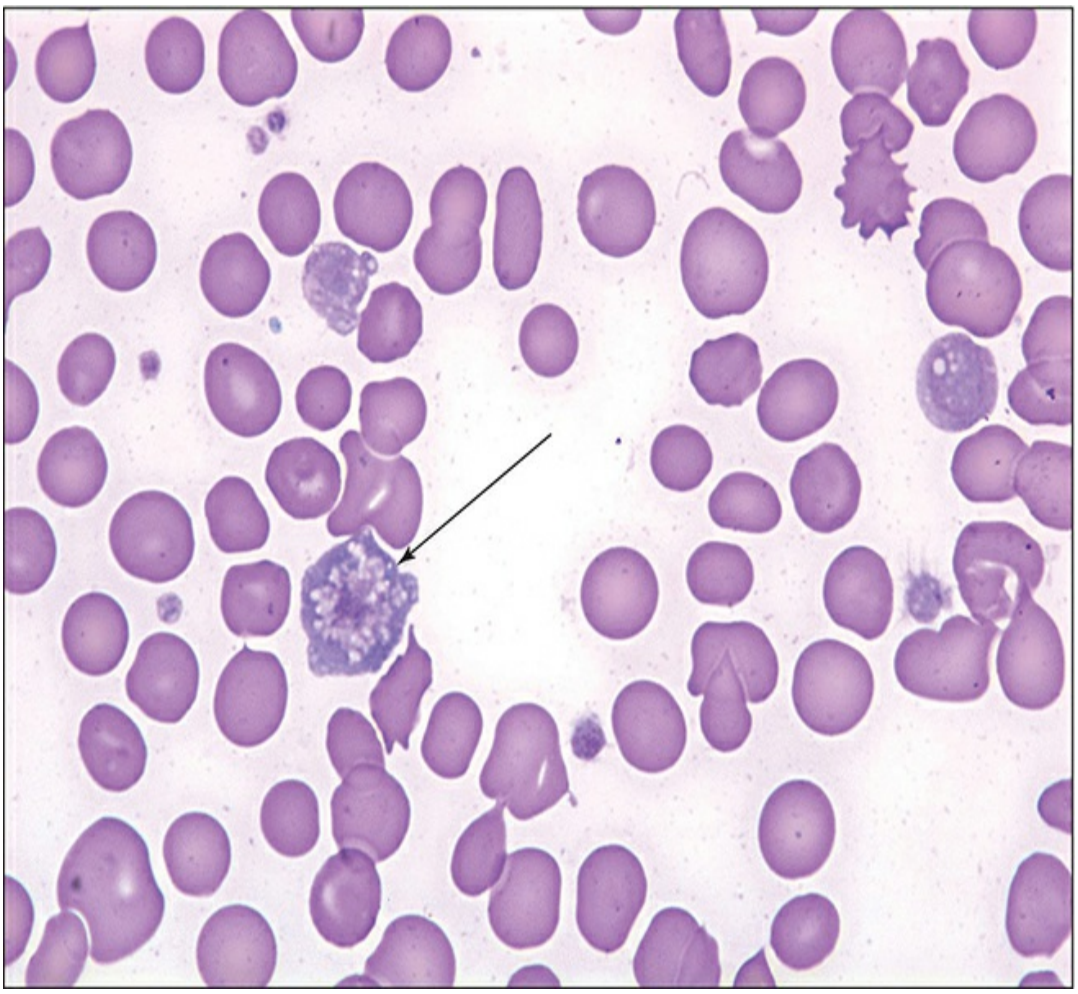


Figure IA3-7

Cell Type

Platelet

Description

Platelet as large as or larger than erythrocytes or granulocytes; light blue with small reddish-blue granules or degranulated (pale blue with no granules)

Clinical Conditions

- May-Hegglin syndrome
- Myelofibrosis
- Thrombasthenia
- Myeloproliferative neoplasms
- Splenectomy
- Myelodysplastic syndromes

Large Megakaryocyte

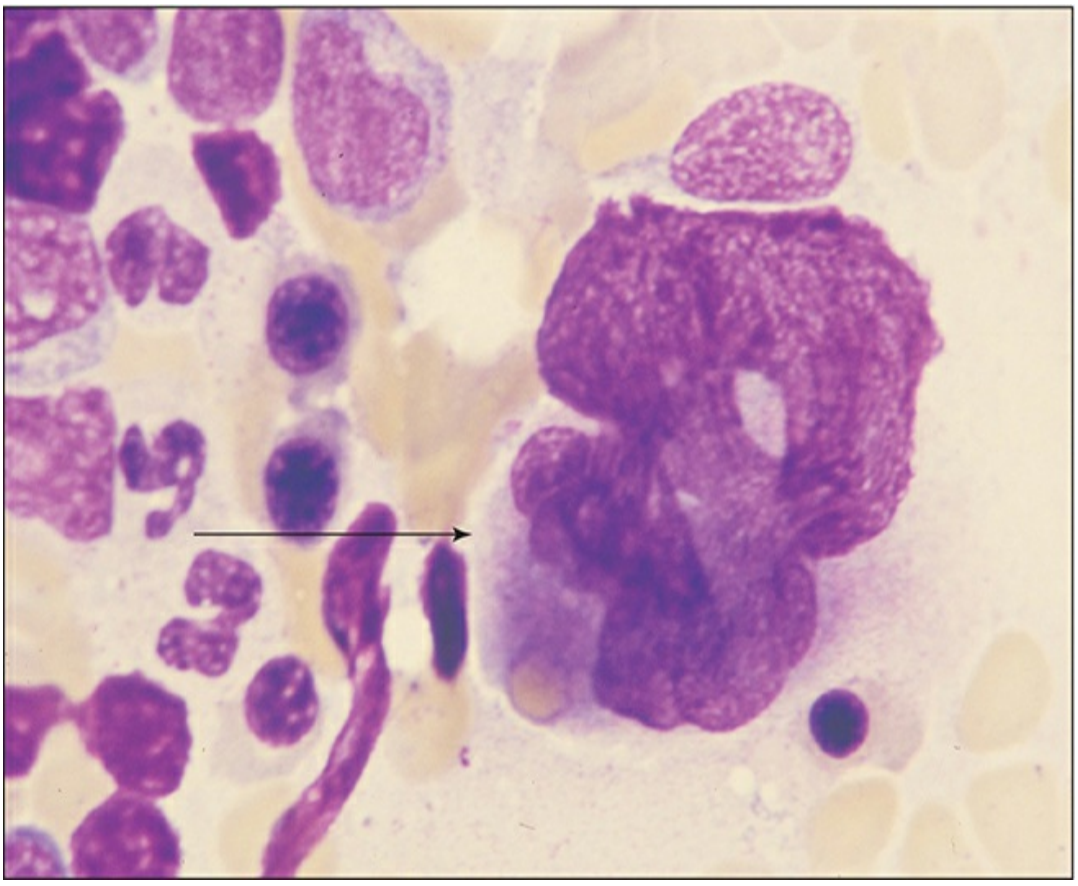


Figure IA3-8

Cell Type

Megakaryocyte

Description

Large megakaryocyte with hyperlobulation

Clinical Conditions

- Vitamin B_{12} deficiency
- Folic acid deficiency
- Myelodysplastic syndromes
- Idiopathic thrombocytopenic purpura

Large Mononuclear Megakaryocyte (Monolobed)

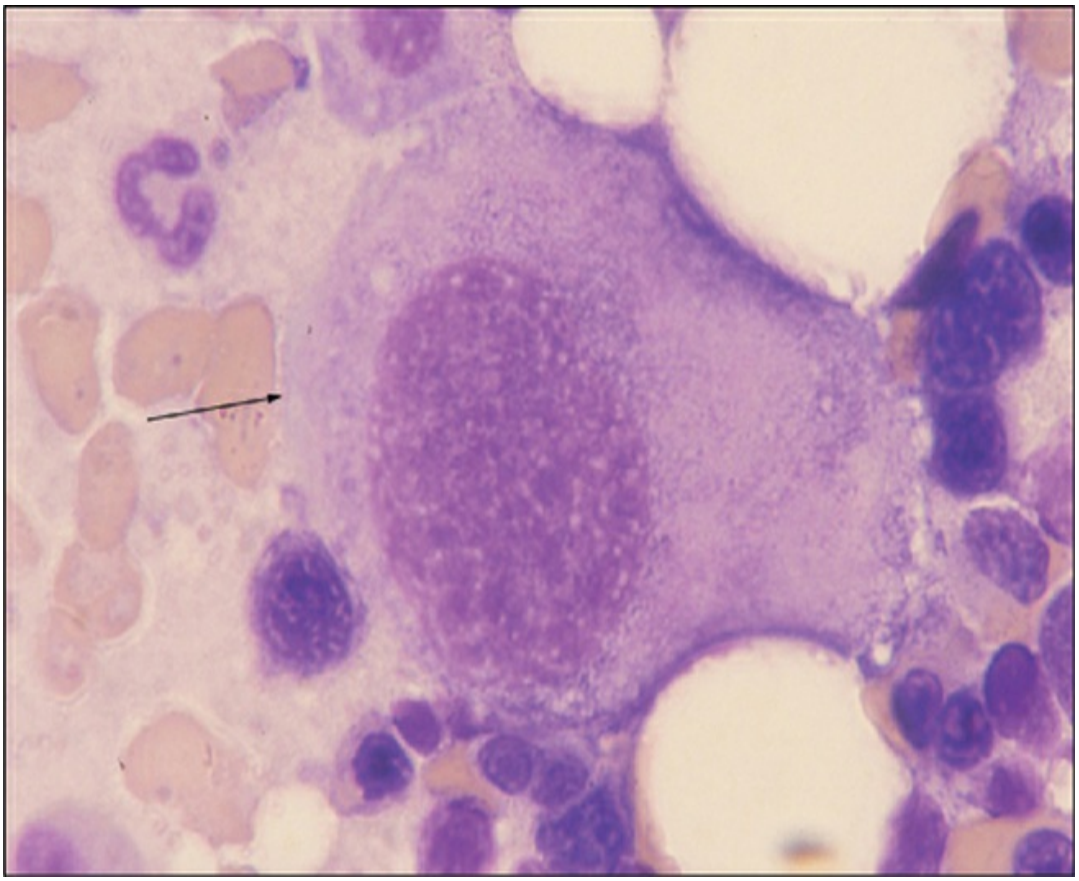


Figure IA3-9

Cell Type

Megakaryocyte

Description

Large megakaryocyte with a single nucleus

Clinical Conditions

- Myelodysplastic syndromes

- Acute megakaryoblastic leukemia (M7) (FAB) (WHO)
- 5q- syndrome

Micromegakaryocyte

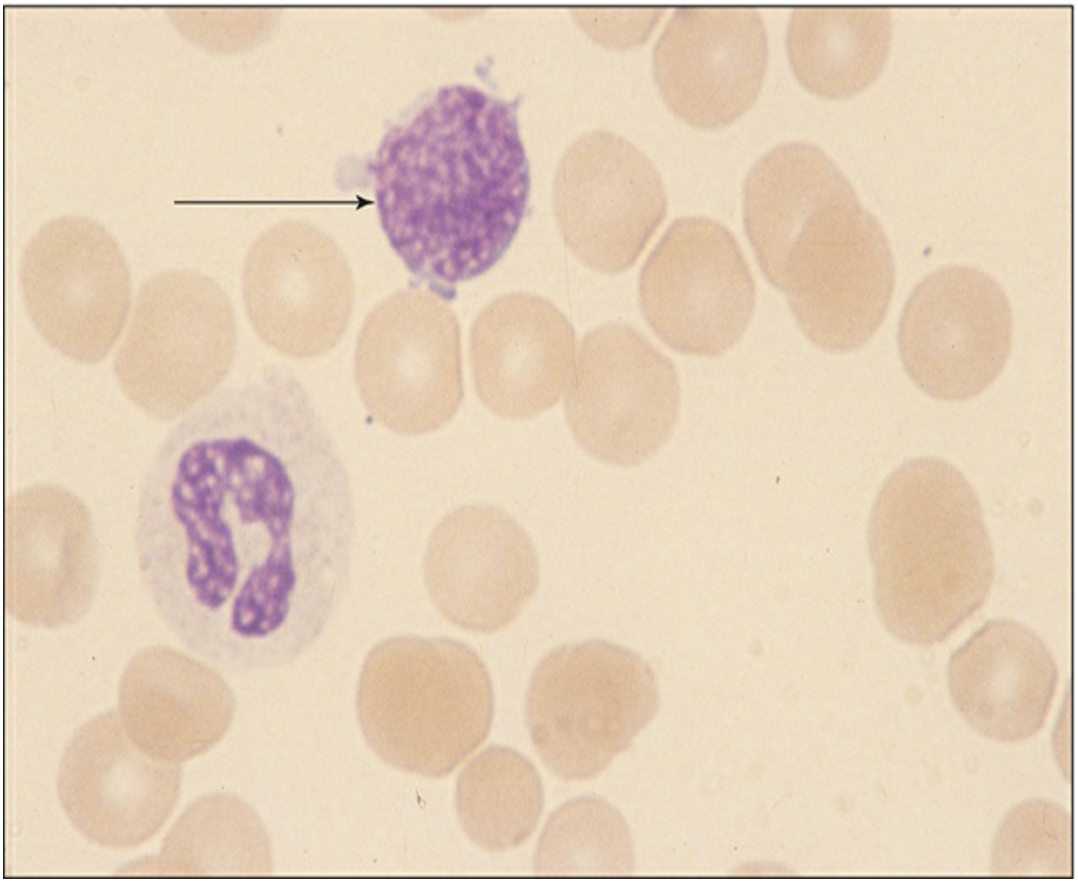


Figure **IA3-10**

Cell Type

Megakaryocyte

Description

Small megakaryocyte about the size of a lymphocyte

Single-lobed nucleus resembles medium-sized lymphocyte

One or more platelet fragments attached to nucleus or scant cytoplasm

Clinical Conditions

- Myeloproliferative neoplasms

- Myelodysplastic syndromes
- Acute megakaryoblastic leukemia (M7) (FAB) (WHO)

Vacuolated Megakaryocyte

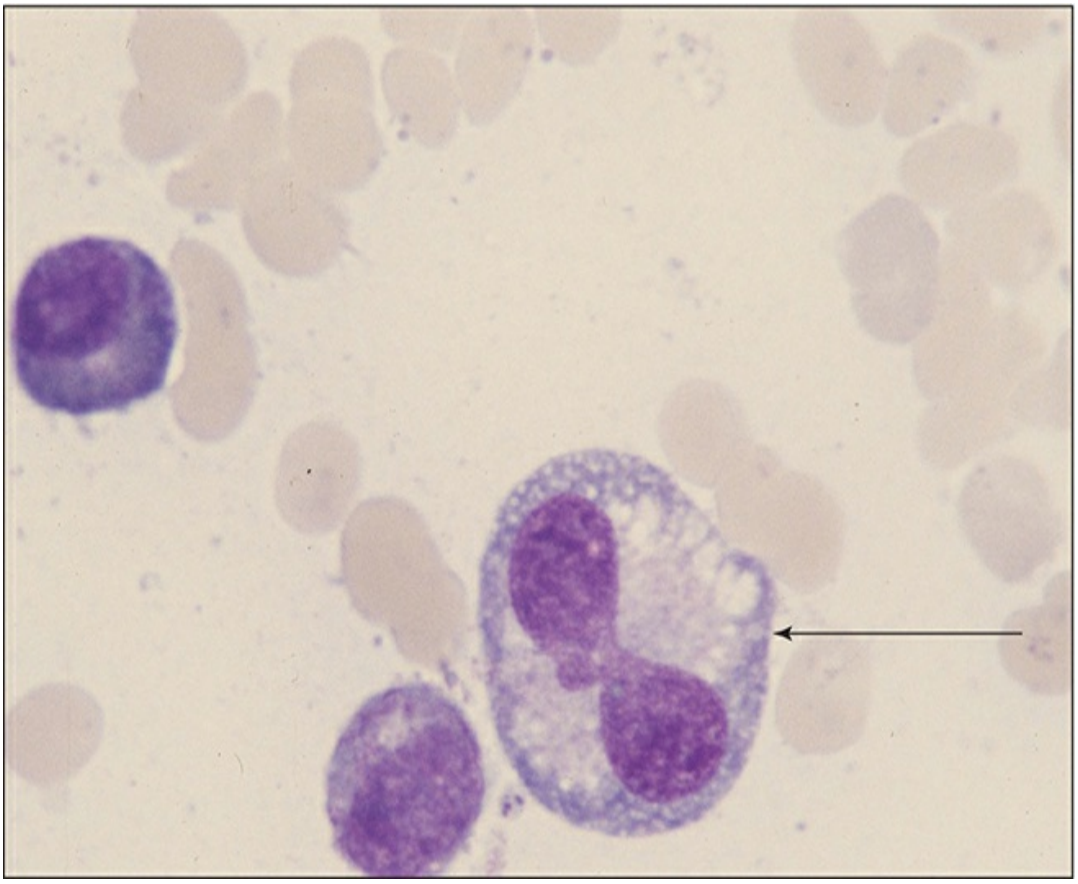


Figure IA3-11

Cell Type

Megakaryocyte

Description

Megakaryocyte or promegakaryocyte with a single or bilobed nucleus

Vacuoles in the basophilic or minimal granule-forming cytoplasm

Clinical Conditions

- Myelodysplastic syndromes

- Acute megakaryoblastic leukemia (M7) (FAB) (WHO)

CHAPTER 4

Comparison of Cells

Myeloblast, Myelocyte

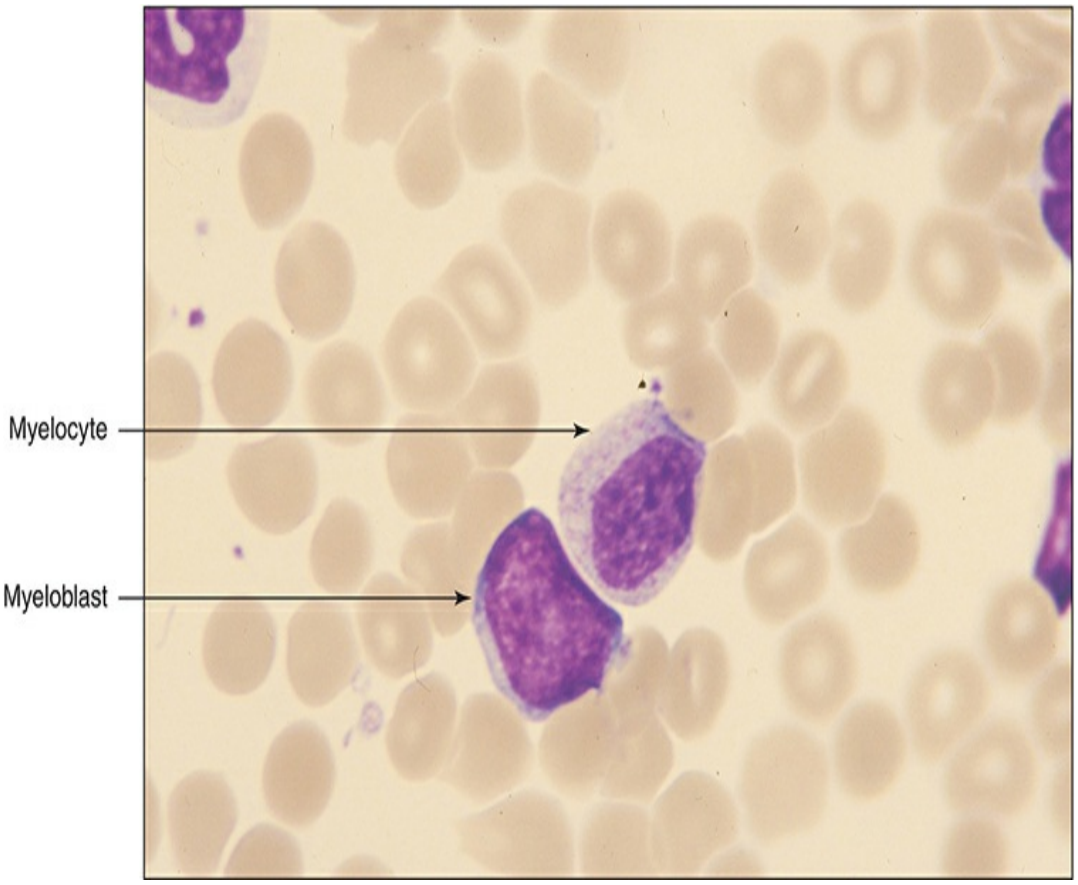


Figure IA4-1

Myeloblast

Fine nuclear chromatin

Moderate amount of agranular blue cytoplasm

N/C ratio higher

Myelocyte

Moderately clumped deep purple nucleus

Presence of some residual primary granules and the beginning of some secondary granule formation in the cytoplasm

Myeloblast, Promyelocyte, Myelocyte

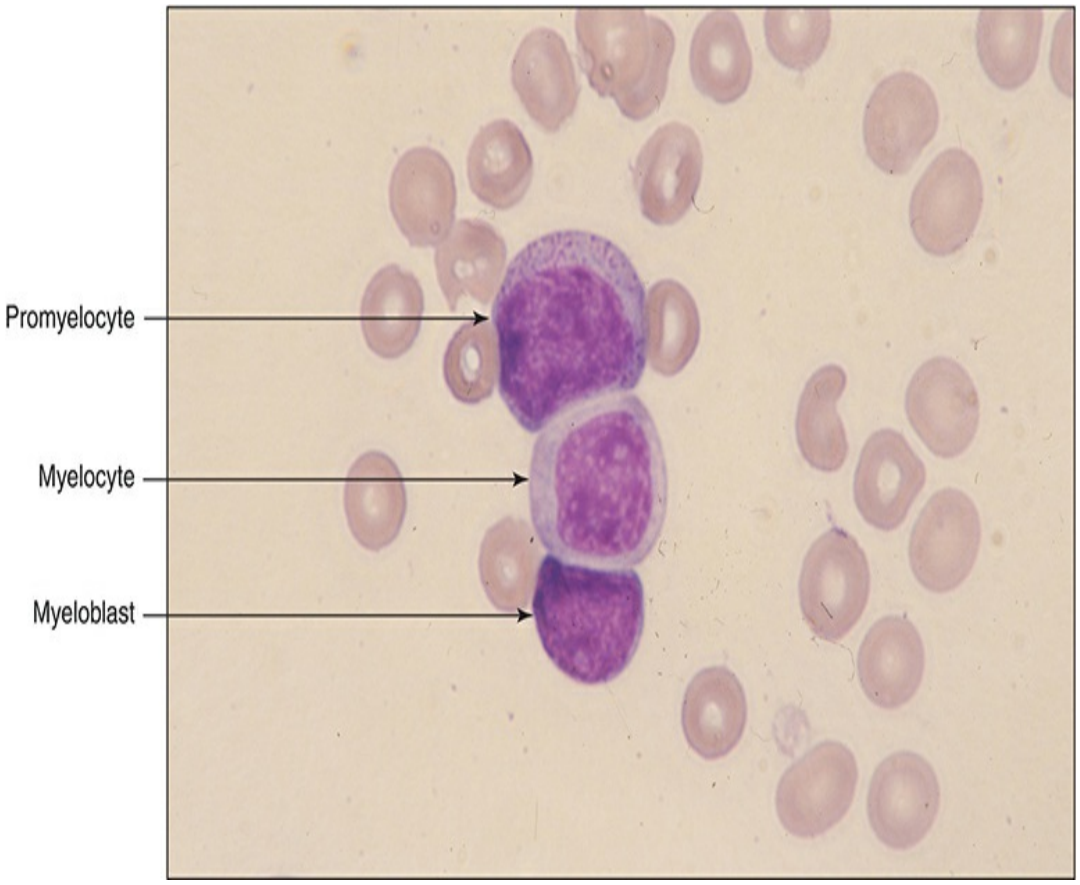


Figure IA4-2

Myeloblast

Highest N/C ratio

Finest nuclear chromatin pattern

Promyelocyte

Presence of primary azurophilic granules

Cytoplasm is moderate blue color

Myelocyte

Lowest N/C ratio

Muddy gray cytoplasmic color

Secondary granules are present

Nuclear chromatin is more clumped

Myeloblast, Basophilic Normoblast

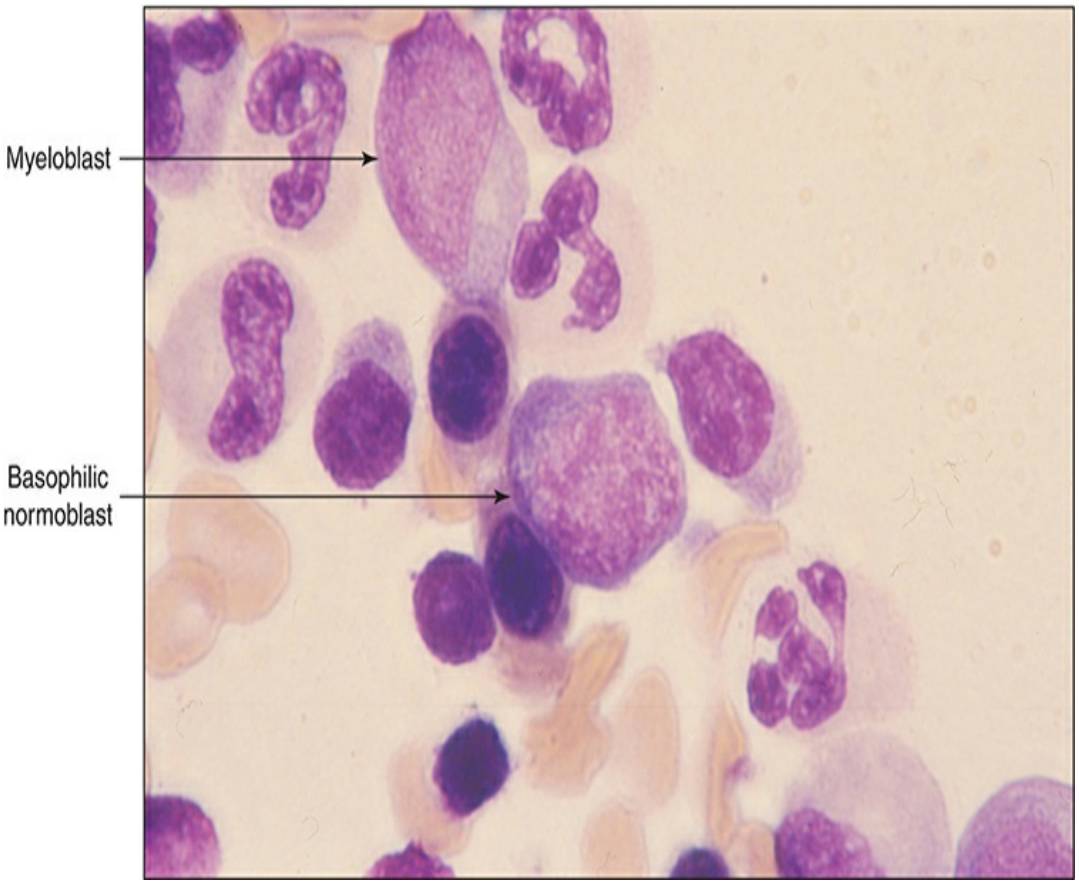


Figure **IA4-3**

Myeloblast

Finer nuclear chromatin pattern with visible nucleoli

Cytoplasm has a lighter blue color

Basophilic Normoblast

Nucleus has a more clumped chromatin pattern

Cytoplasm has a deeper blue color

Late Polychromatophilic Normoblast, Lymphocyte

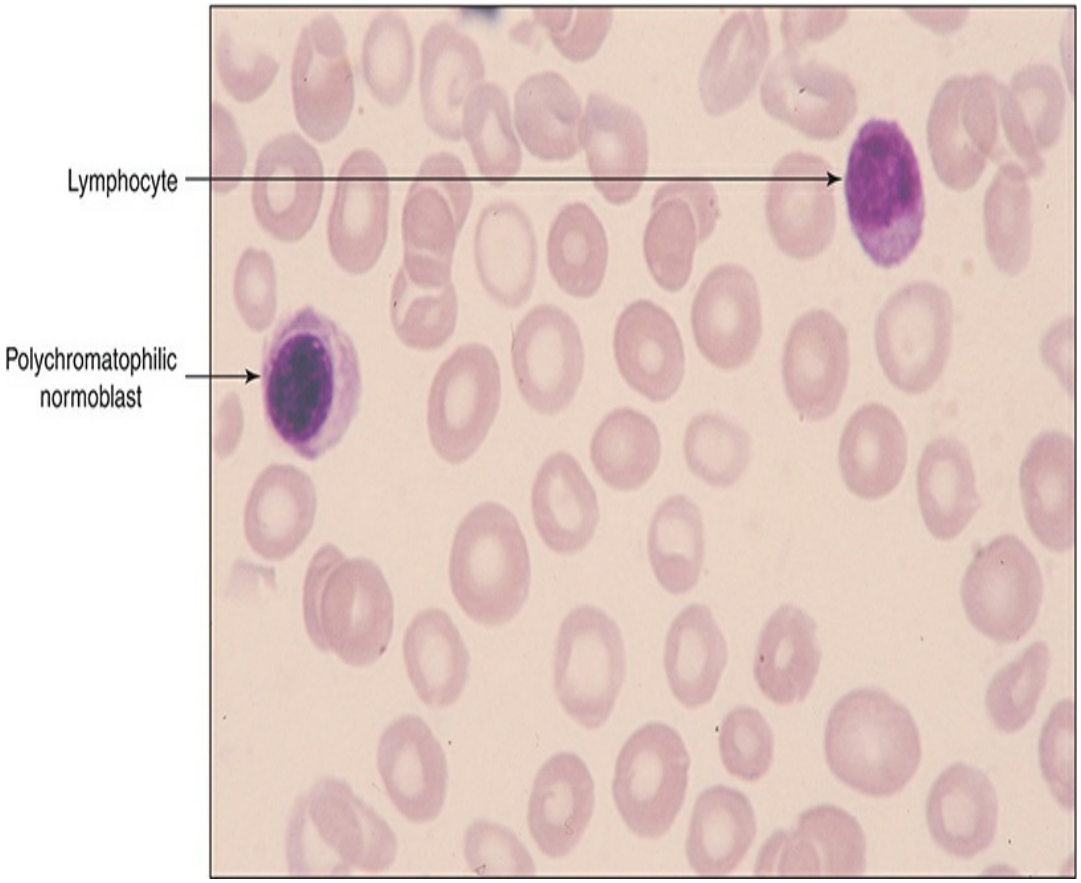


Figure IA4-4

Late Polychromatophilic Normoblast

Nucleus is deep purple and slightly eccentric

Nuclear chromatin is intensely condensed

Cytoplasm is pink with a bluish tinge

Lymphocyte

Nucleus is pale purple and eccentric

Nuclear chromatin is moderately condensed

Cytoplasm is light blue and scanty

Monoblast, Promonocyte

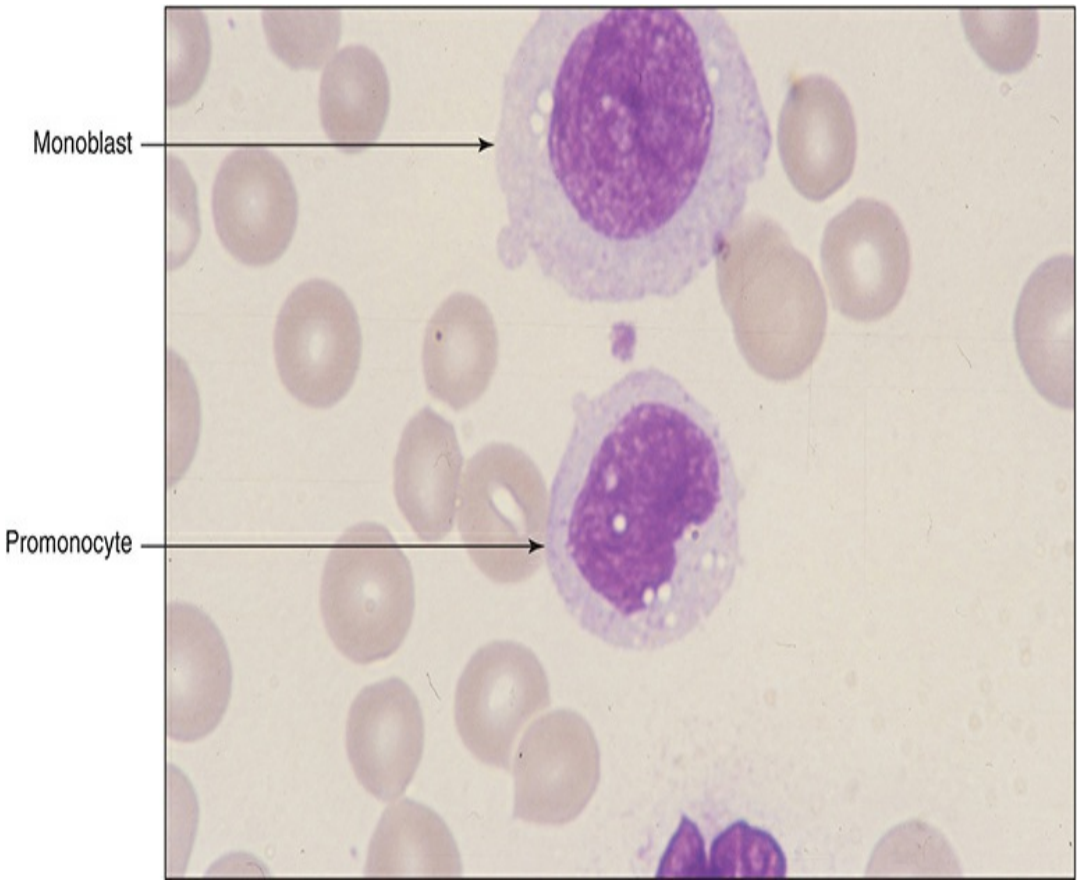


Figure IA4-5

Monoblast

Larger cell

Round nucleus with cleave evident

One single nucleoli present

Similar cytoplasms

Promonocyte

Indented nucleus with more condensed chromatin pattern

Monoblast, Myeloblast

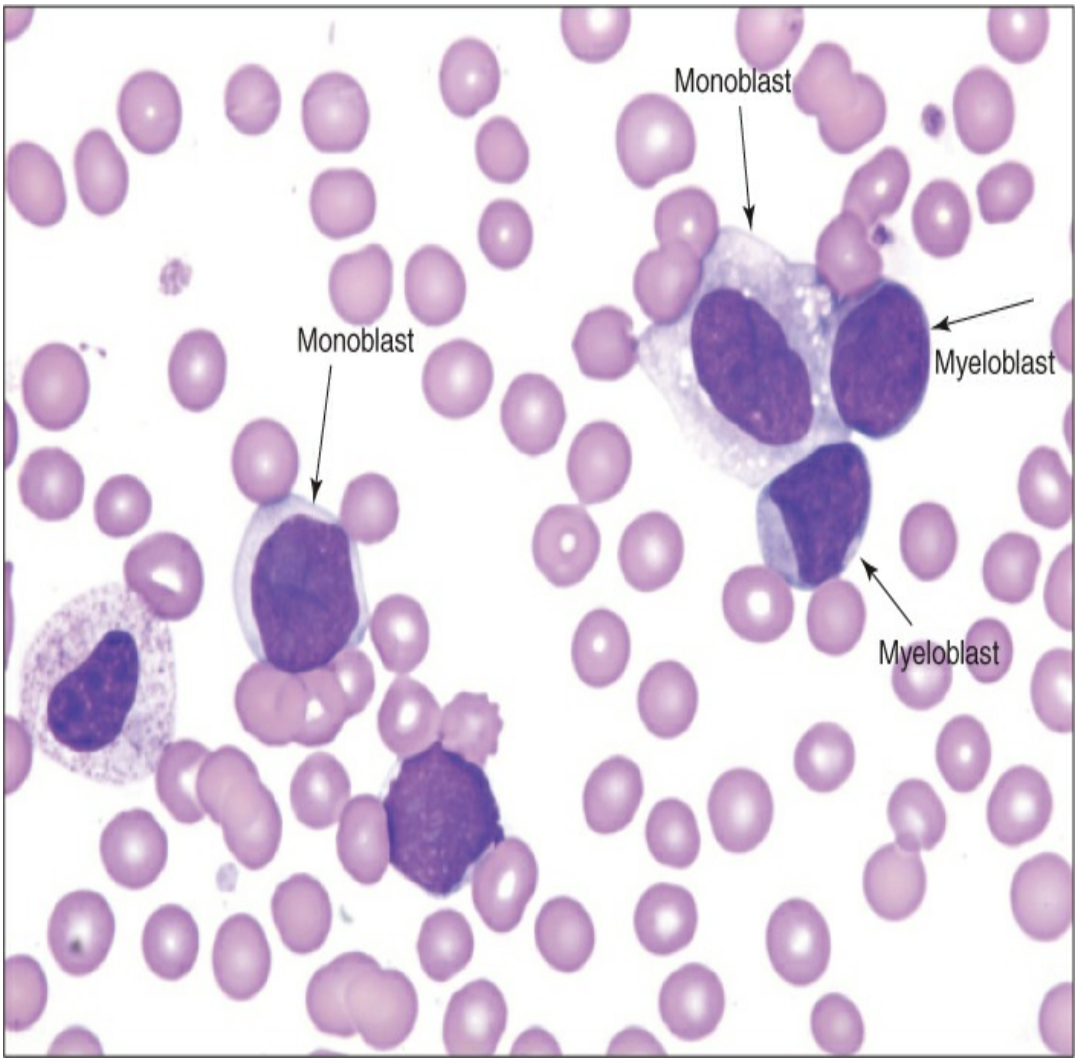


Figure IA4-6

Monoblast

More cytoplasm

Nucleus has finely dispersed chromatin with a vaguely noticeable cleave

Myeloblast

Higher N/C ratio

Finer chromatin pattern

Smaller cell

Monocyte, Reactive Lymphocyte

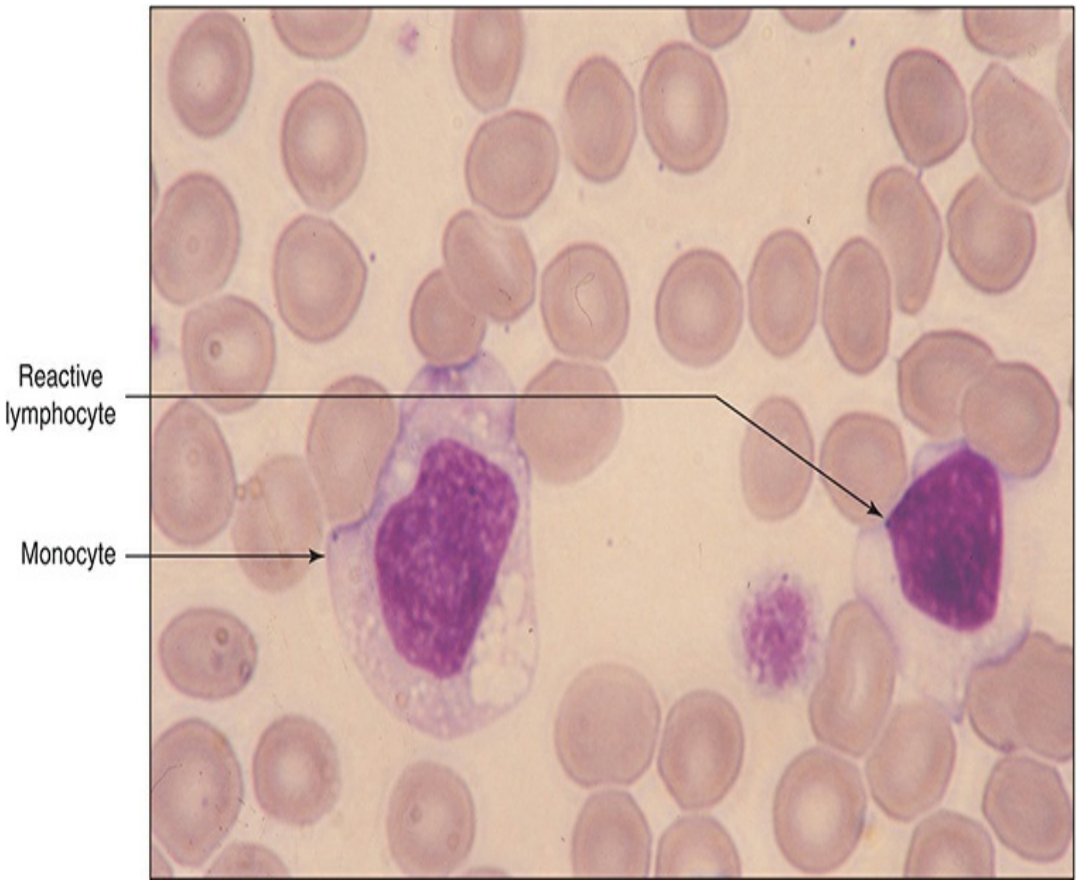


Figure IA4-7

Monocyte

Cell is larger

Lower N/C ratio

Finer nuclear chromatin pattern

Reactive Lymphocyte

Cell is smaller

Condensed nuclear chromatin pattern

Higher N/C ratio

Monocyte, Lymphocyte

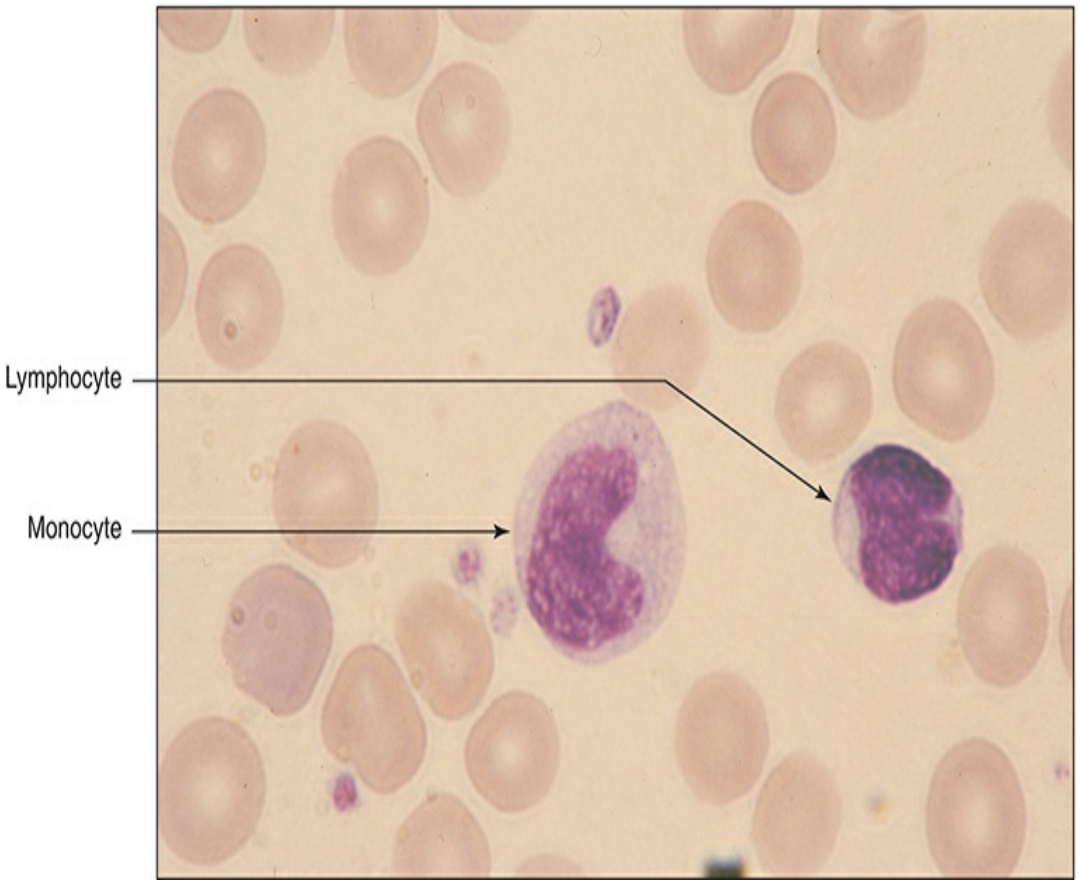


Figure IA4-8

Monocyte

Lower N/C ratio

Finer, lacy nuclear chromatin pattern

Nucleus is indented

Larger cell

Lymphocyte

Nucleus is indented

Intensely clumped nucleus

Higher N/C ratio

Pronormoblast, Myelocyte

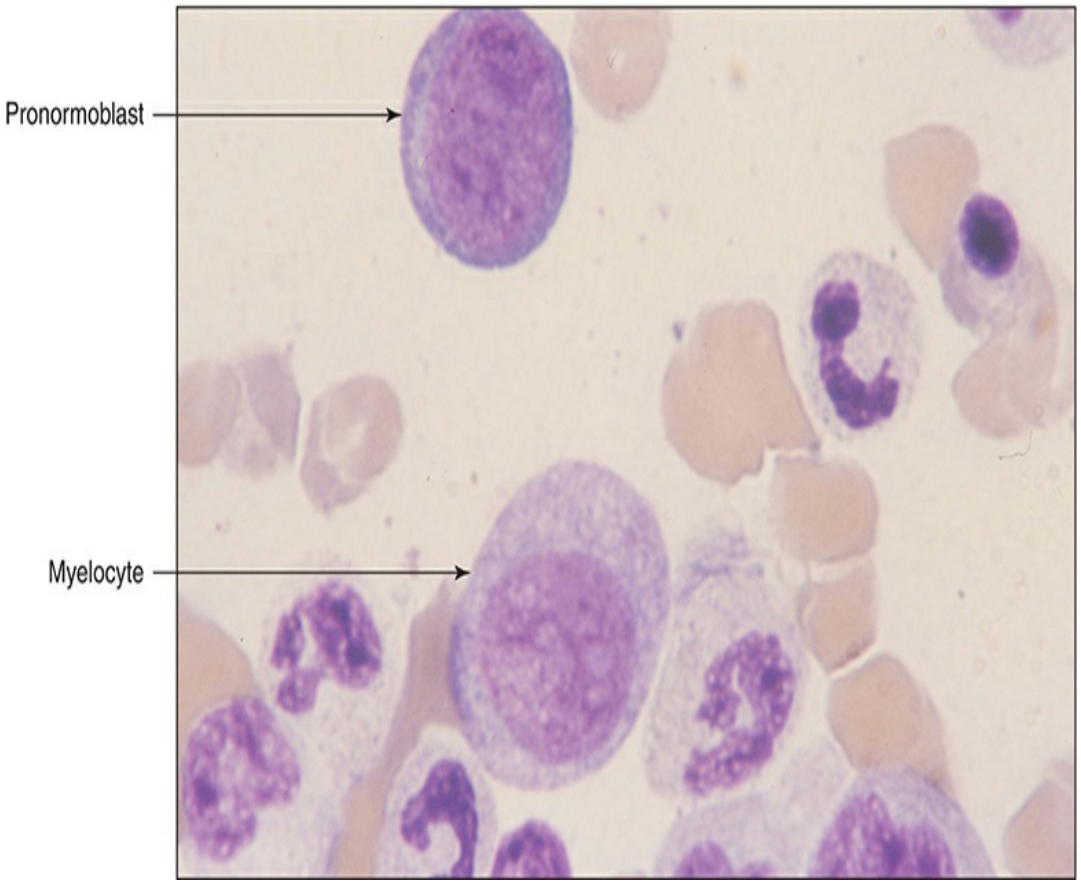


Figure IA4-9

Pronormoblast

Nucleus is large, deep purple, and centrally located

Nuclear chromatin is finely stippled

Cytoplasm is intensely basophilic with light areas of mitochondria

High N/C ratio

Myelocyte

Nucleus is light purple and slightly off center

Nuclear chromatin is moderately condensed with a prominent nucleolus (nucleoli can still be present since this cell can still divide)

Cytoplasm is grayish blue with a hint of pink granulation

Lower N/C ratio

Pronormoblast, Promyelocyte

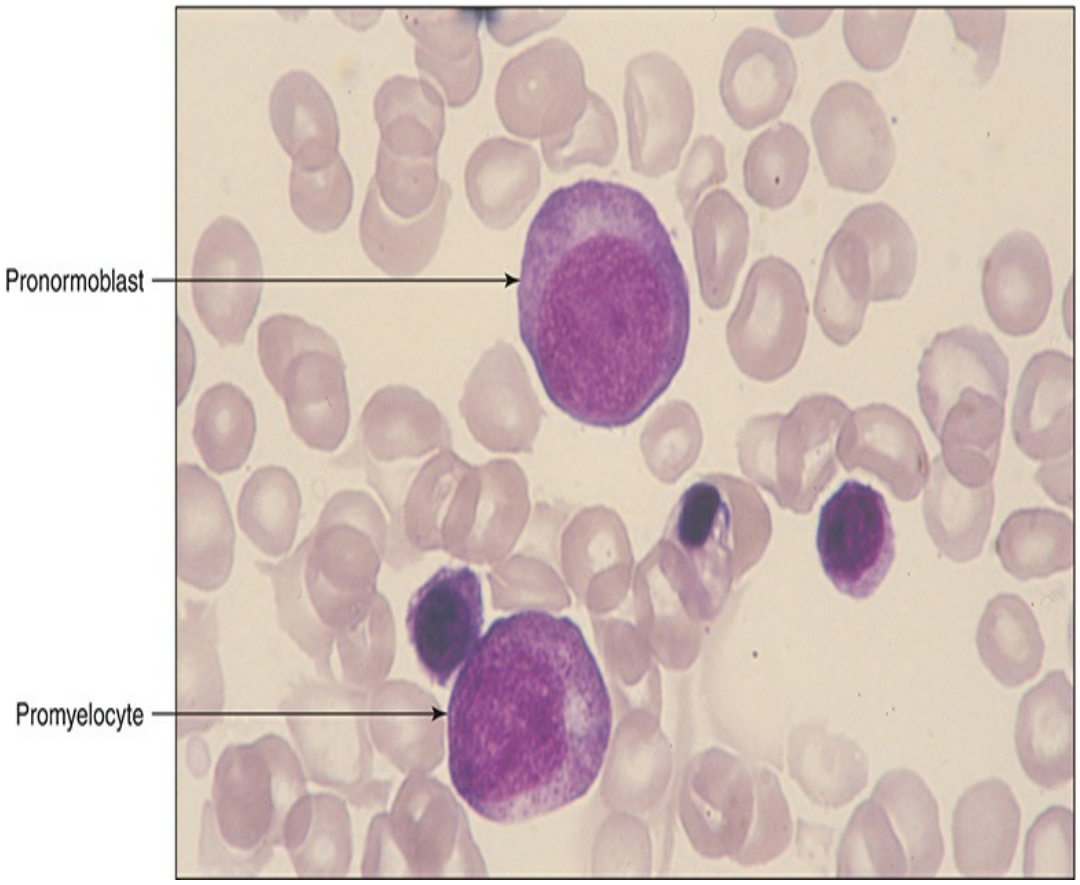


Figure **IA4-10**

Pronormoblast

Nucleus is large, deep purple, and centrally located

Nuclear chromatin is finely stippled

Cytoplasm is intensely basophilic light areas of mitochondria

Light area next to the nucleus is the Golgi

Promyelocyte

Nucleus is purple and eccentrically located

Nuclear chromatin is finely condensed

Cytoplasm has numerous dark, primary granules that have begun to obscure the nucleus

Early Myelocyte, Late Myelocyte

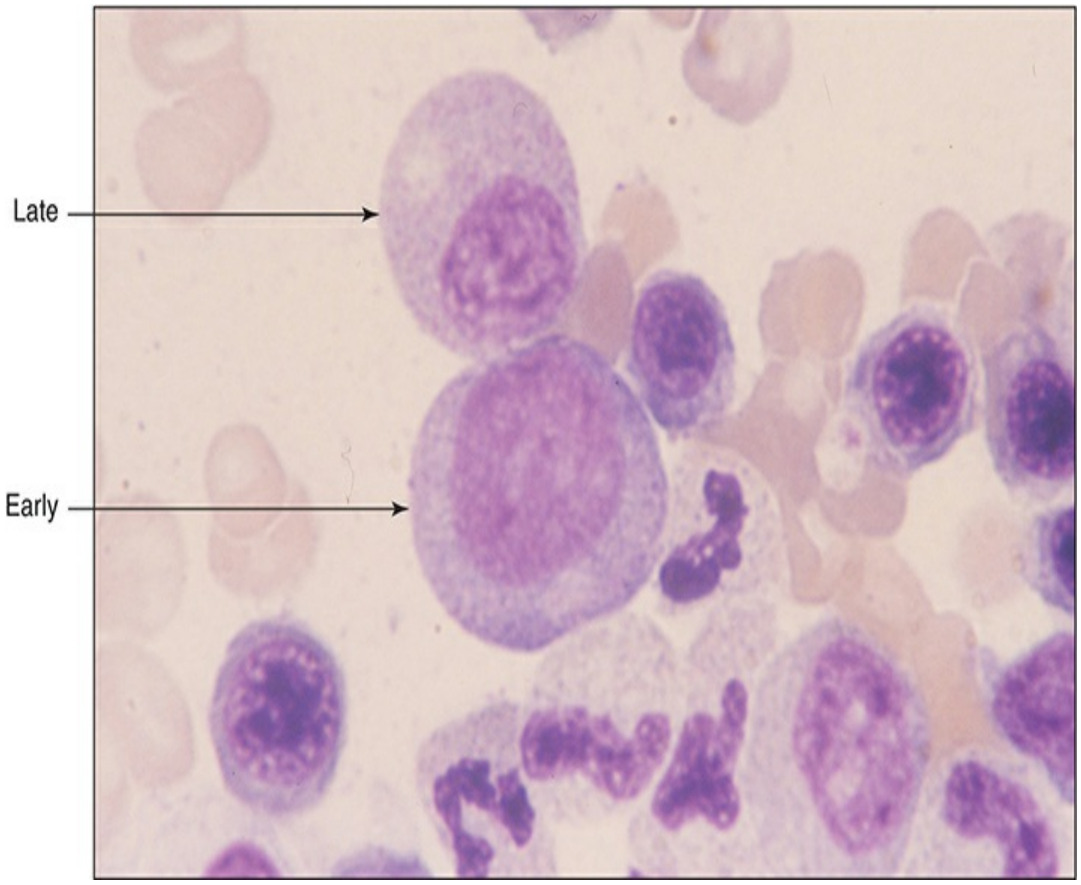


Figure IA4-11

Early Myelocyte

Nucleus is light purple and slightly off center

Nuclear chromatin is moderately condensed with a prominent nucleolus

Cytoplasm is grayish-blue with a hint of pink granulation

Late Myelocyte

Nucleus is purple, oval, and eccentric

Nuclear chromatin is fairly clumped and has an aggregated pattern with no visible nucleoli

Cytoplasm is granulated with pink secondary granules

Metamyelocyte, Neutrophilic Band, Segmented Neutrophil

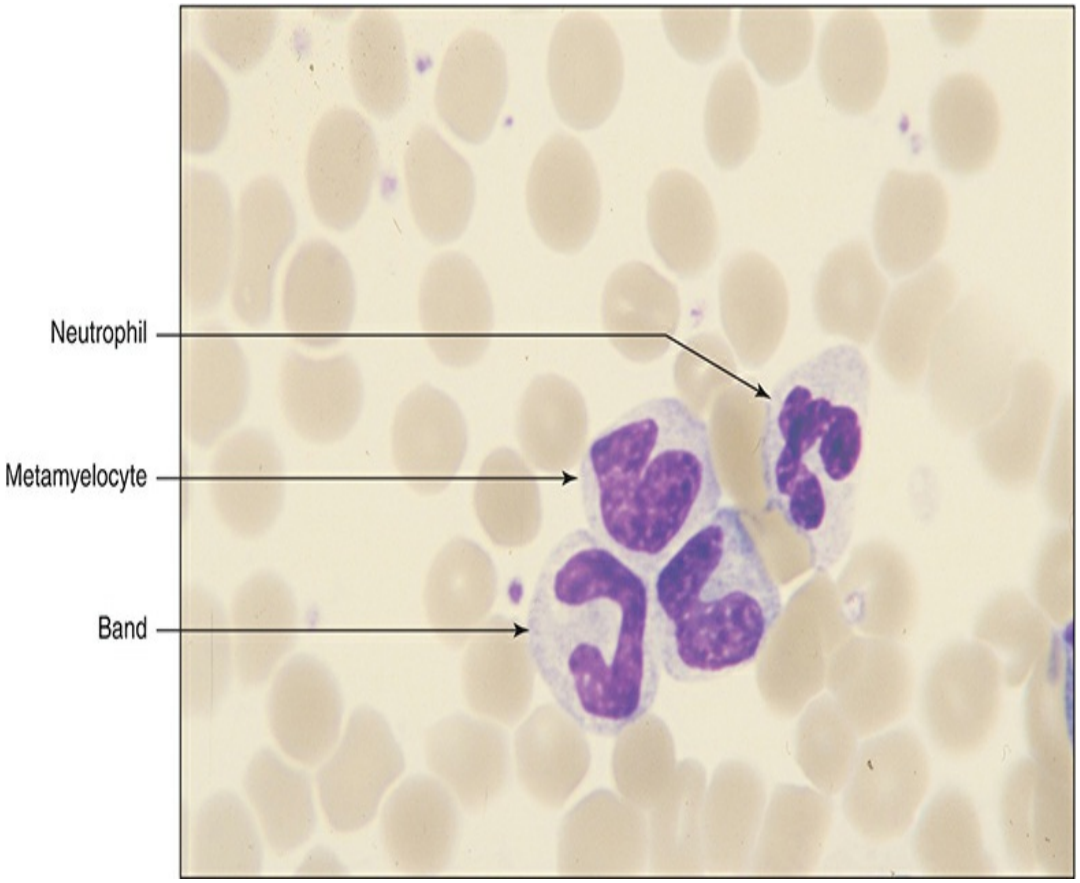


Figure IA4-12

Metamyelocyte

Nucleus is deep purple and has a kidney bean to slightly indented shape

Nuclear chromatin is fairly coarse but not as clumped as the band or segmented neutrophil

Band

Nucleus is deep purple and markedly indented to make a band shape

Nuclear chromatin is intensely clumped

Segmented Neutrophil

Nucleus is deep purple and has a segmented shape
Nuclear chromatin is coarsely clumped
Cytoplasm for all three cells is basically the same and seldom helpful in differentiating the cells

Section B

Bone Marrow

CHAPTER 1

Cellularity

BONE MARROW CELLULARITY

Normal Adult Cellularity

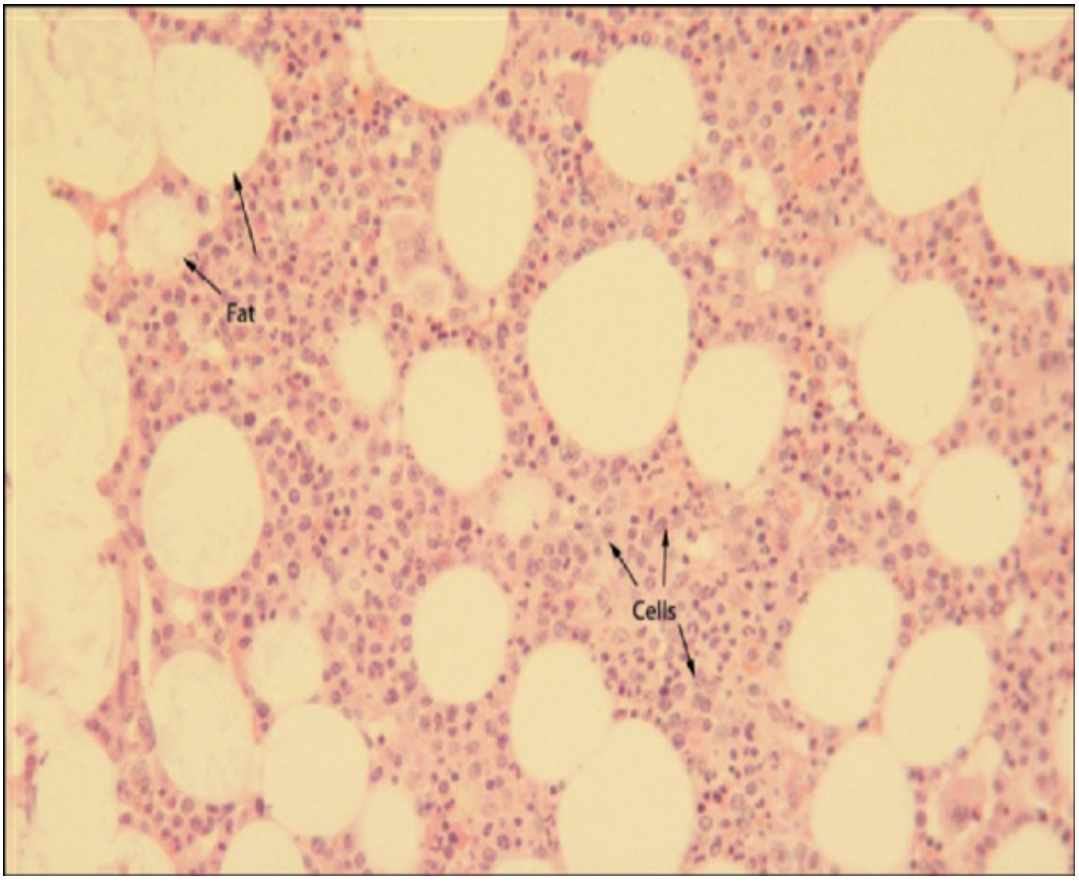


Figure IB1-1

Description

30–80% cellularity

Normal Elderly Cellularity

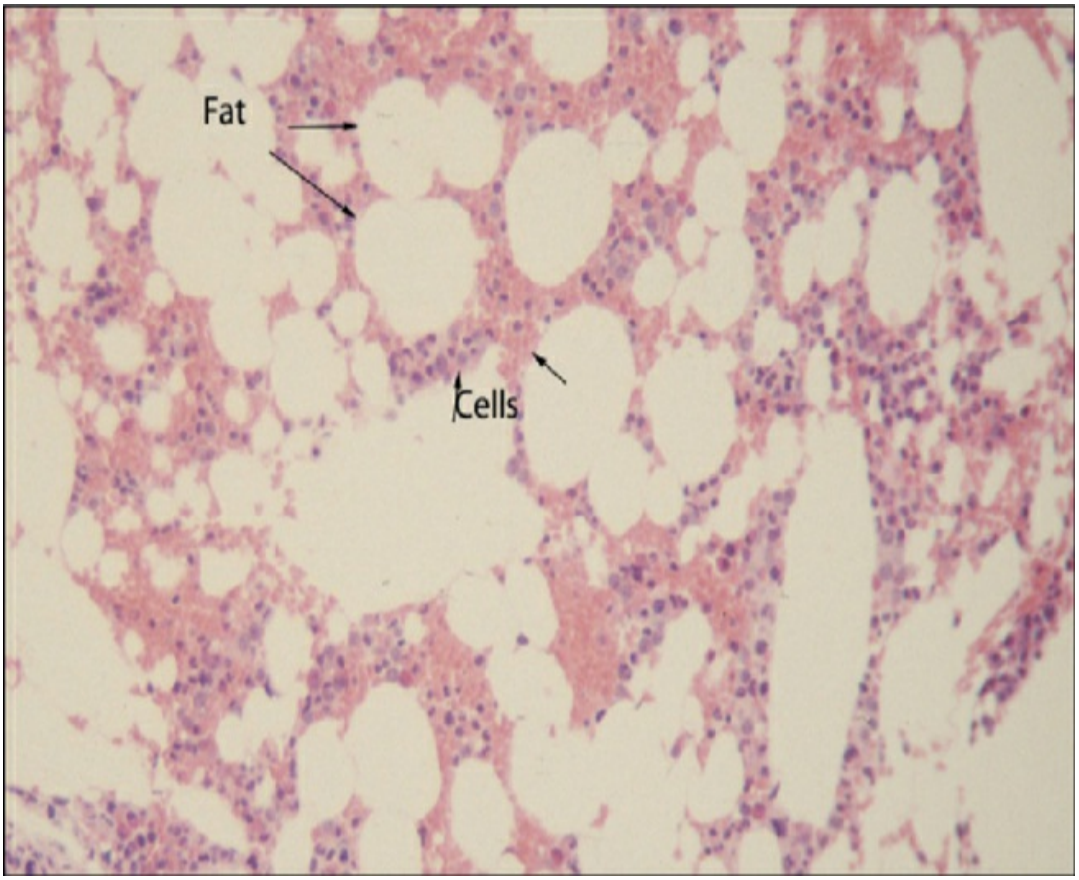


Figure **IB1-2**

Description

20–50% cellularity

Normal Adolescent Cellularity

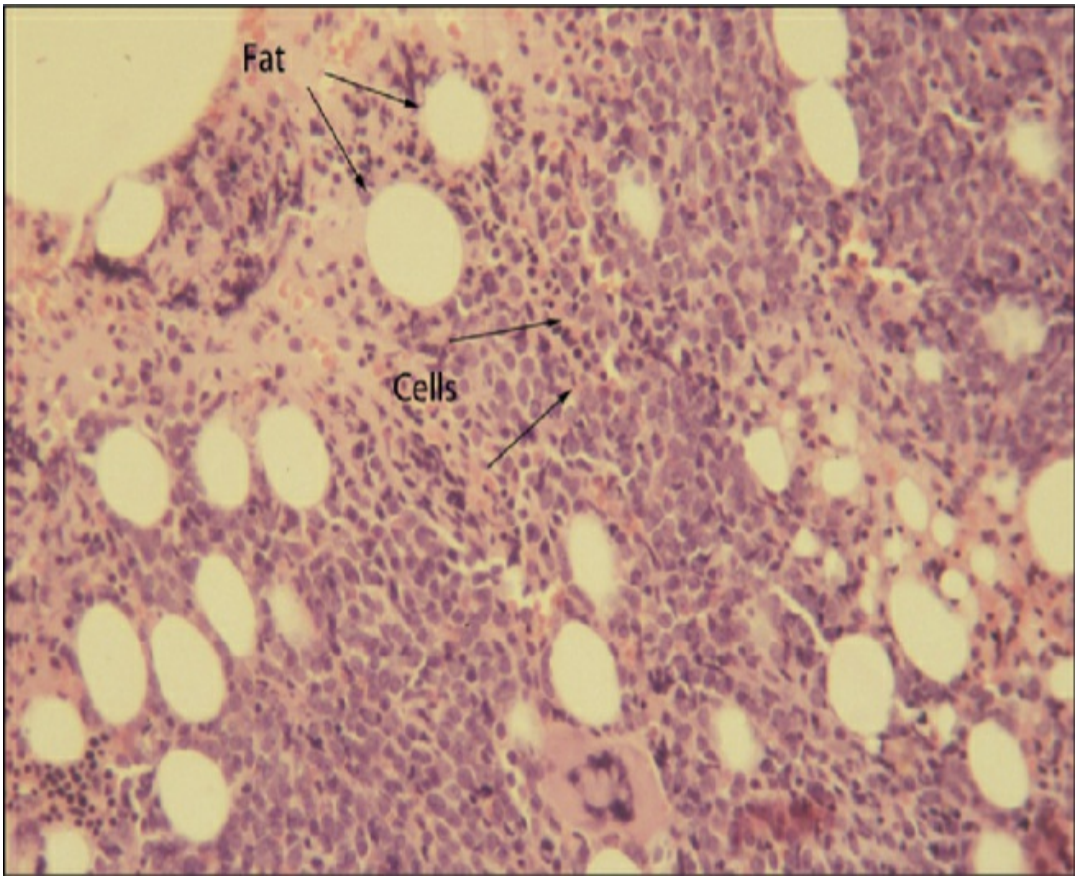


Figure **IB1-3**

Description

50–90% cellularity

Normal Newborn Cellularity

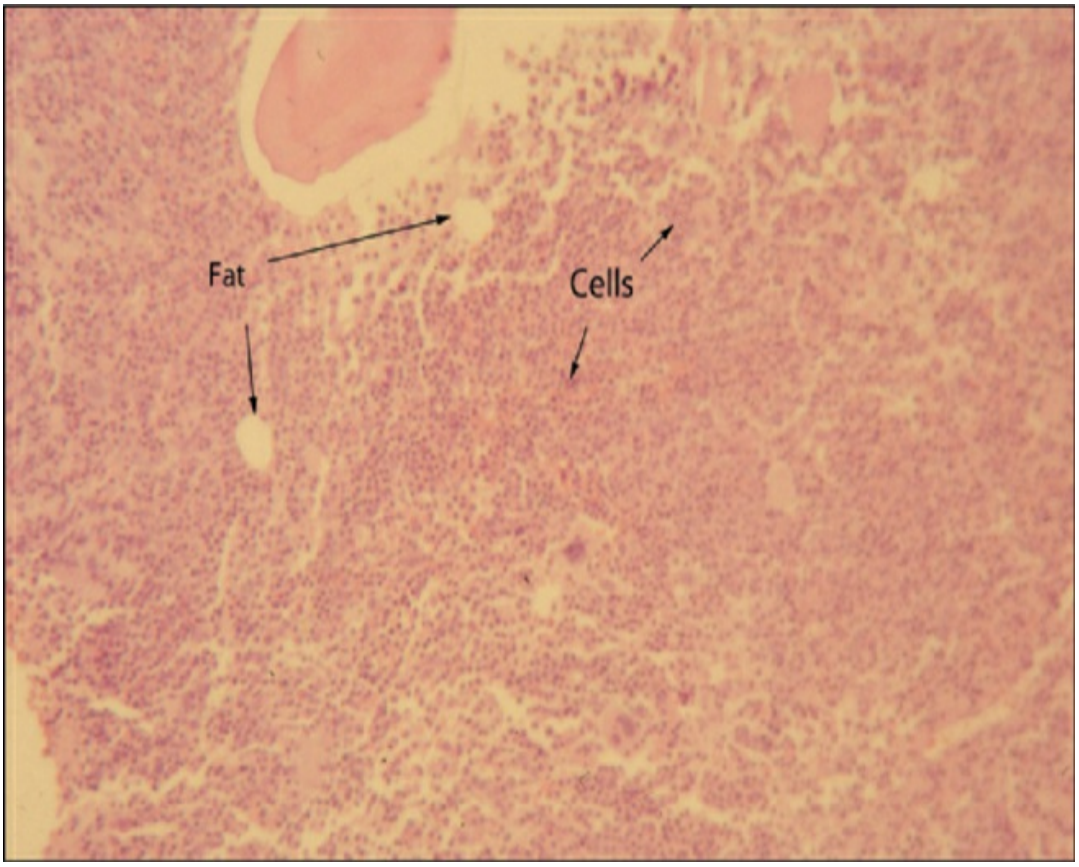


Figure IB1-4

Description

75–100% cellularity

Adult Hypocellularity

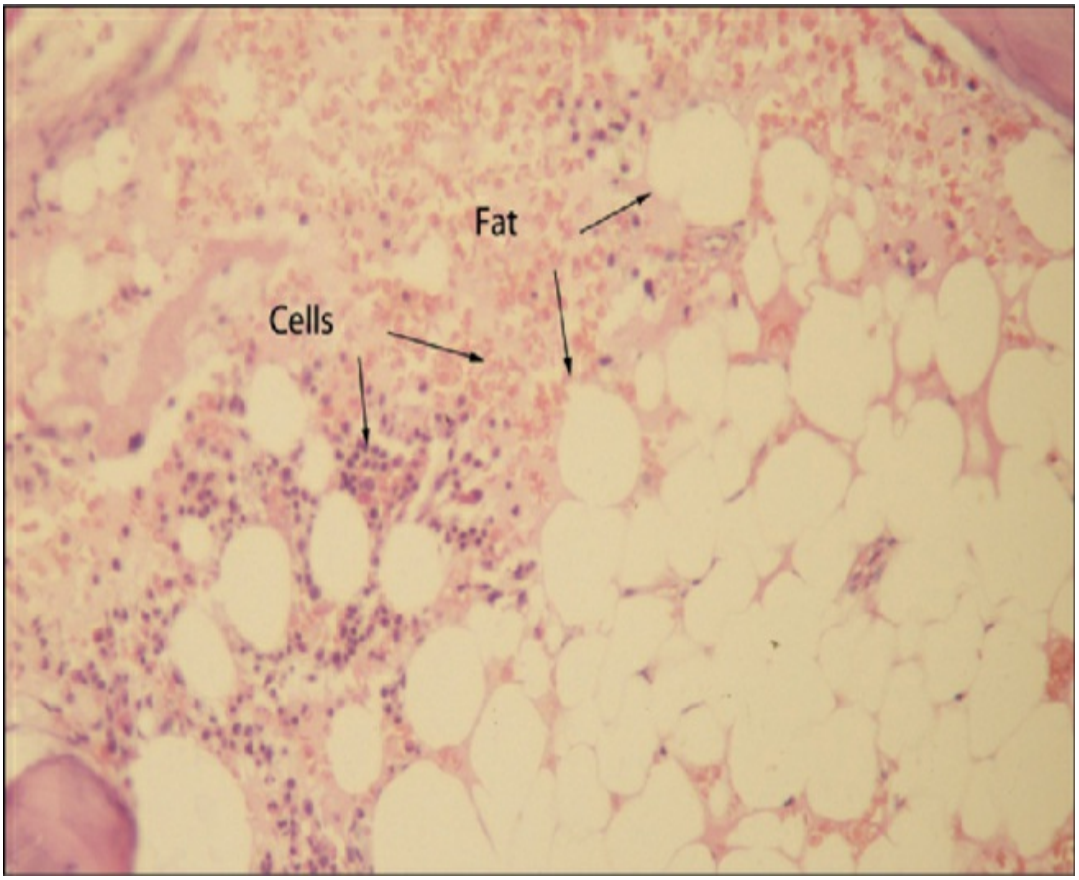


Figure **IB1-5**

Description

<20% cellularity

Clinical Conditions

- Production disorder
- Aplastic anemia
- Anorexia nervosa

Adult Hypercellularity

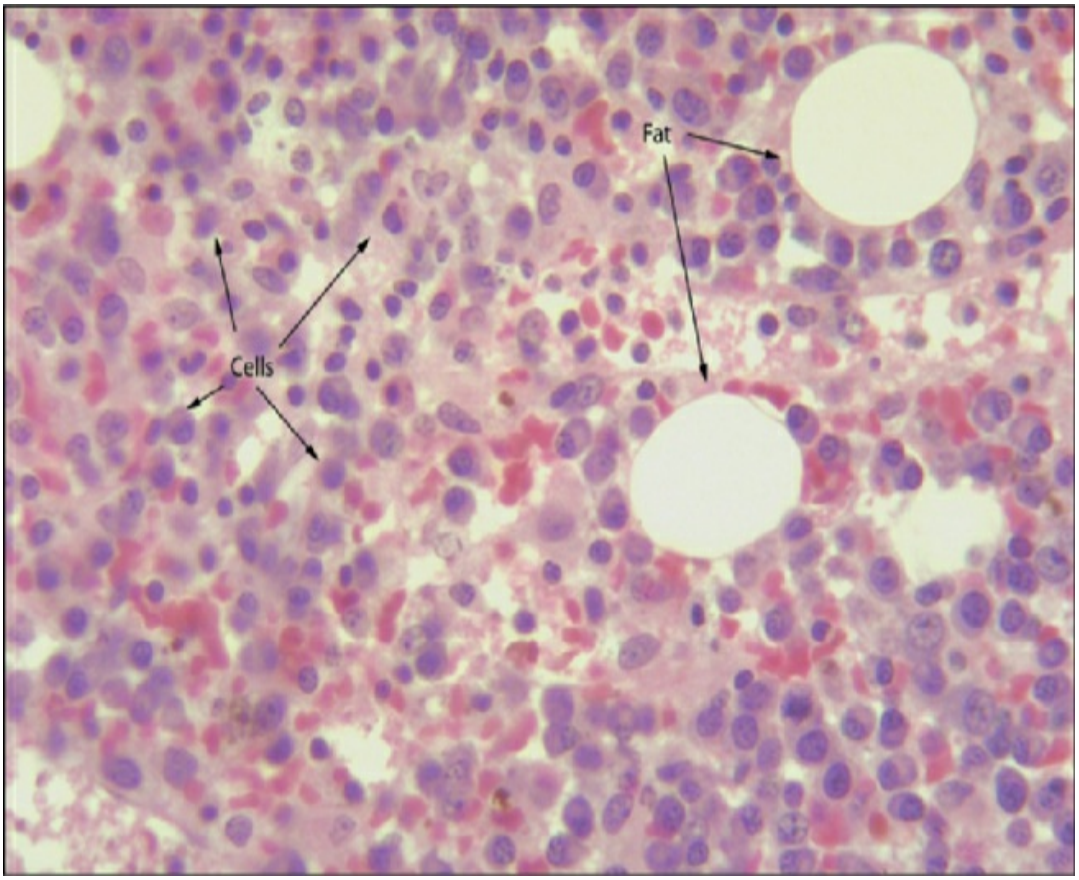


Figure **IB1-6**

Description

>50% cellularity

Clinical Conditions

- Ineffective hematopoiesis; increased peripheral destruction
- Malignancies
- Reactive processes

Erythropoiesis

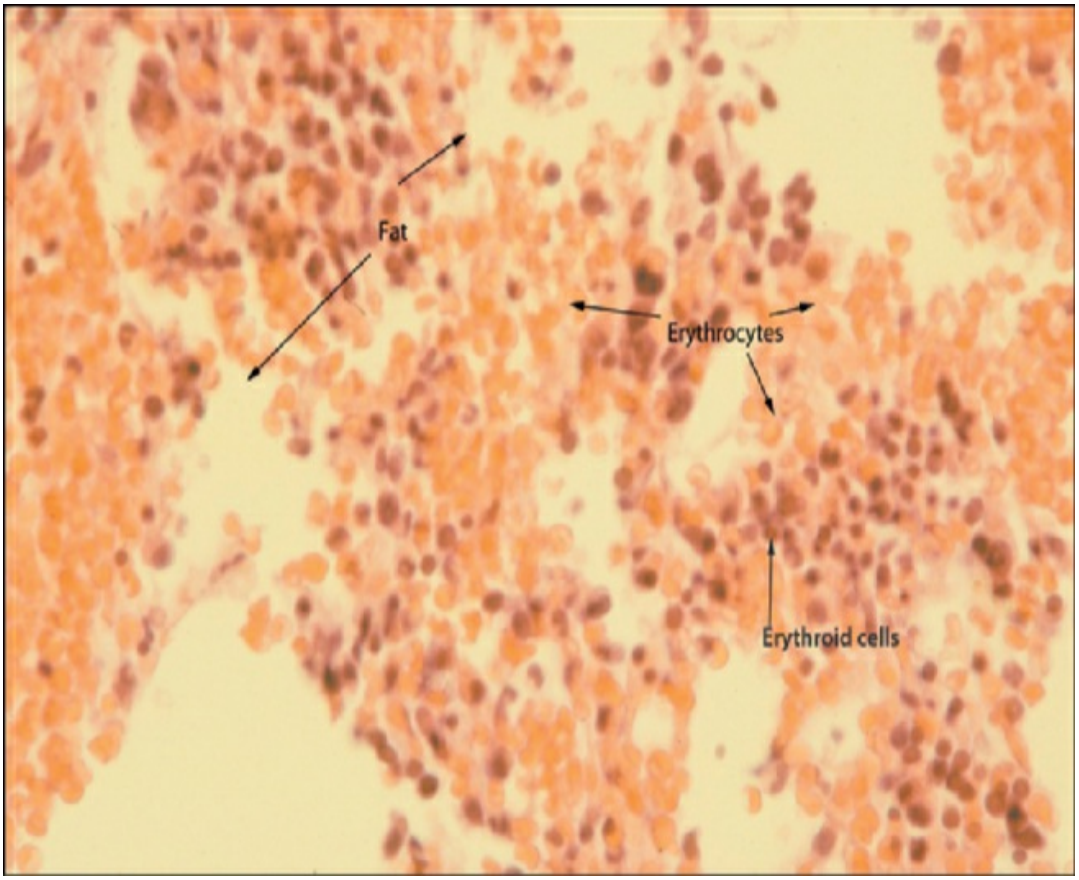


Figure **IB1-7**

Description

>30% of marrow cellularity is erythrocytic

Clinical Conditions

- Decreased M:E ratio—increased production of erythrocytes or ineffective erythropoiesis

Granulopoiesis

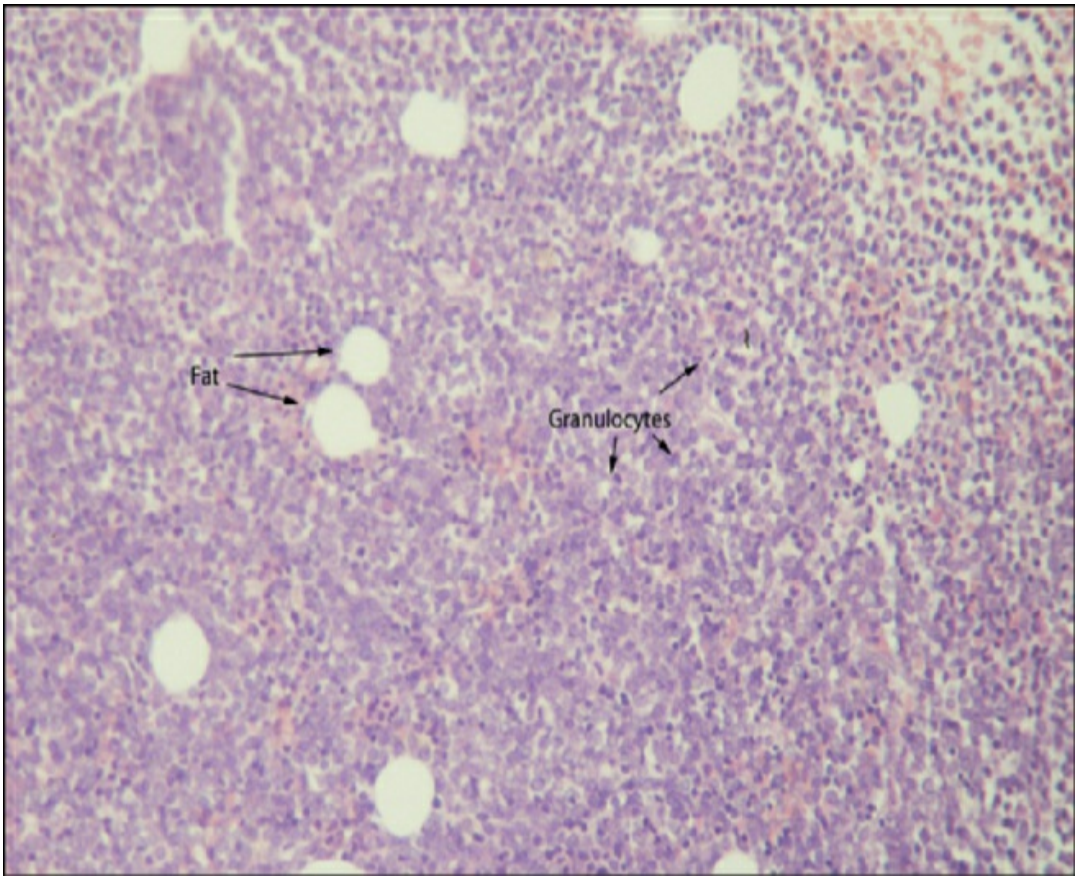


Figure **IB1-8**

Description

>40% of marrow cellularity represents granulopoiesis

Clinical Conditions

- Increased M:E ratio—increased granulocyte production

Lymphopoiesis

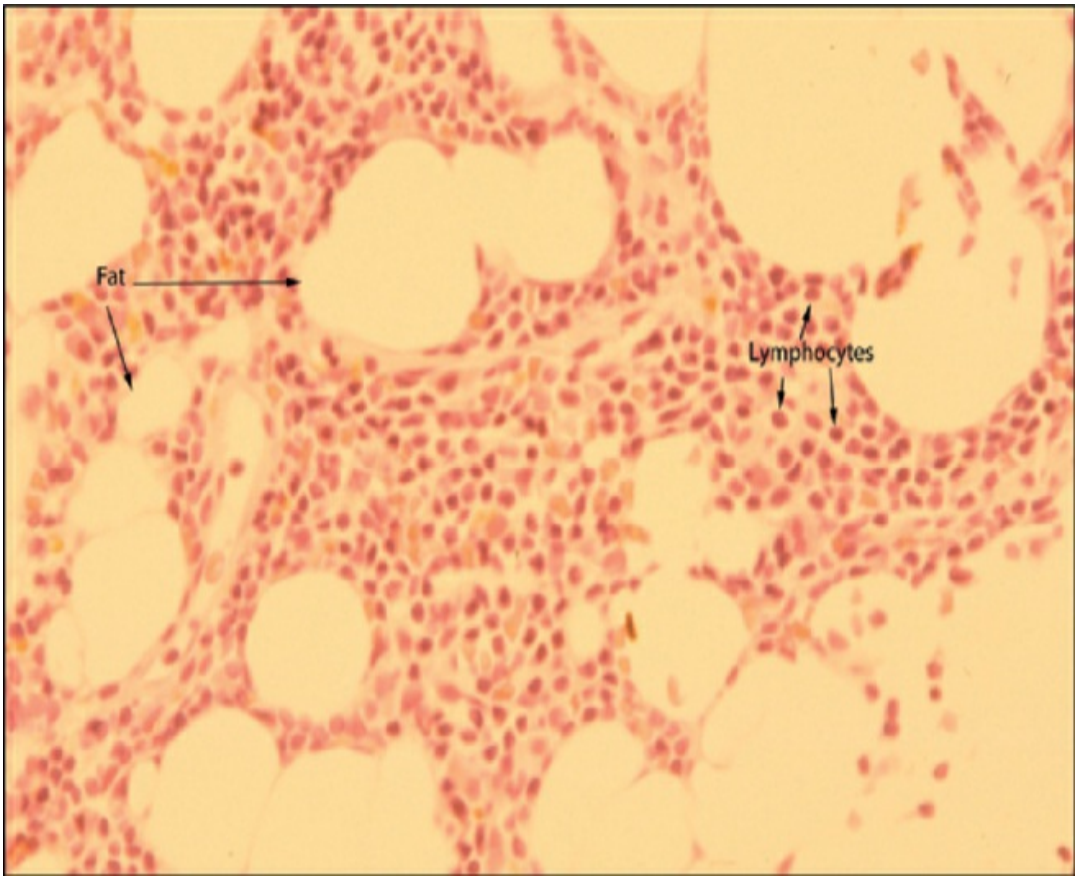


Figure **IB1-9**

Description

>20% of marrow cellularity are lymphocytic cells

Clinical Conditions

- Lymphoproliferative disorders
- Plasmacytomas
- Marrow aplasias
- Chronic lymphocytic leukemia

Megakaryopoiesis

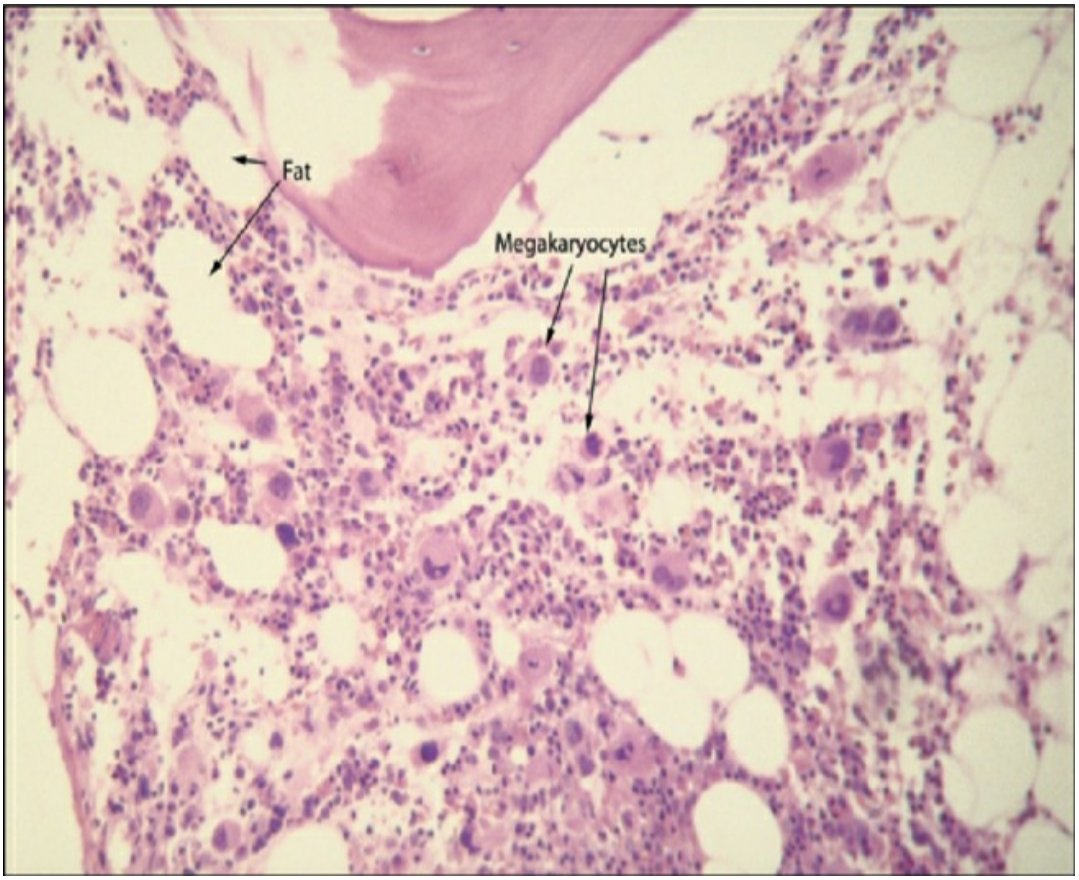


Figure **IB1-10**

Description

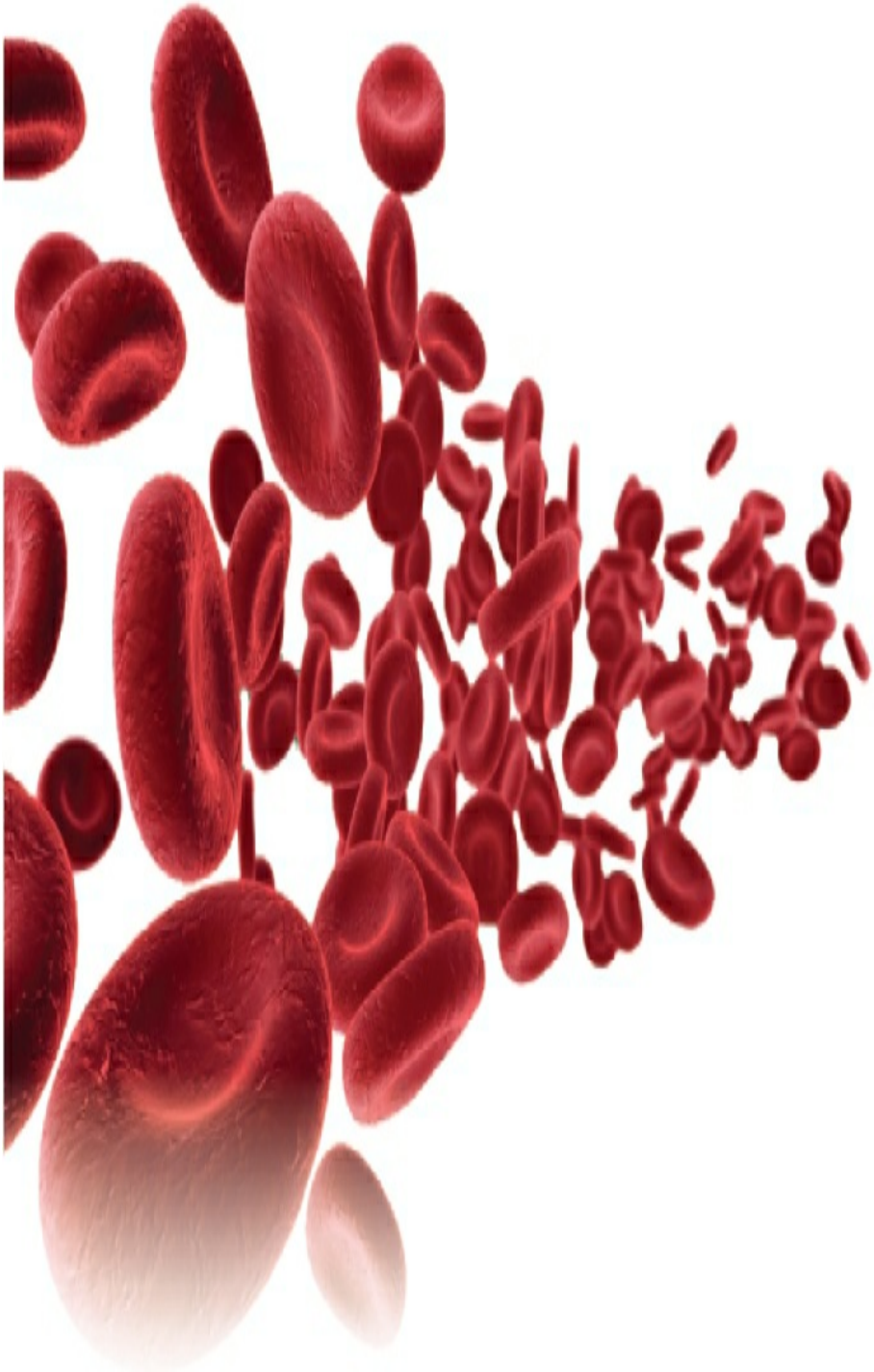
Normally see 1–5 megakaryocytes per 1000 cells

Clinical Conditions

- Idiopathic thrombocytopenic purpura
- Myeloproliferative neoplasms
- Acute megakaryoblastic leukemia (M7) (FAB) (WHO)

CHAPTER 2

Cells of the Reticuloendothelial System



NORMAL CELLS

Macrophage

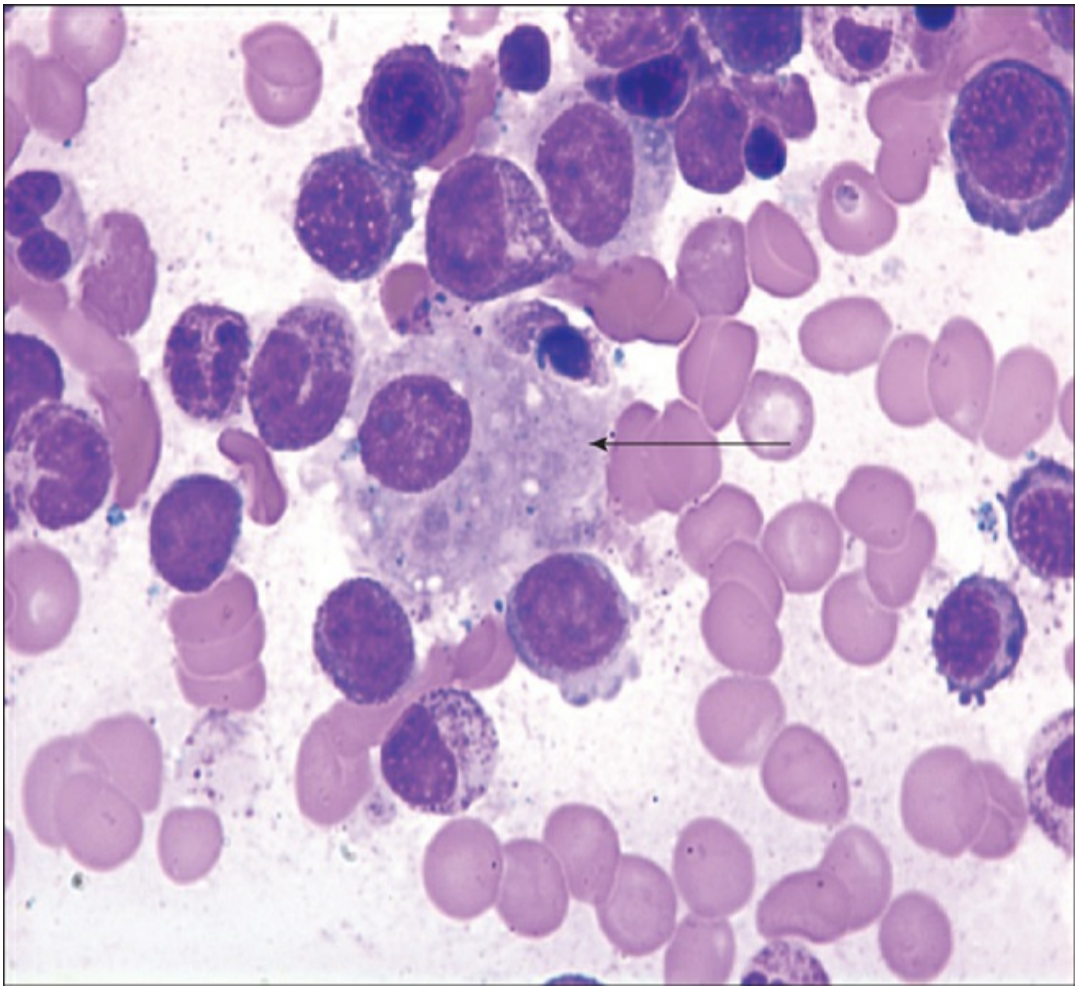


Figure IB2-1

Size: 15–80 µ

Nucleus

Shape: Egg shaped, indented, elongated

N/C Ratio: 2:1–1:1

Color: Purple

Chromatin: Spongy

Nucleoli: None

Cytoplasm

Color: Sky blue

Contents: Coarse, azure granules; vacuoles; many neutral red bodies scattered throughout

Reticulum Cell

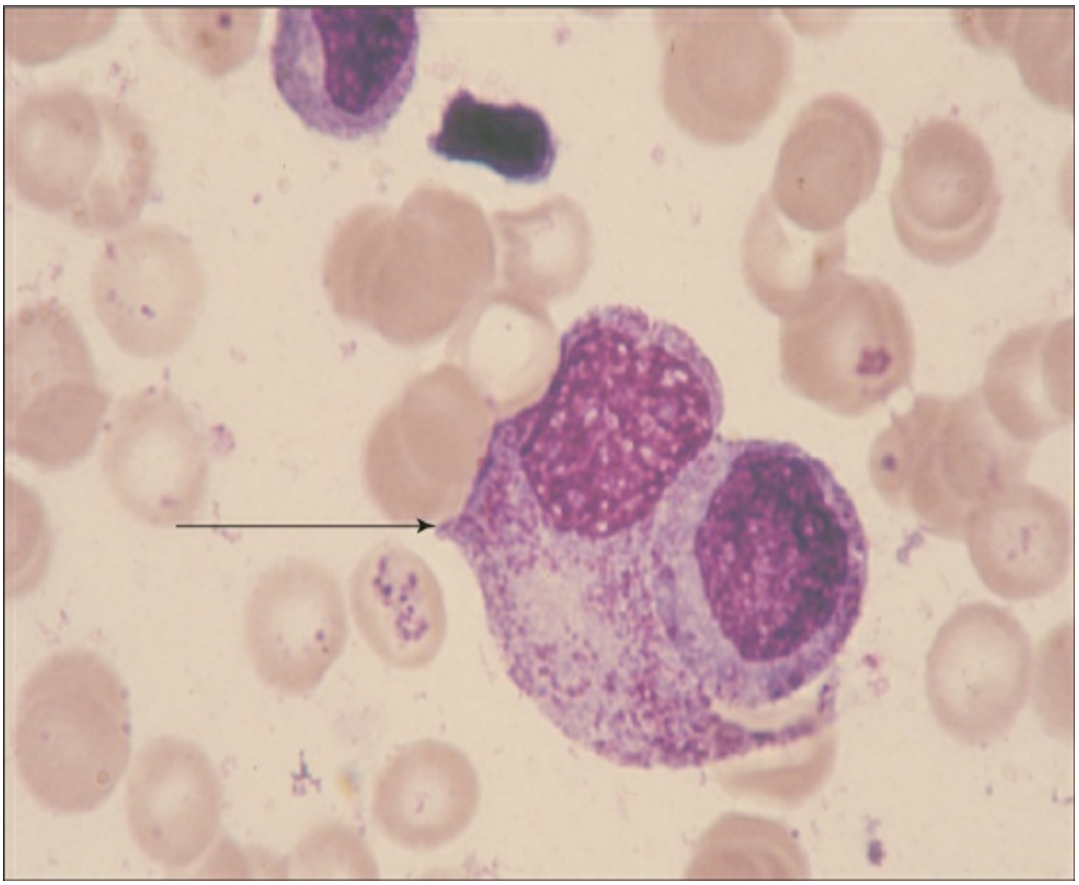


Figure IB2-2

Size: 20–30 µ

Nucleus

Shape: Round to oval

N/C Ratio: 1:1

Color: Purple with reddish hue

Chromatin: Fine, loosely bound but with areas of parachromatin

Nucleoli: 1 or more

Cytoplasm

Cytoplasm

Irregular outline

Color: Pale, blue, often retracted or folded caused by smearing technique

Contents: Reticulin fibers that cause an azurophilic appearance; may contain phagocytized materials

ABNORMAL CELLS

Gaucher Cell

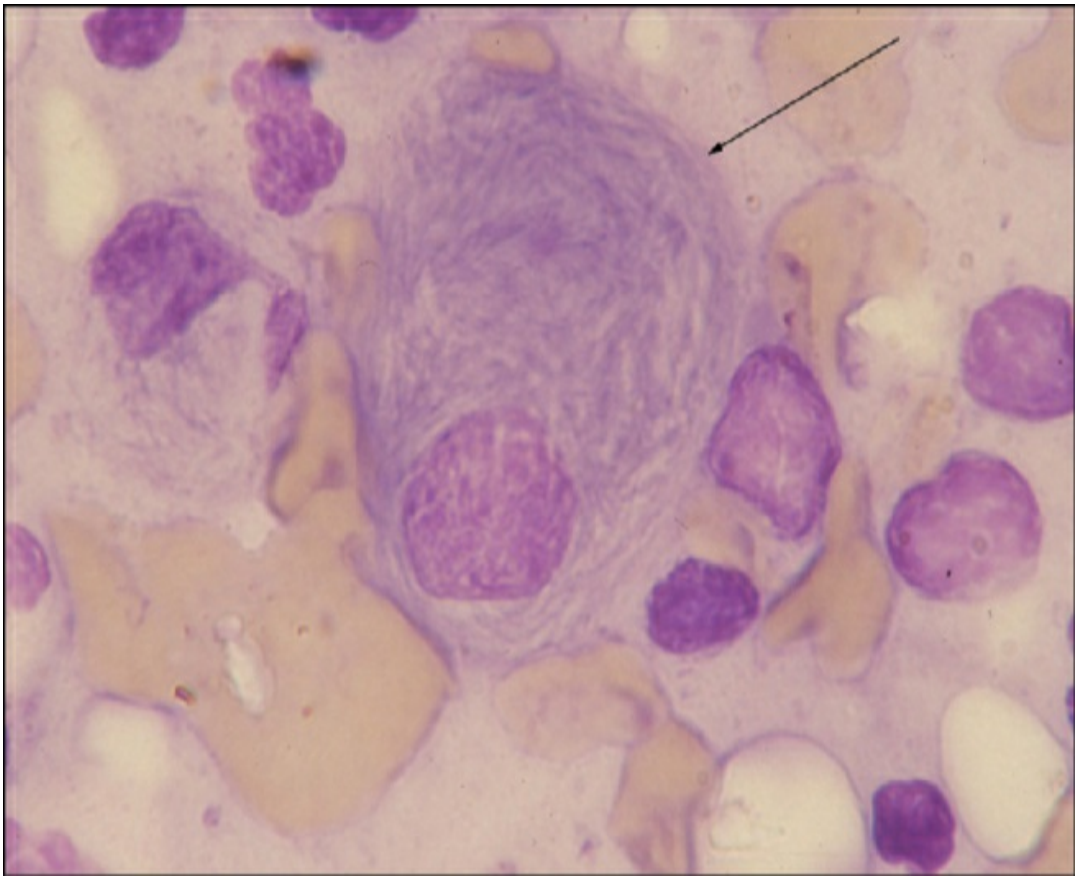


Figure IB2-3

Cell Type

Macrophage

Size: 20–80 µ

Description

A pale staining cell; the cytoplasm is filled with a fibrillar lipid, which gives the appearance of crumpled tissue paper or a wrinkled look; the nucleus is small, round, and eccentrically placed

Clinical Conditions

- Gaucher disease

- Thalassemia (pseudo-Gaucher cells)
- Chronic myelocytic leukemia (pseudo-Gaucher cells)

Niemann-Pick Cell

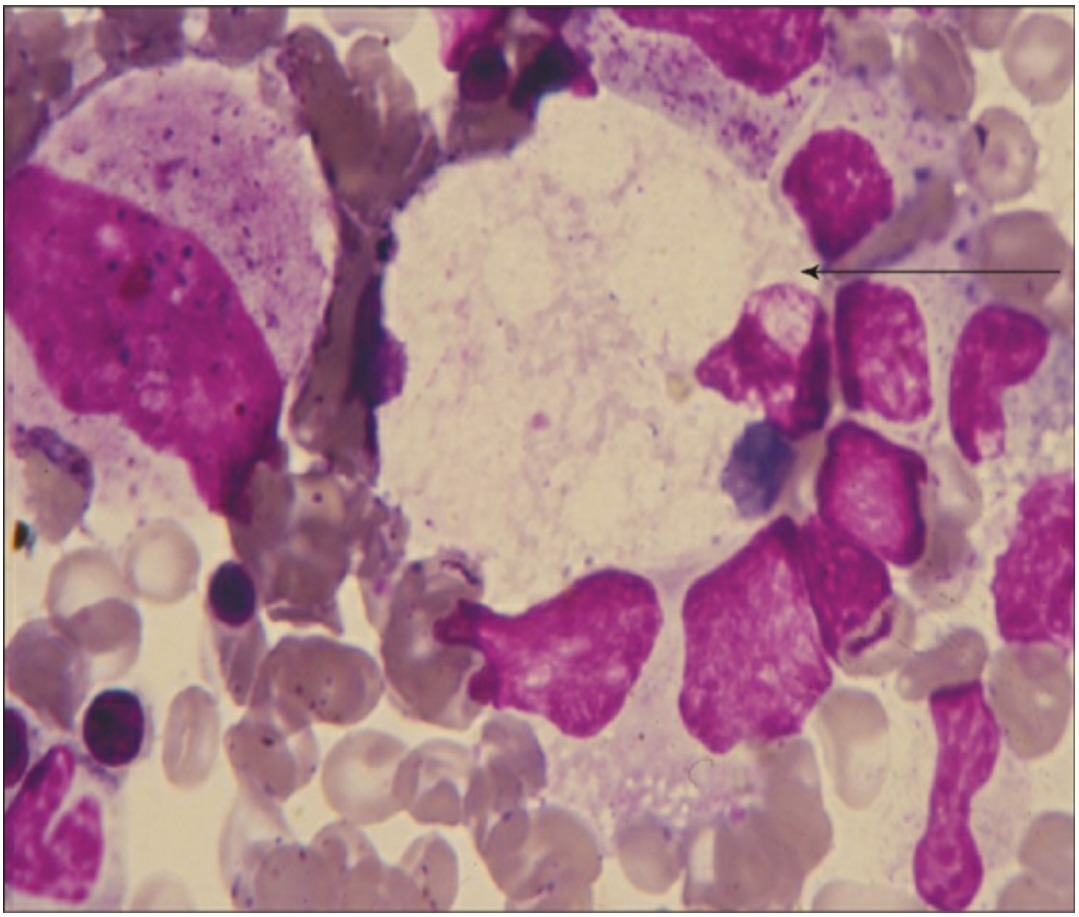


Figure IB2-4

Cell Type

Macrophage

Size: 20–90 μ

Cell Description

Pale staining; cytoplasm contains droplets of sphingomyelin, giving it a globular appearance; the nucleus is small, round, and eccentrically placed

Clinical Condition

- Niemann-Pick disease

Sea-Blue Histiocyte

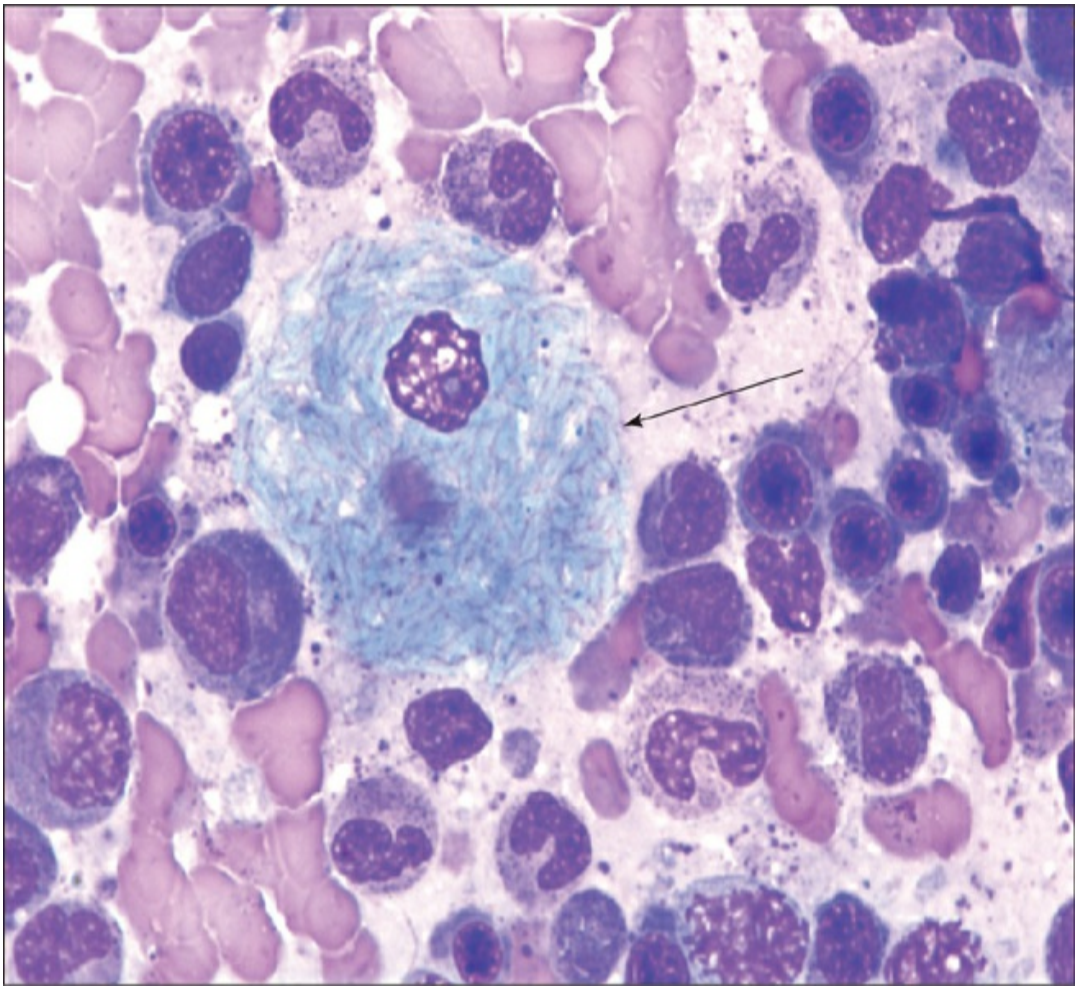


Figure IB2-5

Cell Type

Histiocyte

Size: 20–60 µ

Description

Cell containing granules that stain a sea-blue or blue-green; nucleus is small, round, and eccentric with block chromatin

Clinical Conditions

- Sea-blue histiocytosis
- Pseudo-sea-blue histiocytes are seen in the following:
  - Thalassemia
  - Chronic myelocytic leukemia
  - Polycythemia vera
  - Sickle cell anemia
  - Sarcoidosis
  - Chronic granulomatous disease

CHAPTER 3

Nonhematopoietic Cells

NORMAL CELLS

Osteoblast

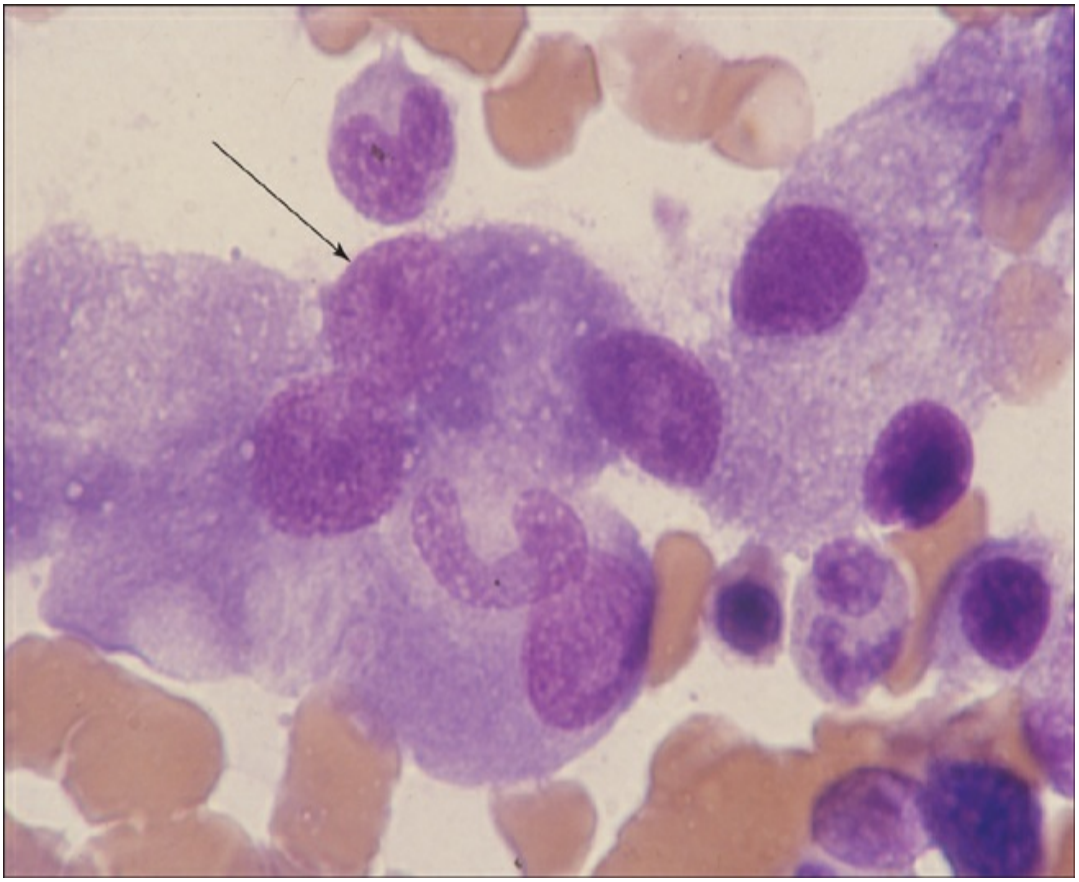


Figure IB3-1

Size: Frequently Found in Clumps but Each Individual Cell Ranges From 25 to 50 µ

Nucleus

Shape: Oval or round; eccentric

N/C Ratio: 1:3–1:4

Color: Purple

Chromatin: Finely granular with clumps; some areas of parachromatin

Nucleoli: 1–3 present, small, light blue

Cytoplasm

Color: Pale blue to dark blue with blurred outlines

Contents: Round, pink-gray areas (archoplasm)

Osteoclast

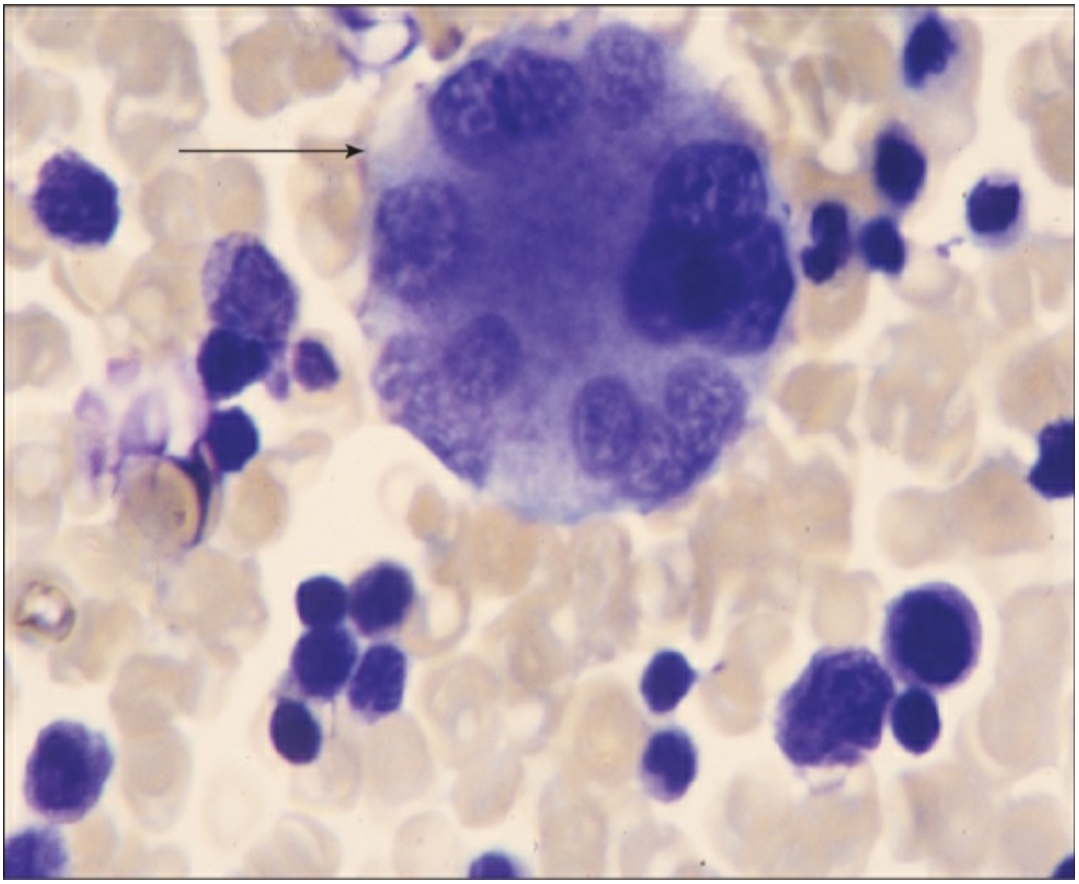


Figure IB3-2

Size: Usually >100 µ

Nucleus

Polyploid and scattered throughout cell; not interconnected

Shape: Round

N/C Ratio: 4:1–2:1–1:1

Color: Purple

Chromatin: Dense

Nucleoli: Usually 1–2 present in each nucleus

Cytoplasm

Color: Light blue to pink, giving a cloudy appearance

Contents: Coarse granules

Section C
Cytochemistry

CHAPTER 1

Cytochemical Stains

ACID PHOSPHATASE REACTION

With Tartrate Inhibition (TRAP)

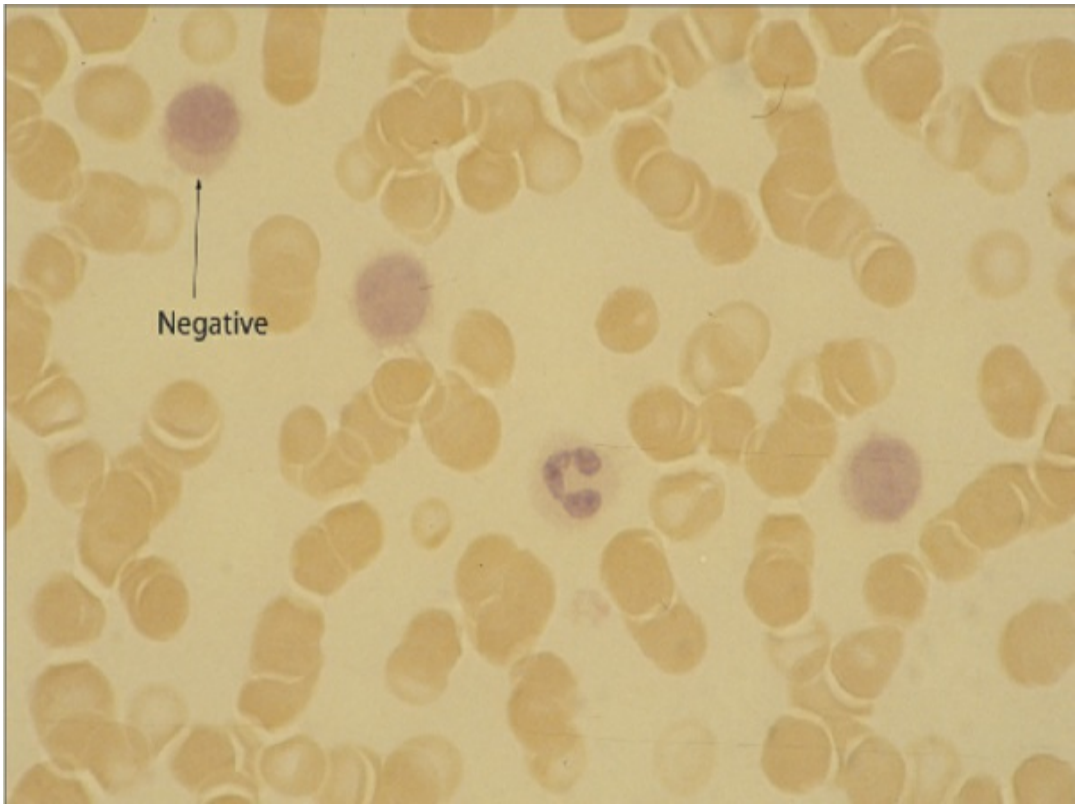


Figure IC1-1

Negative

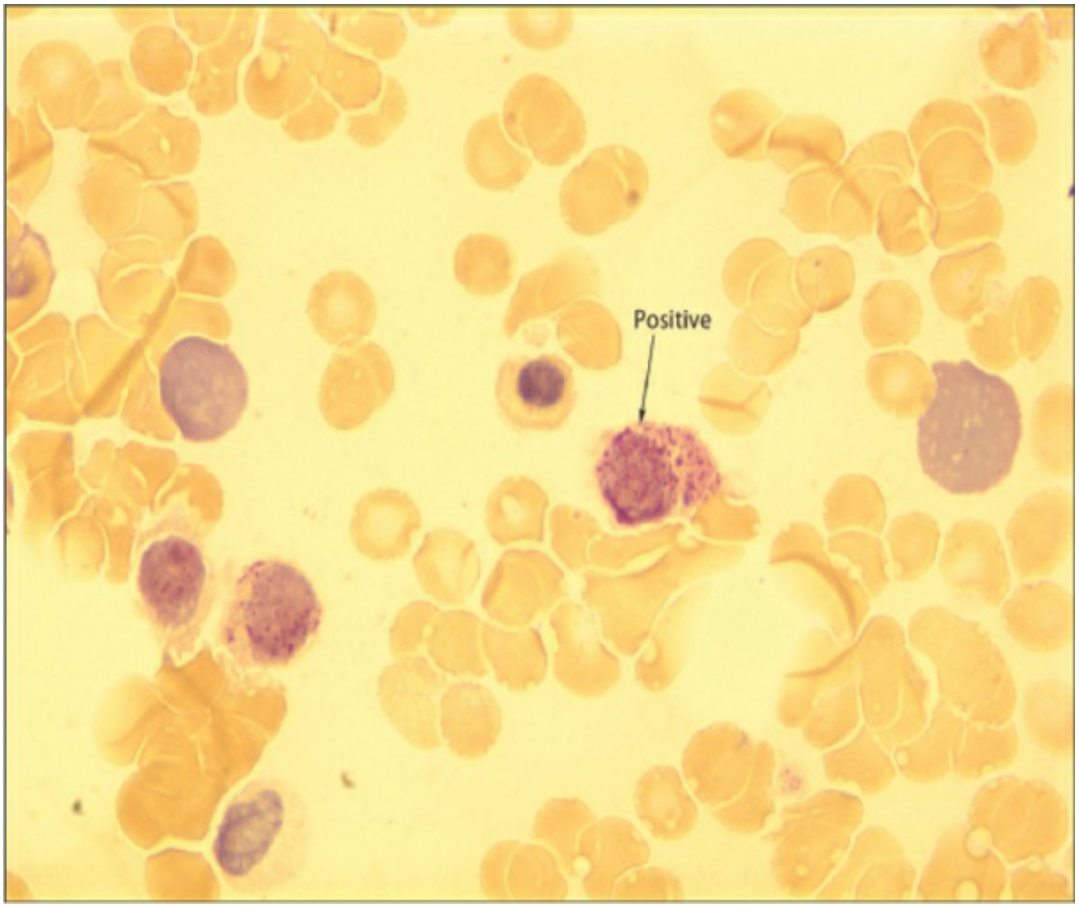


Figure **IC1-2**

Positive

Cell Type

Hairy cell, histiocyte, activated lymphocyte, and activated macrophage

Description

Acid phosphatase (isoenzyme 5) is resistant to tartrate

Hairy cells and histiocytes contain this acid phosphatase, are resistant to inhibition, and will demonstrate positivity (color is dependent on couplers used)

Clinical Condition

- Hairy cell leukemia

ACID PHOSPHATASE REACTION

Without Tartrate Inhibition

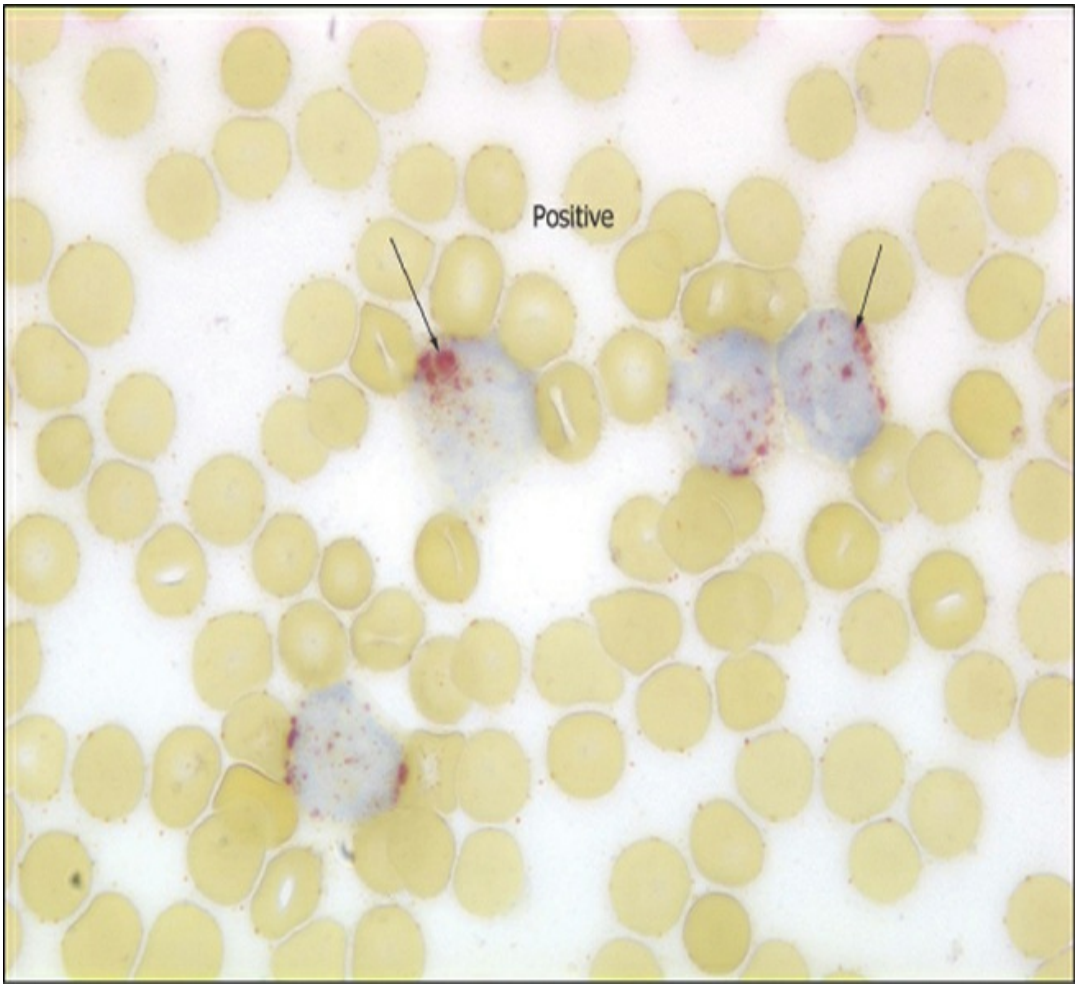


Figure IC1-3

Positive

Cell Type

Most nucleated cells of the hematopoietic system and platelets

Description

Positivity is indicated by a diffuse granular red reaction product

The red product will disappear or contain only a small

amount of reactivity after tartrate is added to the reaction

Focal positivity may be found in blasts of T-cell ALL

Clinical Conditions

- Some T-cell precursor lymphoblastic leukemia
- T-cell chronic lymphocytic leukemia
- T-cell prolymphocytic leukemia
- Sézary syndrome

NONSPECIFIC ESTERASE REACTION

With Fluoride Inhibition

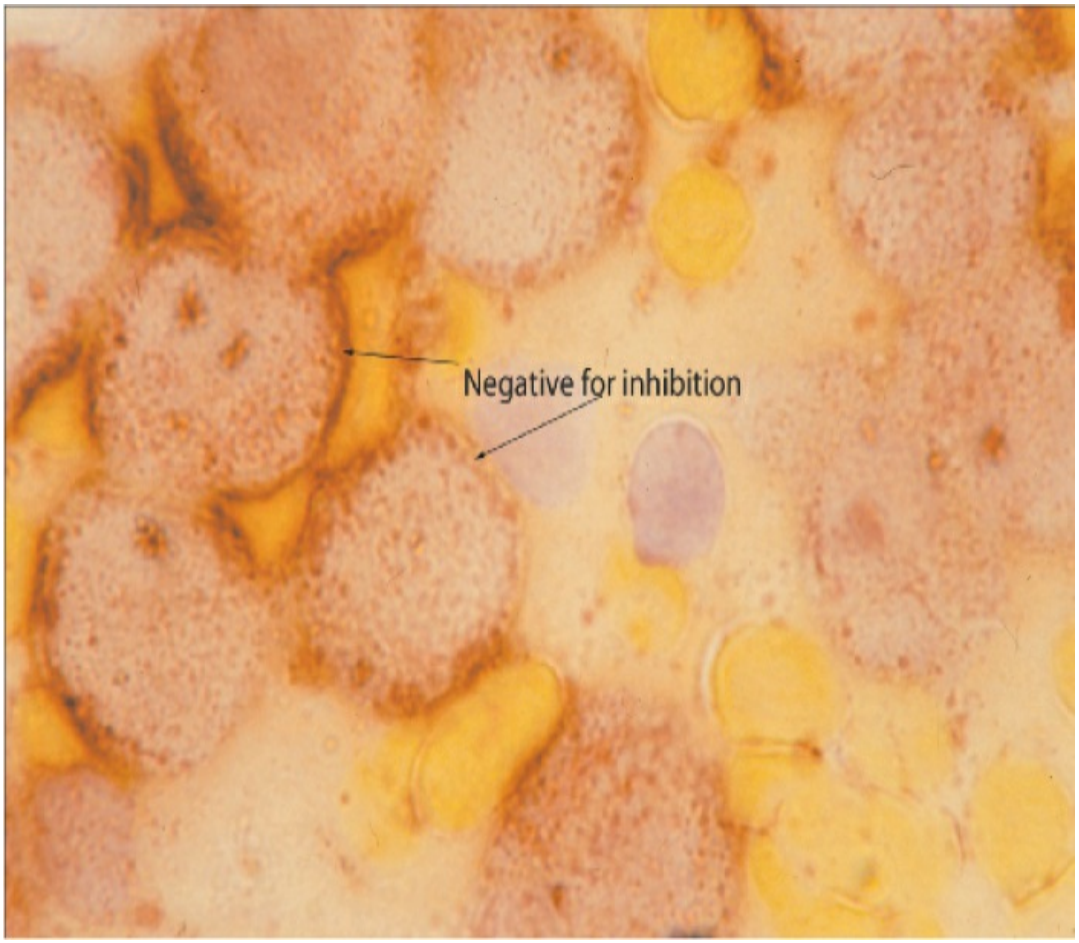


Figure IC1-4

Negative for inhibition.

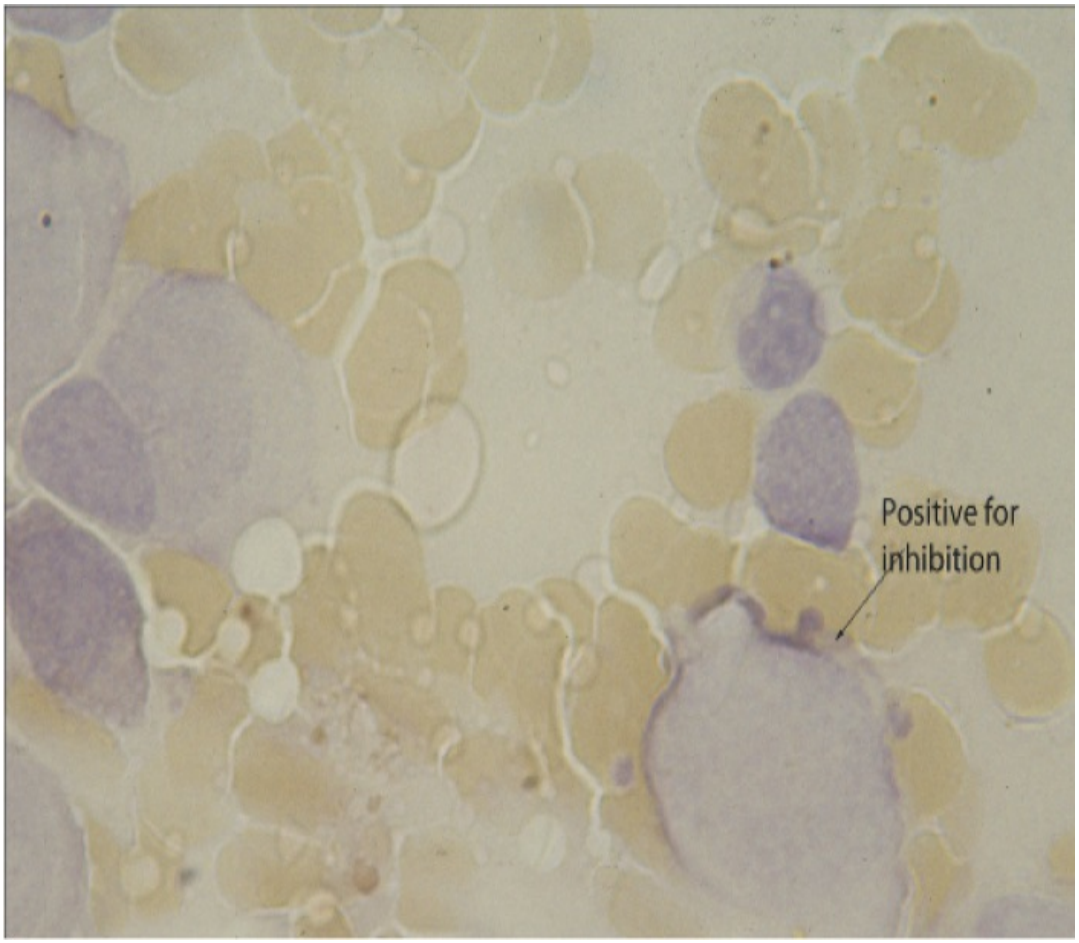


Figure **IC1-5**

Positive for inhibition.

Cell Type

Monocytic line

Description

Megakaryocytes, histiocytes, macrophages demonstrate positivity with a brick-red product

Lymphocytes may have a punctate red product

Monocytes are sensitive to fluoride inhibition and will not show positivity

1+ positivity in granulocytic series

Clinical Conditions

- Acute myelomonocytic (M4) (FAB) (WHO) and

monocytic (M5b) (FAB) (WHO) leukemias are inhibited by fluoride

- Acute lymphocytic leukemia or leukemias of granulocytic origins are not inhibited

NONSPECIFIC ESTERASE REACTION

Without Fluoride Inhibition

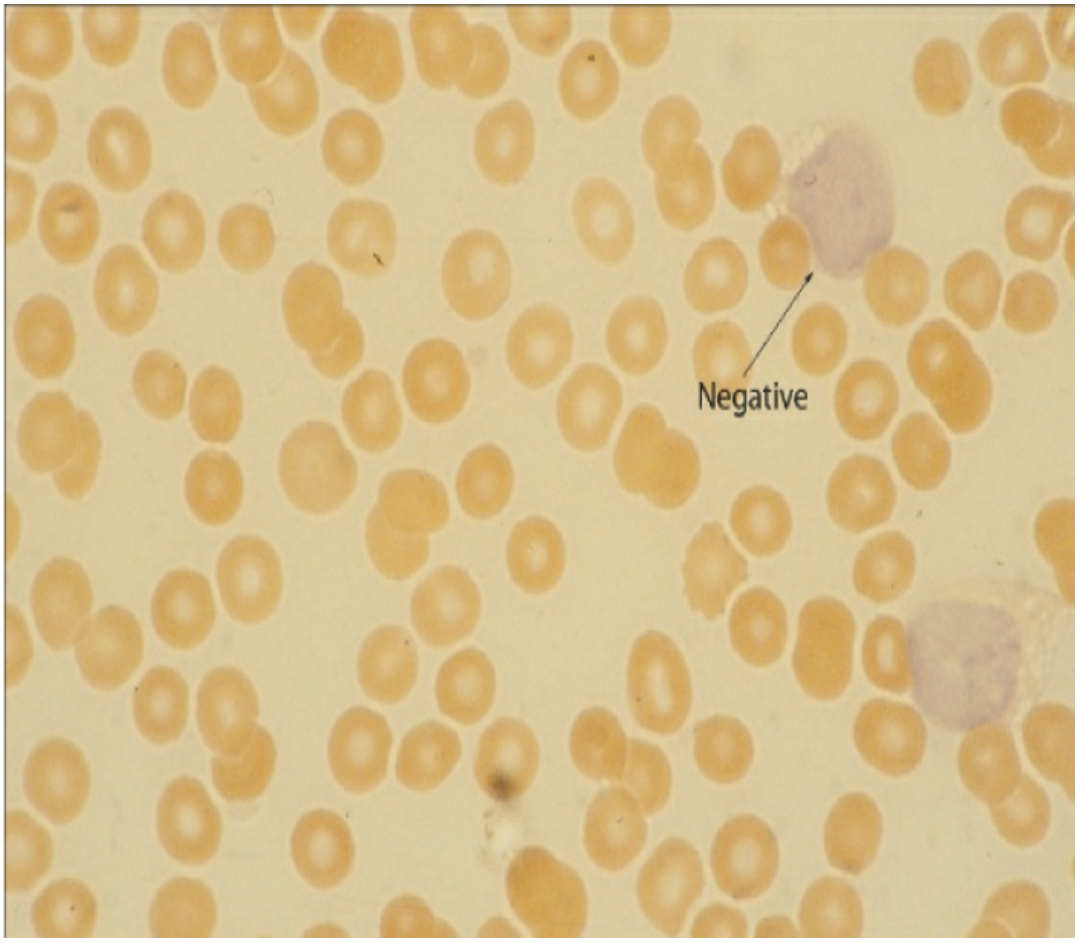


Figure IC1-6

Positive

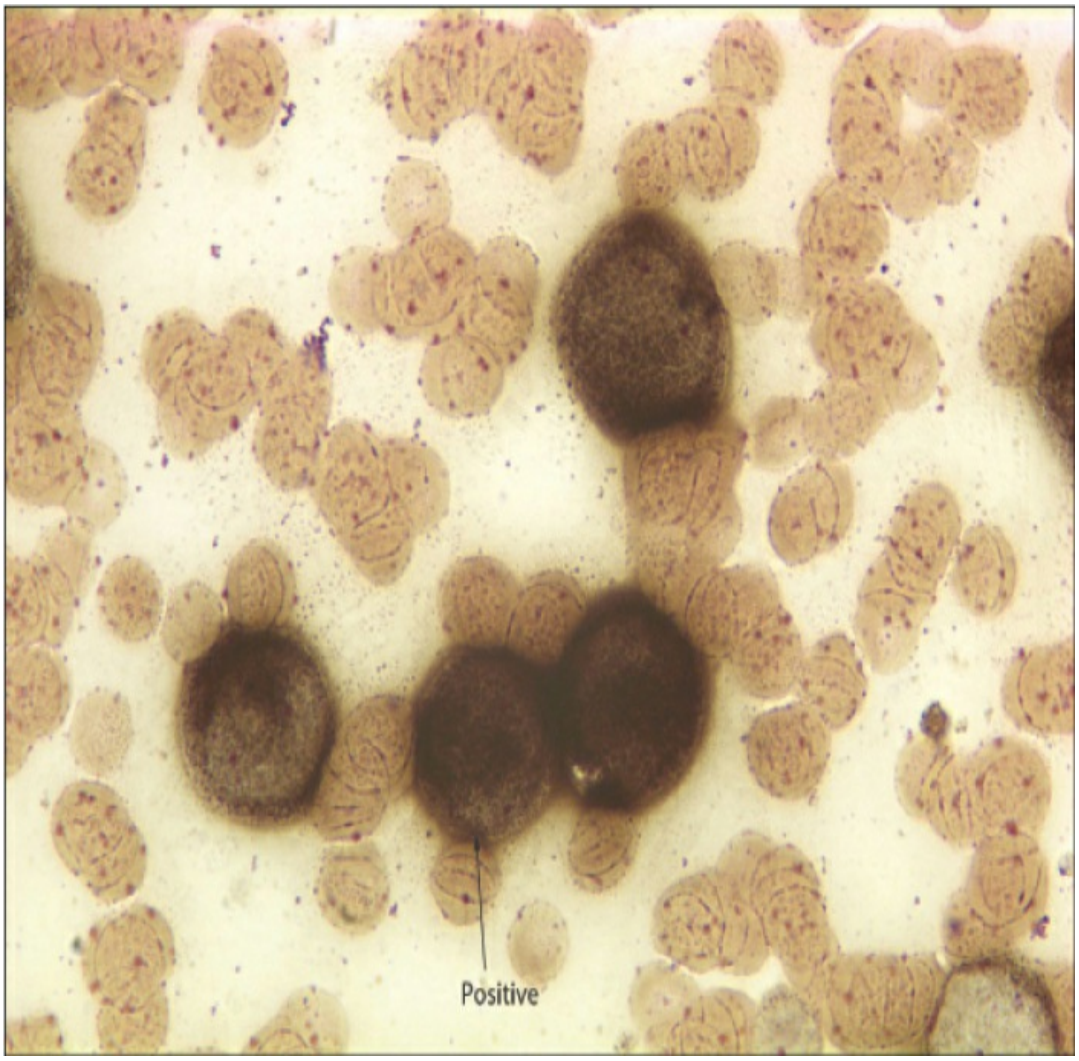


Figure **IC1-7**

Negative

Cell Type

Monocytic line

Description

Megakaryocytes, histiocytes, macrophages demonstrate positivity

Lymphocytes may have a punctate positivity or foci of positivity for T cells

Monocytes are sensitive to fluoride inhibition and will not show positivity

Clinical Conditions

- Acute myelomonocytic (M4) (FAB) (WHO) and monocytic (M5b) (FAB) (WHO) leukemias are inhibited by fluoride
- Acute lymphocytic leukemia or leukemias of granulocytic origins are not inhibited

SPECIFIC ESTERASE REACTION

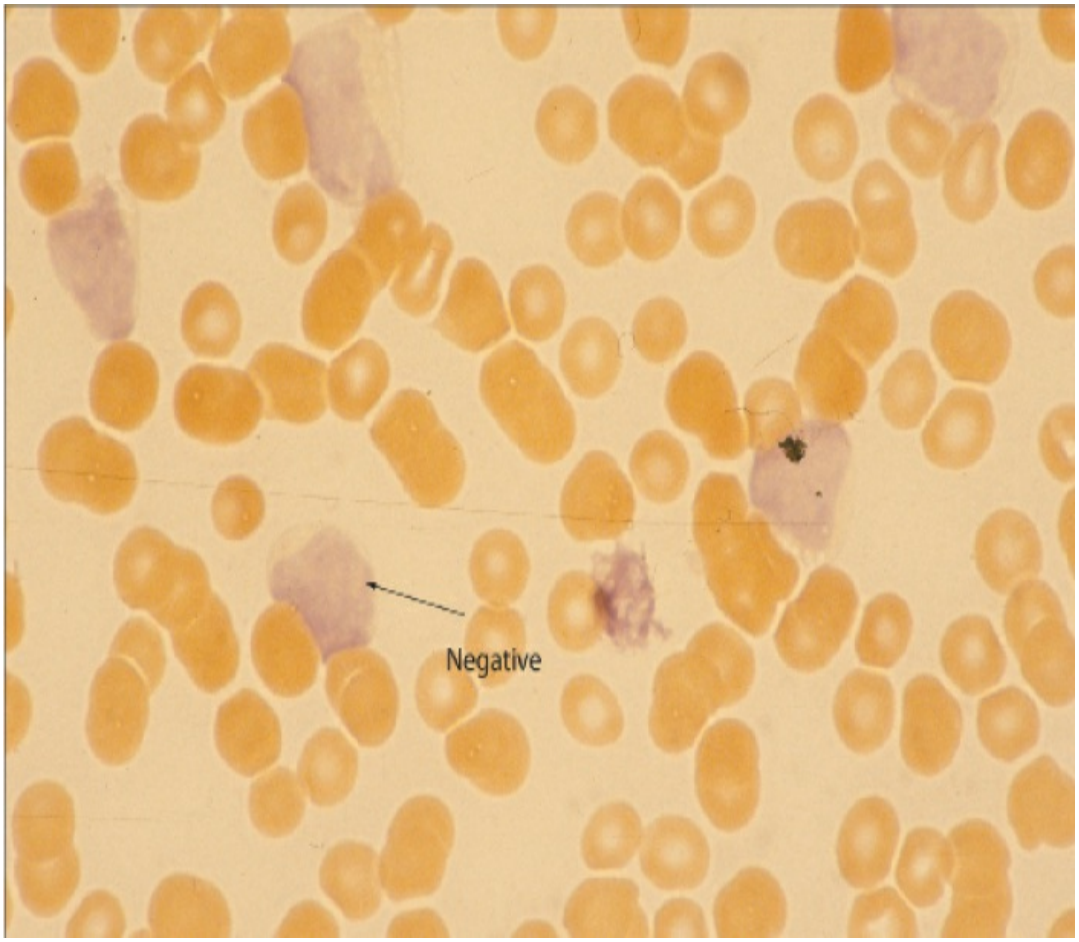


Figure IC1-8

Positive

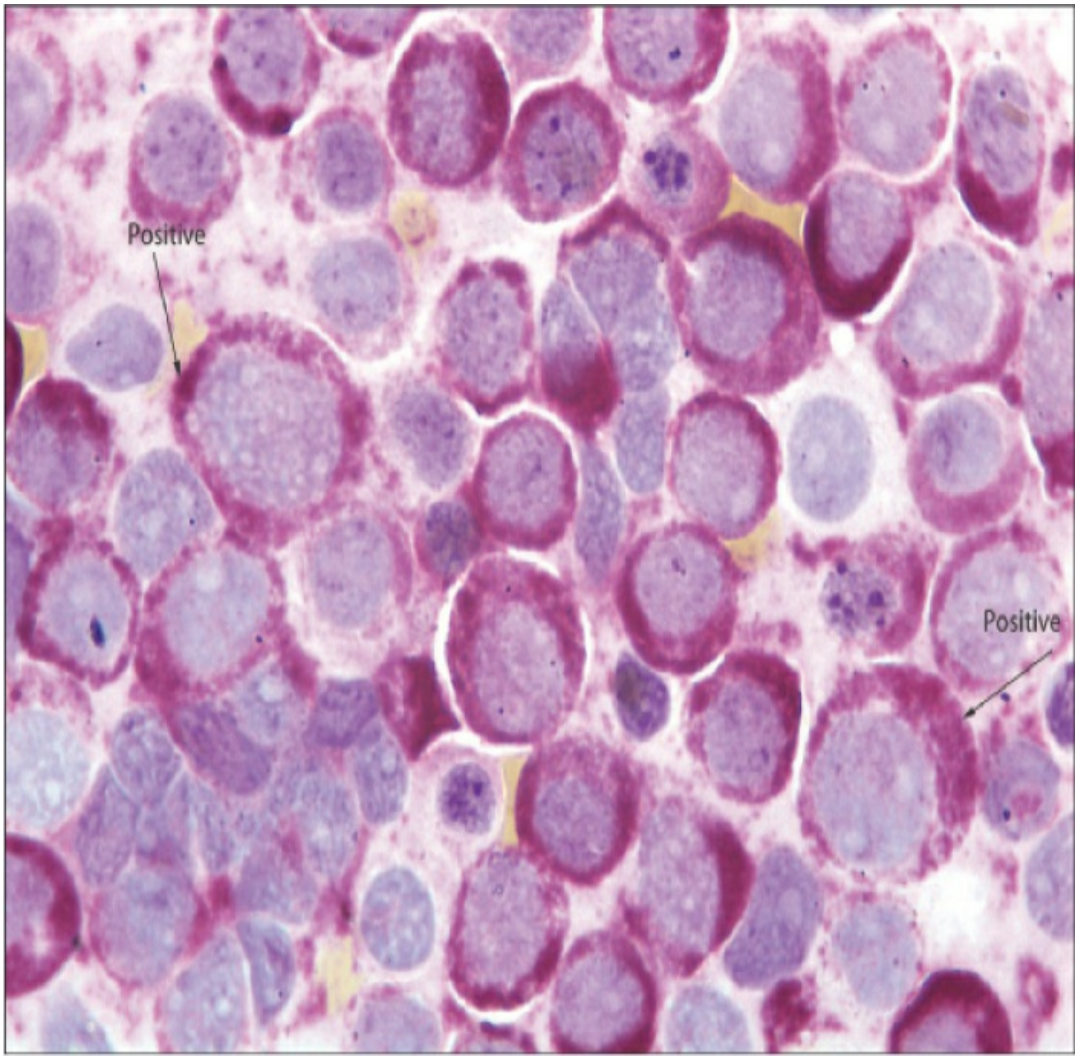


Figure **IC1-9**

Negative

Cell Type

Some myeloblasts, promyelocytes, myelocytes, metamyelocytes, bands, segmented neutrophils, and abnormal eosinophils

Description

Esterases are enzymes that are capable of hydrolyzing the aliphatic and aromatic ester bonds of the substrate naphthol AS-D chloroacetate

Produces a positive reaction indicated by red to magenta

color

Clinical Conditions

- Differentiates granulocytes from lymphocytes and monocytes
- Acute myelocytic leukemia without maturation (M1) (FAB) (WHO)
- Acute myelocytic leukemia with maturation (M2) (FAB) (WHO)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Acute myelomonocytic leukemia with abnormal bone marrow eosinophils
- AML with recurrent genetic abnormalities (WHO)
    - AML with t(8;21)
    - AML with t(15;17)
    - AML with inv16 or t(16;16)

COMBINED ESTERASE REACTION

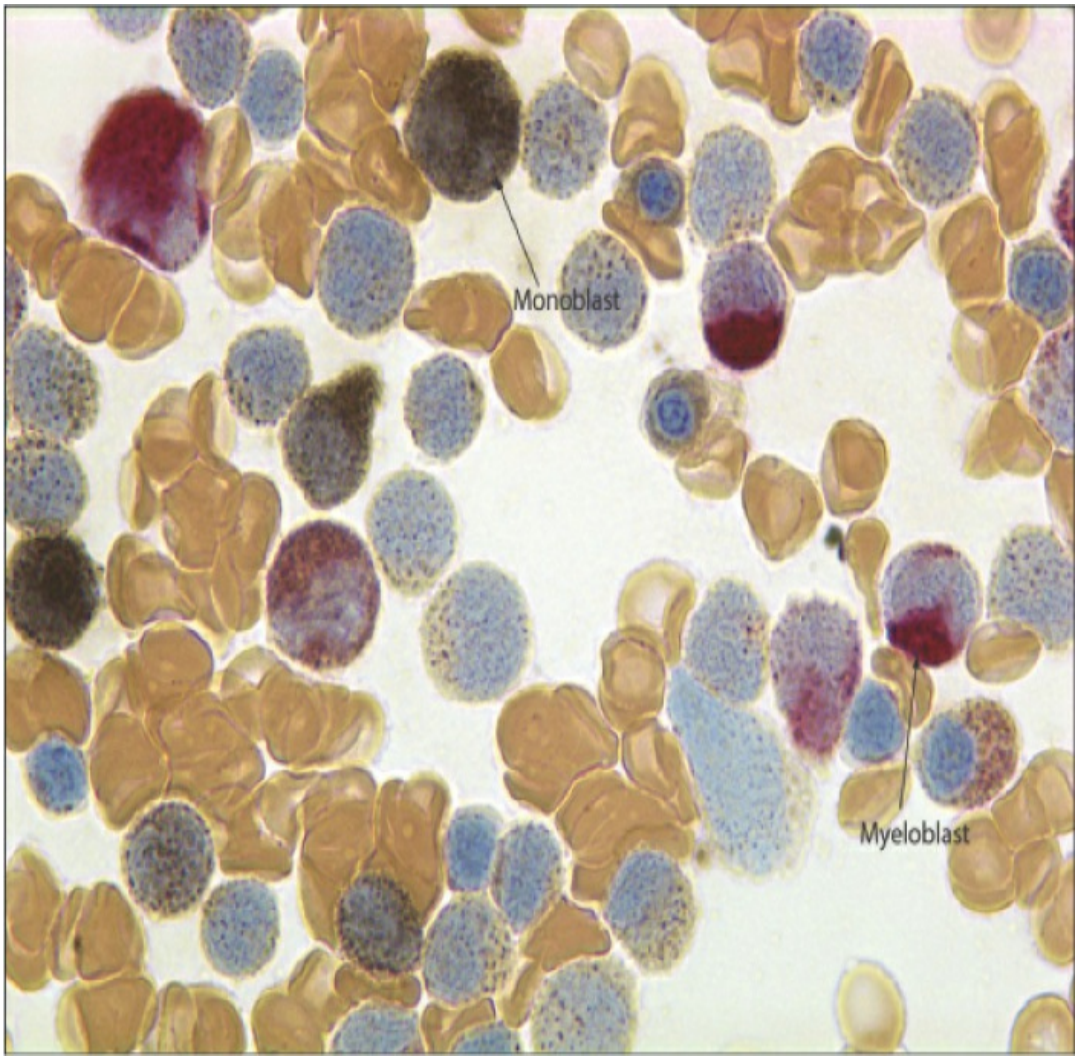


Figure **IC1-10**

Positive replacement.

Cell Type

Differentiation of granulocytic and monocytic series

Description

Both alpha-naphthyl acetate (nonspecific) and naphthyl chloroacetate (specific) are used as substrates

Monocytic series demonstrates positivity with the nonspecific esterase

Granulocytic series demonstrates a positive reaction with

the specific esterase (color depends on couplers used)

Clinical Conditions

- Acute myelomonocytic leukemia (M4) (FAB) (WHO)—demonstrates the coexpression of neutrophilic and monocytic enzymes
- Acute monoblastic leukemia (M5a) (FAB) (WHO)
- Acute monocytic leukemia (M5b) (FAB) (WHO)

IRON STAIN—PRUSSIAN BLUE REACTION

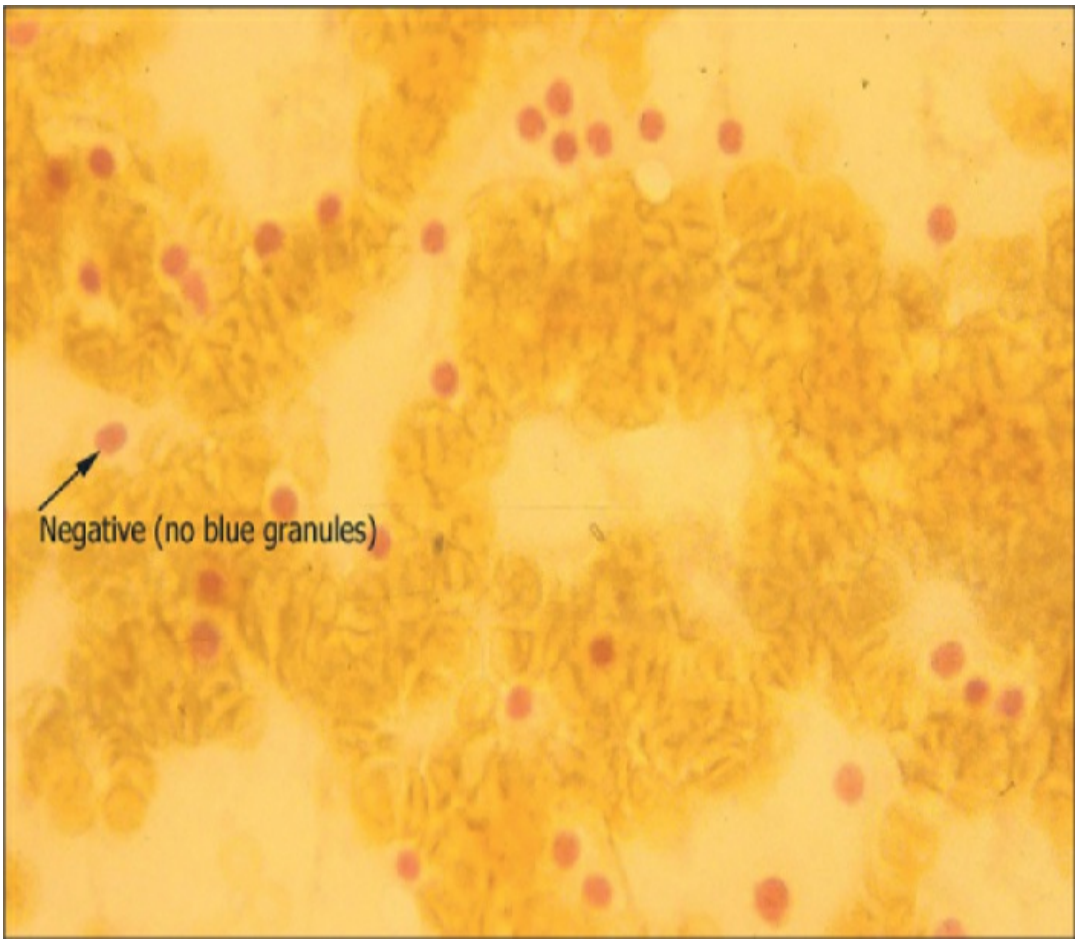


Figure IC1-11

Positive

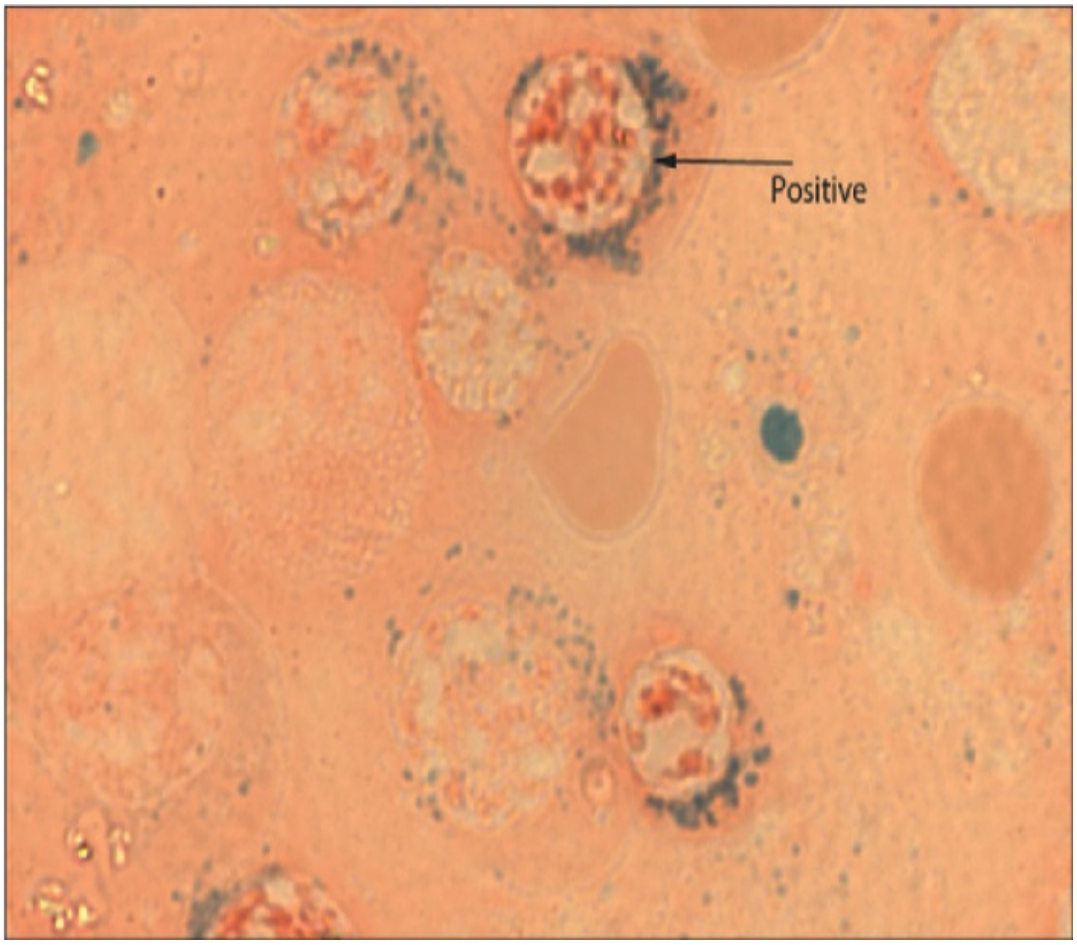


Figure **IC1-12**

Negative

Cell Type

Erythroblast, erythrocyte, macrophage, histiocyte

Description

Iron in the form of hemosiderin is normally present in developing normoblasts and in the reticuloendothelial cells of the bone marrow. A Prussian blue color is produced when ferric iron of hemosiderin reacts with an acid ferrocyanide solution to form ferric ferrocyanide.

Positivity or the presence of iron is indicated by the presence of blue to blue-green granules

May be used to determine the presence of iron stores in the marrow

May be used to demonstrate increased numbers of sideroblasts or the presence of pathologic ferric iron located in mitochondria of the erythroblast (ring sideroblast)

Clinical Conditions

- Myelodysplastic syndromes
- Acute erythroleukemia (M6) (FAB)
- Thalassemias
- Intramacrophage iron is decreased in iron deficiency and increased in hemochromatosis and anemia of chronic diseases

ACID ELUTION (KLEIHAUER-BETKE STAIN)

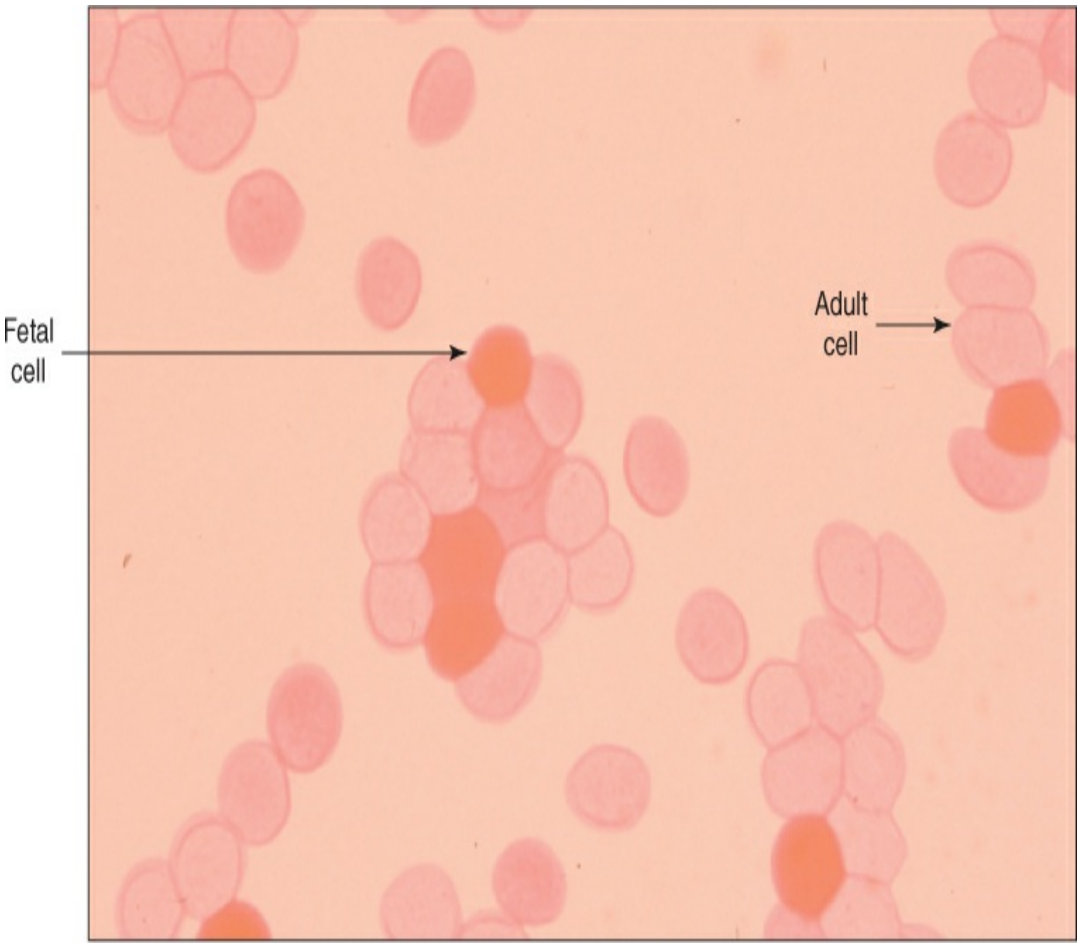


Figure IC1-13

Cell Type

Red blood cell

Description

Cells containing hemoglobin F will appear pink to red

Cells containing no hemoglobin F will only have their outer membrane visible (ghost cells)

Clinical Conditions

- Hereditary persistence of fetal hemoglobin
- Myelodysplastic syndromes

- Some leukemias

LEUKOCYTE ALKALINE PHOSPHATASE STAIN

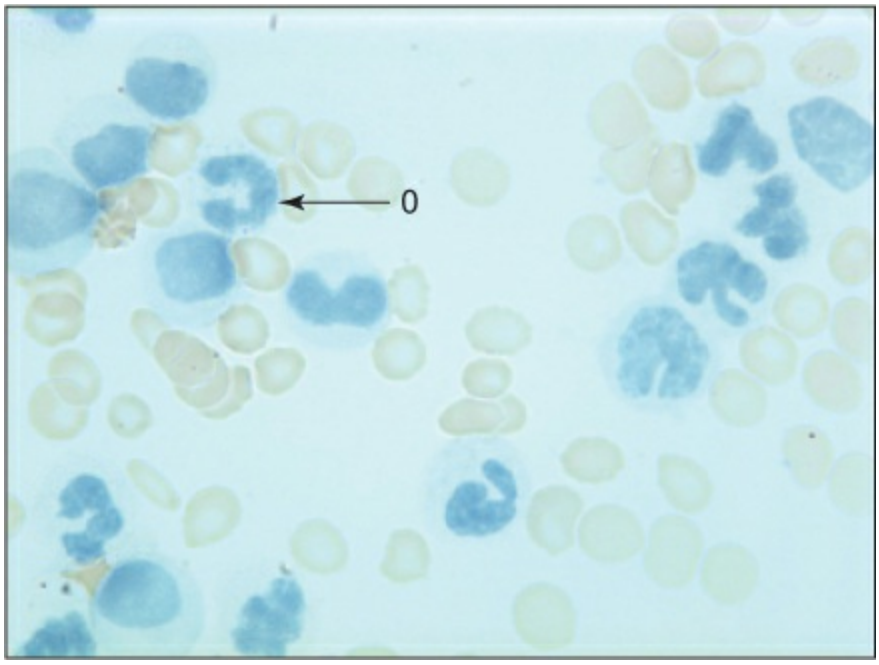


Figure IC1-14

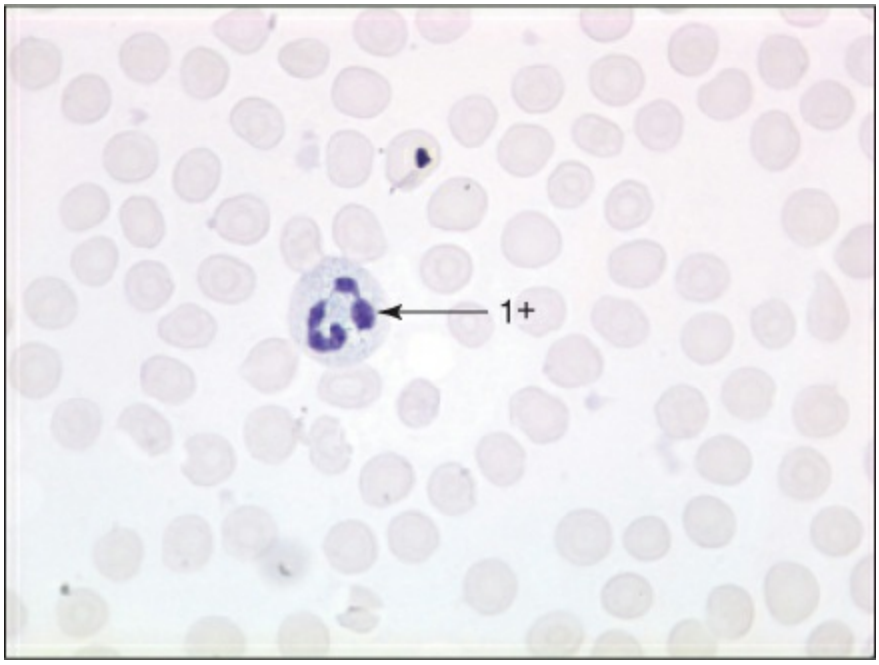


Figure IC1-15

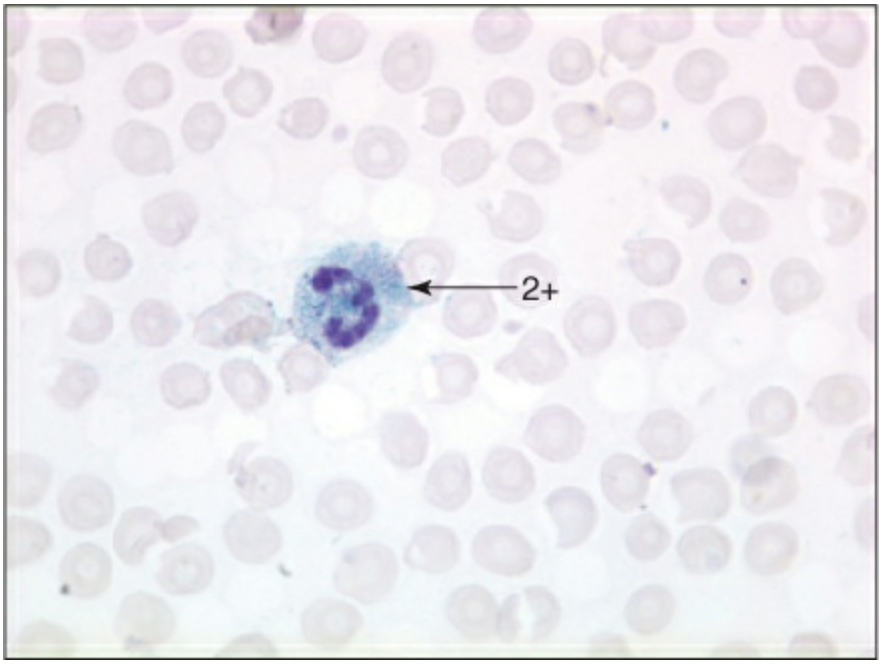


Figure **IC1-16**

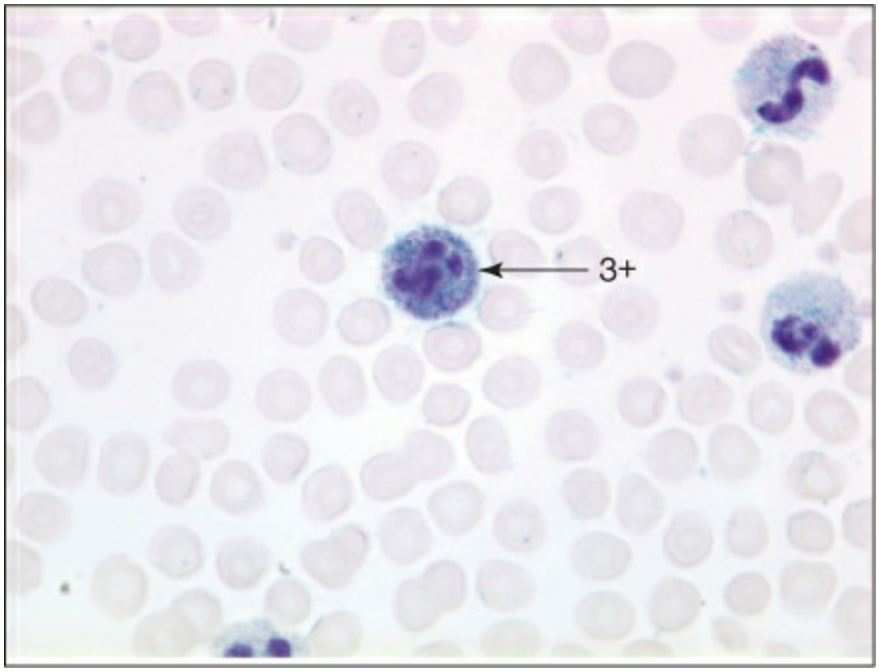


Figure **IC1-17**

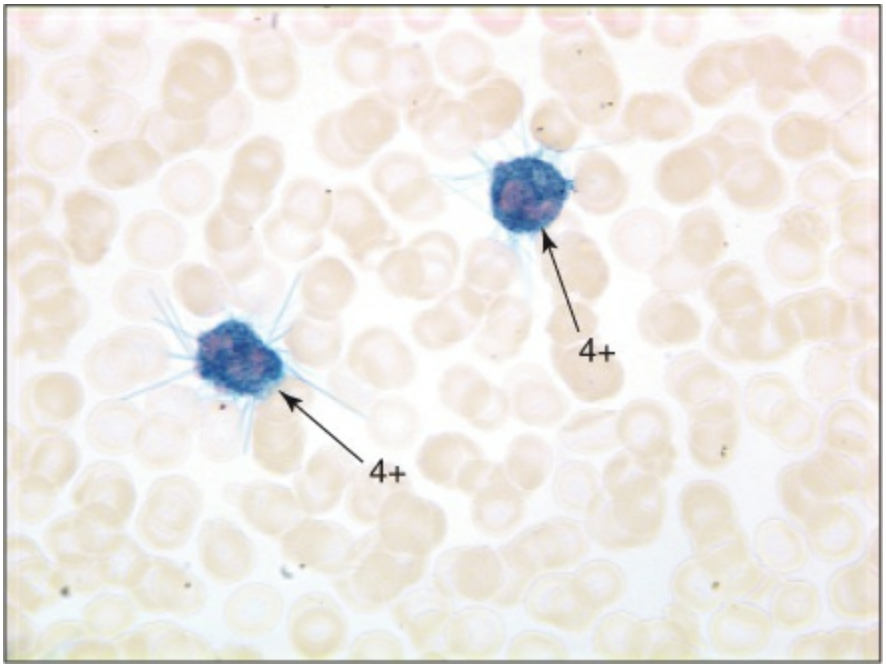


Figure **IC1-18**

Cell Type

Granulocyte distinguishes leukemoid reaction from chronic myelogenous leukemia

Description

LAP is an enzyme associated with the specific granules

Presence of leukocyte alkaline phosphatase activity indicates intracellular metabolic activity

Positivity is indicated by either a ruby red color or a blue-purple color

Positivity is quantitated

100 consecutive bands or segmented neutrophils are scored using the following criteria:

0 Colorless

1 Diffuse positivity; occasional granules

2 Diffuse positivity; moderate numbers of granules

3 Strong positivity; numerous granules

4 Very strong positivity; dark, confluent granules

The scores of the 100 cells are summed

Clinical Conditions

Increased:

- Leukemoid reaction
- Polycythemia vera
- Pregnancy
- Infections
- Chronic myelocytic leukemia blast crisis
- Myelofibrosis

Decreased:

- Chronic myelogenous leukemia
- Paroxysmal nocturnal hemoglobinuria
- Some myelodysplastic syndromes due to degranulation

NEW METHYLENE BLUE AND BRILLIANT CRESYL BLUE STAINS

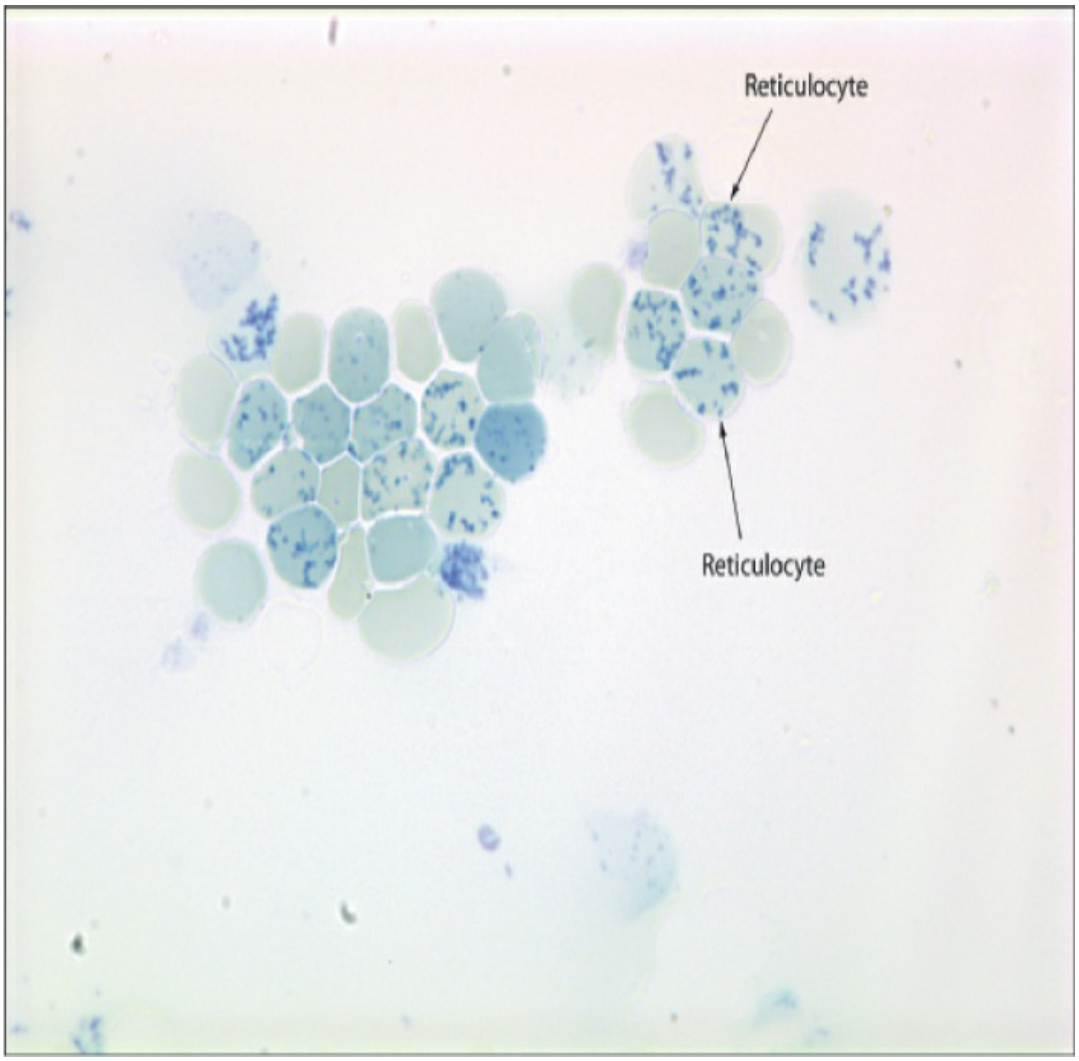


Figure IC1-19

Positive

Cell Type

Red blood cell

Description

Supravital stains commonly used in demonstrating aggregates of RNA in immature erythrocytes (reticulocytes)

Pappenheimer bodies, Howell-Jolly bodies, and Heinz

bodies are also stained

Clinical Conditions

- Hemolytic anemias
- Folate deficiency
- Vitamin B_{12} deficiency
- G-6-PD deficiency
- Hb H disease
- Myelodysplastic syndromes

PERIODIC ACID–SCHIFF REACTION

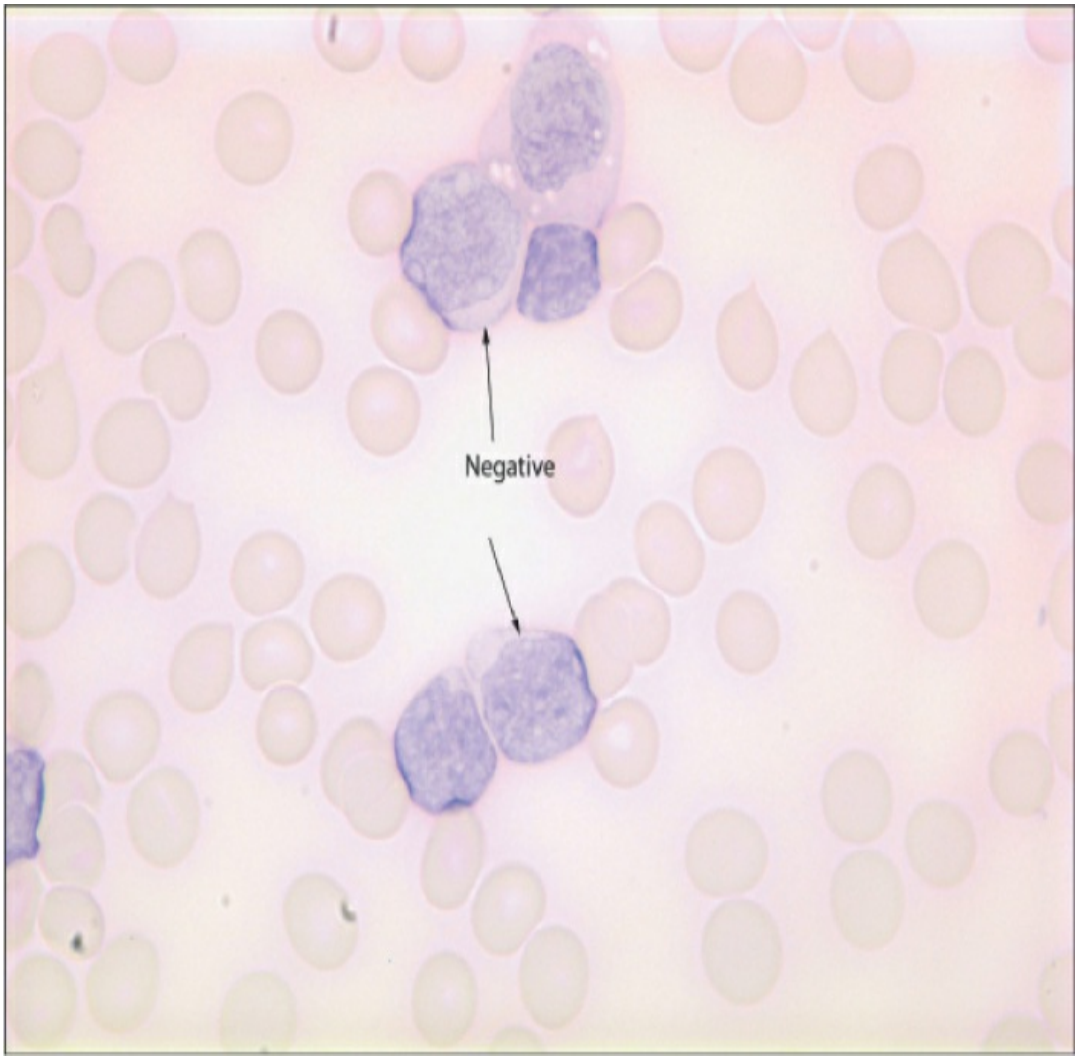


Figure IC1-20

Positive

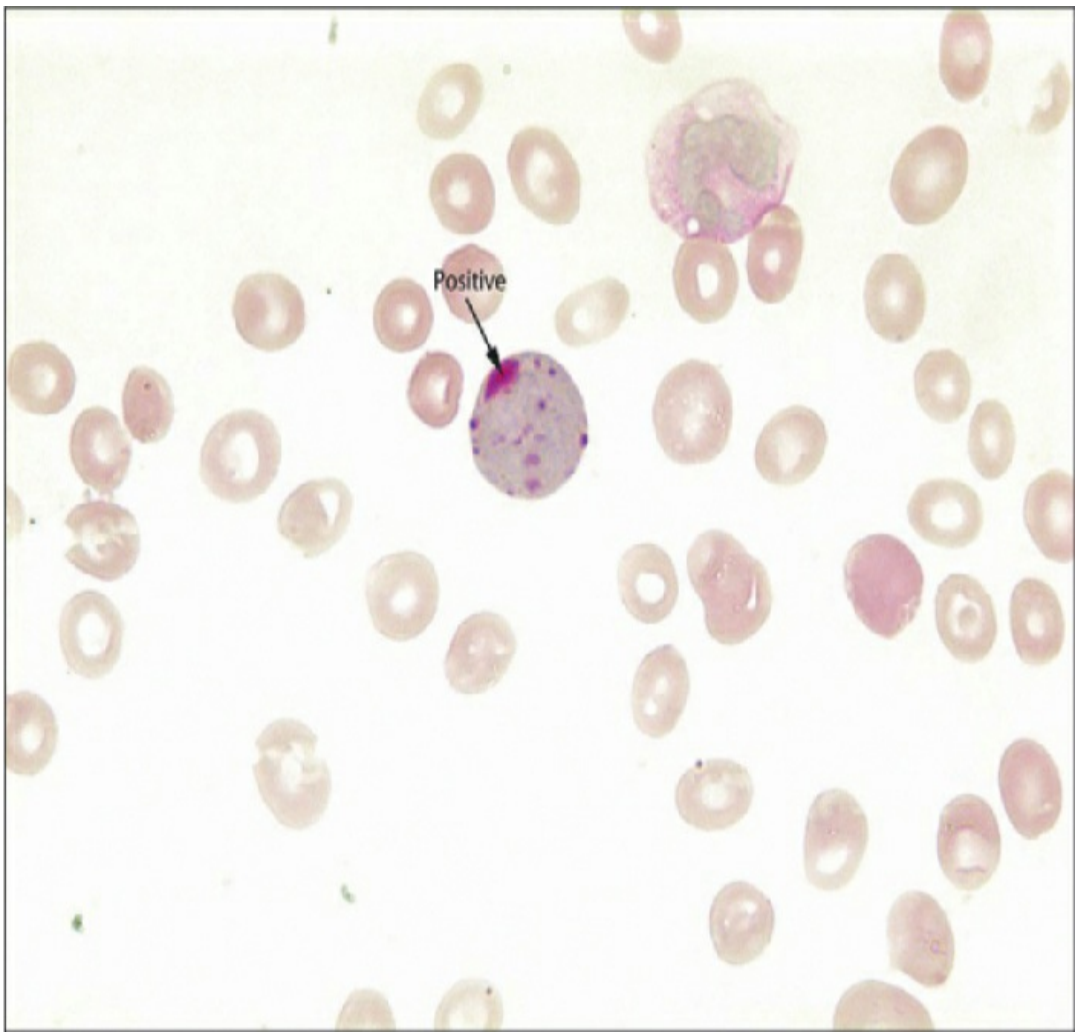


Figure **IC1-21**

Negative

Cell Type

Neoplastic erythroblast, granulocyte, monocyte, lymphoblast, megakaryocyte (most hematopoietic cells in variable quantities)

Description

PAS stains glycogen

Positivity is indicated by a bright pink color

Lymphocytes, granulocytes, monocytes, and megakaryocytes may be positive

Normal erythroblasts are negative

Clinical Conditions

- Acute erythroleukemia (positive)
- Thalassemia, iron deficiency, sideroblastic anemia (may be positive)
- Burkitt lymphoma cells (negative) (L3) (FAB)
- Acute lymphocytic leukemia (may have block positivity) (L1, L2) (FAB) (WHO)
- Any severe dyserythropoiesis
- Acute myelomonocytic leukemia with abnormal bone marrow eosinophils (granules are positive in the abnormal eosinophils)

PEROXIDASE STAIN

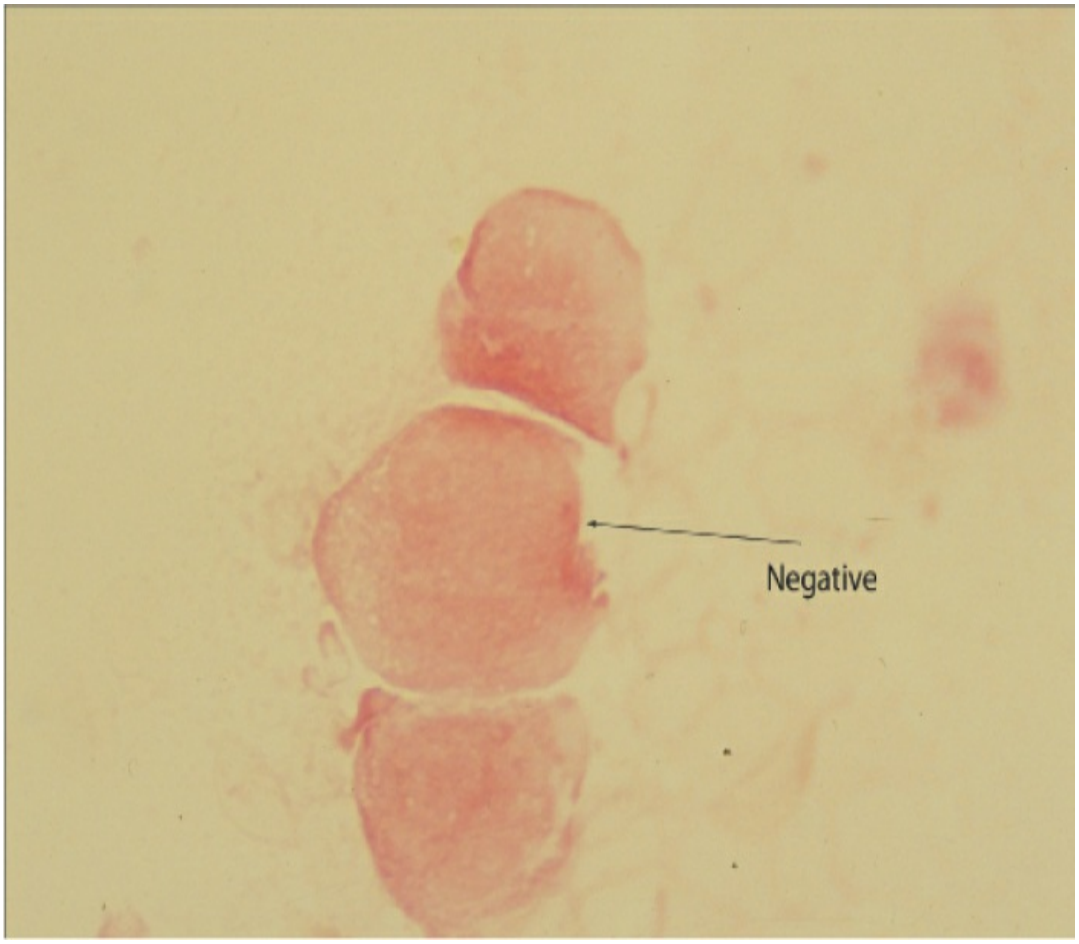


Figure IC1-22

Positive

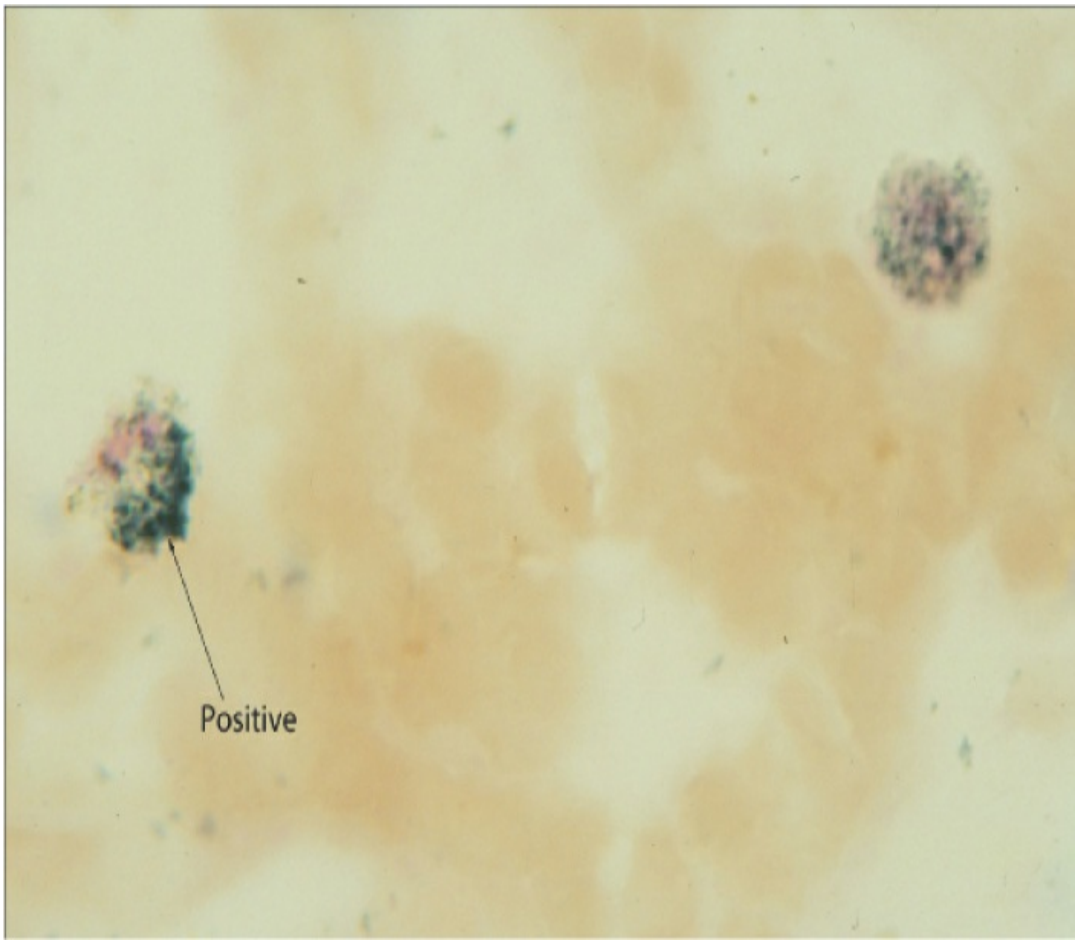


Figure **IC1-23**

Negative

Cell Type

Myeloid cell—primary granules of the neutrophilic and eosinophilic series; monocyte is faintly positive

Description

Myeloperoxidase is an enzyme capable of oxidizing dye substrates in the presence of hydrogen peroxide

Positivity is indicated by the presence of black or red-brown granules (color depends on the substrate)

Positivity is found in some myeloblasts, promyelocytes, myelocytes, metamyelocytes, neutrophils, and eosinophils, and faintly positive in monocytes

Early myeloblasts, basophils, plasma cells, and lymphocytic cells and erythroid cells are negative

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1) (FAB) (WHO)
- Acute myelocytic leukemia with maturation (M2) (FAB) (WHO)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Erythroleukemia (M6a) (FAB)
- AML with recurrent genetic abnormalities (WHO)
  - AML with t(8;21)
  - AML with t(15;17)
  - AML with inv16 or t(16;16)

SUDAN BLACK B STAIN

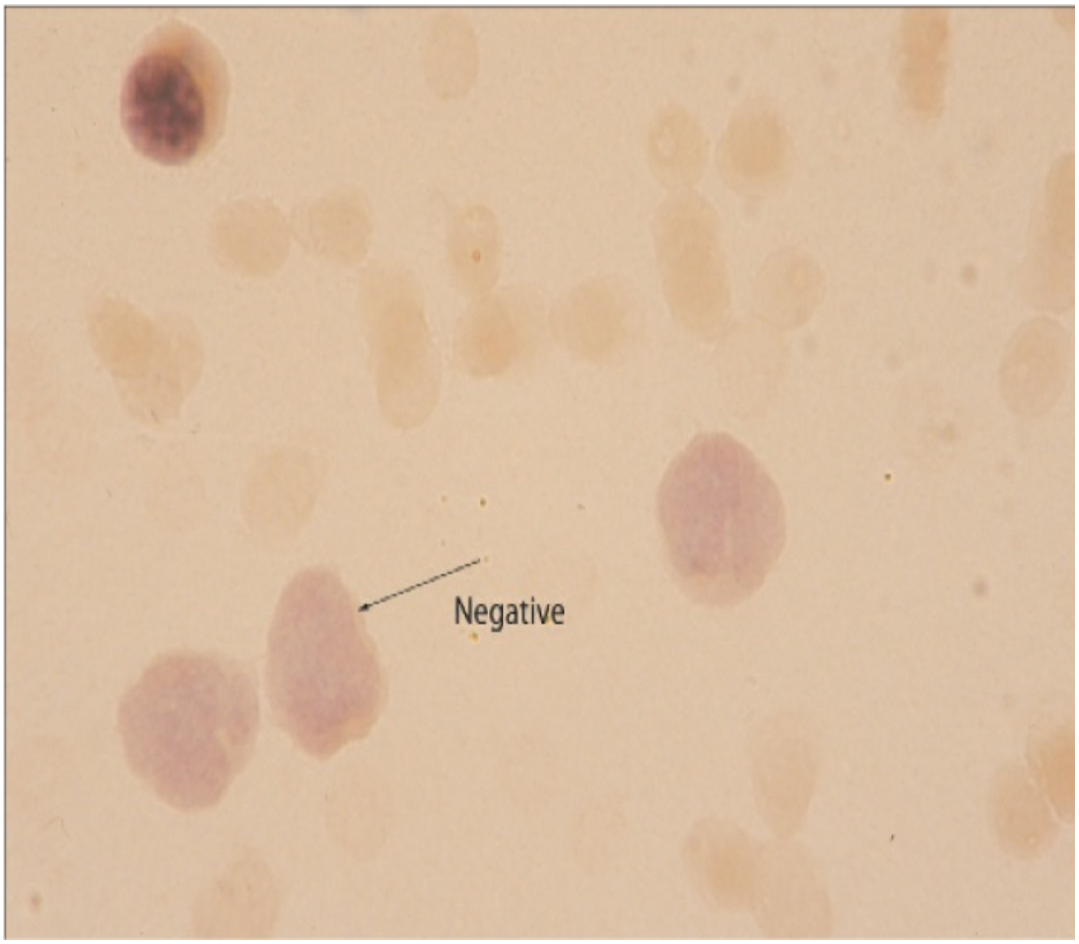


Figure IC1-24

Positive

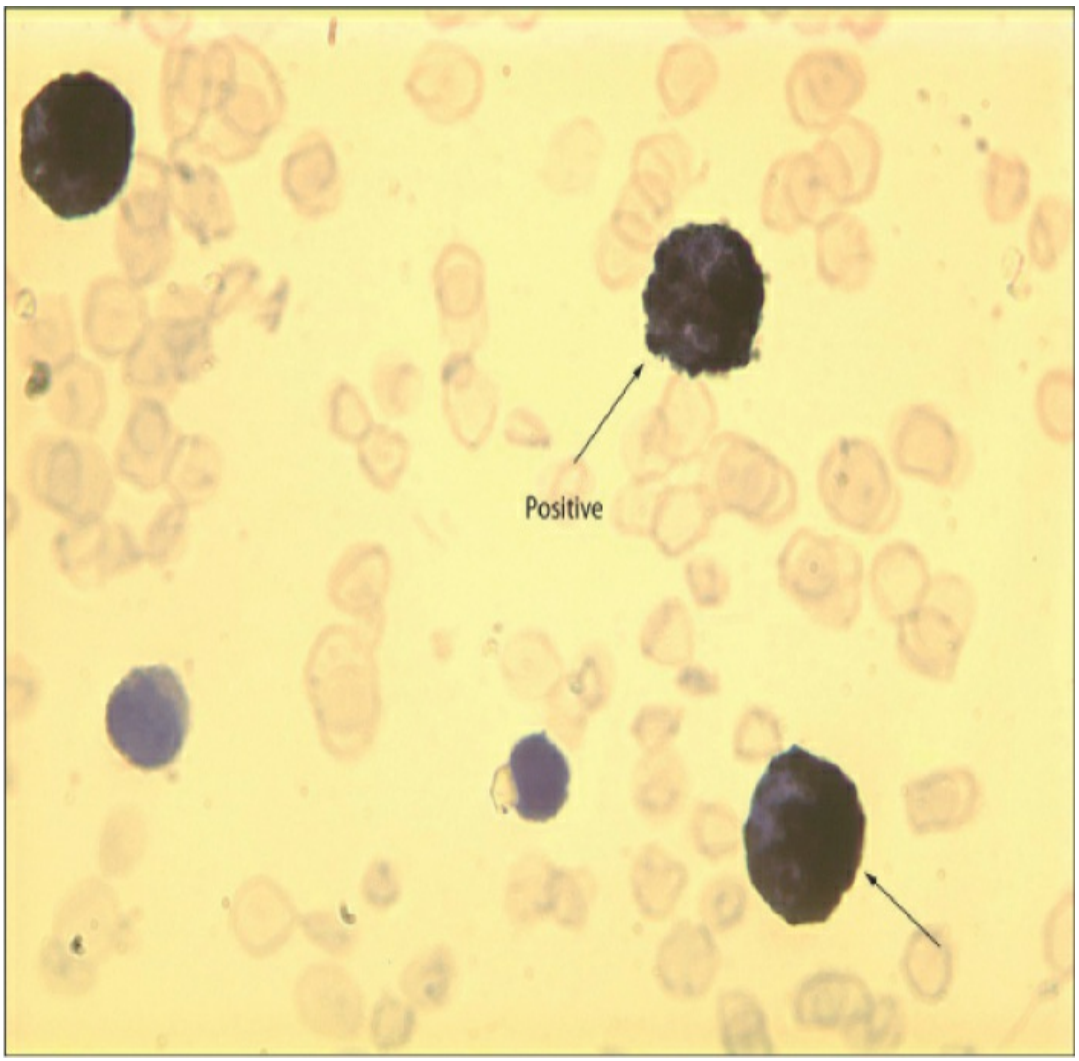


Figure **IC1-25**

Negative

Cell Type

Neutrophilic and eosinophilic cell and its precursor, monocyte, are weakly positive

Description

Separates AML from acute lymphocytic leukemia (ALL)

Sudan Black B stains lipid particles found in primary and secondary granules, as well as giving a weak positivity in lysosomal granules found in the monocytic cells

Lymphocytes may rarely have these granules

Positivity is indicated by a brownish-black colored granule

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1) (FAB) (WHO)
- Acute myelocytic leukemia with maturation (M2) (FAB) (WHO)
- Acute promyelocytic leukemia (M3) (FAB)
- Acute myelomonocytic leukemia (M4) (FAB) (WHO)
- Acute monoblastic leukemia (M5a) (FAB) (WHO) (if myeloblasts present)
- Acute monocytic leukemia (M5b) (FAB) (WHO) (if myeloblasts present)
- Erythroleukemia (M6a) (FAB) (if myeloblasts present)
- AML with recurrent genetic abnormalities (WHO)
    - AML with t(8;21)
    - AML with t(15;17)
    - AML with inv16 or t(16;16)

TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE REACTION

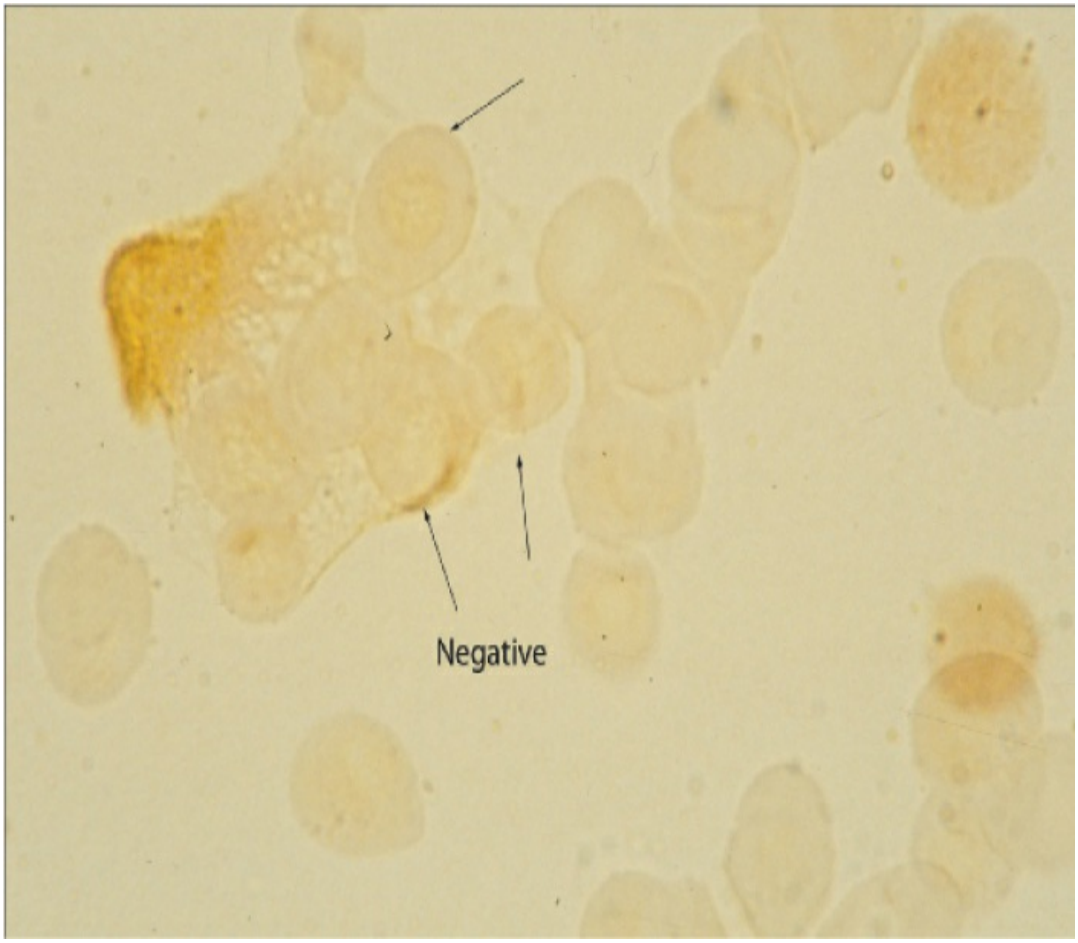


Figure IC1-26

Negative

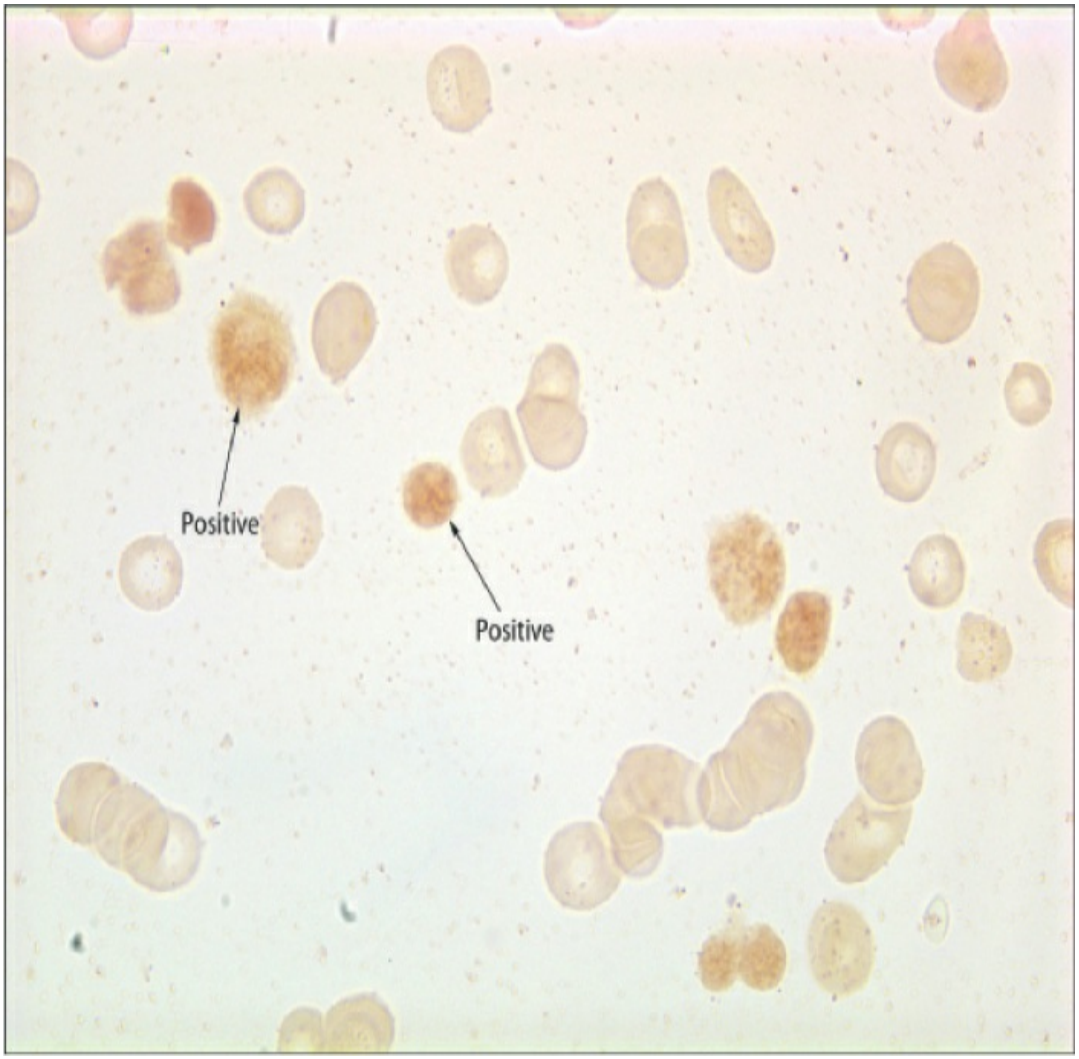


Figure **IC1-27**

Positive

Cell Type

Primitive lymphocytic cells and neoplastic cells

Description

Enzyme (DNA polymerase) found in the nucleus

Demonstrated through immunofluorescent or immunoperoxidase procedures

Positivity is demonstrated by a lime-green fluorescence or red to brownish-red staining

Clinical Conditions

- T-cell acute lymphoblastic leukemia
- Precursor B-cell acute lymphocytic leukemia
- Lymphoblastic lymphoma
- Chronic myelocytic leukemia with lymphoblastic transformation

TOLUIDINE BLUE STAIN

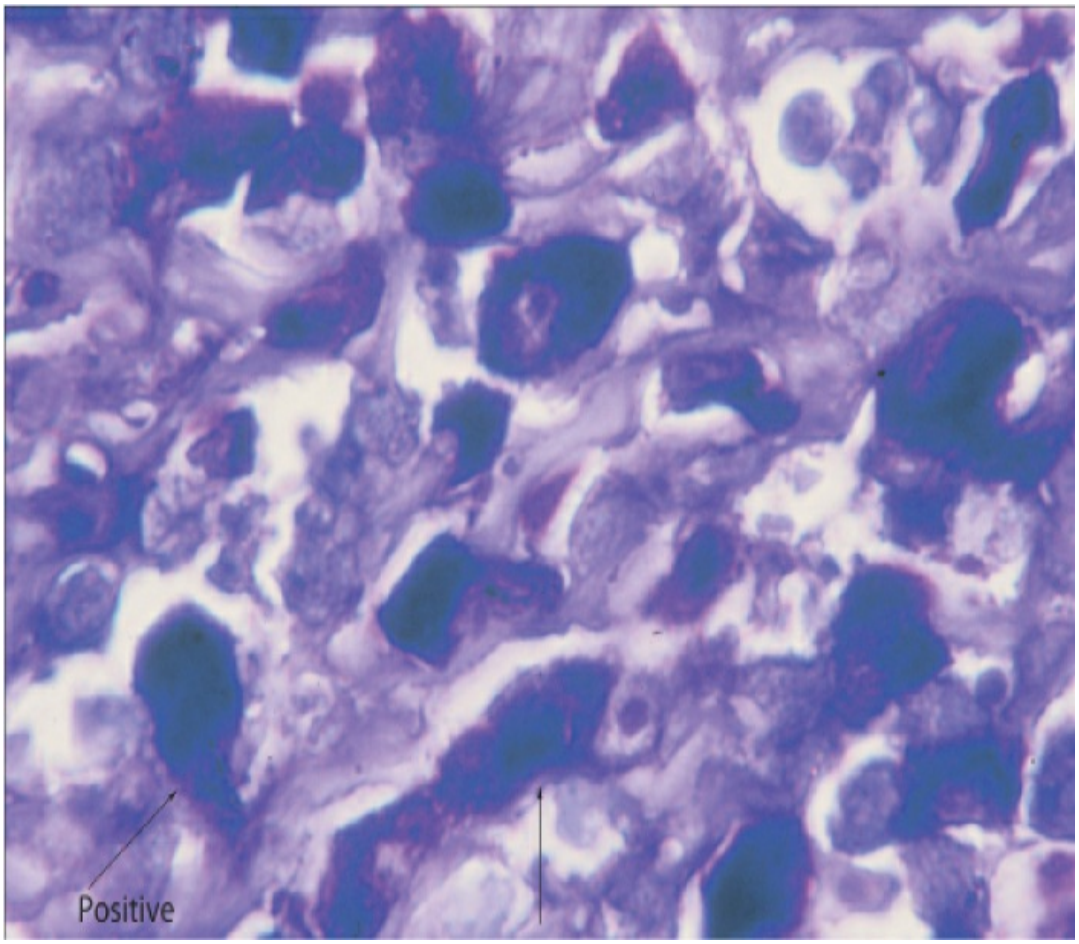


Figure IC1-28

Positive

Cell Type

Basophil and mast cell

Description

Reacts with acid mucopolysaccharides (heparan sulfate) to form metachromatic granules

Positivity is indicated by a red-violet color

May not be positive in neoplastic disorders involving these cells

Clinical Conditions

- Mast cell disease
- Basophilic leukemia

RETICULIN STAIN

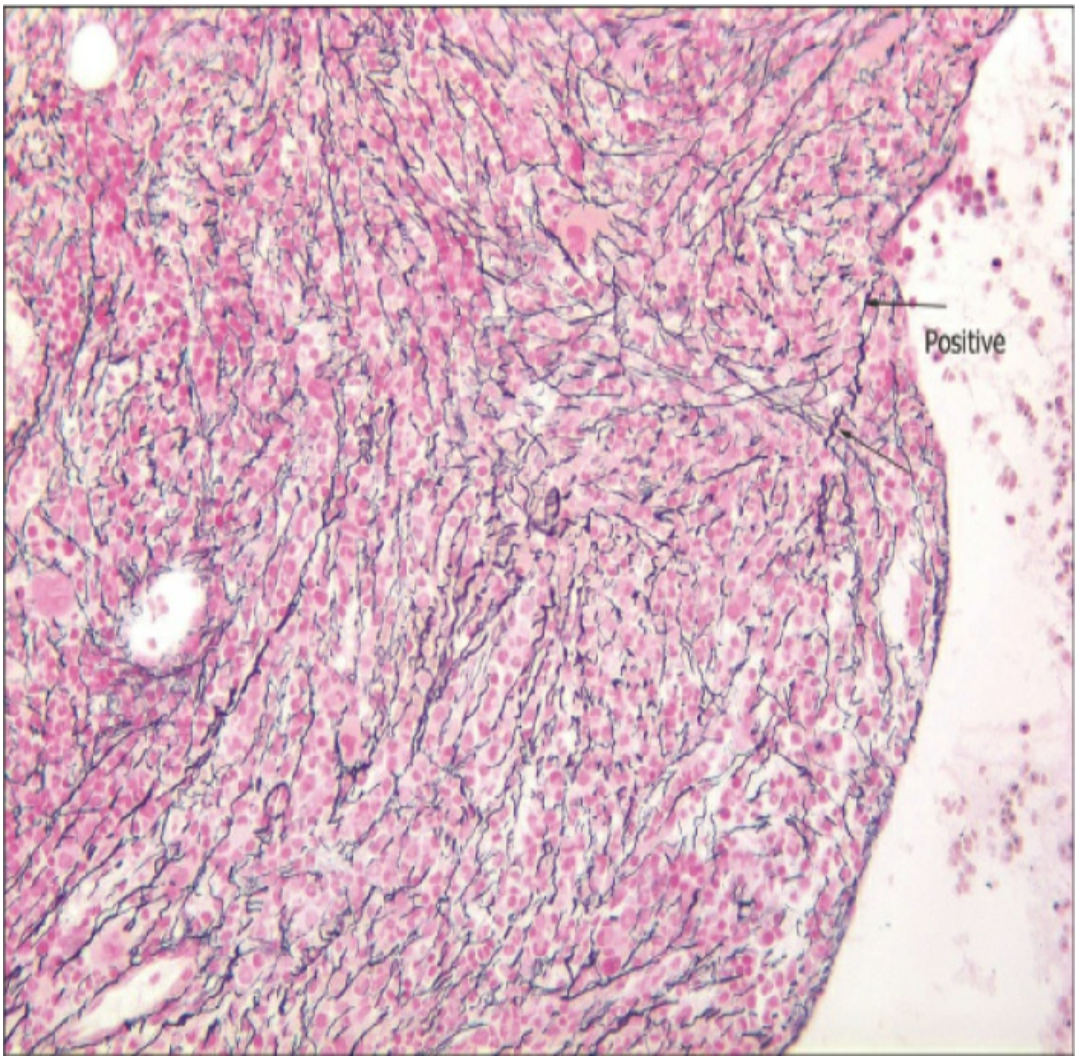


Figure **IC1-29**

Positive

Cell Type

Newly formed collagen

Description

The newly formed collagen is not cross-linked and stains in the biopsy sections

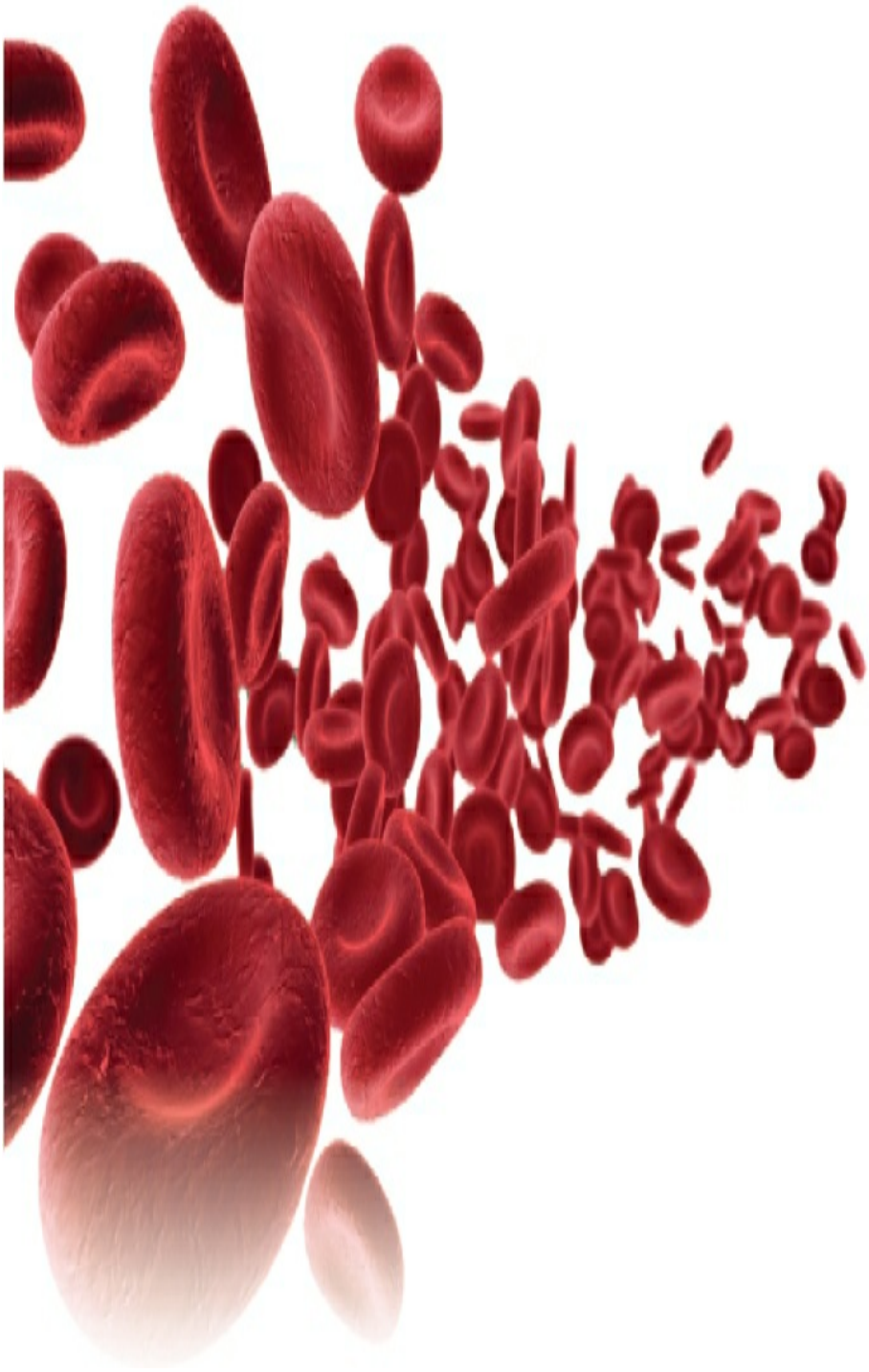
Clinical Conditions

- Elevated numbers of megakaryocytes

- Myeloproliferative neoplasms
- Lymphomas (follicular and Hodgkin)
- Megakaryocytic leukemia
- Hairy cell leukemia

Unit II

Hematologic Disorders



- **Section A** Red Blood Cell Disorders
- **Section B** White Blood Cell Disorders
- **Section C** Miscellaneous Disorders

Section A

Red Blood Cell Disorders

CHAPTER 1

Erythrocytosis

RELATIVE POLYCYTHEMIA (GAISBöCK SYNDROME)

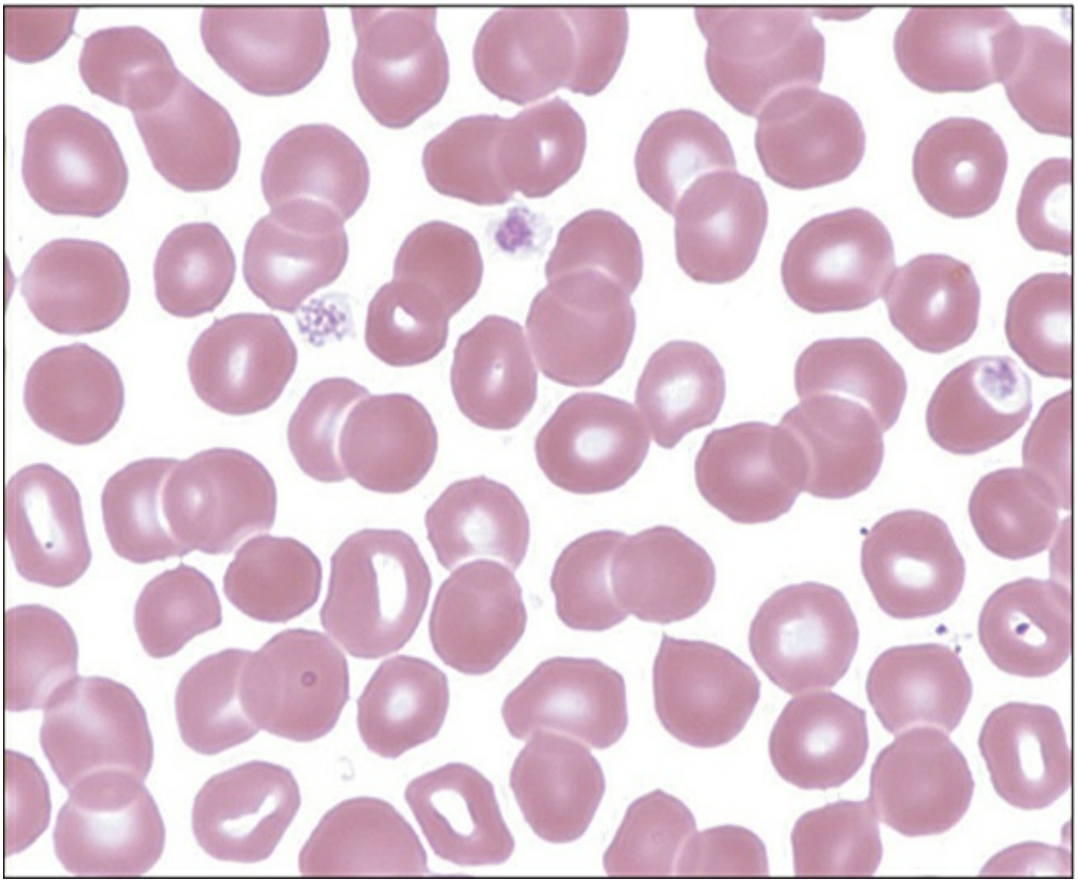


Figure IIA1-1

Peripheral blood smear.

