Acute Leukemia

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Learning Objectives

- By the end of tis lecture students will be able to:
- Define acute leukemia
- Classify acute leukemias
- Discuss pathophysiology of acute leukemia
- Explain how will you diagnose cases of acute leukemia

Leukemia

- Leukemia is caused by mutation of bone marrow pluripotent cells resulting in the formation of abnormal leukemic cells that impaired the production of normal red blood cells ,white blood cells and platelets.

- Hematology in practice .page 160

- Group of malignant disorders of the hematopoietic tissues characteristically associated with increased numbers of premature white cells in the bone marrow and / or peripheral blood

Types of Leukemia

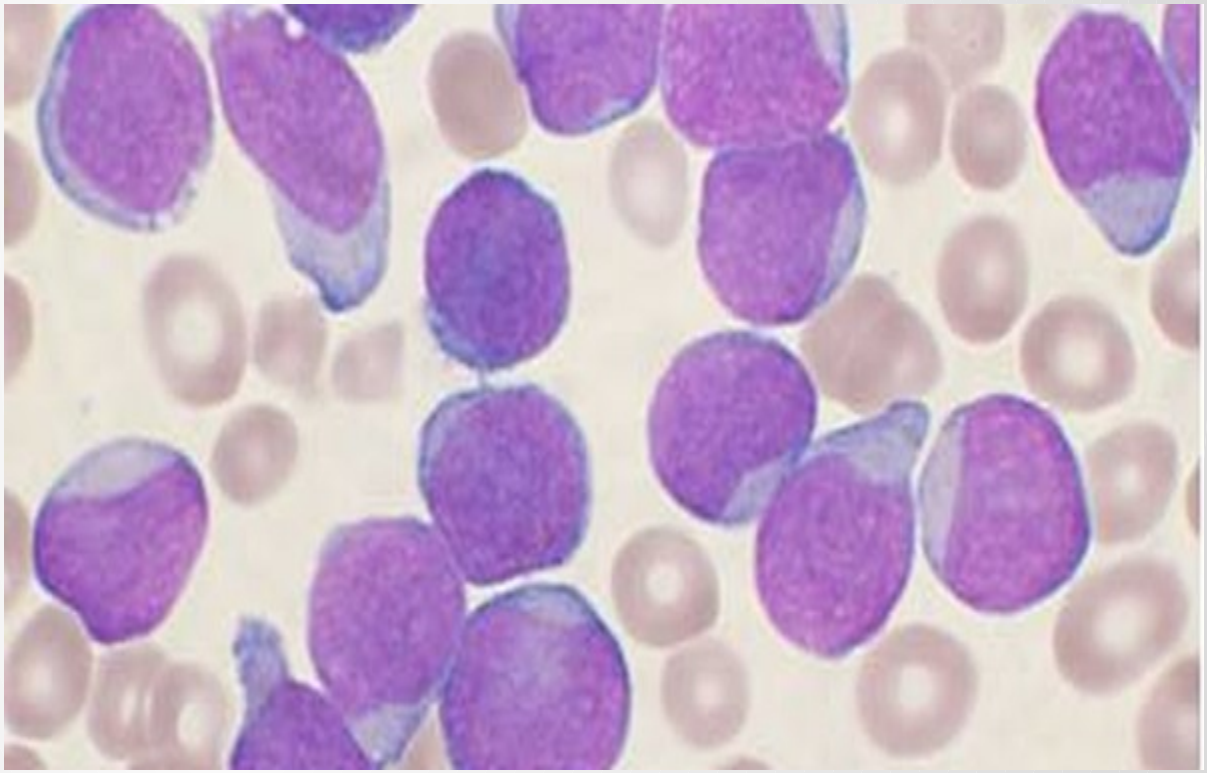
- Acute
- Lymphoid
- Myeloid

- Chronic
- Lymphoid
- Myeloid

Acute lymphoblastic leukemia

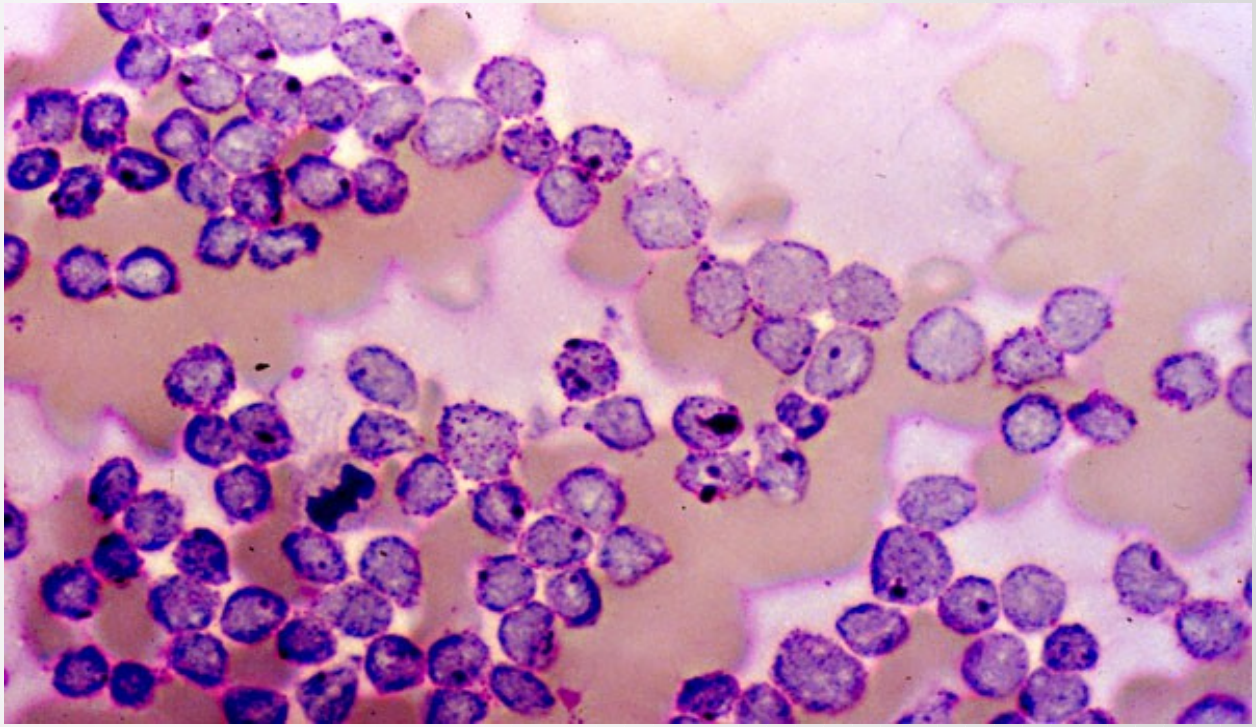
- Composed of immature B (pre-B) or T (pre-T) cells, called as lymphoblasts
- About 85% are B-ALLs
- typically manifest as childhood acute “leukemia.”
- T-ALLs tend to occur in adolescent males as thymic “lymphomas.”

