AML, Not Otherwise Categorized (NOC)

AML, Not Otherwise Categorized (NOC)

- Do not fulfill criteria for insertion into a previously described category

AML, (NOC)

- Blast percentage in bone marrow determined from a 500 cell differential count
- Peripheral blood differential count should include 200 leukocytes

AML, Not Otherwise Categorized (NOC)

Basis for Classification

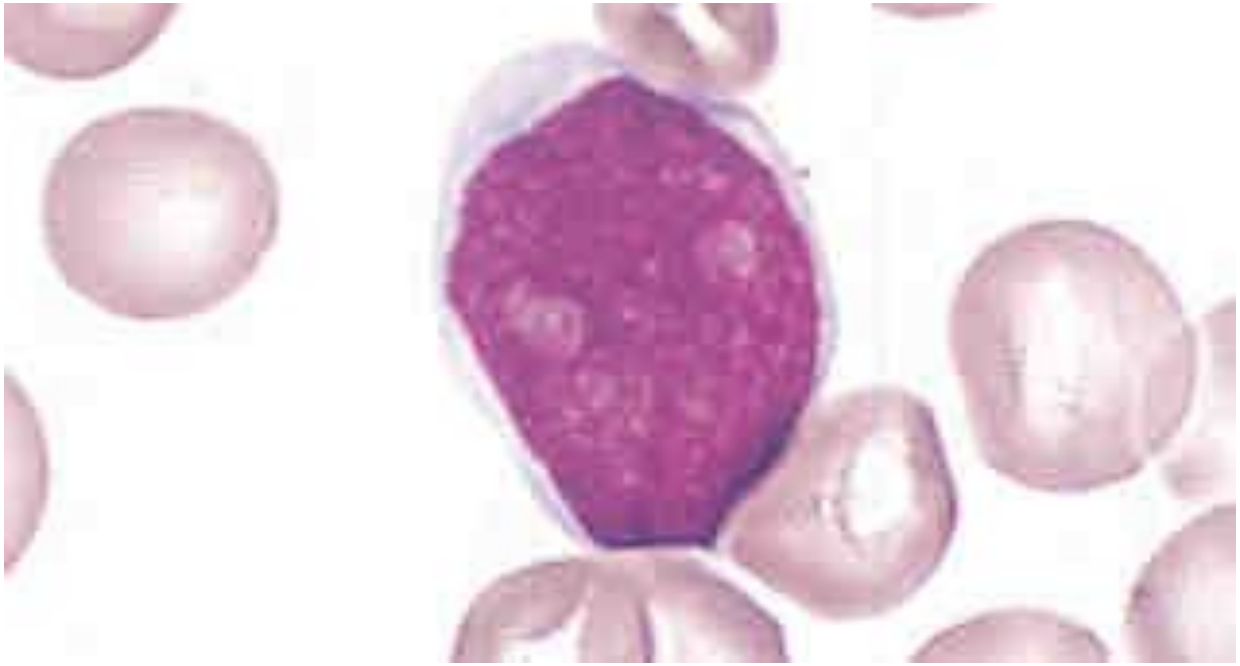
- Morphology
- Cytochemical features
- Maturation

AML, (NOC)