Clinical Features

- Usually occurs in males aged 45–55
- The patients tend to be obese, have hypertension, and are heavy smokers

Pathology

- Normal red blood cell mass and clearly decreased plasma volume
- Red blood cell mass at the upper range of normal; plasma volume at the lower range of normal

- Cause of the low plasma volume is not understood but may be related to a variety of causes including emotional stress, alcoholism, heavy smoking, chronic anxiety, and hypertension

Laboratory Features

White Blood Cells

- Not remarkable

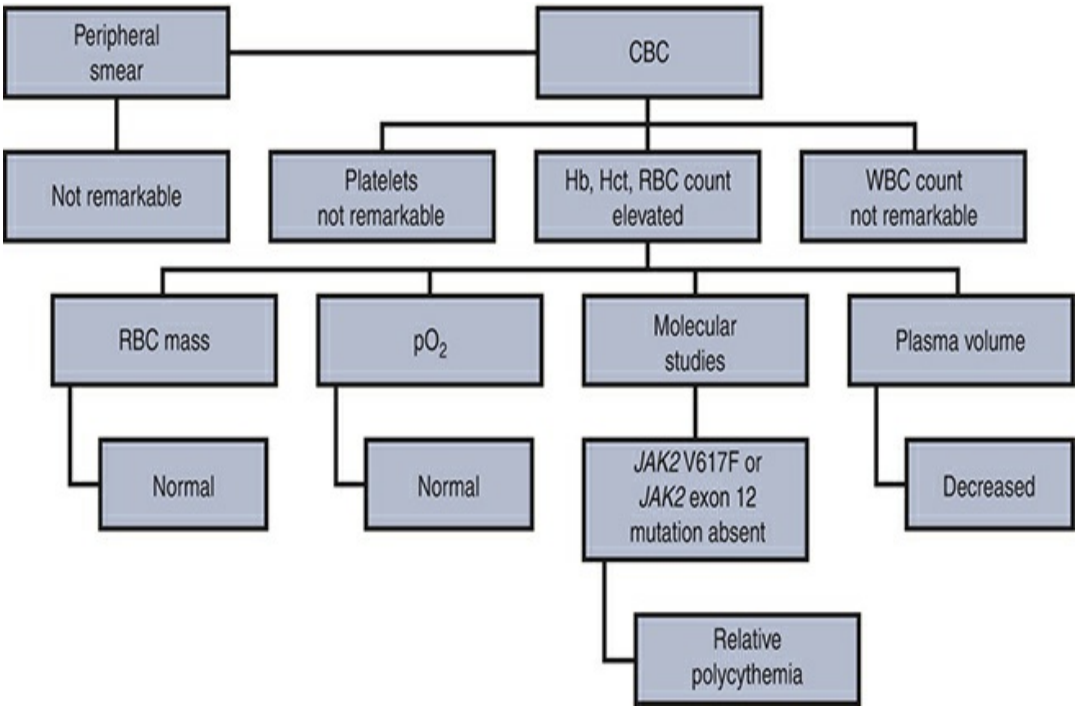
Platelets

- Not remarkable

Red Blood Cells

- Hemoglobin level increased
- Hematocrit level increased
- Red blood cell count increased
- Red blood cell mass normal
- Plasma volume decreased
- Oxygen pressure normal
- Erythropoietin level normal

Diagnostic Scheme


Peripheral smear
CBC
Not remarkable
Platelets not remarkable
Hb, Hct, RBC count elevated
WBC count not remarkable
RBC mass
pO_2
Molecular studies
Plasma volume
Normal
Normal
JAK2 V617F or *JAK2* exon 12 mutation absent
Decreased
Relative polycythemia

SECONDARY POLYCYTHEMIA

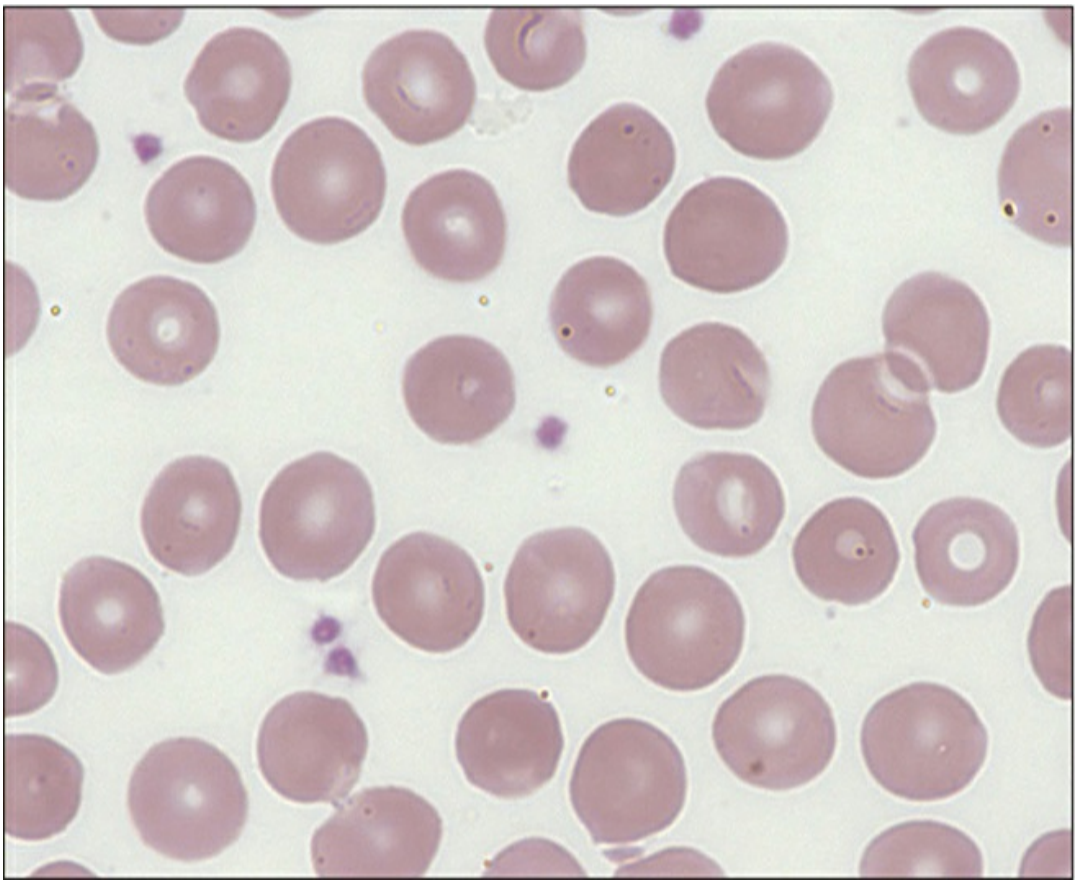


Figure IIA1-2

Peripheral blood smear.

Clinical Features

- Related to the actual cause of the erythrocytosis
- May include plethora, headache, dizziness, visual disturbances, fatigue, paresthesias, decreased mental acuity, obesity, and daytime sleepiness

Pathology

- May be secondary to conditions where there is a decreased delivery of oxygen to the tissues, which results in the release of erythropoietin—appropriate secretion of erythropoietin

- May occur in conditions in which delivery of oxygen to the tissues is normal—inappropriate secretion of erythropoietin
- Conditions associated with appropriate secretion of erythropoietin
  - Living at high altitude
  - High-affinity hemoglobins (e.g., Hb Chesapeake, Rainier, Capetown, Bethesda)
  - Carbon monoxide poisoning
  - Obstructive sleep apnea
  - Drug induced (e.g., testosterone)
  - Obesity hypoventilation syndrome (Pickwickian)
- Conditions associated with inappropriate secretion of erythropoietin
  - Hepatoma
  - Pheochromocytoma
  - Renal cell cancer, renal cyst, or renal artery stenosis
  - Cerebellar hemangioma

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

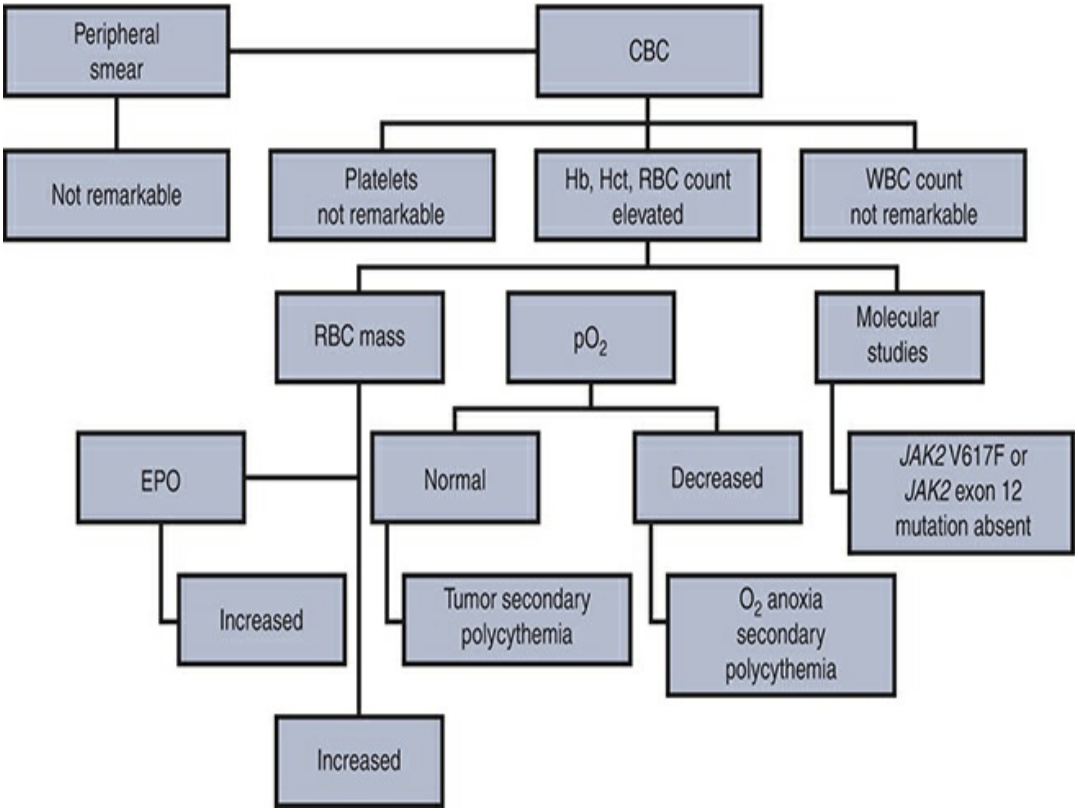
- Not remarkable

Red Blood Cells

- Hemoglobin level increased
- Hematocrit level increased
- Red blood cell count increased
- Red blood cell mass increased

- Increased erythropoietin
- Decreased oxygen pressure if due to anoxia; normal oxygen pressure if due to tumor

Diagnostic Scheme

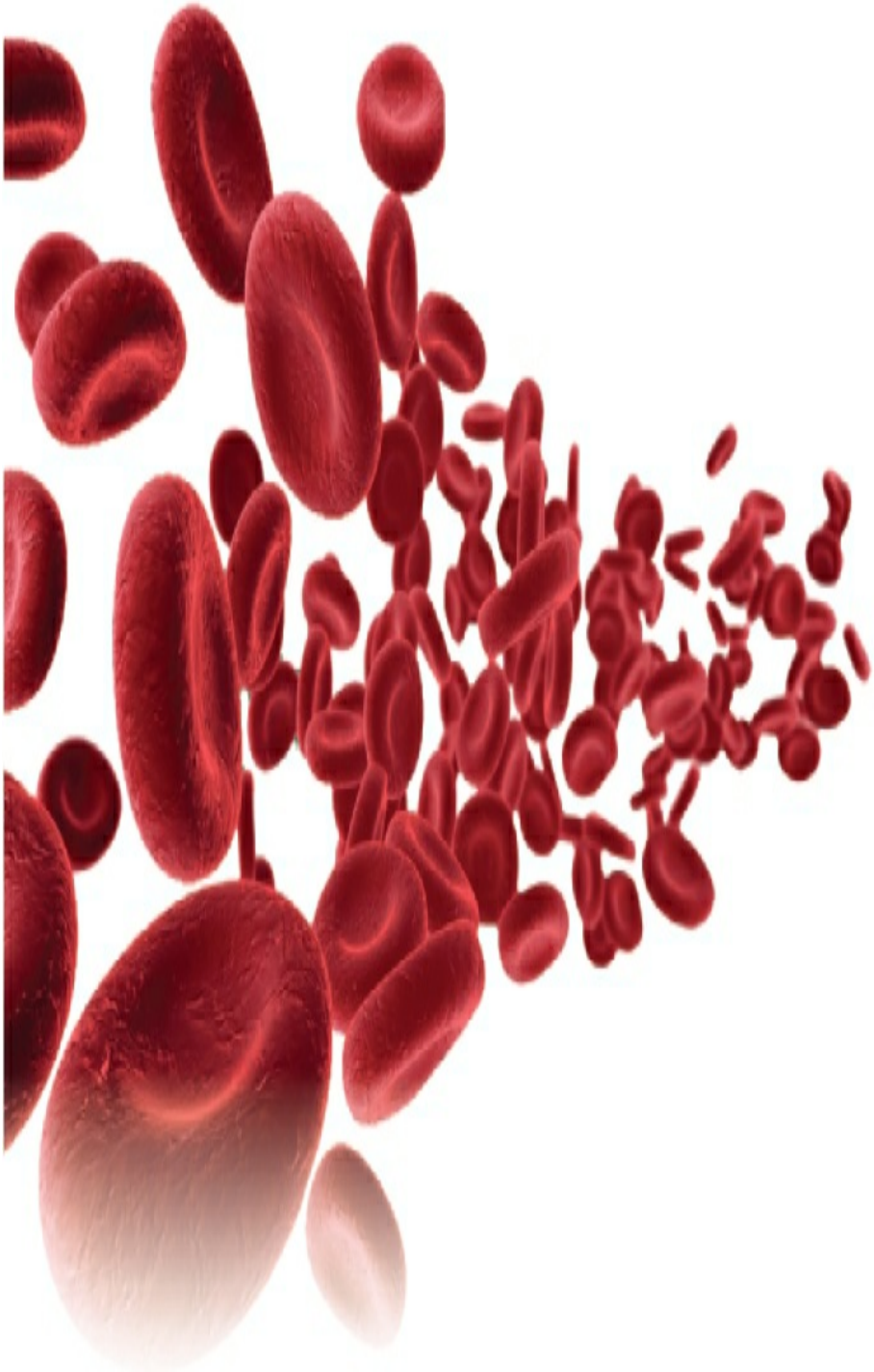


POLYCYTHEMIA VERA

- See Myeloproliferative Neoplasms, **Unit II Section B Chapter 4**

CHAPTER 2

Anemias Due to Disordered Iron Metabolism or Heme Synthesis



ANEMIA OF CHRONIC DISEASE

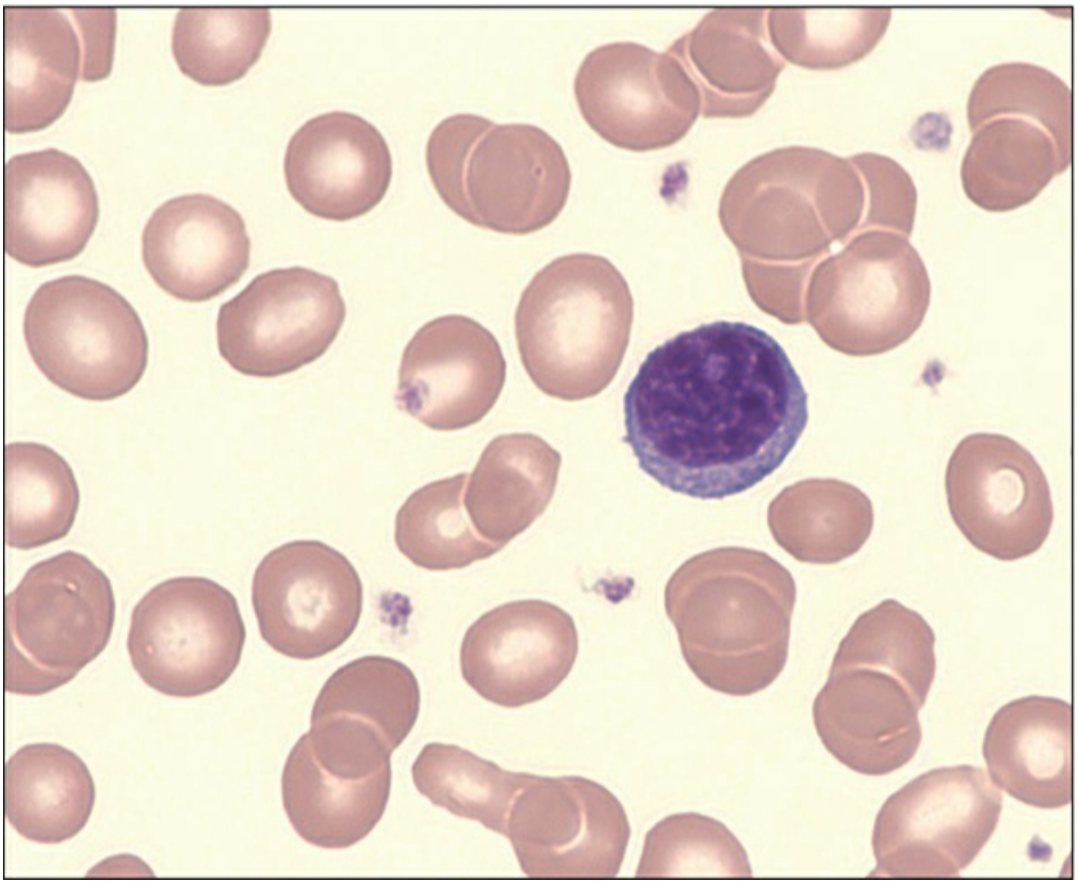


Figure IIA2-1A

Peripheral blood smear.

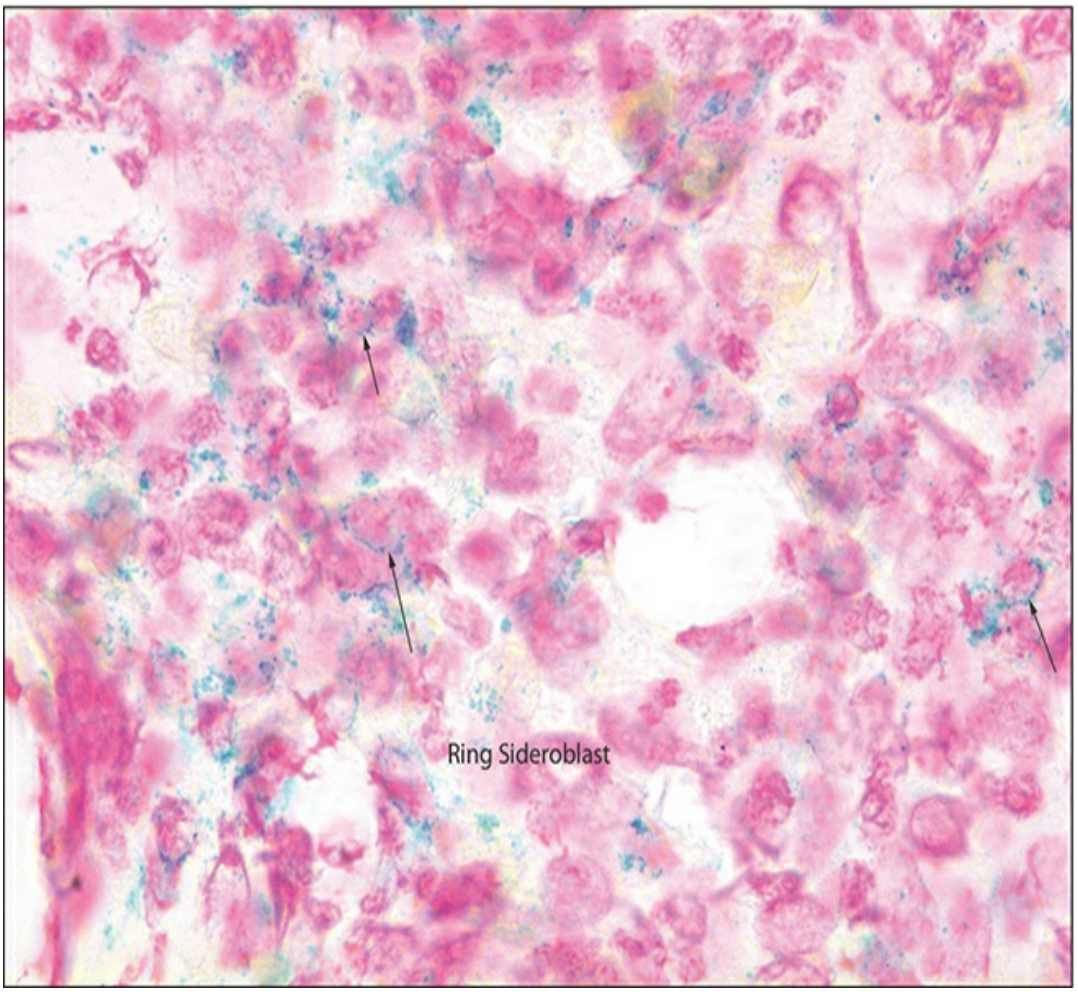


Figure **IIA2-1B**

Prussian blue stain on bone marrow.

Clinical Features

- Those of the underlying disease: Inflammatory, neoplastic, end-stage organ failure, or infectious state

Pathology

- Mild or gradual onset hypoproliferative anemia
- Proinflammatory cytokines cause
  - Blocked differentiation of erythrocyte precursors or progenitors directly
  - Suppression of erythropoietin production secondary to decreased response to tissue hypoxia

    - Decreased erythropoietin, which produces decreased erythropoiesis
    - Inhibited responsiveness of erythrocyte precursors or progenitors to erythropoietin
    - Stimulated hepcidin production, which causes a block in iron absorption
- Decreased red blood cell survival

Laboratory Features

White Blood Cells

- Not consistent—depends on the underlying disease

Platelets

- Not consistent—depends on the underlying disease

Red Blood Cells

- Decreased hemoglobin and hematocrit levels
- Normocytic/normochromic anemia
- Microcytic/hypochromic anemia
- Reticulocyte count normal to slightly increased

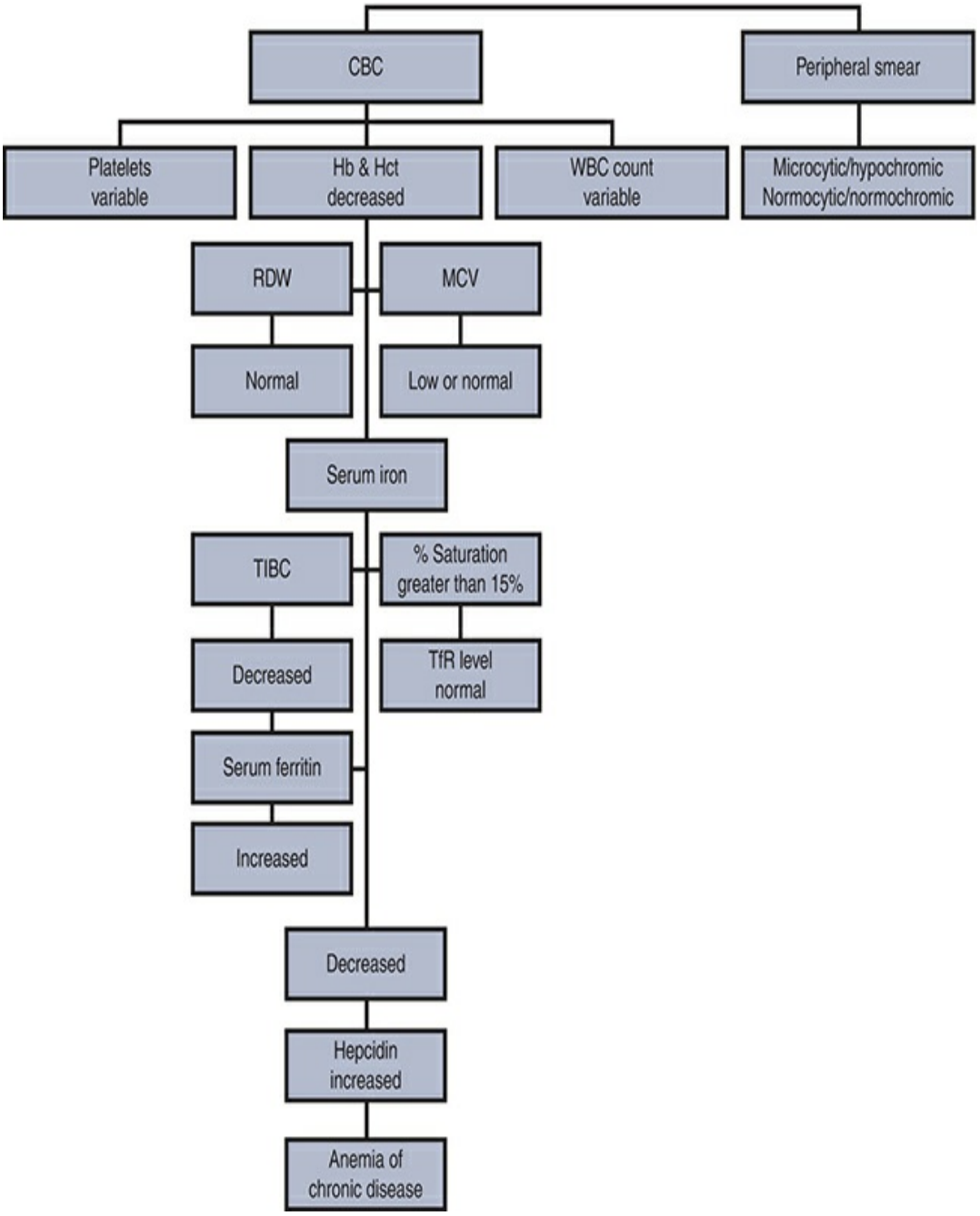
Bone Marrow

- Normal to increased hemosiderin
- Decreased sideroblasts

Chemistries

- Decreased serum iron level
- Normal or decreased total iron-binding capacity
- Decreased % saturation (usually >15%)
- Normal or increased serum ferritin level
- Increased plasma/serum and urine hepcidin (inflammation)
- Decreased erythropoietin levels (chronic renal disease)

Diagnostic Scheme



ERYTHROPOIETIC PORPHYRIA (GUNTHER DISEASE)

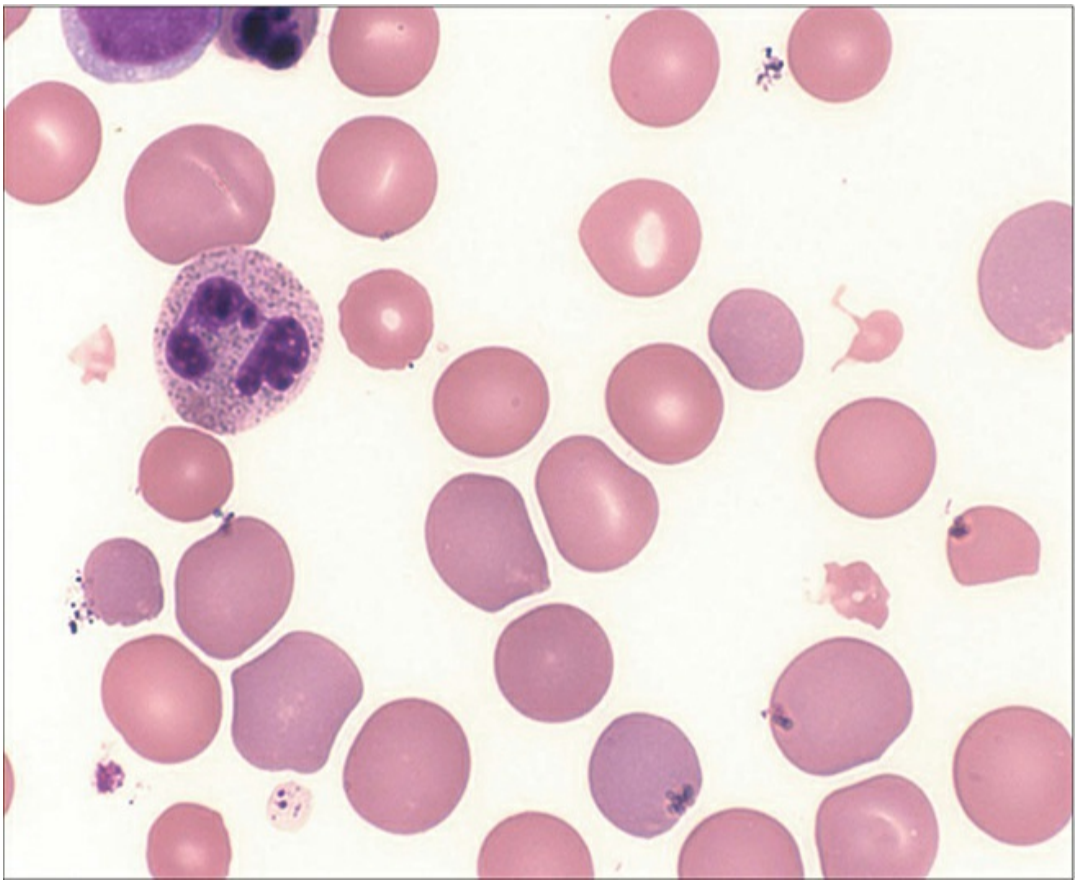


Figure IIA2-2

Peripheral blood smear.

Clinical Features

- Extreme sun sensitivity
- Rare autosomal recessive disease
- Appears in infancy
- Urine is colored pink to reddish brown
- Vesicular or bullous eruptions appear on exposed areas of the body
- Scarring occurs and may lead to severe deformities of the nose, ears, eyes, and fingers
- Teeth fluoresce

- Hypertrichosis affects the entire body
- Splenomegaly

Pathology

- Decreased tissue uroporphyrinogen III cosynthetase
- Hemolytic anemia

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Moderate to severe normocytic/normochromic anemia
- Polychromatophilia
- Nucleated red blood cells in the peripheral blood
- Red cells fluoresce
- Increased reticulocyte count
- Excessive porphyrin deposits in the red blood cells

Bone Marrow

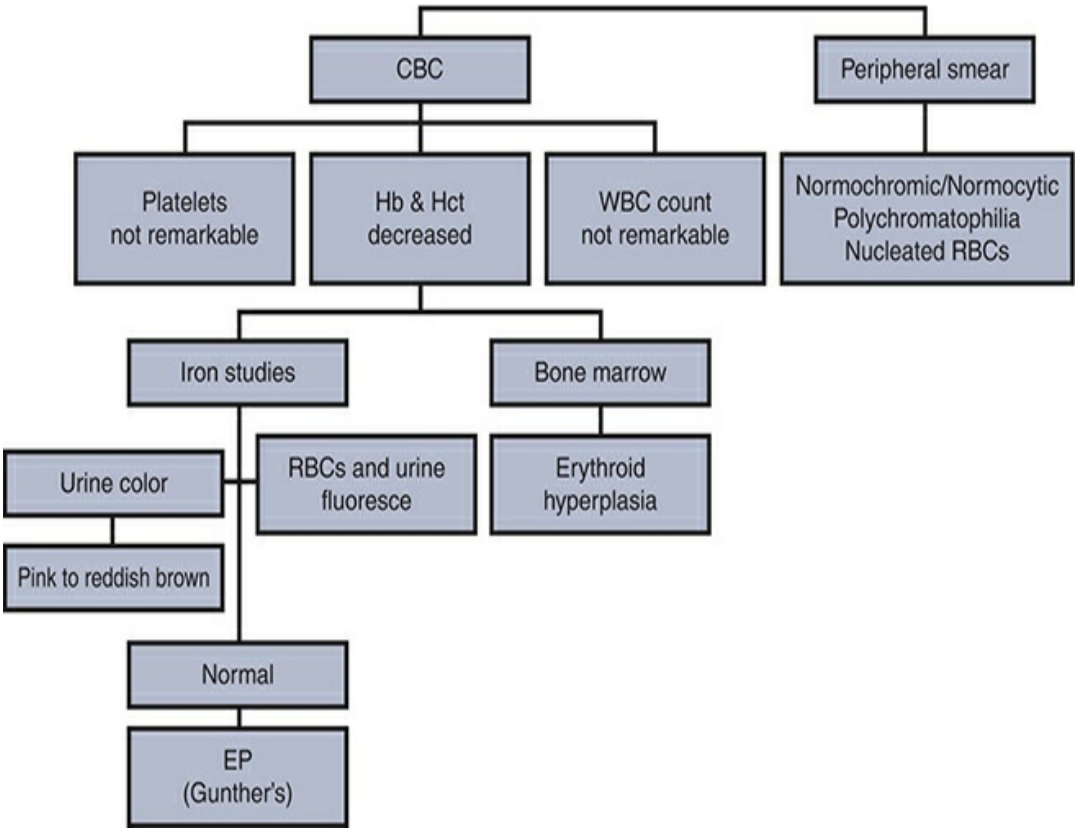
- Erythroid hyperplasia
- Normoblasts fluoresce
- Ineffective erythropoiesis

Chemistries

- Normal serum iron level
- Normal serum ferritin level
- Increased unconjugated bilirubin level
- Increased urine and fecal urobilinogen levels
- Excessive amounts of uroporphyrin I and

coproporphyrin I in urine and feces

Diagnostic Scheme



ERYTHROPOIETIC PROTOPORPHYRIA

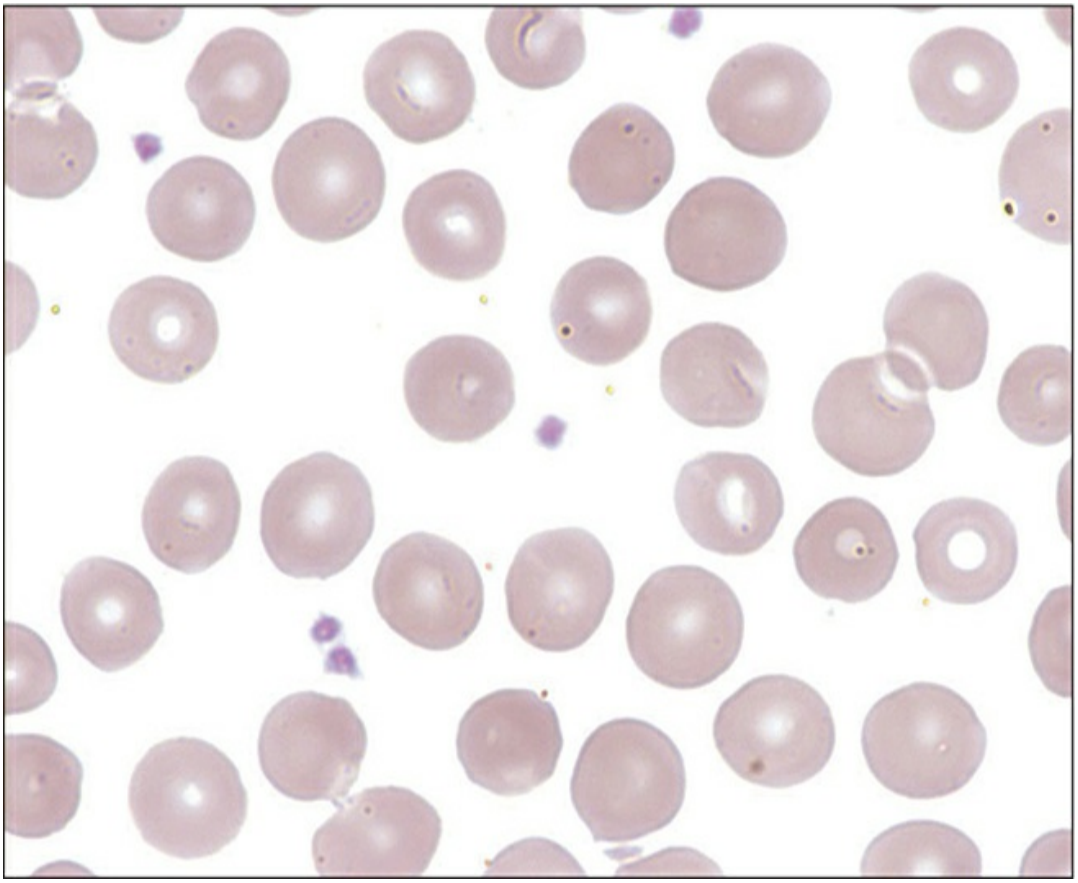


Figure IIA2-3

Peripheral blood smear.

Clinical Features

- Autosomal dominant or recessive transmission
- Usually begins before teen years
- Burning, redness, itching, swelling of skin
- Photosensitivity is not severe
- Relatively mild course

Pathology

- Deficiency of ferrochelatase
- Accumulation of protoporphyrin

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Mild microcytic anemia
- No hemolytic anemia
- No abnormalities
- Red blood cells may accumulate protoporphyrins and fluoresce

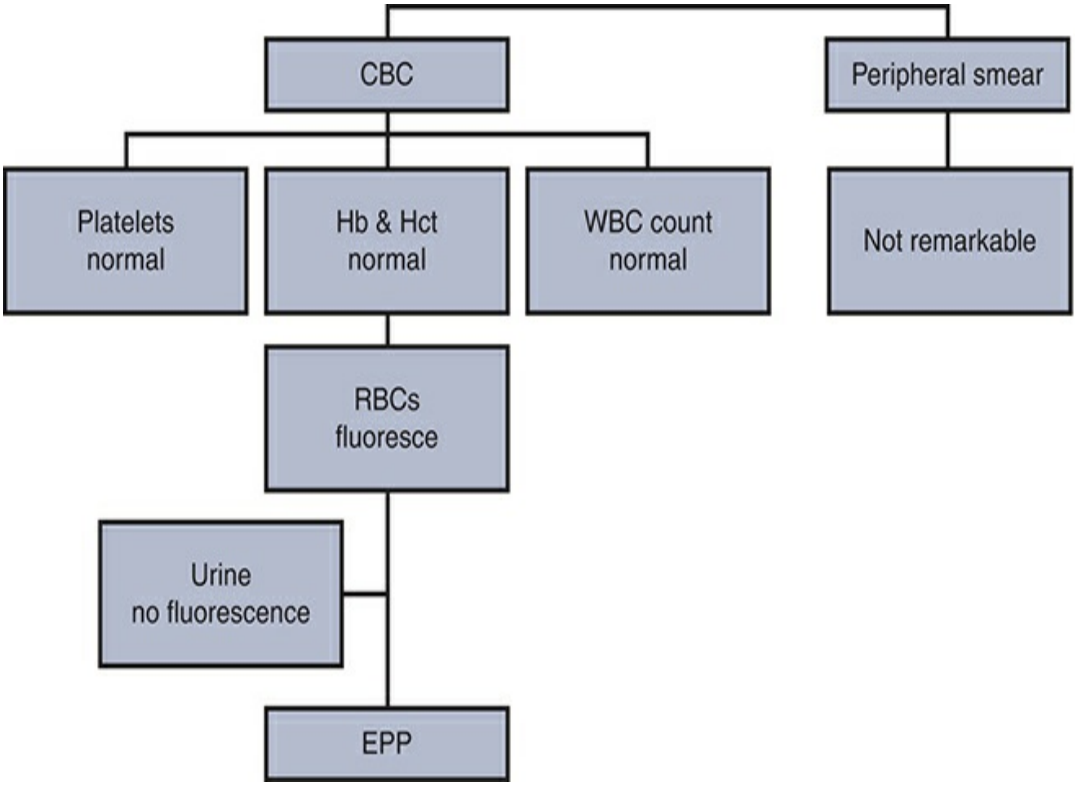
Bone Marrow

- Ring sideroblasts may be seen
- The cytoplasm of normoblasts fluoresce intensely

Chemistries

- Increased levels of protoporphyrin found in red blood cells, plasma, and feces but not in urine

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal
Hb & Hct normal
WBC count normal
Not remarkable
RBCs fluoresce
Urine no fluorescence
EPP

IRON DEFICIENCY ANEMIA

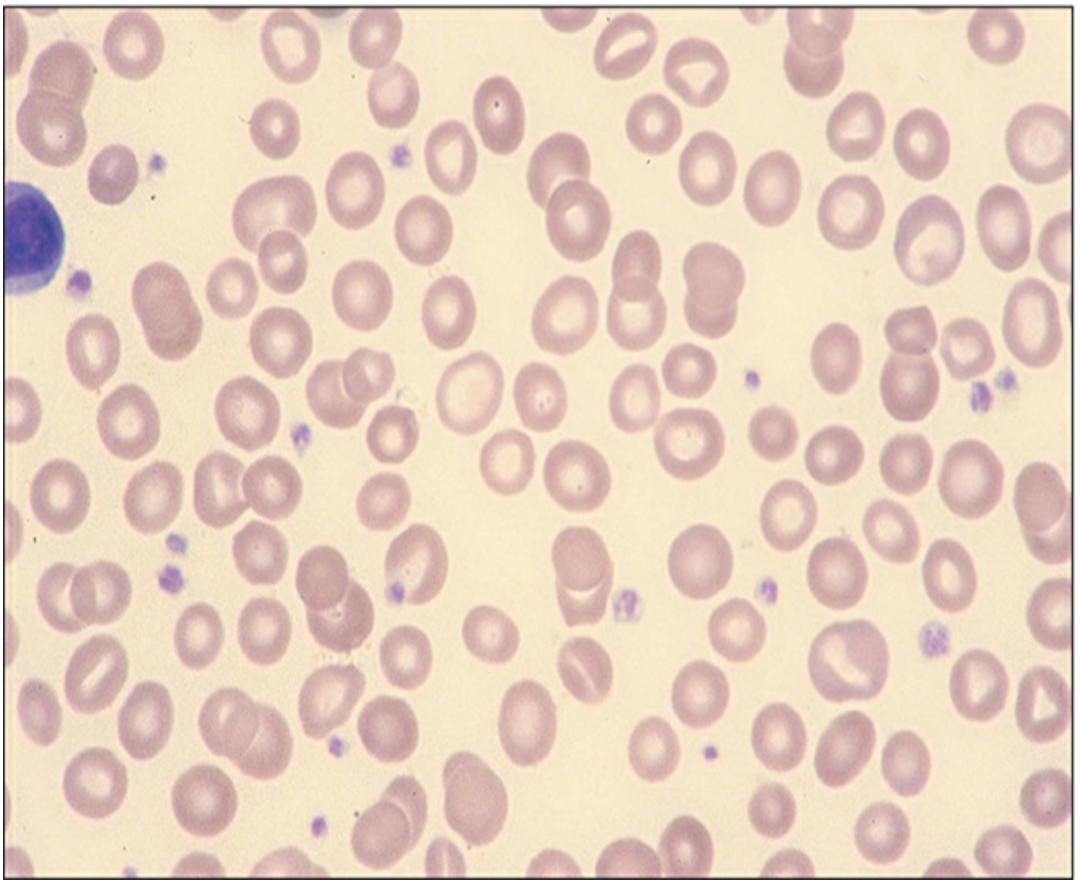


Figure IIA2-4

Peripheral blood smear.

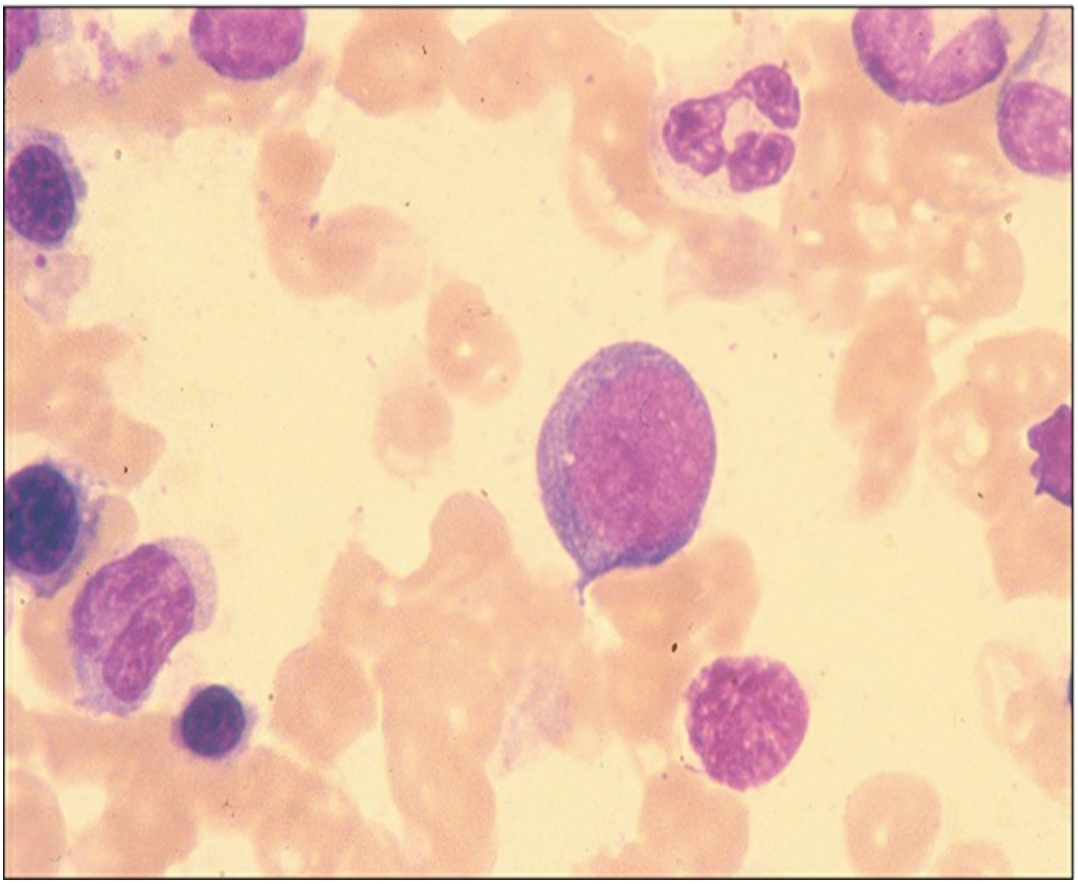


Figure IIA2-5

Bone marrow smear.

Clinical Features

- Insidious onset
- Fatigue, loss of stamina, exercise intolerance
- Delayed growth
- Lethargy
- Dizziness
- Pallor
- Glossitis
- Koilonychia (spoon nails)
- Crave dirt or paint (pica) or ice (pagophagia)

Pathology

- Deficient heme synthesis

- Ineffective erythropoiesis
- Increased iron loss
  - Pregnancy
  - Menstruation
  - Chronic blood loss from gastrointestinal tract
- Low availability of iron
  - Rapid growth period
  - Defective gastric function
  - Achlorhydria
  - Gastrectomy
- Iron-refractory iron deficiency
  - Autosomal recessive disorder due to mutation in TMPRSS6 gene

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Normal or slightly increased

Red Blood Cells

- Decreased red blood cell count
- Hemoglobin and hematocrit levels decreased
- Microcytic/hypochromic anemia
- Decreased mean corpuscular volume
- Reticulocyte count normal or slightly increased
- Increased red blood cell distribution width
- Pencil- or cigar-shaped red blood cells, codocytes

Bone Marrow

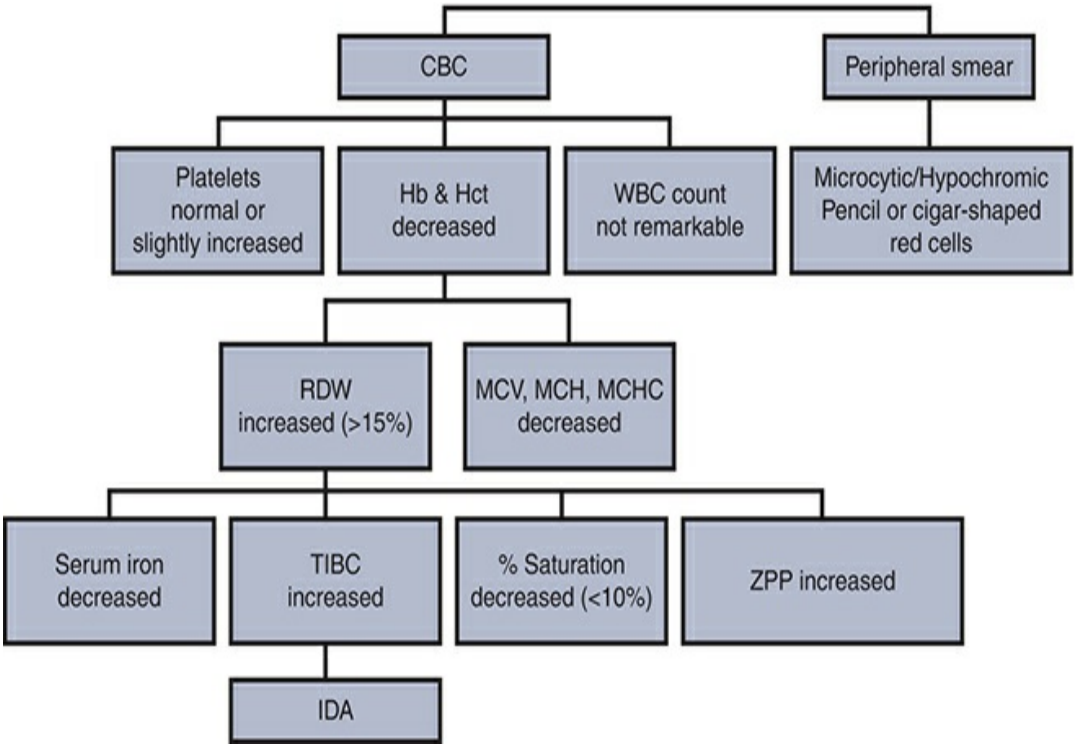
- Erythroblastic hyperplasia

- Absent hemosiderin
- Decreased sideroblasts (<10%)
- Erythroblasts are smaller than normal with ragged rims of cytoplasm containing little hemoglobin

Chemistries

- Decreased serum iron level
- Increased total iron-binding capacity
- Decreased % saturation (<15%)
- Decreased serum ferritin level
- Decreased serum hepcidin levels
- Increased zinc protoporphyrin

Diagnostic Scheme



LEAD INTOXICATION (PLUMBISM)

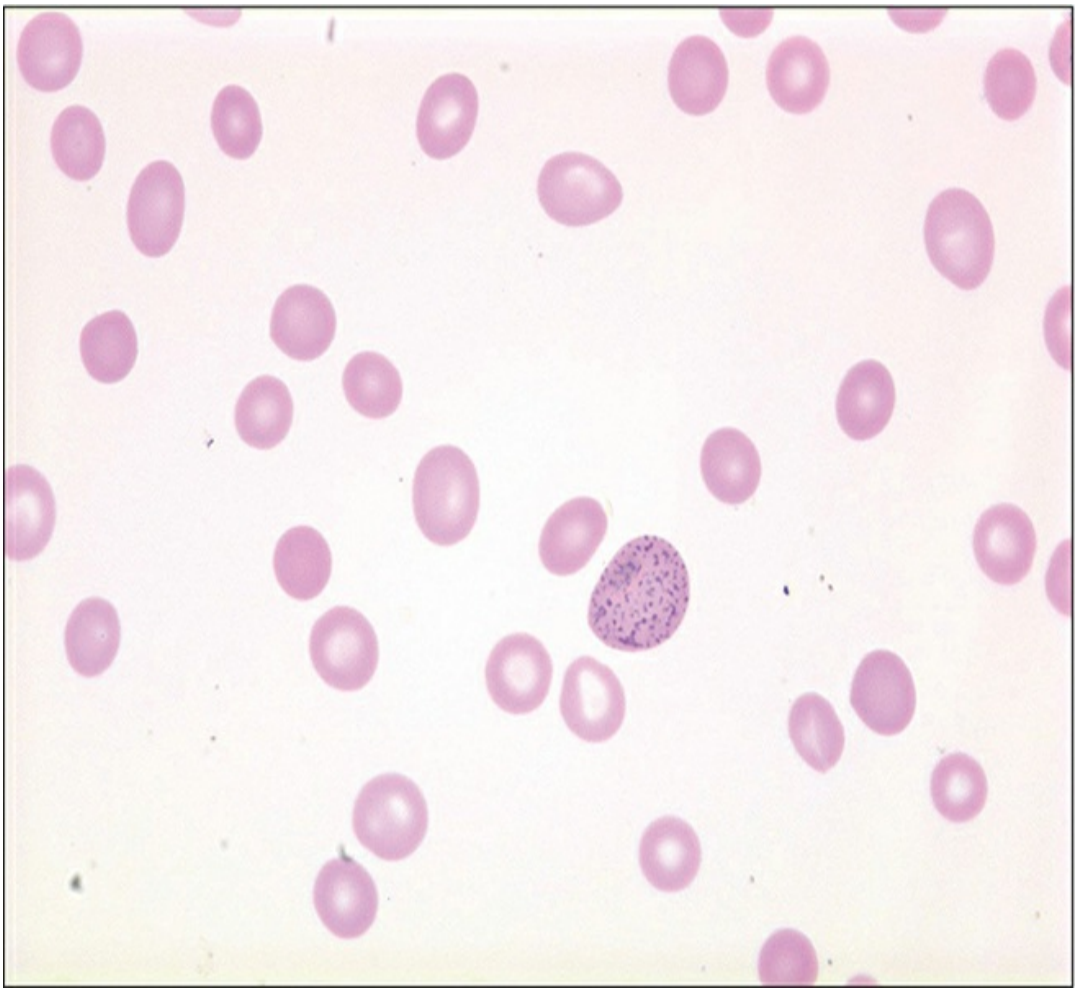


Figure IIA2-6

Peripheral blood smear.

Clinical Features

- Abdominal pain
- Constipation
- Vomiting
- Muscle weakness
- Lead line on gums
- Skin lesions
- Neurologic dysfunctions

Pathology

- Synthesis of heme is impaired
- Interference with iron storage in the mitochondria, which may lead to sideroblastic anemia
- Activity of most enzymes in heme synthesis is inhibited
- Ineffective erythropoiesis (hemolysis because of RNA breakdown)

Laboratory Features

White Blood Cells

- Not consistent findings

Platelets

- Not remarkable

Red Blood Cells

- Microcytic/hypochromic anemia
- Basophilic stippling
- Reticulocyte count normal to increased

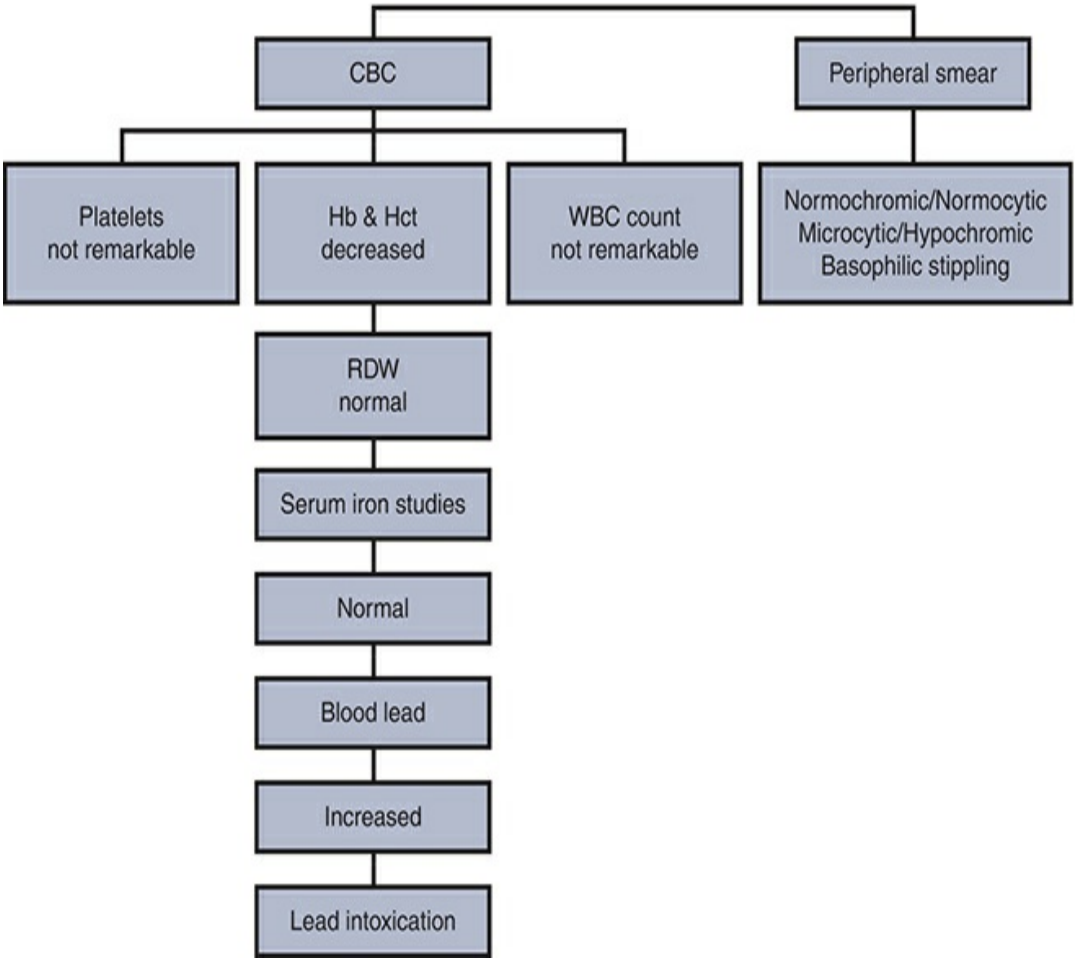
Bone Marrow

- Normal hemosiderin
- Basophilic stippling in normoblasts
- Ring sideroblasts may be seen

Chemistries

- Increased free erythrocyte protoporphyrin
- Normal serum ferritin level
- Increased δ-aminolevulinic acid levels
- Normal porphobilinogen
- Increased blood lead levels

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Normochromic/Normocytic Microcytic/Hypochromic Basophilic stippling
RDW normal
Serum iron studies
Normal
Blood lead
Increased
Lead intoxication

SIDEROBLASTIC ANEMIA

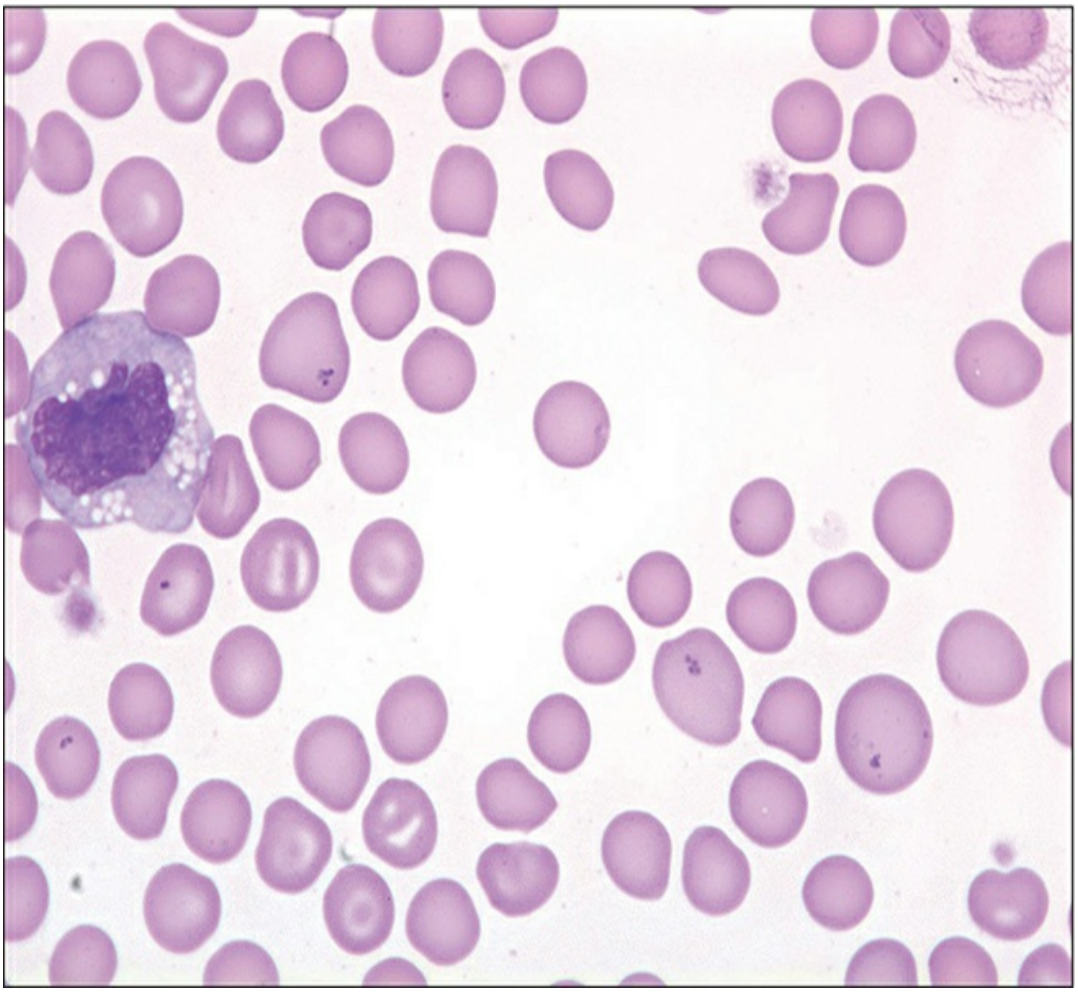


Figure IIA2-7

Peripheral blood smear.

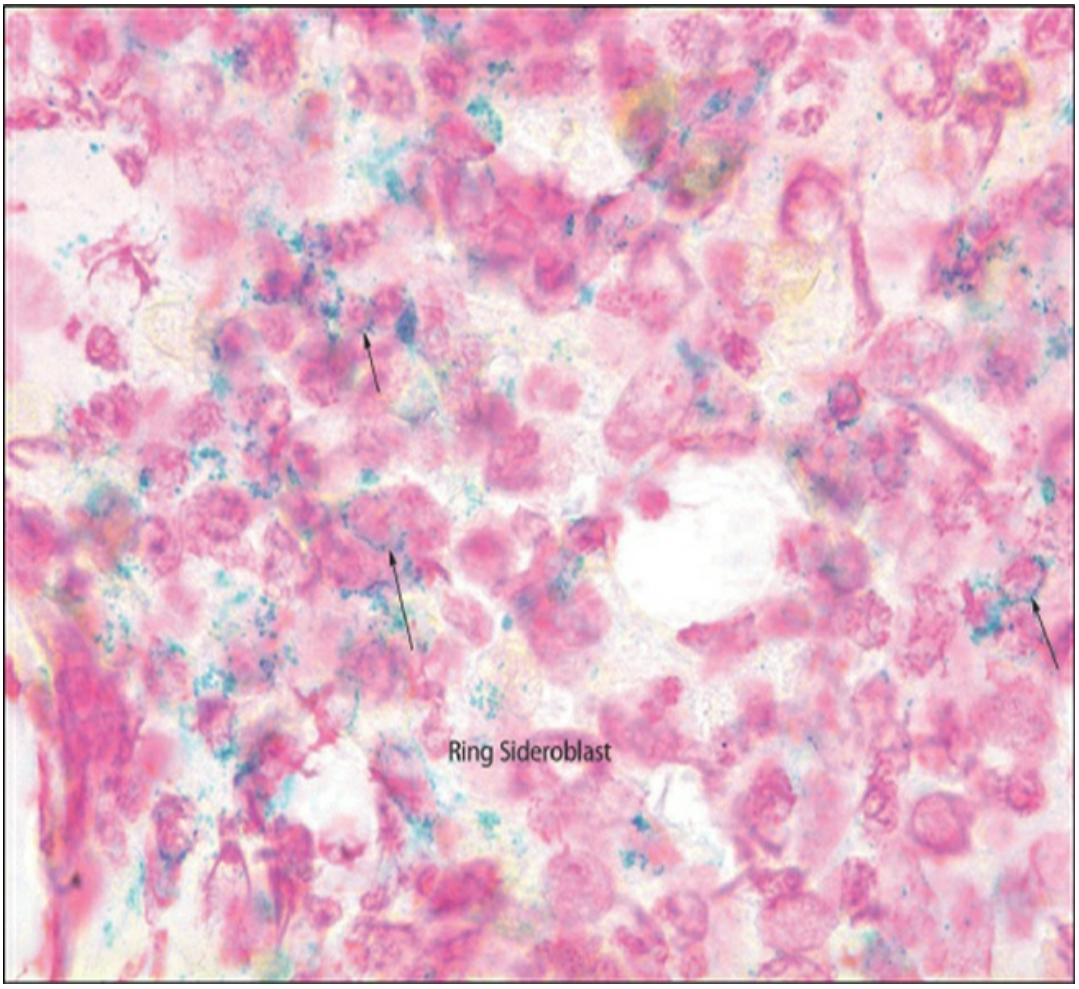


Figure **IIA2-8**

Prussian blue stain on bone marrow.

Clinical Features

- Heterogeneous group of inherited disorders caused by defective heme synthesis and/or accumulation of iron within mitochondria of erythroid precursors
- Hepatosplenomegaly

Pathology

- Common features
  - Ineffective erythropoiesis
  - Mitochondrial iron overload
  - Failure of protoporphyrin and heme synthesis due

to abnormal enzyme activity

- Inherited
  - Gene mutation is related to heme synthesis pathway, mitochondrial iron metabolism, or general mitochondrial functionality
- Secondary
  - Lead exposure, alcohol use, arsenic poisoning, copper deficiency, zinc toxicity, benzene poisoning, certain medications, or vitamin B_6 deficiency

Laboratory Features

White Blood Cells

- Normal to decreased

Platelets

- Not remarkable

Red Blood Cells

- Moderate to severe anemia
- Commonly microcytic/hypochromic anemia
- Dimorphism
- Increased red blood cell distribution width
- Reticulocyte count normal, low, or slightly increased
- Basophilic stippling
- Pappenheimer bodies

Bone Marrow

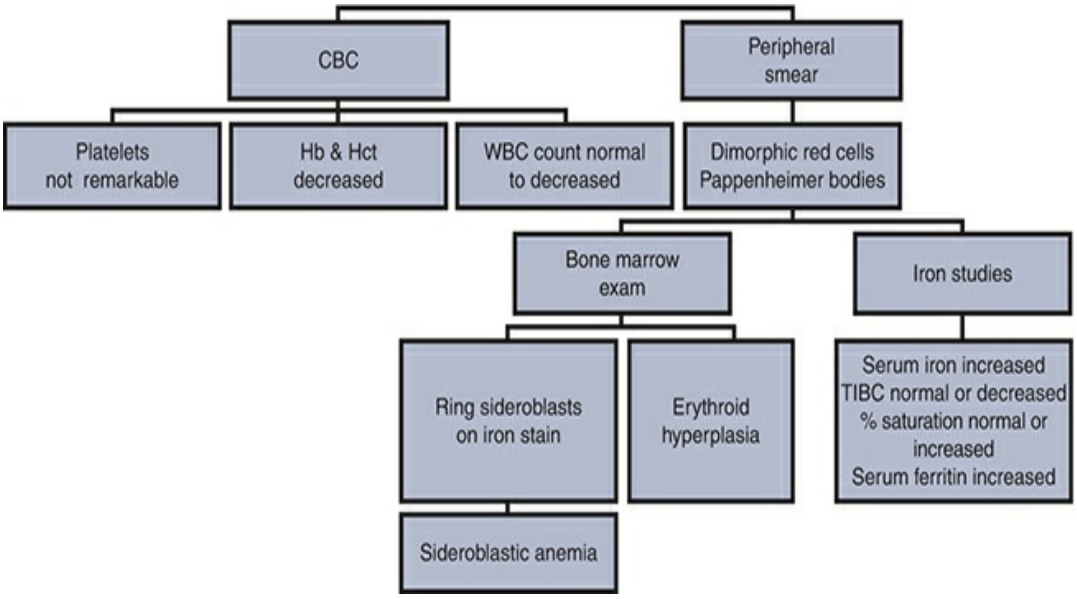
- Erythroid hyperplasia
- Large numbers of sideroblasts and ring sideroblasts

Chemistries

- Increased hemosiderin
- Increased serum iron level

- Normal or decreased total iron-binding capacity
- Normal or increased % saturation
- Increased serum ferritin level

Diagnostic Scheme



CHAPTER 3

Megaloblastic Anemias

FOLIC ACID DEFICIENCY

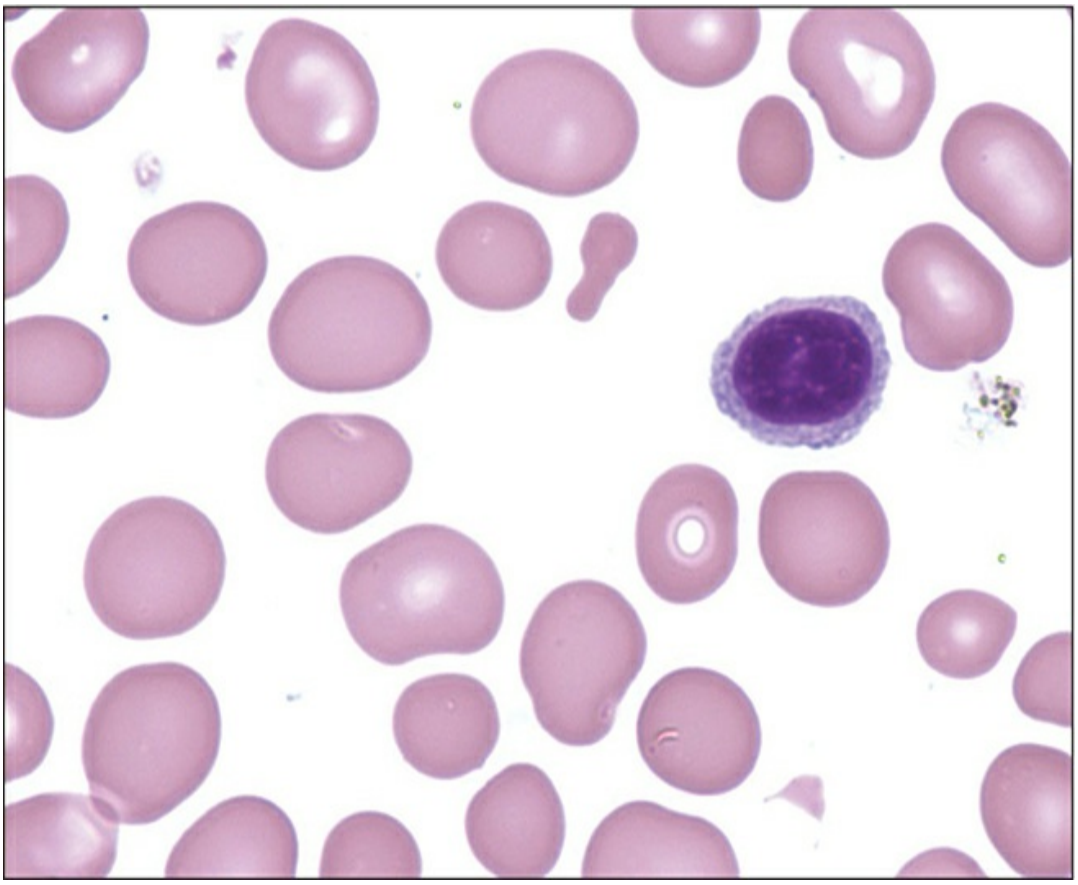


Figure IIA3-1

Peripheral blood smear.

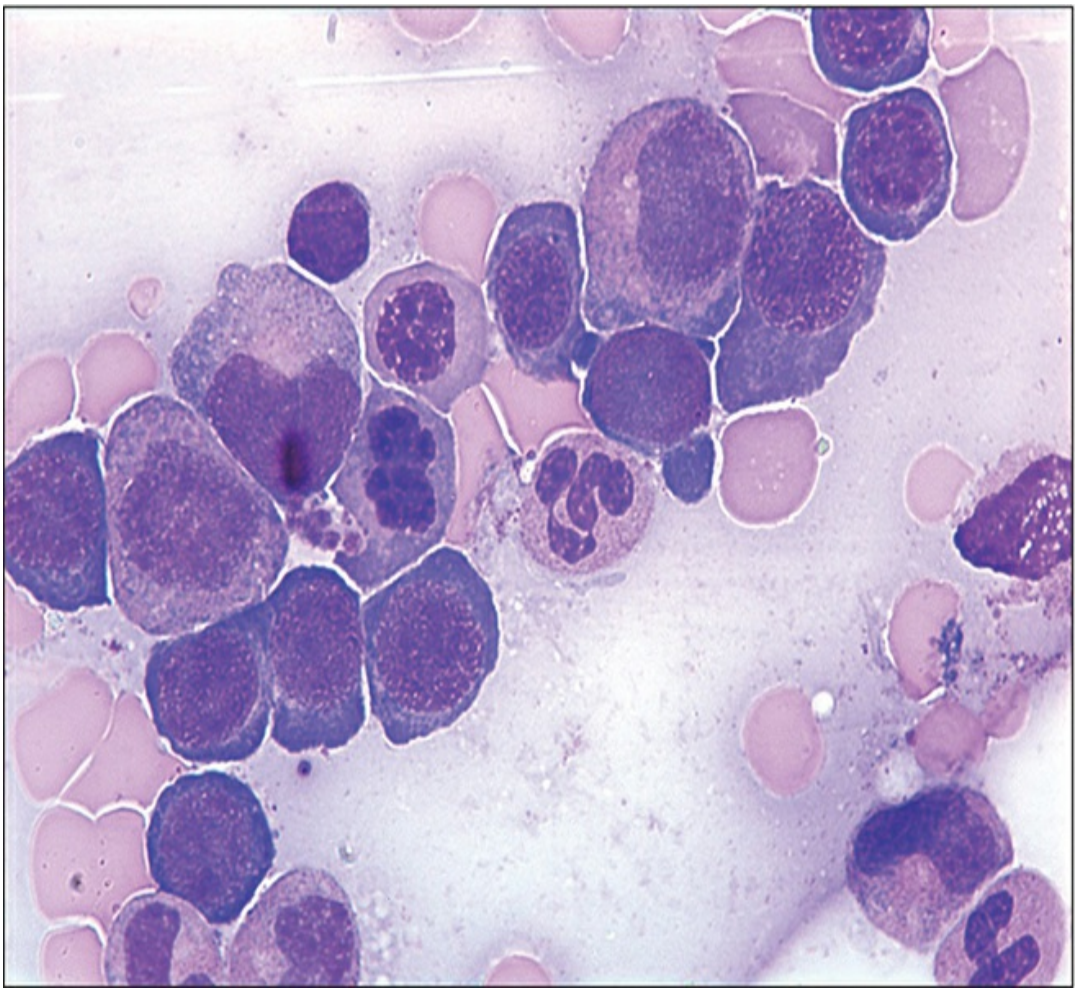


Figure IIA3-2

Bone marrow smear.

Clinical Features

- Usually affects the hematopoietic and gastrointestinal systems
- Neurologic system is not affected
- Anemia onset may occur 2–3 months after deficiency and may be severe
- History of food faddism, alcoholism, or poor dietary intake
- Glossitis

Pathology

- Defective DNA synthesis due to folate deficiency
  - Ineffective hematopoiesis
  - Dietary deficiency—levels can decrease within 1 month of deficient intake
  - Increased demands—pregnancy
  - Malabsorption
    - Nontropical sprue (gluten-sensitive enteropathy)
    - Tropical sprue
  - Medications that impair DNA synthesis
    - Phenytoin
    - Methotrexate

Laboratory Features

White Blood Cells

- Granulocytopenia
- Hypersegmented neutrophils

Platelets

- Thrombocytopenia

Red Blood Cells

- Macrocytic, normochromic anemia
- Presence of macroovalocytes
- Howell-Jolly bodies, Cabot rings, basophilic stippling
- Reticulocyte count normal or decreased
- No polychromasia
- Red blood cell distribution width increased
- Increased mean corpuscular volume

Bone Marrow

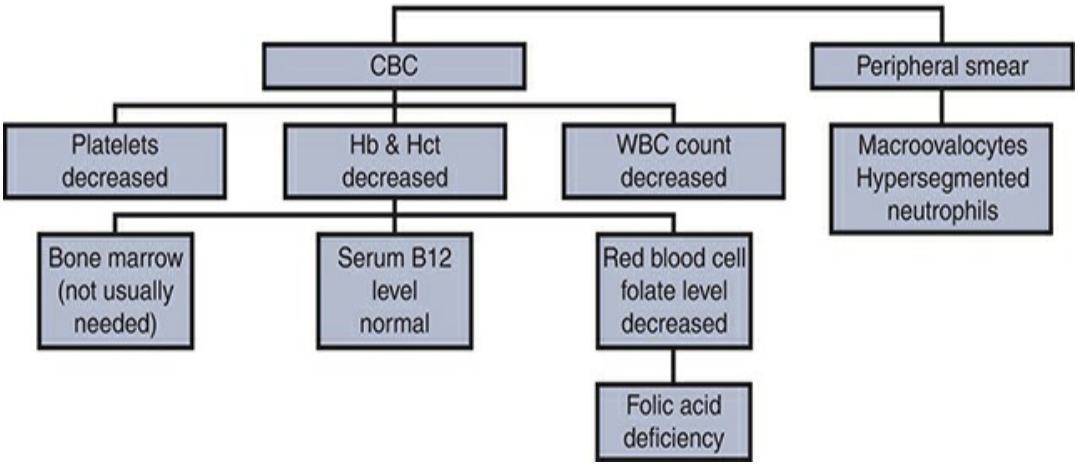
- Megaloblastic erythroid precursors

- Giant myelocytes and metamyelocytes may be seen
- Megakaryocytes may exhibit hyperlobulation and are increased in number

Chemistries

- Indirect bilirubin level increased
- Serum lactic dehydrogenase level increased
- Serum folate level decreased
- Red blood cell folate level is decreased
- Methylmalonic acid level normal
- Serum B_{12} level normal or decreased
- Homocysteine level increased

Diagnostic Scheme



Vitamin B_{12} Deficiency (Pernicious Anemia)

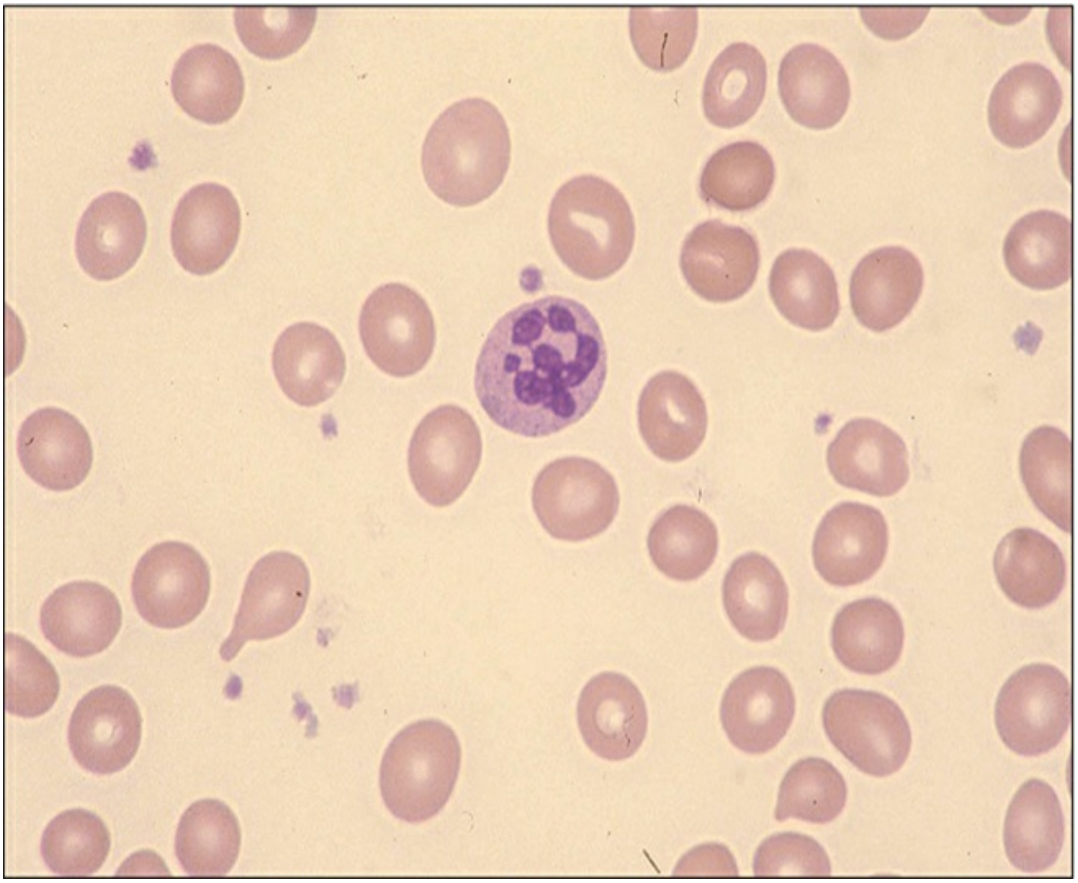


Figure IIA3-3

Peripheral blood smear.

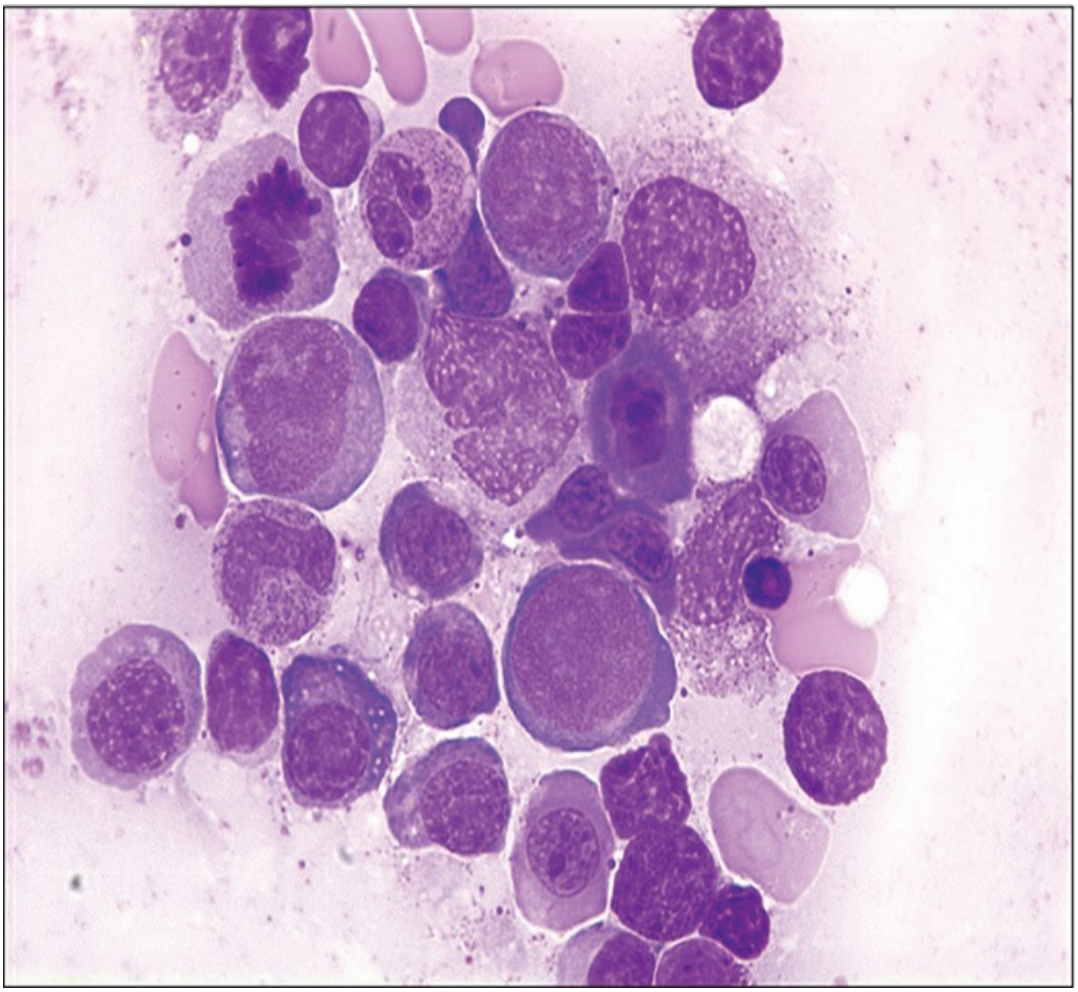


Figure IIA3-4

Bone marrow smear.

Clinical Features

- Usually occurs in persons older than 60 years
- Insidious onset
- Fatigue, weakness, yellowish-waxy pallor
- Smooth tongue
- Gastrointestinal complaints
- Paresthesia, mental changes, spastic gait

Pathology

- Abnormal DNA synthesis
  - Ineffective hematopoiesis

- Causes
  - Dietary lack of vitamin B_{12} (rare in the United States)
  - Antibodies to intrinsic factor or antibodies to the parietal cell components
  - Decreased ileal absorption
  - Decreased availability (anatomic abnormalities)
  - Transcobalamin II deficiency
  - Cellular metabolic disorders (nitrous oxide)

Laboratory Features

White Blood Cells

- Neutropenia
- Hypersegmented neutrophils and eosinophils

Platelets

- Thrombocytopenia
- Large platelets present

Red Blood Cells

- Macrocytic, normochromic anemia
- Oval macrocytes
- Anisocytosis, poikilocytosis
- Howell-Jolly bodies, basophilic stippling, Cabot rings
- Reticulocyte relative number normal but reticulocyte production index <2

Bone Marrow

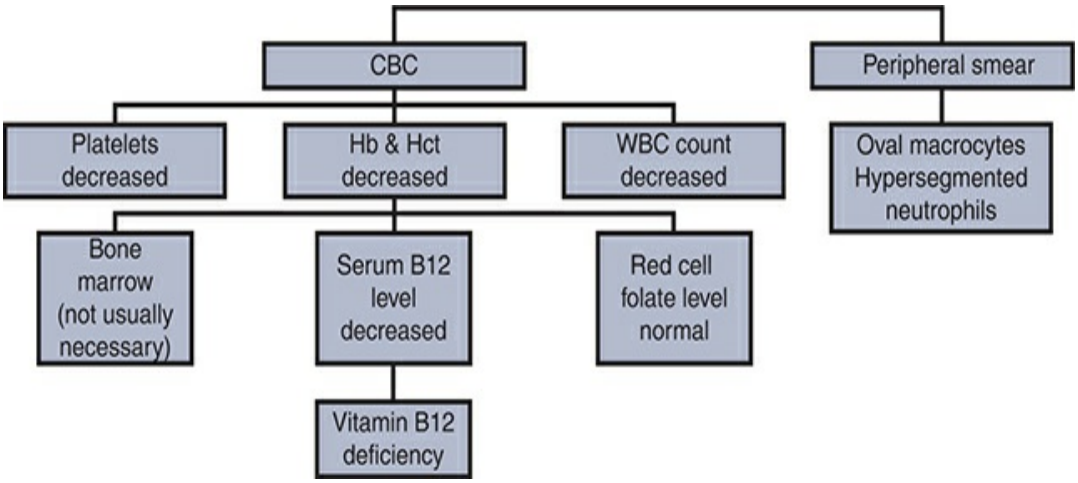
- Hypercellular, myeloid:erythroid ratio about 1:1
- Megaloblastic in erythroid granulocytic and megakaryocytic cell lines
- Giant metamyelocytes present

Chemistries

Chemistries

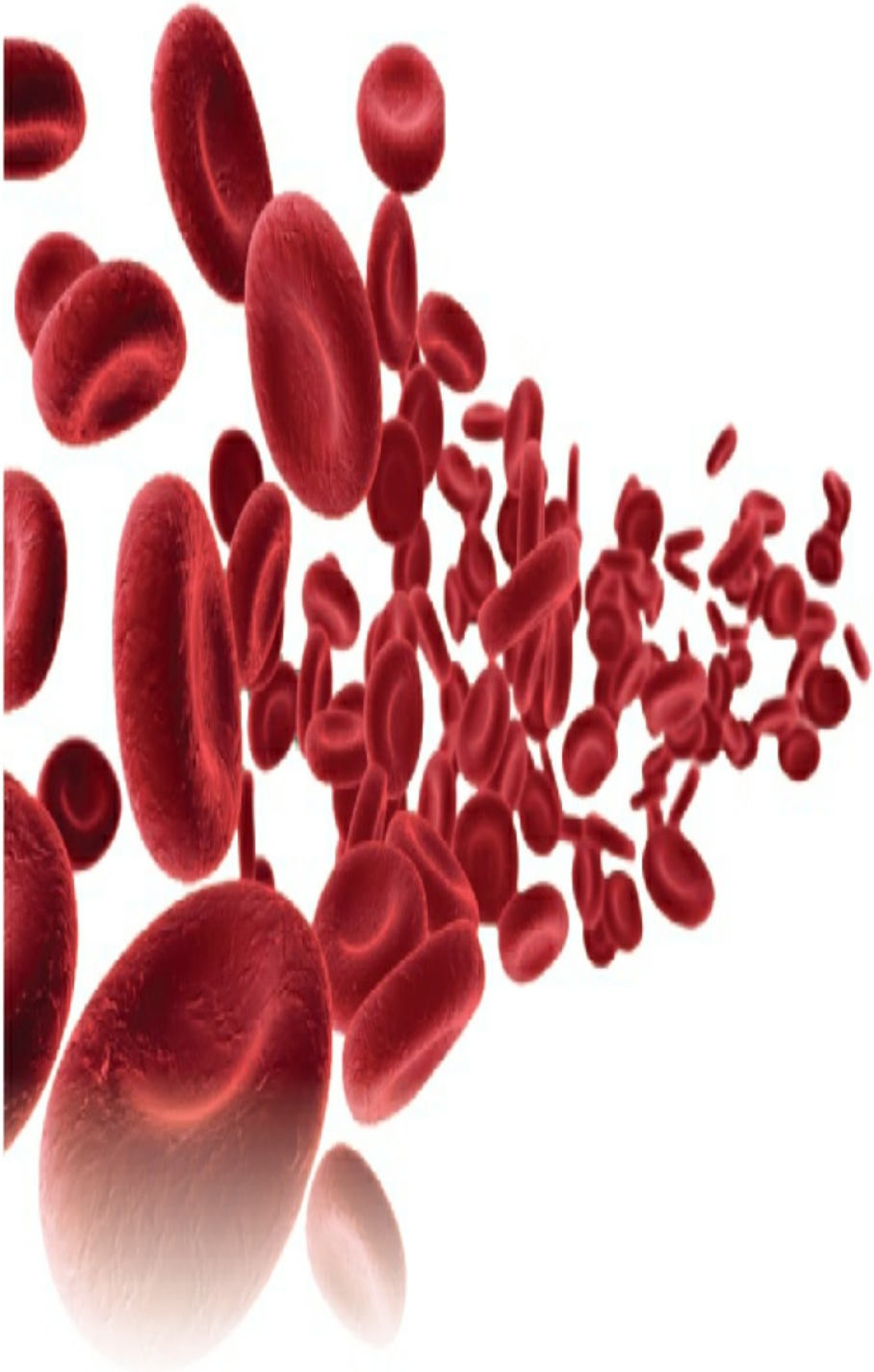
- Increased lactic dehydrogenase level
- Increased unconjugated bilirubin level
- Decreased haptoglobin level
- Decreased B_{12} levels
- Increased homocysteine levels
- Increased methylmalonic acid levels

Diagnostic Scheme



CHAPTER 4

Hypoproliferative Anemias



ANEMIA CAUSED BY MYELOPHTHISIS

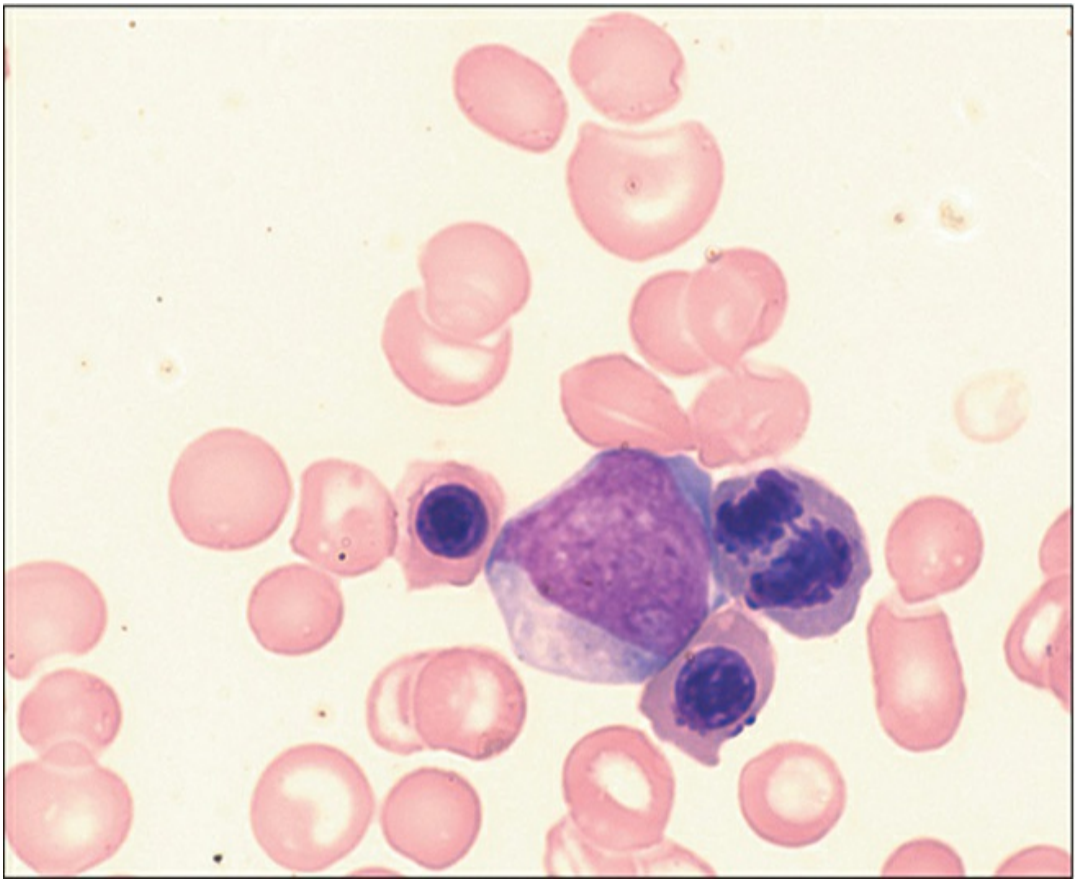


Figure IIA4-1

Peripheral blood smear.

Clinical Features

- Weakness, fatigue
- Hepatosplenomegaly
- Hypersplenism

Pathology

- Marrow invasion (myelophthisis)
  - Tumor
  - Primary myelofibrosis

Laboratory Features

White Blood Cells

- Variable
- Immature granulocytes seen on the peripheral smear

Platelets

- Occasional giant platelets
- Normal to decreased

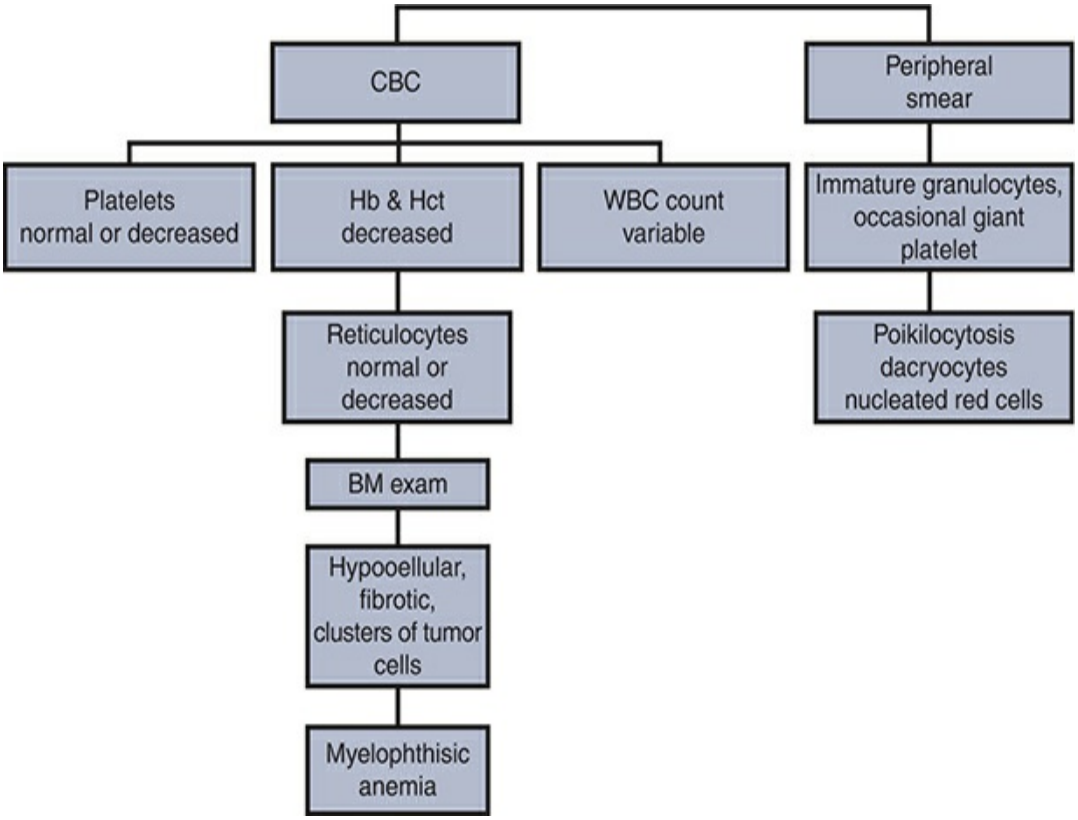
Red Blood Cells

- Normocytic, normochromic
- Poikilocytosis
- Dacryocytes
- Nucleated red blood cells seen on the peripheral smear

Bone Marrow

- Nonspecific changes or even normal morphology
- Bone marrow biopsy may reveal fibrosis or clusters of tumor cells

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal or decreased
Hb & Hct decreased
WBC count variable
Immature granulocytes, occasional giant platelet
Reticulocytes normal or decreased
Poikilocytosis dacryocytes nucleated red cells
BM exam
Hypooellular, fibrotic, clusters of tumor cells
Myelophthisic anemia

ACQUIRED APLASTIC ANEMIA

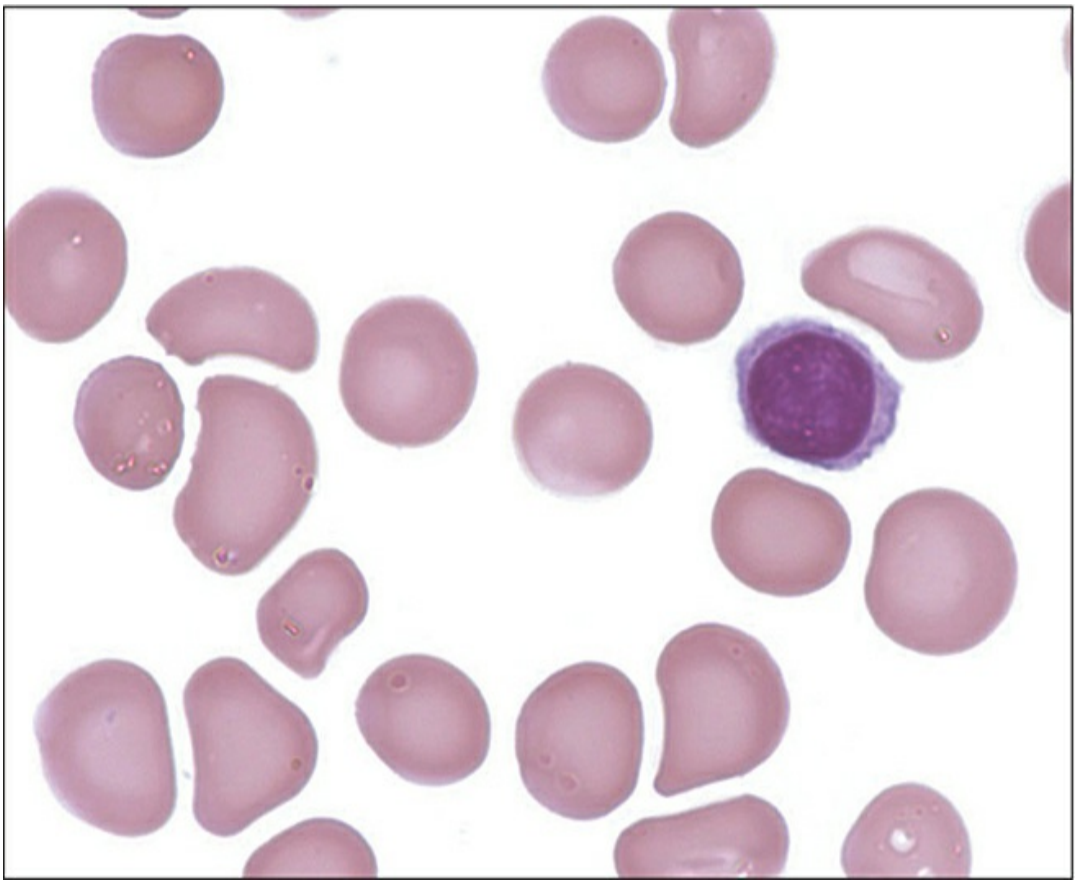


Figure IIA4-2

Peripheral blood smear.

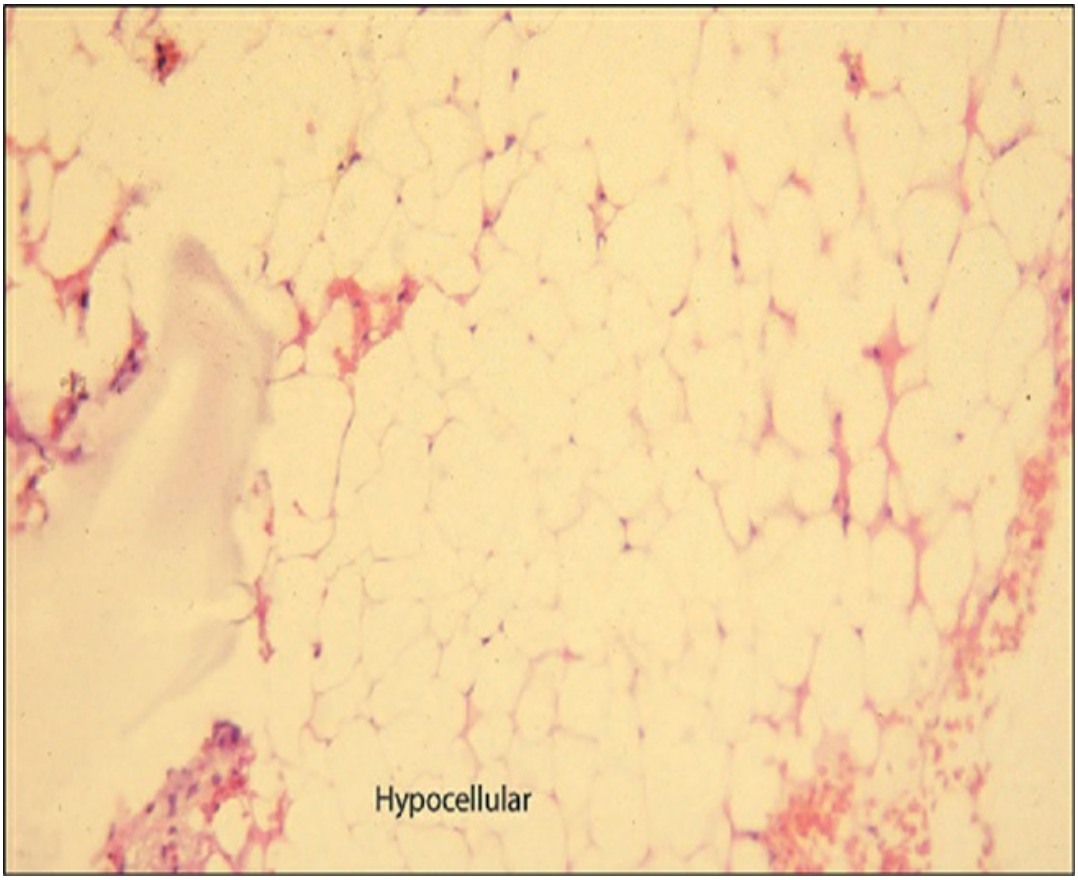


Figure IIA4-3

Bone marrow biopsy.

Clinical Features

- Weakness
- Dizziness
- Increased tendency for bruising
- Infections

Pathology

- Pancytopenia from unknown or multifactorial causes
  - Toxic or therapeutic drugs
  - Immunologic disorders
  - Radiation
  - Viral infections
- Autoimmune attack on stem cells causing decreased

CD34 stem cells
- Paroxysmal nocturnal hemoglobinuria

Laboratory Features

White Blood Cells

- Decreased neutrophils
- Lymphocyte count is normal

Platelets

- Decreased

Red Blood Cells

- Normocytic, normochromic anemia but may be slightly macrocytic
- Red blood cell distribution width normal
- Corrected reticulocyte count decreased

Bone Marrow

- Hypocellular
- Absence of abnormal bone marrow infiltrates
- Absence of bone marrow reticulin fibrosis

Criteria for the Diagnosis

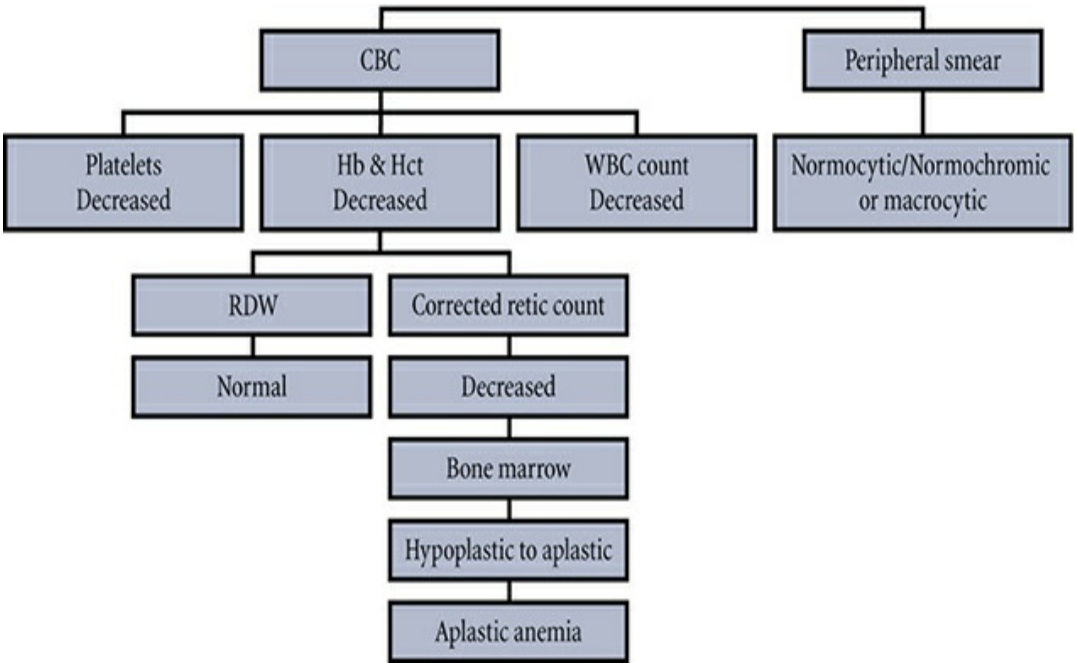
- Patients must exhibit at least two of the following:
  - Absolute neutrophil count $<1.5 \times 10^9$/L
  - Platelets $<50 \times 10^9$/L
  - Hemoglobin <10 g/dL

Criteria for Subclassification of Severe Aplastic Anemia

- Bone marrow cellularity <25% or 25–50% with <30% residual hematopoietic cells and at least two of the following:

- Neutrophil count $<0.5 \times 10^9$/L
- Platelet count $<20 \times 10^9$/L
- Reticulocyte count $<0.6 \times 10^9$/L of red blood cells

Diagnostic Scheme



CONGENITAL DYSERYTHROPOIETIC ANEMIA

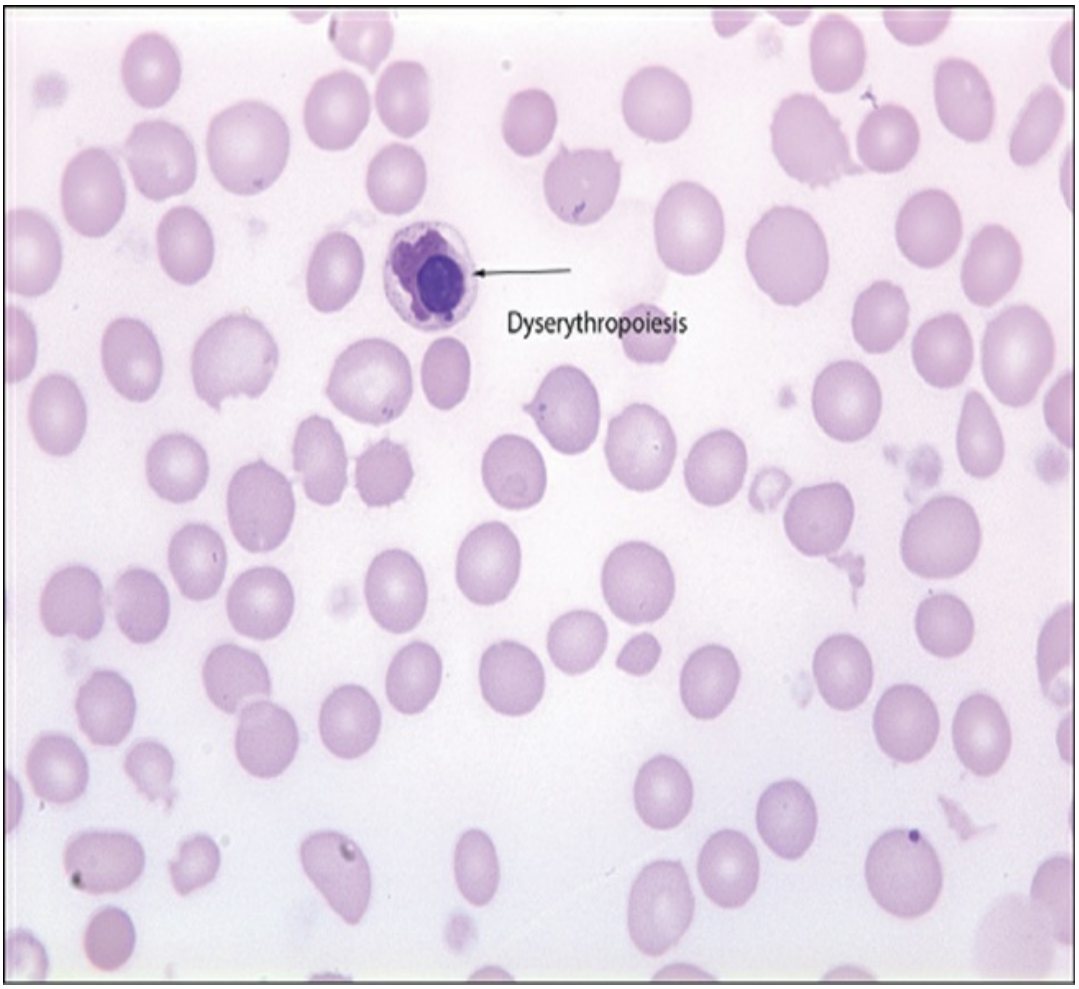


Figure IIA4-4

Peripheral blood smear.

Clinical Features

- Disease manifestation varies from birth to early infancy to middle age
- Type I
  - Autosomal recessive inheritance
  - Male:female ratio 1.25:1
  - Icterus, splenomegaly, brown skin pigmentation, finger, and toe abnormalities

- Type II
  - Autosomal recessive inheritance
  - Male:female ratio 1:1
  - Jaundice, hepatosplenomegaly, gallstones
- Type III
  - Autosomal dominance inheritance
  - Male:female ratio 1.9:1

Pathology

- Genetic defects in mitosis
- Abnormal erythroid production due to ineffective erythropoiesis
- Inherited marrow disorders
- Ineffective erythropoiesis because a discrepancy exists between erythroid output from marrow to circulation, resulting in anemia
- Type I
  - Mutations in CDAN1 , C15orf41
- Type II
  - Mutations in CDAN2 , SEC23B
- Type III
  - Mutations in KIF23

Laboratory Features

Type I

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Mild anemia
  - Normocytic or macrocytic
- Decreased reticulocyte count for degree of anemia
- Reticulocytes 1–7% of red blood cells
- Mean corpuscular volume slightly increased
- Anisocytosis, poikilocytosis
- Basophilic stippling
- Dyserythropoiesis
- Acidified serum test negative

Bone Marrow

- Erythroid hyperplasia
- Megaloblastic
- Chromatin bridging

Type II

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Normocytic or macrocytic anemia
- Anisocytosis, poikilocytosis
- Dacryocytes
- Dyserythropoiesis
- Basophilic stippling
- Acidified serum test positive
- Negative sugar water test

Bone Marrow

- Gaucher-like cells

- Erythroid hyperplasia
- Megaloblastic
- Binuclearity, multinuclearity

Type III

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

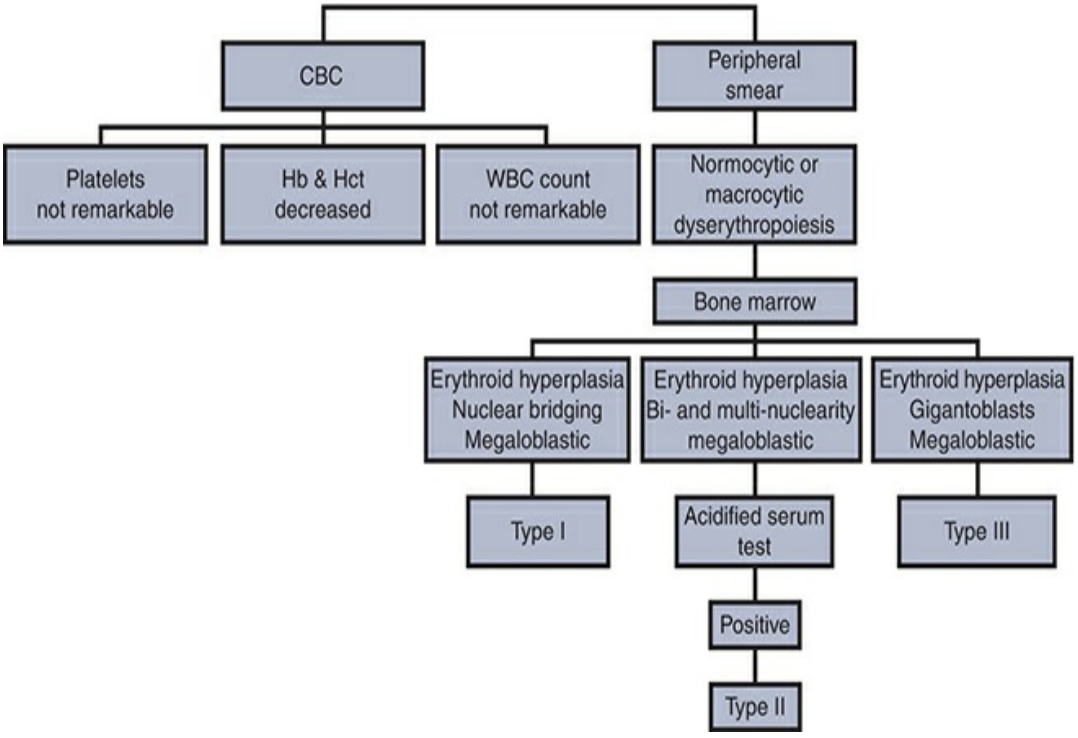
Red Blood Cells

- Mild to moderate anemia
  - Macrocytic
- Dyserythropoiesis
- Mean corpuscular volume normal to slightly increased
- Acidified serum test negative

Bone Marrow

- Erythroid hyperplasia
- Megaloblastic
- Multinuclearity

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Normocytic or macrocytic dyserythropoiesis
Bone marrow
Erythroid hyperplasia Nuclear bridging Megaloblastic
Erythroid hyperplasia Bi- and multi-nuclearity megaloblastic
Erythroid hyperplasia Gigantoblasts Megaloblastic
Type I
Acidified serum test
Type III
Positive
Type II

CONGENITAL PURE RED CELL APLASIA (DIAMOND-BLACKFAN ANEMIA)

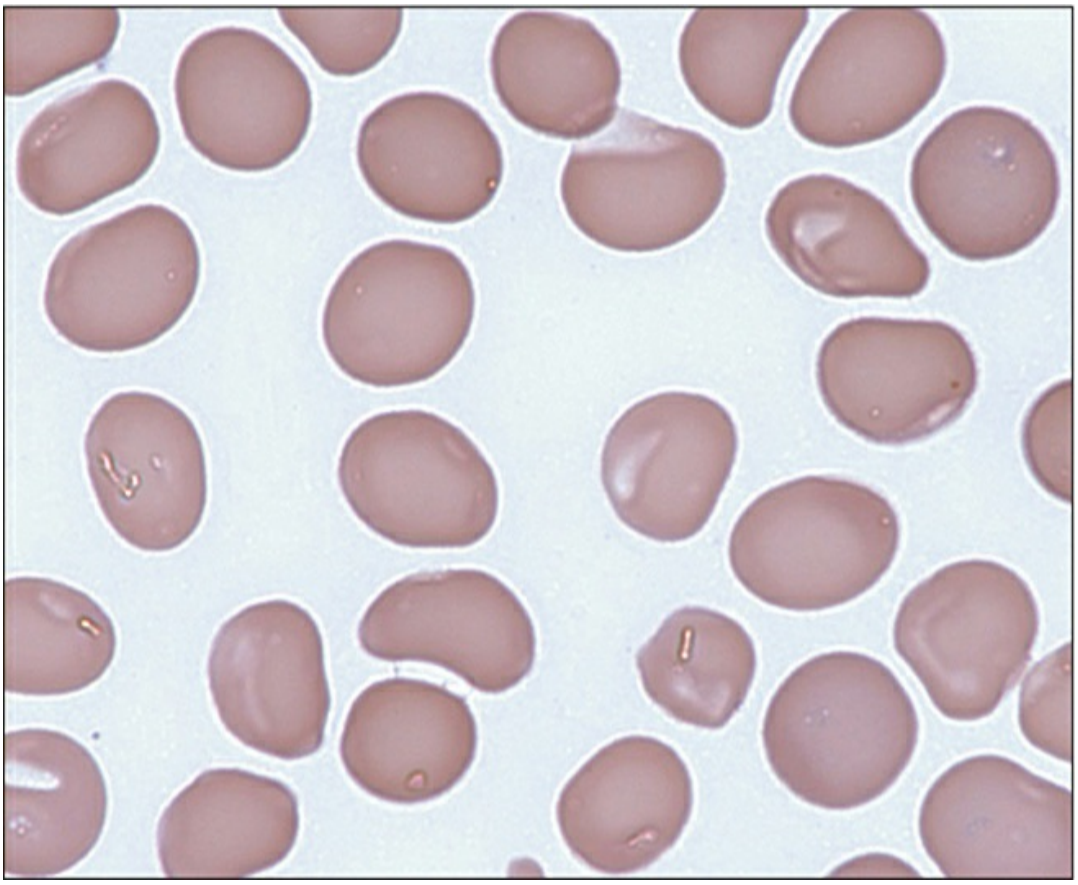


Figure IIA4-5

Peripheral blood smear.

Clinical Features

- Anemia presents within first year of life
- Congenital anomalies of the kidneys, eyes, skeleton, and heart
- Short stature
- Thumb abnormalities
- Microcephaly
- Pallor, listlessness, poor appetite, and failure to thrive, which may progress to congestive heart failure with

breathlessness
- Hepatosplenomegaly

Pathology

- Mutations in genes coding several ribosomal subunit proteins or GATA1 mutations
- Decreased erythroblasts

Laboratory Features

White Blood Cells

- Normal to slightly decreased

Platelets

- Normal to slightly increased

Red Blood Cells

- Decreased
- Reticulocyte count decreased
- Increased fetal hemoglobin
- Increased mean corpuscular volume

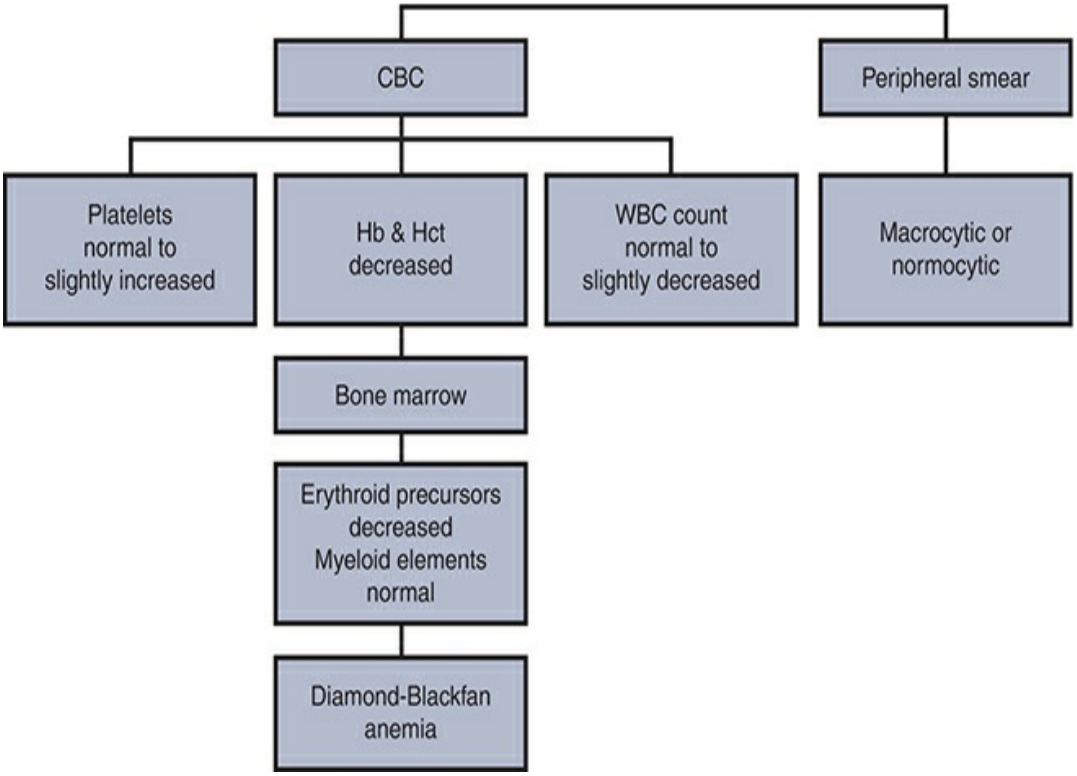
Bone Marrow

- Myeloid elements appear normal
- Erythroid precursors decreased with a predominance of pronormoblasts

Chemistries

- Serum iron level normal to slightly increased
- % Iron saturation increased
- Erythropoietin increased
- Normal erythrocyte adenosine deaminase activity

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal to slightly increased
Hb & Hct decreased
WBC count normal to slightly decreased
Macrocytic or normocytic
Bone marrow
Erythroid precursors decreased
Myeloid elements normal
Diamond-Blackfan anemia

FANCONI ANEMIA

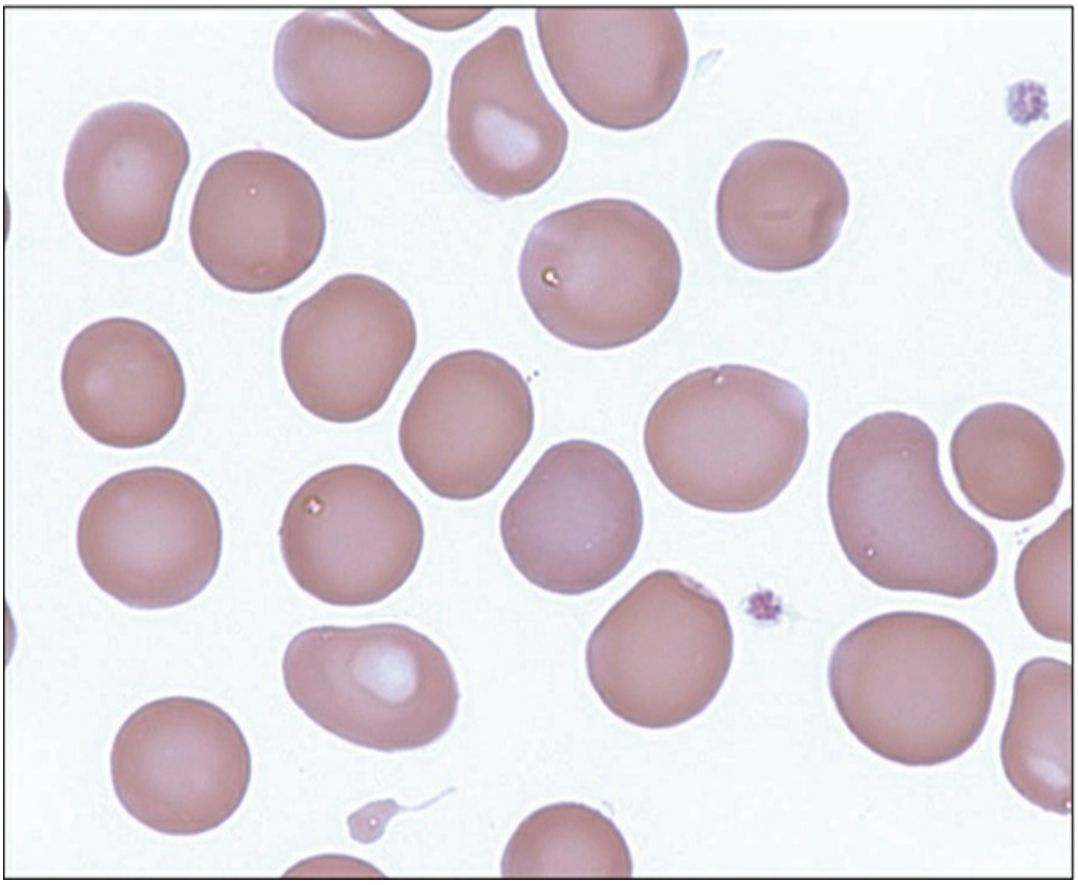


Figure IIA4-6

Peripheral blood smear.

Clinical Features

- Short stature
- Skin pigmentation
- Renal anomalies
- Bone dysplasia
- Microcephaly
- Mental retardation
- Infections
- Male:female ratio 1–3:1
- Bone marrow failure

Pathology

- Autosomal recessive inheritance or X-linked
- Biallelic mutation in any of approximately 19 separate genes resulting in sensing and repairing DNA damage

Laboratory Features

White Blood Cells

- Decreased granulocytes

Platelets

- Decreased

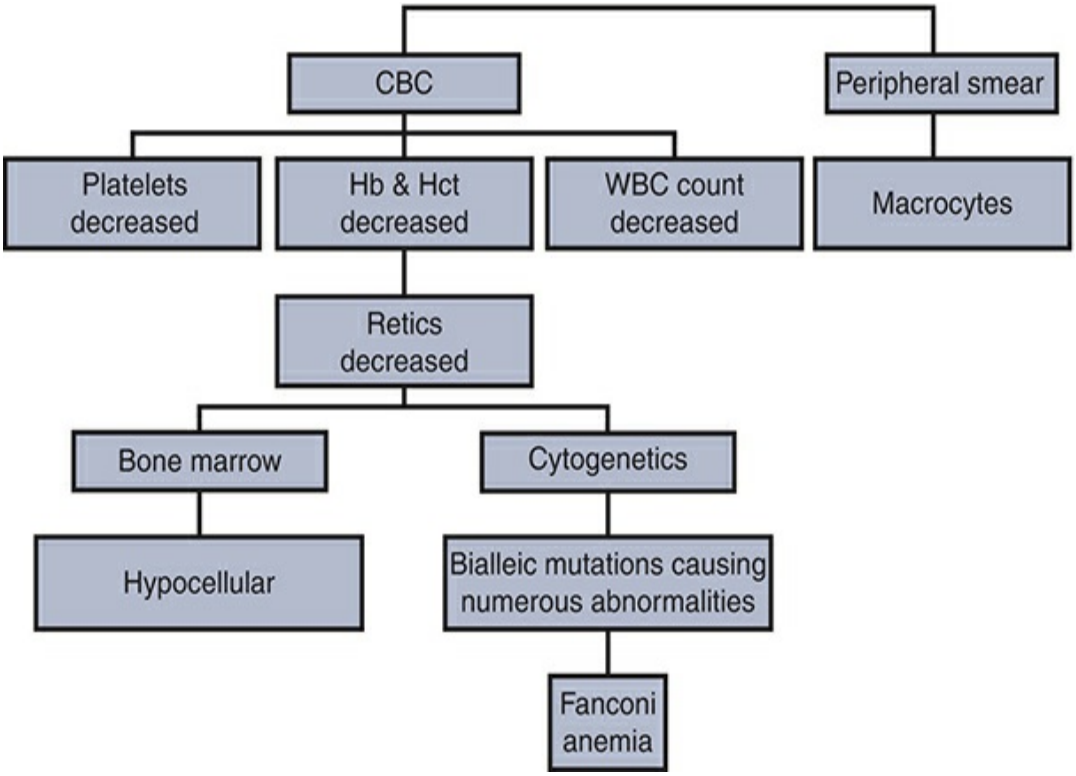
Red Blood Cells

- Macrocytic anemia
- Increased fetal hemoglobin

Bone Marrow

- Hypocellular
- Possible dyserythropoiesis

Diagnostic Scheme


CBC
Peripheral smear
Platelets decreased
Hb & Hct decreased
WBC count decreased
Macrocytes
Retics decreased
Bone marrow
Cytogenetics
Hypocellular
Bialleic mutations causing numerous abnormalities
Fanconi anemia

PURE RED CELL APLASIA

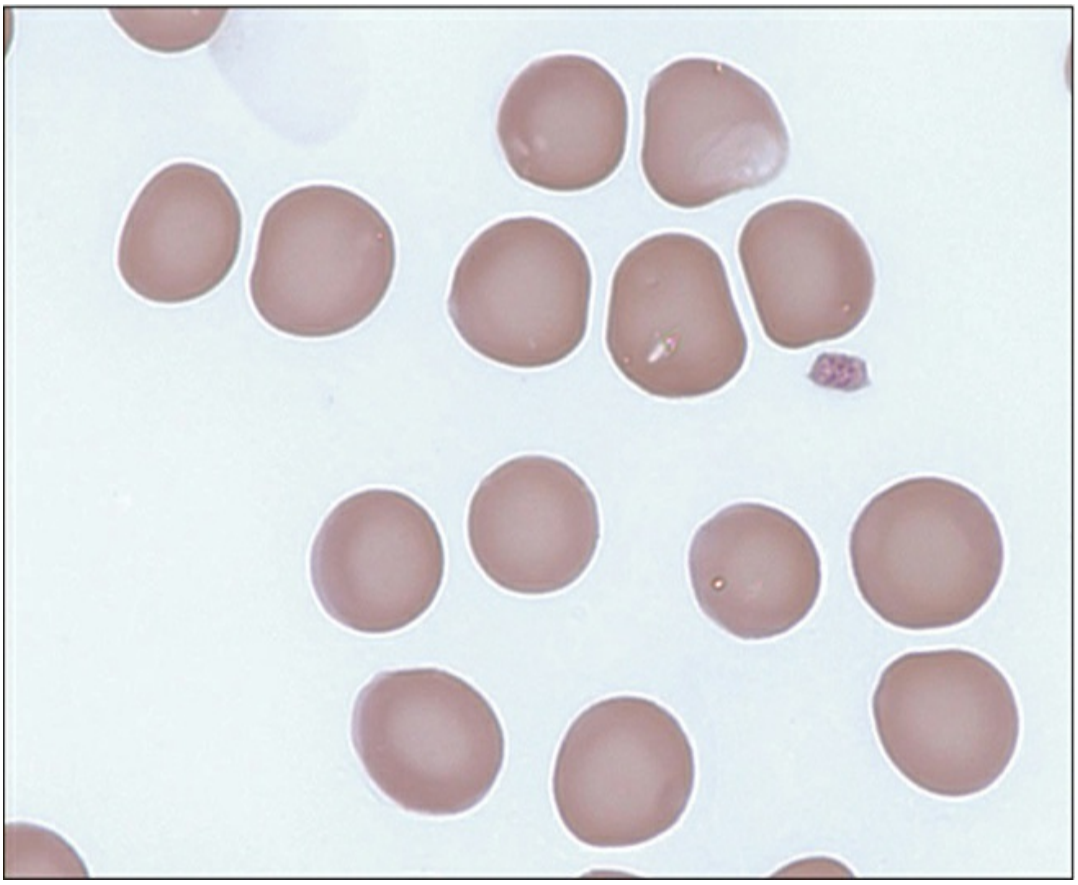


Figure IIA4-7

Peripheral blood smear.

Clinical Features

- Severe anemia—weakness, headache, vertigo, fatigue, tinnitus, and irritability
- Primary
  - Idiopathic
  - Immune mediated
- Secondary
  - Associated with thymoma
  - Neoplasia
  - Drugs
  - Infections

Pathology

- Erythropoiesis inhibited primarily by immune mechanism
- T cells, particularly large granular lymphocytes, may be involved in the suppression of erythropoiesis
- Specific attachment on erythroid precursors by the parvovirus B19
- Clonal abnormality as a prodrome to myelodysplastic syndrome
- Medications may cause a direct toxic effect

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

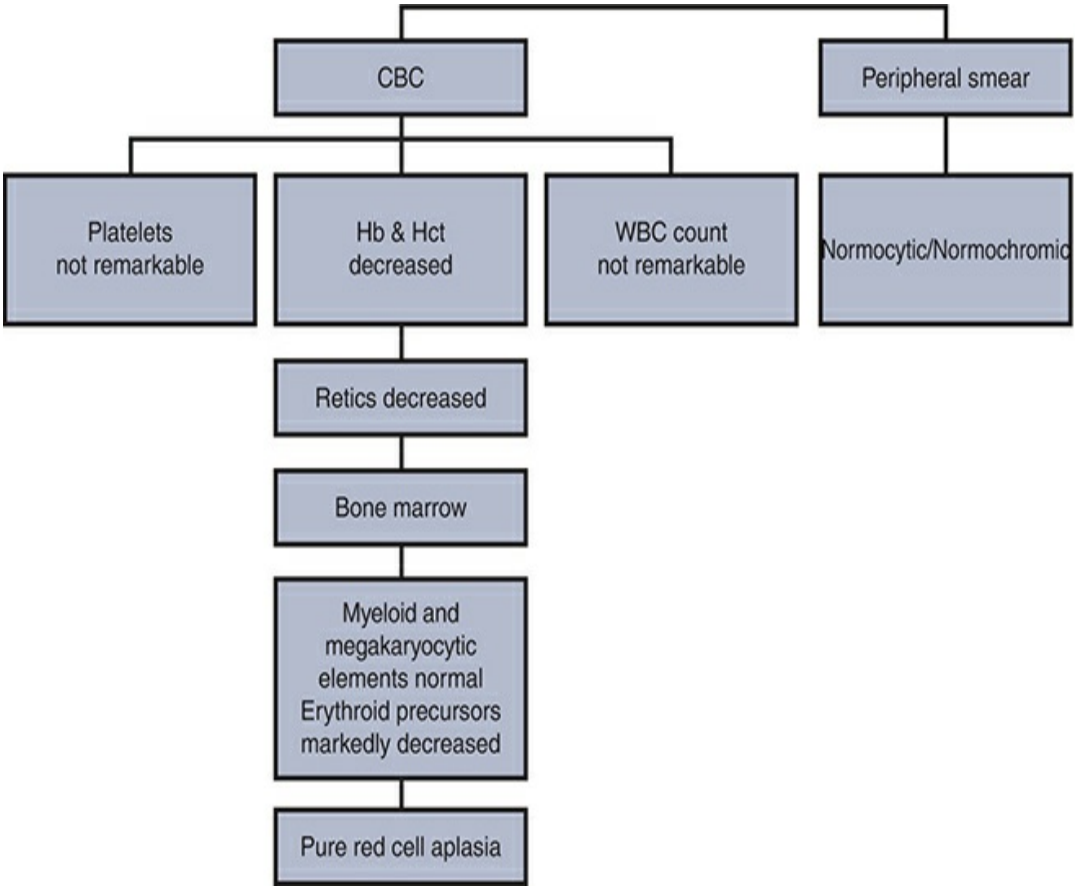
Red Blood Cells

- Normocytic/normochromic anemia
- Hemoglobin level decreased
- Hematocrit level decreased
- Reticulocytes absent

Bone Marrow

- Absence of erythroid cells
- Myeloid and megakaryocytic elements are preserved
- No significant dysplasia

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Normocytic/Normochromic
Retics decreased
Bone marrow
Myeloid and megakaryocytic elements normal
Erythroid precursors markedly decreased
Pure red cell aplasia

CHAPTER 5

Hemoglobinopathies

α -Thalassemia (4-Gene Deletion)

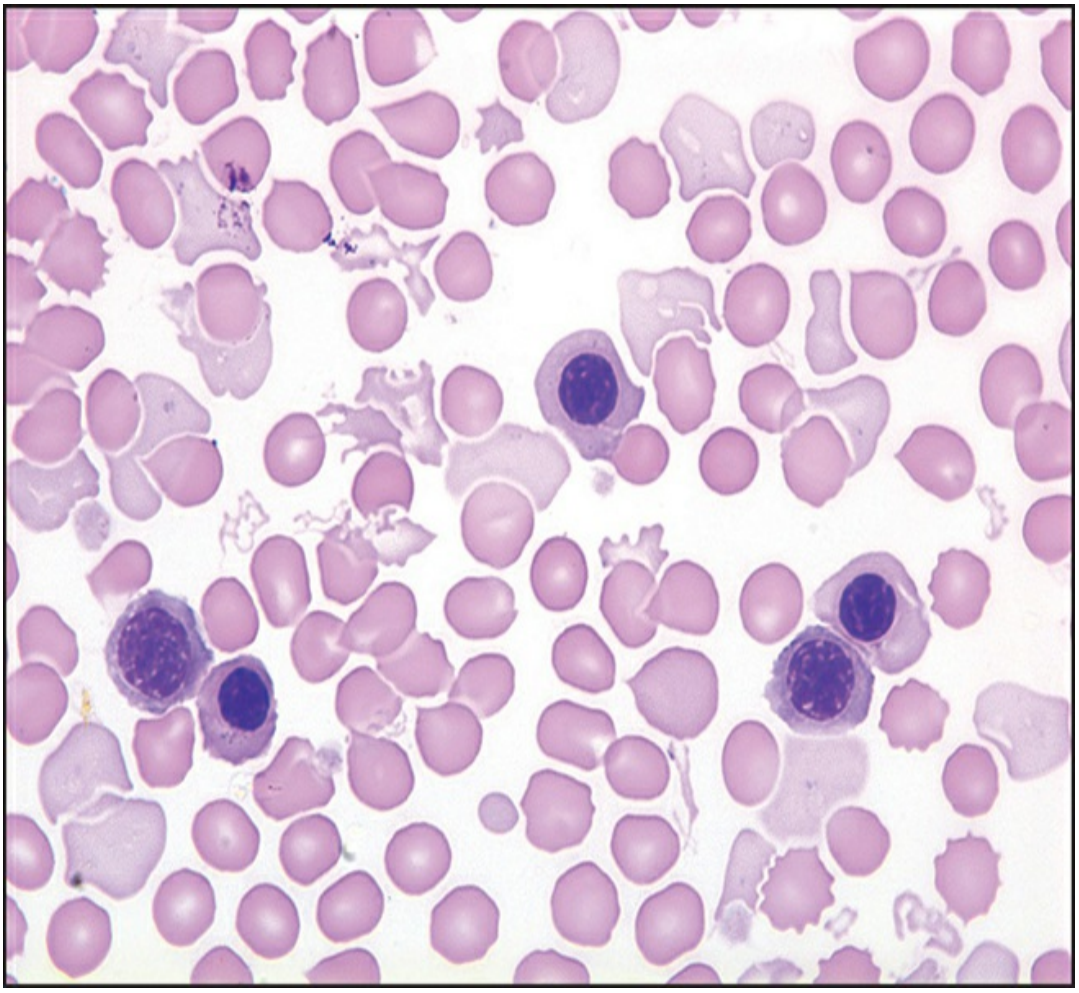


Figure IIA5-1

Cord blood smear.

Clinical Features

- A 4-gene deletion α -thalassemia produces hemoglobin Bart hydrops fetalis syndrome and affected infants are either stillborn or die within hours after birth
- Marked hepatosplenomegaly
- Marked anemia

Pathology

- Parents are usually heterozygous for α -thalassemia (−−/αα)

- No α -chains are produced (−−/−−)
- Free g -chains form tetrads, producing hemoglobin Bart
- Excess β -chains form tetramers and form inclusions in red blood cells, which shortens survival

Laboratory Features

White Blood Cells

- Not remarkable

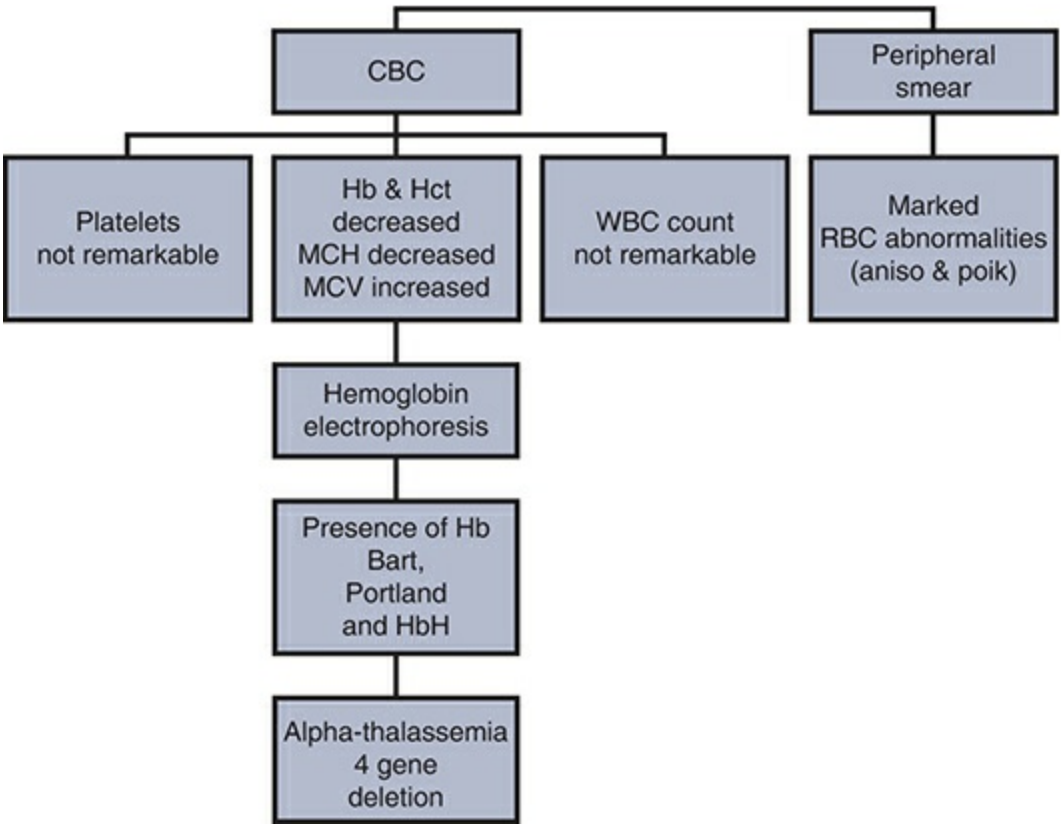
Platelets

- Not remarkable

Red Blood Cells

- Macrocytic/hypochromic anemia
- Mean corpuscular hemoglobin level decreased
- Mean corpuscular volume increased
- Increased nucleated red blood cells
- 80–90% hemoglobin Bart
- 10–20% hemoglobin Portland
- Trace of hemoglobin H

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased MCH decreased MCV increased
WBC count not remarkable
Marked RBC abnormalities (aniso & poik)
Hemoglobin electrophoresis
Presence of Hb Bart, Portland and HbH
Alpha-thalassemia 4 gene deletion

α -Thalassemia (3-Gene Deletion: Hemoglobin H Disease)

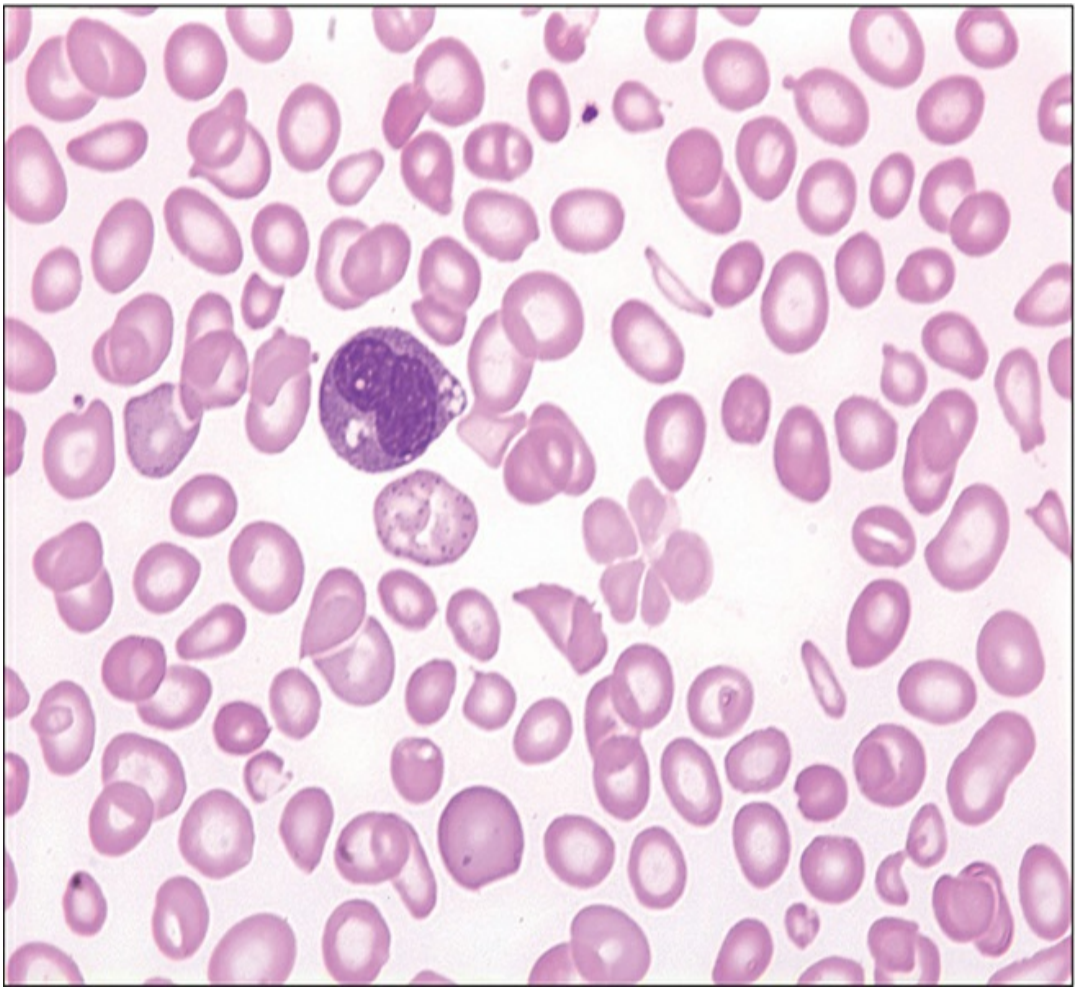


Figure IIA5-2

Peripheral blood smear.

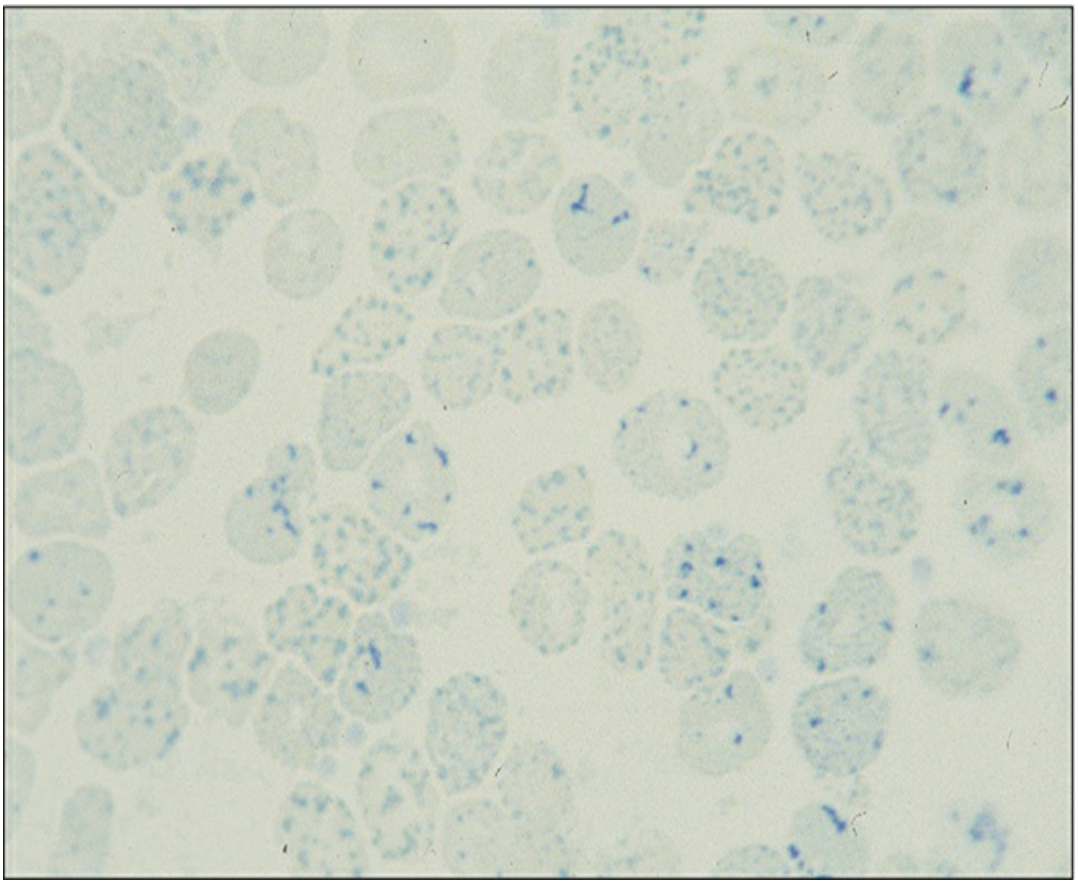


Figure IIA5-3

Brilliant cresyl blue stain.

Clinical Features

- Splenomegaly
- Variable anemia, more severe during pregnancy, infections, and exposure to oxidant drugs

Pathology

- Deletion of three α -genes (−−/−α):
  - Reduced hemoglobin A and thus oxygen delivery
- Excess unpaired β -chains are present and form unstable tetramers (β_4), which forms hemoglobin H
  - Hemoglobin H has a high oxygen affinity, resulting in decreased oxygen delivery
  - Tetramers can cause disturbances in red blood cell

metabolism, membrane function, and deformability, resulting in chronic hemolytic anemia

Laboratory Features

White Blood Cells

- Not remarkable

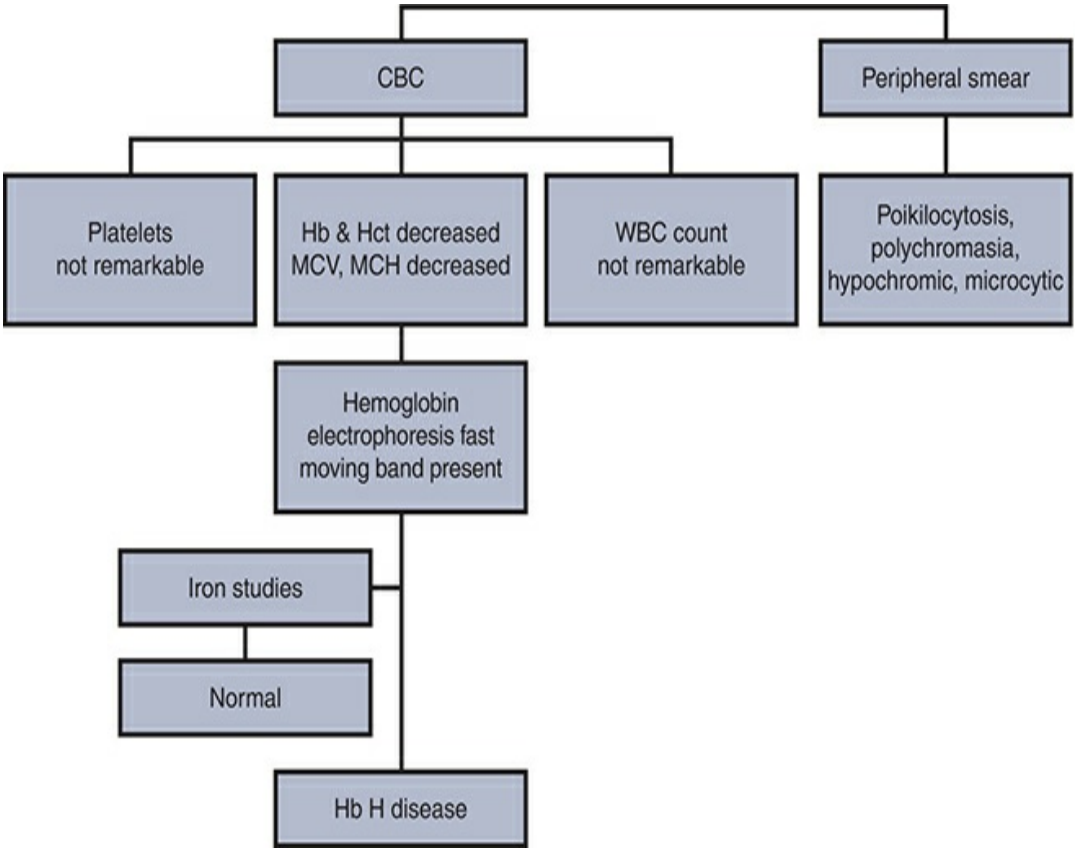
Platelets

- Not remarkable

Red Blood Cells

- Hemoglobin level, 8.0–10.0 g/dL
- Reticulocyte count, 5–10% of red blood cells
- Microcytic/hypochromic anemia
- Increased red blood cell distribution width
- Poikilocytosis
- Polychromasia

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased MCV, MCH decreased
WBC count not remarkable
Poikilocytosis, polychromasia, hypochromic, microcytic
Hemoglobin electrophoresis fast moving band present
Iron studies
Normal
Hb H disease

α -Thalassemia Minor and Silent Carrier

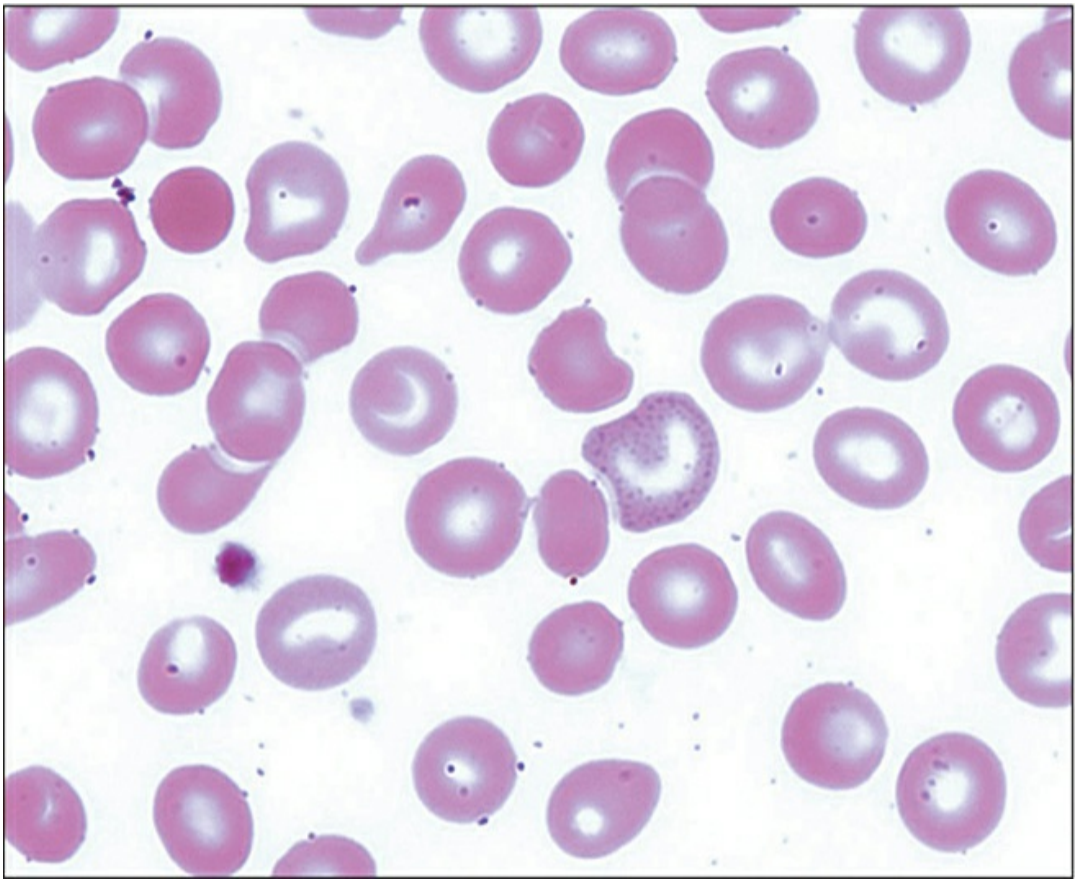


Figure IIA5-4

Peripheral blood smear.

Clinical Features

- No clinical disease is seen with either the trait or the silent carrier

Pathology

Minor or Trait

- Decreased production of α -globin chains
- Exists in two forms:
  - Heterozygous α^0 thalassemia (−−/αα)
  - Homozygous α^+ thalassemia (−α /−α)

- Both forms are common in Southeast Asians, Chinese, and Filipinos
- Homozygous form is common in African American (about 3%)

Silent Carrier

- Heterozygous α^+ ($-\alpha$ /$\alpha\alpha$) is common in Southeast Asians, Chinese, and Filipinos
- About 28% of African Americans have the heterozygous α^+ thalassemia

Laboratory Features

Minor or Trait

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Microcytic and slightly hypochromic anemia
- Poikilocytosis
- Codocytes
- Normal or slightly increased red blood cell distribution width
- Hemoglobin H inclusions may be occasionally found in brilliant cresyl blue (BCB) prep
- 5–15% hemoglobin Bart in cord blood (normal after about 3 months of age)

Silent Carrier

White Blood Cells

- Not remarkable

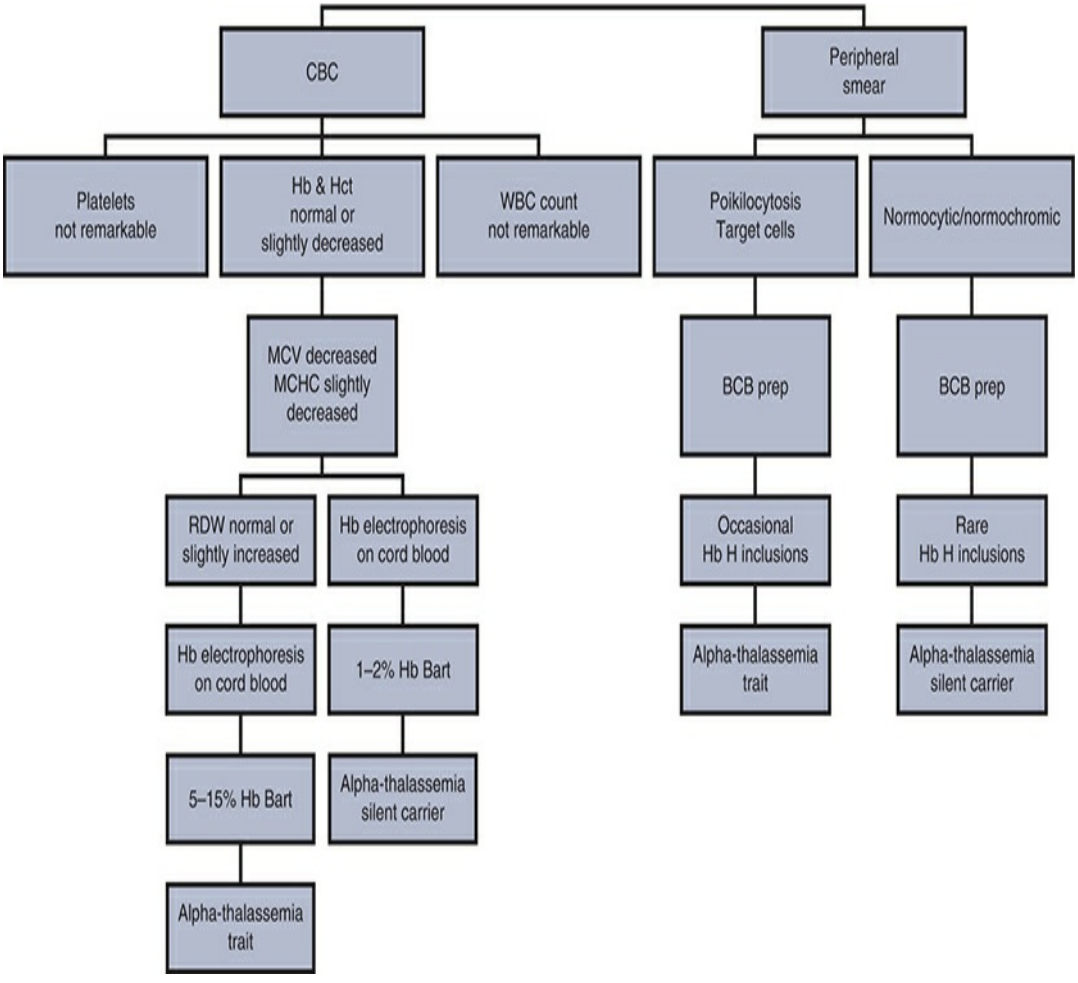
Platelets

- Not remarkable

Red Blood Cells

- No hematologic manifestations
- 1–2% hemoglobin Bart found at birth
- Rare hemoglobin H inclusion found on BCB prep

Diagnostic Scheme



β -Thalassemia

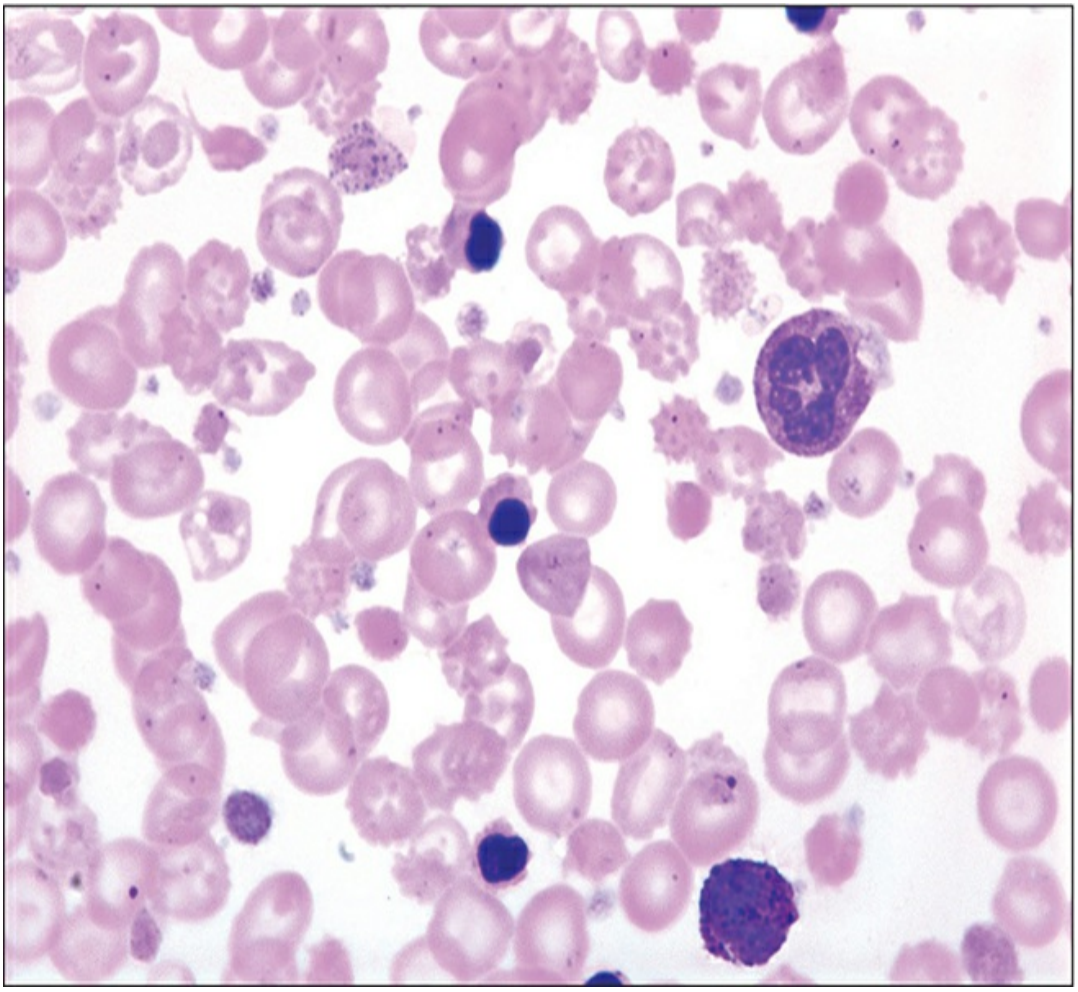


Figure IIA5-5

Peripheral blood smear—major.

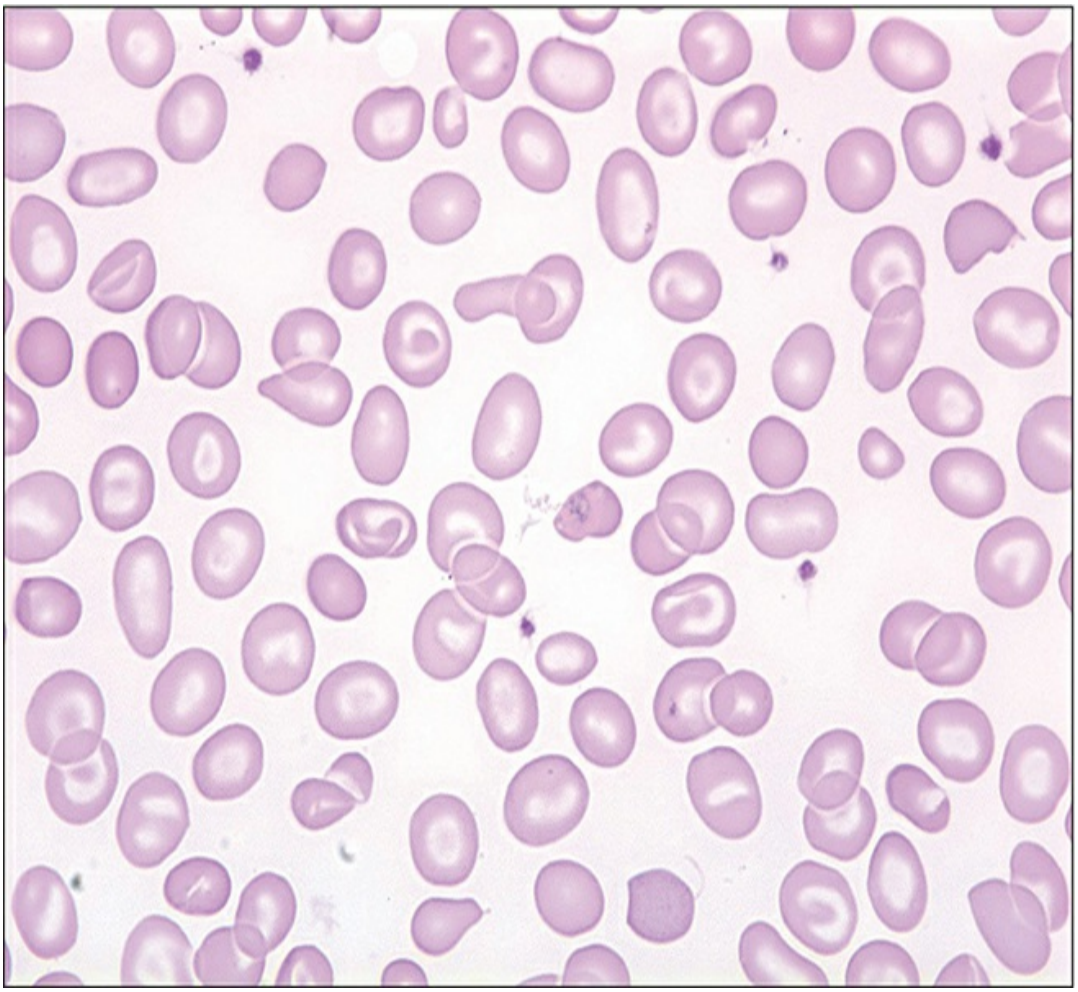


Figure IIA5-6

Peripheral blood smear—intermedia.

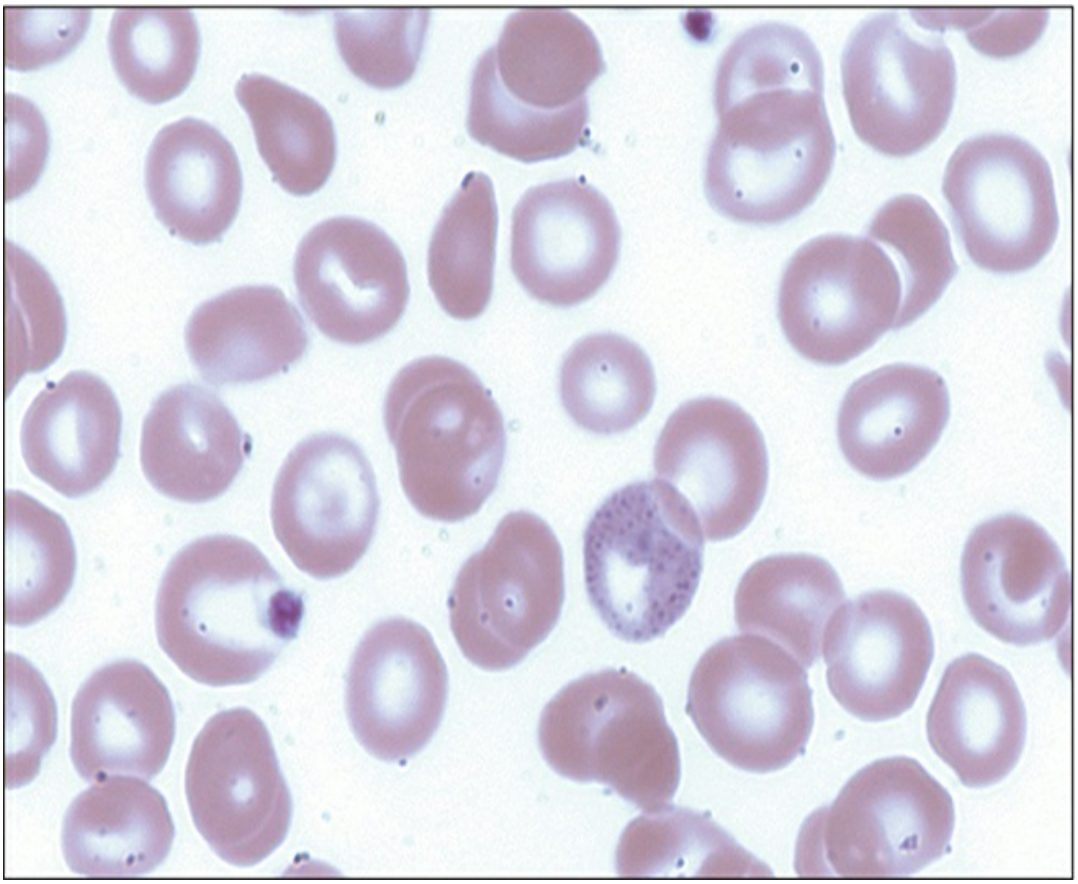


Figure IIA5-7

Peripheral blood smear—minor.

Clinical Features

- Major variant:
  - Severe anemia
  - Transfusion dependent
  - Growth retardation
  - Massive hepatosplenomegaly
  - Severe ineffective erythropoiesis
  - Early death with iron overload
- Intermedia variant:
  - Moderate anemia
  - Splenomegaly
  - Moderate ineffective erythropoiesis

- Minor variant:
  - Mild anemia
  - Usually no symptoms

Pathology

- β -chain production is absent or diminished—the more β -chain produced, the less severe the disease
- Unmatched α -chains accumulate and aggregate:
  - Ineffective erythropoiesis
  - Chronic hemolytic process
- Decreased erythrocyte hemoglobin production

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Nucleated red cells on peripheral smear (found in major and intermedia)
- Hypochromic/microcytic anemia
- Target cells present
- Distorted cells
- Basophilic stippling
- Normal to increased red blood cell distribution width
- Increased red cell count relative to hemoglobin and hematocrit

Bone Marrow

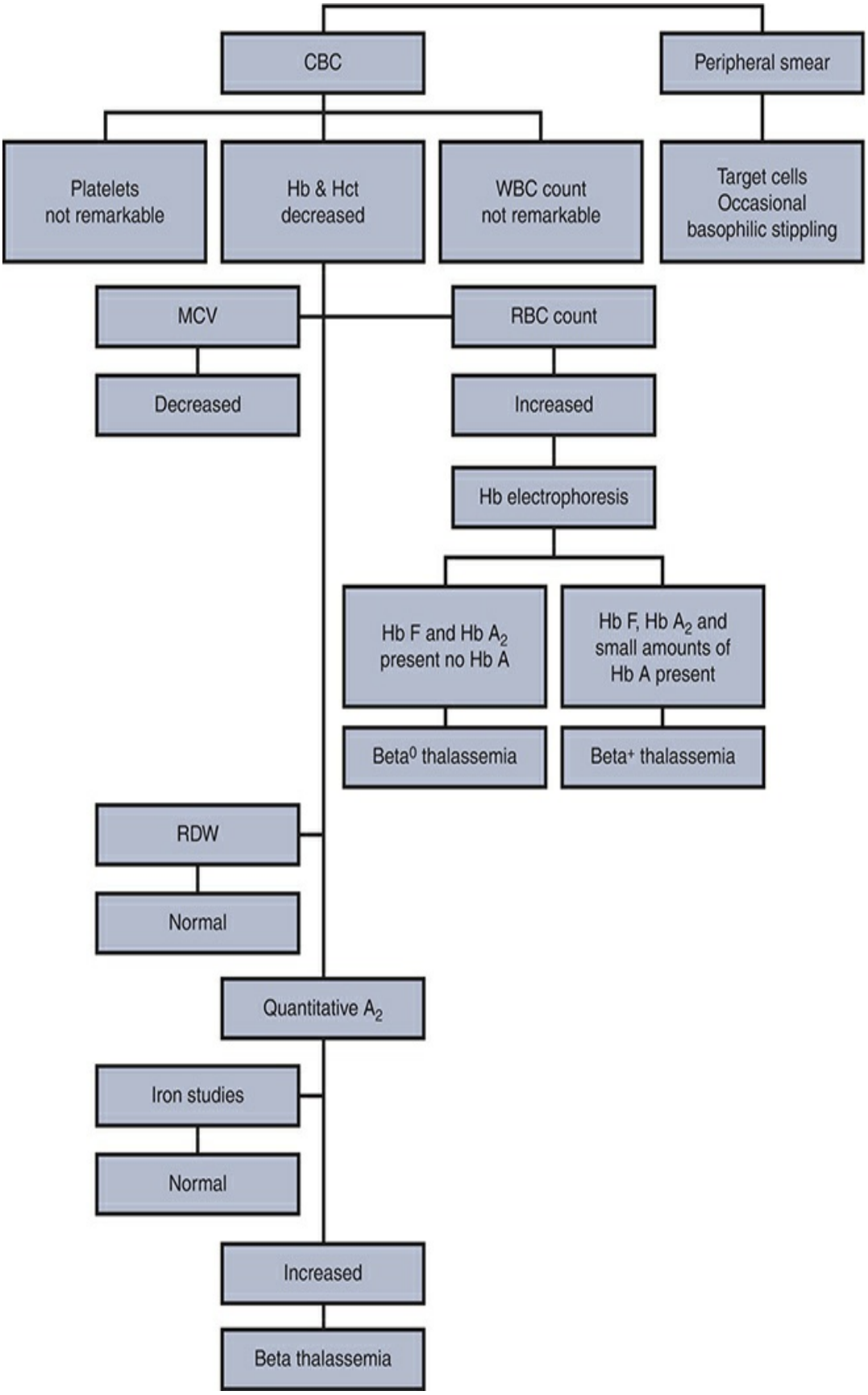
- Ineffective erythropoiesis because of the accumulation of α -globulin chains

- Extremely hyperplastic

Hemoglobin Electrophoresis

- Only hemoglobin F and hemoglobin A_2 are found in β^0 thalassemia
- Small amounts of hemoglobin A may be found in β^+ thalassemia
- Increased hemoglobin A_2 is indicative of β -thalassemia

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Target cells Occasional basophilic stippling
MCV
RBC count
Decreased
Increased
Hb electrophoresis
Hb F and Hb A2 present no Hb A
Hb F, Hb A2 and small amounts of Hb A present
Beta0 thalassemia
Beta+ thalassemia
RDW
Normal
Quantitative A2
Iron studies
Normal
Increased
Beta thalassemia

HEMOGLOBIN C

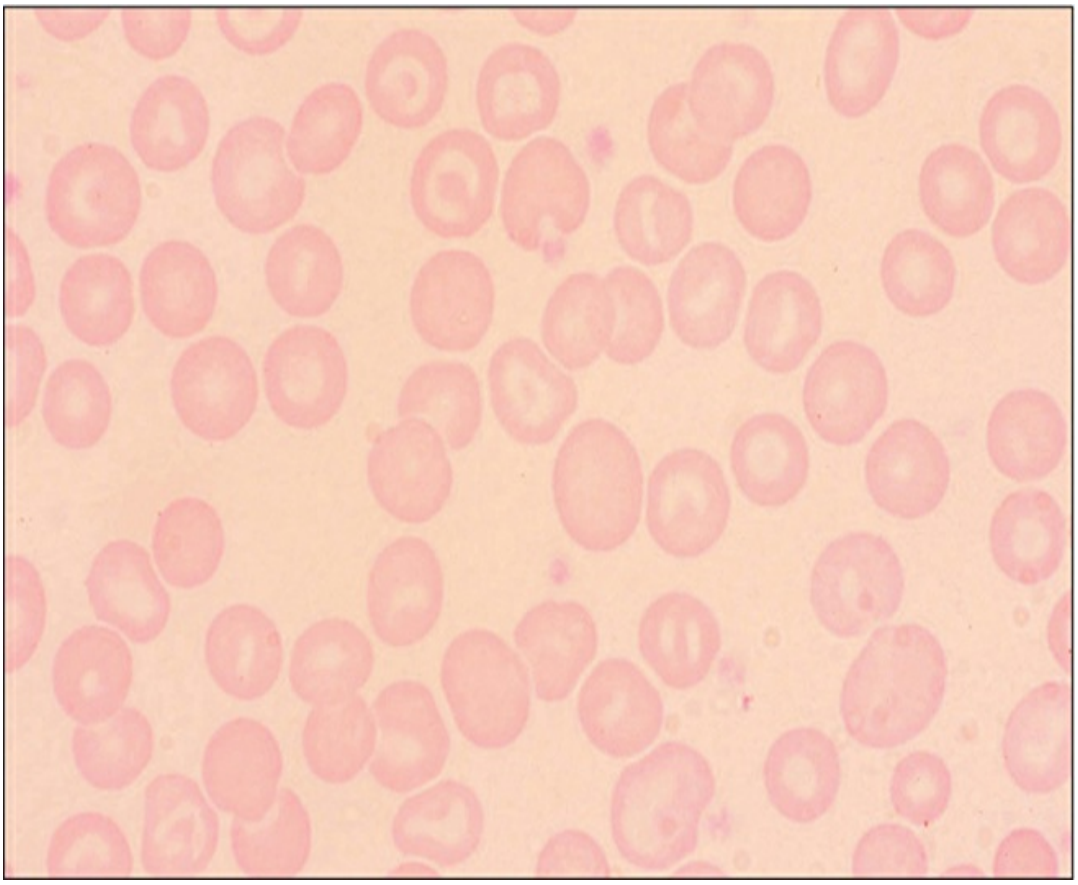


Figure IIA5-8

Peripheral blood smear—heterozygous.

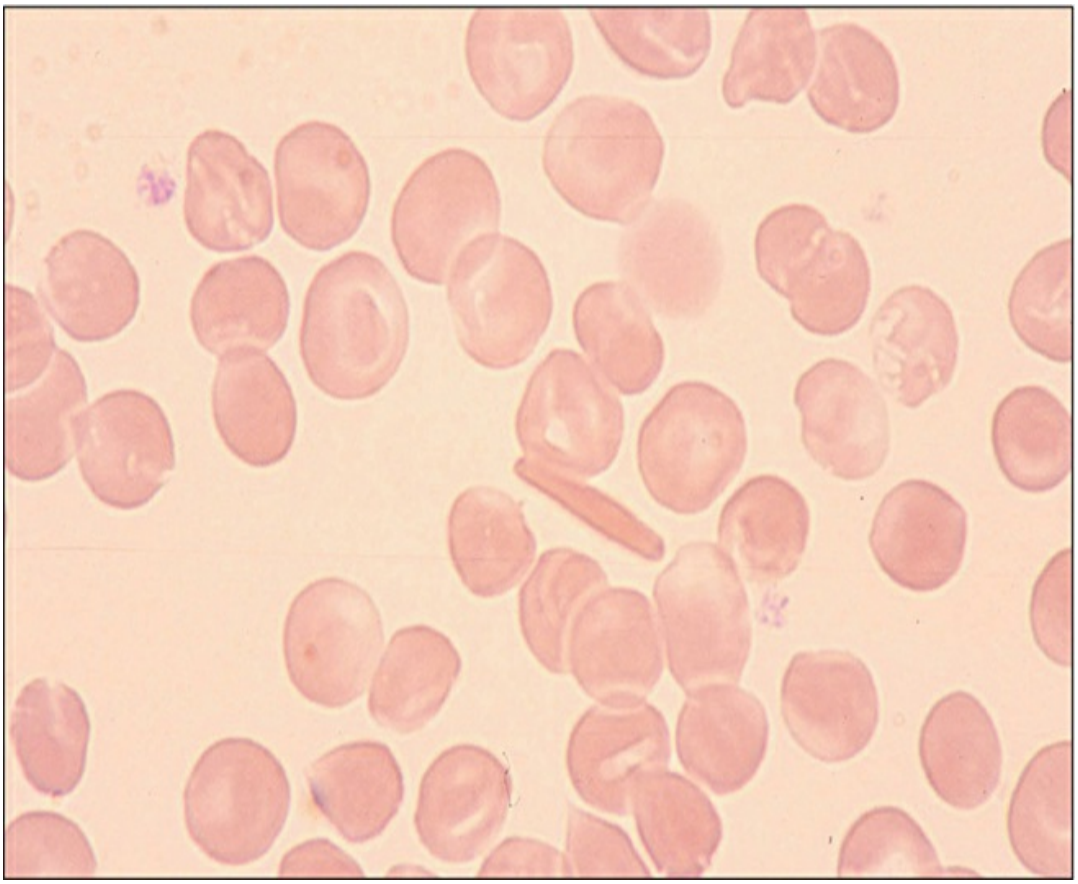


Figure IIA5-9

Peripheral blood smear—homozygous.

Clinical Features

- Mild to moderate hemolysis
- Palpable splenomegaly
- Cholelithiasis and aplastic crises may occur
- Arthralgia is common
- May be abdominal pain
- Hb C trait has no clinical manifestations

Pathology

- α_2/β_2 (glutamic acid replaced by lysine on amino acid 6)
- Relative insolubility of hemoglobin C causes red cells to become rigid

- Loss of potassium and cell hydration
- Cell is subject to fragmentation and loss of membrane material resulting in microspherocytes

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

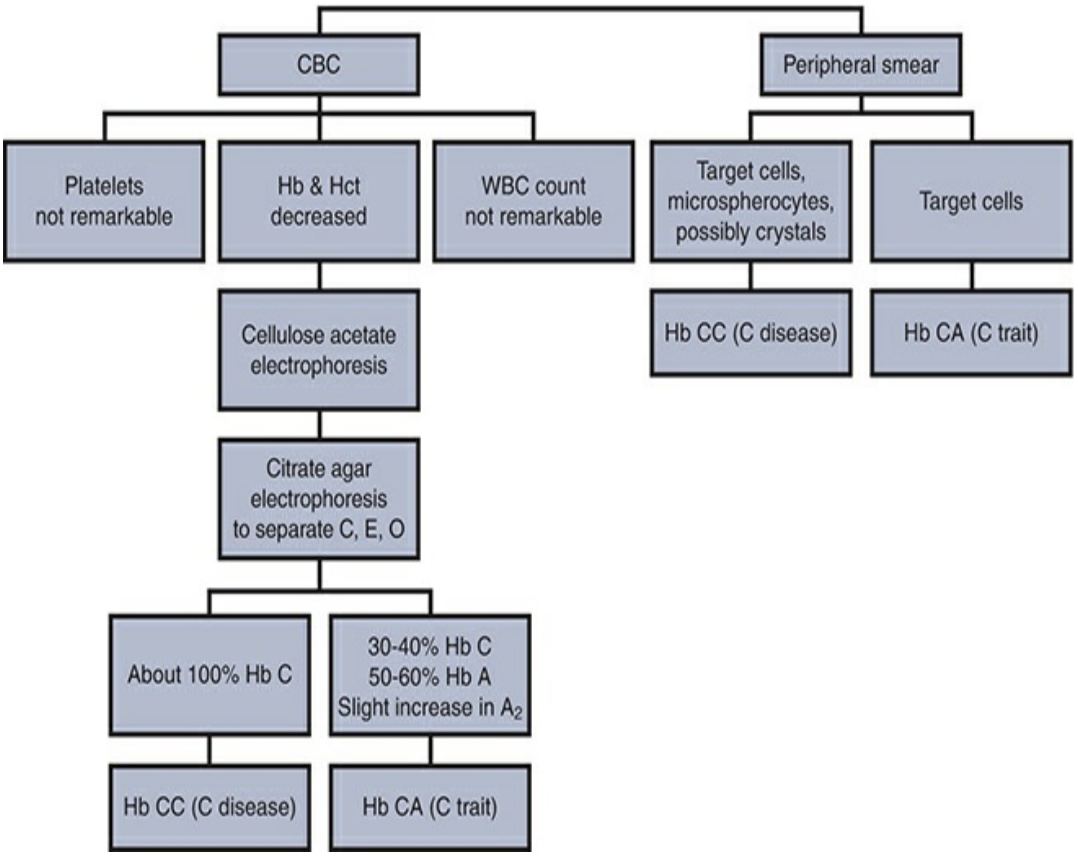
Red Blood Cells

- Microspherocytes present
- Reticulocyte count, 4–8%
- Hematocrit level approximately 25–37%
- Approximately 30–100% target cells
- C crystals seen in oxyhemoglobin state

Hemoglobin Electrophoresis

- Homozygous about 100% Hb C
- Heterozygous 30–40% hemoglobin C, 50–60% hemoglobin A, and slight increase in hemoglobin A_2

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Target cells, microspherocytes, possibly crystals
Target cells
Cellulose acetate electrophoresis
Hb CC (C disease)
Hb CA (C trait)
Citrate agar electrophoresis to separate C, E, O
About 100% Hb C
30-40% Hb C
50-60% Hb A
Slight increase in A_2
Hb CC (C disease)
Hb CA (C trait)

HEMOGLOBIN CONSTANT SPRING SYNDROME

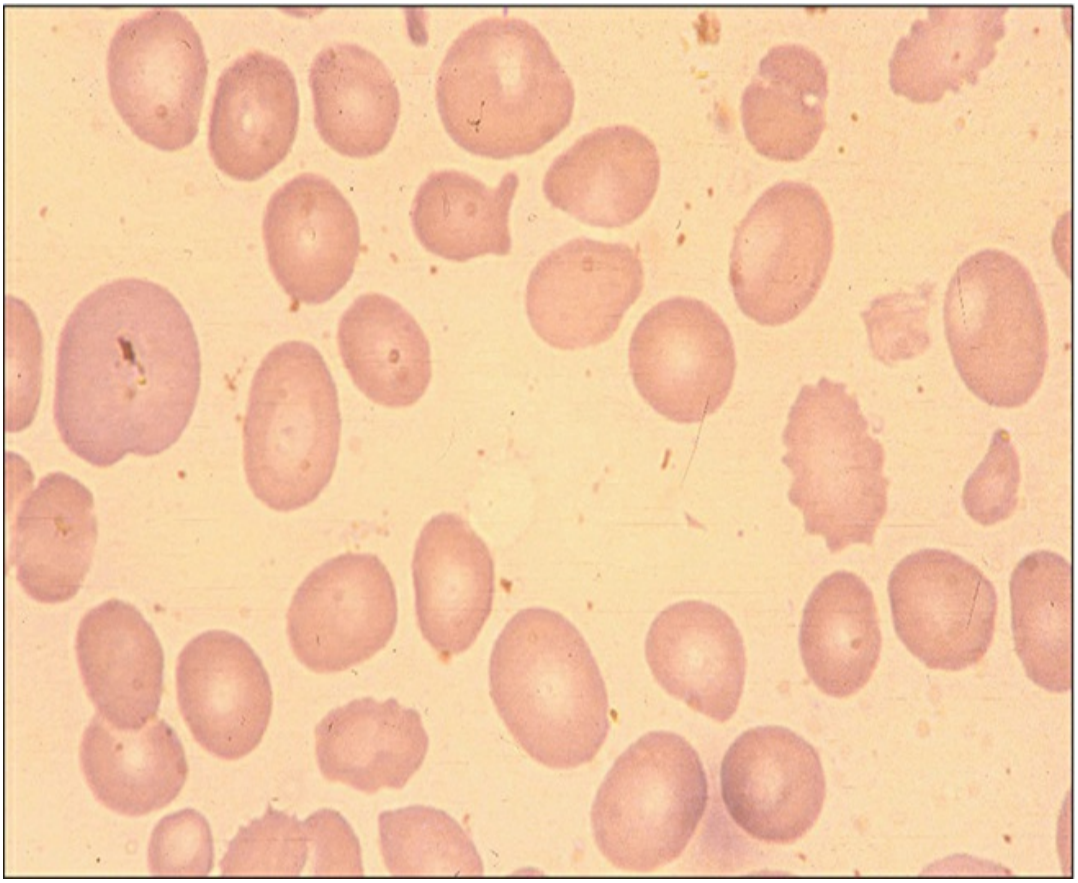


Figure IIA5-10

Peripheral blood smear.

Clinical Features

- Homozygotes have a condition similar to mild α -thalassemia—mild anemia, mild jaundice, and splenomegaly
- Heterozygotes usually have no clinical abnormalities
- Common in Thailand, Chinese, and Greek ancestry with α -thalassemia syndromes
- May occur in about 40% of hemoglobin H disease in Southeast Asians

Pathology

- Four different types of hemoglobins
- Hemoglobin Constant Spring is formed from the combination of two structurally abnormal α -chains, each elongated by 31 amino acids at the C-terminal end and two normal β -chains
- The abnormal α -chains are inefficiently synthesized due to reduced stability of the mRNA translation apparatus
- The deficiency of α -chain synthesis produces an α -thalassemia–like syndrome

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

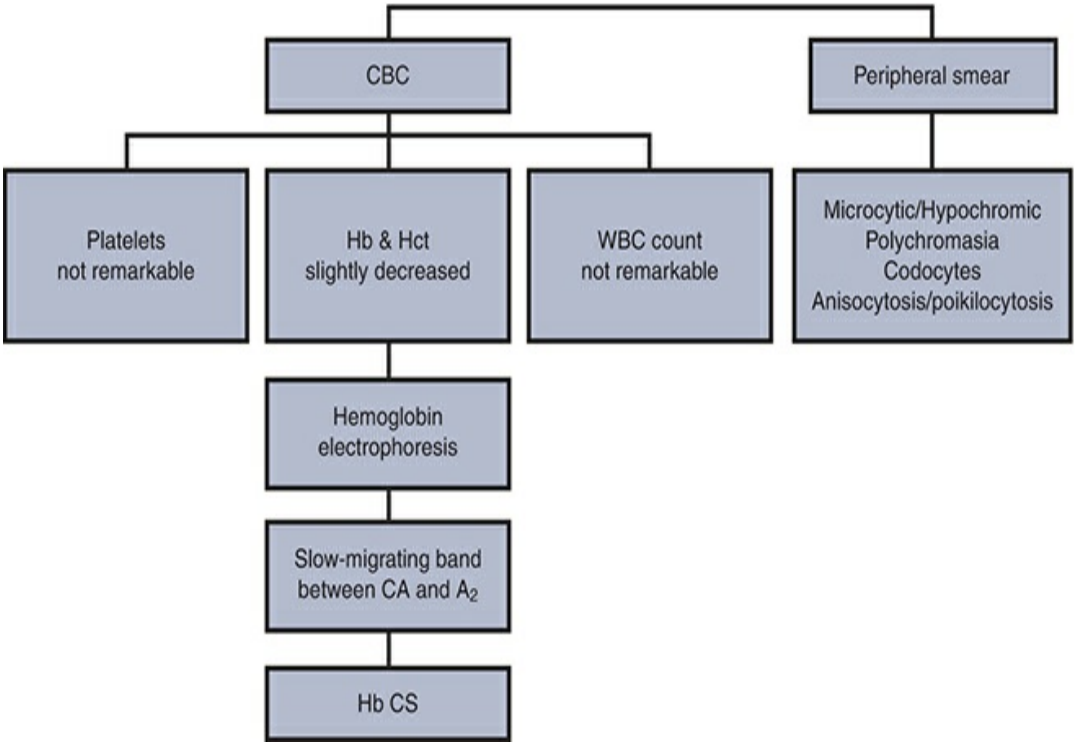
- Mild microcytic, hypochromic anemia
- Hemoglobin level usually 9.0–11.0 g/dL
- Reticulocyte count, 3.5–7.5%
- Anisocytosis and poikilocytosis
- Codocytes

Hemoglobin Electrophoresis (Cellulose Acetate, pH 8.4)

- Migrates on the cathode side of hemoglobin A_2
- In homozygotes
  - Hemoglobin Bart present at birth
  - Hemoglobin Constant Spring 5–7%
  - Hemoglobins A_2 and F normal

- In heterozygotes
  - Hemoglobin Constant Spring 0.2–1.7%

Diagnostic Scheme



HEMOGLOBIN D

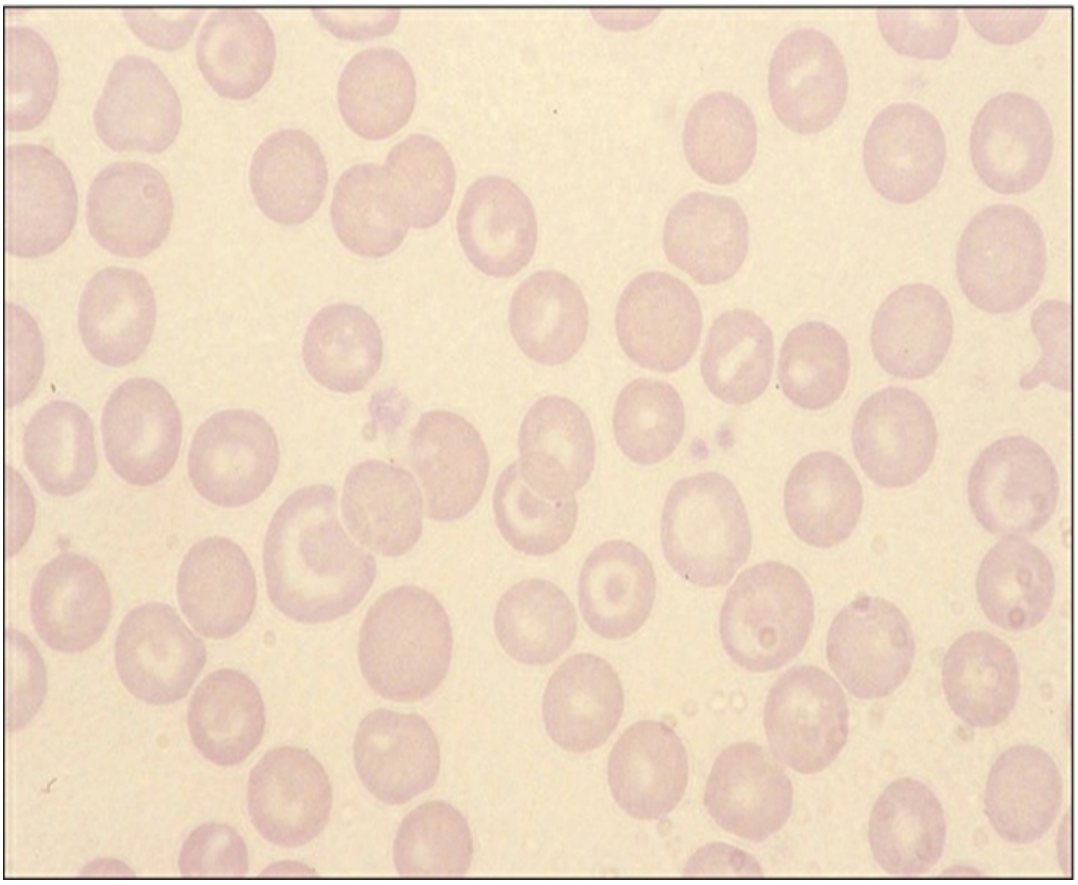


Figure IIA5-11

Peripheral blood smear.

Clinical Features

- Disorder is rare
- Homozygous individuals may have a mild anemia
- Both homozygous and heterozygous individuals are asymptomatic

Pathology

- α /β_2 (glutamic acid replaced by glycine on amino acid 121)
- Many variants are found:
  - Hemoglobin D-Punjab and hemoglobin D Los

Angeles are the most commonly encountered of the D hemoglobins in American Blacks (0.02%)

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

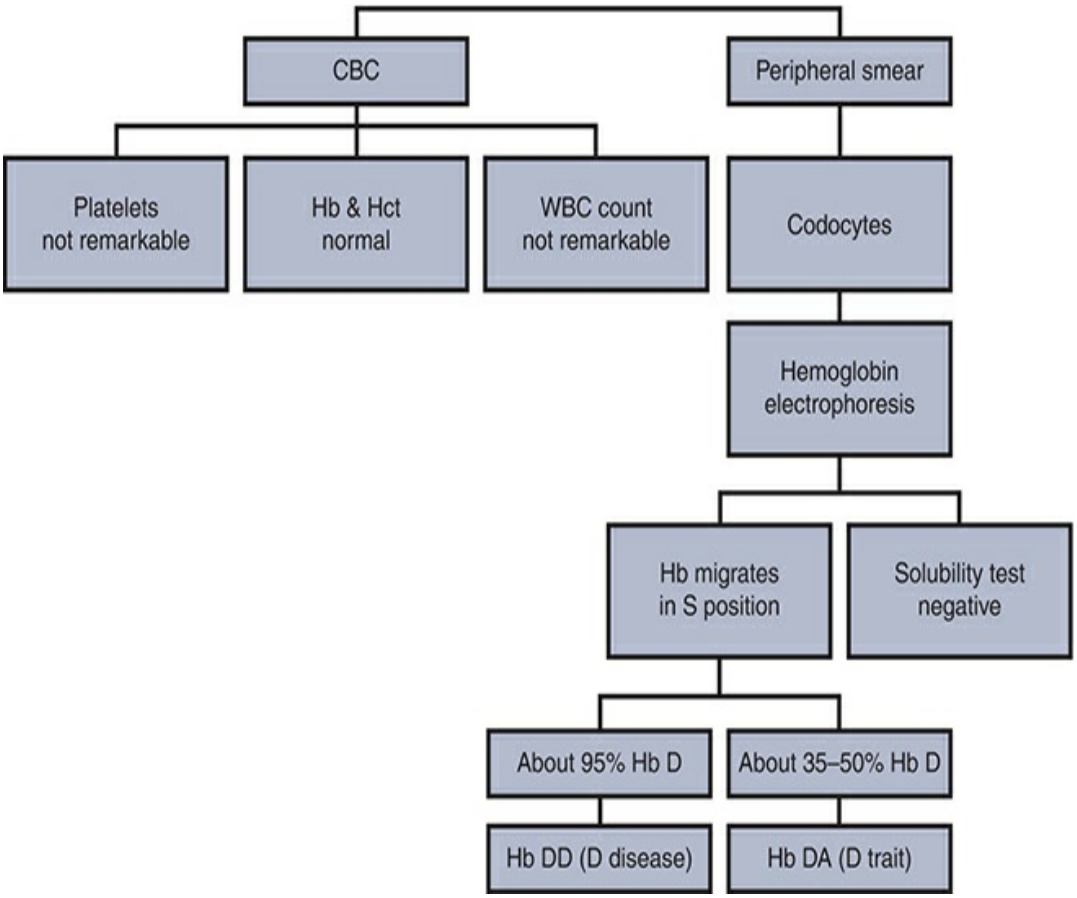
Red Blood Cells

- Homozygotes may have a normal hemoglobin and no evidence of hemolysis
- Indices normal
- May see target cells
- May see decreased osmotic fragility

Hemoglobin Electrophoresis

- Homozygous:
  - 95% hemoglobin D and normal hemoglobin A_2
  - Hemoglobin D migrates with S at pH 8.6 but does not sickle
  - Hemoglobin D migrates with A on acid electrophoresis

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct normal
WBC count not remarkable
Codocytes
Hemoglobin electrophoresis
Hb migrates in S position
Solubility test negative
About 95% Hb D
About 35–50% Hb D
Hb DD (D disease)
Hb DA (D trait)

HEMOGLOBIN E

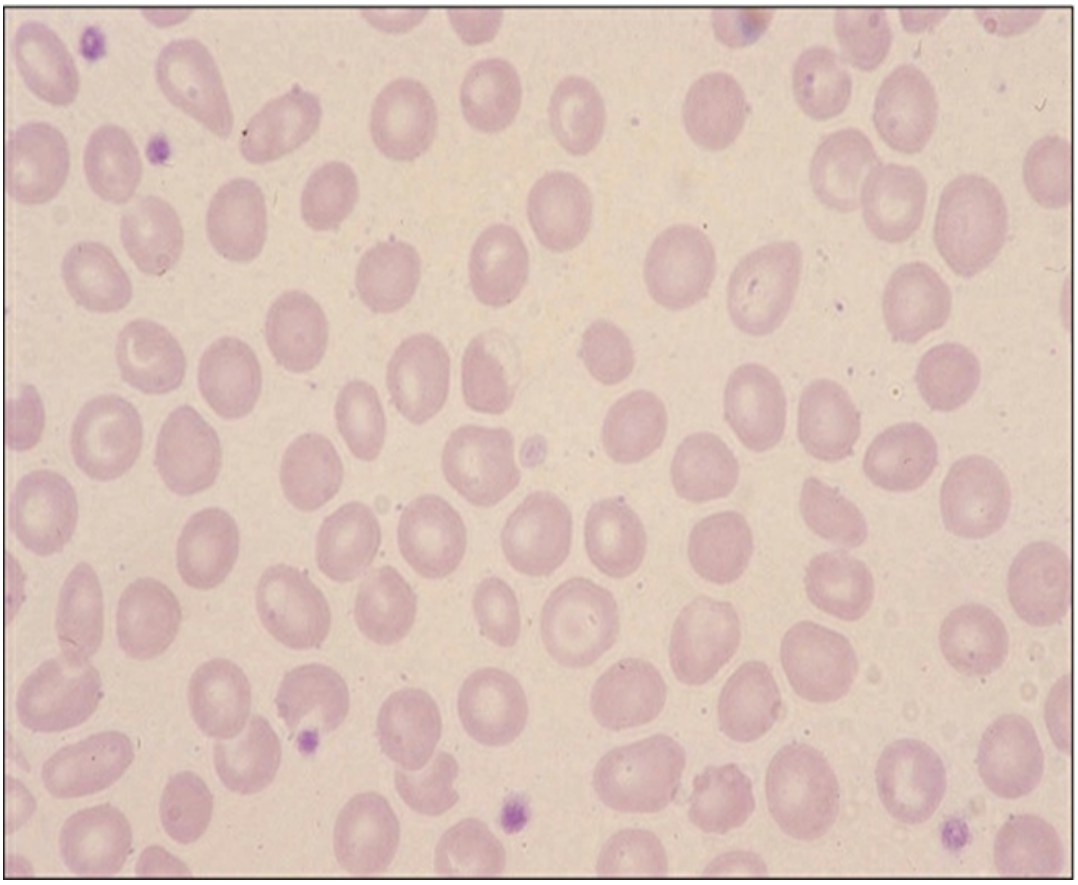


Figure IIA5-12

Peripheral blood smear.