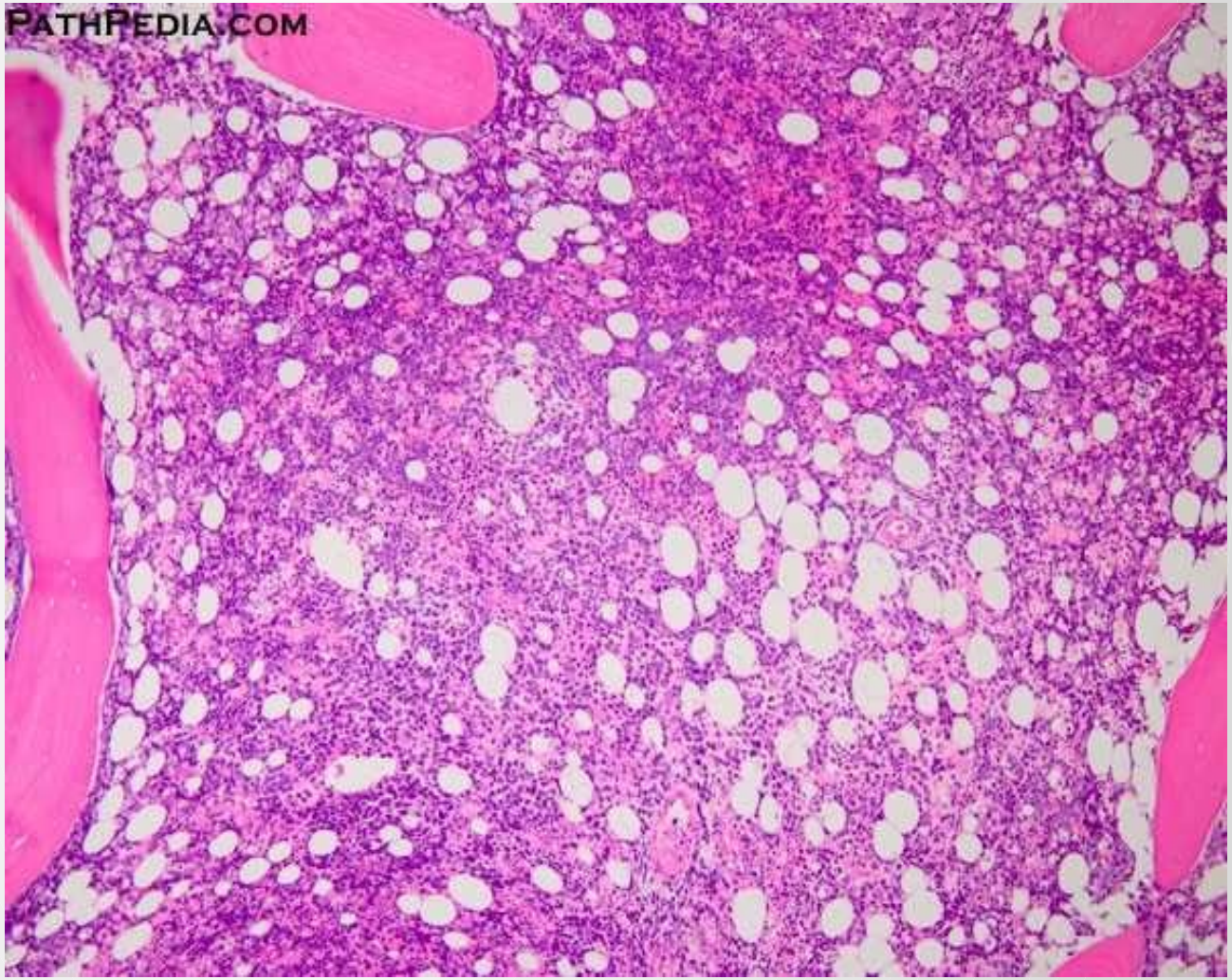
Morphology



- Bone marrow is hypercellular
- Packed with lymphoblasts
- Mediastinal thymic masses occur in 50% to 70% of T-ALLs
- Lymphadenopathy and splenomegaly
- Scanty basophilic cytoplasm in leucoblasts
- High N/C ratio
- High mitotic rate is high

- Special Histochemical stains:
- Myeloperoxidase-negative
- Periodic acid–Schiff-positive

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Immunophenotyping

- Terminal deoxynucleotidyl-transferase (TdT), a specialized DNA polymerase ,expressed only in pre-B and pre-T lymphoblasts, is positive in 95% of cases
- B-ALLs are positive for
- Pan B-cell marker CD19
- Transcription factor PAX5
- CD10 (Negative in vary immature B ALL)
- Late pre-B" ALLs express CD10, CD19, CD20, and cytoplasmic IgM heavy chain (μ chain).
- T-ALLs are positive for
- CD1, CD2, CD5, and CD7
- Vary immature tumors are usually negative for surface CD3, CD4, and CD8
- Late pre-T cell tumors are positive for these markers