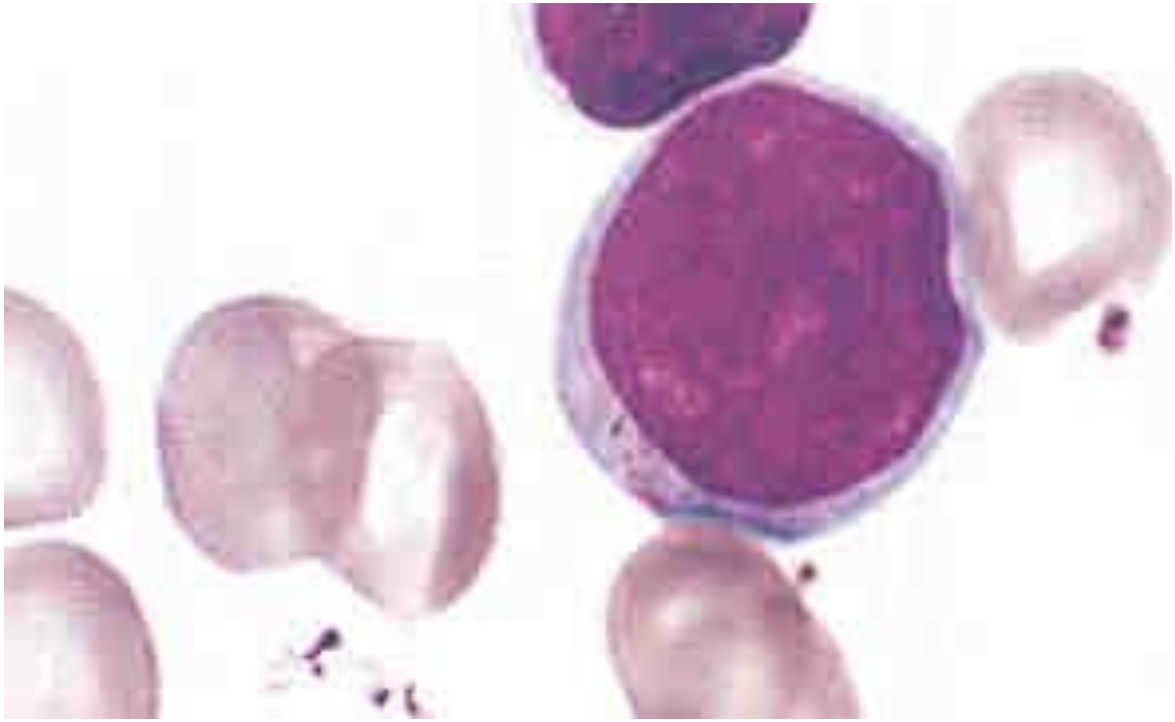
Blast Equivalents

- Promyelocytes in APL
- Promonocytes in AML with monocytic differentiation
- Megakaryoblasts