Clinical Features

- Homozygous: Mild or asymptomatic, microcytic anemia with decreased erythrocyte survival
- Heterozygous: Symptomless and microcytosis

Pathology

- Substitution of lysine for glutamic acid in the β -chain
- Hemoglobin is slightly unstable with oxidant stress
- Oxygen dissociation curve is shifted to the right, indicating the hemoglobin E has decreased oxygen affinity

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

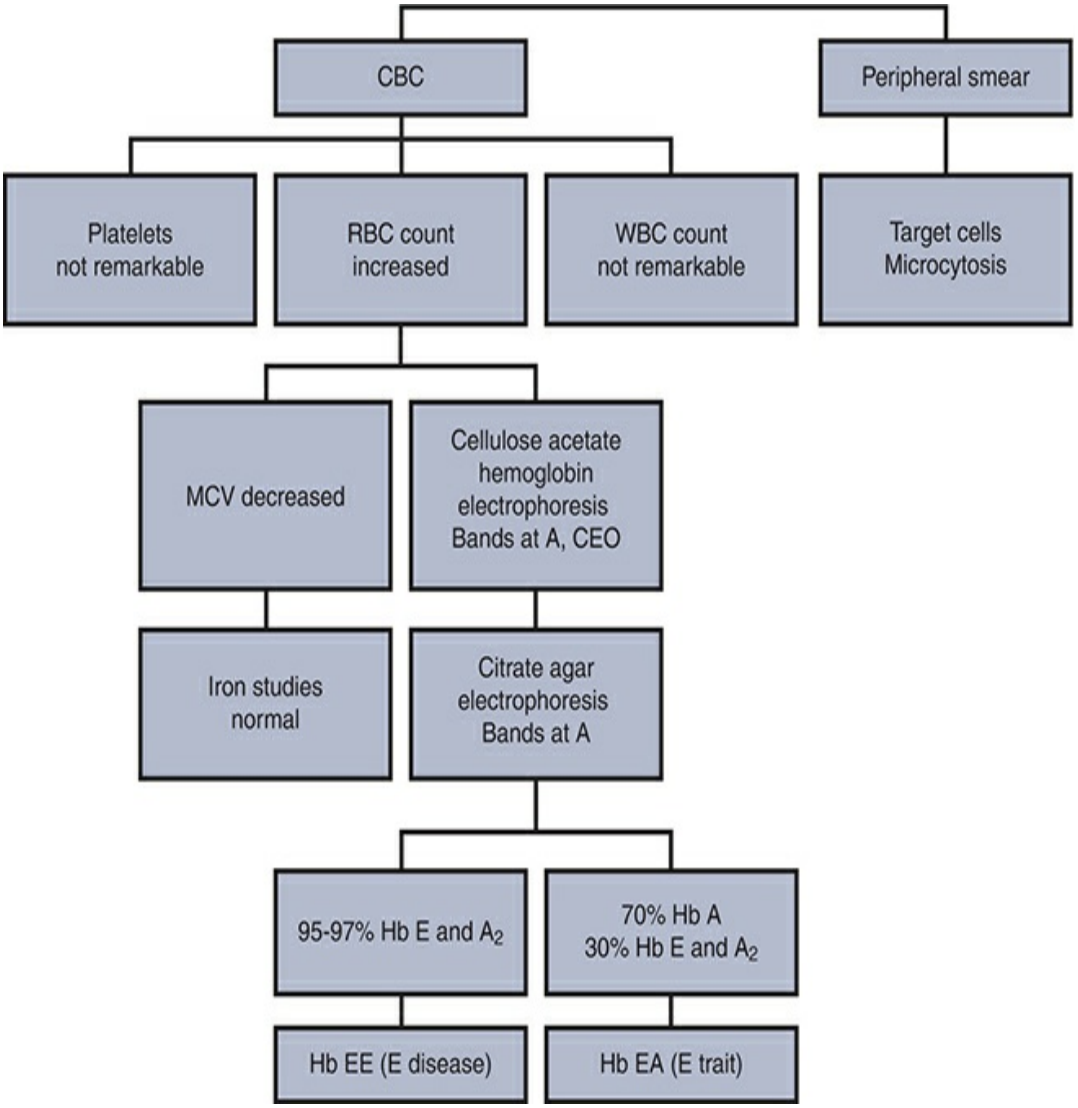
Red Blood Cells

- Hemoglobin level is 12.0–13.0 g/dL
- Decreased mean corpuscular volume
- Target cells present
- Increased red blood cells
- Normal or decreased reticulocyte count

Hemoglobin Electrophoresis

- Presence of hemoglobin E

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
RBC count increased
WBC count not remarkable
Target cells Microcytosis
MCV decreased
Cellulose acetate hemoglobin electrophoresis Bands at A, CEO
Iron studies normal
Citrate agar electrophoresis Bands at A
95-97% Hb E and A_2
70% Hb A 30% Hb E and A_2
Hb EE (E disease)
Hb EA (E trait)

Hemoglobin E/β -Thalassemia

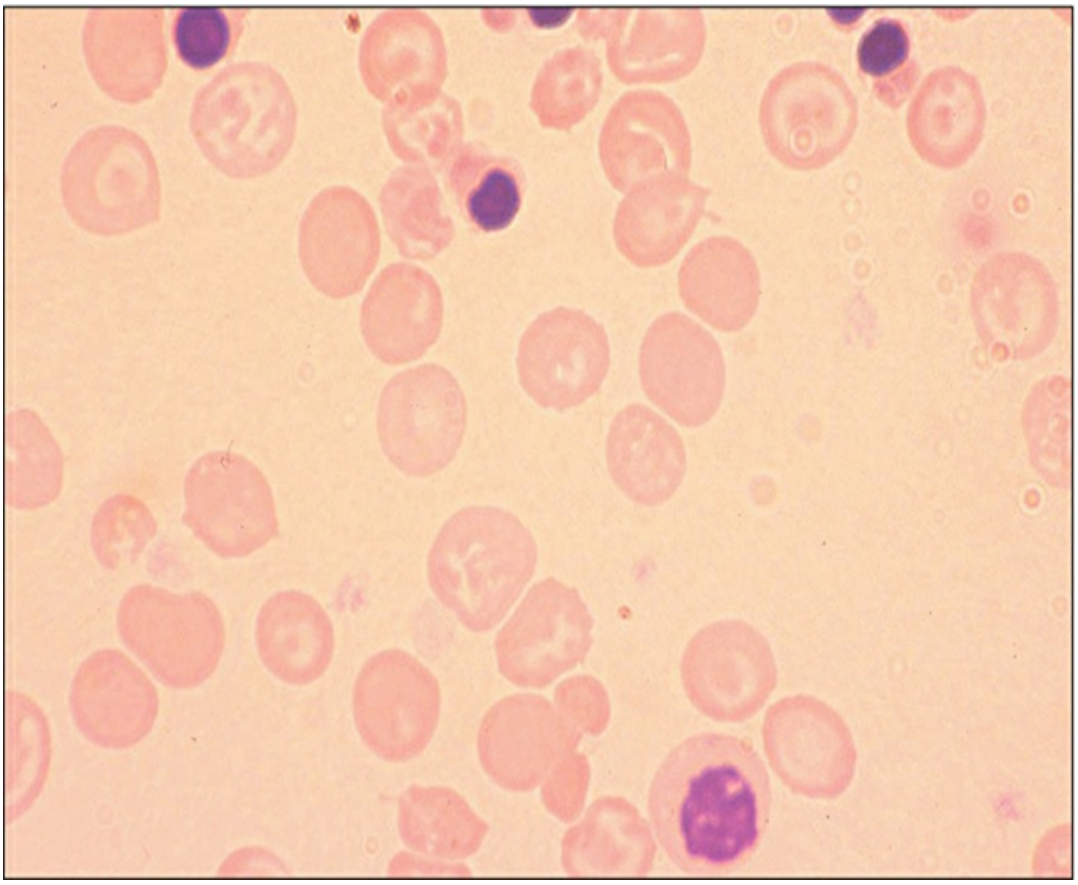


Figure IIA5-13

Peripheral blood smear.

Clinical Features

- Moderate to severe anemia
- The most severe type is E/β^0
- Anemia is generally more severe than in patients with hemoglobin S/β
- Anemia is more severe than in E trait
- Splenomegaly

Pathology

- This is the most common combination in Southeast Asians

- Double heterozygous for hemoglobin E and β - thalassemia

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

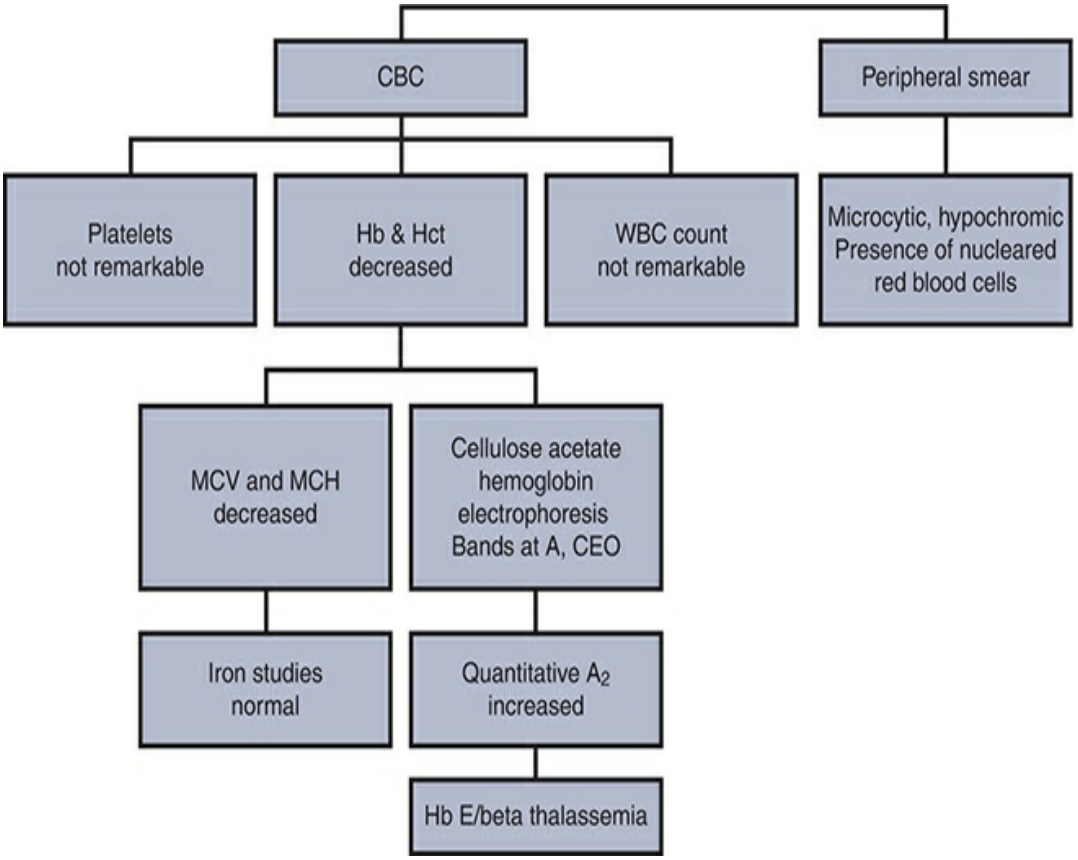
Red Blood Cells

- Decreased hemoglobin and hematocrit levels
- Microcytic, hypochromic anemia
- Presence of nucleated red blood cells

Hemoglobin Electrophoresis (Cellulose Acetate, pH 8.4)

- Bands at A, F, and CEO

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Microcytic, hypochromic Presence of nucleared red blood cells
MCV and MCH decreased
Cellulose acetate hemoglobin electrophoresis Bands at A, CEO
Iron studies normal
Quantitative A_2 increased
Hb E/beta thalassemia

HEMOGLOBIN LEPORE SYNDROME

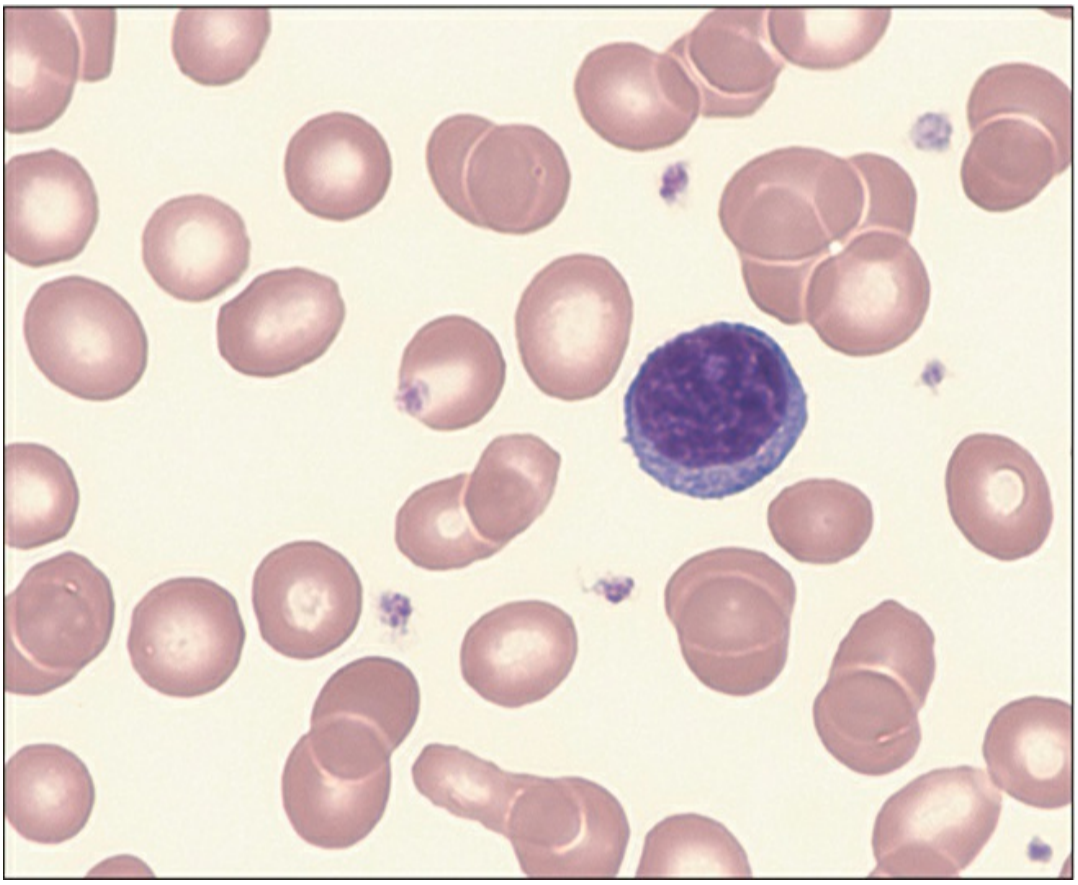


Figure IIA5-14

Peripheral blood smear—heterozygous.

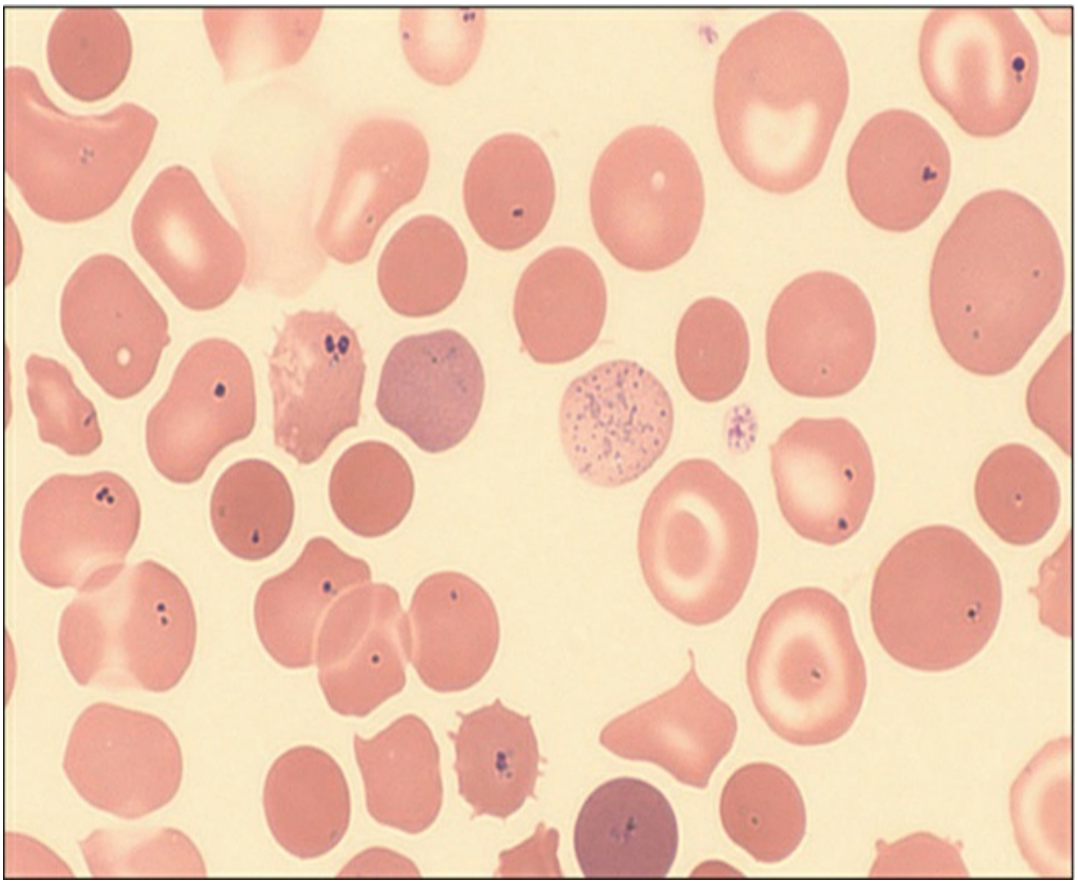


Figure **IIA5-15**

Peripheral blood smear—homozygous.

Clinical Features

- Common in middle and eastern Europe
- Homozygotes:
  - Described as a condition that resembles thalassemia intermedia
  - Variable anemia depending on racial group
  - Symptoms develop with the first 5 years of life
  - Hepatosplenomegaly is significant
  - Skeletal abnormalities may exist also with growth retardation
- Heterozygotes:
  - Mild anemia and the condition resembles thalassemia minor

- May be asymptomatic
- Slight splenomegaly

Pathology

- The non–α -hemoglobin chain is a δ -β globin hybrid in which the N-terminal end of the δ -chain is fused to the C-terminal end of a β -chain
- Believed to arise during meiosis from aberrant recombination of misaligned δ - and β -chains on separate chromosomes
- Two hybrid chains combine with two α -chains to form hemoglobin Lepore
- Hemoglobin Lepore is stable and has normal functional properties, except a slight increase in oxygen
- The abnormal chains are ineffectively synthesized leading to an excess of α -chains, which precipitate leading to cell membrane damage in inflexibility—hemolytic anemia is the result

Laboratory Features

Homozygotes

- Hemoglobin level is usually 4.0–11.0 g/dL
- Microcytic, hypochromic anemia
- Anisocytosis poikilocytosis, codocytes, basophilic stippling, and Pappenheimer bodies

Heterozygotes

- Hemoglobin level is slightly decreased
- Microcytic, hypochromic anemia

Bone Marrow

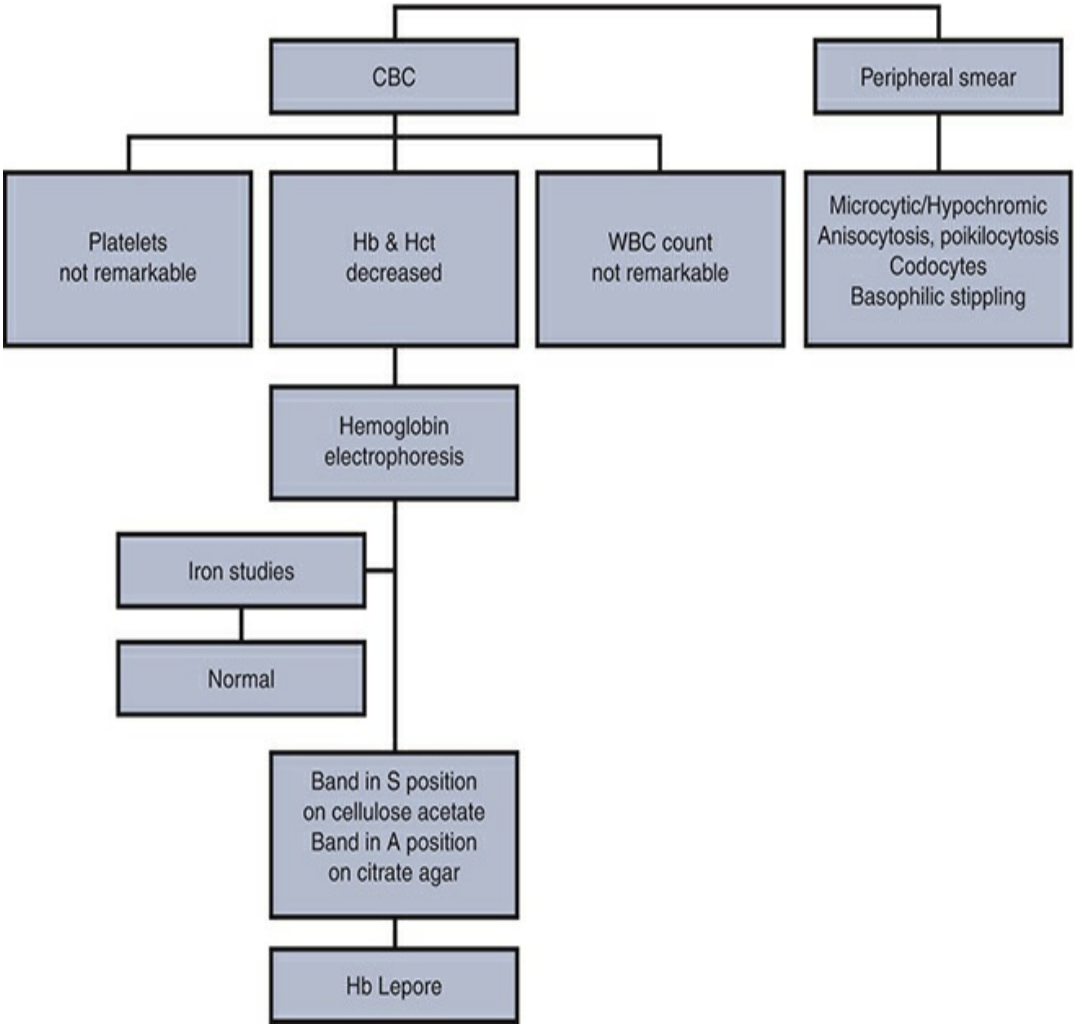
- Erythroid marrow expands and produces abnormal cells

- Ineffective erythropoiesis contributes to the anemia as the abnormal cells are destroyed

Hemoglobin Electrophoresis (Cellulose Acetate, pH 8.4)

- Homozygotes:
  - 0% hemoglobin A
  - 0% hemoglobin A_2
  - 75% hemoglobin F
  - 25% hemoglobin Lepore (hemoglobin Lepore migrates like hemoglobin S)
- Heterozygotes:
  - 75–85% hemoglobin A
  - About 2% hemoglobin A_2
  - 1–6% hemoglobin F
  - 7–15% hemoglobin Lepore

Diagnostic Scheme


CBC
Peripheral smear
Platelets
not remarkable
Hb & Hct
decreased
WBC count
not remarkable
Microcytic/Hypochromic
Anisocytosis, poikilocytosis
Codocytes
Basophilic stippling
Hemoglobin
electrophoresis
Iron studies
Normal
Band in S position
on cellulose acetate
Band in A position
on citrate agar
Hb Lepore

HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

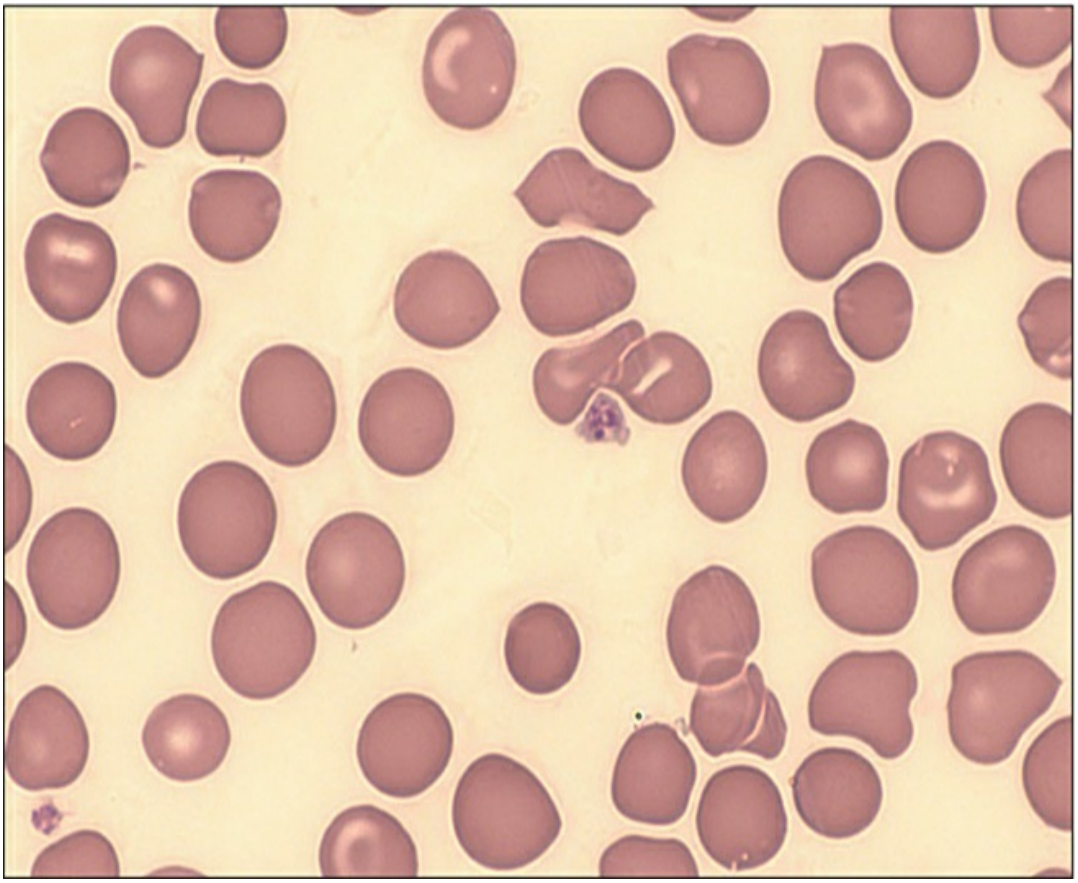


Figure IIA5-16

Peripheral blood smear.

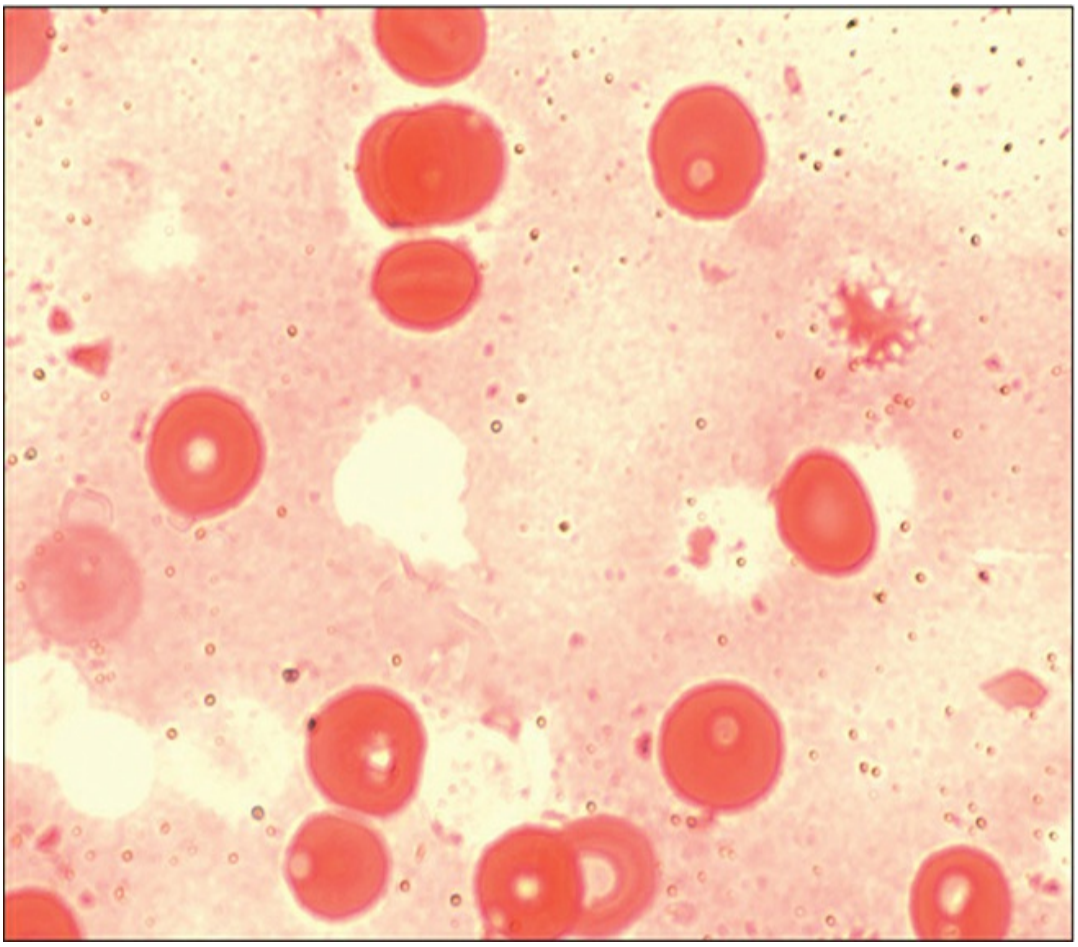


Figure IIA5-17

Kleihauer-Betke stain.

Clinical Features

- Usually no or minimal anemia
- In the homozygous state, there are no findings suggestive of thalassemia (abnormal growth, splenomegaly)

Pathology

- Deletion/inactivation of δ - and β -genes
- Absence of δ - and β -chain synthesis is compensated for by increased g -chain production into adult life causing the increased levels of hemoglobin F
- Two types exist:

    - Pancellular (Black, Greek)
    - Heterocellular (Swiss)
- Hemoglobin F has normal to slightly higher oxygen affinity and thus patients are usually asymptomatic
- Slightly increased oxygen affinity will lead to increased erythropoiesis

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

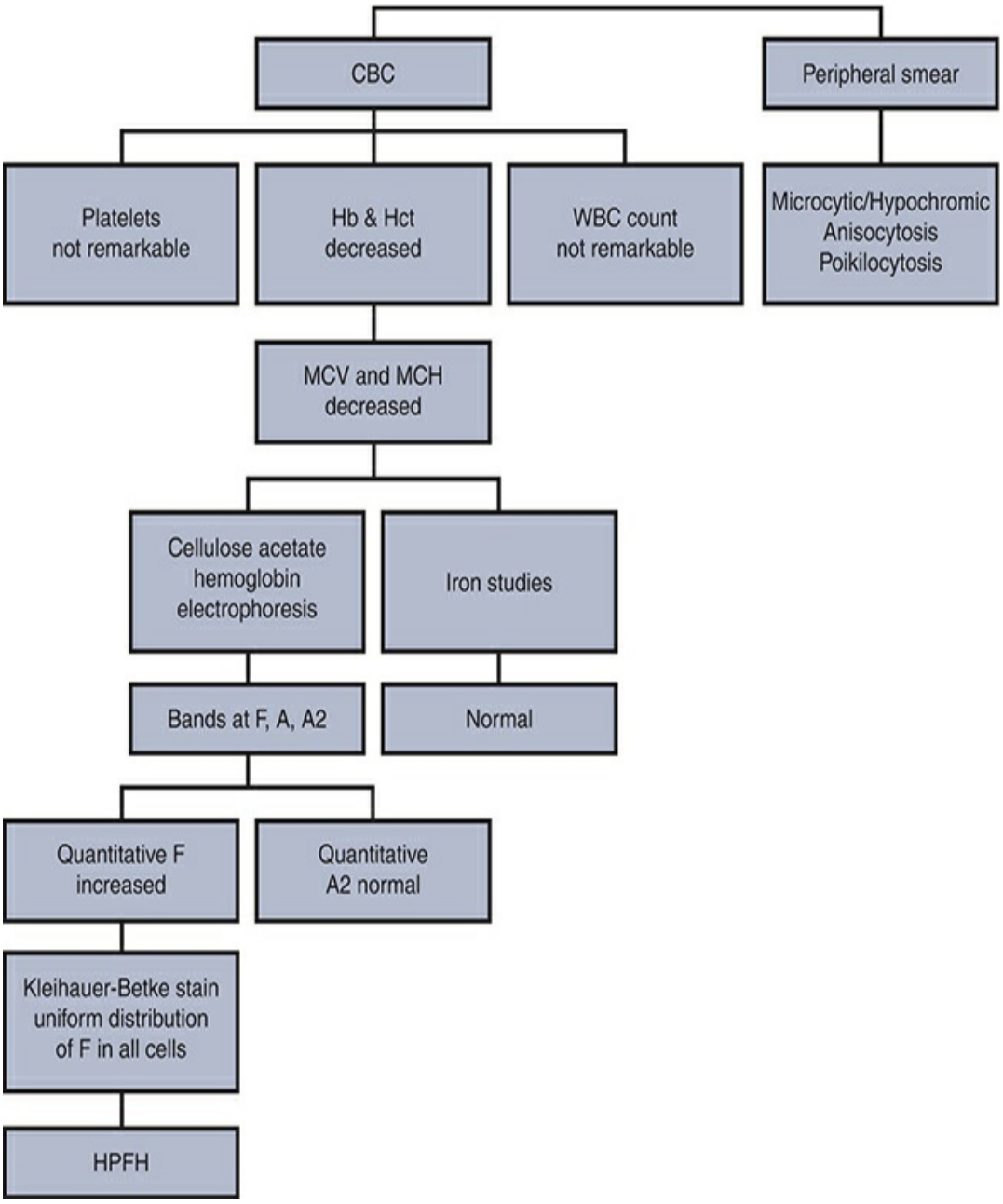
Red cells

- Microcytic/hypochromic anemia
- Mild erythrocytosis
- Mean corpuscular volume decreased
- Anisocytosis
- Poikilocytosis
- Target cells present

Hemoglobin Electrophoresis

- Homozygotes
    - 100% hemoglobin F
- Heterozygotes
    - 10–30% hemoglobin F
    - 1–2% hemoglobin A_2

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Microcytic/Hypochromic Anisocytosis Poikilocytosis
MCV and MCH decreased
Cellulose acetate hemoglobin electrophoresis
Iron studies
Bands at F, A, A2
Normal
Quantitative F increased
Quantitative A2 normal
Kleihauer-Betke stain uniform distribution of F in all cells
HPFH

HEMOGLOBIN S

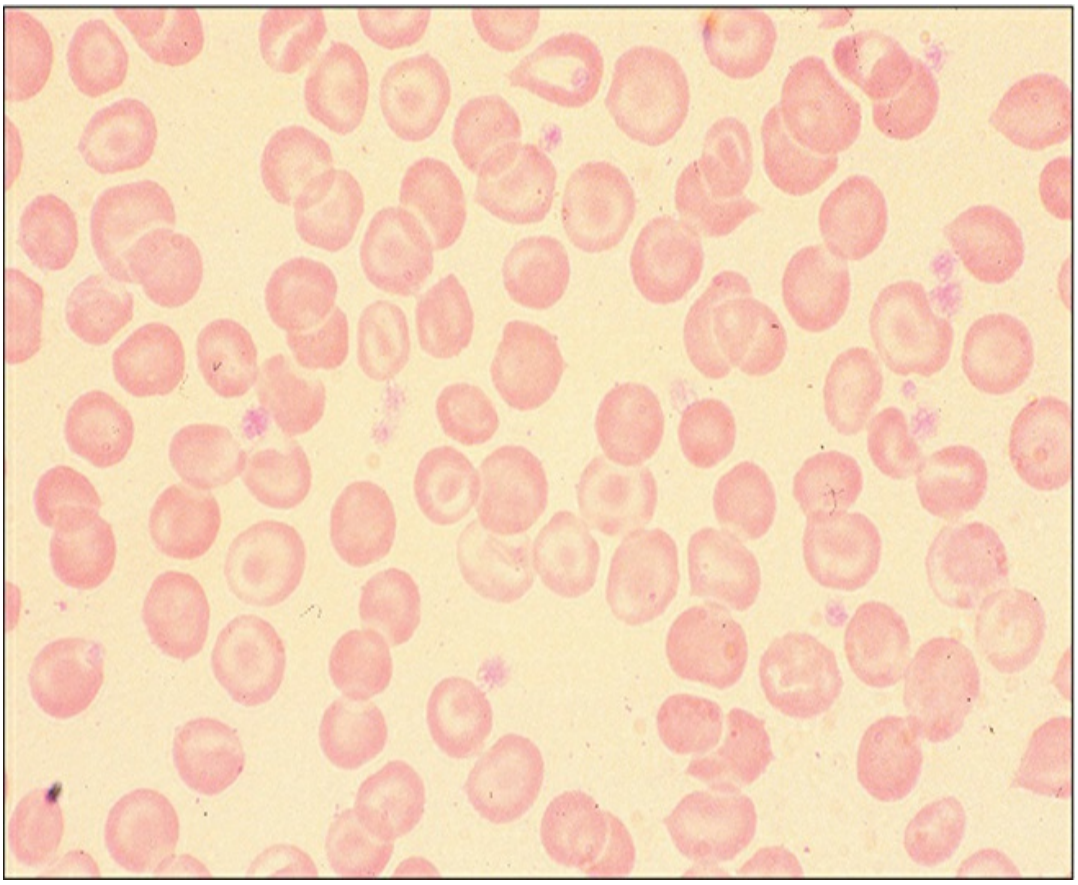


Figure IIA5-18

Peripheral blood smear—heterozygous.

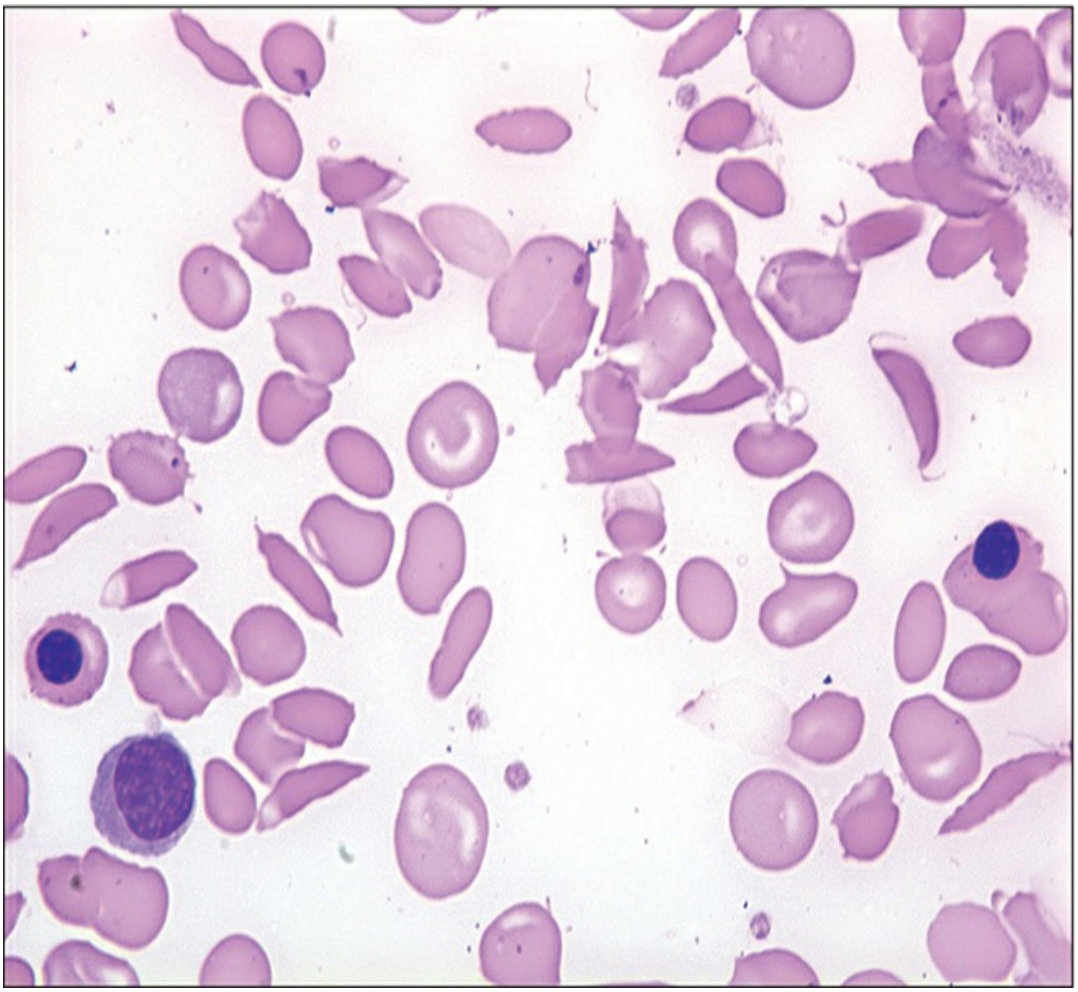


Figure IIA5-19

Peripheral blood smear—homozygous.

Clinical Features

- Homozygous:
  - A disease state that occurs in approximately 0.3–1.3% of American Blacks
  - Person with this disorder may present with fever, effusion of joints, bone deformities, loss of renal function, priapism, enlarged liver, ocular manifestations, leg ulcers, frequent infections, decreased spleen function, complications during pregnancy, and/or cerebrovascular accidents
  - Acute episodes may be manifest

- Heterozygous:
  - The individual possesses one normal β -gene and one S gene
  - In American Blacks, the frequency is approximately 8%
  - No clinical symptoms are associated with the trait, but episodes of hematuria may occur

Pathology

- A single nucleotide base change in the codon responsible for the synthesis of the sixth amino acid in the β -globulin chain, resulting in the substitution of valine for glutamic acid
- The deoxyhemoglobin polymerizes within the red cell
- Extravascular hemolysis of sickled cells takes place, causing a chronic hemolytic anemia

Laboratory Features

Homozygous

White Blood Cells

- Usually increased during a crisis, may be up to 25 × 10^9/L

Platelets

- Normal to increased

Red Blood Cells

- Normocytic/normochromic anemia
- Hemoglobin level 6.5–10.0 g/dL
- Reticulocyte count is increased (10–20%)
- Red blood cell distribution width is increased
- Smear shows polychromasia, codocytes, Howell-Jolly

bodies, nucleated red cells, and drepanocytes

Bone Marrow

- Erythroid hyperplasia caused by chronic hemolysis

Hemoglobin Electrophoresis

- 0% hemoglobin A
- 80–99% hemoglobin S
- Slightly increased hemoglobin A_2
- 1–20% hemoglobin F

Heterozygous

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Codocytes
- Hemoglobin and hematocrit levels normal

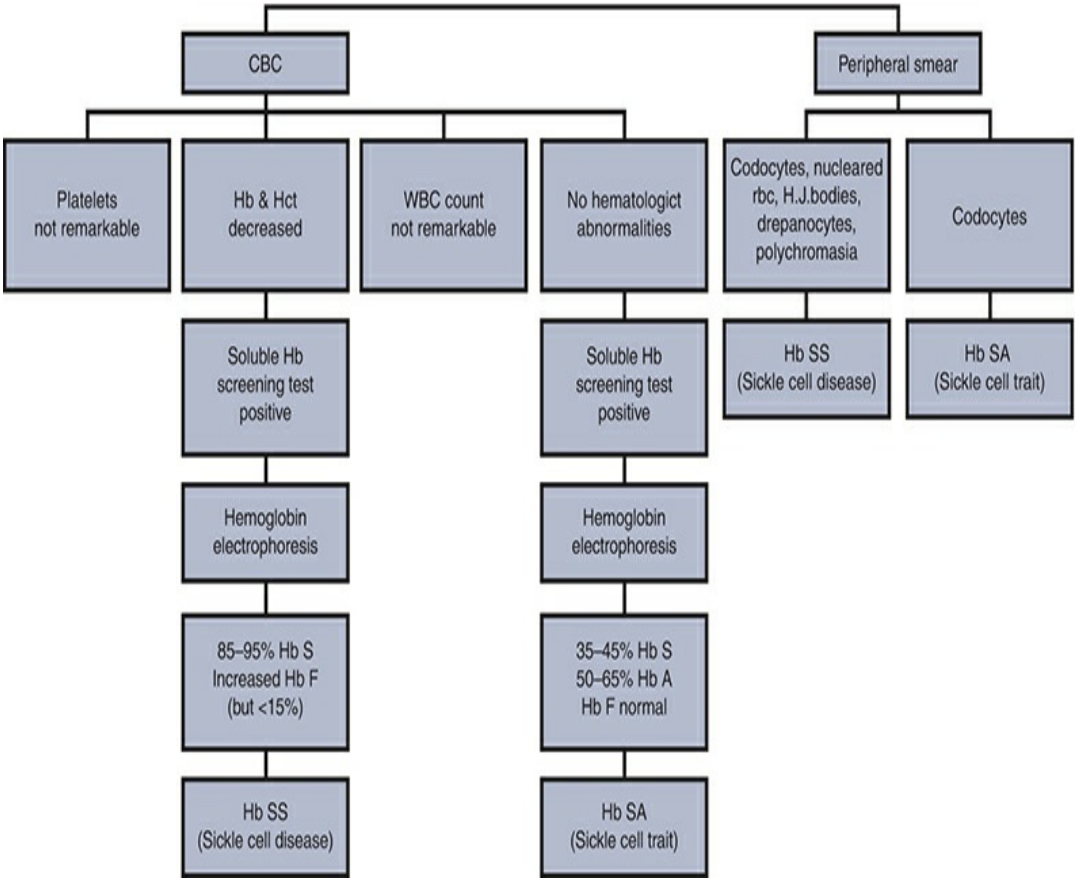
Bone Marrow

- Not remarkable

Hemoglobin Electrophoresis

- 50–65% hemoglobin A
- 35–45% hemoglobin S
- Normal to slightly increased hemoglobin A_2
- Normal hemoglobin F

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
No hematologict abnormalities
Codocytes, nucleared rbc, H.J.bodies, drepanocytes, polychromasia
Codocytes
Soluble Hb screening test positive
Soluble Hb screening test positive
Hb SS (Sickle cell disease)
Hb SA (Sickle cell trait)
Hemoglobin electrophoresis
Hemoglobin electrophoresis
85–95% Hb S Increased Hb F (but <15%)
35–45% Hb S 50–65% Hb A Hb F normal
Hb SS (Sickle cell disease)
Hb SA (Sickle cell trait)

HEMOGLOBIN S/β-THALASSEMIA

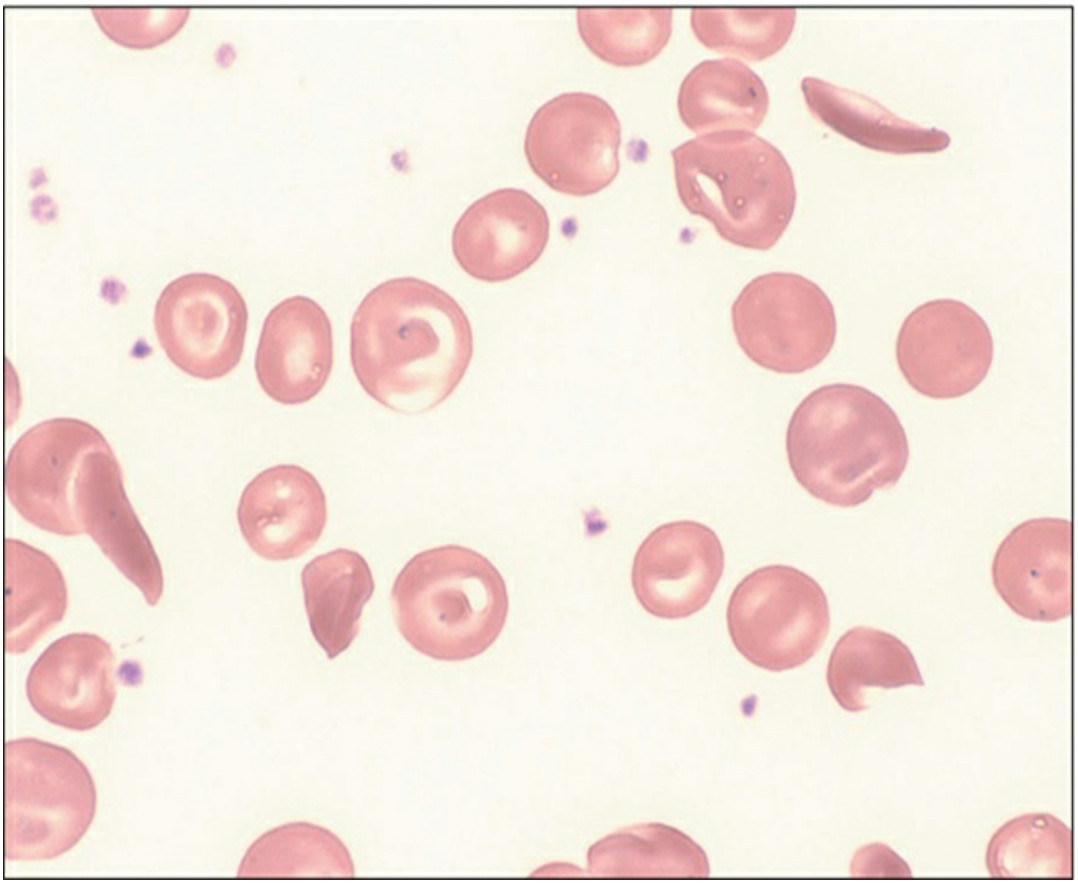


Figure IIA5-20

Peripheral blood smear.

Clinical Features

- S/β^0—severity comparable to that seen in sickle cell anemia
- S/β^+—milder clinical course comparable to SC disease
- Splenomegaly

Pathology

- β -thalassemia gene reduces the rate of synthesis of β^A chain resulting in a predominance of β^S

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

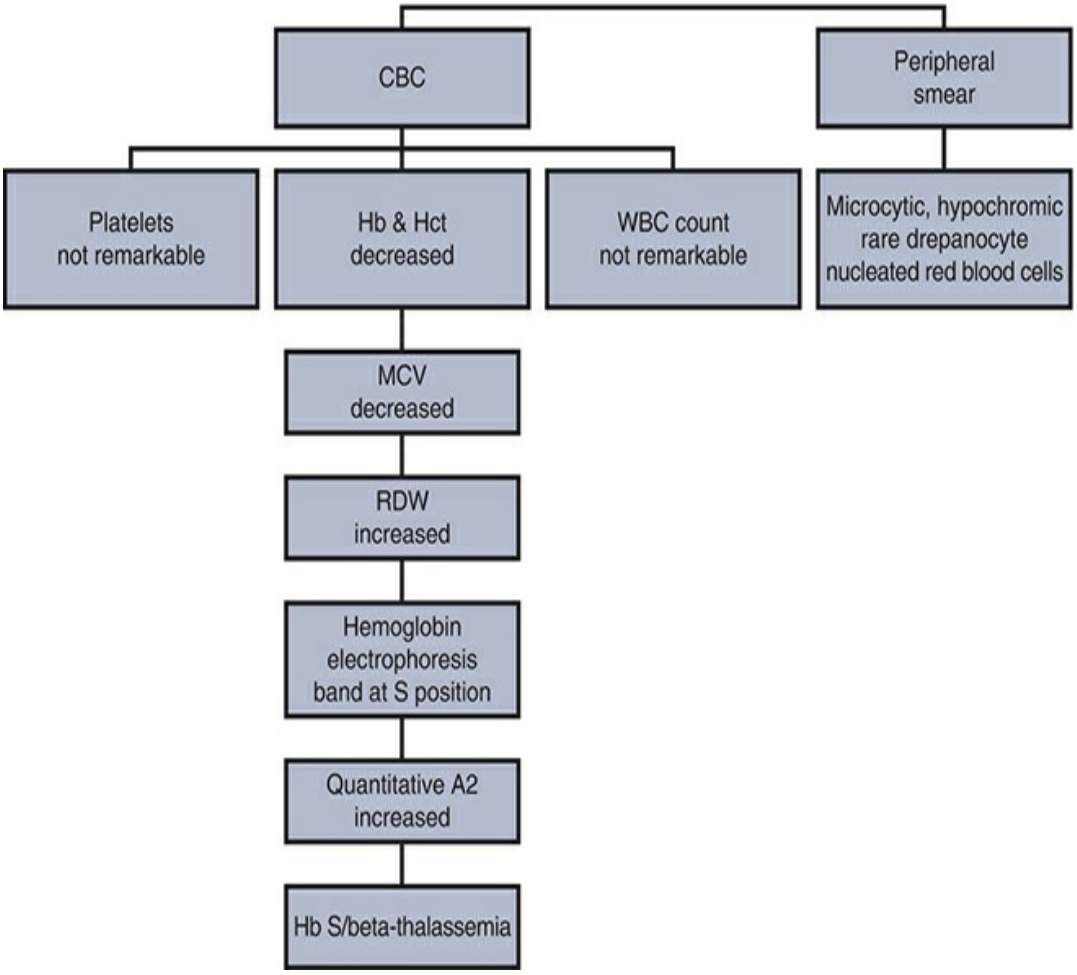
Red Blood Cells

- Microcytic/hypochromic anemia
- Decreased mean corpuscular volume

Hemoglobin electrophoresis

- S/β^0—mostly hemoglobin S, increased hemoglobin A_2, variable hemoglobin F, and no hemoglobin A
- S/β^+—hemoglobin S about 11% and hemoglobin A_2 about 6%

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Microcytic, hypochromic rare drepanocyte nucleated red blood cells
MCV decreased
RDW increased
Hemoglobin electrophoresis band at S position
Quantitative A2 increased
Hb S/beta-thalassemia

HEMOGLOBIN S/C DISEASE

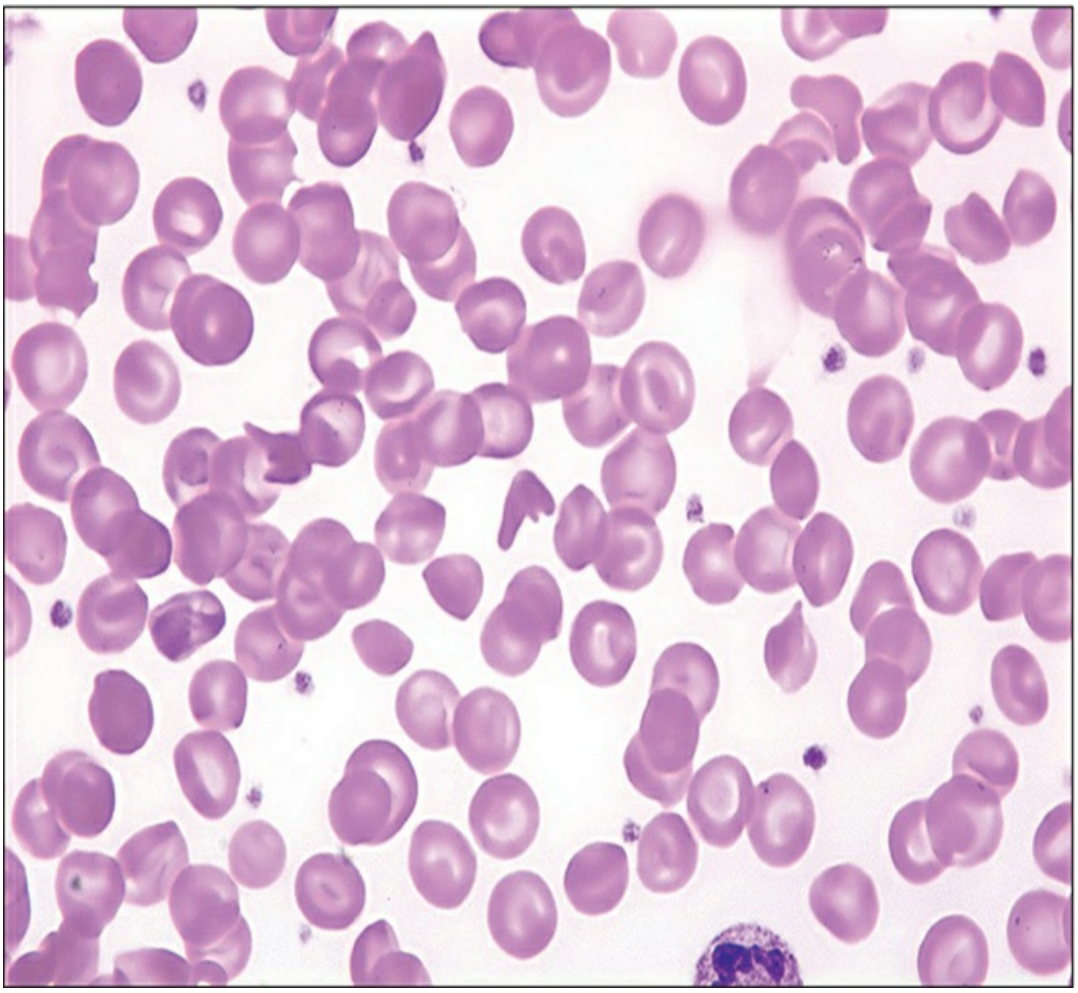


Figure IIA5-21

Peripheral blood smear.

Clinical Features

- Splenomegaly
- Proliferative retinopathy
- Aseptic necrosis of long bones
- Muscle, bone, and joint pain
- Hematuria
- Acute pulmonary disease
- Splenic infarction
- Vaso-occlusive crisis during pregnancy, surgery, or

medical emergency

Pathology

- Both β -chains are abnormal
- Less frequent and less severe than sickle cell anemia
- More severe than sickle trait of C trait

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

Red Blood Cells

- Knizocytes, stomatocytes, and target cells present
- Increased mean corpuscular hemoglobin
- Microcytic anemia
- Sickling not prominent
- SC crystals

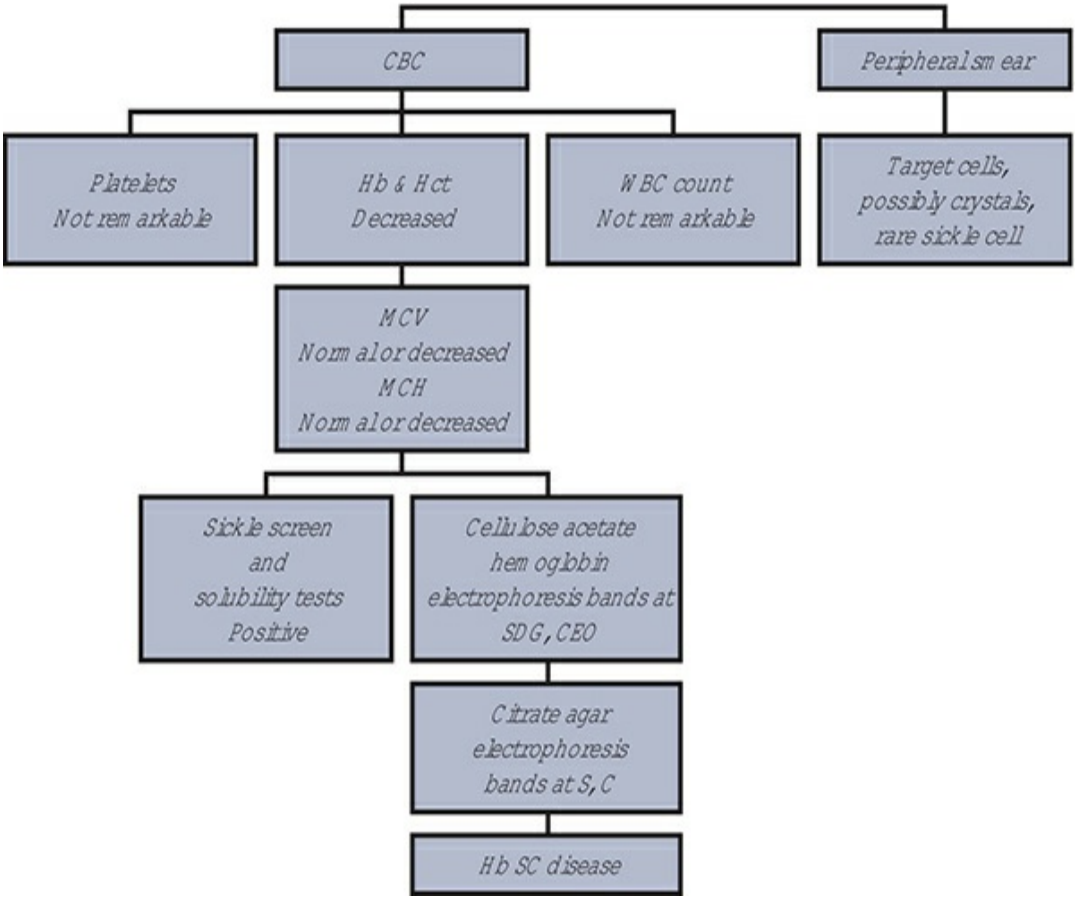
Bone Marrow

- Normoblastic hyperplasia

Hemoglobin Electrophoresis

- Equal amounts of hemoglobin S and hemoglobin C
- 1–2% hemoglobin F
- Trace of hemoglobin A_2

Diagnostic Scheme


CBC
Peripheral smear
Platelets
Not remarkable
Hb & Hct
Decreased
WBC count
Not remarkable
Target cells,
possibly crystals,
rare sickle cell
MCV
Normal or decreased
MCH
Normal or decreased
Sickle screen
and
solubility tests
Positive
Cellulose acetate
hemoglobin
electrophoresis bands at
S D G, C E O
Citrate agar
electrophoresis
bands at S, C
Hb SC disease

UNSTABLE HEMOGLOBINS

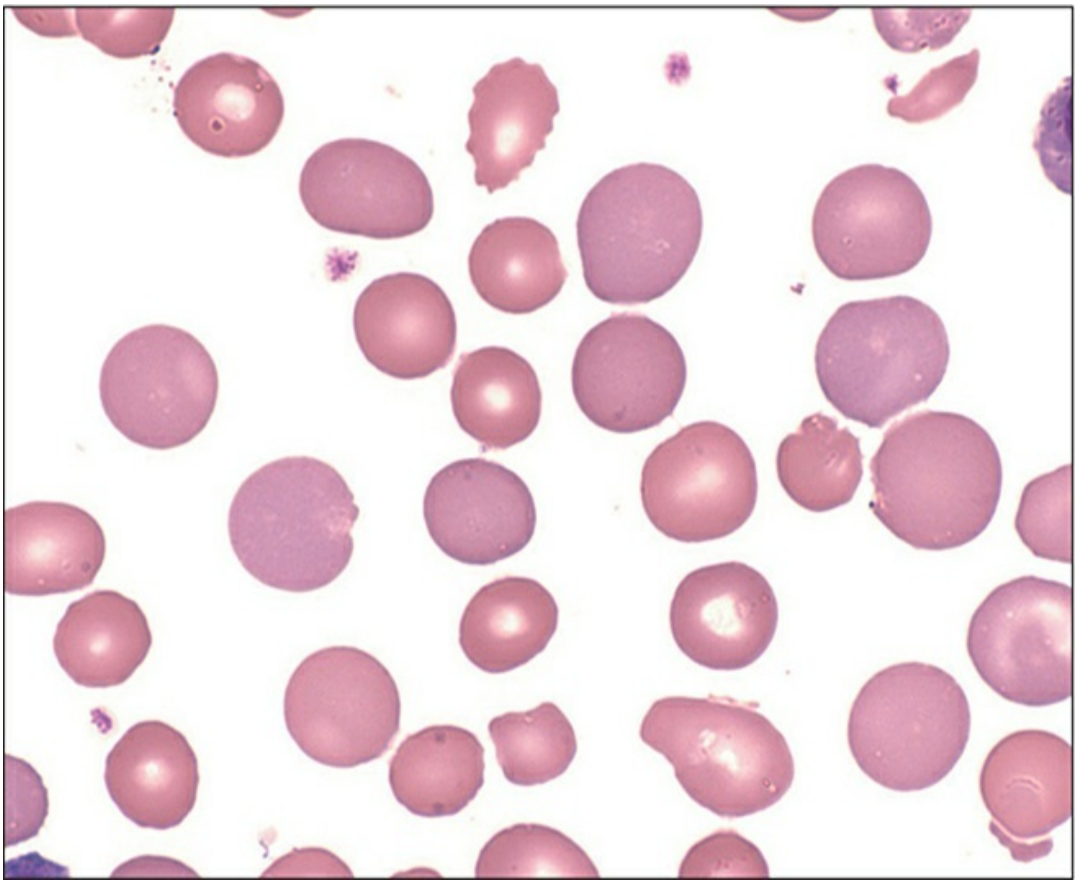


Figure IIA5-22

Peripheral blood smear.

Clinical Features

- Hemoglobin denaturation and hemolysis may occur spontaneously
- Symptoms may occur only after drug administration, infection, or other changes to the normal environment
- Jaundice and splenomegaly occur because of increased red cell hemolysis
- Excretion of dark urine
- Cyanosis may result from the formation of sulfhemoglobin
- Methemoglobin

Pathology

- Amino acid substitutions in critical internal portions of the globin chains
- Abnormal hemoglobin precipitates as Heinz bodies, which attach to the inner surface of the membrane and can cause cell rigidity, membrane damage, and thus erythrocyte hemolysis
- Homozygous state is incompatible with life
- Oxygen stability may be increased or decreased depending on where the amino acid substitution is located
- Hemoglobin with a high oxygen affinity is usually accompanied by erythrocytosis:
    - Oxygen dissociation curve is shifted to the left
    - Decreased amount of oxygen released to the tissues and increased erythropoietin levels
- Hemoglobin with decreased oxygen affinity may be asymptomatic:
    - Oxygen dissociation curve is shifted to the right
    - Increased amount of oxygen delivered to the tissues

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

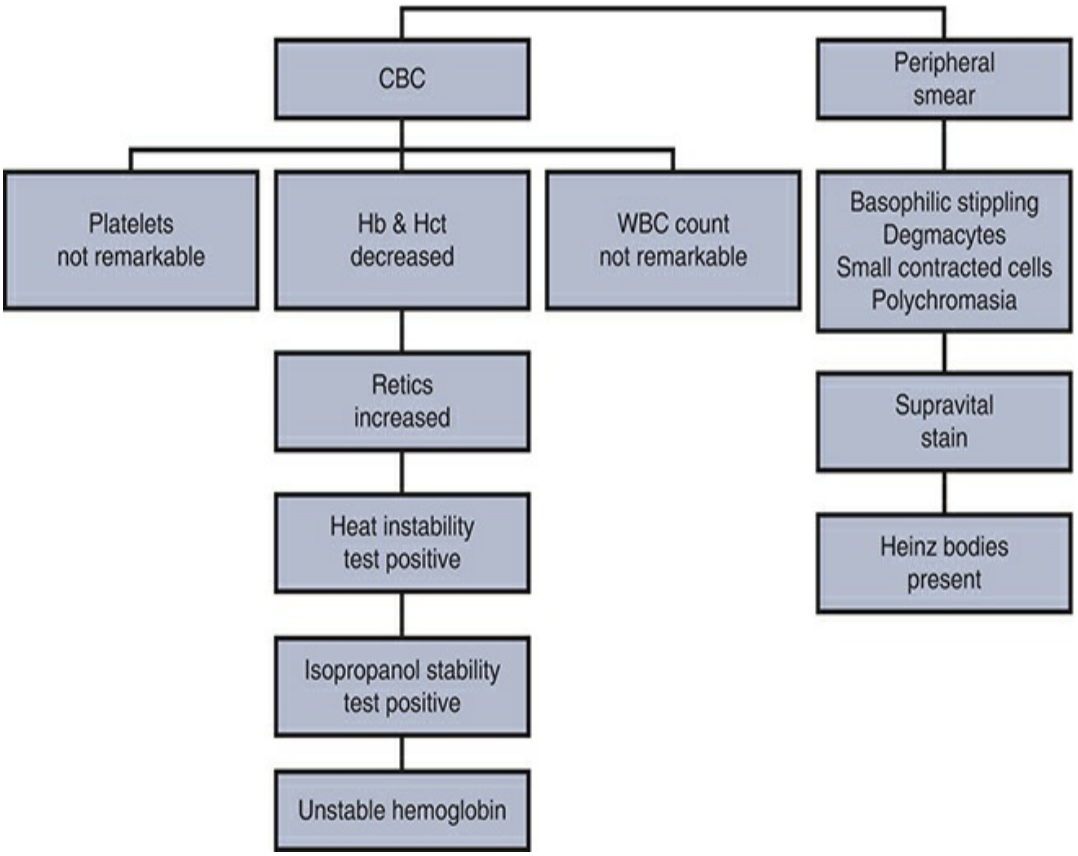
Red Blood Cells

- Normochromic/normocytic anemia
- Slight decrease in mean corpuscular hemoglobin and

mean corpuscular hemoglobin concentration

- Reticulocyte count is increased
- Basophilic stippling, bite cells, and small contracted cells may be present
- Osmotic fragility abnormal after 24-hour incubation
- Heat instability test is positive
- Isopropanol stability test is positive
- Hemoglobin electrophoresis is abnormal in about 45% of cases—hemoglobins A_2 and F are sometimes increased
- Heinz bodies are seen on brilliant cresyl blue stain

Diagnostic Scheme



CHAPTER 6

Hemolytic Anemias

COLD AGGLUTININ SYNDROME

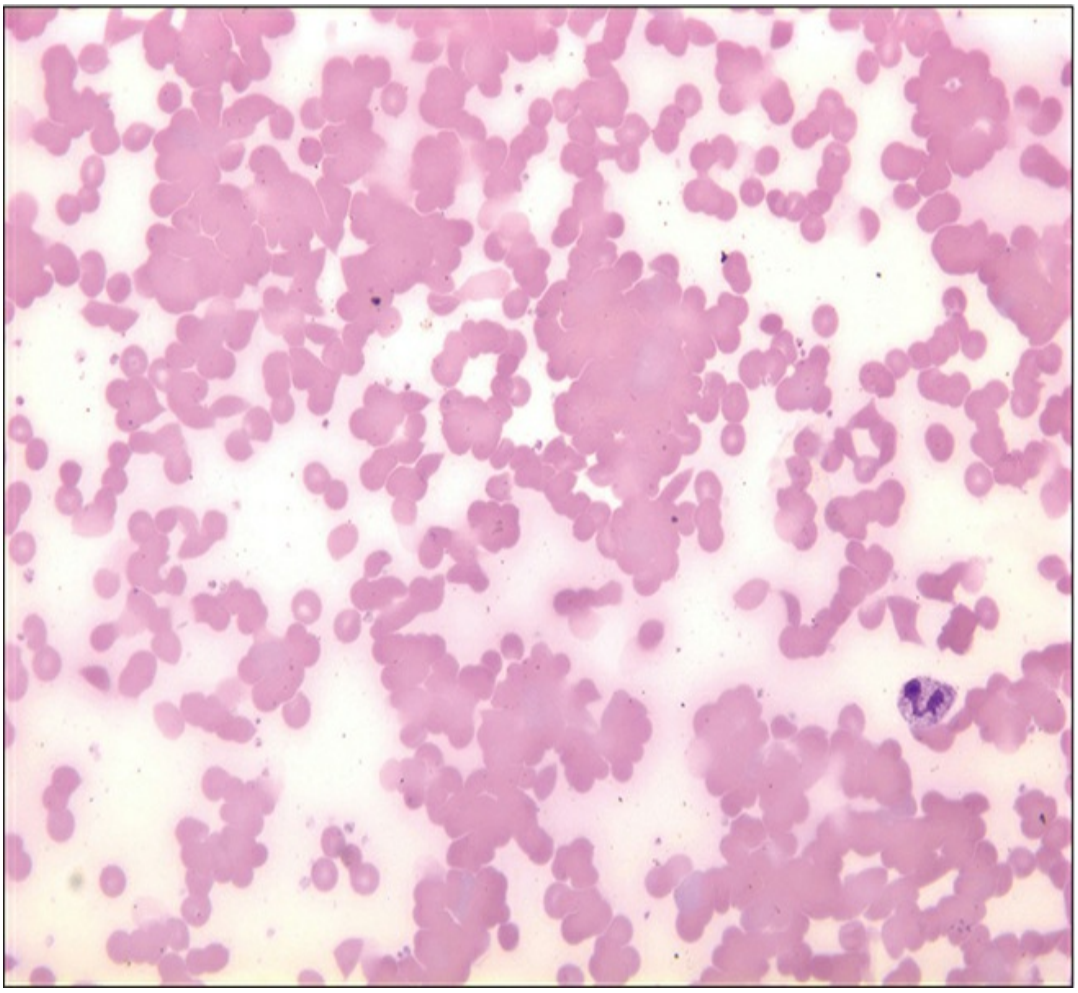


Figure IIA6-1

Peripheral blood smear.

Clinical Features

- Peak incidence in patients older than 50 years
- Onset may be sudden and severe, but usually doesn't last >1–3 weeks
- In adults, the anemia is usually gradual and not as severe as in children
- Purplish discoloration of fingers, toes, nose, ears, or other peripheral areas that are exposed to cold
- Numbness of extremities when exposed to cold

- Splenomegaly

Pathology

- Patients may develop antibodies directed against the I or i antigens on the red blood cells
- Aggressive lymphomas and other malignancies produce an IgM autoantibody that activates complement and hemolysis results
- Can be secondary in patients with lymphoproliferative diseases, infectious mononucleosis, or Mycoplasma pneumoniae infections
- In children and young adults, the syndrome is brought on by viral infections
- Diminished erythropoiesis caused by the infection

Laboratory Features

White Blood Cells

- Normal or falsely elevated

Platelets

- Not remarkable

Red Blood Cells

- Mean corpuscular volume increased when blood cools to room temperature
- Reticulocyte count increased
- Agglutination of red blood cells
- Mild to moderate anisocytosis, poikilocytosis
- Polychromatophilia
- Falsely decreased red blood cell count
- Mean corpuscular hemoglobin concentration falsely increased due to falsely decreased hematocrit levels

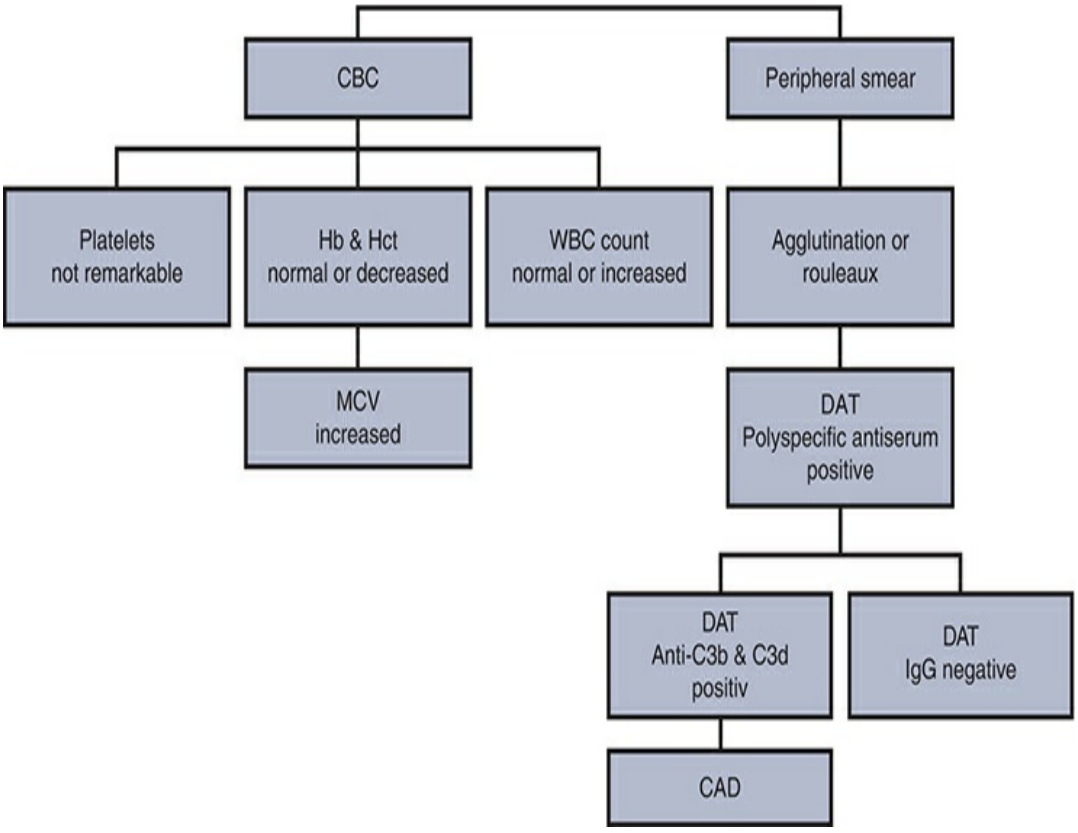
Bone Marrow

- Erythroid hyperplasia

Serologic Tests

- Direct antihuman globulin test positive with polyspecific antisera and anti-C3d
- Cold agglutinin titer of ≥1000 in saline at 4°C

Diagnostic Scheme



GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

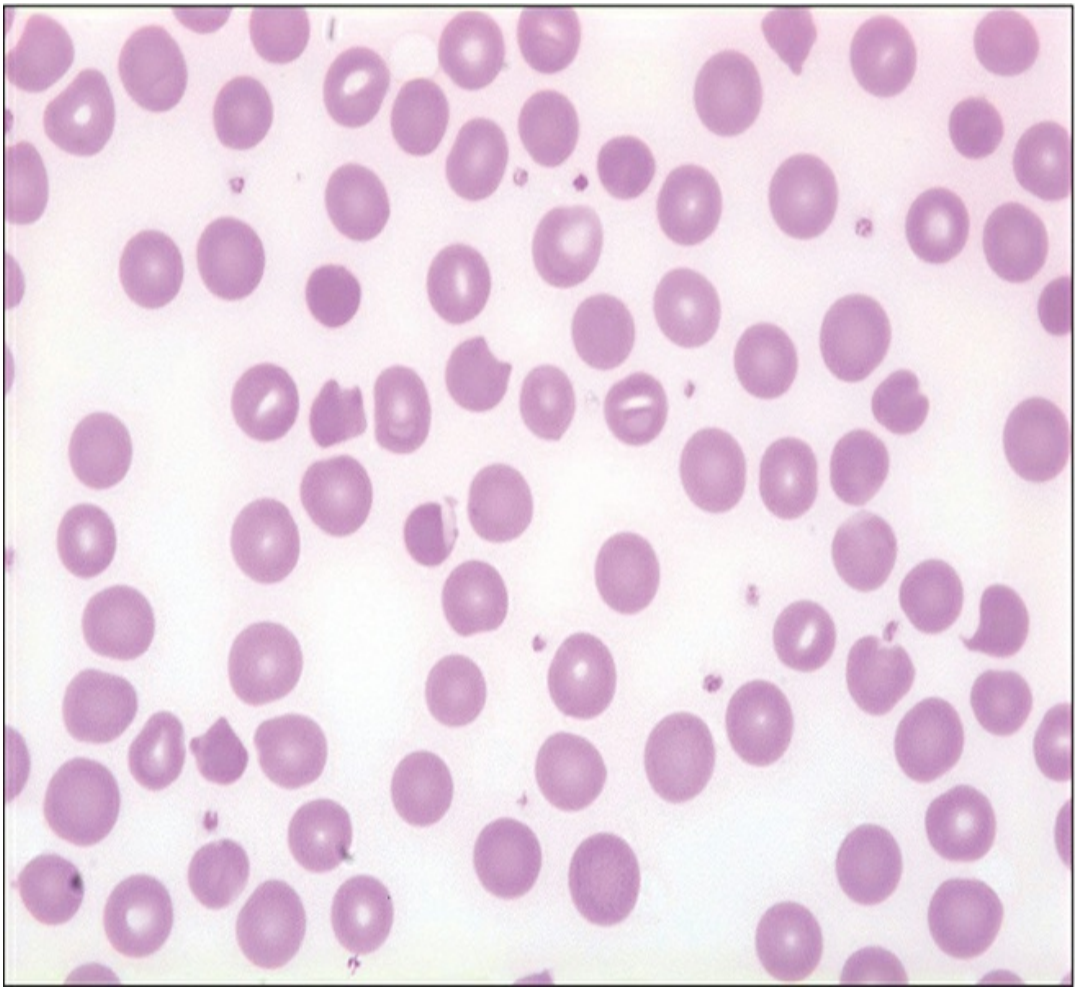


Figure IIA6-2

Peripheral blood smear.

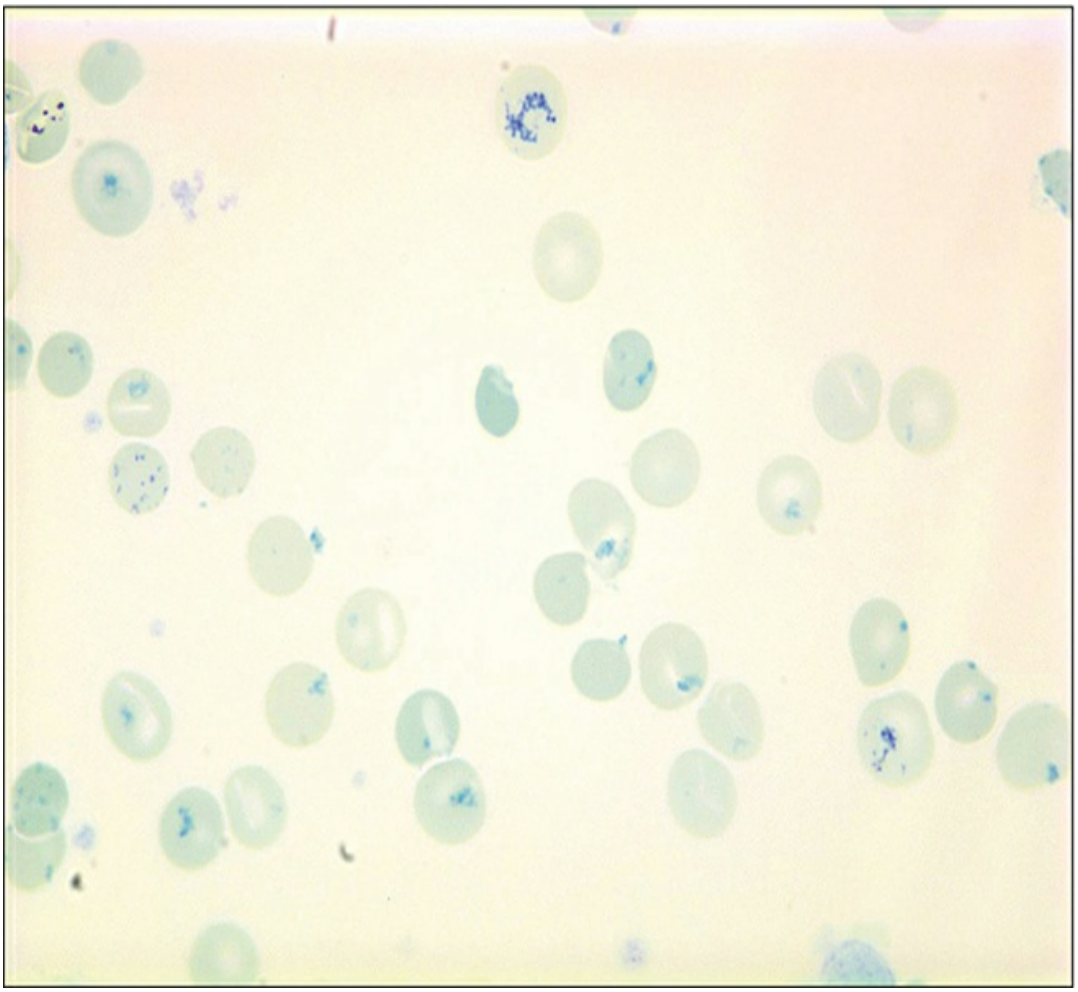


Figure IIA6-3

Brilliant cresyl blue stain.

Clinical Features

- No clinical symptoms unless exposed to chemicals or drug oxidants or severe infections
- Chronic hemolysis
- Jaundice is not prominent
- Abdominal and low back pain
- Urine is dark or black because of hemoglobinuria
- Classification based on degree of hemolysis and enzyme deficiency
- Classes I, II, and III are clinically significant

Pathology

Pathology

- The glucose-6-phosphate dehydrogenase gene is located on the X chromosome
- Red blood cells deficient in glucose-6-phosphate dehydrogenase are susceptible to oxidation and hemolysis
- Nicotinamide adenine dinucleotide phosphate production is impaired
- Buildup of cellular oxidants leads to erythrocyte injury and hemolysis
- Hemoglobin is oxidized to methemoglobin, which precipitates in the form of Heinz bodies
- Heinz bodies attach to the red blood cell membrane, causing increased permeability to cations, osmotic fragility, and cell rigidity
- Red cells have a rigid cell wall, with the hemoglobin confined to one part of the cytosol

Laboratory Features

White Blood Cells

- Increased during attacks

Platelets

- Normal

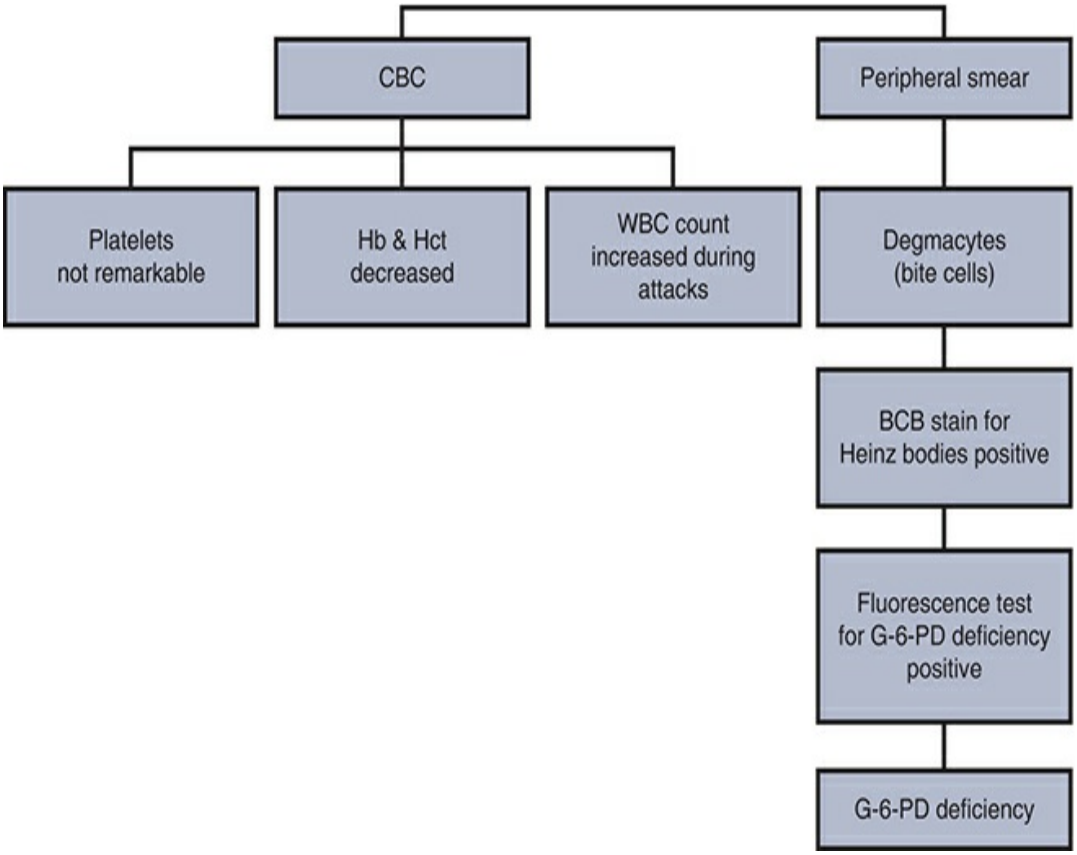
Red Blood Cells

- Normocytic/normochromic anemia
- Increased reticulocyte count after hemolytic crises
- Heinz bodies
- Polychromasia
- Occasional spherocytes
- Degmacytes

Chemistries

- Positive fluorescent screening test for glucose-6-phosphate dehydrogenase deficiency
- Quantitative direct enzyme assay for glucose-6-phosphate dehydrogenase decreased
- Positive Heinz body test
- Indirect bilirubin and lactic dehydrogenase levels may be increased
- Haptoglobin decreased during attacks

Diagnostic Scheme



HEREDITARY ACANTHOCYTOSIS

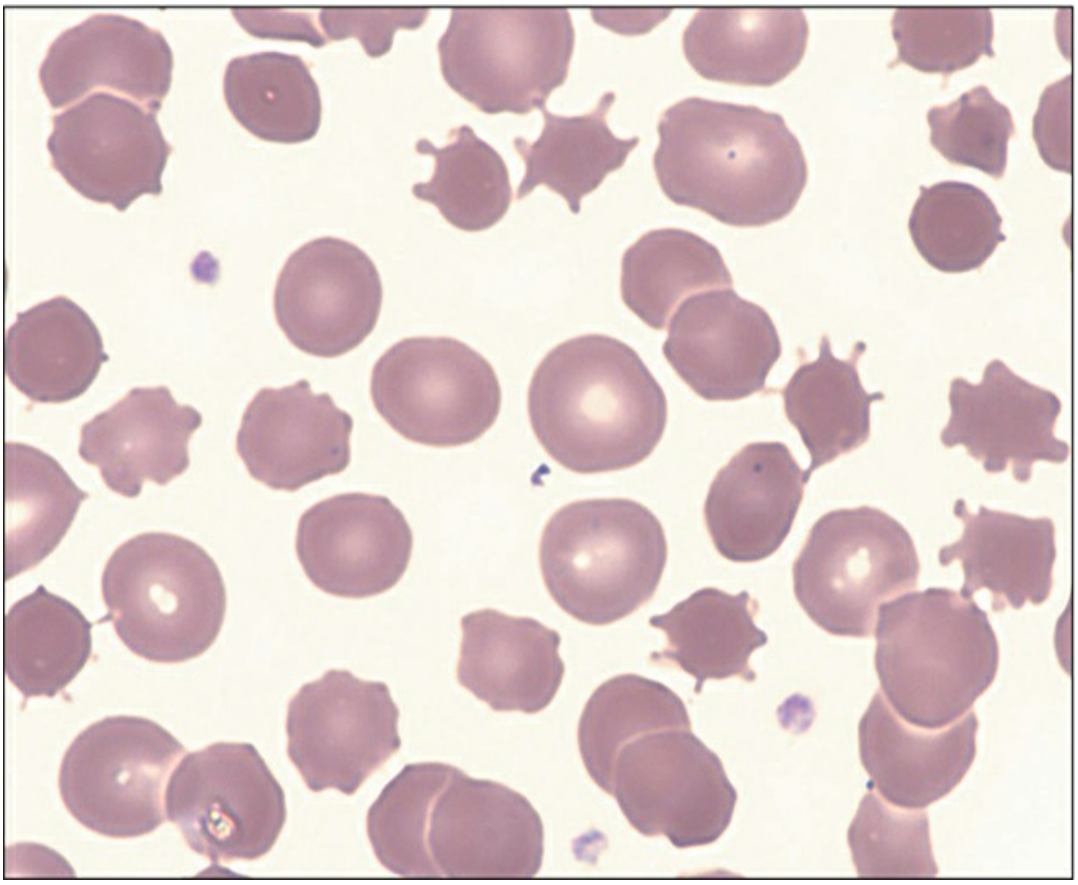


Figure IIA6-4

Peripheral blood smear.

Clinical Features

- Autosomal recessive disease
- Major symptoms due to vitamin E deficiency
- Malabsorption of fat, retinitis pigmentosa, neurologic damage, mental retardation, and delayed growth development

Pathology

- Deficiency in apoprotein
- Defect in the beta-lipoprotein particle assembly and secretion in the intestine and liver

- Deficient absorption and transport of fat-soluble vitamins A, D, E, and K
- Red blood cells have increased sphingomyelin:lecithin ratio that leads to acanthocytosis
- Deficiency in triglyceride microsomal transfer protein, which is necessary for the assembly and secretion of apolipoprotein B–containing lipoproteins from the liver and intestine

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

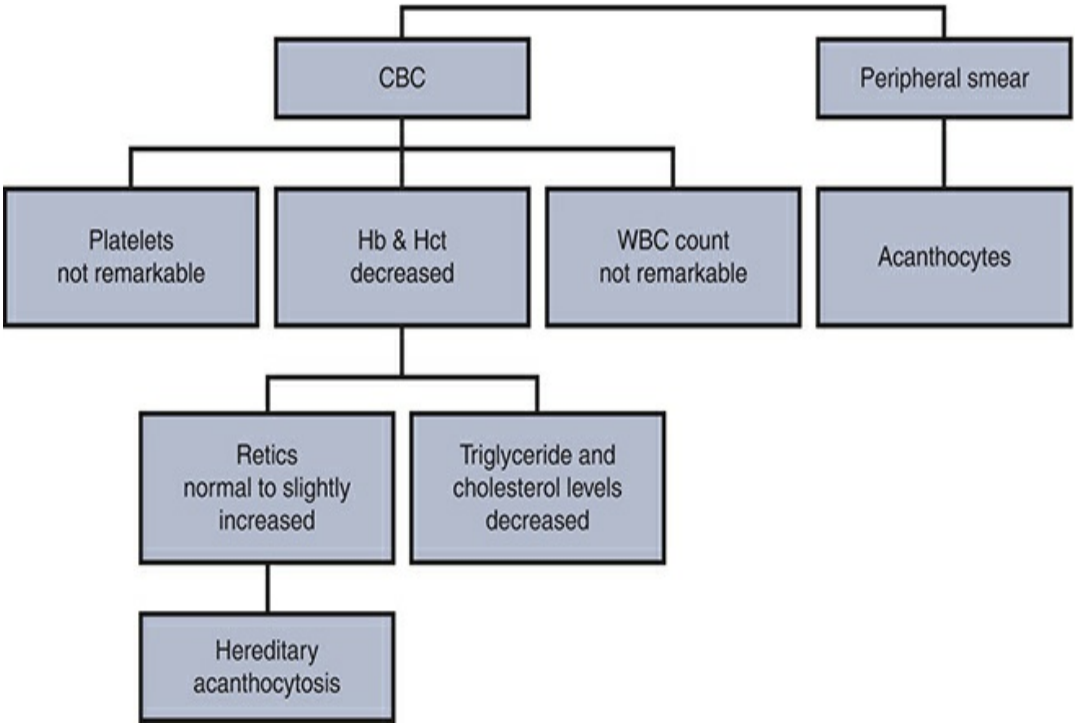
Red Blood Cells

- Mild normocytic/normochromic anemia
- Indices normal
- Reticulocyte count normal or slightly increased
- Acanthocytes
- Increased osmotic fragility

Chemistries

- Triglyceride levels decreased
- Cholesterol level usually <50 mg/dL
- Low-density lipoprotein, very low-density lipoprotein, and chylomicrons decreased

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Acanthocytes
Retics normal to slightly increased
Triglyceride and cholesterol levels decreased
Hereditary acanthocytosis

HEREDITARY ELLIPTOCYTOSIS

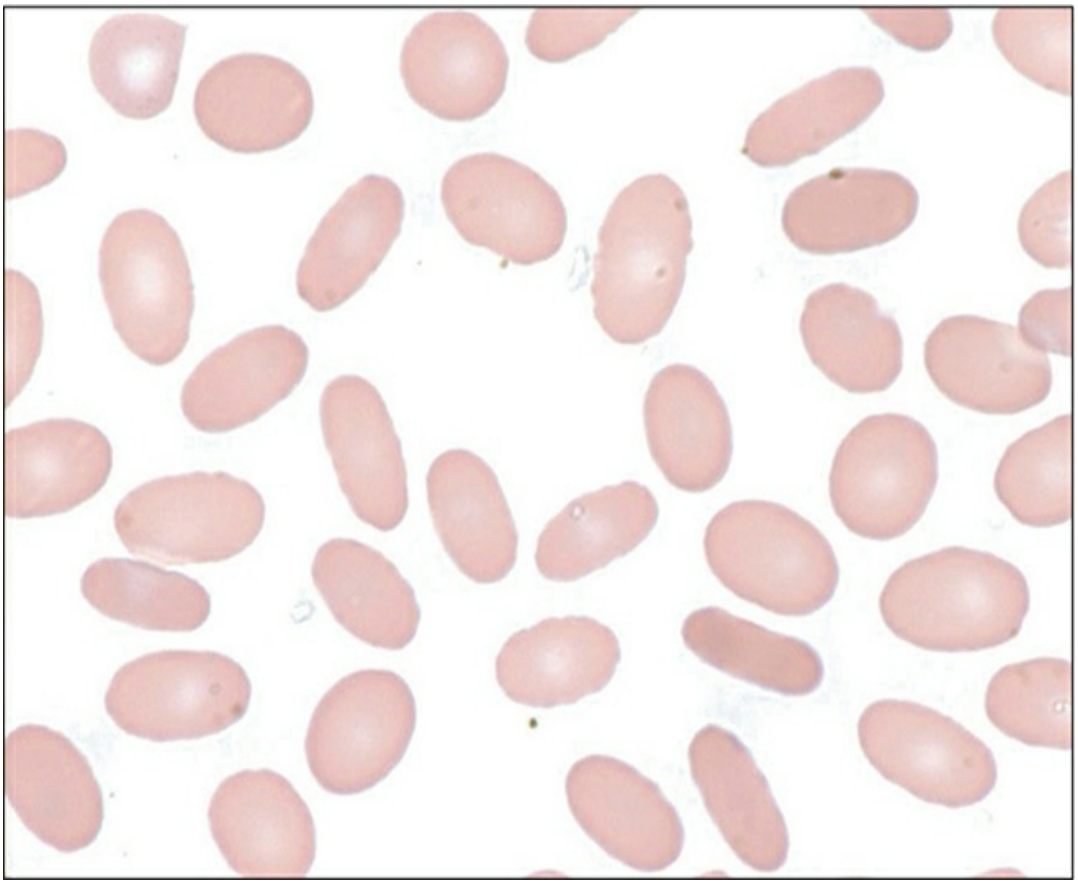


Figure IIA6-5

Peripheral blood smear—common hereditary elliptocytosis.

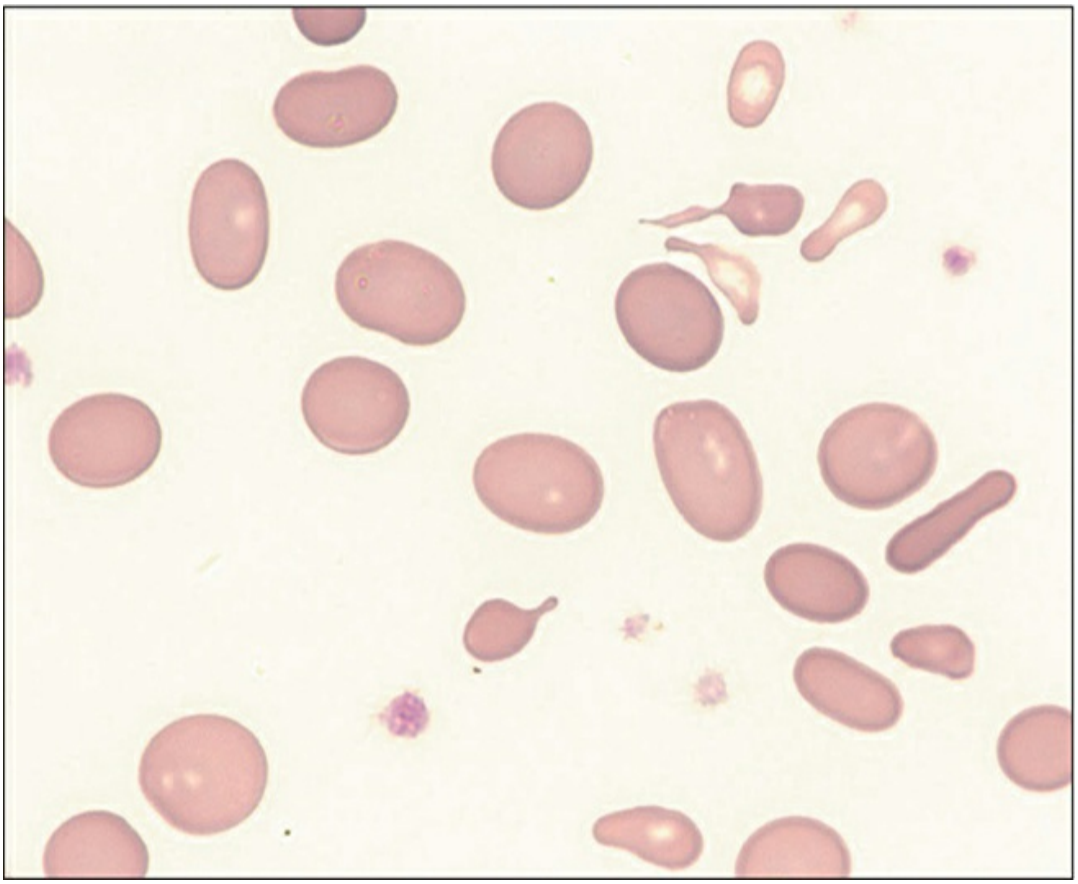


Figure IIA6-6

Peripheral blood smear—hereditary pyropoikilocytosis.

Clinical Features

- About 90% of patients show no overt signs of hemolysis
- Hemolysis is usually mild and well compensated by the bone marrow
- Morphologic classification
  - Common hereditary elliptocytosis
    - Inherited as an autosomal dominant trait
    - Ranges from asymptomatic to severe clinical disease
  - Spherocytic hereditary elliptocytosis
    - Inherited as an autosomal dominant trait
    - Presence of hemolysis

- Stomatocytic hereditary elliptocytosis (Melanesian or Southeast Asian ovalocytosis)
    - Inherited as a recessive trait
    - Occurs in about 0.2–0.5%
    - Mild or absent hemolytic component
    - Cation permeability increased
- Hereditary pyropoikilocytosis
    - Inherited as a recessive trait
    - Presents in infancy or early childhood
    - Microspherocytes
    - Severe red cell fragmentation and hemolysis
    - Hyperbilirubinemia may require exchange transfusion or phototherapy

Pathology

- The defect is in one of the skeletal proteins in the membrane, which is acquired in the circulation (horizontal membrane protein interaction)
    - Decreased associate of spectrin dimers to form tetramers due to defective spectrin chains
    - Deficient or defective band 4.1, which aids in binding spectrin to actin
    - Abnormalities of integral proteins (glycophorin C and band 3)
- Membrane fragmentation causes a decrease in cell surface and reduced cell deformability and thus a shortened life span
- Abnormal permeability to sodium and thus increased demands on adenosine triphosphate availability
- In hereditary pyropoikilocytosis, there is a mutant alpha or beta spectrin that shows severe impairment of

spectrin dimer self-association and a partial deficiency of spectrin due to decreased alpha spectrin synthesis or an unstable spectrin deficiency

Laboratory Features

White Blood Cells

- Not remarkable

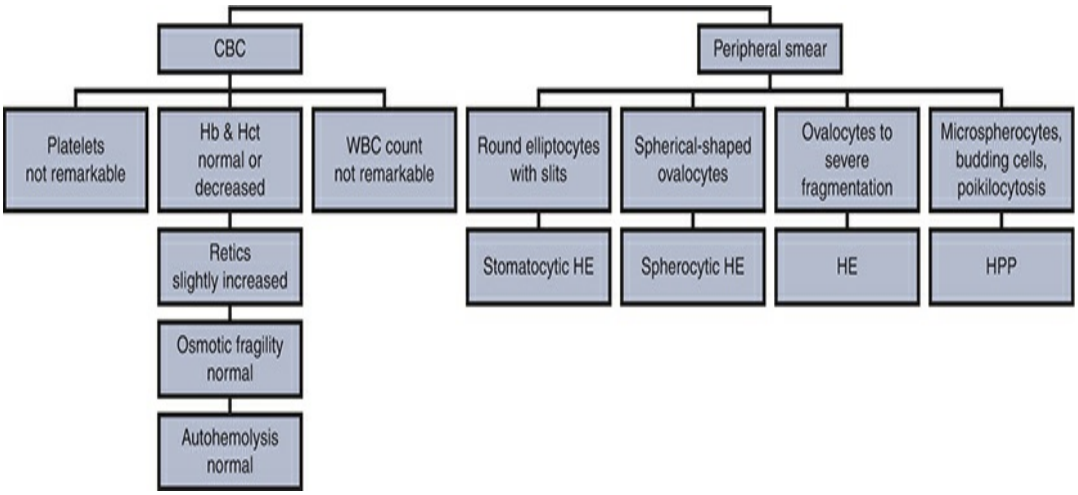
Platelets

- Not remarkable

Red Blood Cells

- Common hereditary elliptocytosis: mild elliptocytosis (15%) to severe fragmentation and poikilocytes
- Spherocytic hereditary elliptocytosis: morphology between spherocytes and elliptocytes
- Stomatocytic hereditary elliptocytosis: round elliptocytes with slit
- Hereditary pyropoikilocytosis: poikilocytosis, microspherocytes, budding of cells

Diagnostic Scheme



HEREDITARY SPHEROCYTOSIS

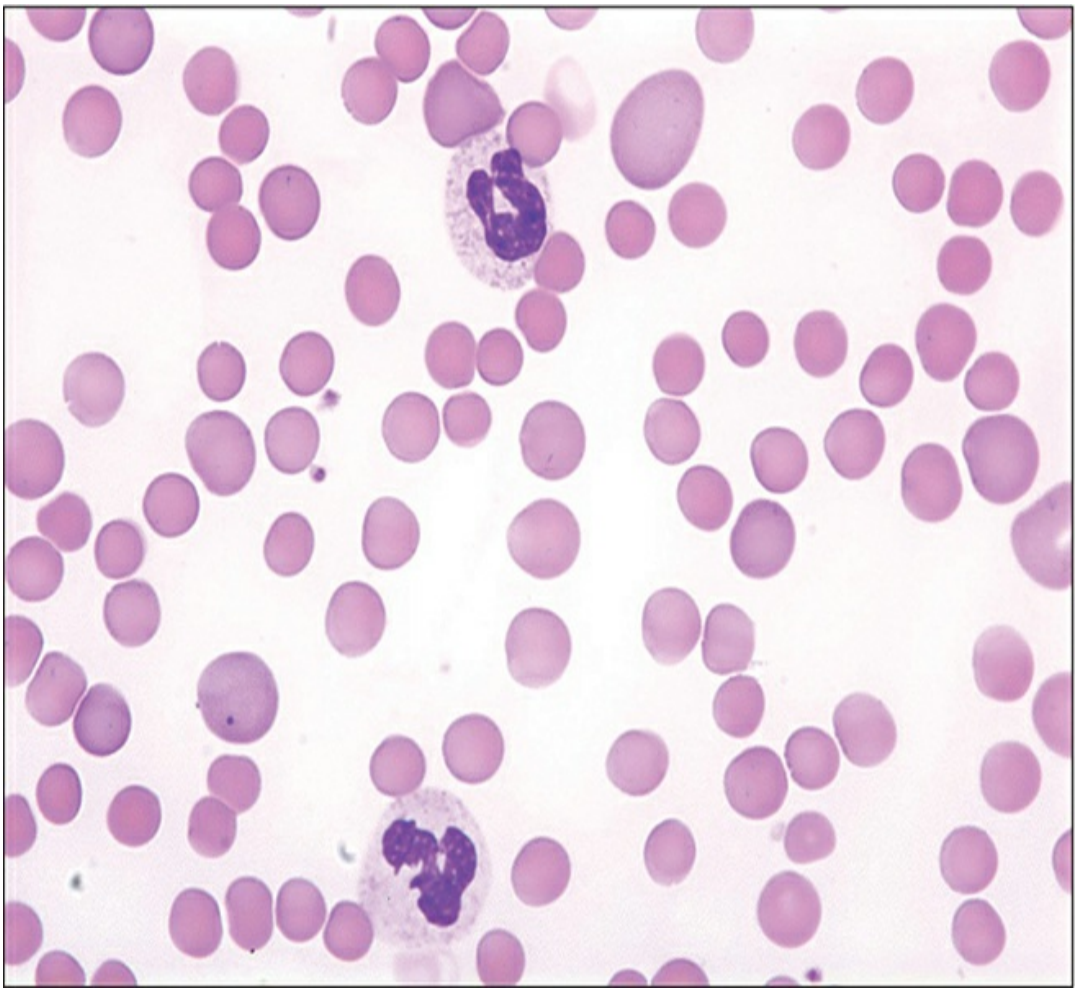


Figure IIA6-7

Peripheral blood smear.

Clinical Features

- Usually inherited as an autosomal dominant trait, but can be recessive
- Classically, the patient will have anemia, jaundice, and splenomegaly; however, the symptoms are variable
- Gallstone formation is not uncommon

Pathology

- Group of hemolytic anemias characterized by mutations in red blood cell membrane protein genes

- Red blood cell membranes abnormalities
  - Spectrin deficiency
  - Ankyrin deficiency
  - Protein 3 deficiency
  - Protein 4.1 deficiency
  - Protein 4.2 defect
- Because of the membrane disorder, microspherocytes are formed, which are not deformable and are sequestered in the spleen and hemolytic anemia may result

Laboratory Features

White Blood Cells

- Usually normal

Platelets

- Usually normal

Red Blood Cells

- Increased mean corpuscular hemoglobin concentration
- Normal to decreased mean corpuscular volume
- Normal mean corpuscular hemoglobin
- Reticulocyte count increased (5–20%)
- Diffusely basophilic erythrocytes, spherocytes, anisocytosis, and poikilocytosis seen on smear
- Osmotic fragility increased

Bone Marrow

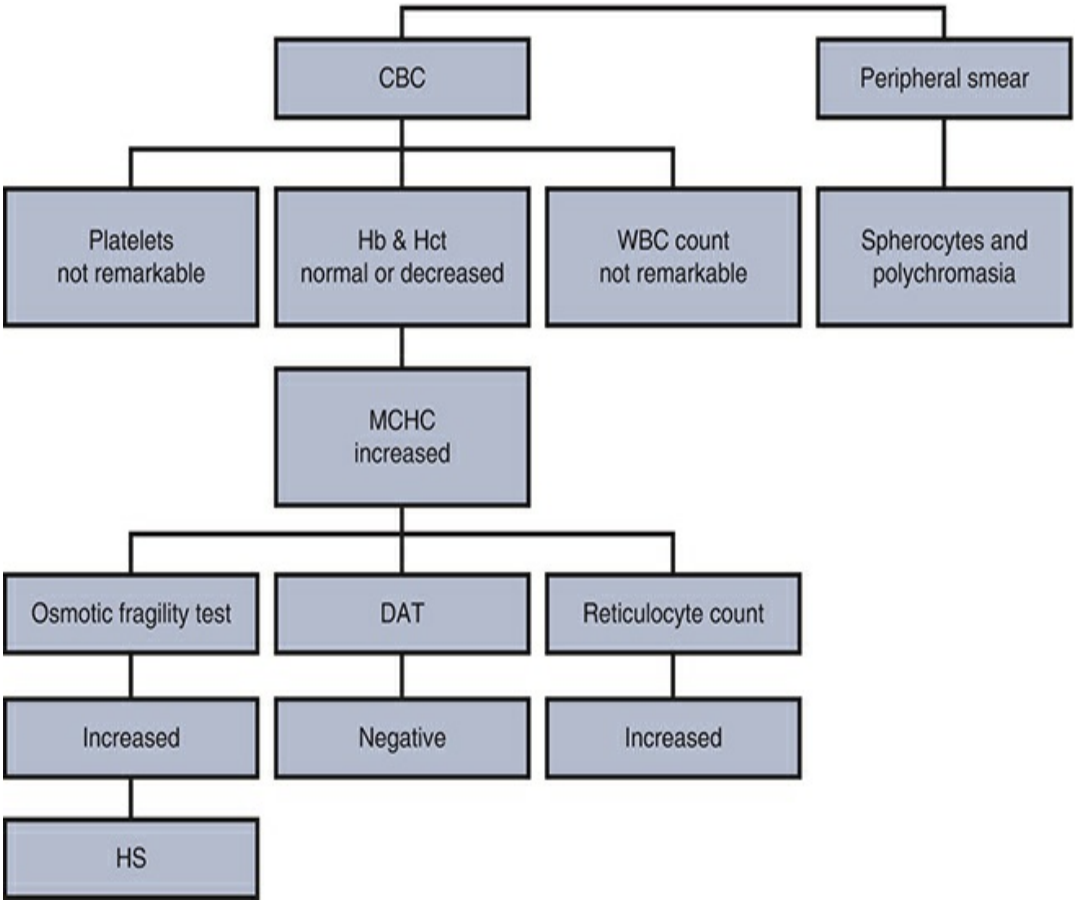
- Erythroid hyperplasia

Chemistries

- Indirect bilirubin level increased
- Fecal and urine urobilinogen levels increased

- Lactic dehydrogenase level increased
- Haptoglobin level decreased

Diagnostic Scheme



HEREDITARY STOMATOCYTOSIS

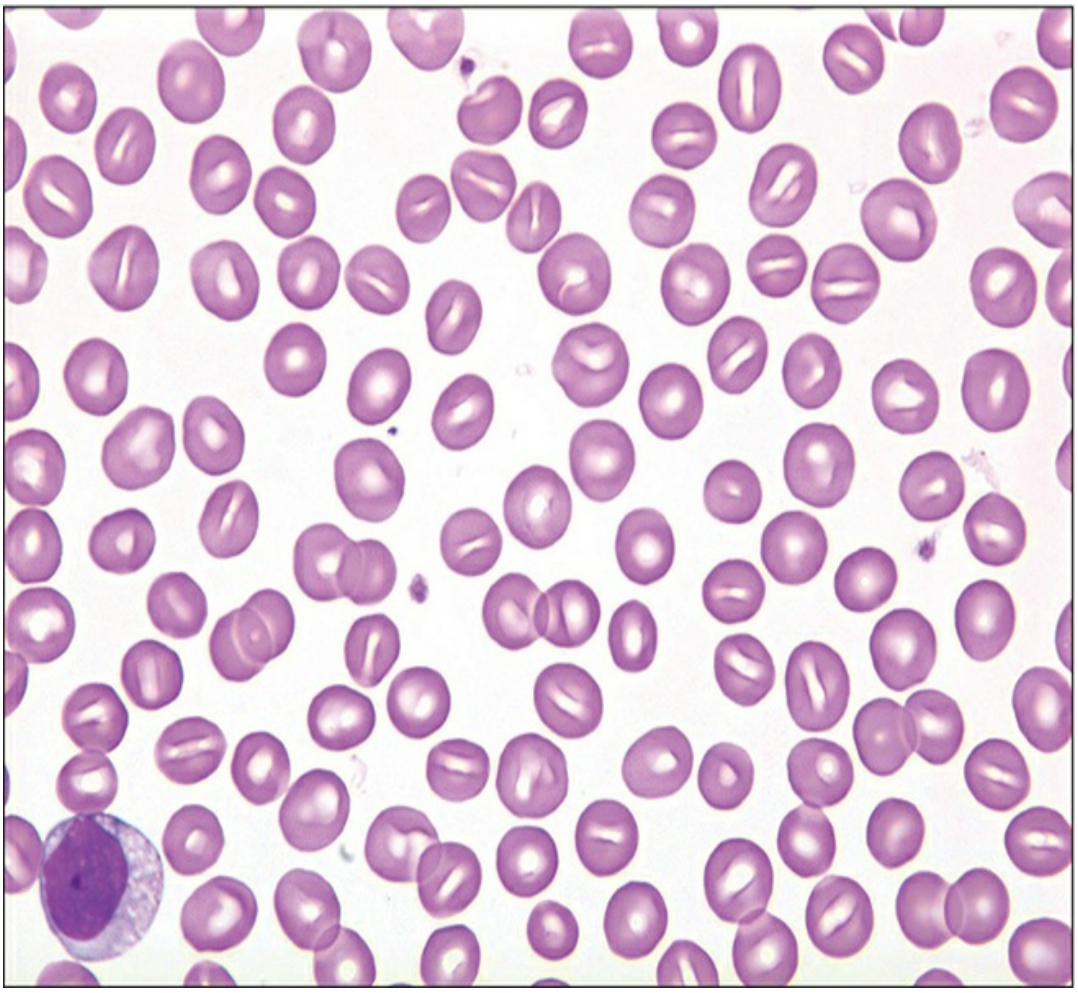


Figure IIA6-8

Peripheral blood smear.

Clinical Features

- On occasion, the patient may have a palpable spleen

Pathology

- Passive influx of sodium ions exceeds the loss of potassium ions
- The enzyme, sodium–potassium adenosine triphosphatase, is overwhelmed and the water content of the cell is increased
- The surface area:volume is decreased

- The most common defect is one of the red cell membrane protein in the band 7.2b (stomatin)
- Cells are more avid, which increased thrombotic events

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

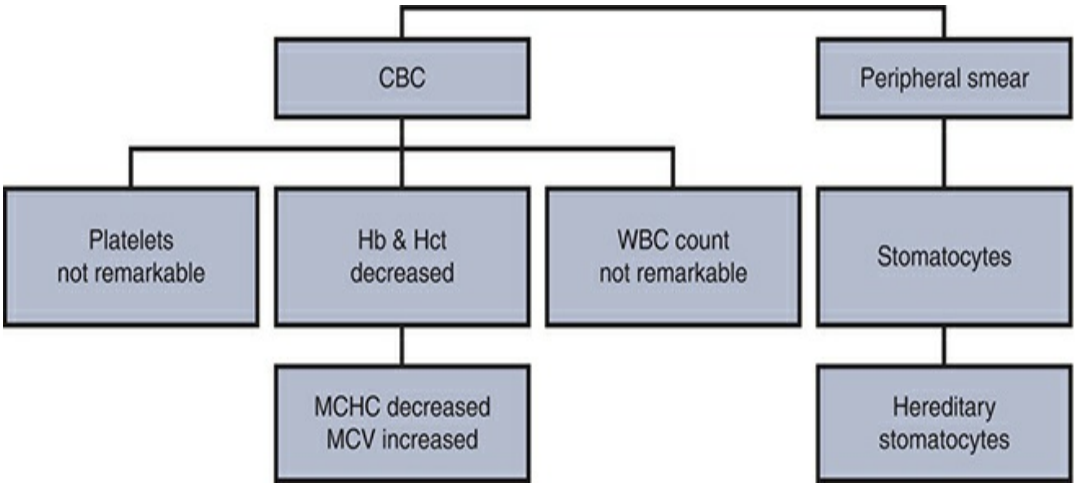
Red Blood Cells

- Mild to moderate anemia
- Stomatocytes present
- Moderate reticulocytosis
- Osmotic fragility increased

Chemistries

- Increased bilirubin
- Autohemolysis increased

Diagnostic Scheme



IMMUNE HEMOLYTIC ANEMIA

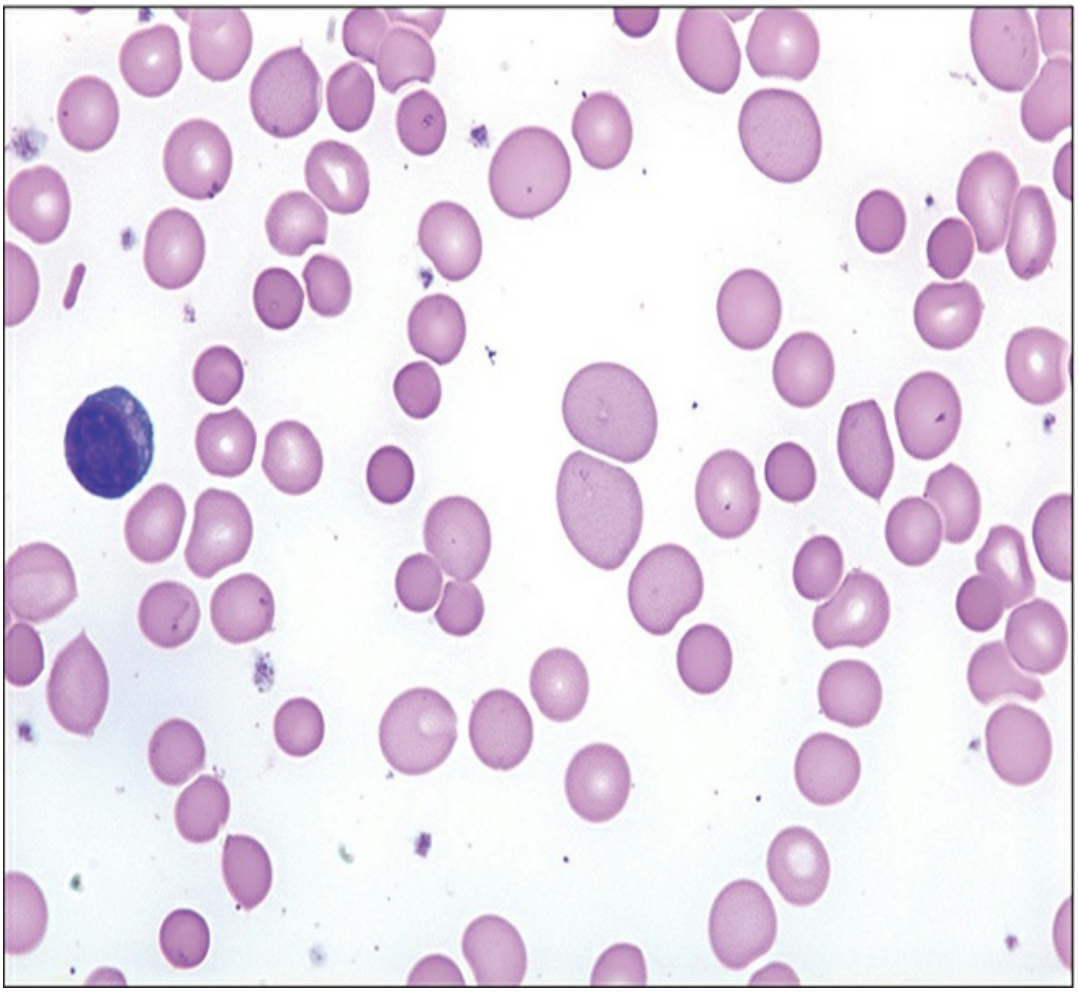


Figure IIA6-9

Peripheral blood smear.

Clinical Features

- Mild fatigue to dyspnea, syncope, and angina result because of decreased oxygen delivery to tissues
- Pallor
- Jaundice

Pathology

- Destruction of red cells by antibodies produced by the patient
- Destruction of red cells by these antibodies is brought

about primarily by a mechanism that depends on immune adherence

Laboratory Features

White Blood Cells

- May be elevated due to an increased in neutrophils
- Counts may approach 30×10^9/L

Platelets

- Usually normal

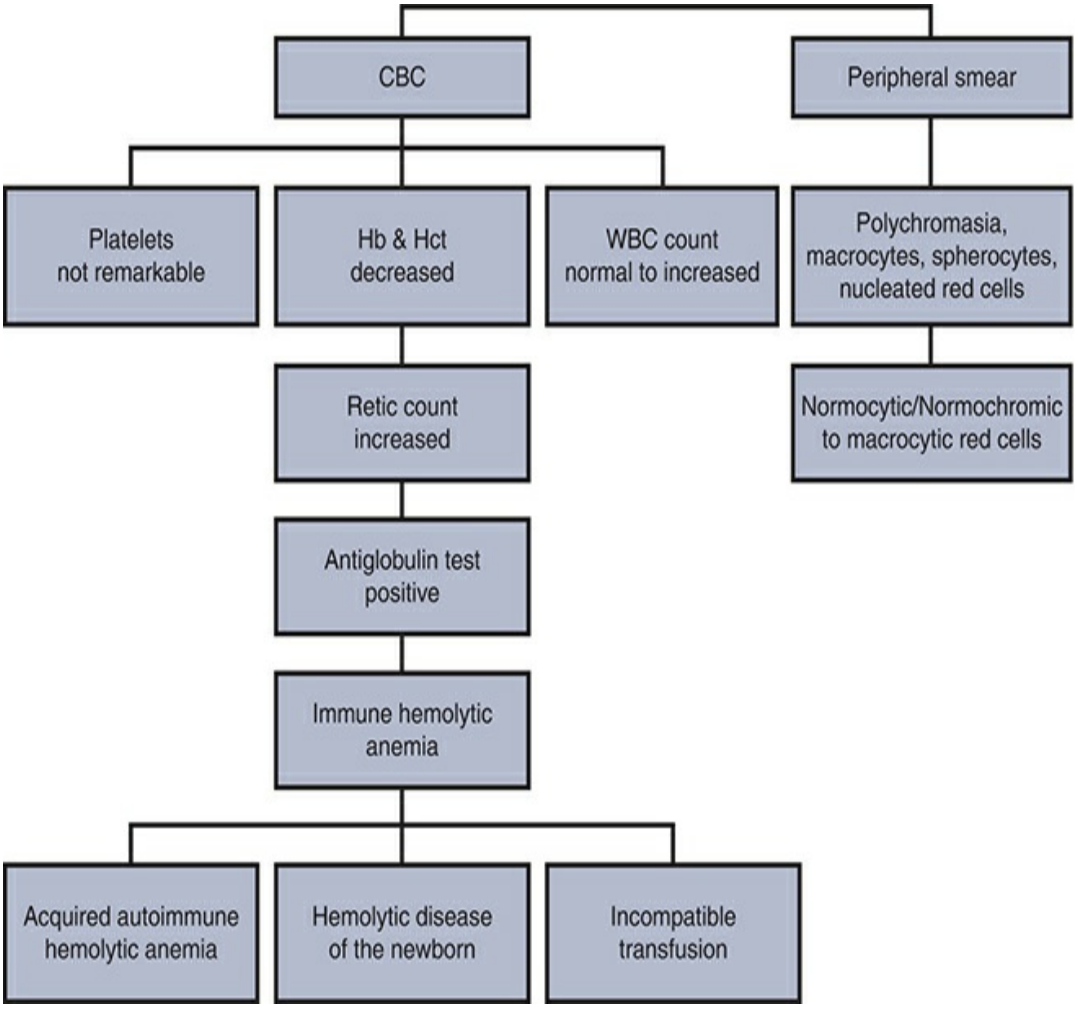
Red cells

- Hemoglobin and hematocrit levels decreased
- Normocytic/normochromic anemia
- Reticulocyte count increased
- Increased mean corpuscular volume is due to prominent reticulocytosis
- Spherocytes

Bone marrow

- Hypercellular with erythroid precursors

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count normal to increased
Polychromasia, macrocytes, spherocytes, nucleated red cells
Retic count increased
Normocytic/Normochromic to macrocytic red cells
Antiglobulin test positive
Immune hemolytic anemia
Acquired autoimmune hemolytic anemia
Hemolytic disease of the newborn
Incompatible transfusion

MICROANGIOPATHIC HEMOLYTIC ANEMIA

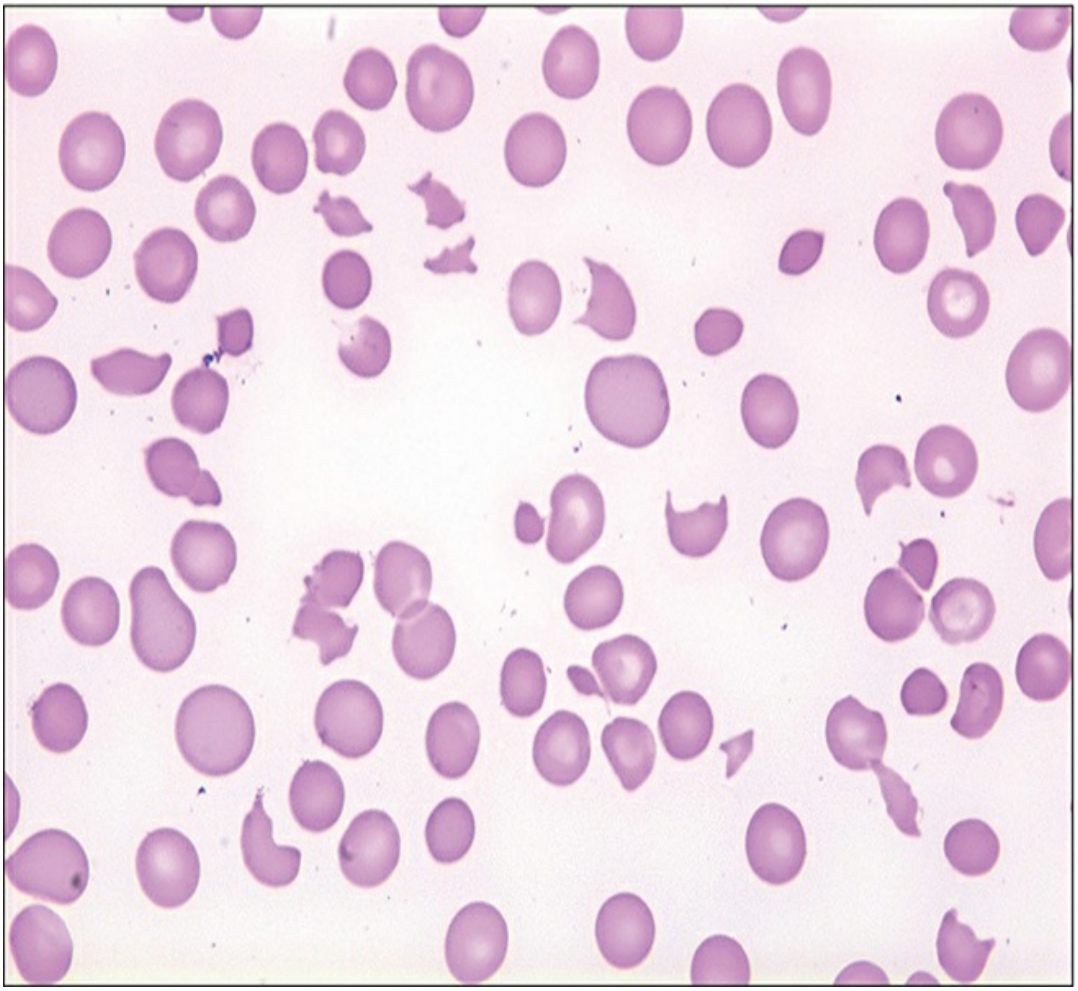


Figure IIA6-10

Peripheral blood smear.

Clinical Features

- Hemolysis—intravascular
- Thrombotic thrombocytopenic purpura
  - Occurs frequently in young adults
  - Hemorrhage into the tissues
  - Fever, weakness, gastrointestinal symptoms
  - Purpura
  - Neurologic abnormalities

- Hemolytic uremic syndrome
  - Disease of children that occurs abruptly after ingestions of contaminated food often with bloody diarrhea where the causative agent produces a Shiga-like toxin
  - Fever
  - Acute renal failure
  - Hypertension and electrolyte abnormalities
- Disseminated intravascular coagulation
  - Abrupt onset
  - Associated with trauma, massive transfusion, obstetric complications, sepsis, carcinoma, and others
  - Hemorrhagic tendencies
  - Progressive renal dysfunction
- Transplant-associated thrombotic microangiopathy
  - Associated with allogenic stem cell transplantation

Pathology

- Common pathway complement activation
- Localized intravascular coagulation in which fibrin strands bridge the arteriolar lumen when supplying blood in inflamed or neoplastic tissue
- Fibrin strands lop off fragments of red blood cells whose membranes seal, leaving distorted cells
- Thrombotic thrombocytopenic purpura
  - Mutations lead to ADAMTS13 deficiency in the hereditary form
  - Autoantibodies cause inhibition of the ADAMTS13 activity in the acquired form
  - Deficiency of ADAMTS13 leads to ultra-large von

Willebrand factor multimers, which react with platelets and induce thrombi formation

- Hemolytic uremic syndrome
  - Microthrombi are formed, complement is activated, and red blood cells and endothelial cells are damaged
    - 75% of cases are caused by E. coli infections that release a Shiga-like toxin, which blocks ADAMTS13 causing ultra-large multimers of von Willebrand factor
    - Sporadic form may be due to Streptococcus pneumonia infection, which causes injury to endothelial cells through the production of neuraminidase
    - Complement activation leads to endothelial and red blood cell damage and thrombotic microangiopathy and then intravascular hemolysis
- Disseminated intravascular coagulation
  - Tissue factor or bacterial toxin can activate the coagulation cascade that results in the overproduction of thrombin producing fibrin monomers, which form polymers:
    - Fibrin polymers deposit in microvasculature and lead to tissue ischemia
    - Endothelial cells respond and cause excessive fibrinolysis
- Transplant-associated thrombotic microangiopathy
  - Likely due to endothelial cell damage with subsequent dysregulation of the complement

pathway

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Decreased

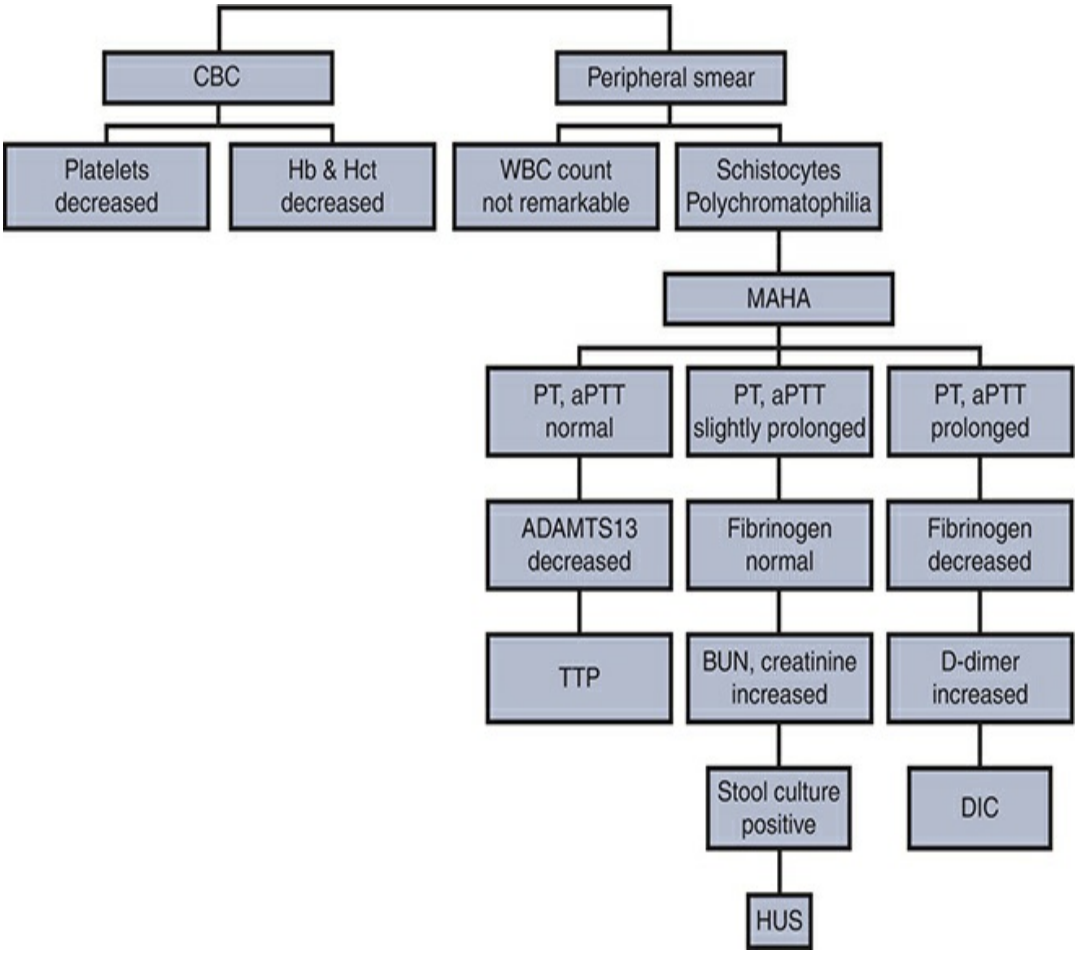
Red Blood Cells

- Normocytic/normochromic anemia
- Increased reticulocyte count
- Schistocytes
- Polychromatophilia

Other Laboratory Tests

- Increased serum lactate dehydrogenase level
- Decreased ADAMTS13 activity in thrombotic thrombocytopenic purpura
- Positive stool culture in Shiga-like toxin hemolytic uremic syndrome
- Elevated D-dimer test in disseminated intravascular coagulation

Diagnostic Scheme


CBC
Peripheral smear
Platelets decreased
Hb & Hct decreased
WBC count not remarkable
Schistocytes Polychromatophilia
MAHA
PT, aPTT normal
PT, aPTT slightly prolonged
PT, aPTT prolonged
ADAMTS13 decreased
Fibrinogen normal
Fibrinogen decreased
TTP
BUN, creatinine increased
D-dimer increased
Stool culture positive
DIC
HUS

NONIMMUNE HEMOLYTIC ANEMIA

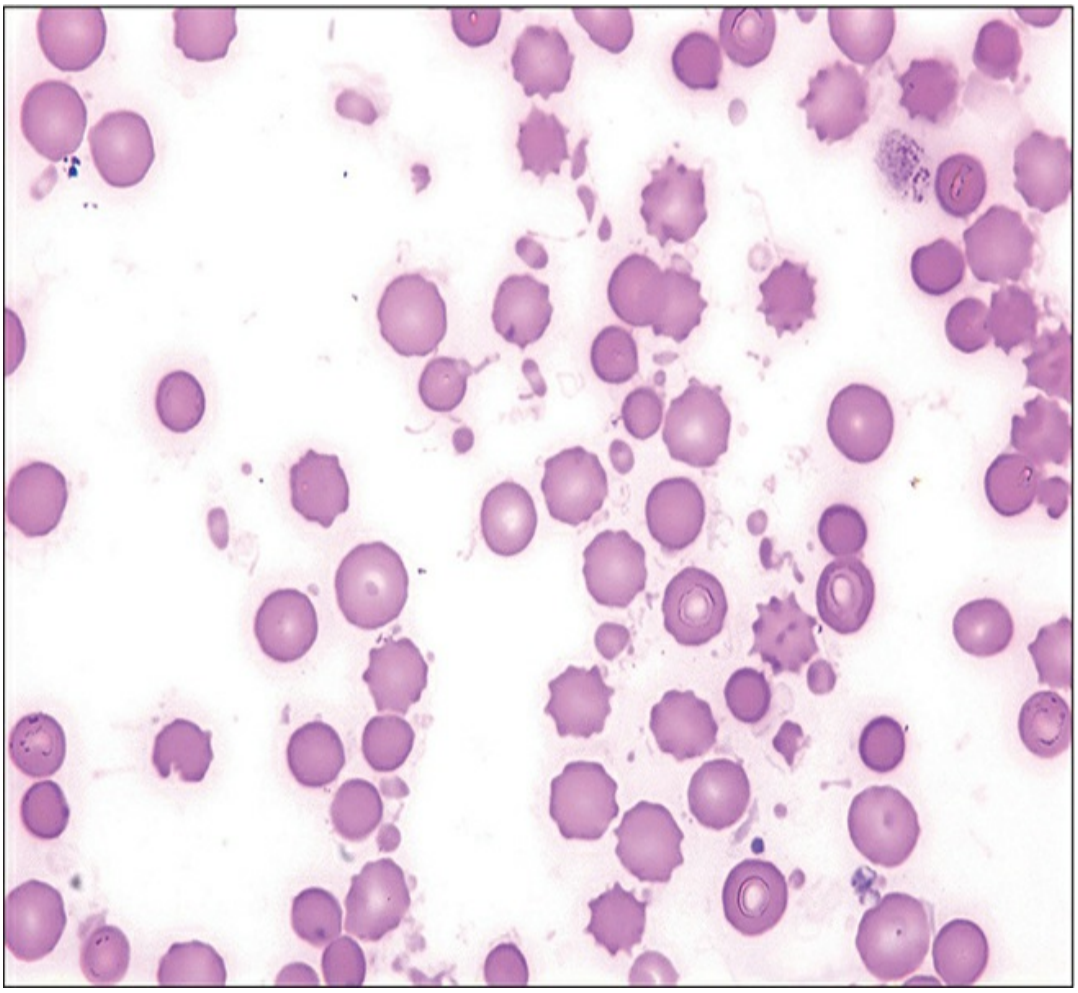


Figure IIA6-11

Peripheral blood smear.

Clinical Features

- Hemolysis—intravascular or extravascular
- Evidence of hemolysis—jaundice, hemoglobinuria, and hemoglobinemia

Pathology

- Thermal injury
  - Red cells within the vessels exposed to temperatures above about 50°C are destroyed, causing immediate intravascular fragmentation

and lysis
    - Because of increased capillary permeability, plasma is lost from the vessels resulting in hemoconcentration
- Mechanical injury
    - Red cells disintegrate when subjected to strong stretching or shearing forces
    - March hemoglobinuria occurs with prolonged marching or running, and red cells are destroyed in the vessels of the feet

Laboratory Features

Thermal Injury

White Blood Cells

- Increased

Platelets

- Not remarkable

Red Blood Cells

- Microspherocytes
- Budding of membrane

Mechanical Injury

White Blood Cells

- Not remarkable

Platelets

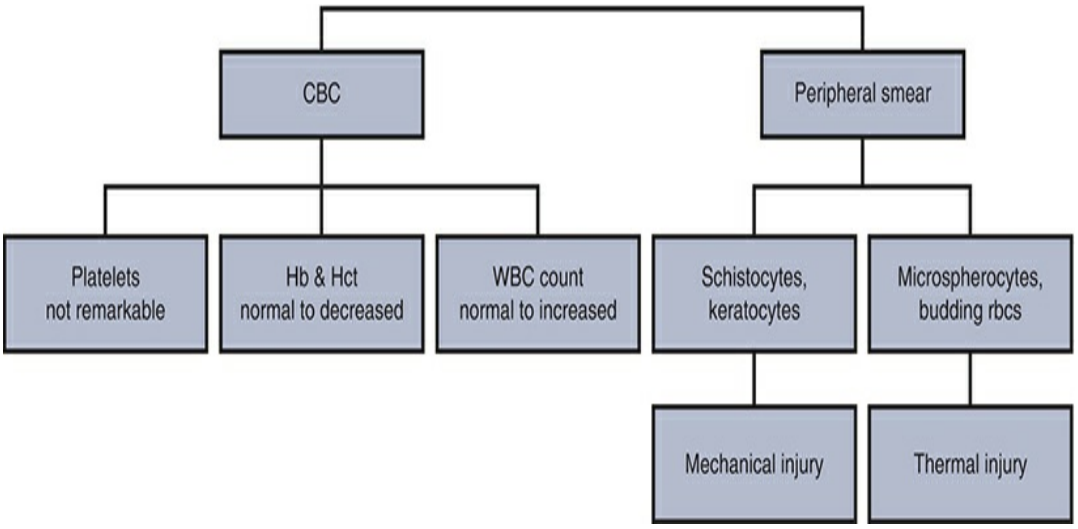
- Not remarkable

Red Blood Cells

- Schistocytes
- Keratocytes

- Reticulocyte count increased

Diagnostic Scheme



PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

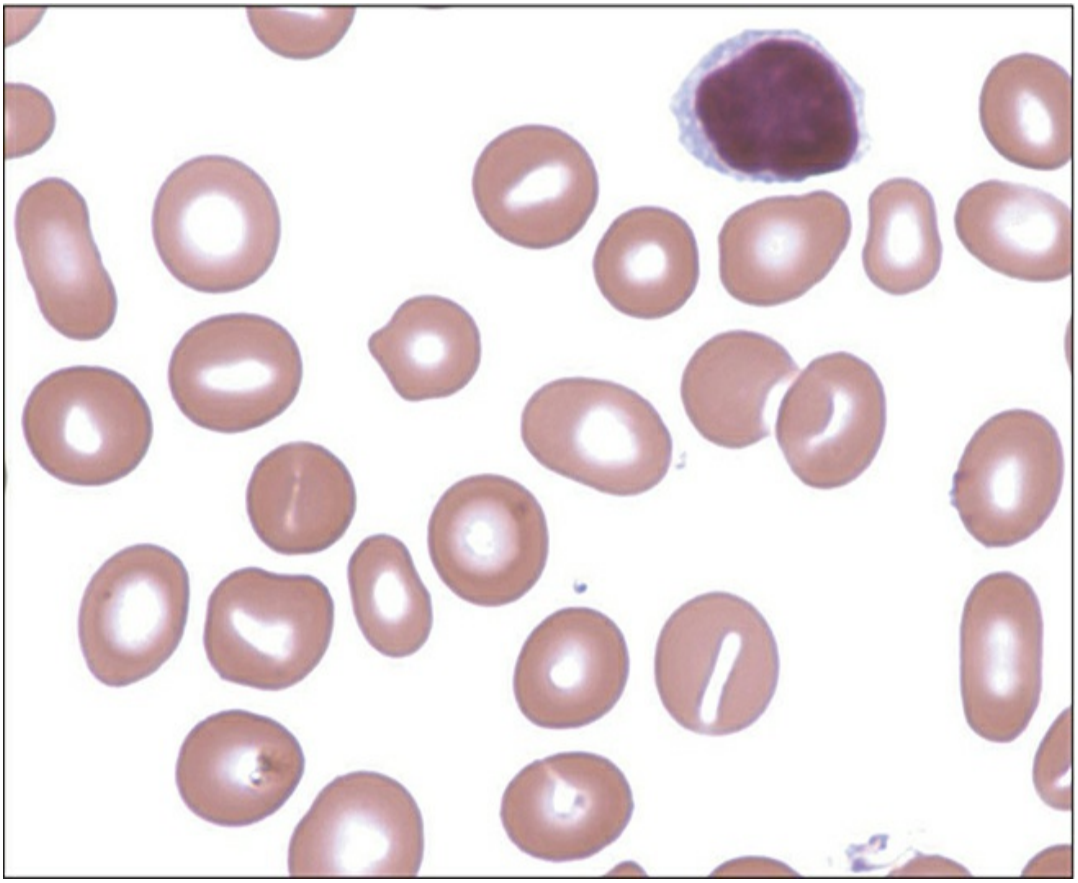


Figure IIA6-12

Peripheral blood smear.

Clinical Features

- Rare disorder with severe anemia possible
- Acute episodes of intravascular hemolysis are superimposed on a background of chronic hemolysis
- Hemoglobinuria on voiding after sleep is not a universal finding
- Recurrent venous occlusions may lead to pulmonary embolisms and hepatic and mesenteric vein thrombosis
- May be precipitated by surgery, transfusion, or infections

- Three types of paroxysmal nocturnal hemoglobinuria cell may be observed and are associated with the severity of the disease

Pathology

- Somatic mutation in marrow stem cells
- Clonal disorder of hematopoiesis caused by a deficiency of phosphatidylinositol glycan class A
- Abnormal susceptibility to complement-mediated lysis
- The decay-accelerating factor that regulates the activity of C3 convertase is one of the missing proteins
- Loss of surface protein linkage caused by deficiency of glycophosphatidylinositol anchors
- Can progress to acute myelogenous leukemia or myelodysplasia syndromes

Laboratory Features

White Blood Cells

- Neutropenia
- Decreased leukocyte alkaline phosphatase activity

Platelets

- Thrombocytopenia
- Abnormal platelet function

Red Blood Cells

- Hemolytic anemia
- Iron deficiency may develop with chronic hemolysis
- Acetylcholinesterase activity decreased

Bone Marrow

- Marrow hypoplasia

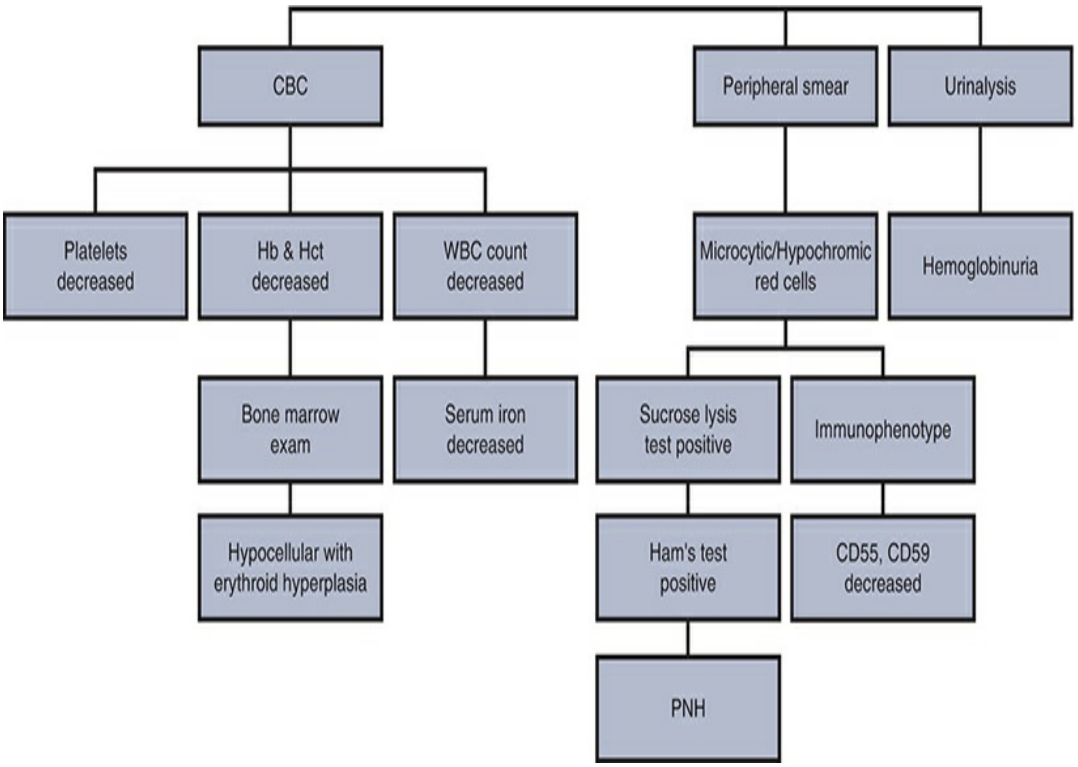
Chemistries

- Serum haptoglobin level decreased
- Methemalbumin level increased
- Hemoglobinuria
- Hemosiderinuria
- Ham test result positive
- Sucrose lysis test is the most common screening test

Immunophenotype

- Decreased CD55, CD59

Diagnostic Scheme



PYRUVATE KINASE DEFICIENCY

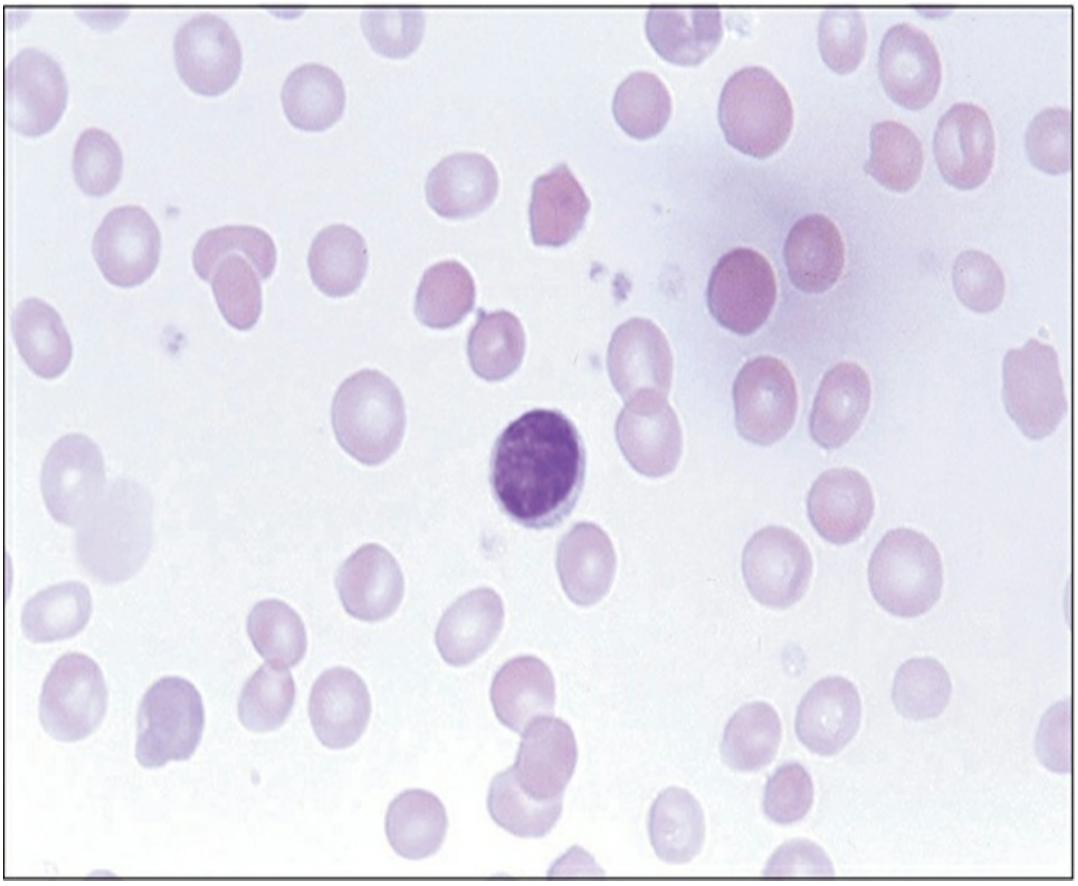


Figure IIA6-13

Peripheral blood smear.

Clinical Features

- Autosomal recessive inheritance
- Most severe types manifest in infancy
- Homozygosity produces clinical disease
- Acquired pyruvate kinase deficiency has been reported
- Severity ranges from severe neonatal anemia to asymptomatic
- May see splenomegaly, icterus, and gallstones

Pathology

- Most common enzyme deficiency in the Embden-

Meyerhof pathway and second most common red blood cell enzyme deficiency

- Adenosine triphosphate levels cannot be maintained at normal levels, and the red cell membrane is altered
- Potassium is lost and dehydration results
- Echinocytes are formed and cannot deform in splenic cords—hemolysis results

Laboratory Features

White Blood Cells

- Not remarkable

Platelets

- Not remarkable

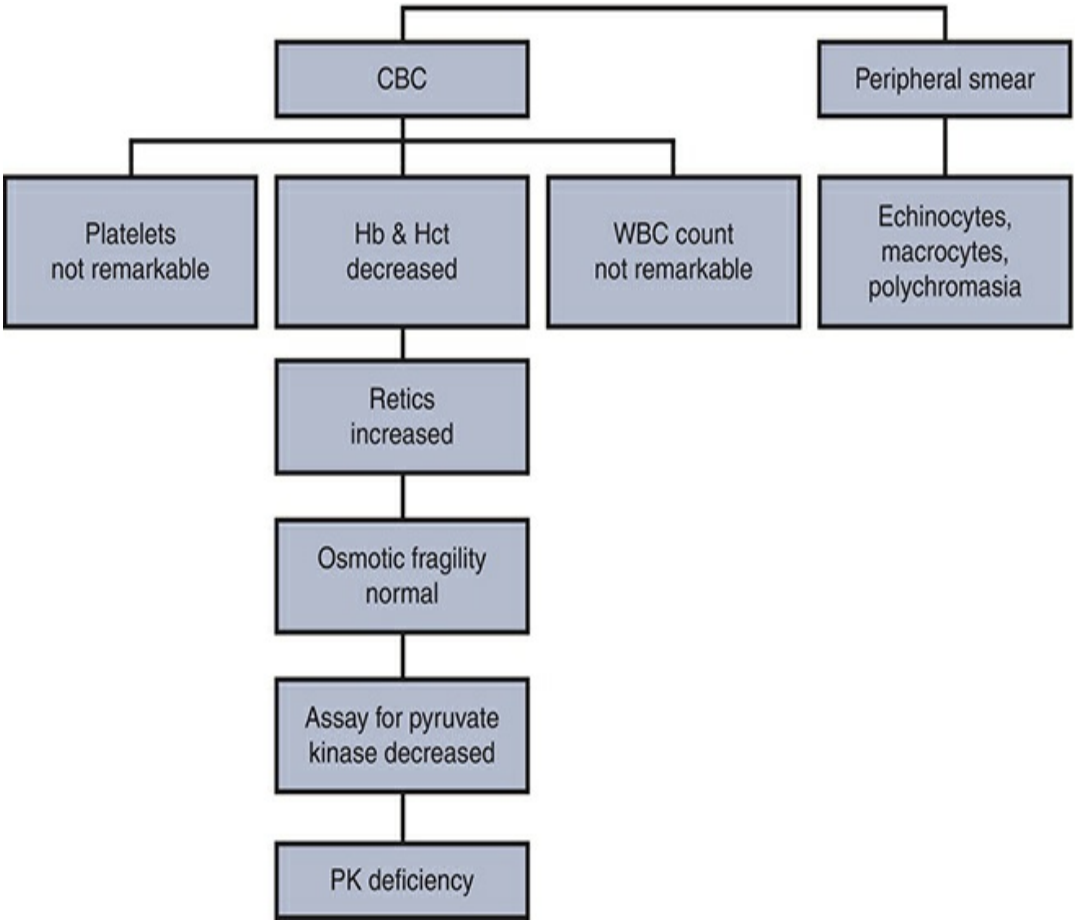
Red Blood Cells

- No characteristic cells
- May see echinocytes, macrocytes
- Increased reticulocyte count
- Normocytic/normochromic anemia
- Osmotic fragility normal

Bone Marrow

- Erythroid hyperplasia

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct decreased
WBC count not remarkable
Echinocytes, macrocytes, polychromasia
Retics increased
Osmotic fragility normal
Assay for pyruvate kinase decreased
PK deficiency

CHAPTER 7

Acute Blood Loss

ANEMIA OF ACUTE BLOOD LOSS

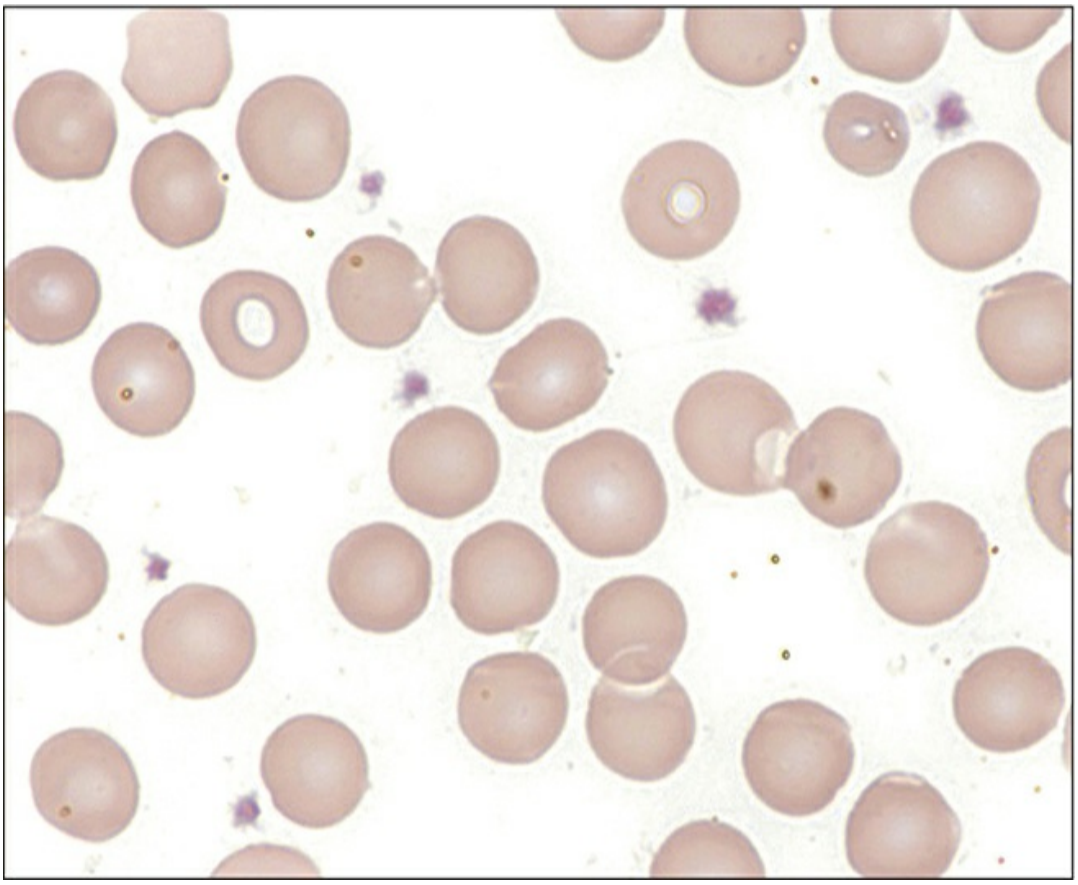


Figure IIA7-1

Peripheral blood smear.

Clinical Features

- Symptoms depend on the amount of blood loss and how fast it was lost
- Light-headedness, hypotension, and rapid pulse
- Cool, clammy skin
- Unconsciousness and severe shock
- Death

Pathology

- An injury that allows blood to escape from blood vessels into surrounding tissues or outside the body

- If >20% of the total blood volume is lost, oxygen perfusion of tissue is disrupted, resulting in subsequent cell death

Laboratory Features (3–4 Hours After the Event)

White Blood Cells

- Increased with shift to the left

Platelets

- Increased

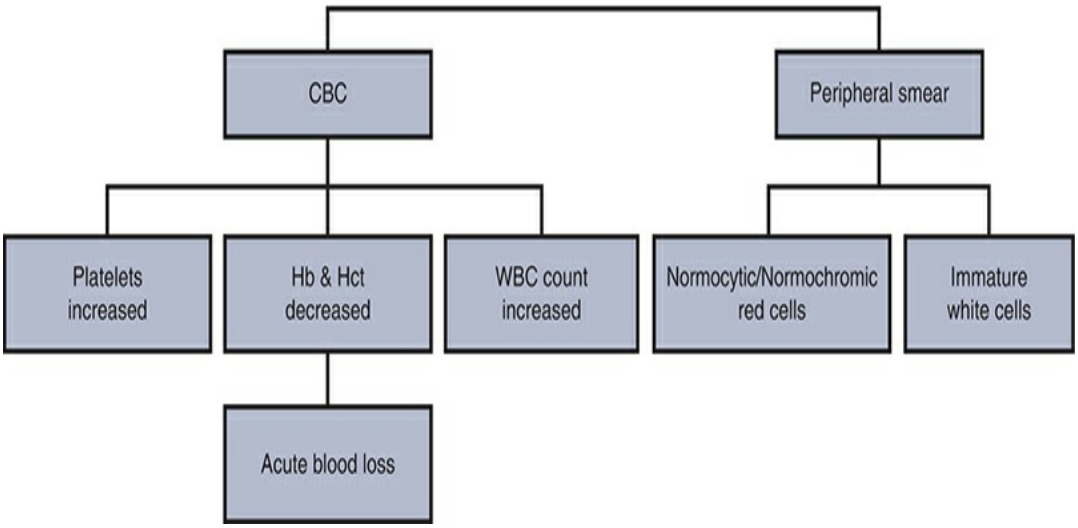
Red Blood Cells

- Hemoglobin and hematocrit levels begin to decrease
- Normocytic/normochromic anemia
- Increased reticulocytes occur 2–5 days after the event

Bone Marrow

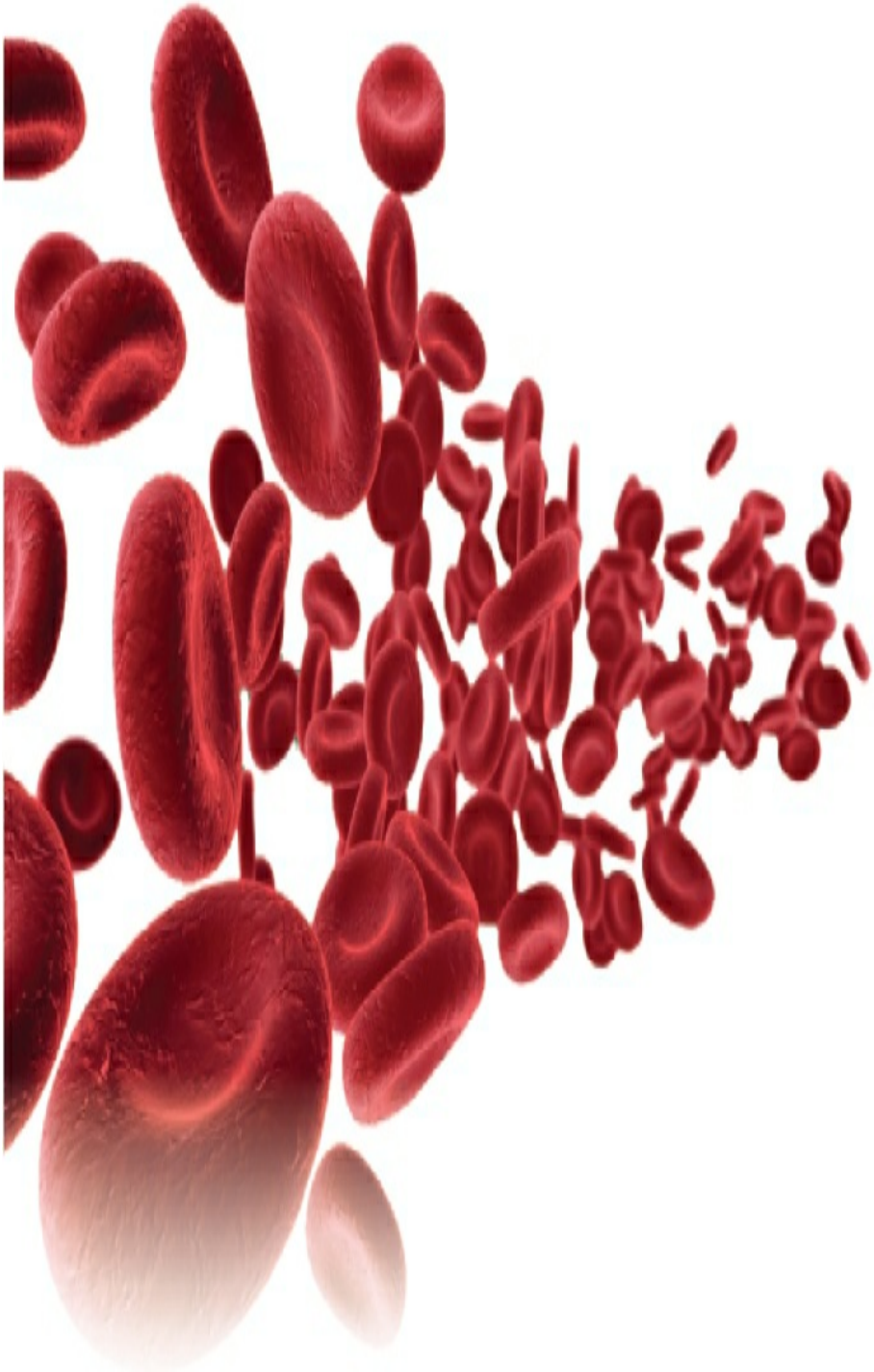
- Erythroid hyperplasia

Diagnostic Scheme



CHAPTER 8

Anemias Associated With Systemic Disorders



CHRONIC RENAL DISEASE

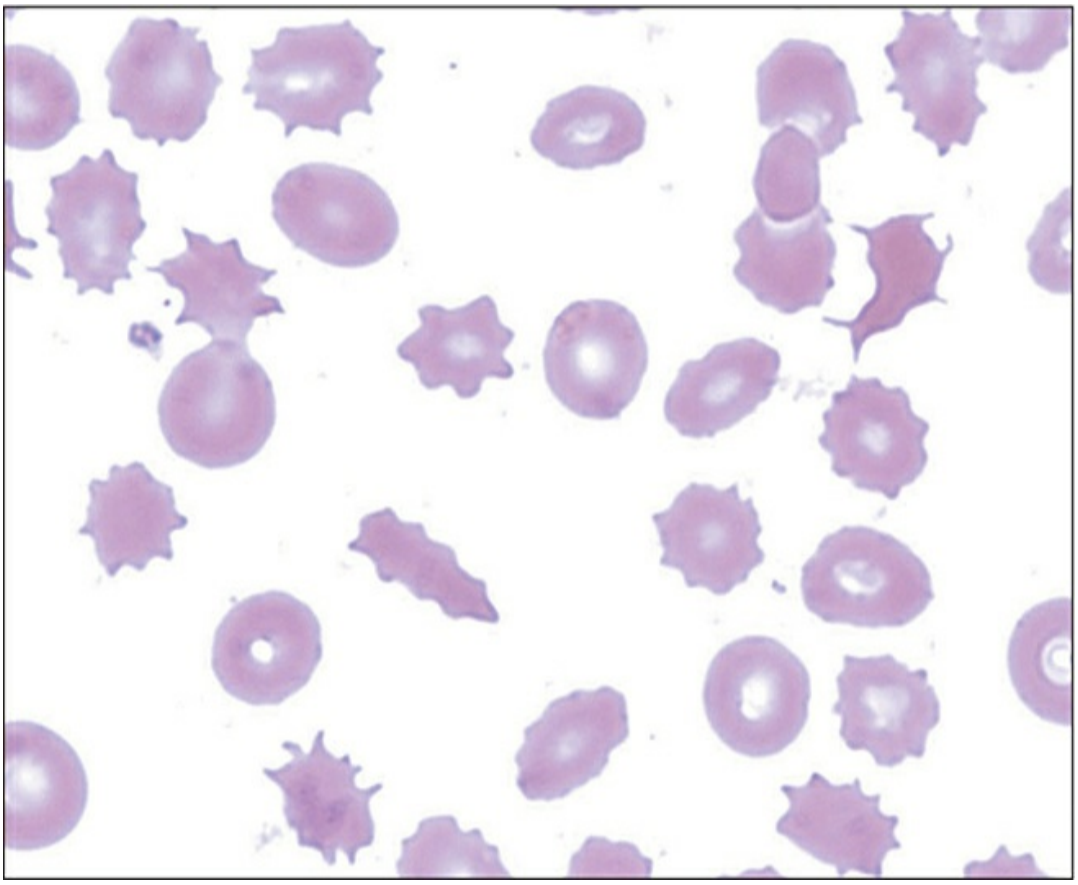


Figure IIA8-1

Peripheral blood smear.

Clinical Features

- Symptoms depend on severity of anemia
- May manifest with gastrointestinal or gynecologic bleeding
- Fatigue

Pathology

- Failure of renal excretory function and accumulation of waste products in plasma cause
  - Decreased red cell survival and mild hemolytic anemia

- Failure of renal production of erythropoietin
- Failure of release of erythropoietin

Laboratory Features

White Blood Cells

- Not remarkable

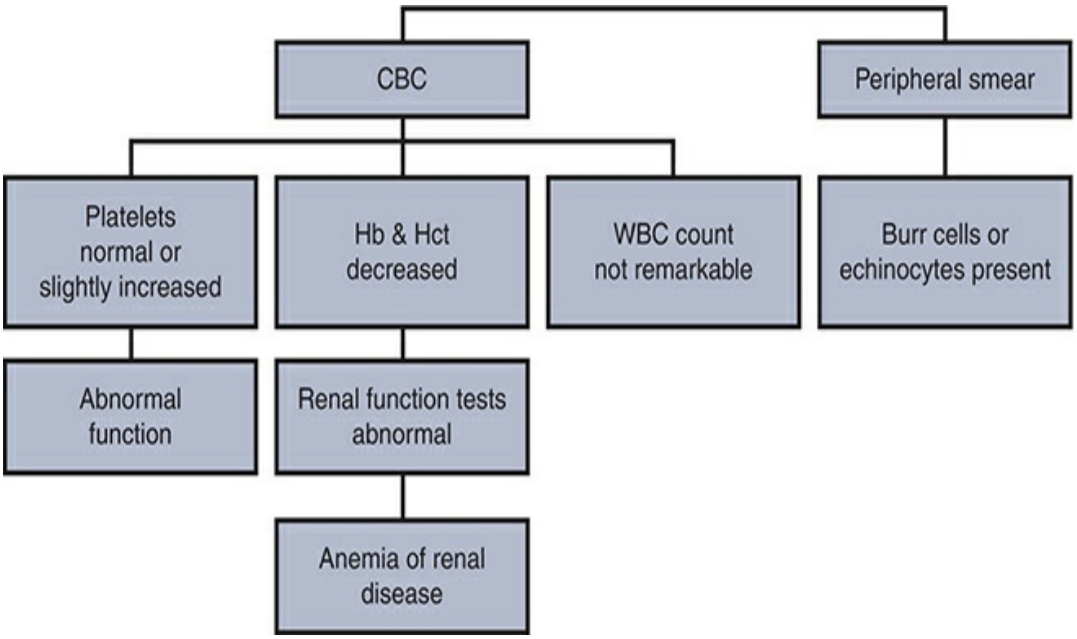
Platelets

- Normal to slightly increased
- Function may be abnormal

Red Blood Cells

- Normocytic/normochromic anemia
- Burr cells (echinocytes)
- Reticulocyte count normal

Diagnostic Scheme



ENDOCRINE DISEASES

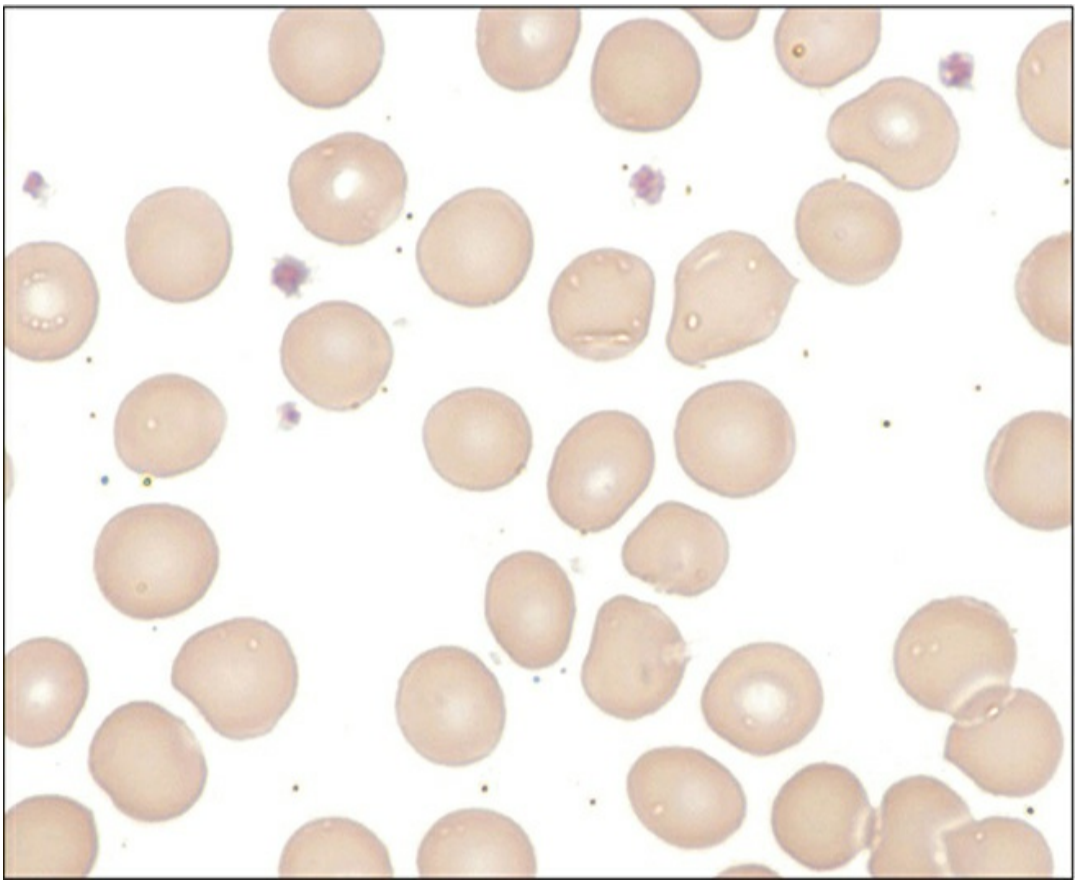


Figure IIA8-2

Peripheral blood smear.

Clinical Features

- Symptoms are specific to the type of endocrine disorder
  - Hyperthyroidism
  - Hypothyroidism
  - Hypercortisolism
  - Hypocortisolism
  - Hypoandrogenemia
  - Diabetes mellitus

Pathology

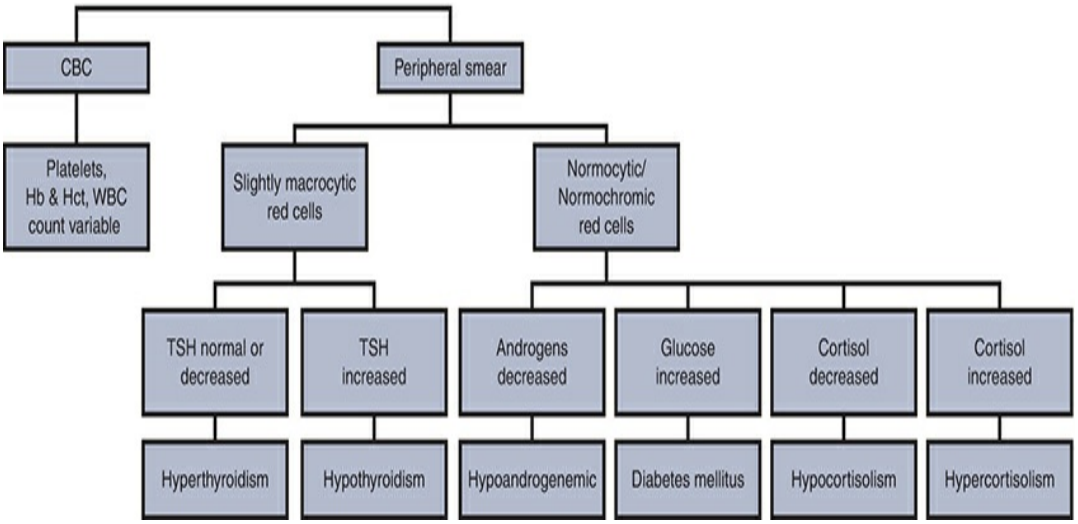
- Hyperthyroidism
  - Elevated red blood cell mass secondary to enhanced BFU-E proliferation
  - Increased requirement for folic acid to accommodate the increased red blood cell production
- Hypothyroidism
  - Reduced red blood cell mass secondary to decreased oxygen requirements
- Hypercortisolism
  - Modest polycythemic state due to increased androgens
- Hypocortisolism
  - Hemoconcentrated state with a normal to slightly increased hematocrit level due to lack of the salt-retaining hormones
- Hypogonadism
  - Anemia due to reduced level of androgens
- Diabetes mellitus
  - Acute hemolysis may occur in ketoacidosis

Laboratory Features

- Hyperthyroidism
  - Macrocytic anemia
- Hypothyroidism
  - Usually macrocytic anemia
  - Iron deficiency anemia may occur when menorrhagia is present
- Hypercortisolism
  - Modest polycythemic picture
- Hypocortisolism

- Normal or slightly increased hematocrit level
- Hyperandrogenemia
  - Slight normocytic/normochromic anemia
- Diabetes mellitus
  - Falsely elevated hematocrit level

Diagnostic Scheme



LIVER DISEASE

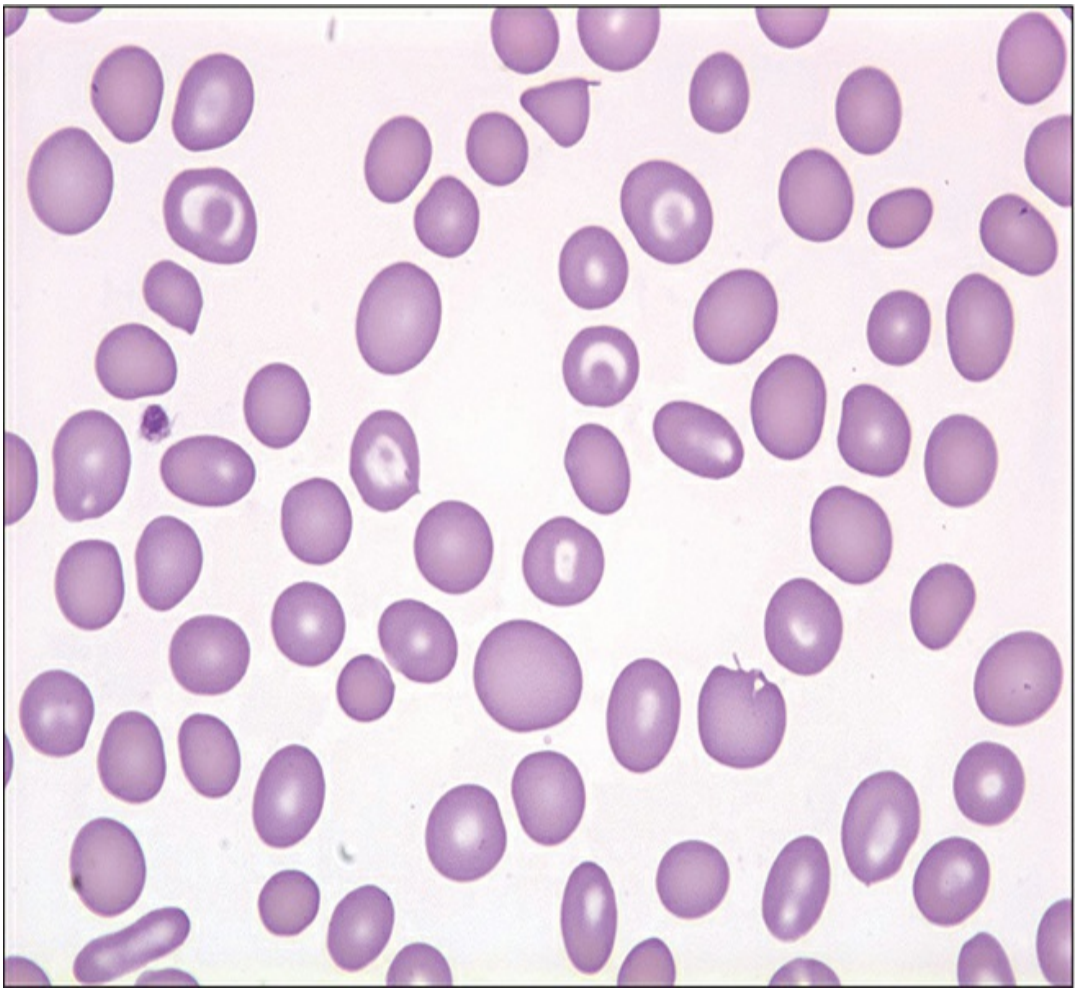


Figure IIA8-3

Peripheral blood smear.

Clinical Features

- Anemia is secondary to the abnormalities in liver function
- The most common cause of nonmegaloblastic, macrocytic anemia
- Occurs in about 50% of patients with liver disease

Pathology

- Multifaceted
  - Hemolysis

    - Impaired bone marrow response
    - Folate deficiency
    - Blood loss
- Abnormalities in red cell membrane lipid composition are common
- Ethanol and its by-products have a toxic effect on the bone marrow

Laboratory Features

White Blood Cells

- Neutropenia, neutrophilia, or lymphopenia

Platelets

- Decreased
- Abnormal function

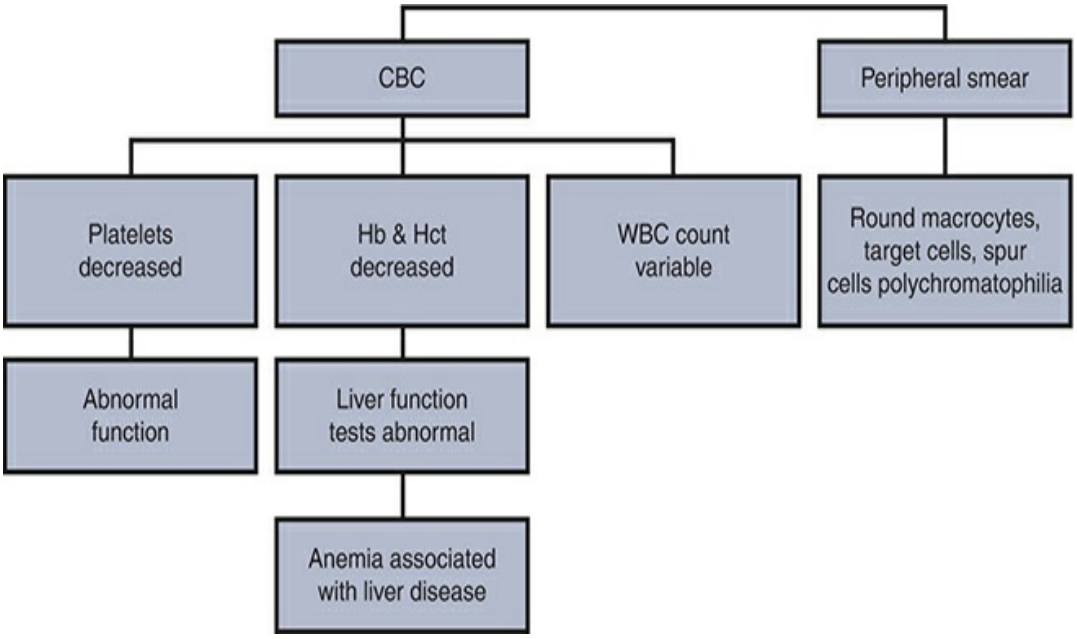
Red Blood Cells

- Mild to moderate anemia
    - Macrocytic, normocytic, or microcytic
- Round macrocytes
- Target cells, spur cells, acanthocytes
- Increased reticulocyte count

Bone Marrow

- Normocellular or hypercellular with erythroid hyperplasia
- Vacuolization of red cell precursors

Diagnostic Scheme


CBC
Peripheral smear
Platelets decreased
Hb & Hct decreased
WBC count variable
Round macrocytes, target cells, spur cells polychromatophilia
Abnormal function
Liver function tests abnormal
Anemia associated with liver disease

SYSTEMIC LUPUS ERYTHEMATOSUS

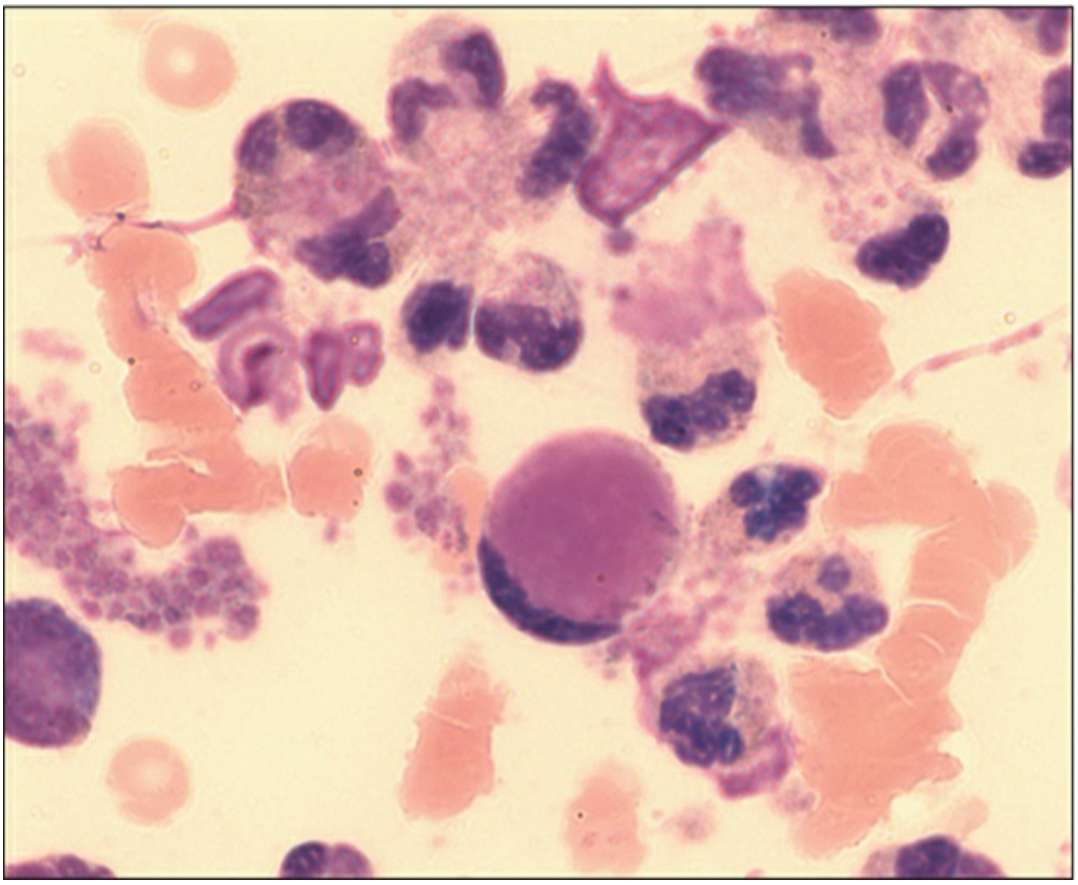


Figure IIA8-4

Buffy coat smear.

Clinical Features

- Low-grade fever
- Arthritis and arthralgia
- Skin lesions
- Nervous system disorders (psychological and neurologic changes)
- Pericarditis
- Pleuritic chest pain
- Anorexia, nausea, vomiting, and abdominal pain
- Hepatomegaly

Pathology

- Decreased cellular immunity
- Circulating immune complexes may cause tissue injury in many organ systems

Laboratory Features

White Blood Cells

- Decreased count but usually >2.0 × 10^9/L

Differential

- Normal

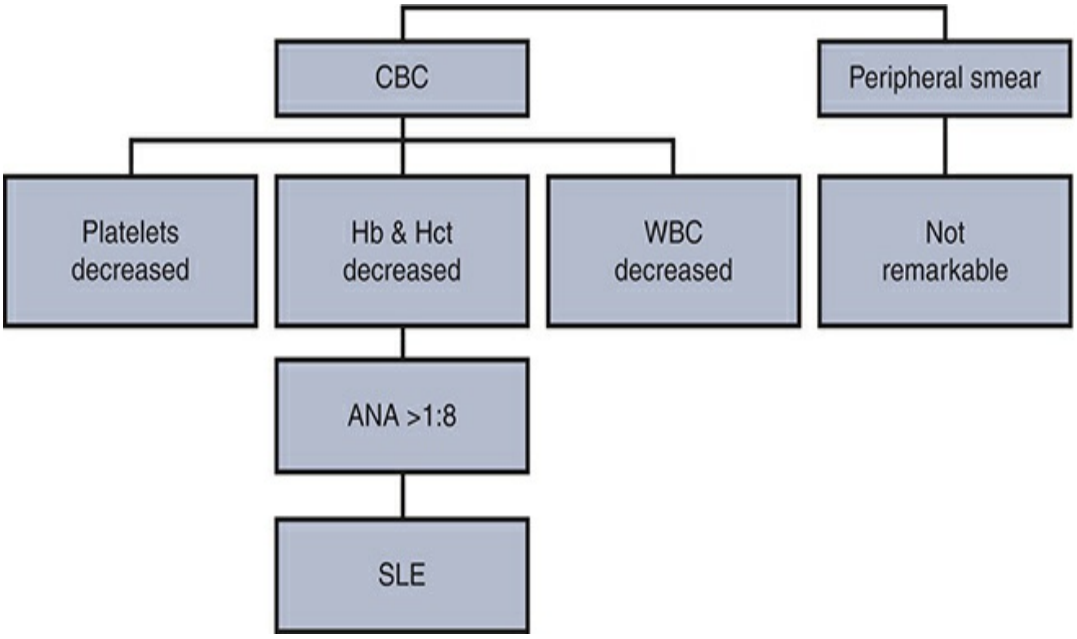
Platelets

- Decreased

Red Blood Cells

- Normocytic/normochromic anemia
- Hemolysis due to autoantibodies
- Circulating anticoagulants may cause prolongation of partial thromboplastin times
- Antinuclear antibodies may be present and may result in presence of lupus erythematosus cells
- Complement levels decreased

Diagnostic Scheme

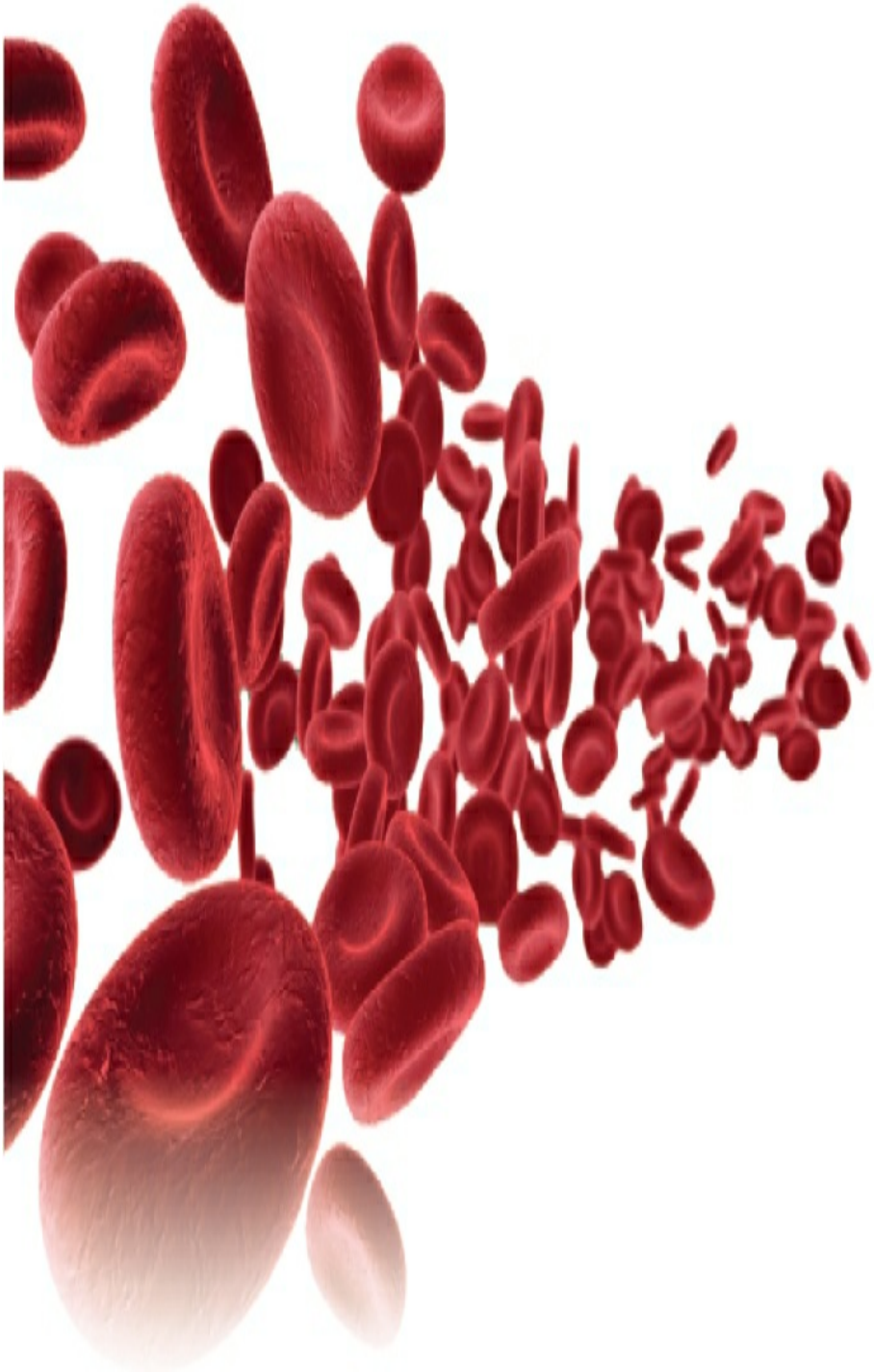

CBC
Peripheral smear
Platelets decreased
Hb & Hct decreased
WBC decreased
Not remarkable
ANA >1:8
SLE

Section B

White Blood Cell Disorders

CHAPTER 1

Nonmalignant Leukocyte Disorders



BASOPHILIA

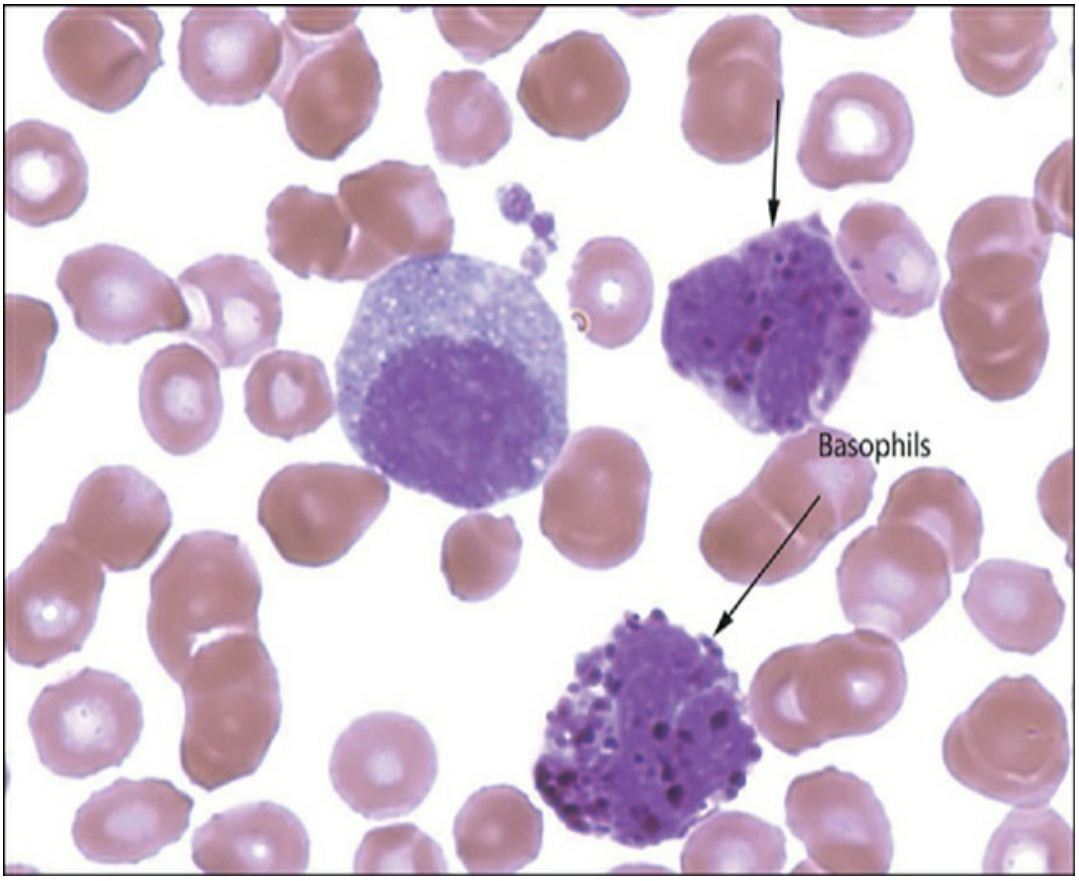


Figure IIB1-1

Peripheral blood smear.

Clinical Features

- Defined as >0.15 × 10^9/L basophils
- Varies with the etiology
  - Hypothyroidism with myxedema
  - Myeloproliferative neoplasms
    - Chronic myelogenous leukemia
    - Polycythemia vera
    - Primary myelofibrosis
  - Acute myeloid leukemia with t(6:9) translocation
  - After radiation exposure

Pathology

Pathology

- Associated with immediate hypersensitivity reactions
  - When IgE binds to the basophil receptors, the cell degranulates and releases histamine and other inflammatory mediators
- Specific to the disorders that cause the secondary basophilia

Laboratory Features

White Blood Cells

- Increased numbers of basophils

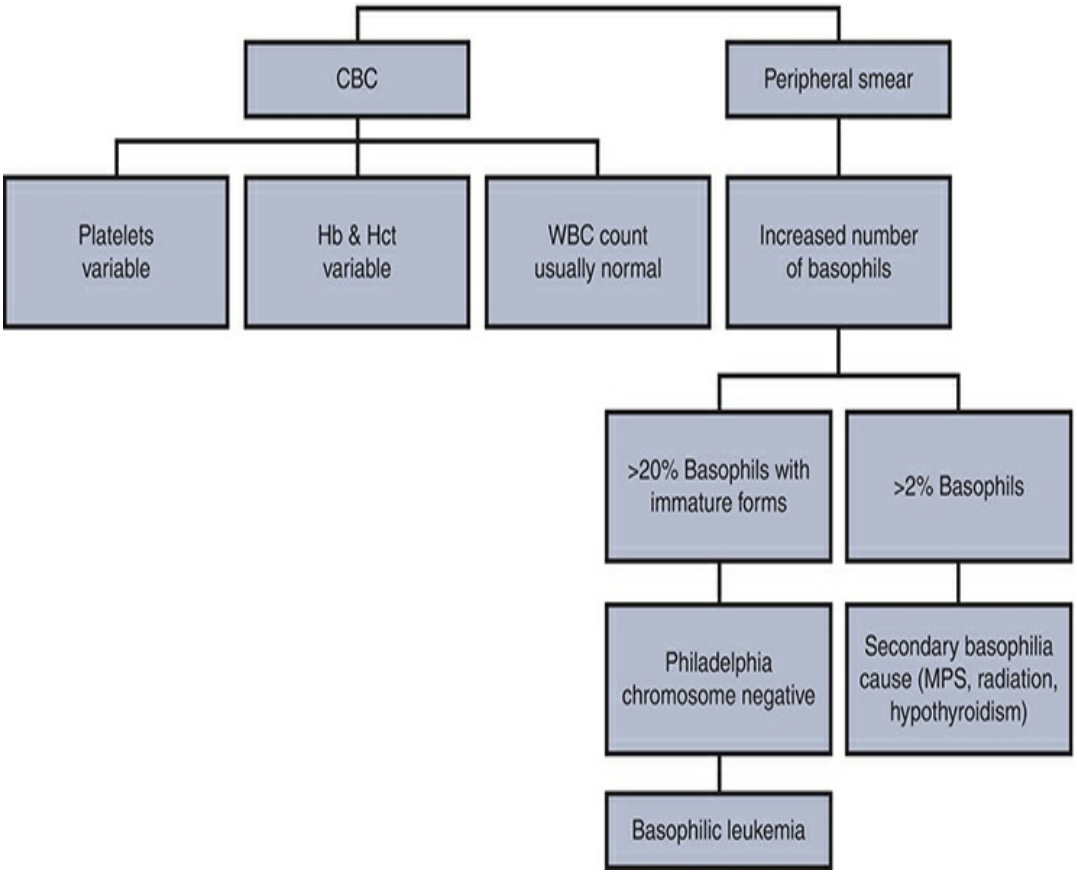
Red Blood Cells

- Variable

Platelets

- Variable

Diagnostic Scheme


CBC
Peripheral smear
Platelets variable
Hb & Hct variable
WBC count usually normal
Increased number of basophils
>20% Basophils with immature forms
>2% Basophils
Philadelphia chromosome negative
Secondary basophilia cause (MPS, radiation, hypothyroidism)
Basophilic leukemia

CHEDIAK-HIGASHI ANOMALY

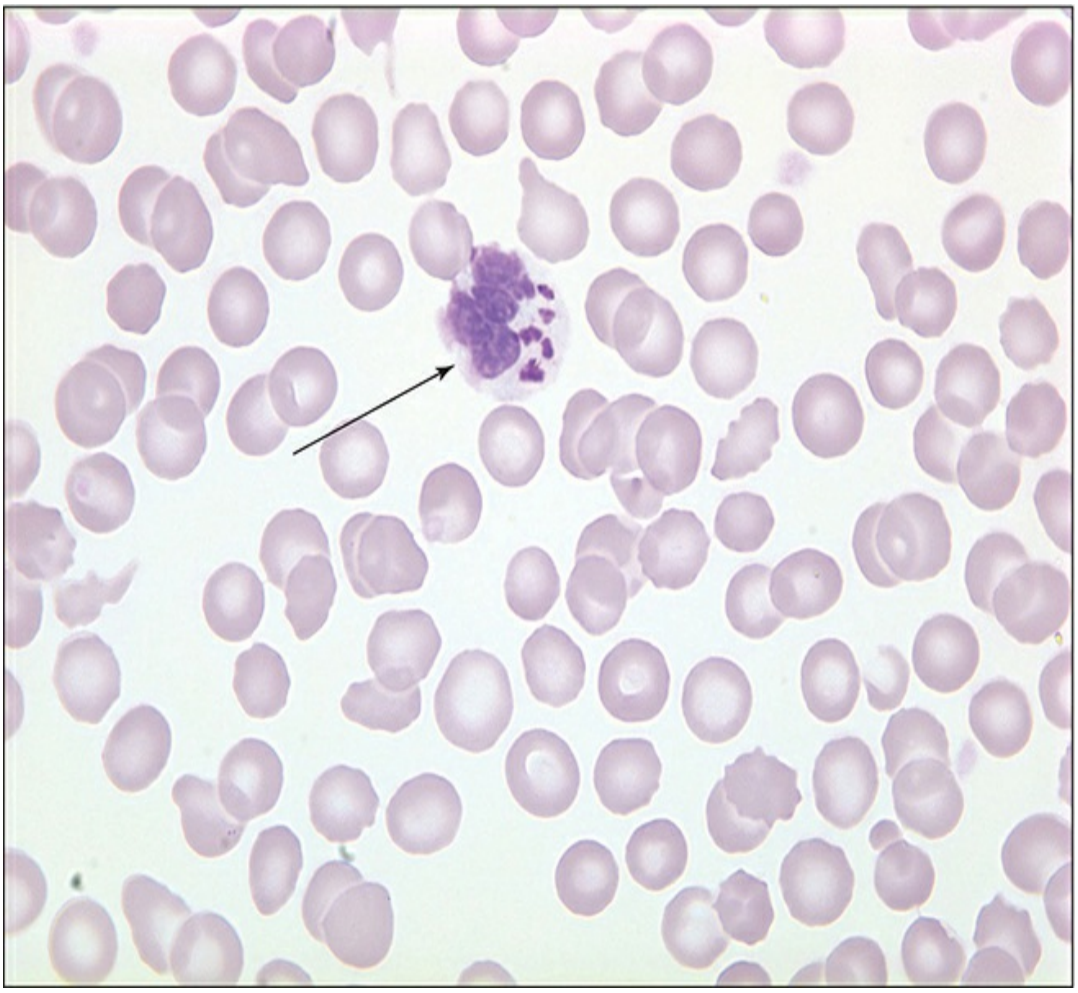


Figure IIB1-2

Peripheral blood smear.

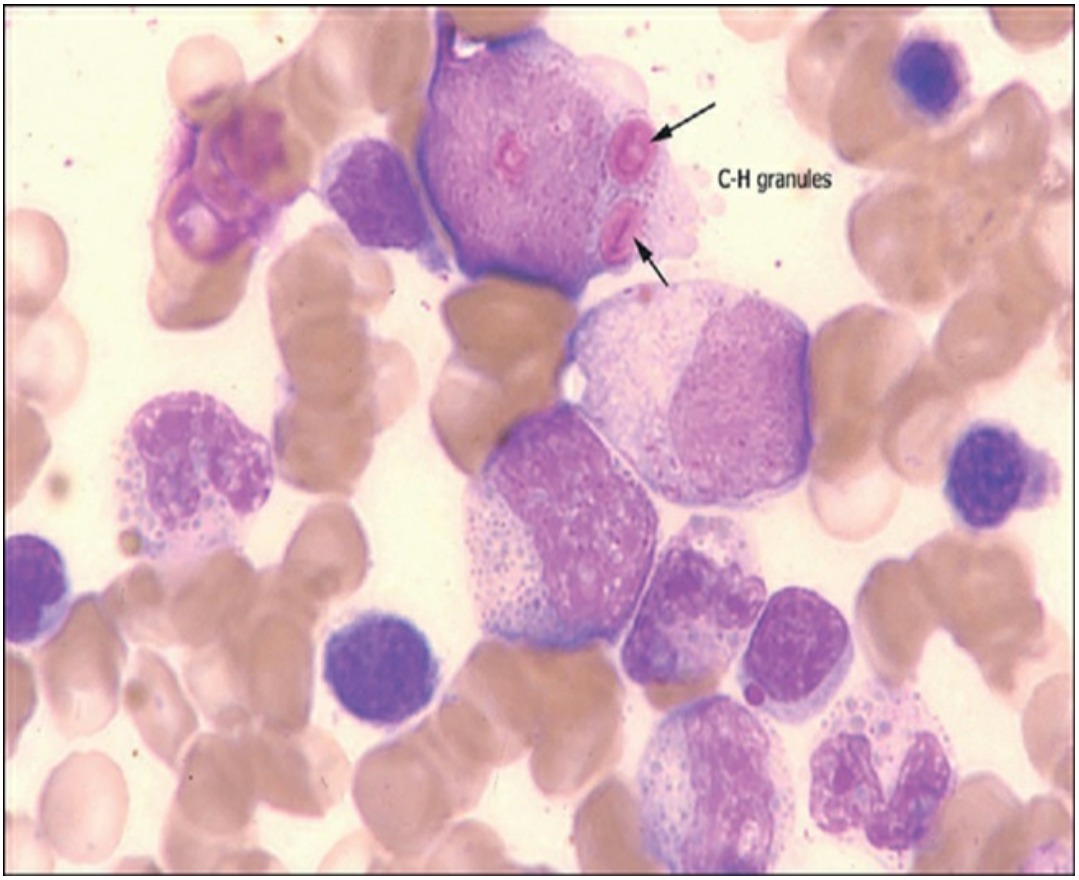


Figure IIB1-3

Bone marrow smear.