Classification of ALL

B-lineage ALL	CD10	CD19	cCD22	cCD79a	TDT	Ig	PAX5
Early precursor (pro-B-ALL)	–	+	+	+	+	–	+
Common (cALL)	+	+	+	+	+	–	+
Pre-B-ALL	+/–	+	+	+	+	c-μ	+
T-lineage ALL	**CD1a**	**CD2**	**CD3**	**CD4**	**CD7**	**CD8**	**CD34**
Pro-T	–	–	c	–	+	–	+/–
Pre-T	–	+	c	–	+	–	+/–
Cortical T	+	+	c	+	+	+	–
Medullary T	-	+	c, s	+/–	+	+/–	–

Classification of ALL

- French-American-British (FAB) classification

- ALL-L1: small uniform cells
- ALL-L2: large varied cells
- ALL-L3: large varied cells with vacuoles

Pathogenesis

- Single mutations are not for ALL pathogenesis
- 90% of ALLs have numerical or structural chromosomal changes
- Most common is hyperploidy (>50 chromosomes)
- Hypoploidy
- Chromosomal translocations

- These chromosomal aberrations dysregulate the expression and function of transcription factors required for normal B- and T-cell development
- In T ALL gain-of-function mutations in NOTCH1 predominate
- In B-ALLs loss-of-function mutations in genes such as PAX5, E2A, and EBF are common
- In B-ALL balanced t(12;21) involving the genes TEL and AML1 genes are also important

Clinical Presentation

- Abrupt onset with in days to weeks

- Symptoms of marrow function failure
- Fatigue due to anemia
- Fever, reflecting infections secondary to neutropenia;
- Bleeding due to thrombocytopenia

- Mass effects due to neoplastic infiltration including
  - Bone pain resulting from marrow expansion
  - Generalized lymphadenopathy
  - Splenomegaly and hepatomegaly
  - Testicular enlargement

- Central nervous system manifestations such as headache, vomiting, and nerve palsies

Prognosis

- Excellent response to chemotherapy in Pediatric ALL
- Complete remission achieved in 95% of children.
- However only 35% to 40% of adults can be cured
- Several factors associated with a worse prognosis include:

  (1) Age under 2, largely because of the strong association of infantile ALL with translocations involving the MLL gene

  (2) Adolescence or adulthood

(3) Peripheral blood blast counts greater than 100,000 reflecting high tumor burden

(4) Presence of particular cytogenetic aberrations such as t(9;22) (the Philadelphia chromosome)

The t(9;22) is present in only 3% of childhood ALL but up to 25% of adult cases responsible for poor prognosis in adults

Acute Myeloid Leukemia

- More common in male
- Increase incidence associated with genetic disorders like Bloom disease, Fanconi anemia, Wiskott aldrich syndrome
- Tobacco
- Herbicides, Pesticides
- Benzene exposure
- X ray

Classification

- Two types of classification

1. FAB classification
2. WHO classification of 2008

1.FAB classification:

In the 1970s, a group of French, American, and British leukemia experts divided AML into subtype

- From M0 through M7

Subclass	Description
M0	Acute non-differentiated leukemia – immature blast cells with minimal differentiation
M1	Acute myeloblastic leukemia without maturation – immature blast cells without signs of myeloid differentiation
M2	Acute myeloblastic leukemia with granulocytic maturation
M3	Promyelocytic or acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4eo	Myelomonocytic leukemia with bone marrow eosinophilia
M5	M5a – acute monocytic leukemia without maturation M5b – acute monocytic leukemia with partial maturation
M6	Acute erythromyelosis
M7	Acute megakaryoblastic leukemia

WHO classification

- A new proposed classification from the WHO subdivides AML into four categories
- The first includes forms of AML that are associated with recurrent cytogenetic aberrations
- AML arising after a myelodysplastic disorder (MDS)
- Therapy-related AML
- A fourth one is AML not otherwise

WHO classification

WHO Classification of Acute Myeloid Leukemias (AML)