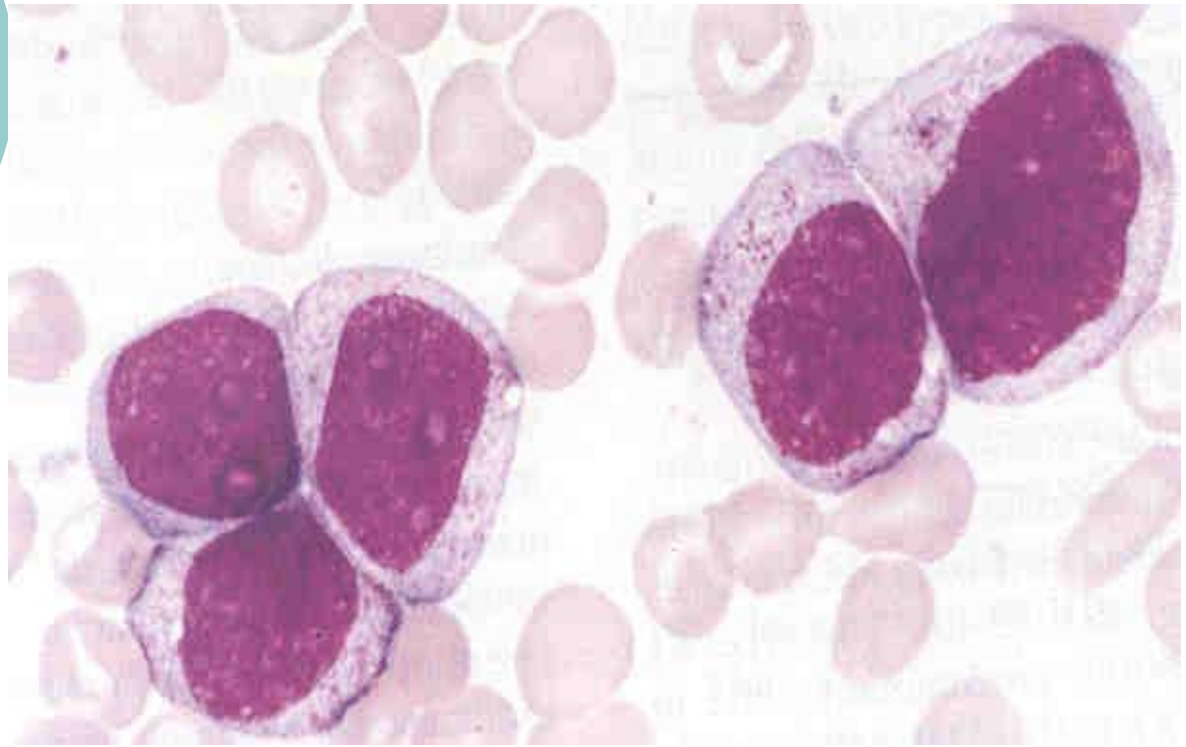
Type I blasts



Type II blasts



Type III blasts



Acute Myeloblastic Leukemia, Minimally Differentiated

Acute Myeloblastic Leukemia, Minimally Differentiated

Synonym

- FAB: Acute Myeloid Leukemia, M0
- 5% of all AMLs
- Mostly adults

Acute Myeloblastic Leukemia, Minimally Differentiated

- No evidence of myeloid differentiation by morphology or light microscopy cytochemistry
- Myeloblast nature determined by immunologic markers and ultrastructural studies (ultrastructural cytochemistry)

Acute Myeloblastic Leukemia, Minimally Differentiated

- Patients present with marrow failure
- Anemia
- Neutropenia
- Thrombocytopenia
- May be leukocytosis and increased blasts in peripheral blood

Acute Myeloblastic Leukemia, Minimally Differentiated

Morphology

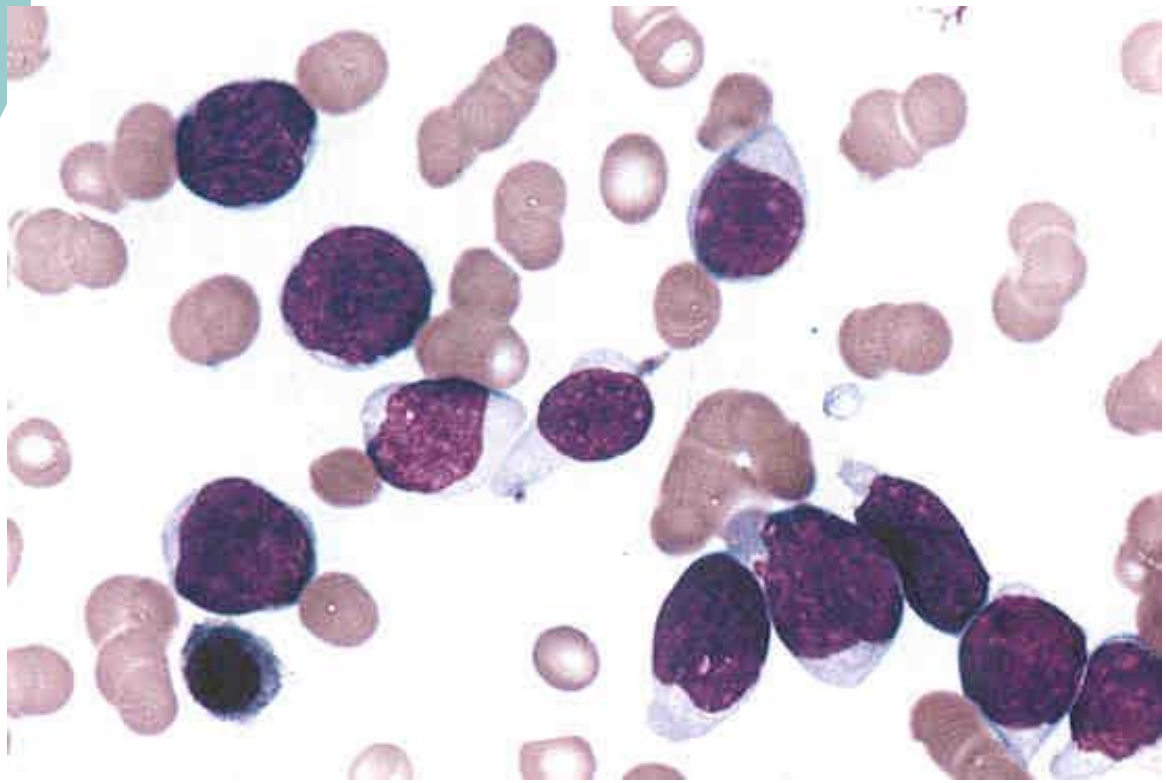
- Medium sized blasts (less often smaller)
- Round (or slightly indented) nucleus
- Dispersed nuclear chromatin (less often condensed)
- One or two nucleoli (less often inconspicuous)