Clinical Features

- Increased susceptibility to bacterial infections
- Fever
- Silvery-white hair
- Photophobia
- Enlarged lymph nodes
- Hepatosplenomegaly

Pathology

- Autosomal recessive inherited disorder of granule formation
- LYST mutation, which is a regulator of lysosome size and trafficking

- Produces serious abnormalities in the function of affected phagocytes
  - Bacterial killing is impaired
  - Degranulation is delayed and incomplete
  - Chemotaxis is defective
- Lymphocytes show an impairment of both antibody-dependent and natural killer cell–mediated cytotoxicities

Laboratory Features

White Blood Cells

- Typical count of 1–3 × 10^9/L
- Giant gray-green peroxidase-positive granules are found in the cytoplasm of leukocytes
- Neutropenia

Red Blood Cells

- Normal

Platelets

- Thrombocytopenia
- Aggregation is abnormal

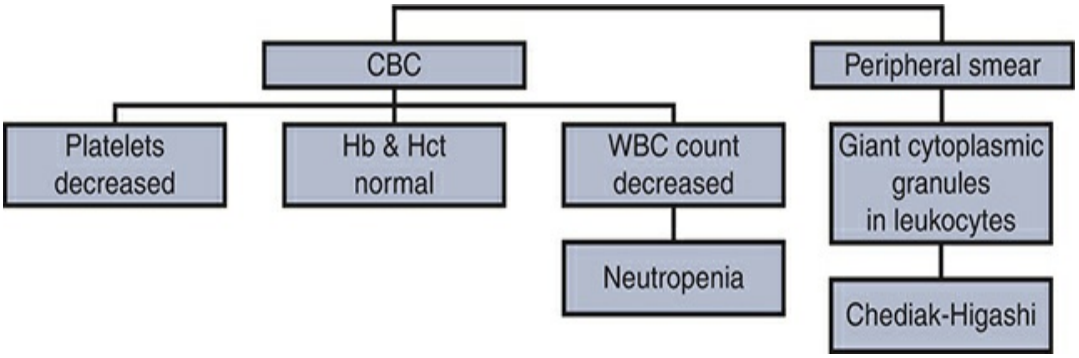
Coagulation Studies

- Bleeding time is abnormal

Bone Marrow

- The abnormal granules from precursor vacuoles undergo fusion

Diagnostic Scheme


CBC
Peripheral smear
Platelets decreased
Hb & Hct normal
WBC count decreased
Neutropenia
Giant cytoplasmic granules in leukocytes
Chediak-Higashi

CHRONIC GRANULOMATOUS DISEASE

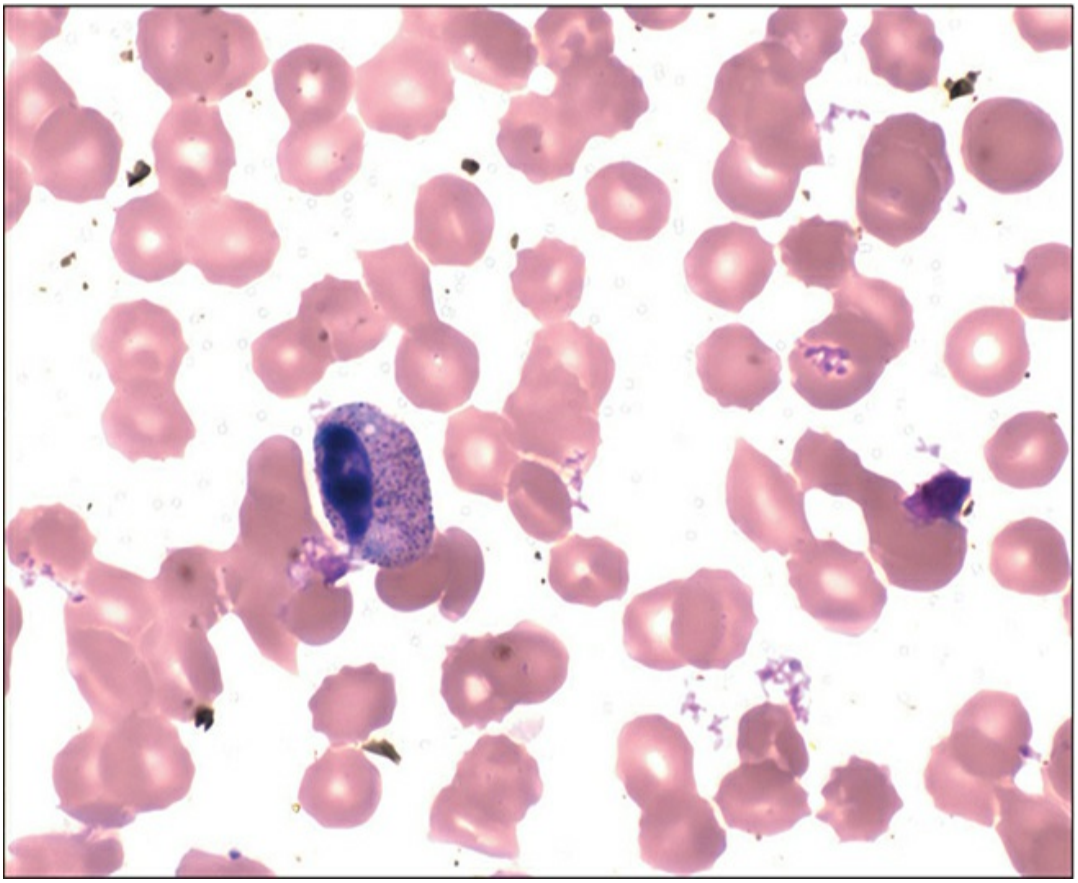


Figure IIB1-4

Nitroblue tetrazolium stain—negative.

Clinical Features

- Recurrent bacterial and fungal infections during the first 12 months of life
- Lymphadenitis
- Deep tissue infections
- Infected eczema-like rash
- Visceral and hepatic abscesses
- Recurrent pulmonary infections
- Organomegaly

Pathology

- May be inherited as an X-linked or as an autosomal recessive trait
- Mutation of CYUBB affecting any of the subunits NADPH oxidative complex, which is responsible for the respiratory burst in the phagocytic leukocytes
- Failure in the activation of the respiratory burst
- Formation of granulomas during chronic inflammatory reactions

Laboratory Features

White Blood Cells

- Neutrophilia
- Traditional nitroblue tetrazolium reduction test results negative
    - In this test, neutrophils are incubated in the presence of nitroblue tetrazolium along with an activating agent
    - The superoxide that is released reduces the dye to an insoluble dark blue formazan that can be seen as a granular precipitate in the neutrophils

Red Blood Cells

- Not remarkable

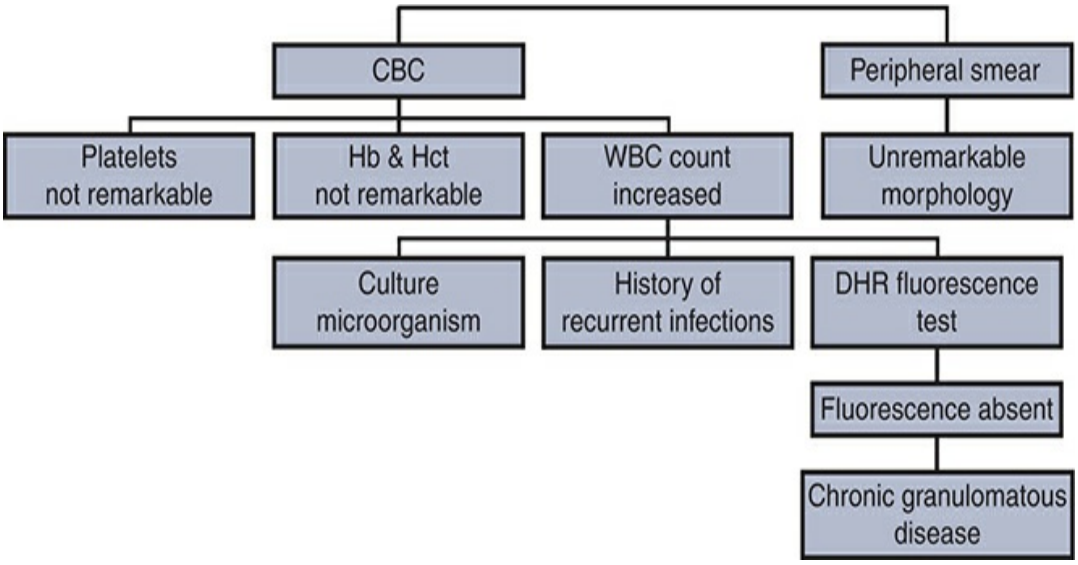
Platelets

- Not remarkable

Flow Cytometry

- Dihydroxy rhodamine (DHR) fluorescence test (no fluorescence)

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct not remarkable
WBC count increased
Unremarkable morphology
Culture microorganism
History of recurrent infections
DHR fluorescence test
Fluorescence absent
Chronic granulomatous disease

EOSINOPHILIA

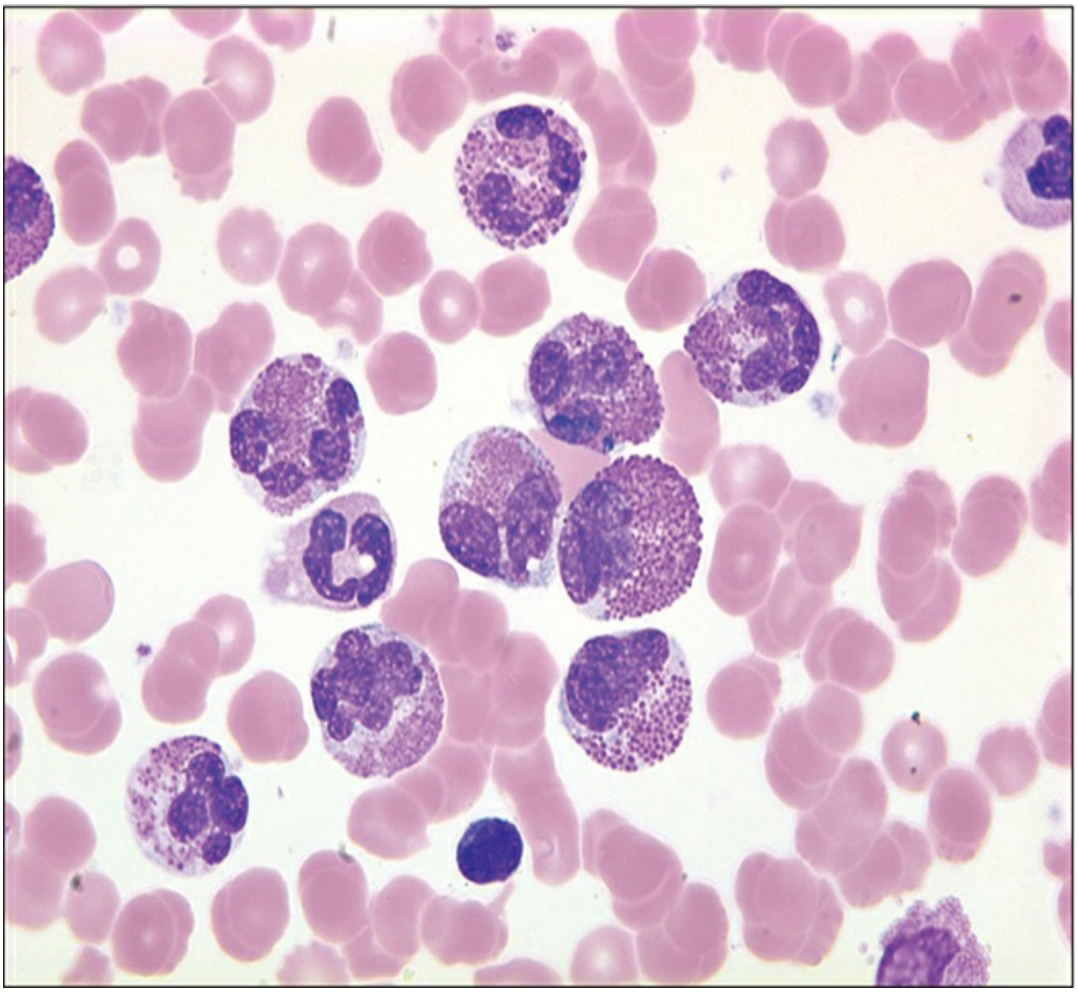


Figure IIB1-5

Peripheral blood smear.

Clinical Features

- Depends on the etiology—may see fever, skin rash, adenopathy, cough, pulmonary infiltrates, muscle pain, and hepatosplenomegaly

Pathology

- Absolute eosinophil count of $>0.6 \times 10^9$/L
- Causes include the following:
  - Parasitic infection
  - Allergic reaction

- Respiratory disorders
- Neoplastic diseases
- Inflammatory or autoimmune diseases
- Skin disorders

Laboratory Features

White Blood Cells

- Count normal to increased
- Eosinophils increased

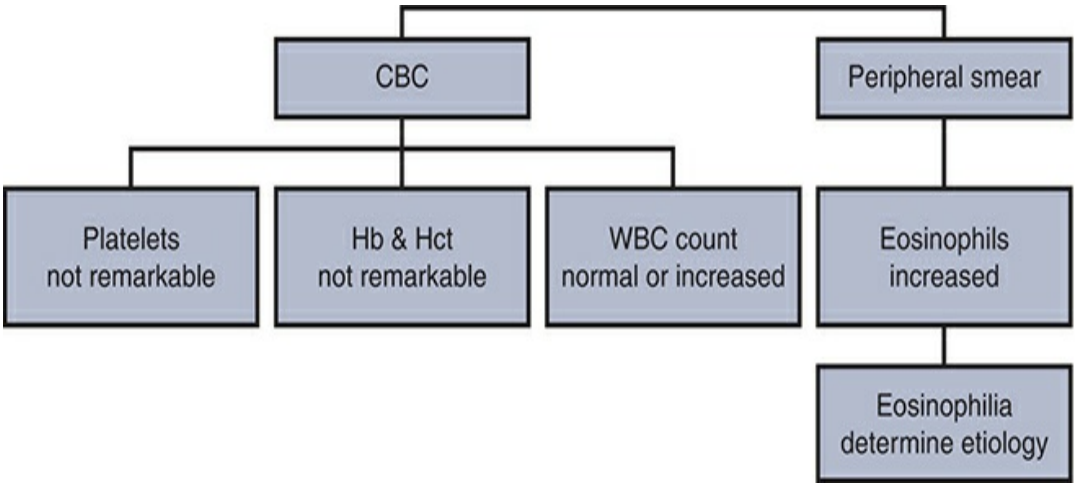
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme



INFECTIOUS MONONUCLEOSIS

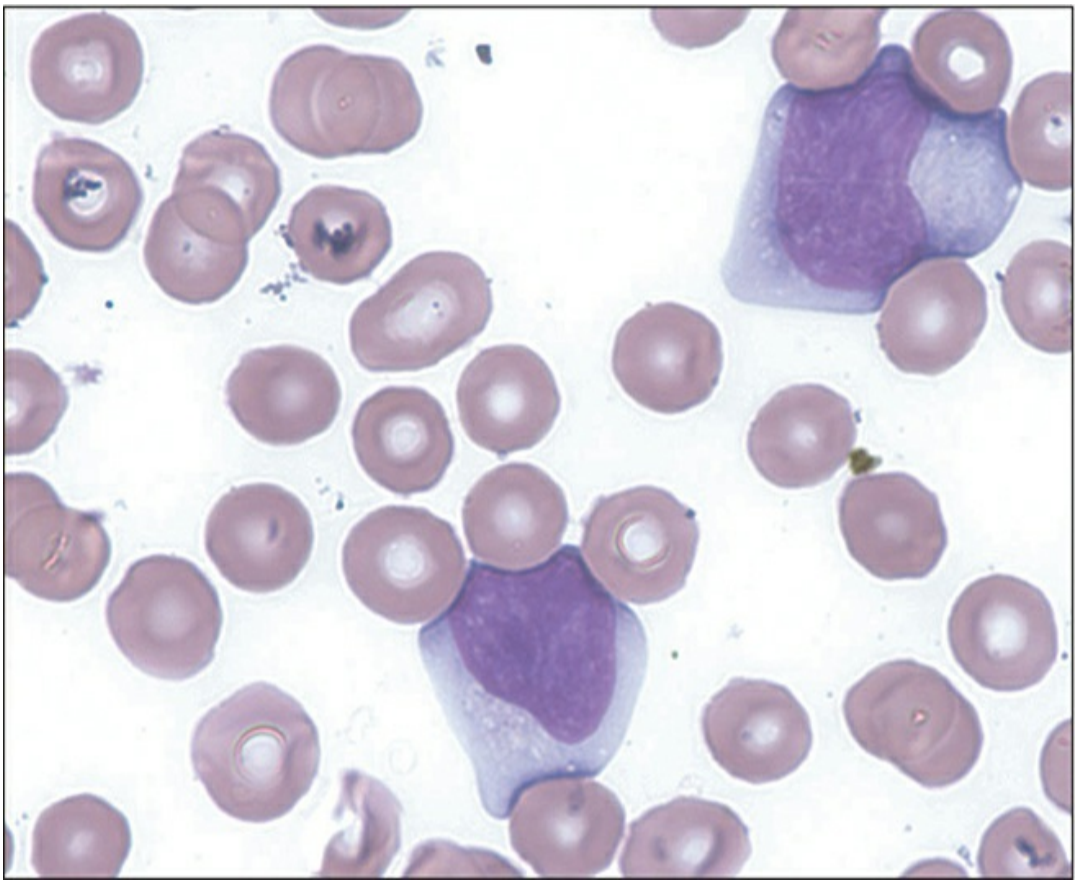


Figure IIB1-6

Peripheral blood smear.

Clinical Features

- Usually occurs in young adults aged 14–24 years
- Lethargy, anorexia, nausea, headache, chills, fever, pharyngitis, lymphadenopathy, splenomegaly, hepatomegaly
- Usually self-limited

Pathology

- Epstein-Barr virus attaches to the B lymphocytes by means of a specific Epstein-Barr virus receptor on the lymphocyte membrane

- B lymphocytes and lymphoid tissues throughout the body are involved
- Incubation period is about 30–50 days

Laboratory Features

White Blood Cells

- Agranulocytosis
- Proliferation of lymphocytes (12.0–25.0 × 10^9/L)
- >20% reactive lymphocytes
- Immunoblasts may be present
- Plasmacytoid lymphocytes may be present

Red Blood Cells

- May have an autoimmune hemolytic anemia

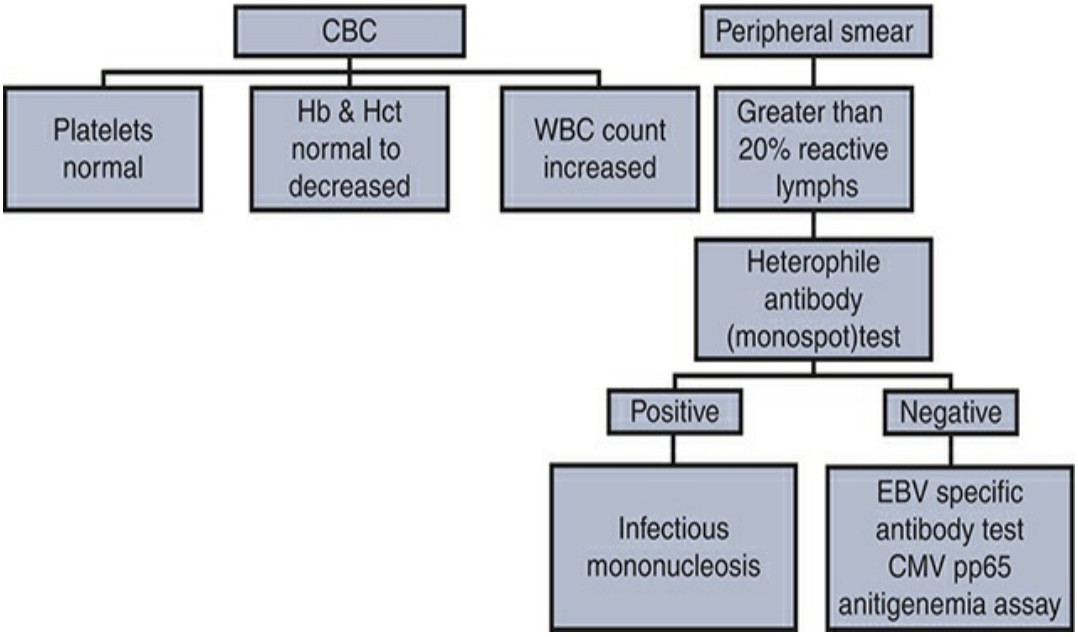
Platelets

- Normal to decreased

Serologic Tests

- Heterophile antibodies (monospot) test positive in majority of Epstein-Barr virus infections
- If monospot test is negative, EBV-specific antibody tests by indirect immunofluorescence or CMV testing is required

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal
Hb & Hct normal to decreased
WBC count increased
Greater than 20% reactive lymphs
Heterophile antibody (monospot)test
Positive
Negative
Infectious mononucleosis
EBV specific antibody test CMV pp65 anitigenemia assay

LYMPHOCYTOSIS

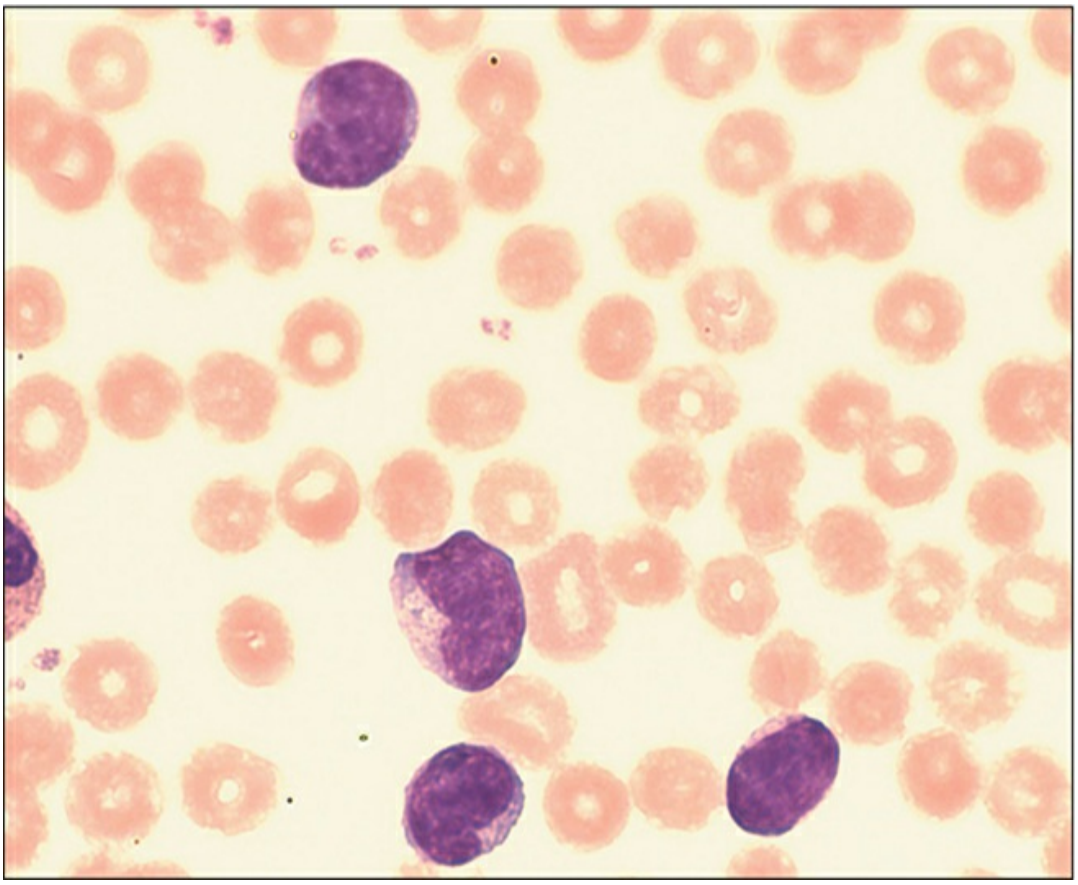


Figure IIB1-7

Peripheral blood smear—whooping cough.

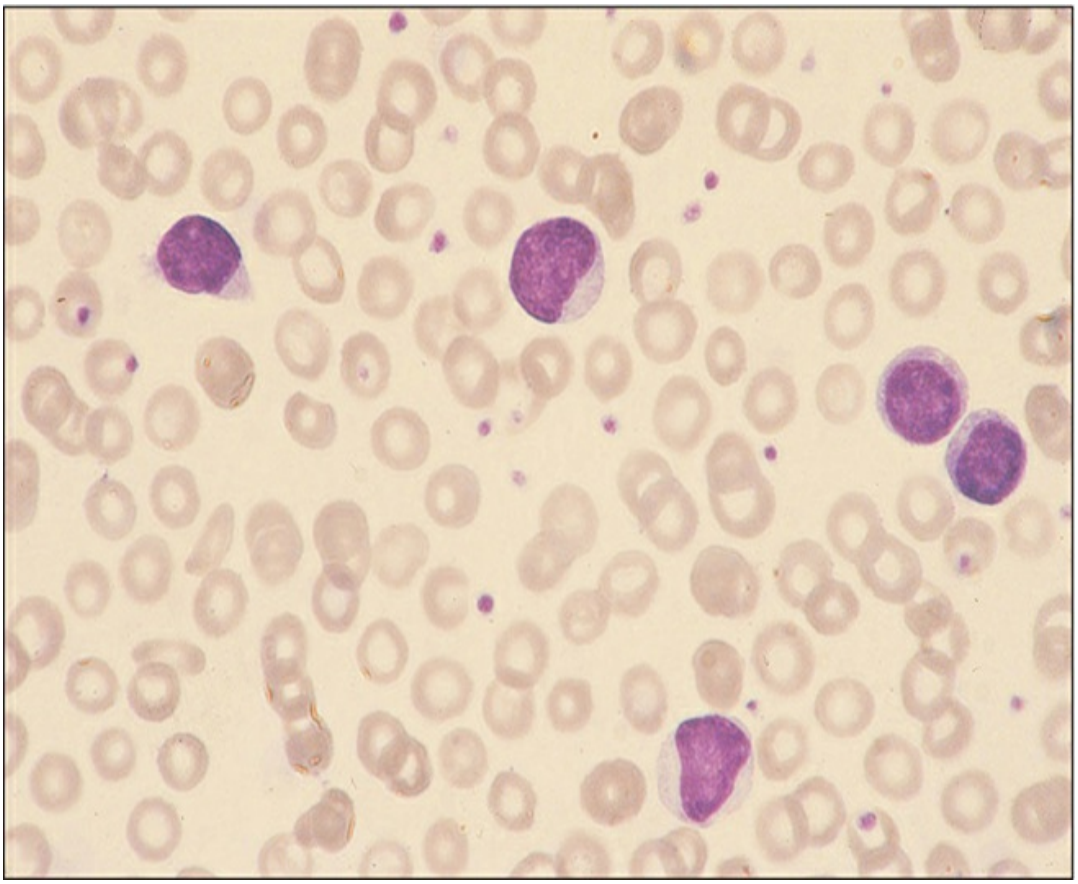


Figure IIB1-8

Peripheral blood smear—infectious lymphocytosis.

Clinical Features

- Benign conditions
  - Viral infections
  - Bacterial infections
  - Protozoal infections
  - Other
- Malignant conditions

Bacterial Infections

- Incubation period is about 2 weeks
- Head cold, paroxysmal cough, pain in the neck and chest

Protozoal Infections (Toxoplasmosis)

- Congenital—hepatosplenomegaly, jaundice, microcephaly, mental retardation
- Acquired—lethargy, anorexia, nausea, headache, chills and fever, pharyngitis, lymphadenopathy to asymptomatic

Viral Infections (Cytomegalovirus)

- Congenital—only 10% of infected newborns show the clinical features, which include microcephaly, hepatosplenomegaly, and jaundice
- Acquired—lethargy, anorexia, nausea, headache, chills, fever, lymphadenopathy, splenomegaly, and hepatomegaly

Infectious Lymphocytosis

- Usually affects young children aged 1–10 years
- Occurs in epidemics
- Incubation time is about 2–3 weeks
- Usually asymptomatic

Pathology

Bacterial Infections

- Bordetella pertussis infection (whooping cough)
- Usually in nonimmunized children

Protozoal Infections

- Usually the result of infection by Toxoplasma gondii
- Multiply in all body cells except red cells
- Congenital—results from placental transmission from parasitized mother
- Acquired—ingestion of oocytes from undercooked meat or inhalation from cat feces

Viral Infections

- Commonly from the cytomegalovirus
- Virus infects leukocytes, which transport it to other location
- Virus suppresses cell-mediated immune function
- Congenital—transplacental transmission from an infected mother
- Acquired—may be spread by close contact or by blood transfusion

Infectious Lymphocytosis

- Caused by a virus, probably of the Coxsackie group
- Usually affects children under the age of 10 years
- Usually no symptoms

Laboratory Features

Bacterial Infections

White Blood Cells

- Increased lymphocyte count (up to 15.0–56.0 × 10^9/L)

Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Protozoal Infections

White Blood Cells

- Increased
- Lymphocytosis with the presence of reactive lymphocytes
- Eosinophilia may be present

Red Blood Cells

- Hemolytic anemia

Platelets

- Variable

Serologic Tests

- Heterophile antibody test negative

Viral Infections

White Blood Cells

- Increased
- Lymphocytosis with the presence of reactive lymphocytes

Red Blood Cells

- Hemolytic anemia

Platelets

- Variable

Serologic Tests

- Heterophile antibody test negative

Infectious Lymphocytosis

White Blood Cells

- Usually 20.0–30.0 × 10^9/L
- 50–95% normal-appearing, small lymphocytes

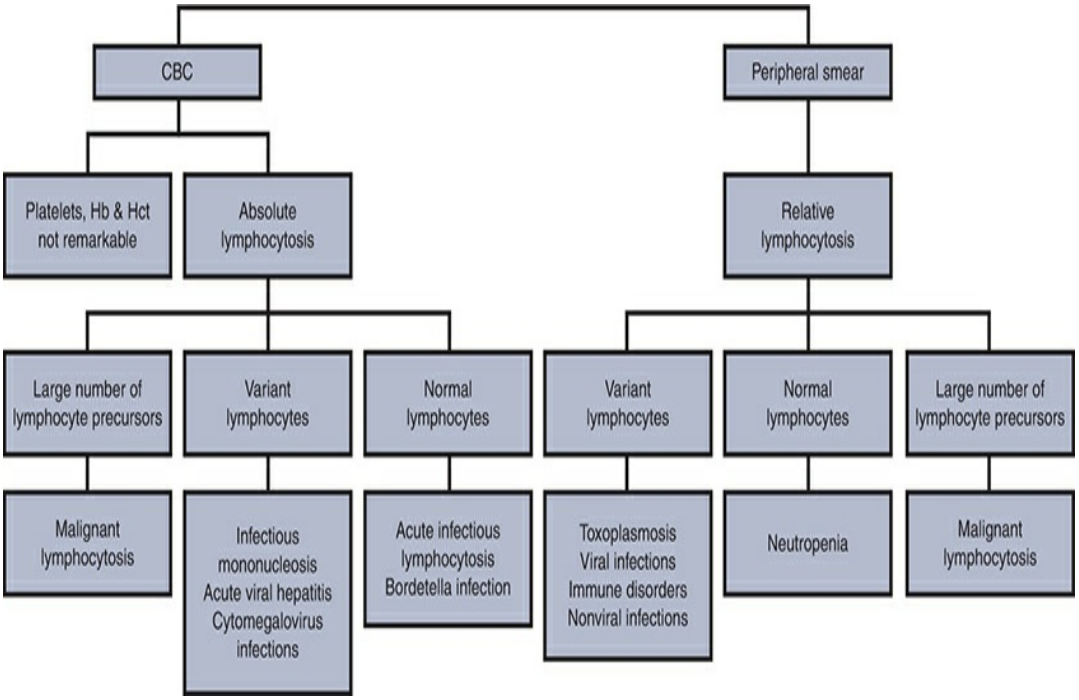
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets, Hb & Hct not remarkable
Absolute lymphocytosis
Relative lymphocytosis
Large number of lymphocyte precursors
Variant lymphocytes
Normal lymphocytes
Variant lymphocytes
Normal lymphocytes
Large number of lymphocyte precursors
Malignant lymphocytosis
Infectious mononucleosis
Acute viral hepatitis
Cytomegalovirus infections
Acute infectious lymphocytosis
Bordetella infection
Toxoplasmosis
Viral infections
Immune disorders
Nonviral infections
Neutropenia
Malignant lymphocytosis

MAY-HEGGLIN ANOMALY

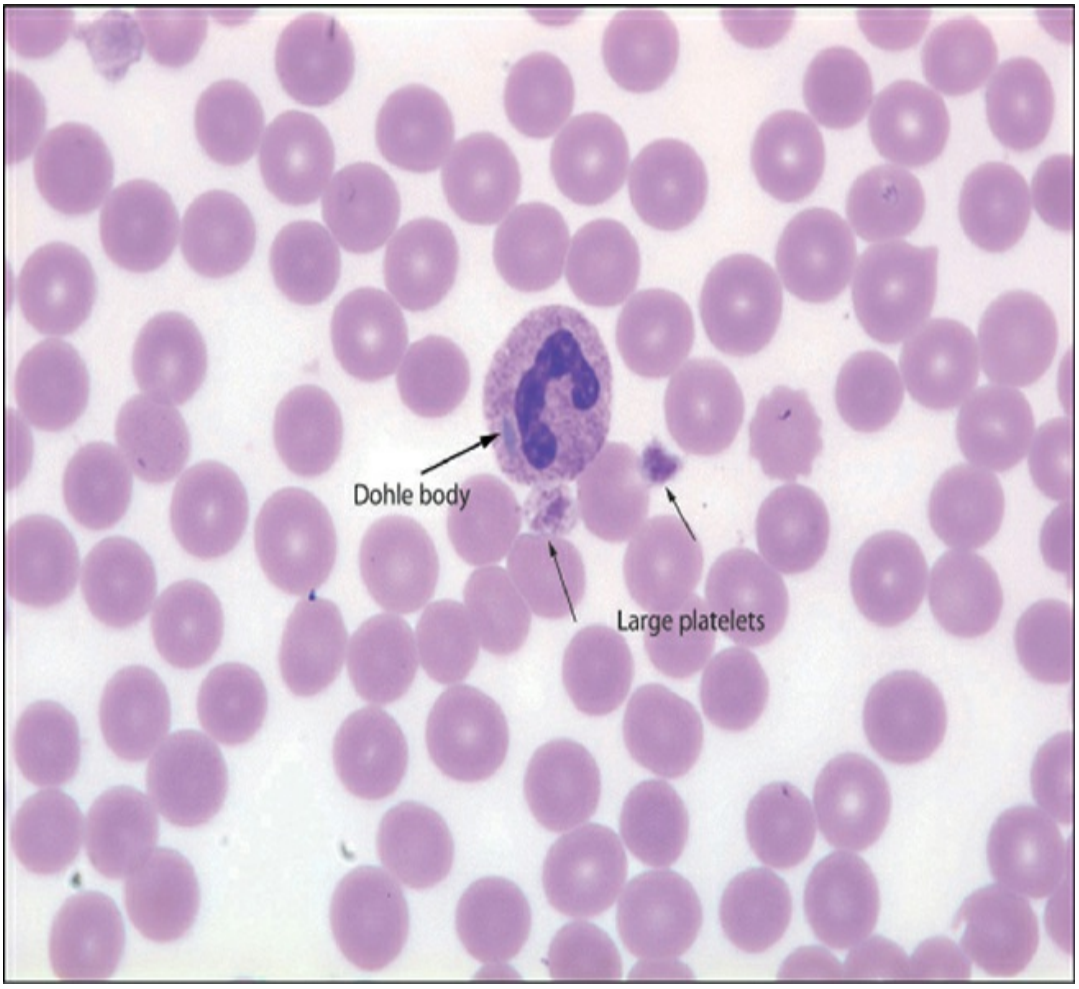


Figure IIB1-9

Peripheral blood smear.

Clinical Features

- Usually a mild bleeding disorder—epistaxis, bruising, gingival bleeding, dysmenorrhea, and abnormal bleeding following dental extractions or surgery

Pathology

- Inherited as an autosomal dominant trait caused by MYH9 (myosine9) mutation affecting white cell and platelets

Laboratory Features

Laboratory Features

White Blood Cells

- A few neutrophils contain small homogeneous blue inclusions
- Inclusions are larger than Döhle bodies, spindle or crescent shaped, and light blue
- Found in neutrophils, eosinophils, basophils, monocytes, and occasionally even lymphocytes

Red Blood Cells

- Normal

Platelets

- Giant platelets
- Mean platelet volume increased
- Number decreased

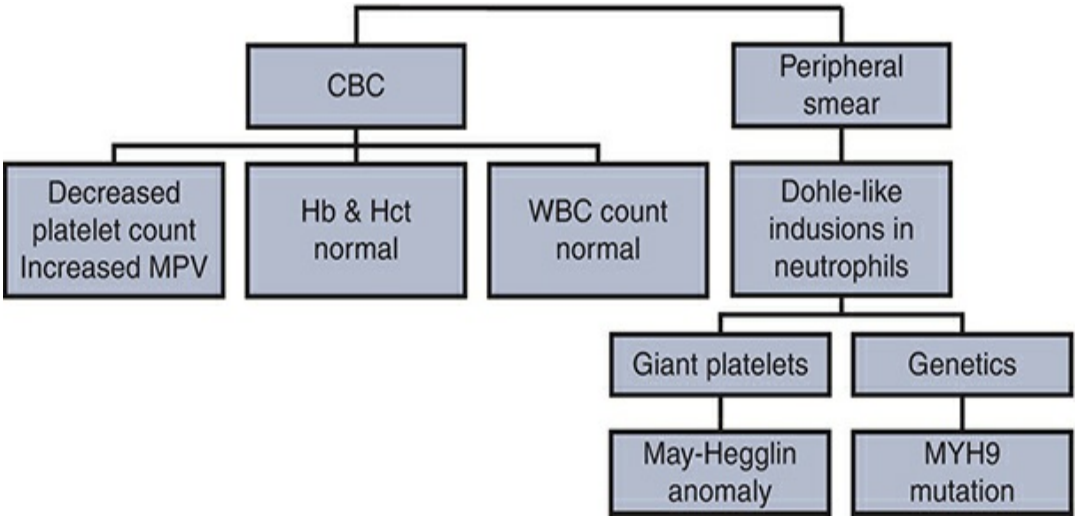
Coagulation Studies

- Bleeding time is prolonged

Bone Marrow

- A number of megakaryocytes are normal but show some large hypergranular platelets in the cytoplasm

Diagnostic Scheme


CBC
Peripheral smear
Decreased platelet count Increased MPV
Hb & Hct normal
WBC count normal
Dohle-like indusions in neutrophils
Giant platelets
Genetics
May-Hegglin anomaly
MYH9 mutation

MONOCYTOSIS

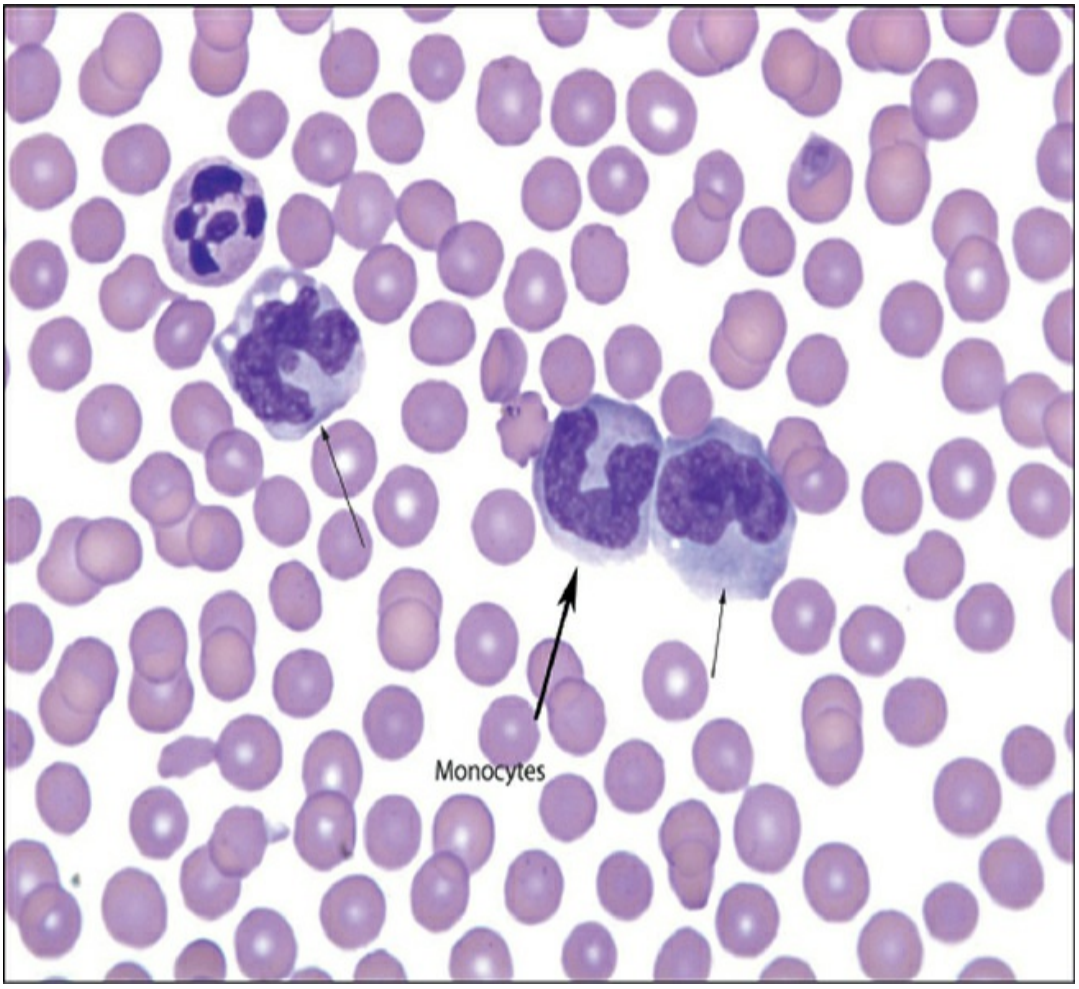


Figure IIB1-10

Peripheral blood smear.

Clinical Features

- In adults, defined as >0.95 × 10^9/L monocytes
- In infants and children, defined as >1.0 × 10^9/L monocytes
- Causes of neutrophilia may be accompanied by absolute monocytosis
- Relative monocytosis may indicate a recovery from agranulocytosis or marrow hypoplasia

Pathology

- Monocytes play a role in inflammation and immune reactions
- Monocytosis is associated with several conditions
  - Tuberculosis
  - Malignancies
  - Myelodysplastic syndromes
  - Myeloproliferative neoplasms
  - Myelodysplastic/myeloproliferative neoplasms
  - Lymphocytic tumors
  - Inflammatory disorders

Laboratory Features

White Blood Cells

- Increased monocytes

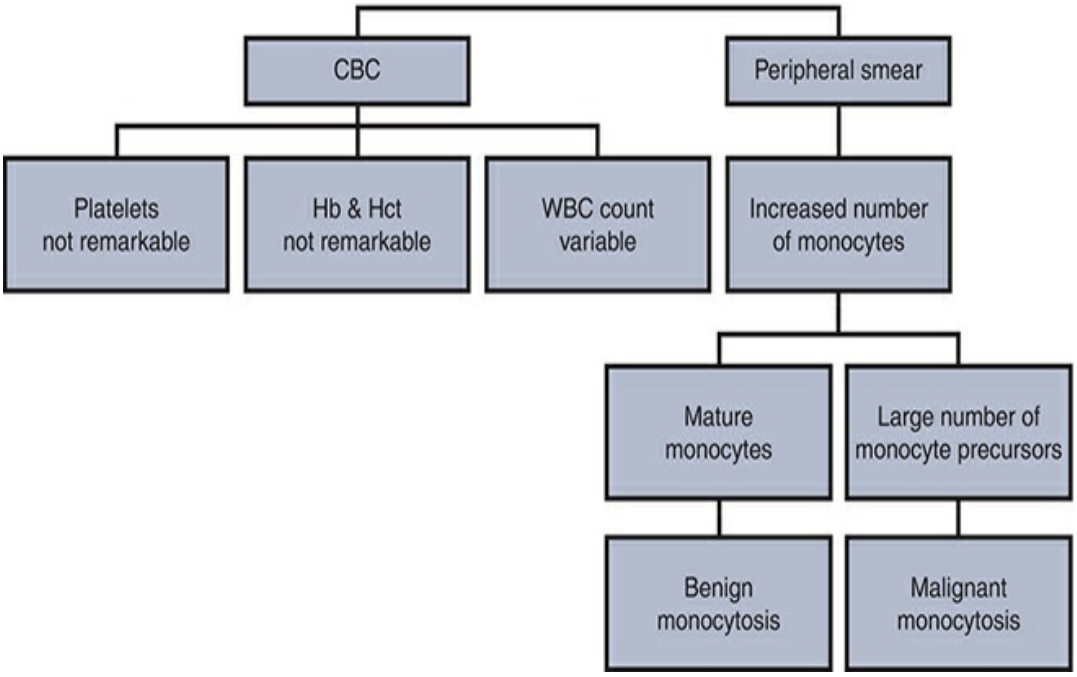
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct not remarkable
WBC count variable
Increased number of monocytes
Mature monocytes
Large number of monocyte precursors
Benign monocytosis
Malignant monocytosis

NEUTROPENIA

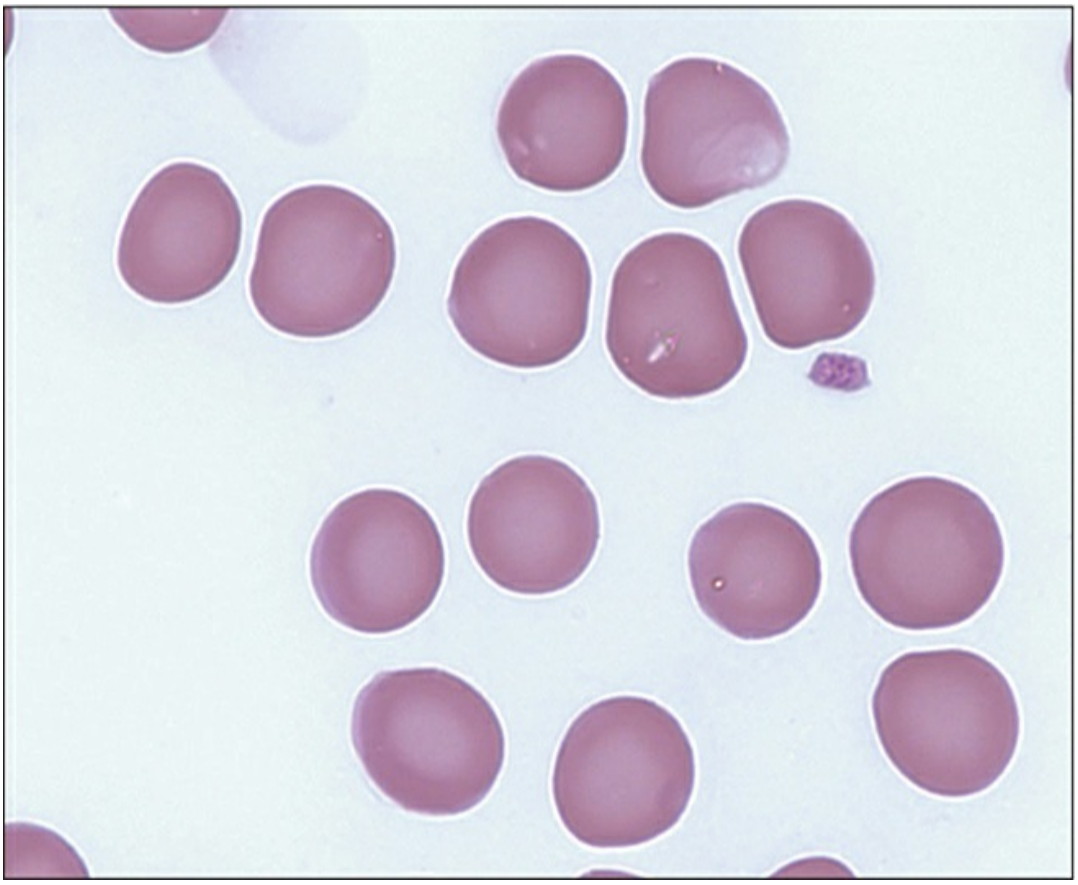


Figure IIB1-11

Peripheral blood smear.

Clinical Features

- Defined as an absolute neutrophil count of $<1.5 \times 10^9/L$
- May have no symptoms or may present with sudden overwhelming sepsis
  - Fever
  - Enlarged lymph nodes
  - Sternal tenderness
  - Oral lesions
- Hepatosplenomegaly

Pathology

Pathology

- Decreased or ineffective production
- Reduced survival
- Abnormal distribution and sequestration

Laboratory Features

White Blood Cells

- Total number decreased
- Neutrophils count decreased

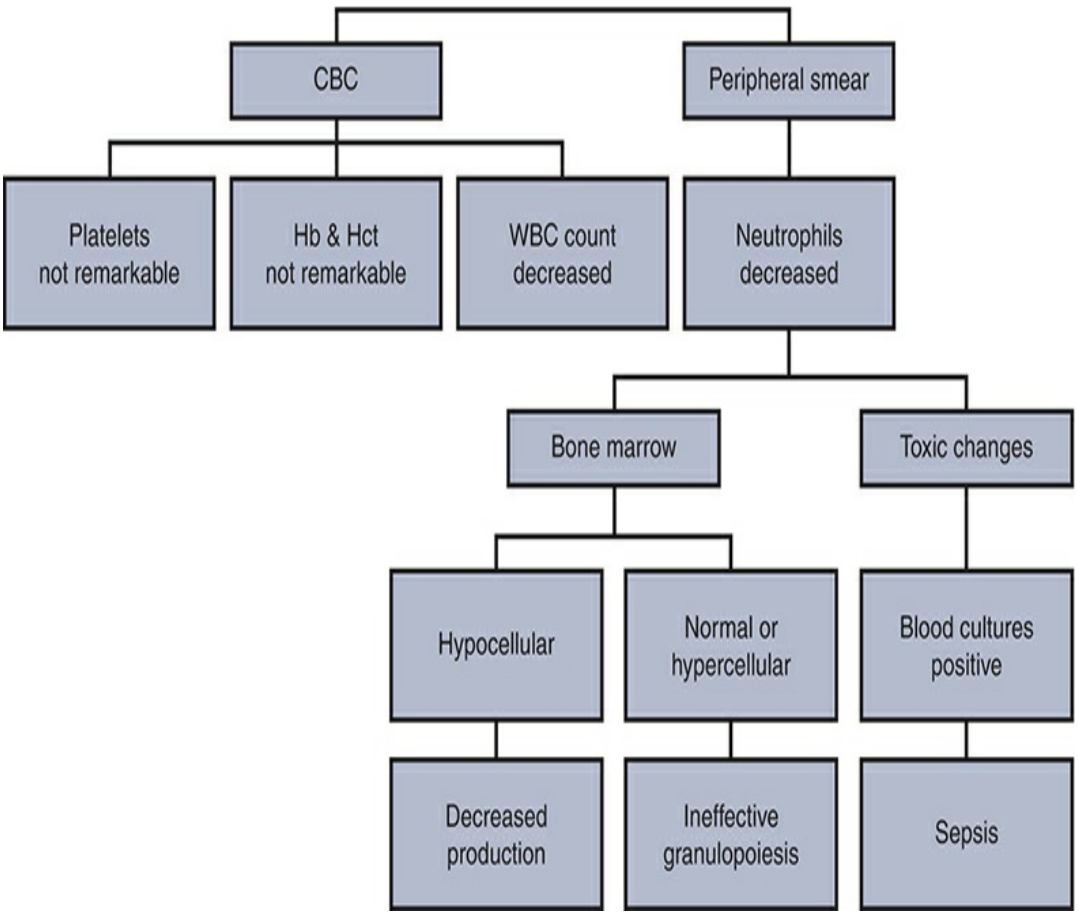
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme



NEUTROPHILIA

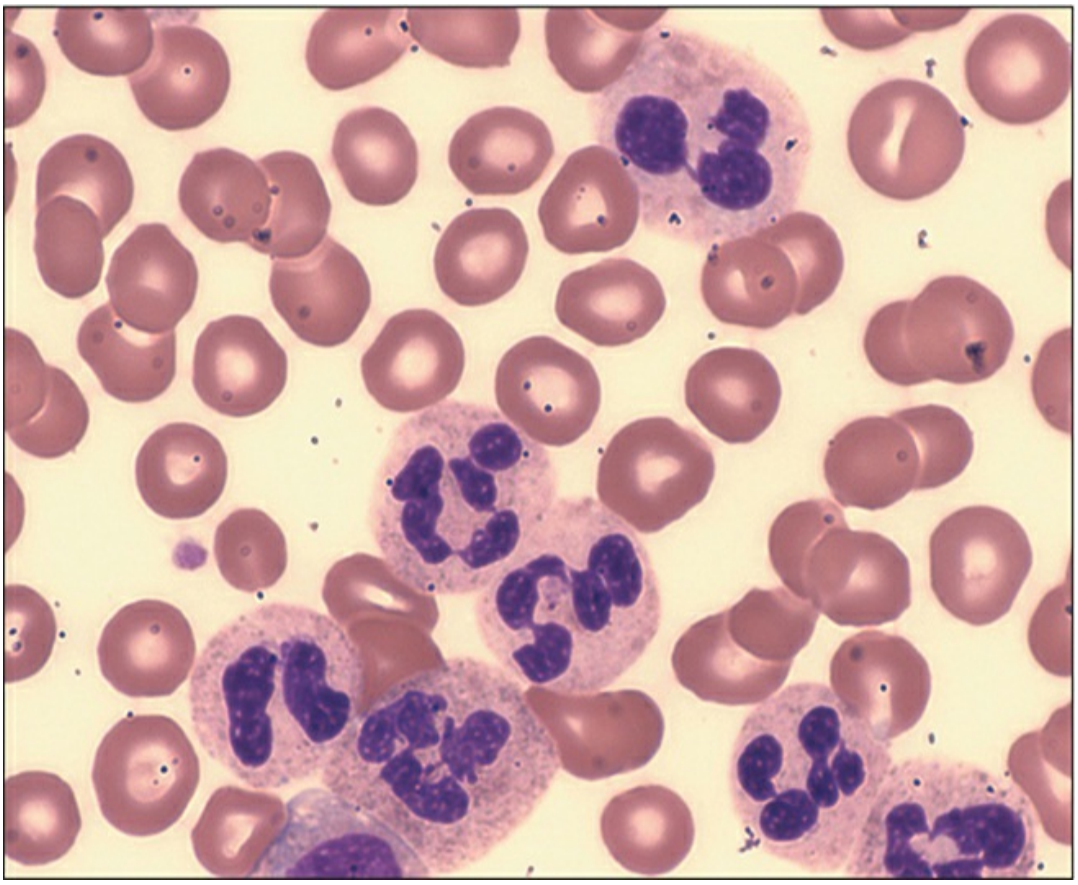


Figure IIB1-12

Peripheral blood smear.

Clinical Features

- Defined as an absolute count of >7.0 × 10^9/L
- Acute neutrophilia may be caused by exercise, stress, drugs, and hormones, and the most frequent cause is bacterial infection
- Chronic neutrophilia may be seen with infection, chronic inflammation, tumors, or hematologic disorders

Pathology

- Increased production by the bone marrow
- Increased release from the marrow reserve or impaired

egress from the peripheral blood
- Decreased neutrophils in the marginating pool with increased neutrophil count in the circulating pool
- Extreme neutrophilic reactions to severe infections or necrotizing tissue may produce a leukemoid reaction (usually >50.0 × 10^9/L)
- Neoplastic disorders

Laboratory Features

White Blood Cells

- Physiologic neutrophilia
  - Increased count
- Pathologic neutrophilia
  - Increased count
  - Shift to the left
  - Vacuolization and toxic granulation
  - Döhle bodies

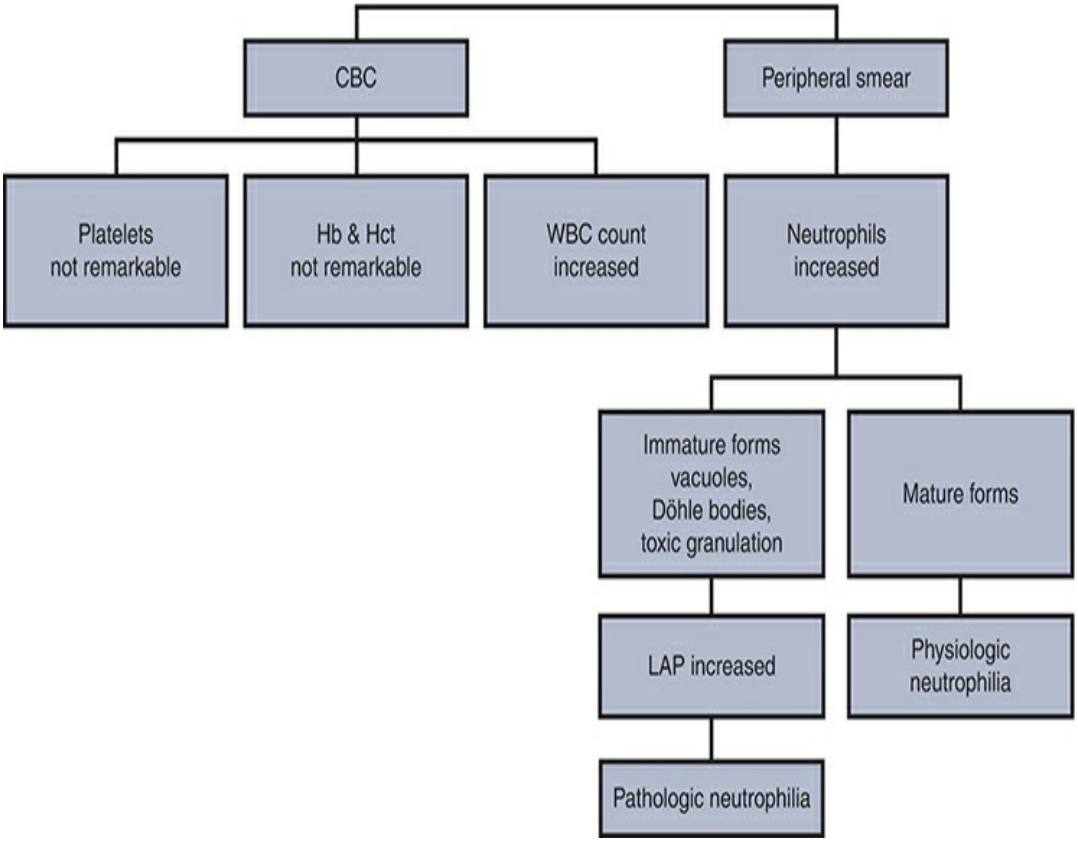
Red Blood Cells

- Not remarkable

Platelets

- Not remarkable

Diagnostic Scheme


CBC
Peripheral smear
Platelets not remarkable
Hb & Hct not remarkable
WBC count increased
Neutrophils increased
Immature forms vacuoles, Döhle bodies, toxic granulation
Mature forms
LAP increased
Physiologic neutrophilia
Pathologic neutrophilia

PELGER-HUëT ANOMALY

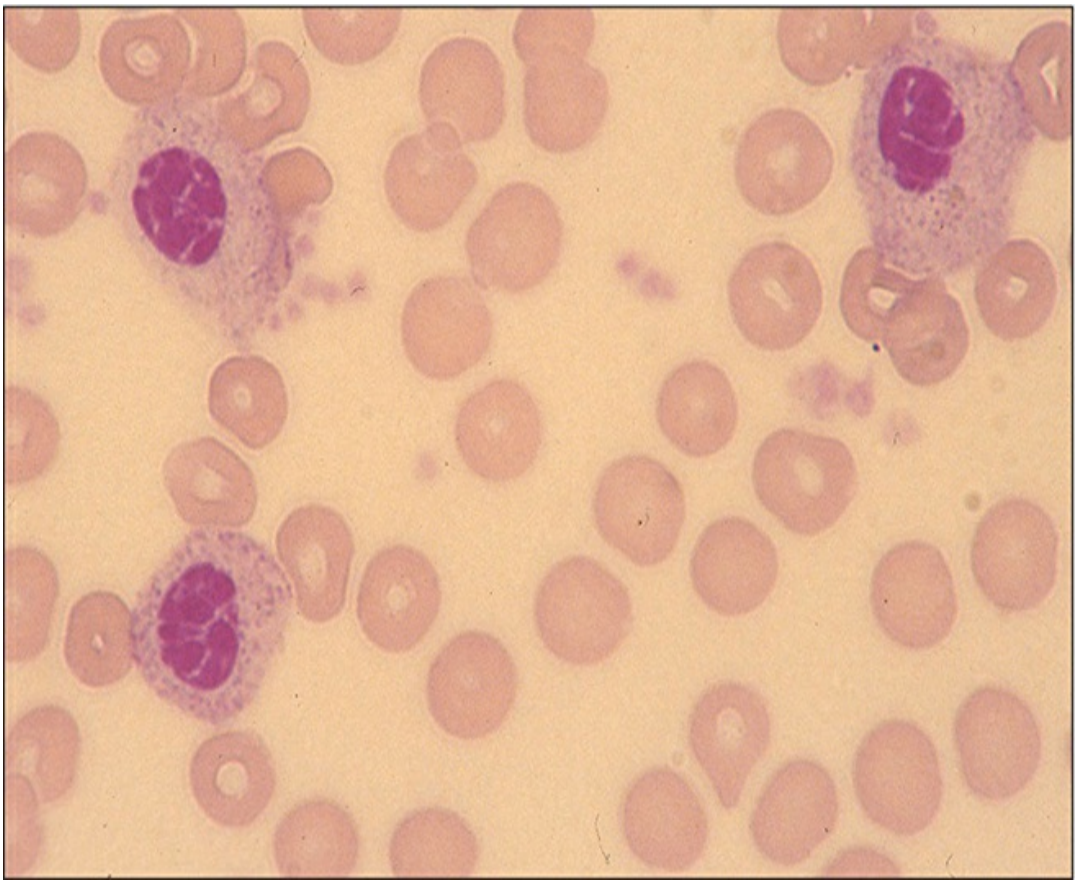


Figure IIB1-13

Peripheral blood smear—homozygous.

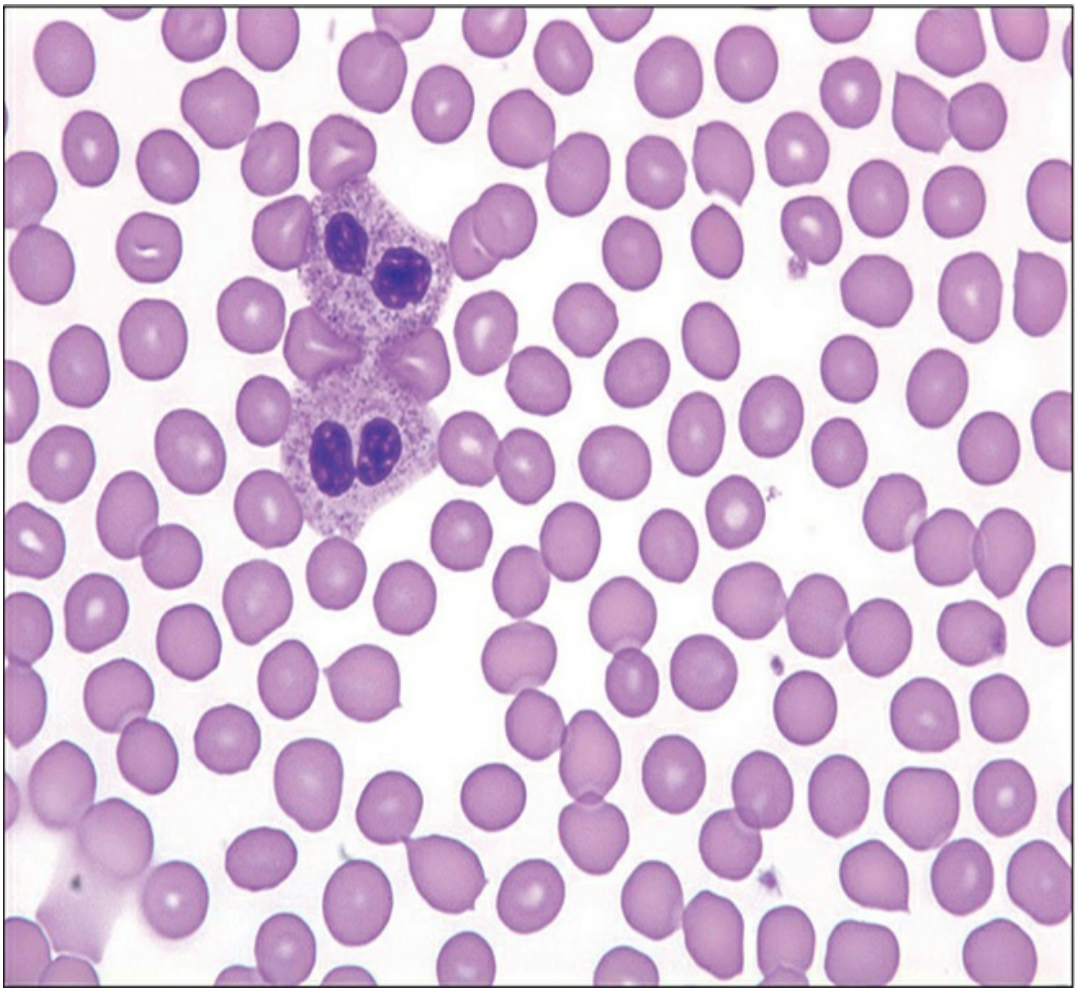


Figure IIB1-14

Peripheral blood smear—heterozygous.

Clinical Features

- No clinical significance is associated with this anomaly
- Neutrophils have normal function

Pathology

- Inherited as an autosomal dominant
- Mutations in lamin β-receptor gene
  - Results in defects in scaffolding proteins that control the shape of the nuclear membrane
  - Reduced levels of lamin β-receptor result in hypolobation of nucleus

- Marked condensation of nuclear chromatin
- Normal cytoplasmic maturation

Laboratory Features

White Blood Cells

- In the heterozygous state, the granulocyte nucleus is bilobed or dumbbell shaped (Pince-Nez)
- In the homozygous state, the nucleus is round or oval (Stodtmeister)

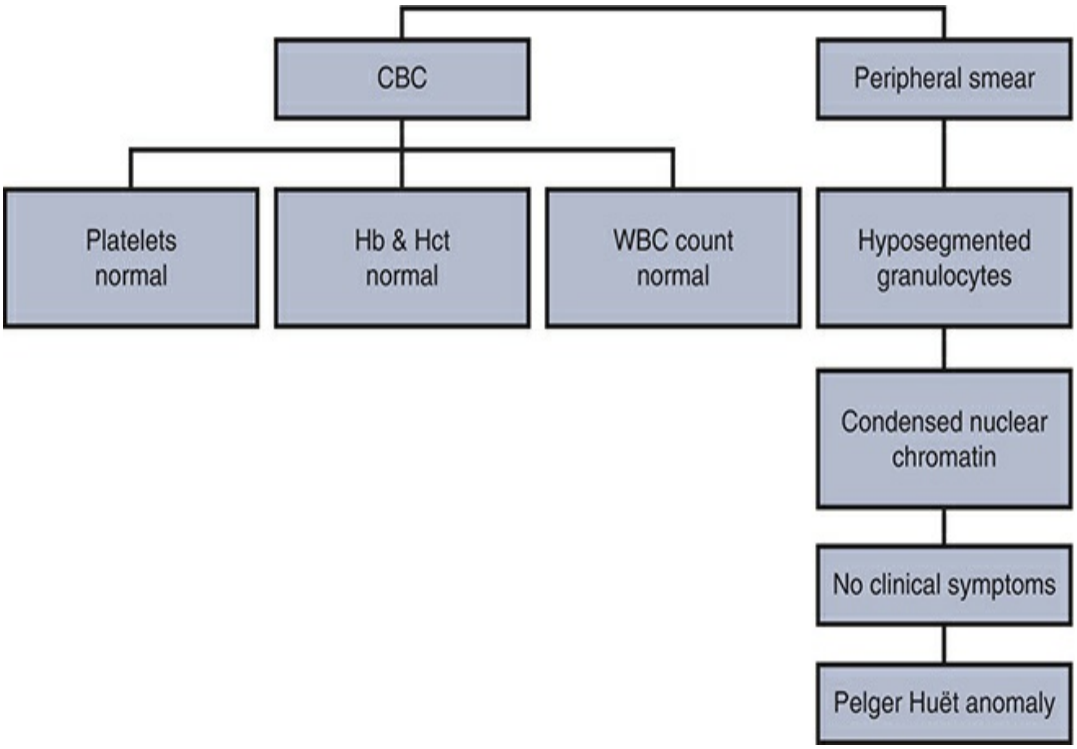
Red Blood Cells

- Not remarkable

Platelets

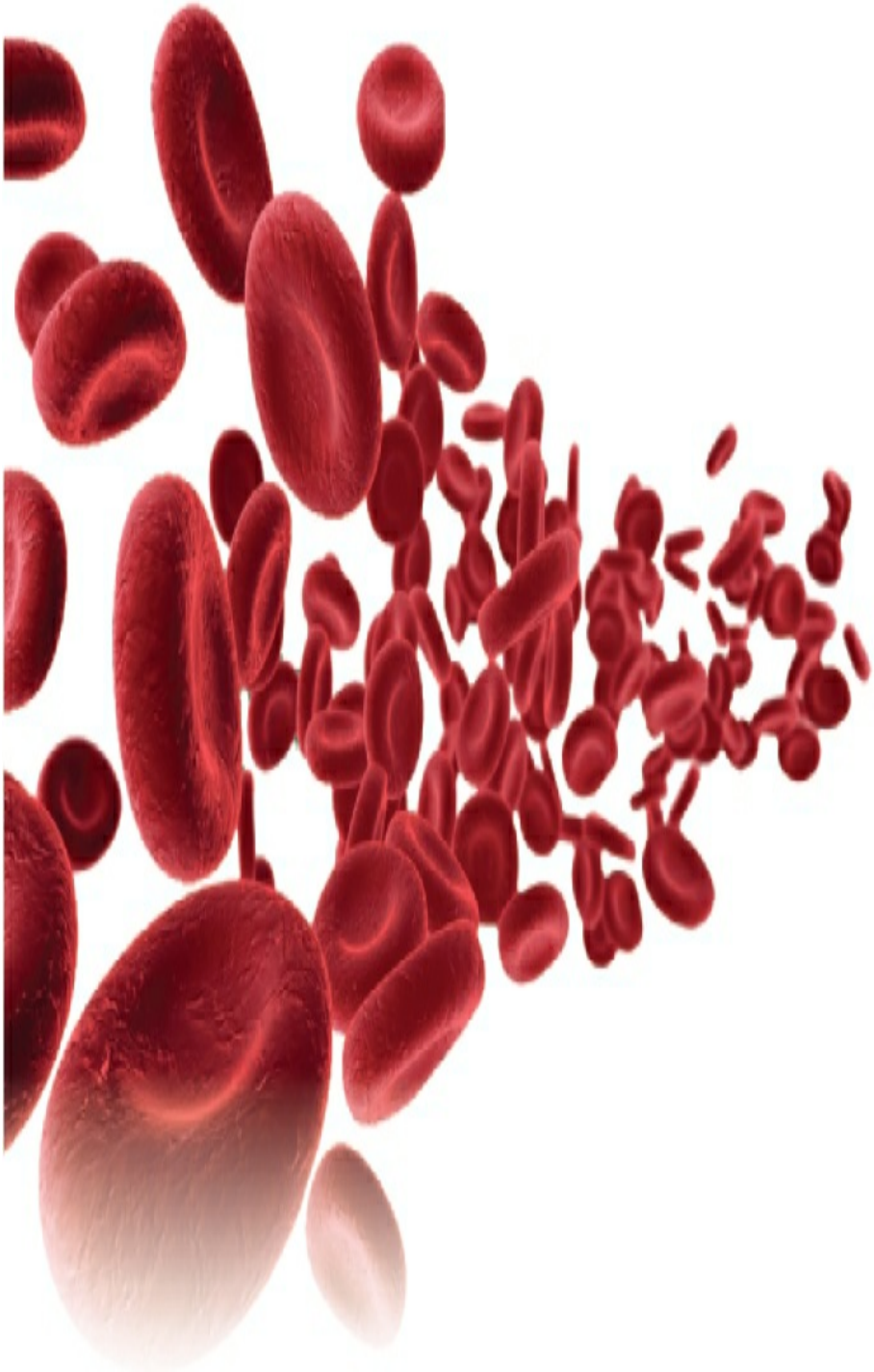
- Not remarkable

Diagnostic Scheme



CHAPTER 2

French–American–British (FAB) Classification of Leukemia



FAB CLASSIFICATION OF LEUKEMIAS

Background

- Organized in 1976 in an attempt to provide a uniform means of discussing the leukemias worldwide. The classifications were based on morphology and cytochemistry

Peripheral Blood Findings

- 90% of patients have moderate to severe neutropenia
- 50% of patients have a leukocytosis
- 30% of patients have a leukopenia
- The blasts are of variable size
- 70–80% of the patients have normochromic, normocytic anemia
- 60% of the patients have hematocrits of <30%
- Thrombocytopenia is usually present

Bone Marrow Findings

- Blast count of ≥30% is diagnostic of acute leukemia

Cytochemistry

- Type I, II, and III myeloblasts show ≥3% positivity of blasts for myeloperoxidase, Sudan black B, or specific esterase
- Monoblasts and promonocytes are positive with the nonspecific esterase
- Erythroblasts and megakaryoblasts are positive with the periodic acid–Schiff

Definitions

Type I Myeloblast

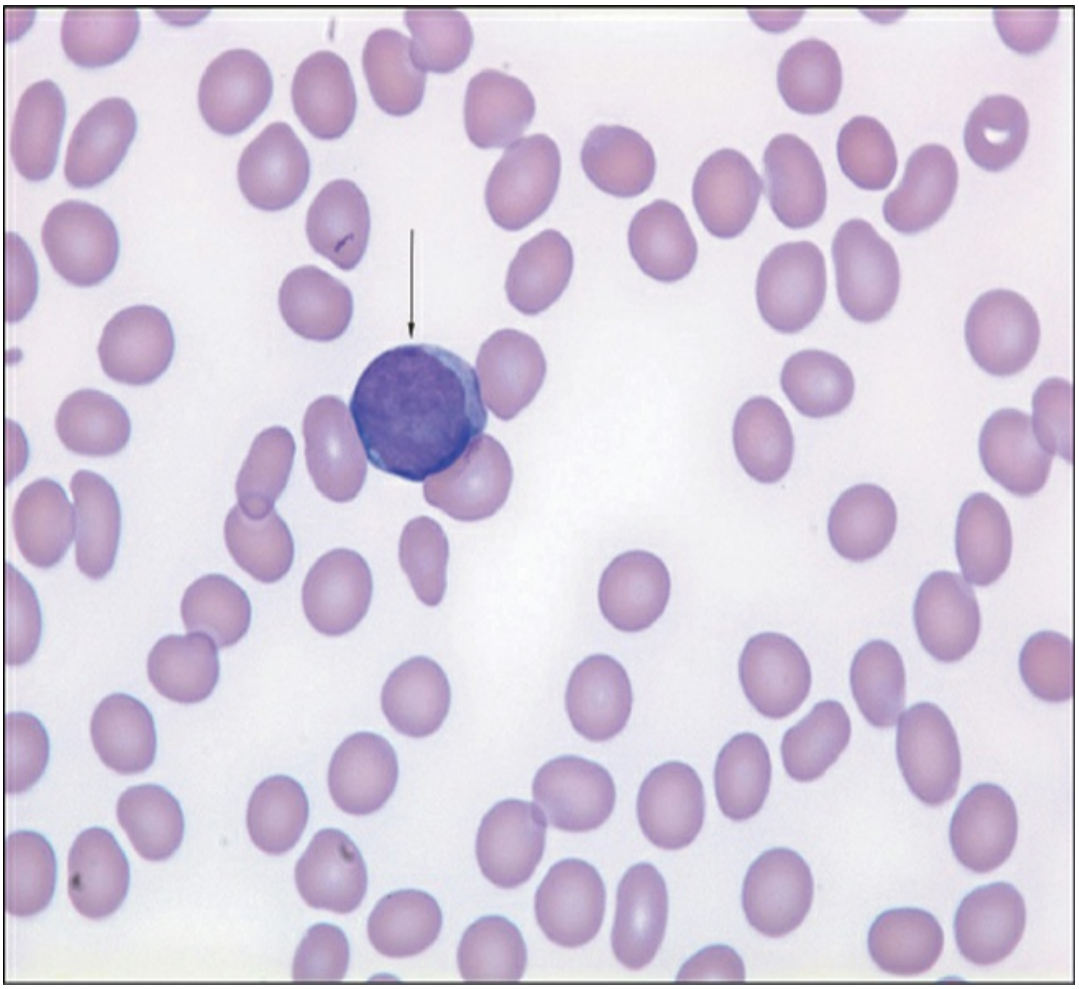


Figure **IIB2-1**

Peripheral blood smear.

Size: 10–18 µ

Nucleus

Shape: Oval or round

N/C Ratio: 6:1–7:1

Color: Dark purple

Chromatin: Fine

Nucleoli: 1–3

Cytoplasm

Color: Light to medium blue

Contents: Without azurophilic granules

Clinical Conditions

- Acute myelocytic leukemia minimally differentiated (M0)
- Acute myelocytic leukemia without maturation (M1)
- Acute myelocytic leukemia with maturation (M2)
- Acute myelomonocytic leukemia (M4)
- Erythroleukemia (M6a)
- Myeloproliferative neoplasms—chronic myelogenous leukemia, primary myelofibrosis

Type II Myeloblast

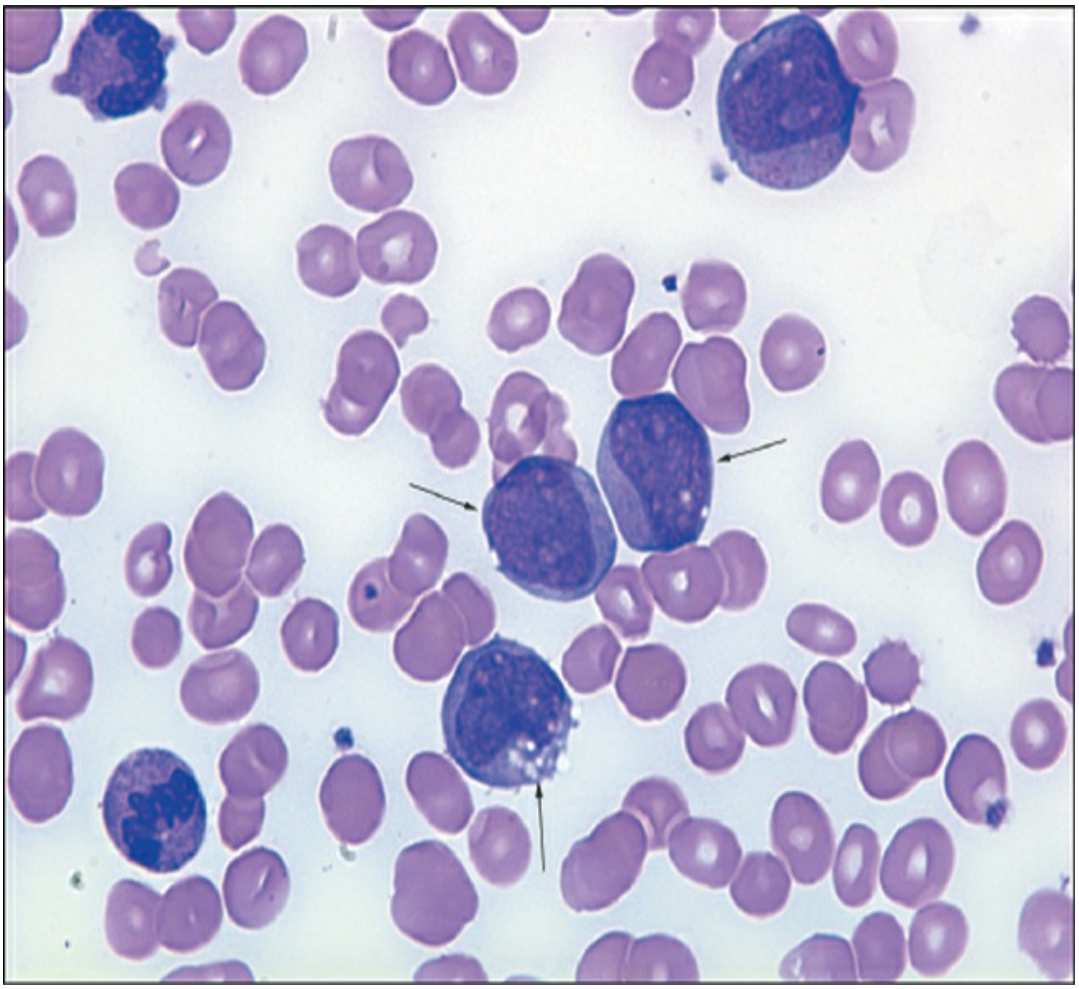


Figure **IIB2-2**

Peripheral blood smear.

Size: 10–18 µ

Nucleus

Shape: Oval or round

N/C Ratio: Slightly lower than a type I

Color: Dark purple

Chromatin: Slightly more condensed than a type I

Nucleoli: 2–5

Cytoplasm

Color: Medium blue

Contents: <20 azurophilic granules and may have Auer rods

Clinical Conditions

- Acute myelocytic leukemia without maturation (M1)
- Acute myelocytic leukemia with maturation (M2)
- Acute myelomonocytic leukemia (M4)
- Erythroleukemia (M6a)
- Myeloproliferative neoplasms—chronic myelogenous leukemia, primary myelofibrosis

Type III Myeloblast

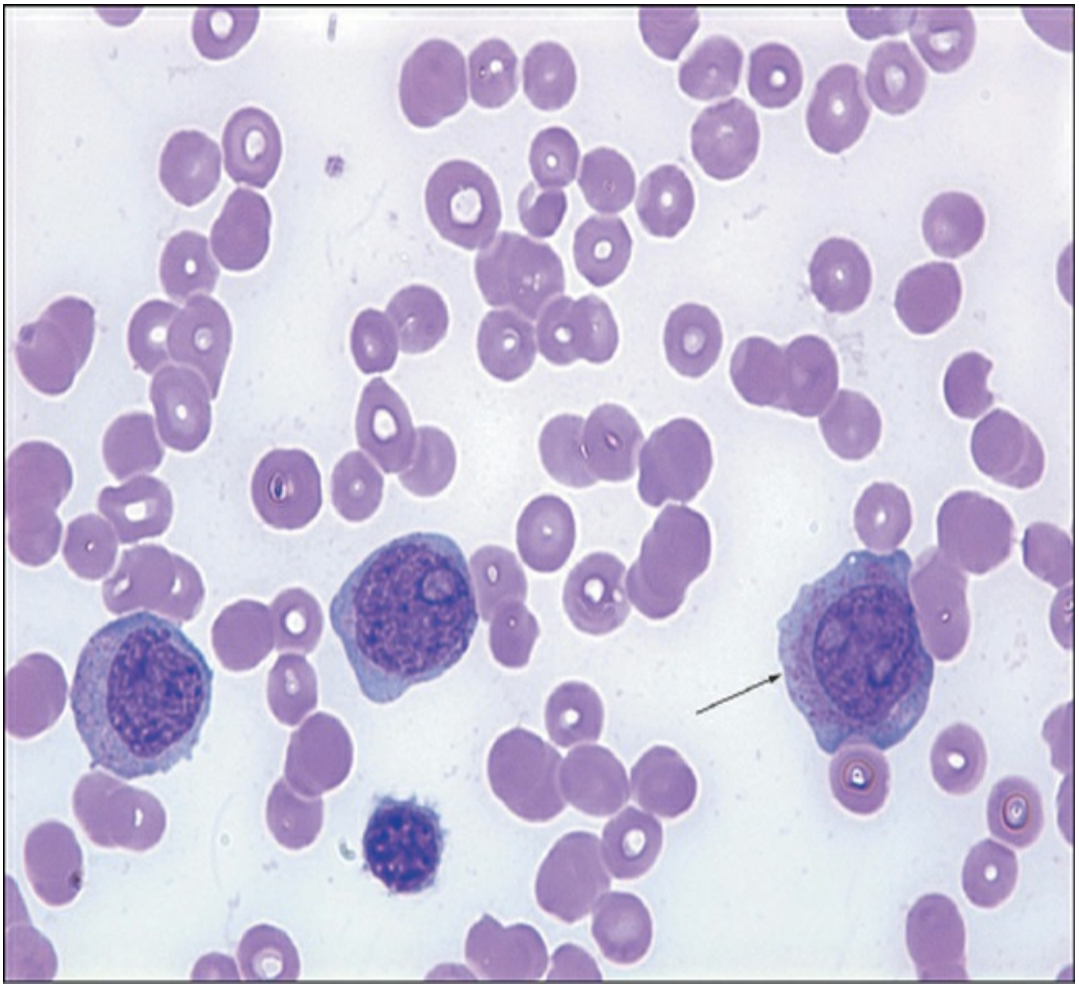


Figure **IIB2-3**

Peripheral blood smear.

Size: 10–18 µ

Nucleus

Shape: Oval or round

N/C Ratio: Lower than a type I

Location: Centrally located

Color: Dark purple

Chromatin: Slightly more condensed than type II

Nucleoli: Less visible

Cytoplasm

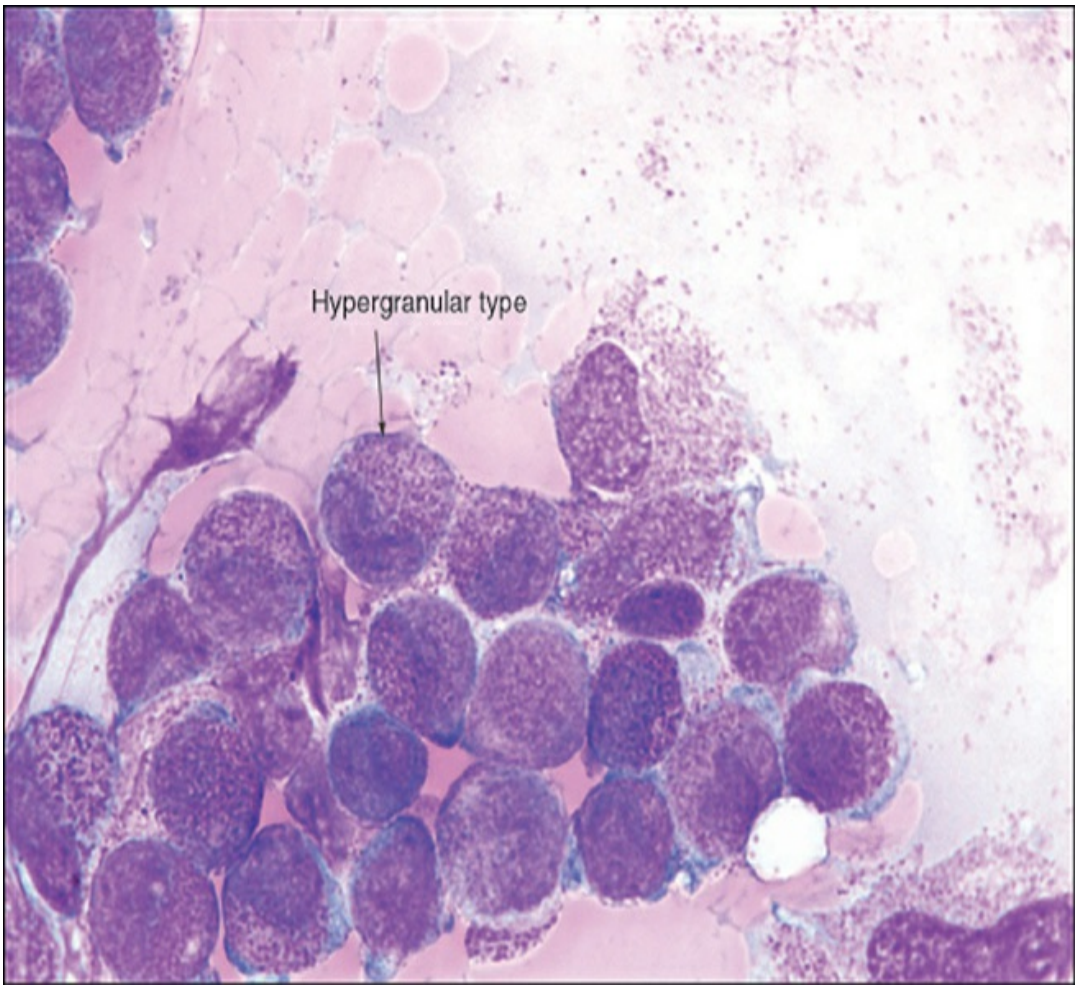
Color: Medium blue

Contents: >20 azurophilic granules but don't obscure the nucleus

Clinical Conditions

- Acute myelocytic leukemia with maturation (M2)

Abnormal Promyelocyte



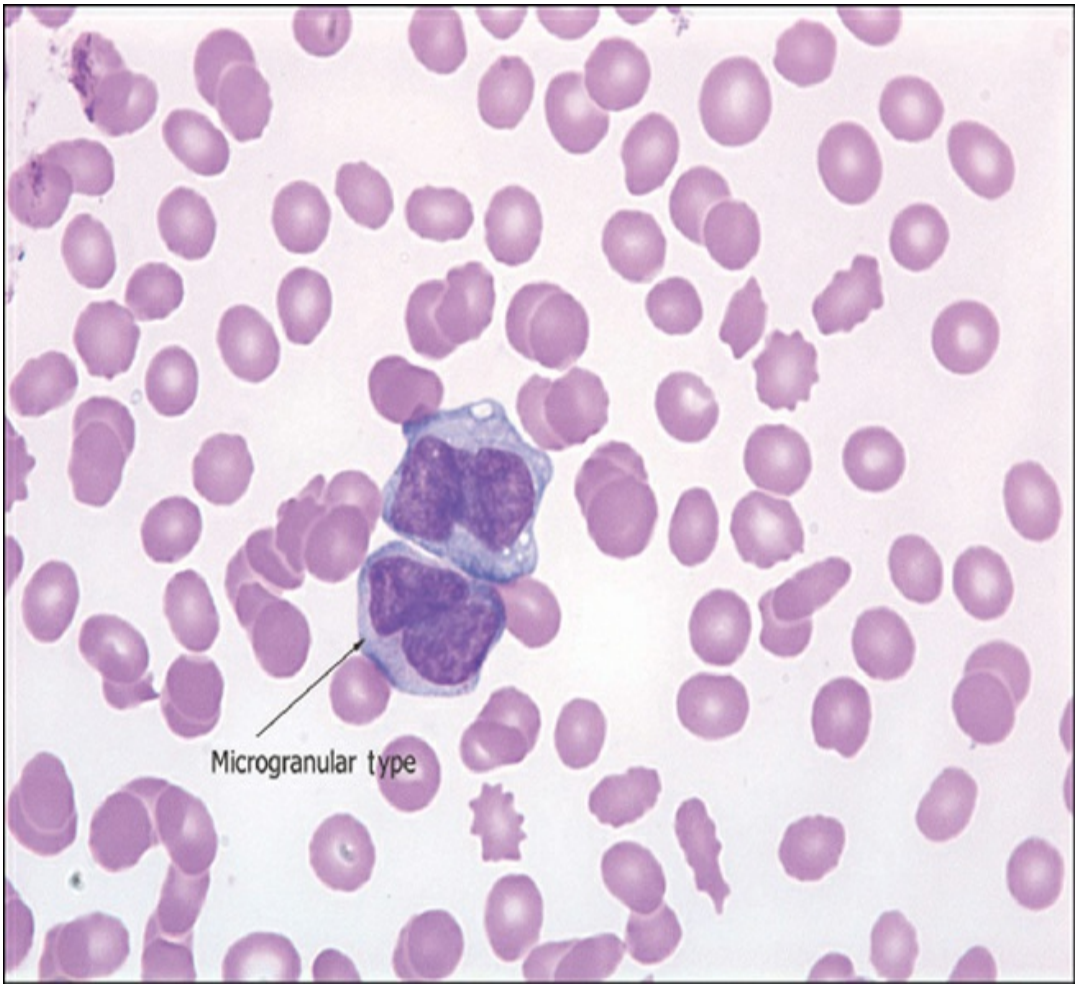


Figure **IIB2-4**

A. Bone marrow smear.

B. Peripheral blood smear.

Size: 18–25 µ

Nucleus

Shape: Round or, more commonly, reniform or bilobed

N/C Ratio: 2:1

Color: Purple

Chromatin: Relatively fine, becoming coarser

Nucleoli: 2–3 varying from visible to indistinct

Cytoplasm

Hypergranular type:

Color: Intensely basophilic

Contents: Large red to purple granules; Auer rods may be numerous and intertwined, giving haystack appearance (faggot cells); may obscure the nucleus

Microgranular type:

Color: Moderately basophilic

Contents: Small, indistinct granules that are difficult to see with the light microscope; Auer rods are often found but not as abundant as those found in the hypergranular type

Clinical Conditions

- Acute promyelocytic leukemia (M3, M3v)

L1 Lymphoblast

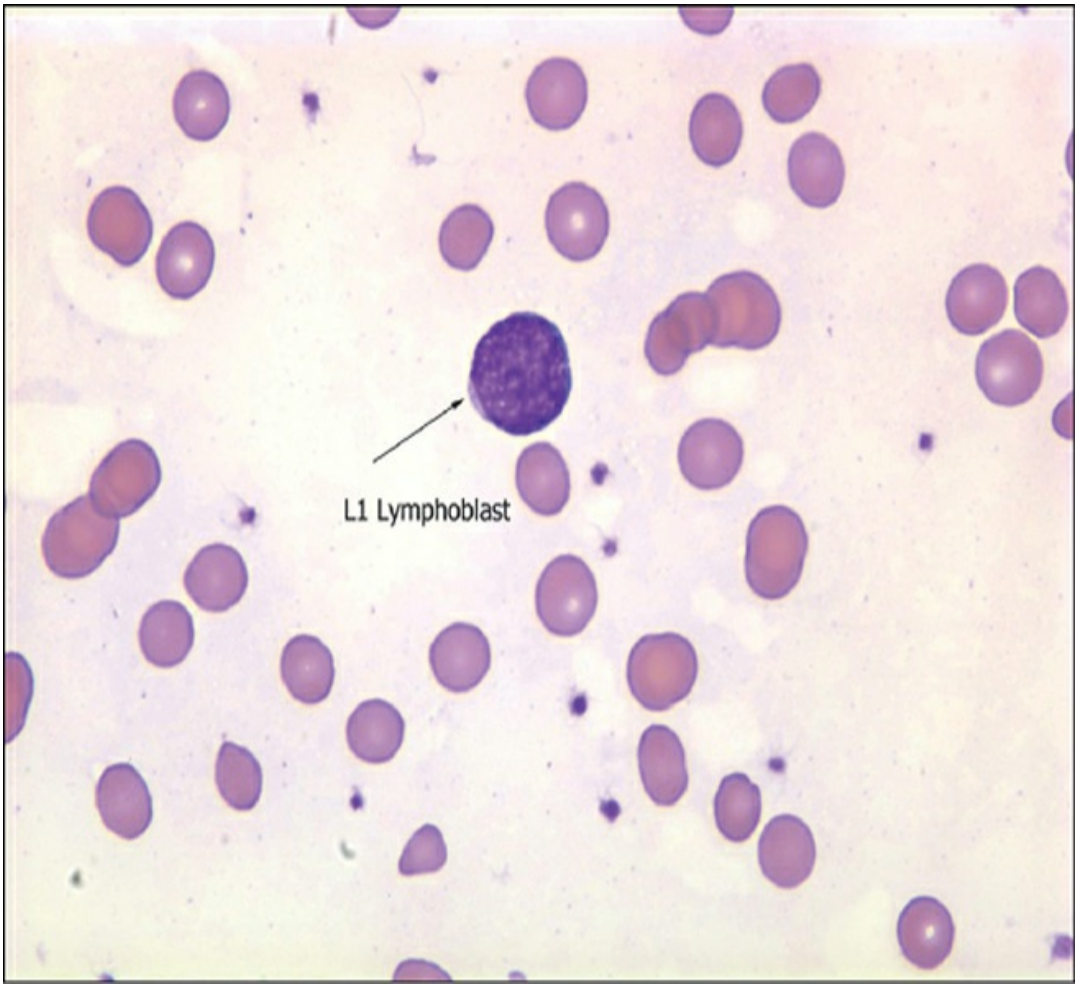


Figure **IIB2-5**

Peripheral blood smear.

Cell Type

Lymphoblast

Size: 14–22 µ

Description

Nuclear shape is regular or small cleaved and indented

Purple nucleus has a homogeneous and condensed chromatin pattern

Nucleoli are inconspicuous or not visible (0–1)

Scanty cytoplasm is moderately basophilic and rarely vacuolated

Clinical Condition

- Precursor lymphoblastic leukemia

L2 Lymphoblast

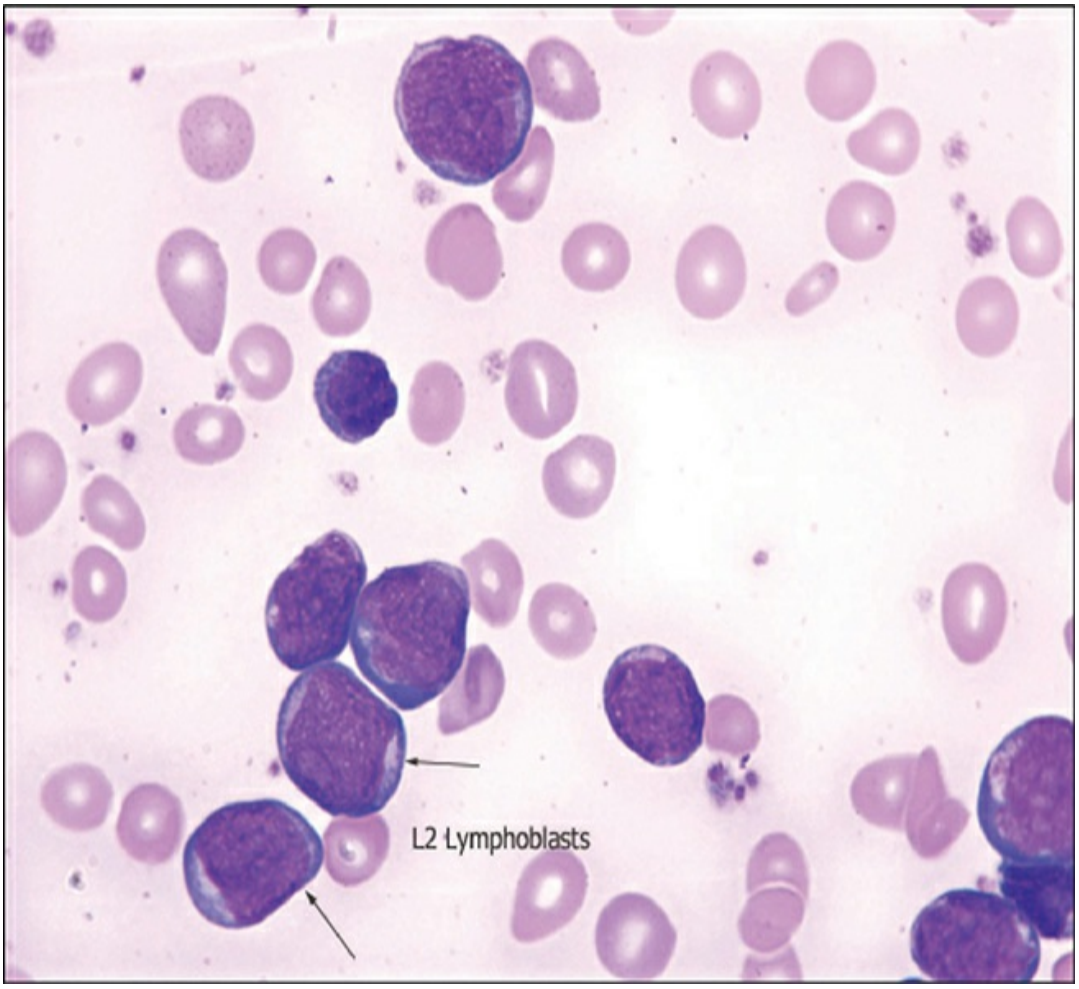


Figure **IIB2-6**

Peripheral blood smear.

Cell Type

Lymphoblast

Size: 14–22 µ

Description

Nucleus has an irregular or indented shape

N/C ratio is average (4:1)

Nucleus is purplish-red with variable heterogeneous chromatin

One to two nucleoli are often prominent

Cytoplasm is variable but occasionally intensely basophilic and rarely vacuolated

Clinical Condition

- Precursor lymphoblastic leukemia

L3 Lymphoblast

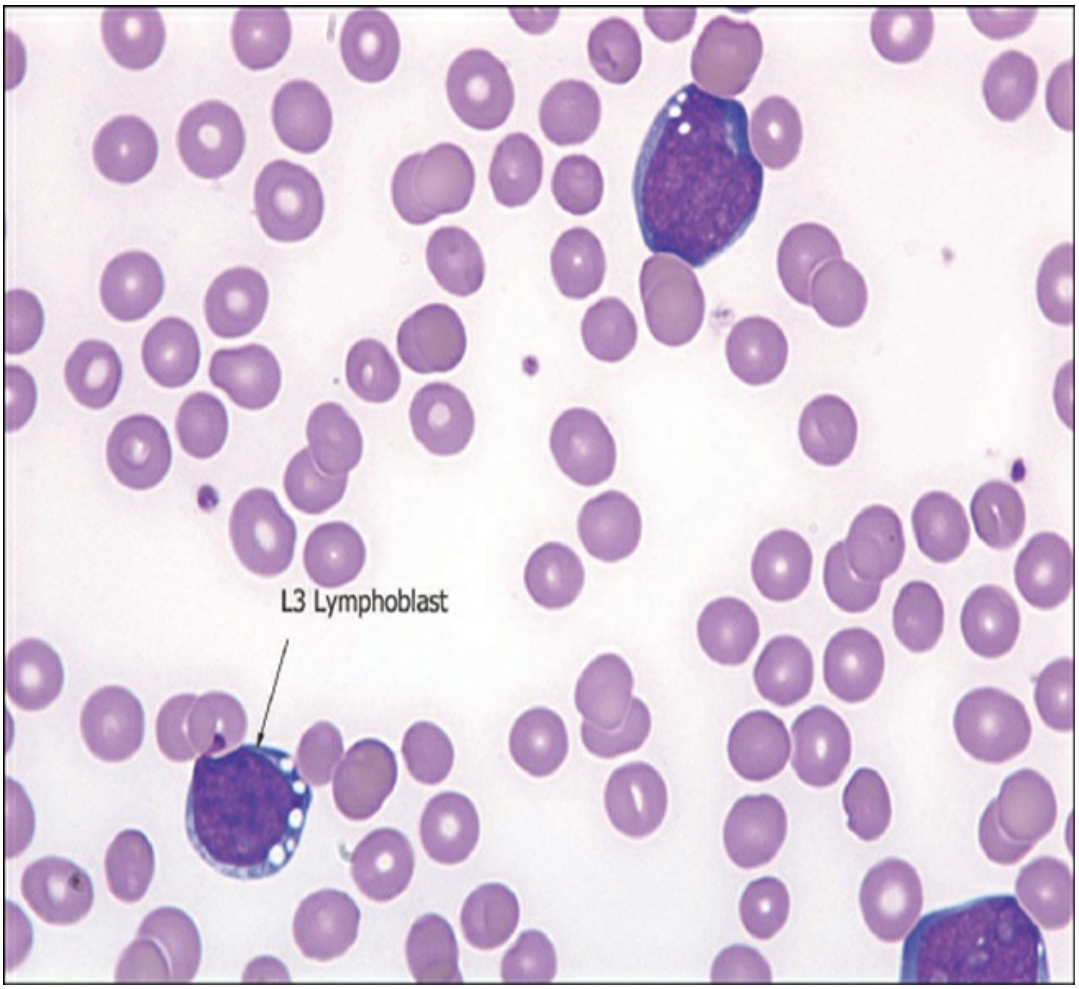


Figure **IIB2-7**

Peripheral blood smear.

Cell Type

Lymphoblast

Size: 14–18 μ

Description

Cell size ranges from 14 to 18 μ

Nucleus is oval to round, is purple, and has a finely stippled and homogeneous chromatin pattern

N/C ratio is 5:1–4:1

One to two nucleoli are often prominent

Cytoplasm is intensely basophilic with prominent vacuolization

Clinical Conditions

- Burkitt lymphoma
- Acute lymphoblastic leukemia (L3)
- Burkitt leukemia/lymphoma

M0 (Acute Myeloid Leukemia With Minimal Differentiation)

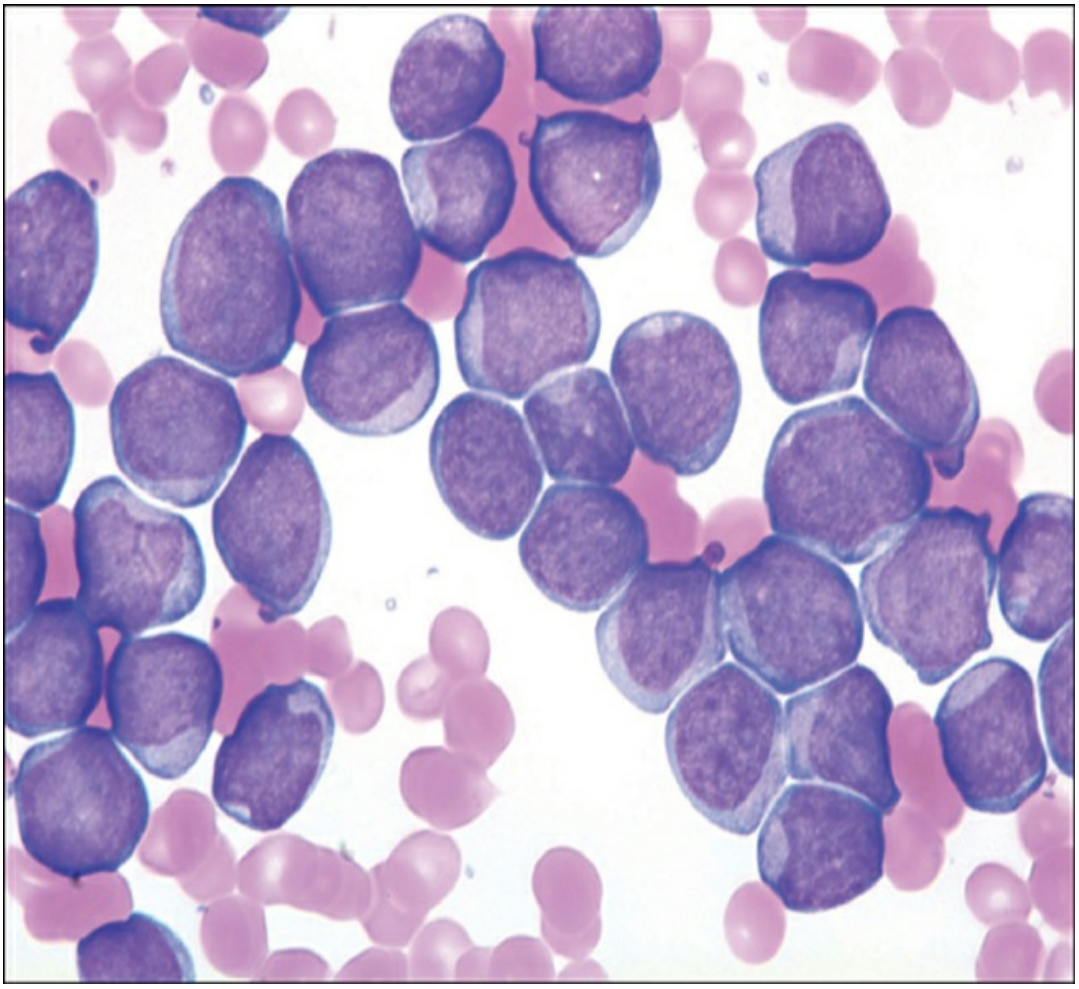


Figure **IIB2-8**

Peripheral blood smear.

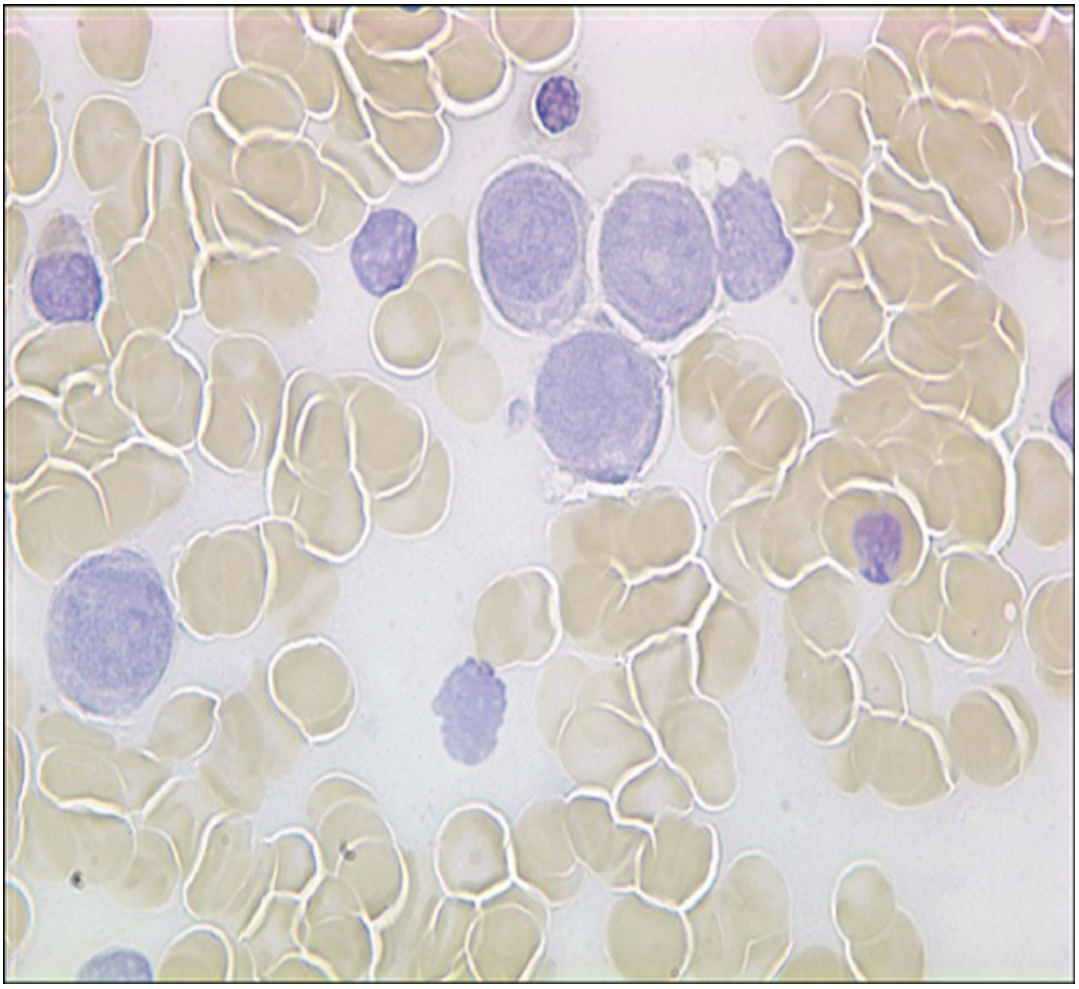


Figure **IIB2-9**

Sudan black B stain. Negative.

Criteria

Peripheral Blood

- Blasts are agranular
- Platelets are decreased

Bone Marrow

- ≥30% blasts
- ≥20% blasts are reactive for myeloid-associated antigen
- Myeloblasts are type I
- No Auer rods

- Blasts are negative for lymphoid-associated antigens
- Blasts are positive for myeloid-associated antigens

Cytochemistry

- <3% blasts are myeloperoxidase, Sudan black B, and specific esterase (chloroacetate) positive

M1 (Acute Myeloid Leukemia Without Maturation)

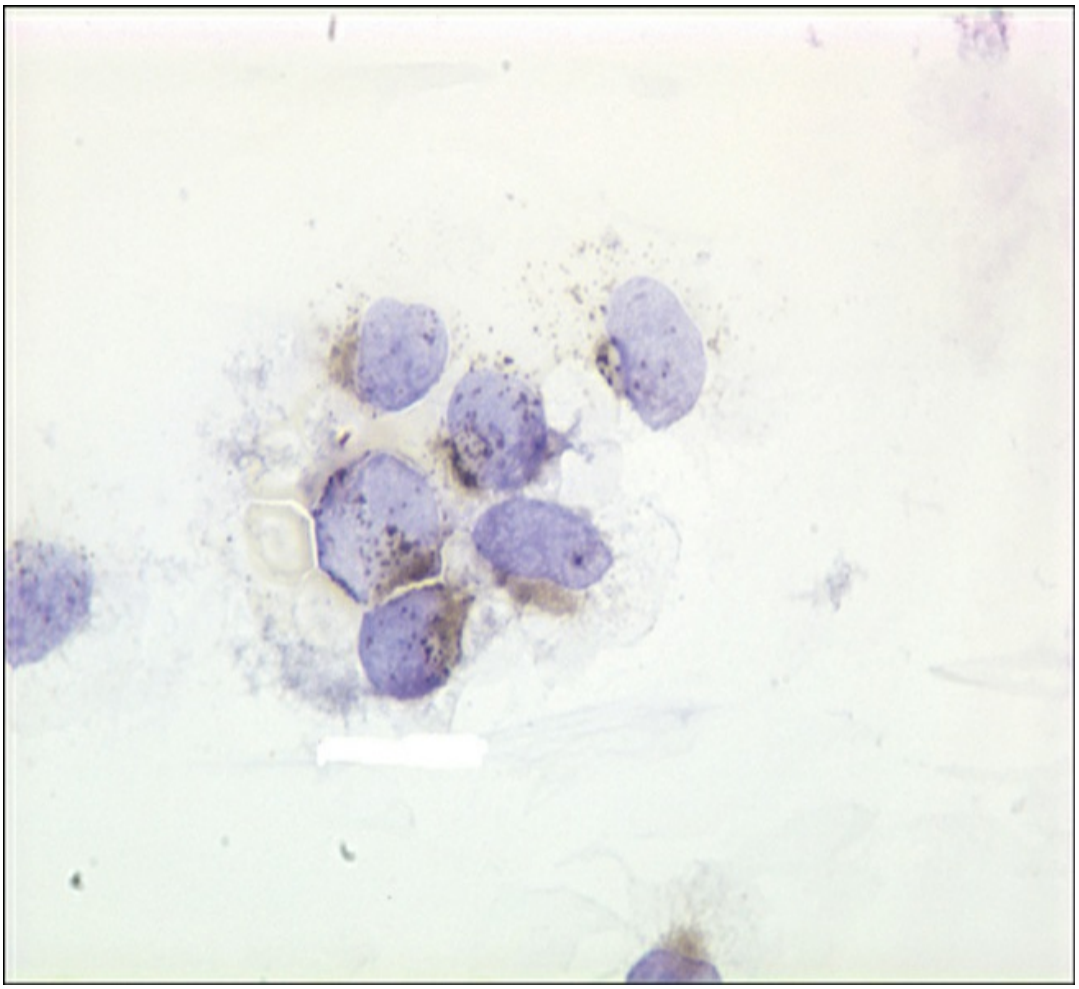


Figure IIB2-10

Peripheral blood smear.

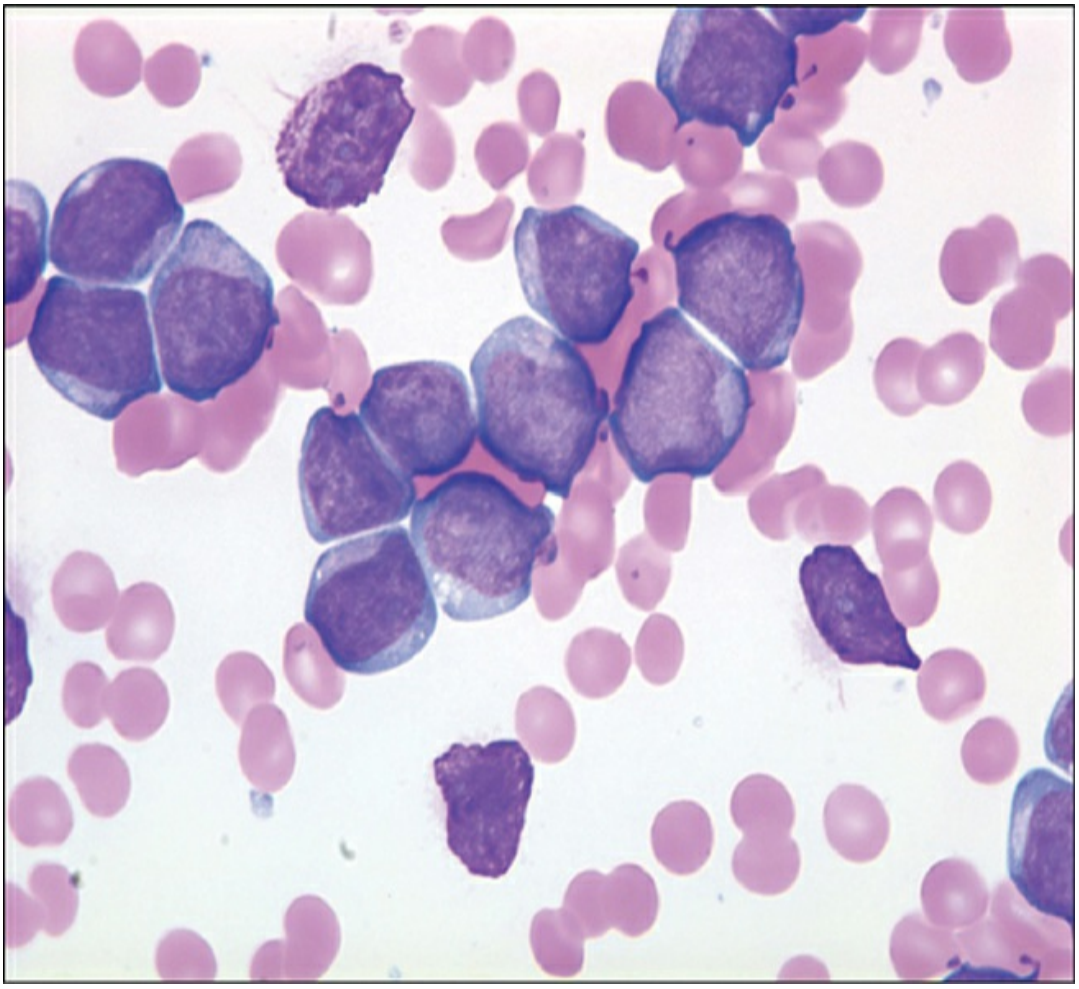


Figure **IIB2-11**

Sudan black B stain. Positive.

Criteria

Peripheral Blood

- The predominant cell is usually a type I myeloblast
- Auer rods are rare

Bone Marrow

- ≥30% blasts
- ≥90% or more of the nonerythroid cells are myeloblasts
- <10% promyelocytes or more mature cells of the granulocytic series

Cytochemistry

- Myeloperoxidase and Sudan black B are positive in ≥3% of the blasts
- Naphthol AS-D chloroacetate (specific esterase) may be positive
- Nonspecific esterases are negative

M2 (Acute Myeloid Leukemia With Maturation)

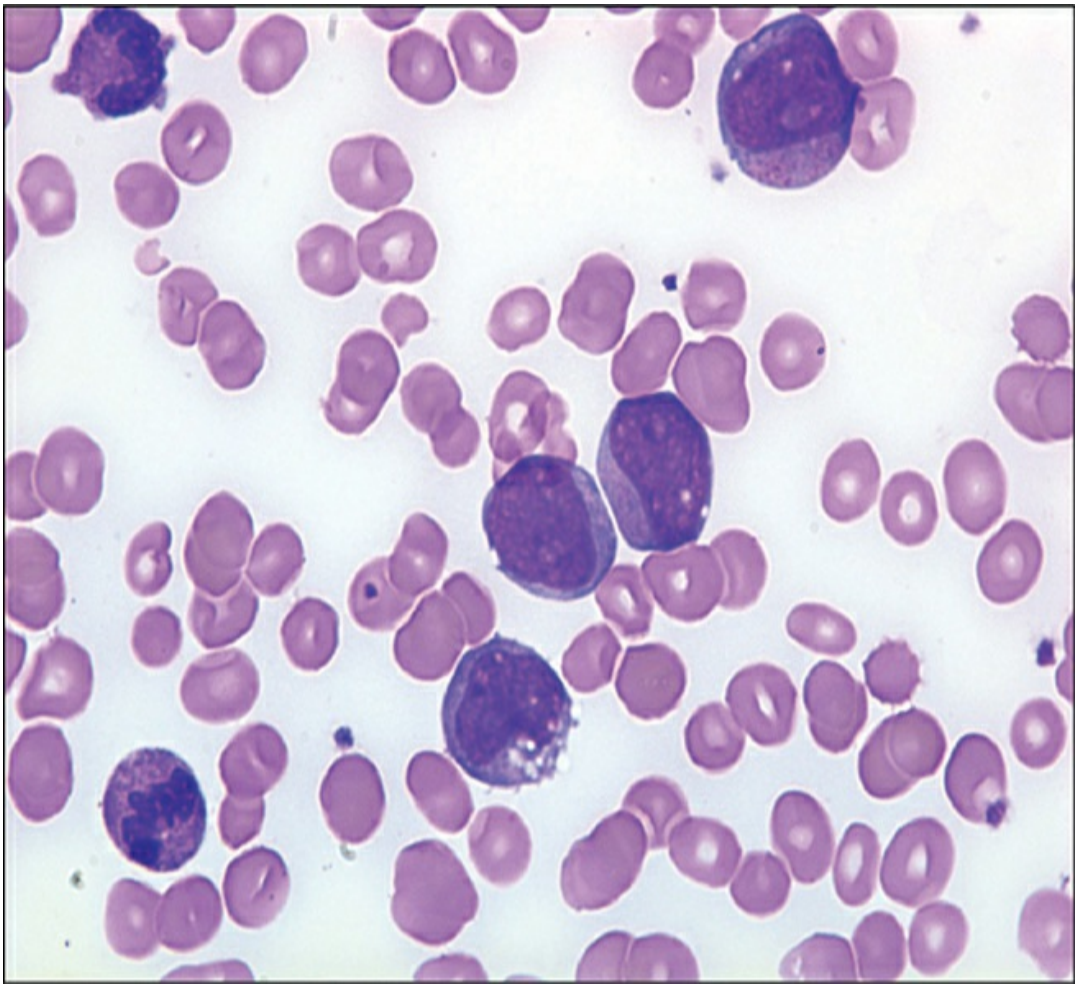


Figure IIB2-12

Peripheral blood smear.

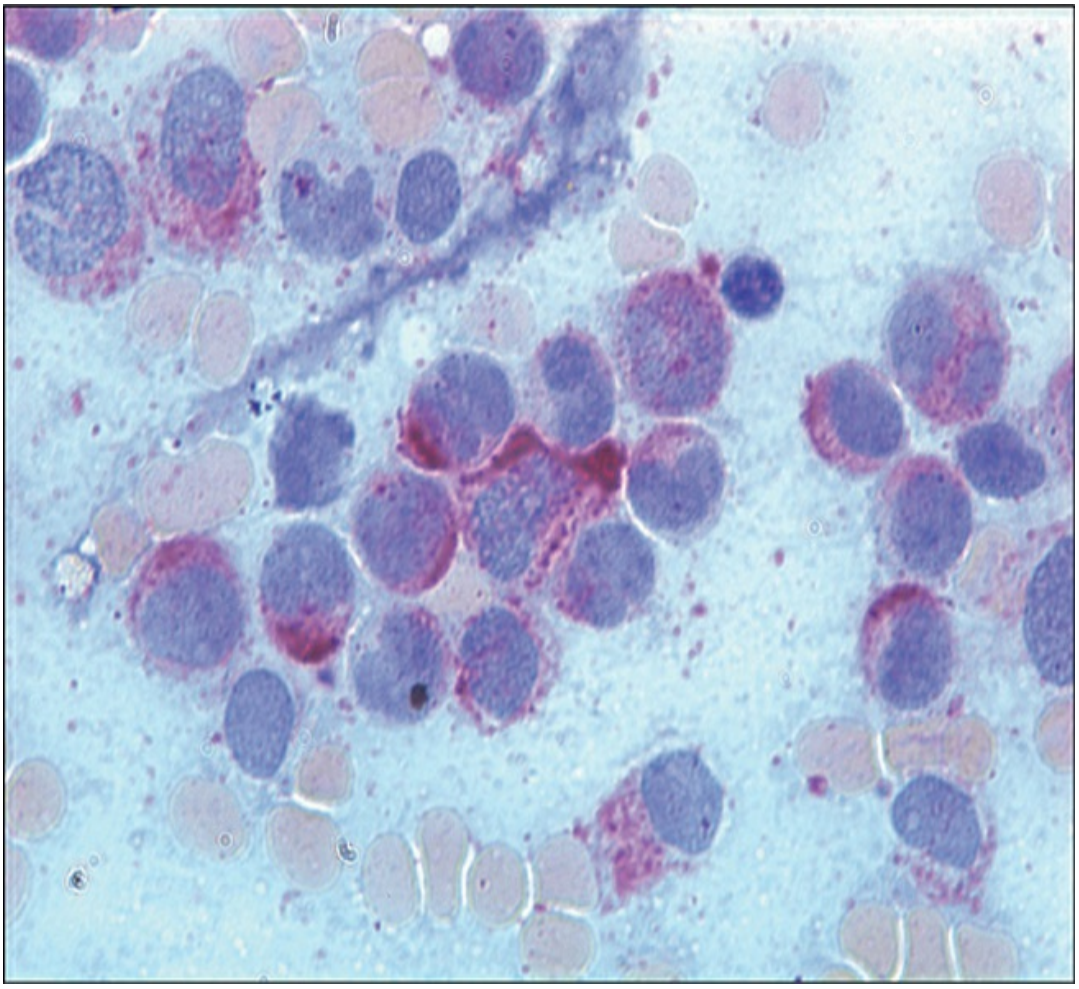


Figure **IIB2-13**

Specific esterase stain. Positive.

Criteria

Peripheral Blood

- Type II myeloblasts may be the predominant cell
- Auer rods typically present

Bone Marrow

- ≥30% blasts
- 30–89% or more of the nonerythroid cells are myeloblasts
- ≥10% are promyelocytes or more mature granulocytes
- Blasts are predominantly type II or type III

Cytochemistry

- ≥3% blasts are myeloperoxidase and Sudan black B positive
- Naphthol AS-D chloroacetate (specific esterase) positive

M3 (Acute Promyelocytic Leukemia—Hypergranular)

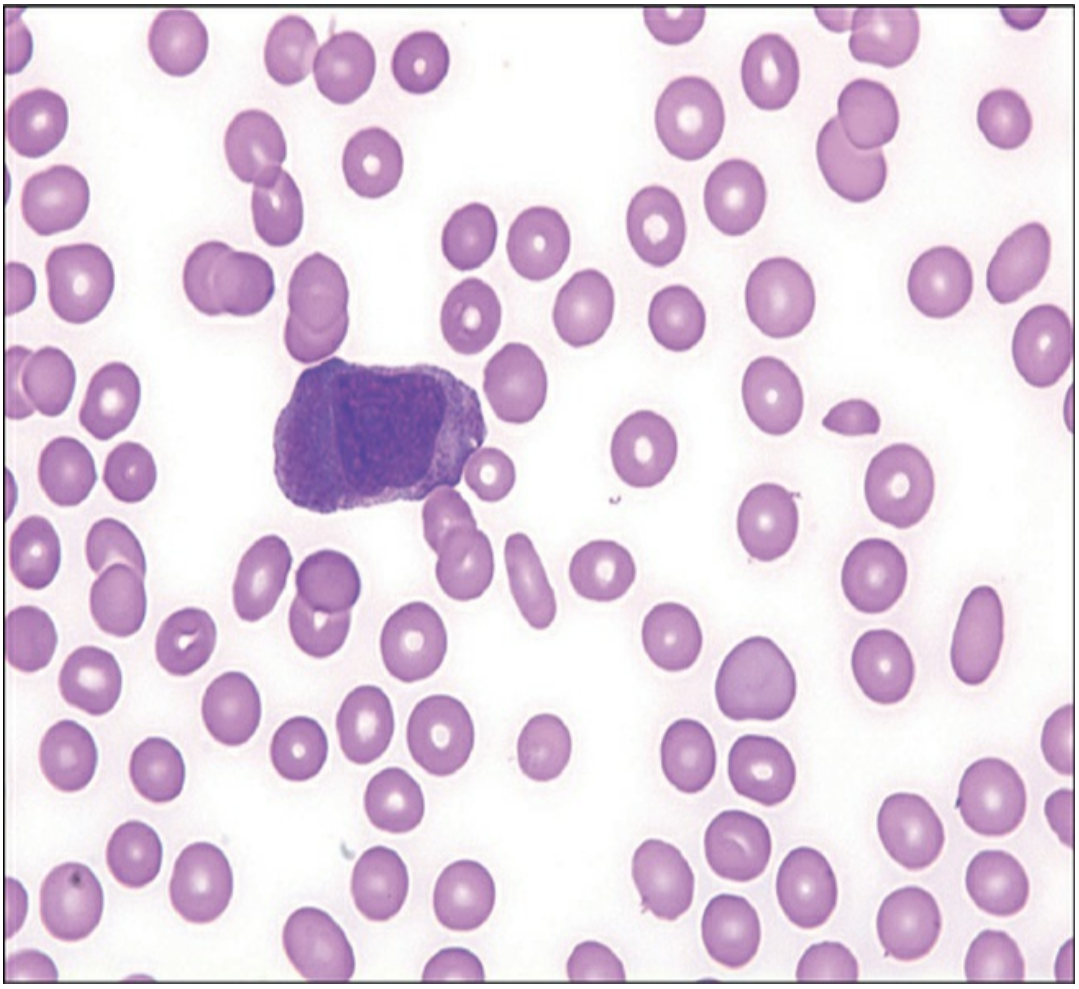


Figure IIB2-14

Peripheral blood smear.

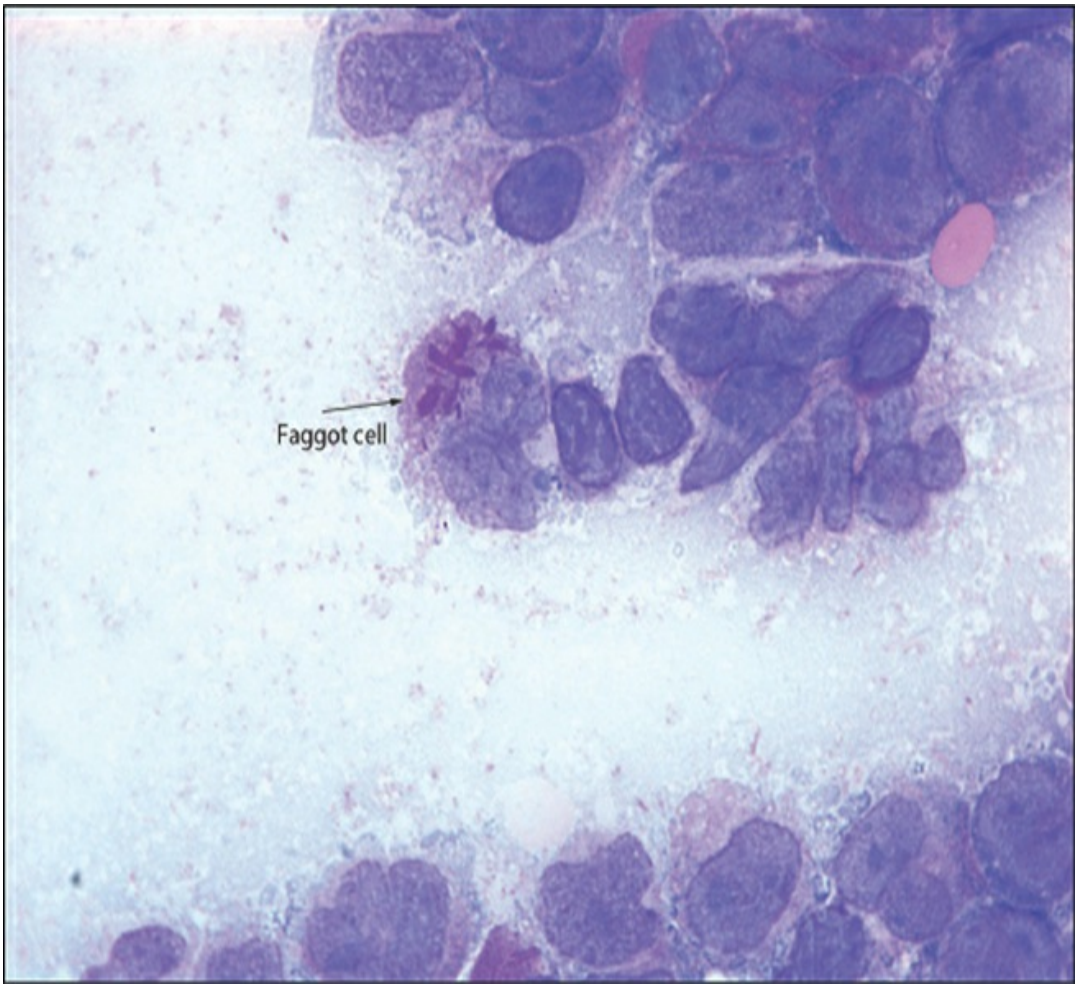


Figure **IIB2-15**

Bone marrow smear.

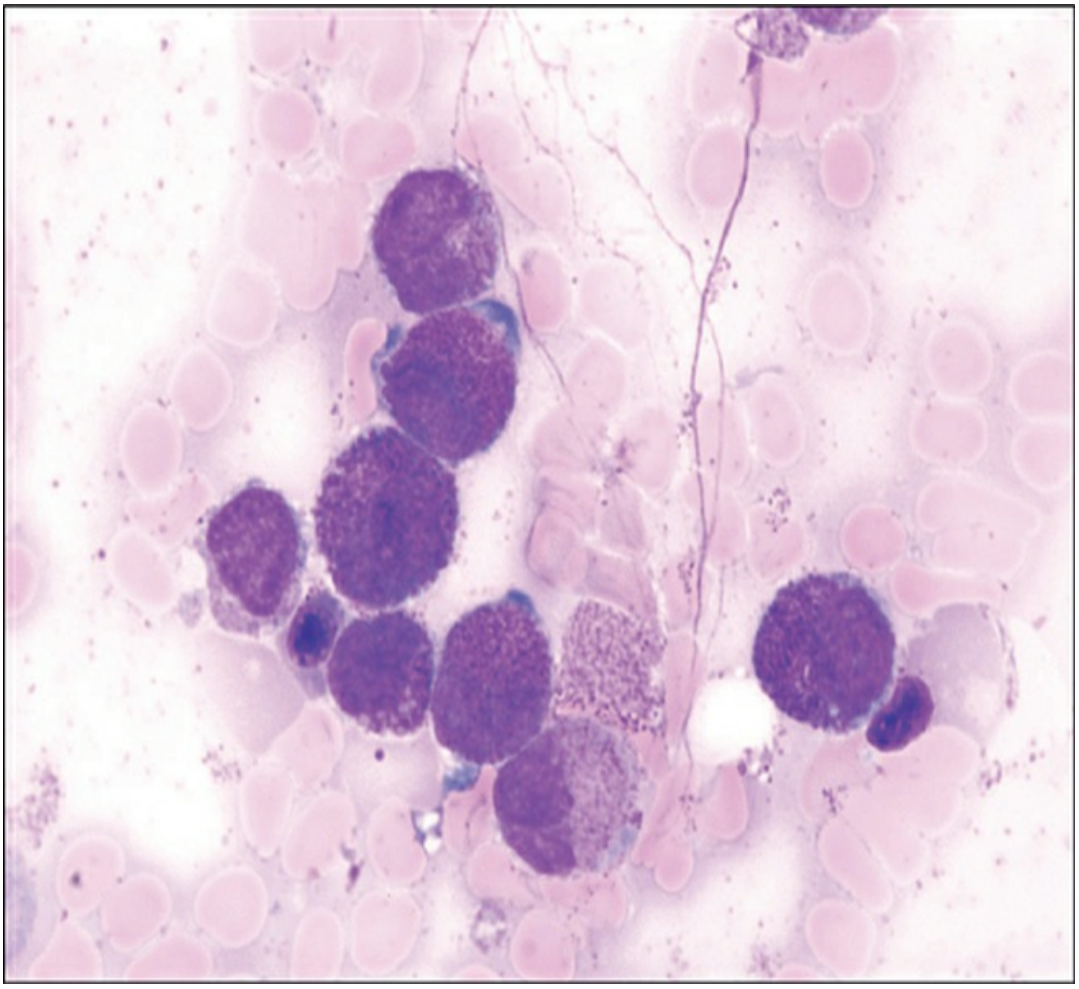


Figure **IIB2-16**

Bone marrow smear.

Criteria

- 70–80% of cases are hypergranular

Peripheral Blood

- Blasts and promyelocytes show heavy granulation and multiple Auer rods
- White blood cell count is usually decreased <5.0 × 10^9/L, but the range is 3.0–15.0 × 10^9/L
- Auer rods range from 10 to 20 per cell (faggot cells) and the rods may be intertwined or single. Few Auer rods are possible

Bone Marrow

- Most of the cells are abnormal promyelocytes with heavy azurophilic granulation
- Multiple Auer rods found in promyelocytes (faggot cells)

M3v (Acute Promyelocytic Leukemia —Microgranular Variant)

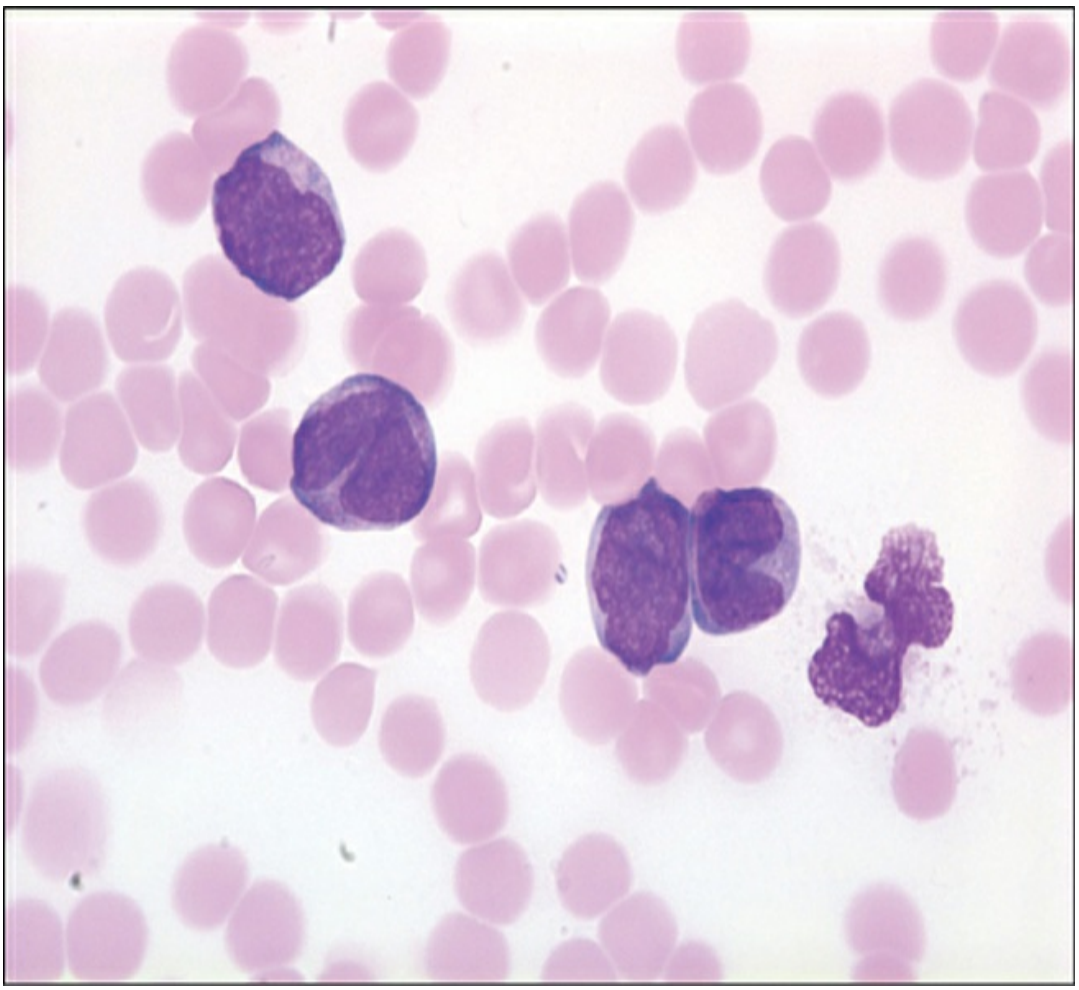


Figure IIB2-17

Peripheral blood smear.

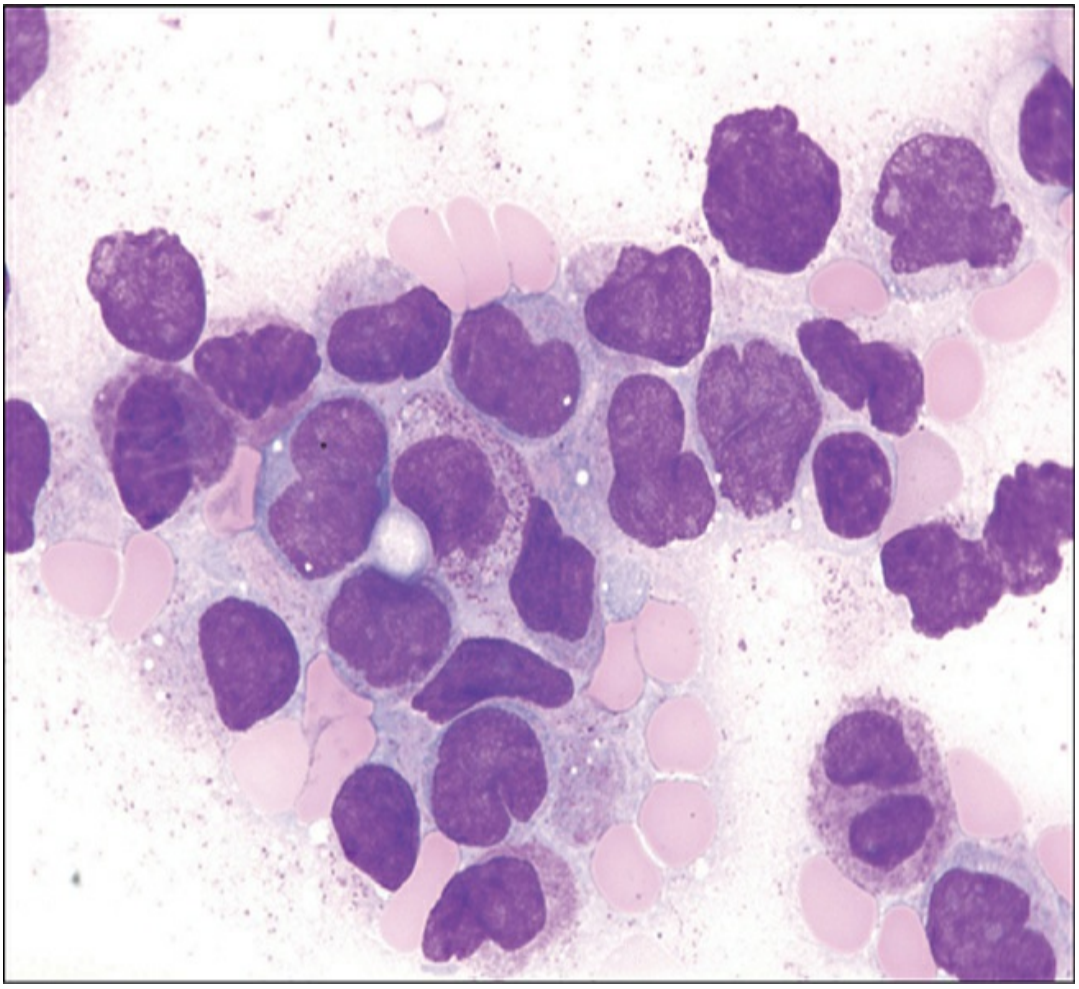


Figure **IIB2-18**

Bone marrow smear.

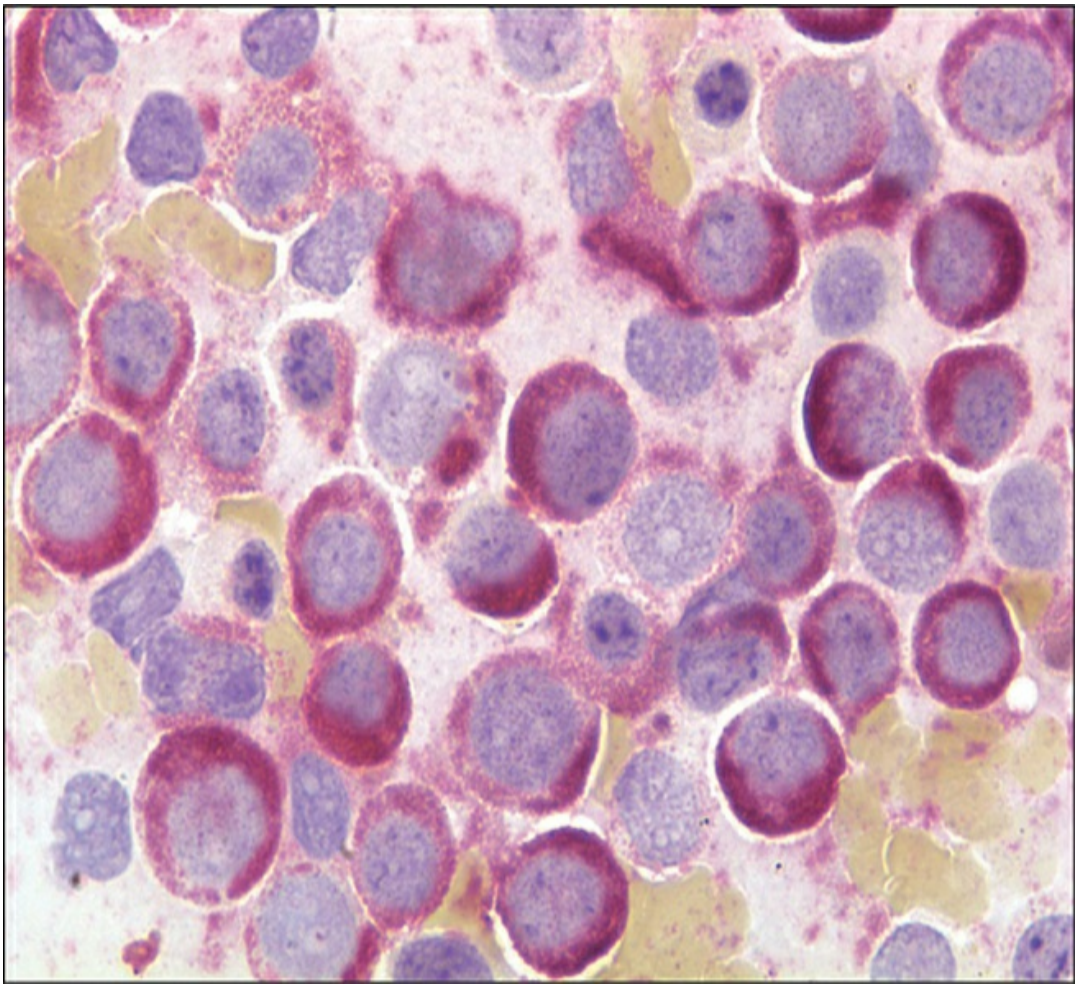


Figure **IIB2-19**

Specific esterase stain. Positive.

Criteria

- 20–30% of cases are microgranular

Peripheral Blood

- White blood cells are markedly increased
- Promyelocytes are usually bilobed and the cytoplasm contains only a few granules

Bone Marrow

- Azurophilic granules are small and difficult to see with light microscopy (<250 nm)
- Promyelocytes are large with a lower N/C ratio

- The nucleus is usually lobulated, irregular, folded, bilobed, or monocytoid in appearance

Cytochemistry

- Myeloperoxidase, Sudan black B, and specific esterase positive

M4 (Acute Myelomonocytic Leukemia)

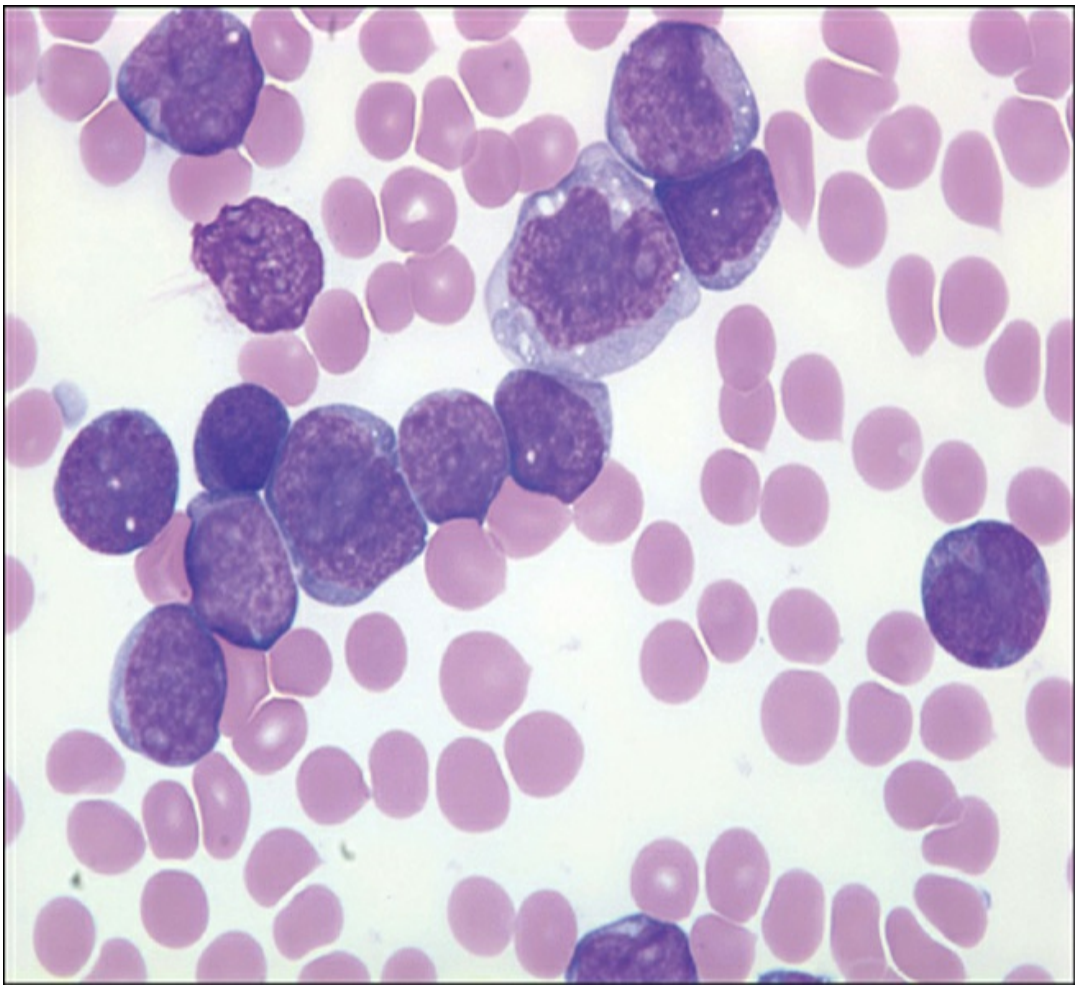


Figure IIB2-20

Peripheral blood smear.

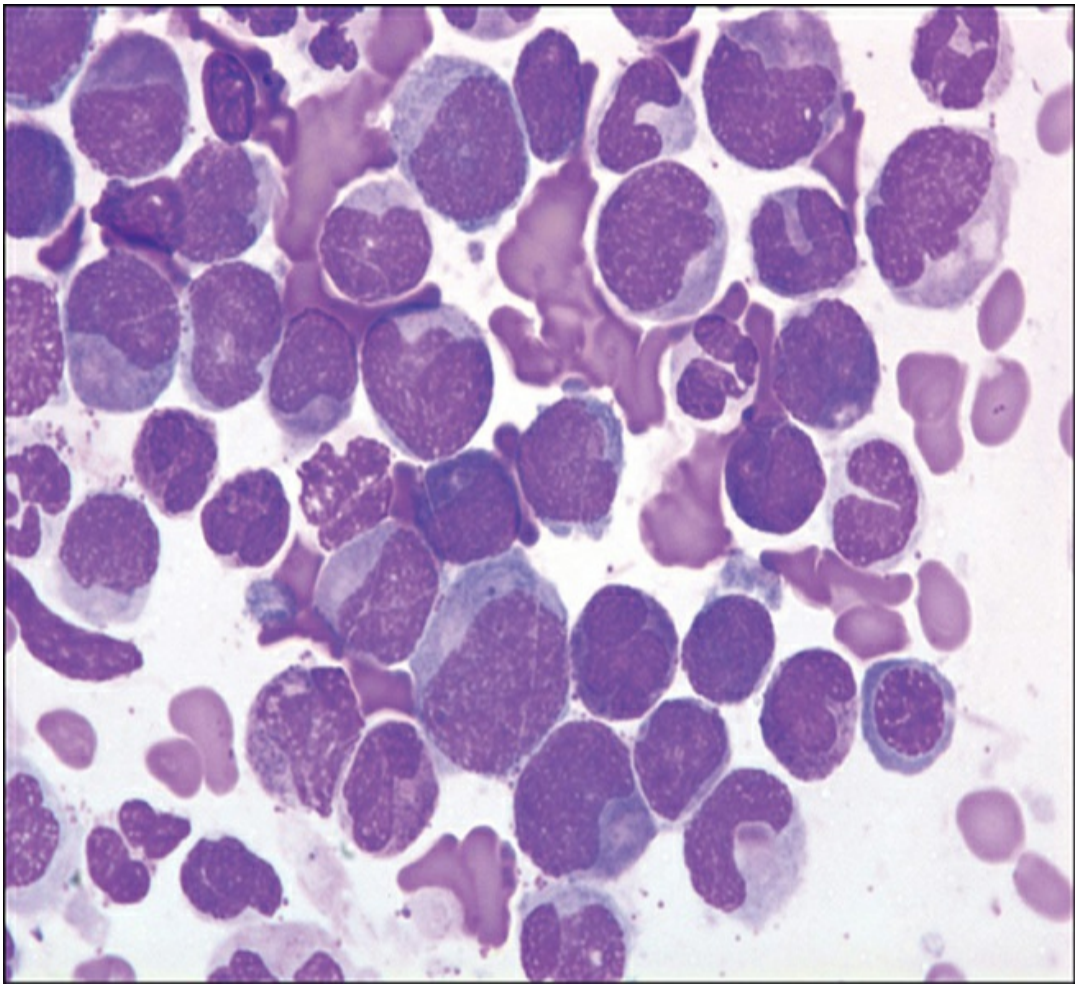


Figure **IIB2-21**

Bone marrow smear.

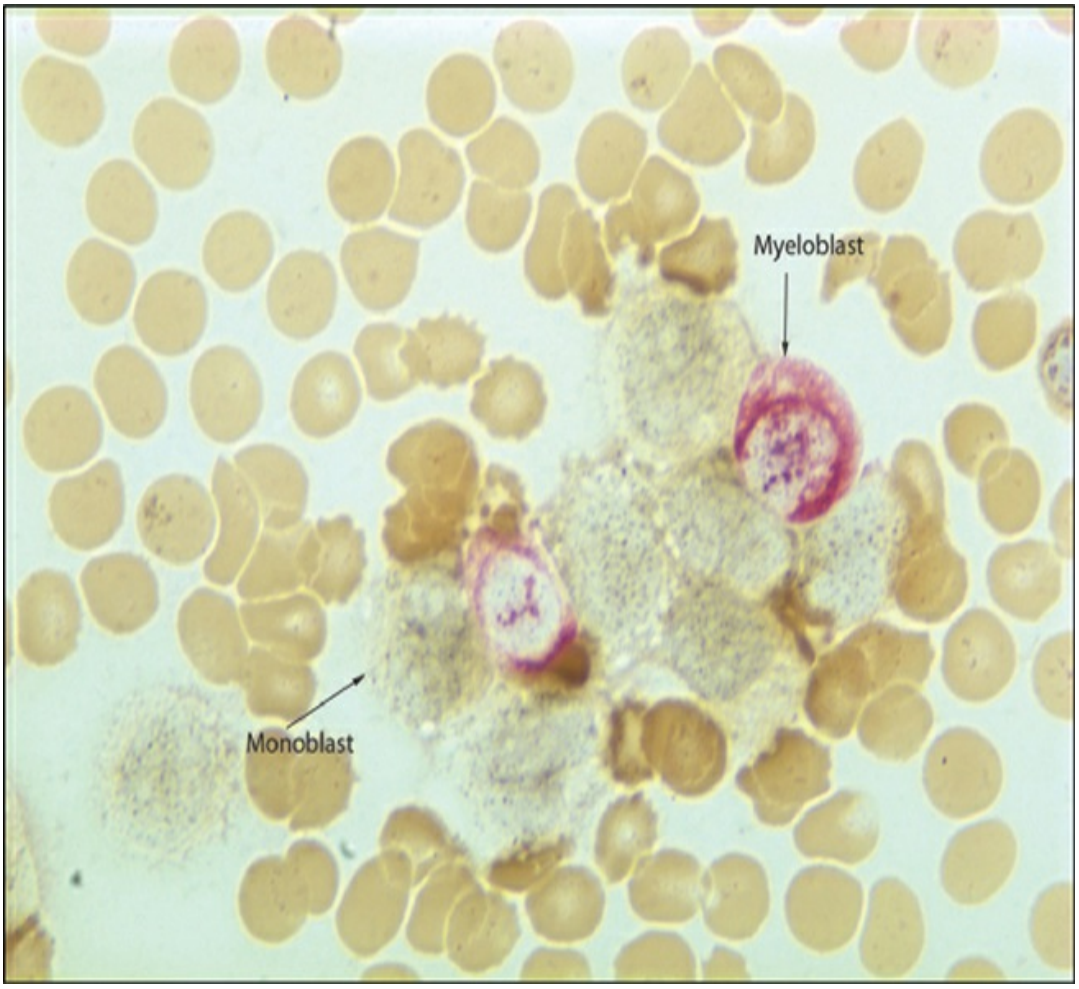


Figure **IIB2-22**

Combined esterase stain. Positive for two cell lines.

Criteria

Peripheral Blood

- White count is usually increased
- Both myelocytic and monocytic differentiations are found
- ≥5 × 10^9/L monocytes and precursors are found
- Auer rods may be present

Bone Marrow

- ≥30% myeloblasts, monoblasts, and promonocytes
- ≥20% granulocytic precursors

- ≥20% monocytic precursors
- If the bone marrow has <20% monocytic component, then it must have a peripheral blood monocytosis of ≥5 × 10^9/L (monocytes and precursors)
- Blast percentage includes type I and type II myeloblasts, monoblasts, and promonocytes

Cytochemistry

- Myeloblasts are positive for myeloperoxidase, Sudan black B, and specific esterase and negative with nonspecific esterases
- Monoblasts and promonocytes are negative or only slightly positive with myeloperoxidase and negative with Sudan black B
- Nonspecific esterase is positive and inhibited by sodium fluoride

$M4_{eo}$ (Acute Myelomonocytic Leukemia With Increased Bone Marrow Eosinophils)

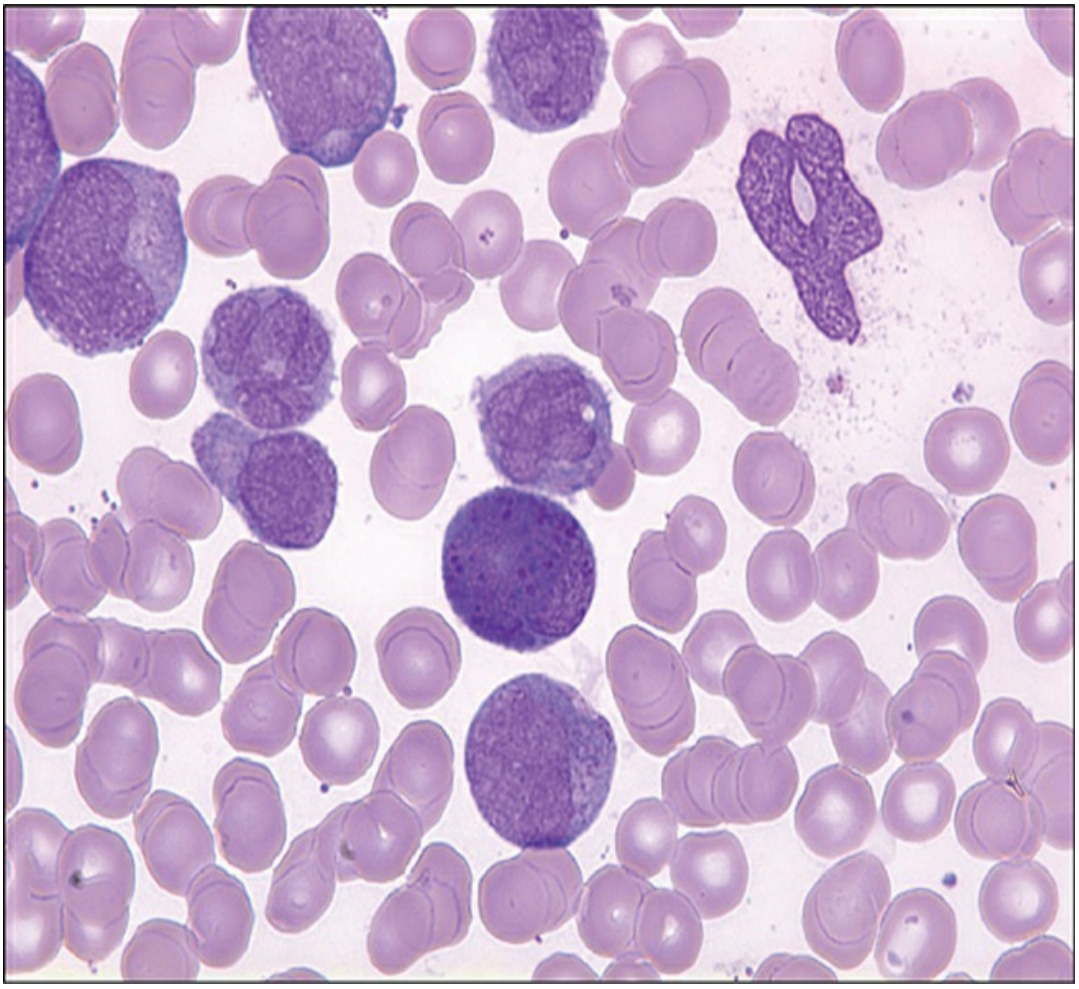


Figure **IIB2-23**

Bone marrow smear.

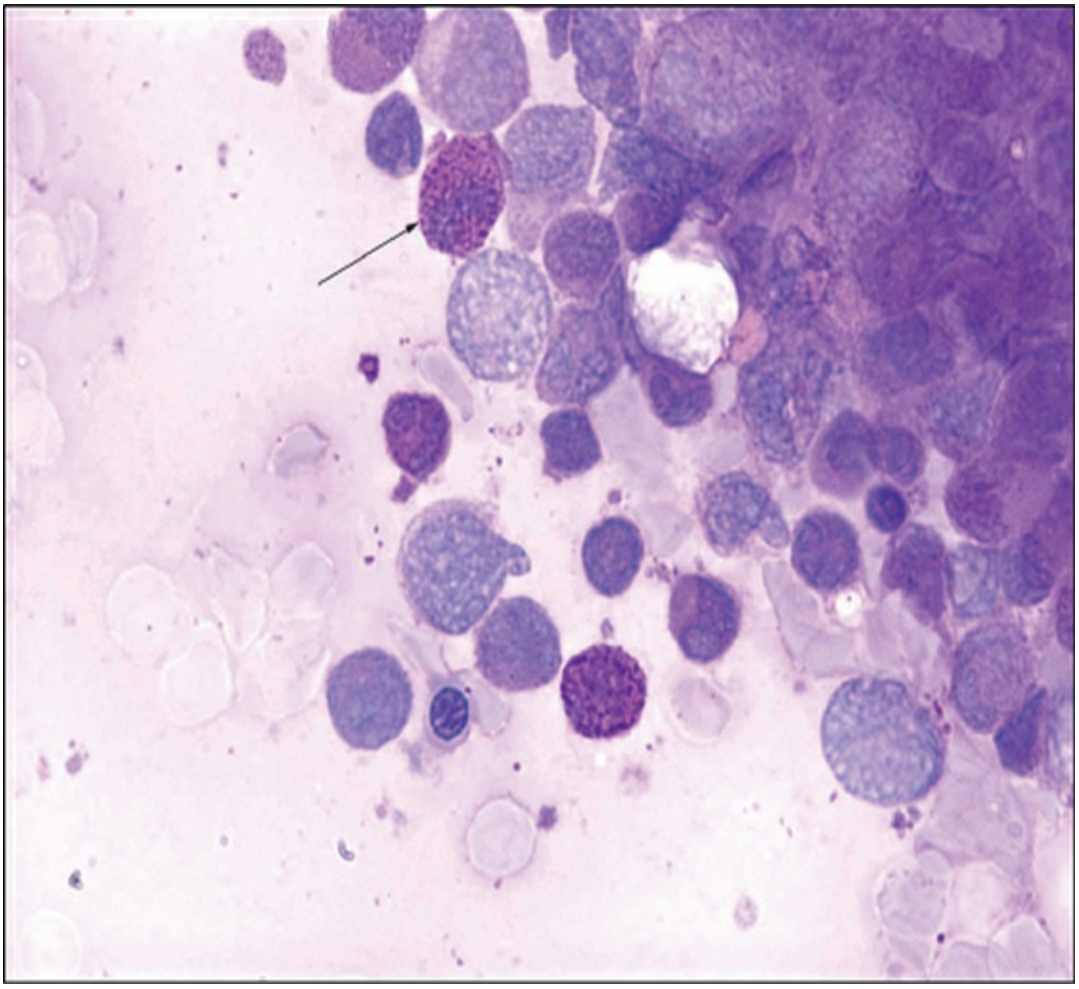


Figure **IIB2-24**

Periodic acid–Schiff stain. Positive.

Criteria

Peripheral Blood

- WBC is usually increased (range 30 × 10^9/L to 100 × 10^9/L)
  - Abnormal eosinophils are not found
  - Myeloblasts and monoblasts present

Bone Marrow

- ≥5% and <30% abnormal eosinophils
- Atypical eosinophils with possible pseudo-Pelger-Huët features in the nuclei and abnormal basophilic granules

Cytochemistry

- Abnormal eosinophils are specific esterase and periodic acid–Schiff positive

M5a (Acute Monoblastic Leukemia)

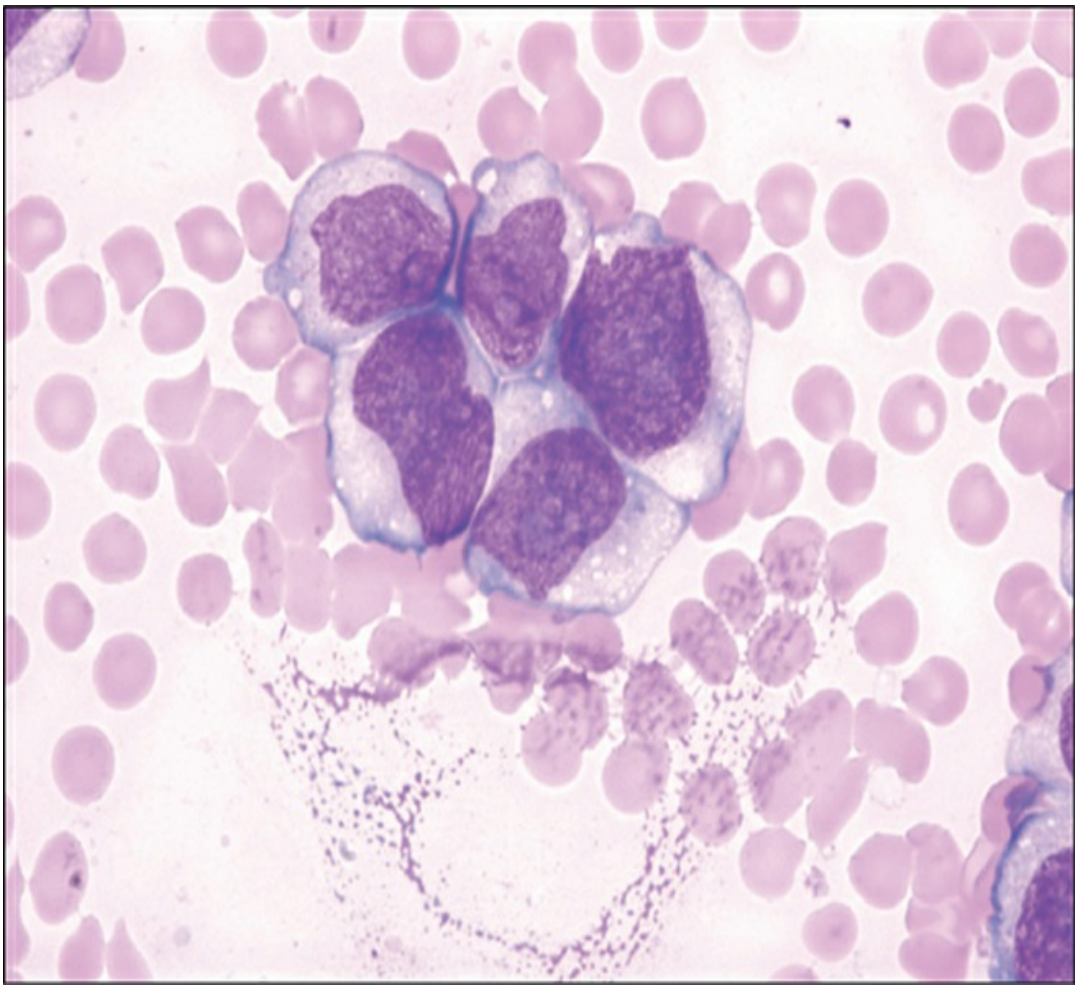


Figure IIB2-25

Peripheral blood smear.

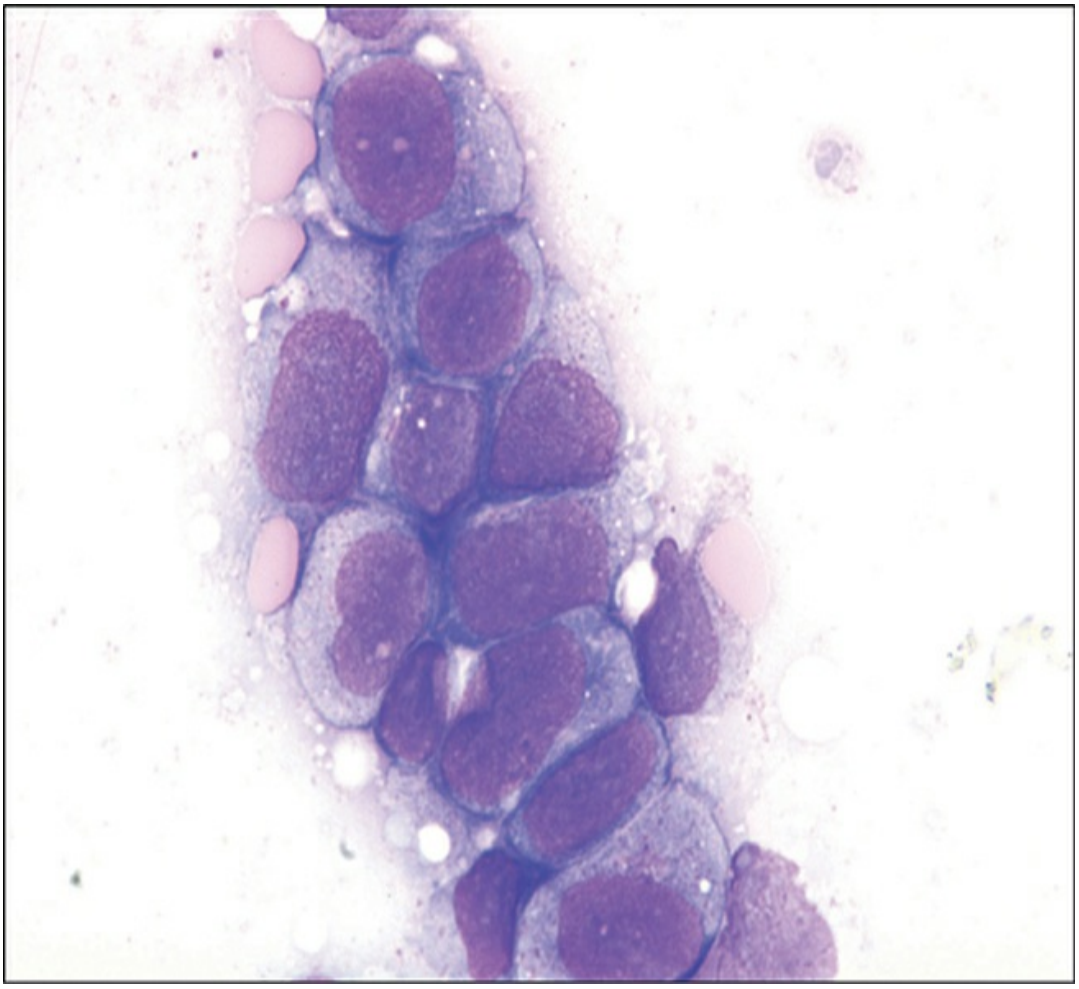


Figure **IIB2-26**

Bone marrow smear.

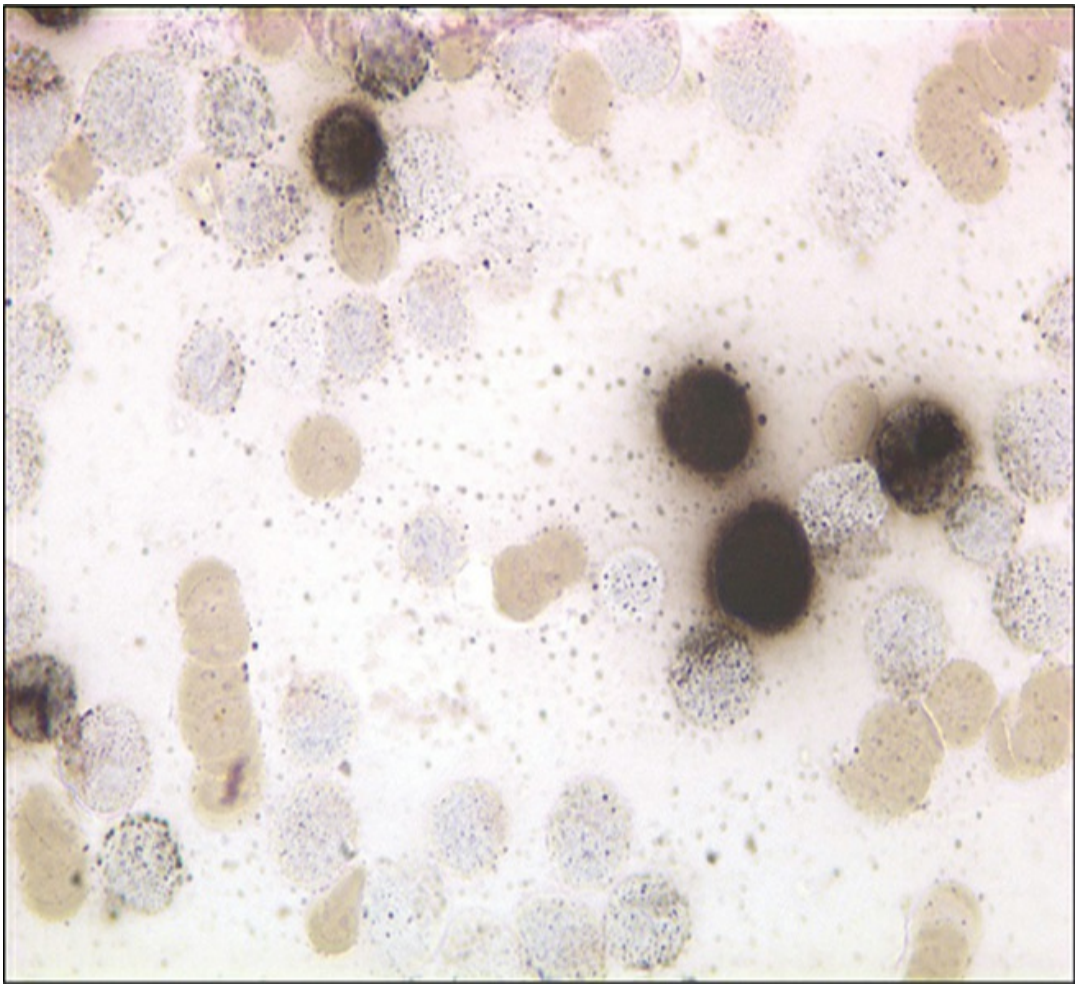


Figure **IIB2-27**

Nonspecific esterase stain. Positive.

Criteria

- Acute leukemia with almost total monocytic dominance

Peripheral Blood

- White blood cells are usually increased
- Blast morphology is variable
- Auer rods are usually absent

Bone Marrow

- <20% granulocytic precursors
- ≥80% are typically monoblasts
- Auer rods are usually absent

Cytochemistry

- <20% are myeloperoxidase positive
- ≥80% are nonspecific esterase positive
- Naphthol AS-D chloroacetate negative
- Naphthol AS-D acetate esterase is ++++ (strong positivity) and inhibited by sodium fluoride (1+ or negative)

M5b (Acute Monocytic Leukemia)

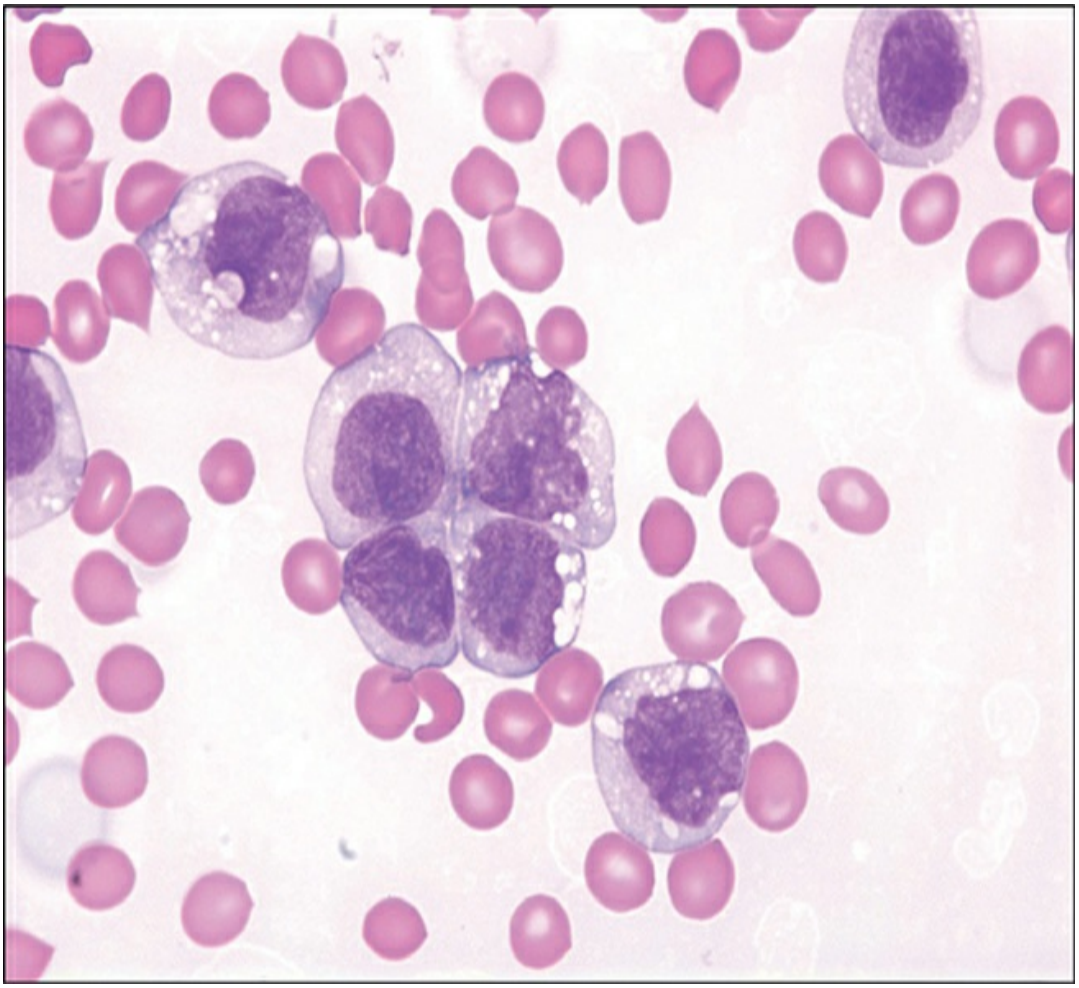


Figure IIB2-28

Peripheral blood smear.

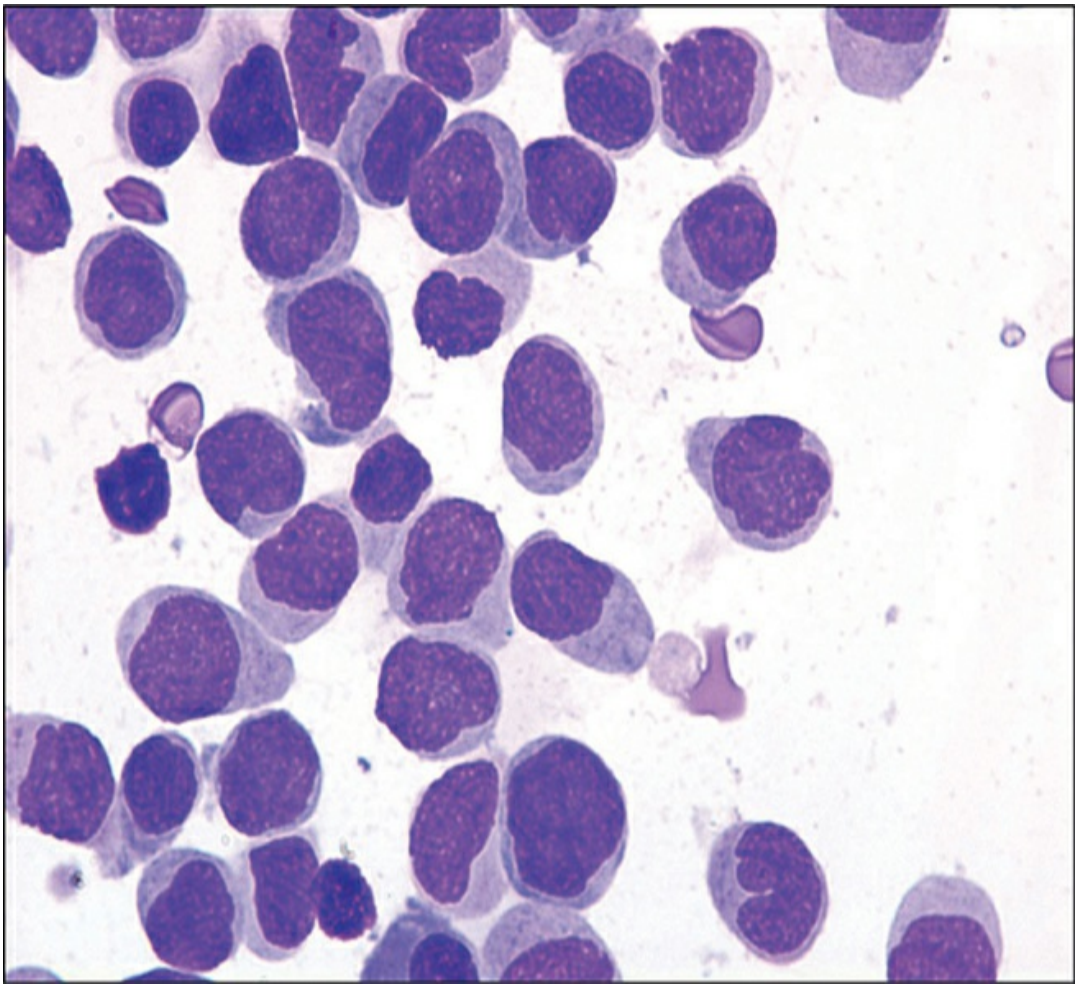


Figure **IIB2-29**

Bone marrow smear.

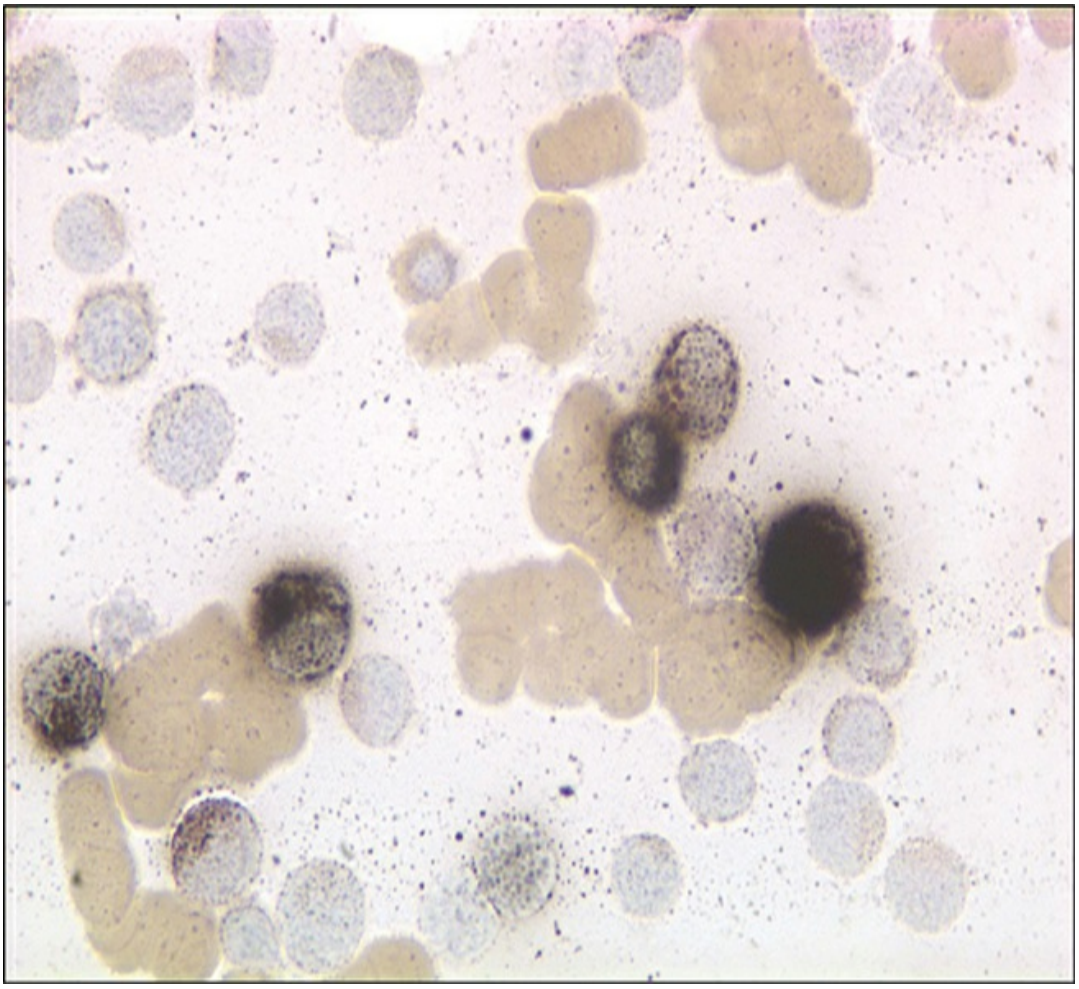


Figure **IIB2-30**

Nonspecific esterase stain. Positive.

Criteria

Peripheral Blood

- Monocytosis with the promonocyte as the predominant cell

Bone Marrow

- ≥80% immature monocytic component with the promonocyte as the predominant cell
- <20% are the granulocytic component

Cytochemistry

- <20% are myeloperoxidase positive cells

- Promonocytes may show some weak positivity with myeloperoxidase and are Sudan black B negative
- ≥80% of the cells are nonspecific esterase positive
- ≥80% of the cells are nonspecific esterase negative with sodium fluoride inhibition

M6a (Erythroleukemia)

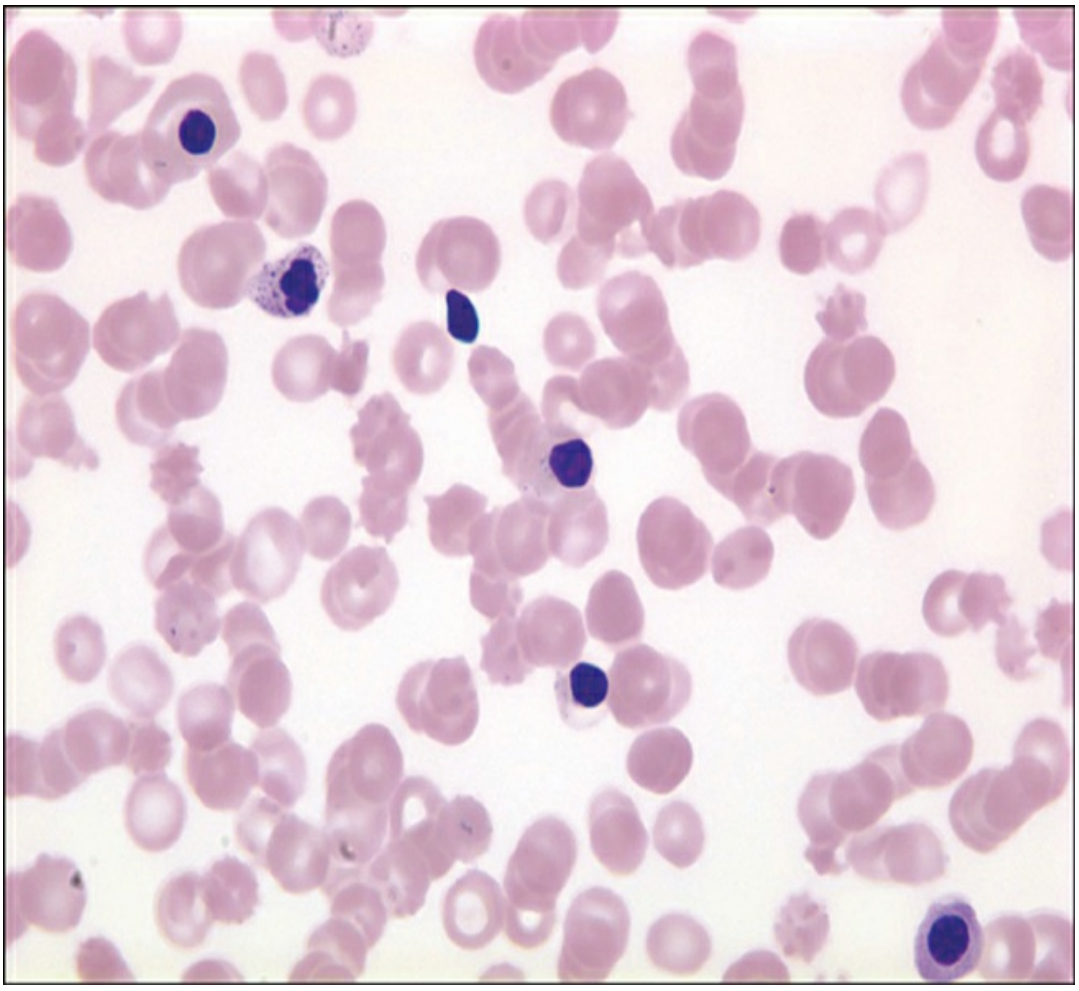


Figure IIB2-31

Peripheral blood smear.

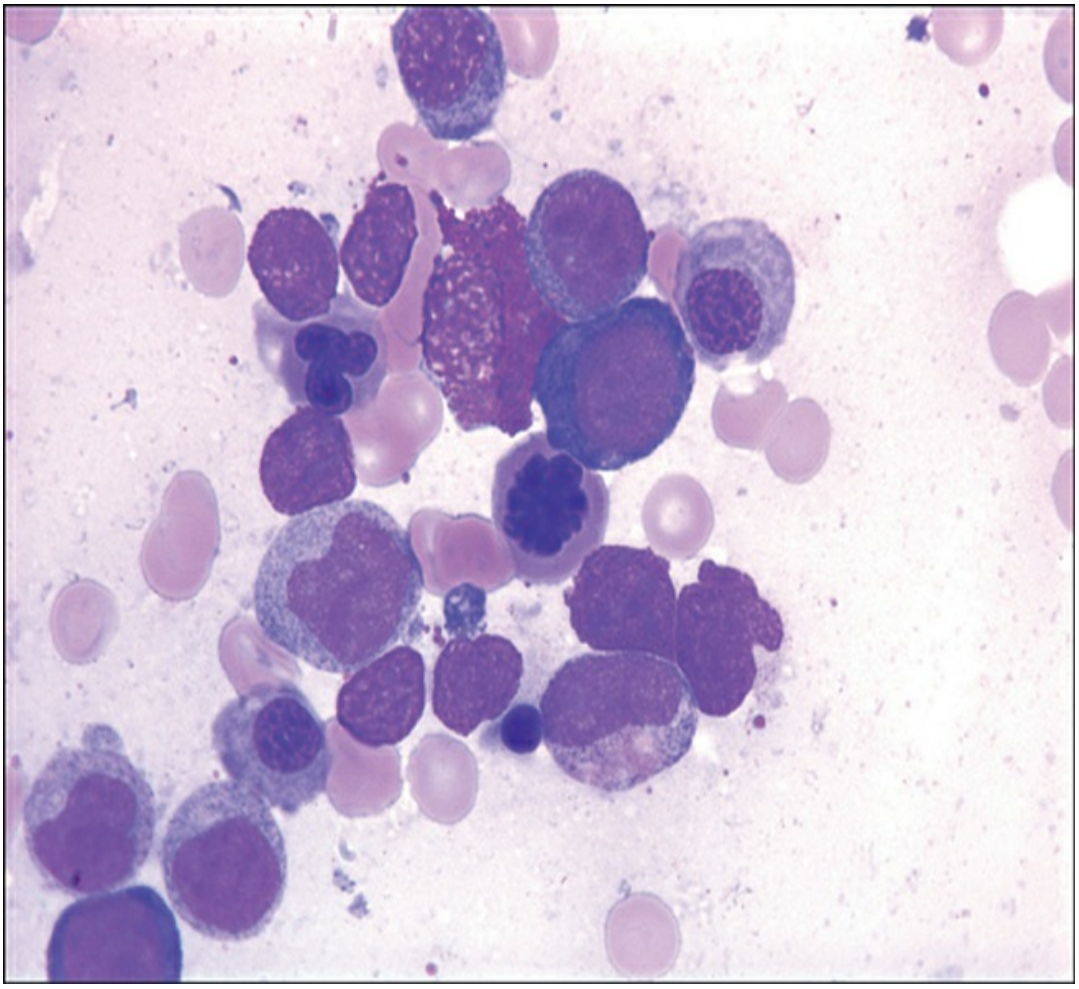


Figure **IIB2-32**

Bone marrow smear.

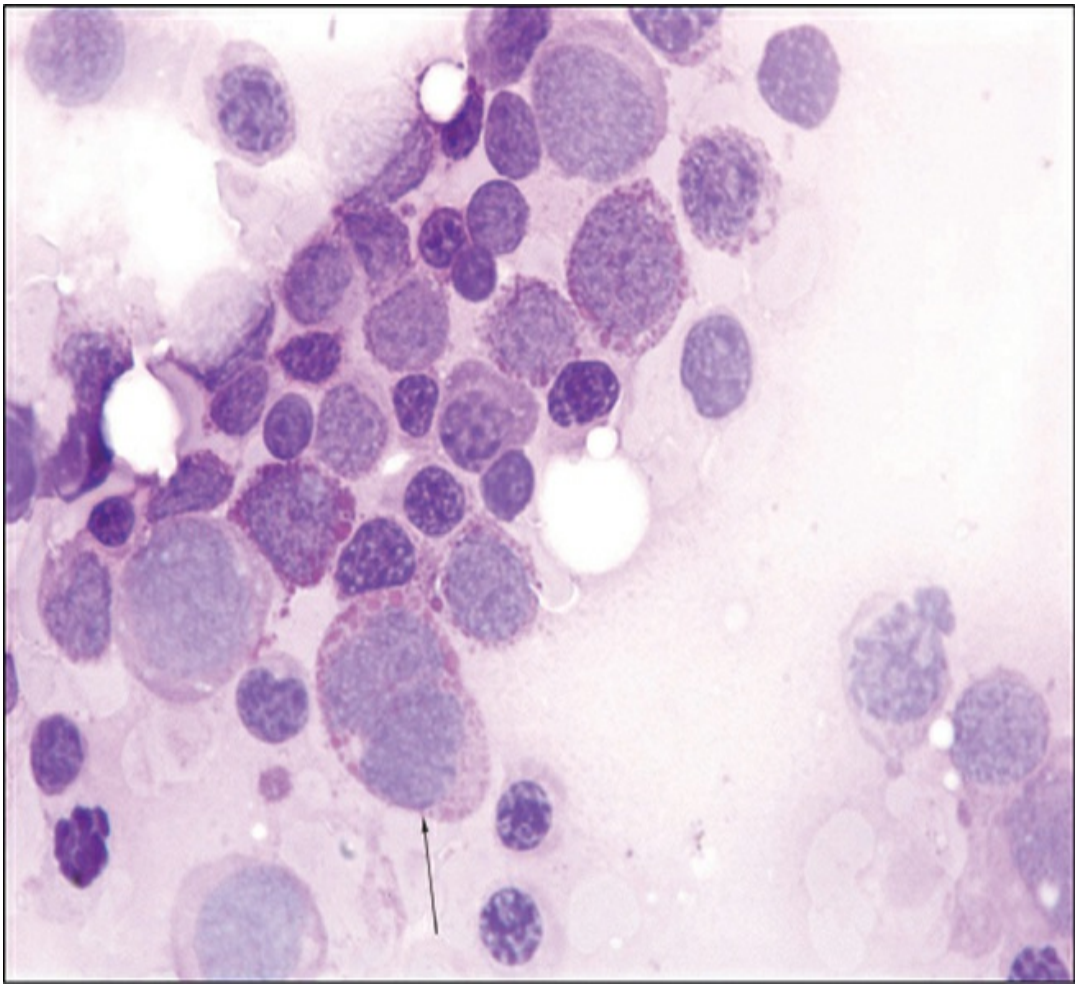


Figure **IIB2-33**

Periodic acid–Schiff stain. Positive.

Criteria

- Usually exhibits three phases and there is more myeloid involvement as the disease progresses

Peripheral Blood

- Normocytic/normochromic to macrocytic/normochromic anemia
- Anisocytosis, poikilocytosis, basophilic stippling, and nucleated red blood cells

Bone Marrow

- Acute and abnormal proliferation of erythroid and

myeloid precursors

- ≥50% erythroblasts (all nucleated cells)
- ≥30% myeloblasts (nonerythroid cells) type I and type II
- Trilineage dysplasia common—dyserythropoiesis, dysmegakaryopoiesis, and dysgranulopoiesis

Cytochemistry

- Periodic acid–Schiff positive in early erythrocytic precursors
- Myeloperoxidase and Sudan black B show ≥3% positive in myeloblasts

M6b (Pure Erythroid Leukemia)

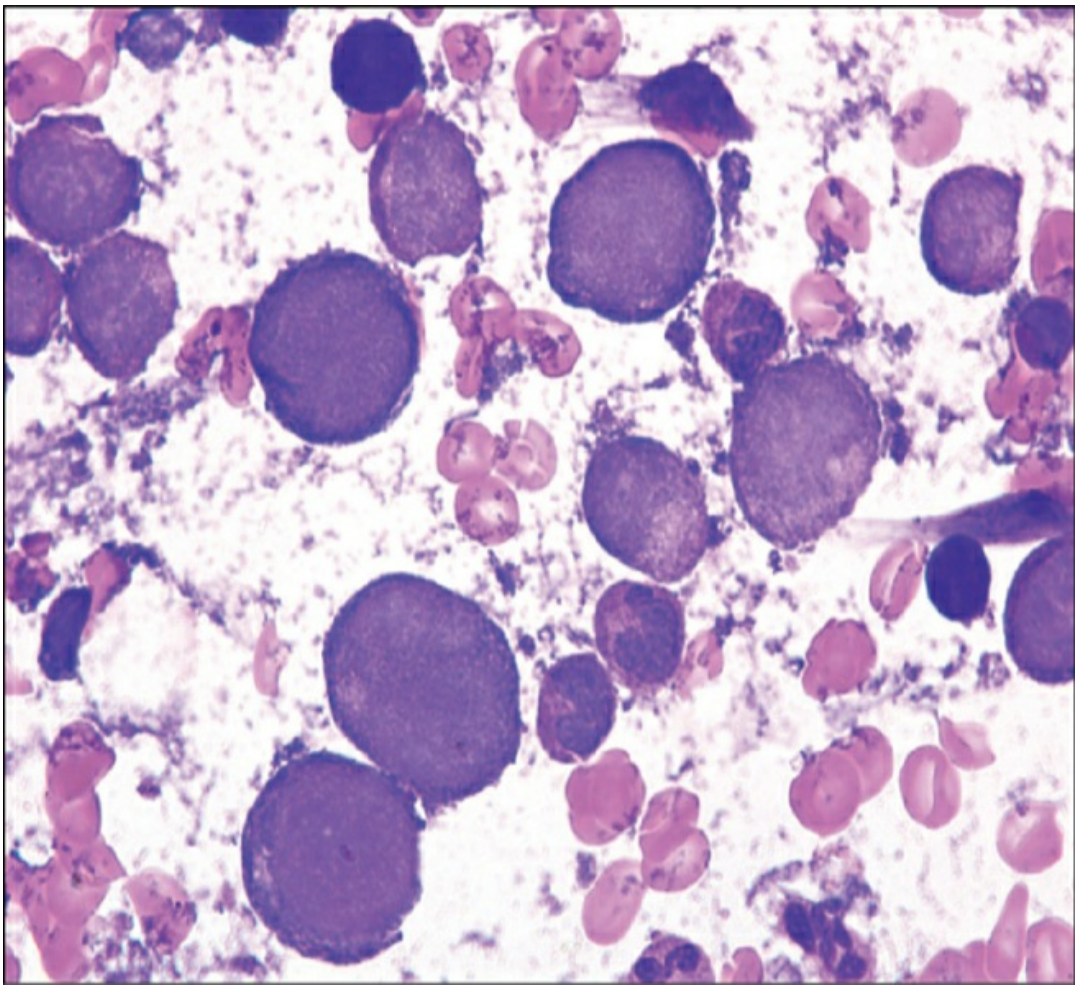


Figure IIB2-34

Bone marrow smear.

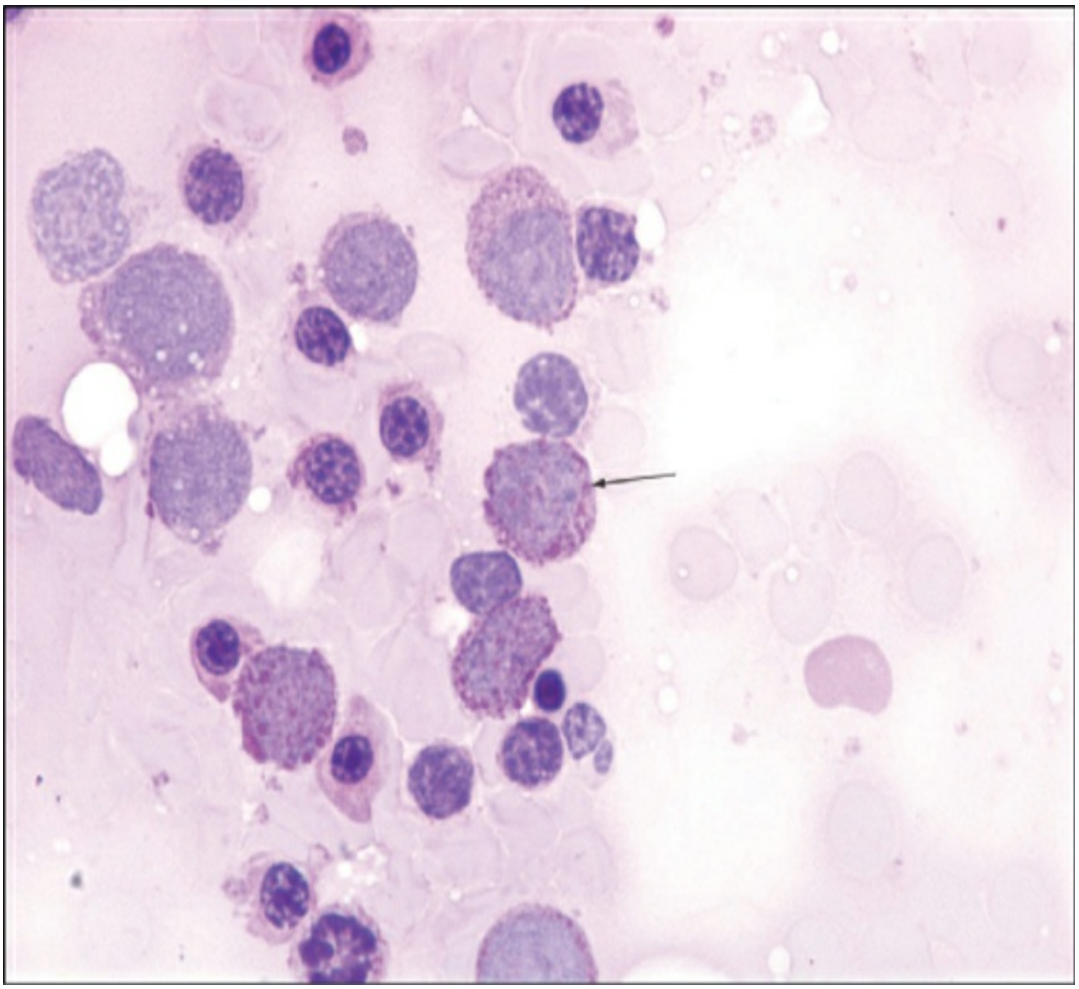


Figure IIB2-35

Periodic acid–Schiff stain. Positive.

Criteria

- Erythroid cell line malignancy with no myeloid involvement

Peripheral Blood

- Platelets are decreased
- Usually a macrocytic anemia

Bone Marrow

- ≥80% of the cell are of erythroid lineage (≥30% must be proerythroblastic)

Cytochemistry

- Myeloperoxidase, nonspecific esterase, and Sudan black B negative
- Block positivity with the periodic acid–Schiff

M7 (Acute Megakaryoblastic Leukemia)

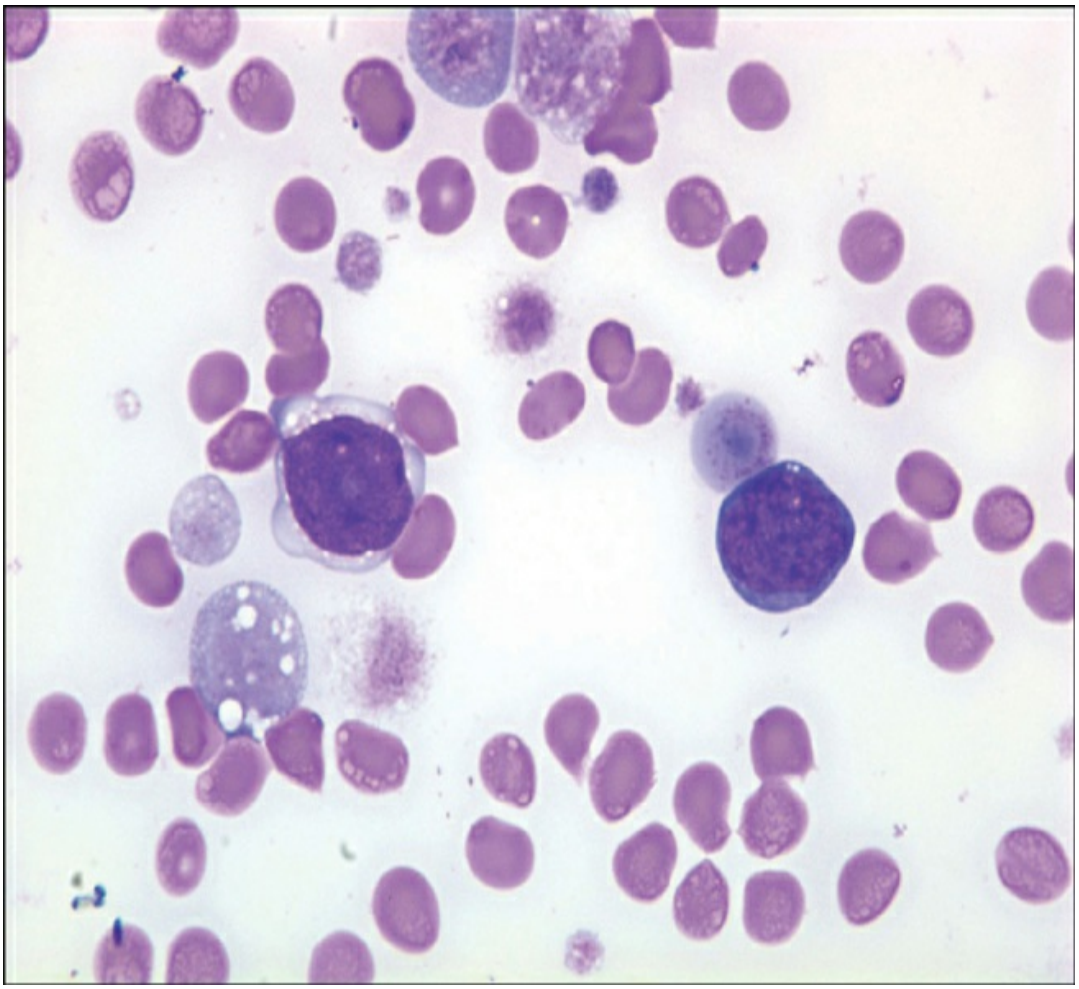


Figure IIB2-36

Peripheral blood smear.

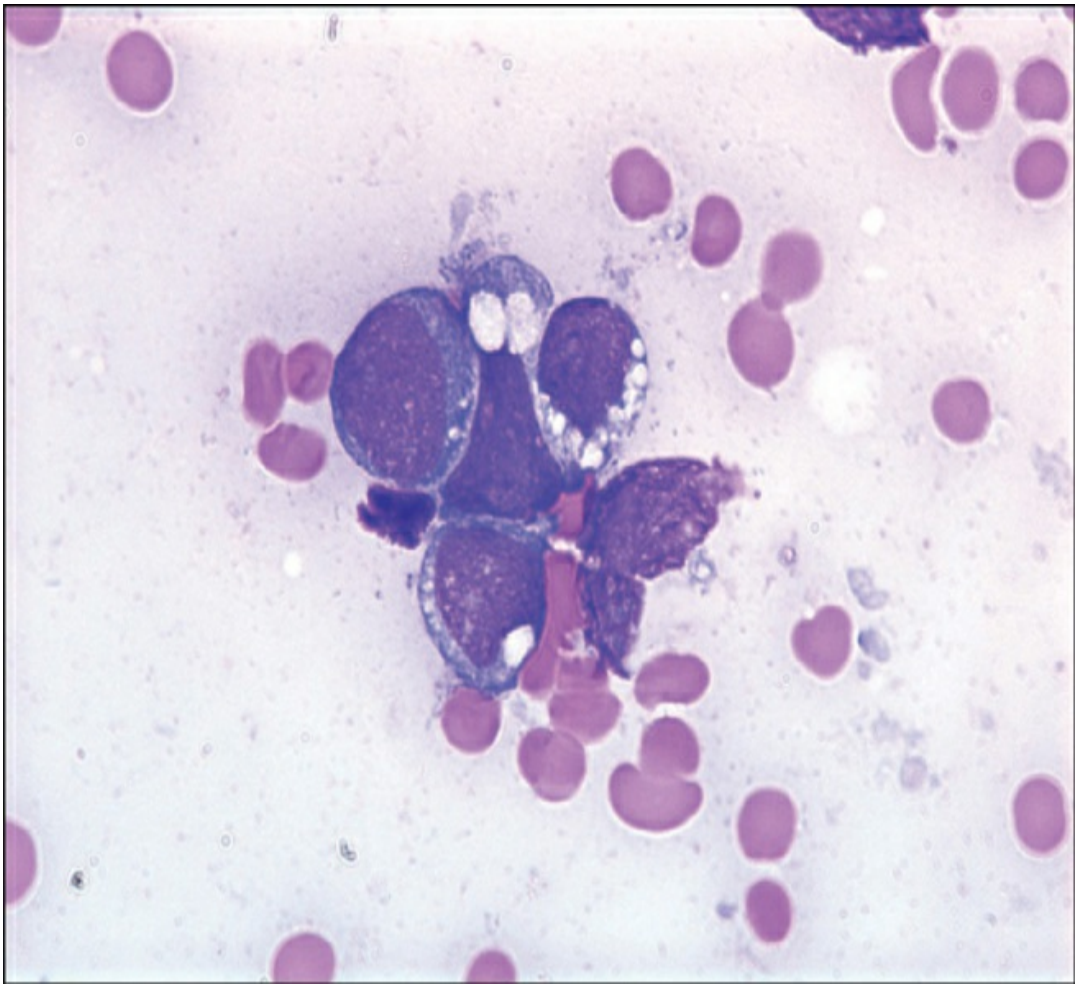


Figure **IIB2-37**

Bone marrow smear.