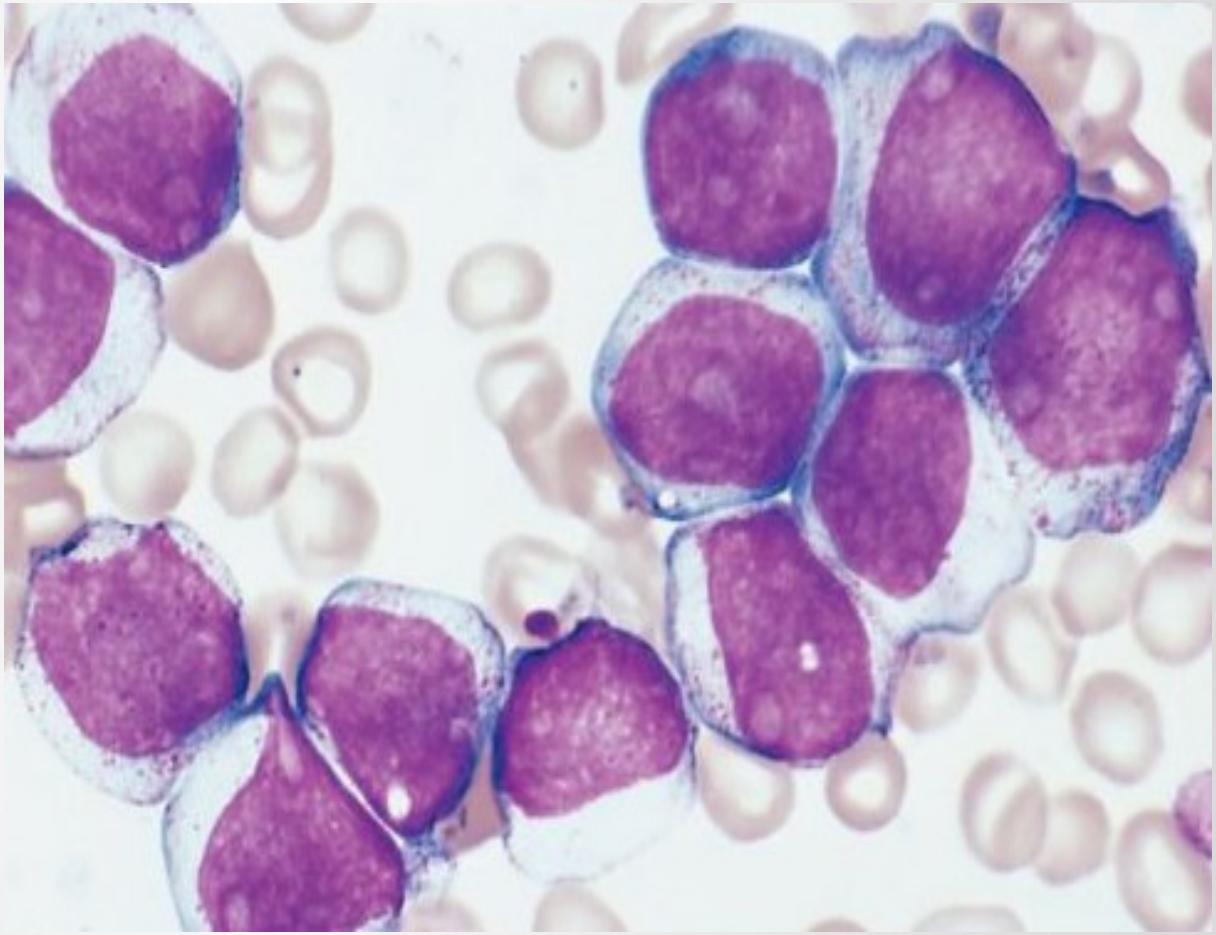
Group	Subgroups
AML with recurrent genetic abnormalities	AML with t(8;21)(q22;q22), *AML1(CBFα)/ETO*
	Acute promyelocytic leukemia, AML with t(15;17)(q22;q12), (*PML/RARα*), and variants (FAB M3)
	AML with abnormal bone marrow eosinophils: inv(16)(p13q22) or t(16;16)(p13;q22), (*CBFβ/MYH11*)
	AML with 11q23(*MLL*) abnormalities
AML with multilineage dysplasia	Following myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative disorder
	Without prior myelodysplastic syndrome
AML and MDS—therapy-related	Alkylating agent related
	Topoisomerase type II inhibitor-related (some can be lymphoid)
	Other types
AML not otherwise categorized	AML minimally differentiated (FAB M0)
	AML without maturation (FAB M1)
	AML with maturation (FAB M2)
	Acute myelomonocytic leukemia (FAB M4)
	Acute monoblastic and monocytic leukemia (FAB M5)
	Acute erythroid leukemia (FAB M6)
	Acute megakaryoblastic leukemia (FAB M7)
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis
	Myeloid sarcoma

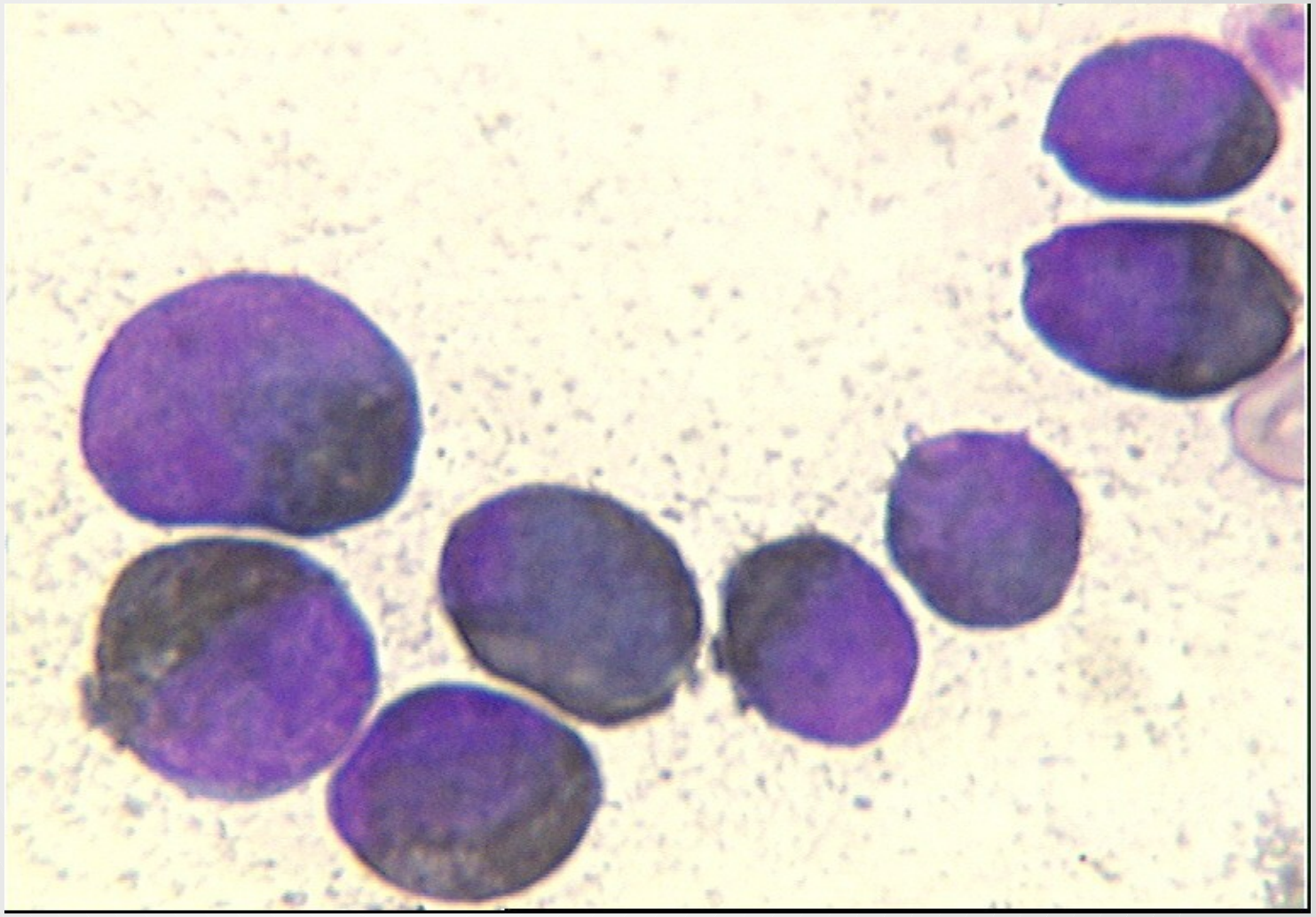
Morphology

- Hypercellular
- Decreased fat spaces in marrow
- Normal hemopoeitic cells replaced by leucoblasts
- 20% myeloid blasts in the bone marrow
- Myeloblasts have delicate nuclear chromatin
- Two to four nucleoli