Acute Myeloblastic Leukemia, Minimally Differentiated

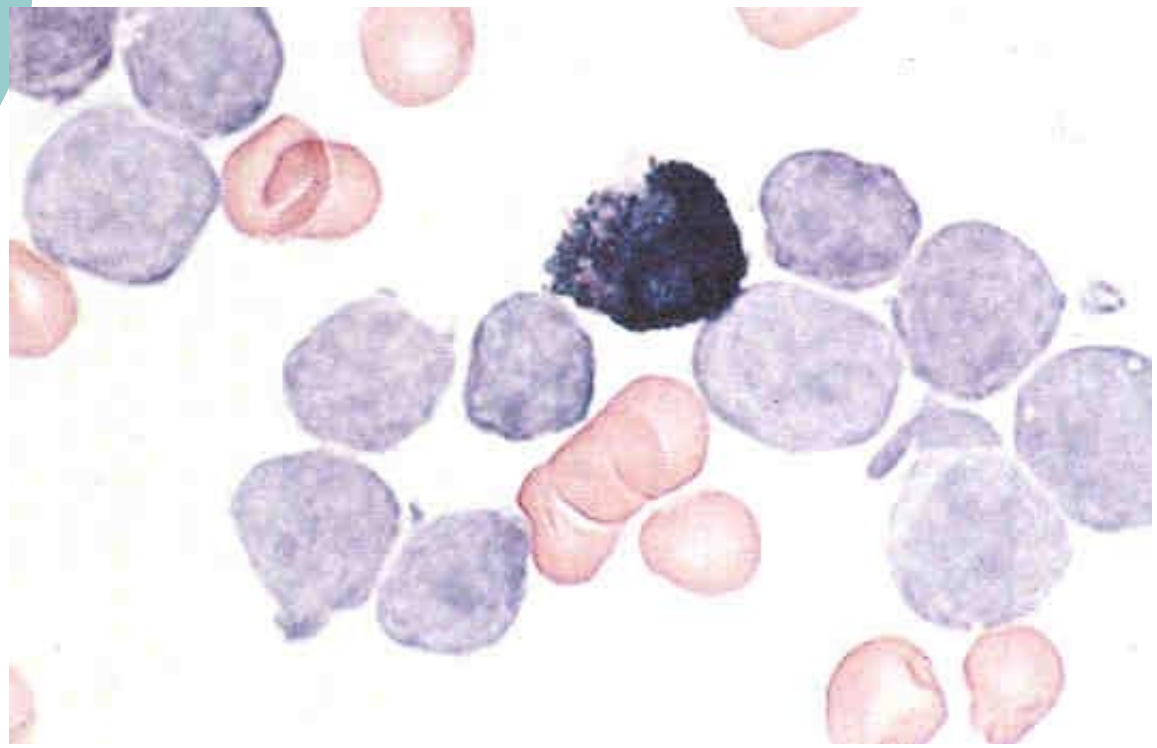
Morphology

- Agranular cytoplasm (varying basophilia)
- No Auer rods
- Bone marrow usually hypercellular

AML M0



AML M0



Negative MPO

Acute Myeloblastic Leukemia, Minimally Differentiated

Cytochemistry

- Myeloperoxidase (MPO), Sudan Black B (SBB), and naphthol ASD chloroacetate esterase cytochemical stains are all negative (less than 3% positivity in all blasts)

Acute Myeloblastic Leukemia, Minimally Differentiated

Cytochemistry

- Alpha naphthyl acetate esterase and alpha naphthyl butyrate esterase stains are all negative (no monocytic differentiation)

Acute Myeloblastic Leukemia, Minimally Differentiated

Ultrastructural Cytochemistry

- More sensitive
- MPO activity in small granules, endoplasic reticulum, Golgi area, and/or nuclear membranes

Acute Myeloblastic Leukemia, Minimally Differentiated

Immunophenotype

- CD34+, CD117+, HLA-DR+, CD13+, CD33+, TdT+ (in one-third)
- Negative for B and T restricted markers (cCD3, cCD79a, cCD22)

Acute Myeloblastic Leukemia, Minimally Differentiated

Immunophenotype

- Negative for myelomonocytic differentiation markers (CD11b, CD15, CD14, CD65)
- CD7, CD2, CD19 occasionally weakly positive (lymphoid differentiation)