Criteria

Peripheral Blood

- Variable white blood cell count but usually decreased
- Normocytic/normochromic anemia
- Platelets are variable, bizarre, and atypical

Bone Marrow

- ≥30% blasts (usually hard to get an aspirate for quantitation of blasts)
- ≥50% megakaryocytic cells (megakaryoblasts, promegakaryocytes, and megakaryocytes)

- Megakaryoblasts are highly pleomorphic
- Small round cells with scant cytoplasm and dense heavy chromatin or larger vacuolated blasts

Cytochemistry

- Myeloperoxidase and Sudan black B negative
- Periodic acid–Schiff positive
- Nonspecific esterase (acetate) positive
- Nonspecific esterase (butyrate) negative

L1 (Precursor Lymphoblastic Leukemia)

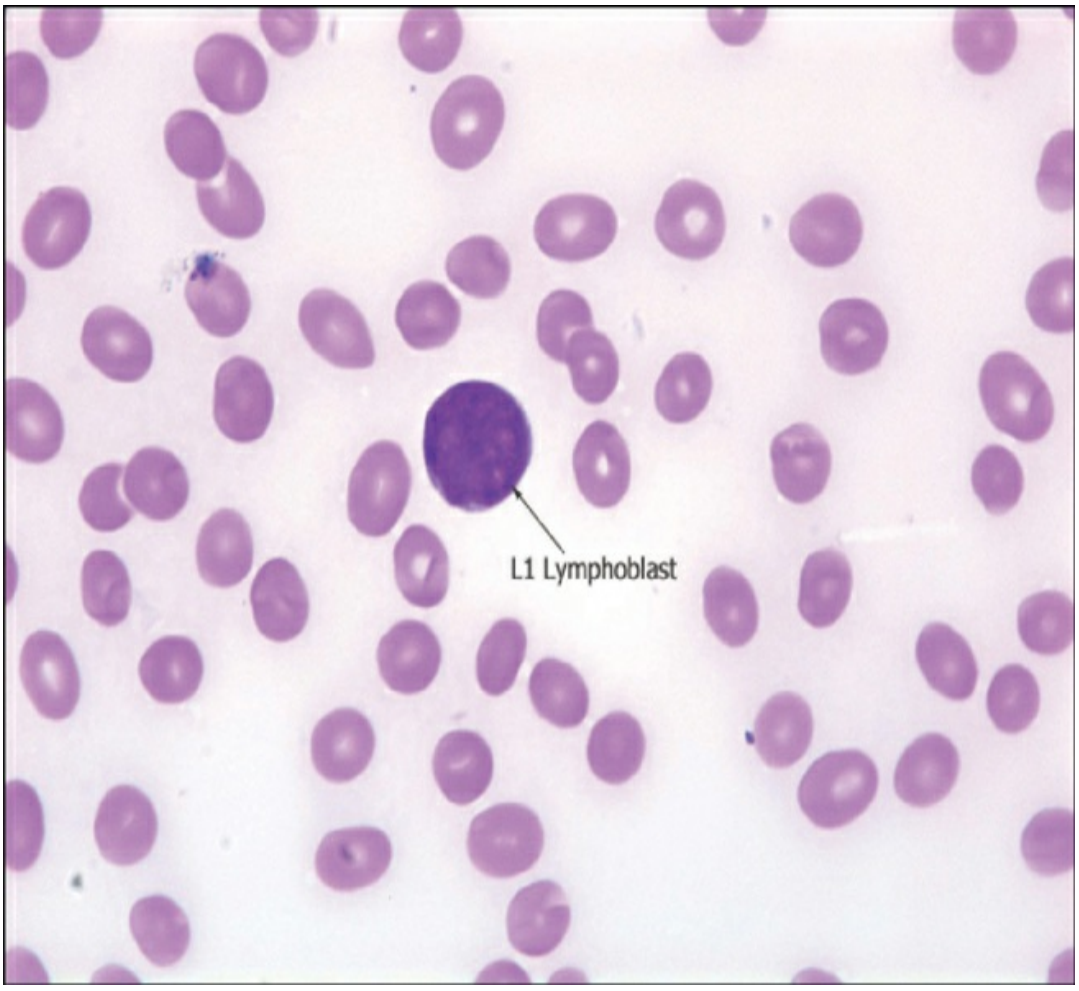


Figure IIB2-38

Peripheral blood smear.

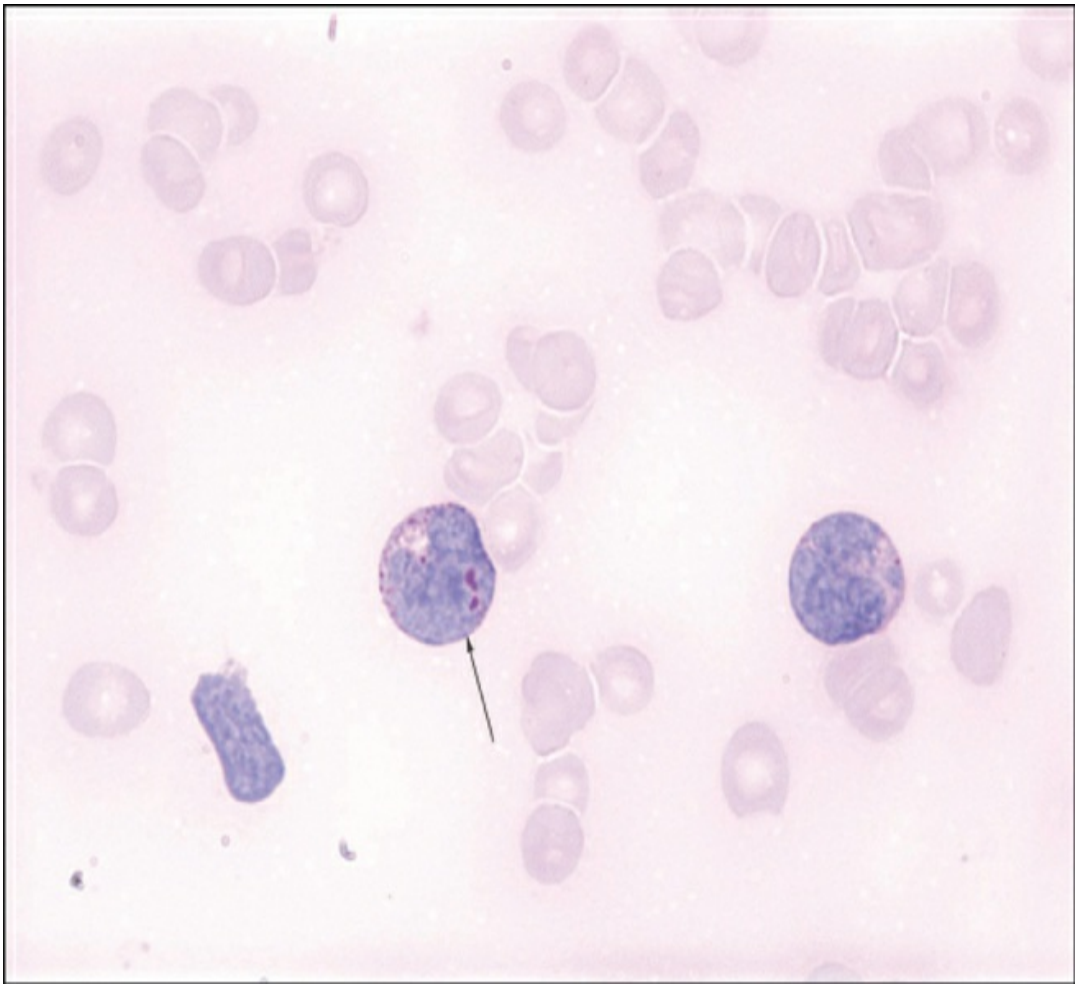


Figure **IIB2-39**

Periodic acid–Schiff stain. Positive.

Criteria

- Mutation of a single lymphoid stem cell causing proliferation of malignant lymphoblasts

Peripheral Smear

- Normocytic/normochromic anemia
- Decreased platelets
- White blood cells may be increased, decreased, or normal

Bone Marrow

- Hypercellular

- ≥25% blasts that are predominantly small blasts, up to twice the size of a normal small lymphocyte, nucleoli are not present and the cytoplasm is scant and only slightly or moderately basophilic

Cytochemistry

- Sudan black B, peroxidase, specific esterase, and nonspecific esterase are negative
- Large block positivity with the periodic acid–Schiff
- Focal positivity with acid phosphatase in T-cell blasts
- Terminal deoxynucleotidyl transferase is positive in 90–95% in L1 and L2 and negative in L3

L2 (Precursor Lymphoblastic Leukemia)

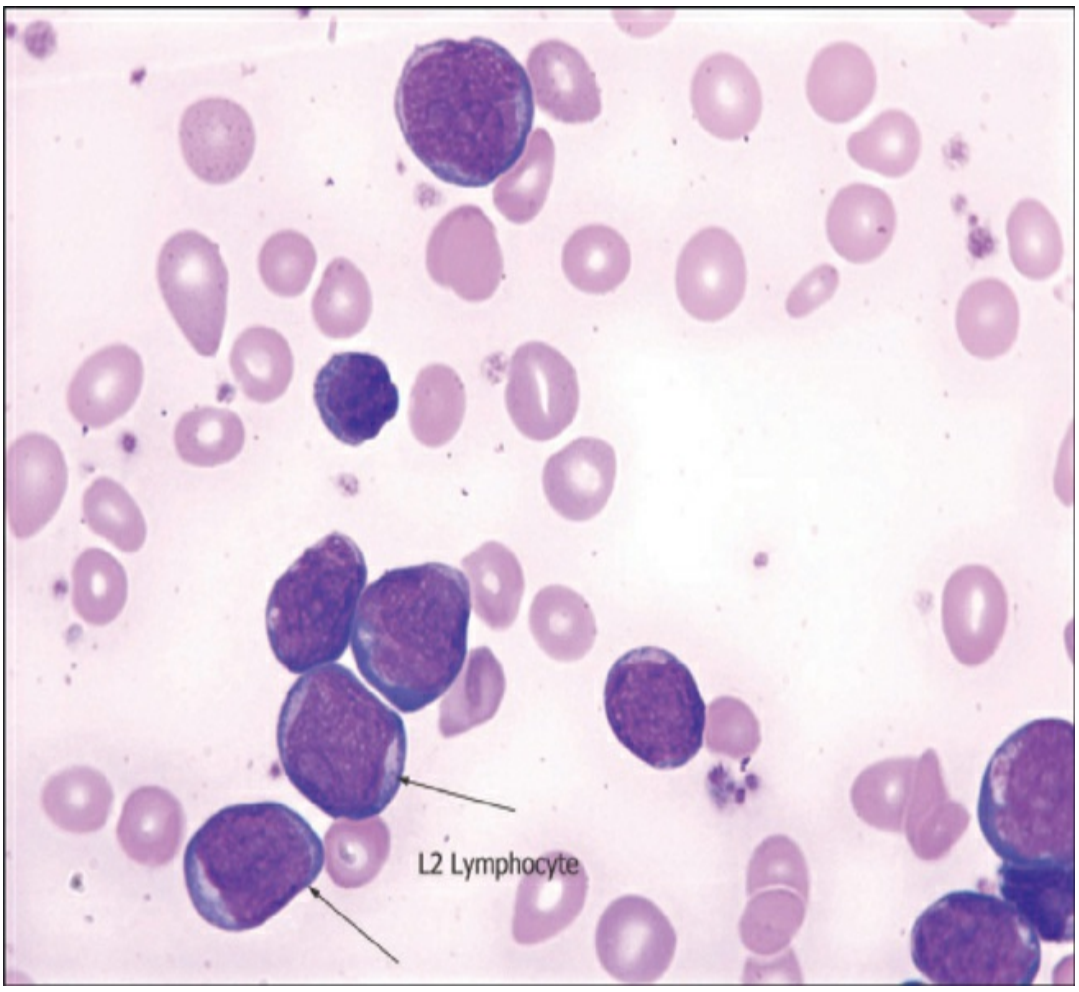


Figure IIB2-40

Peripheral blood smear.

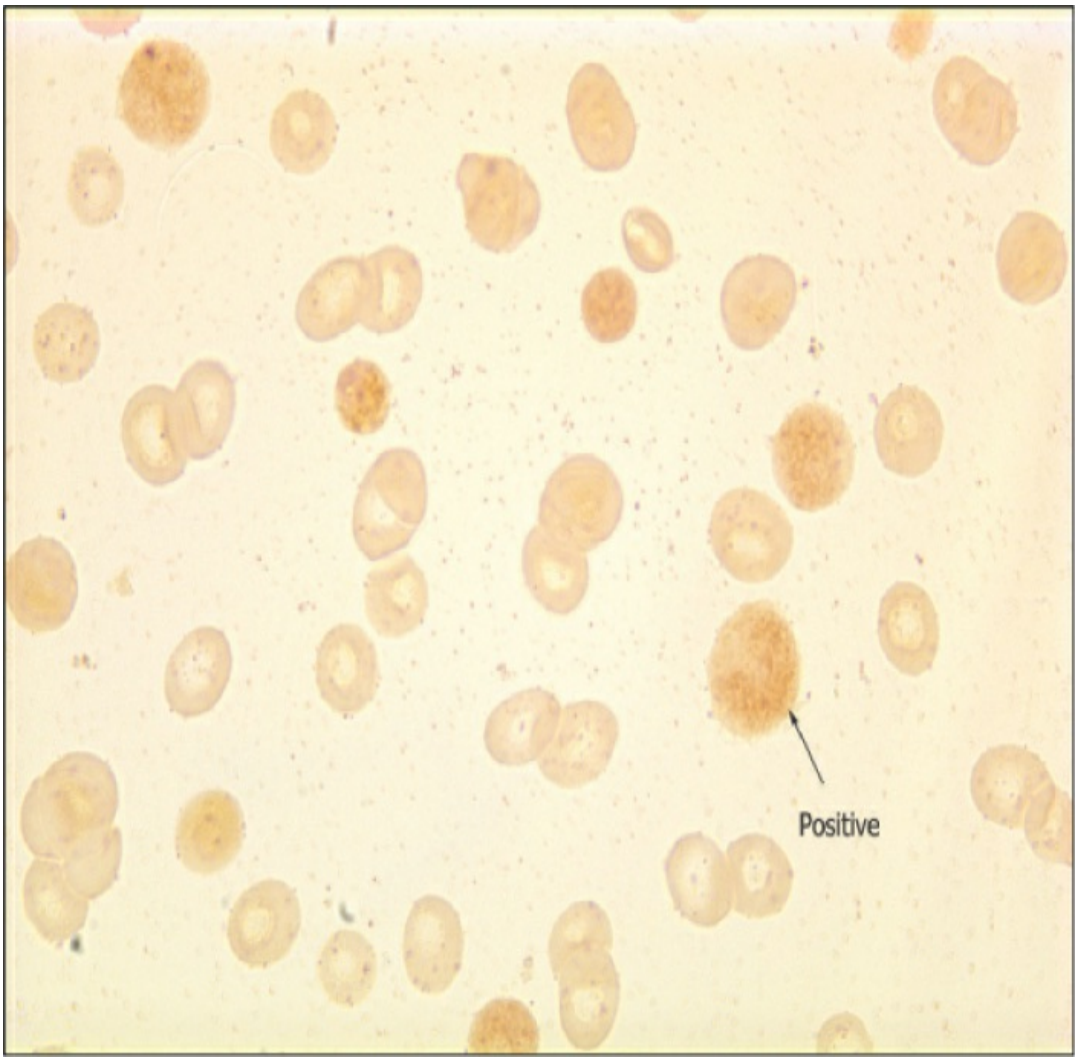


Figure IIB2-41

TdT stain (nuclear stain). Positive.

Criteria

- Mutation of a single lymphoid stem cell causing proliferation of malignant lymphoblasts

Peripheral Blood

- Normocytic/normochromic anemia
- Platelets are often decreased
- White blood cells may be increased, normal, or

decreased

Bone Marrow

- The blasts are larger than L1, heterogeneous in size, the nucleus is irregular with clefting, and nucleoli are present

Cytochemistry

- Sudan black B, peroxidase, specific esterase, and nonspecific esterase negative
- Large block positivity with the periodic acid–Schiff
- Focal positivity with acid phosphatase in T-cell blasts
- Terminal deoxynucleotidyl transferase is positive in 90–95% in L1 and L2 and negative in L3

L3 (Burkitt Type)

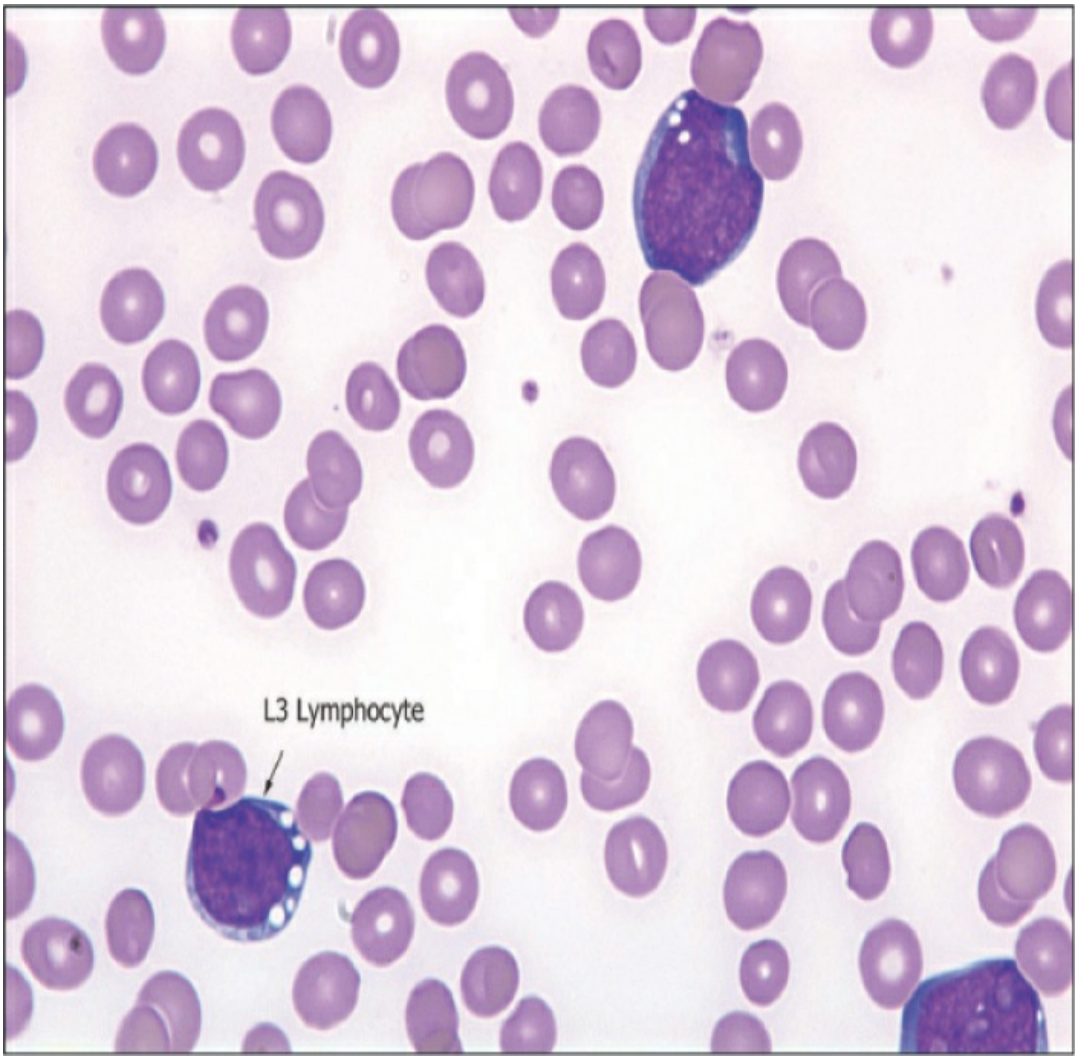


Figure **IIB2-42**

Peripheral blood smear.

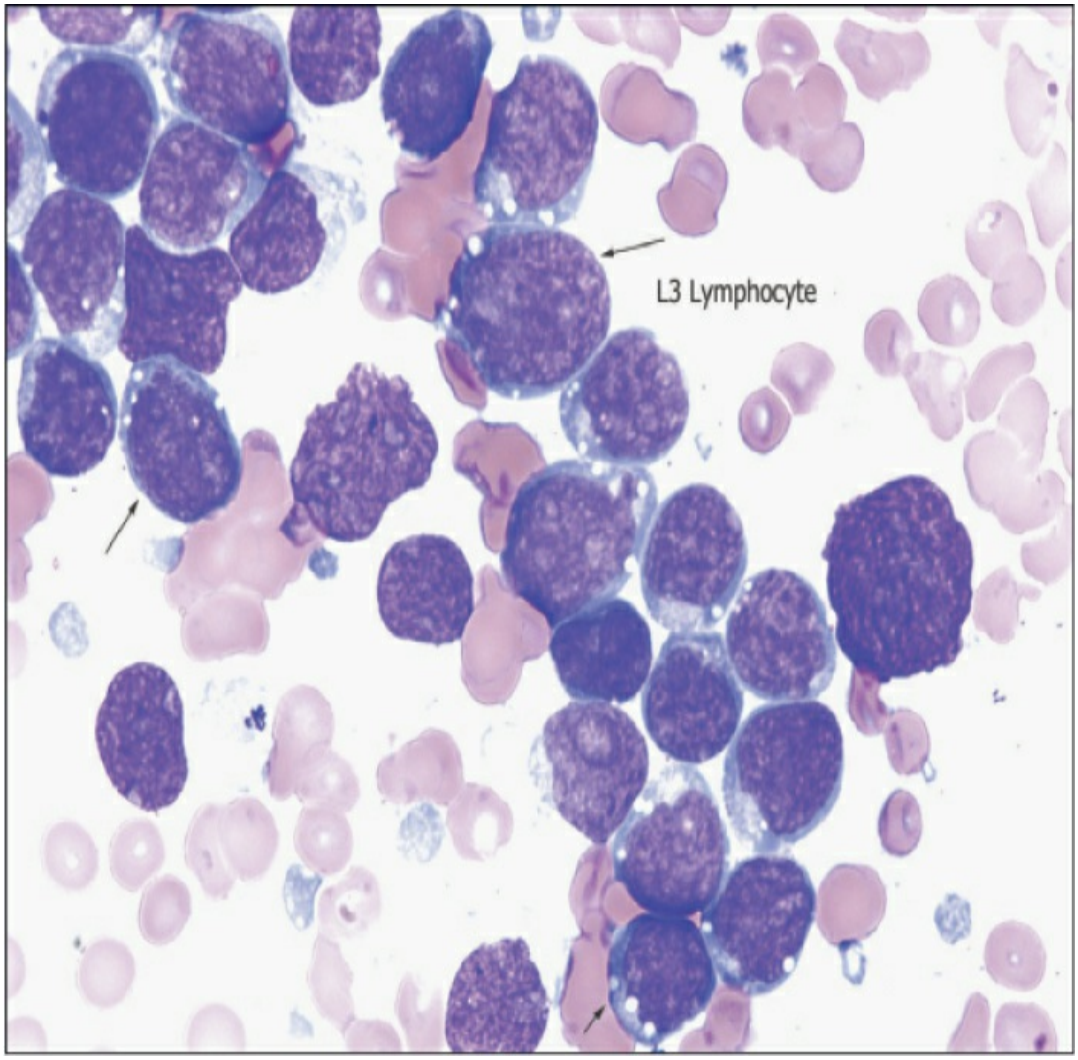


Figure **IIB2-43**

Bone marrow smear.

Criteria

- The lymphoblasts are similar in appearance to those found in Burkitt lymphoma
- Constitutes about 3–4% of precursor lymphoblastic leukemias in children and adults

Peripheral Blood

- Normocytic/normochromic anemia
- Decreased platelets are often seen
- White blood cells may be increased, decreased, or

normal

- Blasts are larger than L1 and have round to oval nucleoli with fine, homogenous chromatin, and one or more nucleoli may be seen
- Cytoplasm of the blasts is deeply basophilic and vacuolated

Bone Marrow

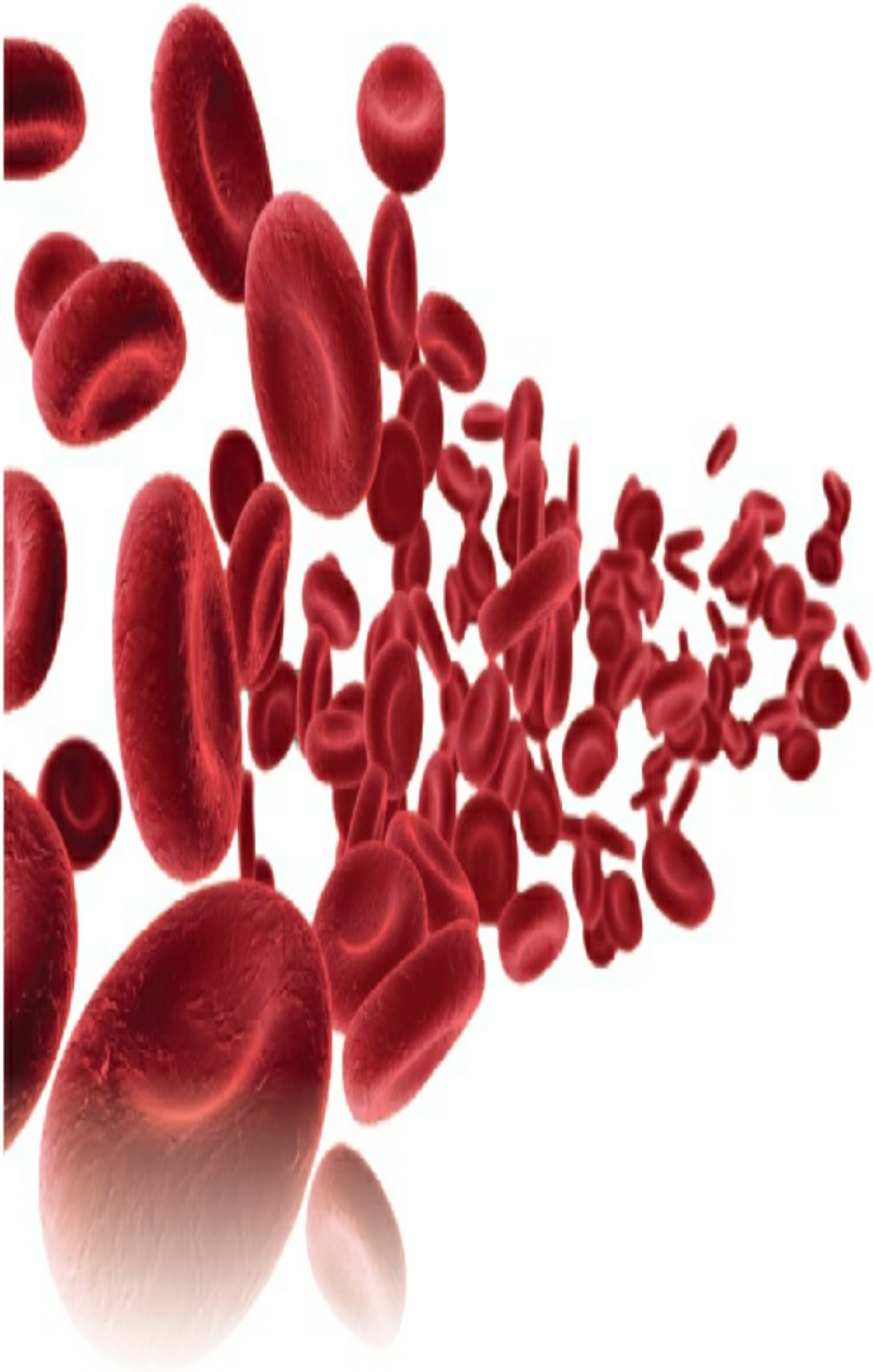
- Hypercellular with blasts that are larger than L1, have a round- to oval-shaped nucleus with fine, homogenous chromatin, and one or more nucleoli present
- Cytoplasm of the blasts is deeply basophilic and vacuolated

Cytochemistry

- Sudan black B, peroxidase, specific esterase, and nonspecific esterase negative
- Periodic acid–Schiff negative
- Terminal deoxynucleotidyl transferase negative
- Oil red O positive

CHAPTER 3

World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Neoplasms



WHO CLASSIFICATION OF HEMATOLOGIC NEOPLASMS

Background

- First published in 2001, revised in 2008, and again in 2016/2017 to stratify neoplasms according to lineage using clinical features, morphology including myeloid, lymphoid, and histiocytic/dendritic cells, immunophenotypes, and genetic features

Classification

- The classification of myeloid neoplasms includes myeloproliferative neoplasms, mastocytosis, myelodysplastic/myeloproliferative neoplasms, myelodysplastic syndromes, acute myeloid leukemia, and acute leukemias of ambiguous lineage
- The classification of lymphoid neoplasms includes precursor lymphoid neoplasms, mature B-cell neoplasms, mature T- and NK-cell neoplasms, and Hodgkin lymphomas

Peripheral Blood Smear

- Well-stained blood smears should be examined for white blood cell, red blood cell, and platelet abnormalities
- Manual 200-cell leukocyte differentials are recommended

Bone Marrow Aspiration and Bone Marrow Trephine Biopsy

- 500 nucleated bone marrow cells should be counted

Cytochemistry

- Usually performed on peripheral blood and bone marrow aspirate smears

Immunophenotype Studies

- Analysis should be performed by flow cytometry on each case
- Differentiation antigens appear at various stages of hematopoietic development and in various myeloid and lymphoid neoplasms

Genetics Profile

- Specific gene abnormalities including rearrangements due to translocations, deletions, and mutations are of primary importance
- Performance of a cytogenetic analysis of bone marrow by conventional karyotyping should be conducted at initial evaluation and at regular intervals
- Molecular genetic features may be utilized for diagnosis, prognosis, and treatment purposes

Definitions

Agranular Blast

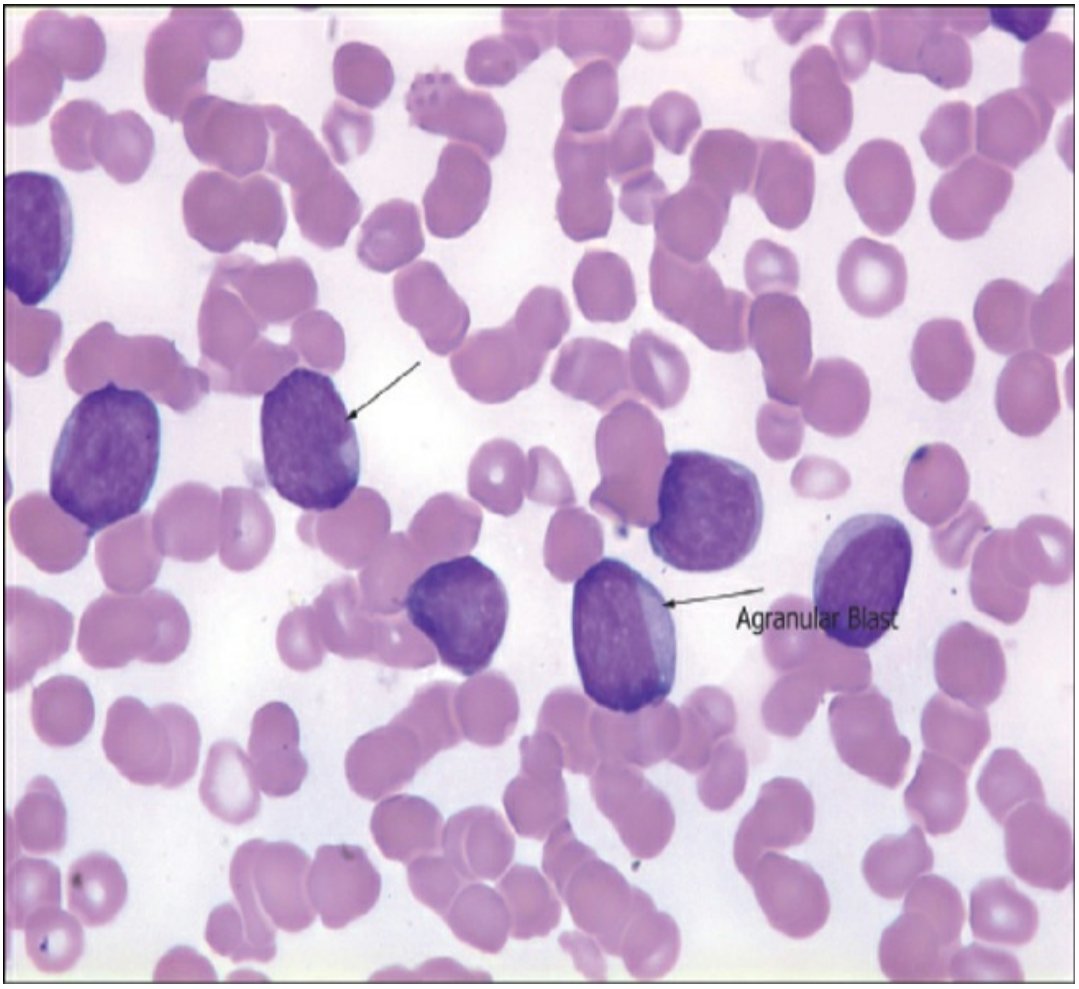


Figure **IIB3-1**

Peripheral blood smear.

Size: 10–18 µ

Nucleus

Shape: Oval or round

N/C Ratio: 6:1–7:1

Color: Dark purple

Chromatin: Fine

Nucleoli: 1–3

Cytoplasm

Color: Light to medium blue

Contents: Without azurophilic granules

Granular Blast

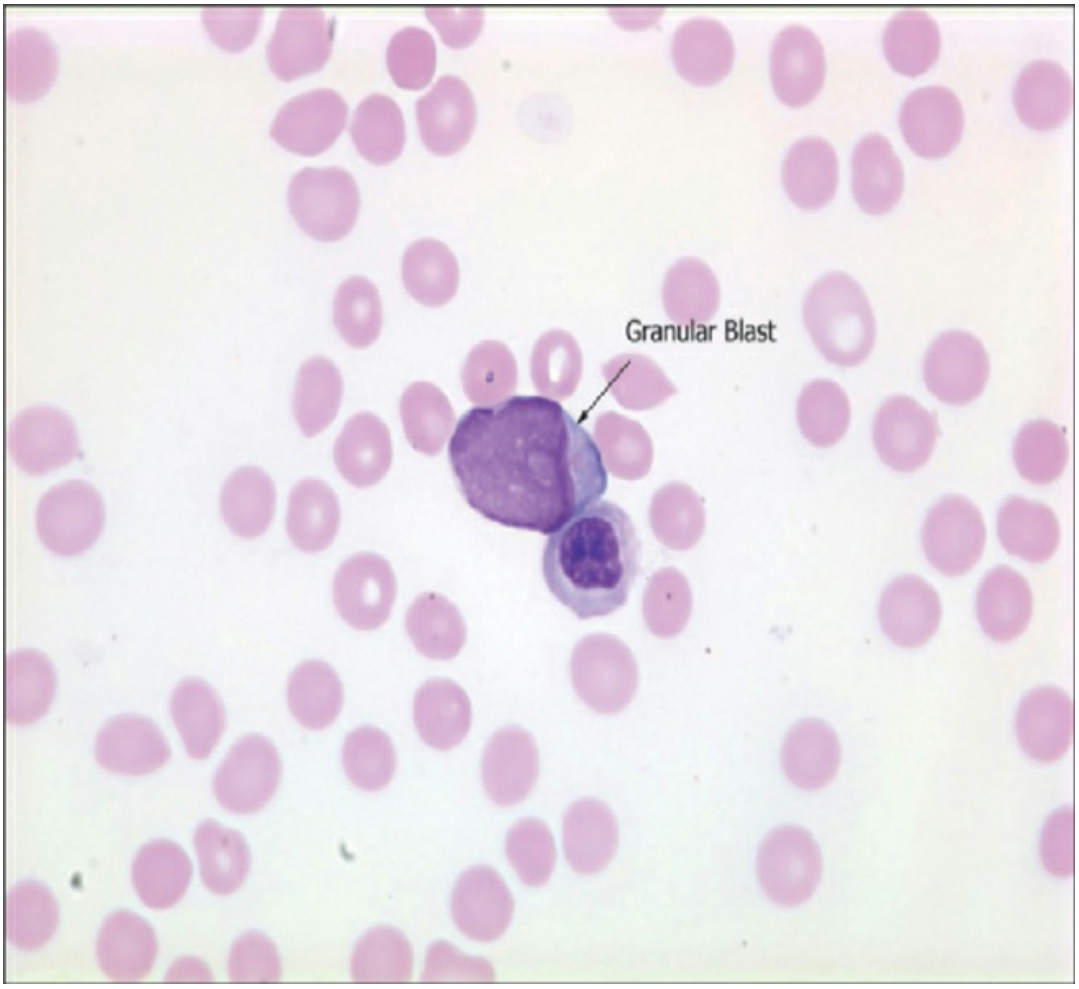


Figure IIB3-2

Peripheral blood smear.

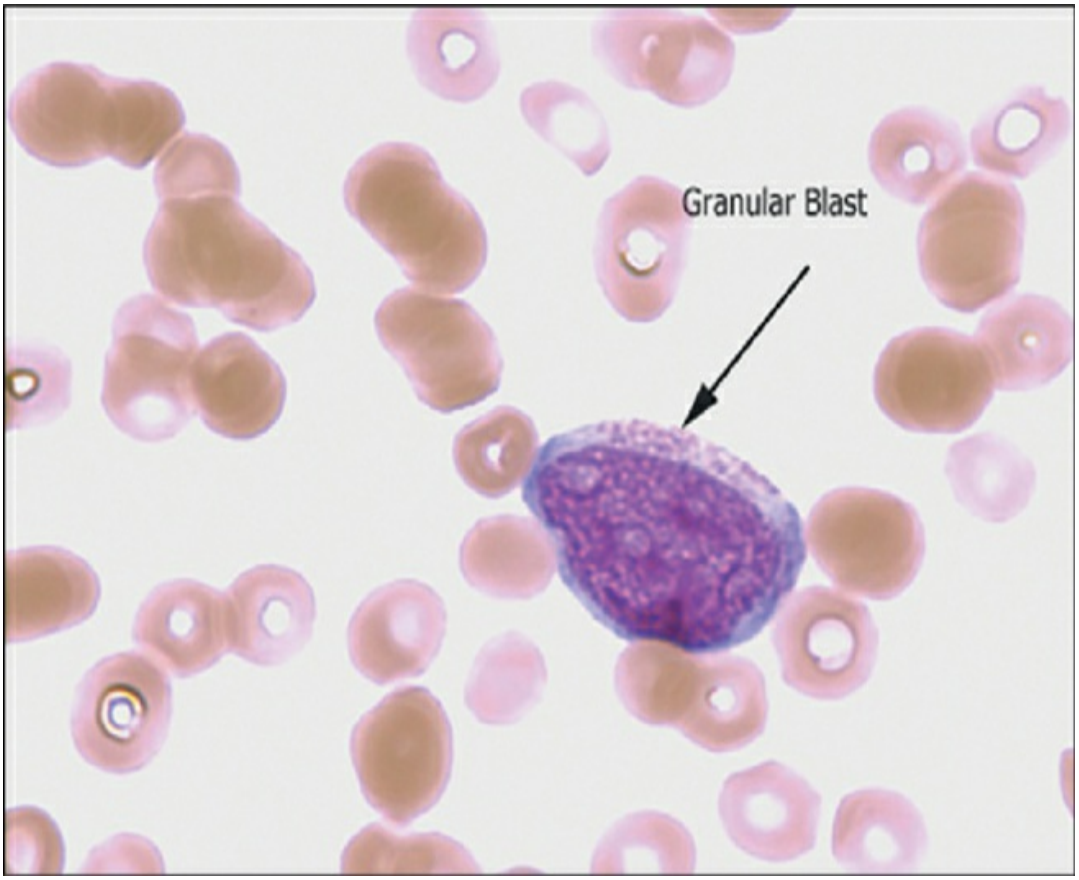


Figure **IIB3-3**

Peripheral blood smear.

Size: 10–18 µ

Nucleus

Shape: Oval or round

N/C Ratio: Slightly lower than an agranular

Color: Dark purple

Chromatin: Slightly more condensed than an agranular

Nucleoli: 2–5

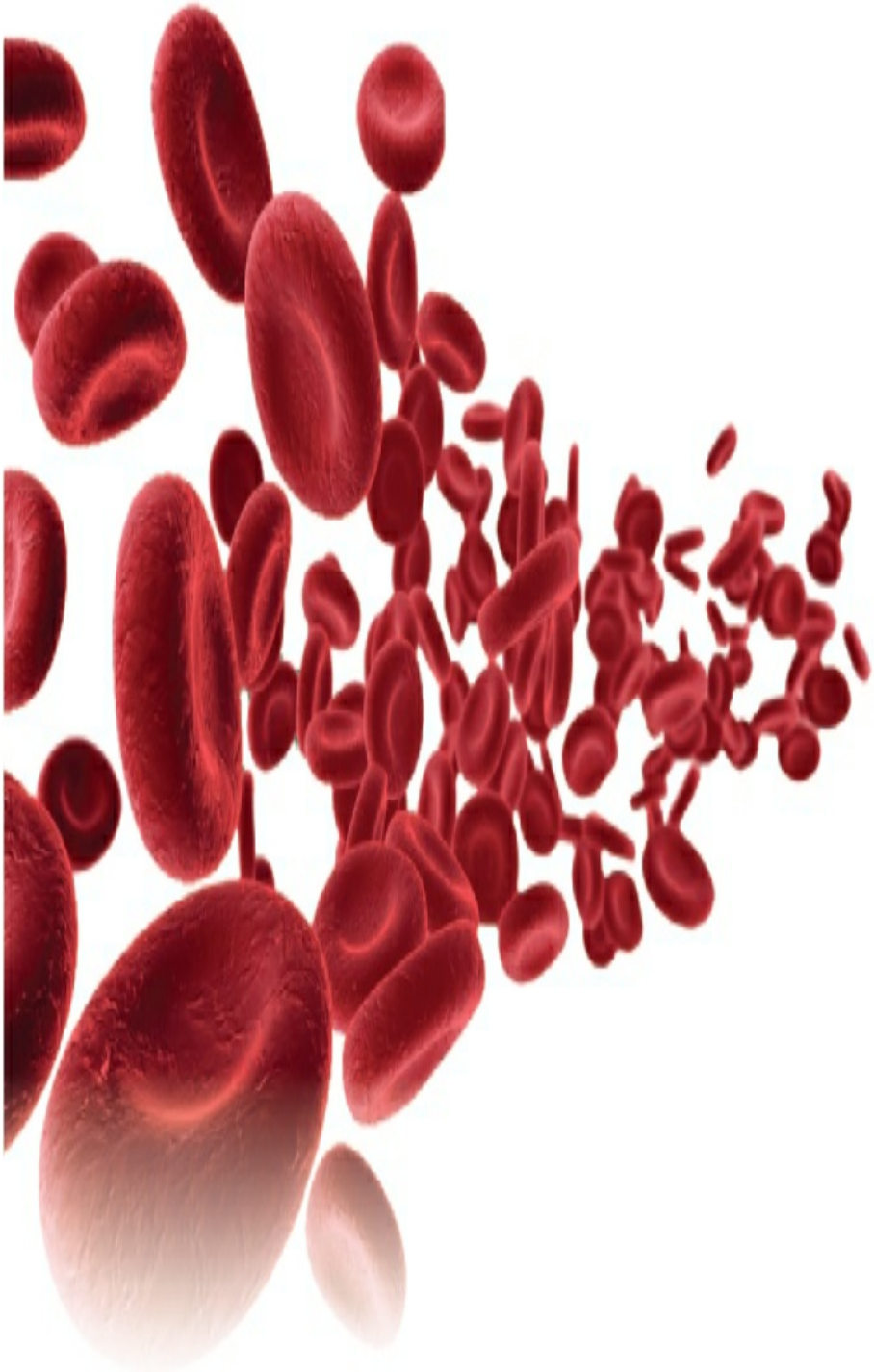
Cytoplasm

Color: Medium blue

Contents: Azurophilic granules present and may have Auer rods

CHAPTER 4

Myeloproliferative Neoplasms



MYELOPROLIFERATIVE NEOPLASMS

Criteria

- At least one hematopoietic cell line is elevated in the blood
- Significant dysplasia and cytopenias are not present in the stable phase
- The percentage of blasts is not significantly increased in the bone marrow during the stable phase
- Mutations in the tyrosine kinase genes are present
    - BCR-ABL1 fusion gene defines chronic myeloid leukemia
    - JAK2 mutations are present in polycythemia vera
    - JAK2/CALR/MPL mutations are seen in essential thrombocytopenia and primary myelofibrosis

Chronic Myeloid Leukemia, BCR-ABL1 Positive

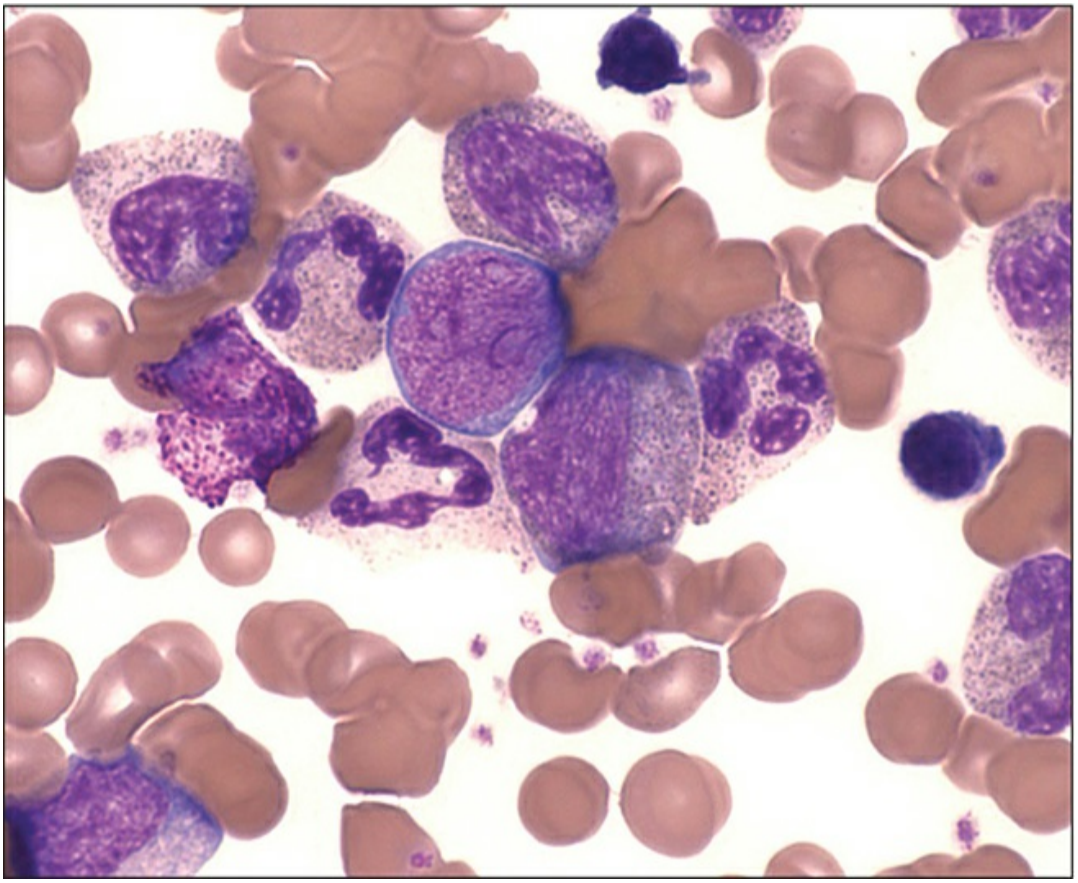


Figure IIB4-1

Peripheral blood smear.

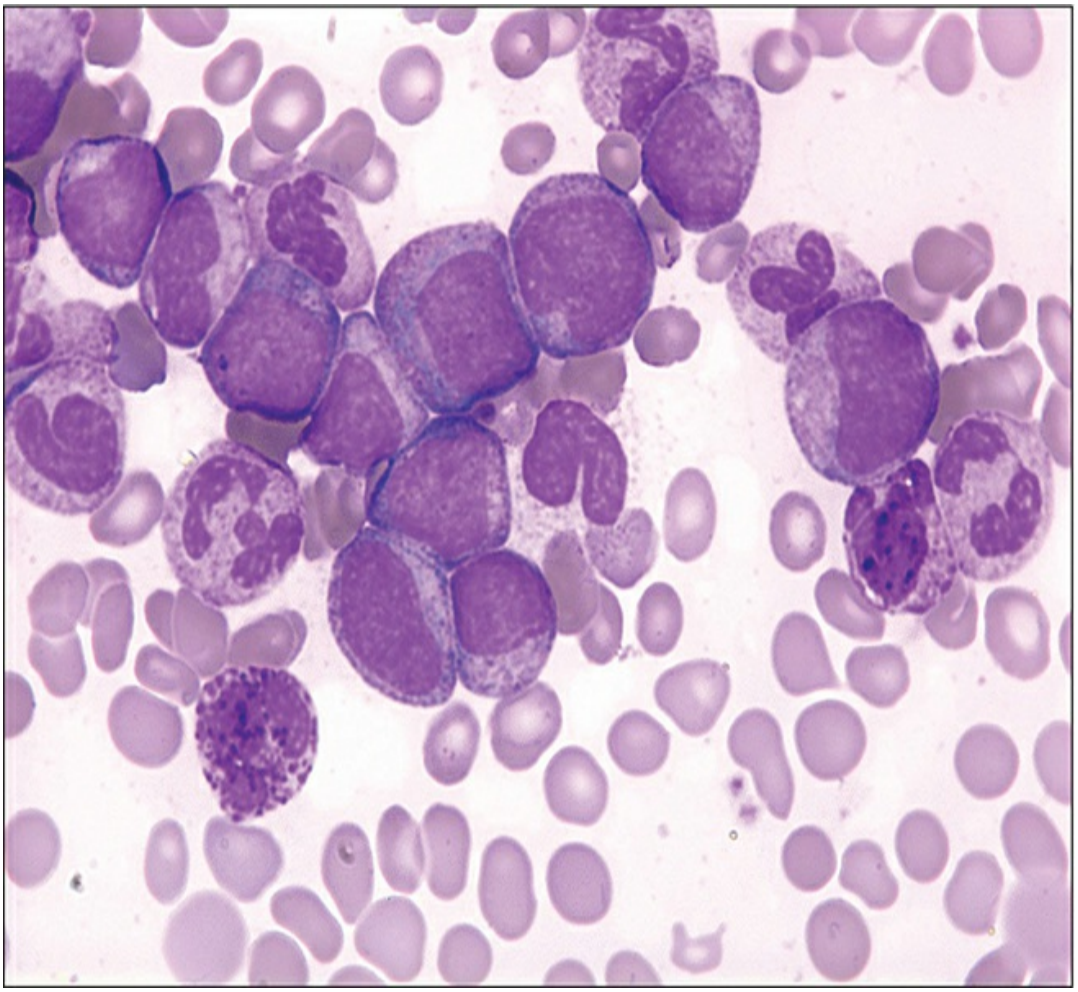


Figure **IIB4-2**

Bone marrow smear.

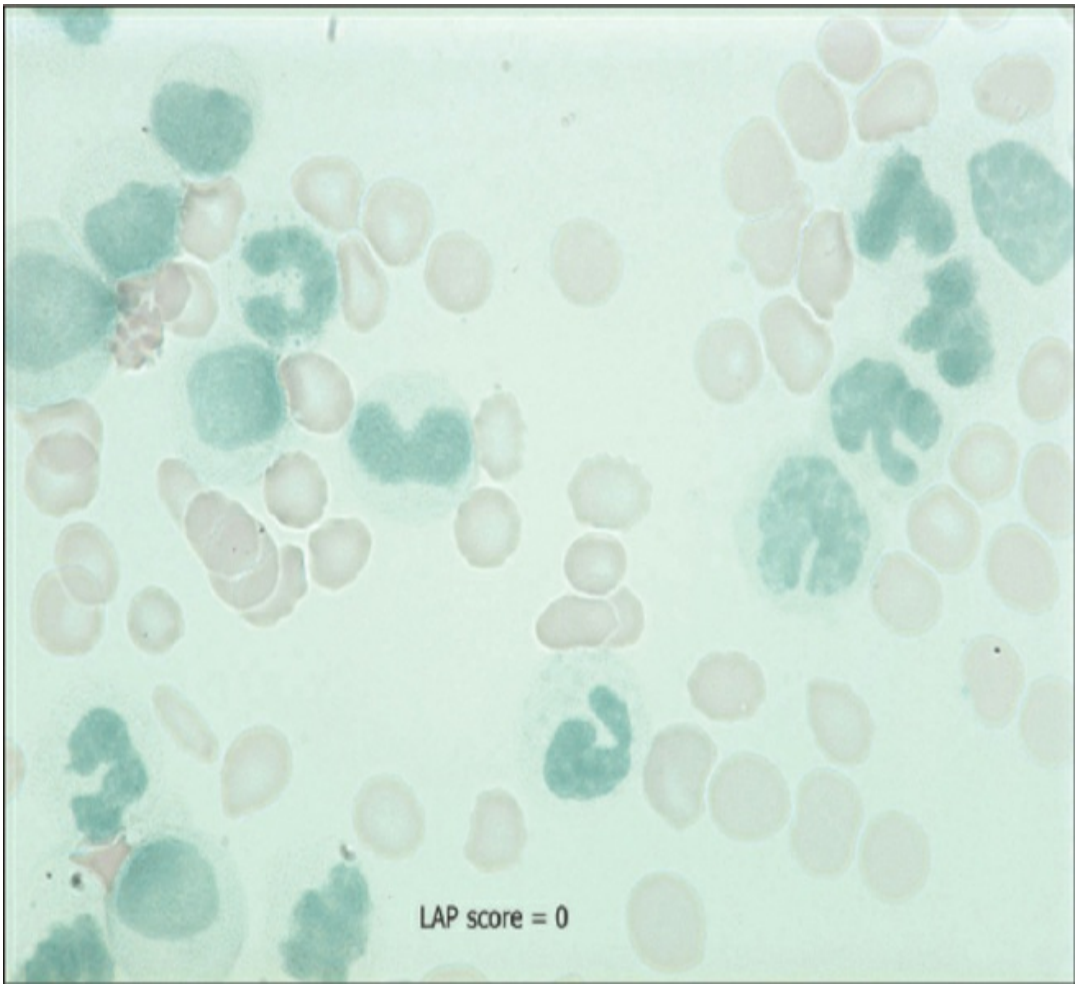


Figure **IIB4-3**

LAP stain. Decreased score.

Clinical Features

- Occurs most frequently in middle-aged people—peak age 50–70 years
- Accounts for about 25% of adult leukemias
- Weight loss, night sweats, anorexia, visual disturbances, bleeding disorders, and bone pain
- Splenomegaly and hepatomegaly

Pathology

- Philadelphia chromosome—t(9;22)(q34.1;q11.2)
- BCR-ABL1 genetic fusion

    - Causes continual production of tyrosine kinase
    - Tyrosine kinase activity causes disease
- Three stages
    - Chronic phase
    - Accelerated phase
    - Blast phase

Laboratory Features—Chronic Phase

White Blood Cells

- Granulocytic leukocytosis with shift to the left (entire maturation series of granulocytes is seen)
- <5% blasts
- Basophilia and often eosinophilia
- No granulocytic dysplasia or toxic changes

Red Blood Cells

- No or mild anemia
- Rare nucleated red blood cells

Platelets

- Normal to elevated count
- Atypical large platelets, megakaryocytic cytoplasmic fragments, or megakaryocytic nuclei

Bone Marrow

- ≥95% cellularity
- Myeloid:erythroid ratio ≥10:1
- <5% blasts
- Minimal or no granulocytic dysplasia
- Increased small and monolobulated megakaryocytes
- Pseudo-Gaucher cells and sea-blue histiocytes can be observed if there is increased cell turnover

Cytochemistry

- Neutrophils in the chronic phase have markedly decreased leukocyte alkaline phosphatase score (score is usually ≤10)

Laboratory Features—Accelerated Phase

White Blood Cells

- Persistent and increasing white blood cell count
- 10–19% myeloid blasts
- Entire maturation series of granulocytes is seen but no toxic changes
- Basophilia ≥20%

Red Blood Cells

- Normocytic/normochromic anemia
- Occasional nucleated red blood cells

Platelets

- Persistent thrombocytosis (>1000 × 10^9/L) or persistent thrombocytopenia (<100 × 10^9/L)

Bone Marrow

- 90–100% cellularity
- Myeloid:erythroid ratio 10:1–50:1
- Increased small abnormal megakaryocytes
- Pseudo-Gaucher cells and sea-blue histiocytes can be observed if there is increased cell turnover

Laboratory Features—Blast Phase

Peripheral Blood/Bone Marrow

- ≥20% blasts
- Extramedullary proliferation of blasts

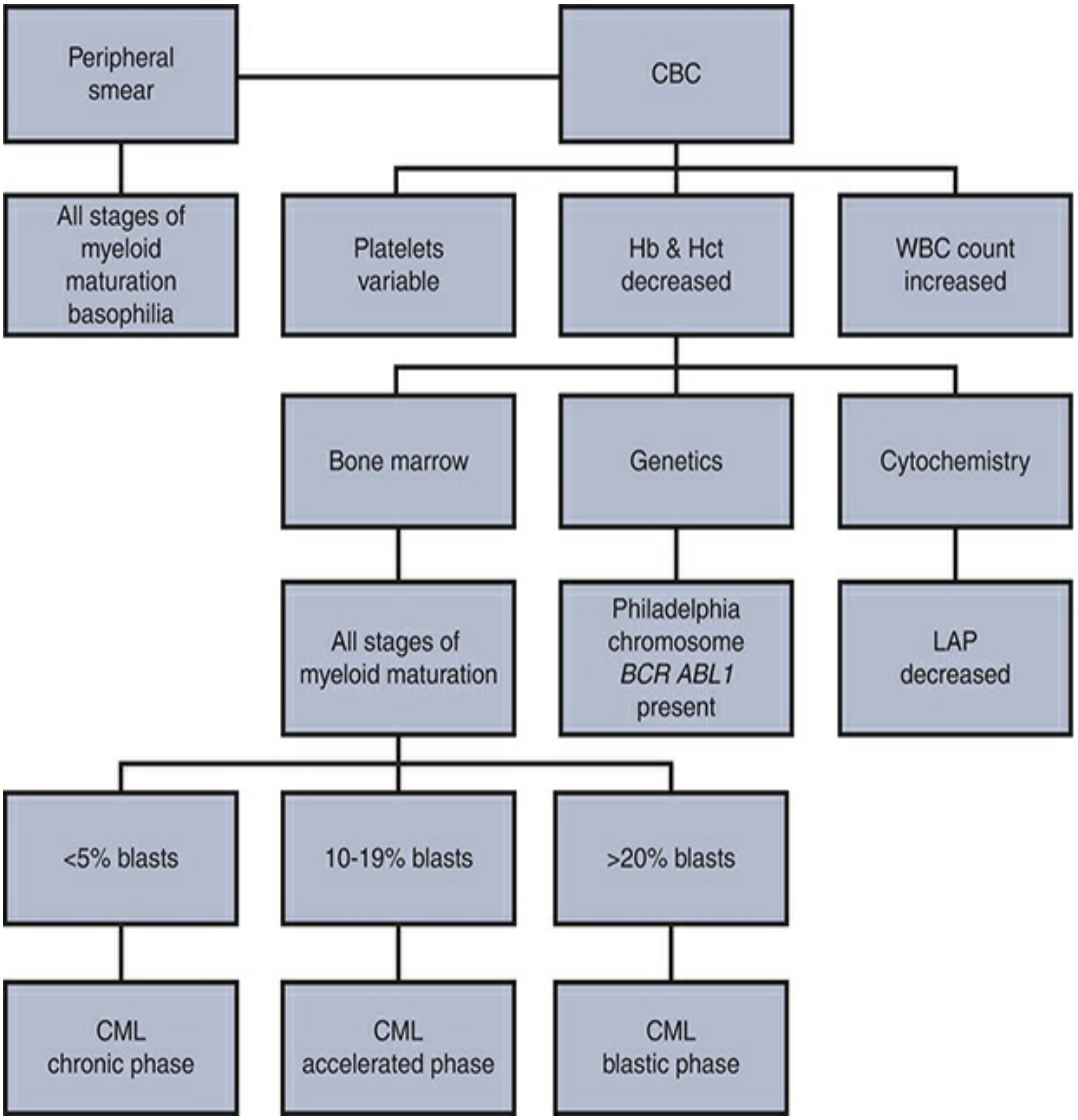
(hepatosplenomegaly)

- Presence of large clusters of blasts in the bone marrow
- In the blast phase, the blasts may have strong, weak, or no myeloperoxidase activity, but express antigen associated with granulocytic, monocytic, megakaryoblastic, and/or erythroid differentiation
- 20% of blast phase leukemias are lymphoblastic (typically B cell)

Genetics

- Translocation of material from the long arm of 22 to the long arm of 9 and from 9 to 22
- Fuses the BCR gene from chromosome 22 with regions of the ABL gene on chromosome 9 (BCR-ABL1 fusion protein)

Diagnostic Scheme


Peripheral smear
CBC
All stages of myeloid maturation basophilia
Platelets variable
Hb & Hct decreased
WBC count increased
Bone marrow
Genetics
Cytochemistry
All stages of myeloid maturation
Philadelphia chromosome BCR ABL1 present
LAP decreased
<5% blasts
10-19% blasts
>20% blasts
CML chronic phase
CML accelerated phase
CML blastic phase

CHRONIC NEUTROPHILIC LEUKEMIA

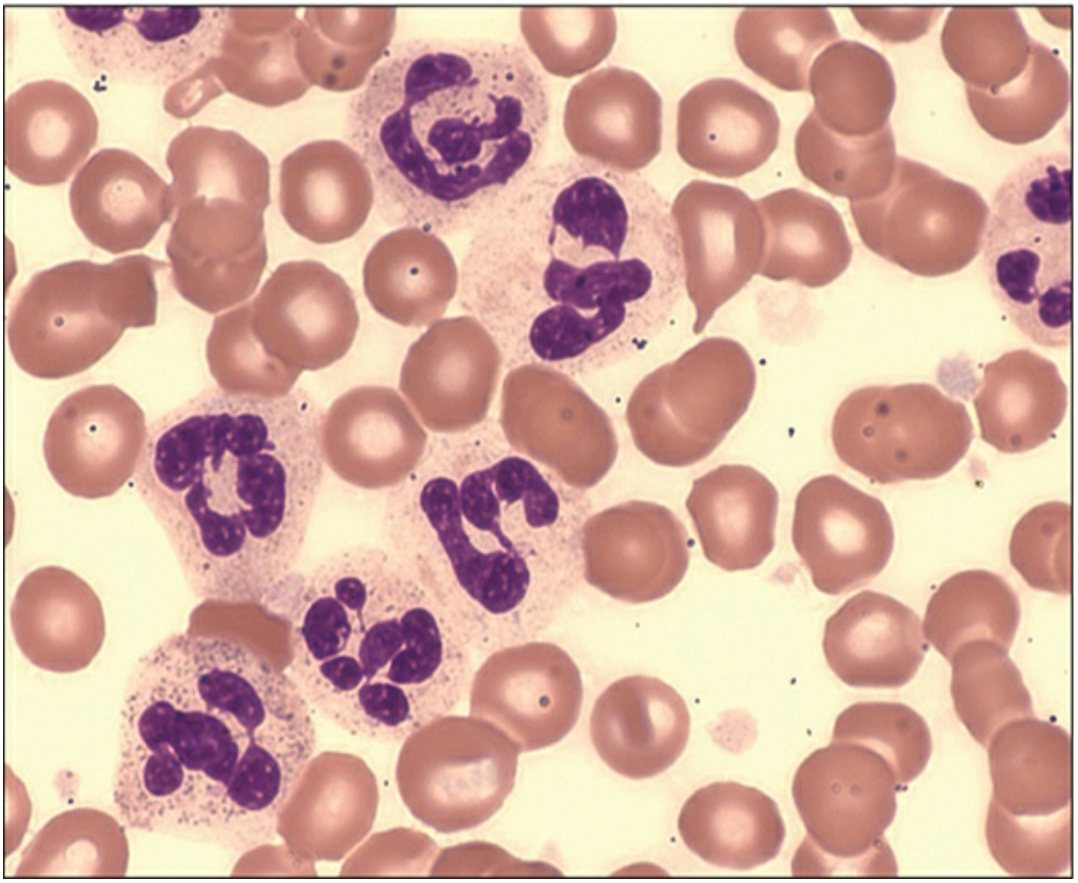


Figure IIB4-4

Peripheral blood smear.

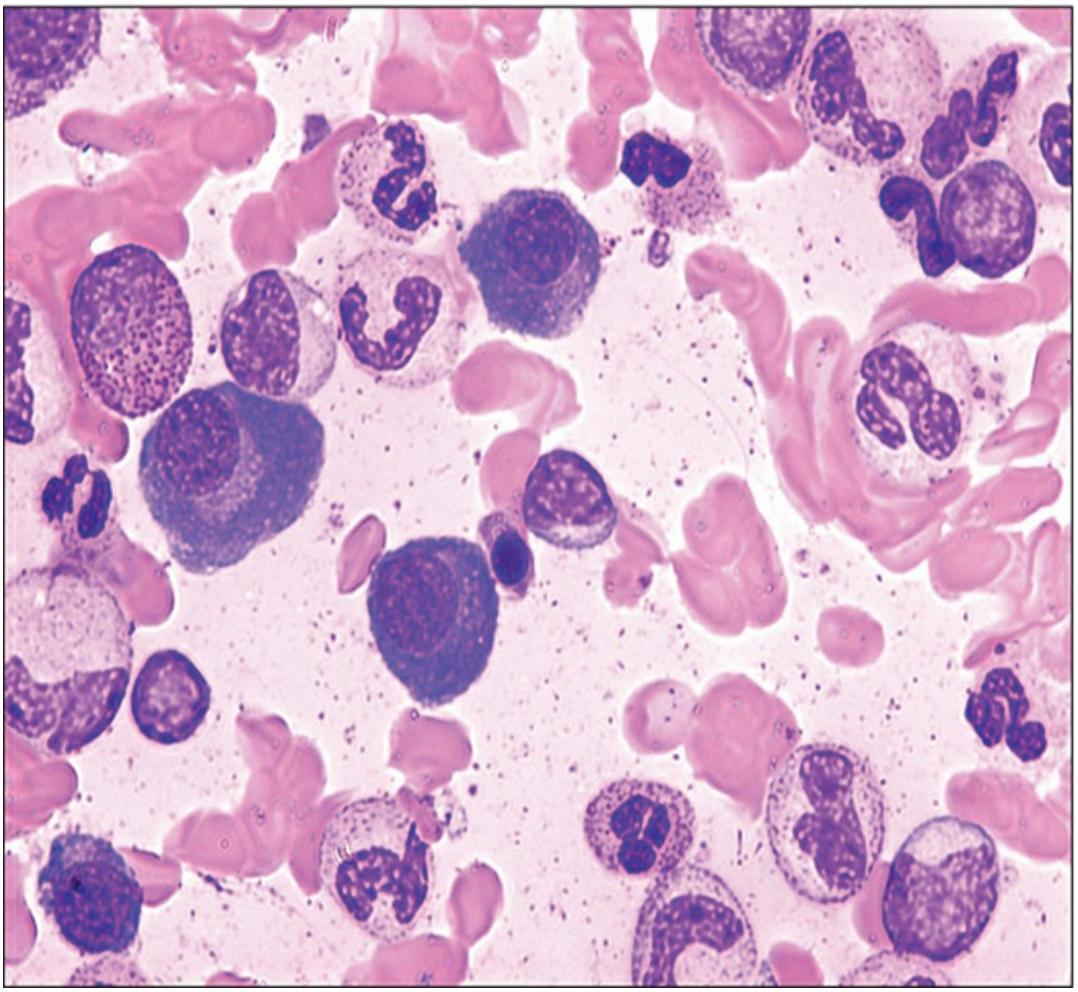


Figure IIB4-5

Bone marrow smear.

Clinical Features

- Majority of patients are asymptomatic; some may have weight loss
- Usually 50 years or older
- Slight male predominance
- Splenomegaly
- Hepatomegaly
- Bruising and purpura

Pathology

- Mutation of CSF3R gene

- Very rare
- Seen with possible increased plasma cells in the bone marrow
- Synthesis of granulocyte colony–stimulating factor by plasma cells

Laboratory Features

White Blood Cells

- Persistent neutrophilia with ≥25 × 10^9/L white blood cell count
- Predominant cell is the neutrophil (≥80%) with a possible increase in bands
- Neutrophils often show toxic granulation
- No significant basophilia
- <10% immature granulocytes (promyelocytes, myelocytes, metamyelocytes)
- Monocytes <1 × 10^9/L

Red Blood Cells

- Variable normocytic/normochromic anemia

Platelets

- Variable thrombocytopenia

Bone Marrow

- Granulocytic hypercellularity
- Myeloid:erythroid ratio about 5:1–25:1
- <5% myeloblasts
- No myelofibrosis
- Possible increase in plasma cells; exclude plasma cell dyscrasia

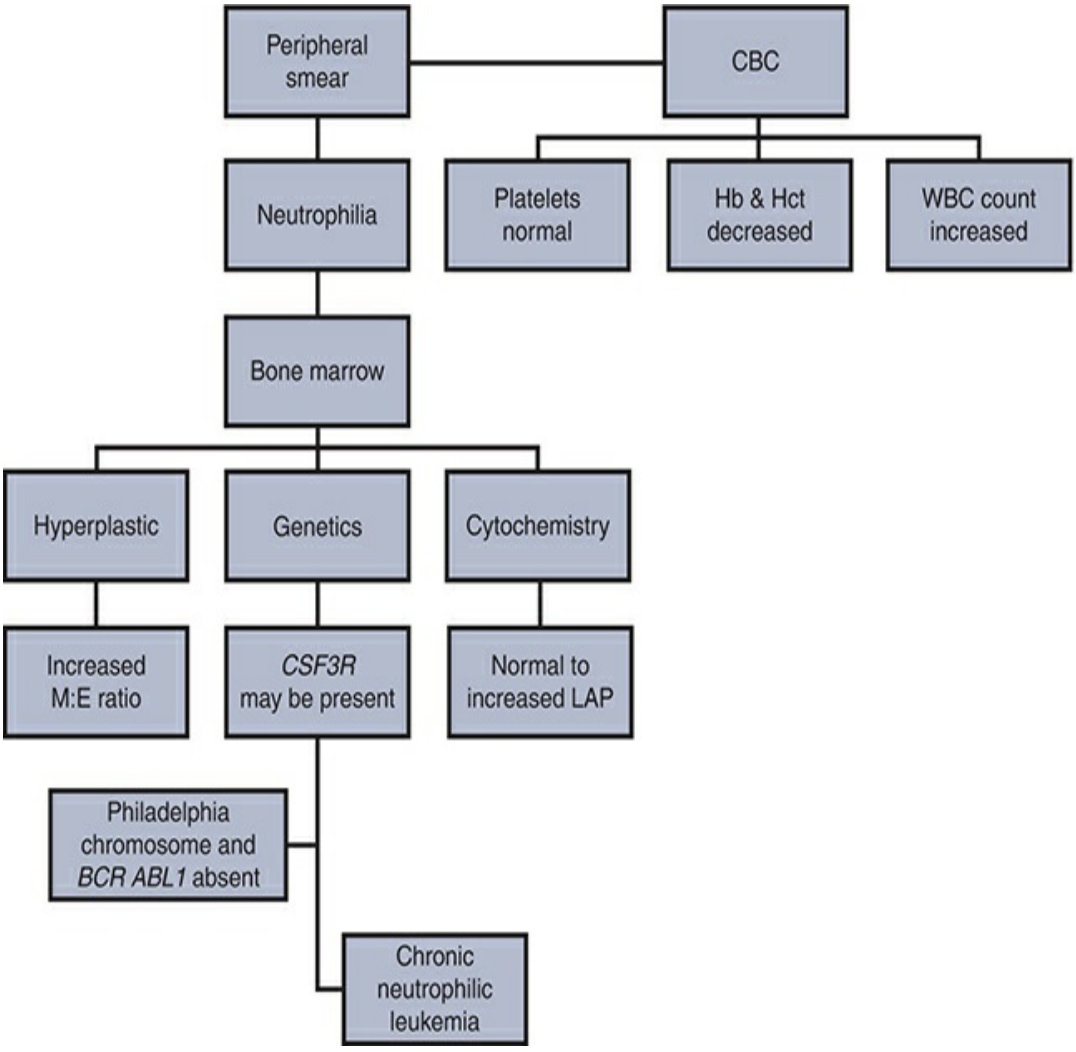
Cytochemistry

- Leukocyte alkaline phosphatase is normal or increased
- Myeloperoxidase is positive

Genetics

- CSF3R mutations seen in ≥80% of cases
- Philadelphia chromosome or BCR-ABL1 fusion genes are absent

Diagnostic Scheme



POLYCYTHEMIA VERA

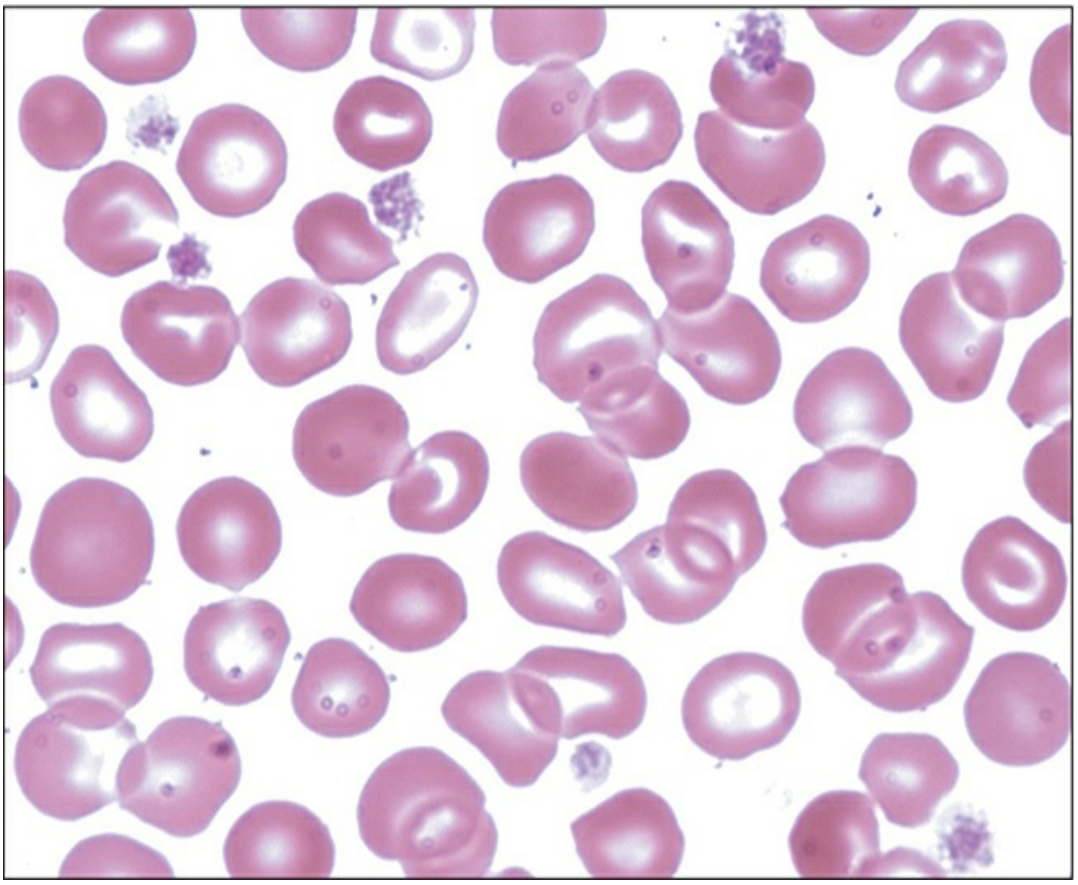


Figure IIB4-6

Peripheral blood smear.

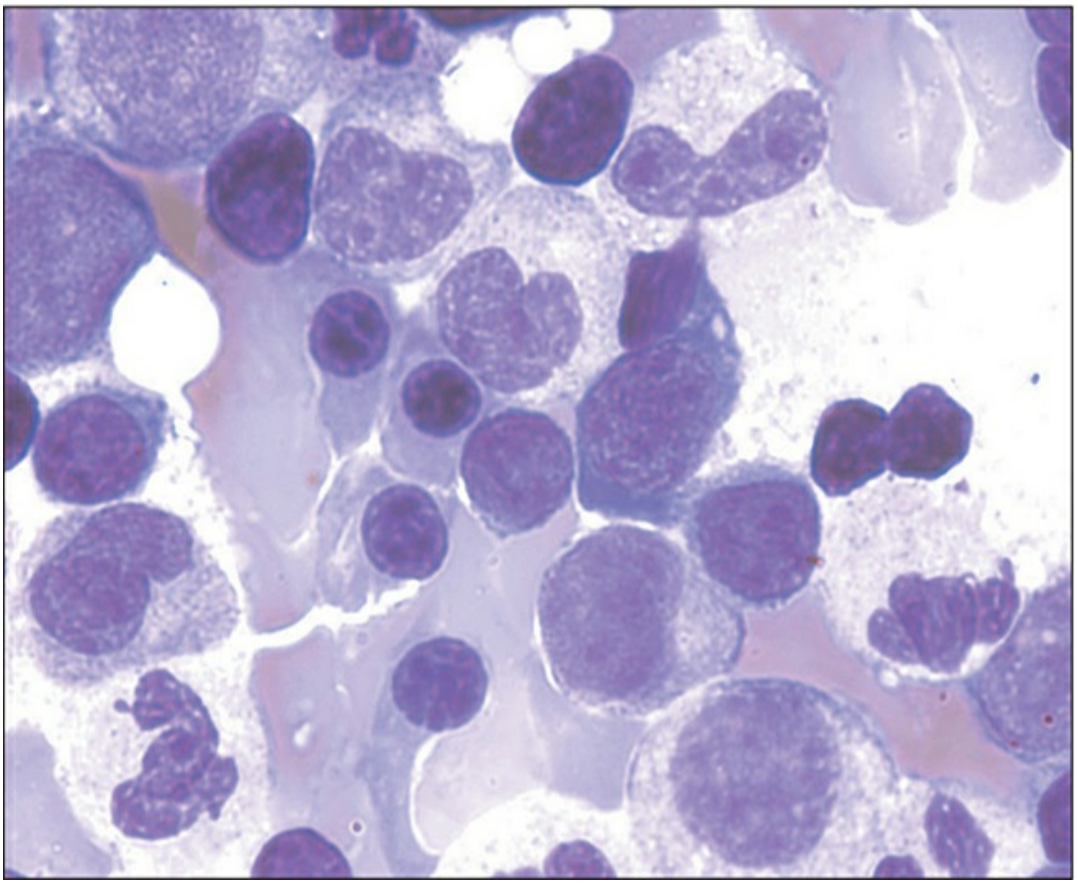


Figure IIB4-7

Bone marrow smear.

Clinical Features

- Usually diagnosed in persons aged 55–70 years
- Slight male predominance
- Headache, confusion, altered mental status, dizziness, visual changes, tinnitus, and paresthesia
- Weight loss, epigastric pain, gout, pruritus, thrombosis, and hemorrhage
- Plethora, hypertension, and a mild to moderate degree of splenomegaly and hepatomegaly

Pathology

- Excessive bone marrow production of red blood cells and an increase in total red blood cell volume

- Increased blood viscosity
- White blood cell and platelet counts may also increase to a lesser extent
- Thrombosis is a complication in more than half of the cases
- Myelofibrosis or acute myeloid leukemia may develop in the polycythemia phase
    - Anemia
    - Bone marrow fibrosis
    - Extramedullary hematopoiesis
    - Hypersplenism
    - Three phases exist:
        - Prepolycythemic phase with a mild erythrocytosis
        - Overt polycythemic phase with an increased red blood cell mass
        - Spent phase and postpolycythemic myelofibrosis with a decreased red blood cell mass

Laboratory Features

White Blood Cells

- Increased in about two-thirds of patients
- Immature forms usually not seen
- Basophils may be increased
- Leukocyte alkaline phosphatase increased in three-quarters of cases

Platelets

- Normal to increased

Red Blood Cells

- Hemoglobin level increased
- Hematocrit level increased
- Red blood cell mass increased

Bone Marrow

- Hyperplastic
- Erythroid hyperplasia
- Increased megakaryocytes
- Granulocytic hyperplasia
- Increased reticulin in postpolycythemic myelofibrosis and myeloid metaplasia
- Iron stores are often depleted

World Health Organization Criteria for Diagnosis

- Meet all three major criteria or the first two major and minor criteria

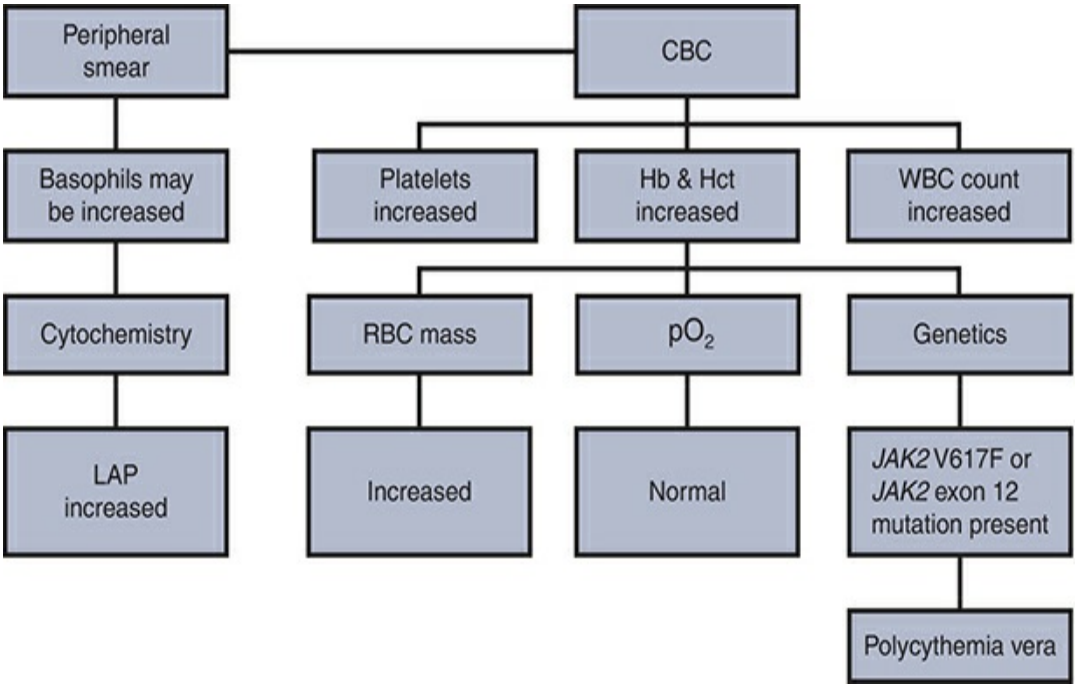
Major Criteria

- Hemoglobin >16.5 g/dL in men and 16.0 g/dL in women or hematocrit >49% in men and >48% in women or increased red cell mass (>25% above mean normal predicted value)
- Bone marrow showing panmyelosis with pleomorphic megakaryocytes
- Presence of JAK2 V617F or JAK2 exon 12 mutation

Minor Criteria

- Decreased serum erythropoietin level

Diagnostic Scheme


Peripheral smear
CBC
Basophils may be increased
Platelets increased
Hb & Hct increased
WBC count increased
Cytochemistry
RBC mass
pO_2
Genetics
LAP increased
Increased
Normal
JAK2 V617F or *JAK2* exon 12 mutation present
Polycythemia vera

PRIMARY MYELOFIBROSIS

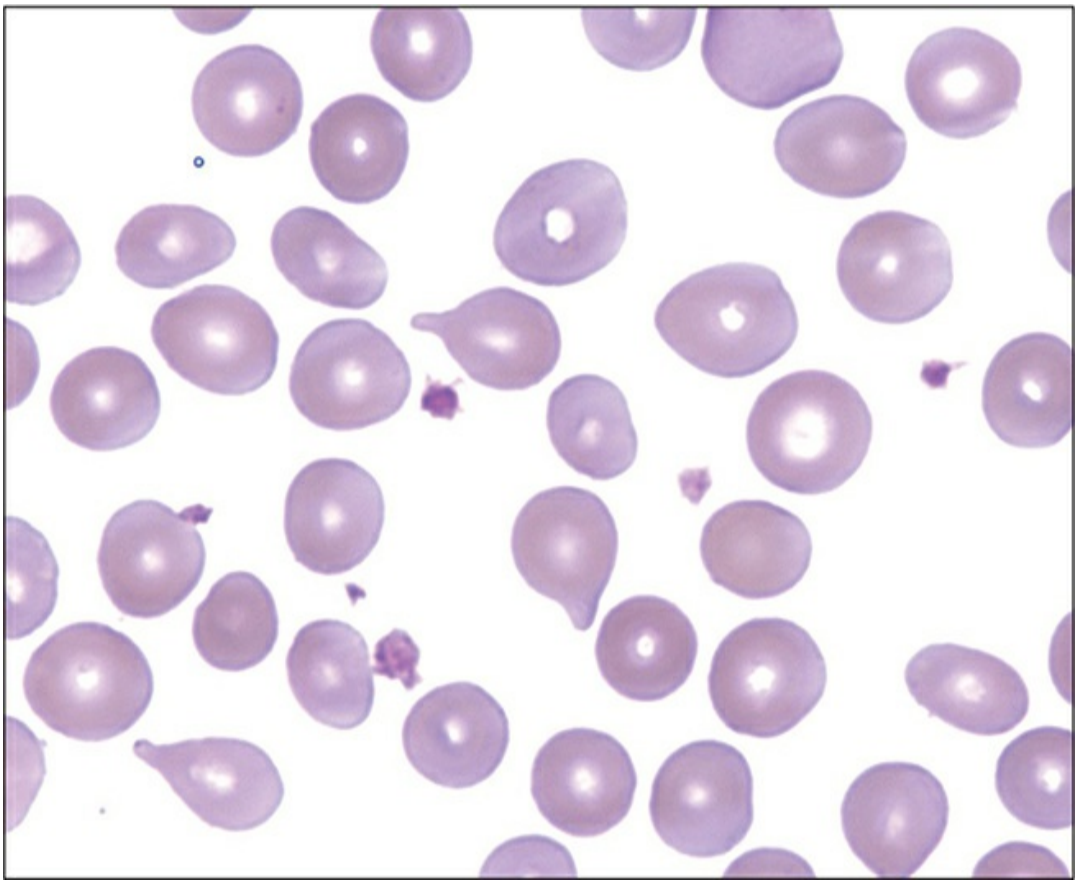


Figure IIB4-8

Peripheral blood smear.

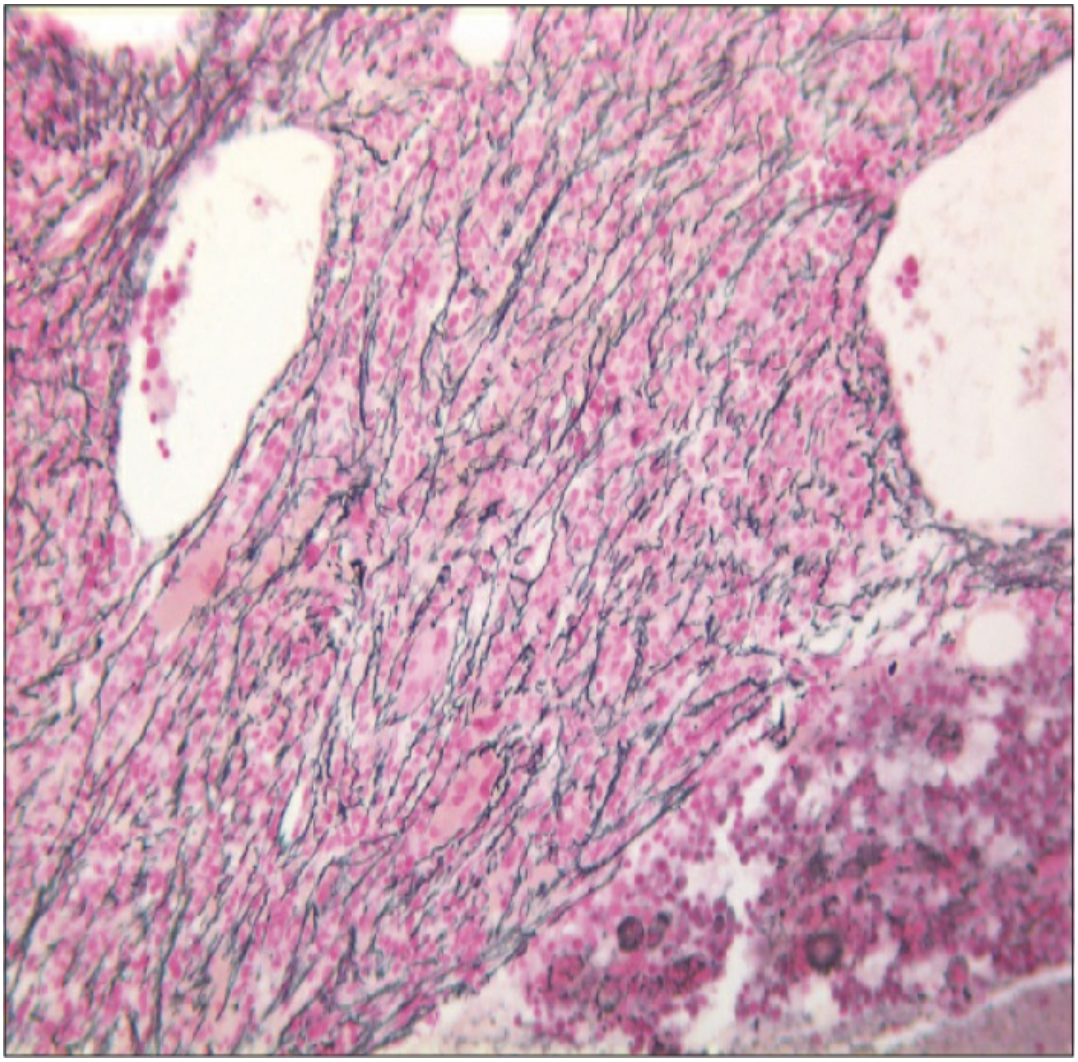


Figure **IIB4-9**

Bone marrow biopsy. Reticulin stain is increased.

Also known as agnogenic myeloid metaplasia (AMM) or chronic idiopathic myelofibrosis (CIMF) or myelofibrosis/sclerosis with myeloid metaplasia (MMM) or idiopathic myelofibrosis

Clinical Features

- Occurs in older persons
- Fatigue, weakness, weight loss, gouty arthritis, petechiae, and purpura
- Low-grade fever, night sweats
- Thrombosis

- No or mild hepatosplenomegaly in the early/prefibrotic stage and moderate to marked hepatosplenomegaly in the fibrotic state
- Anemia and pallor

Pathology

- Molecular mutations
  - JAK2 V617F
  - MPL
  - CALR
- Clonal stem cell disorder with the proliferation of abnormal megakaryocytes and granulocytes
- Fibrosis is a secondary abnormality
- Extramedullary hematopoiesis

Early/Prefibrotic Stage

- Mild anemia
- No or mild leukoerythroblastosis
- No or minimal poikilocytosis
- Mild to moderate leukocytosis
- Mild to marked thrombocytosis
- Hypercellular marrow
- Neutrophilic and megakaryocytic proliferation

Fibrotic Stage

- Leukoerythroblastosis
- Anisopoikilocytosis, including teardrop forms
- Moderate to marked anemia
- Variable white blood cell count
- Variable platelet count
- Decreased marrow cellularity
- Increased marrow reticulin and collagen

- Megakaryocytic proliferation

Laboratory Features

White Blood Cells

- Count is usually <30.0 × 10^9/L
- Immature cells in the myeloid series

Red Blood Cells

- Nucleated red blood cells
- Normocytic/normochromic anemia
- Dacryocytes (tear-shaped red blood cells) are present

Platelets

- Normal, decreased, or increased
- Morphology may be abnormal

Bone Marrow

- In the early/prefibrotic phase, the aspirate is hypercellular, trilineage hematopoiesis present, and megakaryocytic atypia
- Blasts <5%
- During the fibrotic phase, it is inaspirable or results in a dry tap

Cytochemistry

- Reticulin stain is increased

Immunophenotype

- No abnormal phenotypic features

Genetics

- 60% of patients have the JAK2 V617F mutation
- CALR mutations in 25% of cases
- MPL mutations in 6–7% of cases

- May have additional mutations but no Philadelphia chromosome or BCR-ABL1 fusion gene

WHO Diagnostic Criteria for Early/Prefibrotic Primary Myelofibrosis

- Diagnosis requires meeting all three major criteria and at least one minor criterion

Major Criteria

- Hypercellular bone marrow with megakaryocytic hyperplasia and atypia, granulocytic hyperplasia, and normal or decreased erythropoiesis with grade 0 or 1 (of 3) reticulin fibrosis
- Exclusion of other WHO-defined myeloid neoplasms
- Presence of a JAK2 , CALR , or MPL mutation or presence of other clonal marker and absence of other causes of reactive reticulin fibrosis

Minor Criteria

- Leukocytosis $\geq 11 \times 10^9$/L
- Increased serum lactate dehydrogenase
- Anemia (not attributable to other underlying condition)
- Palpable splenomegaly

WHO Diagnostic Criteria for Overt Primary Myelofibrosis

Major Criteria

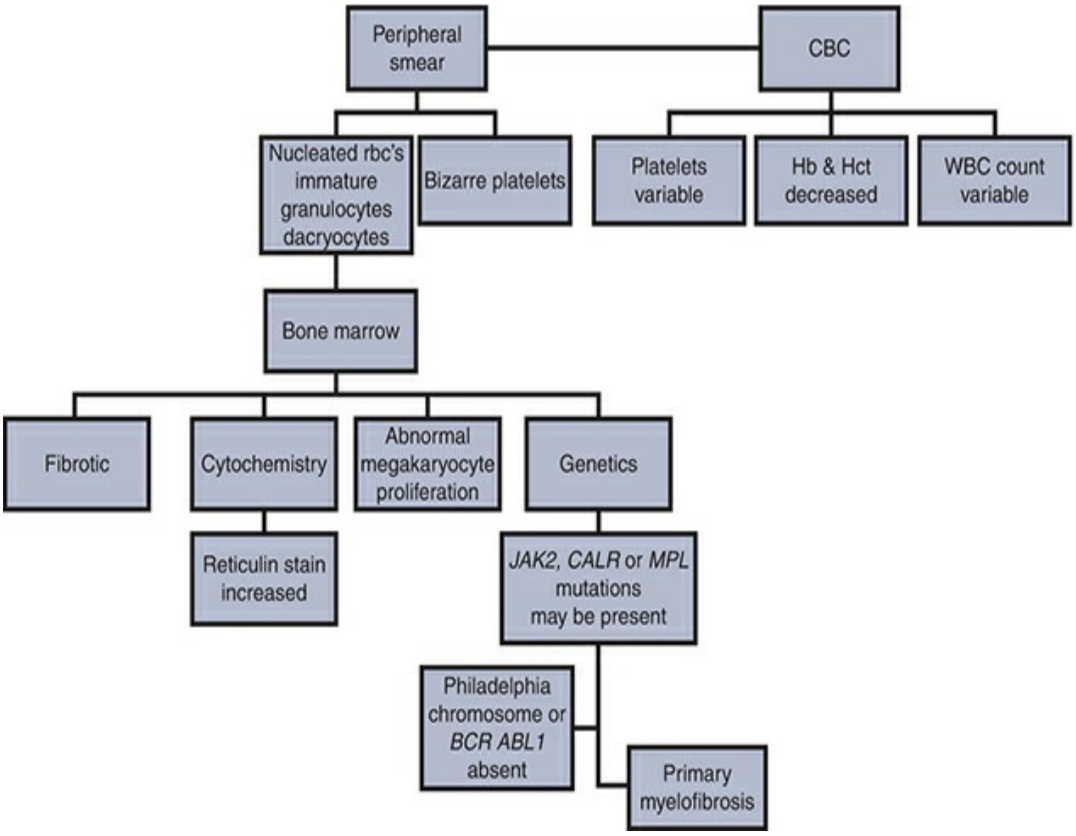
- Megakaryocytic proliferation and atypia with grade 2 or 3 (of 3) reticulin fibrosis or collagen fibrosis
- Exclusion of other WHO-defined myeloid neoplasms
- Presence of JAK2 , CALR , or MPL mutation or presence

of other clonal marker and absence of other causes of reactive reticulin fibrosis

Minor Criteria

- Leukocytosis ≥11 × 10^9/L
- Increased serum lactic dehydrogenase
- Anemia (not attributable to other underlying condition)
- Palpable splenomegaly
- Leukoerythroblastosis

Diagnostic Scheme



ESSENTIAL THROMBOCYTHEMIA

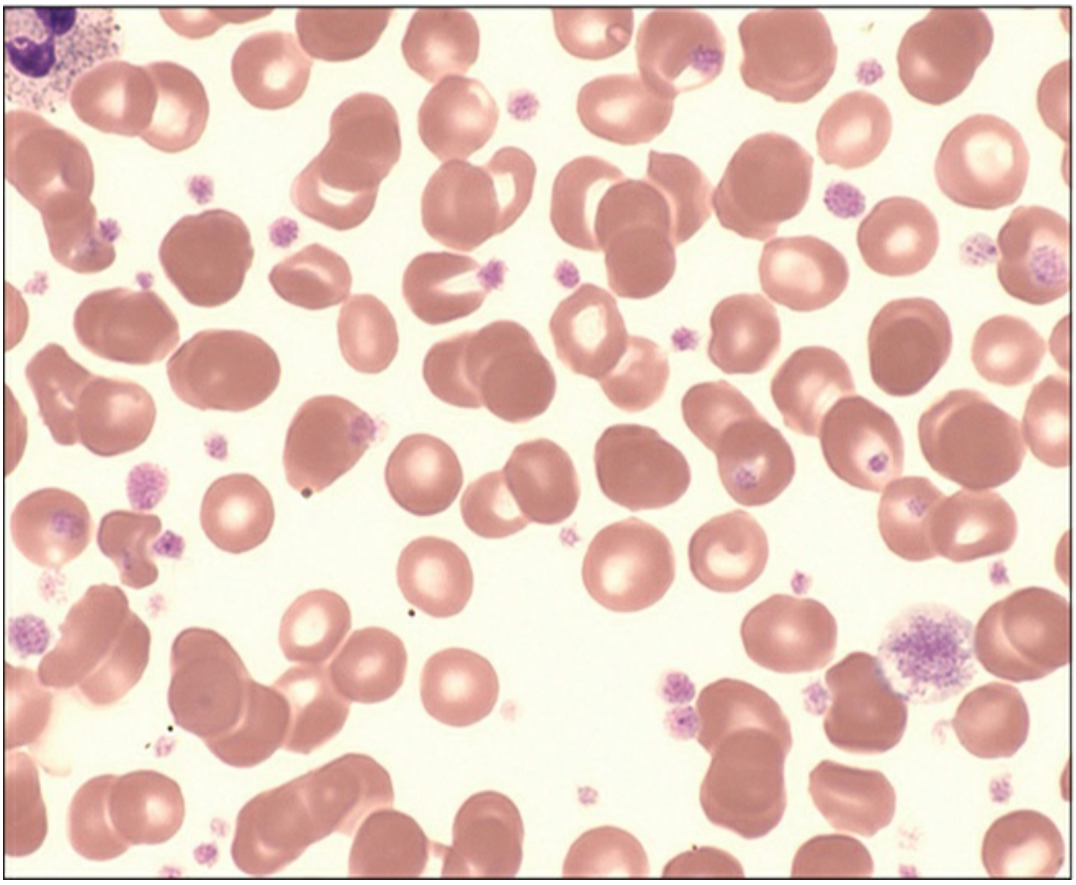


Figure **IIB4-10**

Peripheral blood smear.

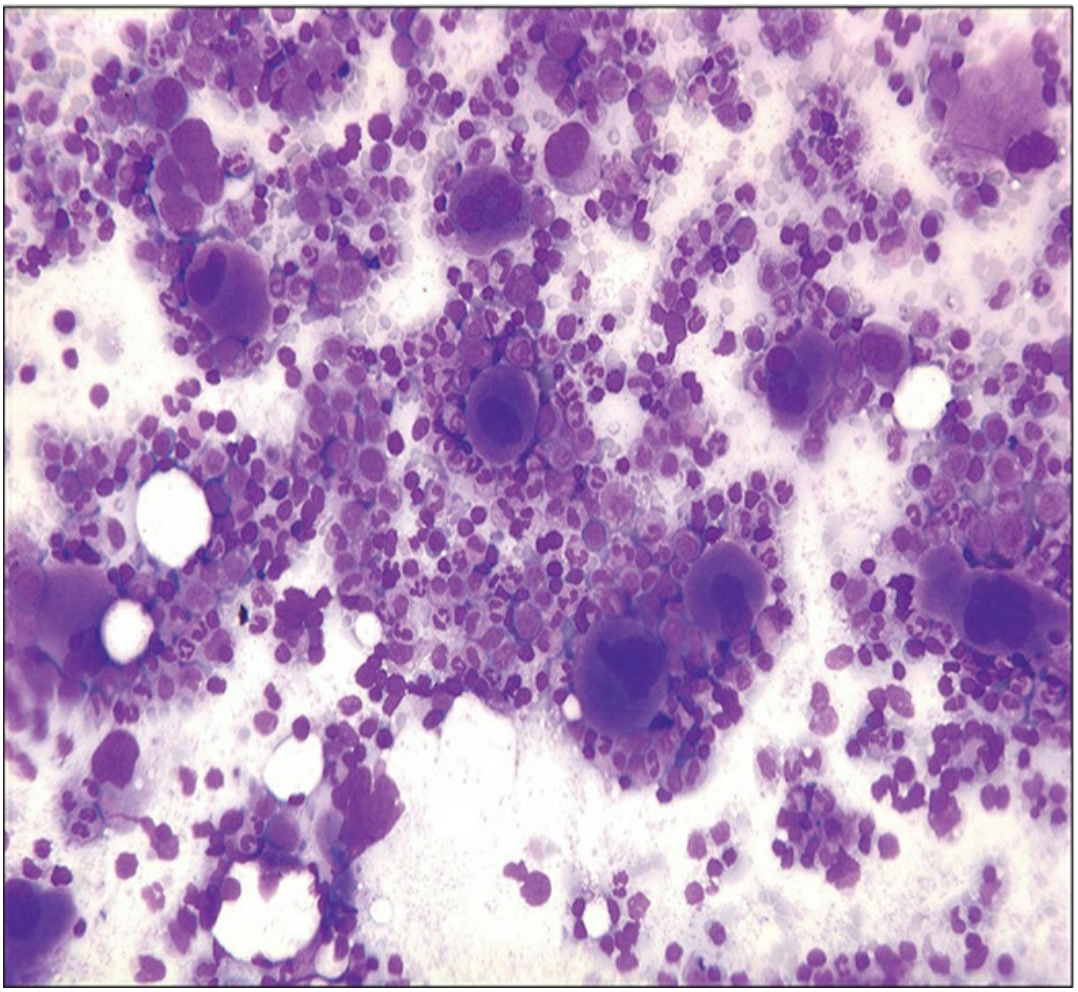


Figure IIB4-11

Bone marrow smear.

Also known as primary thrombocytosis or idiopathic thrombocytosis

Clinical Features

- Patients are usually older than 50 years
- Splenomegaly
- Epistaxis, hemorrhage, or thrombosis
- Digital ischemia paresthesia

Pathology

- Molecular mutations
  - JAK2V617F

    - MPL
    - CALR
- Clonal abnormality involving the megakaryocytic lineage
- Absence of Philadelphia chromosome
- Other causes for thrombocytosis must be excluded

Laboratory Features

White Blood Cells

- Usually normal or mildly increased
- Basophilia absent or minimal

Red Blood Cells

- Normocytic/normochromic anemia
- Microcytic, hypochromic anemia if there is gastrointestinal tract blood loss
- Red blood cell mass not elevated
- No dacryocytes or leukoerythroblastosis

Platelets

- Thrombocytosis with counts $\geq 450 \times 10^9$/L but typically higher
- Platelets vary in size
- Bizarre shapes with agranular forms are not uncommon

Bone Marrow

- Normocellular or moderately hypercellular
- Increased numbers of large to giant megakaryocytes
- Megakaryocytes mass increased
- Increased megakaryocytes arranged in clusters or evenly dispersed
- Blasts <5%

- Absent or minimal reticulin fibrosis
- Normal iron stores

Immunophenotype

- No abnormal phenotypes

Genetics

- 60% of cases harbor JAK2 V617F (exon 14) mutation
- 20–25% of cases have CALR mutations
- 3–5% of cases have MPL mutations
- JAK2 exon 12 mutations absent

Diagnostic Criteria for Essential Thrombocythemia

- Diagnosis of ET requires meeting all four major criteria or the first three major and minor criteria

Major Criteria

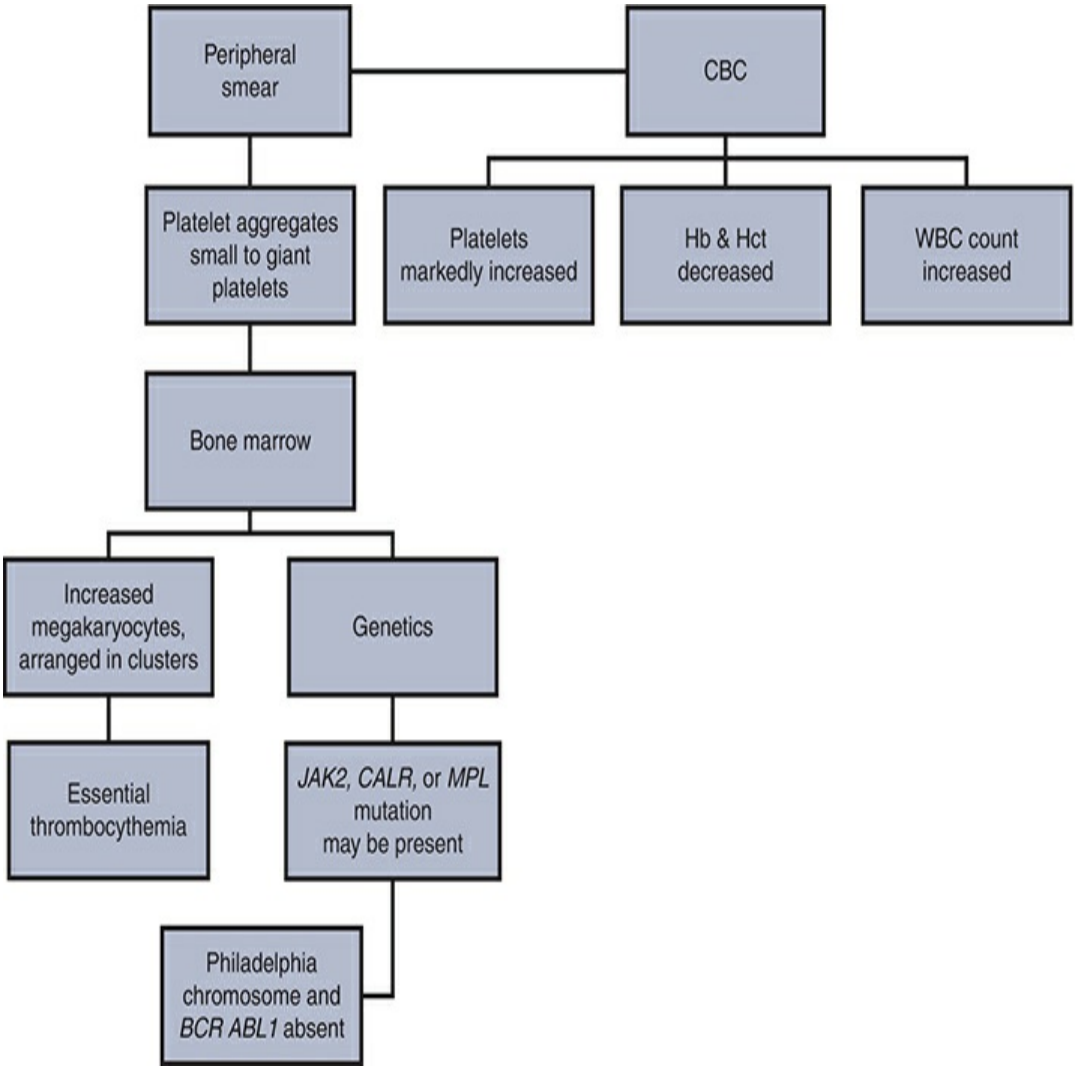
- Persistent platelet count ≥450 × 10^9/L
- Bone marrow biopsy findings
- Megakaryocytic proliferation with loose cluster formation
- Enlarged, hyperlobulated megakaryocytes
- No significant granulocytic or erythroid proliferation or granulocytic shift to the left
- No significant granulocytic or erythroid dysplasia
- No significant reticulin fibrosis
- Exclusion of other myeloproliferative neoplasms
- t(9;22)(q34.1;q11.2); BCR-ABL1 negative
- Presence of JAK2 , CALR , or MPL mutation

Minor Criteria

- Another clonal abnormality or exclusion of reactive

thrombocytosis

Diagnostic Scheme



CHRONIC EOSINOPHILIC LEUKEMIA, NOT OTHERWISE SPECIFIED

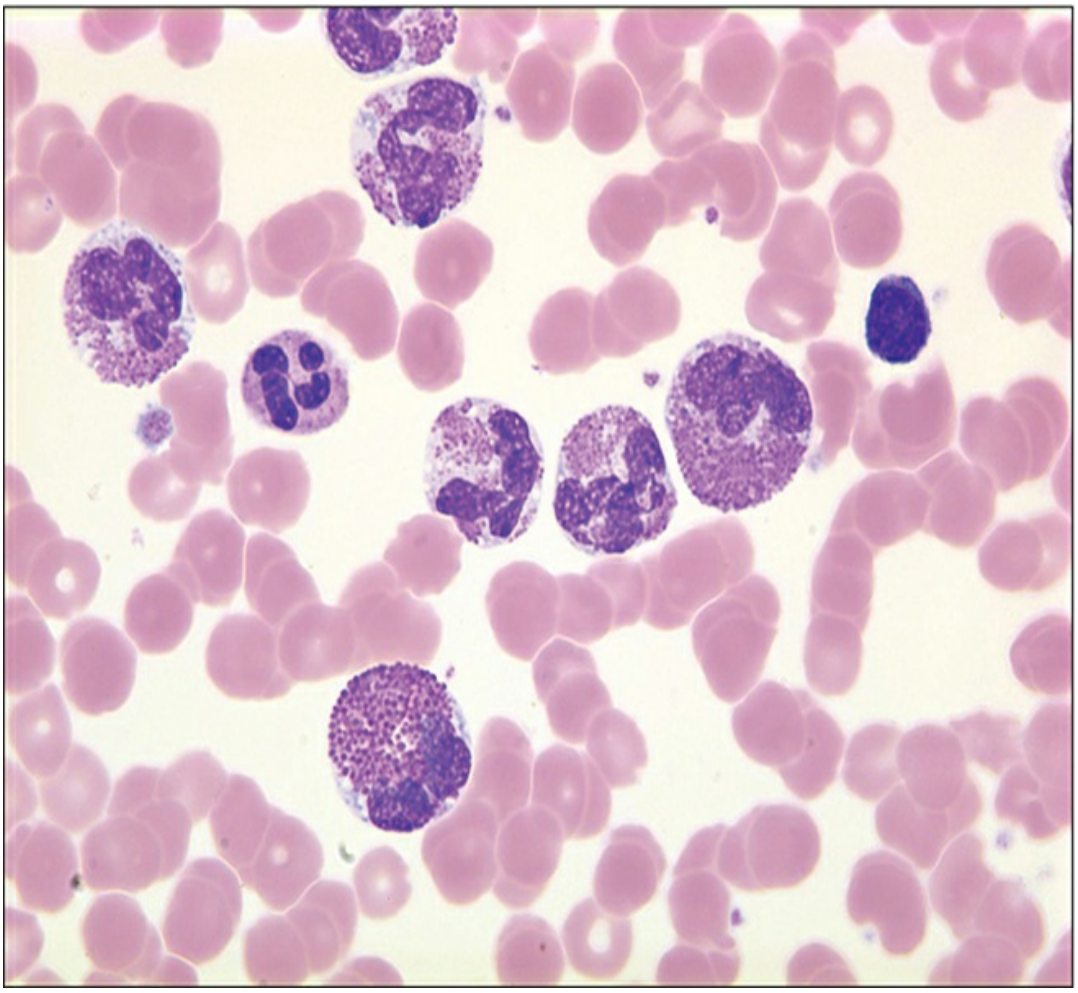


Figure IIB4-12

Peripheral blood smear.

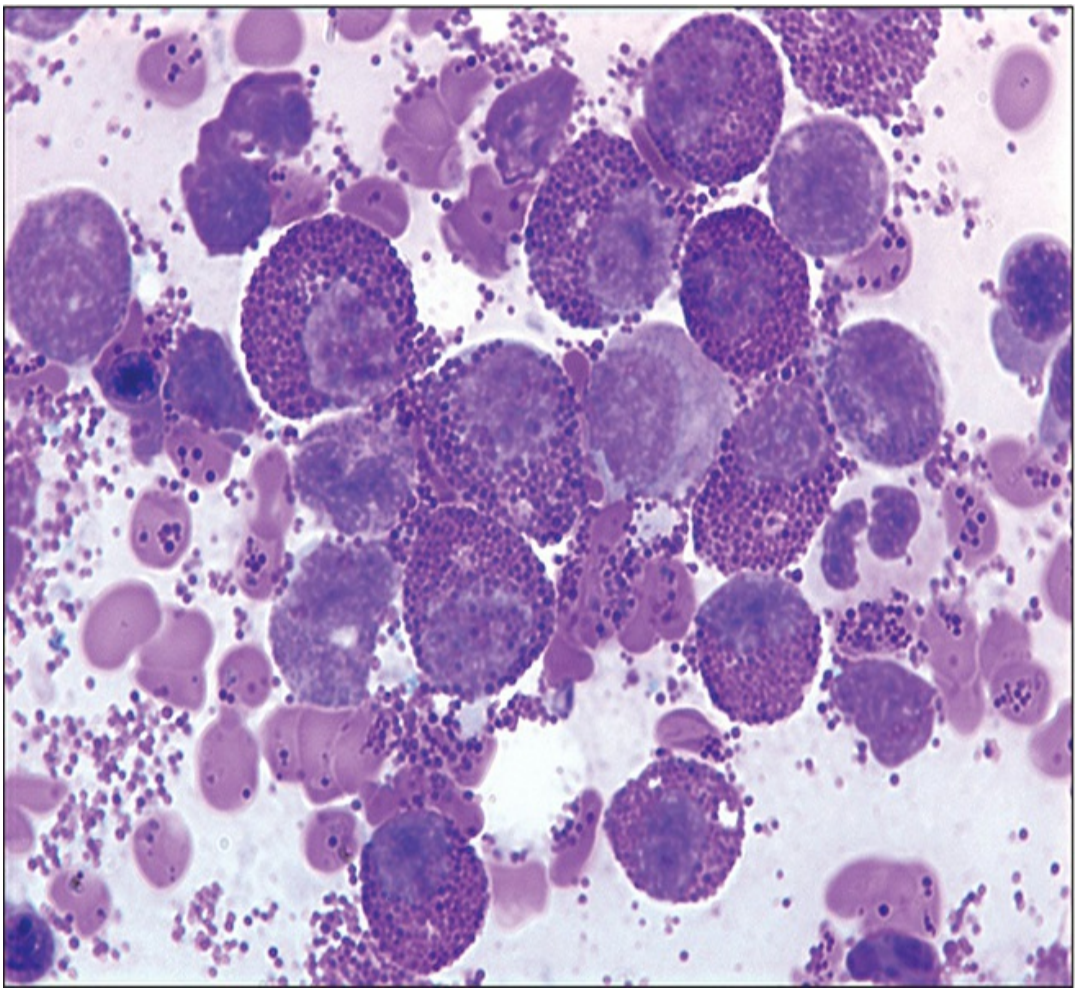


Figure IIB4-13

Bone marrow smear.

Clinical Features

- Many patients are asymptomatic
- Hepatosplenomegaly
- Skin involvement
- Fever, night sweats, cough, and weight loss
- Central nervous system irregularities, congestive heart failure, and pulmonary fibrosis

Pathology

- Rare
- Usually middle-aged males are affected

- Tissue eosinophil infiltration causes organ damage
- Clonal abnormality

Laboratory Features

White Blood Cells

- Persistent absolute eosinophilia ($\geq 1.5 \times 10^9$/L)
- 30–70% eosinophils
- Count is usually $\geq 30.0 \times 10^9$/L
- <20% blasts
- Eosinophils exhibit sparse granulation with clear areas of cytoplasm and vacuoles and may be increased in size

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Eosinophilia with increasing myeloid immaturity
- <20% blasts
- Charcot-Leyden crystals are often present
- Increased number of eosinophilic myelocytes

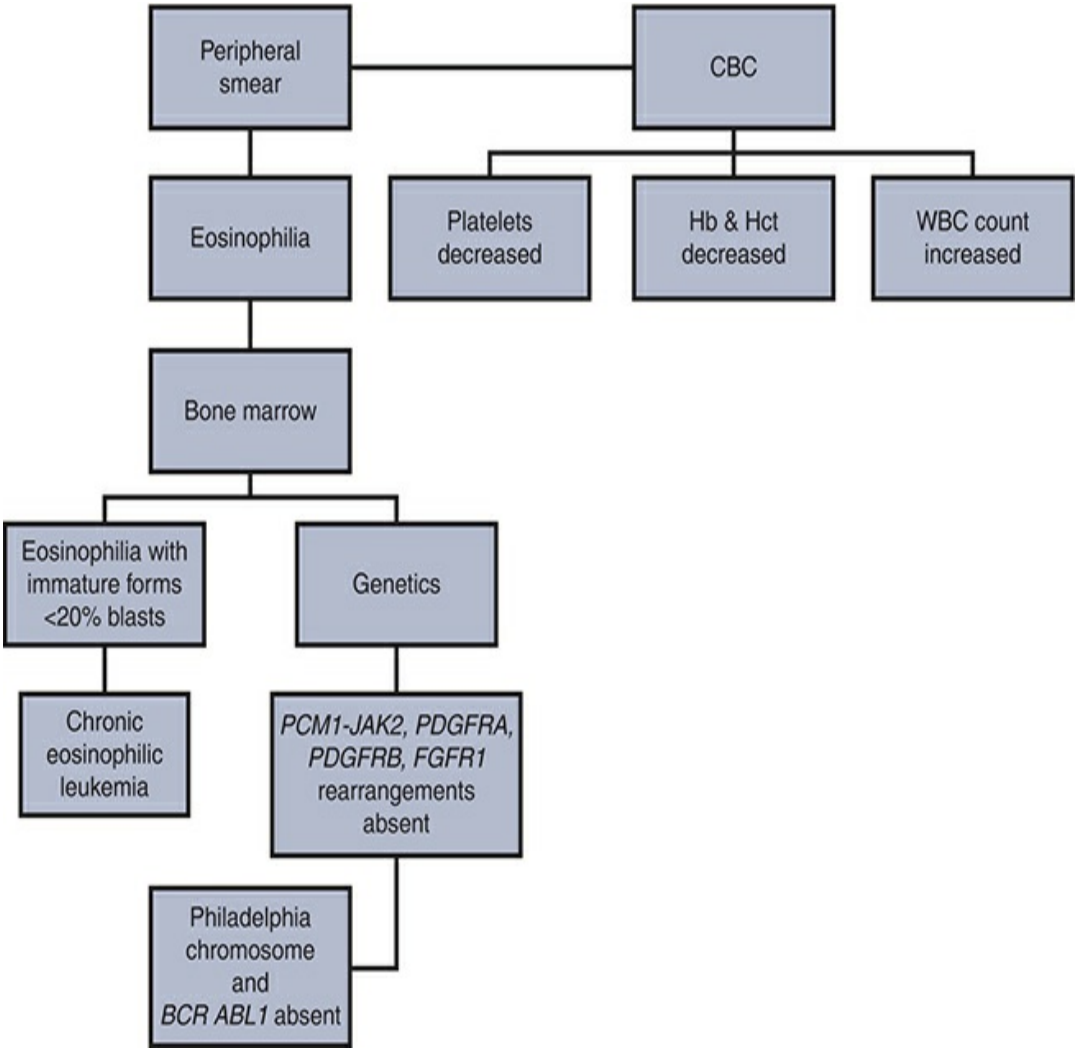
Immunophenotype

- No specific abnormalities

Genetics

- No single or specific cytogenetic or molecular genetic abnormalities
- Cases with rearrangement of PDGFRA , PDGFRB , or FGFR1 , or with PCM1-JAK2 are specifically excluded

Diagnostic Scheme



CHAPTER 5

Mastocytosis

MASTOCYTOSIS

Criteria

- Classified as a separate disease category because of its unique clinical and pathologic features
- Ranges from indolent cutaneous disease to aggressive systemic disease

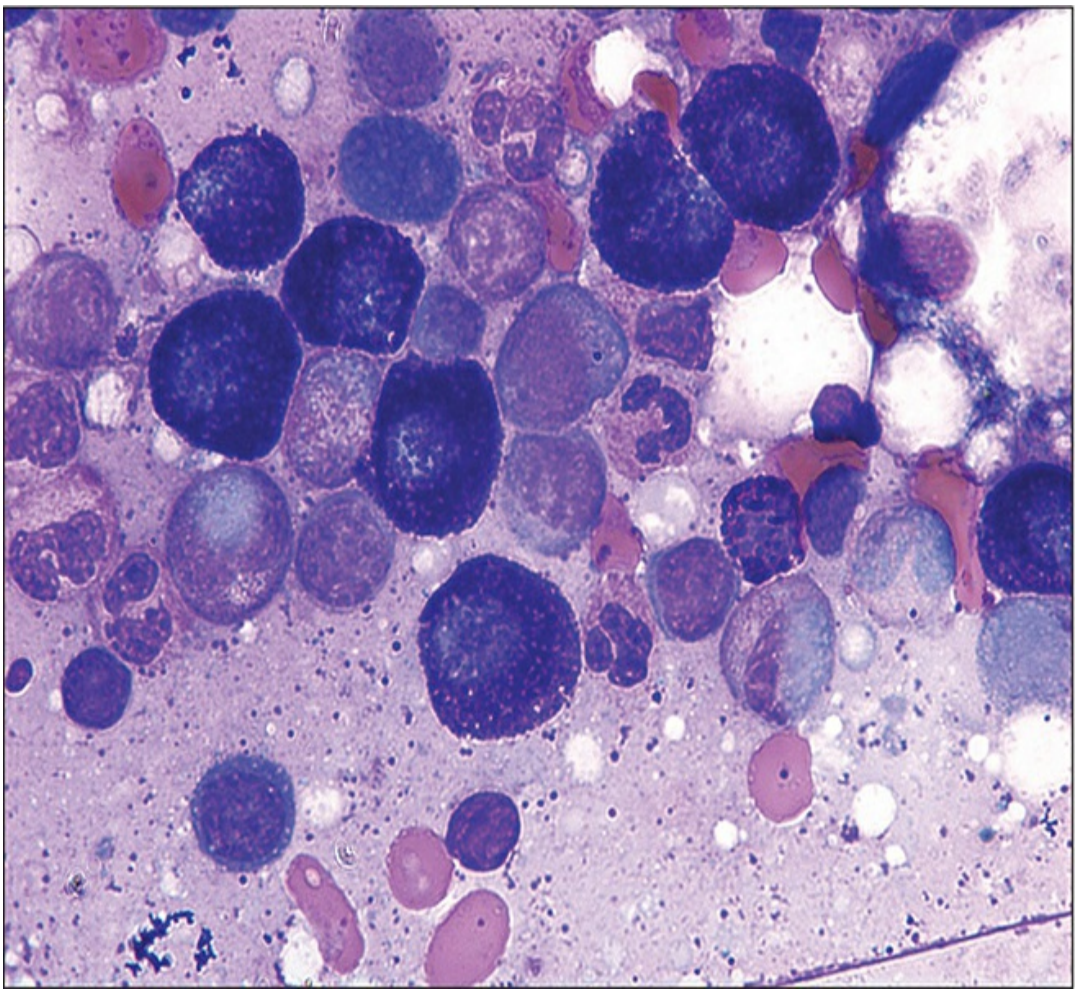


Figure IIB5-1

Bone marrow smear.

Classification

- Cutaneous mastocytosis
- Systemic mastocytosis
  - Indolent systemic mastocytosis

    - Systemic mastocytosis with an associated hematologic neoplasm; at least one extracutaneous organ is involved
    - Aggressive systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma

Clinical Features

- Fever, fatigue, and weight loss
- Skin manifestations such as pruritus, urticaria, and flushing
- Abdominal pain, gastrointestinal distress, headache, and hypotension
- Bone pain, fractures, arthralgias, and myalgias
- Splenomegaly, lymphadenopathy, and hepatomegaly

MastocytosisPathology

- A clonal, neoplastic proliferation of mast cells that accumulate in one or more organ systems
- Presence of clusters of abnormal mast cells

Laboratory Features

White Blood Cells

- May have 10% or more mast cells
- Mast cells are morphologically abnormal
- Eosinophilia is a common finding

Red Blood Cells

- Mild to moderate normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- ≥20% mast cells
- Diffuse, compact infiltrate with reduction in fat cells and normal hematopoietic cells
- Mast cells are atypical with hypogranular cytoplasm and irregularly shaped monocytoid or bilobulated nuclei

Cytochemistry

- Toluidine blue may be positive

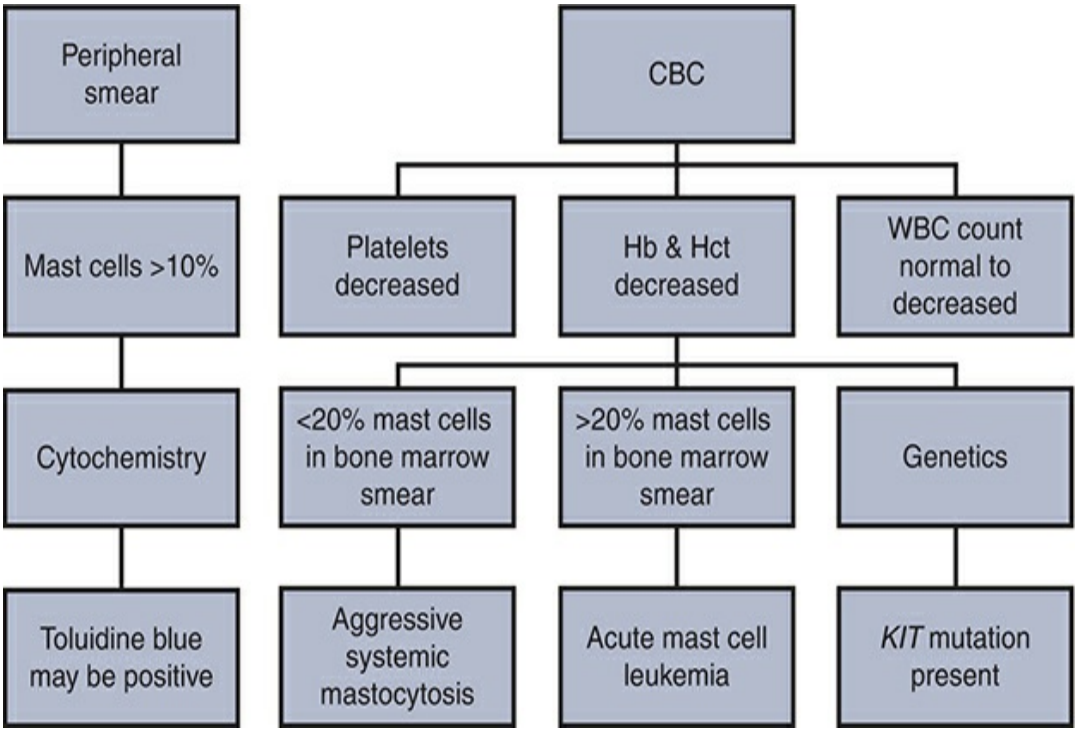
Immunophenotype

- Expresses CD9, CD33, CD45, CD68, and CD117
- Lacks CD14, CD15, and CD16
- Reacts with antibodies against tryptase

Genetics

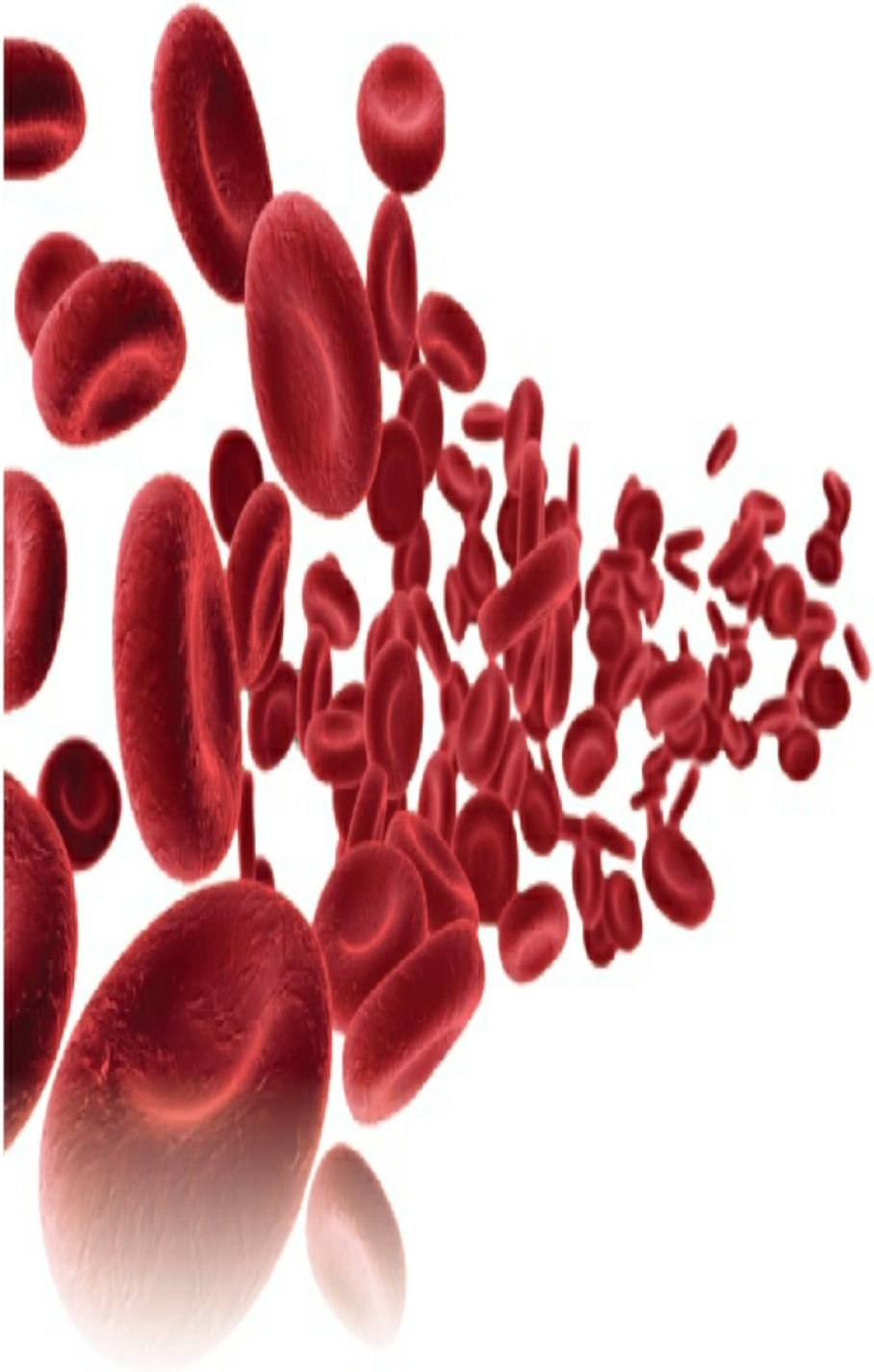
- ≥90% of cases associated with point mutations within KIT
- TET2 mutations seen in about 30% of cases but not specific to mastocytosis
- ASXL1 and CBL mutations may be predictive of survival in advanced systemic mastocytosis
- SRSF2 and RUNX1 may be associated with higher-risk disease in advanced systemic mastocytosis

Diagnostic Scheme


Peripheral smear
CBC
Mast cells >10%
Platelets decreased
Hb & Hct decreased
WBC count normal to decreased
Cytochemistry
<20% mast cells in bone marrow smear
>20% mast cells in bone marrow smear
Genetics
Toluidine blue may be positive
Aggressive systemic mastocytosis
Acute mast cell leukemia
KIT mutation present

CHAPTER 6

Myelodysplastic Syndromes (MDS)



MYELODYSPLASTIC SYNDROMES

Criteria

- Group of clonal hematopoietic stem cell diseases characterized by
  - Ineffective hematopoiesis
  - <20% blasts in peripheral blood and bone marrow
  - Dysplasia in ≥10% of cells in one or more myeloid lineages
  - Cytopenia in at least one hematopoietic lineage
  - Persistent cytopenias
    - The increased degree of apoptosis within the bone marrow progenitors contributes to the cytopenias

Definitions

Dyserythropoiesis

Peripheral Blood

- Dual (dimorphic) red blood cell population:
  - Normochromic/hypochromic
  - Normocytic/macrocytic or microcytic

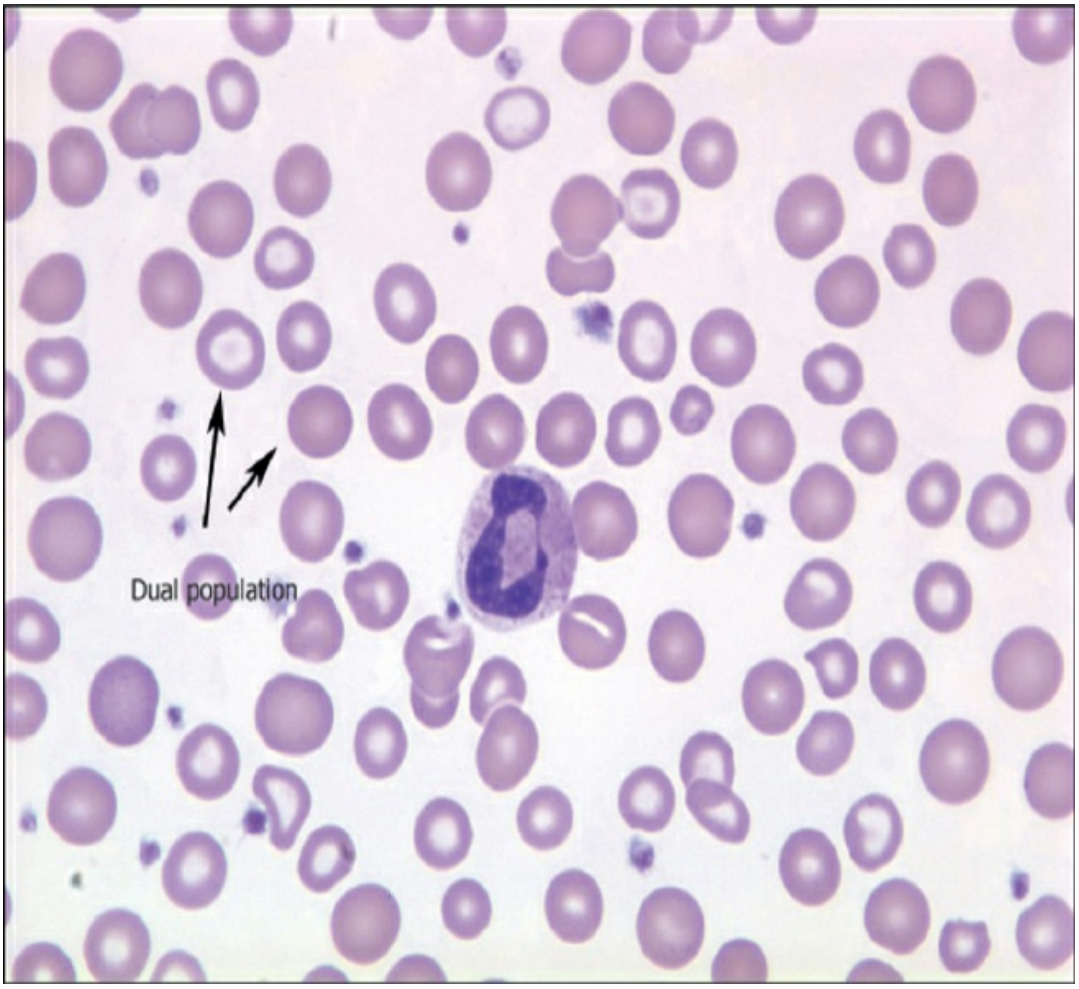


Figure **IIB6-1**

Peripheral blood smear.

- Basophilic stippling

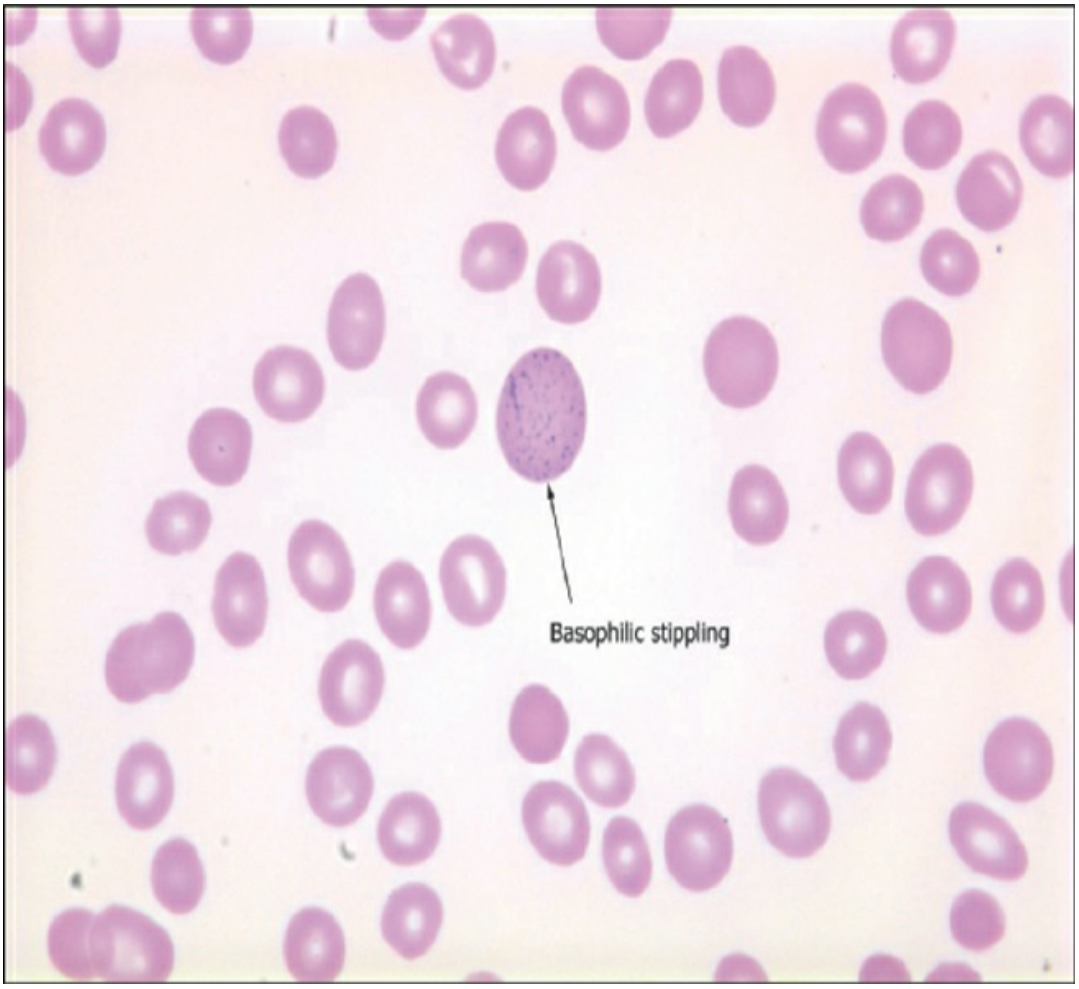


Figure **IIB6-2**

Peripheral blood smear.

- Pappenheimer bodies

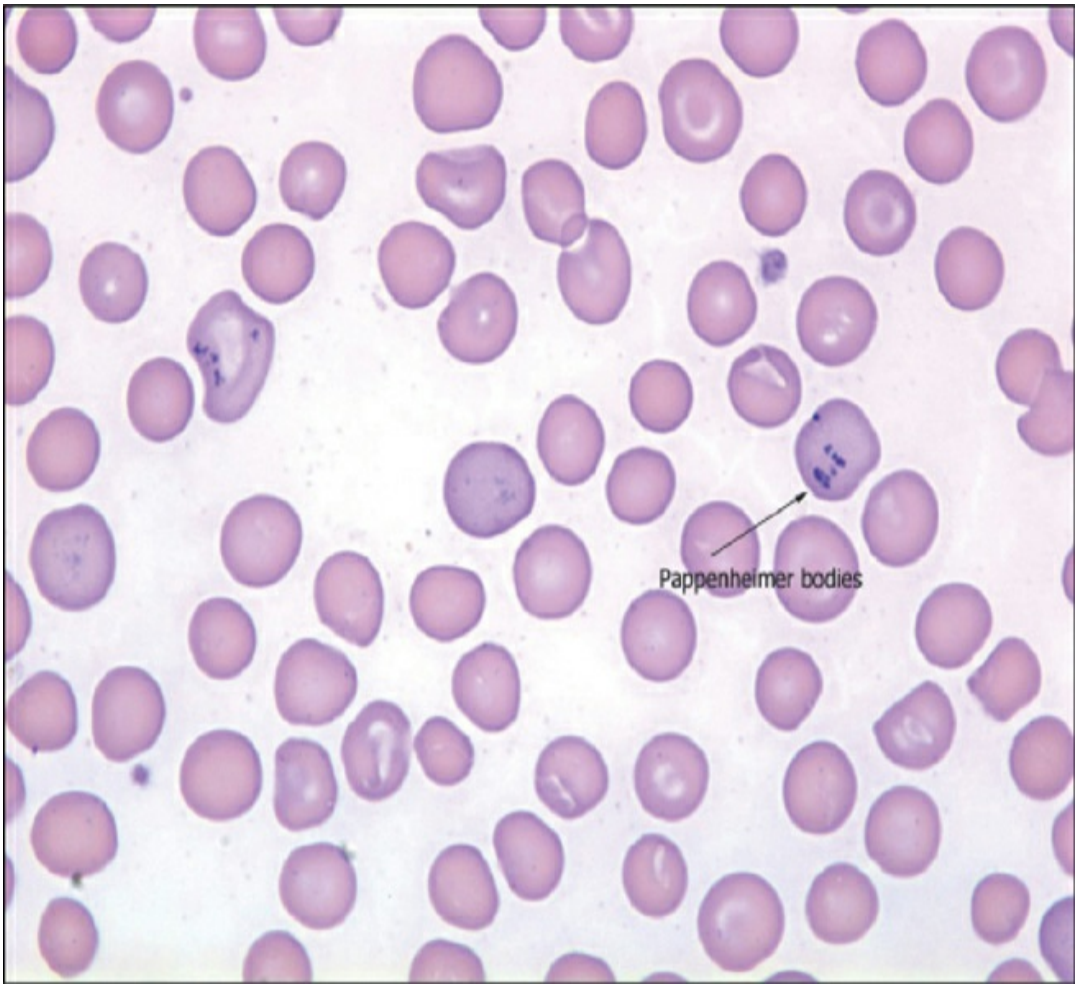


Figure **IIB6-3**

Peripheral blood smear.

Bone Marrow

- Megaloblastic changes

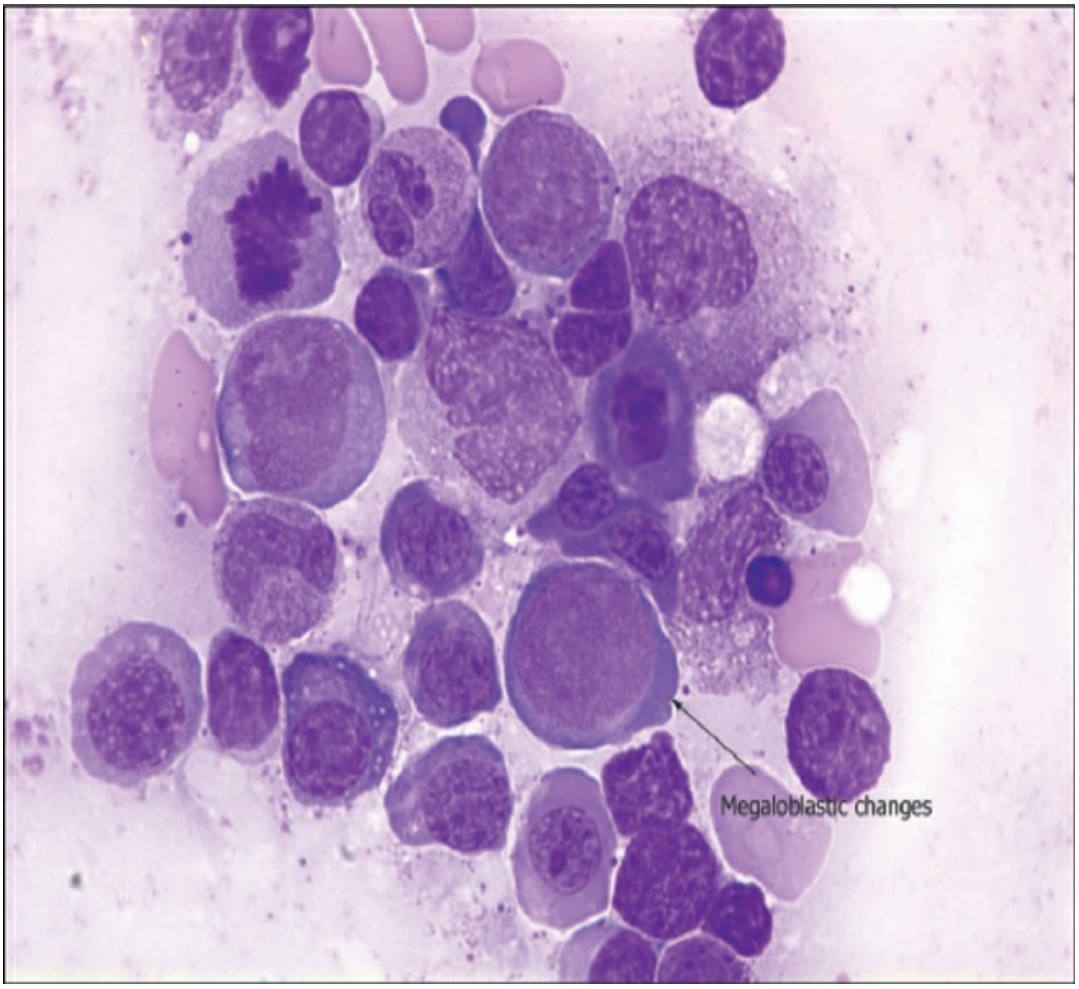


Figure **IIB6-4**

Bone marrow smear.

- Megaloblastoid changes
- Abnormal mitotic figures

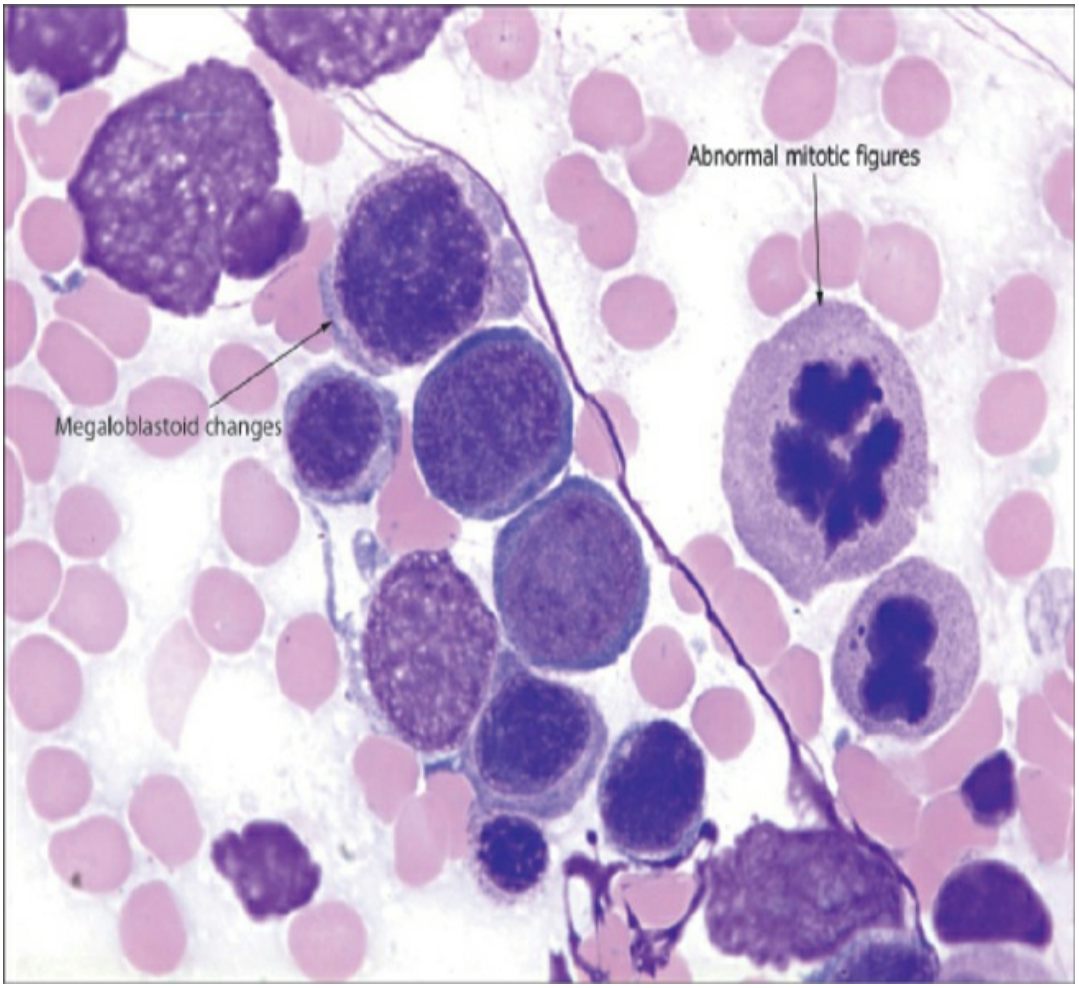


Figure **IIB6-5**

Bone marrow smear.

- Nuclear budding
- Karyorrhexis

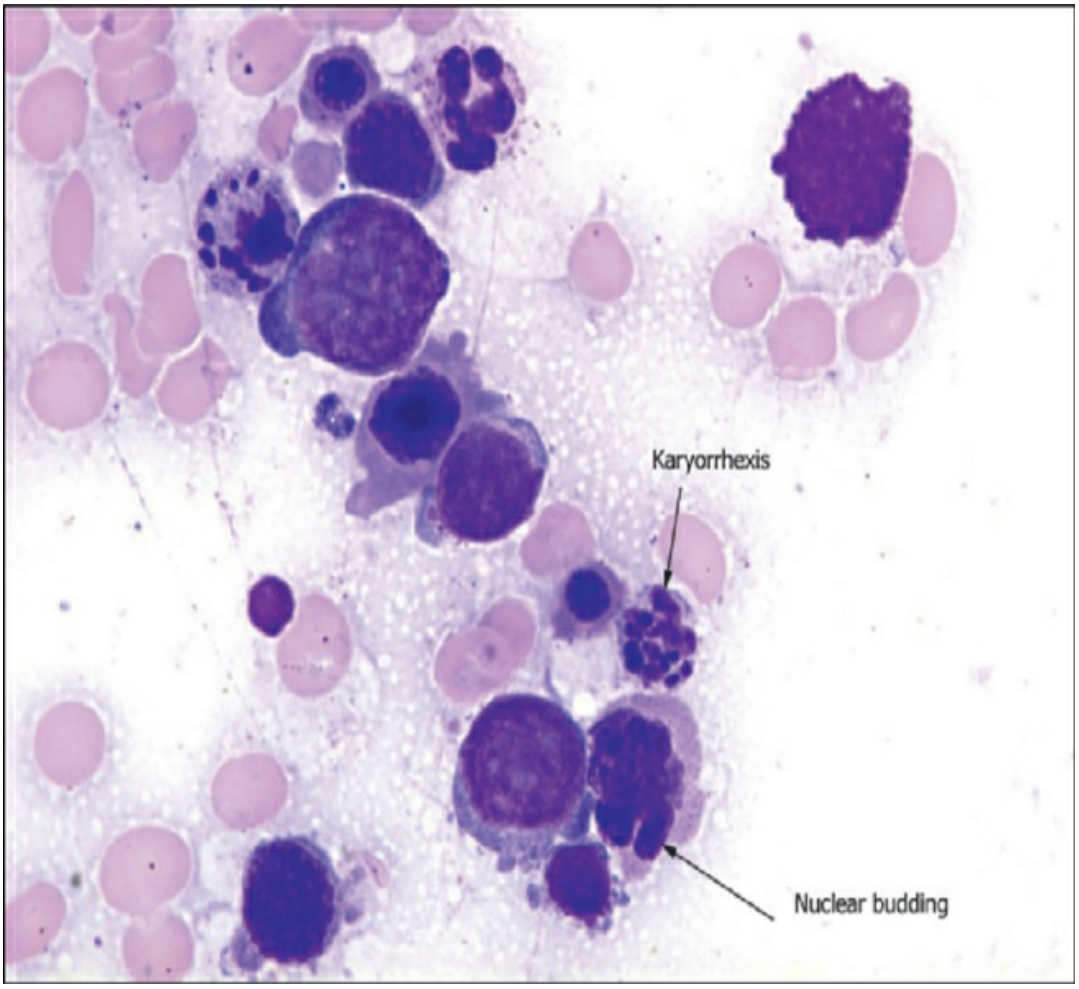


Figure **IIB6-6**

Bone marrow smear.

- Multinuclearity

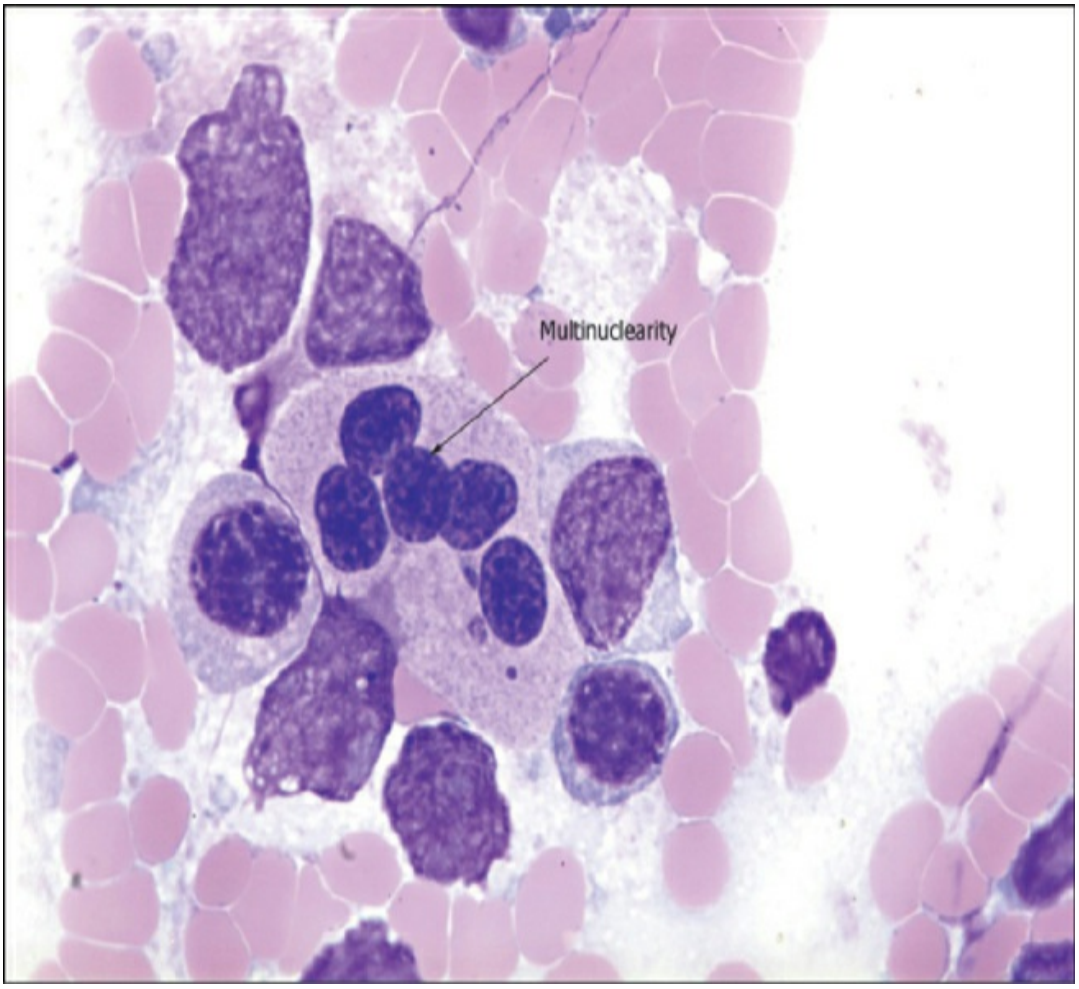


Figure **IIB6-7**

Bone marrow smear.

- Vacuolated erythroblasts

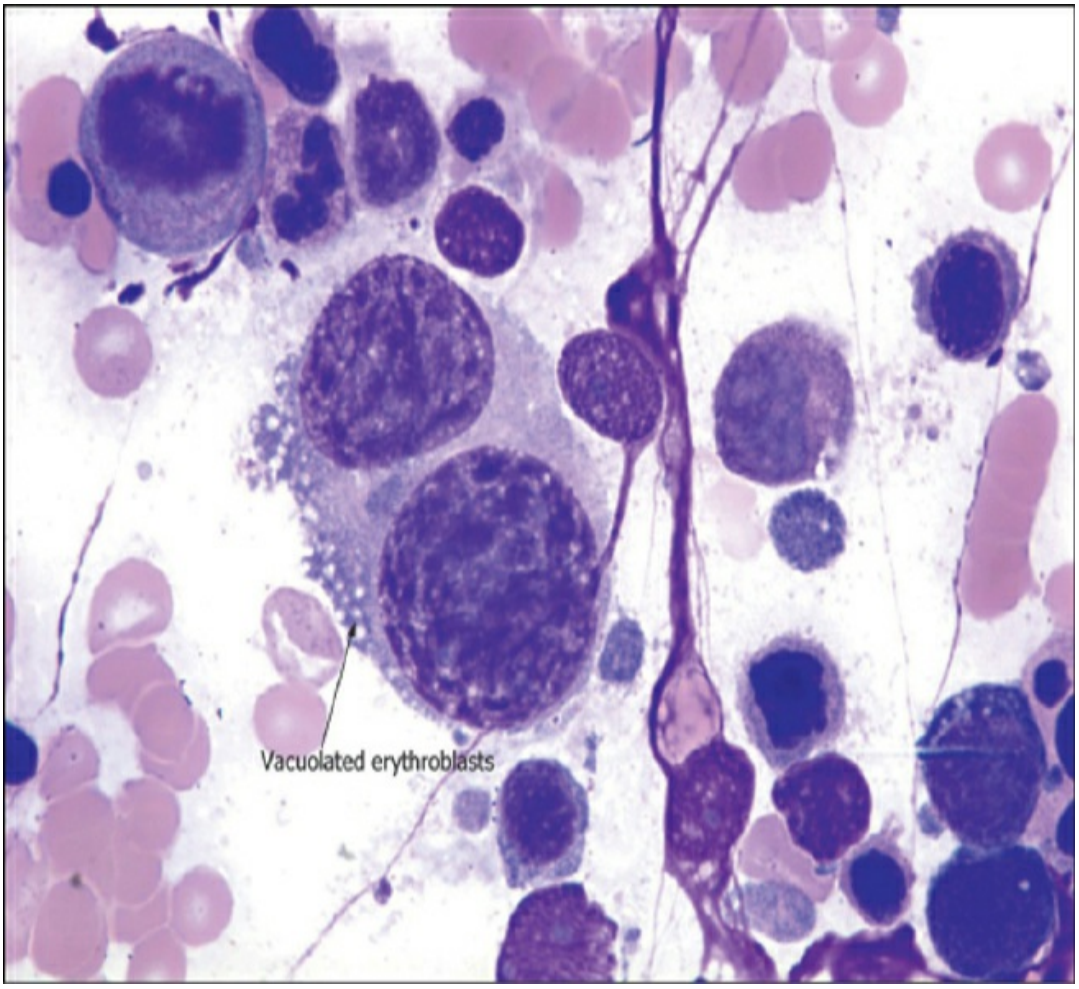


Figure **IIB6-8**

Bone marrow smear.

- Ring sideroblasts (erythroblast with at least five iron granules covering at least one-third the circumference of the nucleus)

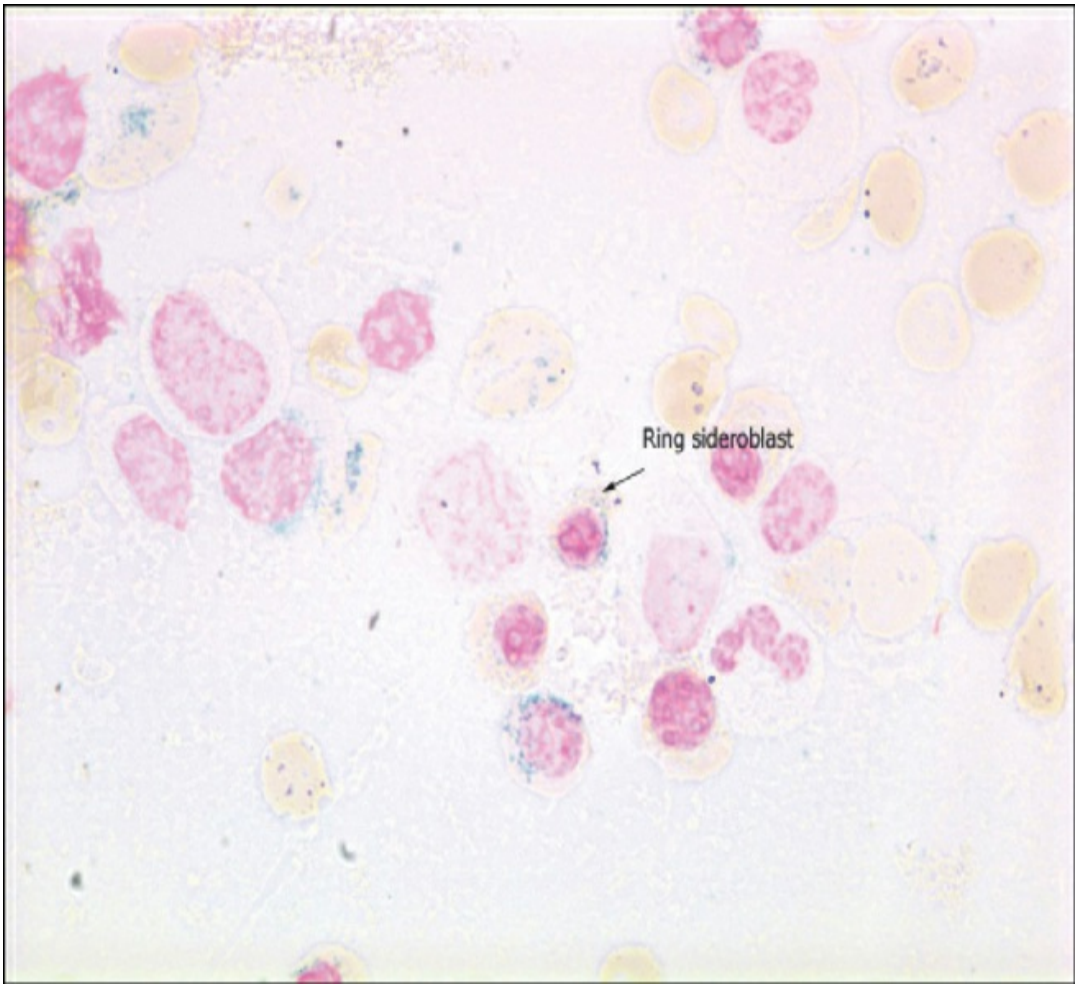


Figure **IIB6-9**

Bone marrow smear. Prussian blue stain.

- Defective hemoglobinization

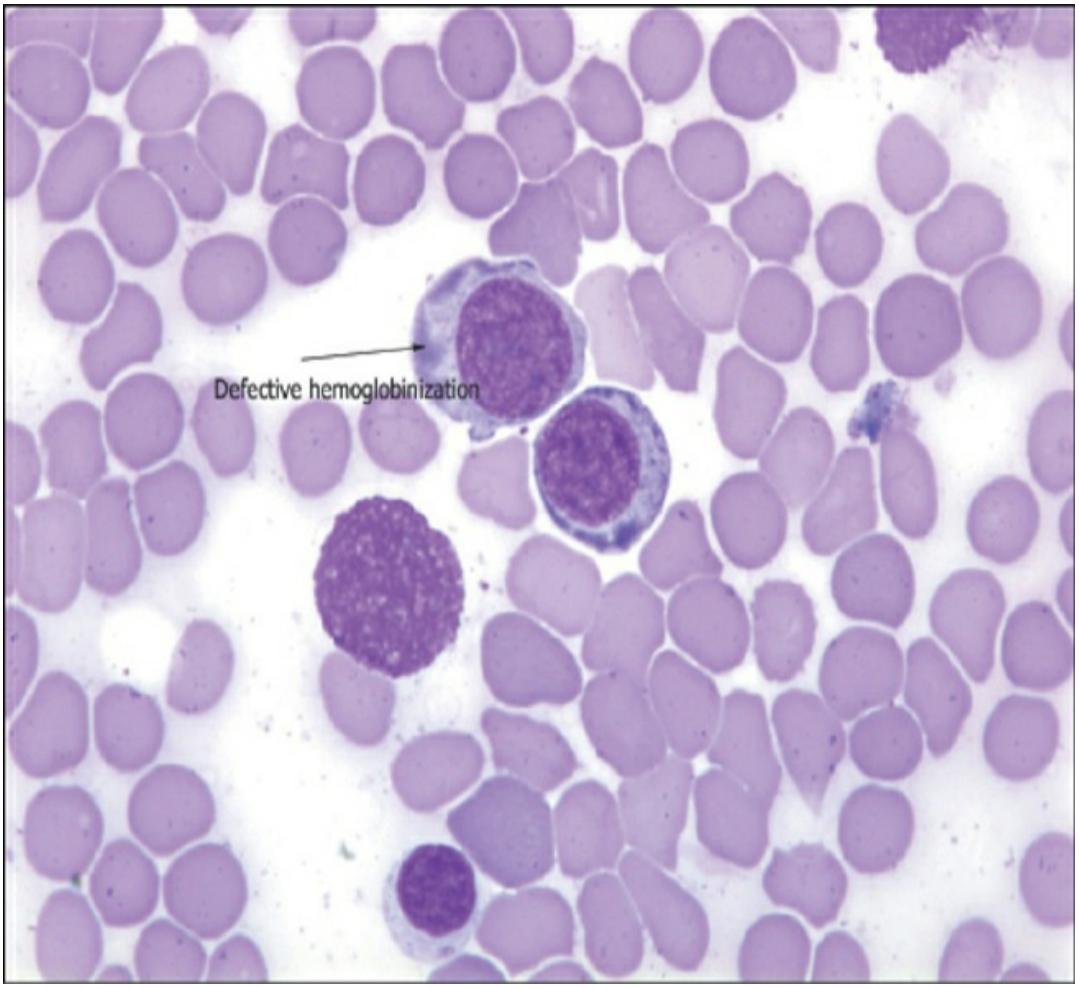


Figure **IIB6-10**

Bone marrow smear.

- Irregular nuclear outlines

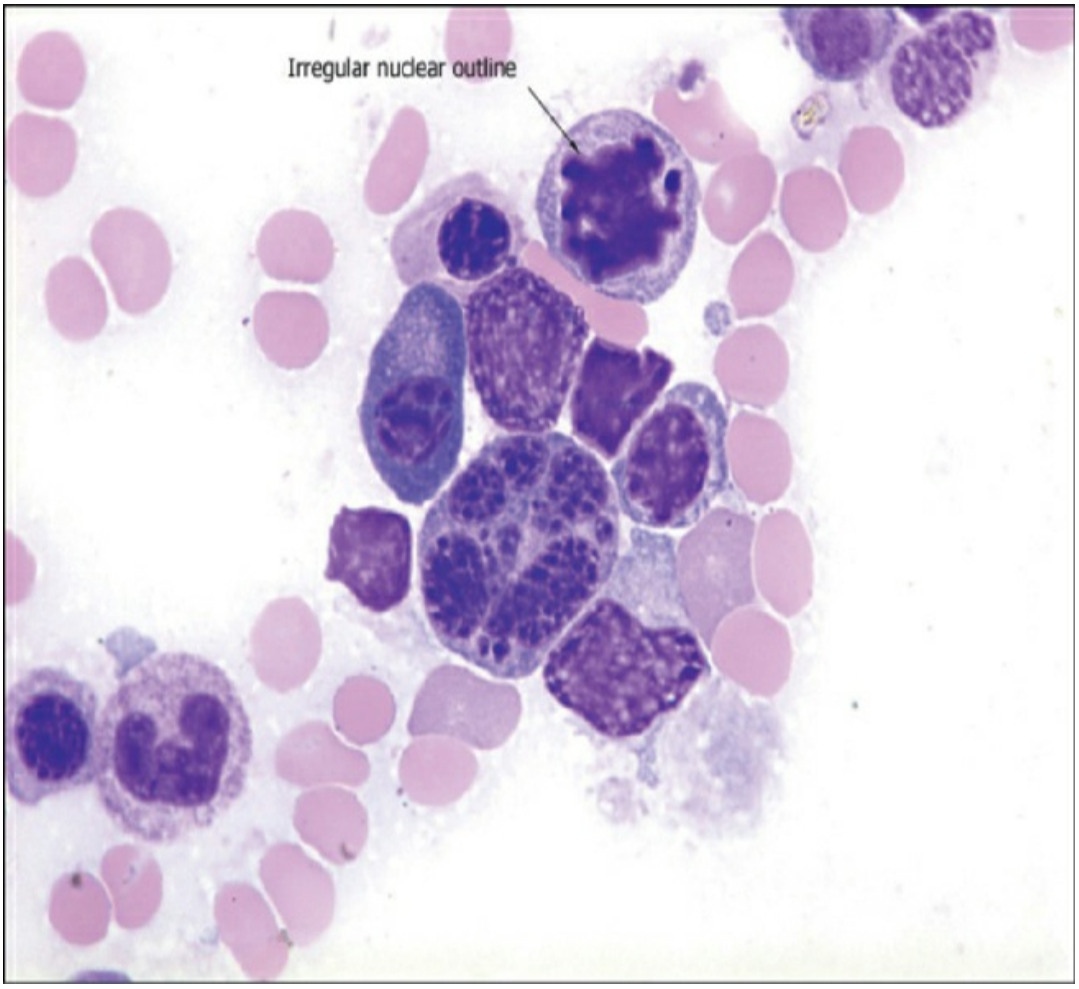


Figure **IIB6-11**

Bone marrow smear.

- Irregular clefts of cytoplasm

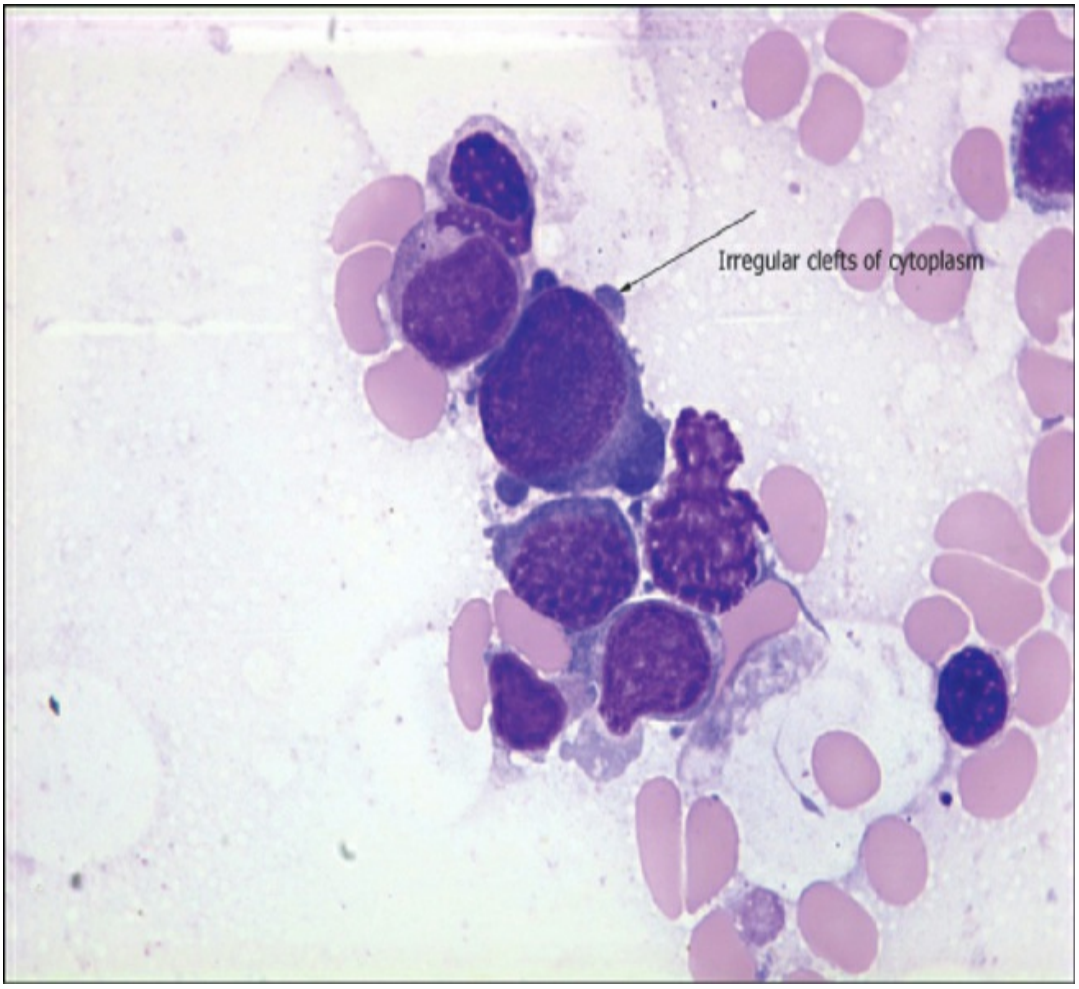


Figure **IIB6-12**

Bone marrow smear.

- Erythroid hyperplasia with shift to the left in erythroid precursors

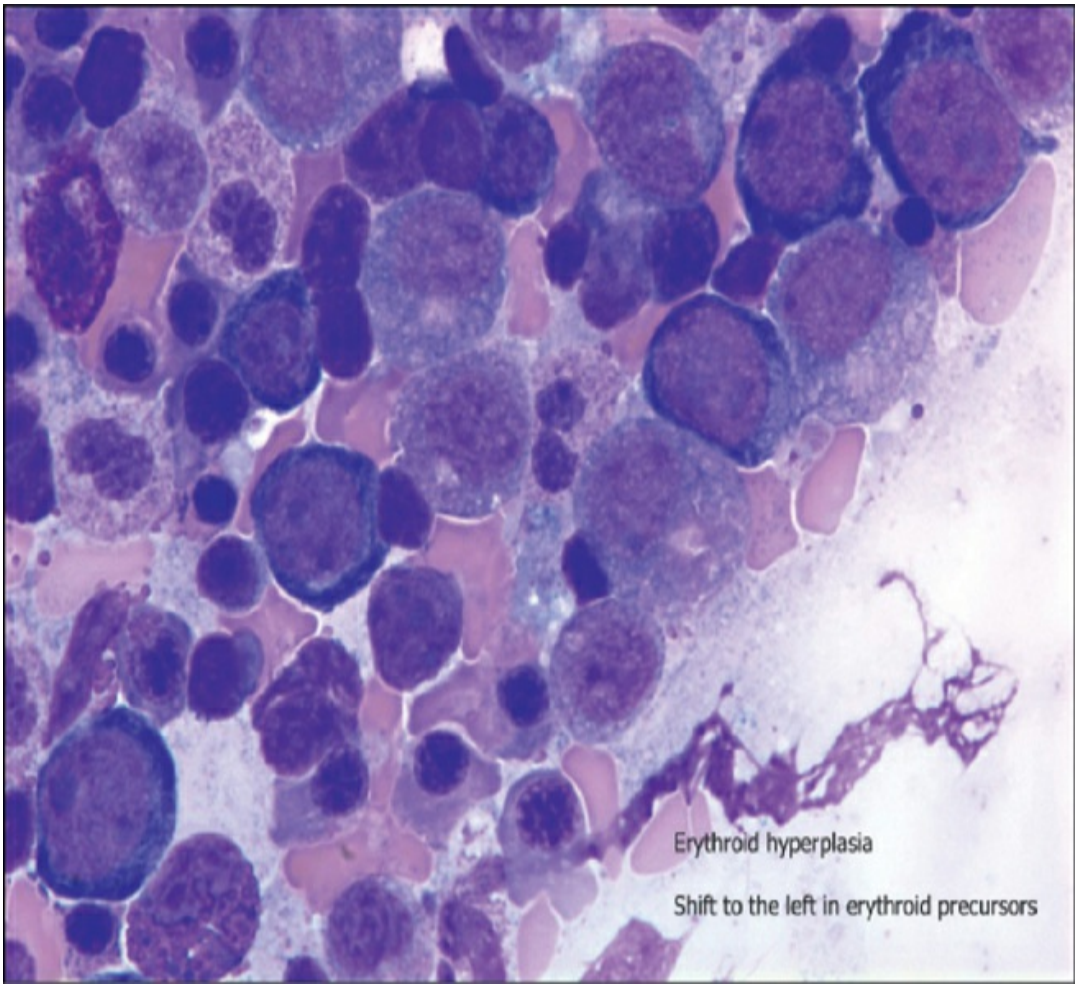


Figure **IIB6-13**

Bone marrow smear.

Dysgranulopoiesis

Peripheral Blood

- Pseudo Pelger-Huët nucleus/abnormal segmentation

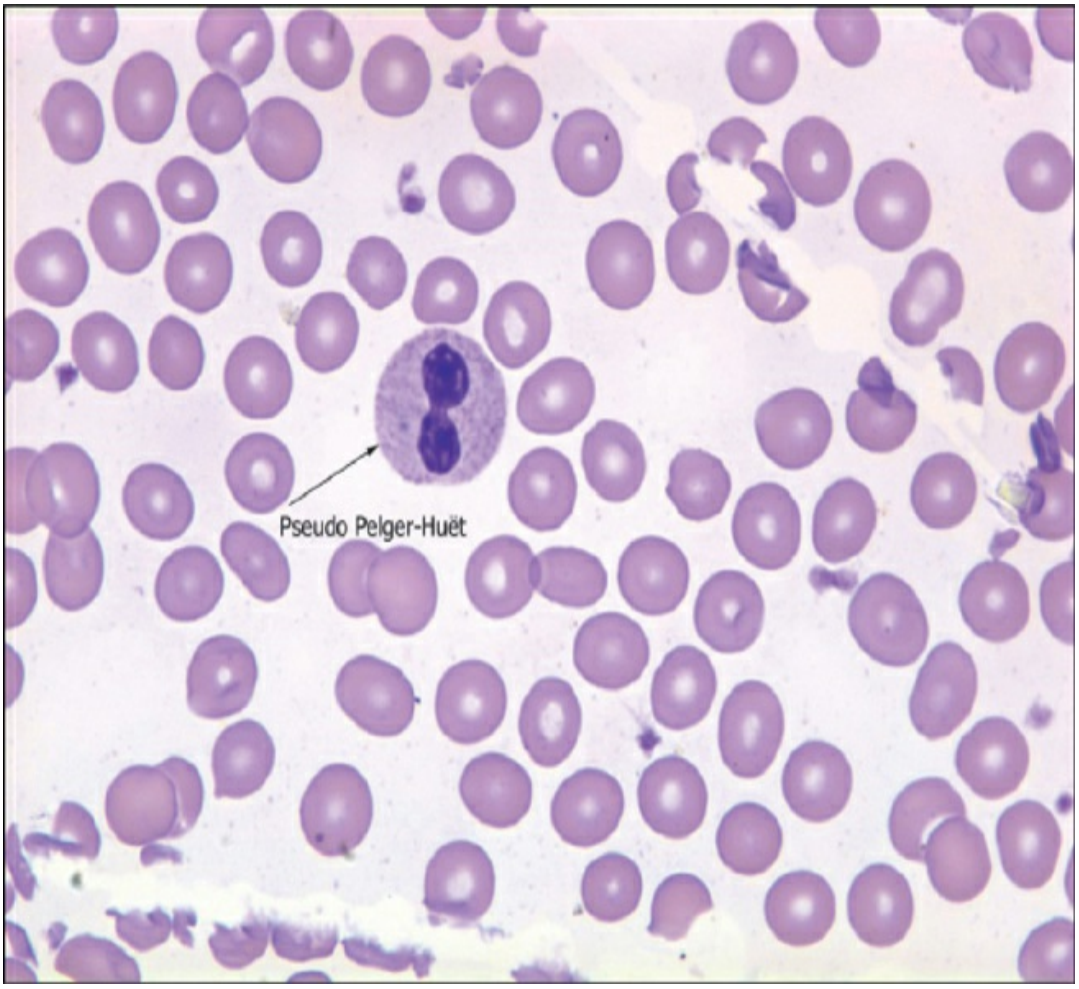


Figure **IIB6-14**

Peripheral blood smear.

- Pseudo Chediak-Higashi granules

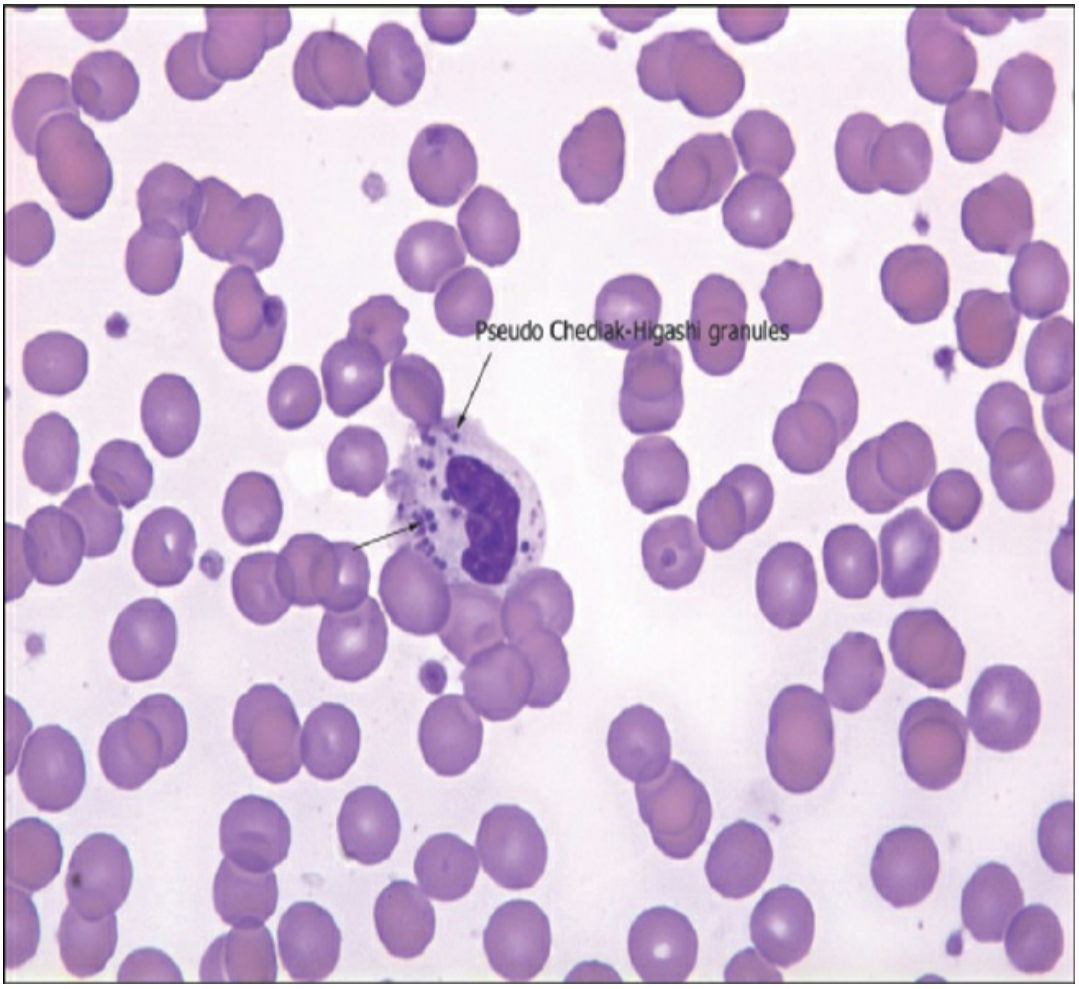


Figure **IIB6-15**

Peripheral blood smear.

- Hyperclumped neutrophil nuclei

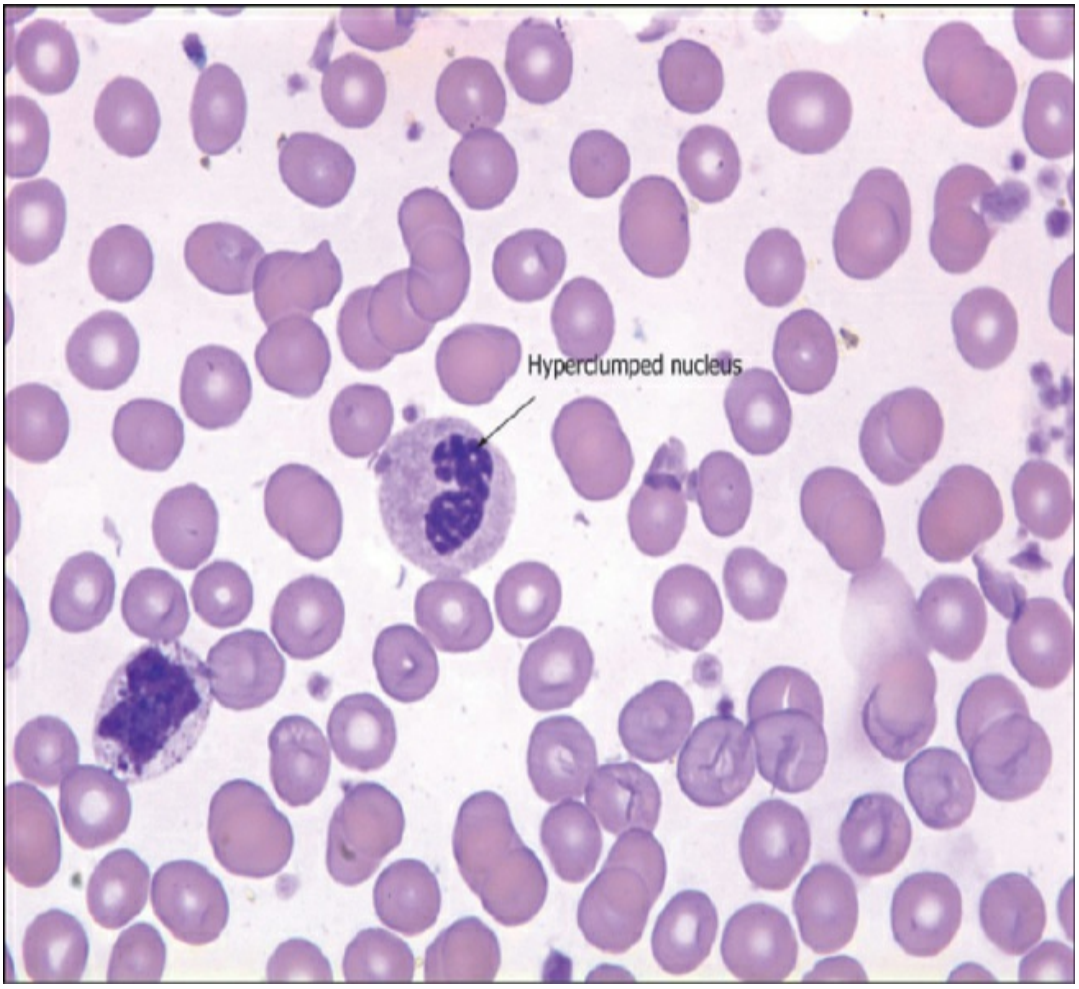


Figure **IIB6-16**

Peripheral blood smear.

- Monocytosis

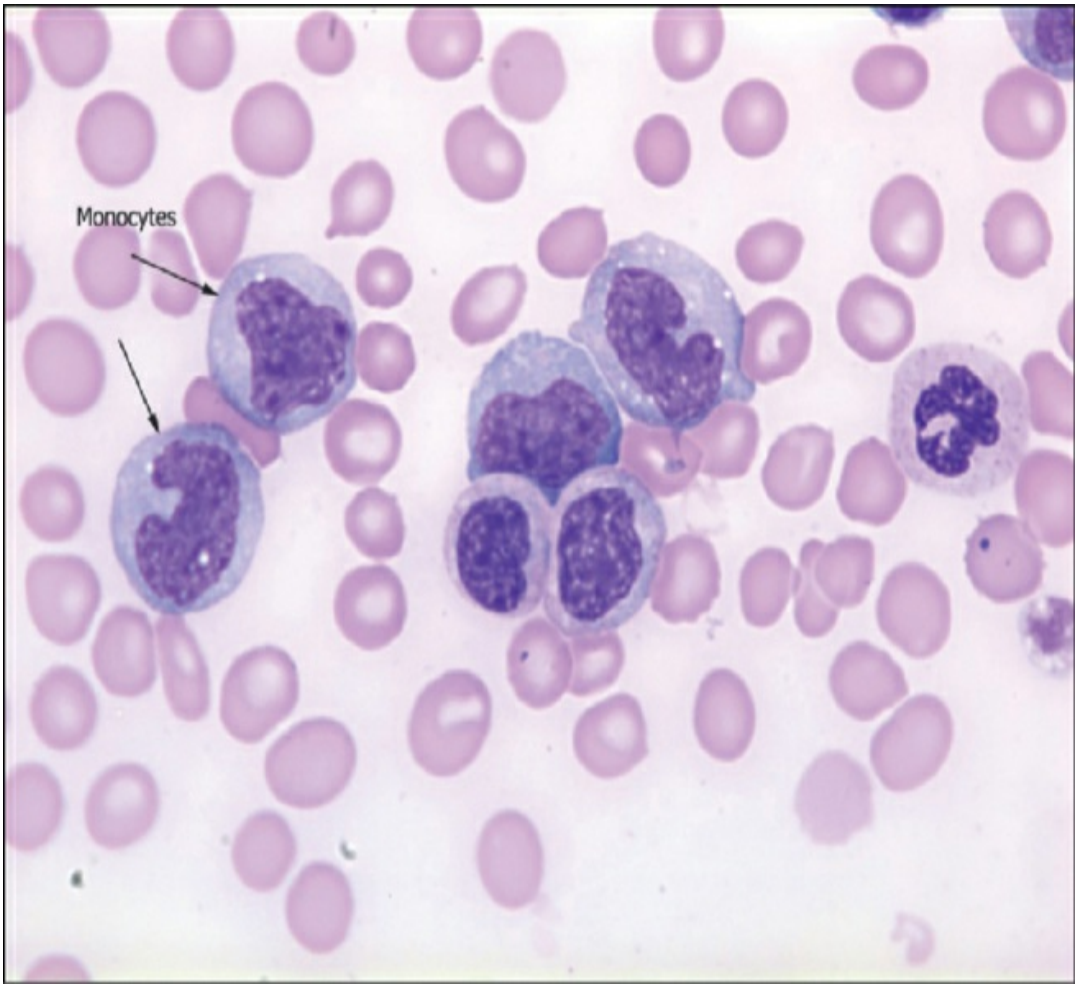


Figure **IIB6-17**

Peripheral blood smear.

- Ring nucleus

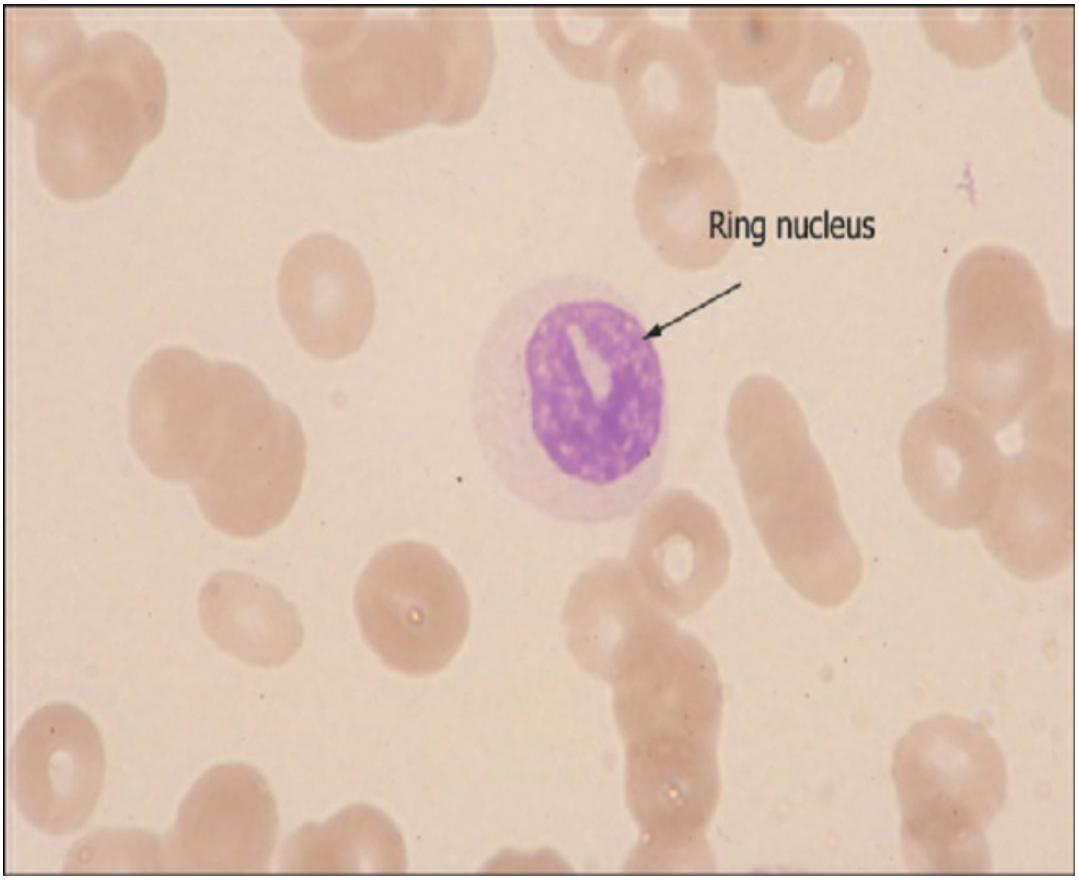


Figure **IIB6-18**

Peripheral blood smear.

- Abnormal segmentation

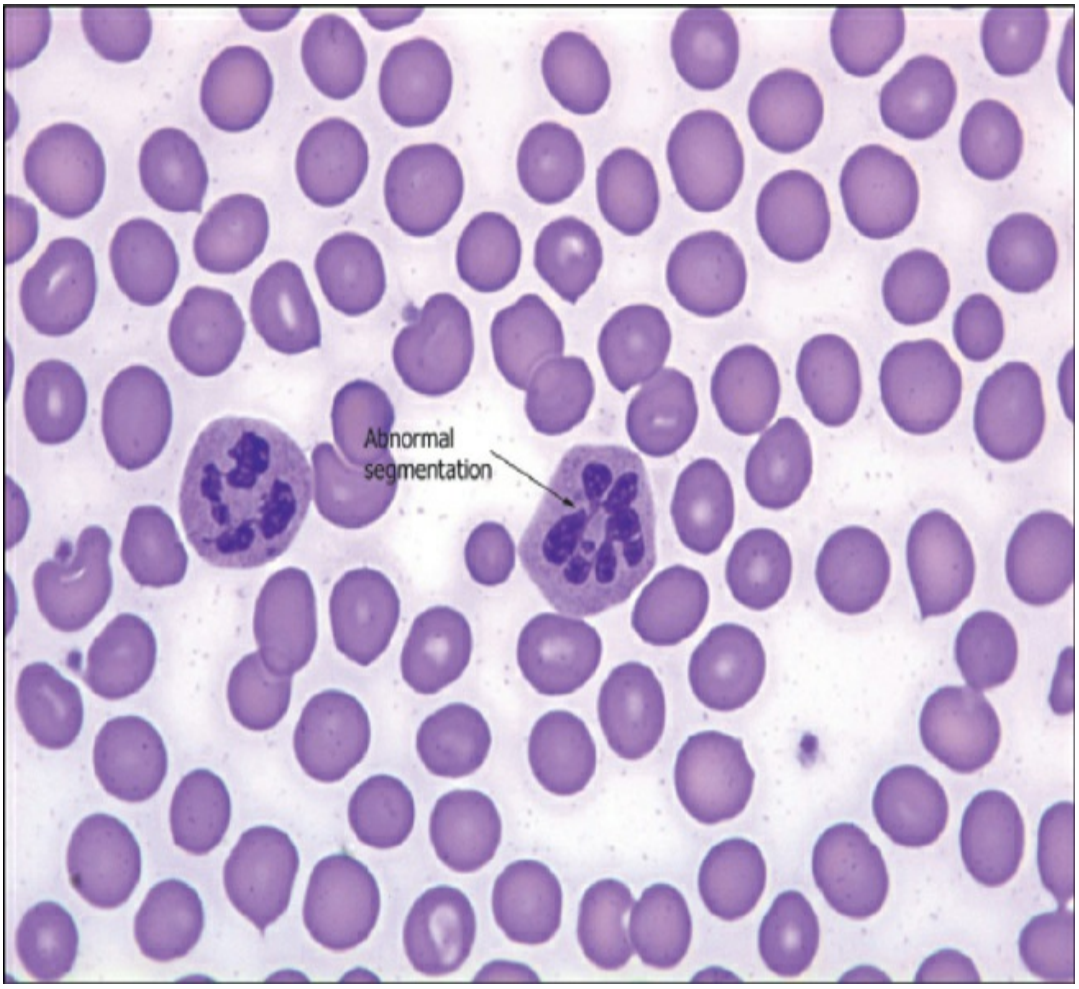


Figure **IIB6-19**

Peripheral blood smear.

- Auer rod

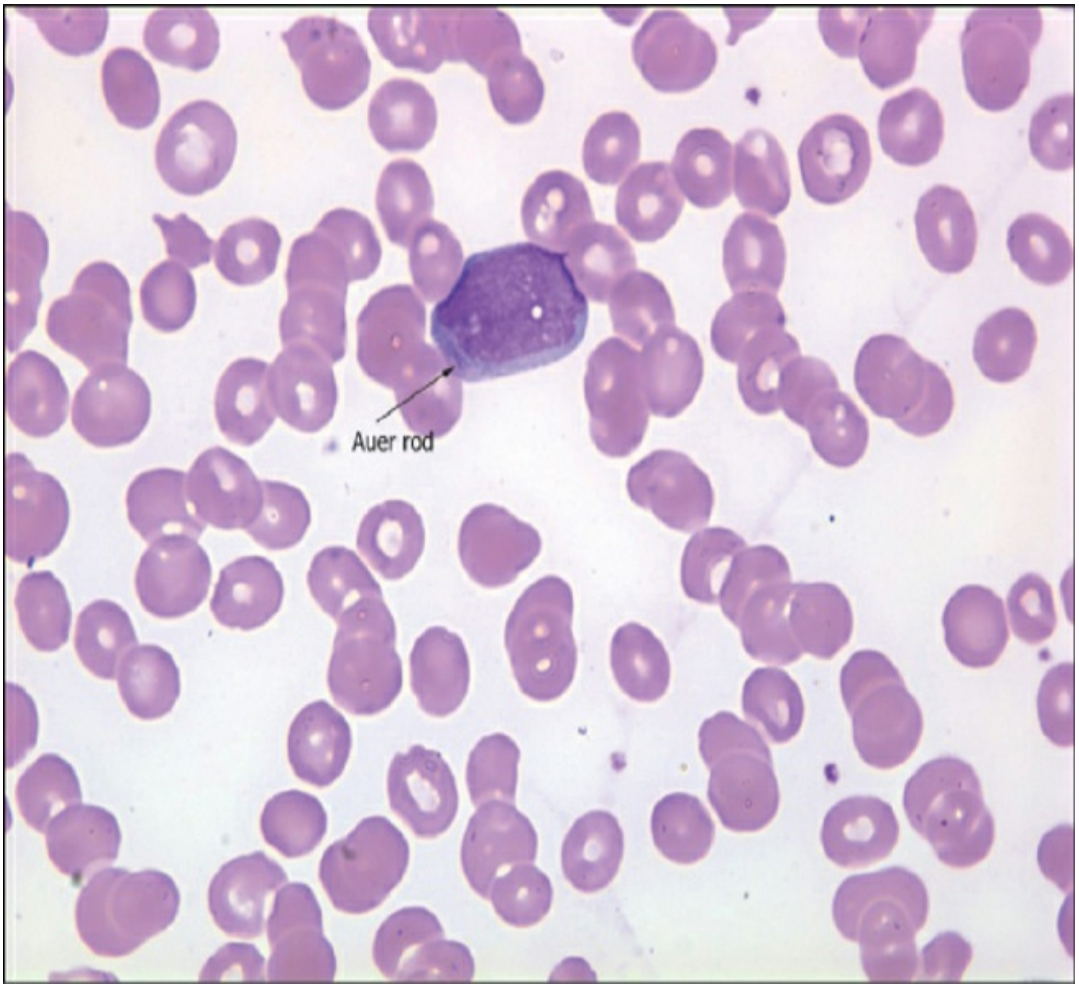


Figure **IIB6-20**

Peripheral blood smear.

Bone Marrow

- Myeloid hyperplasia with shift to the left in granulocyte precursors

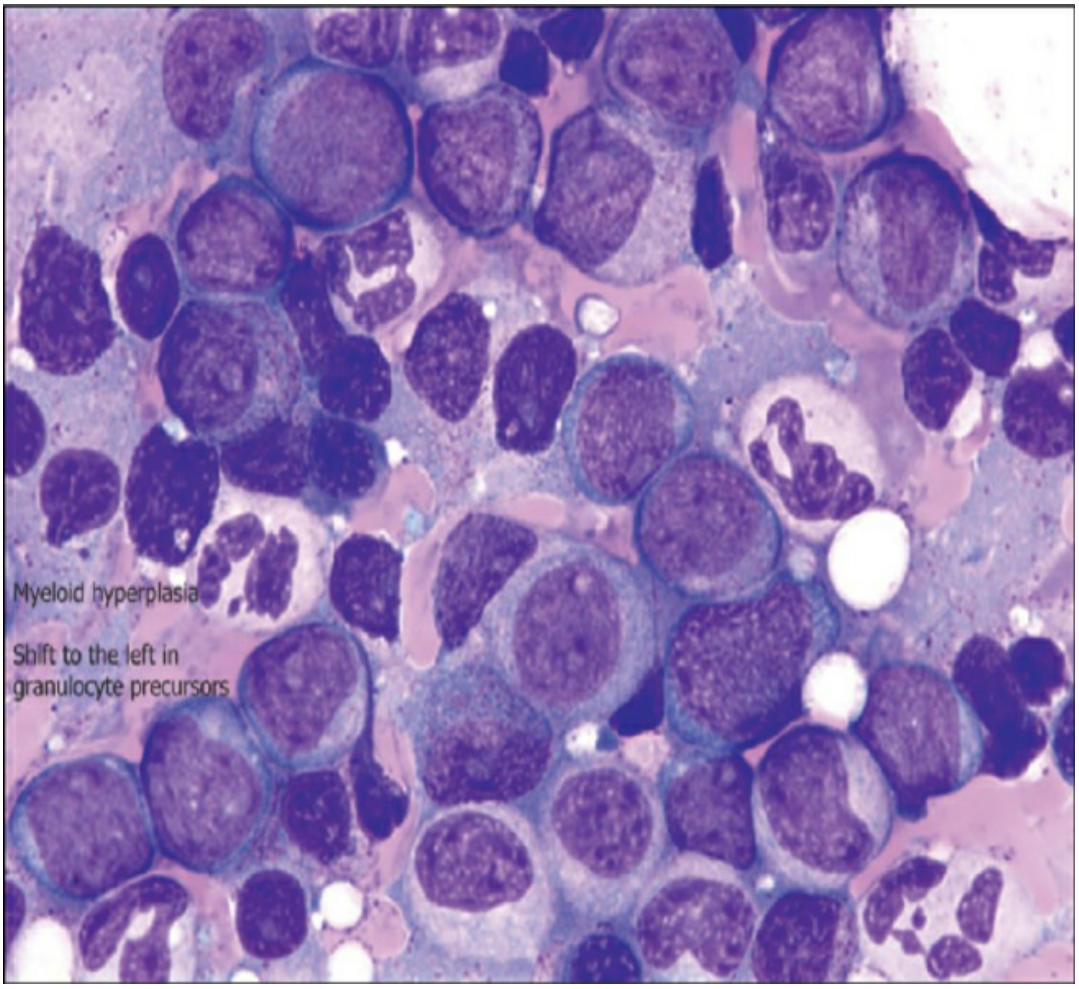


Figure **IIB6-21**

- Hypogranular neutrophils

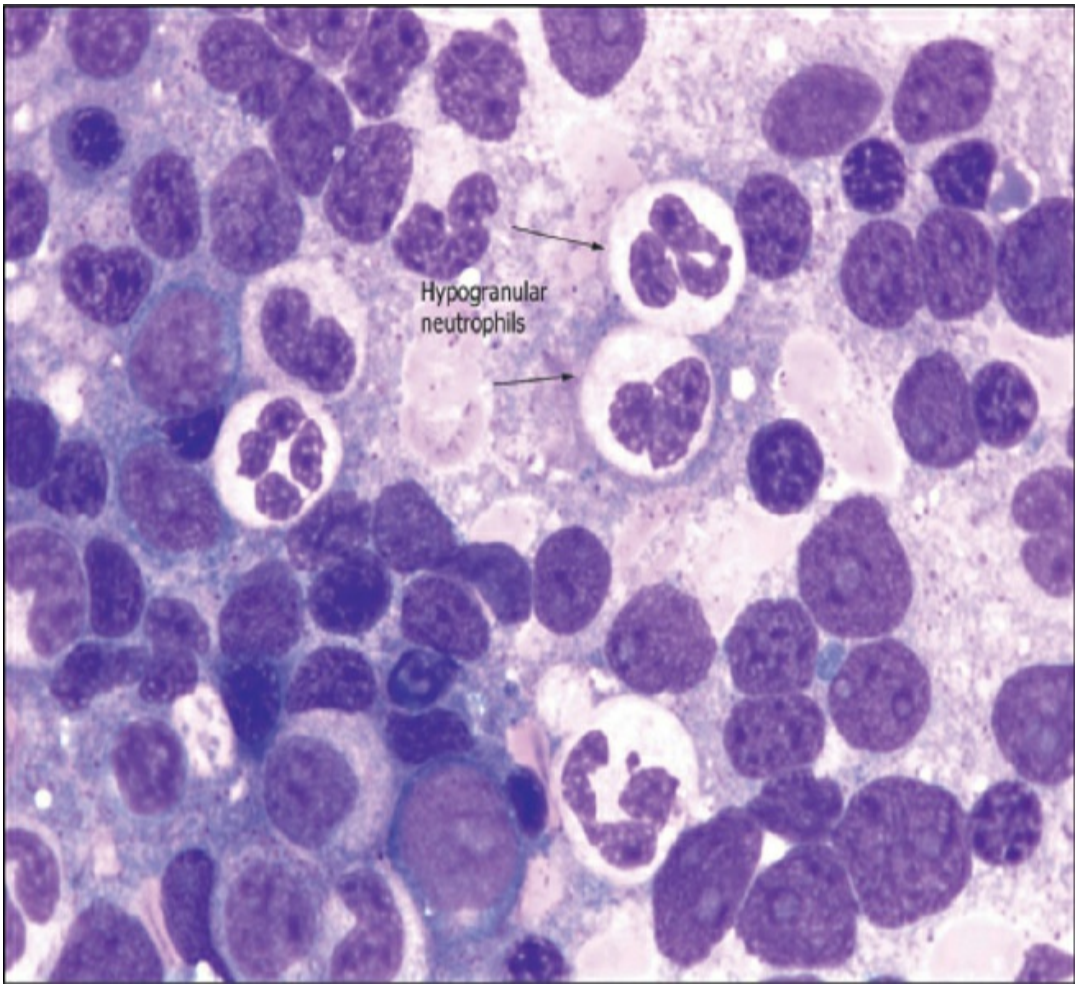


Figure **IIB6-22**

Peripheral blood smear.

Dysmegakaryopoiesis

- Dysplasia (≥10% based on evaluation of ≥30 megakaryocytes)

Peripheral Blood

- Micromegakaryocytes/micromegakaryoblasts (can also be found in bone marrow)

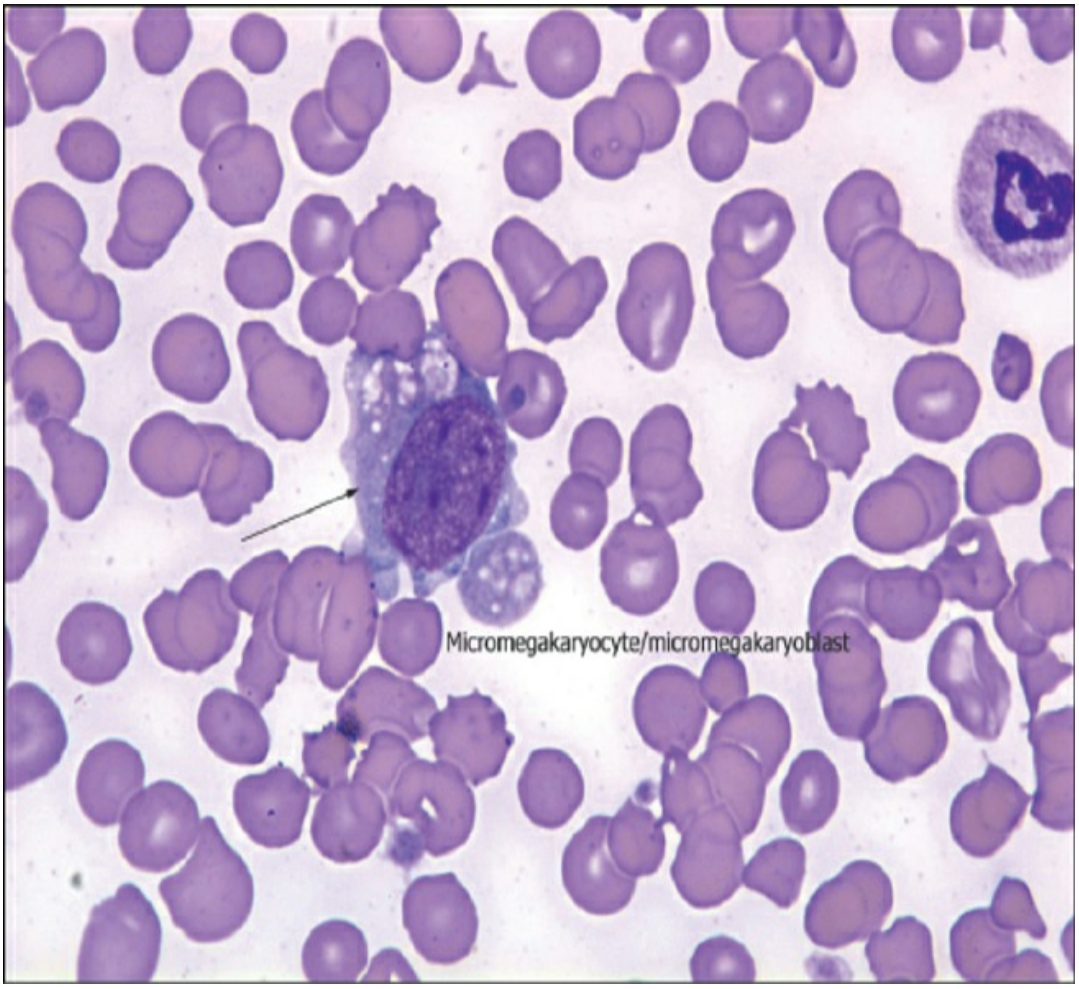


Figure **IIB6-23**

Peripheral blood smear.