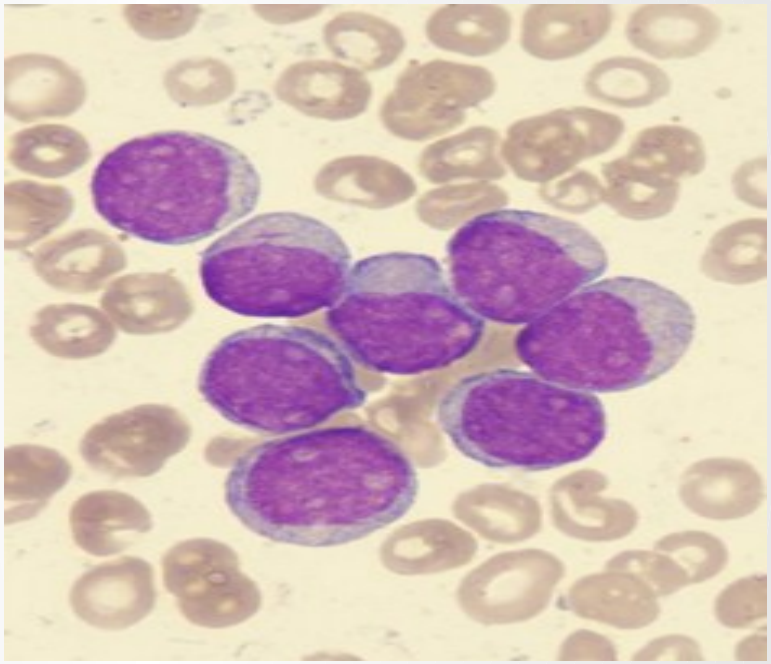
- Sufficient cytoplasm than lymphoblasts
- The cytoplasm contains fine, peroxidase-positive azurophilic granules
- Auer rods, needle-like azurophilic granules
- Numerous in AML with the t(15;17)
- Monoblasts are nonspecific esterase-positive

- M0

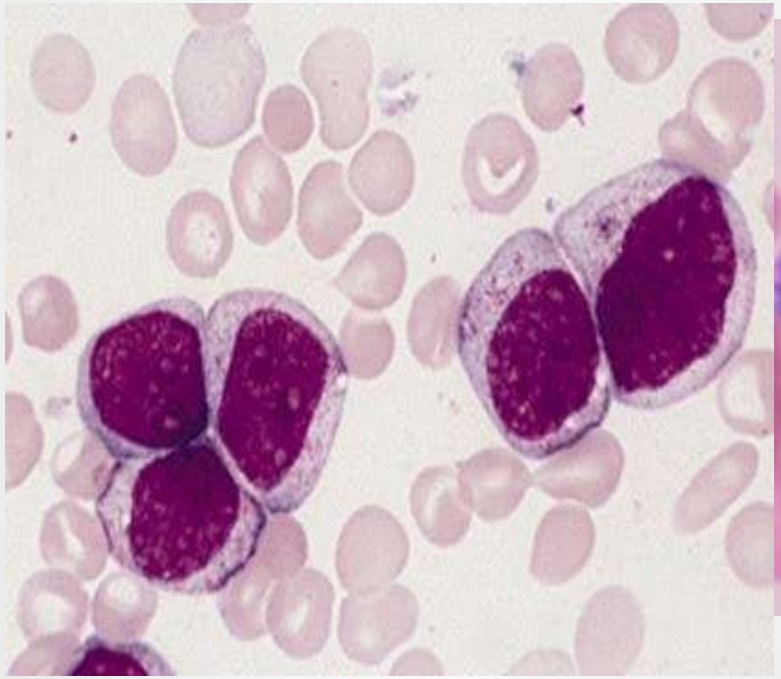


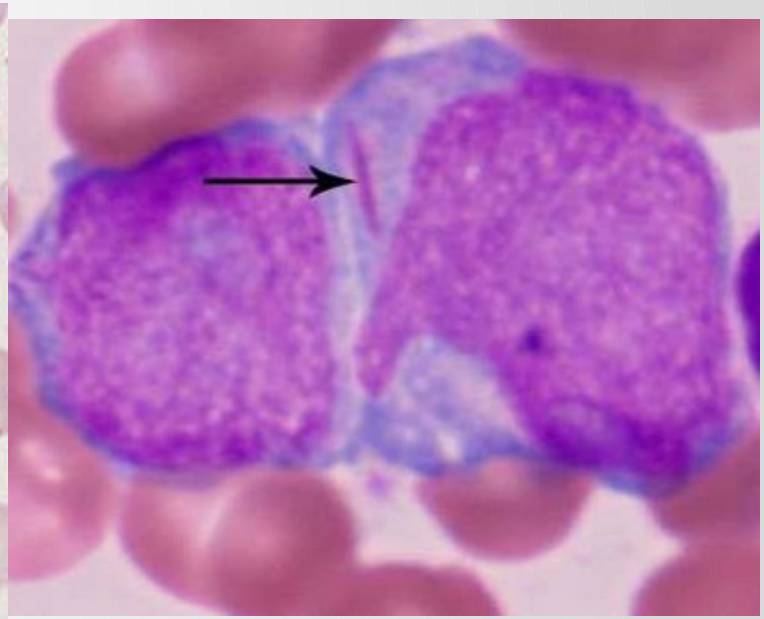


- M1

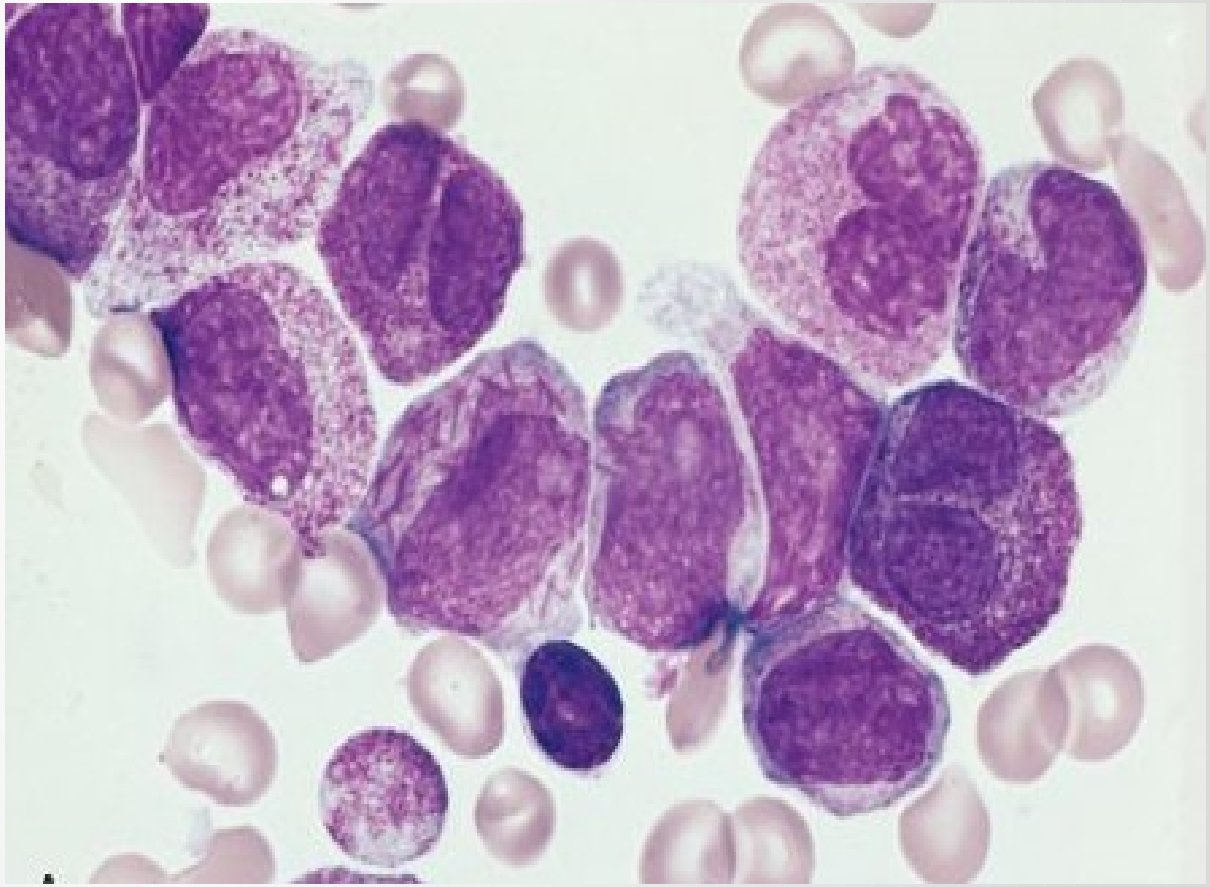


- M2

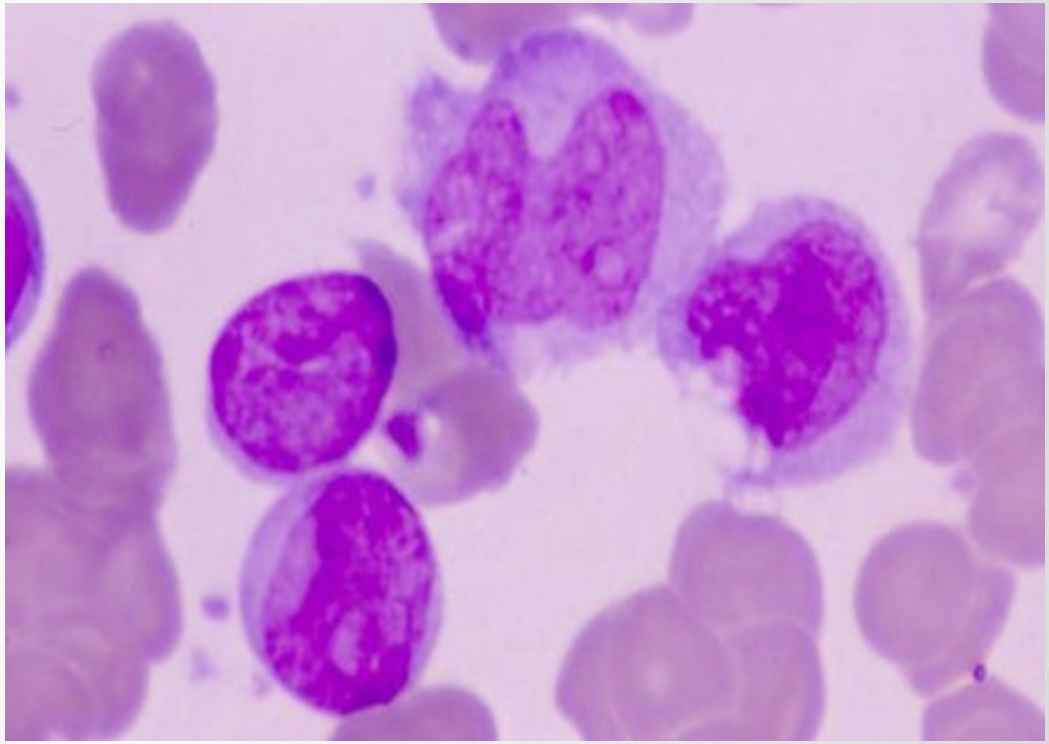




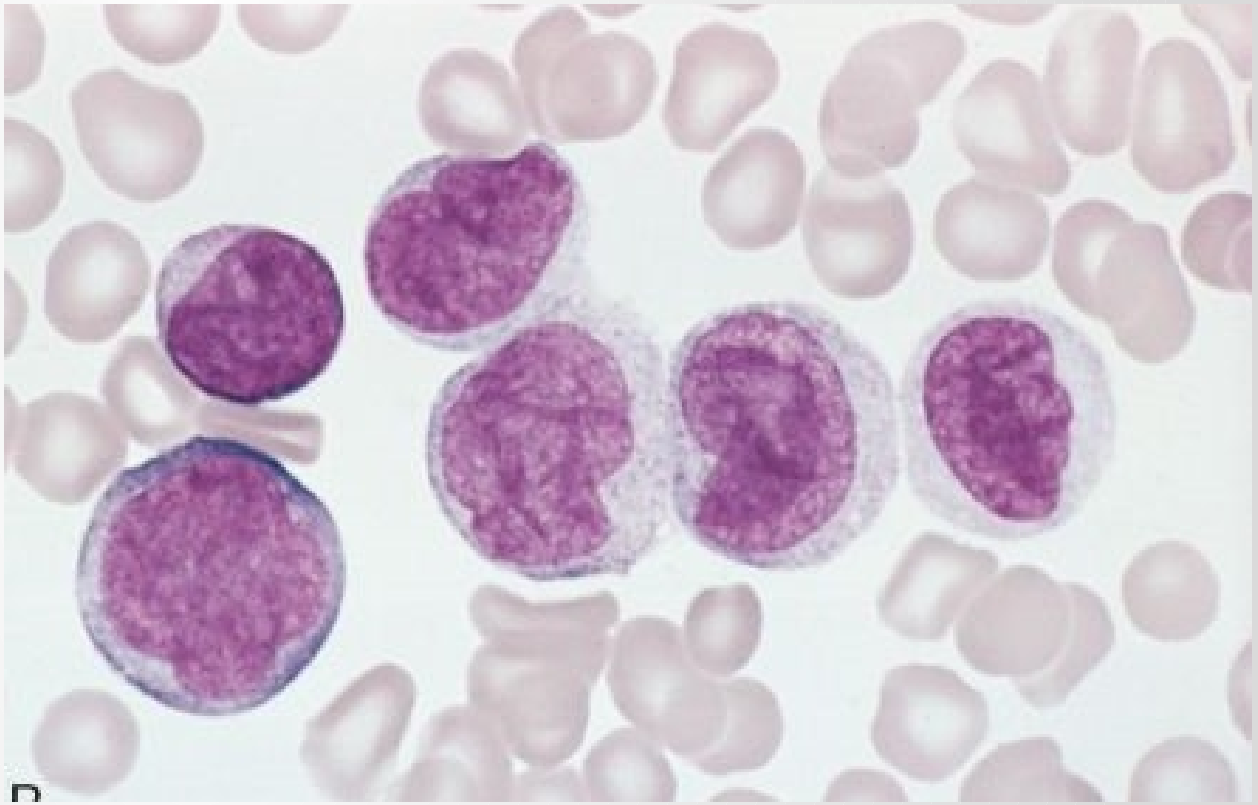
- M3



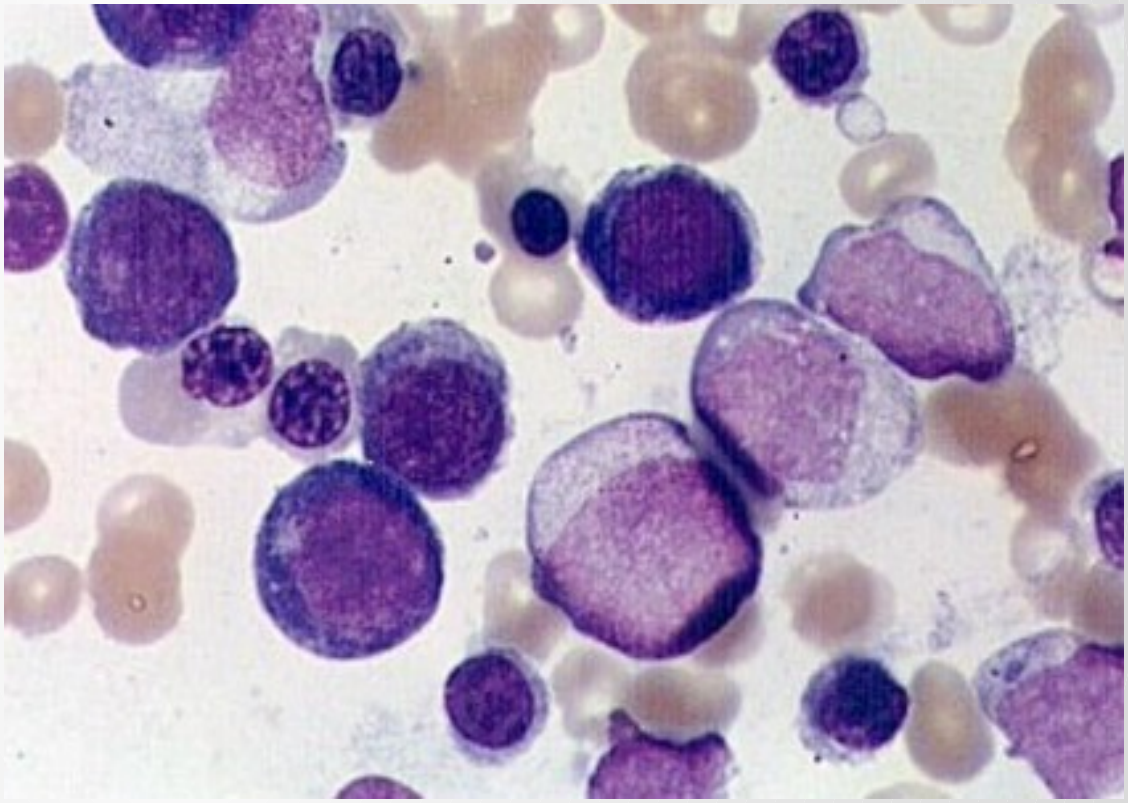
- M4



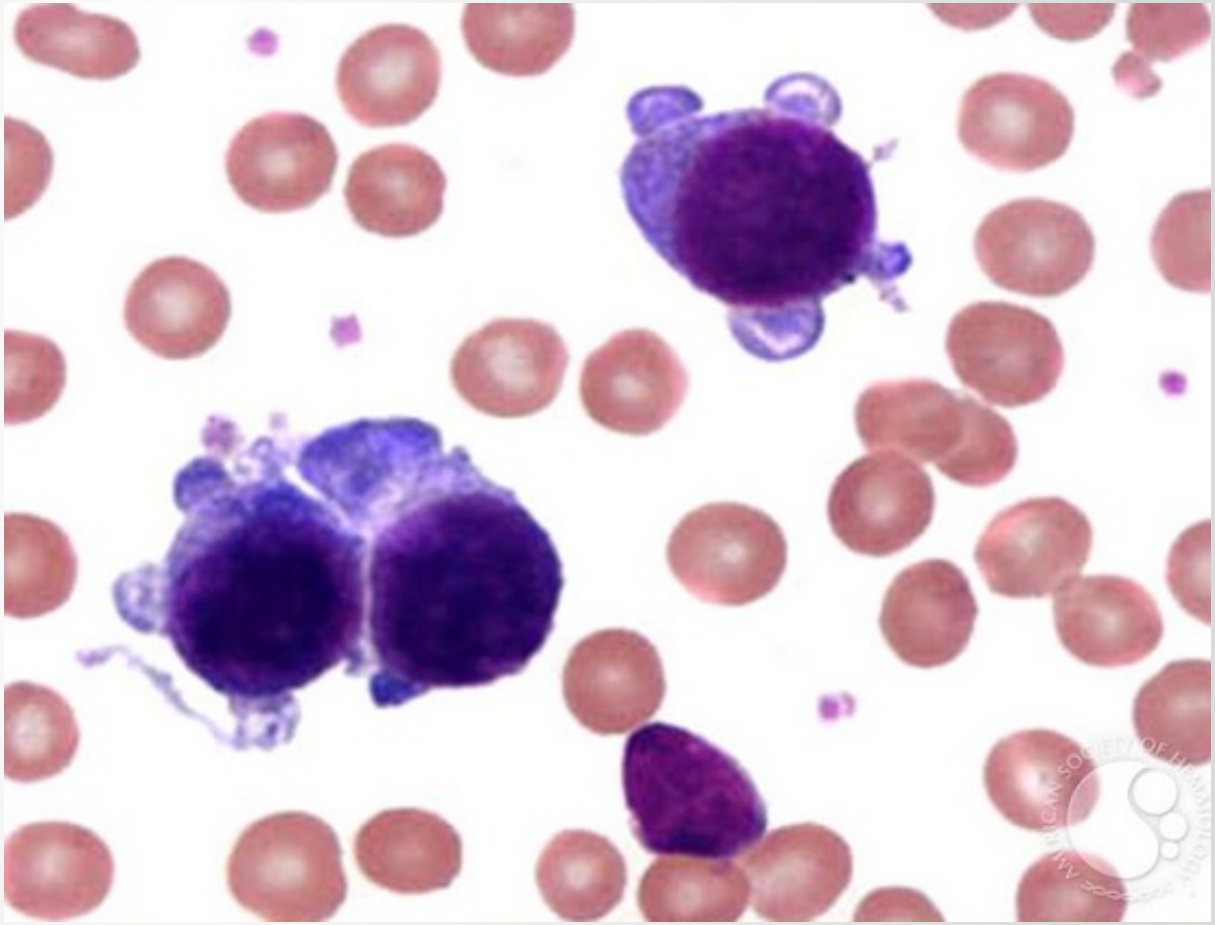
- M5



- M6



- M7



Cytogenetics

- Essential for classifying AML
- Karyotypic changes detected in 50% to 70% of cases
- AMLs arising de novo in younger adults have balanced chromosomal translocations, particularly t(8;21), inv(16), and t(15;17)