- Large atypical platelets

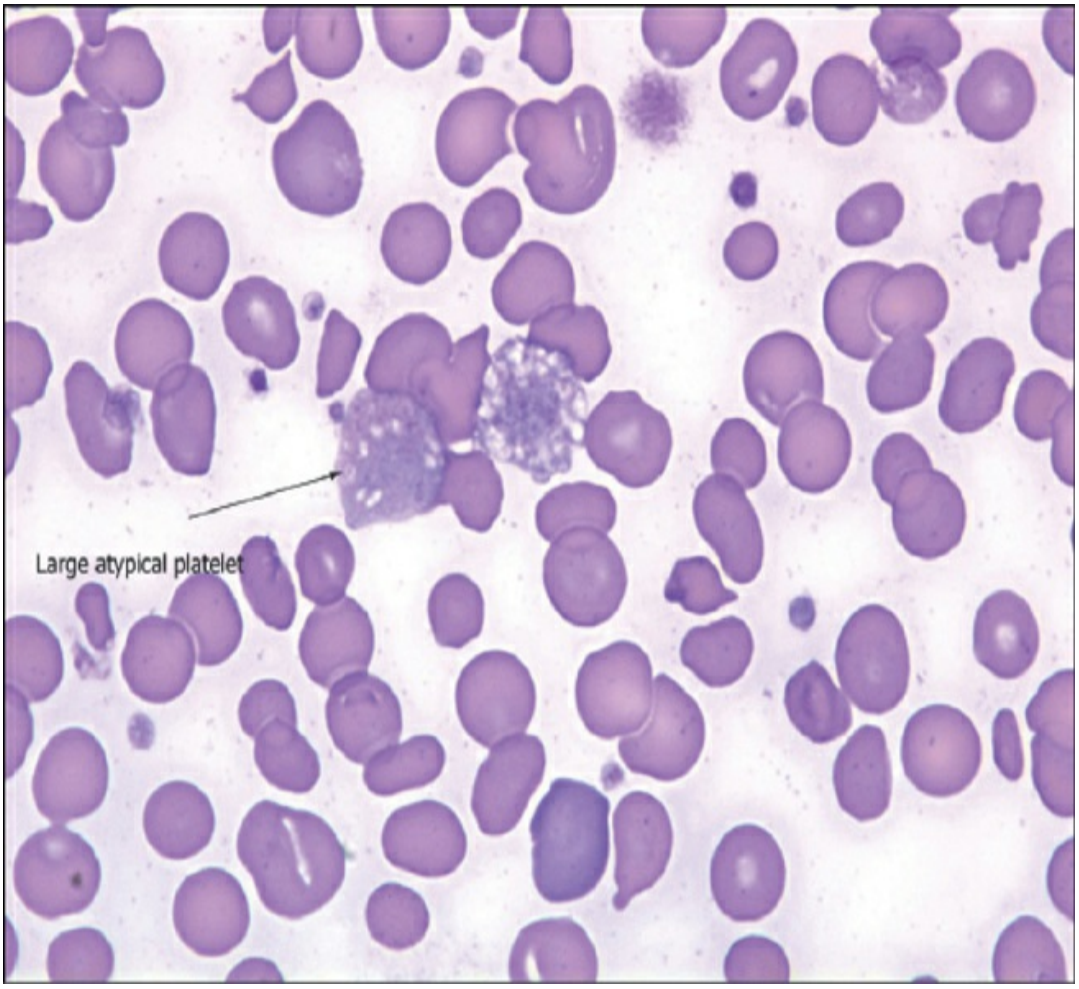


Figure **IIB6-24**

Peripheral blood smear.

- Degranulated platelets

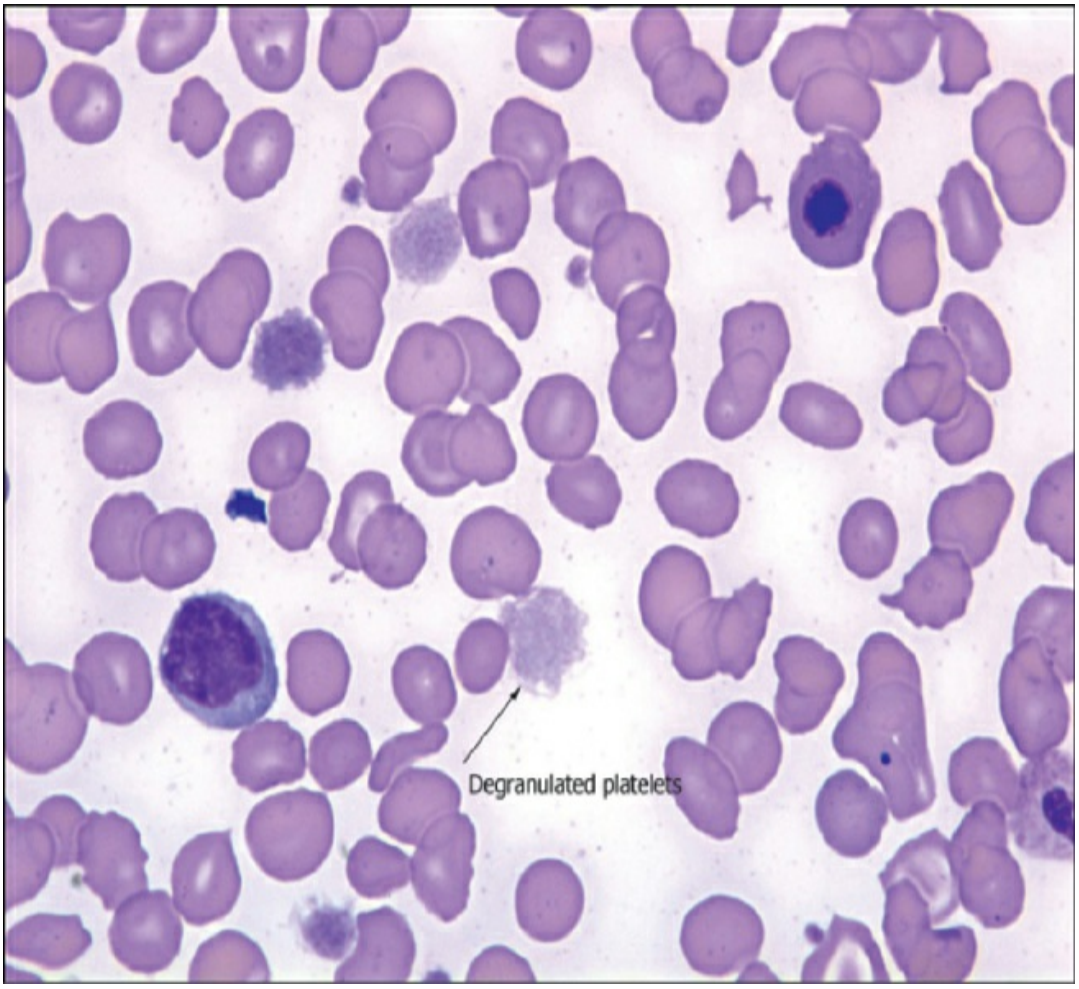


Figure **IIB6-25**

Peripheral blood smear.

Bone Marrow

- Mononuclear megakaryocytes

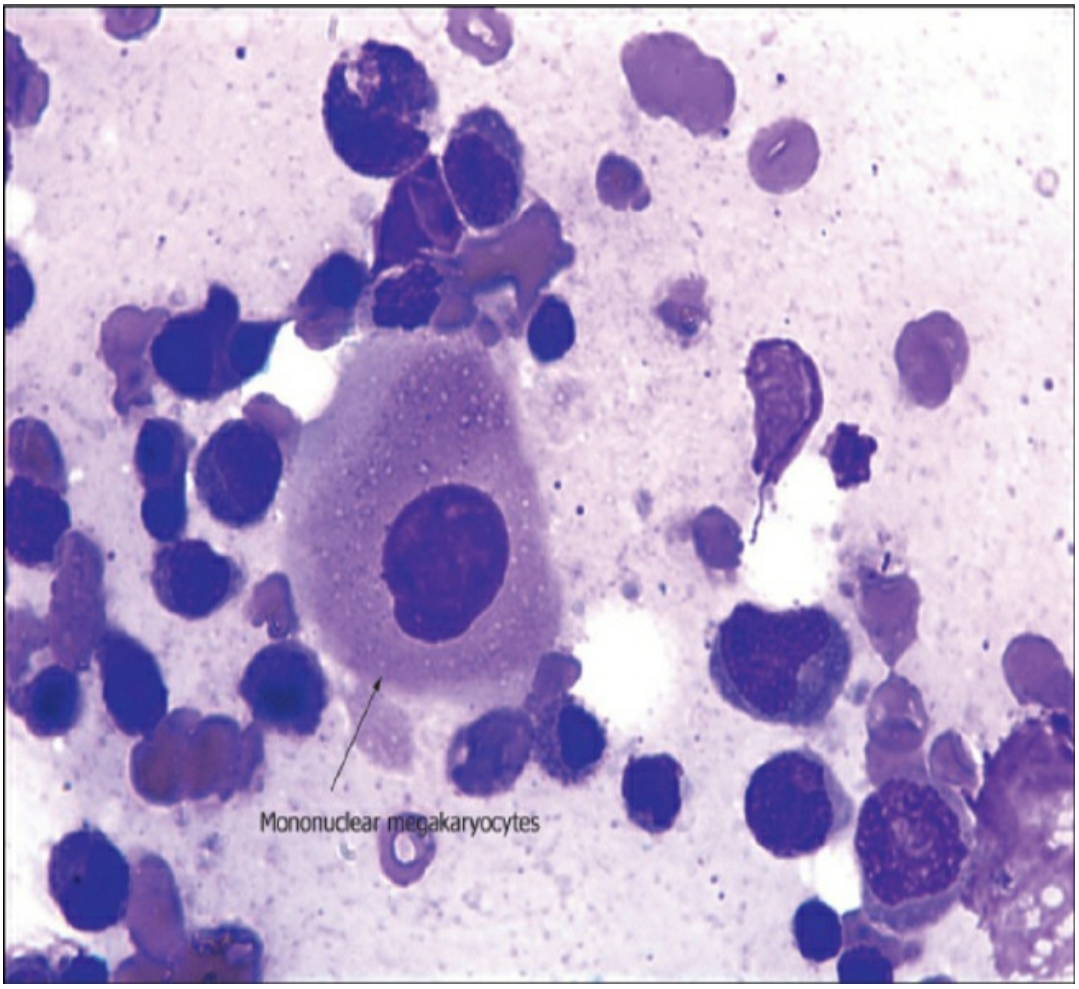


Figure **IIB6-26**

Bone marrow smear.

- Abnormal granulation

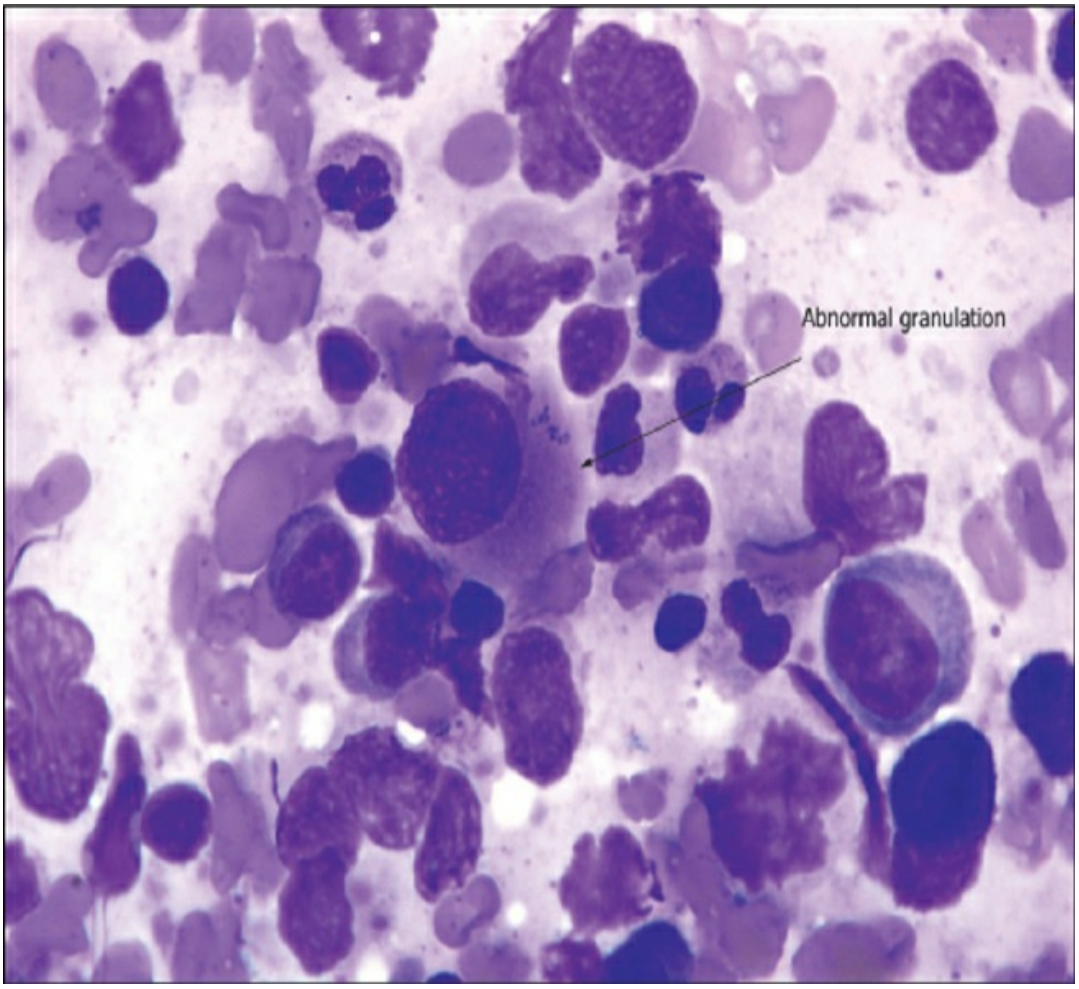


Figure **IIB6-27**

Bone marrow smear.

- Vacuolated cytoplasm

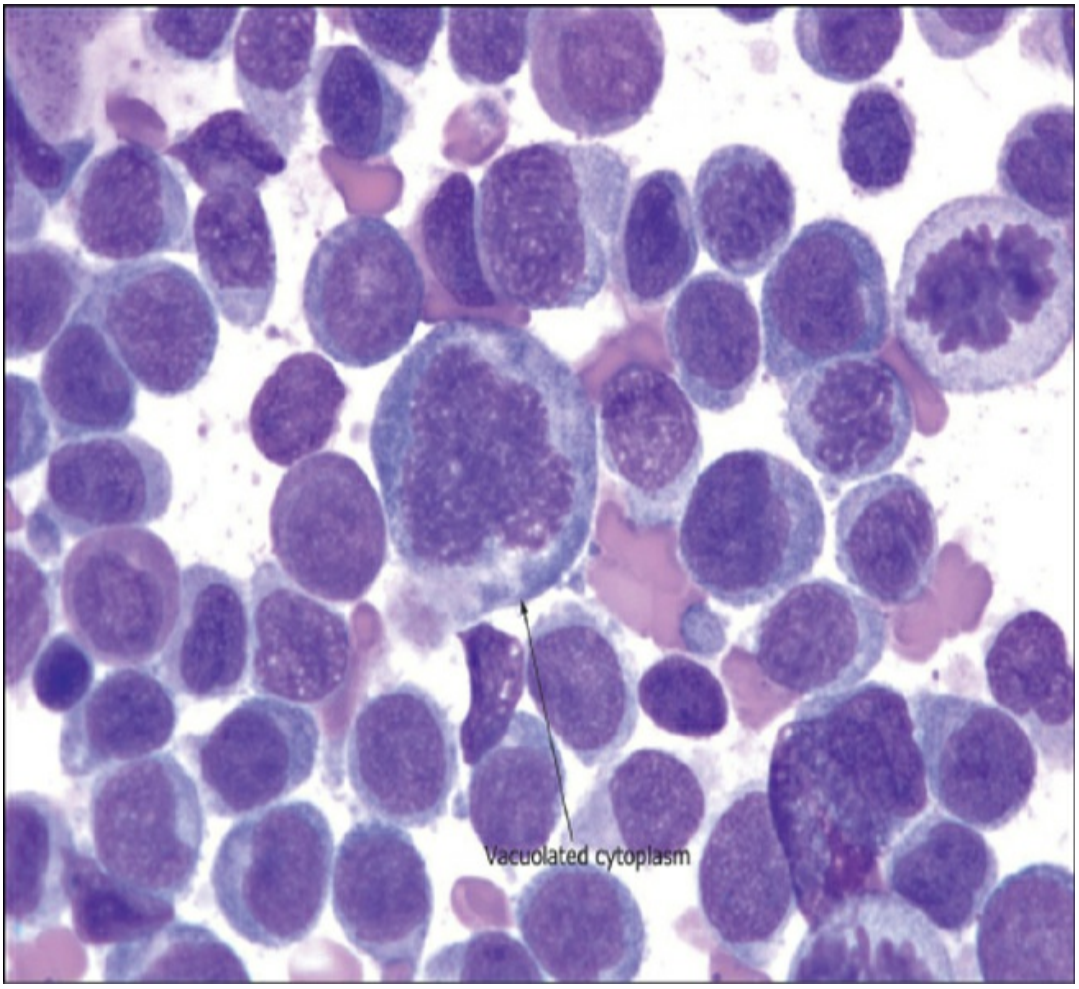


Figure **IIB6-28**

Bone marrow smear.

- Abnormal nuclear changes

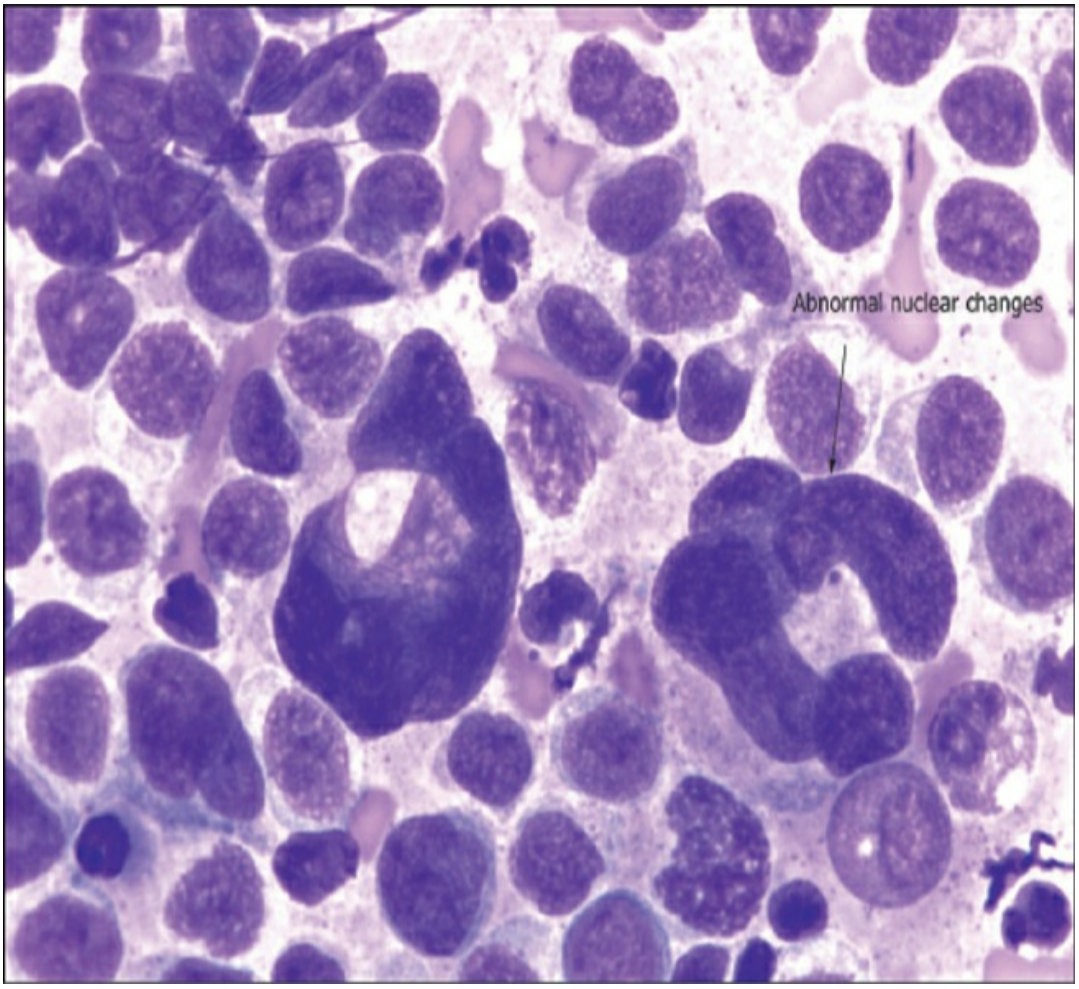


Figure **IIB6-29**

Bone marrow smear.

- Bilobed nuclei

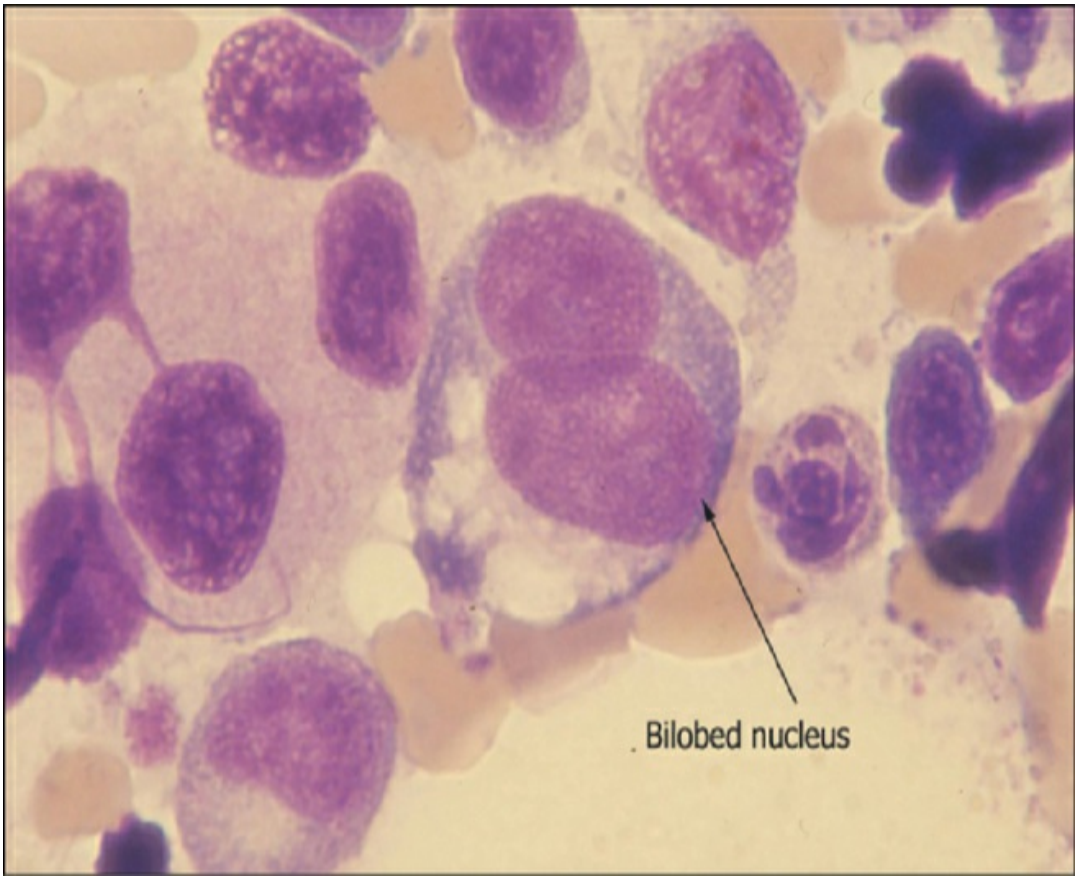


Figure **IIB6-30**

Bone marrow smear.

- Hypersegmented nuclei

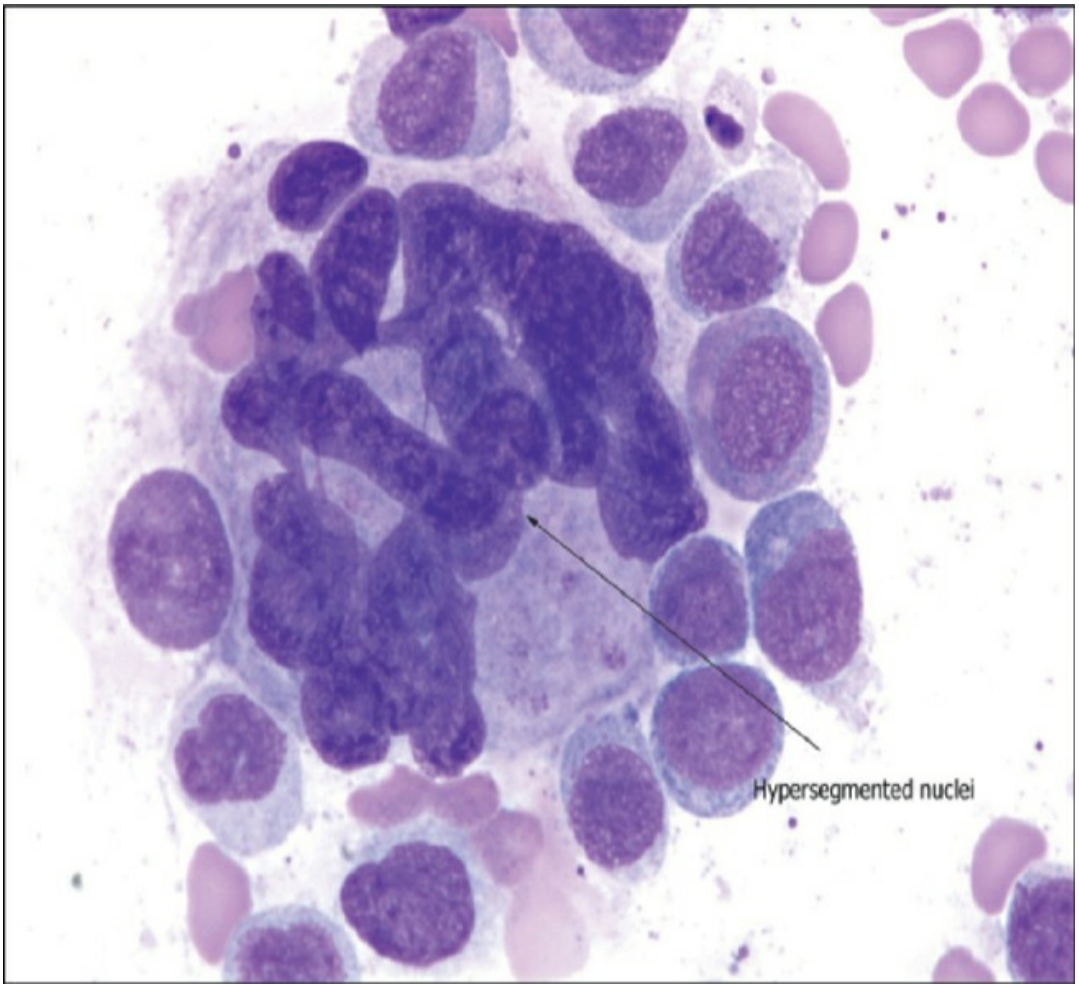


Figure **IIB6-31**

Bone marrow smear.

- Separated nuclear lobes

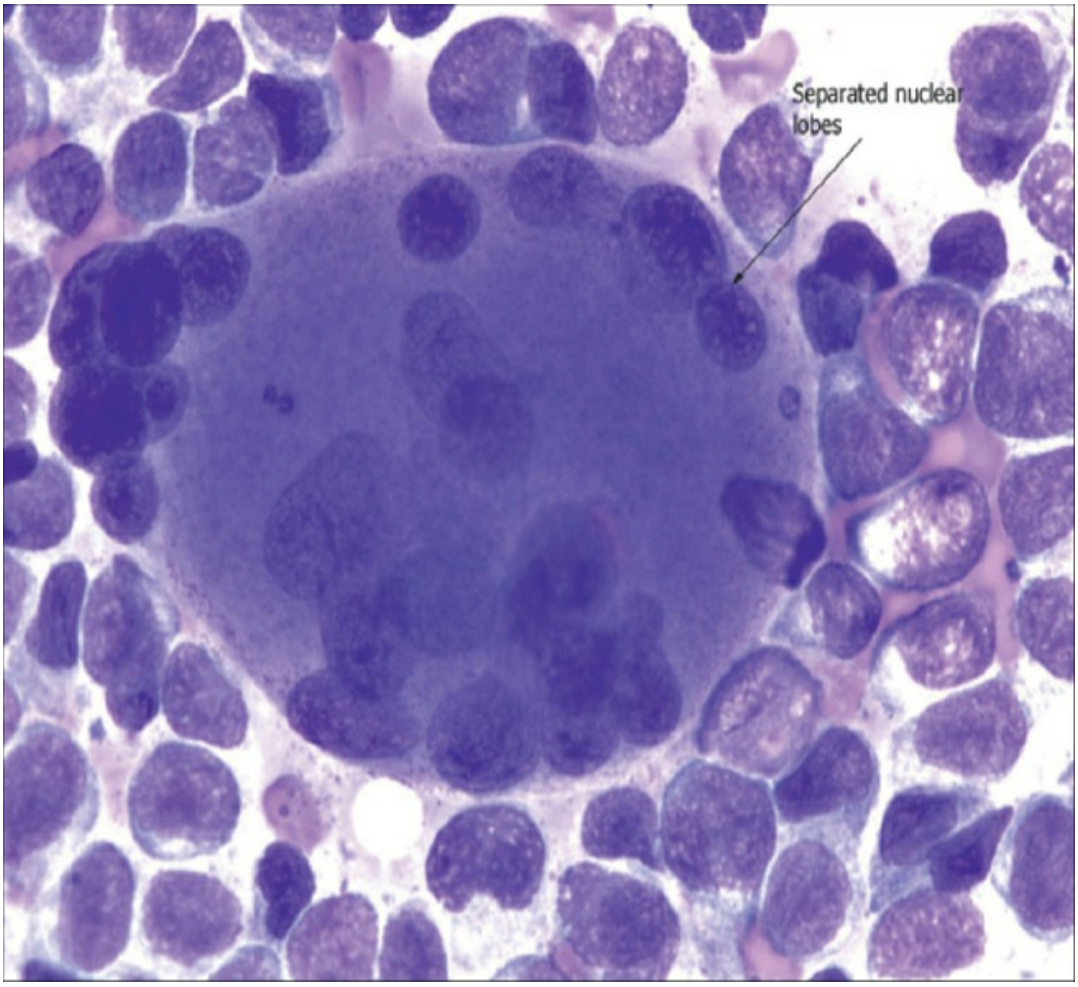


Figure **IIB6-32**

Bone marrow smear.

MYELODYSPLASTIC SYNDROME WITH SINGLE-LINEAGE DYSPLASIA (MDS-SLD)

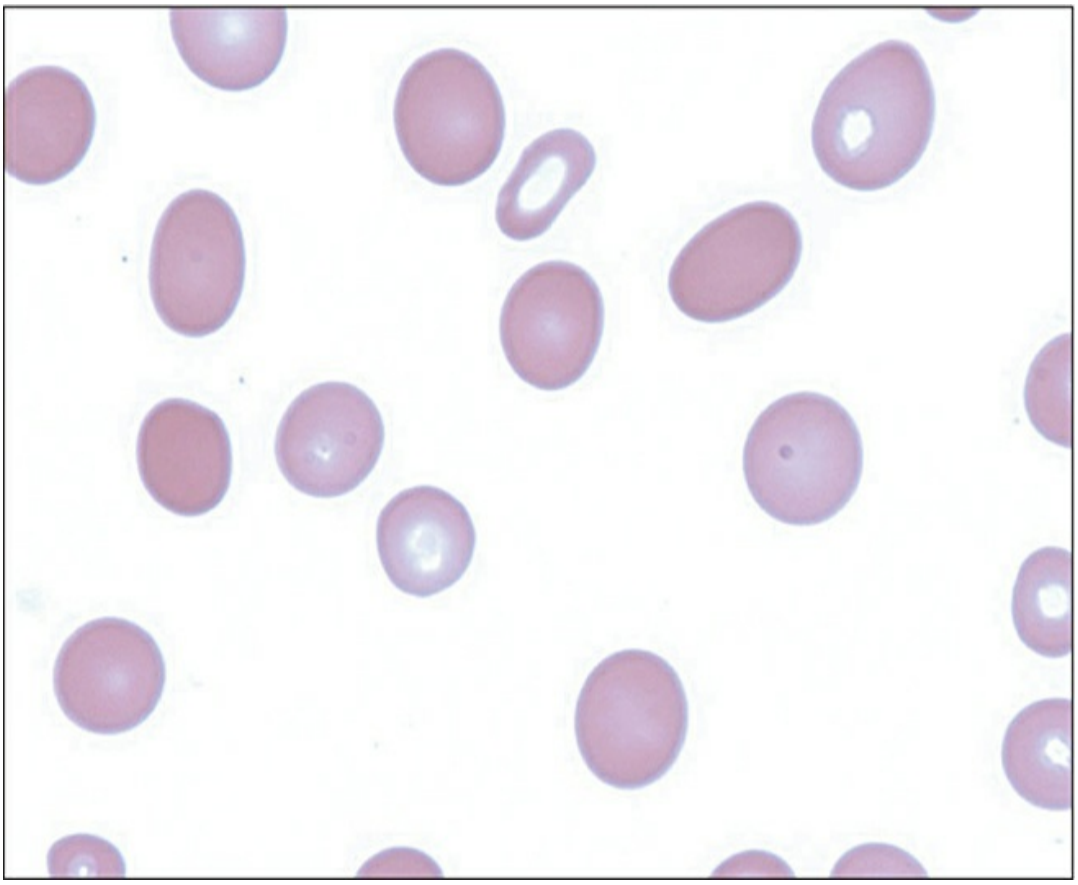


Figure IIB6-33

Peripheral blood smear.

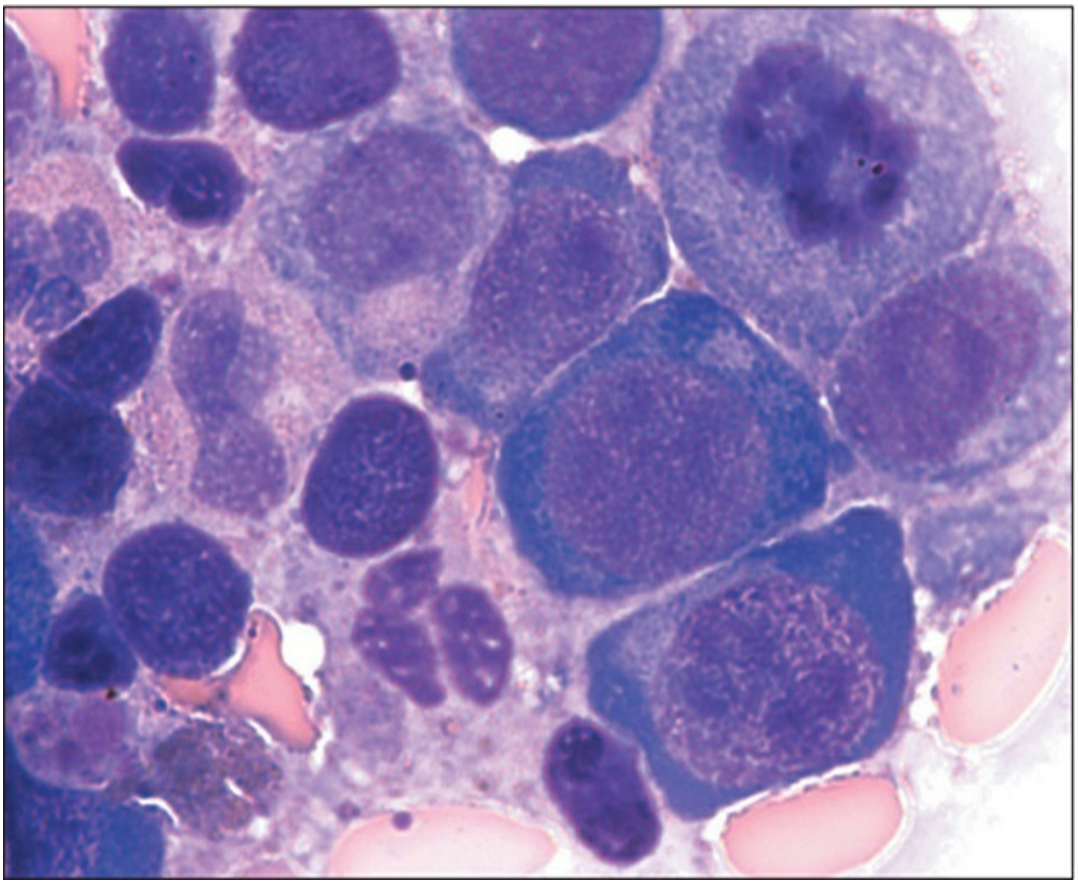


Figure **IIB6-34**

Bone marrow smear.

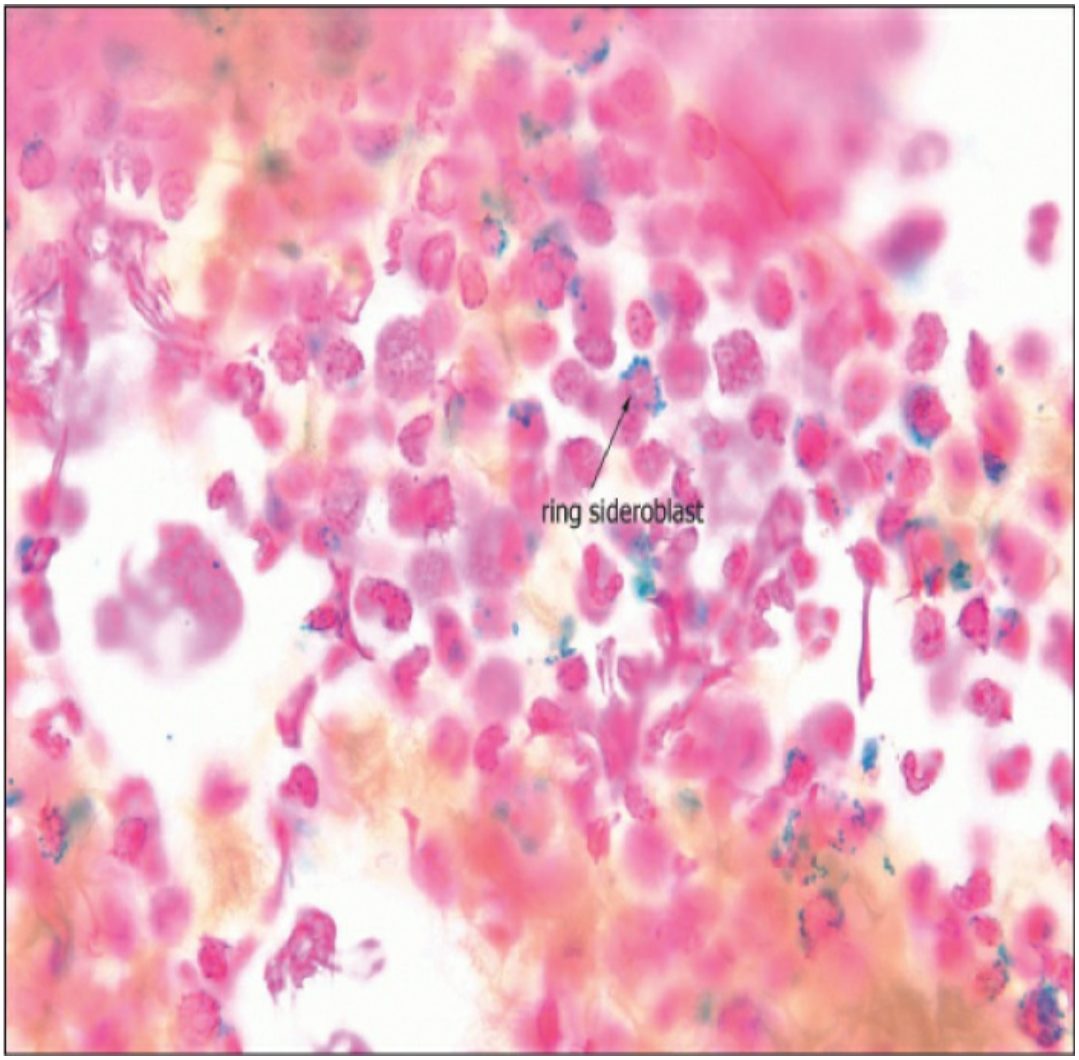


Figure **IIB6-35**

Prussian blue stain.

Criteria

- ≥10% dysplastic cells in affected cell lineage
- Red blood cells—hemoglobin concentration <10 g/dL
- White blood cells—absolute neutrophil count <1.8 × 10^9/L
- Platelets—platelet count <100 × 10^9/L
- Erythroid precursors contain <15% ring sideroblasts if no SF3B1 mutation and <5% if SF3B1 mutation

Clinical Features

- Symptoms related to the type of cytopenia
  - Anemia (red blood cells)
  - Infections (white blood cells)
  - Bleeding (platelets)
- Occurs in older adults

Pathology

- Cell of origin is a hematopoietic stem cell
  - Neutropenia or thrombocytopenia with dysplasia is a rare presentation of MDS-SLD
  - Erythroid dysplasia is the most common type of MDS-SLD

Laboratory Features

Red Blood Cells

- Normocytic/normochromic or macrocytic/normochromic anemia (<10 g/dL)
- Anisochromasia or dimorphic population
- <1% blasts

White Blood Cells

- If affected line, neutropenia ($<1.8 \times 10^9$/L)

Platelets

- If affected line, thrombocytopenia ($<100 \times 10^9$/L)

Bone Marrow

- <5% blasts, no Auer rods
- Markedly decreased to markedly increased erythroid precursors
- Dysplasia present in ≥10% of single lineage
- Hypercellular or normocellular
- Ring sideroblasts may be present but account for

<15% of the erythroid precursors or <5% if SF3B1 mutation is present
- Iron stores may be increased

Genetics

- 50% have cytogenetic abnormalities but they are not specific
- Del(20q), gain of 8, and abnormalities of 5 and 7
- 60–70% of cases have somatic driver mutations that affect the stem cell
- Most commonly mutated genes are TET2 and ASXL1

Diagnostic Scheme

See Diagnostic Scheme under MDS-RS-SLD (page 441)

MYELODYSPLASTIC SYNDROME WITH RING SIDEROBLASTS AND SINGLE-LINEAGE DYSPLASIA (MDS-RS-SLD)

Clinical Features

- Related to anemia—fatigue and pallor

Pathology

- Clonal stem cell disorder
- Defect in mitochondrial iron metabolism
- Usually occurs in adults over 50 years of age
- SF3B1 mutation may be present

Laboratory Features

White Blood Cells

- <1% blasts

Red Blood Cells

- Normochromic, macrocytic or normochromic, normocytic anemia
- Dimorphic pattern with hypochromic microcytes and normocytic or macrocytic cells

Bone Marrow

- Increase in erythroid precursors with dyserythropoiesis
- No significant dysplasia in nonerythroid lineages
- <5% myeloblasts in nucleated bone marrow cells and no Auer rods

Cytochemistry

- Prussian blue stain
  - ≥15% ringed sideroblasts as defined by ≥5 iron

granules encircling one-third or more of the nucleus (≥5% if SF3B1 mutation is present)

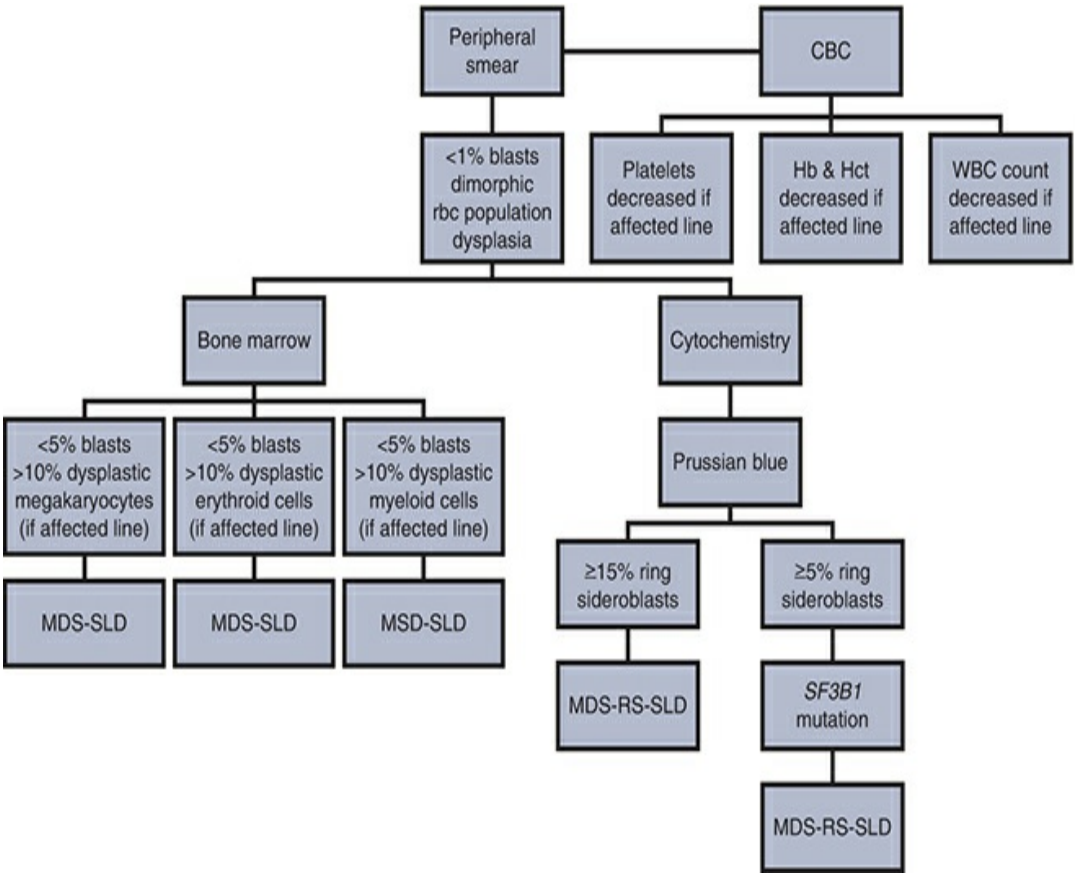
Immunophenotype

- Aberrance in the immature erythroid progenitor compartment
- CD34+ cells (blasts) are typically <5%

Genetics

- SF3B1 mutation detected in 64–83% of cases

Diagnostic Scheme



MYELODYSPLASTIC SYNDROME WITH MULTILINEAGE DYSPLASIA (MDS-MLD)

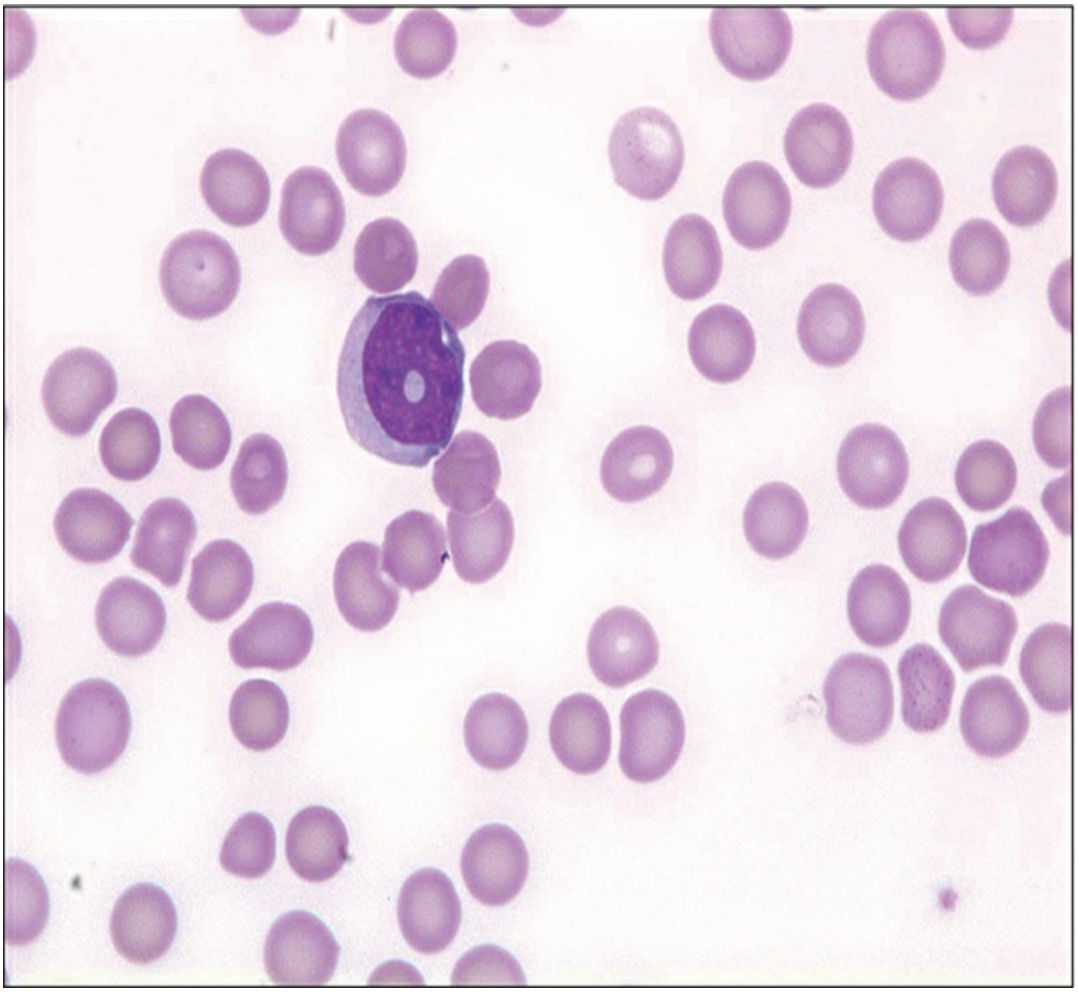


Figure IIB6-36

Peripheral blood smear.

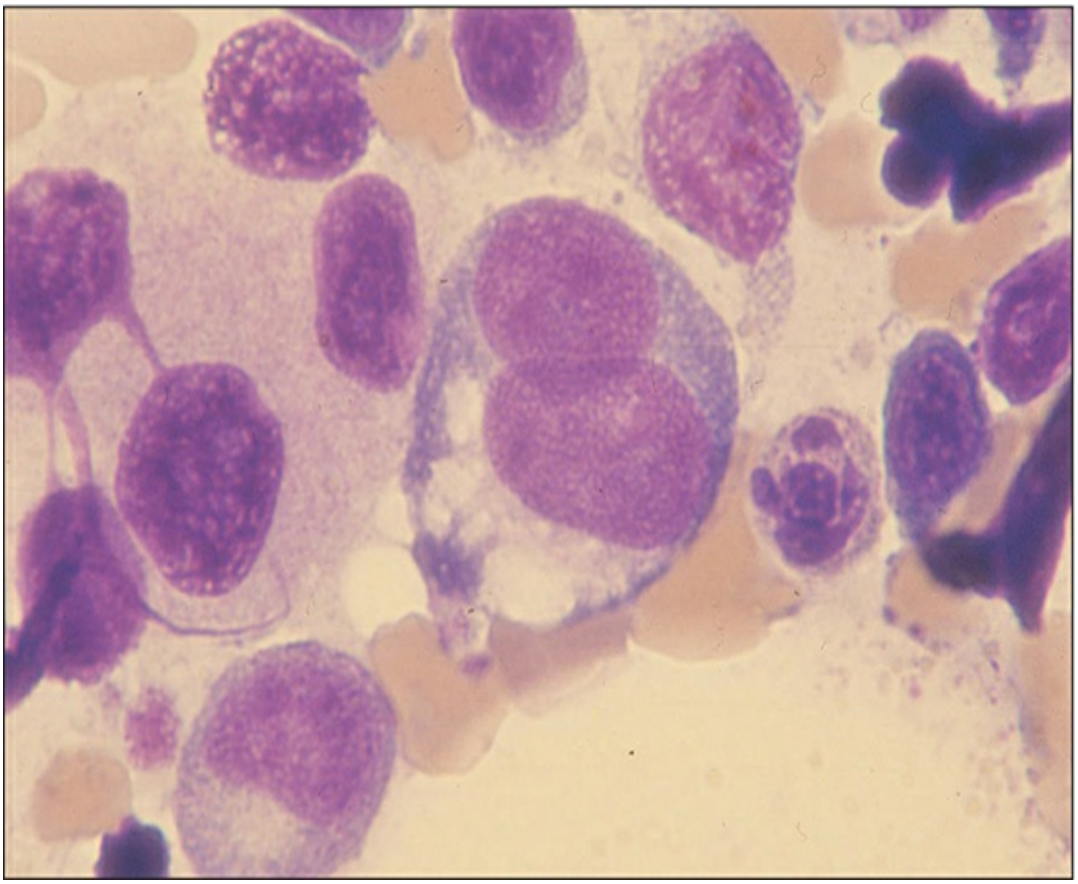


Figure **IIB6-37**

Bone marrow smear.

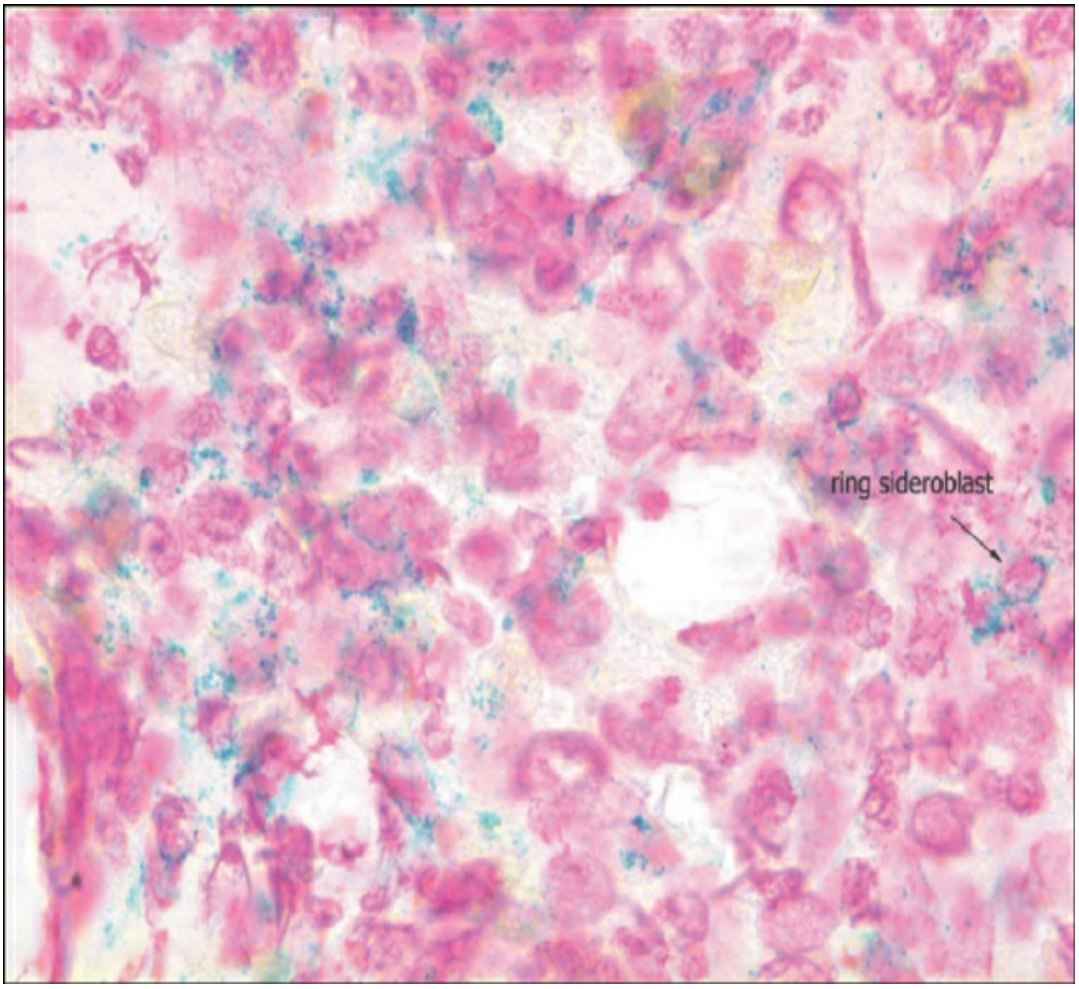


Figure **IIB6-38**

Prussian blue stain.

Criteria

- One or more cytopenias
- Dysplasia of ≥10% of cells in two or more lineages
- <1% blasts in peripheral blood and <5% in bone marrow
- No Auer rods
- No monocytosis
- Erythroid precursors contain <15% ring sideroblasts if no SF3B1 mutation and <5% if SF3B1 mutation

Clinical Features

- Pallor
- Infections
- Bleeding

Pathology

- Usually occurs in adults over 50 years of age
- Higher incidence in males
- Accounts for about 30% of all cases of MDS

Laboratory Features

White Blood Cells

- Dysgranulopoiesis
- Absolute neutrophil count $<1.8 \times 10^9$/L
- <1% blasts
- No Auer rods
- $<l \times 10^9$/L monocytes

Red Blood Cells

- Hemoglobin <10 g/dL
- Dimorphic population

Platelets

- Platelet count $<100 \times 10^9$/L
- May have abnormal morphology

Bone Marrow

- Normocellular or hypercellular but hypocellular can be seen
- Dysplasia in ≥10% of the cells in two or more myeloid cell lines (erythroid, granulocytic, and megakaryocytic)
- <5% blasts
- No Auer rods
- Megakaryocyte abnormalities may be seen

Cytochemistry

- Prussian blue stain to evaluate presence of ring sideroblasts and increased iron stores

Immunophenotype

- CD34+ cells (blasts) are typically <5%

Genetics

- Abnormalities include trisomy 8, monosomy 7, del(7q) monosomy 5, del(5q), and del(20q)
- Several gene mutations can be present

Diagnostic Scheme

See Diagnostic Scheme under MDS-RS-MLD (page 446)

MYELODYSPLASTIC SYNDROME WITH RING SIDEROBLASTS AND MULTILINEAGE DYSPLASIA (MDS-RS-MLD)

Clinical Features

- Related to anemia—fatigue and pallor
- Infection
- Bleeding

Pathology

- Clonal stem cell disorder
- Defect in mitochondrial iron metabolism
- Usually occurs in adults over 50 years of age
- SF3B1 mutation may be present

Laboratory Features

White Blood Cells

- <1% blasts
- Dysgranulopoiesis

Red Blood Cells

- Normochromic, macrocytic or normochromic, normocytic anemia
- Dimorphic pattern with hypochromic microcytes and normocytic or macrocytic cells

Platelets

- Abnormal platelet morphology

Bone Marrow

- Increase in erythroid precursors with dyserythropoiesis
- Granulocytes or megakaryocytes show ≥10%

dysplastic forms

- <5% myeloblasts in nucleated bone marrow cells and no Auer rods

Cytochemistry

- Prussian blue stain
  - ≥15% ringed sideroblasts as defined by ≥5 iron granules encircling one-third or more of the nucleus (≥5% if SF3B1 mutation is present)

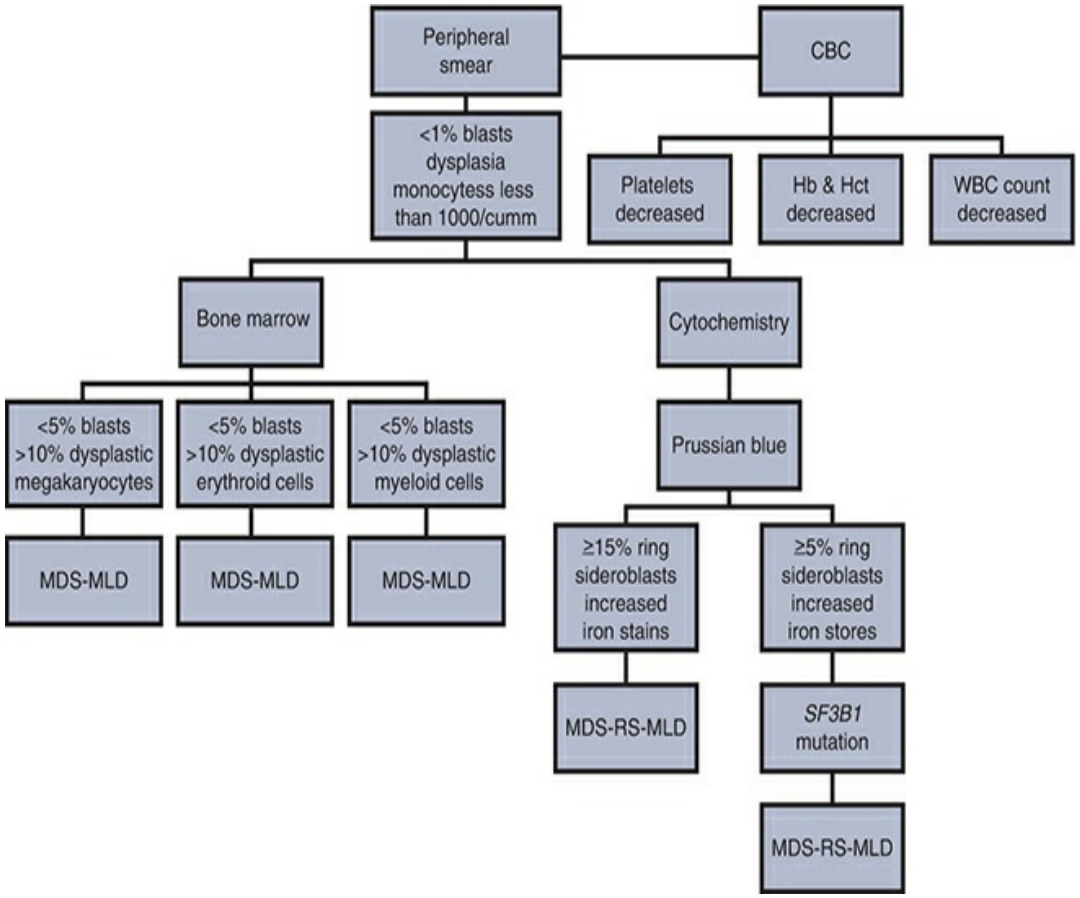
Immunophenotype

- Aberrance in the immature progenitor compartment:
  - Abnormal maturation in granulopoiesis, the monocytic compartment, and erythropoiesis
- CD34+ cells (blasts) are typically <5%

Genetics

- SF3B1 mutation detected in 57–76% of cases

Diagnostic Scheme


Peripheral smear
CBC
<1% blasts dysplasia monocytess less than 1000/cumm
Platelets decreased
Hb & Hct decreased
WBC count decreased
Bone marrow
Cytochemistry
<5% blasts >10% dysplastic megakaryocytes
<5% blasts >10% dysplastic erythroid cells
<5% blasts >10% dysplastic myeloid cells
Prussian blue
MDS-MLD
MDS-MLD
MDS-MLD
≥15% ring sideroblasts increased iron stains
≥5% ring sideroblasts increased iron stores
MDS-RS-MLD
SF3B1 mutation
MDS-RS-MLD

MYELODYSPLASTIC SYNDROME WITH EXCESS BLASTS (MDS-EB)

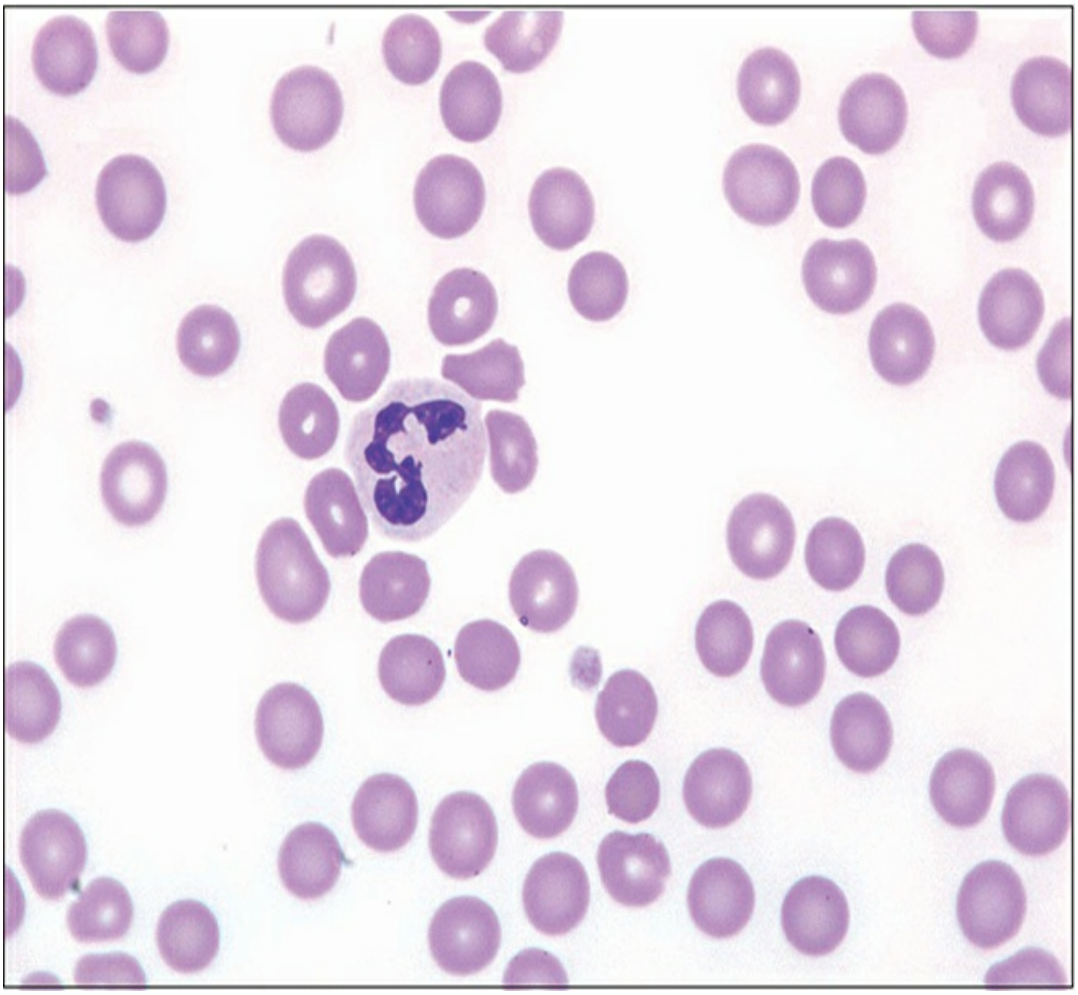


Figure IIB6-39

MDS-EB-1 Peripheral blood smear.

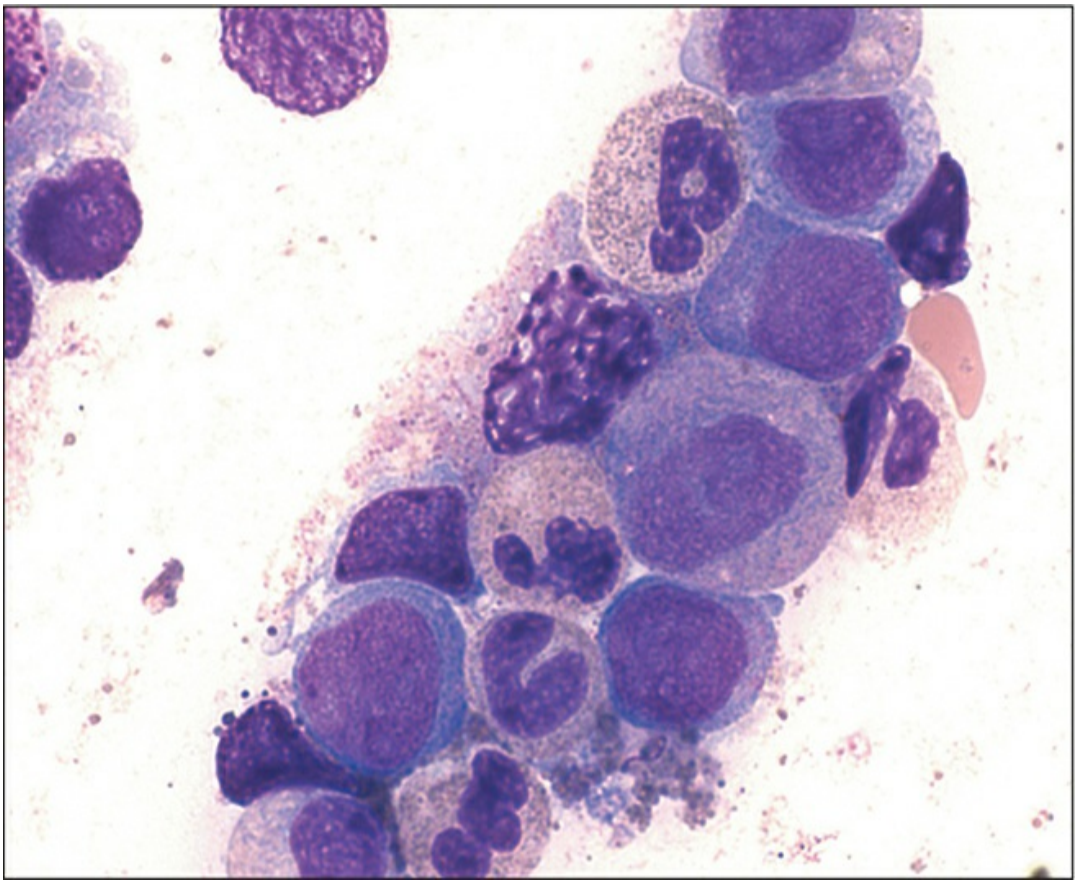


Figure **IIB6-40**

MDS-EB-1 Bone marrow smear.

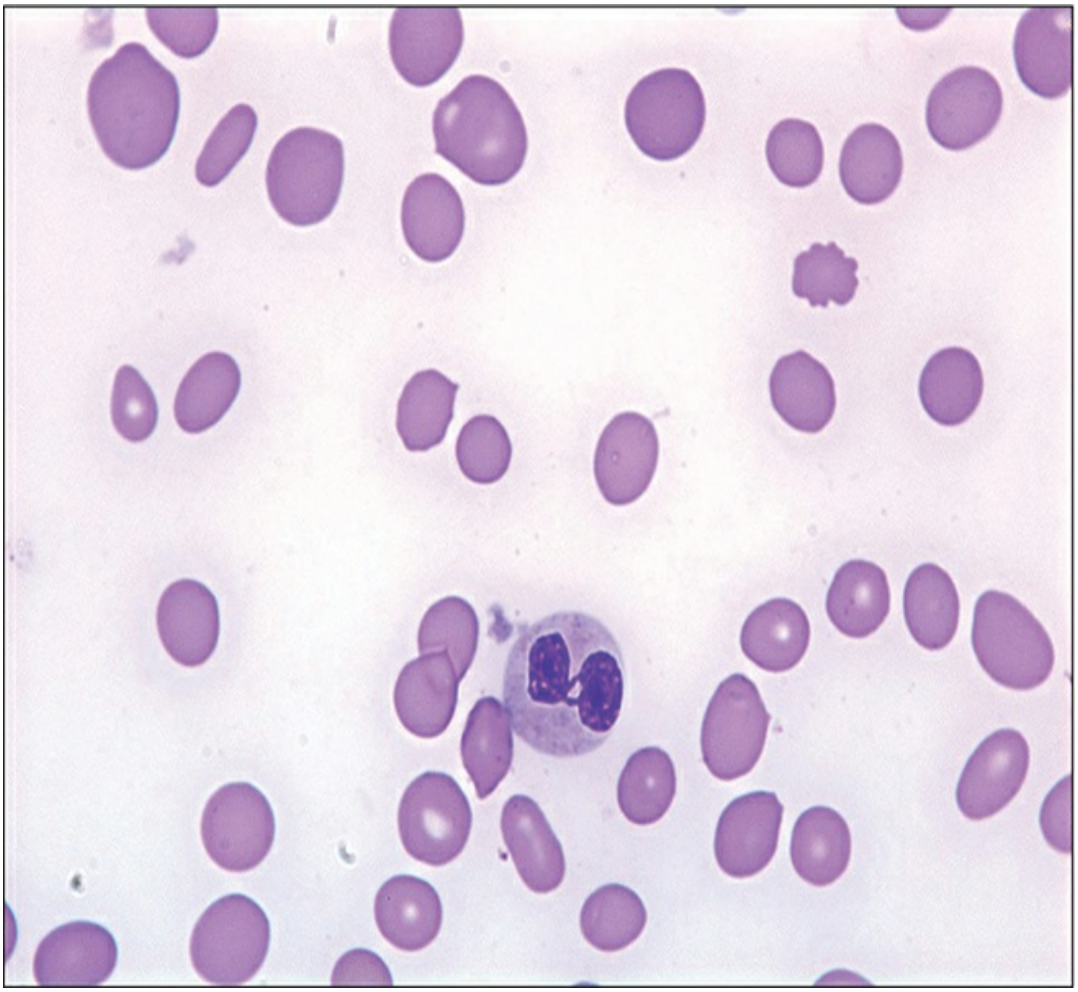


Figure **IIB6-41**

MDS-EB-2 Peripheral blood smear.

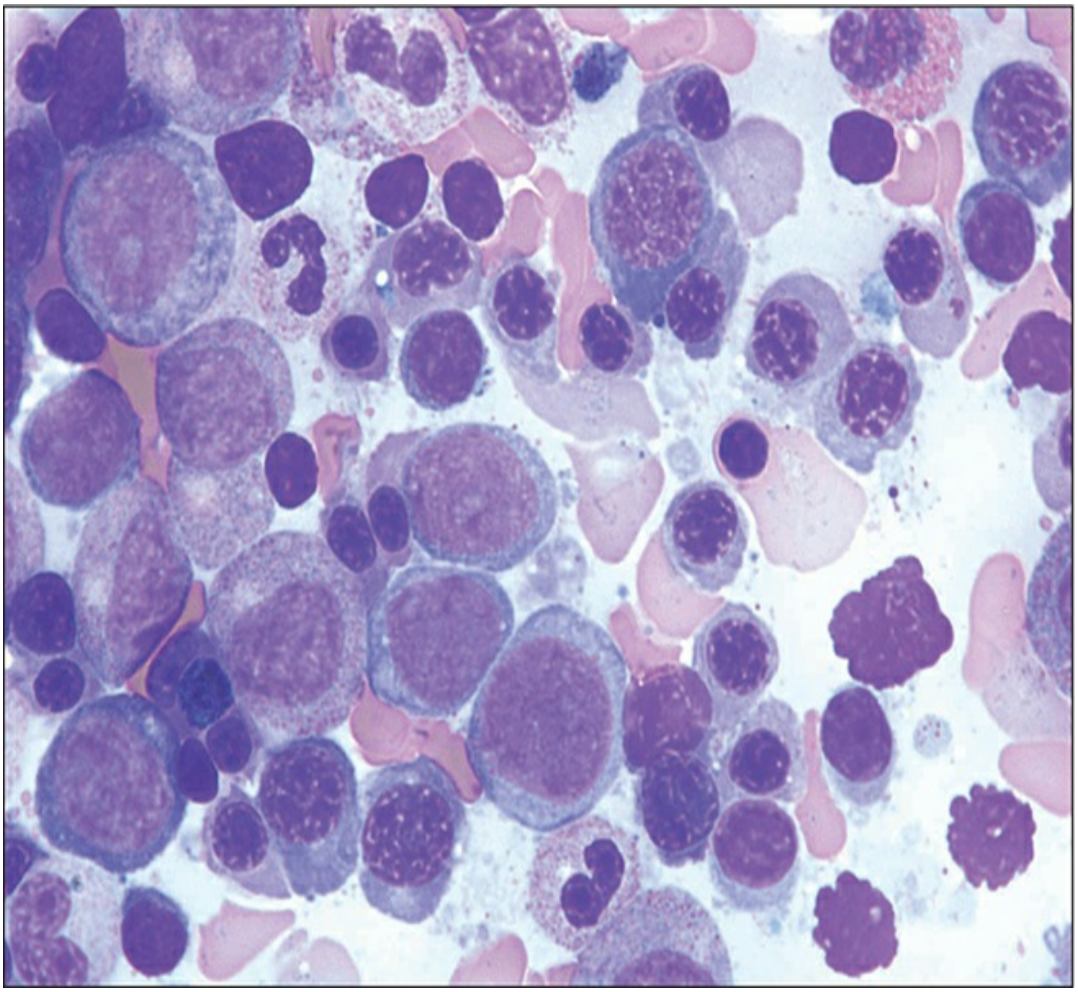


Figure **IIB6-42**

MDS-EB-2 Bone marrow smear.

Criteria

- Characterized by 2–19% blasts in the peripheral blood or 5–19% myeloblasts in the bone marrow

Subcategories

- MDS-EB-1:
  - 2–4% blasts in peripheral blood or 5–9% blasts in bone marrow
- MDS-EB-2:
  - 5–19% blasts in peripheral blood or 10–19% blasts in bone marrow

- If Auer rods are present, it is MDS-EB-2 regardless of blast numbers

Clinical Features

- Fatigue and weakness
- Hemorrhagic symptoms
- Infection
- Hepatomegaly and splenomegaly may be present

Pathology

- Occurs most commonly in older adults
- Accounts for about 40% of all cases of MDS
- Unknown etiology but associated with environmental toxins and cigarettes

Laboratory FeaturesWhite Blood Cells

- Neutropenia
- Dysgranulopoiesis

Red Blood Cells

- Anisopoikilocytosis with macrocytes
- Dimorphic population
- Decreased reticulocytes

Platelets

- Decreased
- Large, giant, or hypogranular

Bone Marrow

- Usually hypercellular; may be hypocellular or normocellular
- Clusters or aggregates of blasts
- Erythropoiesis, granulopoiesis, and megakaryopoiesis may be increased with variable dysplasia

Cytochemistry

- Peroxidase stain is positive

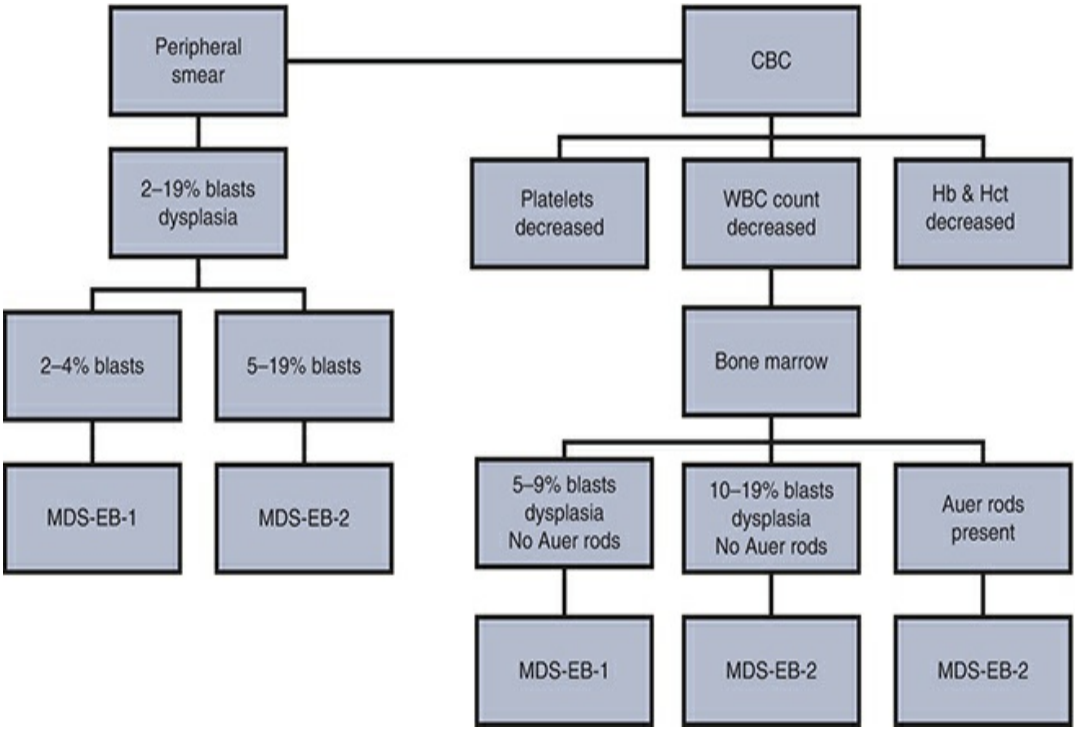
Immunophenotype

- CD34, CD117, or CD33 positive

Genetics

- 30–50% of cases have clonal cytogenetic abnormalities and can include +8, −5, del(5q), −7, del(7q), and del(20q)
- Splicing gene mutations are common (SRSF2)

Diagnostic Scheme



MYELODYSPLASTIC SYNDROME WITH ISOLATED DEL(5Q)

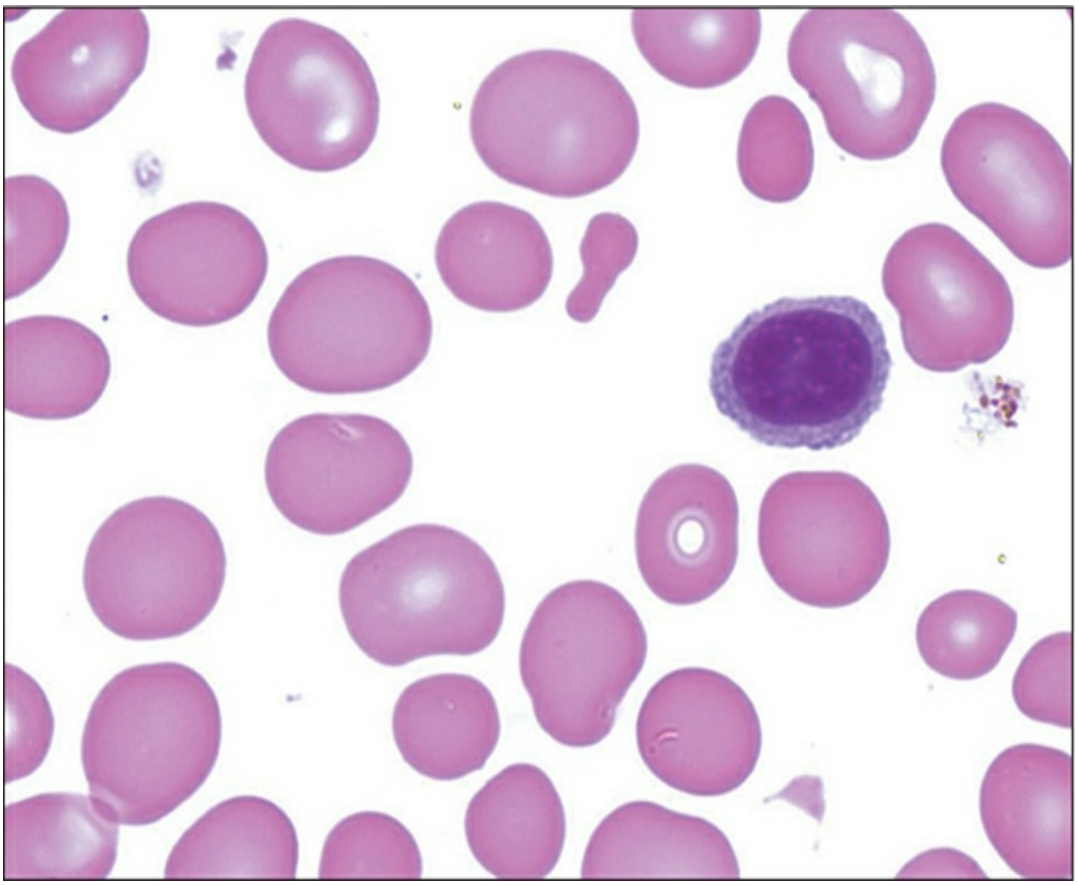


Figure IIB6-43

Peripheral blood smear.

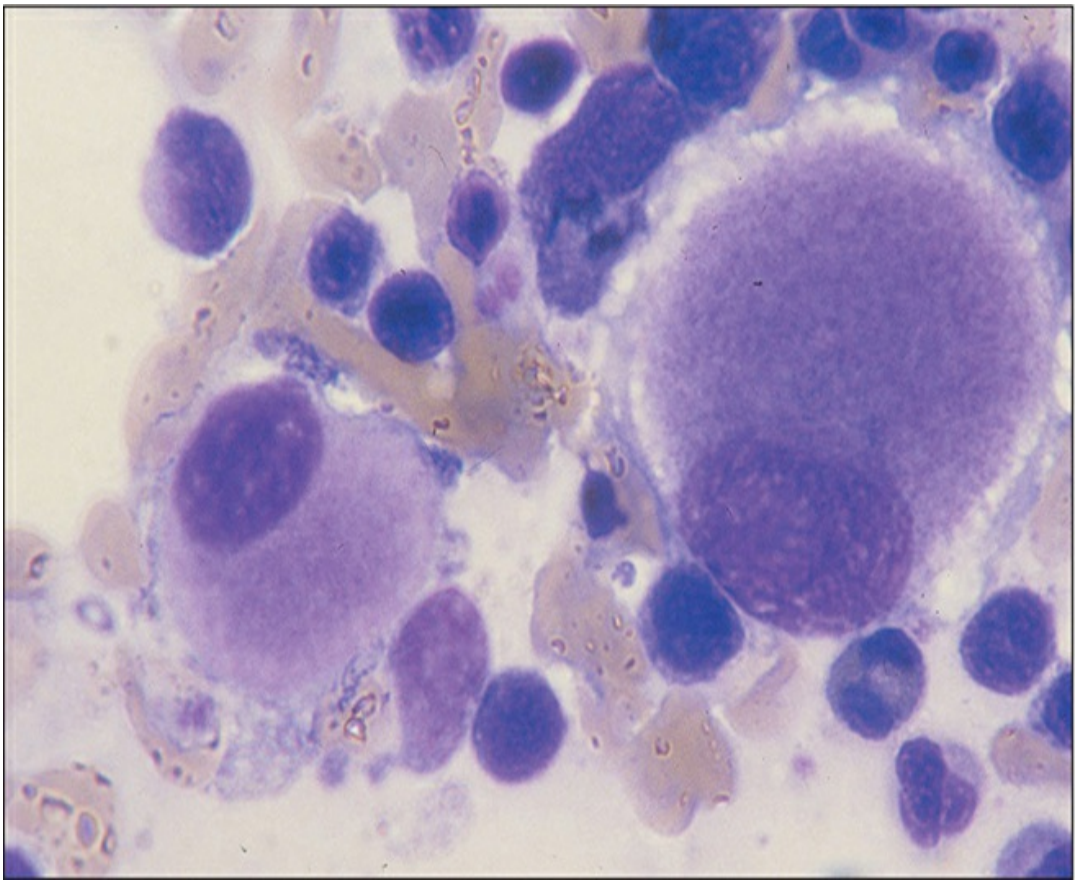


Figure **IIB6-44**

Bone marrow smear.

Criteria

- Anemia with or without other cytopenias
- Del(5q) occurs either in isolation or with one other cytogenetic abnormality other than monosomy 7/del(7q)
- <1% of the peripheral blood leukocytes and <5% blasts of nucleated cells in bone marrow
- Auer rods are absent

Clinical Features

- Symptoms related to anemia usually macrocytic
- Fatigue and weakness may be the presenting symptoms

Pathology

- Usually occurs in older females
- Loss of a portion of the long arm of chromosome 5
- Loss of a tumor suppressor gene or genes
- Haploinsufficiency of RPS14

Laboratory Features

White Blood Cells

- Normal

Red Blood Cells

- Macrocytic anemia
- Hemoglobin level often <8.0 g/dL

Platelets

- Normal or elevated count

Bone Marrow

- <5% blasts of nucleated cells
- No Auer rods
- Increased megakaryocytes, which are normal to slightly decreased in size
- Dysmegakaryopoiesis
- Monolobated or hypolobated nuclei in megakaryocytes
- Hypercellular or normocellular
- May have dysplastic erythroid precursors but less pronounced

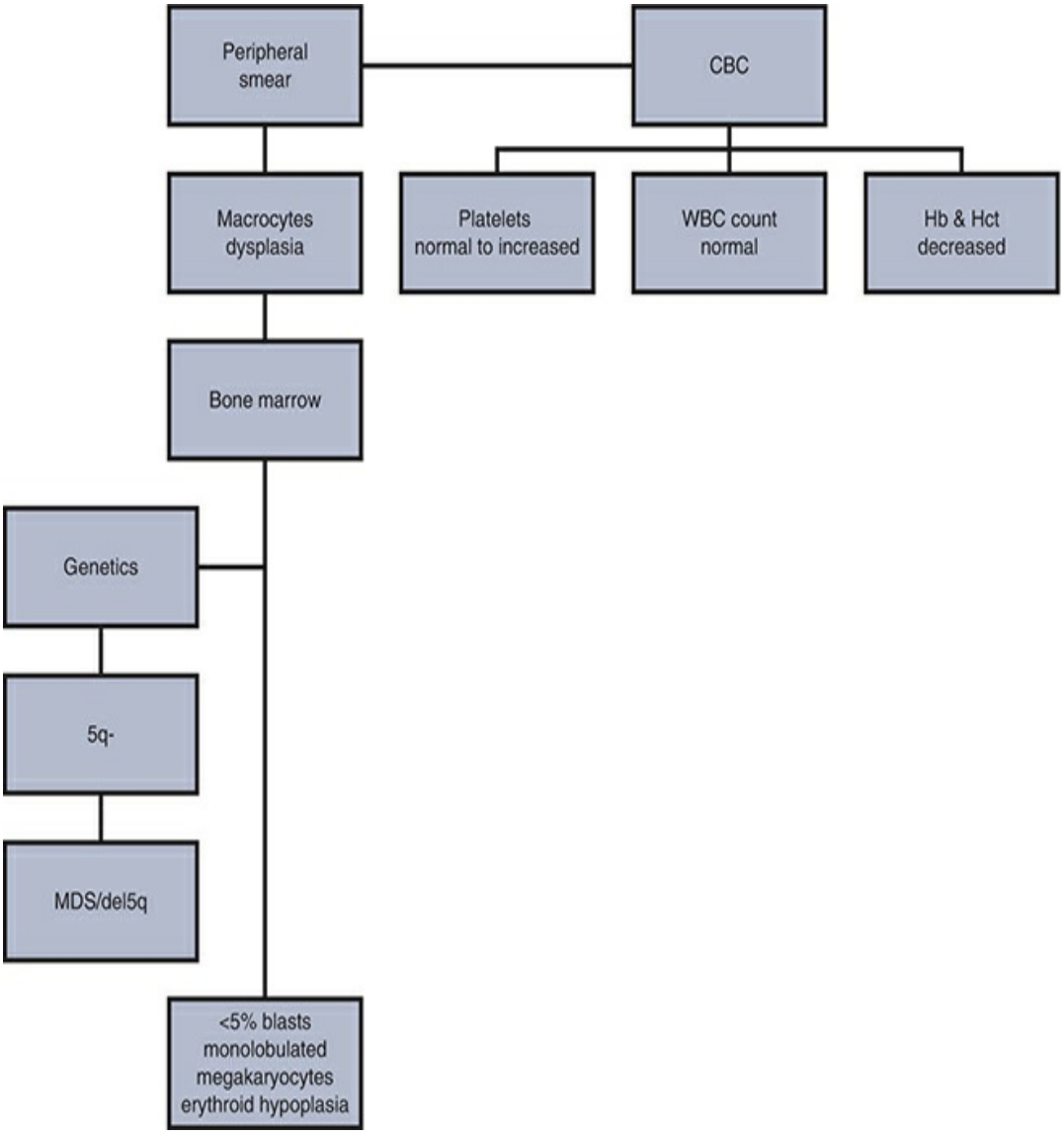
Cytochemistry

- Prussian blue stain revealing ring sideroblasts may be present

Genetics

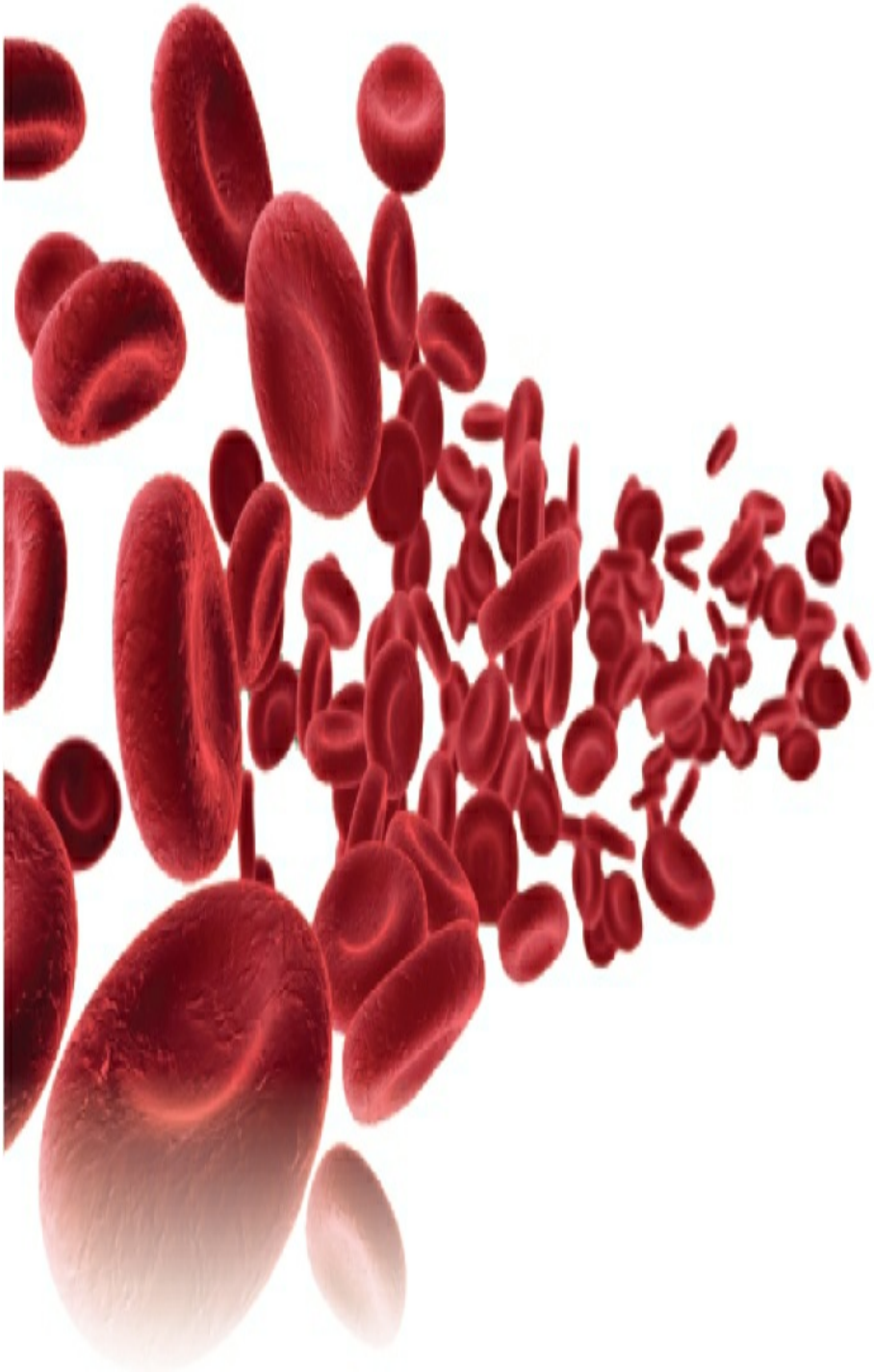
- Deletion of bands q31–q33 on the long arm of chromosome 5
- Cases with one additional cytogenetic abnormality (except monosomy 7 or del (7q)) have similar outcome

Diagnostic Scheme



CHAPTER 7

Myelodysplastic/Myeloprolife Syndromes



MYELODYSPLASTIC/MYELOPROLIFERATIV NEOPLASMS

Criteria

- Clonal chronic myeloid neoplasm characterized by myelodysplastic and myeloproliferative features manifested by at least one dysplasia and at least one cytosis in blood
- Blasts are ≤20% in blood and bone marrow
- Mature cells predominate

CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

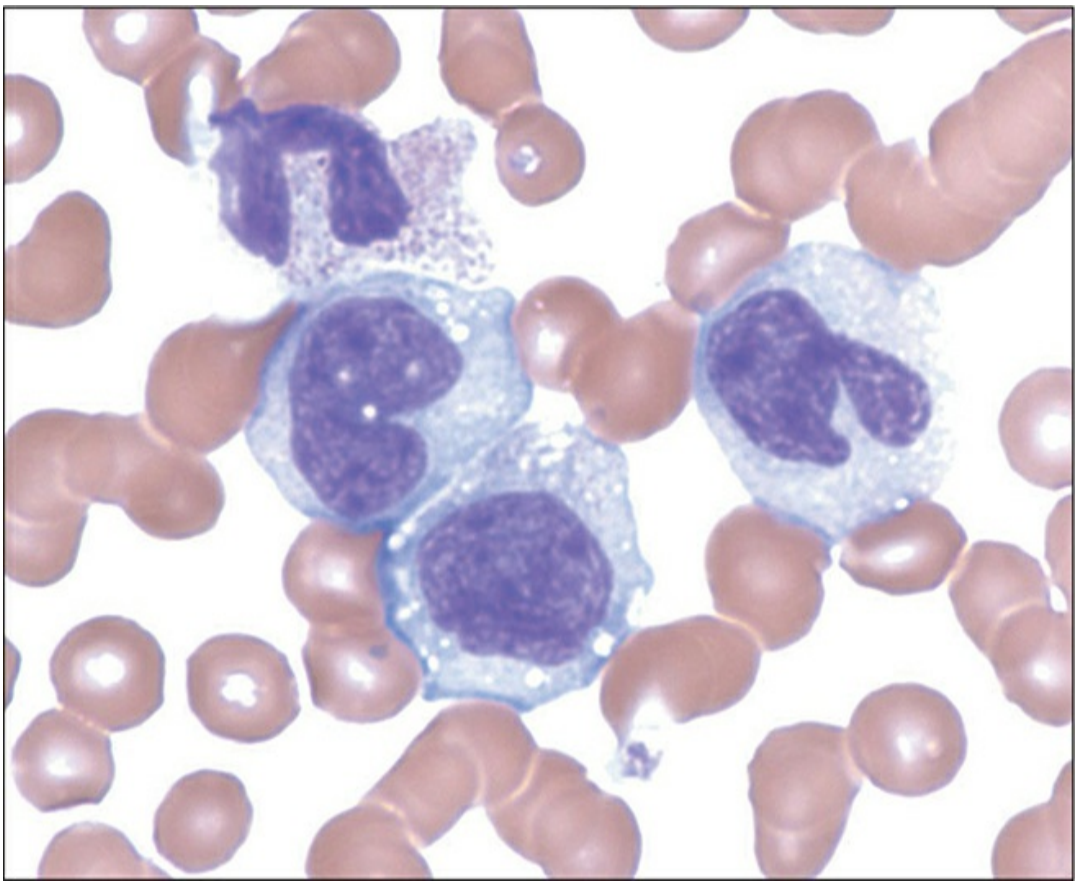


Figure IIB7-1

Peripheral blood smear.

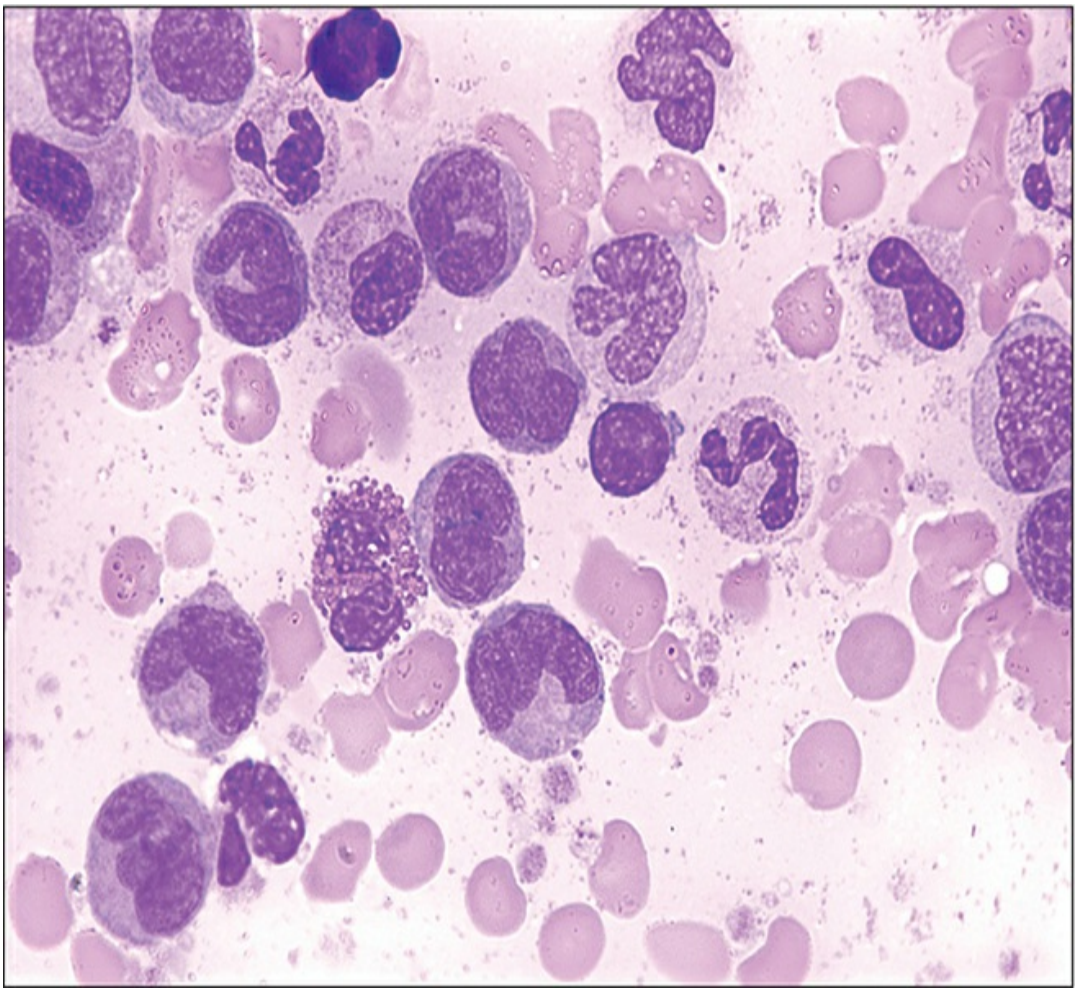


Figure **IIB7-2**

Bone marrow smear.

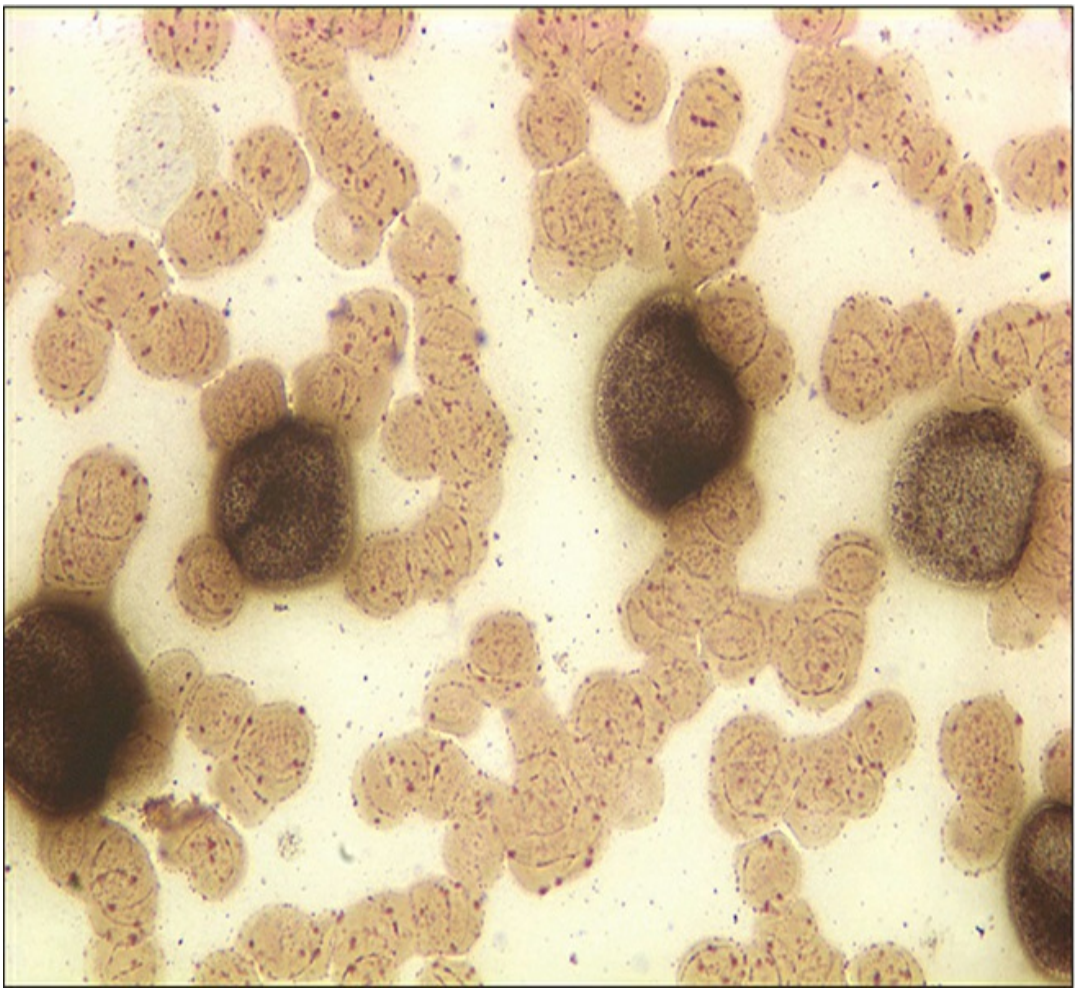


Figure **IIB7-3**

Nonspecific esterase stain. Positive.

Criteria

- Persistent peripheral blood monocytosis defined as >1.0 × 10^9/L and >10% monocytes
- Absence of Philadelphia chromosome, BCR-ABL1 fusion, or myeloproliferative neoplasm
- Absence of PDGFRA , PDGFRB , FGFR1 , or PCM1-JAK2
- <20% blasts or blast equivalents in peripheral blood or bone marrow
- Dysplasia in one or more of the myeloid lineages
- Subcategories
  - CMML-0

    - Blasts <2% in peripheral blood and <5% in bone marrow and no Auer rods
- CMML-1
    - Blasts 2–4% in peripheral blood or 5–9% in bone marrow and no Auer rods
- CMML-2
    - Blasts between 5% and 19% in peripheral blood or 10–19% in bone marrow or Auer rods are present

Clinical Features

- Occurs most commonly in persons over 50 years
- Fatigue and weakness
- Hemorrhagic symptoms
- Infection is the most common cause of death
- Hepatomegaly and splenomegaly may be present especially when the white blood cell count is elevated
- May have skin infiltrations

Pathology

- Expansion of abnormal cells in the bone marrow and a decrease in normal cells
- Rearrangements of genetic material may be important in the activation of protooncogenes to oncogenes

Laboratory Features

White Blood Cells

- Usually normal to decreased
- Monocytes range from 2 to 5 × 10^9/L but may be above 80 × 10^9/L
- Monocytes are >10% of the leukocytes

- Monocytes are mature but can exhibit abnormal granulation or nuclear lobulation
- Blasts and promonocytes are <20% of the white blood cell count
- There are <10% neutrophil precursors
- Dysgranulopoiesis is common
- Basophilia is typically mild but rare cases of increased eosinophils have been described

Red Blood Cells

- Anemia is usually normocytic but sometimes macrocytic
- Dimorphic population

Platelets

- Decreased count
- Abnormal forms may be found

Bone Marrow

- Usually hypercellular
- Granulocytic proliferation
- Slight dysgranulopoiesis
- <20% blasts and promonocytes
- Dyserythropoiesis
- Slight dysmegakaryopoiesis
- Increased monocytic precursors

Cytochemistry

- Nonspecific esterase positive for monocytic cells
- Myeloperoxidase and Sudan black B positive in granulocytic cells
- Periodic acid–Schiff negative

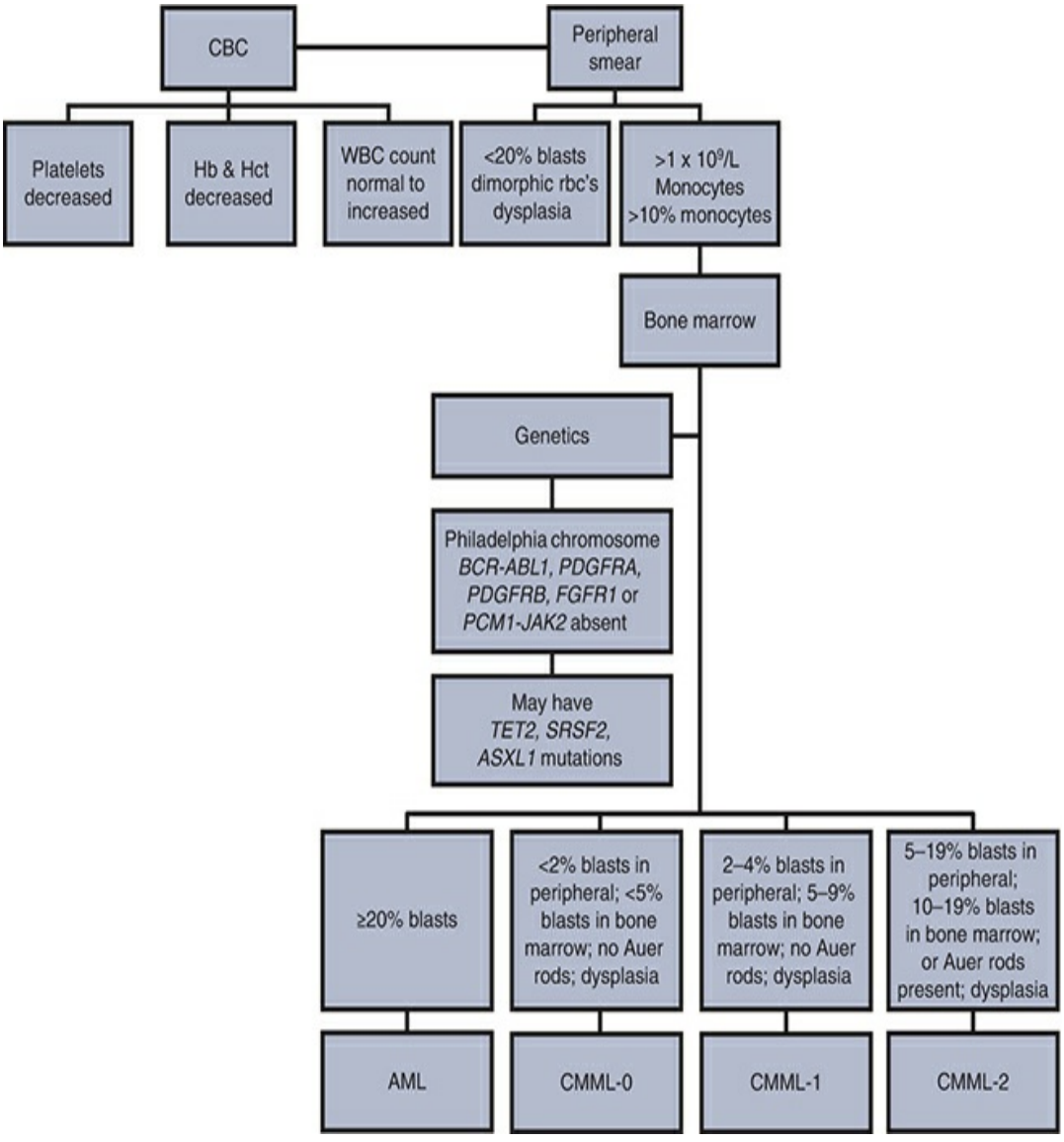
Immunophenotype

- Expresses the myelomonocytic antigen such as CD33 and CD13
- Variable expression of CD14, CD68, and CD64

Genetics

- 60% of cases show TET2 mutations
- 50% of cases have SRSF2 mutations
- 40% of cases have ASXL1 mutations

Diagnostic Scheme



Atypical Chronic Myeloid Leukemia (aCML) BCR-ABL1 Negative

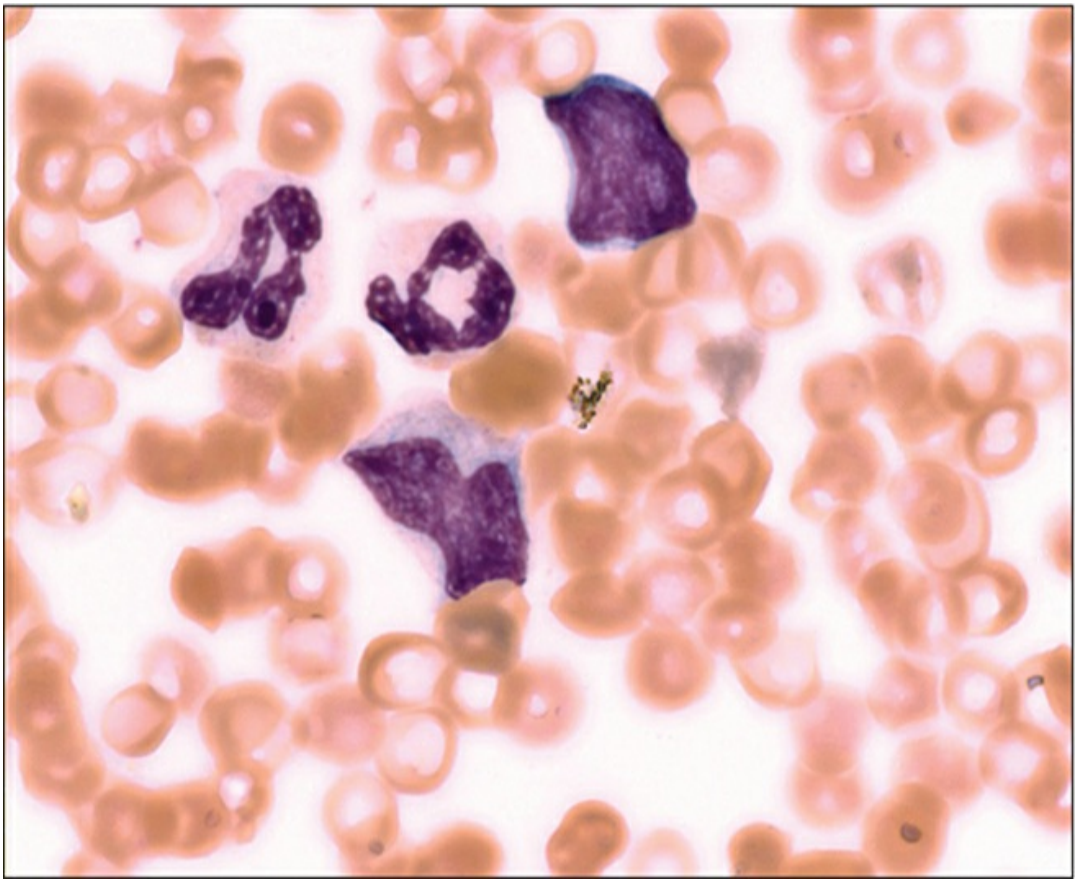


Figure IIB7-4

Peripheral blood smear.

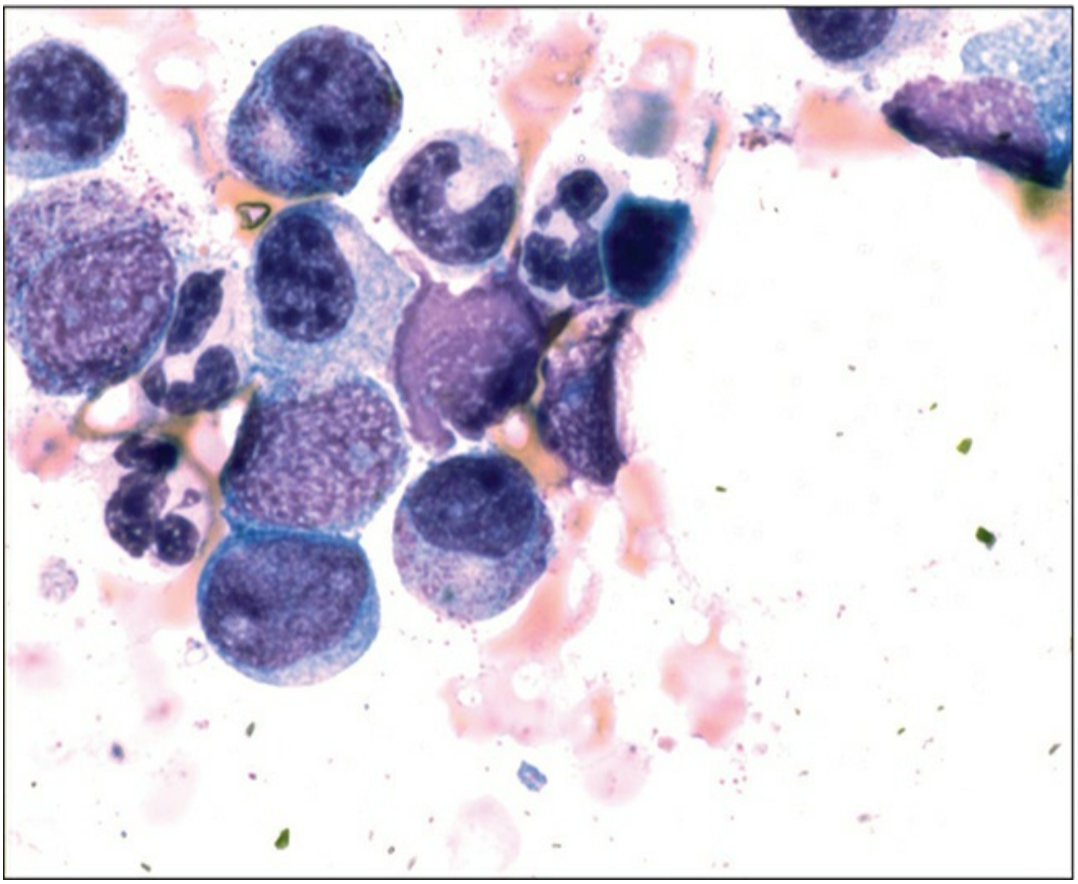


Figure IIB7-5

Bone marrow smear.

Clinical Features

- Occurs in about 1–2% of the chronic myelogenous leukemias
- Patients are usually elderly
- Fatigue, bleeding disorders
- Splenomegaly and hepatomegaly may also be present

Pathology

- Myelodysplastic as well as myeloproliferative features at the time of initial diagnosis
- Principal involvement of the granulocytic line
- No Philadelphia chromosome or BCR-ABL1 fusion gene
- No specific chromosomal abnormalities but may see

+8, +13, del(20q), inv(17q), and del(12p)

Laboratory Features

White Blood Cells

- Leukocytosis with counts ≥13.0 × 10^9/L but most have counts from 24.0 to 96.0 × 10^9/L
- Immature and dysplastic
- 10–20% immature cells (promyelocytes, myelocytes, and metamyelocytes)
- Blasts are usually <5% but must be <20%
- Monocytes are usually <10%
- Basophilia <2%
- Dysgranulopoiesis is pronounced with pseudo Pelger-Huët cells, abnormally clumped chromatin, or bizarre segmentation

Red Blood Cells

- Anemia
- Dyserythropoiesis
- Macro-ovalocytosis may be present

Platelets

- Count is variable but decreased numbers are common

Bone Marrow

- Hypercellular due to increased neutrophils and their precursors
- Increased myeloid to erythroid ratio with >10:1 common
- Blasts are typically <5% but always <20%
- Dysgranulopoiesis, dyserythropoiesis, and dysmegakaryopoiesis

- Some cases have over 30% erythroid precursors

Cytochemistry

- No diagnostic abnormalities

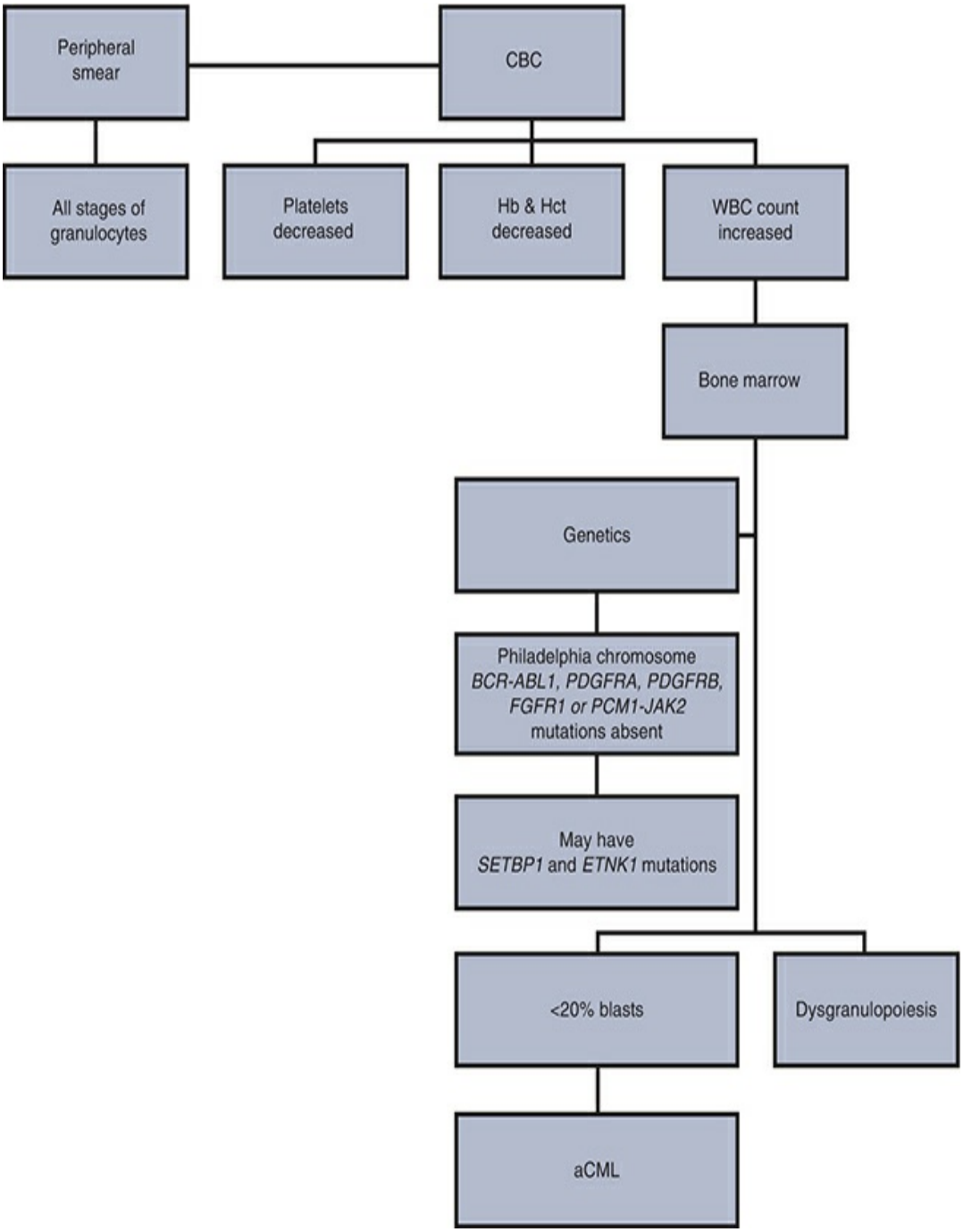
Immunophenotype

- Neutrophils and precursors are positive for CD33, CD13, and CD15

Genetics

- SETBP1 and ETNK1 mutations are relatively common
- The CSF3R mutation is present in <10% of cases
- Common cytogenetic abnormalities are inv(17q), trisomy 8, and deletion of long arm of chromosome 20

Diagnostic Scheme


Peripheral smear
CBC
All stages of granulocytes
Platelets decreased
Hb & Hct decreased
WBC count increased
Bone marrow
Genetics
Philadelphia chromosome
BCR-ABL1, PDGFRA, PDGFRB, FGFR1 or PCM1-JAK2
mutations absent
May have
SETBP1 and *ETNK1* mutations
<20% blasts
Dysgranulopoiesis
aCML

JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML)

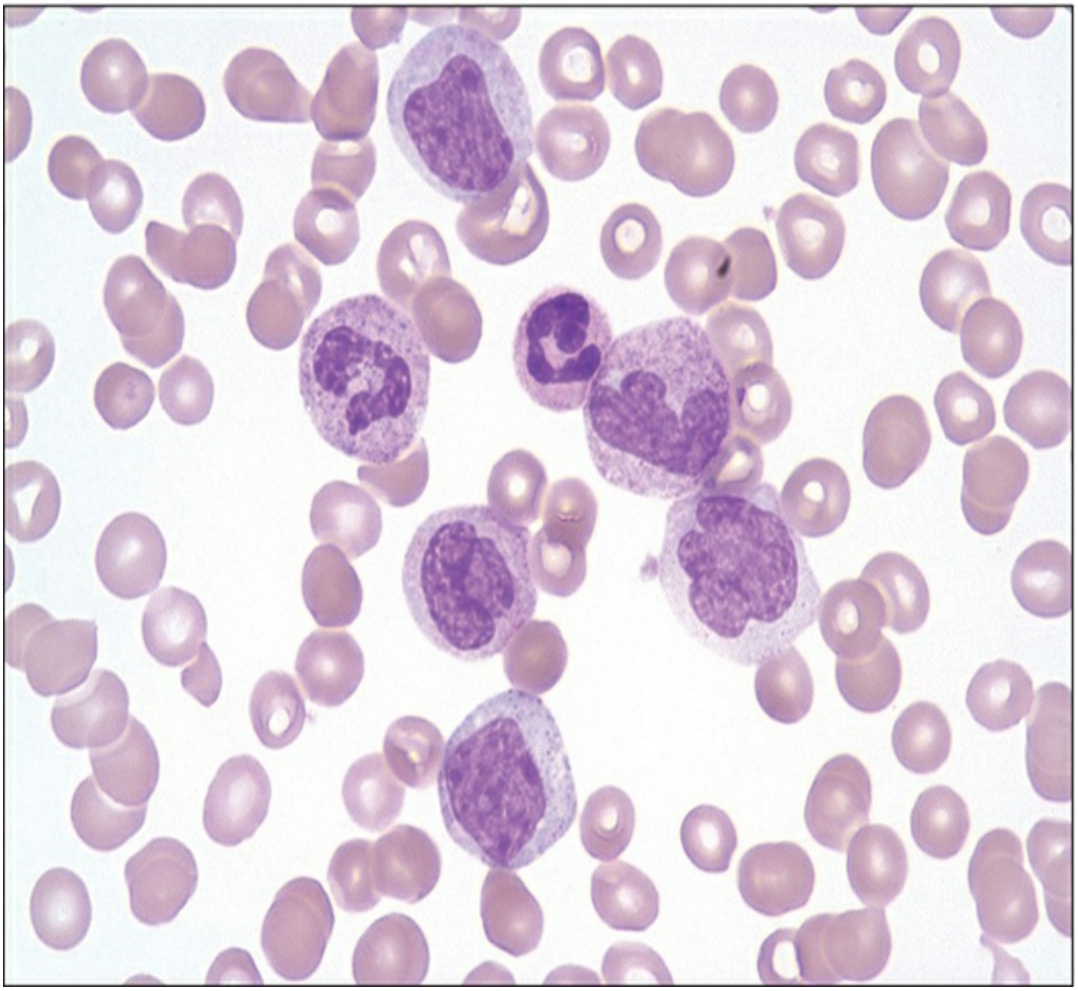


Figure IIB7-6

Peripheral blood smear.

Clinical Features

- Age of onset ranges from 1 month to early adolescence; 70% of cases occur in children <3 years of age
- 2–3% of all leukemias in children
- 20–30% of all myelodysplastic and myeloproliferative diseases in children
- Approximately 75% of the cases occur in children <3

years

- Malaise, pallor, fever, and recurrent infections
- Leukemic infiltrates are common in the skin
- Most patients have infections and hepatosplenomegaly

Pathology

- Associated with RAS/MAPK mutations
- Loss of NF1 tumor suppressor gene function causes activation of RAS signaling pathway
- 10–15% of cases have CBL mutations
- Mutations lead to increased sensitivity to granulocyte–macrophage colony–stimulating factors in myeloid cells

Laboratory Features

White Blood Cells

- White blood cell count varies from 25.0 to 30.0 $\times 10^9$/L
- Mainly neutrophils with some immature cells such as promyelocytes and myelocytes
- Monocytes are increased (1.0 $\times 10^9$/L)
- Blasts and promonocytes usually account for <5% and always <20%

Red Blood Cells

- Nucleated red blood cells are frequent
- Marked increased in hemoglobin F

Platelets

- Variable but may be decreased and may be severe

Bone Marrow

- Hypercellularity
- Granulocytic proliferation but rarely erythroid precursors can predominate

- Monocytes account for about 5–10% or cells
- Blasts and promonocytes are <20%
- No Auer rods
- Dysplasias are minimal but pseudo Pelger-Huët cells or hypogranular forms may be seen
- Megakaryocytes are often decreased

Cytochemistry

- Nonspecific esterase stain is positive in monocytic precursors
- Myeloperoxidase and Sudan black B positive in granulocytic cells

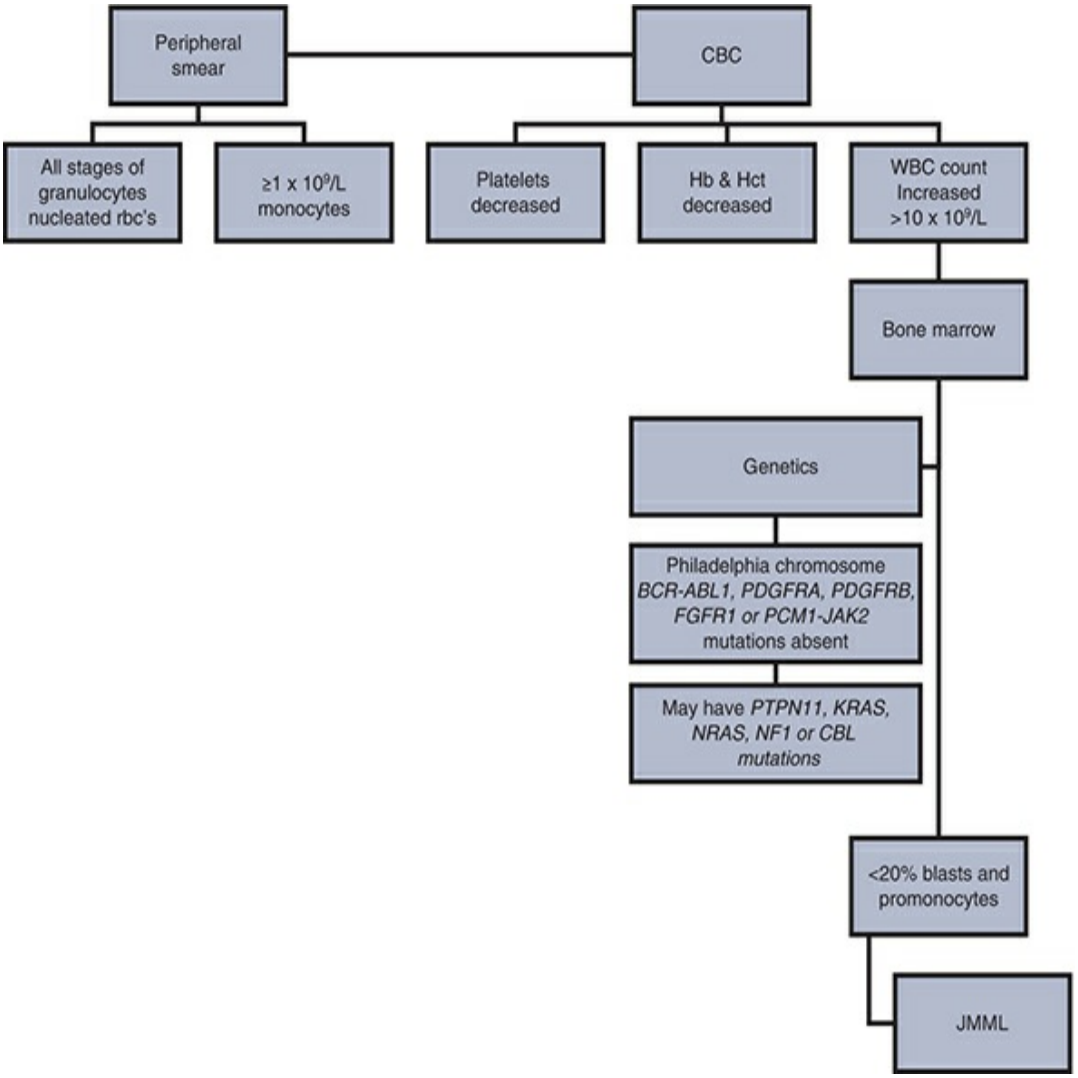
Immunophenotype

- No specific immunophenotypic abnormalities have been reported

Genetics

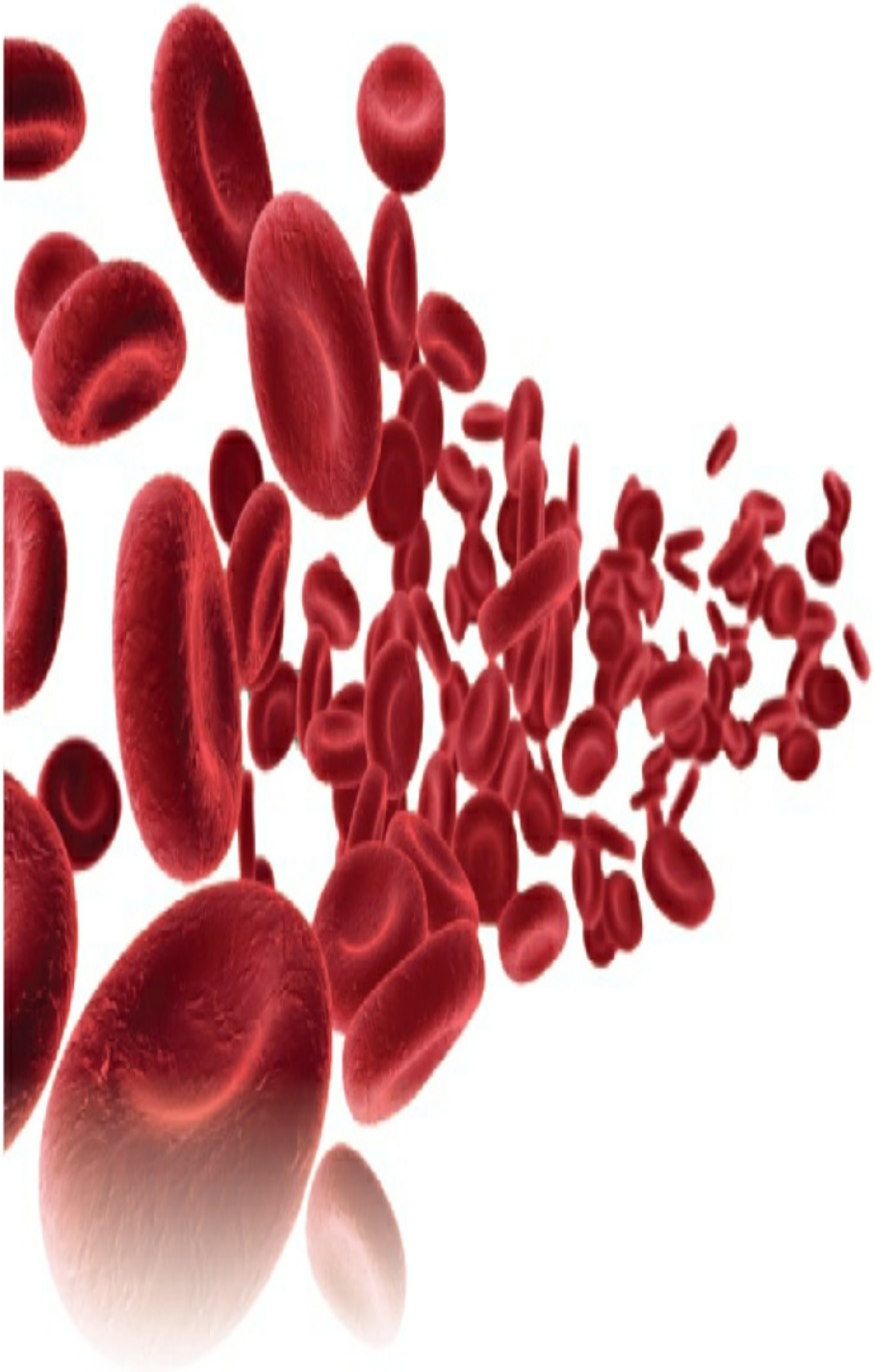
- 25% of cases have monosomy 7
- 65% of cases have a normal karyotype

Diagnostic Scheme


Peripheral smear
CBC
All stages of granulocytes nucleated rbc's
≥1 x 10⁹/L monocytes
Platelets decreased
Hb & Hct decreased
WBC count Increased >10 x 10⁹/L
Bone marrow
Genetics
Philadelphia chromosome BCR-ABL1, PDGFRA, PDGFRB, FGFR1 or PCM1-JAK2 mutations absent
May have PTPN11, KRAS, NRAS, NF1 or CBL mutations
<20% blasts and promonocytes
JMML

CHAPTER 8

Acute Myeloid Leukemia and Related Precursor Neoplasms



ACUTE MYELOID LEUKEMIA WITH RECURRENT GENETIC ABNORMALITIES

Criteria

- Clonal hematopoietic neoplasm
- When there is an associated t(8;21)(q22;q22.1), inv(16)(p13.1q22) or t(16;16)(p13.1;q22) chromosomal abnormality or t(15;17)(q22;q11-12); PML-RARA fusion, the blast count in peripheral blood and/or bone marrow may be <20% for the diagnosis of acute leukemia
- ≥20% blasts

Classification

Acute Myeloid Leukemia With Balanced Translocations/Inversions

- Most commonly identified are balanced abnormalities
- These structural chromosomal rearrangements create a fusion gene
  - Acute myeloid leukemia with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
  - Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
  - Acute promyelocytic leukemia with t(15;17)(q22;q11–12); PML-RARA
  - Acute myeloid leukemia with t(9;11)(p21.3;q23.3); KMT2A-MLLT3
  - Acute myeloid leukemia with t(6;9)(p23;q34.1); DEK-NUP214
  - Acute myeloid leukemia with inv(3)(q21.3q26.2) or

t(3;3)(q21.3;q26.2); GATA2 , MECOM
    - Acute myeloid leukemia (megakaryoblastic) with t(1;22)(p13.3;q13.1); RBM15-MKL1
    - Acute myeloid leukemia with BCR-ABL1 (provisional)

Acute Myeloid Leukemia With Gene Mutations

- Translocations and inversion mutations are common in acute myeloid leukemias
    - NPM1
    - Biallelic CEBPA
    - RUNX1 (provisional)

Acute Myeloid Leukemia With t(8;21)(q22;q22.1); RUNX1-RUNX1T1

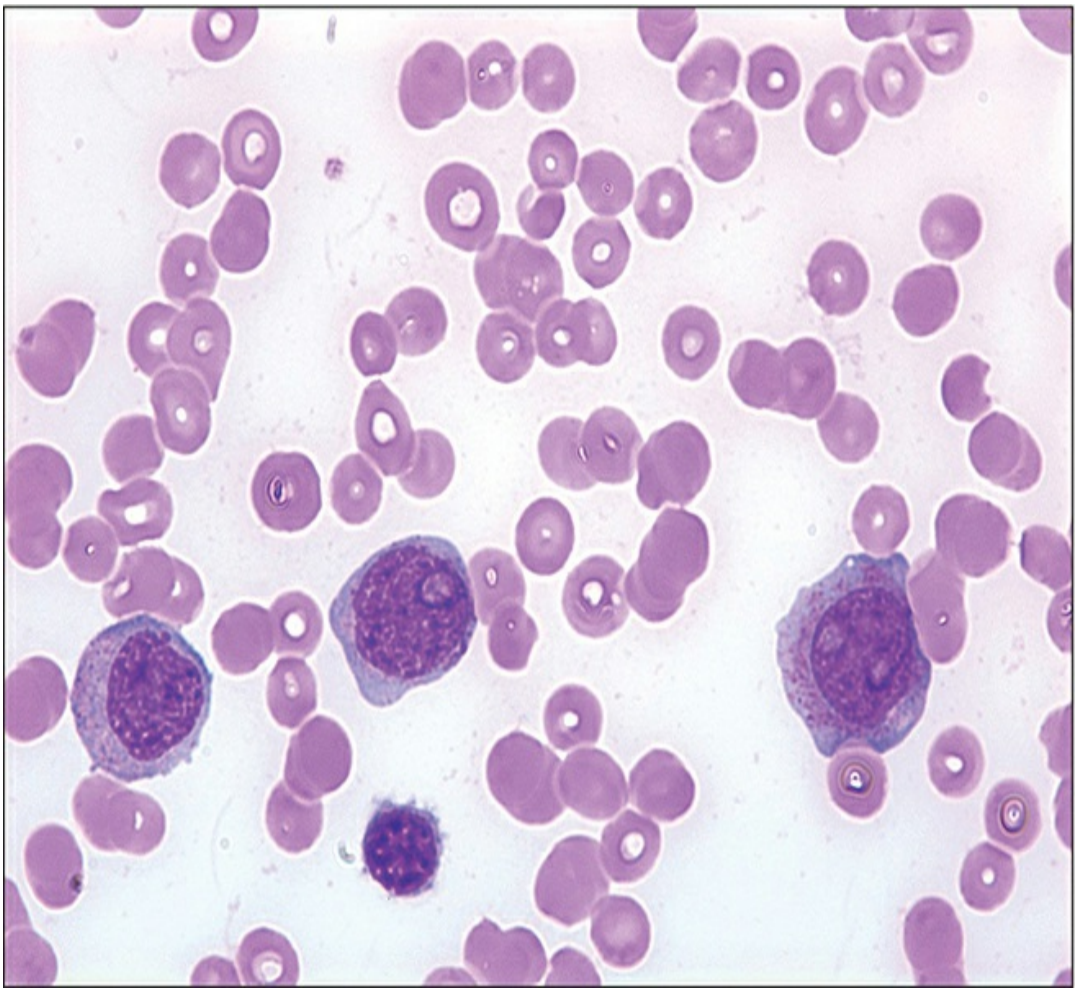


Figure IIB8-1

Peripheral blood smear.

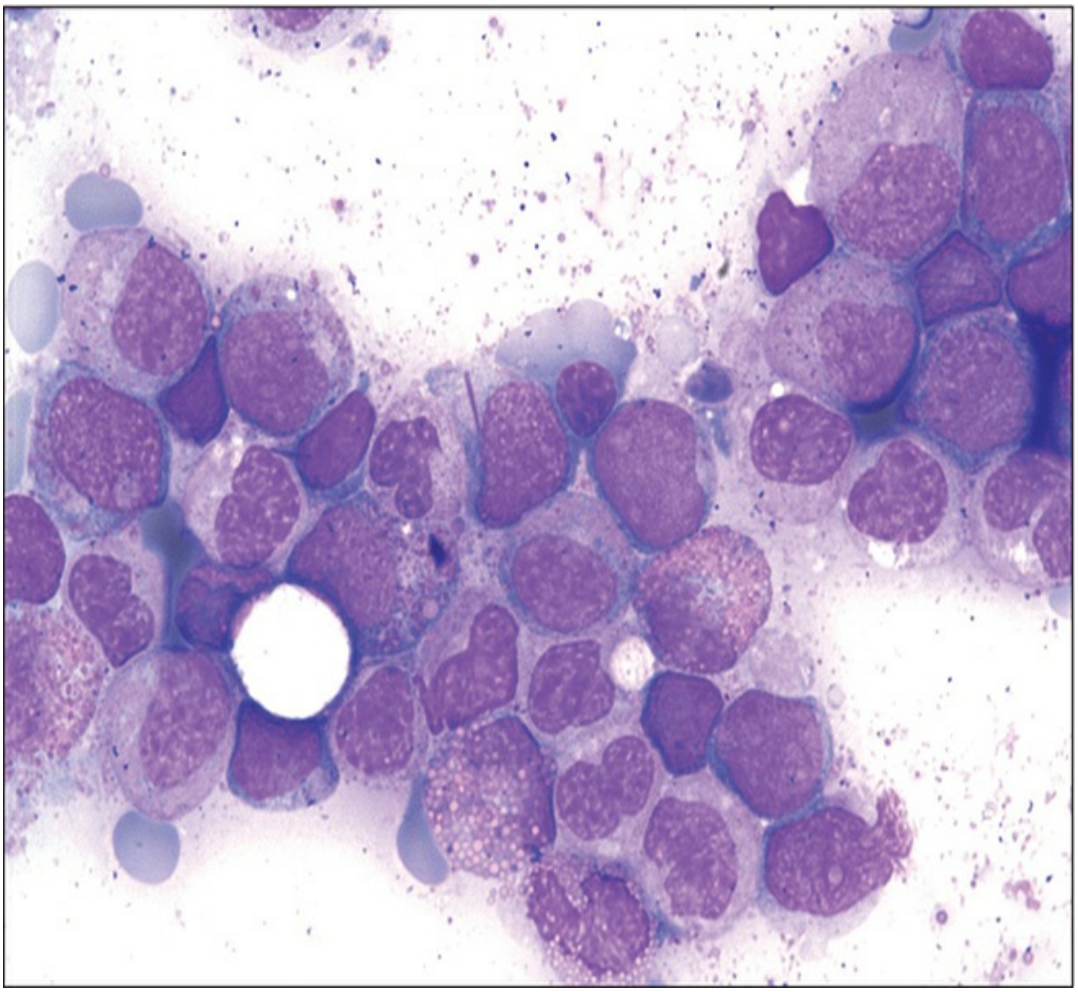


Figure **IIB8-2**

Bone marrow smear.

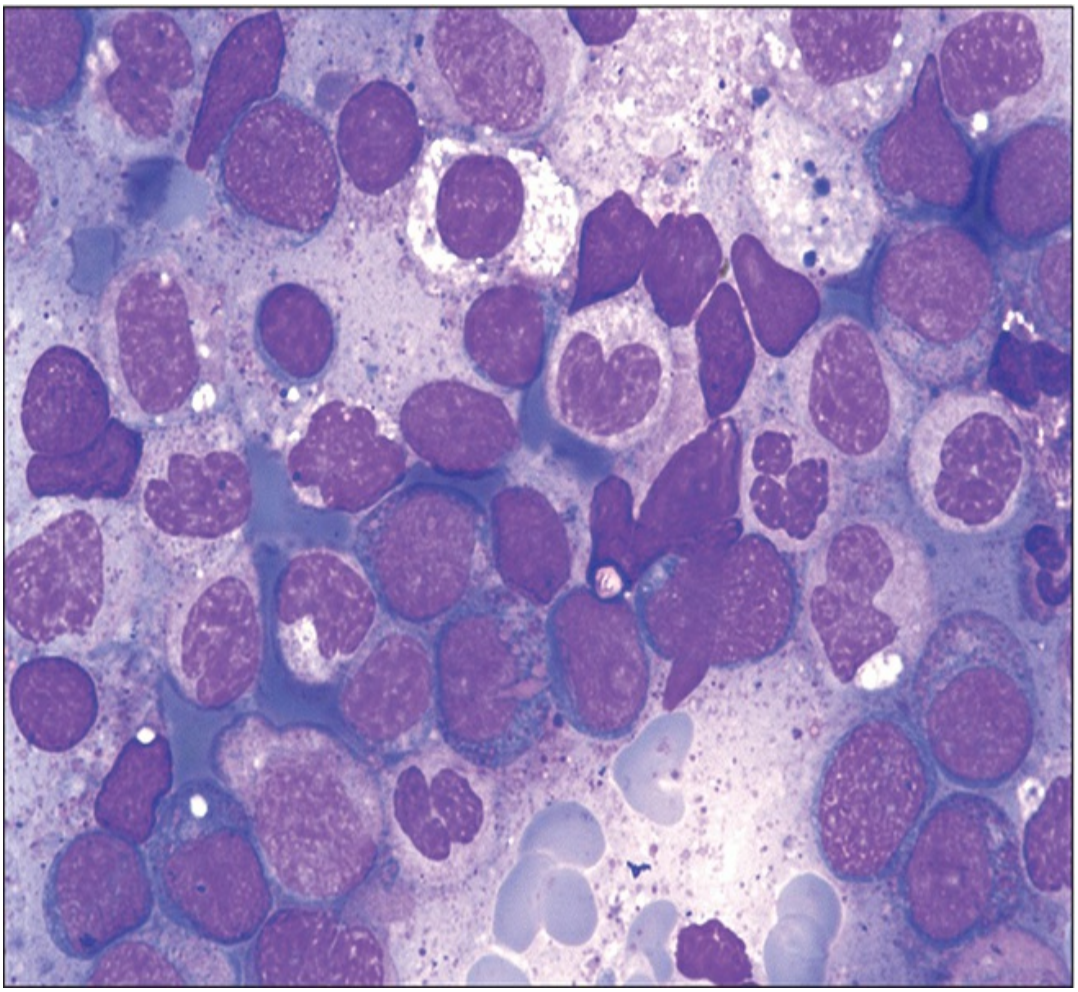


Figure IIB8-3

Bone marrow smear.

Clinical Features

- Myeloid sarcomas may be present at the time of diagnosis
- Weakness and pallor associated with anemia
- Bleeding due to decreased platelet count
- Infection if neutropenia exists

Pathology

- Translocations result in a fusion of RUNX1-RUNX1T1
- Found in 10–15% or pediatric cases of acute myeloid leukemias

- Found in about 7% of adult cases of acute myeloid leukemias
- Occurs predominantly in younger people
- Shows maturation in the neutrophilic lineage
- Down-regulates normal transcriptional activity

Laboratory Features

White Blood Cells

- Large blasts with abundant basophilic cytoplasm
- Smaller blasts may be present
- Auer rods are common with abnormally long pointed ends
- Granular myeloblasts may be the predominant cell
- Dysplasia in granulocytes

Red Blood Cells

- Anemia may be present

Platelets

- May be decreased

Bone Marrow

- Typically hypercellular
- ≥20% blasts
- If the 8;21 translocation is present, may have <20% blasts for a diagnosis
- Some blasts may show pseudo-Chediak-Higashi granules
- Large salmon-colored granules in some blasts
- Auer rods are frequently found with long pointed ends
- Blasts may show a hof next to the nucleus
- Granulocytic series show variable dysplasia

- Eosinophil precursors are frequently increased but don't have cytoplasmic granule abnormalities

Cytochemistry

- Myeloblasts myeloperoxidase positive

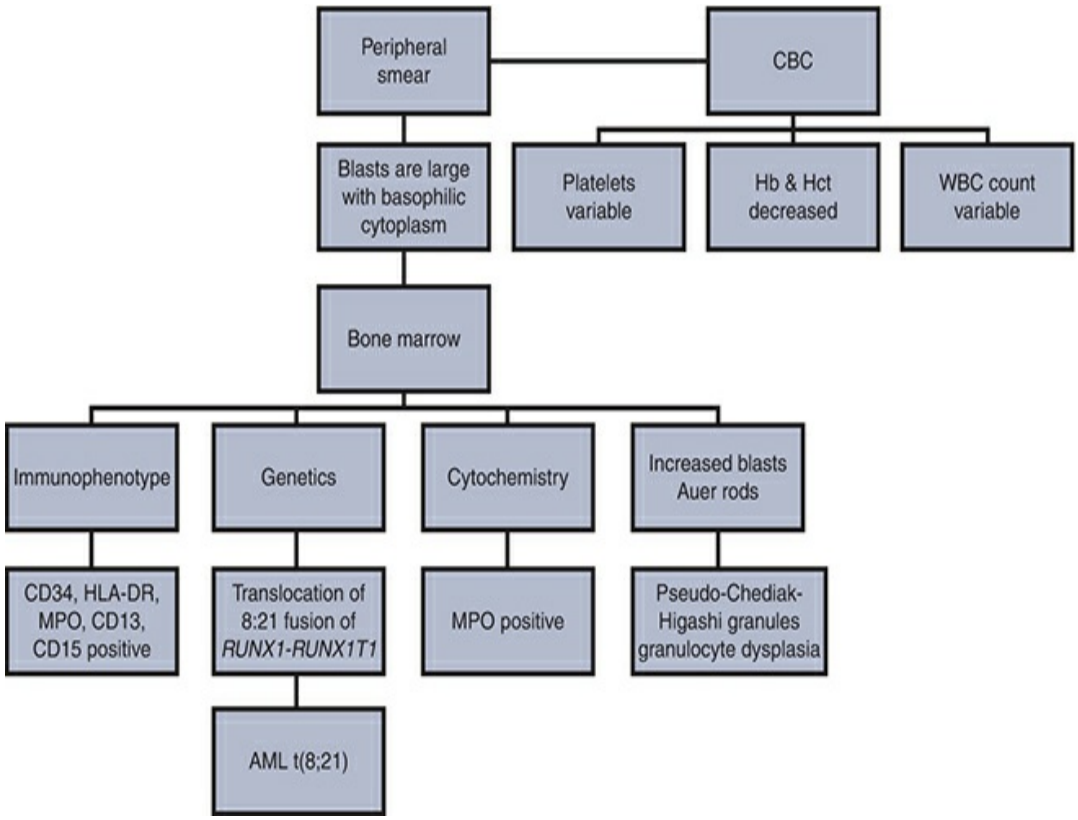
Immunophenotype

- Weak expression of CD33
- Will also show CD34, MPO, HLA-DR, CD13, and CD15
- If CD56 is present, it indicates a poorer prognosis

Genetics

- Balanced abnormalities of t(8;21)(q22;q22.1)
- Additional chromosomal abnormalities can be seen in approximately 70% of the cases
- ASXL1 mutations occur in approximately 10% patient, mostly adults
- ASXL2 mutations occur in 20–25% of patients of all ages

Diagnostic Scheme


Peripheral smear
CBC
Blasts are large with basophilic cytoplasm
Platelets variable
Hb & Hct decreased
WBC count variable
Bone marrow
Immunophenotype
Genetics
Cytochemistry
Increased blasts Auer rods
CD34, HLA-DR, MPO, CD13, CD15 positive
Translocation of 8:21 fusion of RUNX1-RUNX1T1
MPO positive
Pseudo-Chediak-Higashi granules granulocyte dysplasia
AML t(8;21)

Acute Myeloid Leukemia With inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11

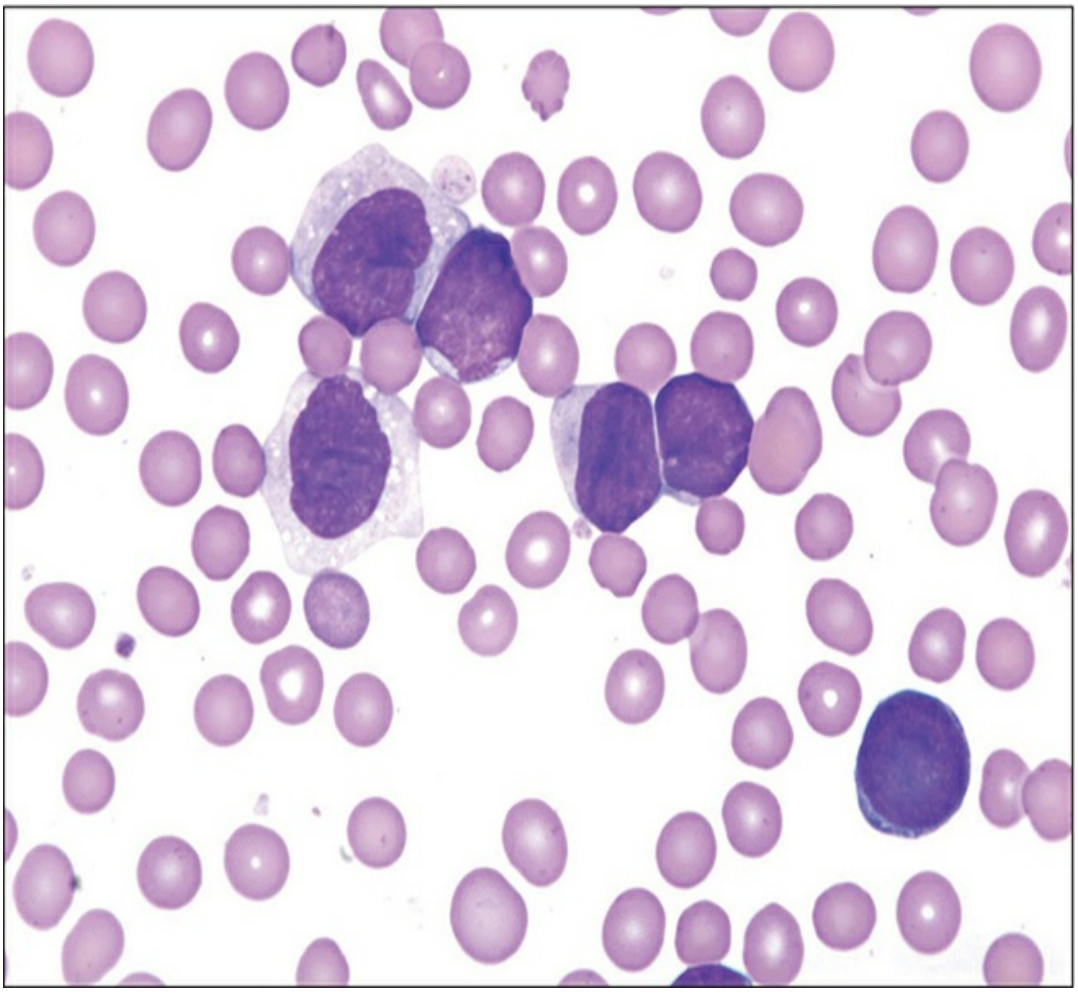


Figure IIB8-4

Peripheral blood smear.

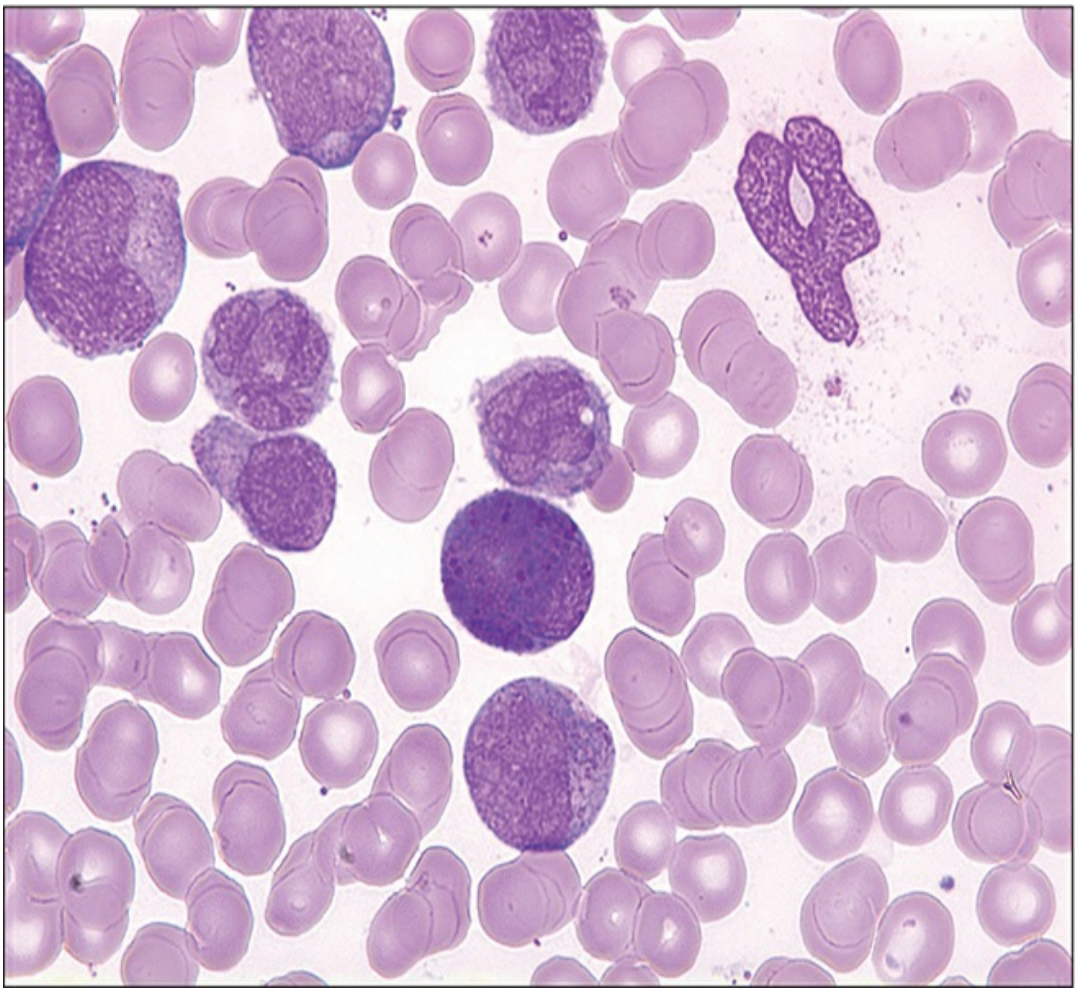


Figure **IIB8-5**

Bone marrow smear.

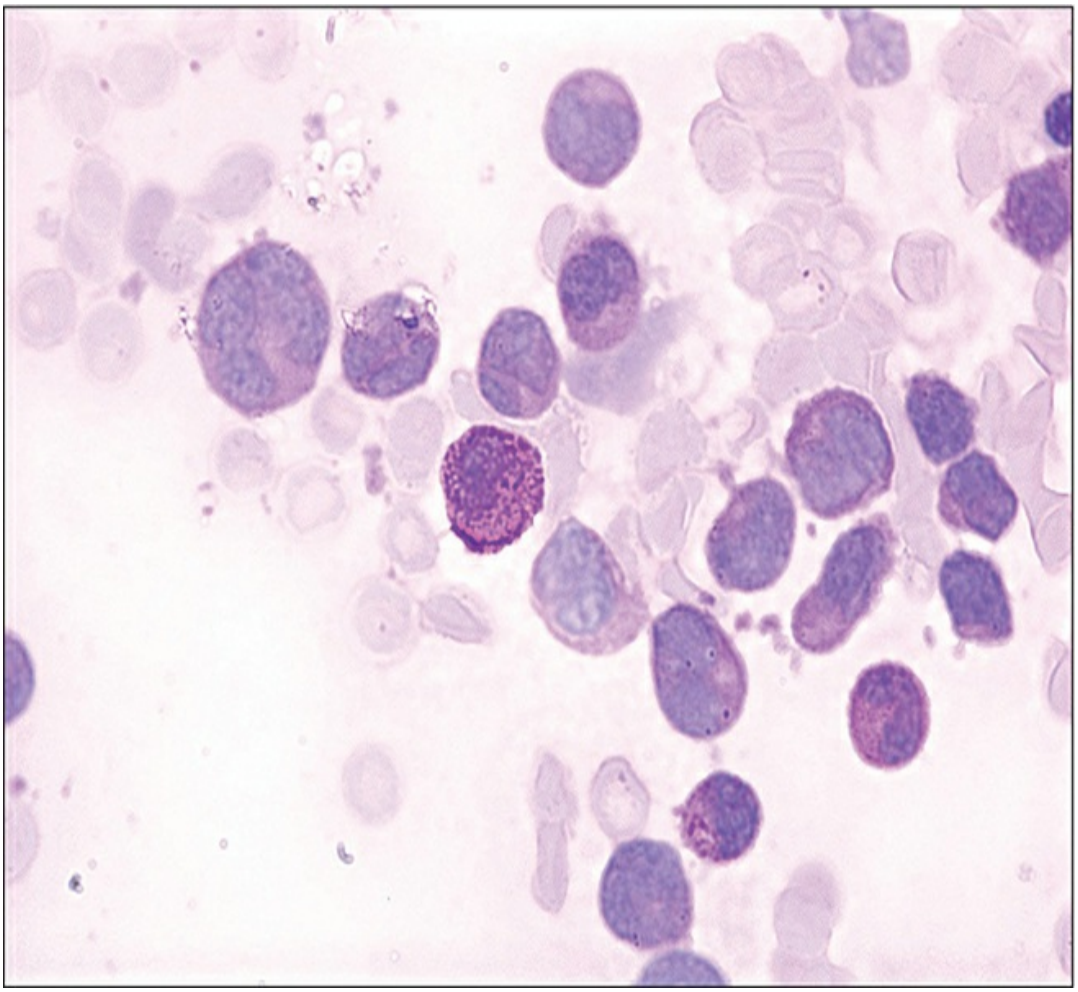


Figure IIB8-6

Periodic acid–Schiff stain. Positive.

Clinical Features

- Occurs at all age groups but more likely in younger patients
- Myeloid sarcomas may be present
- Pallor, fatigues, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Bone tenderness, hepatosplenomegaly, and lymphadenopathy

Pathology

- Found in about 5–8% of all patients with acute myeloid leukemias
- Shows acute myelomonocytic leukemia
- Exhibits an abnormal eosinophilic component in the bone marrow
- CBFB-MYH11 molecular fusion

Laboratory Features

White Blood Cells

- Variable white blood cell count
- Neutropenia
- Variable blast count
- Monoblasts, promonocytes, and myeloblasts are present
- Absolute monocytosis common

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- ≥20% blasts
- If inv(16) or t(16:16) translocation is present, may have <20% blasts for a diagnosis
- Predominant myelomonocytic and abnormal eosinophilic component
- Decreased number of mature neutrophils
- Variable number of eosinophils but usually increased and at all stages of maturation
- Eosinophilic granules are larger than normal and have

an intense basophilic purple-violet color in eosinophilic precursors (Harlequin cell)
- Auer rods may be seen in myeloblasts

Cytochemistry

- Naphthol AS-D chloroacetate esterase is positive in the abnormal eosinophils
- Periodic acid–Schiff is positive in the abnormal eosinophils
- Myeloblasts are myeloperoxidase positive
- Monoblasts and promonocytes usually show nonspecific esterase positive

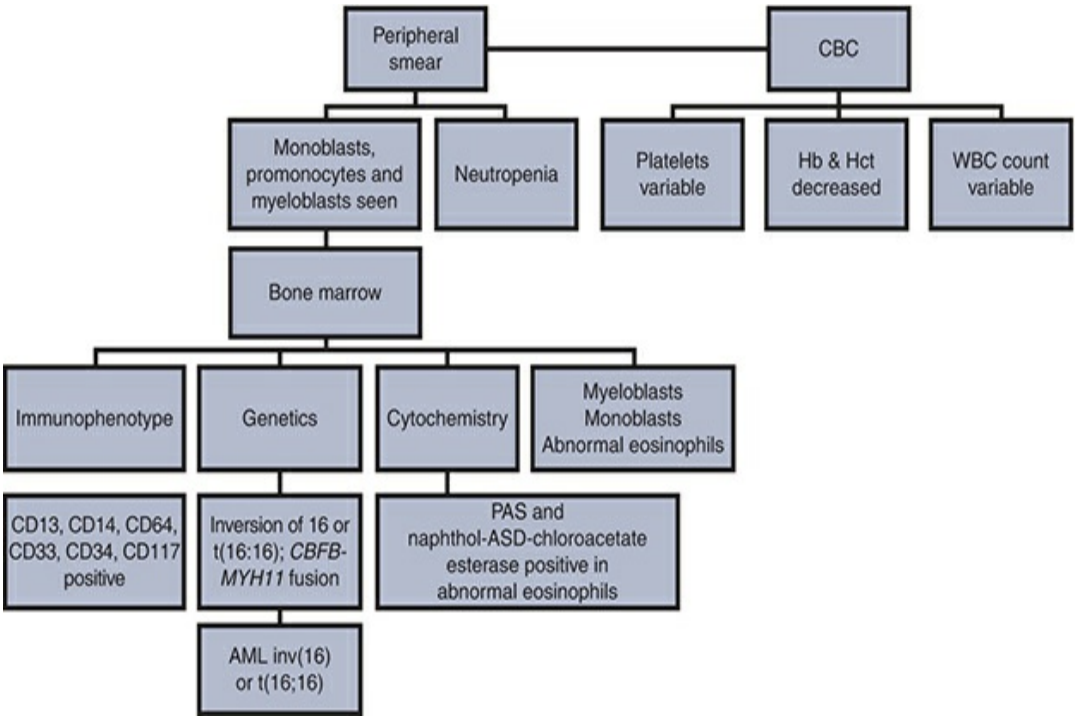
Immunophenotype

- Complex with the presence of multiple blast populations
- Increased myeloblasts show CD34, CD117, and CD33
- Monocytic cells show CD36, CD64, CD33, HLA-DR, CD14, and CD45

Genetics

- Inv(16)(p13.1q22) found in the majority of cases
- t(16;16)(p13.1;q22) found less commonly
- Abnormal genetics rearrangements result in the fusion of the CBFB gene to the MYH11 gene

Diagnostic Scheme


Peripheral smear
CBC
Monoblasts, promonocytes and myeloblasts seen
Neutropenia
Platelets variable
Hb & Hct decreased
WBC count variable
Bone marrow
Immunophenotype
Genetics
Cytochemistry
Myeloblasts Monoblasts Abnormal eosinophils
CD13, CD14, CD64, CD33, CD34, CD117 positive
Inversion of 16 or t(16:16); CBFB-MYH11 fusion
PAS and naphthol-ASD-chloroacetate esterase positive in abnormal eosinophils
AML inv(16) or t(16;16)

Acute Promyelocytic Leukemia (APL) With t(15;17)(q22;q11–12); PML-RARA

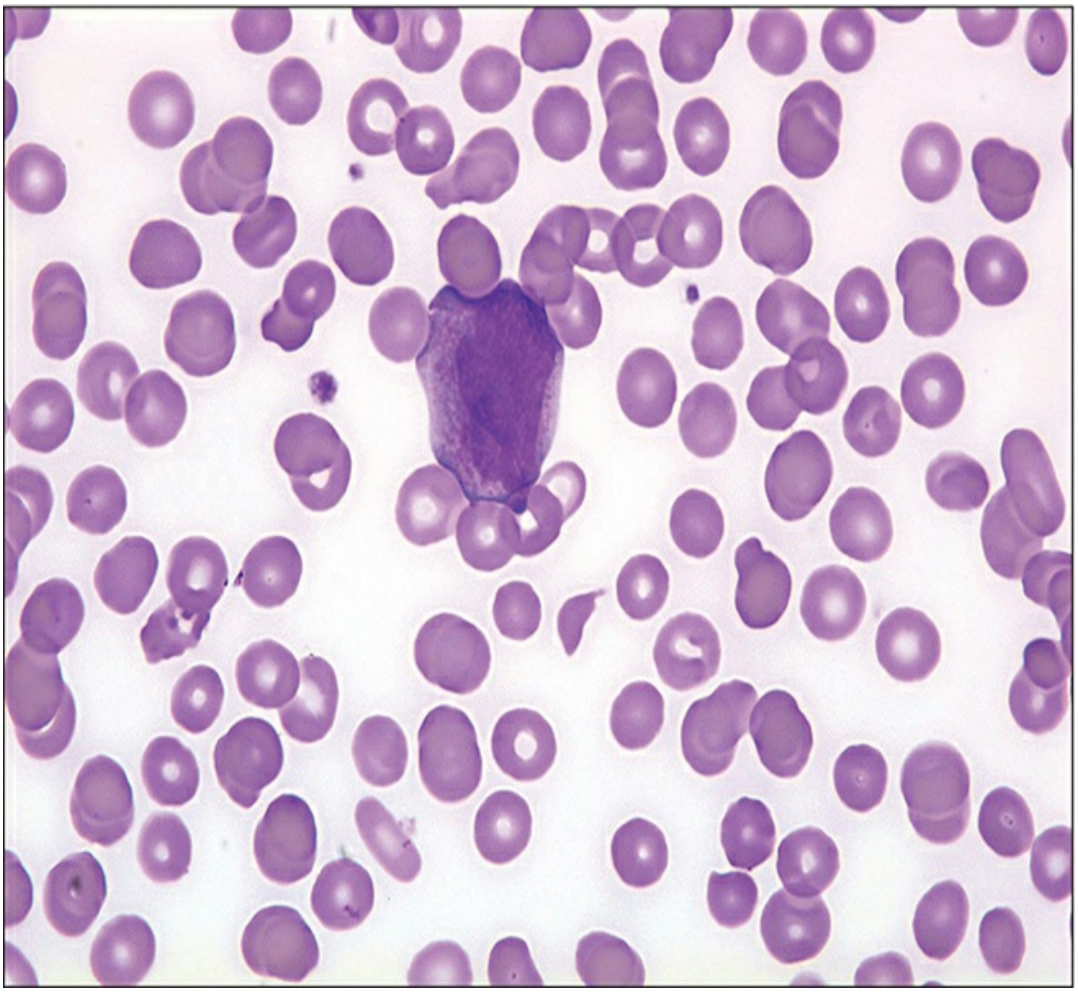


Figure IIB8-7

Peripheral blood smear. Hypergranular.

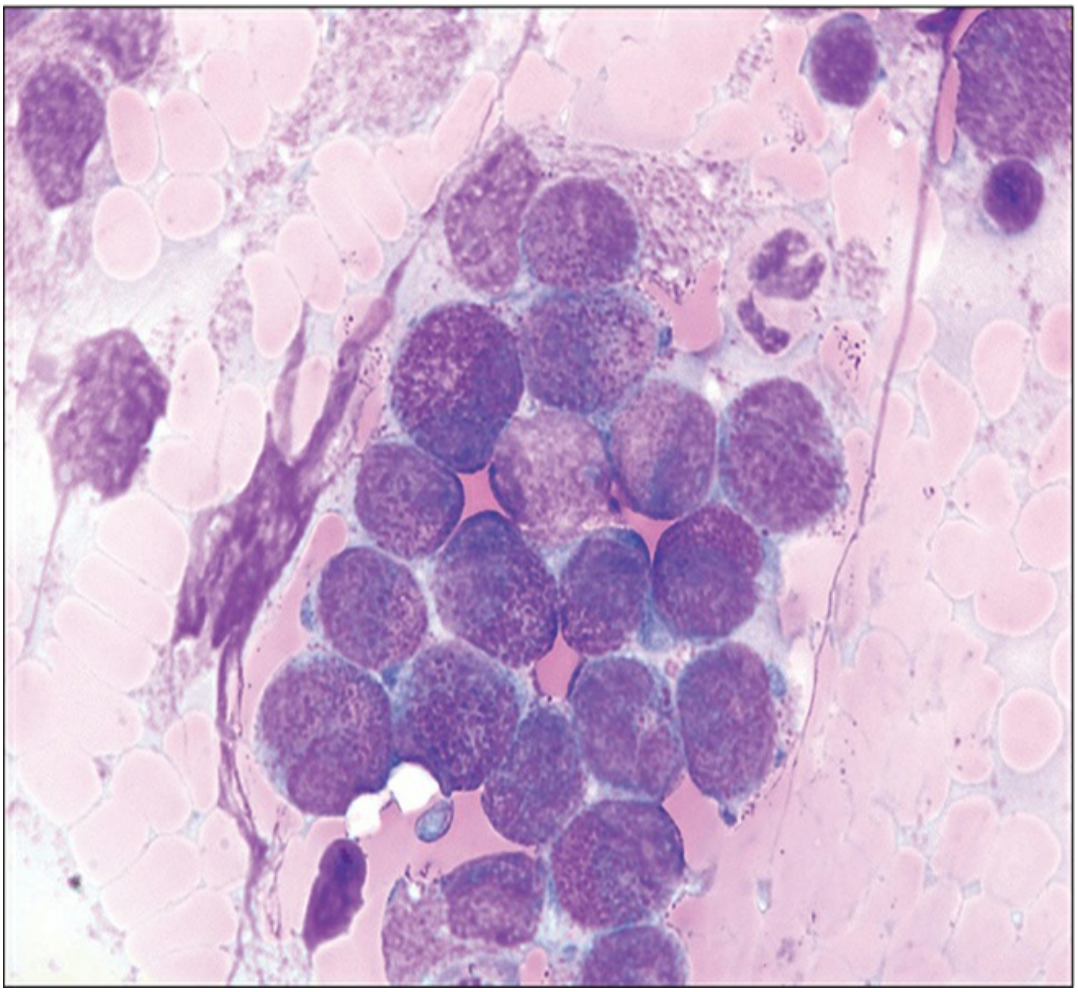


Figure **IIB8-8**

Bone marrow smear. Hypergranular.

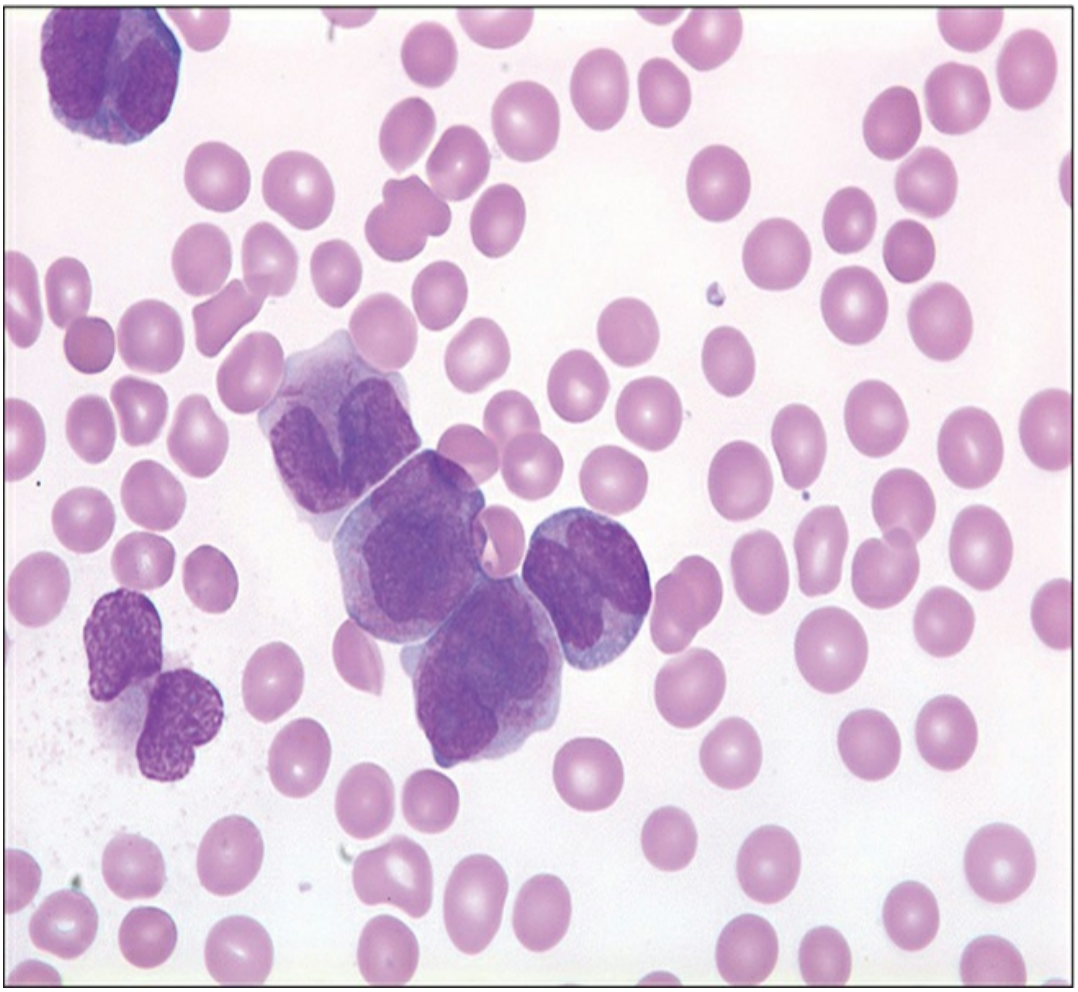


Figure **IIB8-9**

Peripheral blood smear. Microgranular variant.

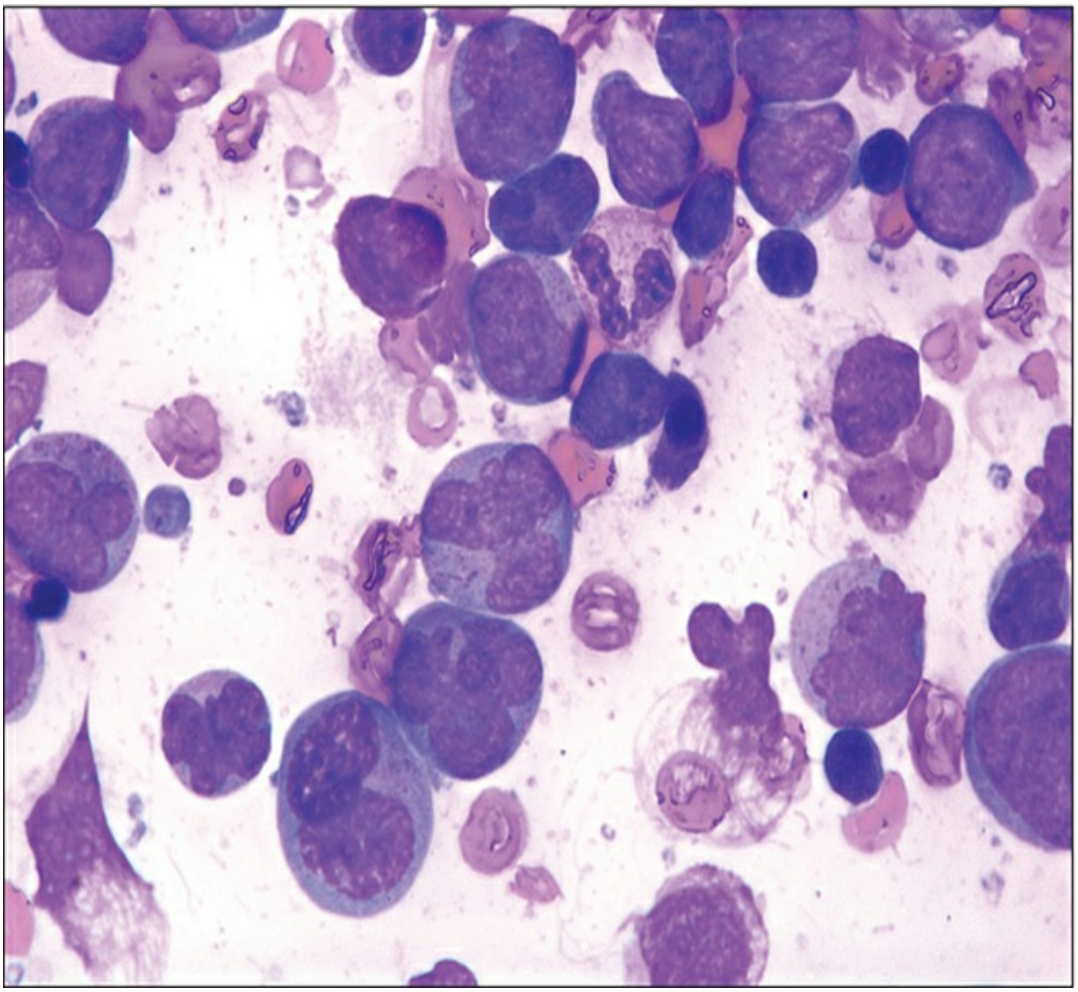


Figure **IIB8-10**

Bone marrow smear. Microgranular variant.

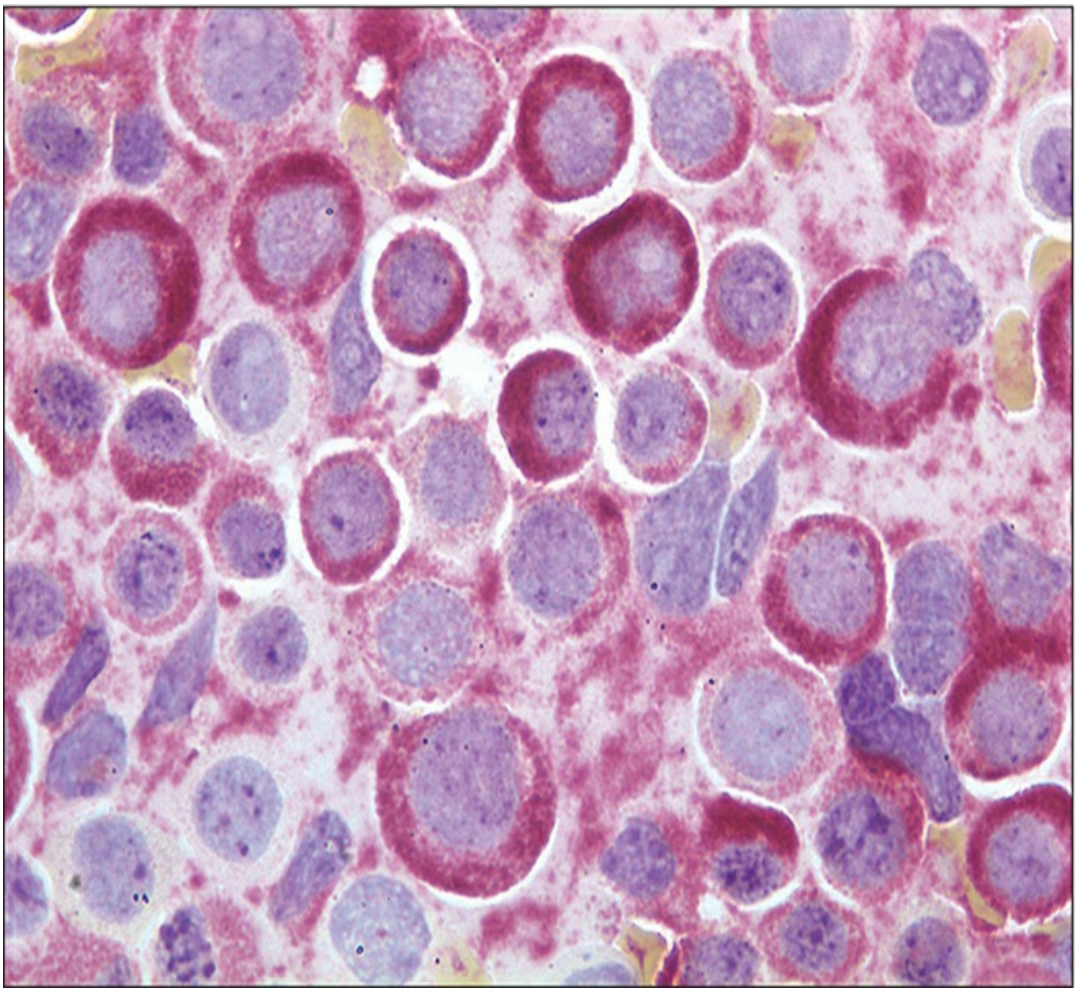


Figure **IIB8-11**

Specific esterase stain.

Clinical Features

- Associated with disseminated intravascular coagulation (DIC) and increased fibrinolysis
- Pallor, fatigue, and weakness

Pathology

- Occurs in about 5–8% of the acute myeloid leukemia cases in younger patients
- Occurs at any age but most cases are young to middle-aged adults
- Hypergranular and microgranular (hypogranular) forms

exist

Laboratory Features—Hypergranular Type

White Blood Cells

- Low count in hypergranular type
- ≥20% blasts (promyelocytes included in blast count)
- If the 15;17 translocation is present, may have <20% blasts for a diagnosis
- Count markedly elevated with numerous abnormal microgranular promyelocytes showing reniform, irregular, or bilobed nuclei in hypogranular type

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- ≥20% blasts
- The nucleus in the abnormal promyelocytes is irregular and often kidney-shaped or bilobed
- Large granules in the cytoplasm of the promyelocytes are dense and stain a deep blue or purple
- Promyelocytes may have bundles of Auer rods randomly distributed in the cytoplasm (faggot cells)

Laboratory Features—Microgranular (Hypogranular) Type

White Blood Cells

- Count markedly elevated with numerous abnormal microgranular promyelocytes showing reniform,

irregular, or bilobed nuclei

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- ≥20% blasts (promyelocytes included in blast count)
- If the 15;17 translocation is present, may have <20% blasts for a diagnosis
- Predominantly bilobed and irregular nucleus in promyelocytes
- Cytoplasmic granules are present but smaller than the resolution of the microscope and so appear absent or decreased in number
- A small number of promyelocytes will demonstrate clearly visible granules and bundles of Auer rods (faggot cells)

Cytochemistry

- Myeloperoxidase is strongly positive in promyelocytes
- Specific esterase is strongly positive in 75% of cases
- Nonspecific esterase is typically negative but may be weakly positive

Immunophenotype

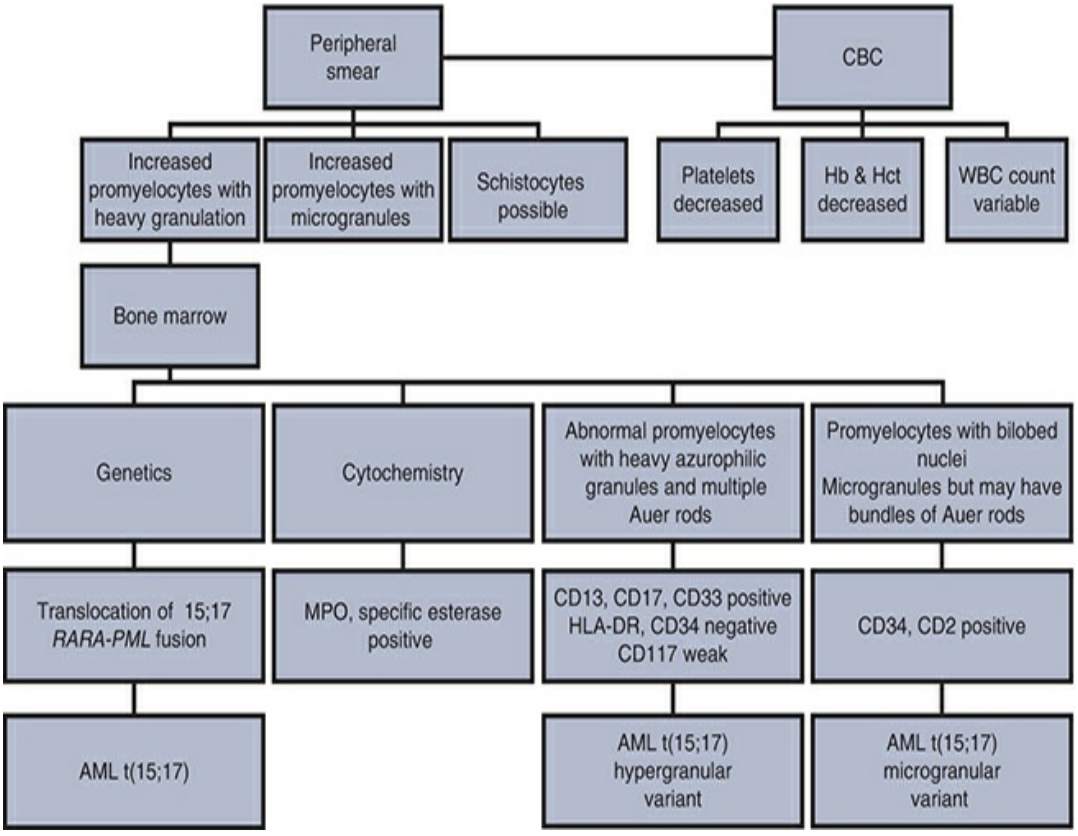
- Hypergranular type shows bright expression of CD13, CD33, and CD17 in most cases
- Absence of CD34, HLA-DR, and CD117 is a typical finding
- CD15 and CD65 are weak or negative

- If CD56 is present, it is a worse prognosis
- In the microgranular type, there is a frequent expression of CD34 and CD2

Genetics

- t(15;17)(q24.1;q21.2)
- Translocation results in the fusion of the RARA gene and the PML gene

Diagnostic Scheme



Acute Myeloid Leukemia With t(9;11)(p21.3;q23.3); KMT2A-MLLT3

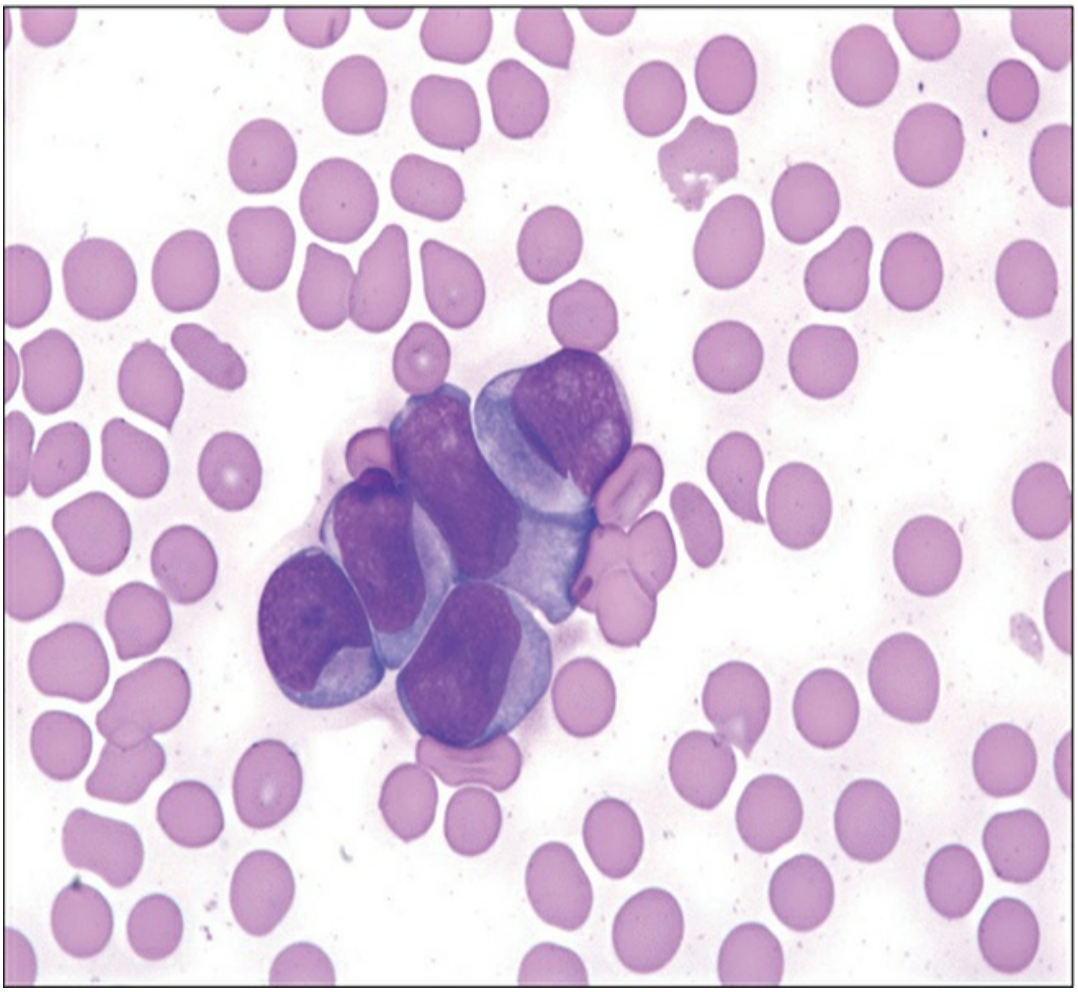


Figure IIB8-12

Peripheral blood smear.

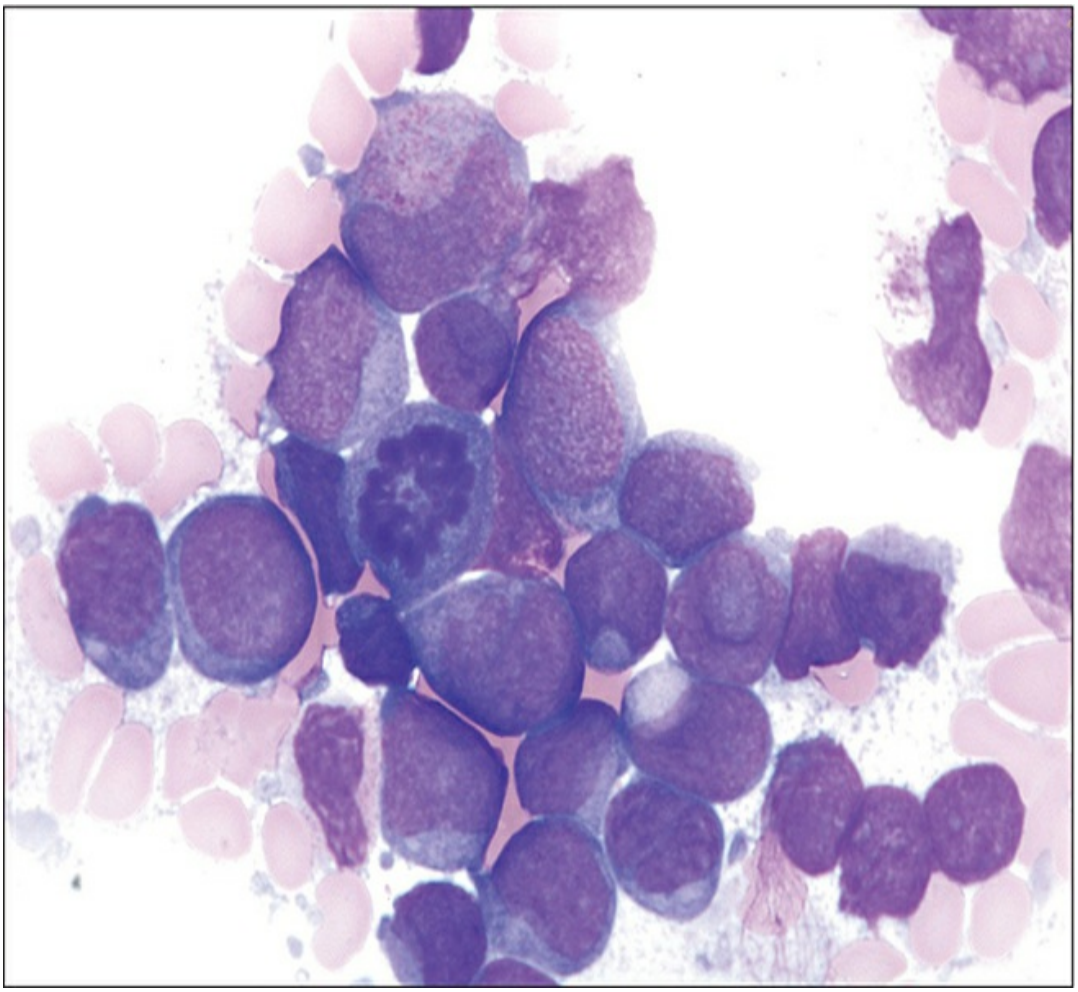


Figure **IIB8-13**

Bone marrow smear.

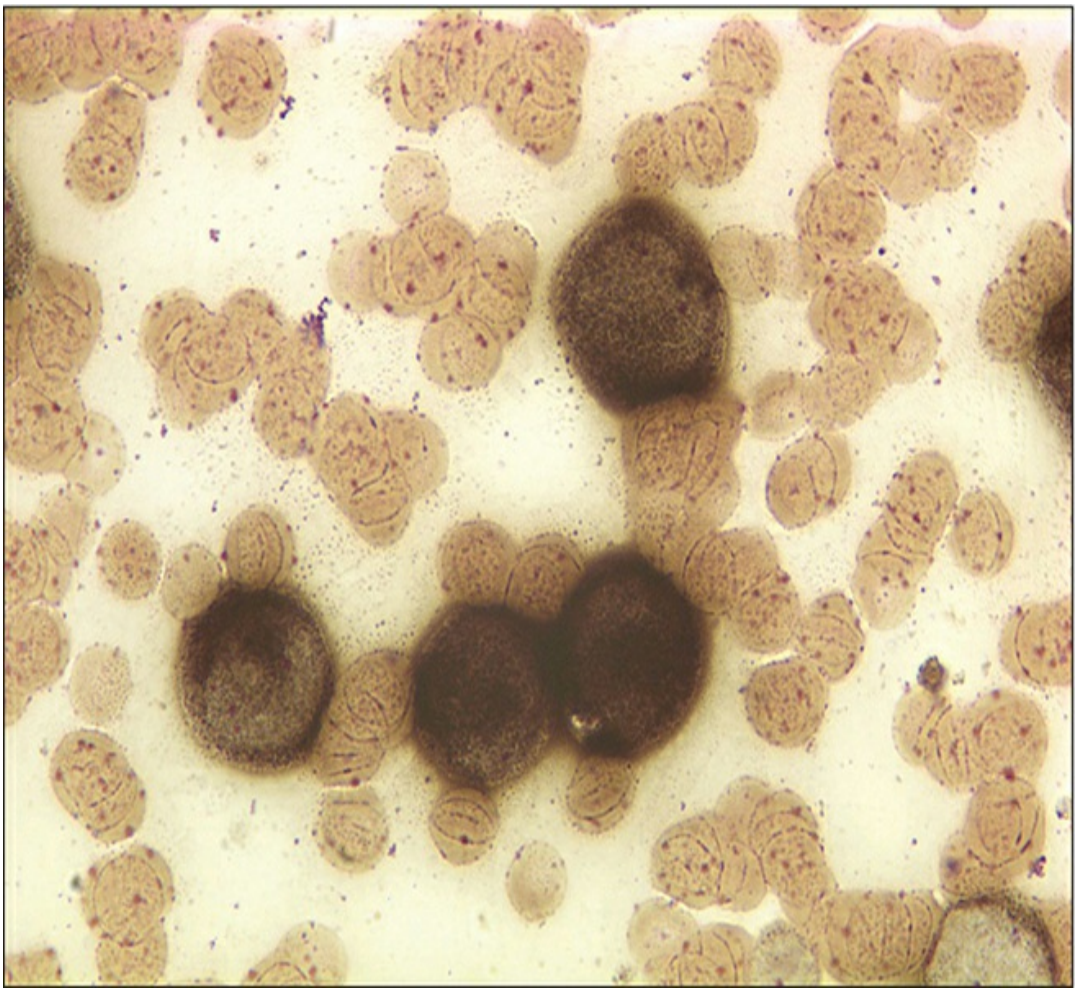


Figure IIB8-14

Nonspecific esterase stain.

Clinical Features

- Patients may present with disseminated intravascular coagulation
- May have extramedullary myeloid sarcomas and/or tissue infiltration in gingiva and/or skin

Pathology

- Occurs at any age but is more common in children
- Constitutes about 9–12% of pediatric and 2% of adult leukemias

Laboratory Features

White Blood Cells

- Count may be low or high
- ≥20% circulating monoblasts and promonocytes
- Variable % of myeloblasts
- Auer rods are usually absent

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Hypercellular
- ≥20% blasts
- Monoblasts and promonocytes typically predominate (>80% nucleated cells)
- Monoblasts are large with abundant intensely basophilic cytoplasm and may have pseudopod formation
- Monoblasts may have fine azurophilic granules and vacuoles
- Monoblasts usually contain round nuclei with delicate chromatin
- Promonocytes have a less basophilic cytoplasm but the nuclei are more irregular

Cytochemistry

- Nonspecific esterase reaction is strongly positive for monocytic lineage
- Monoblasts are myeloperoxidase negative

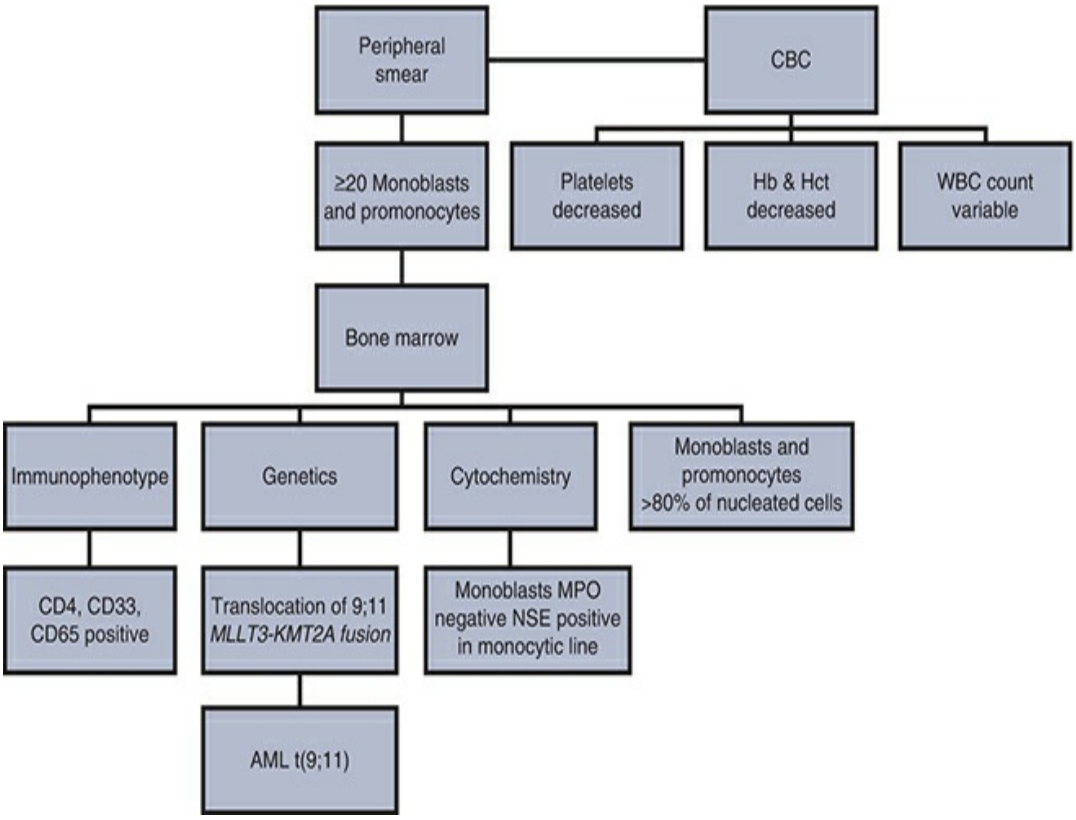
Immunophenotype

- Strong expression of CD33, CD65, CD4, and HLA-DR
- Monocytic markers, CD14, CD11b, CD11c, CD64, and CD36, may be present

Genetics

- t(9;11)(p21.3;q23.3)
- Translocations cause fusion genes of MLLT3 and KMT2A

Diagnostic Scheme



Acute Myeloid Leukemia With t(6;9)(p23;q34.1); DEK-NUP214

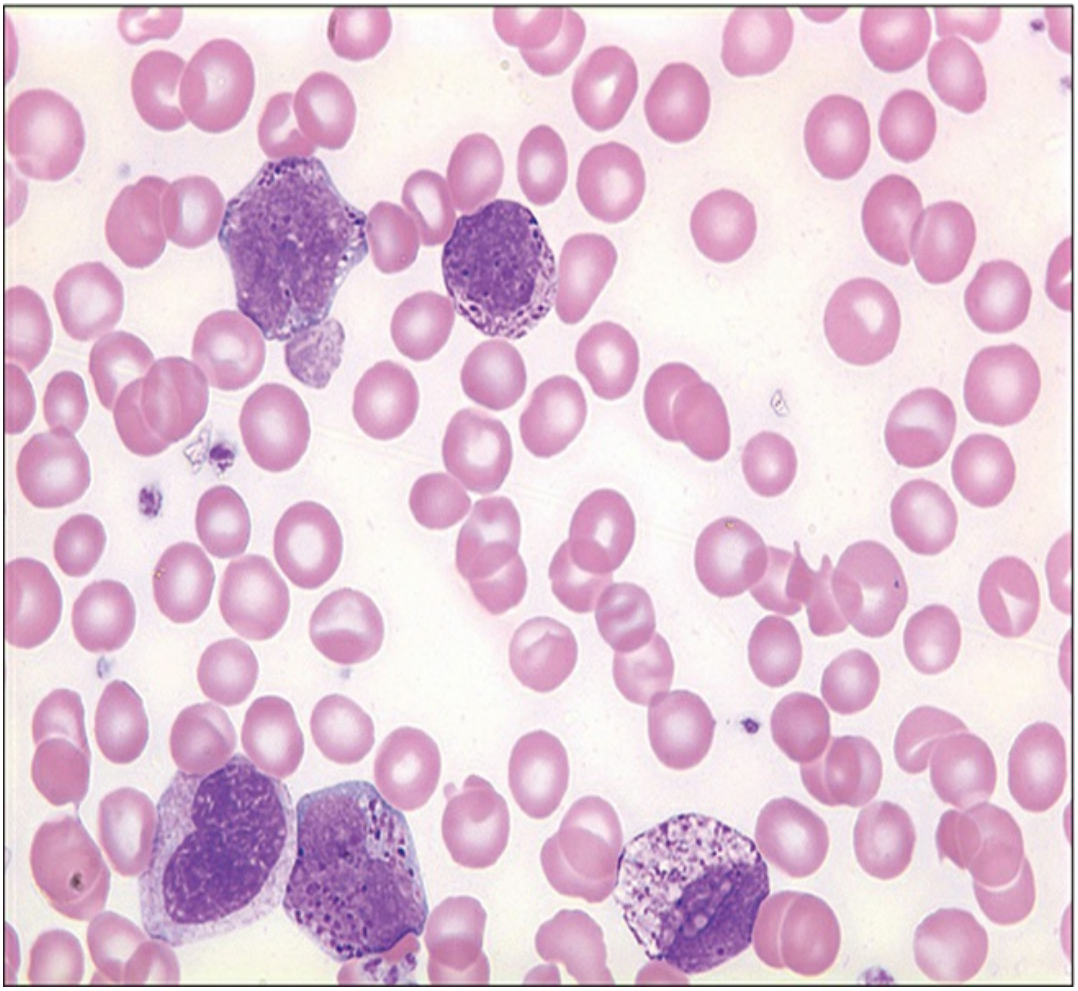


Figure IIB8-15

Peripheral blood smear.

Clinical Features

- Patients may present with a pancytopenia but usually present with anemia and thrombocytopenia

Pathology

- DEK-NUP214 fusion causes altered nuclear transportation and aberrant transcription factor
- Occurs in both children and adults
- Associated with any subtype of acute myeloid leukemia

except promyelocytic and megakaryocytic leukemias
- The most common are myelomonocytic leukemia and leukemia with maturation

Laboratory Features

White Blood Cells

- ≥20% peripheral or bone marrow blasts
- Count is usually lower than other acute myeloid leukemias (about 12×10^9/L)
- ≥2% basophilia
- Granulocytic dysplasia

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- ≥20% blasts
- Auer rods may be present
- Granulocytic and erythrocytic dysplasia
- ≥2% basophilia
- Ring sideroblasts are present in some cases

Cytochemistry

- Myeloperoxidase reaction is strong
- Nonspecific esterase is positive if a monocytic component is present in the leukemia

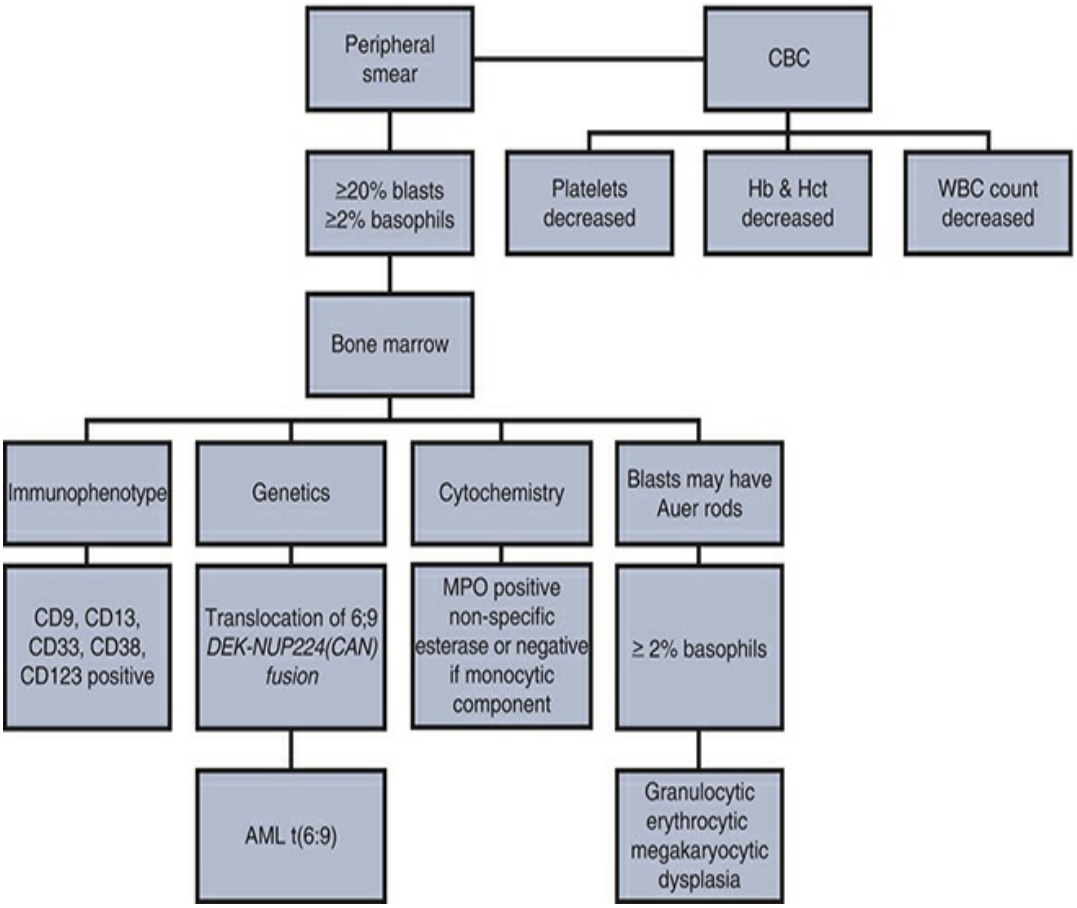
Immunophenotype

- Expression of CD9, CD13, CD33, CD38, CD123, and HLA-DR
- May have the CD64 monocytic marker

Genetics

- t(6;9)(p23;q34.1)
- Translocation results in the fusion of DEK and NUP214(CAN)

Diagnostic Scheme



Acute Myeloid Leukemia With inv(3)(q21.3q26.2) OR t(3;3)(q21.3;q26.2); GATA2, MECOM

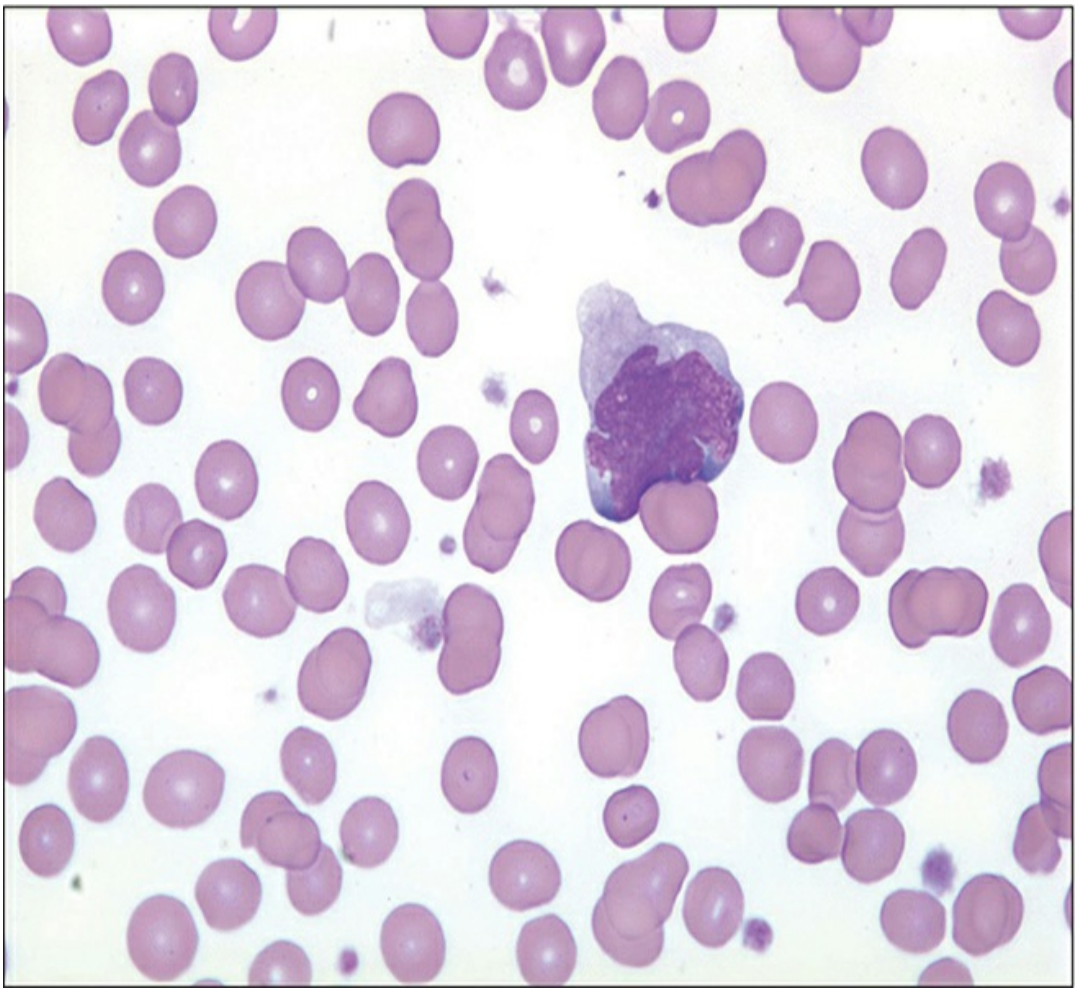


Figure IIB8-16

Peripheral blood smear.

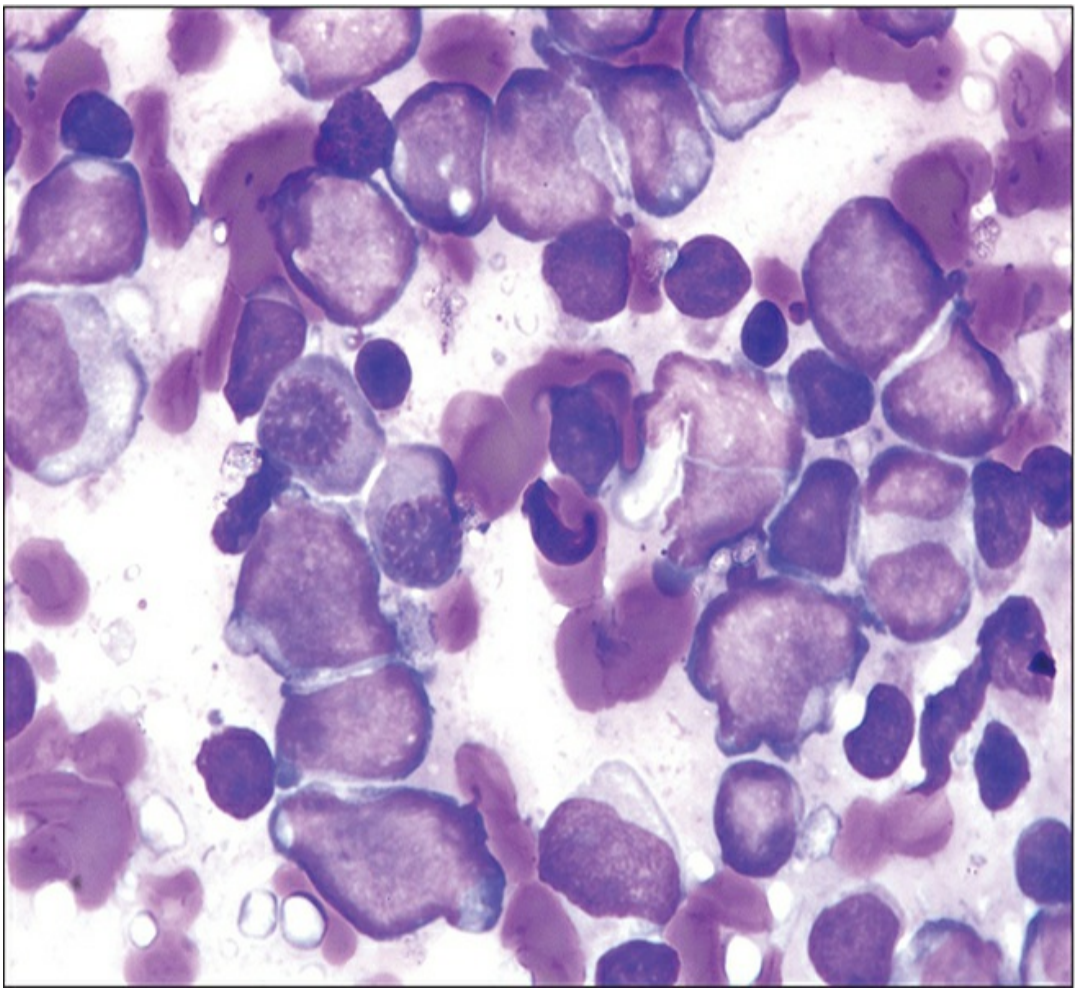


Figure IIB8-17

Bone marrow smear.

Clinical Features

- Most patients present with anemia and a normal platelet count
- Normal platelet count but 7–22% have thrombocythemia
- Some patients have hepatosplenomegaly

Pathology

- Occurs most commonly in adults

Laboratory Features

White Blood Cells

- ≥20% peripheral blood blasts
- Hypogranular neutrophils with pseudo-Pelger-Huët anomaly

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Count may be normal or elevated
- Giant and hypogranular

Bone Marrow

- ≥20% blasts
- Increased megakaryocytes but atypical or dysplastic
- Megakaryocytes may be small and mono- or bilobed
- Basophils, eosinophils, and mast cells may be increased
- Multilineage dysplasia is seen

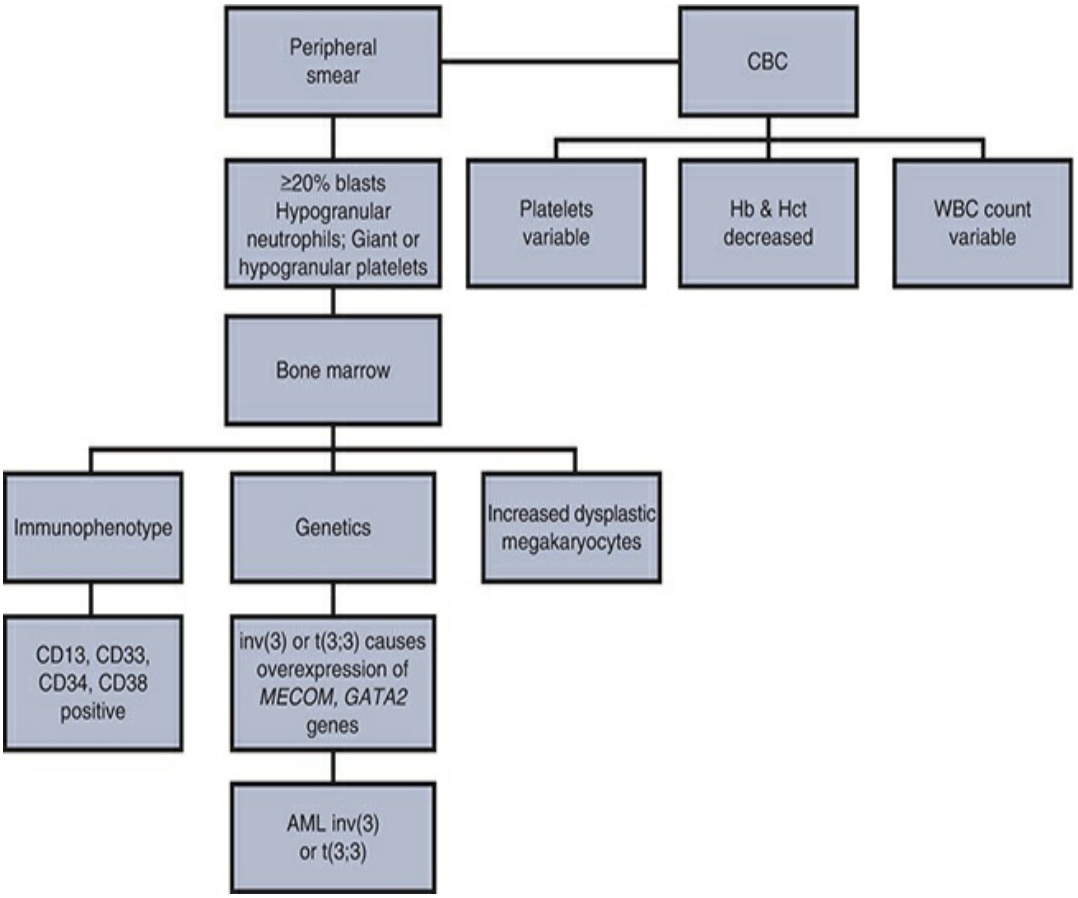
Immunophenotype

- Blasts cells usually express CD13, CD33, HLA-DR, CD34, and CD38
- Megakaryocytic markers of CD41 and CD61 may be expressed

Genetics

- A variety of abnormalities of the long arm of chromosome 3 but inv(3)(q21.3q26.2) and t(3;3)(q21.3;q26.2) are the most common
- The abnormalities involve the oncogene MECOM
- GATA2 enhances the activation of MECOM

Diagnostic Scheme


Peripheral smear
CBC
≥20% blasts Hypogranular neutrophils; Giant or hypogranular platelets
Platelets variable
Hb & Hct decreased
WBC count variable
Bone marrow
Immunophenotype
Genetics
Increased dysplastic megakaryocytes
CD13, CD33, CD34, CD38 positive
inv(3) or t(3;3) causes overexpression of *MECOM, GATA2* genes
AML inv(3) or t(3;3)

Acute Myeloid Leukemia (Megakaryoblastic) With t(1;22)(p13.3;q13.1); RBM15-MKL1

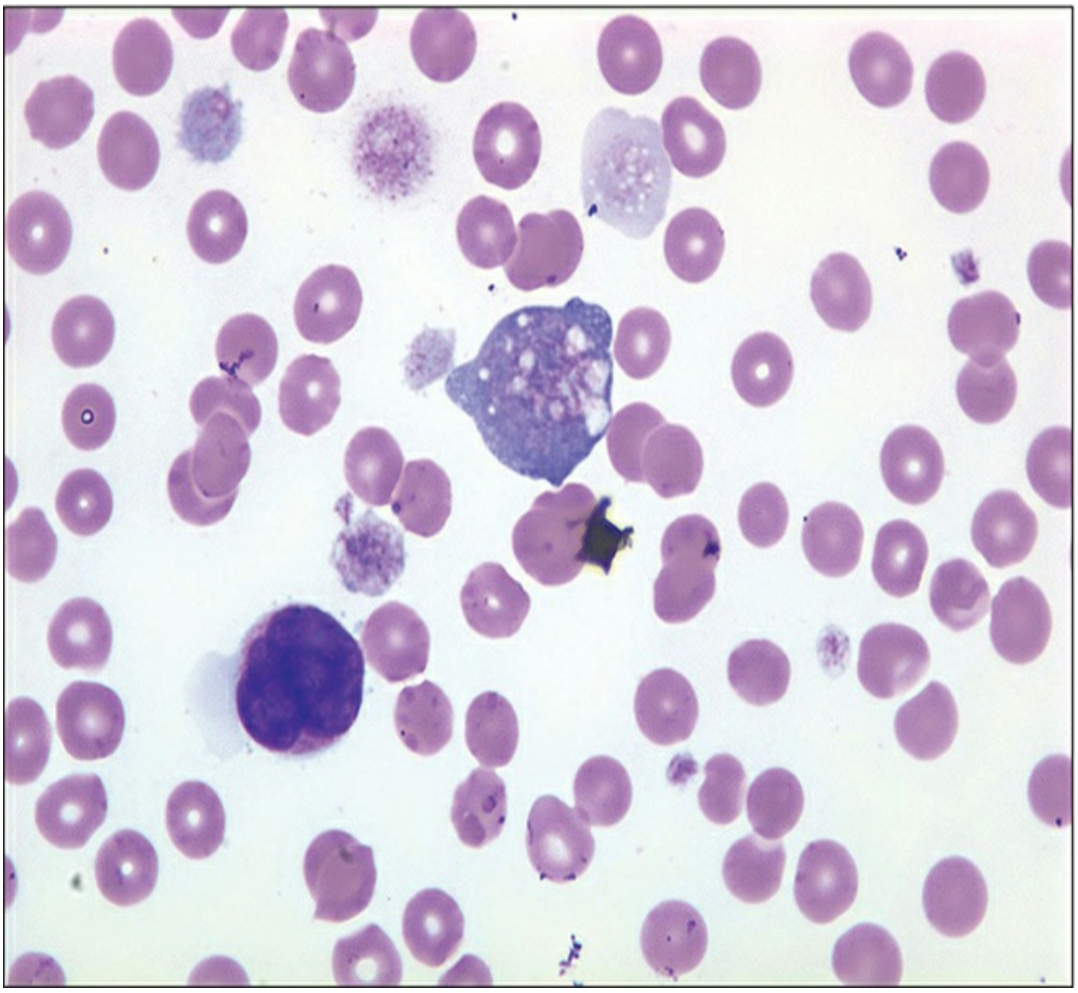


Figure IIB8-18

Peripheral blood smear.

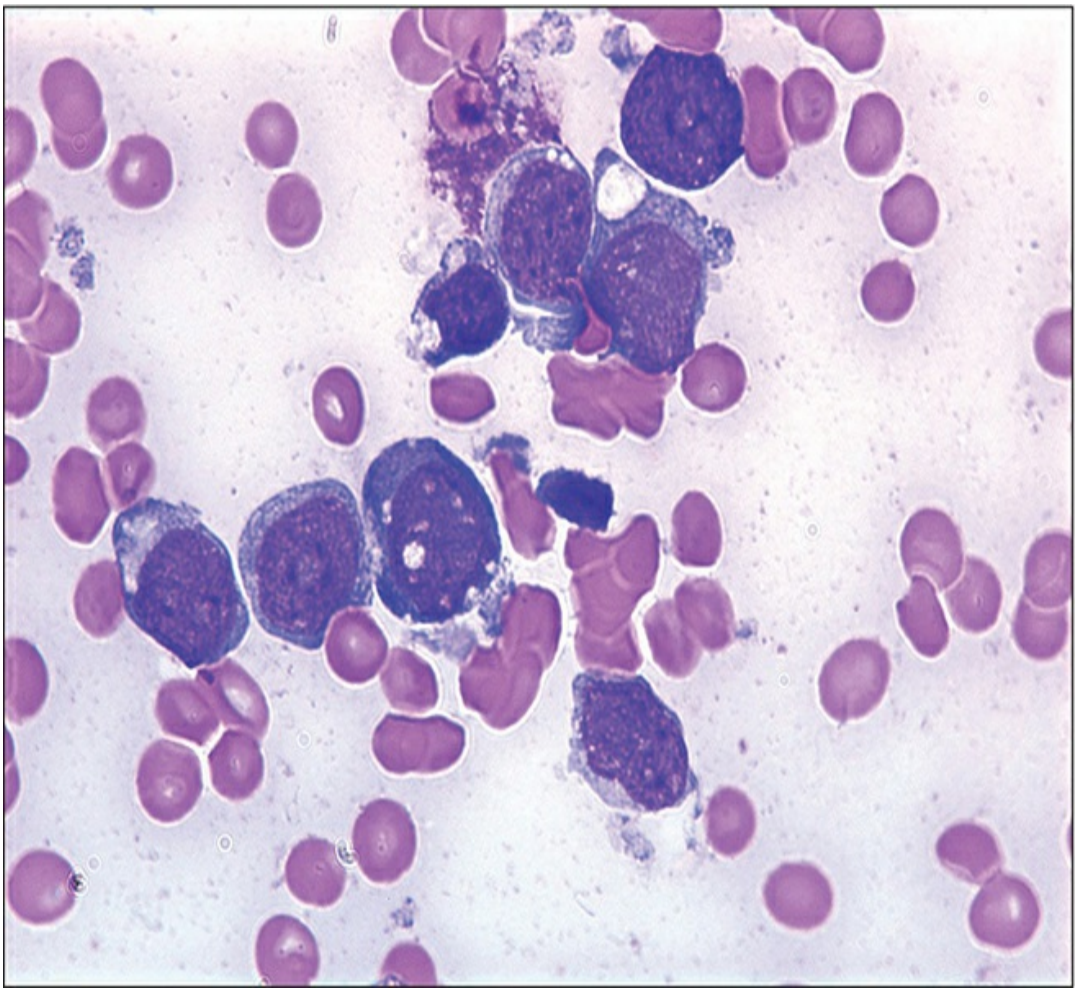


Figure IIB8-19

Bone marrow smear.

Clinical Features

- Cases usually restricted to infants and children <3 years of age
- Marked hepatosplenomegaly
- Often presents with anemia and thrombocytopenia

Pathology

- Represents <1% of cases of acute myeloid leukemias
- Commonly in infants without Down syndrome with a female predominance

Laboratory Features

White Blood Cells

- Moderately elevated

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Variable
- Bizarre and atypical forms

Bone Marrow

- ≥20% blasts
- Small and large megakaryoblasts may be present but are usually of medium to large size
- Megakaryocytes have basophilic, agranular cytoplasm showing pseudopod formation
- Megakaryocyte nuclei are irregular or indented

Cytochemistry

- Sudan black B and myeloperoxidase reactions are negative
- Periodic acid–Schiff may be positive

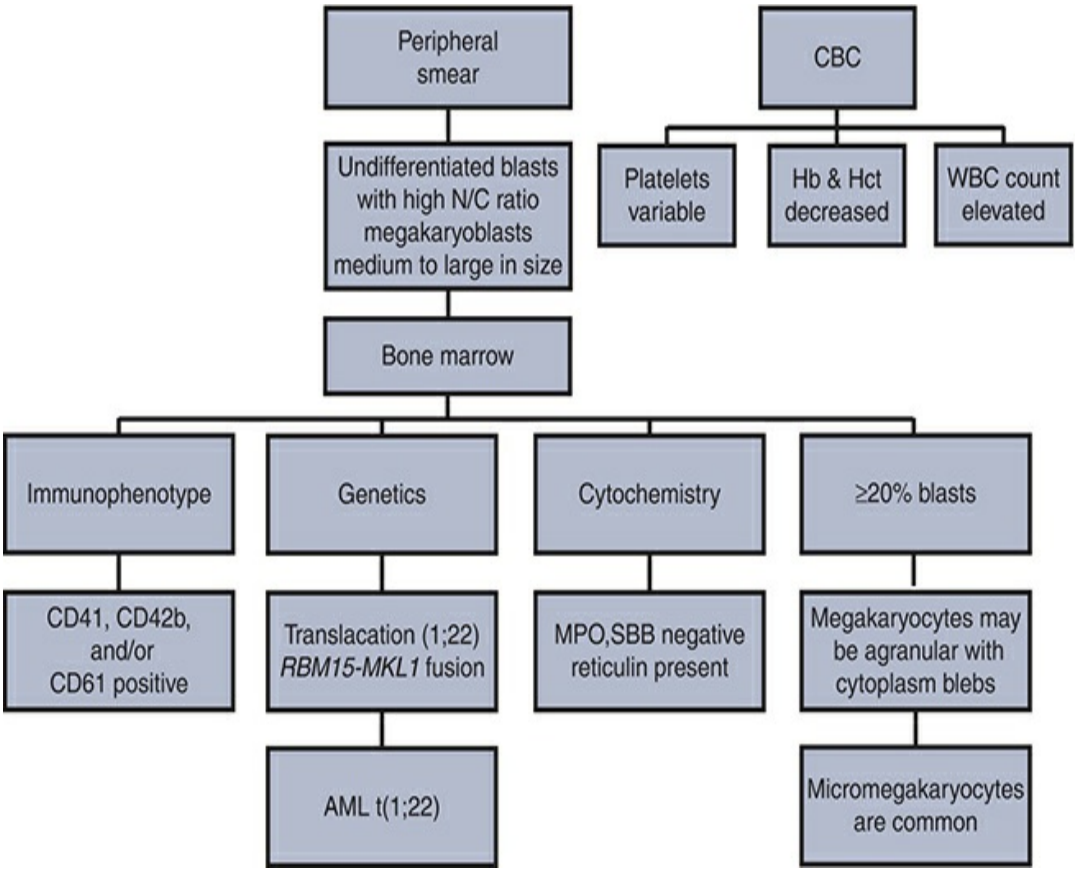
Immunophenotype

- Expression of CD41, CD42b, and/or CD61
- CD13 and CD33 may be positive
- CD34, CD45, and HLA-DR are often negative

Genetics

- In most cases, t(1;22)(p13.3;q13.1) is the sole karyotypic abnormality
- A fusion gene is produced (RBM15-MKL1)

Diagnostic Scheme


Peripheral smear
CBC
Undifferentiated blasts with high N/C ratio megakaryoblasts medium to large in size
Platelets variable
Hb & Hct decreased
WBC count elevated
Bone marrow
Immunophenotype
Genetics
Cytochemistry
≥20% blasts
CD41, CD42b, and/or CD61 positive
Translacation (1;22) *RBM15-MKL1* fusion
MPO,SBB negative reticulin present
Megakaryocytes may be agranular with cytoplasm blebs
AML t(1;22)
Micromegakaryocytes are common

Acute Myeloid Leukemia With Mutated NPM1

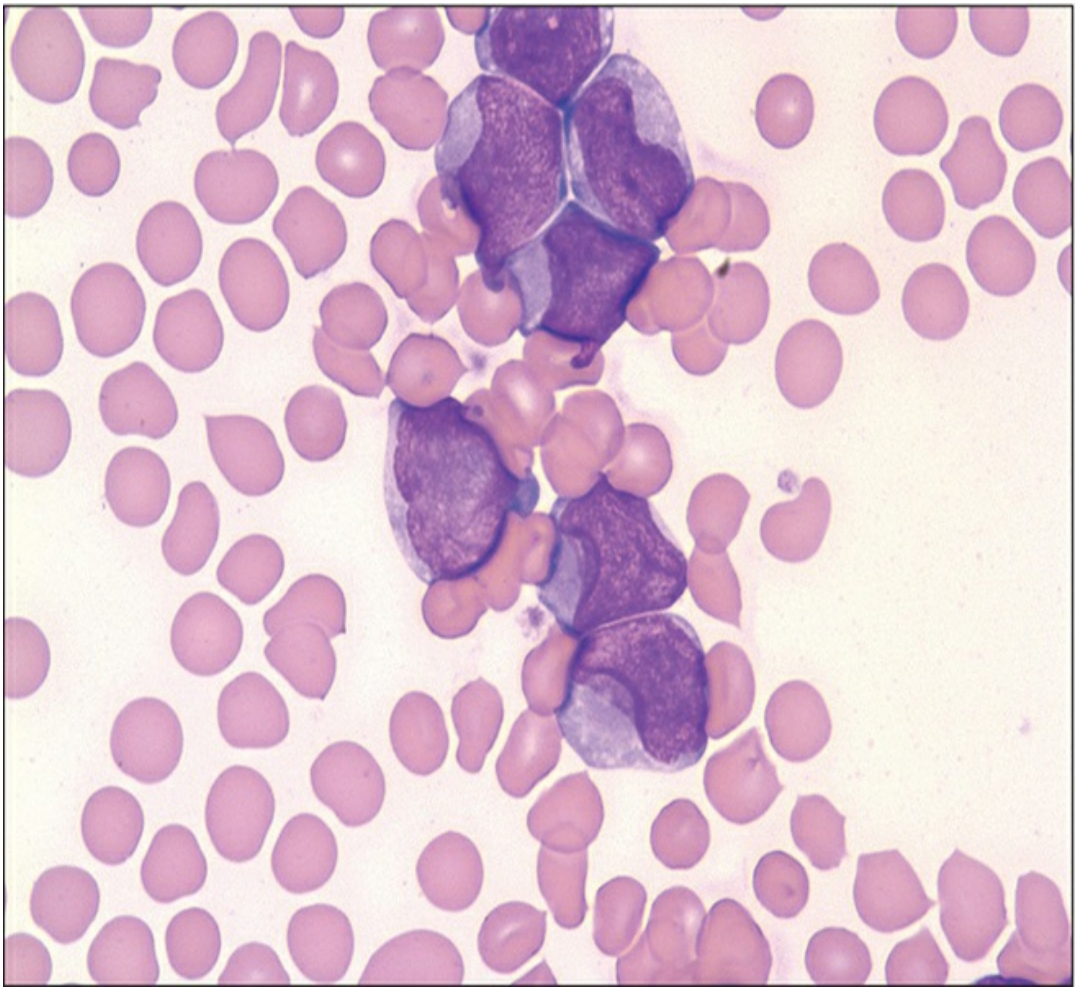


Figure IIB8-20

Peripheral blood smear.

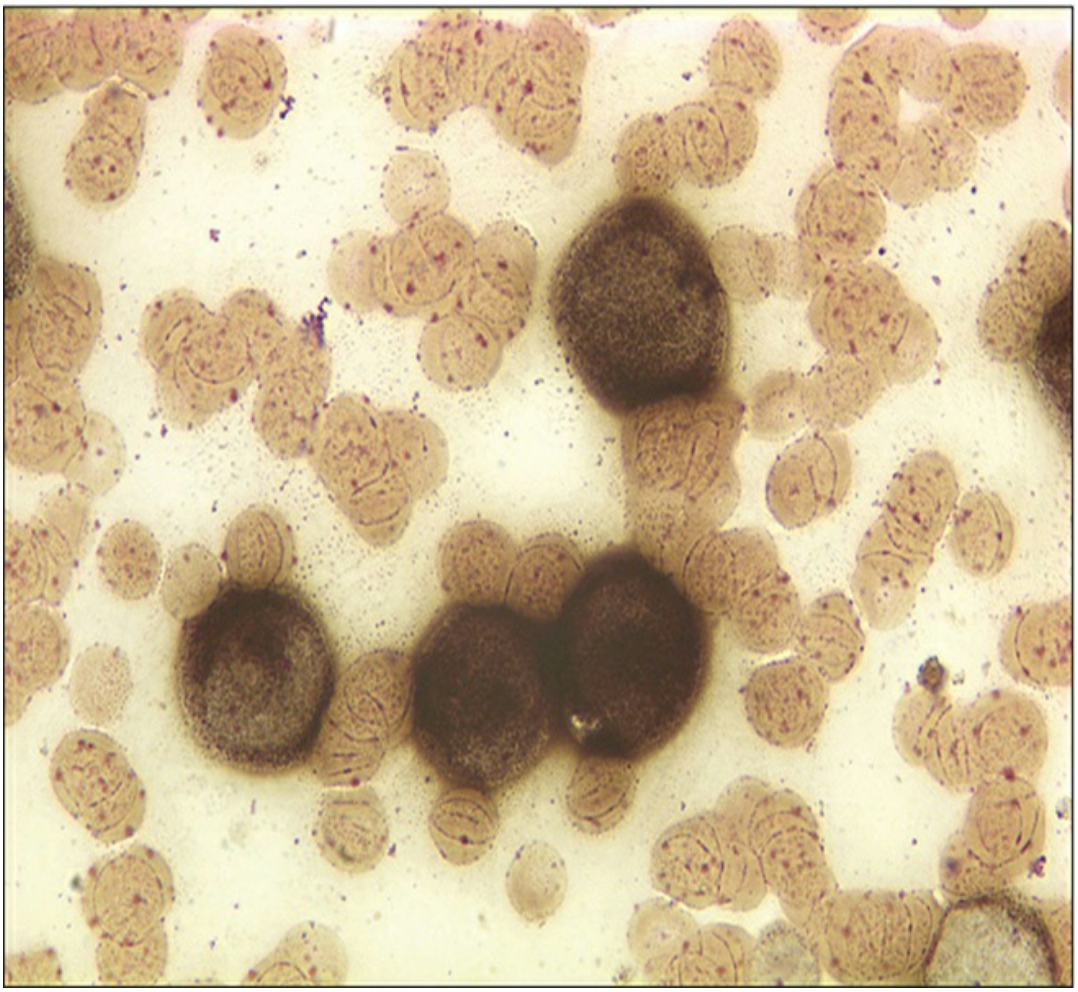


Figure IIB8-21

Nonspecific esterase stain.

Clinical Features

- Patients usually have no history of myelodysplastic syndromes or myeloproliferative neoplasms
- May present with anemia and thrombocytopenia
- May have infiltration of gingiva, lymph nodes, and skin

Pathology

- Accounts for 2–8% of childhood and 27–35% of adult acute myeloid leukemia cases
- About 80–90% of acute monocytic leukemias show NPM1 mutation

Laboratory Features

White Blood Cells

- Count is usually high

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Higher platelet count than other acute myeloid leukemias without NPM1 mutation

Bone Marrow

- ≥20% blasts
- Multilineage involvement but monocytic or myelomonocytic is common

Cytochemistry

- Specific to the cell lines involved

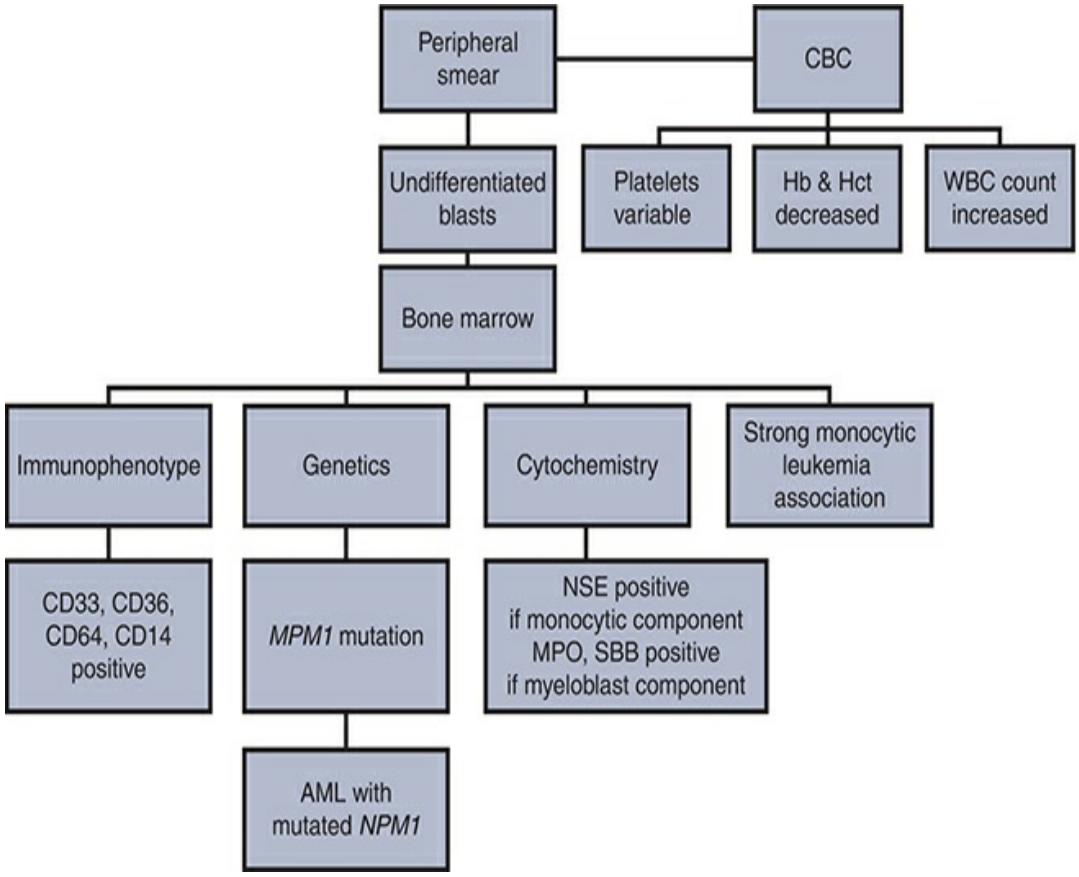
Immunophenotype

- Expression of CD13, CD33, and possibly CD14, CD11b, and CD68

Genetics

- Mutated NPM1
- Usually associated with a normal karyotype

Diagnostic Scheme


Peripheral smear
CBC
Undifferentiated blasts
Platelets variable
Hb & Hct decreased
WBC count increased
Bone marrow
Immunophenotype
Genetics
Cytochemistry
Strong monocytic leukemia association
CD33, CD36, CD64, CD14 positive
MPM1 mutation
NSE positive if monocytic component MPO, SBB positive if myeloblast component
AML with mutated NPM1

Acute Myeloid Leukemia With Biallelic Mutation of CEBPA

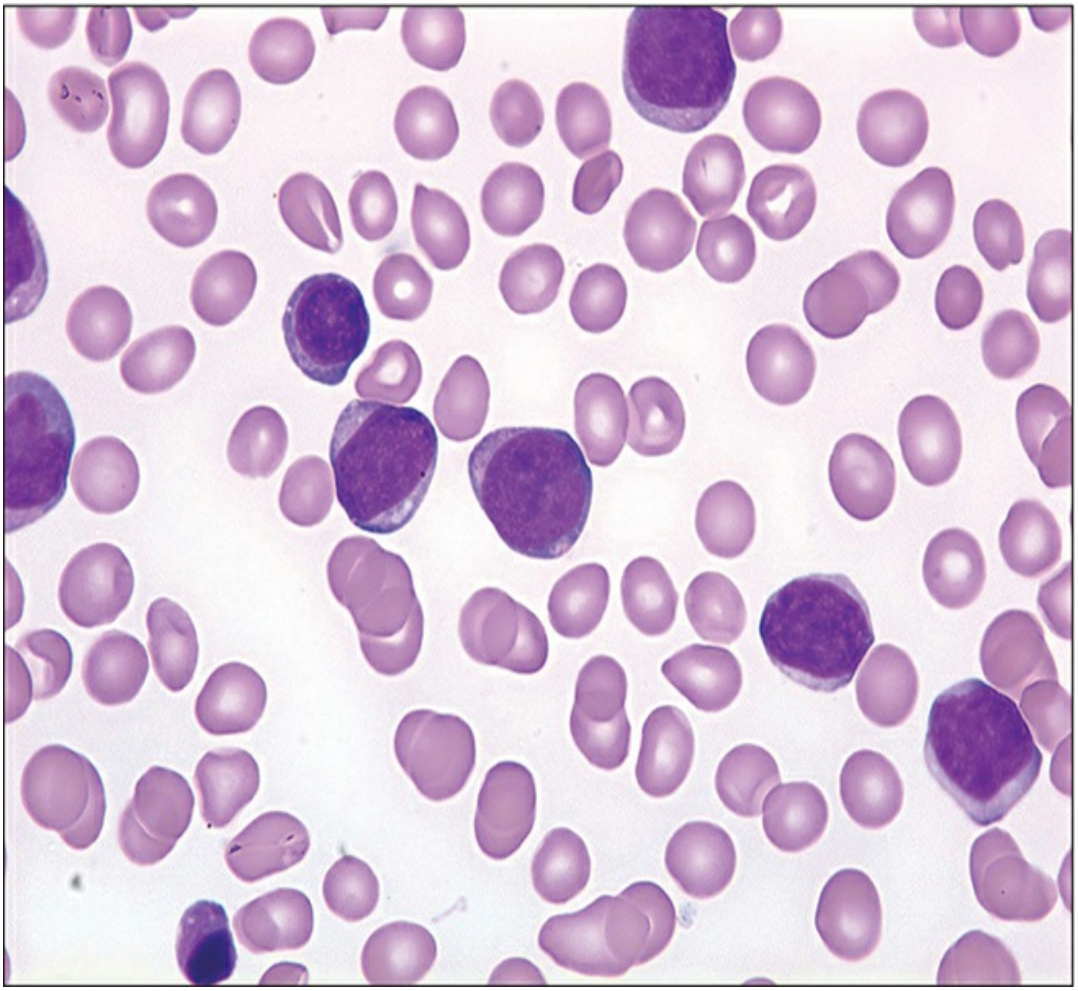


Figure IIB8-22

Peripheral blood smear.

Clinical Features

- Usually presents de novo

Pathology

- Occurs in about 6–15% of de novo acute myeloid leukemias
- Occurs in about 15–18% of acute myeloid leukemias with normal karyotypes

Laboratory Features

White Blood Cells

- Count is typically increased

Red Blood Cells

- Normocytic/normochromic anemia but hemoglobin is higher than in most leukemias

Platelets

- Numbers decreased

Bone Marrow

- ≥20% blasts
- Most are associated with acute myeloid leukemias with or without maturation
- Some cases have monocytic or myelomonocytic features

Cytochemistry

- Myeloperoxidase or Sudan black B is positive if a myeloblast component is present
- Nonspecific esterase is positive when a monocytic population is present

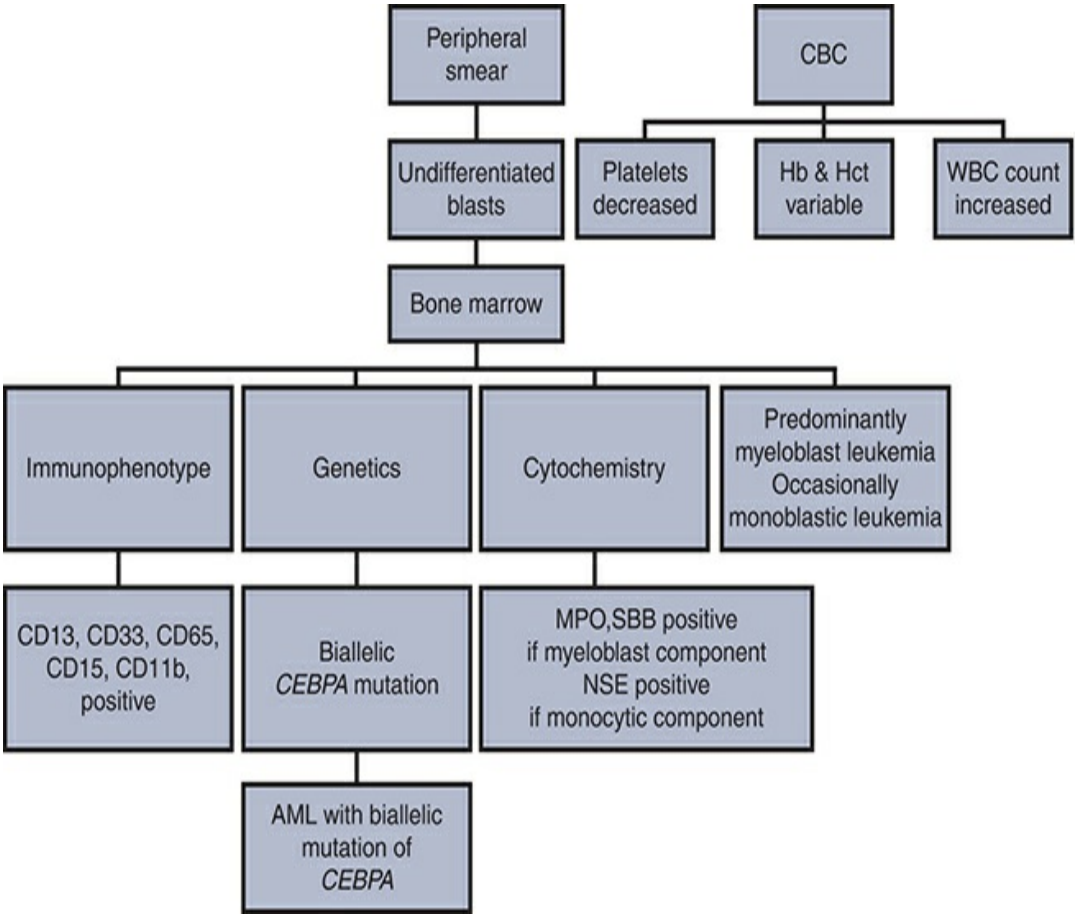
Immunophenotype

- Blasts usually express one or more of the following: CD13, CD33, CD65, CD11b, and CD15
- The majority of blasts express HLA-DR and CD34

Genetics

- Biallelic mutation of CEBPA
- Approximately 70% of the cases have a normal karyotype

Diagnostic Scheme



ACUTE MYELOID LEUKEMIAS WITH MYELODYSPLASIA-RELATED CHANGES

Criteria

- ≥20% blasts in peripheral blood or bone marrow
- Morphologic features of multilineage dysplasia
- Occurring in patients with a prior history of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm, with myelodysplastic-related cytogenic abnormalities
- Specific genetic abnormalities characteristic of acute myeloid leukemia with recurrent genetic abnormalities absent
- No history of prior cytotoxic or radiation therapy

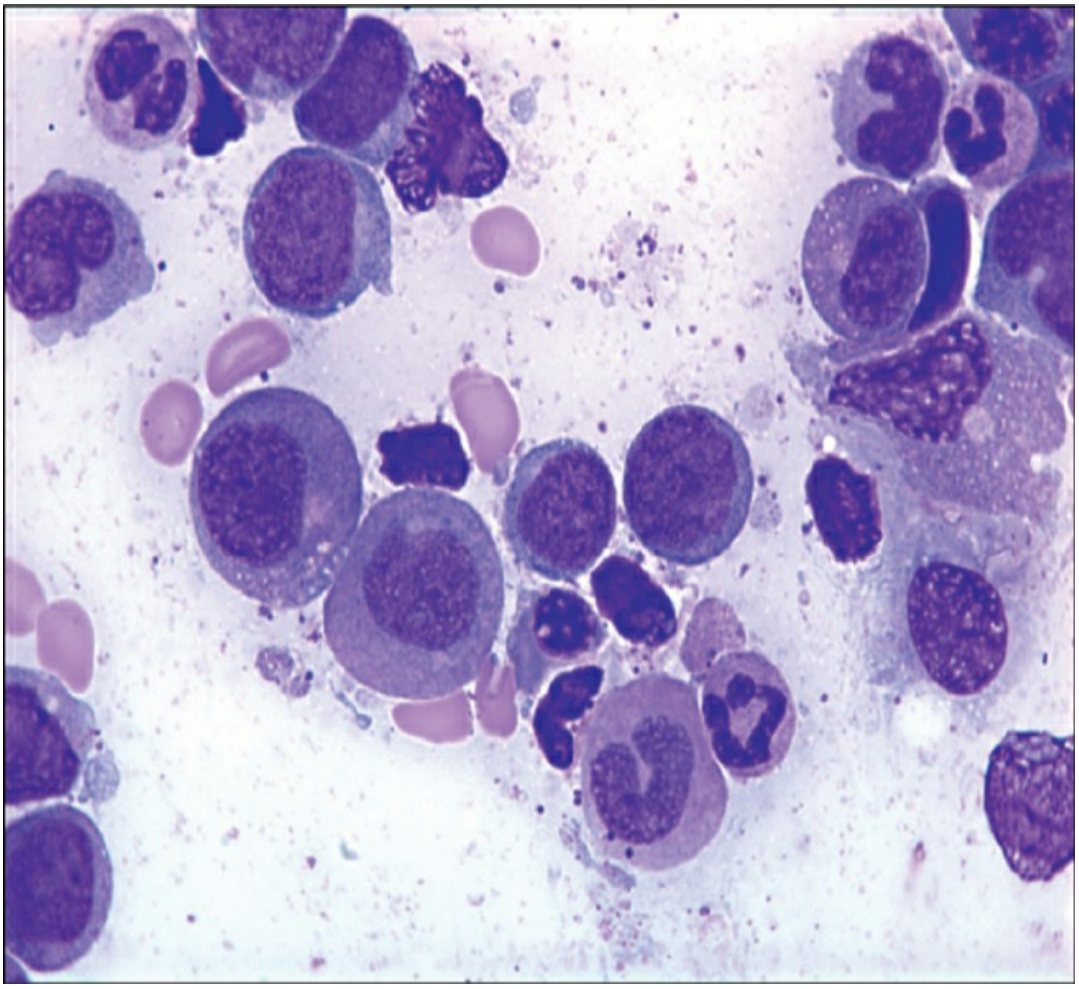


Figure IIB8-23

Bone marrow smear.

Clinical Features

- Often presents with severe pancytopenia

Pathology

- Makes up about 24–35% of all cases of acute myeloid leukemias
- Occurs mainly in elderly patients
- Dysplasia in ≥50% of the cells in at least two hematopoietic cell lines

Laboratory Features

White Blood Cells

- Dysgranulopoiesis in peripheral blood and bone marrow
- Neutrophils with hypogranular cytoplasms and hyposegmented or bizarrely segmented nuclei

Red Blood Cells

- Decreased

Platelets

- Decreased

Bone Marrow

- ≥20% blasts
- Dyserythropoiesis
  - Megaloblastosis, karyorrhexis and clear irregularity, fragmentation, or multinucleation
- Ring sideroblasts, cytoplasmic vacuoles
- Dysmegakaryopoiesis
  - Micromegakaryocytes and normal-sized or large megakaryocytes with nonlobulated or multiple nuclei

Cytochemistry

- Periodic acid–Schiff may be positive in dysplastic erythroid precursors
- Prussian blue demonstrates ring sideroblasts

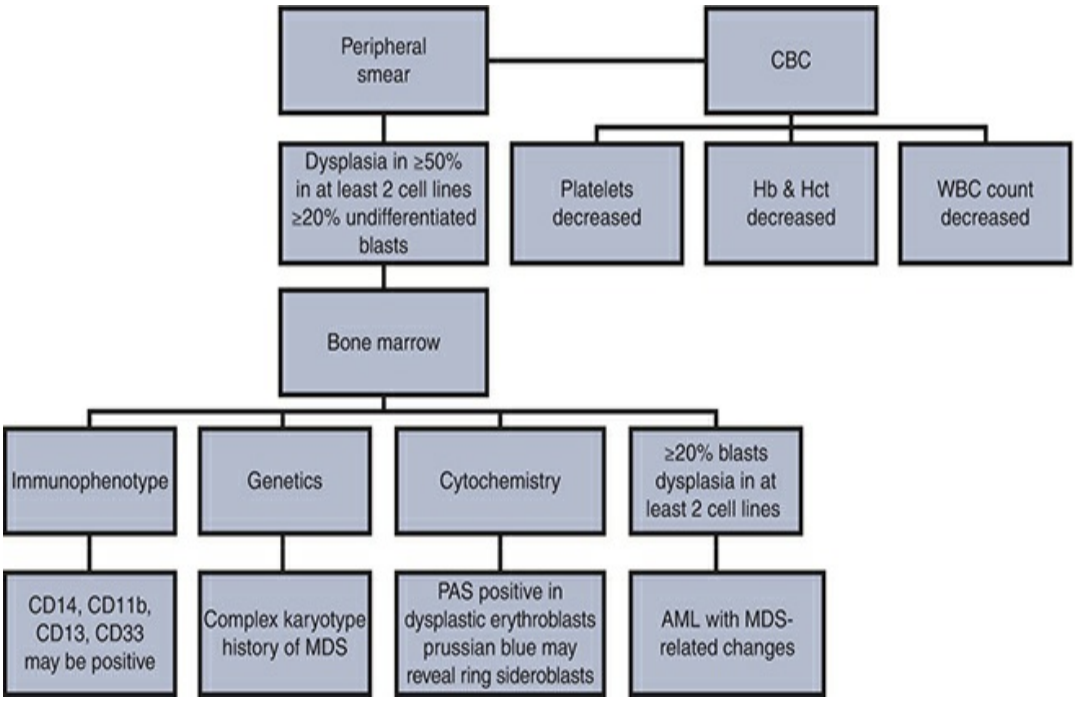
Immunophenotype

- Variable results due to the heterogeneity of the underlying genetic changes
- Increase in CD14 expressions on blasts is related to a poor prognosis

Genetics

- Gain or loss of major segments of certain chromosomes with complex karyotype (≥3 abnormalities)

Diagnostic Scheme



THERAPY-RELATED MYELOID NEOPLASMS

Criteria

- Therapy-related cases of acute myeloid leukemia (t-AML), myelodysplastic syndromes (t-MDS), and myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN) that occur as a late complication of cytotoxic chemotherapy and/or radiation therapy applied to prior disorders

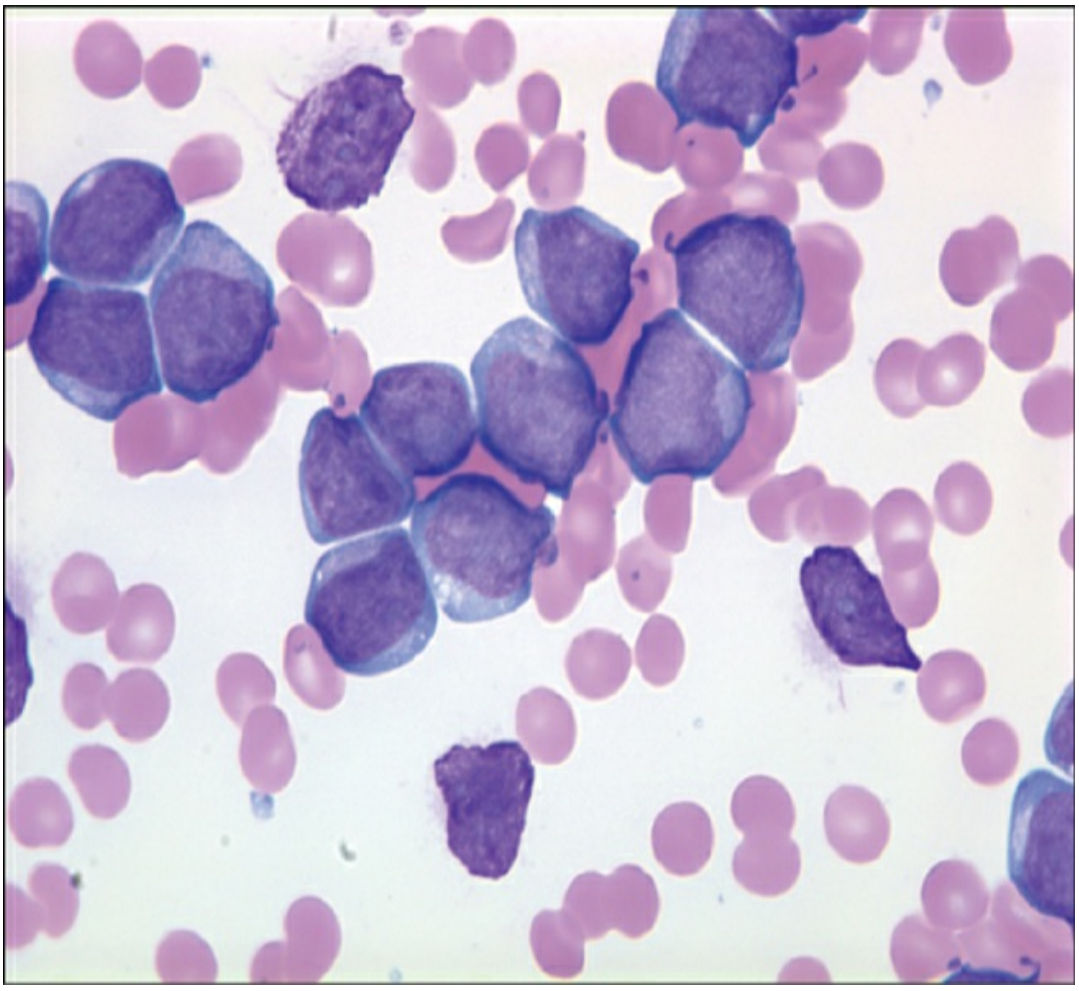


Figure IIB8-24

Peripheral blood smear.

Clinical Features

- Commonly occurs 5–10 years after exposure to alkylating agents and/or ionizing radiation
- Presents with an MDS with marrow failure and one or more cytopenias

Pathology

- Accounts for 10–20% of all cases of acute myeloid leukemias, myelodysplastic syndromes, and myelodysplastic/myeloproliferative neoplasms
- About 70% of cases have been treated for solid tumors
- About 30% of cases have been treated for hematologic tumors

Laboratory Features

White Blood Cells

- Dysplastic changes in neutrophils with abnormal nuclear segmentation and hypogranular cytoplasm
- Basophilia is frequently present

Red Blood Cells

- Decreased
- Macrocytosis and poikilocytosis

Platelets

- May be decreased

Bone Marrow

- ≥20% blasts
- Hypercellular, normocellular, or hypocellular
- Reticulin fibrosis is common
- Multilineage dysplasia

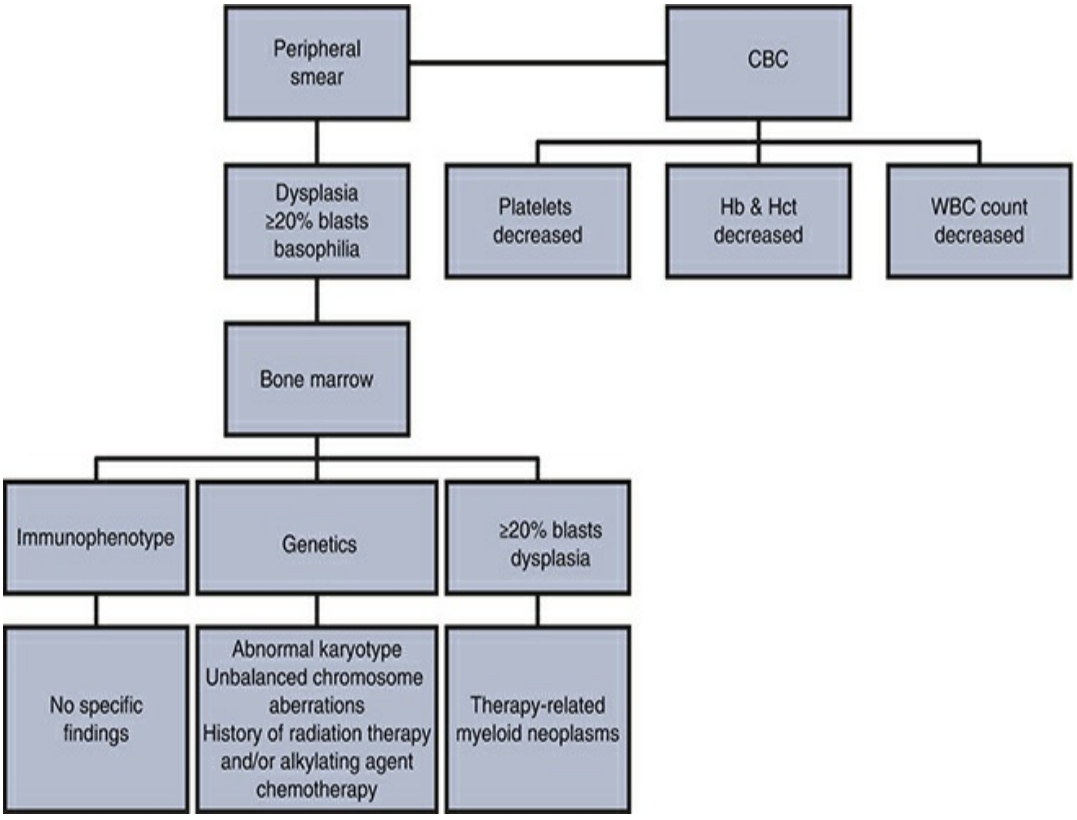
Immunophenotype

- No specific immunophenotypic findings

Genetics

- The leukemic cells of >90% of patients show an abnormal karyotype that correlates with the latent period between the initial therapy and the onset of the leukemic disorder and the cytotoxic agent
- About 70% of cases harbor unbalance chromosomal aberrations—partial loss of 5q, loss of chromosome 7, or deletion of 7q associated with one or more additional chromosomal abnormalities

Diagnostic Scheme



ACUTE MYELOID LEUKEMIAS, NOT OTHERWISE SPECIFIED (NOS)

Criteria

- Do not fit the criteria for acute myeloid leukemias with recurrent genetic abnormalities, myelodysplastic-related changes, or therapy-related acute myeloid leukemias
- Define criteria for the diagnosis of acute myeloid leukemias across a diverse morphologic spectrum
- Include the specific diagnostic criteria for pure erythroid leukemia
- Mutation analysis and cytogenetic studies are required before a case can be placed into this category
- Cytochemical studies are used to subtype the acute myeloid leukemias, not otherwise specified
- Subclassification is based on morphologic and cytochemical/immunophenotypic features of the leukemic cells
- Presence of ≥20% blasts in peripheral blood or bone marrow—bone marrow blast percentage should be determined from a 500-cell differential
- Peripheral blood differential should include 200 leukocytes
- If leukopenia is present, a buffy coat can be used

ACUTE MYELOID LEUKEMIA WITH MINIMAL DIFFERENTIATION

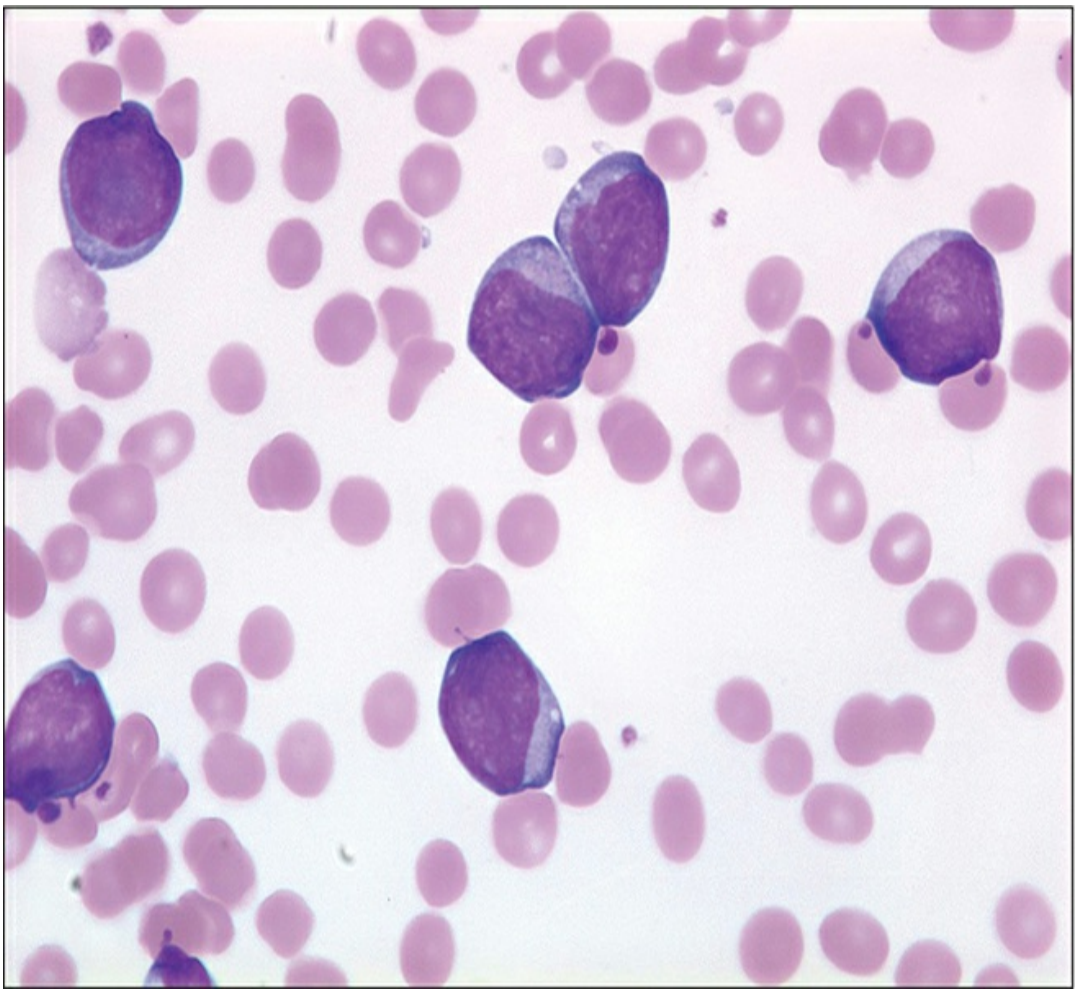


Figure IIB8-25

Peripheral blood smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- Makes up <5% of acute myeloid leukemias
- Patients are usually infants or older adults

Laboratory Features

White Blood Cells

- Increased in 50% of patients but may be normal or decreased
- Predominant cell in peripheral blood is the myeloblast

Red Blood Cells

- Normocytic/normochromic anemia
- Nucleated red blood cells may be seen

Platelets

- Decreased

Bone Marrow

- Hypercellular
- ≥20% blasts
- Blasts are usually of medium size with dispersed nuclear chromatin
- Round or slightly indented nuclei with one or two nucleoli
- Cytoplasm is agranular with a varying degree of basophilia
- Auer rods are absent

Cytochemistry

- Myeloperoxidase, Sudan black B, and naphthol AS-D chloroacetate esterase are negative (<3% of blasts are positive)
- Alpha–naphthyl acetate and butyrate esterases are negative

Immunophenotype

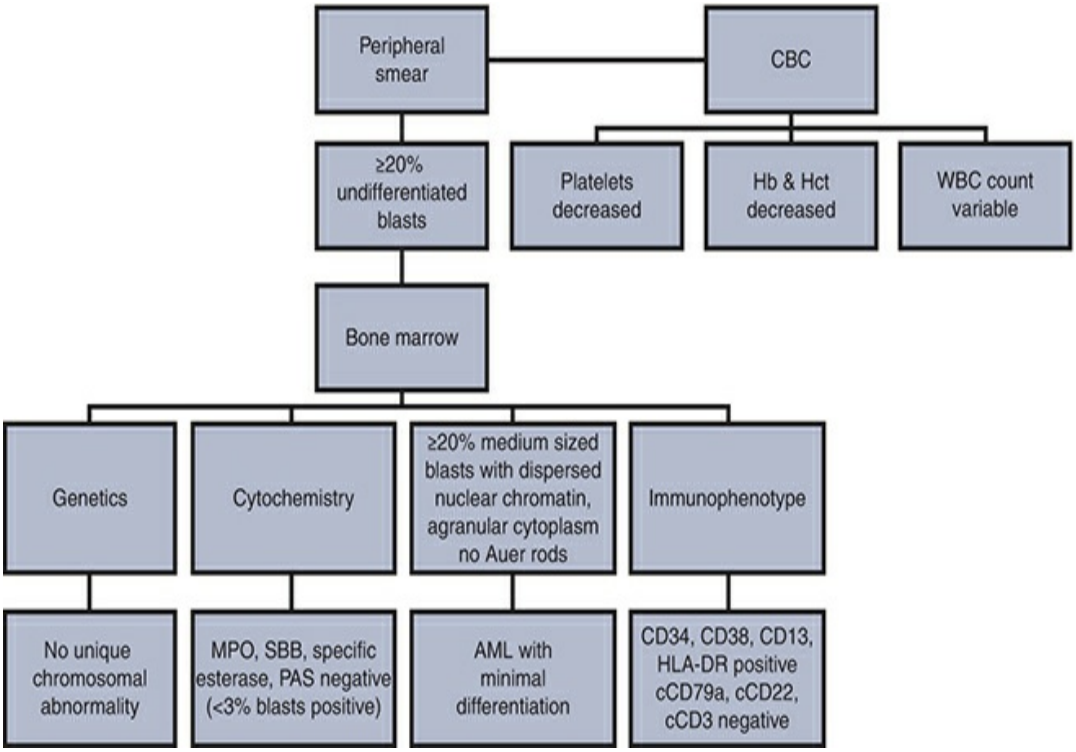
- Most cases express CD34, CD38, and HLA-DR

- CD11b, CD15, CD14, CD64, and CD65 are usually negative
- Negative for B- or T-cell–associated antigens
- Blast cells exhibit at least two myeloid markers (CD13, CD117, CD33)

Genetics

- No specific chromosomal abnormality has been identified

Diagnostic Scheme



ACUTE MYELOID LEUKEMIA WITHOUT MATURATION

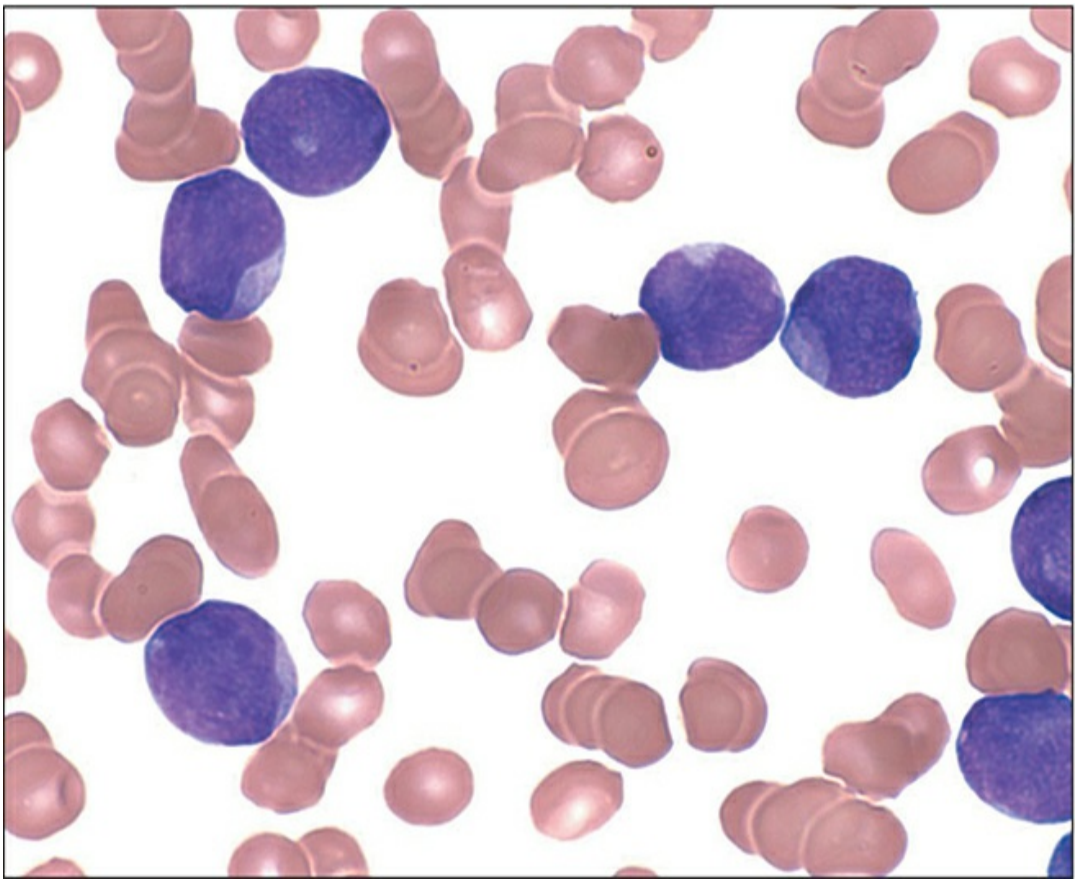


Figure IIB8-26

Peripheral blood smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- 5–10% of cases of acute myeloid leukemias
- Majority of patients are adults but it may occur at any age

Laboratory Features

White Blood Cells

- Usually increased but may be normal or decreased
- Predominant cell in peripheral blood is a myeloblast

Red Blood Cells

- Normocytic/normochromic anemia
- Nucleated red blood cells may be seen

Platelets

- Decreased

Bone Marrow

- Hypercellular
- ≥20% blasts
- 90% or more are myeloblasts
- Myeloblasts may have azurophilic granules and/or Auer rods

Cytochemistry

- Myeloperoxidase and Sudan black B are positive in a variable number of blasts but more than 3%
- Nonspecific esterases are negative

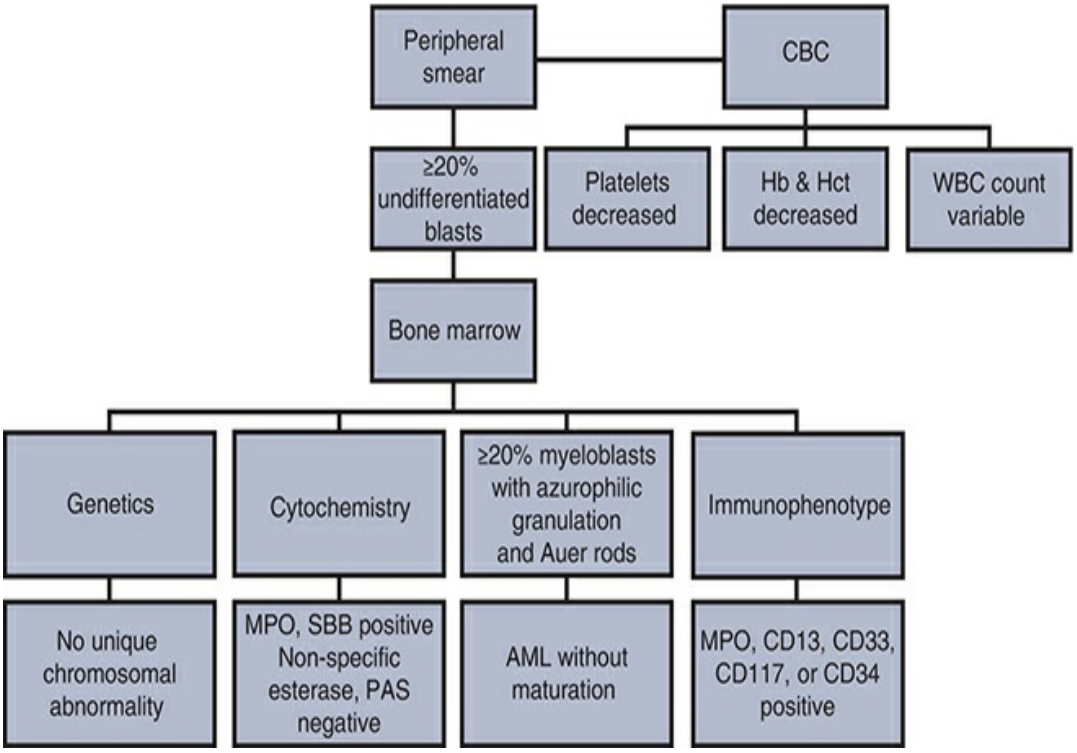
Immunophenotype

- Cells express one or more of the following: CD13, CD33, and CD117
- CD34 and HLA-DR may be positive; CD15, CD65, CD14, and CD64 are negative

Genetics

- There are no specific associated abnormalities

Diagnostic Scheme


Peripheral smear
CBC
≥20% undifferentiated blasts
Platelets decreased
Hb & Hct decreased
WBC count variable
Bone marrow
Genetics
Cytochemistry
≥20% myeloblasts with azurophilic granulation and Auer rods
Immunophenotype
No unique chromosomal abnormality
MPO, SBB positive Non-specific esterase, PAS negative
AML without maturation
MPO, CD13, CD33, CD117, or CD34 positive

ACUTE MYELOID LEUKEMIA WITH MATURATION

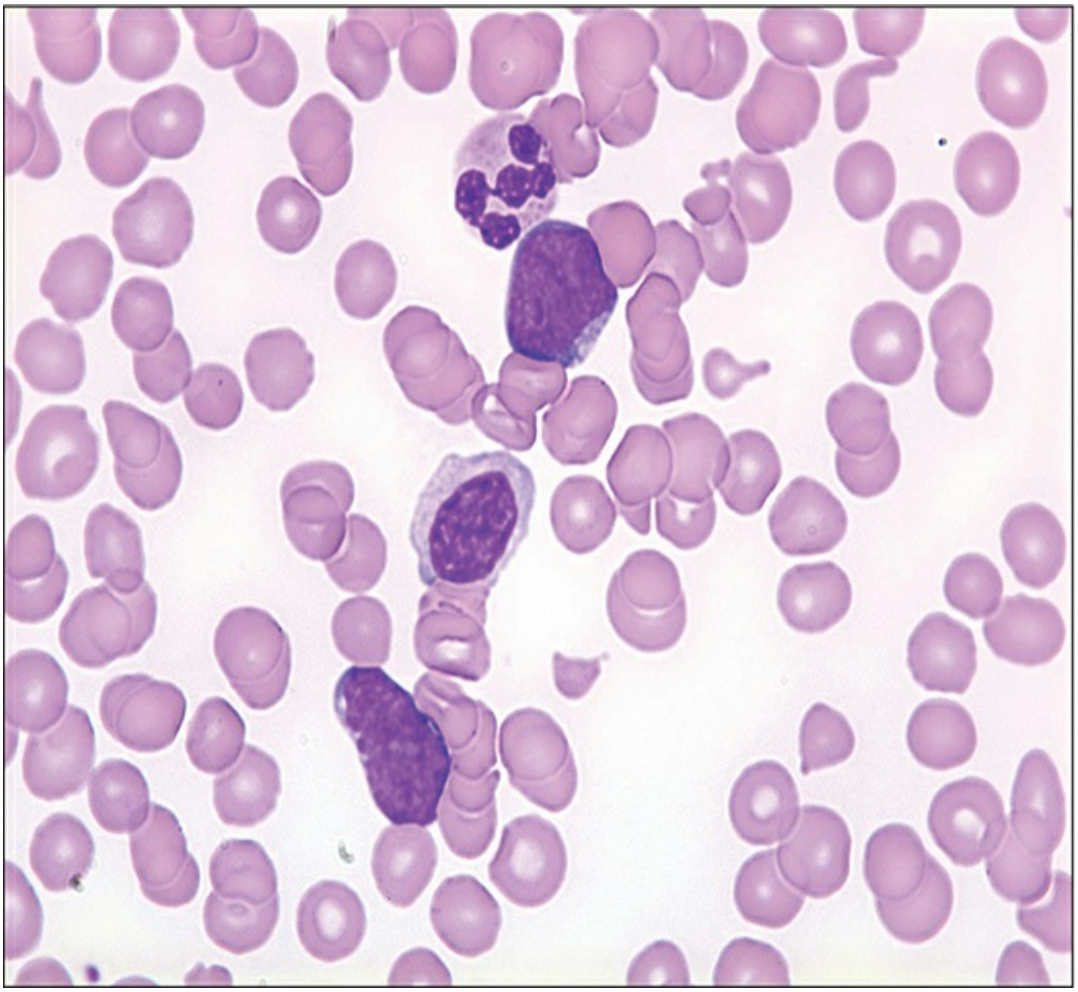


Figure IIB8-27

Peripheral blood smear.

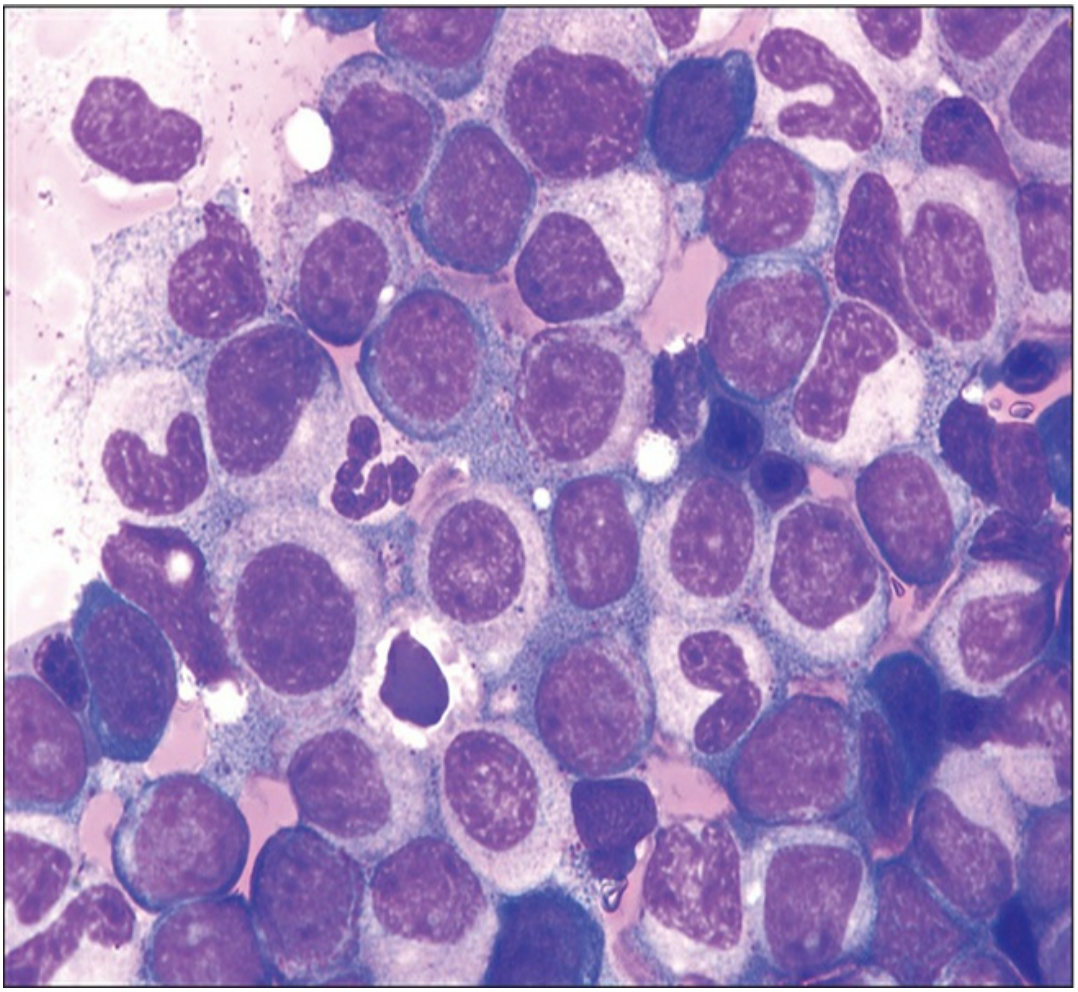


Figure IIB8-28

Bone marrow smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- Accounts for about 10% of cases of acute myeloid leukemias
- Occurs at any age but about 20% are <25 years of age and 40% ≥60 years of age

Laboratory Features

White Blood Cells

- Count is variable
- ≥20% blasts in peripheral blood and 10% or more of the cells show granulocyte maturation
- <20% are of the monocyte lineage

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Usually decreased

Bone Marrow

- Hypercellular
- ≥20% blasts with or without azurophilic granulation and Auer rods are common
- Maturation indicated by promyelocytes and more mature granulocytic forms present in ≥10% of nucleated cells
- Dysplasia if often present but ≤50% of cells in two lineages
- Eosinophil precursors may be present but do not have the cytologic abnormalities
- Basophils or mast cells may be slightly increased

Cytochemistry

- Myeloperoxidase and Sudan black B positive
- Specific esterase positive

Immunophenotype

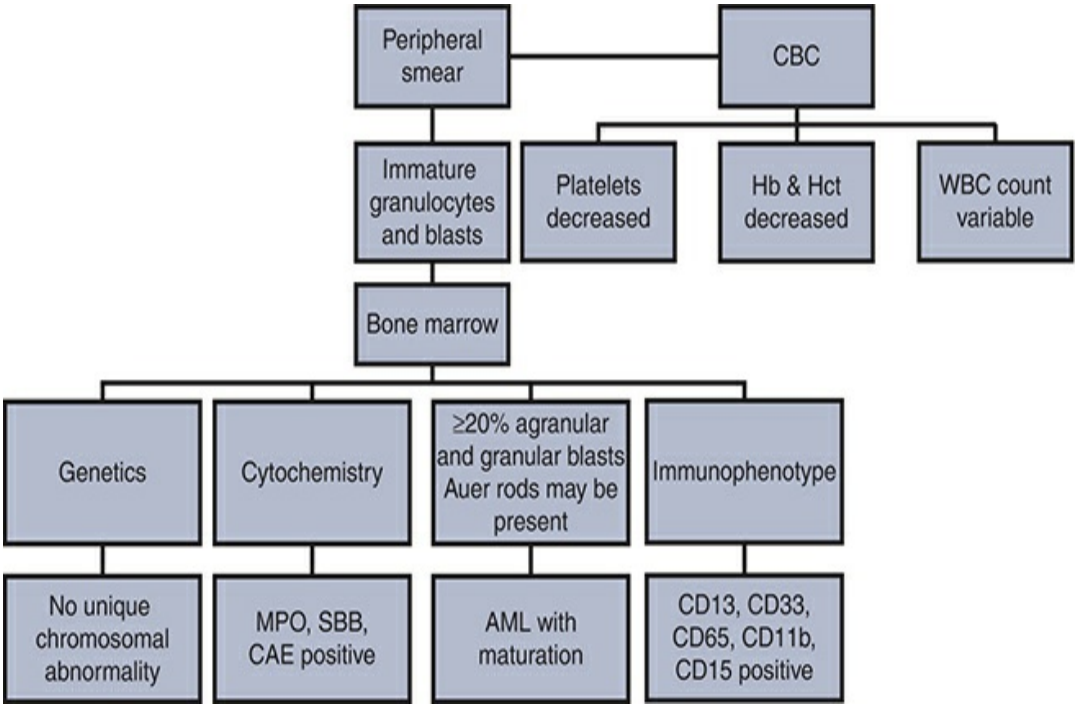
- Expression of one or more of the following: CD13, CD33, CD65, CD11b, and CD15

- CD14 and CD64 are usually absent

Genetics

- No association with recurrent genetic abnormalities

Diagnostic Scheme



ACUTE MYELOMONOCYTIC LEUKEMIA

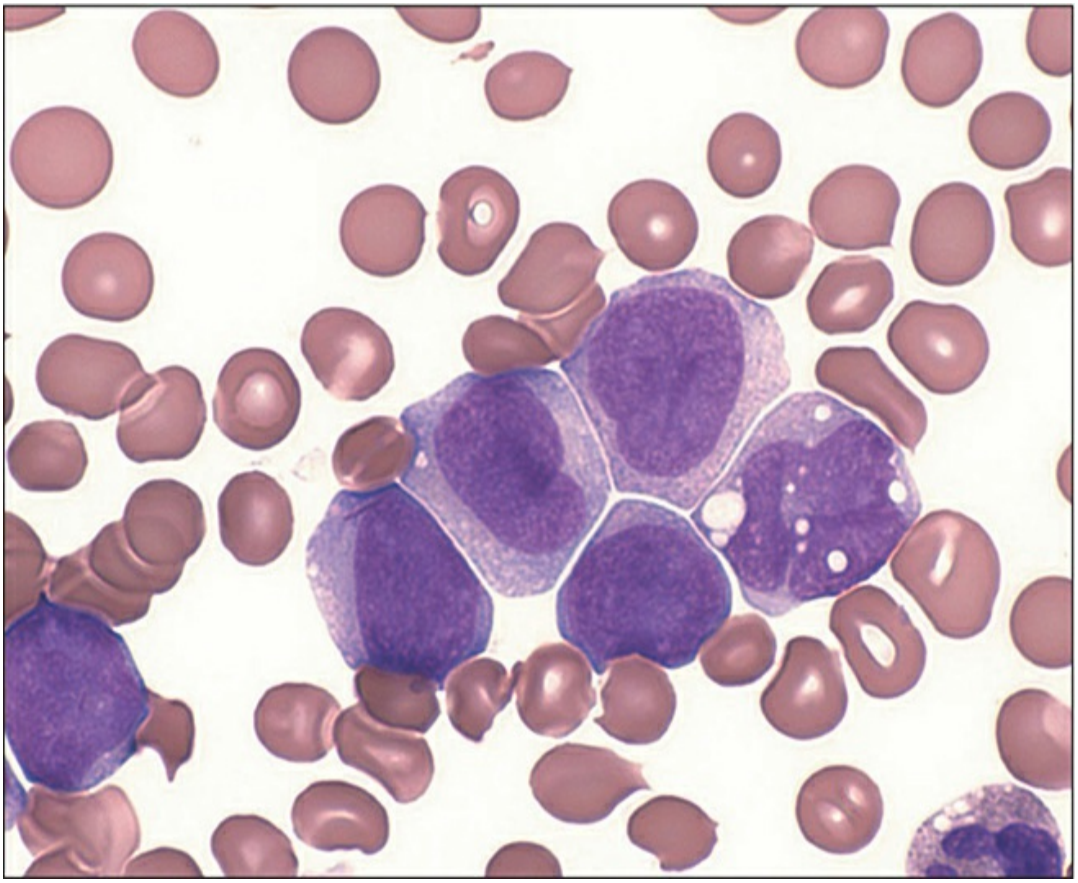


Figure IIB8-29

Peripheral blood smear.

Clinical Features

- Pallor, fatigue, and weakness from anemia
- Bleeding bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy
- Bone tenderness, hepatosplenomegaly, and lymphadenopathy
- Infiltration of leukemia cells in extramedullary sites
- Gingival hyperplasia is found in some cases

Pathology

- Accounts for about 5–10% of cases of acute myeloid leukemias
- Occurs in all age groups but is more common in individuals over 50 years of age
- Male to female ratio is about 1.4:1

Laboratory Features

White Blood Cells

- Count is usually increased
- Both myelocytic and monocytic differentiation occurs
- High number of monocytic cells may be present

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased but may be normal

Bone Marrow

- ≥20% blasts (including promonocytes)
- ≥20% neutrophils and precursors
- Scattered fine azurophil granules, vacuoles, and Auer rods may be present
- ≥20% monocytes and precursors
- Monoblasts are large cells with abundant cytoplasm that is moderately to intensely basophilic and may have pseudopod formation
- Promonocytes have irregular and delicately convoluted nuclear configuration; cytoplasm is usually less basophilic and more granulated with occasional large azurophilic granules and vacuoles

Cytochemistry

- Myeloblasts are positive for myeloperoxidase (at least 3%), Sudan black B, and specific esterase and negative with nonspecific esterases
- Monoblasts are negative for myeloperoxidase and Sudan black B
- Monoblasts are positive for nonspecific esterases

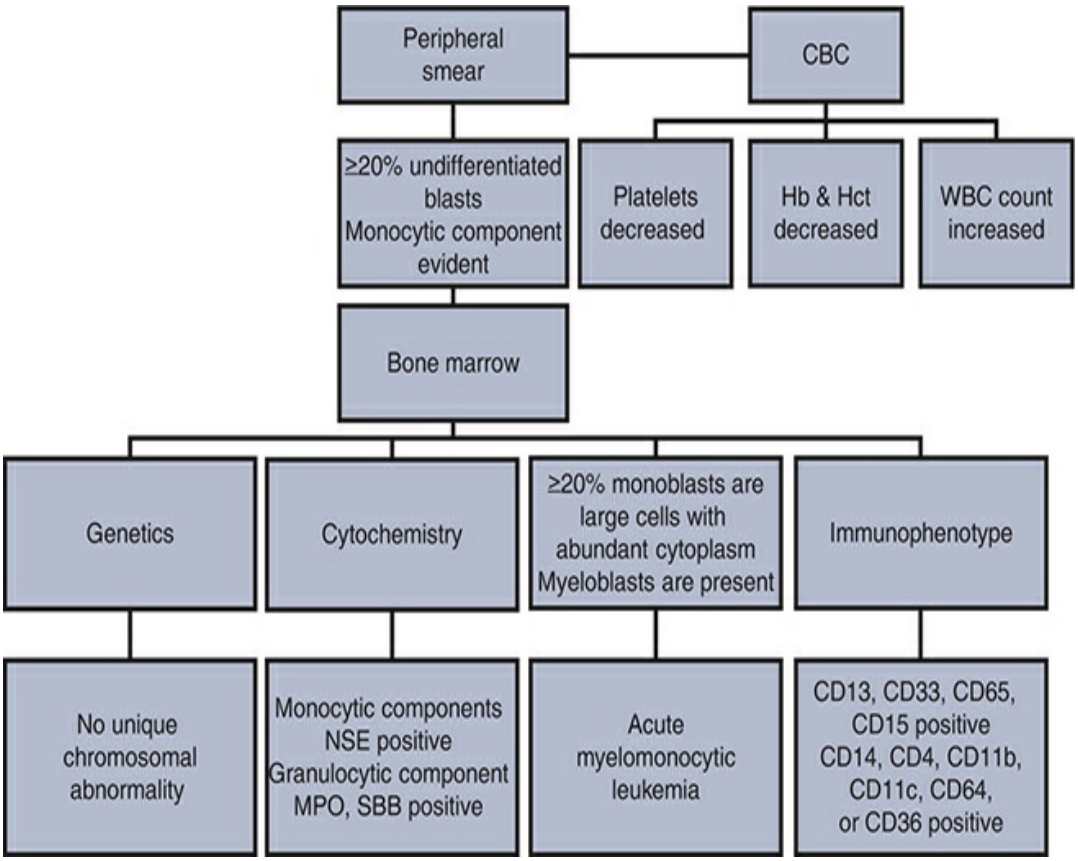
Immunophenotype

- Positive for myeloid antigen—CD13 and CD33
- Positive for monocytic markers—CD14, CD4, CD11b, CD64, and CD36

Genetics

- Nonspecific cytogenetic abnormality but +8 is present in the majority of cases

Diagnostic Scheme



ACUTE MONOBLASTIC AND MONOCYTIC LEUKEMIA

Monoblastic

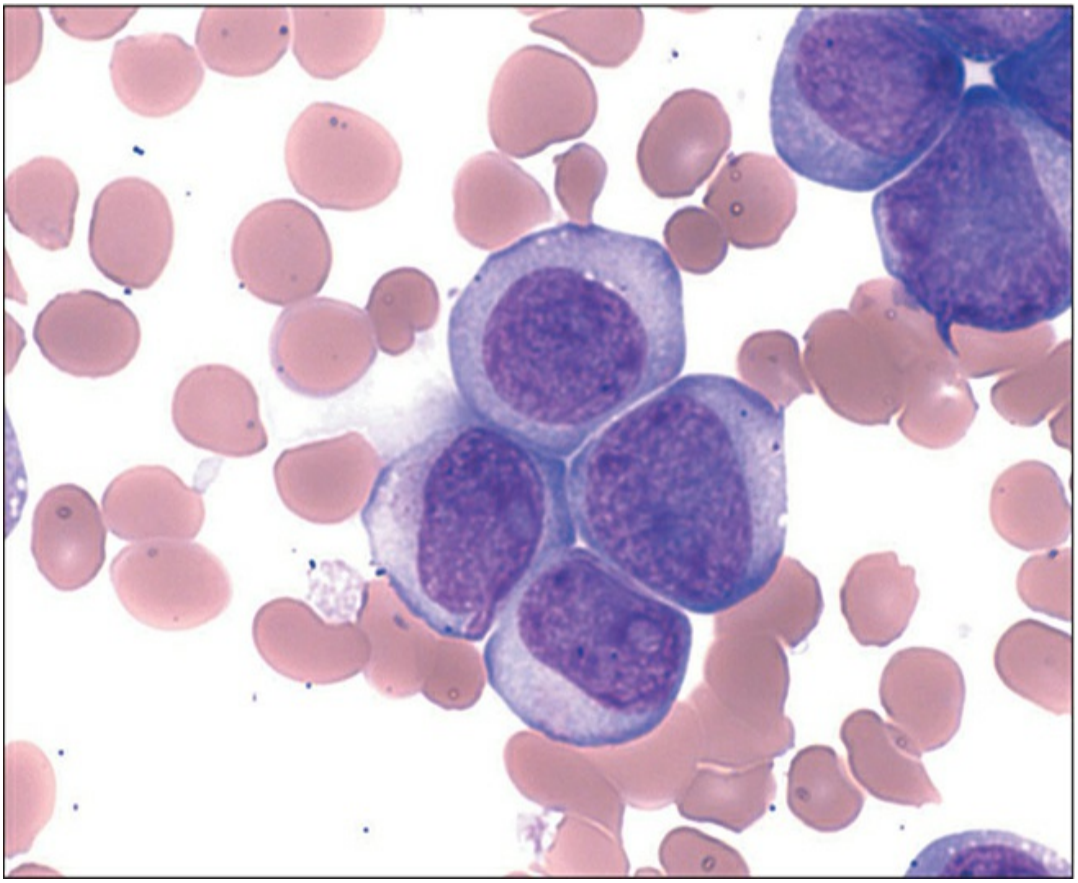


Figure IIB8-30

Peripheral blood smear.

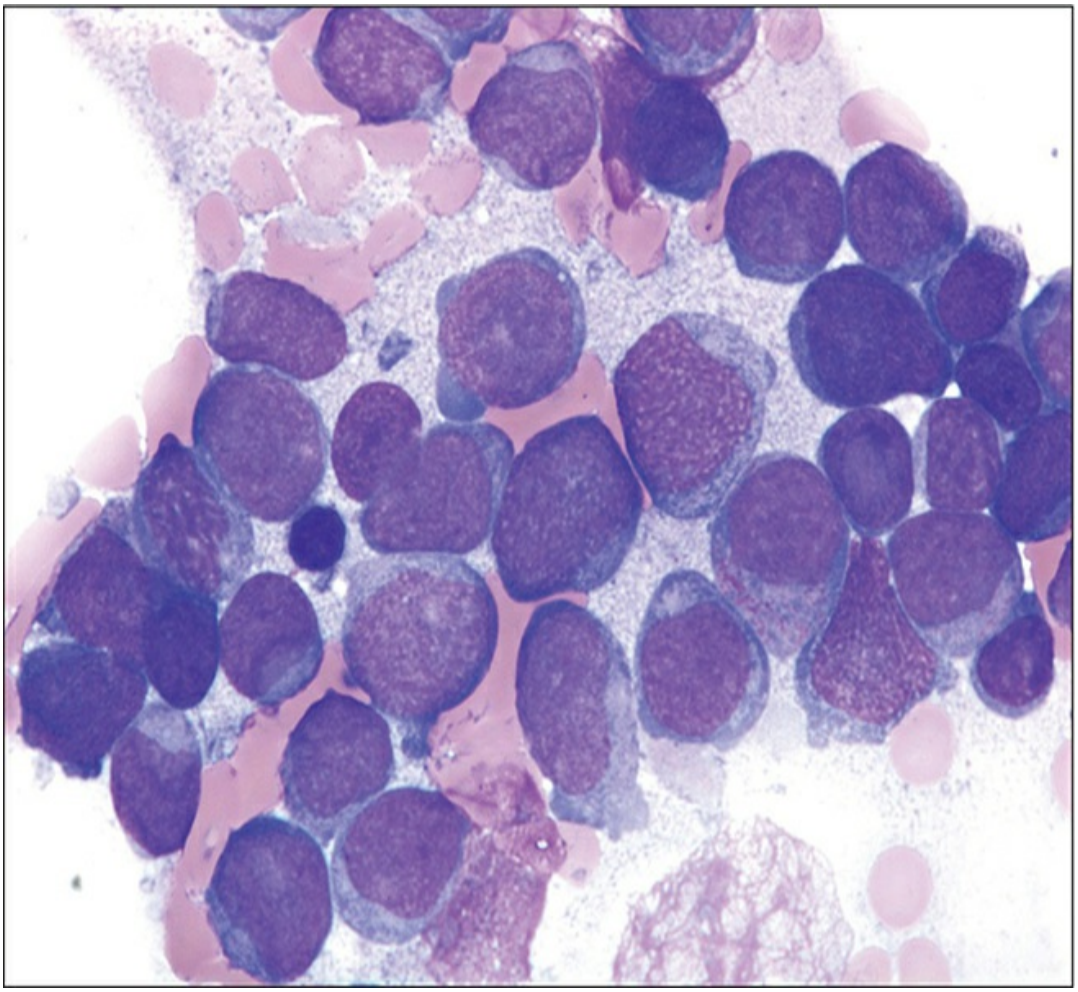


Figure IIB8-31

Bone marrow smear.

Monocytic

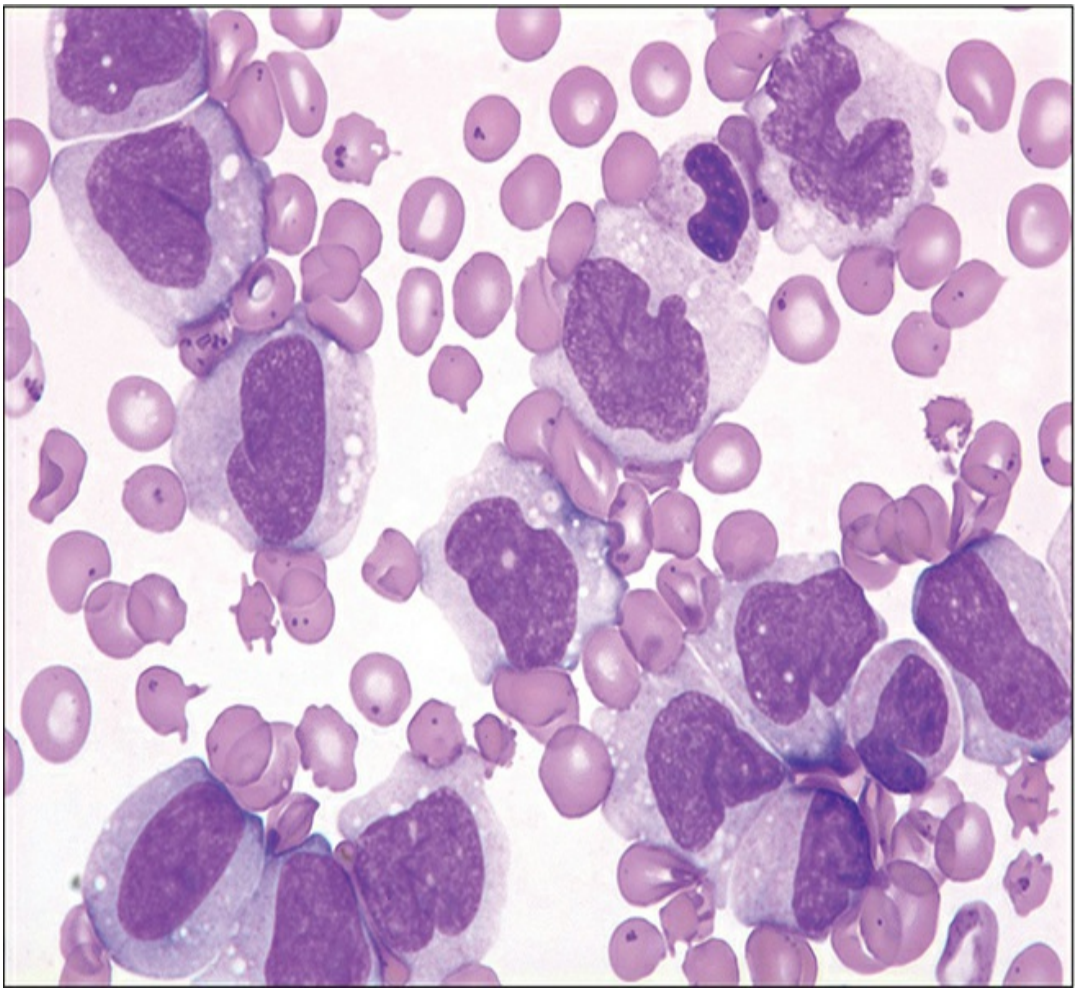


Figure **IIB8-32**

Peripheral blood smear.

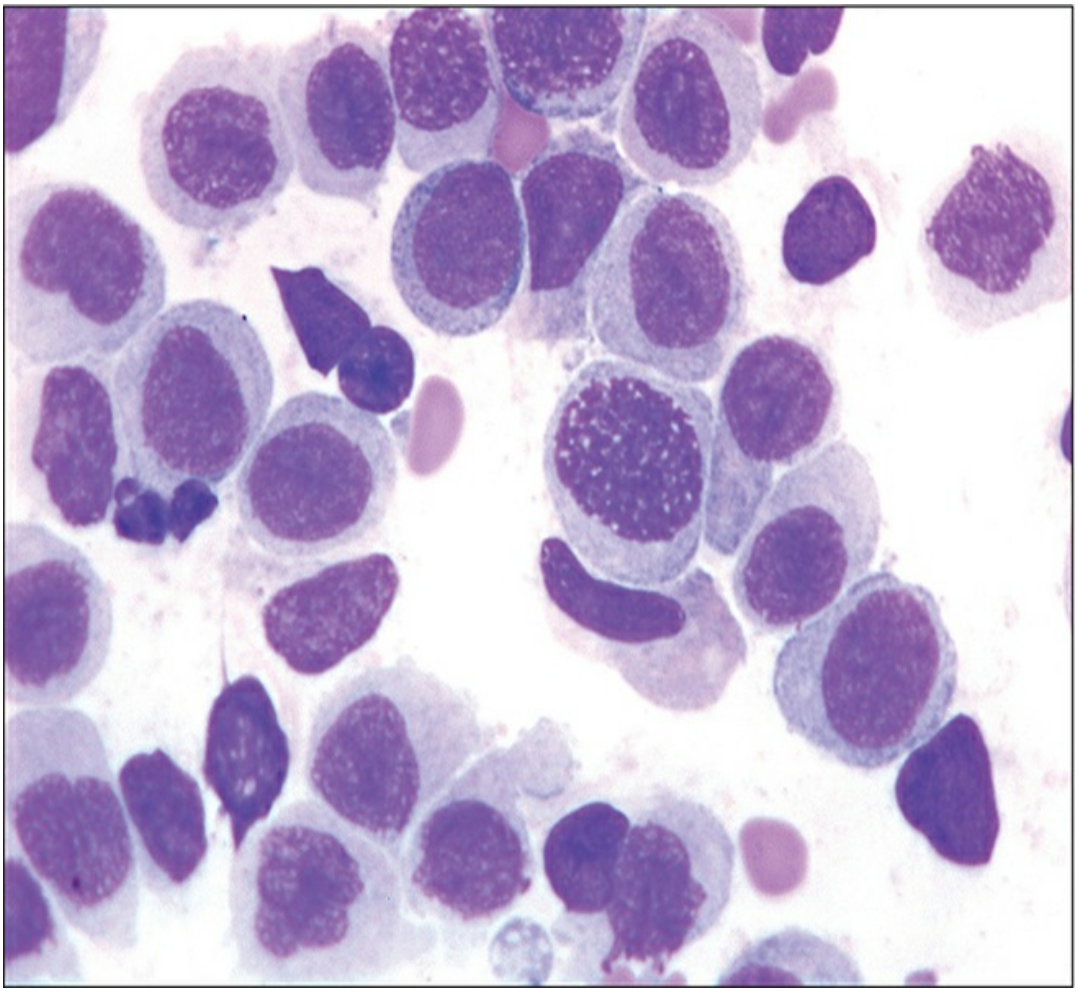


Figure IIB8-33

Bone marrow smear.

Clinical Features

- Bleeding disorders are the most common presentation
- Gum hyperplasia
- Splenomegaly
- Infections
- Extramedullary involvement: lymph nodes, liver, skin, spleen, central nervous system

Pathology

- Accounts for <5% of acute myeloid leukemias
- More common in young individuals

- The male to female ratio is 1.8:1

Laboratory Features

White Blood Cells

- Usually increased
- ≥20% blasts (including promonocytes)
- Blast morphology is variable
- Monoblasts are the predominant cells in the monoblastic type
- Promonocytes are the predominant cells in the monocytic type

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Hypercellular
- ≥20% blasts
- ≥80% of the cells are of the monocytic lineage including monoblasts, promonocytes, and monocytes
- <20% are of the neutrophilic origin
- In acute monoblastic leukemia, the majority of the cells are monoblasts
- In acute monocytic leukemia, the majority of the cells are promonocytes

Cytochemistry

- Myeloperoxidase is typically negative or very weakly positive
- Nonspecific esterase is typically positive

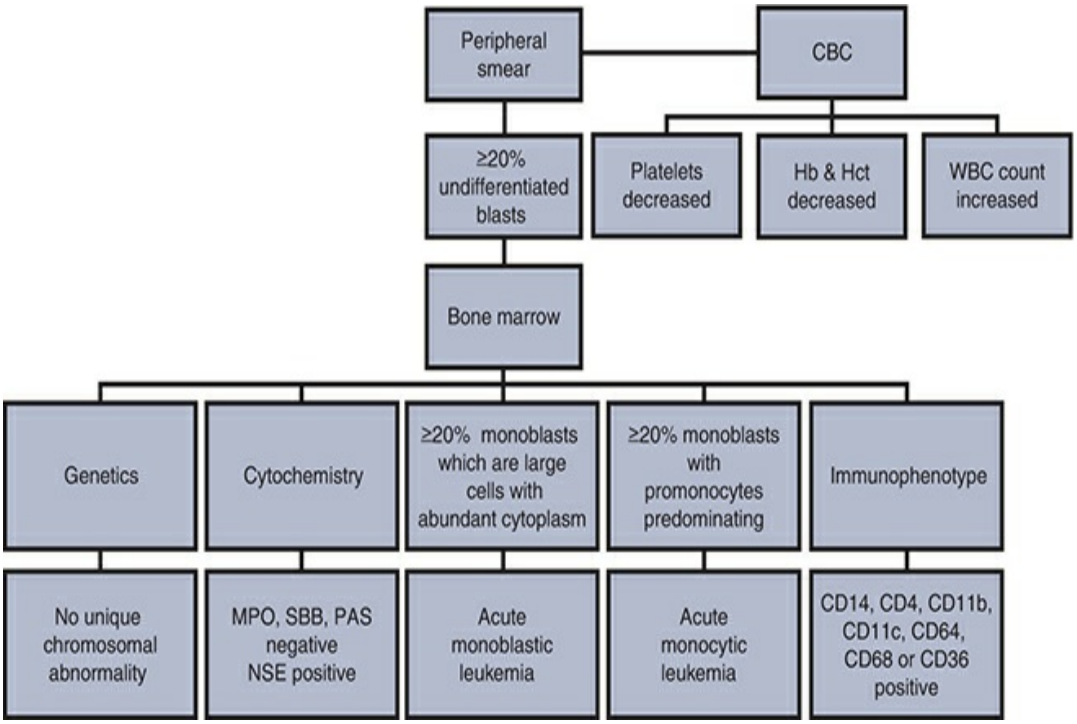
Immunophenotype

- Variable expression of CD13, CD33, CD15, and CD65
- At least two of the following markers are present: CD14, CD4, CD11b, CD11c, CD64, CD68, CD36, and lysozyme

Genetics

- Nonspecific cytogenetic abnormalities are present in most cases

Diagnostic Scheme



PURE ERYTHROID LEUKEMIA

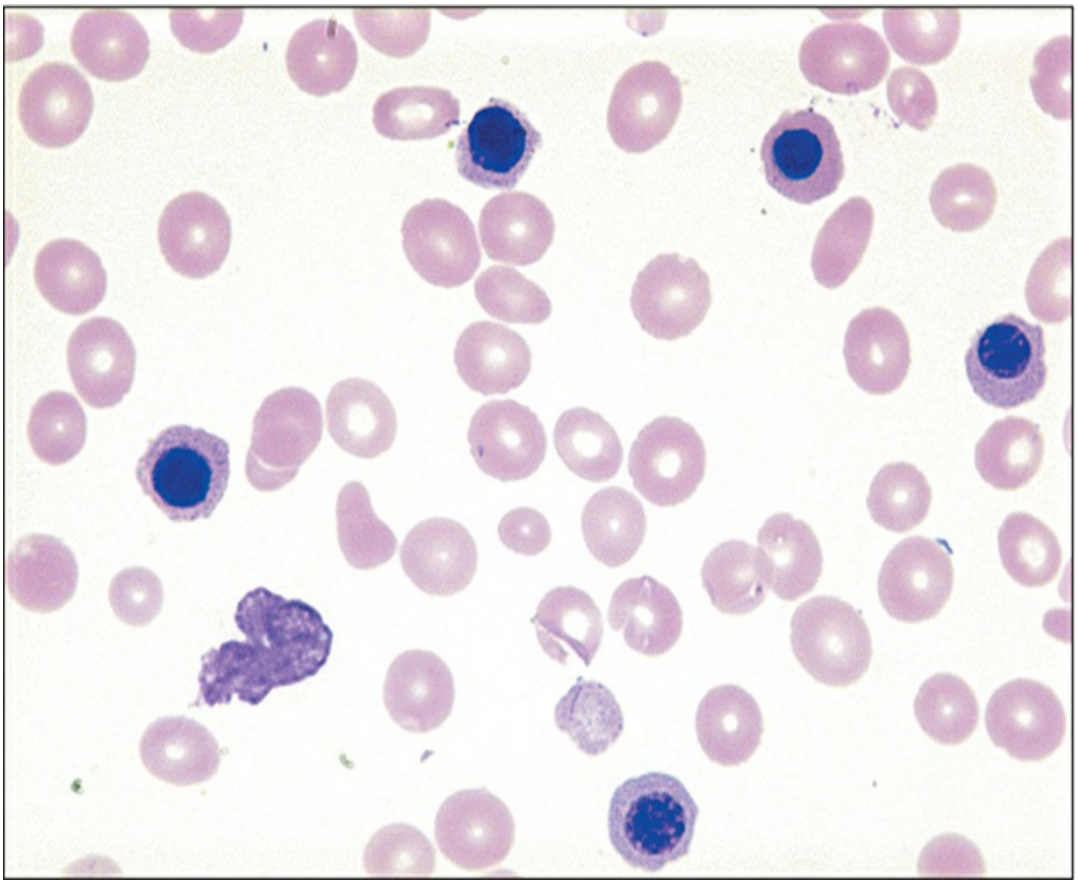


Figure IIB8-34

Peripheral blood smear.

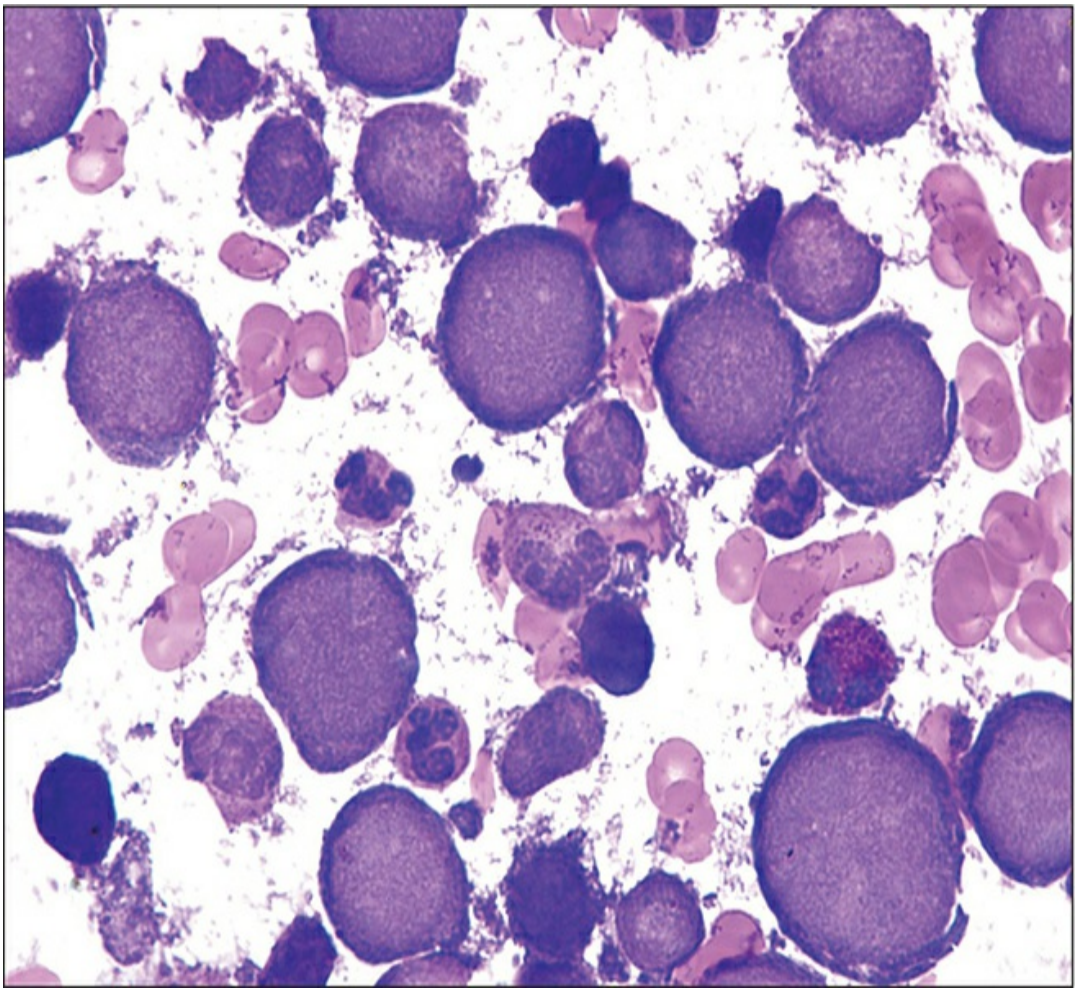


Figure IIB8-35

Bone marrow smear.

Clinical Features

- Weakness, fatigue, weight loss, fever
- Hepatosplenomegaly
- Petechiae, purpura

Pathology

- Neoplastic proliferation of immature cells committed to erythroid lineage
- Pure erythroid leukemia is very rare and can occur at any age

Laboratory Features

White Blood Cells

- Count is variable

Red Blood Cells

- Normocytic/normochromic to macrocytic/normochromic anemia
- Anisocytosis and poikilocytosis
- Basophilic stippling
- Nucleated red blood cells

Platelets

- Variable

Bone Marrow

- >80% of cells are erythroid with ≥30% proerythroblasts
- If the neoplastic erythroblasts occur in sheets, erythroblasts may constitute <80% of the cells, but proerythroblasts should constitute ≥30% of the cells
- No significant myeloblastic component
- Dysmegakaryopoiesis is common
- Ring sideroblasts may be present
- Presence of medium- to large-sized erythroblasts containing round nuclei, fine chromatin, and one or more nucleoli
- Cytoplasm is deeply basophilic

Cytochemistry

- Negative for myeloperoxidase and Sudan black B
- Periodic acid–Schiff, alpha–naphthyl acetate esterase, and acid phosphatase positive

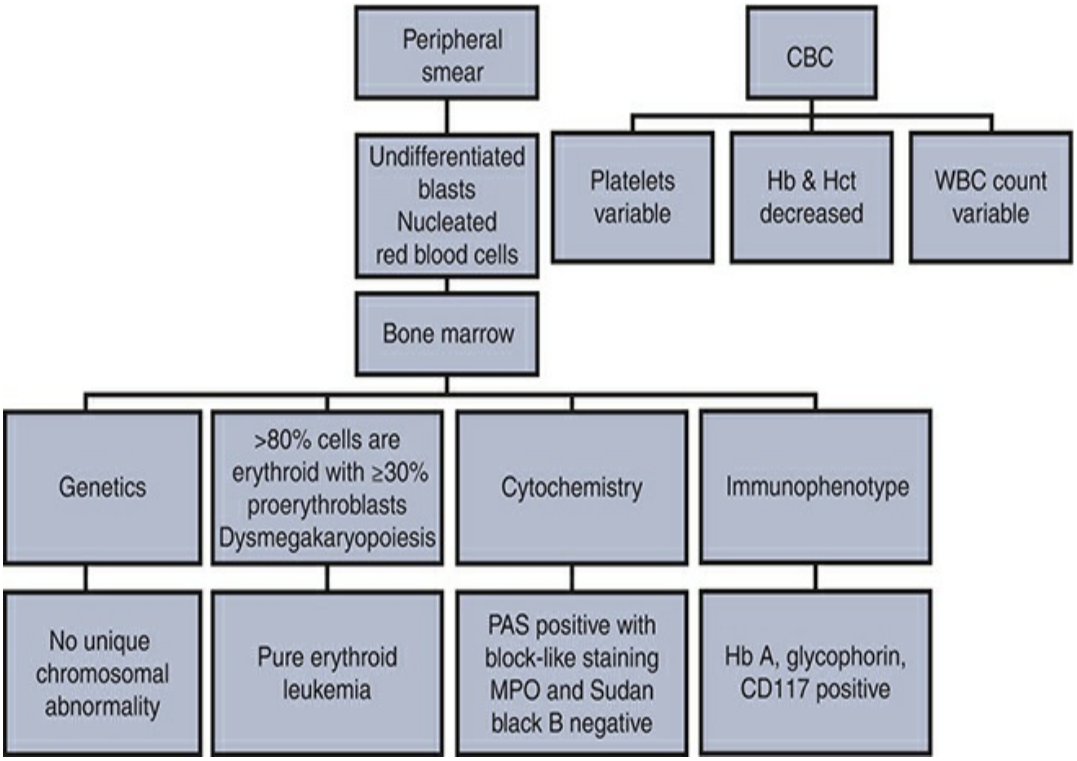
Immunophenotype

- Erythroid precursors are for hemoglobin A, glycophorin, and CD117
- HLA-DR and CD34 are negative

Genetics

- No specific chromosomal abnormalities are described
- Multiple structural abnormalities are commonly found such as −5/del(5q) and −7/del(7q)

Diagnostic Scheme



ACUTE MEGAKARYOBLASTIC LEUKEMIA

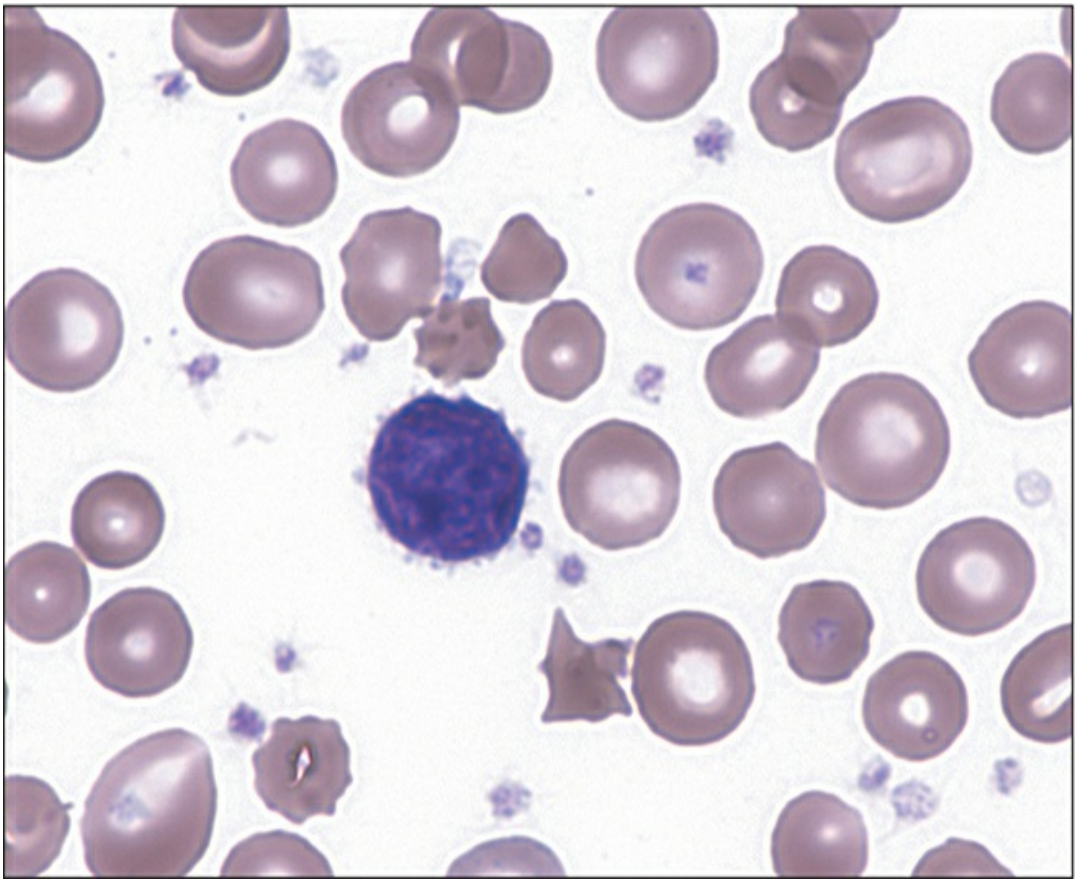


Figure IIB8-36

Peripheral blood smear.

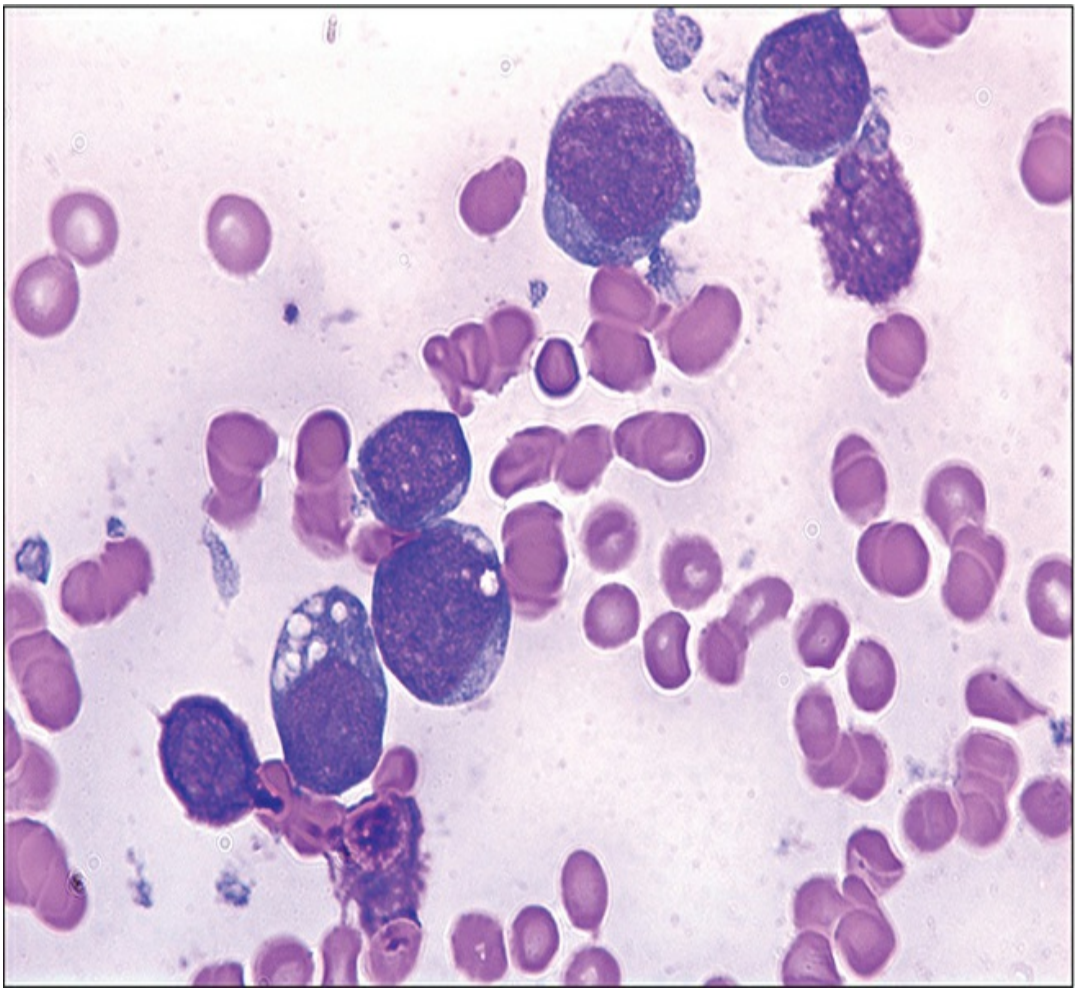


Figure IIB8-37

Bone marrow smear.

Clinical Features

- Pale, fatigue, and weakness from anemia
- Bleeding, bruising, and petechial hemorrhages caused by thrombocytopenia
- Infections that fail to respond to appropriate therapy

Pathology

- Accounts for <5% cases of the acute myeloid leukemias
- Occurs in both adults and children

Laboratory Features

White Blood Cells

- Variable but usually decreased

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Count is variable and may be normal or increased
- Bizarre and atypical forms

Bone Marrow

- Megakaryoblasts are highly pleomorphic
- Medium-sized to large blasts with a round, slightly irregular or indented nucleus with fine reticular chromatin and 1–3 nucleoli
- Cytoplasm is basophilic and mostly agranular with distinct blebs or pseudopods
- Increased reticulum fibrosis may result in a dry tap
- ≥20% blasts in which ≥50% are of the megakaryocytic lineage

Cytochemistry

- Myeloperoxidase and Sudan black B negative
- Periodic acid–Schiff positive
- Nonspecific esterase (acetate) positive
- Nonspecific esterase (butyrate) negative

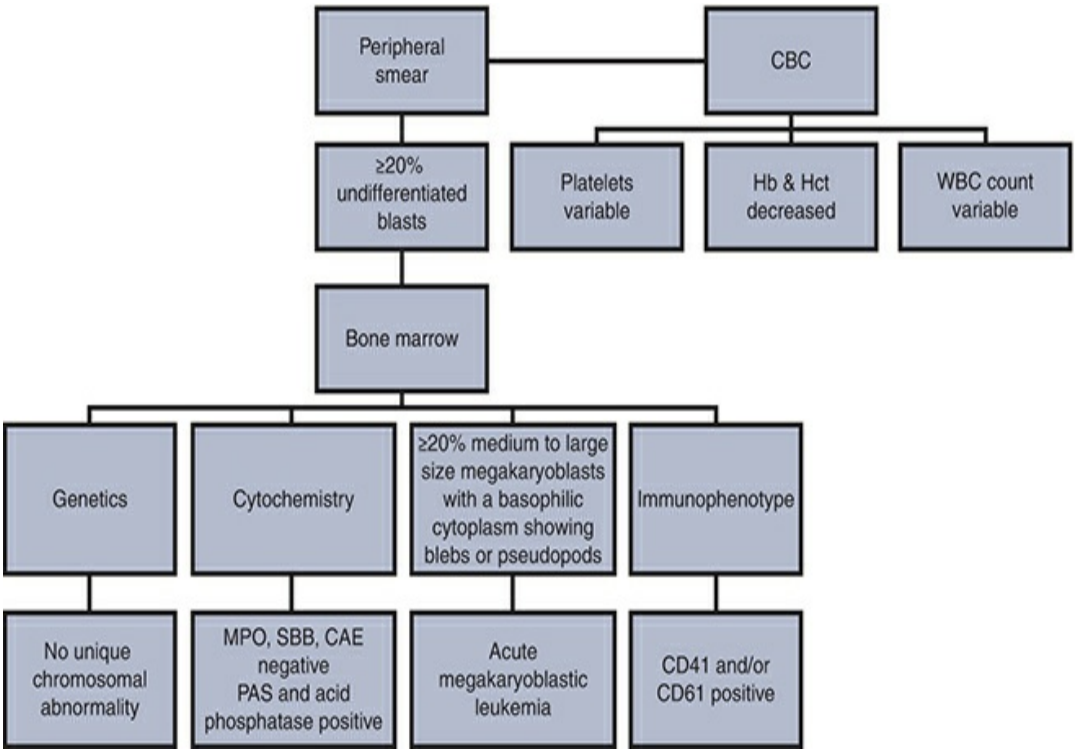
Immunophenotype

- Expression of one or more of the following: CD41 or CD61 or CD42b

Genetics

- No specific chromosomal abnormalities are associated

Diagnostic Scheme


Peripheral smear
CBC
≥20% undifferentiated blasts
Platelets variable
Hb & Hct decreased
WBC count variable
Bone marrow
Genetics
Cytochemistry
≥20% medium to large size megakaryoblasts with a basophilic cytoplasm showing blebs or pseudopods
Immunophenotype
No unique chromosomal abnormality
MPO, SBB, CAE negative PAS and acid phosphatase positive
Acute megakaryoblastic leukemia
CD41 and/or CD61 positive

ACUTE BASOPHILIC LEUKEMIA

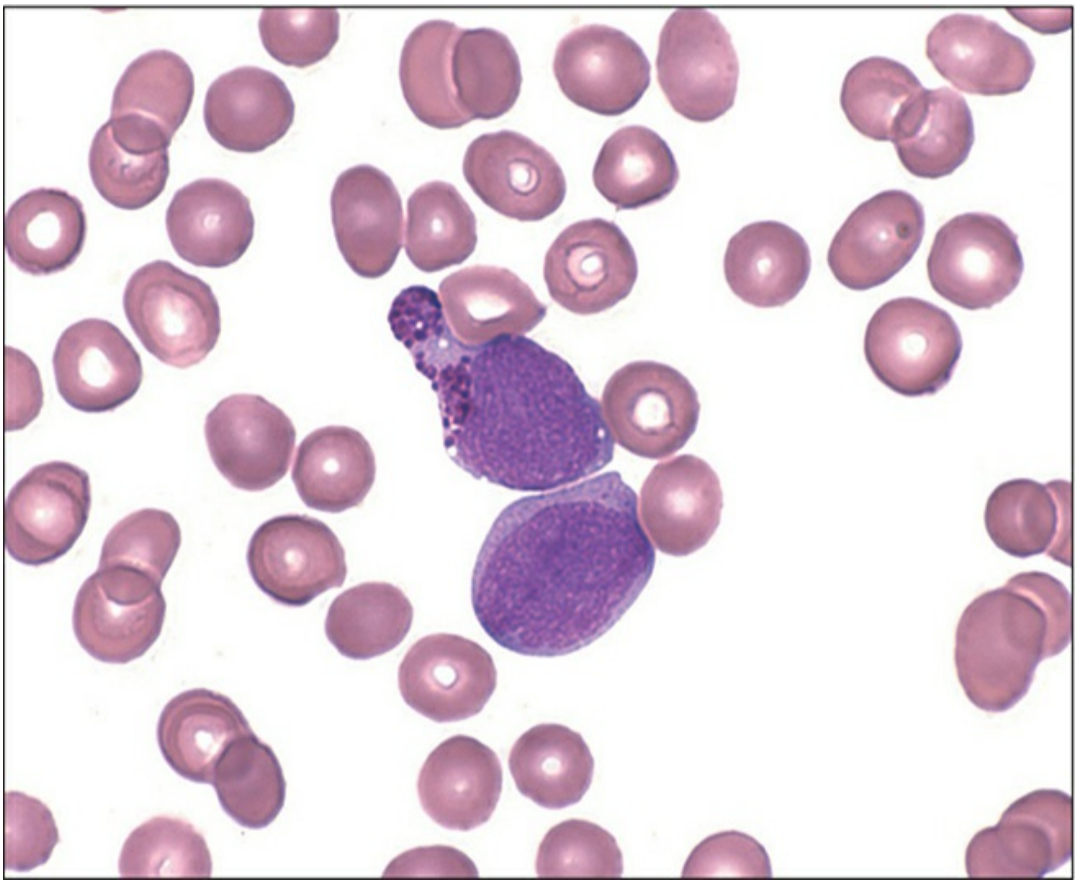


Figure IIB8-38

Peripheral blood smear.

Clinical Features

- Weakness, fatigue, fever, wheezing, urticaria, diarrhea, pruritus, hepatosplenomegaly

Pathology

- Very rare occurrence
- Release of basophil granules may cause shock or severe disseminated intravascular coagulation

Laboratory Features

White Blood Cells

- Normal to increased

- Increased basophils
- Abnormal basophils that resemble mast cells

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- ≥20% blasts
- Increased basophils with immature form
- Medium-sized with a high N/C ratio; oval, round, or irregular nucleus with dispersed chromatin and 1–3 prominent nucleoli
- Cytoplasm is moderately basophil and contains a variable number of coarse basophilic granules (positive with metachromatic staining)

Cytochemistry

- Myeloperoxidase and Sudan black B positive
- Toluidine blue positive

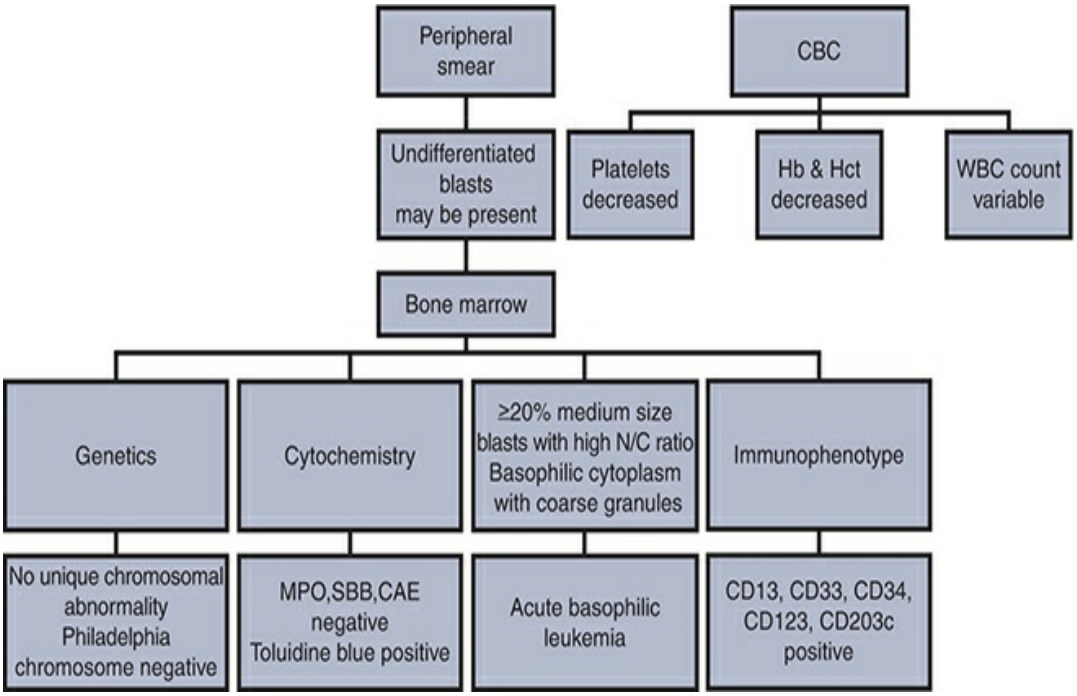
Immunophenotype

- Positive for CD13 and/or CD33
- Usually positive for CD12, CD203c, and CD11b

Genetics

- No specific chromosomal abnormalities

Diagnostic Scheme


Peripheral smear
CBC
Undifferentiated blasts may be present
Platelets decreased
Hb & Hct decreased
WBC count variable
Bone marrow
Genetics
Cytochemistry
≥20% medium size blasts with high N/C ratio Basophilic cytoplasm with coarse granules
Immunophenotype
No unique chromosomal abnormality Philadelphia chromosome negative
MPO,SBB,CAE negative Toluidine blue positive
Acute basophilic leukemia
CD13, CD33, CD34, CD123, CD203c positive

ACUTE PANMYELOSIS WITH MYELOFIBROSIS (APMF)

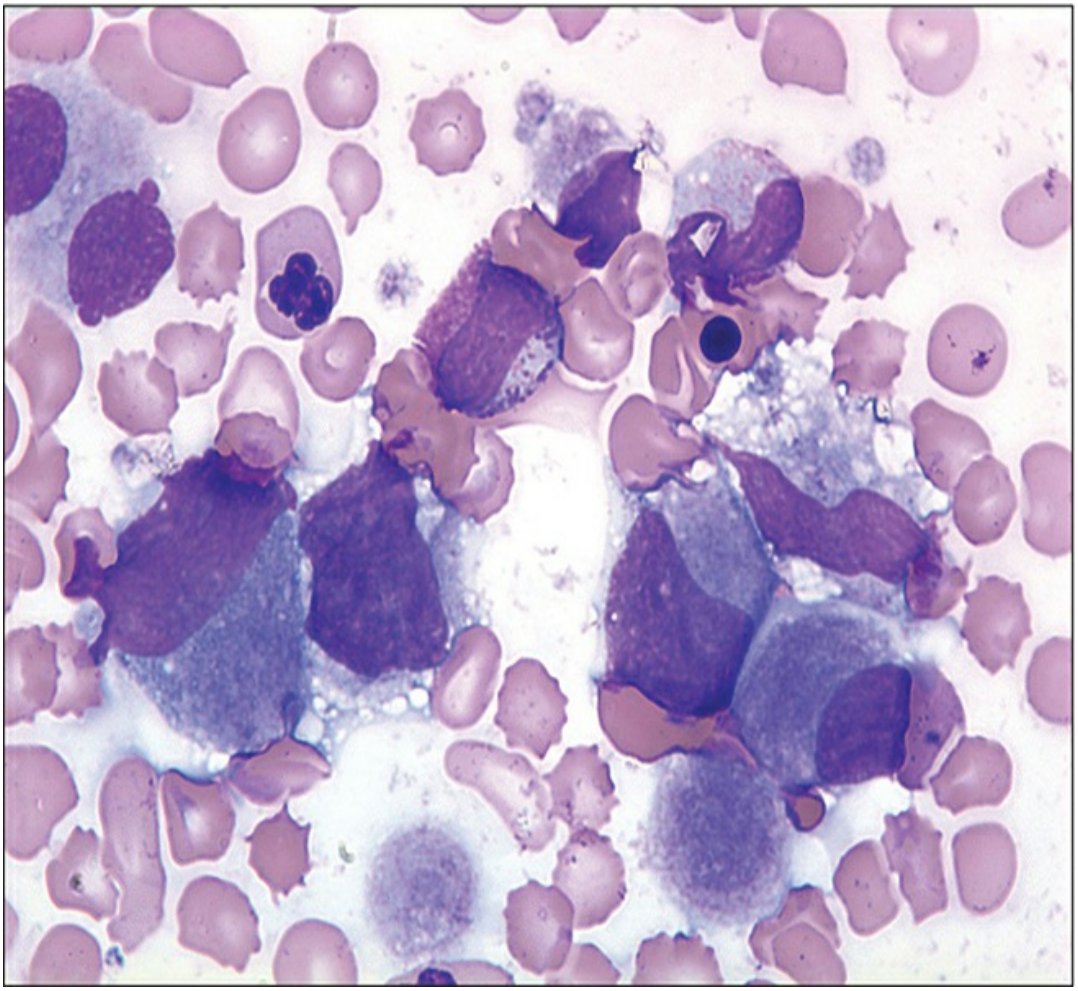


Figure IIB8-39

Peripheral blood smear.

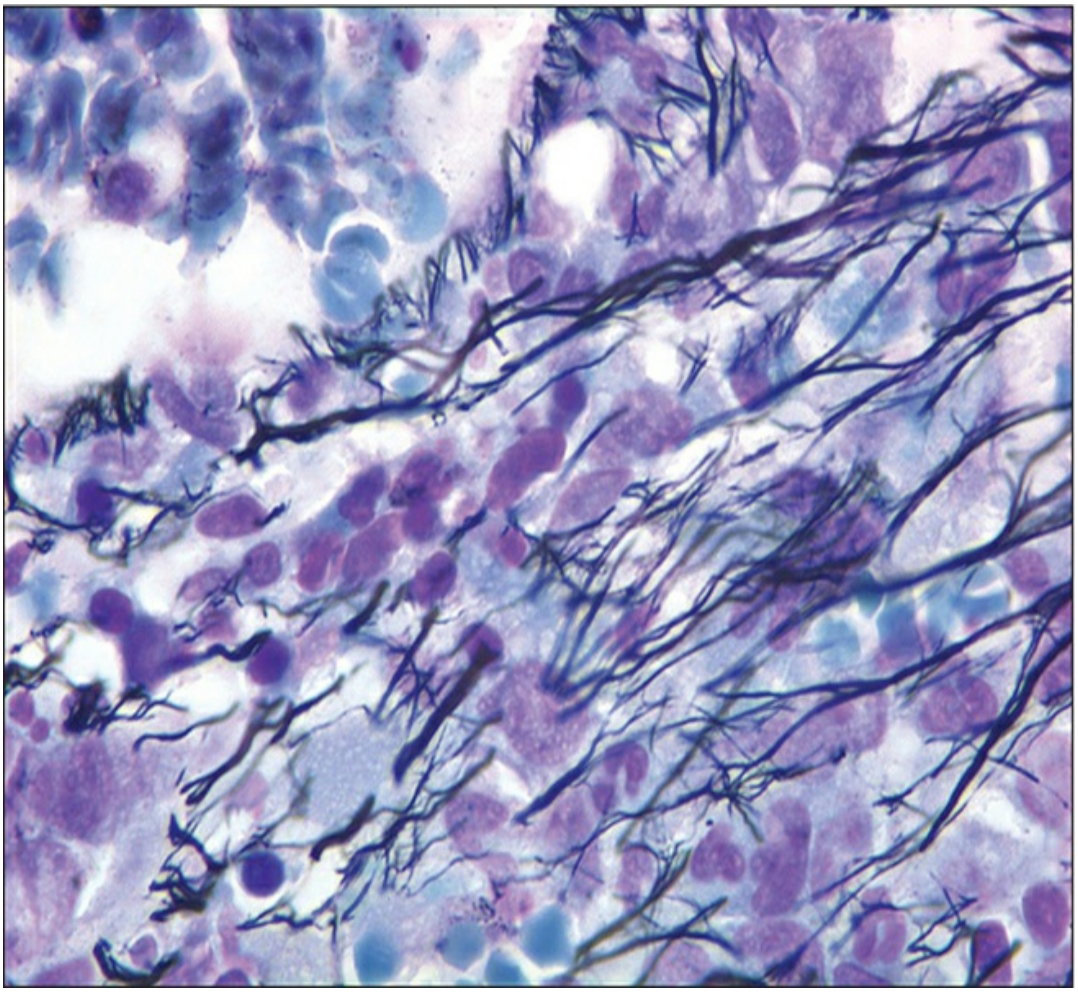


Figure **IIB8-40**

Reticulin stain.

Clinical Features

- Weakness, fatigue, fever, and bone pain
- Rapidly progressive
- Pancytopenia is present

Pathology

- Very rare form of acute myeloid leukemias
- Occurs de novo
- Primarily affects adults

Laboratory Features

White Blood Cells

- Count is decreased
- Dysplasia is common

Red Blood Cells

- Normocytic/normochromic anemia—variable macrocytosis

Platelets

- Count is decreased
- Abnormal forms are observed

Bone Marrow

- ≥20% blasts
- Hypercellular
- Increased fibrotic stroma, resulting in inadequate sample
- Increased erythroid, granulocyte, and megakaryocyte precursors
- Megakaryocytes are typically dysplastic

Cytochemistry

- Myeloperoxidase is negative

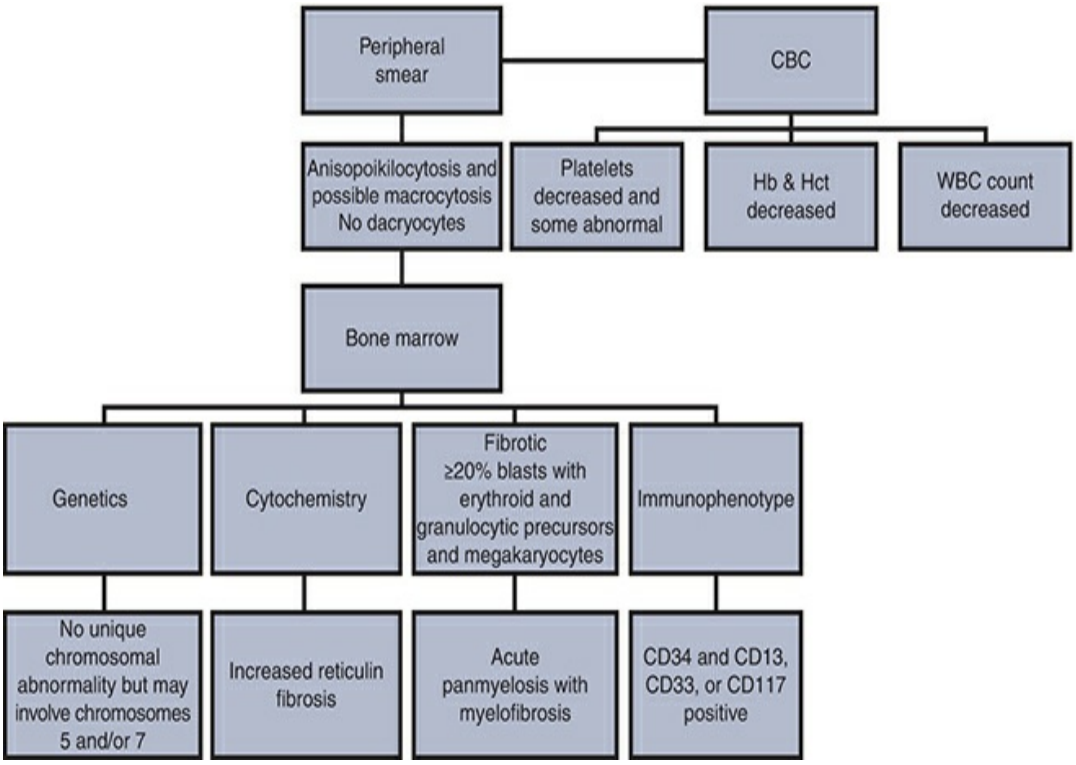
Immunophenotype

- Blasts are usually positive for CD34 and one or more of the following: CD13, CD33, and CD117

Genetics

- Usually abnormal involving chromosome 5 and/or 7

Diagnostic Scheme


Peripheral smear
CBC
Anisopoikilocytosis and possible macrocytosis No dacryocytes
Platelets decreased and some abnormal
Hb & Hct decreased
WBC count decreased
Bone marrow
Genetics
Cytochemistry
Fibrotic ≥20% blasts with erythroid and granulocytic precursors and megakaryocytes
Immunophenotype
No unique chromosomal abnormality but may involve chromosomes 5 and/or 7
Increased reticulin fibrosis
Acute panmyelosis with myelofibrosis
CD34 and CD13, CD33, or CD117 positive

MYELOID PROLIFERATIONS ASSOCIATED WITH DOWN SYNDROME

Criteria

- Ratio of lymphoblastic leukemia to acute myeloid leukemia in children aged >4 years with Down syndrome is 1.0:1.2
- There is a 150-fold increase in acute myeloid leukemias in children aged >5 years with Down syndrome
- 70% of cases are acute megakaryoblastic leukemia

TRANSIENT ABNORMAL MYELOPOIESIS ASSOCIATED WITH DOWN SYNDROME

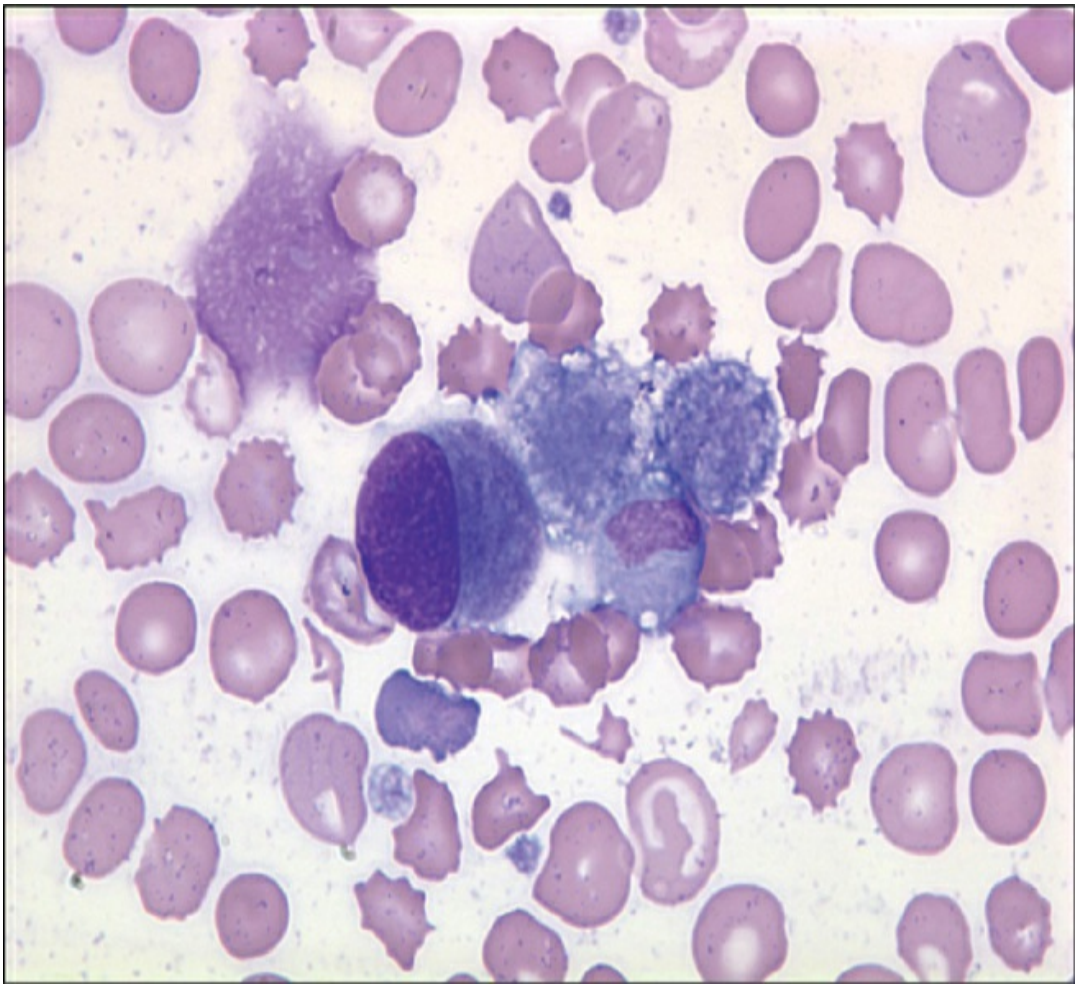


Figure IIB8-41

Peripheral blood smear.

Clinical Features

- Symptoms are usually the same as those of acute myeloid leukemias and usually diagnosed at age 3–7 days
- May have jaundice, ascites, respiratory distress, bleeding, and pericardial or pleural effusions
- Hepatosplenomegaly is often present

Pathology

- Unique disorder of newborns with Down syndrome
- Diagnosed in approximately 10% of newborns with Down syndrome
- Undergoes spontaneous remission within the first 3 months of life
- 20–30% of children develop acute myeloid leukemias 1–3 years later

Laboratory Features

White Blood Cells

- May be marked leukocytosis
- Increased basophils
- % of blasts may exceed the blast % in bone marrow

Red Blood Cells

- Anemia

Platelets

- Decreased

Bone Marrow

- ≥20% blasts
- Blasts often have basophilic cytoplasm with coarse basophilic granules and cytoplasmic blebbing suggestive of megakaryoblasts
- Erythroid and megakaryocytic dysplasia

Cytochemistry

- Granules in blasts are myeloperoxidase negative

Immunophenotype

- Blasts are positive for CD34, CD117, CD13, CD33, HLA-

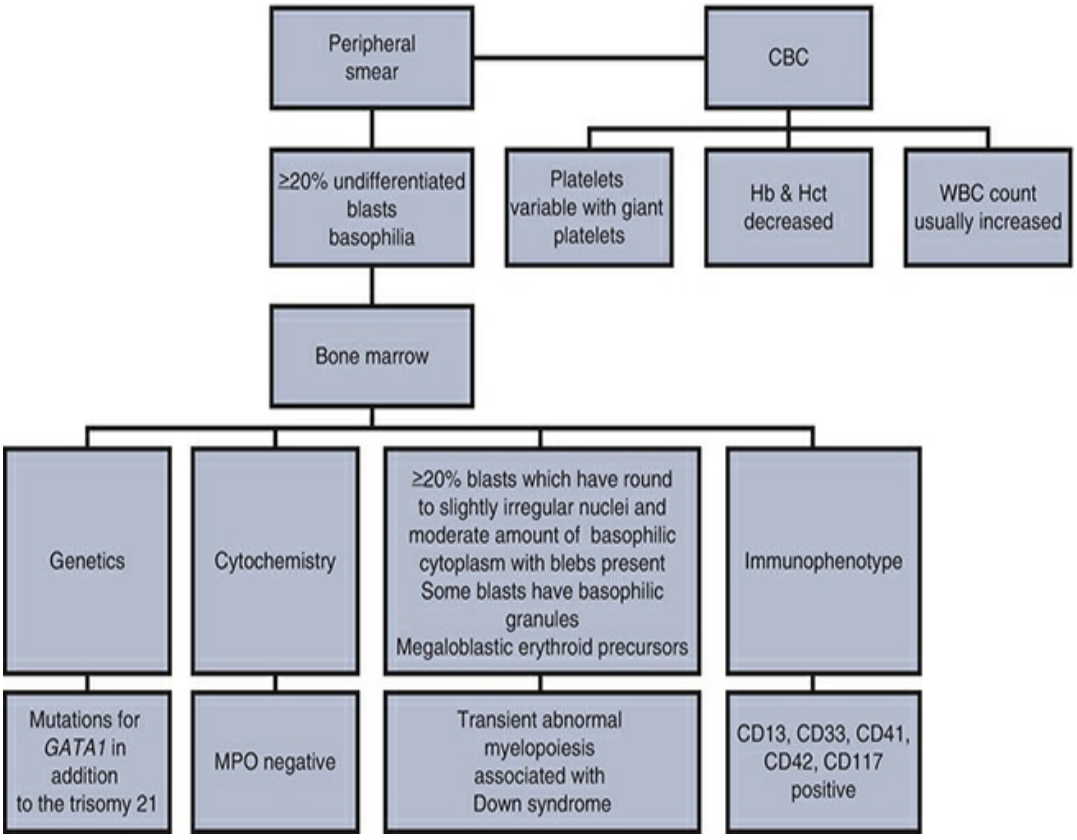
DR, CD41, CD42, CD110 (TPOR), IL3R, CD36, CD61, and CD71

- Negative for CD15, CD14, CD11a, and glycophorin A
- 50% are negative for CD34

Genetics

- Trisomy 21 and acquired mutations of the gene encoding GATA1 in blast cells

Diagnostic Scheme



MYELOID LEUKEMIA ASSOCIATED WITH DOWN SYNDROME

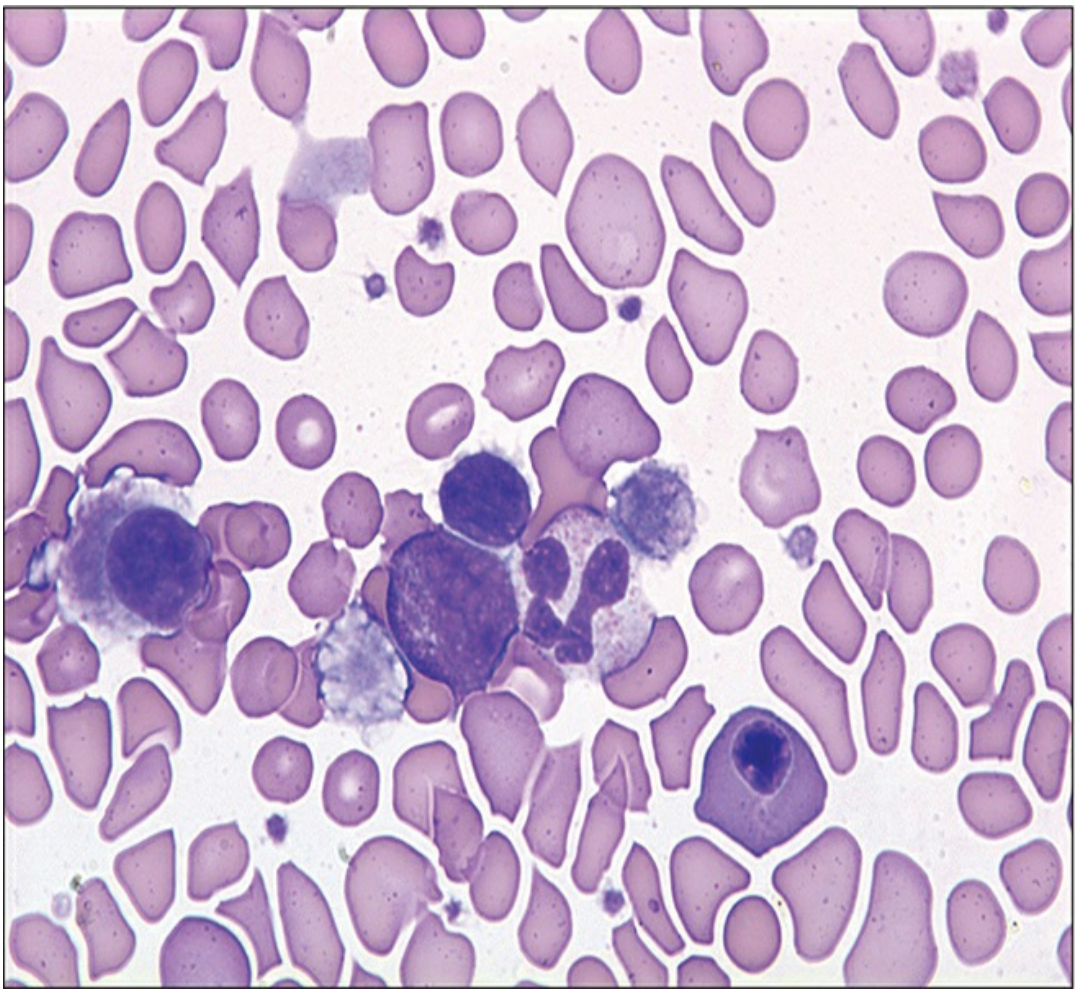


Figure IIB8-42

Peripheral blood smear.

Clinical Features

- Manifests predominantly in the first 3 years of life

If <20% blast cells in the bone marrow appears to be relatively indolent present with complications due to thrombocytopenia

Pathology

- Occurs in 20–30% of children with a history of transient

abnormal myelopoiesis (TAM) and the leukemia usually occurs 1–3 years after TAM

- About 1–2% of children with Down syndrome develop acute myeloid leukemia during first 5 years of birth
- Down syndrome patients account for 20% of all pediatric patients with acute myeloid leukemias/myelodysplastic syndromes

Laboratory Features

White Blood Cells

- Decreased
- Blasts may be present

Red Blood Cells

- Macrocytic anemia
- Anisopoikilocytosis
- Erythroid precursors may be seen
- Dacryocytes

Platelets

- Decreased
- Giant platelets may be seen

Bone Marrow

- ≥20% blasts
- Blasts have slightly irregular to round nucleus
- A variable number of blasts contain coarse granules
- Cytoplasm of blasts is basophilic and blebs are usually present
- Erythroid precursors may show megaloblastic and dysplastic changes
- Dysgranulopoiesis may also be present
- Megakaryocytic series is extremely dysplastic

Cytochemistry

- Granules in blasts are myeloperoxidase positive

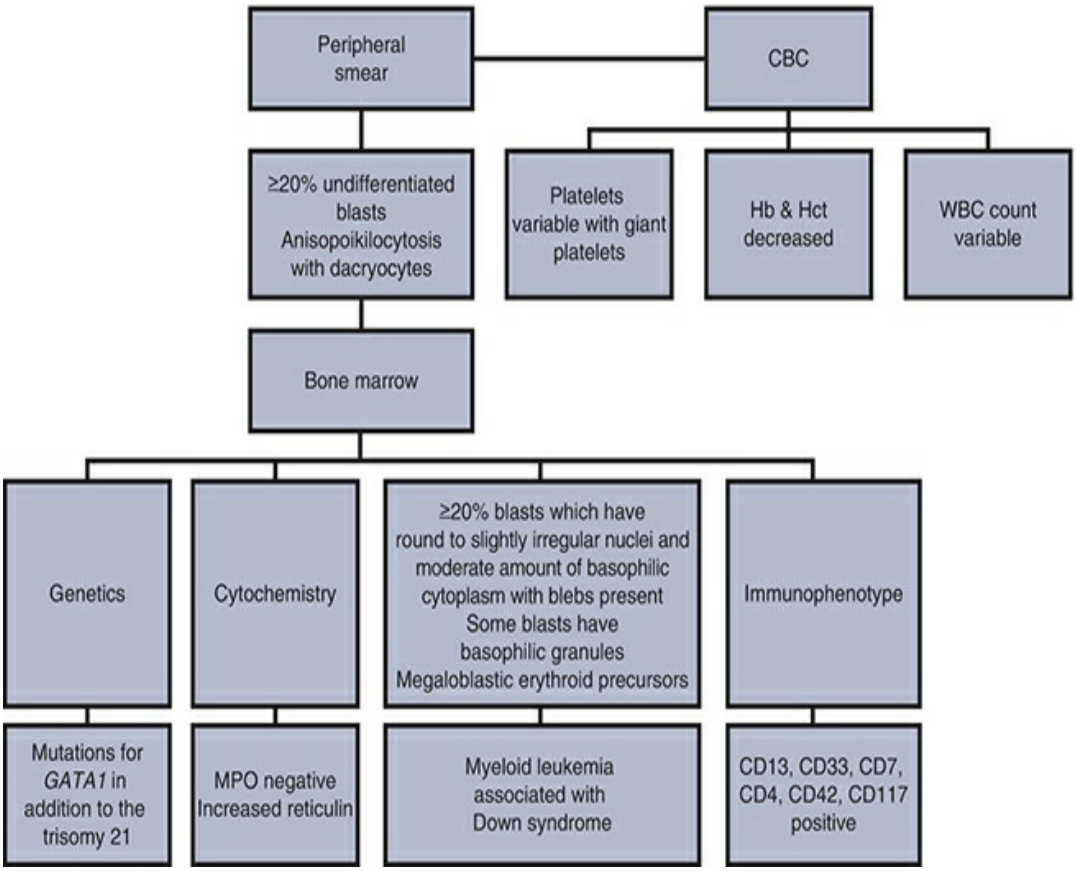
Immunophenotype

- Blasts are positive for CD117, CD13, CD33, CD7, CD4, CD42, TPO-R, IL-3R, CD36, CD41, CD61, and CD71
- Negative for CD15, CD14, and glycophorin A
- 50% are negative for CD34

Genetics

- Trisomy 21 and somatic mutations of the gene encoding GATA1
- 13–44% of cases have trisomy 8

Diagnostic Scheme



MYELOID SARCOMA

Criteria

- Tumor mass consisting of myeloid blasts with or without maturation
- Occurring at sites other than bone marrow

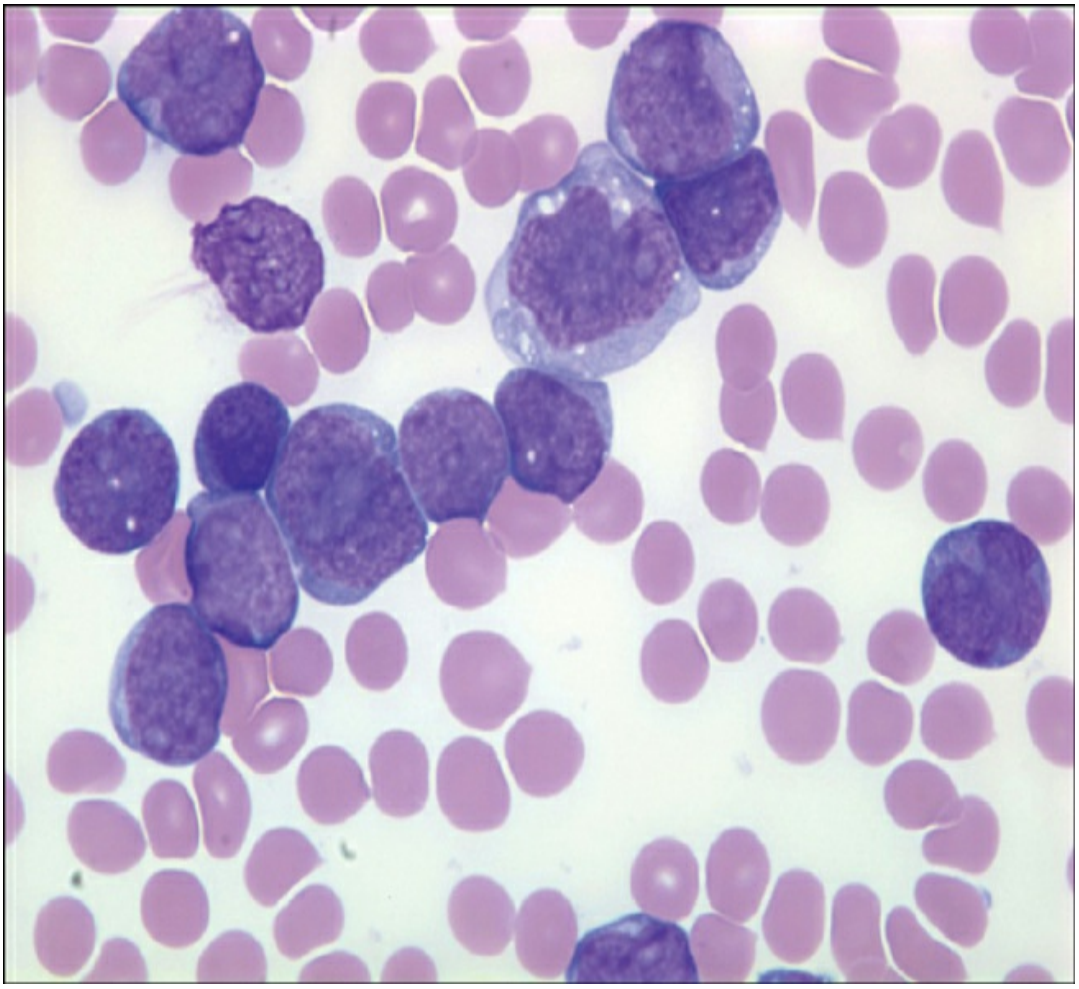


Figure IIB8-43

Peripheral blood smear.

Clinical Features

- Tumors that occur in any site in the body such as skin, lymph nodes, gastrointestinal tract, bone, soft tissue, and testes

Pathology

Pathology

- Most tumors occur as de novo neoplasms
- ¼ of cases occur in the absence of an underlying acute myeloid leukemia or other myeloid neoplasms
- 8–20% of cases have undergone allogeneic stem cell transplantation
- May be the initial manifestation of relapse in a patient with previously diagnosed acute myeloid leukemias
- Can be associated with simultaneous or previously treated non-Hodgkin lymphoma

Laboratory Features

White Blood Cells

- Normal to increased
- Blasts may be present

Red Blood Cells

- Normal to decreased

Platelets

- Normal to decreased

Bone Marrow

- Blasts may be present

Biopsy

- Consists of myeloblasts with or without maturation
- In some cases, it displays myelomonocytic or pure monoblastic morphology
- Rare tumors consist of erythroid precursors or megakaryoblasts but can be seen in blast transformation of myeloproliferative neoplasm

Cytochemistry

- Granulocytic lineage shows myeloperoxidase and naphthol AS-D chloroacetate esterase (CAE) positivity
- Monoblastic forms show nonspecific esterase positivity

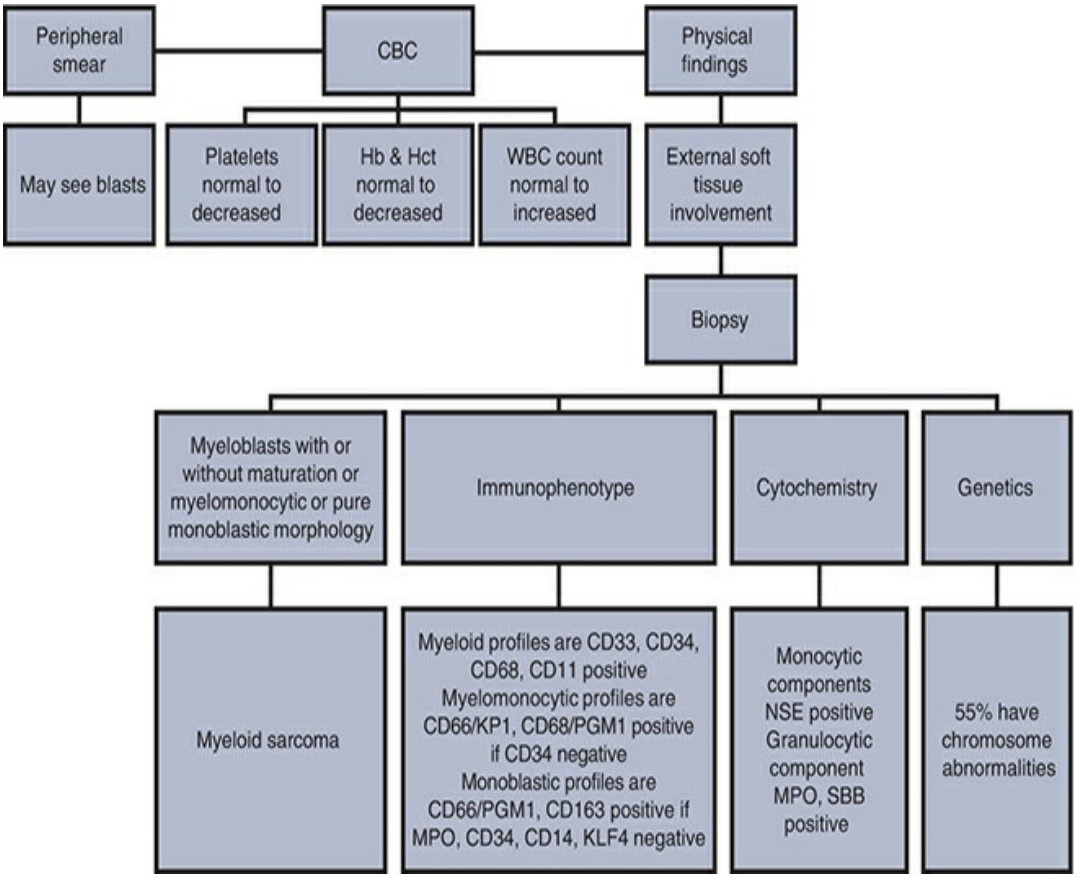
Immunophenotype

- Immature myeloid profiles express CD33, CD34, CD68, and CD11
- Myelomonocytic tumors are positive for CD66/KP1 with MPO and CD68/PGM1 in populations that are CD34 negative
- Monoblastic tumors are positive for CD66/PGM1 and CD163 and lack MPO and CD34, CD14, and KLF4

Genetics

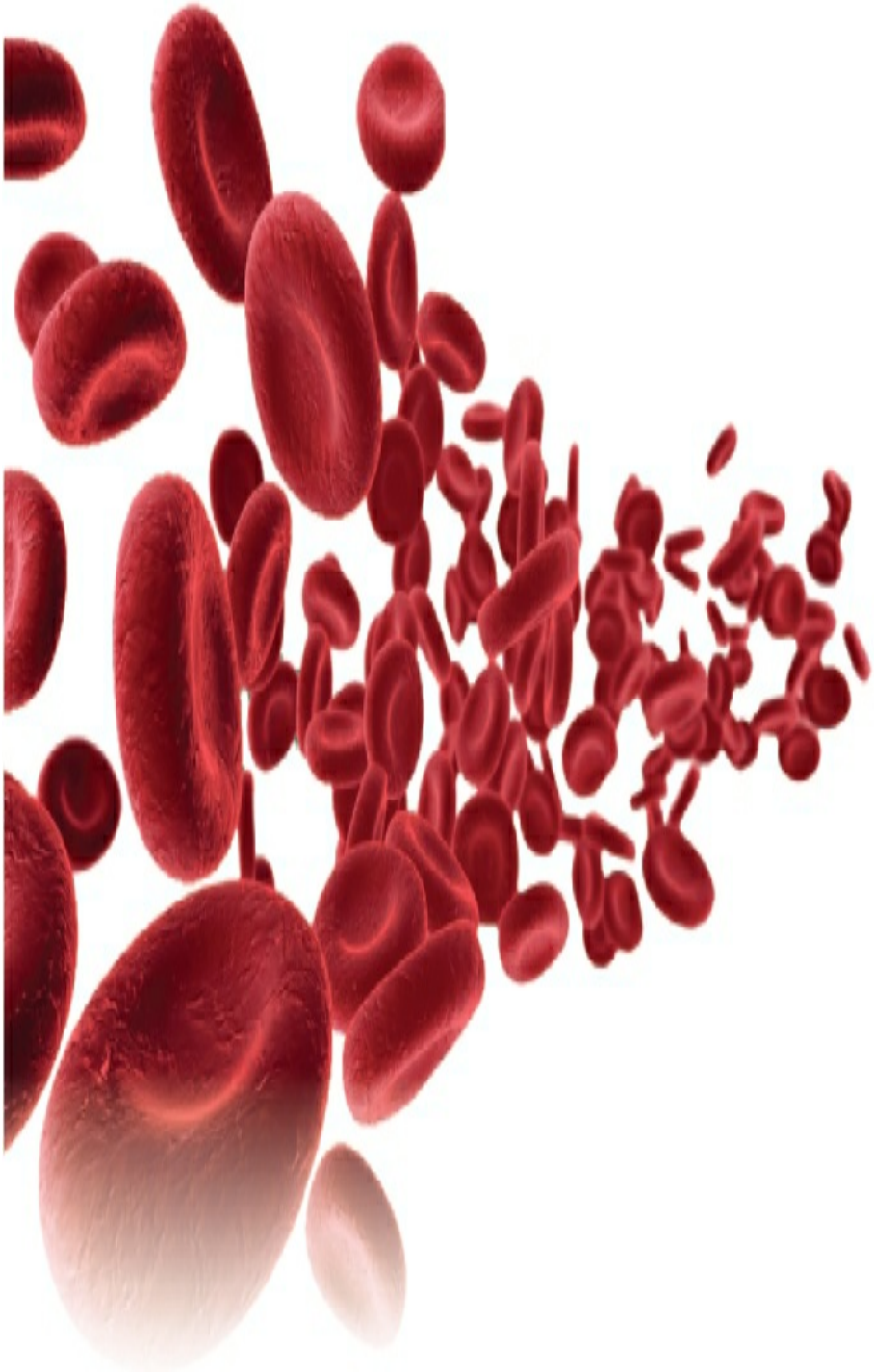
- 55% of cases have chromosome aberrations
- Monosomy 7; trisomy 8; KMT2A rearrangement; inv(16); trisomy 4; monosomy 16; loss of 16q, 5q, or 20q; and trisomy 11
- 16% of cases carry NPM1 mutations

Diagnostic Scheme


Peripheral smear
CBC
Physical findings
May see blasts
Platelets normal to decreased
Hb & Hct normal to decreased
WBC count normal to increased
External soft tissue involvement
Biopsy
Myeloblasts with or without maturation or myelomonocytic or pure monoblastic morphology
Immunophenotype
Cytochemistry
Genetics
Myeloid sarcoma
Myeloid profiles are CD33, CD34, CD68, CD11 positive
Myelomonocytic profiles are CD66/KP1, CD68/PGM1 positive if CD34 negative
Monoblastic profiles are CD66/PGM1, CD163 positive if MPO, CD34, CD14, KLF4 negative
Monocytic components NSE positive
Granulocytic component MPO, SBB positive
55% have chromosome abnormalities

CHAPTER 9

Precursor Lymphoid Neoplasms



PRECURSOR LYMPHOID NEOPLASMS

Criteria

- ≥20% or ≥ 25% (WHO) bone marrow blast countMorphology and immunophenotype are sufficient for the diagnosis of most lymphoid neoplasms
- No one antigenic marker is specific for any neoplasm, and a combination of morphologic features and a panel of antigenic markers are necessary for correct diagnosis
- Most B-cell lymphomas have characteristic immunophenotypic profiles that are very helpful in diagnosis
- Immunophenotypic profiling is somewhat less helpful in the subclassification of T-cell lymphomas
- Genetic features are playing an increasingly important role in the classification of lymphoid malignancies. They are valuable tools to determine the clonality in B-cell and T-cell proliferations.
- Precursor lymphoid neoplasms are primarily diseases of children
- Infectious agents have been shown to contribute to the development of several types of mature B-cell, T-cell, and NK-cell lymphomas

B-LYMPHOBLASTIC LEUKEMIA/LYMPHOMA, NOT OTHERWISE SPECIFIED (NOS)

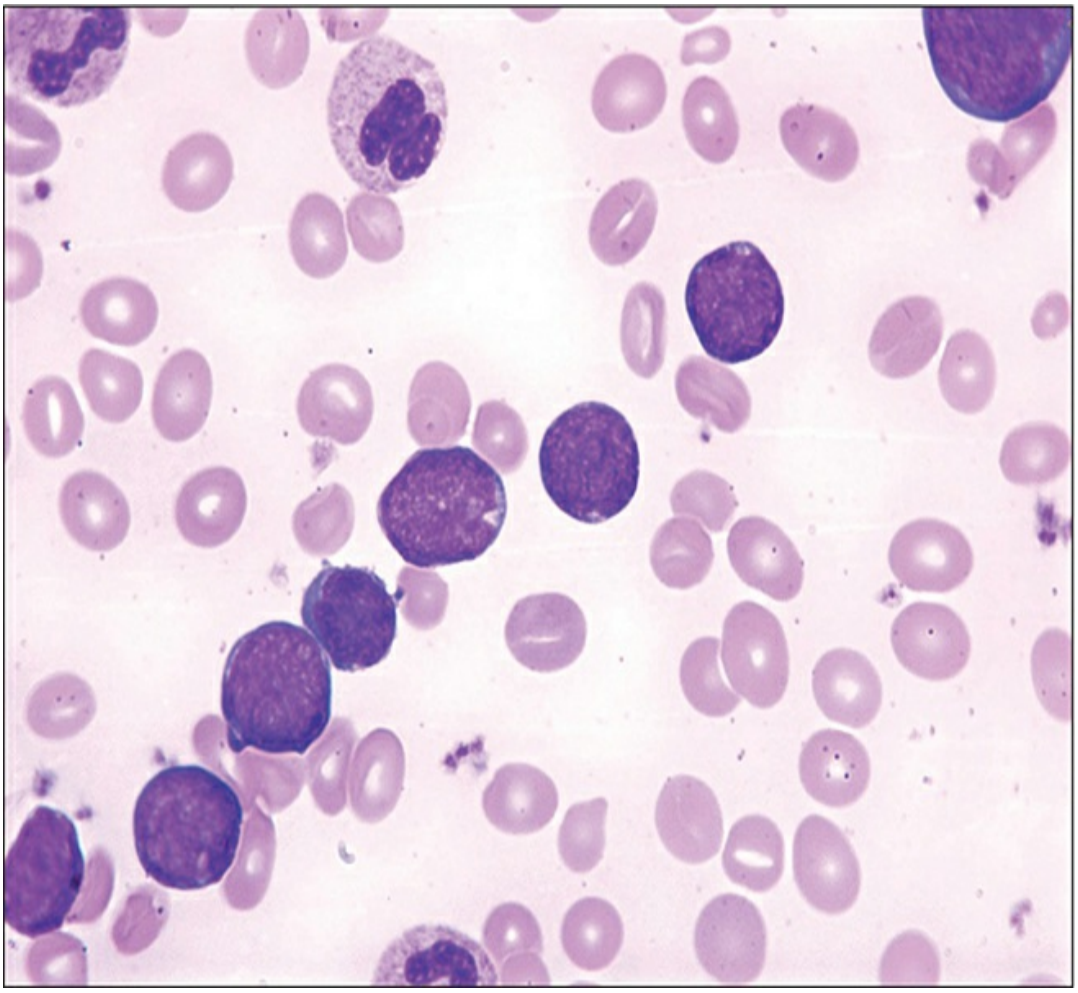


Figure IIB9-1

Peripheral blood smear.

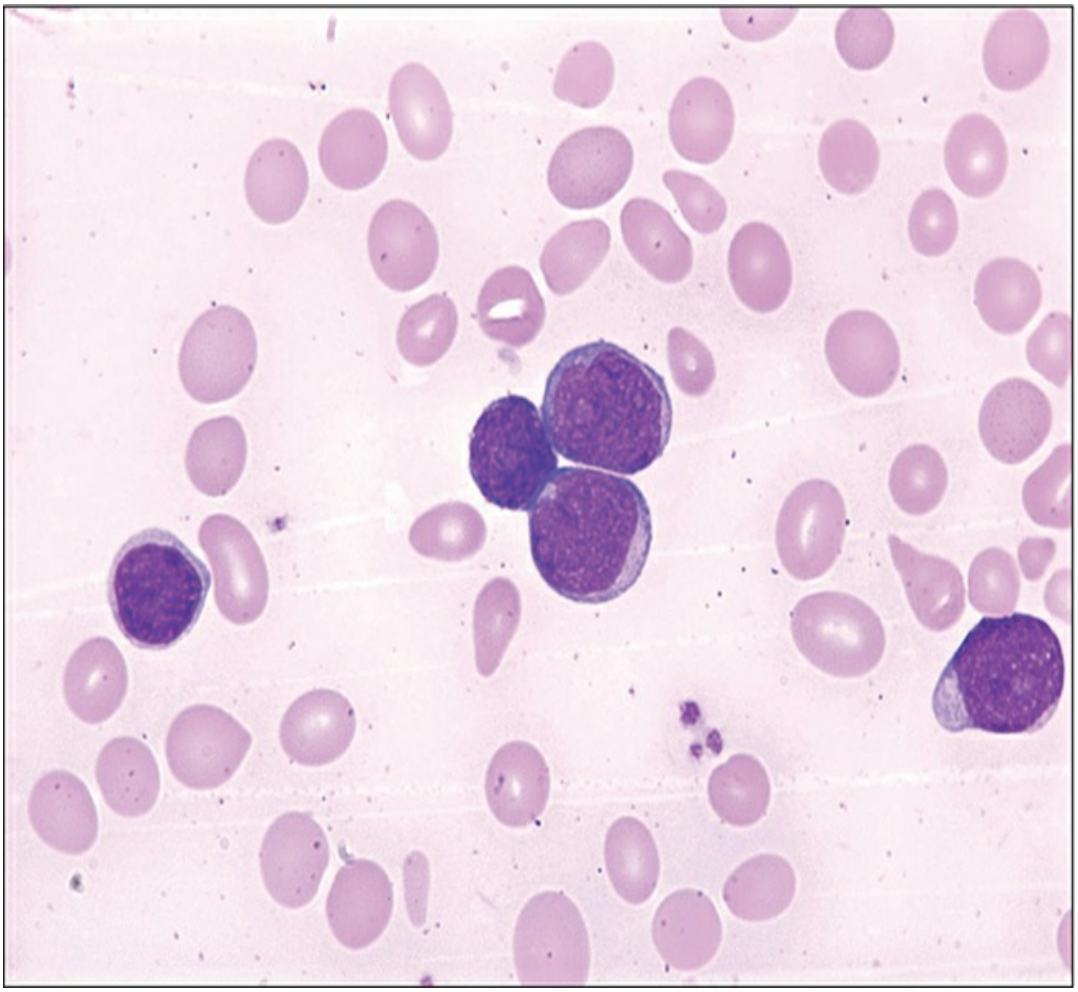


Figure IIB9-2

Peripheral blood smear.

Clinical Features

- Patients usually present with anemia, thrombocytopenia, and/or infections
- Lymphadenopathy, hepatomegaly, and splenomegaly are common
- Bone pain is a prominent feature

Pathology

- Acute lymphoblastic leukemia is primarily a disease of children under 6 years of age but also can occur at any age

- 80–85% are B-cell precursor types
- B-lymphoblastic leukemia/lymphoma accounts for about 10% of lymphoblastic lymphomas, and the rest are of T lineage

Laboratory Features

White Blood Cells

- May be decreased, normal, or increased

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Small to medium-sized blasts with scanty cytoplasm to larger blasts with a lower N/C ratio and irregular nuclear outline
- Nuclei are moderately condensed to dispersed and nucleoli are inconspicuous

Cytochemistry

- Myeloperoxidase negative
- Periodic acid–Schiff and TdT positive

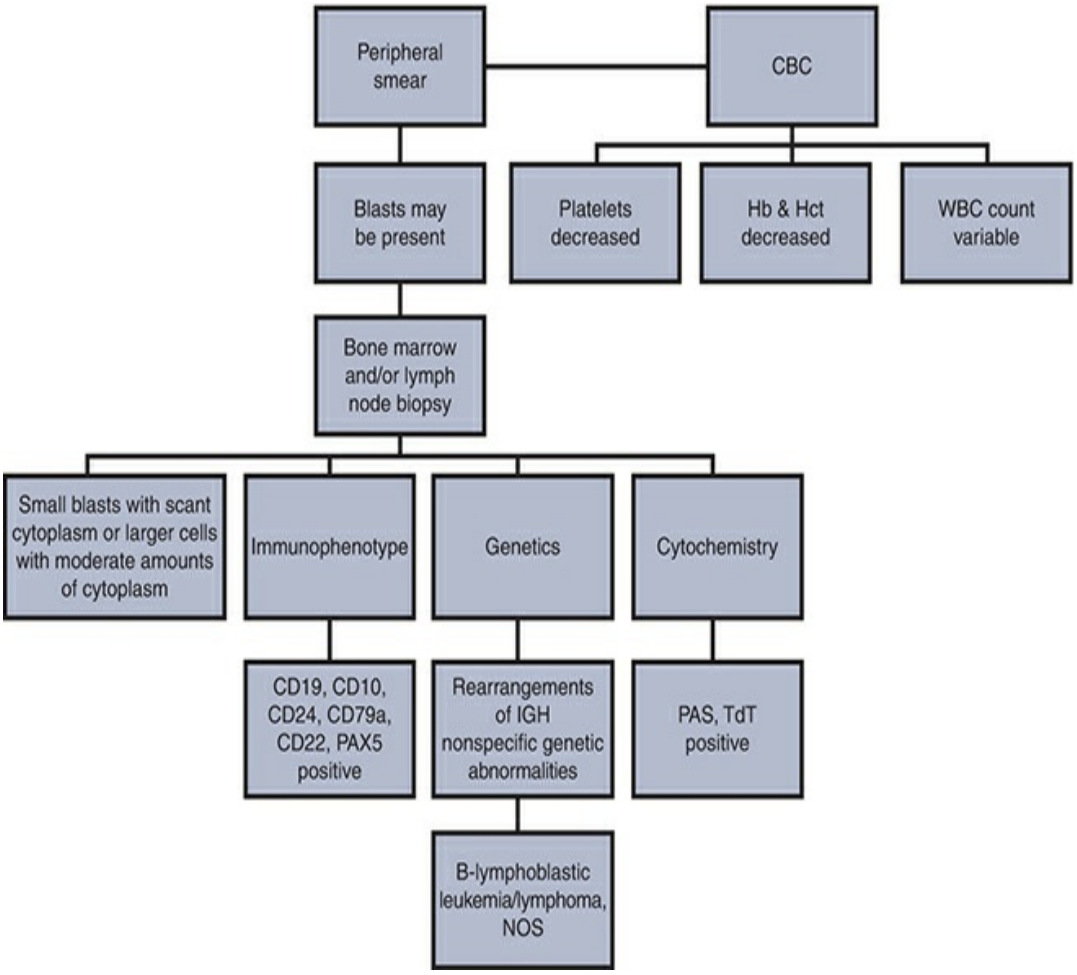
Immunophenotype

- Positive for CD19, CD10, CD24, CD79a, CD22, PAX5, and nuclear TdT

Genetics

- Most cases have a rearrangement of IGH
- Nonspecific genetic abnormalities

Diagnostic Scheme


Peripheral smear
CBC
Blasts may be present
Platelets decreased
Hb & Hct decreased
WBC count variable
Bone marrow and/or lymph node biopsy
Small blasts with scant cytoplasm or larger cells with moderate amounts of cytoplasm
Immunophenotype
Genetics
Cytochemistry
CD19, CD10, CD24, CD79a, CD22, PAX5 positive
Rearrangements of IGH nonspecific genetic abnormalities
PAS, TdT positive
B-lymphoblastic leukemia/lymphoma, NOS

B-LYMPHOBLASTIC LEUKEMIA/LYMPHOMA, WITH RECURRENT GENETIC ABNORMALITIES

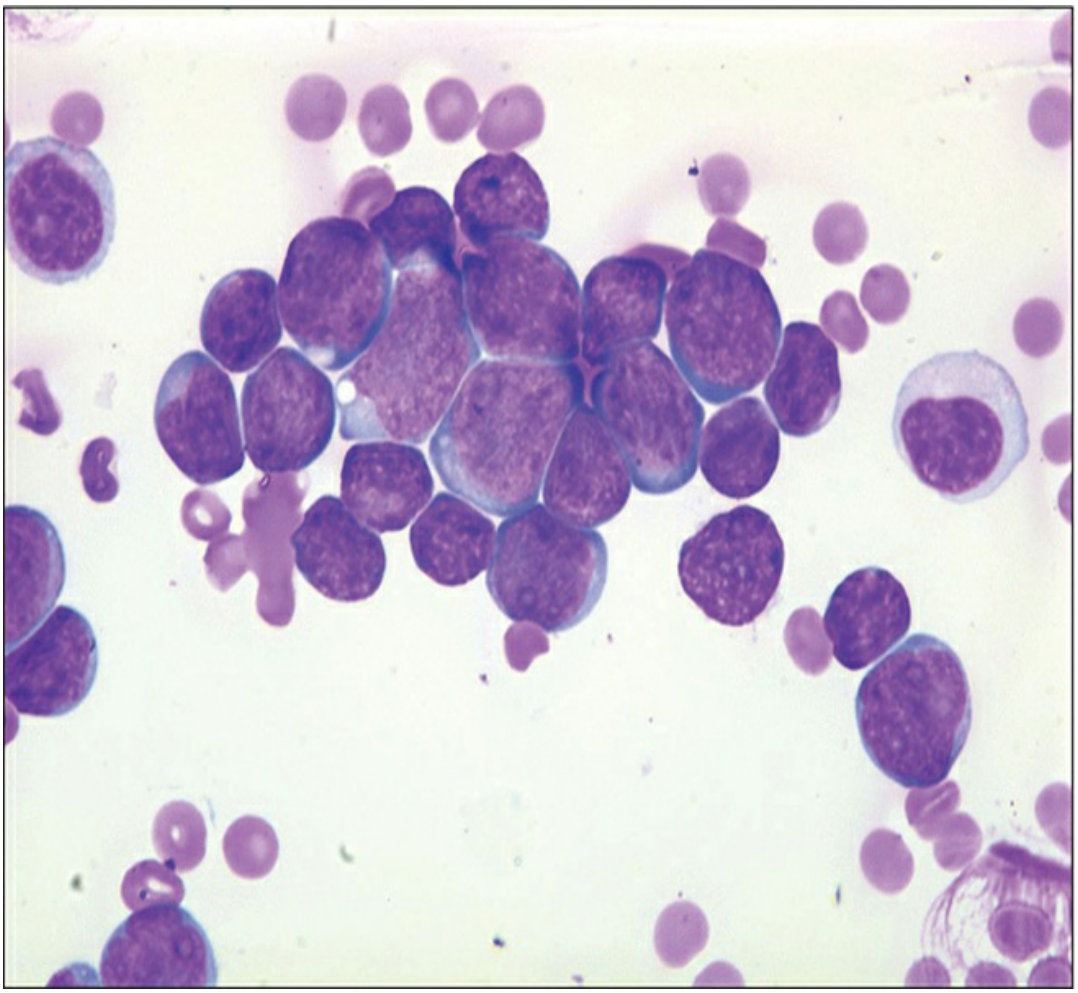


Figure IIB9-3

Bone marrow smear.

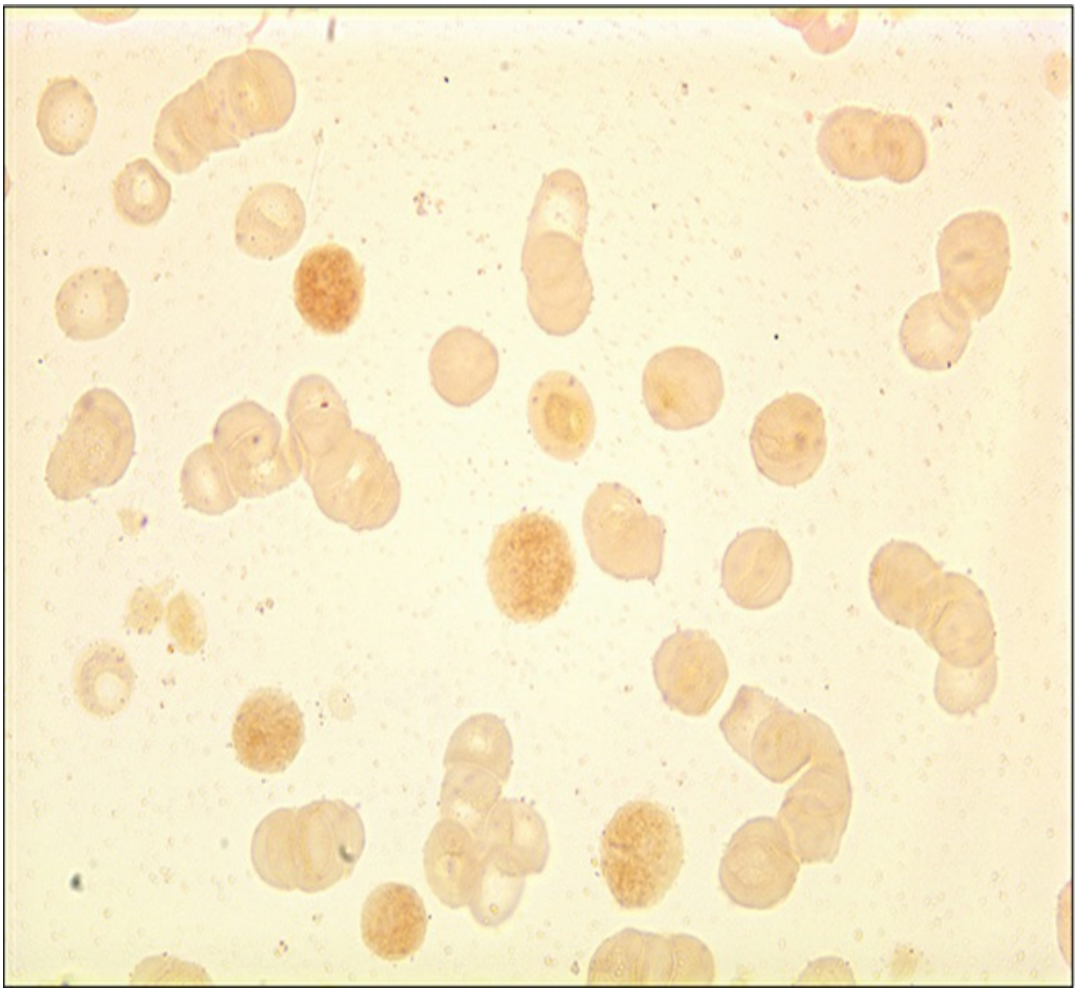


Figure **IIB9-4**

TdT stain. Positive.

Clinical Features

- Patients usually present with features similar to those with other B-ALLs
- Cases with BCR-ABL1 are at high risk
- BCR-ABL1 patients may have organ involvement
- CNS involvement is found in KMT2A rearrangement patients

Pathology

- B-ALL with BCR-ABL1 cases have the worse prognosis
- B-ALL with KMT2A rearrangements is the most

common leukemia in infants (< 1 year old)
- KMTSA-AFF translocations have a poor prognosis
- Translocations of ETV6-RUNX1 are common in children but not seen in infants but have a favorable prognosis
- > 25% of all B-ALL cases are hyperdiploid
- Hypodiploid B-ALL cases have a poor prognosis

Laboratory Features

White Blood Cells

- May be decreased, normal, or increased
- KMT2A rearrangement patients have very high white counts of >100 x 10^9/L
- Translocation between IL3 and IGH genes result in variable eosinophilia and blasts may be absent in peripheral blood

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Small to medium sized blasts with scanty cytoplasm to larger blasts with a lower N/C ratio and irregular nuclear outline
- Nuclei are moderately condensed to dispersed and nucleoli are inconspicuous

Cytochemistry

- Myeloperoxidase negative
- Periodic acid-Schiff and TdT positive

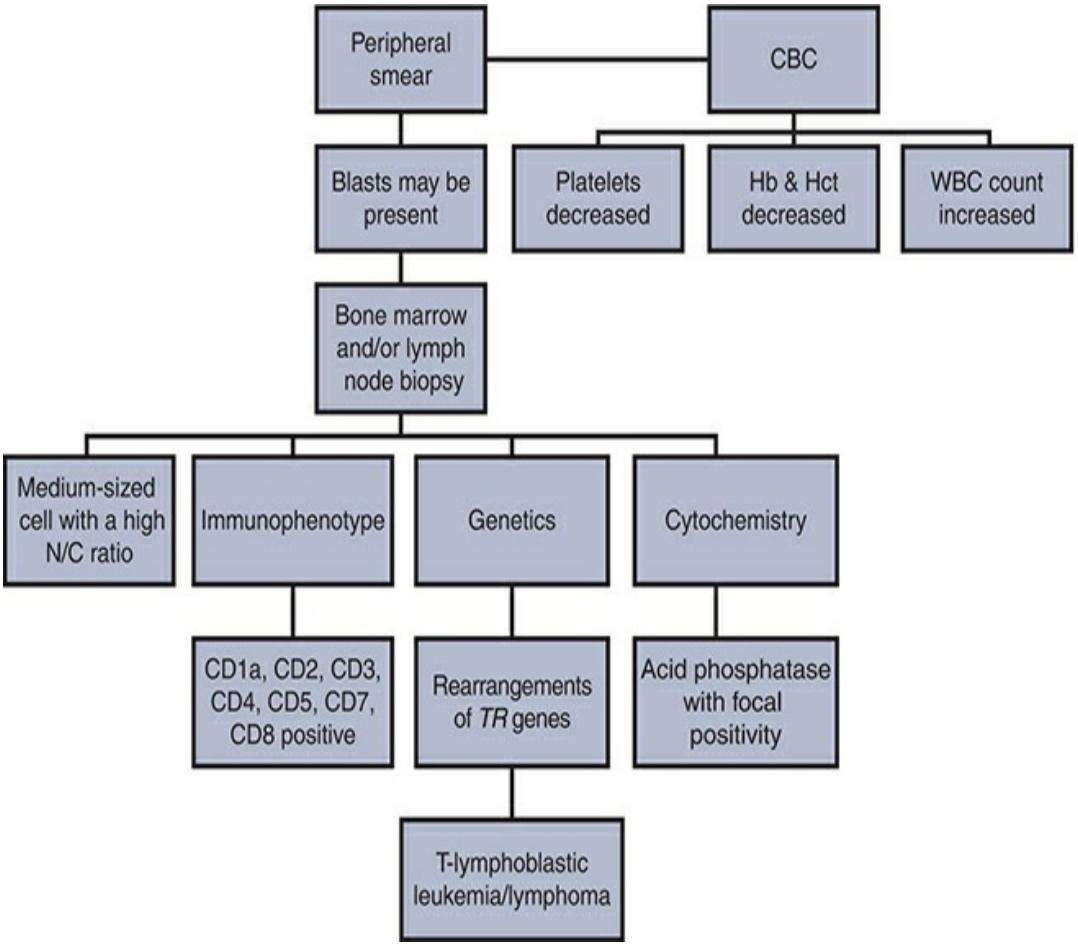
Immunophenotype

- B-ALL with BCR-ABL1 is positive for CD 10, CD19, CD15 and TdT
- KMT2A rearrangements, especially t(4;11) are CD19 positive but CD10 and CD24 are negative
- ETV6-RUNX1 translocations have CD19, CD10, and CD34 and CD9, CD20 and CD66c are negative

Genetics

- Cytogenetic abnormalities are seen in most cases and define specific entities with unique phenotypic and prognostic features
- t(9;22)(q34.1;q11.2); BCR-ABL1
- t(v;11q23.3); KMT2A -rearranged
- t(12;21)(p13.2;q22.1); ETV6-RUNX1
- Hyperdiploidy
- Hypodiploidy
- t(5;14)(q31.1;q32.1); IGH/IL3
- t(1;19)(q23;p13.3); TCF3-PBX1
- BCR-ABL1 -like
- iAMP21

Diagnostic Scheme


Peripheral smear
CBC
Blasts may be present
Platelets decreased
Hb & Hct decreased
WBC count increased
Bone marrow and/or lymph node biopsy
Medium-sized cell with a high N/C ratio
Immunophenotype
Genetics
Cytochemistry
CD1a, CD2, CD3, CD4, CD5, CD7, CD8 positive
Rearrangements of TR genes
Acid phosphatase with focal positivity
T-lymphoblastic leukemia/lymphoma

T-LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

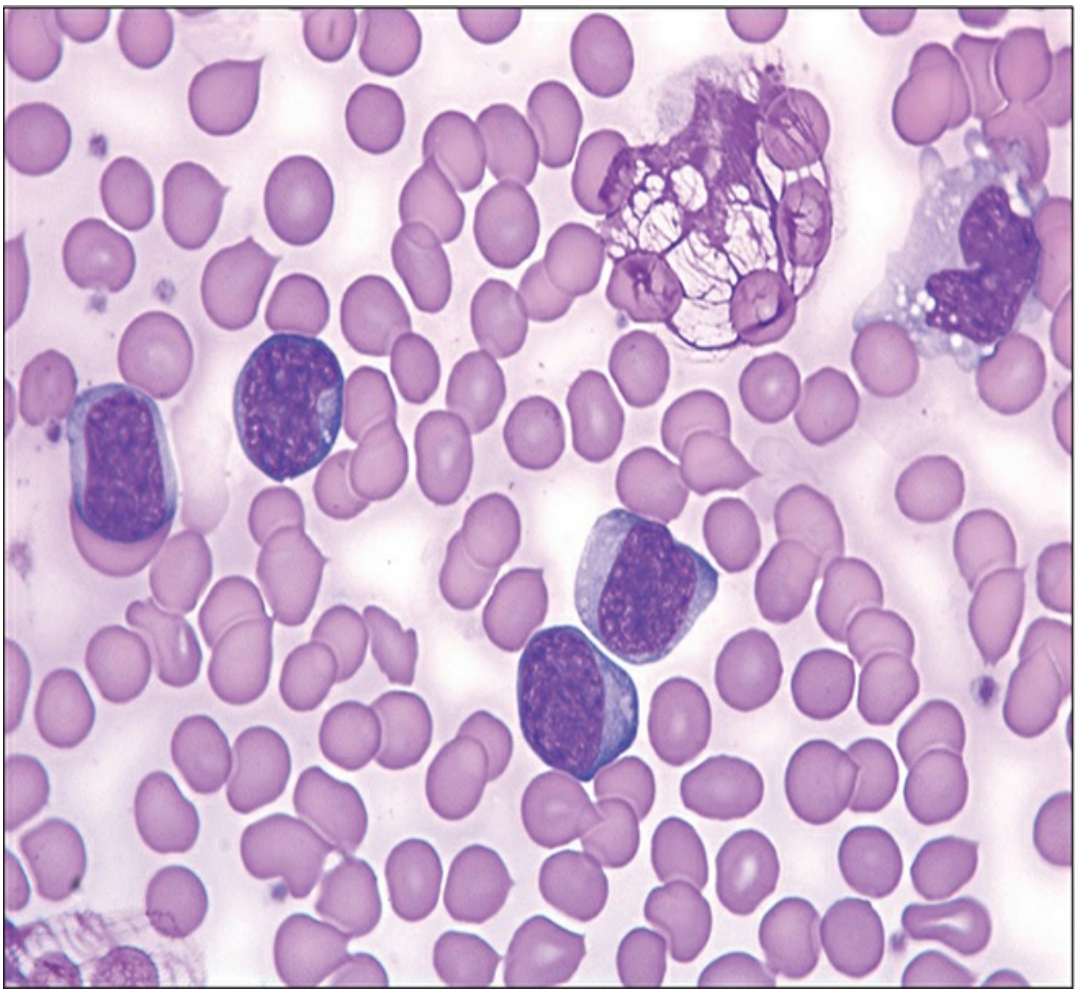


Figure IIB9-5

Peripheral blood smear.

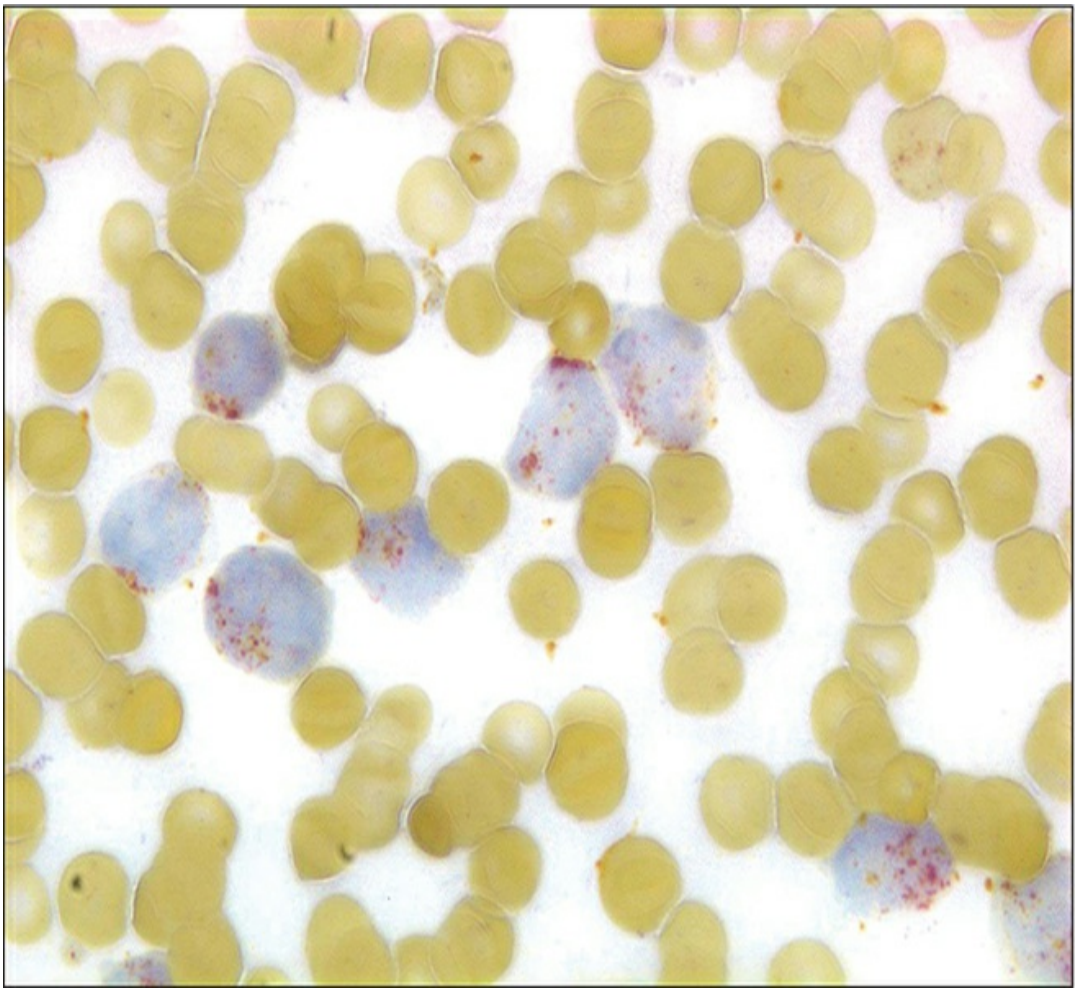


Figure **IIB9-6**

Acid phosphatase stain. Positive.