- AMLs following MDS or exposure to DNA-damaging agents have deletions or monosomies involving chromosomes 5 and 7

Molecular Pathogenesis

- Recurrent cytogenetic abnormalities in AML disrupt genes required for normal myeloid differentiation
- The two most common chromosomal rearrangements are t(8;21) and inv(16)
- Normally CBF1α/CBF1β genes encode polypeptides that bind one another to form transcription factor required for normal maturation
- The t(8;21) and the inv(16) create fusion proteins interfering with the function of CBF1α/CBF1β and block the maturation of myeloid cells

Clinical Features

- Gum hypertrophy especially in the monocytic variants (M4 or M5)
- Pallor, petechiae , ecchymoses
- Bone tenderness
- Retinal hemorrhage
- CNS infiltration (more common in M4 and M5)
- Skin, soft tissue infiltration
- Extramedullary disease (ie, myeloid sarcoma)
- Hepatosplenomegaly

Progostic Factors

- **Favorable**

  younger age (<50)

  WBC <30,000

  t(8;21) ,inv(16) ,t(15;17)

- **Unfavorable**

  Older age (>60)

  WBC >100,000

  Elevated LDH

  Prior MDS or hematogic malignancy

  CD34 positive phenotype, MRD1 postive phenotype

  del (5), del (7), trisomy 8

  t(6;9), t(9;22)

  FLT3 gene mutation (seen in 30% of patients)

Thanks