Clinical Features

- Presents with high white count and may have mediastinal mass
- Skin, tonsils, liver, spleen, central nervous system, and testes may be involved

Pathology

- Neoplasm of lymphoblasts committed to the T-cell lineage
- Makes up about 15% of childhood acute lymphoblastic leukemia

- Is more common in adolescents than younger children

Laboratory Features

White Blood Cells

- Usually high count

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Medium-sized blast cells with a high N/C ratio, a scant cytoplasm, and usually an irregular nuclear outline
- Chromatin in the nucleus is condensed to dispersed and nucleoli are inconspicuous
- Lymphoblasts are indistinguishable from those of the B-lymphoblastic leukemia/lymphoma type
- The number of mitotic figures is higher than in B-lymphoblastic leukemia/lymphoma

Cytochemistry

- Show focal acid phosphatase positivity

Immunophenotype

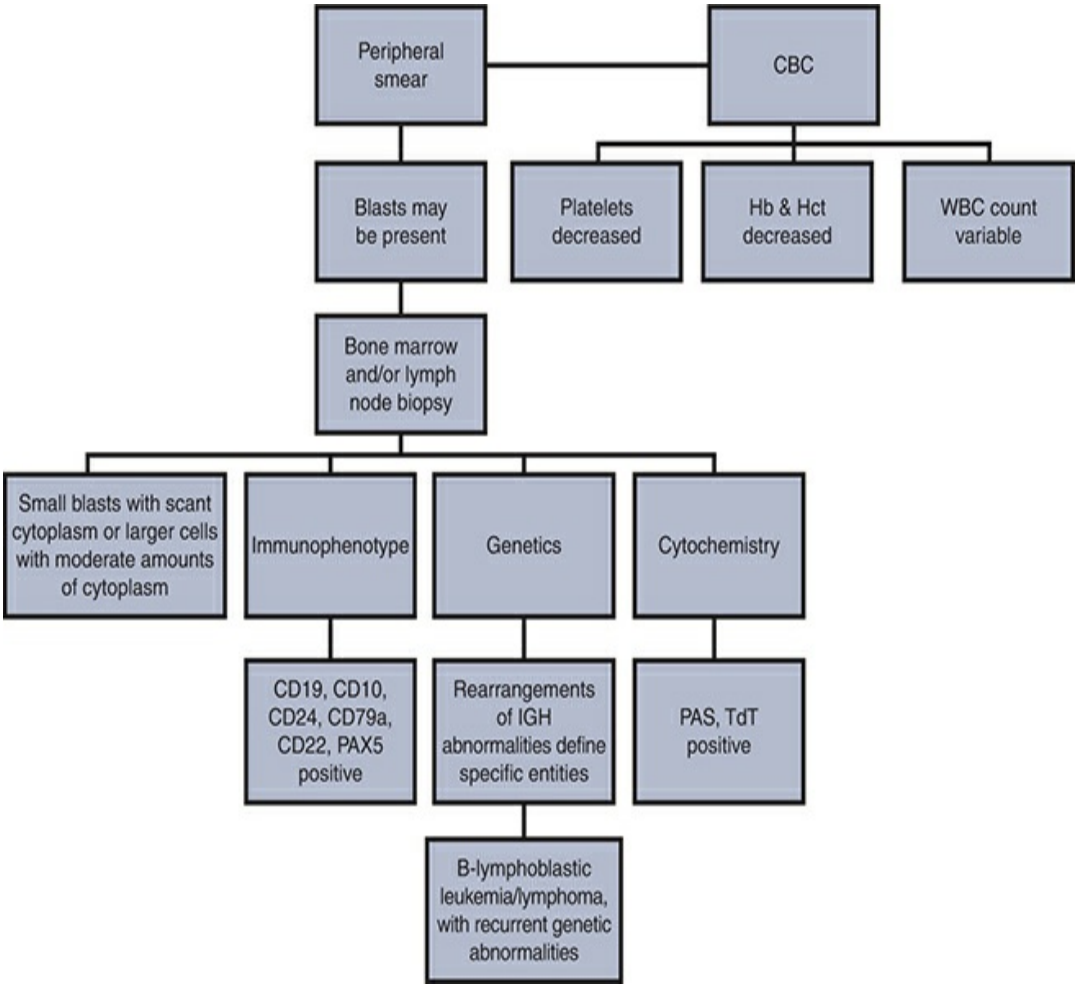
- Usually TdT positive and may express CD1a, CD2, CD3, CD4, CD5, CD7, and CD8
- CD7 and cCD3 are expressed the strongest

Genetics

- Most cases show rearrangements of the TR gene
- About 20% of cases also show the presence of IGH gene rearrangements

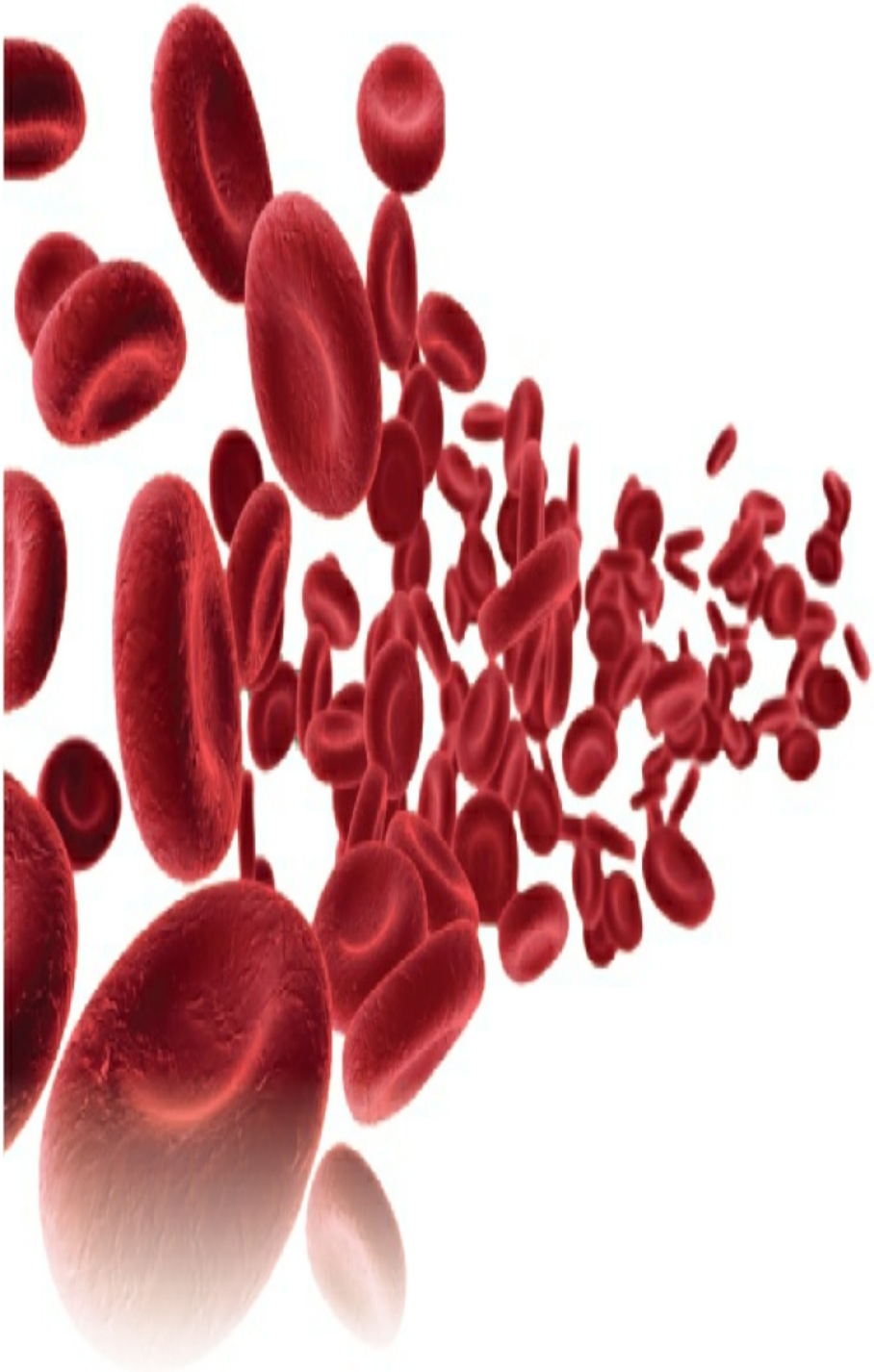
- 50–70% of cases have an abnormal karyotype involving the alpha and delta TR loci at 14q11.2, the beta locus at 7q35, and the gamma locus at 7p14-15

Diagnostic Scheme



CHAPTER 10

Mature B-cell Neoplasms



MATURE B-CELL NEOPLASMS

Criteria

- Clonal mature lymphoid lineage neoplasm derived from B cells or plasma cells
- Immunohistochemistry and/or flow cytometry determines lineage, maturity, and immunophenotypic profiles
- Many of the B-cell leukemias have distinctive immunophenotypic profiles

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

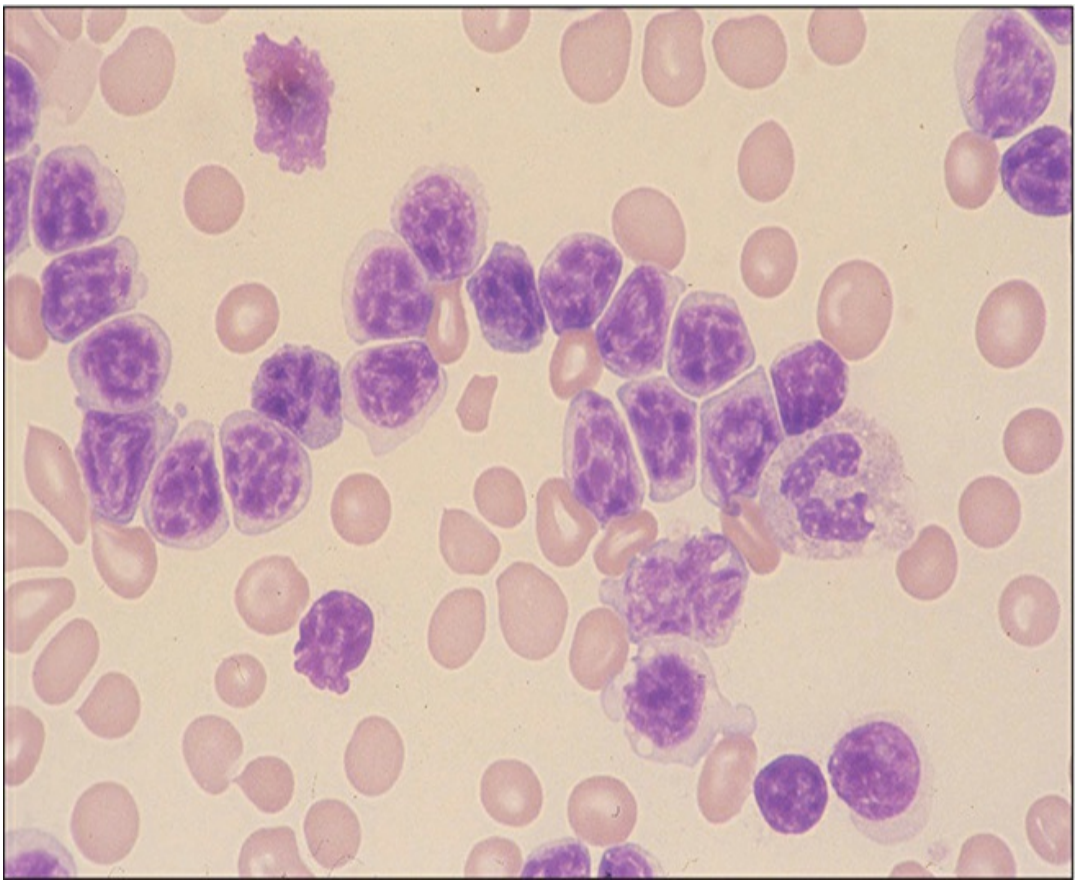


Figure IIB10-1

Peripheral blood smear.

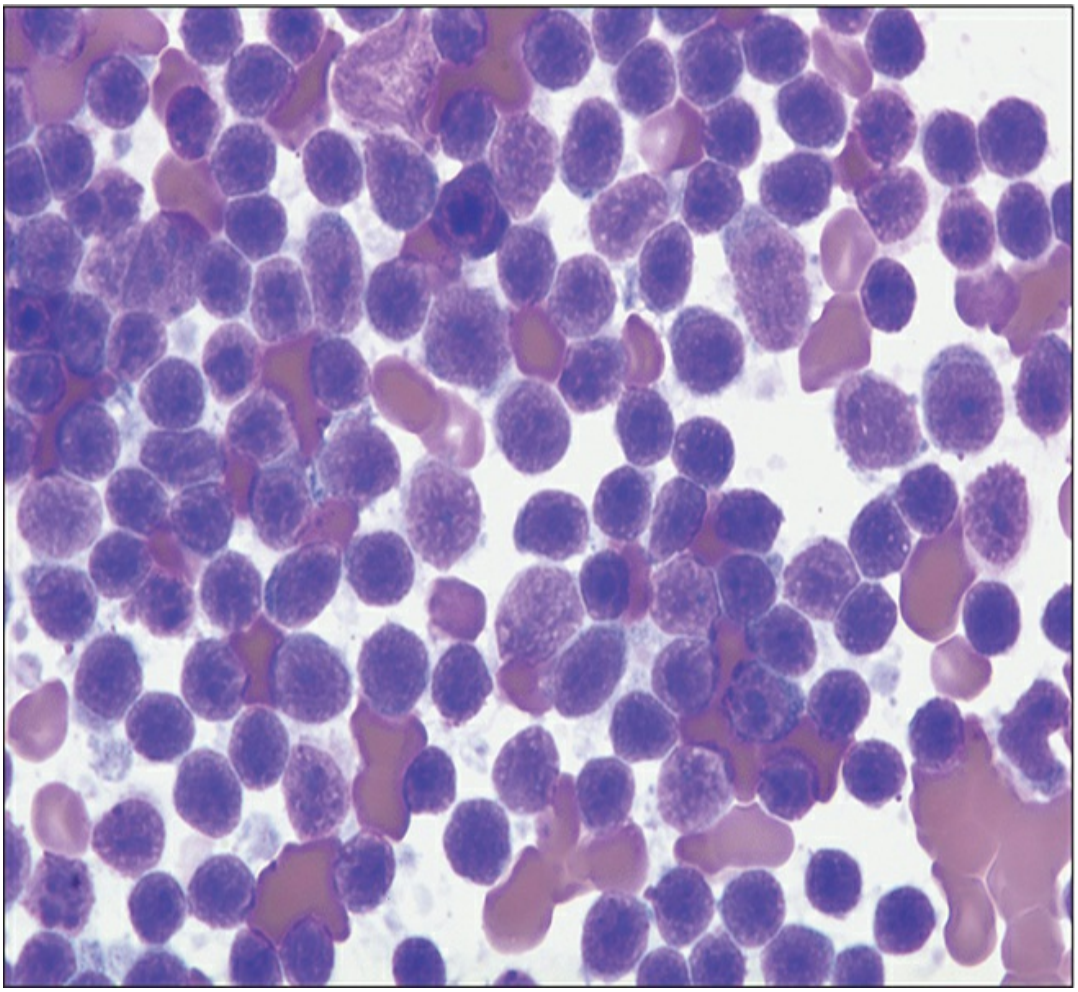


Figure **IIB10-2**

Bone marrow smear.

Clinical Features

- Occurs most frequently in persons older than 50 years with a median age of 70 years
- Most common leukemia in Western countries
- Enlargement of superficial lymph nodes is common
- With disease progression, hepatosplenomegaly develops
- Infections are frequent
- May develop a secondary warm autoimmune hemolytic anemia
- >80% of patients are initially asymptomatic

Pathology

- Proliferation and accumulation of B lymphocytes due to prolonged cell survival
- Monoclonal B-cell population with low-density surface immunoglobulin
- Approximately 3.5% of chronic lymphocytic leukemia cases transform into a more aggressive stage of high-grade large-cell lymphoma cells
- Deletions in microRNA genes, which normally function as tumor suppressor genes
- Defects in B-cell receptor, which plays a role in oncogenesis

Laboratory Features

White Blood Cells

- White blood cell count is increased to 20–200 × 10^9/L
- Absolute lymphocytosis
- Typical, small lymphocytes, with a hypermature-appearing nucleus
- Smudge cells present
- <10% prolymphocytes

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Normal
- Often decreased with disease progression

Bone Marrow

- >30% lymphocytes
- ≤10% prolymphocytes

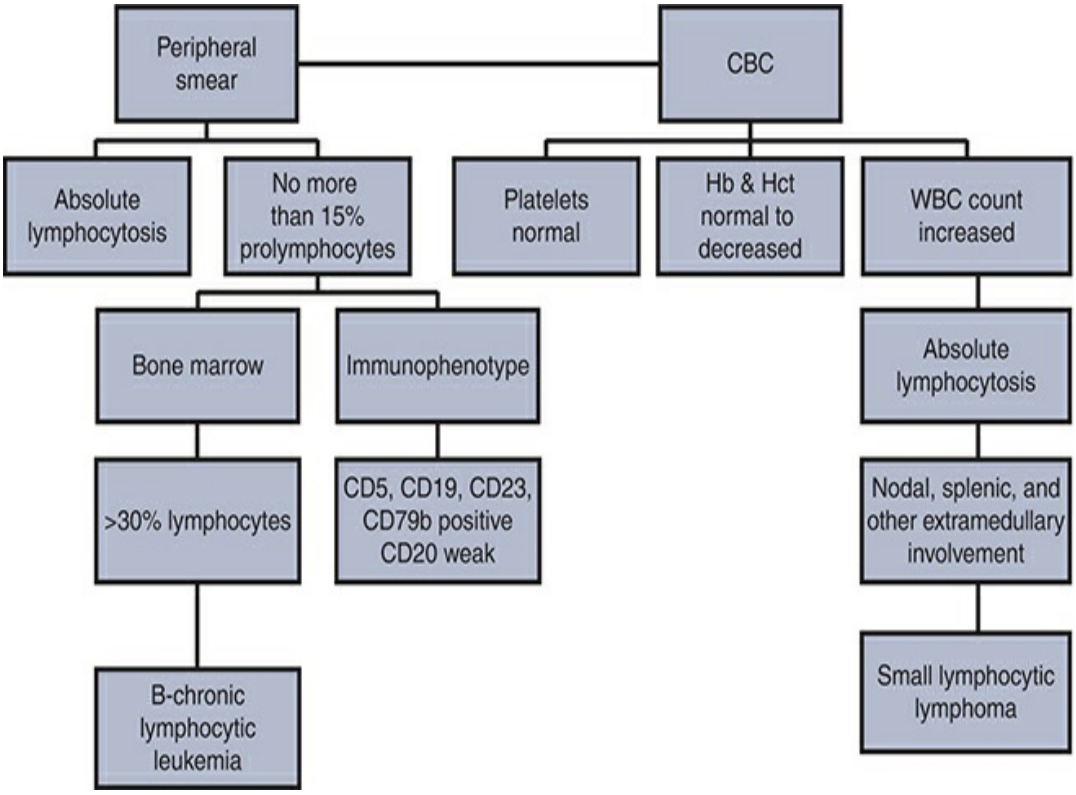
Immunophenotype

- CD5, CD19, CD23, and CD79b positive
- CD20 and sIg weak

Genetics

- 13q14.3 deletion, which is the most common chromosomal abnormality
- Most common mutated genes are NOTCH1 , SF3B1 , TP53 , ATM , BIRC3 , POT1 , and MYD88

Diagnostic Scheme



B-CELL PROLYMPHOCYTIC LEUKEMIA

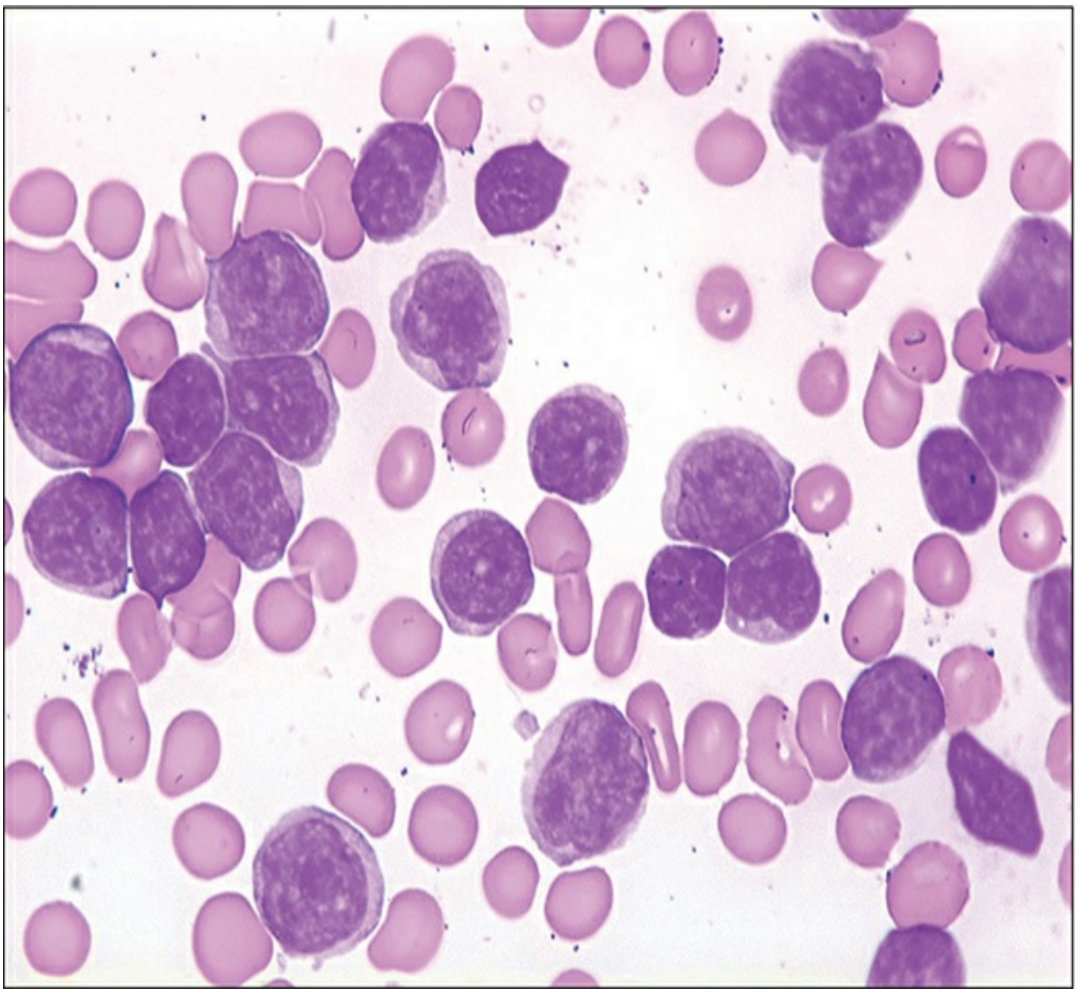


Figure IIB10-3

Peripheral blood smear.

Clinical Features

- Systemic symptoms such as weakness, fatigue, weight loss, fever, and possibly abdominal pain are seen
- Absent or minimal lymphadenopathy
- Massive splenomegaly, hepatomegaly, and bone marrow infiltration

Pathology

- Neoplasm of B-cell prolymphocytes

- Median age of occurrence is 65–69 years of age
- Rare, only accounts for 1% of lymphocytic leukemias

Laboratory Features

White Blood Cells

- Typically >100 × 10^9/L
- >55% prolymphocytes and usually >90% (WHO)
- Medium-sized cells that contain a large, vesicular nucleolus and condensed nuclear chromatin and have lower N/C ratio

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Decreased

Bone Marrow

- Same types of prolymphocytes seen in the peripheral blood

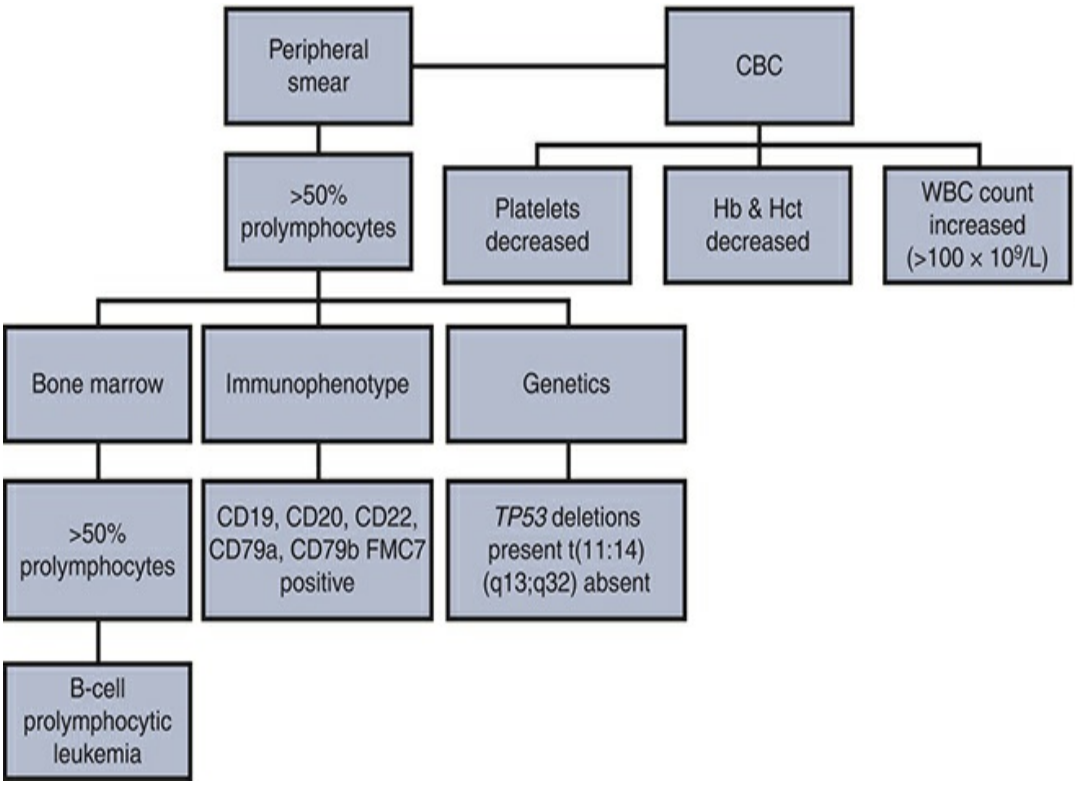
Immunophenotype

- CD19, CD20, CD22, CD79a, CD79b, FMC7, and sIg positive
- CD5 and CD23 positive in less than one-third of cases

Genetics

- Exhibit heavy- and light-chain Ig gene rearrangements
- Cells express much more sIg than do chronic lymphocytic leukemia cells
- MYC abnormalities are common
- May see TP53 deletions
- Must lack t(11;14)(q13;q32), which is found in mantle cell lymphoma

Diagnostic Scheme



HAIRY CELL LEUKEMIA

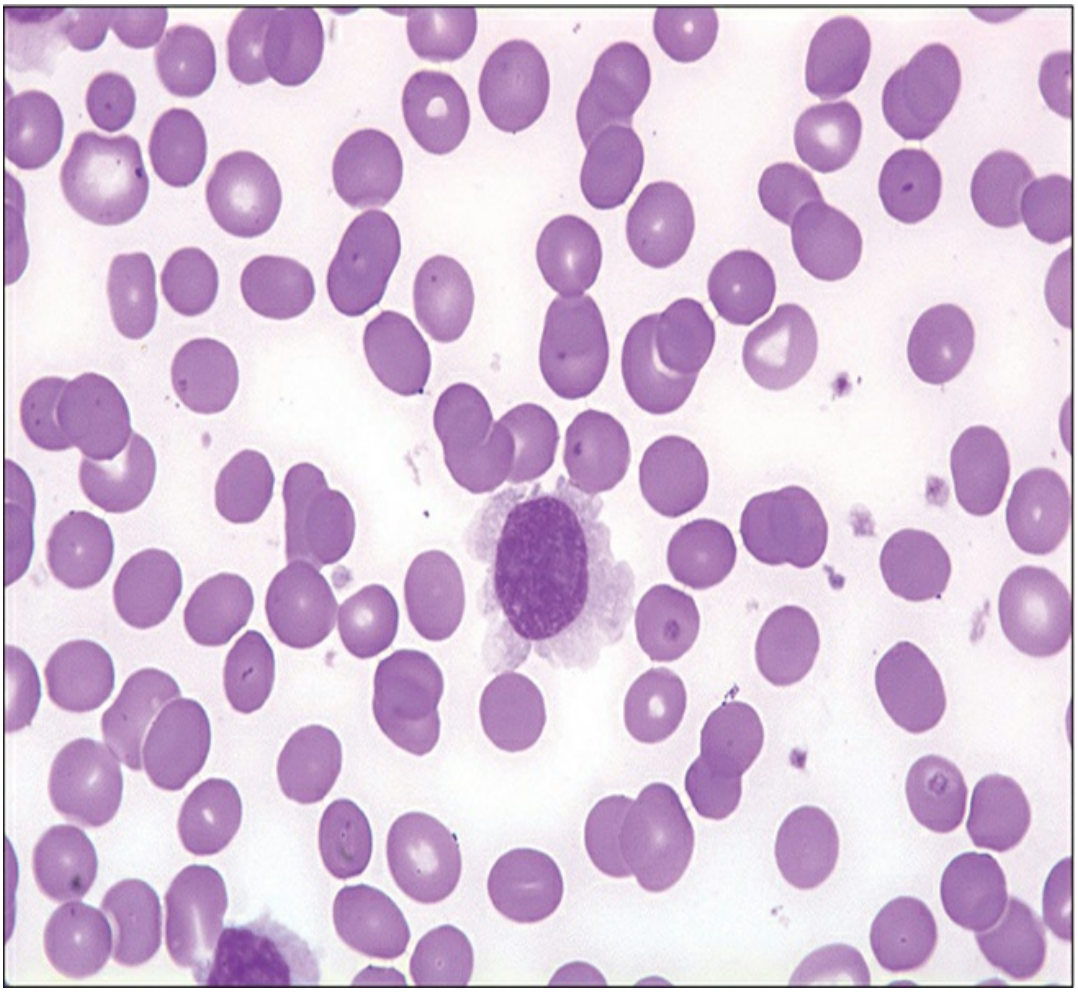


Figure IIB10-4

Peripheral blood smear.

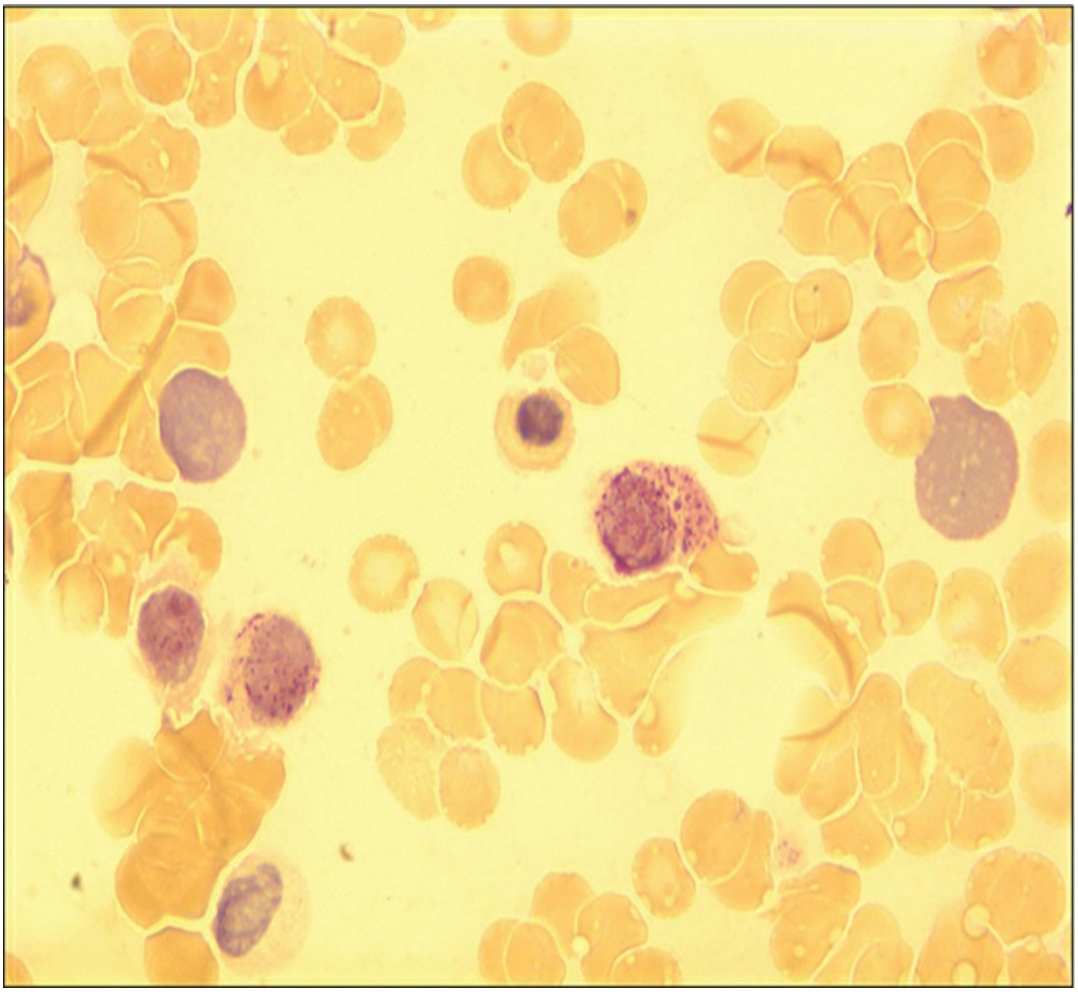


Figure **IIB10-5**

TRAP stain. Positive.

Clinical Features

- Weakness and fatigue
- Easy bruising and bleeding tendency
- Recurrent infections
- Splenomegaly common (left upper quadrant pain)

Pathology

- Neoplasm of small mature lymphoid cells characterized by distinctive cytoplasmic (hairy) projections
- Rare disease accounting for 2% lymphoid leukemias
- Male predominance (4:1)

- Median age of onset is about 58 years
- BRAF V600E mutation

Laboratory Features

White Blood Cells

- Usually decreased
- Presence of hairy cells
- Monocytopenia
- Neutropenia

Red Blood Cells

- Moderate normocytic/normochromic anemia

Platelets

- Thrombocytosis in 80% of patients

Bone Marrow

- Cannot be aspirated in more than half of the cases because of reticulin fibers
- Small to medium-sized lymphoid cells with oval or bean-shaped nucleus
- The pale blue cytoplasm is abundant and has “hairy” projections

Cytochemistry

- Tartrate-resistant acid phosphatase positive
- Specific esterase (naphthol AS-D chloroacetate esterase) and myeloperoxidase reactions are negative

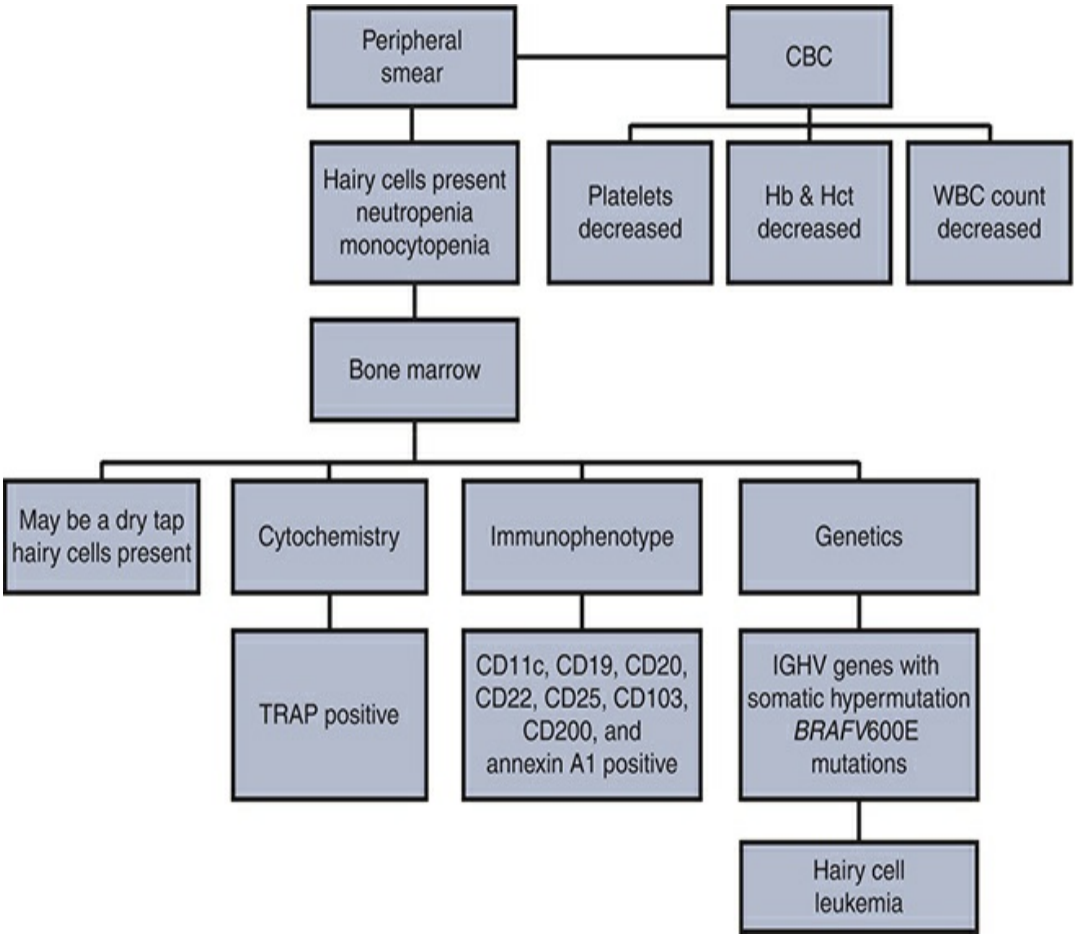
Immunophenotype

- CD103, CD20, CD19, CD22, CD11c, CD25, CD200, and annexin A1 positive

Genetics

- About 85% of cases demonstrate IGHV genes with somatic hypermutation
- BRAF V600E mutations

Diagnostic Scheme



PLASMA CELL MYELOMA

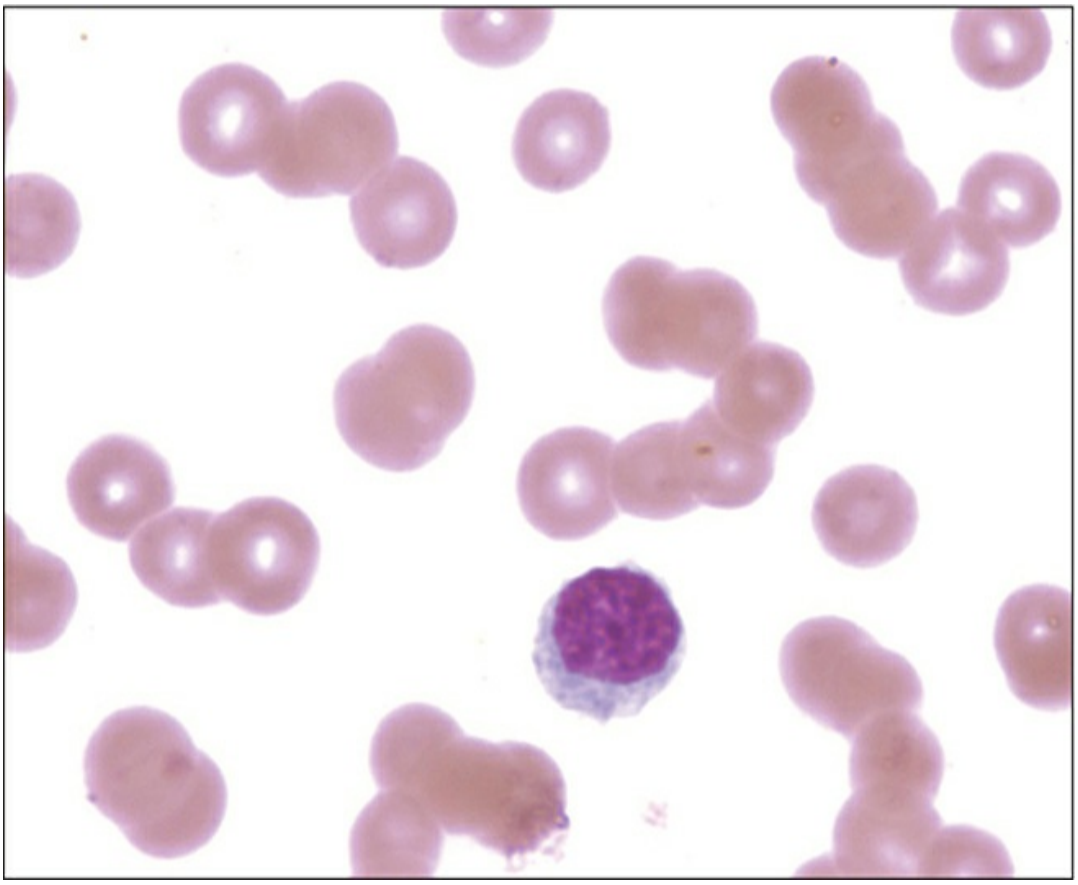


Figure **IIB10-6**

Peripheral blood smear.

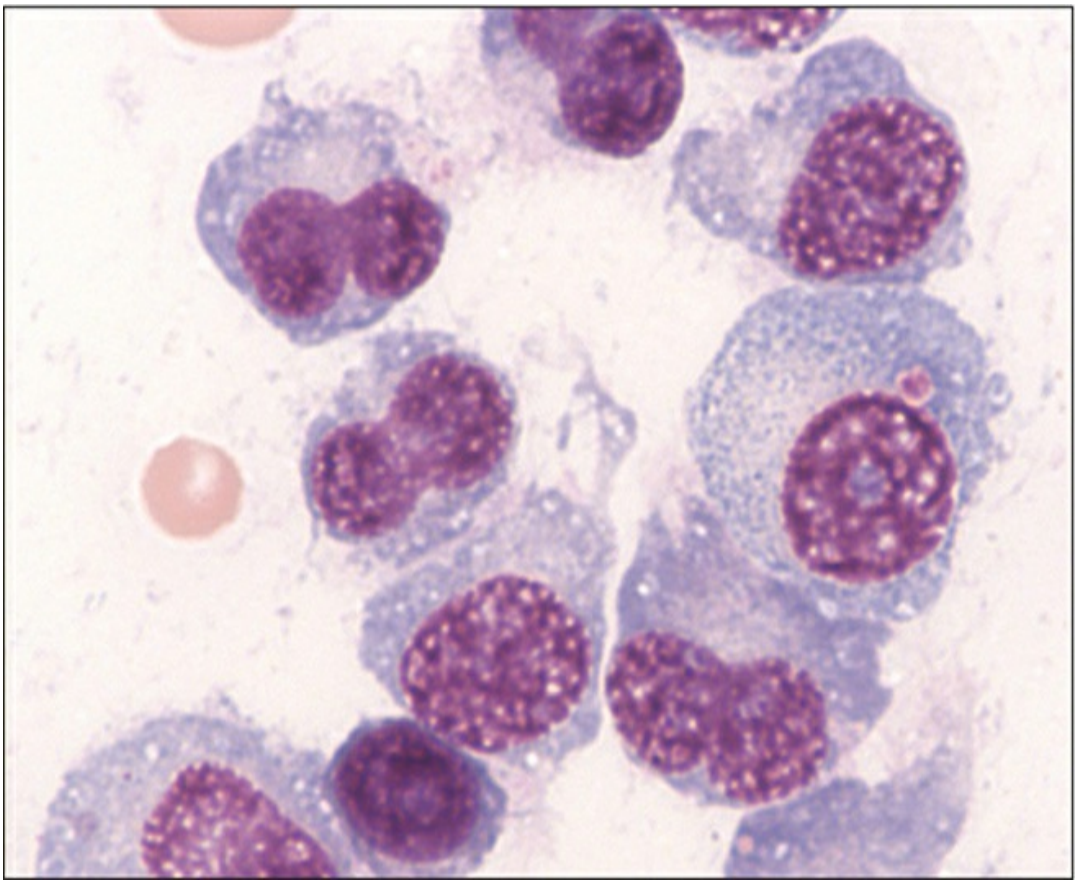


Figure IIB10-7

Bone marrow smear.

Clinical Features

- Fatigue and generalized aching
- Bone pain with lytic lesions
- Neurologic abnormalities
- Infections and renal failure

Pathology

- Median age of onset is about 70 years
- Bone marrow–based, multifocal neoplastic proliferation of plasma cells
- Plasma cells secrete complete or incomplete monoclonal immunoglobulins
- Prolonged excretion of Bence Jones protein in the urine

often results in renal failure
- Increased susceptibility to infections

Laboratory Features

White Blood Cells

- Count is usually normal
- Few plasma cells may be present

Red Blood Cells

- Normocytic/normochromic anemia
- Rouleaux
- Increased sedimentation rate

Platelets

- Normal to decreased
- Abnormal function

Bone Marrow

- >10% plasmacytosis
- Myeloma cells are present, which have a single eccentrically placed nucleus, and nucleoli may be seen in finely divided chromatin. Various types of inclusions may be present.

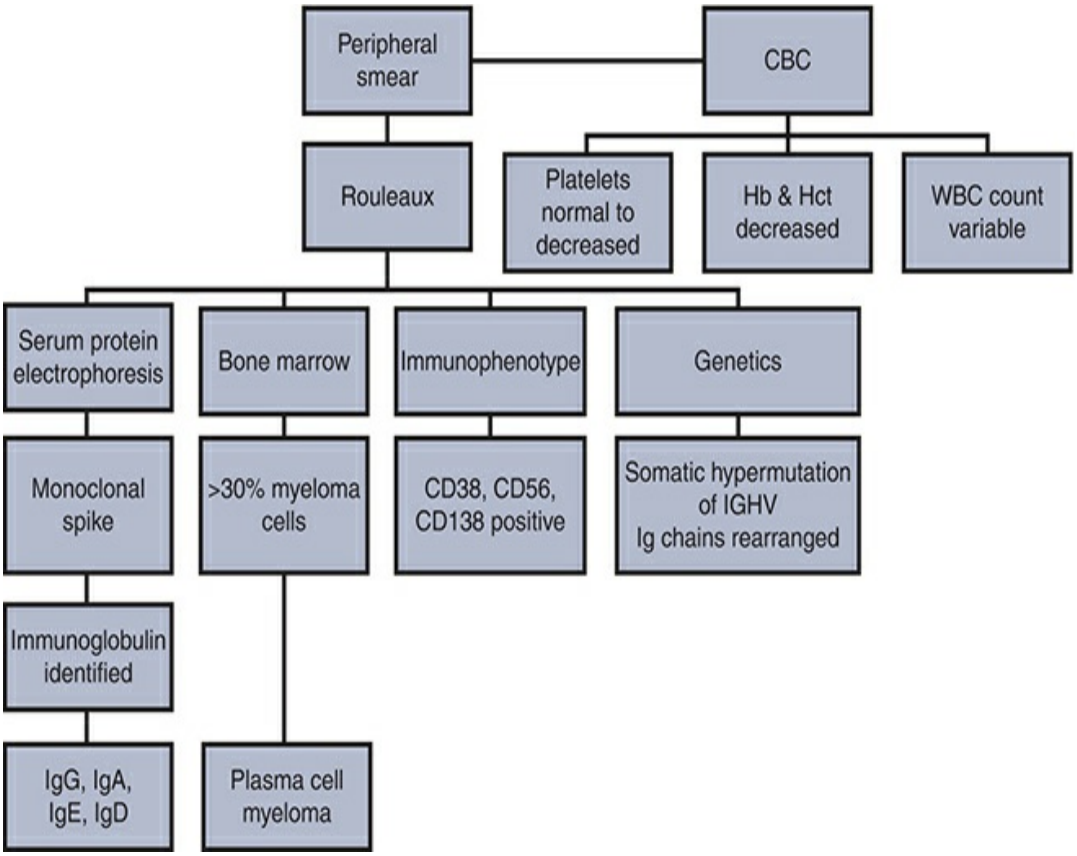
Immunophenotype

- CD38, CD56, and CD138 positive

Genetics

- High load of IGHV gene somatic hypermutation
- Heavy and light chains of the immunoglobulins are clonally rearranged

Diagnostic Scheme


Peripheral smear
CBC
Rouleaux
Platelets normal to decreased
Hb & Hct decreased
WBC count variable
Serum protein electrophoresis
Bone marrow
Immunophenotype
Genetics
Monoclonal spike
>30% myeloma cells
CD38, CD56, CD138 positive
Somatic hypermutation of IGHV
Ig chains rearranged
Immunoglobulin identified
IgG, IgA, IgE, IgD
Plasma cell myeloma

PLASMA CELL LEUKEMIA

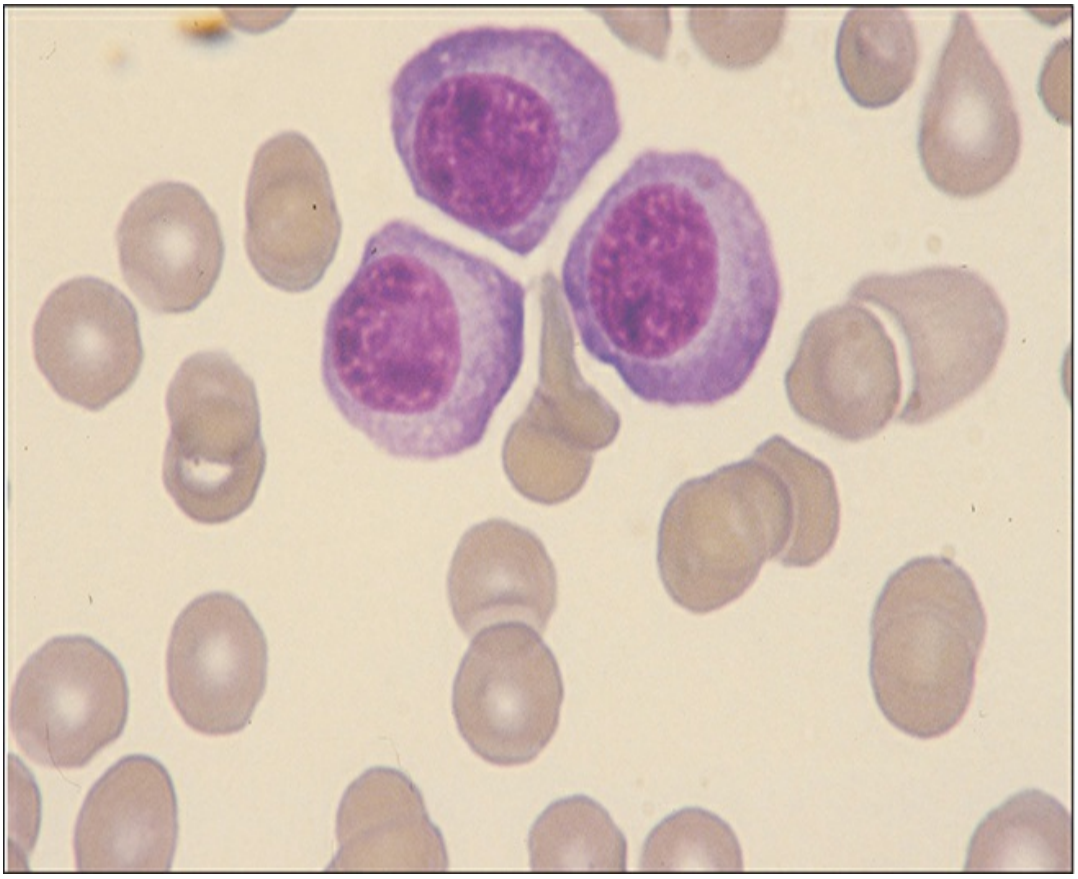


Figure IIB10-8

Peripheral blood smear.

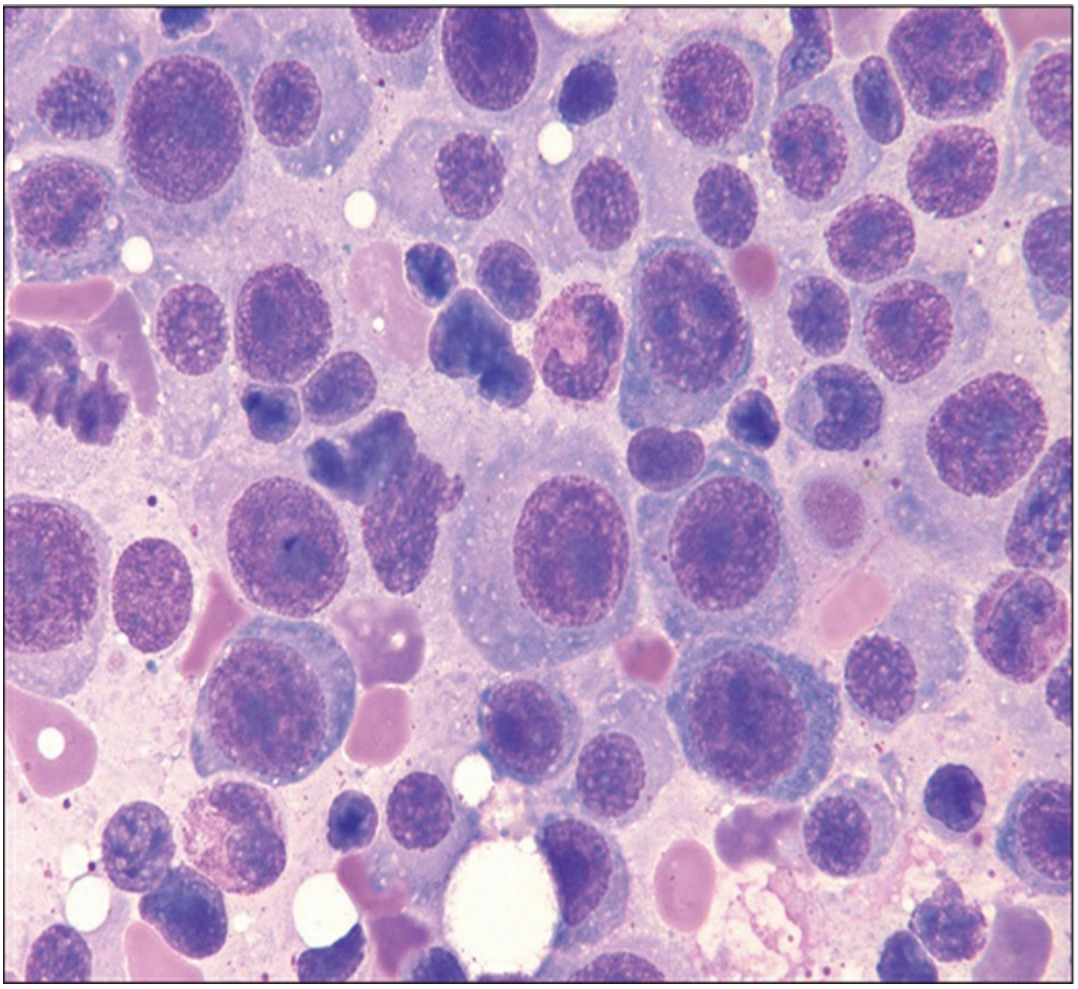


Figure **IIB10-9**

Bone marrow smear.

Clinical Features

- Hepatosplenomegaly
- Lymphadenopathy
- Renal failure
- Severe anemia

Pathology

- Primary plasma cell leukemia demonstrates circulating myeloma cells at the time of diagnosis and is found in 2–4% of myelomas
- Secondary plasma cell leukemia represents the

advanced stage of myeloma (a leukemic phase), which occurs as a terminal event in about 1% of cases
- Median age of patient at diagnosis is younger than plasma cell myeloma

Laboratory Features

White Blood Cells

- Plasma cells represent >20% of leukocytes in the peripheral blood
- Absolute plasma cell count is >2.0 × 10^9/L

Red Blood Cells

- Severe normocytic/normochromic anemia
- Rouleaux

Platelets

- Decreased

Bone Marrow

- Diffuse plasma cell infiltration is variable but may be as high as 90%
- Plasma cells are well differentiated
- Binucleated plasma cells may be present

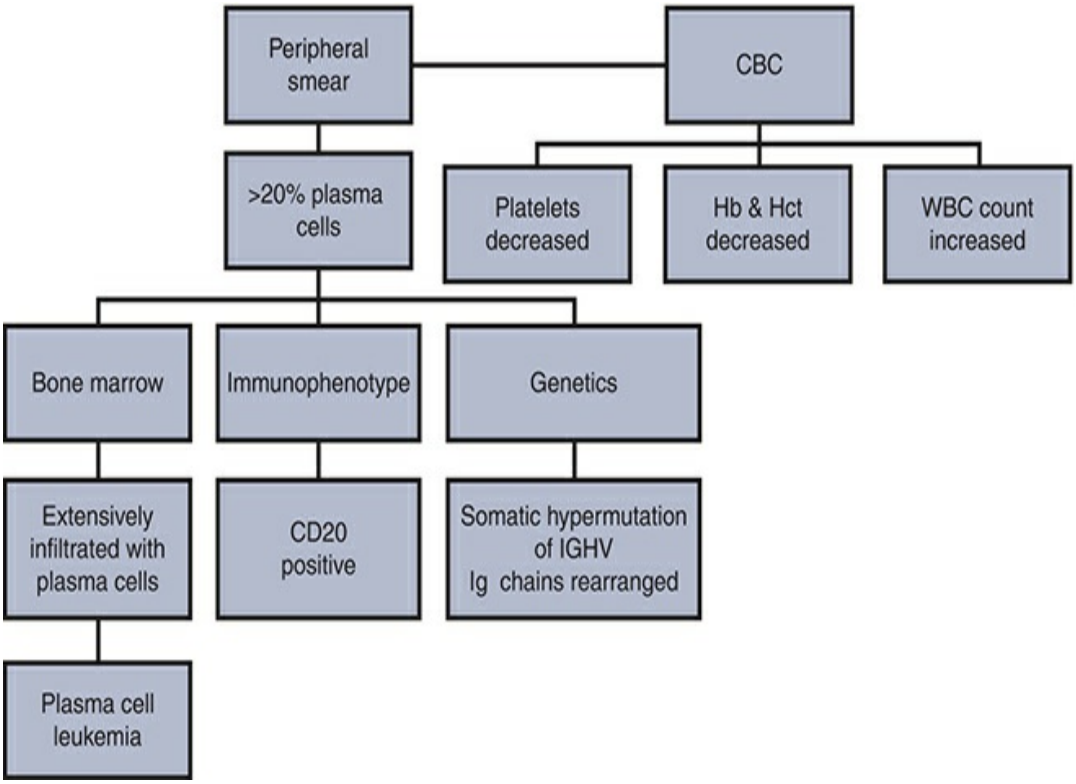
Immunophenotype

- Frequent expression of CD20
- CD56 is negative in 80% of cases

Genetics

- High load of IGHV gene somatic hypermutation
- Heavy and light chains of the immunoglobulins are clonally rearranged

Diagnostic Scheme


Peripheral smear
CBC
>20% plasma cells
Platelets decreased
Hb & Hct decreased
WBC count increased
Bone marrow
Immunophenotype
Genetics
Extensively infiltrated with plasma cells
CD20 positive
Somatic hypermutation of IGHV
Ig chains rearranged
Plasma cell leukemia

BURKITT LYMPHOMA

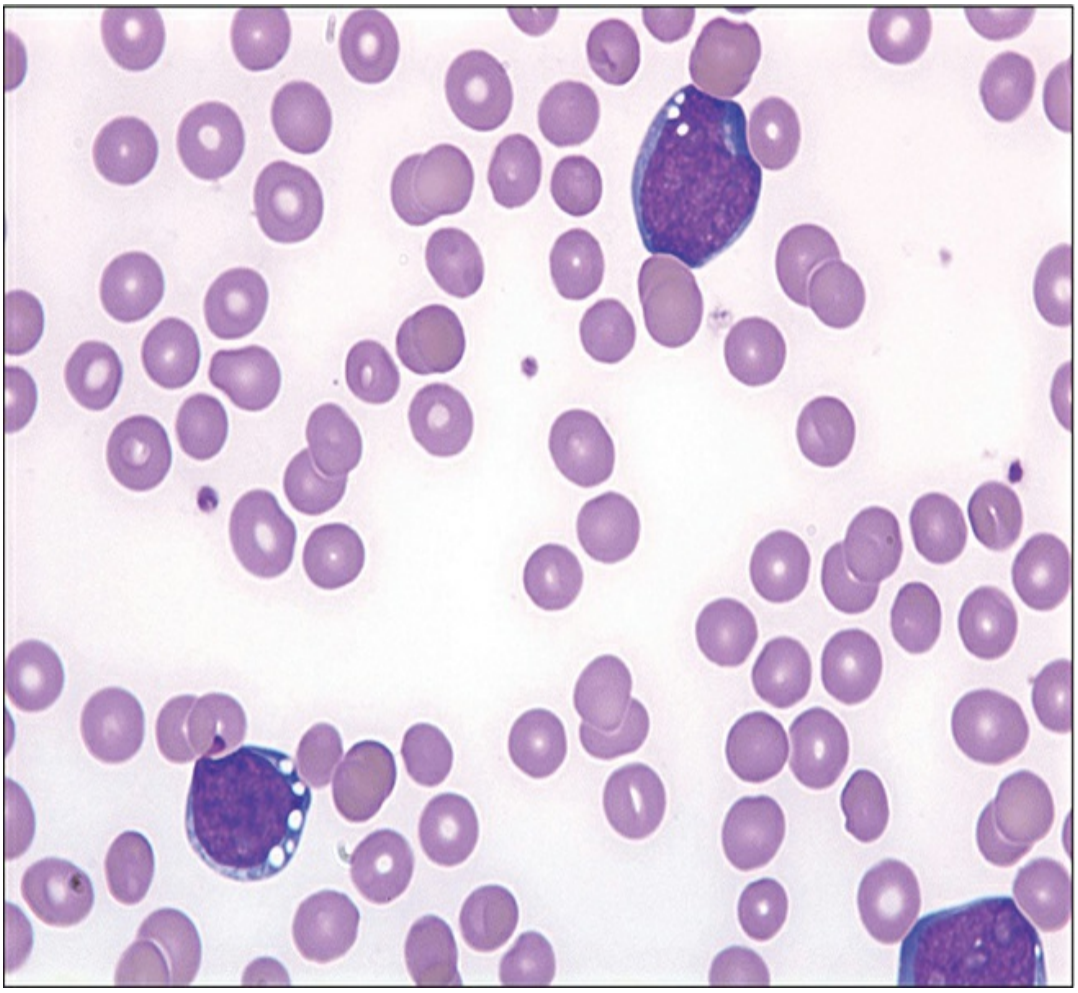


Figure IIB10-10

Peripheral blood smear.

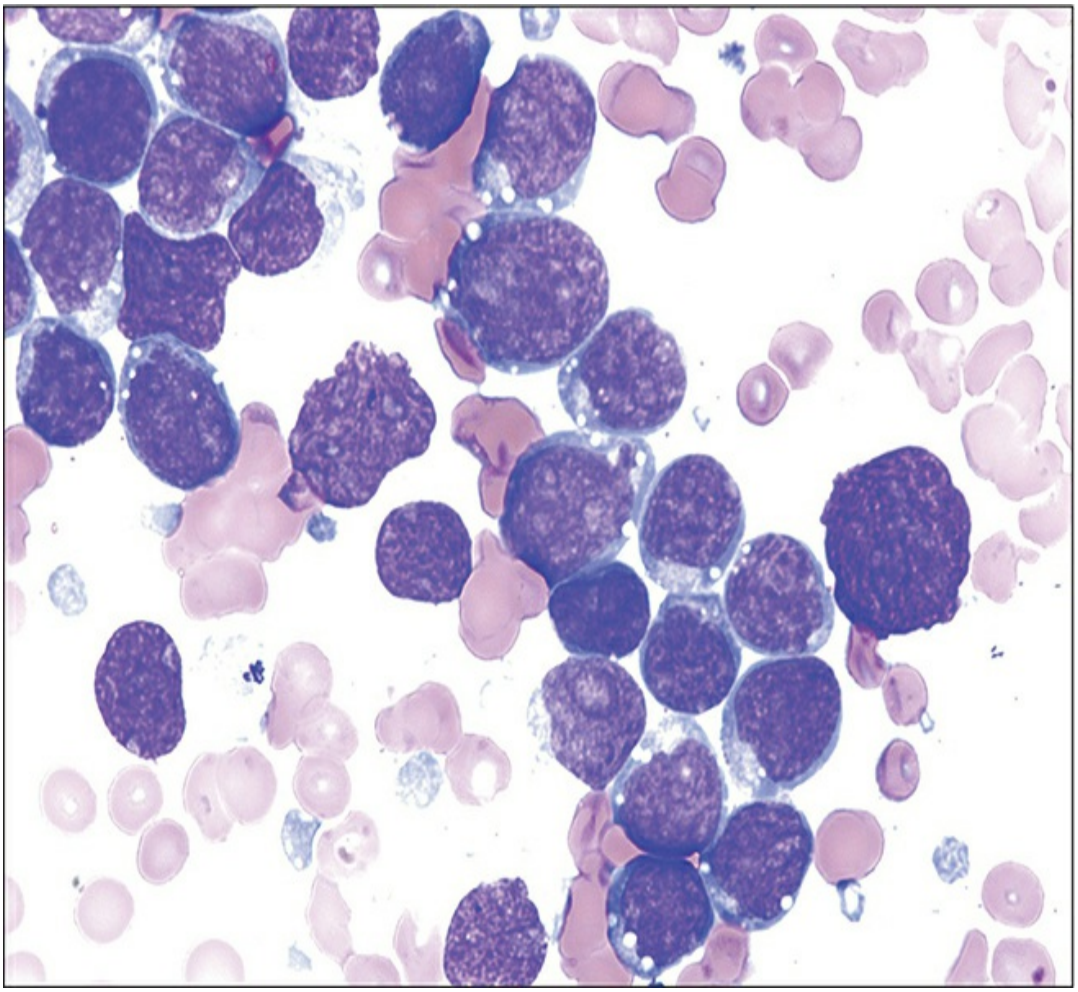


Figure **IIB10-11**

Bone marrow smear.

Clinical Features

- Extranodal sites are most often involved
- Rapidly growing mass may be present, especially in the jaw bone, but abdominal masses are more common

Pathology

- Usually occurs in children or young adults
- Accounts for about 1–2% of lymphomas but varies by country
- Epstein-Barr virus and human immunodeficiency virus as well as Plasmodium falciparum may be associated

with the lymphoma
- Highly aggressive

Laboratory Features

Cell Types

- Monomorphic medium-sized cell
- Round nucleus
- 2–5 prominent nucleoli
- Moderate basophilic cytoplasm with vacuoles

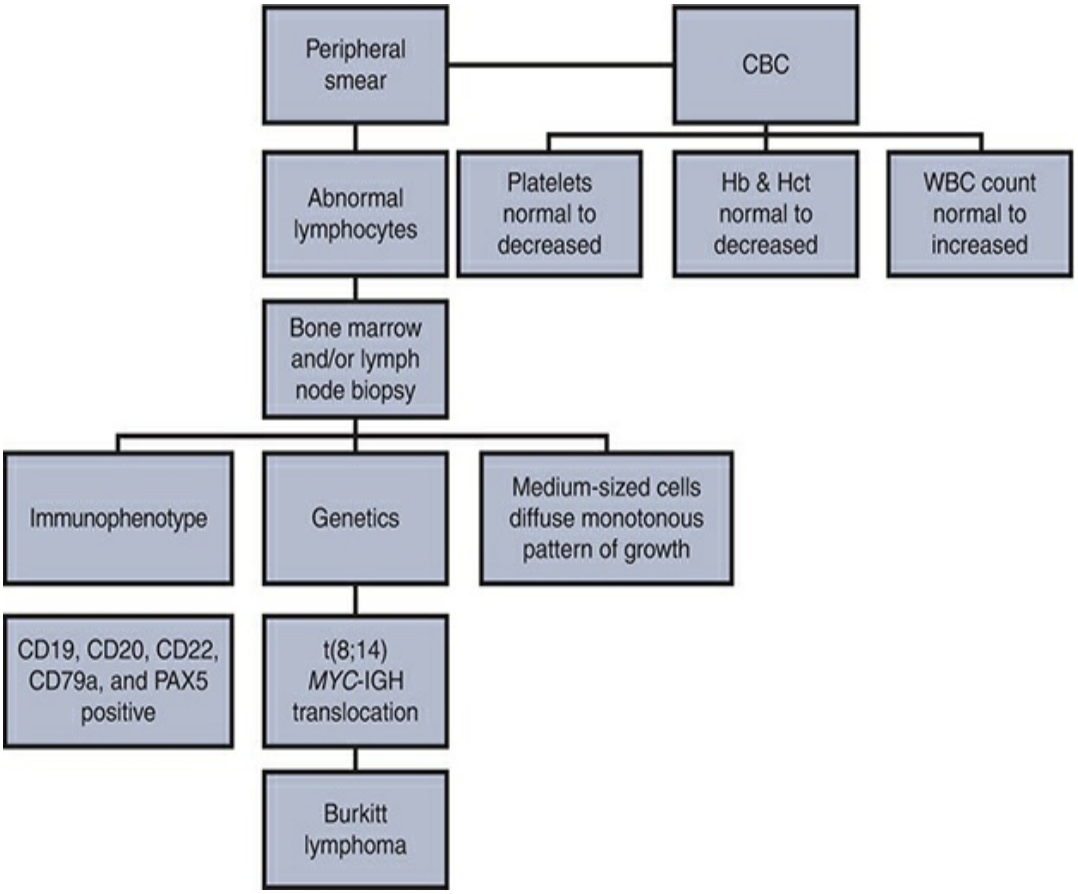
Immunophenotype

- CD19, CD20, CD22, CD79a, and PAX5 are present
- CD5, CD23, and BCL2 negative

Genetics

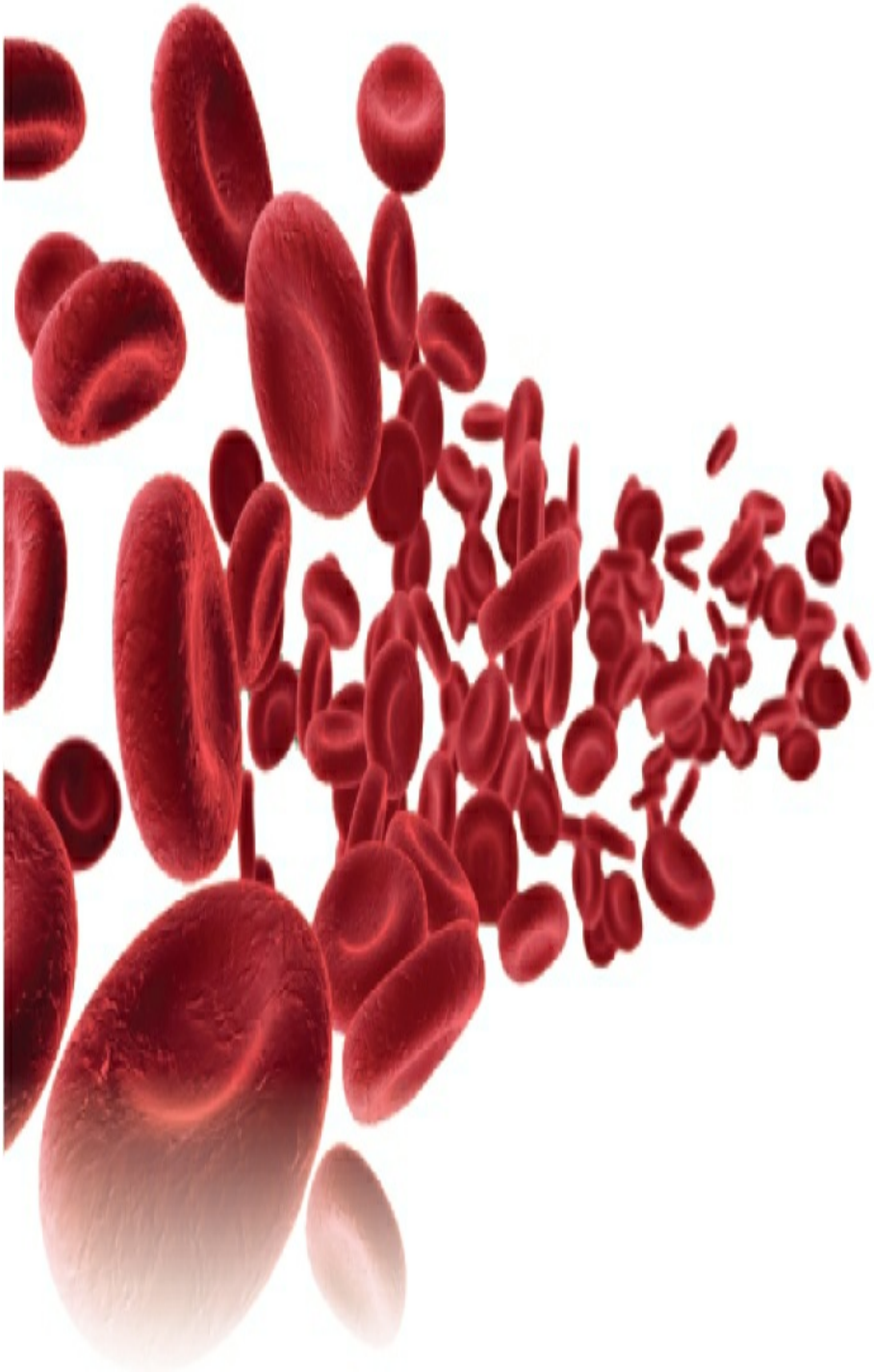
- Translocation of MYC at band 8q24 to the IGH region on chromosome 14q32, t(8;14)(q24;q32) is a hallmark of the lymphoma

Diagnostic Scheme


Peripheral smear
CBC
Abnormal lymphocytes
Platelets normal to decreased
Hb & Hct normal to decreased
WBC count normal to increased
Bone marrow and/or lymph node biopsy
Immunophenotype
Genetics
Medium-sized cells diffuse monotonous pattern of growth
CD19, CD20, CD22, CD79a, and PAX5 positive
t(8;14) *MYC*-IGH translocation
Burkitt lymphoma

CHAPTER 11

Mature T-cell Neoplasms



MATURE T-CELL NEOPLASMS

Criteria

- Neoplasms composed of morphologically and/or immunophenotypically mature T cells
- These are relatively uncommon neoplasms and account for only 12% of all non-Hodgkin lymphomas
- Geographical regions and racial populations show variations in incidence
- Human T-cell leukemia virus type 1 and Epstein-Barr virus infections are associated with the incidence in some populations

T-CELL LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

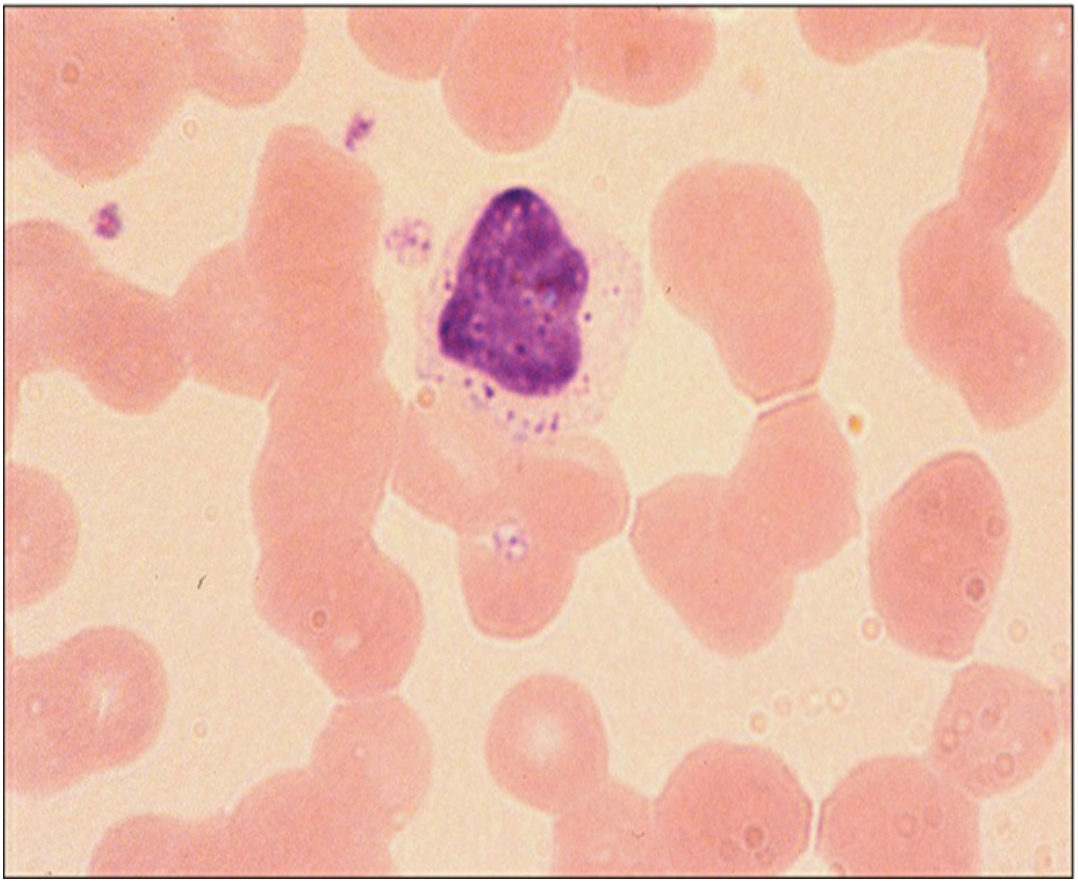


Figure IIB11-1

Peripheral blood smear.

Clinical Features

- Some patients are asymptomatic
- Characterized by a persistent (>6 months) increase in the number of peripheral blood large granular lymphocytes
- Recurrent infections
- Rheumatoid arthritis
- Splenomegaly
- Median age of onset is 60 years

Pathology

- STAT3 mutations in about one-third of cases
- Inhibition of apoptosis results in the accumulation of T-large granular lymphocytic cells
- Accounts for 2–3% of mature small lymphocytic leukemias
- Viral infections may be an initial stimulus

Laboratory Features

White Blood Cells

- Persistent neutropenia
- Lymphocytosis in the range of 4.0–10.0 × 10^9/L
- Presence of large granular lymphocytes, generally >2.0 × 10^9/L
- Predominant lymphocytes have moderate to abundant cytoplasm and fine or course azurophilic granules

Red Blood Cells

- May have a macrocytic anemia

Platelets

- Normal to decreased

Bone Marrow

- Lymphocytic infiltration is variable
- Left-shifted granulocytic maturation is common

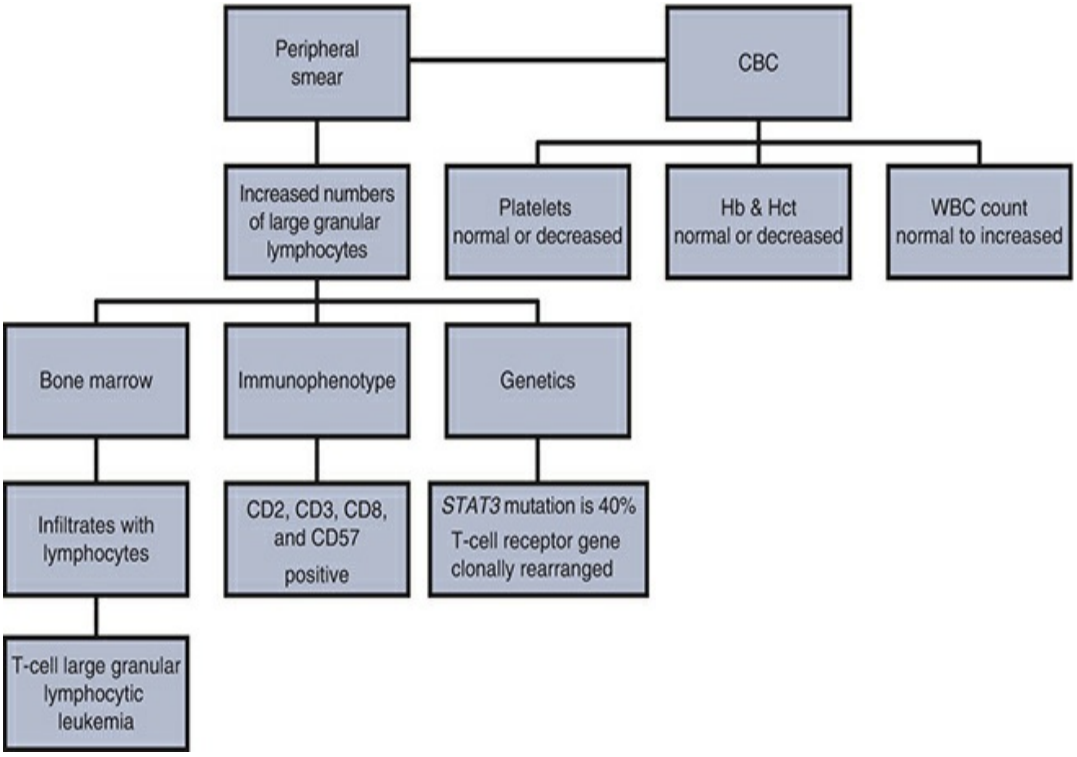
Immunophenotype

- CD2, CD3, CD8, CD16, and CD57 positive

Genetics

- T-cell receptor gene clonally rearranged
- STAT3 mutation is present in about one-third of cases

Diagnostic Scheme


Peripheral smear
CBC
Increased numbers of large granular lymphocytes
Platelets normal or decreased
Hb & Hct normal or decreased
WBC count normal to increased
Bone marrow
Immunophenotype
Genetics
Infiltrates with lymphocytes
CD2, CD3, CD8, and CD57 positive
STAT3 mutation is 40%
T-cell receptor gene clonally rearranged
T-cell large granular lymphocytic leukemia

ADULT T-CELL LEUKEMIA/LYMPHOMA

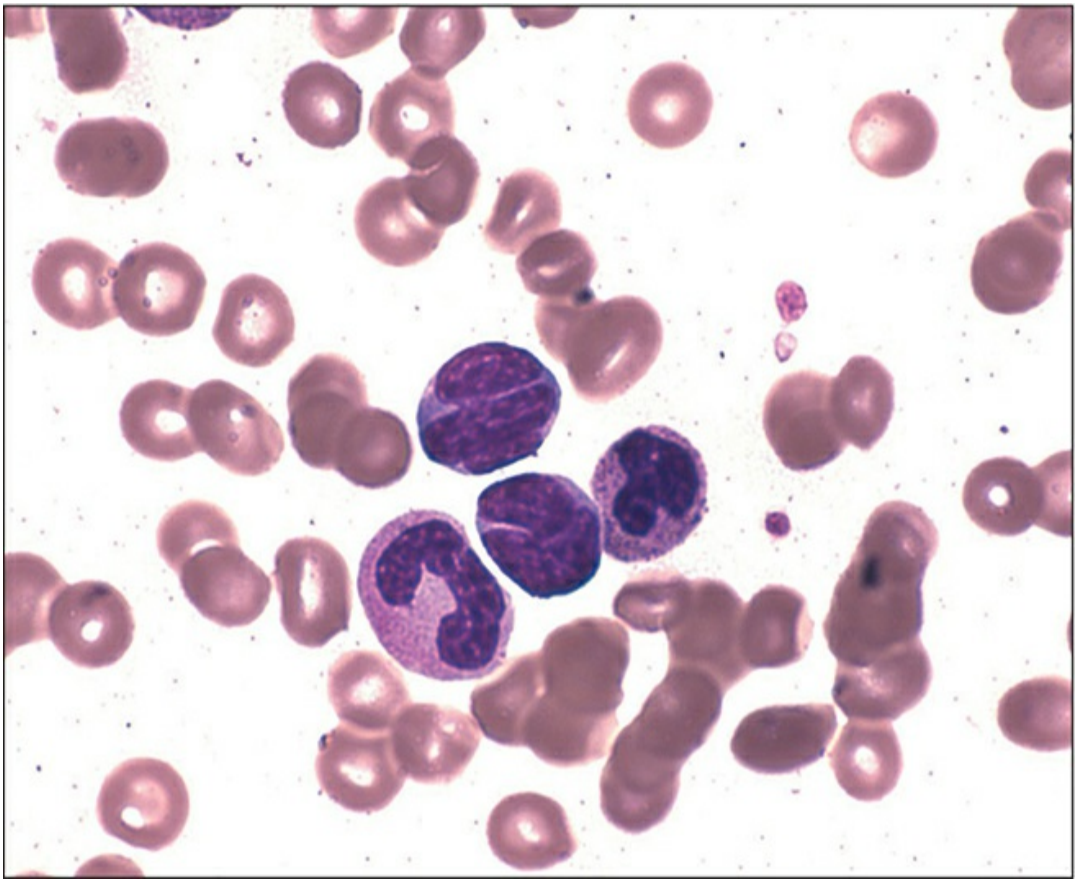


Figure IIB11-2

Peripheral blood smear.

Clinical Features

- Evolves rapidly
- Skin lesions
- Hepatosplenomegaly
- Generalized lymphadenopathy

Pathology

- The disease is usually widely disseminated and is caused by the retrovirus, human T-cell leukemia virus type 1

- Invasion of cells by the virus causes cell proliferation

Laboratory Features

White Blood Cells

- May be only a few abnormal cells in the peripheral blood
- Cells have highly convoluted nuclei with deep multilobulated indentation
- Cell size and N/C ratio are larger than that of normal lymphocytes

Red Blood Cells

- Normocytic/normochromic anemia

Platelets

- Normal to decreased

Bone Marrow

- Presence of infiltrates and evidence of bony remodeling and fibrosis

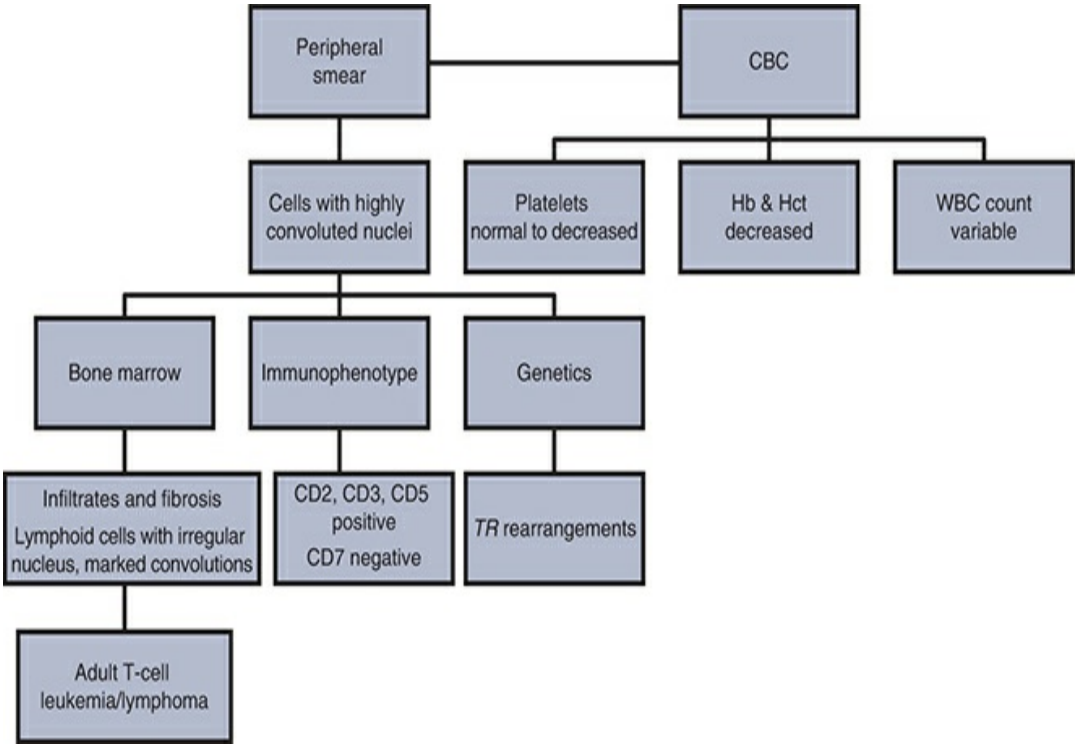
Immunophenotype

- CD2, CD3, and CD5 are positive
- CD7 is negative

Genetics

- Rearrangement of TR genes

Diagnostic Scheme


Peripheral smear
CBC
Cells with highly convoluted nuclei
Platelets normal to decreased
Hb & Hct decreased
WBC count variable
Bone marrow
Immunophenotype
Genetics
Infiltrates and fibrosis
Lymphoid cells with irregular nucleus, marked convolutions
CD2, CD3, CD5 positive
CD7 negative
TR rearrangements
Adult T-cell leukemia/lymphoma

SéZARY SYNDROME

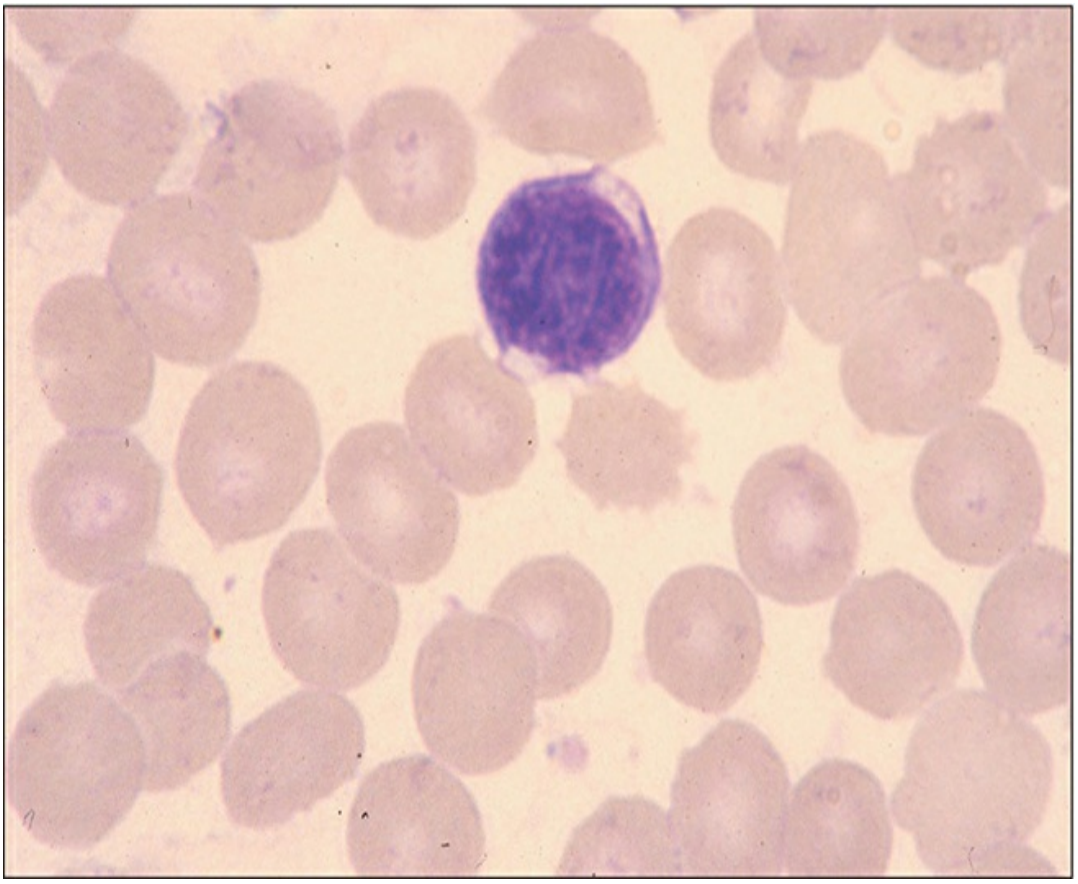


Figure IIB11-3

Peripheral blood smear.

Clinical Features

- Erythroderma
- Generalized lymphadenopathy
- Presence of neoplastic T cells in skin, lymph nodes, and peripheral blood
- Pruritus
- Infections

Pathology

- Rare disease, which accounts for <5% of the cutaneous lymphomas

- Seen more commonly in males (2:1) and in patients over 60 years of age
- Systemic phase of cutaneous T-cell lymphoma
- Malignant proliferation of T lymphocytes
- Aggressive disease

Laboratory Features

White Blood Cells

- Hyperconvoluted lymphoid cells in peripheral blood

Red Blood Cells

- May have a normocytic/normochromic anemia

Platelets

- Normal to decreased

Bone Marrow

- Eosinophilia
- Monocytosis
- Plasmacytosis
- Rare infiltrates of Sézary cells

Cytochemistry

- Focal positivity with acid phosphatase
- Myeloperoxidase, alkaline phosphatase, and specific esterase (chloroacetate esterase) negative

Immunophenotype

- CD3 and CD4 positive
- CD8, CD7, and CD26 negative

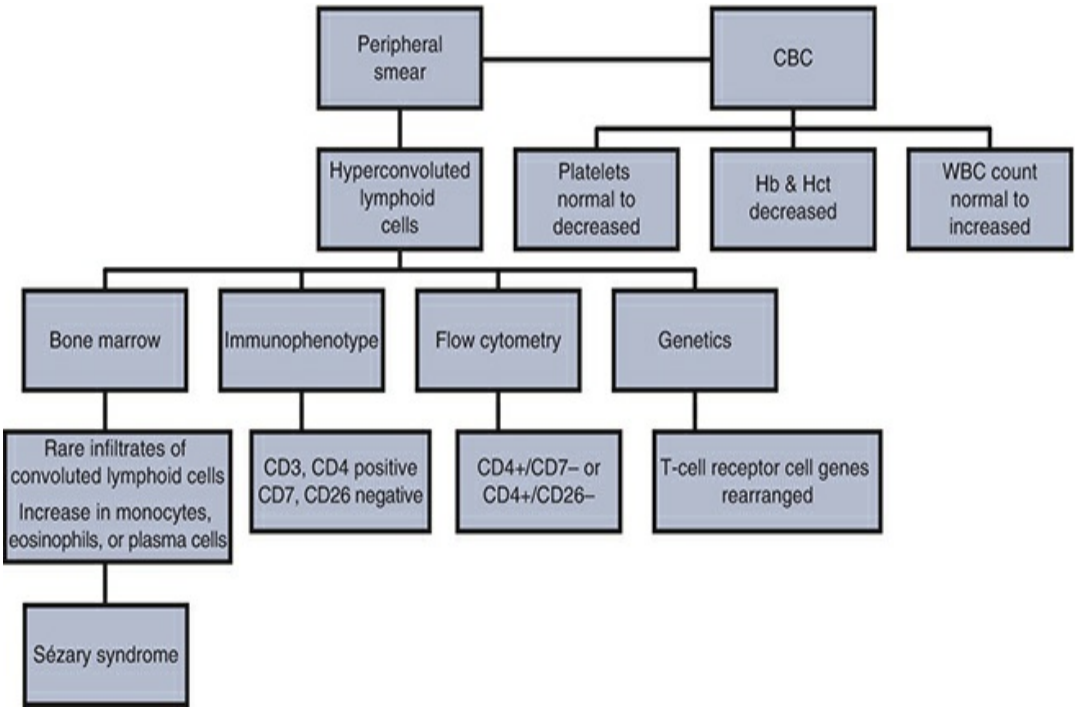
Flow Cytometry

- CD4+/CD7− in >30% of cases or CD4+/CD26− in >40% or T-cell population

Genetics

- T-cell receptor genes are clonally rearranged
- Overexpression of PLS3 , DNM3 , TWIST1 , and EPHA4

Diagnostic Scheme

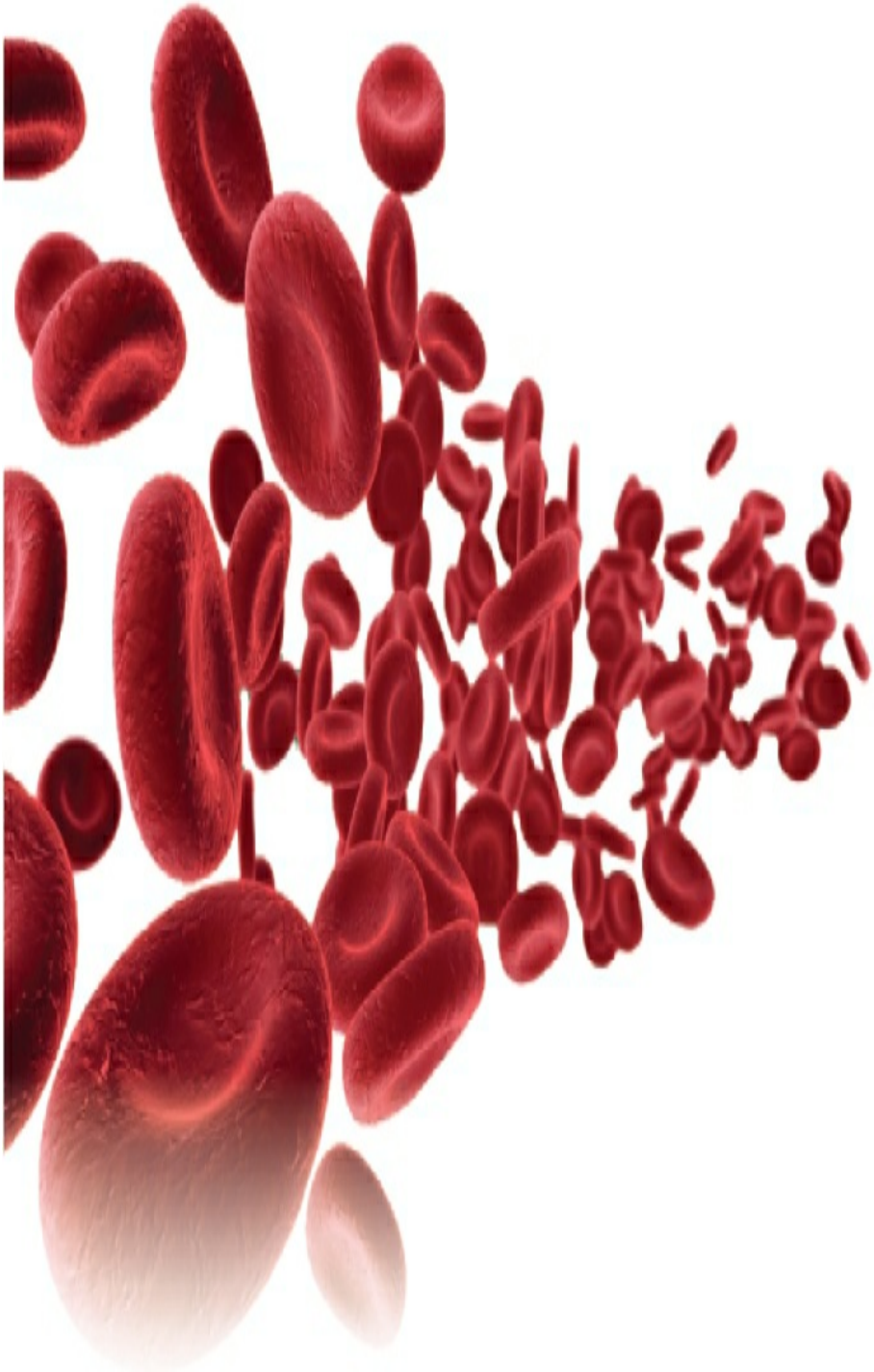


Section C

Miscellaneous Disorders

CHAPTER 1

Quantitative Platelet Disorders



THROMBOCYTOPENIA

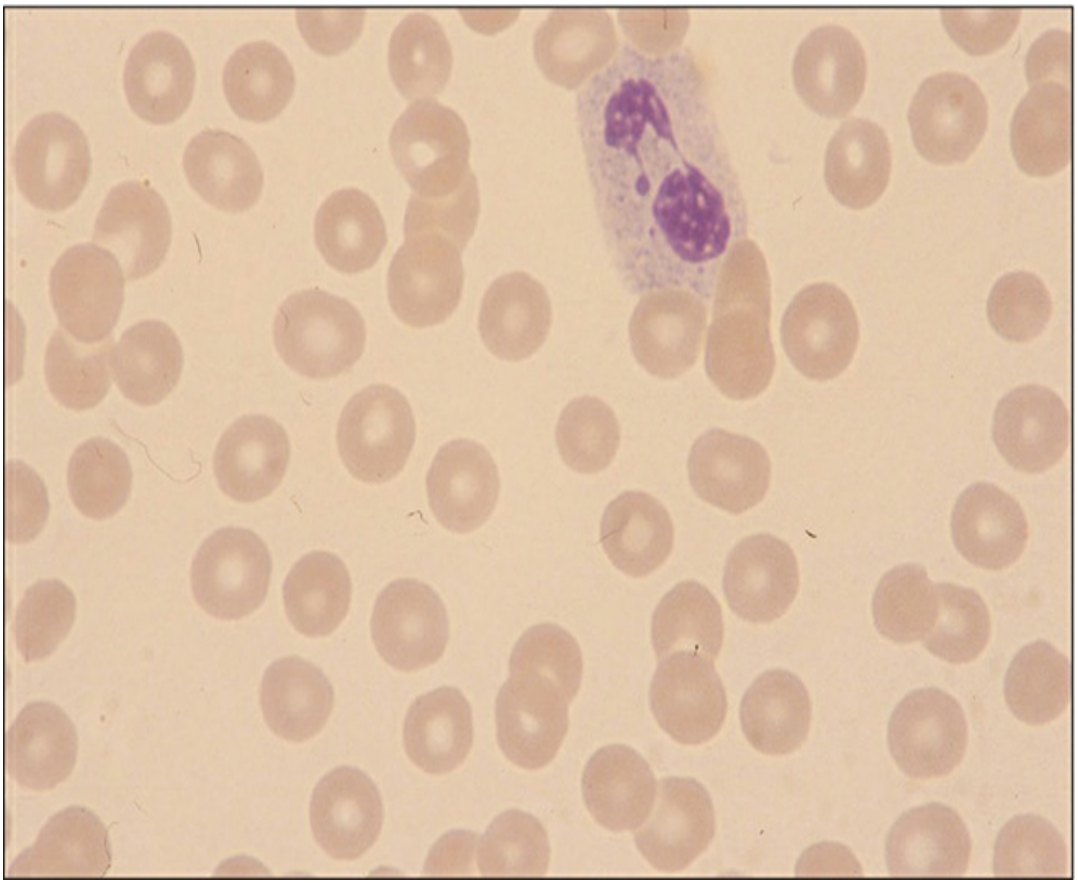


Figure IIC1-1

Peripheral blood smear.

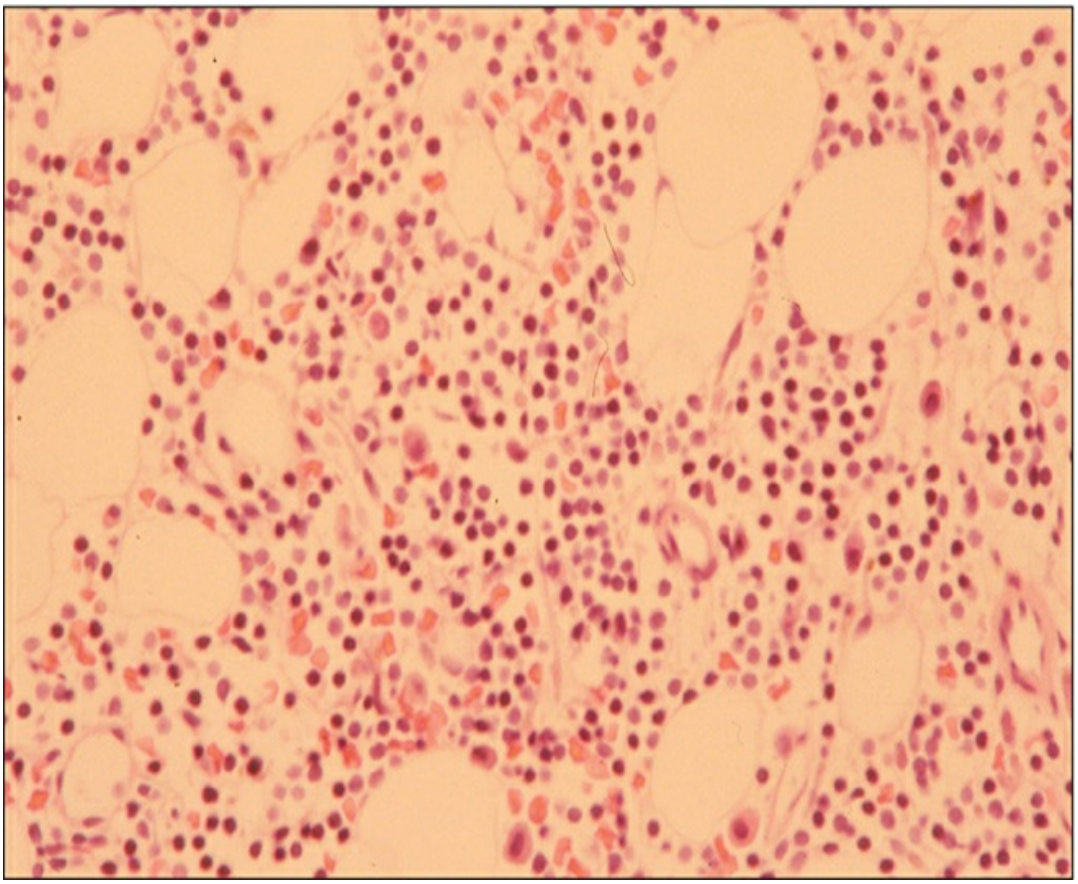


Figure IIC1-2

Bone marrow biopsy.

Criteria

- Platelet count of $<150 \times 10^9$/L

Clinical Features

- Petechiae and purpura
- Mild to moderate mucosal bleeding
- Gingival bleeding

Pathology

- Classified as hereditary or acquired; may be subclassified by platelet count and number of megakaryocytes

Hereditary Thrombocytopenia

- Hereditary may occur as an isolated phenomenon or associated with bone marrow failure

Congenital Amegakaryocytic Thrombocytopenia

- Platelet count about 21.0 × 10^9/L
- Normal-sized platelets
- Normal cellularity of bone marrow with decreased megakaryocytes
- Autosomal recessive disorder
- Mutations in the MPL gene (receptor for thrombopoietin)

Thrombocytopenia-absent Radius Syndrome

- Platelet count ranges from 10 to 100 × 10^9/L
- Normal-sized platelets
- Megakaryocytes deceased in size and number
- Skeletal abnormalities
- Chromosomal deletions involving RBM8A gene

Platelet Disorders

Small Platelets

- Wiskott-Aldrich syndrome—X-linked thrombocytopenia

Large Platelets

- MYH9 -related disorder
- X-linked GATA1 macrothrombocytopenia
- Bernard-Soulier

Normal-sized Platelets

- Gray platelet syndrome—reduced α-granules
- Platelet count is from 50 to 100 × 10^9/L

Bone Marrow Failure Syndrome

- Fanconi anemia

Acquired Thrombocytopenia

Increased or Normal Number of Bone Marrow Megakaryocytes

Immune Thrombocytopenia

- Platelets decreased due to autoantibodies
- Large (giant) platelets
- Bone marrow megakaryocytes are increased

Decreased Megakaryocytes

- Bone marrow hypoplasia or aplasia
- Bone marrow myelosuppression

Laboratory Features

White Blood Cells

- Varies with etiology

Red Blood Cells

- Varies with etiology

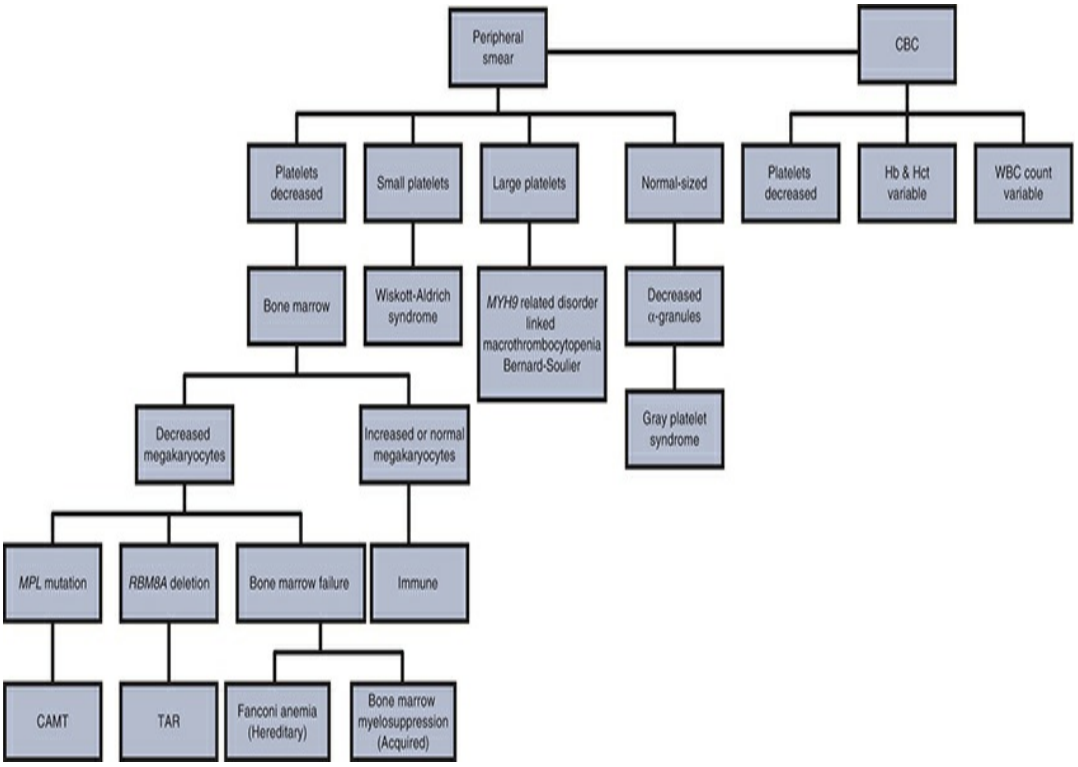
Platelets

- Decreased

Bone Marrow

- Increased, normal, or decreased megakaryocytes

Diagnostic Scheme


Peripheral smear
CBC
Platelets decreased
Small platelets
Large platelets
Normal-sized
Platelets decreased
Hb & Hct variable
WBC count variable
Bone marrow
Wiskott-Aldrich syndrome
MYH9 related disorder linked macrothrombocytopenia Bernard-Soulier
Decreased α-granules
Gray platelet syndrome
Decreased megakaryocytes
Increased or normal megakaryocytes
MPL mutation
RBM8A deletion
Bone marrow failure
Immune
CAMT
TAR
Fanconi anemia (Hereditary)
Bone marrow myelosuppression (Acquired)

THROMBOCYTOSIS

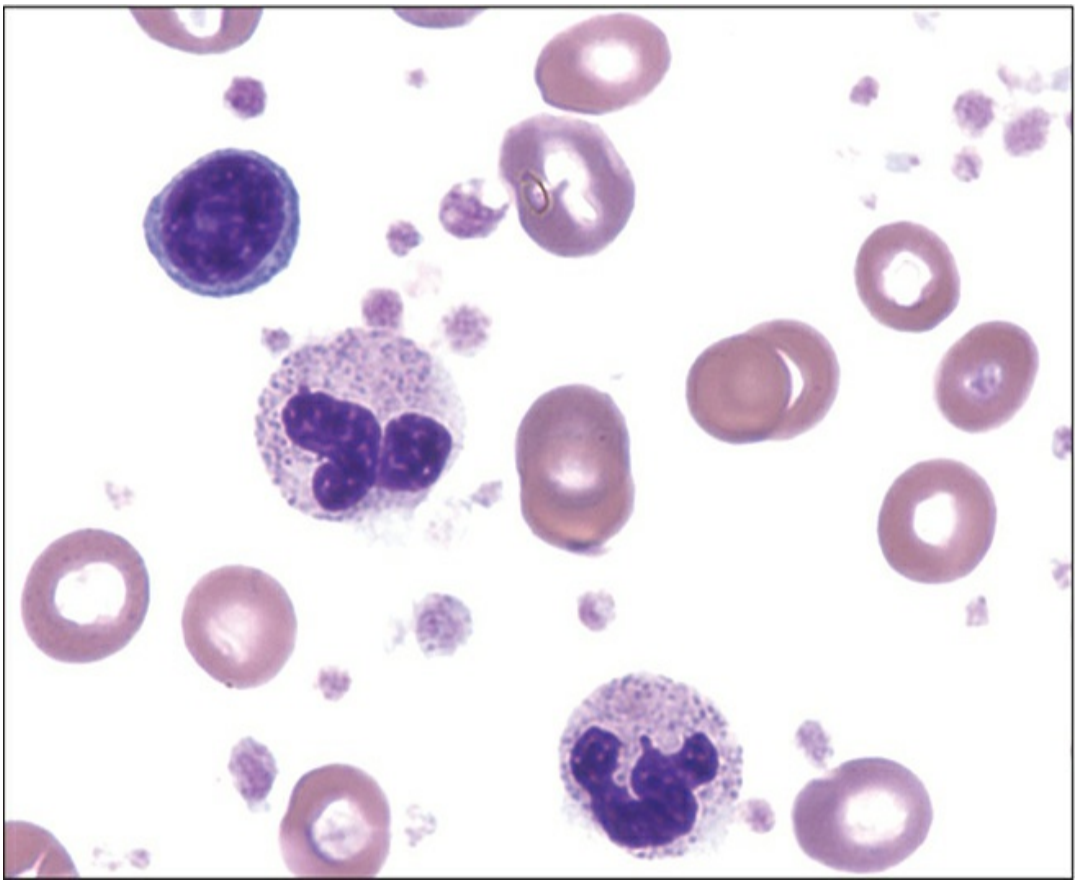


Figure IIC1-3

Peripheral blood smear.

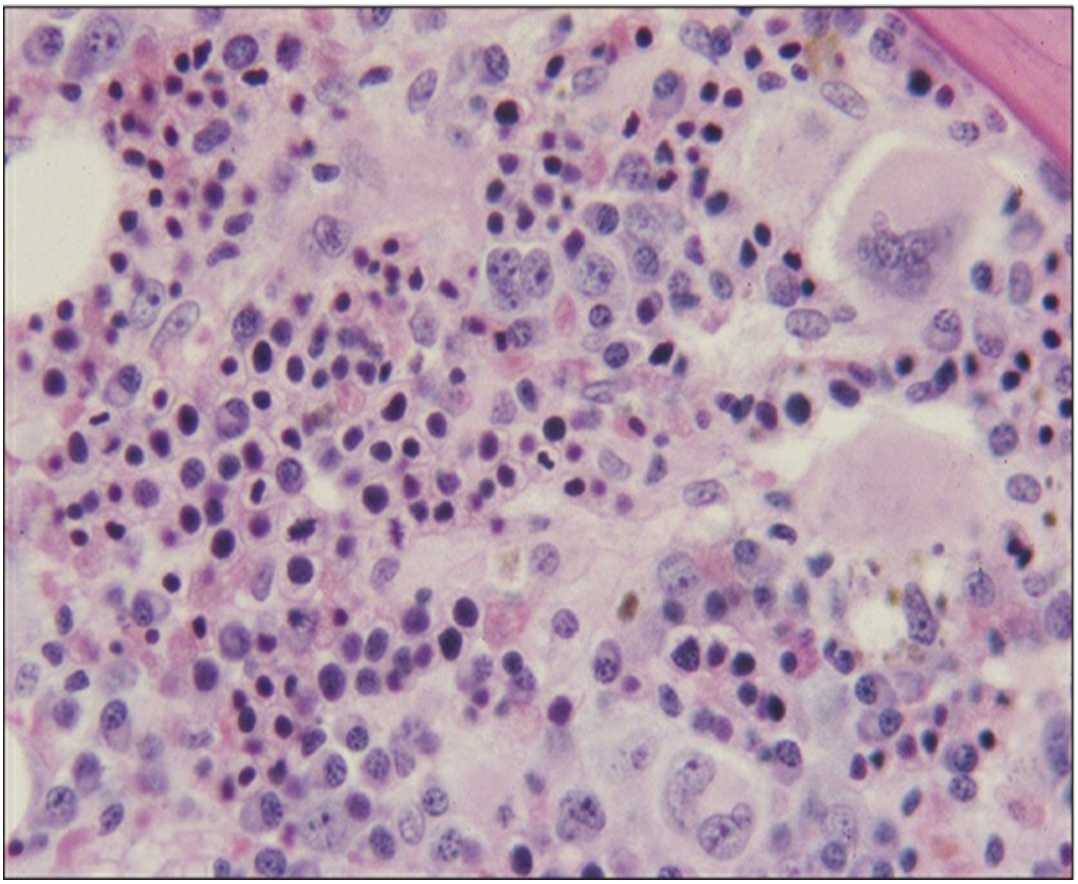


Figure IIC1-4

Bone marrow biopsy.

Criteria

- Platelet count of >450 × 10^9/L

Clinical Features

- Reactive thrombocytosis is usually asymptomatic
- Autonomous thrombocytosis may be associated with bleeding and/or thrombosis

Pathology

- Classified as hereditary or acquired; may be subclassified by platelet count and number of megakaryocytes

Hereditary Thrombocytosis

- Mutations in thrombopoietin
- Mutations in receptor for thrombopoietin

Acquired, Nonneoplastic Thrombocytosis

Reactive Thrombocytosis

- Stress, trauma, postoperative inflammatory conditions, autoimmune conditions, and iron deficiency anemia
- Overproduction of thrombopoietic factors
  - Thrombopoietin
  - IL-6
  - Cross-reactivity of erythropoietin with thrombopoietin receptors

Malignancies With Thrombocytosis

Myeloproliferative Neoplasms

- Megakaryocytes and platelets are overproduced by clonal proliferation
- JAK2 V617F genetic mutation
- MPL W515L/K genetic mutation
- CALR genetic mutations and exon 9

Laboratory Features

White Blood Cells

- Varies with etiology

Red Blood Cells

- Varies with etiology

Platelets

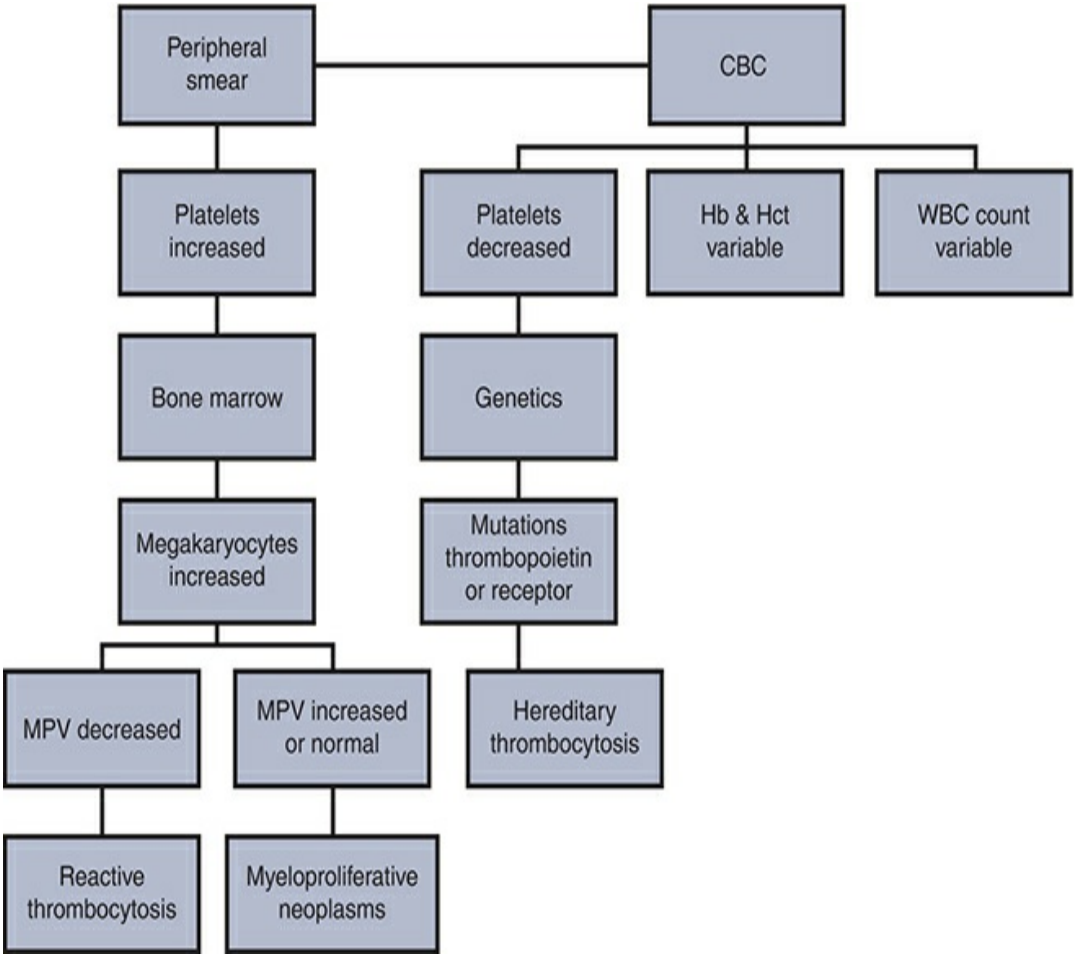
Reactive Thrombocytosis

- Platelets increased
- Megakaryocytes increased
- Mean platelet volume is decreased

Malignancies With Thrombocytosis

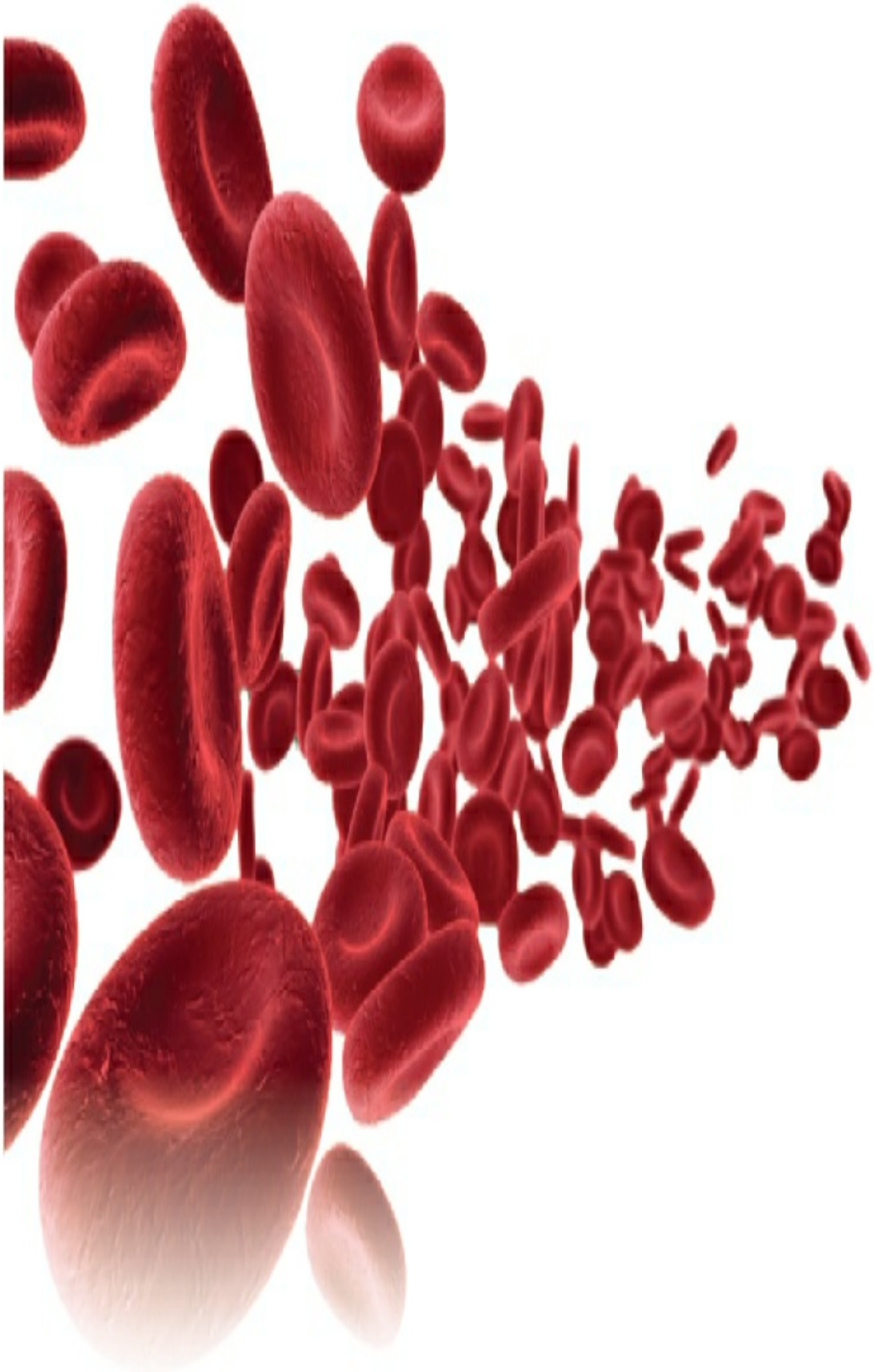
- Platelets greatly increased
- Megakaryocytes increased
- Mean platelet volume is increased (chronic myelogenous leukemia, primary myelofibrosis)
- Mean platelet volume is normal (essential thrombocythemia, polycythemia vera)

Diagnostic Scheme



CHAPTER 2

Hematologic Disease Associated With Microorganisms



BABESIOSIS

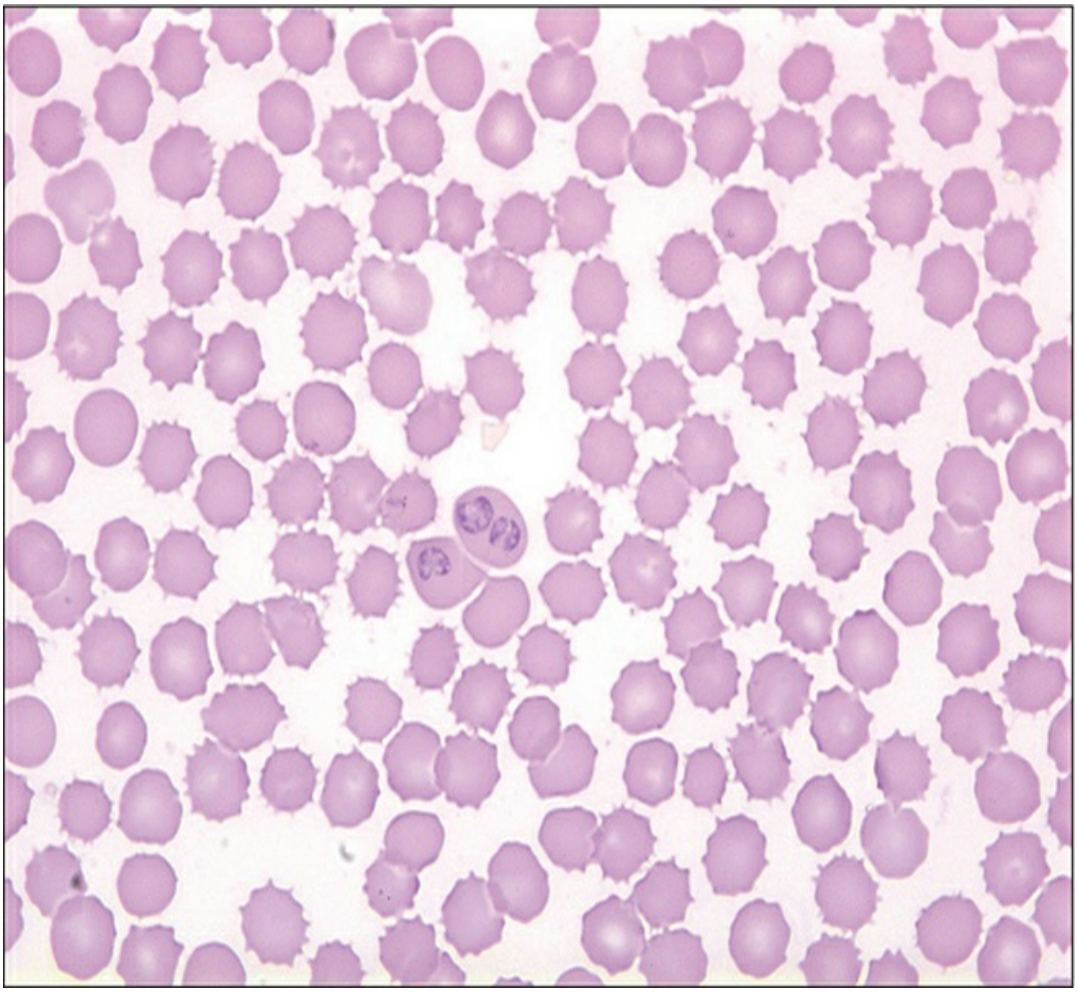


Figure IIC2-1

Peripheral blood smear.

Clinical Features

- May be asymptomatic from many months to years
- Malaise, fever, chills, fatigue, myalgia, and arthralgia
- Hepatosplenomegaly with jaundice
- Complications seen in about 40% of hospitalized patients

Pathology

- Rodents are the main reservoir, but some human infections with cattle and dog species of Babesia have

been reported
- Babesia are major pathogens in wild and domestic animals that nearly destroyed the American cattle industry during the late 19th century
- Human infections are still rare but have similar epidemiology to Lyme disease but are less widely spread
- Transmitted by the bite of the deer tick but can be transmitted transplacentally and by blood transfusion
- B. microti is responsible for most infections in the United States

Laboratory Features

White Blood Cells

- Mild neutropenia

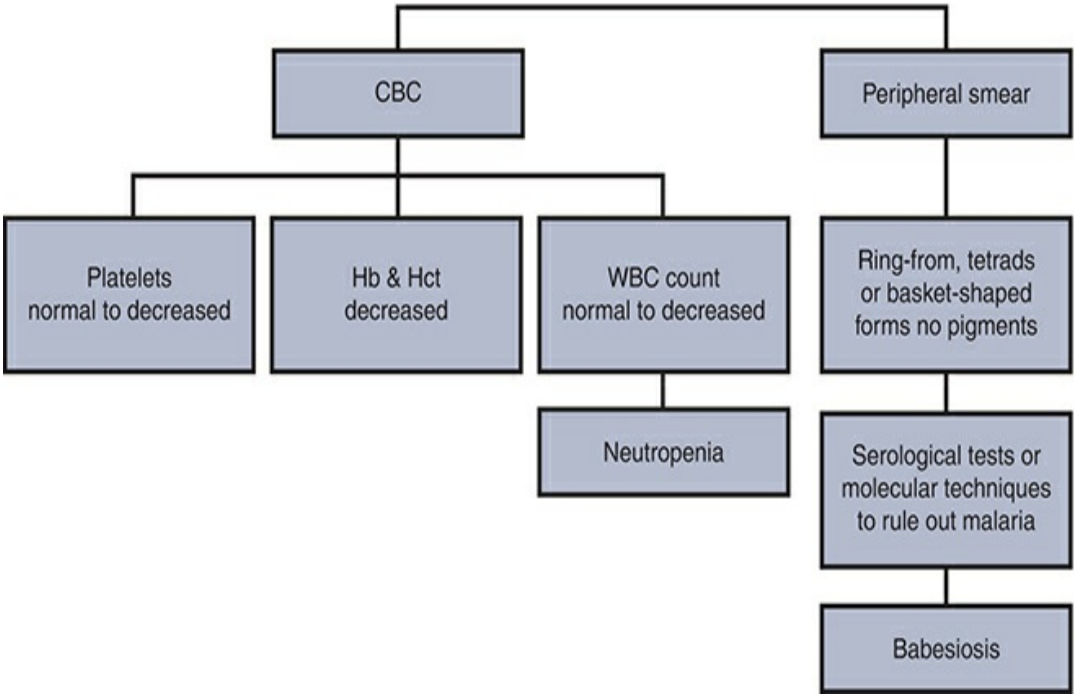
Red Blood Cells

- Mild to severe hemolytic anemia

Platelets

- Thrombocytopenia may occur
- Babesia organisms found on the blood smear
- Intraerythrocytic ring-shaped or pleomorphic parasites (piroplasms)
- Extraerythrocytic parasites found
- Unlike malaria, there is no pigment

Diagnostic Scheme


CBC
Peripheral smear
Platelets
normal to decreased
Hb & Hct
decreased
WBC count
normal to decreased
Ring-from, tetrads
or basket-shaped
forms no pigments
Neutropenia
Serological tests or
molecular techniques
to rule out malaria
Babesiosis

BORRELIOSIS

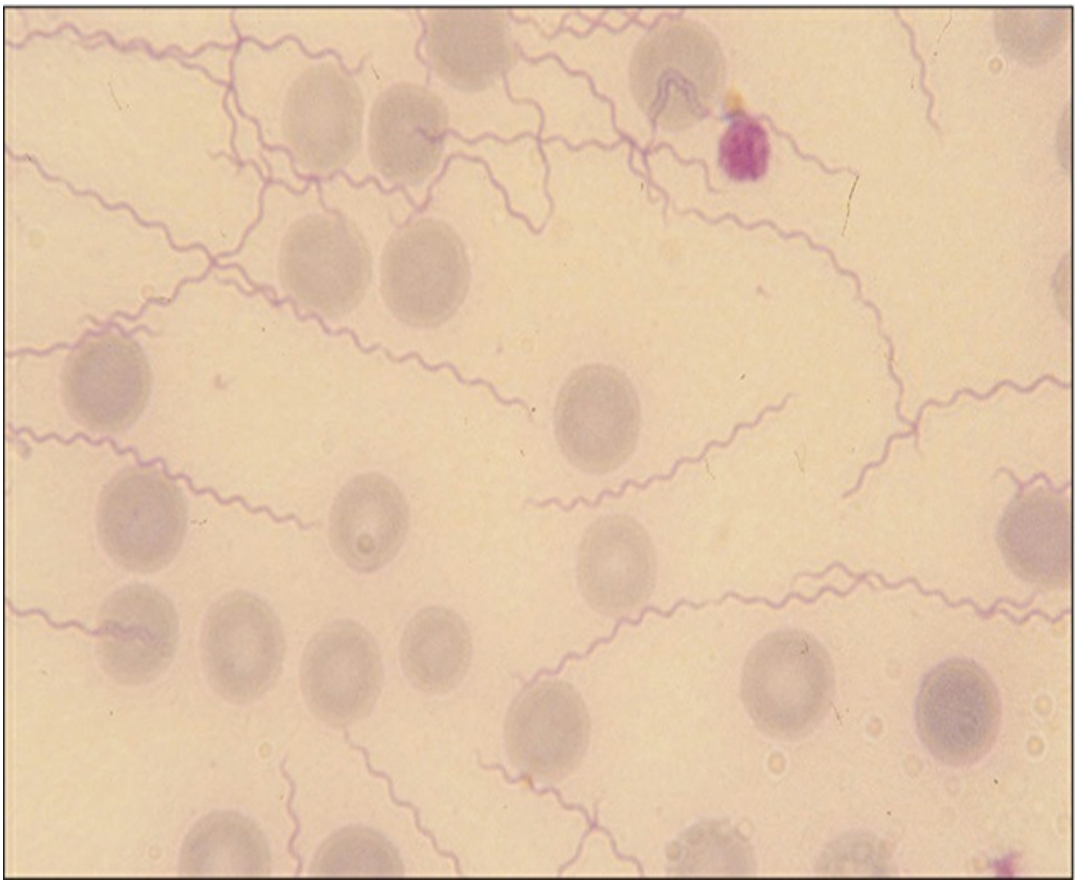


Figure IIC2-2

Peripheral blood smear.

Clinical Features

- High fever, shaking chills, delirium, headache, and muscle aches
- Cyclic pattern of symptoms corresponds to parasite development
- Pains in bones and joints
- Hepatosplenomegaly with tenderness
- Jaundice

Pathology

- Several species of Borrelia spirochetes

- Enter the body through the bite of a tick or through contamination of abraded skin with materials from crushed body lice

Laboratory Features

White Blood Cells

- Leukocytosis
- Neutrophilia

Red Blood Cells

- Not remarkable

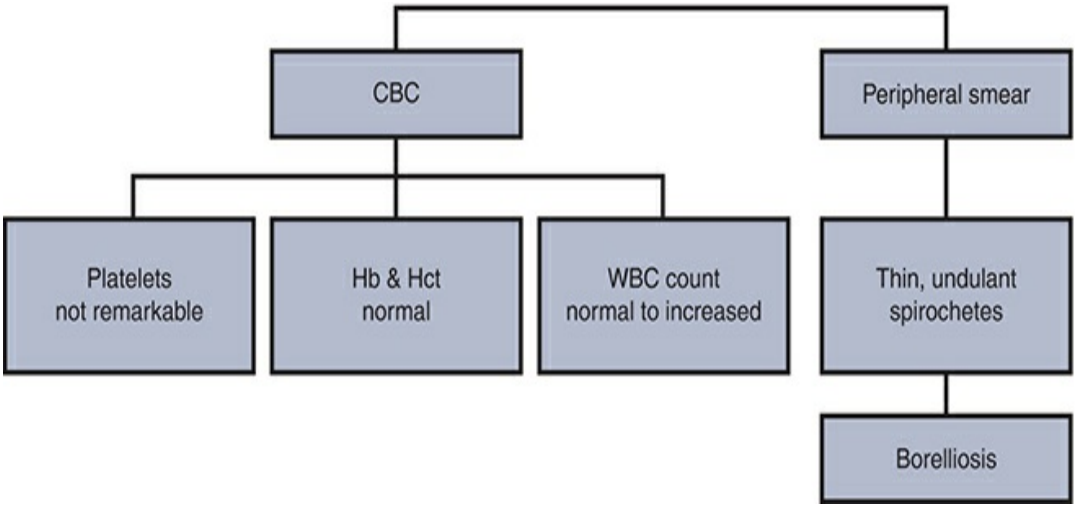
Platelets

- Not remarkable

Presence of Spirochetes in Blood During a Febrile Episode

- Thin, undulant, and overtly spiral organisms
- Located between red cells

Diagnostic Scheme



CANDIDIASIS

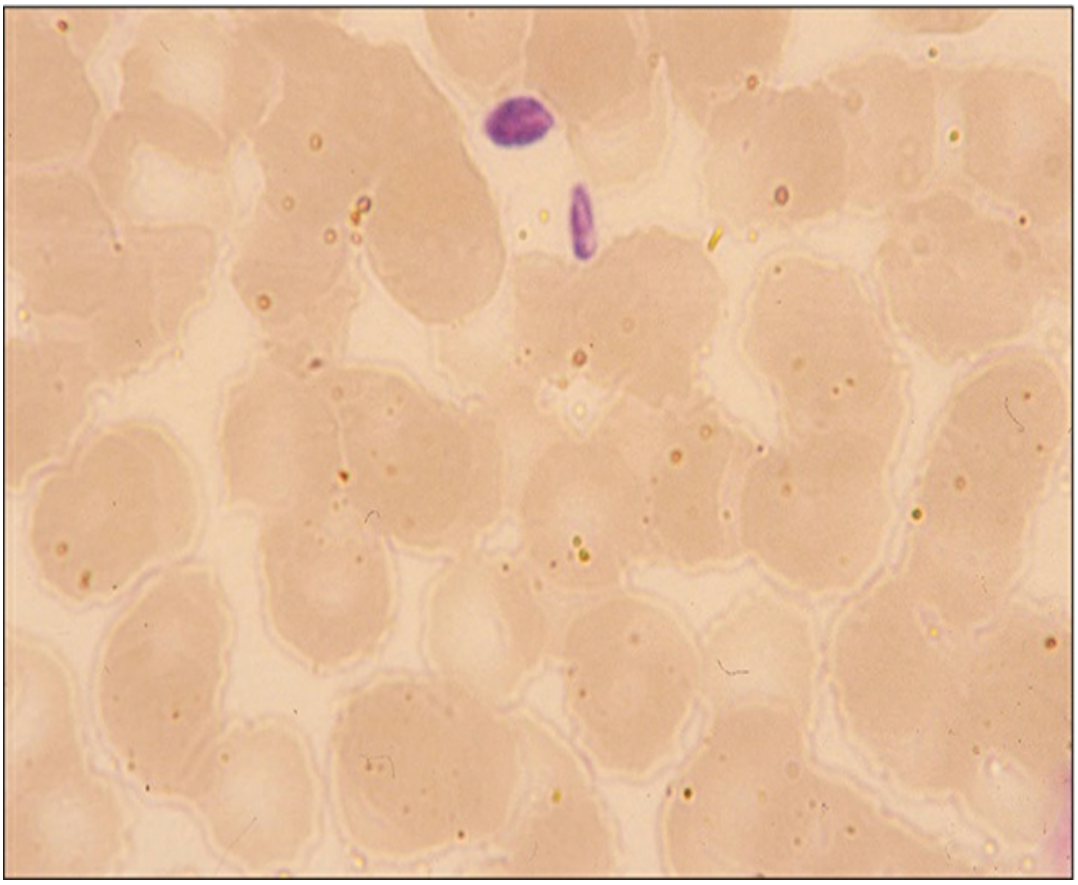


Figure IIC2-3

Peripheral blood smear.

Clinical Features

- Dysphagia, cough, itching, and burning
- Discharge—depends on primary location of infection
- Fever, chills, and headache
- May include shock, renal shutdown, and disseminated intravascular coagulation

Pathology

- Species of Candida , which are commensal organisms
- Candida albicans is the most common agent
- Immunocompromised people are at risk of infection

- Persons treated with broad-spectrum antibiotics and corticosteroids are at risk

Laboratory Features

White Blood Cells

- Leukocytosis

Red Blood Cells

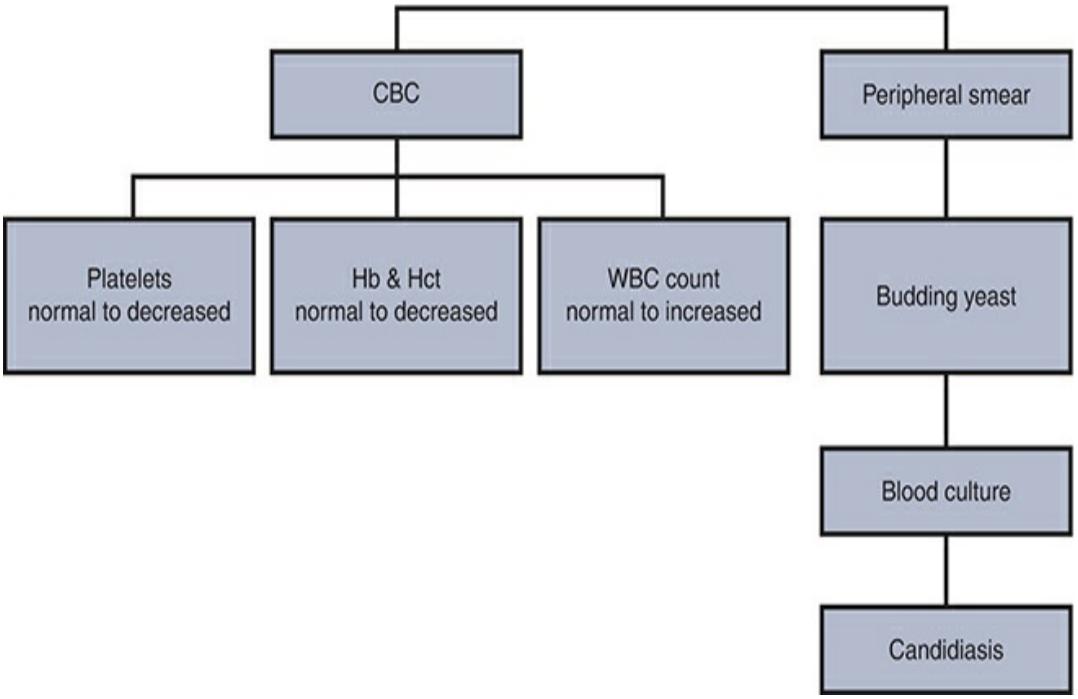
- Anemia develops in severe infections

Platelets

- Thrombocytopenia may develop

Budding Yeast With Pseudo or True Hyphae Can Be Observed in the Blood

Diagnostic Scheme



FILARIASIS

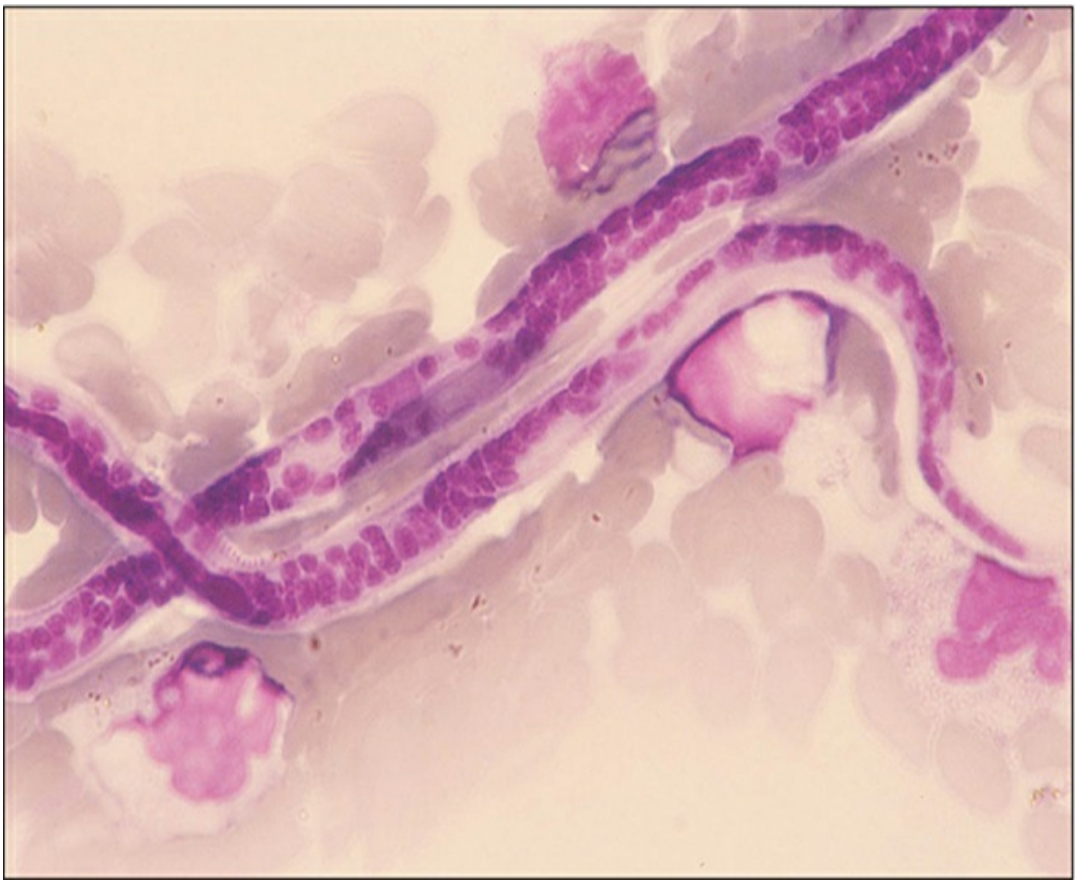


Figure IIC2-4

Peripheral blood smear.

Clinical Features

- Tissue-dwelling nematodes producing larvae that appear in blood, skin, and serous fluids
- May be asymptomatic
- Lymphadenitis to disruption of lymphatic vessels or drainage of lymph fluid
- Low-grade fever
- Maculopapular rash
- Urticaria

Pathology

- May be caused by Wuchereria bancrofti , Brugia malayi , Brugia timori , or Loa loa
- Spread by mosquitoes or tabanid fly when infective larvae escape from the mosquito, enter the puncture wound, and migrate to the lymphatics
- Adult worms develop in the lymphatics
- Gravid females produce microfilariae that circulate in blood
- Bancroftian filariasis present in tropical areas of Africa, Asia, the Pacific, and the Americas
- Brugian filariasis is found in South and Southeast Asia
- Loiasis is confined to the rain forest belt of Western and Central Africa and equatorial Sudan

Laboratory Features

White Blood Cells

- Normal to increased
- Eosinophilia possible

Red Blood Cells

- Not remarkable

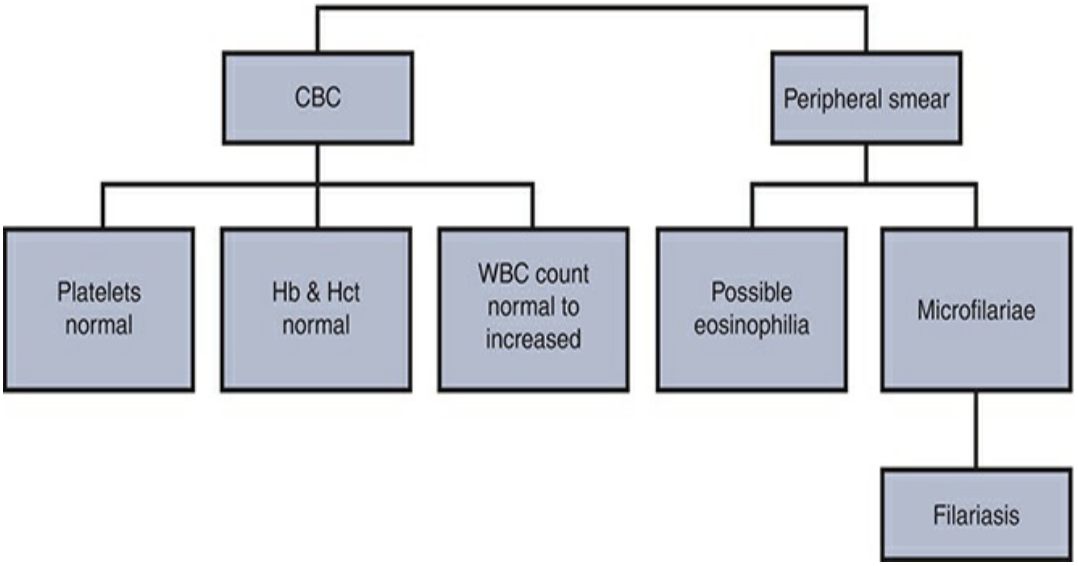
Platelets

- Not remarkable

Microfilariae in Blood May Be Seen on Stained Thick Films

- Species identification may be made by microfilaria morphology

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal
Hb & Hct normal
WBC count normal to increased
Possible eosinophilia
Microfilariae
Filariasis

HISTOPLASMOSIS

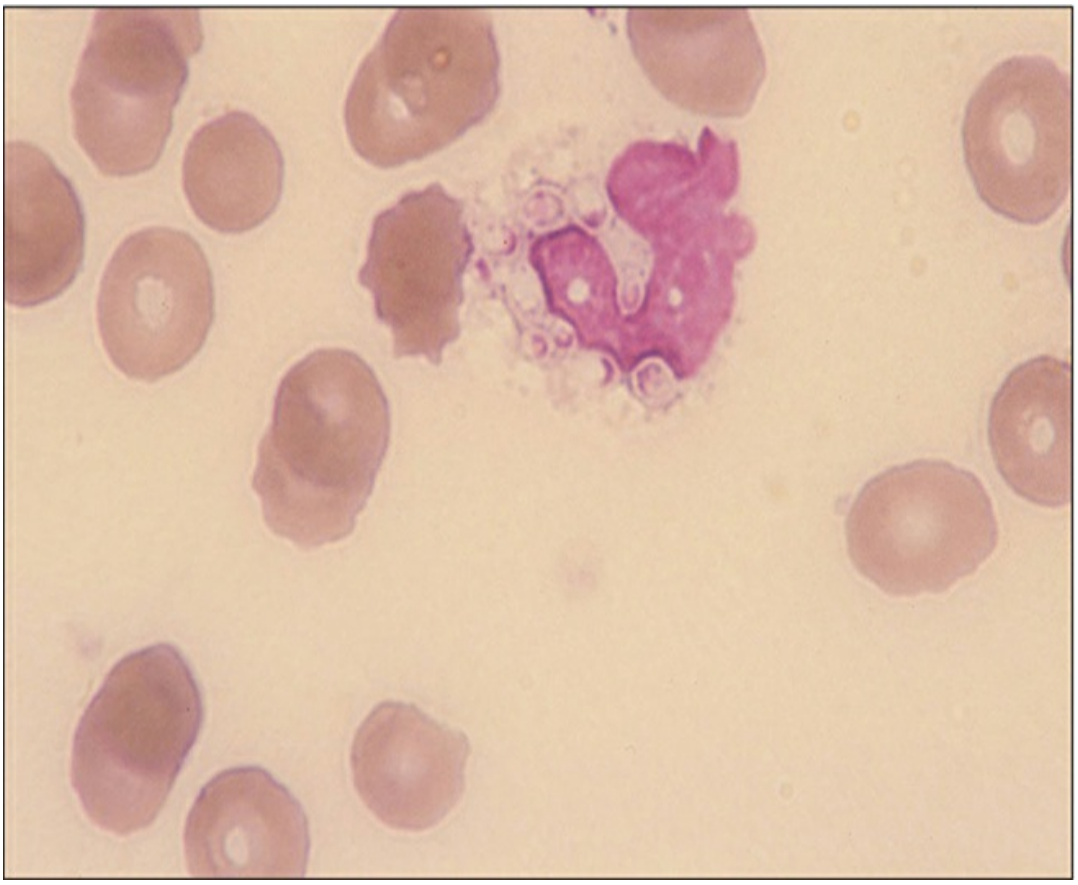


Figure IIC2-5

Peripheral blood smear.

Clinical Features

- Three stages
  - Acute primary
    - Asymptomatic to fever, cough, and malaise
  - Progressive disseminated
    - Hepatosplenomegaly, lymphadenopathy or gastrointestinal ulcerations, fatigue, weakness, malaise
  - Chronic cavitary
    - Pulmonary lesions, worsening cough, dyspnea, decreasing pulmonary function

Pathology

- Infection occurs worldwide; the endemic areas in the United States are the Ohio–Mississippi river valleys
- Histoplasma capsulatum is the causative agent
- Inhalation of spores in soil or dust contaminated with bird or bat droppings is the mode of exposure

Laboratory Features

White Blood Cells

- Normal to increased

Red Blood Cells

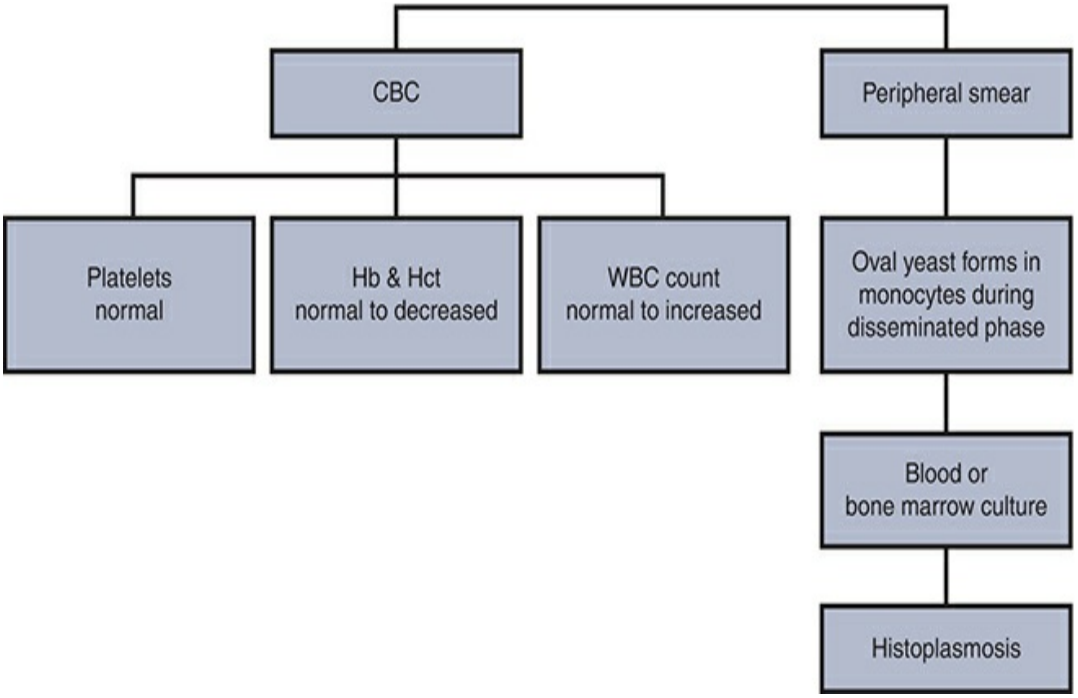
- Anemia in severe infections

Platelets

- Not remarkable

Small Oval Yeast Forms May Be Seen Within Macrophages or Monocytes on Peripheral Blood, Bone Marrow, or Buffy Coat Smears

Diagnostic Scheme


CBC
Peripheral smear
Platelets
normal
Hb & Hct
normal to decreased
WBC count
normal to increased
Oval yeast forms in
monocytes during
disseminated phase
Blood or
bone marrow culture
Histoplasmosis

LEISHMANIASIS

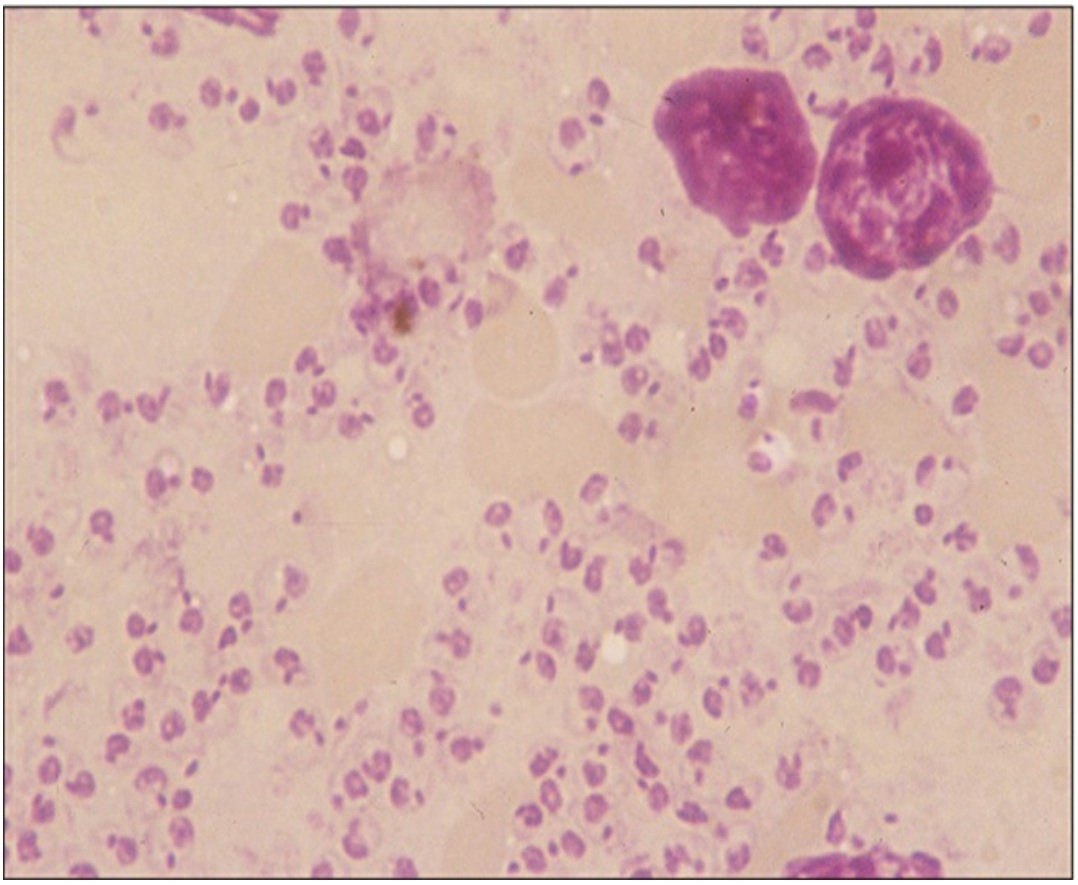


Figure IIC2-6

Splenic biopsy.

Clinical Features

- Three forms exist:
  - Visceral leishmaniasis (kala-azar, dumdum fever)
    - Irregular fever, hepatosplenomegaly, and emaciation
  - Cutaneous leishmaniasis (oriental or tropical sore)
    - Sharply demarcated skin lesion at the site of infective bite
    - Multiple lesions are rare and take months to heal
  - Mucocutaneous leishmaniasis (espundia)

    - Primary cutaneous ulcer appears but can metastasize to nasopharyngeal tissue and cause gross mutilations of the nose, palate, maxillary, etc.

Pathology

- Blood and tissue flagellates that are zoonotic infections from dogs, rodents, and other reservoirs

Visceral Leishmaniasis

- Present worldwide in tropical and some temperate areas
- Caused by Leishmania donovani complex
- Transmitted by the bite of sandflies
- Parasites disseminated from the skin to the lymph nodes, spleen, liver, and bone marrow
- Parasites are intracellular in macrophages
- Highly fatal without treatment

Cutaneous Leishmaniasis

- Occurs in Southern Europe, Asia, Africa, Middle East, Mexico, and Central and South America
- Causative agents are Leishmania major , Leishmania tropica , Leishmania mexicana , and Leishmania braziliensis
- Does not respond well to treatment but once ulcers are healed, permanent immunity results

Mucocutaneous Leishmaniasis

- Caused mainly by Leishmania (Viannia) braziliensis
- Parasites develop in nasopharyngeal macrophages
- Greatly feared because of gross deformities
- All forms of leishmaniasis are difficult to treat

Laboratory Features

White Blood Cells

- Leukopenia may occur in chronic forms

Red Blood Cells

- Anemia may develop in chronic forms

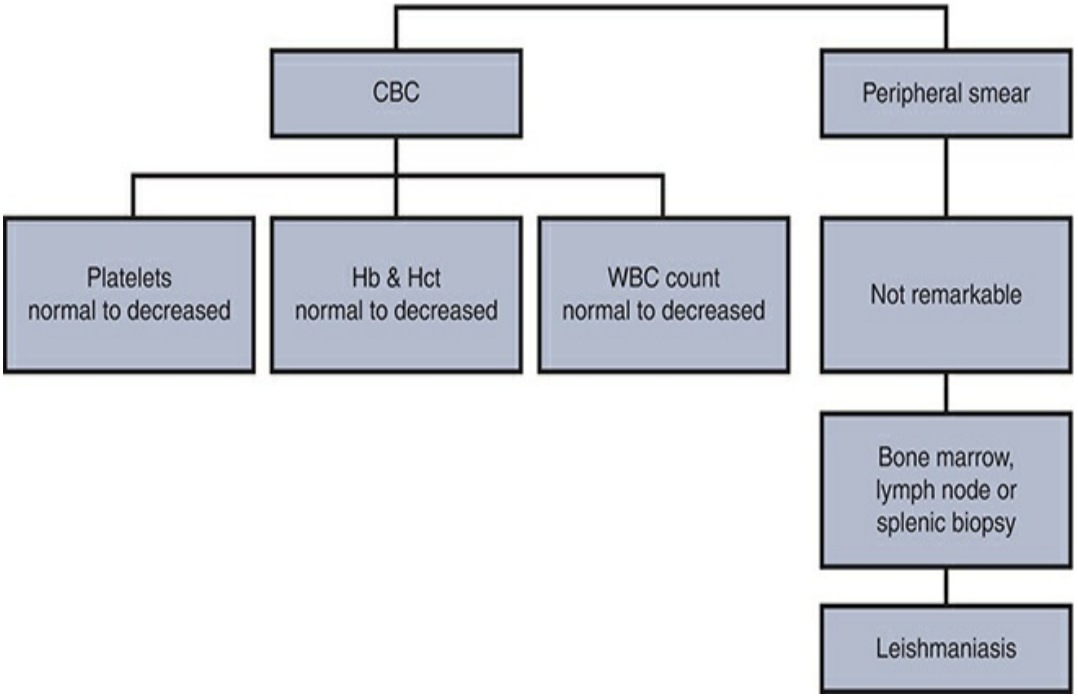
Platelets

- Thrombocytopenia may develop in chronic forms

The Intracellular Amastigotes May Be Seen in Stained Smears Containing Macrophages (i.e., Bone Marrow, Splenic Punctures)

- More difficult to see in cutaneous lesions

Diagnostic Scheme



MALARIA

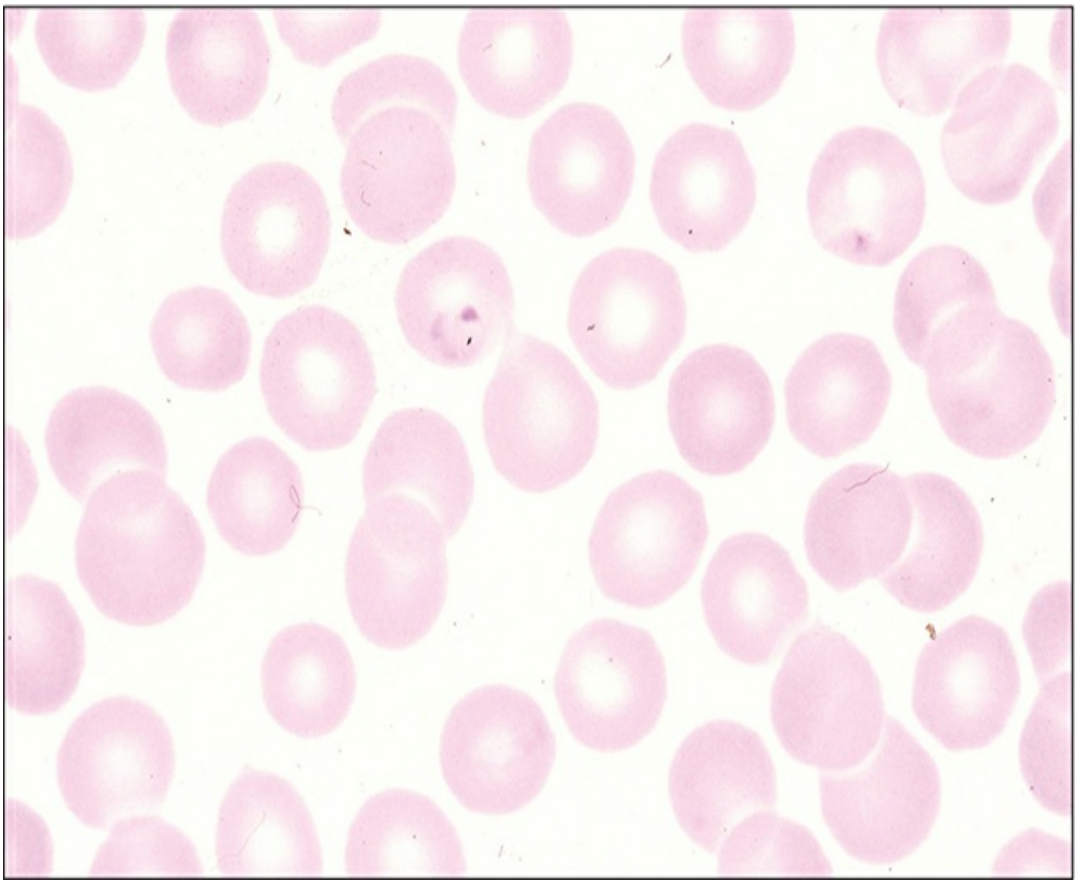


Figure IIC2-7

Peripheral blood smear.

Clinical Features

- Malaise, chills, and fever
- Thready pulse, headache, and nausea
- Anemia
- Jaundice
- Diarrhea
- Hepatosplenomegaly

Pathology

- Worldwide, there are about 198 million cases with about 584,000 deaths per year

- Endemic in Africa, South and Southeast Asia, Central America, and northern South America
- Caused by four different species: Plasmodium falciparum , P. vivax , P. ovale , and P. malariae
- P. knowlesi can be found in most Southeast Asian countries
- Transmitted by the female Anopheles mosquitoes, which are strictly nighttime feeders

Laboratory Features

White Blood Cells

- Not remarkable

Red Blood Cells

- Hemolytic anemia

Platelets

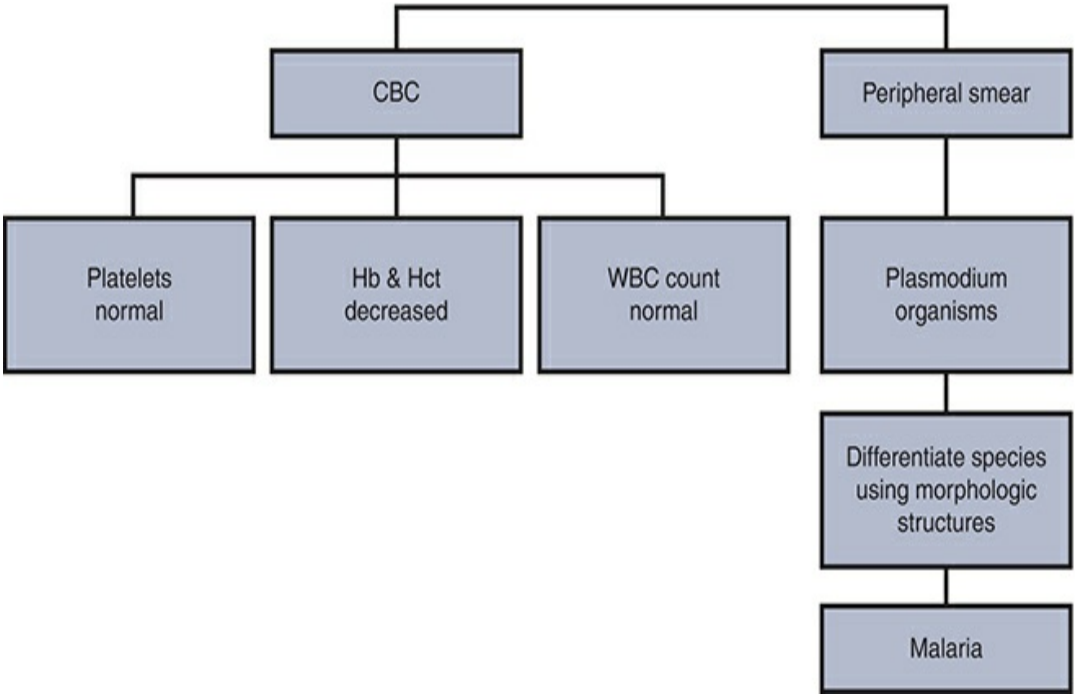
- Not remarkable

Plasmodium Organisms May Be Found on Thin and Thick Peripheral Blood Smear

- Species diagnosis is made by ring-stage morphology

Rapid Diagnostic Tests as Well as Species-specific PCR

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal
Hb & Hct decreased
WBC count normal
Plasmodium organisms
Differentiate species using morphologic structures
Malaria

TOXOPLASMOSIS

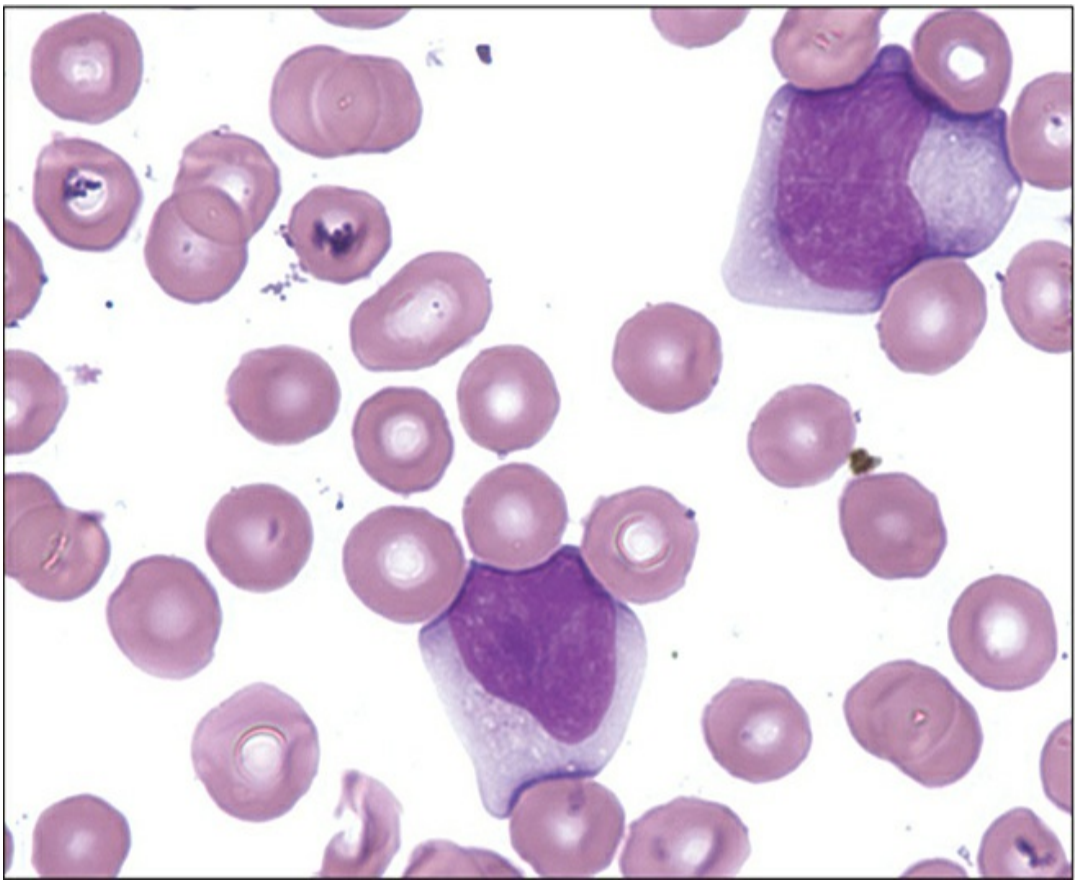


Figure IIC2-8

Peripheral blood smear.

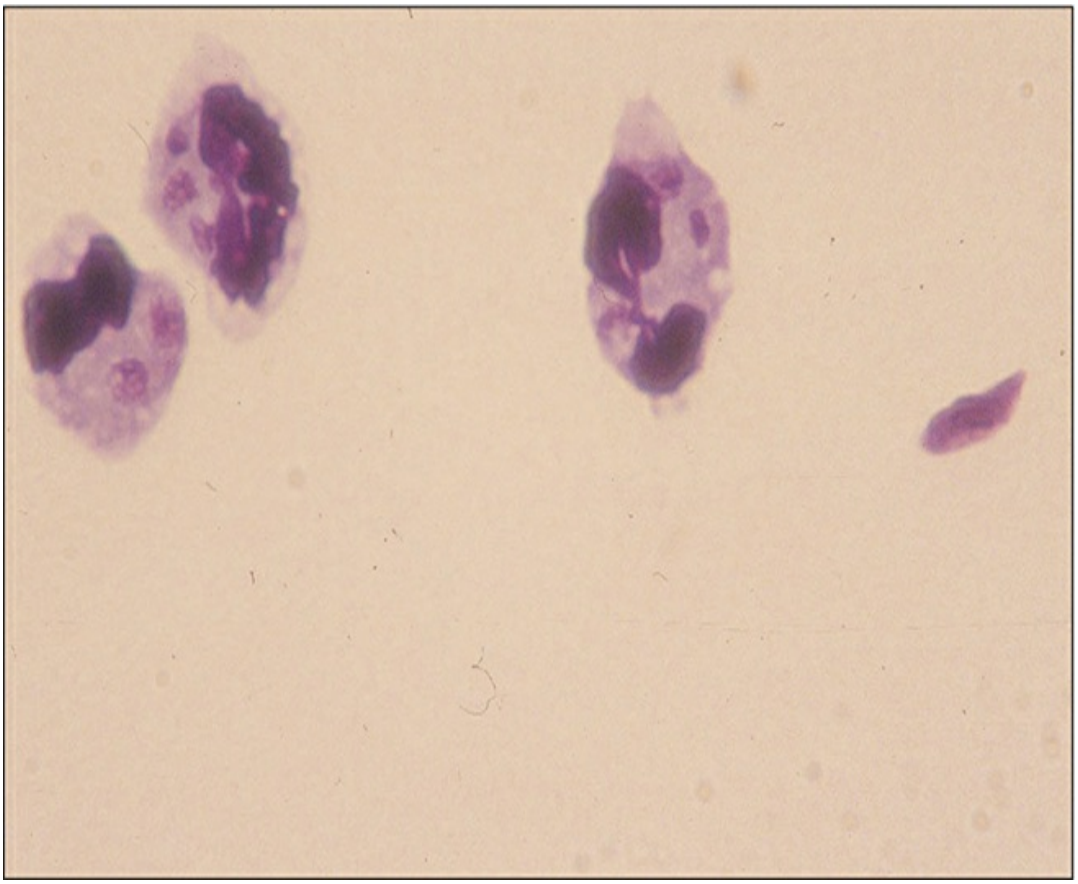


Figure IIC2-9

Lymph node impression.

Clinical Features

- Usually asymptomatic
- Principal health risk is to neonates of infected women, and it is an important cause of death in patients with AIDS
- May cause malaise, fever, myalgia, and pharyngitis
- Lymphadenopathy and hepatosplenomegaly
- Severe form—pneumonitis, myocarditis, meningoencephalitis, high fever, and chills

Pathology

- Immunocompromised patients may be at risk for a severe form of the infection

- Caused by Toxoplasma gondii , which is a ubiquitous protozoan parasite of birds and mammals
- Ingestion of oocysts from cat feces is the most common mode of oral infection
- Undercooked meats may be infective
- Can be transmitted transplacentally

Laboratory Features

White Blood Cells

- Lymphocytosis
- Atypical lymphocytes

Red Blood Cells

- Not remarkable

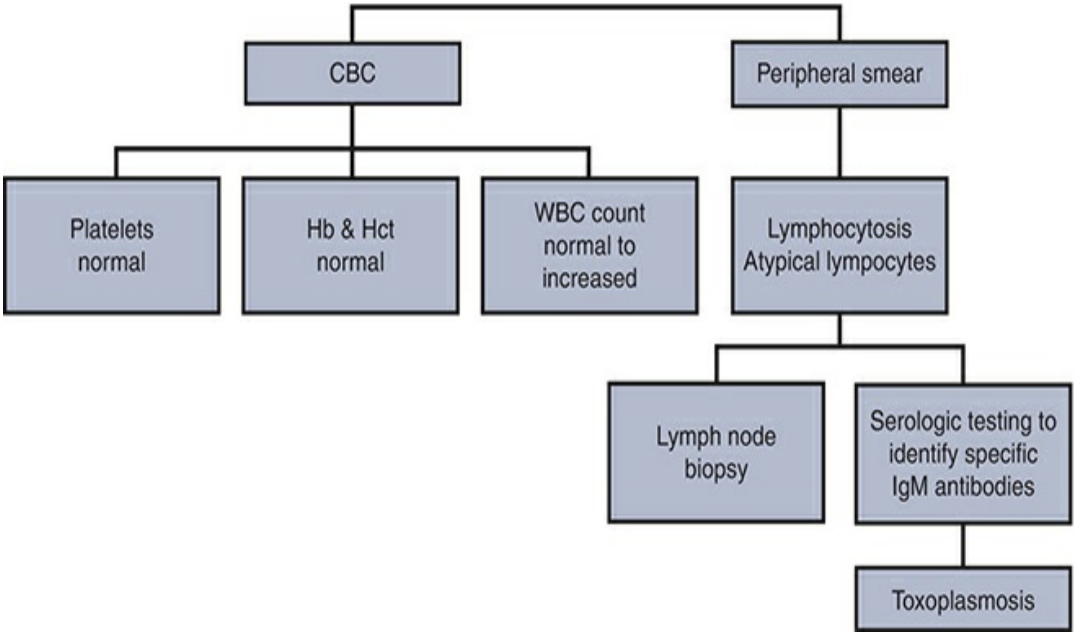
Platelets

- Not remarkable

Cluster of Tachyzoites May Be Observed in Tissue Sections or Impression Smears

- Organisms may be seen in the white blood cells or macrophages in the bone marrow

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal
Hb & Hct normal
WBC count normal to increased
Lymphocytosis Atypical lympocytes
Lymph node biopsy
Serologic testing to identify specific IgM antibodies
Toxoplasmosis

TRYPANOSOMIASIS

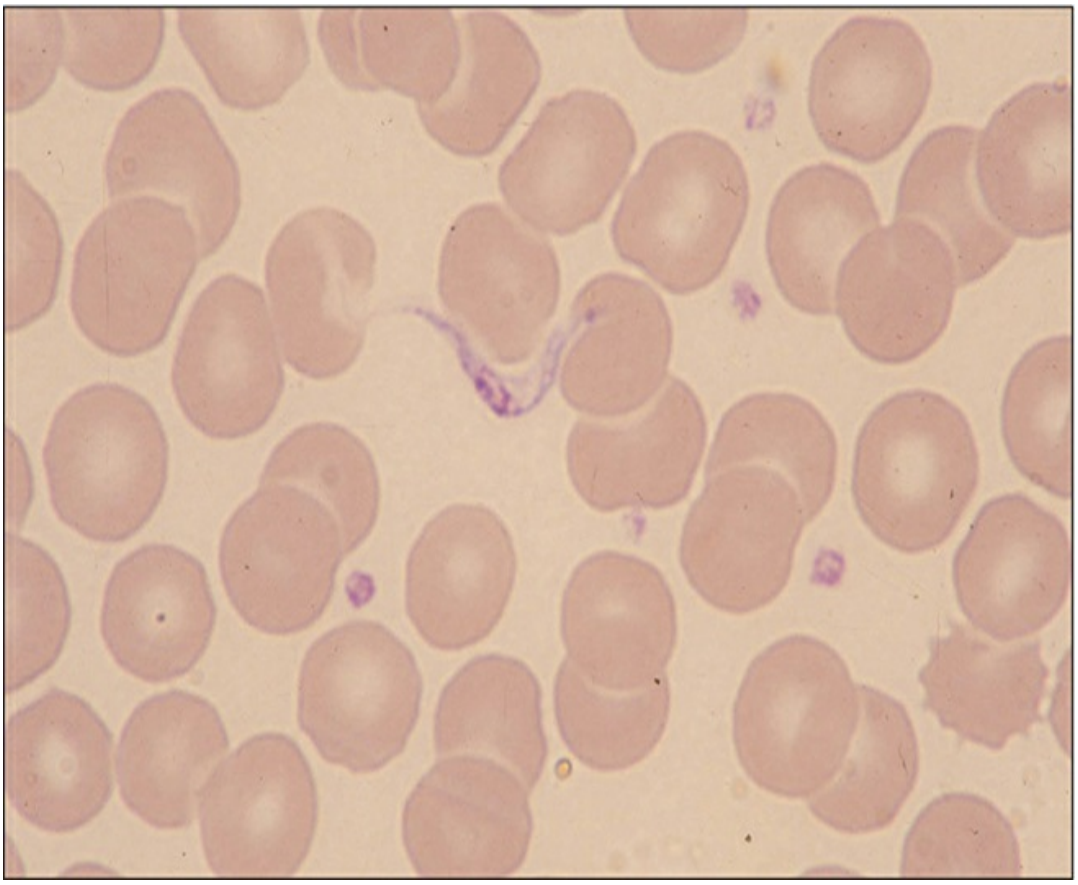


Figure IIC2-10

Peripheral blood smear.

Clinical Features

African Trypanosomiasis (African Sleeping Sickness)

- Papule develops and resolves spontaneously
- Fever, headache, edematous swellings, and red rash
- Lymphadenopathy
- Central nervous system involvement—headache, personality changes, somnolence, tremor, ataxia, and coma

American Trypanosomiasis (Chagas Disease)

- Initial infection is usually asymptomatic

- May have indurated skin lesion at site of entry
- Fever and malaise
- Generalized lymphadenopathy and hepatosplenomegaly
- Major cause of heart disease in South America, chronic cardiomyopathy occurs in some cases

Pathology

African Trypanosomiasis

- Caused by Trypanosoma brucei gambiense in Western and Central Africa
- Caused by Trypanosoma brucei rhodesiense in Eastern Africa
- Transmitted by tsetse flies
- May be transmitted by blood transfusion

American Trypanosomiasis

- Caused by Trypanosoma cruzi
- Transmitted by triatomine (reduviid) bugs
- Infected bugs deposit feces containing the organisms while feeding
- The organisms enter through the bite and invade macrophages at the site of entry
- Eventually, they reach other cells of the reticuloendothelial system
- Primary damage is to neuroconductivity of the heart, esophagus, and colon
- Can be transmitted by blood transfusion

Laboratory Findings

White Blood Cells

- Not remarkable

Red Blood Cells

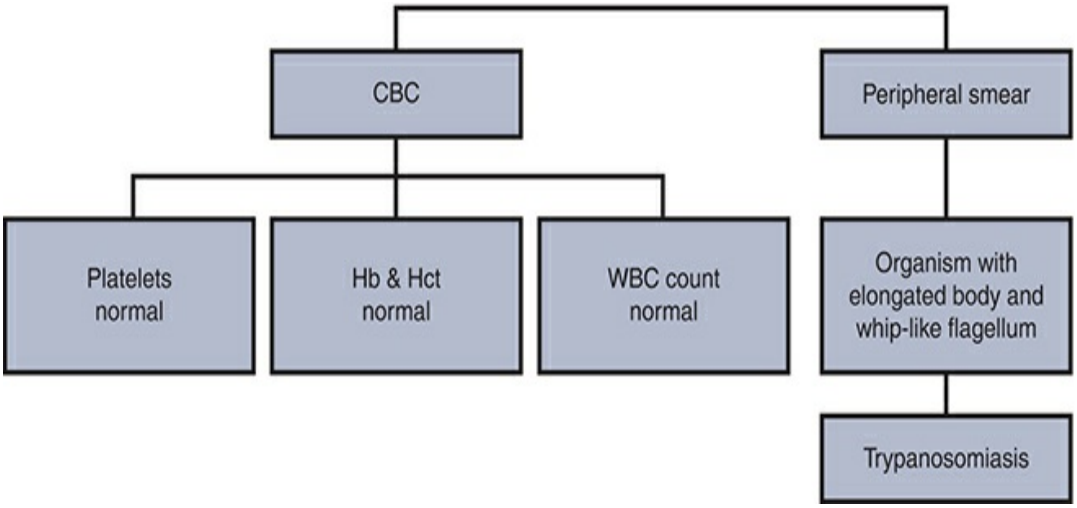
- Not remarkable

Platelets

- Not remarkable

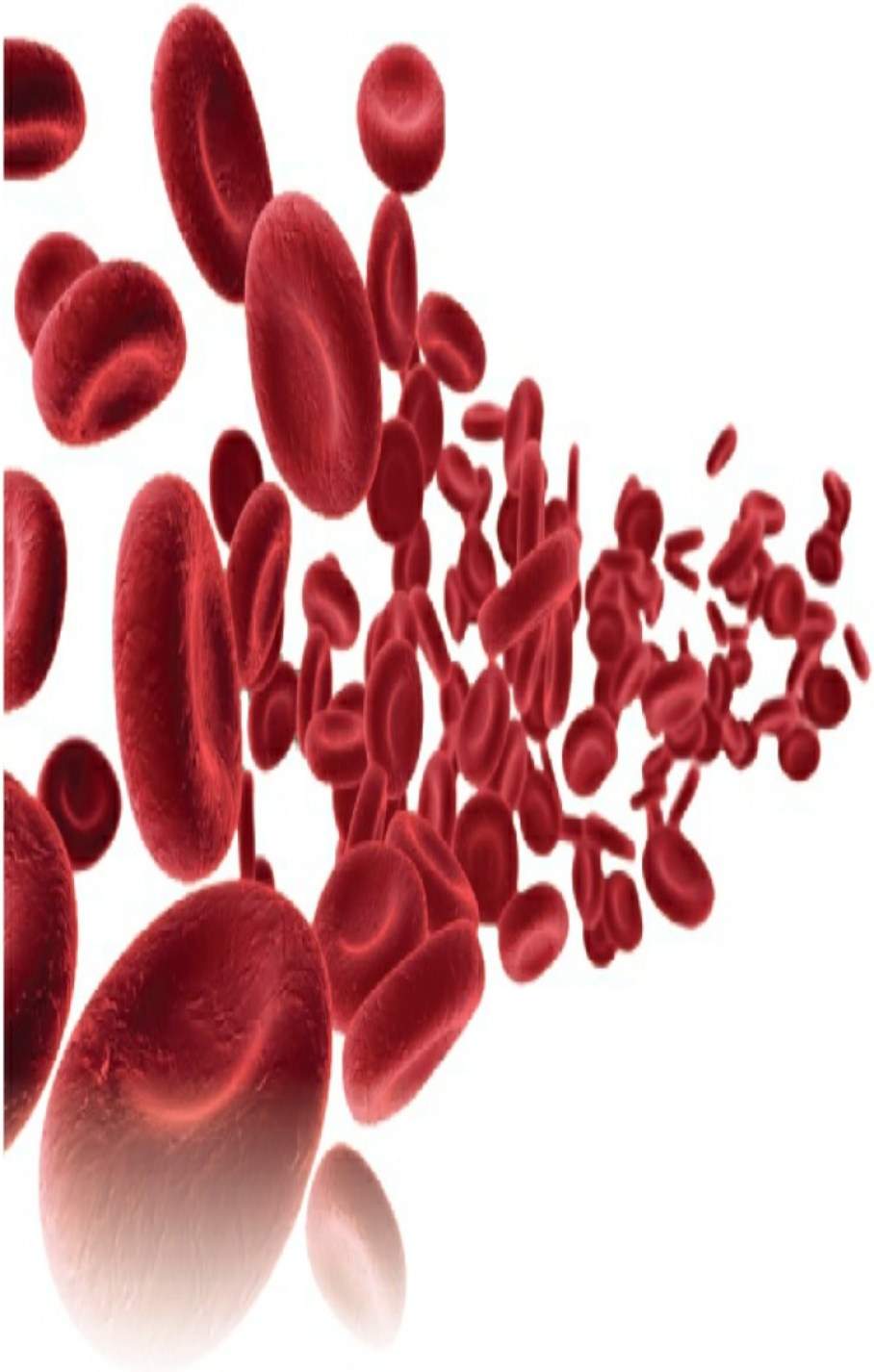
Organisms May Be Observed in Thin and Thick Smears of Peripheral Blood During the Acute Phase of Infection

Diagnostic Scheme



CHAPTER 3

RETICULOENDOTHELIAL SYSTEM STORAGE DISORDERS



GAUCHER DISEASE

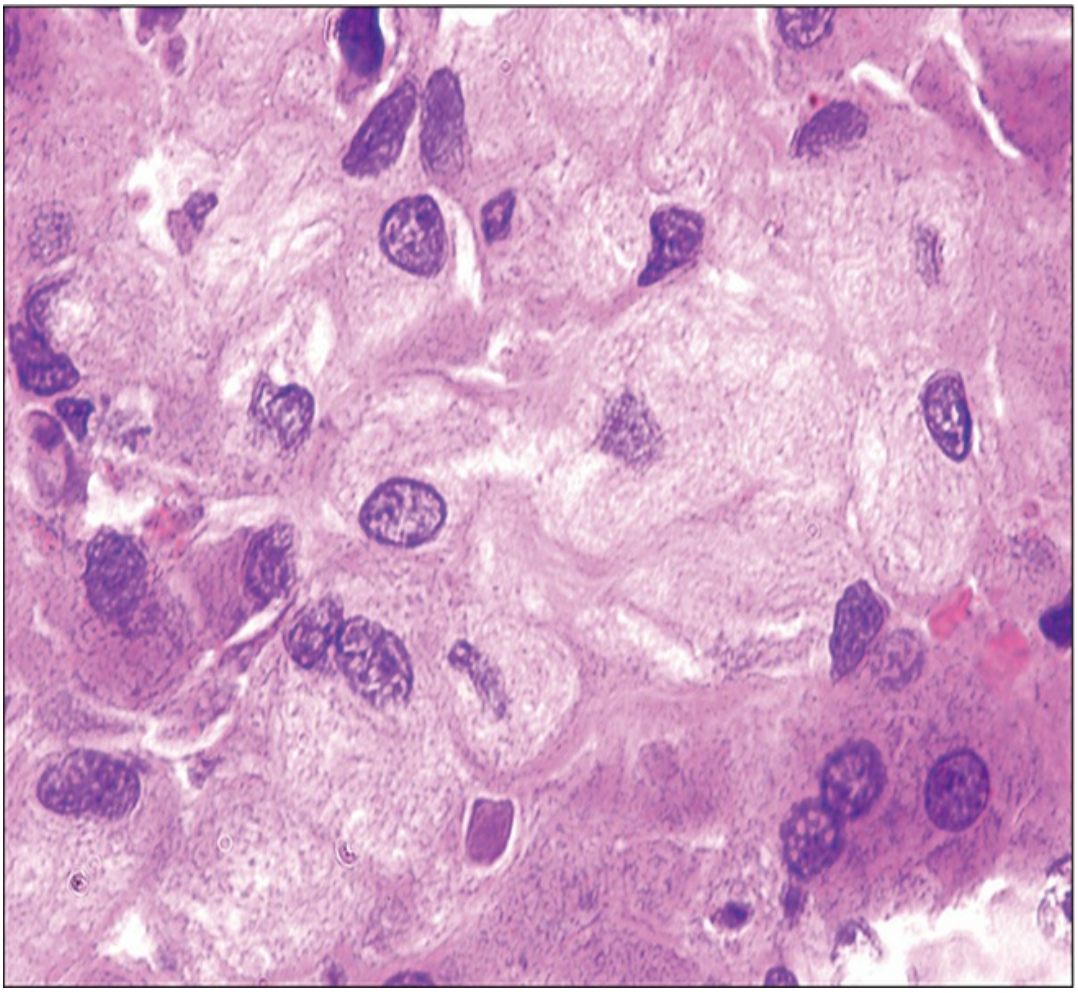


Figure IIC3-1

Bone marrow smear.

Clinical Features

- Splenomegaly
- Hepatomegaly
- Destruction of bone
- Pigmentation of skin in exposed areas
- Purpura and abnormal bleeding

Pathology

- Most common storage disease
- Inherited as an autosomal recessive trait

- Deficiency of beta-glucocerebrosidase
- Accumulation of glucocerebroside in macrophages of the lymphoid tissue, spleen, liver, and bone marrow

Laboratory Features

White Blood Cells

- Leukopenia (2.0–3.0 × 10^9/L)
- Relative lymphocytosis

Red Blood Cells

- Normocytic/hypochromic anemia

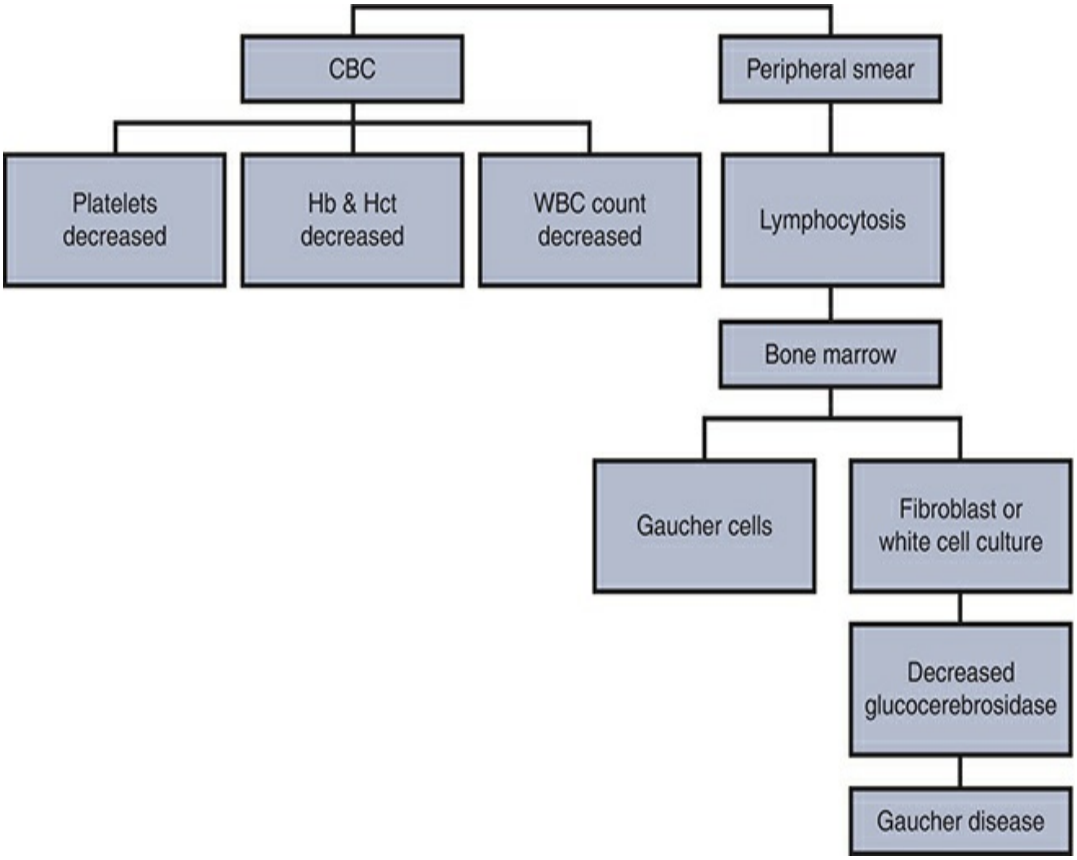
Platelets

- Moderate thrombocytopenia (50–100 × 10^9/L)

Bone Marrow

- Presence of Gaucher cells in the bone marrow, spleen, and liver
    - Cell is large with relatively small eccentric nucleus with coarsely clumped cytoplasm that is filled with a fibrillar pale-staining lipid

Diagnostic Scheme


CBC
Peripheral smear
Platelets decreased
Hb & Hct decreased
WBC count decreased
Lymphocytosis
Bone marrow
Gaucher cells
Fibroblast or white cell culture
Decreased glucocerebrosidase
Gaucher disease

MUCOPOLYSACCHARIDOSES

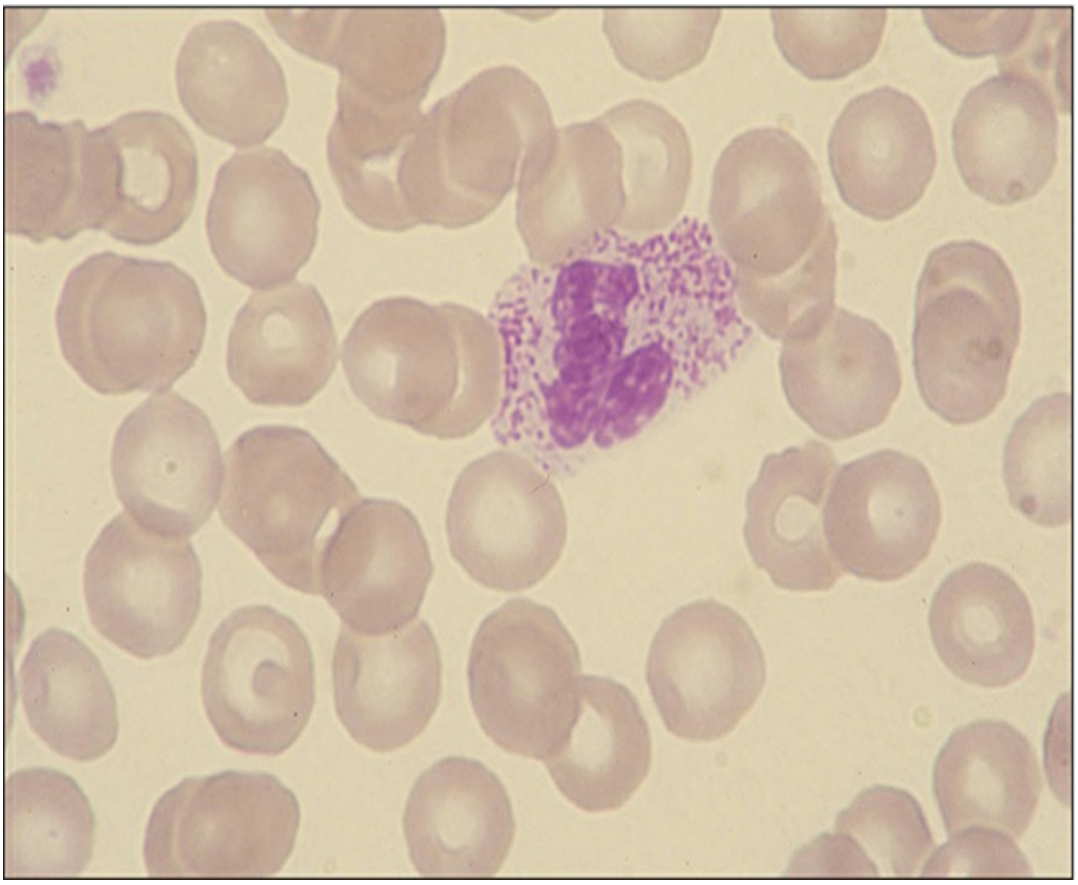


Figure IIC3-2

Peripheral blood smear.

Clinical Features

- Coarse facial features—flat nose and thick lips
- Skeletal abnormalities including bone dysplasias and joint movement restriction
- Dwarfism
- Neurologic manifestations
  - Psychomotor retardation
  - Deafness
  - Ataxia
  - Mental status disturbances
- Severity varies with the type of mucopolysaccharide

present
- Hepatosplenomegaly

Pathology

- A group of inherited diseases with enzyme deficiencies
- Excessive accumulation of mucopolysaccharides in body tissues
  - Arteries
  - Skeleton
  - Eyes
  - Joints
  - Skin
  - Liver
  - Bone marrow
  - Central nervous system
- Inherited as autosomal recessive genes except for Hunter syndrome, which is X-linked
- Depending on enzyme deficiency, different syndromes occur
  - Hurler/Schele Syndrome
  - Hurler Disease
  - Hunter Syndrome
  - Sanfilippo Syndrome
  - Hyaluronidase Deficiency
  - Morquio Syndrome (no Alder-Reilly inclusions seen)
  - Maroteaux-Lamy Syndrome
  - Sly Syndrome

Laboratory Features

White Blood Cells

- Presence of Alder-Reilly bodies in neutrophils, eosinophils, and basophil
- Inclusions may occasionally be seen in lymphocytes and monocytes

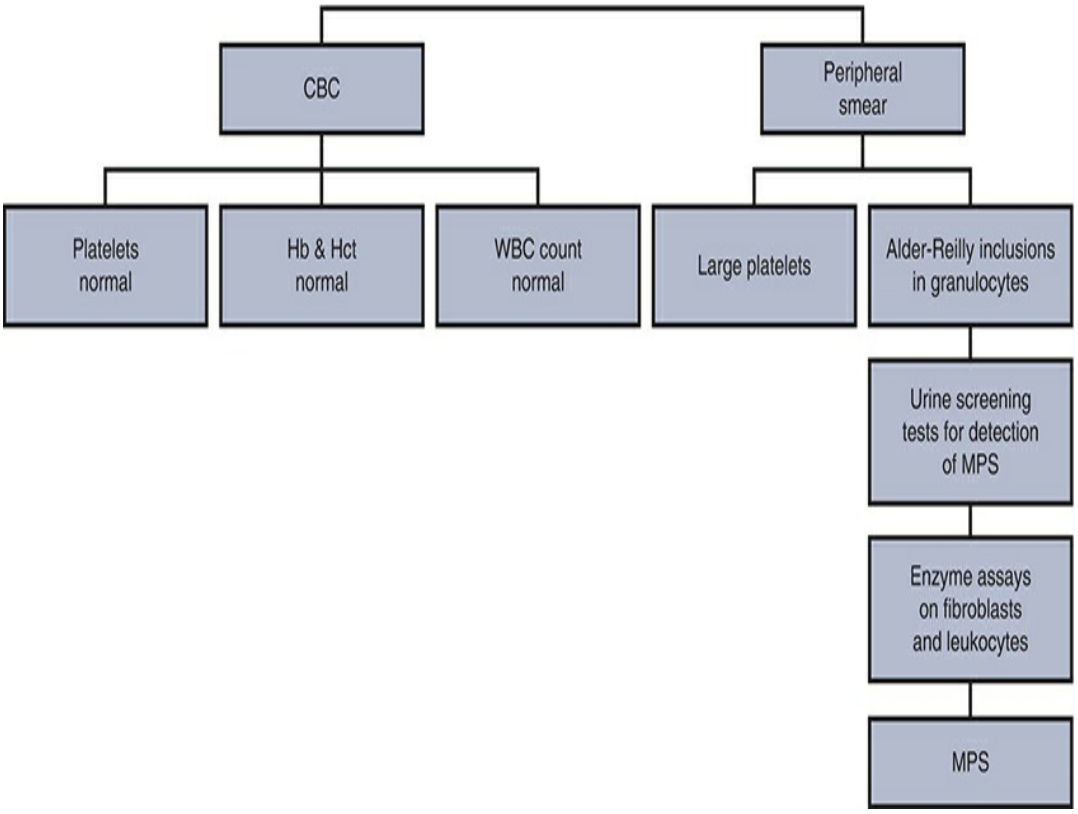
Red Blood Cells

- Not remarkable

Platelets

- Abnormally large

Diagnostic Scheme



NIEMANN-PICK DISEASE

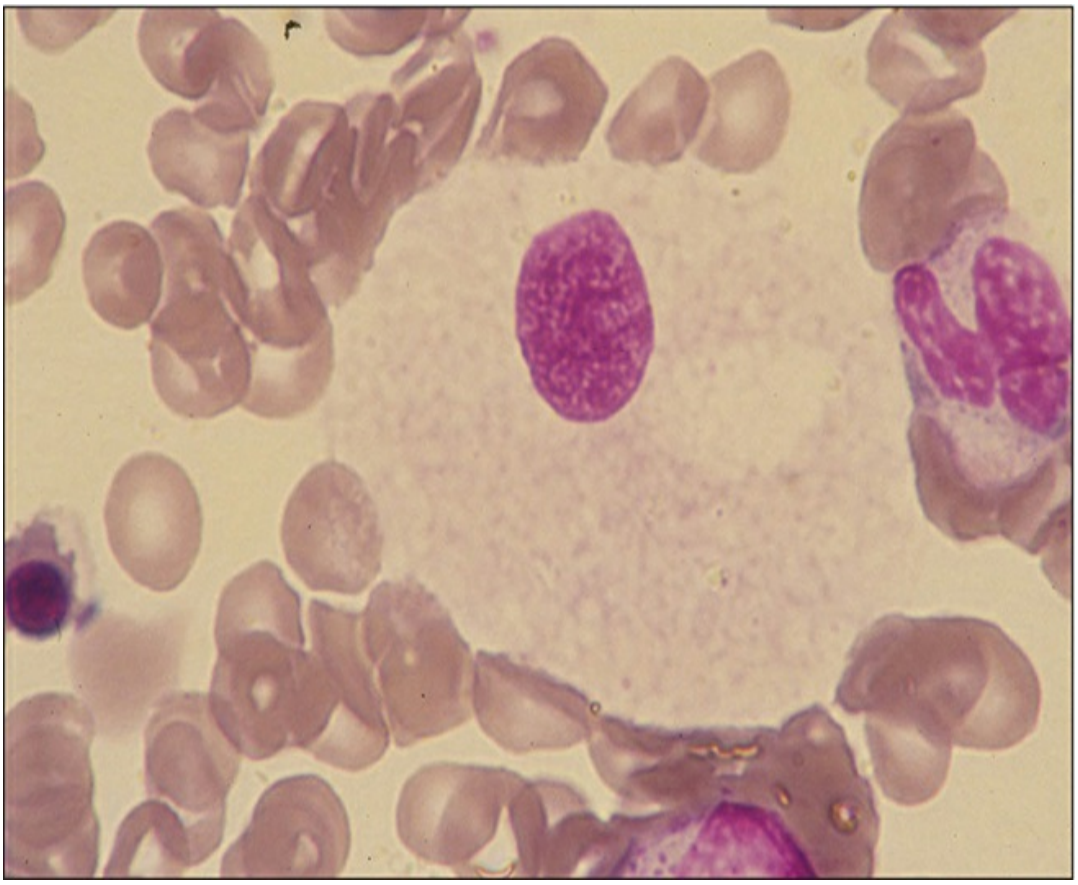


Figure IIC3-3

Bone marrow smear.

Clinical Features

- Splenomegaly
- Hepatomegaly
- Severely impaired development
- About one-third of patients have a cherry-red spot on the macula of the retina
- It affects girls more often than boys

Pathology

- An autosomal recessive inherited disorder
- Deficiency of sphingomyelinase

- Accumulation of sphingomyelin in macrophages in the lymphoid system

Laboratory Features

White Blood Cells

- Leukopenia may occur
- Monocytes and lymphocytes may show characteristic vacuoles

Red Blood Cells

- Mild anemia

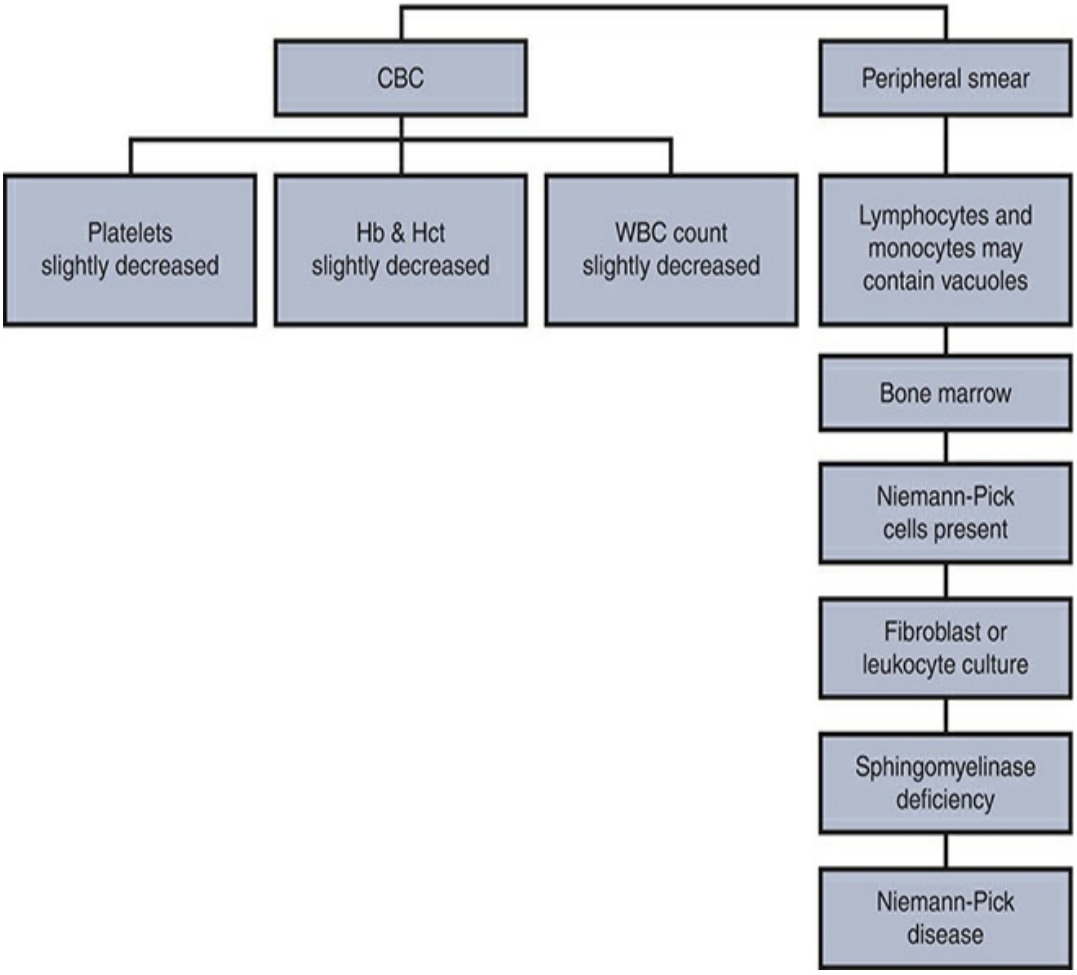
Platelets

- Mild thrombocytopenia

Bone marrow

- Finding Niemann-Pick cells in bone marrow or other tissues
    - These cells are filled with droplets of sphingomyelin material

Diagnostic Scheme


CBC
Peripheral smear
Platelets slightly decreased
Hb & Hct slightly decreased
WBC count slightly decreased
Lymphocytes and monocytes may contain vacuoles
Bone marrow
Niemann-Pick cells present
Fibroblast or leukocyte culture
Sphingomyelinase deficiency
Niemann-Pick disease

SEA-BLUE HISTIOCYTOSIS

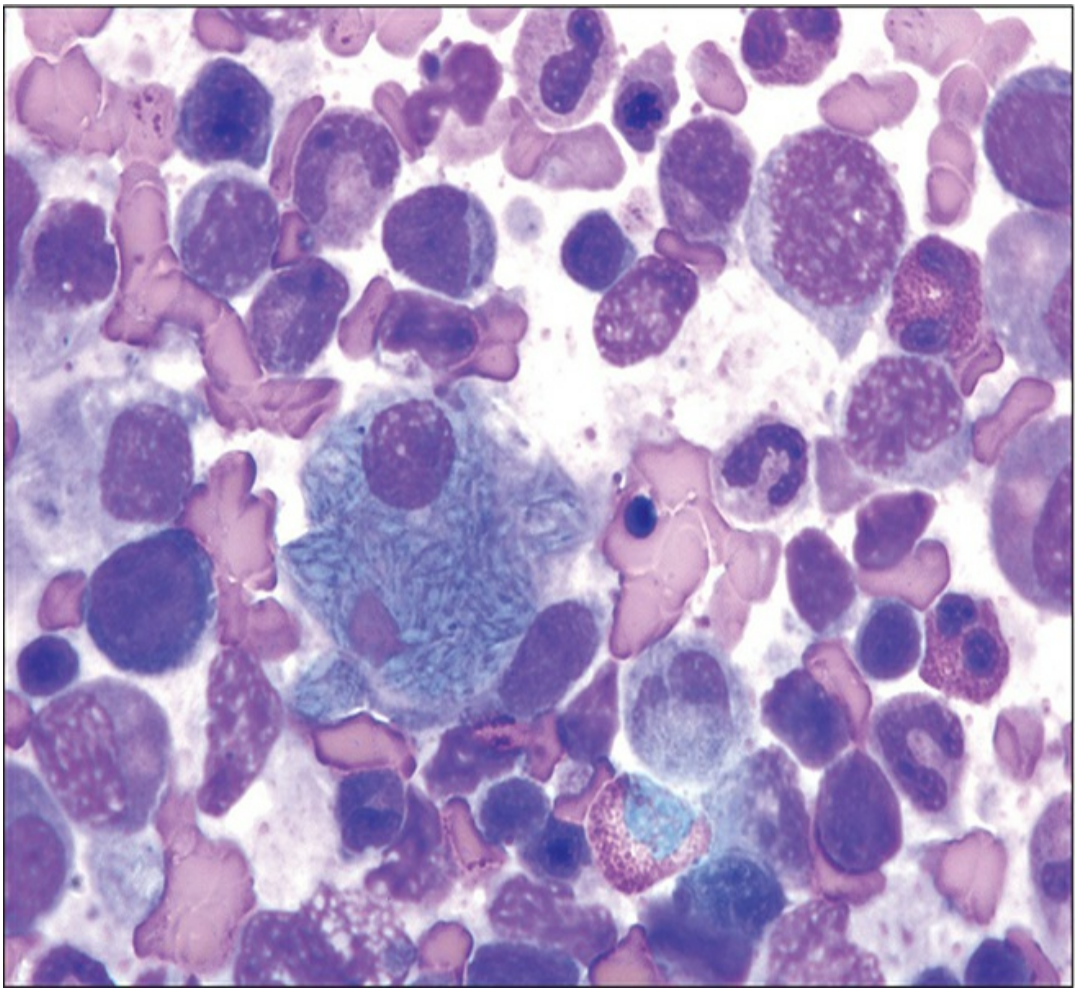


Figure IIC3-4

Bone marrow smear.

Clinical Features

- Splenomegaly
- Hepatomegaly
- Purpura seen in about half of the cases
- Occasional neurologic damage

Pathology

- Familial disorder in which macrophages contain blue or blue-green granules in the cytoplasm
- No specific enzyme deficiency

- Course of the disease is usually benign
- An acquired type of this disease is associated with several conditions

Laboratory Features

White Blood Cells

- Not remarkable

Red Blood Cells

- Not remarkable

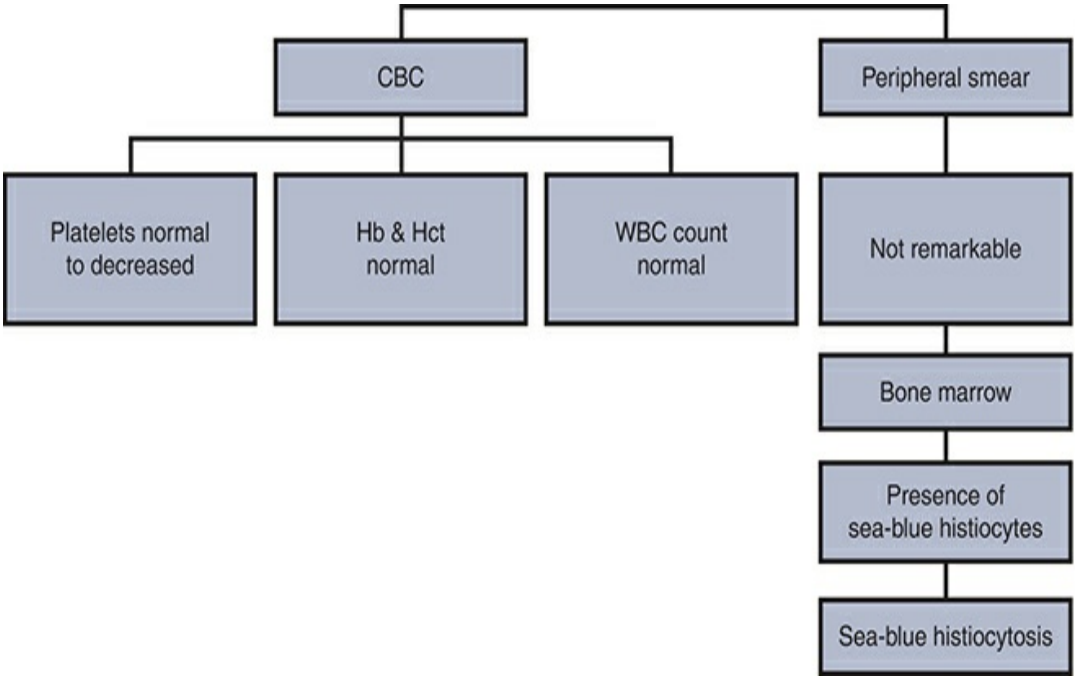
Platelets

- Normal to decreased

Bone Marrow

- Sea-blue histiocytes are found in the bone marrow and spleen
    - Large cells
    - Eccentric nucleus
    - Cytoplasm contains blue or blue-green granules

Diagnostic Scheme


CBC
Peripheral smear
Platelets normal to decreased
Hb & Hct normal
WBC count normal
Not remarkable
Bone marrow
Presence of sea-blue histiocytes
Sea-blue histiocytosis

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