Acute Myeloblastic Leukemia, Minimally Differentiated

Genetics

- None specific
- Complex karyotypes, trisomy 13, trisomy 8, trisomy 4, monosomy 7

Acute Myeloblastic Leukemia, Minimally Differentiated

Differential Diagnoses

- ALL
- Acute megakaryoblastic leukemia
- Biphenotypic/mixed lineage acute leukemias

Acute Myeloblastic Leukemia, Minimally Differentiated

- Poor prognosis
- Lower remission rate
- Shorter survival

Acute Myeloblastic Leukemia without Maturation

Acute Myeloblastic Leukemia without Maturation

Synonym

- FAB: Acute Myeloid Leukemia, M1

Acute Myeloblastic Leukemia without Maturation

- Blasts greater than or equal to 90% of non-erythroid nucleated cells
- Granulocytic elements <10%
- No maturation
- MPO or SBB positivity >3% of blasts
- Auer rods may be present

Acute Myeloblastic Leukemia without Maturation

- 10% of all AMLs
- Adults (but can occur at any age)
- Median age: 46 years

Acute Myeloblastic Leukemia without Maturation

Presentation

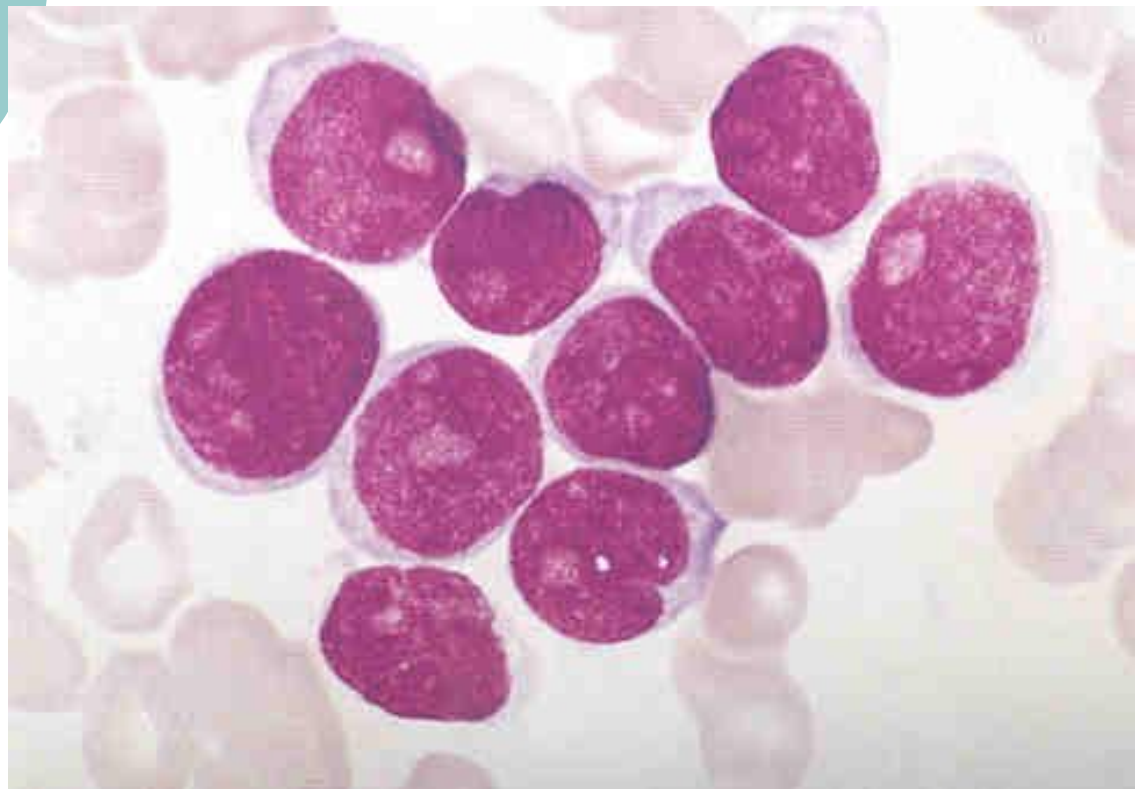
- Bone marrow failure
- Anemia
- Thrombocytopenia
- Neutropenia
- Leukocytosis with increased blasts in blood

Acute Myeloblastic Leukemia without Maturation

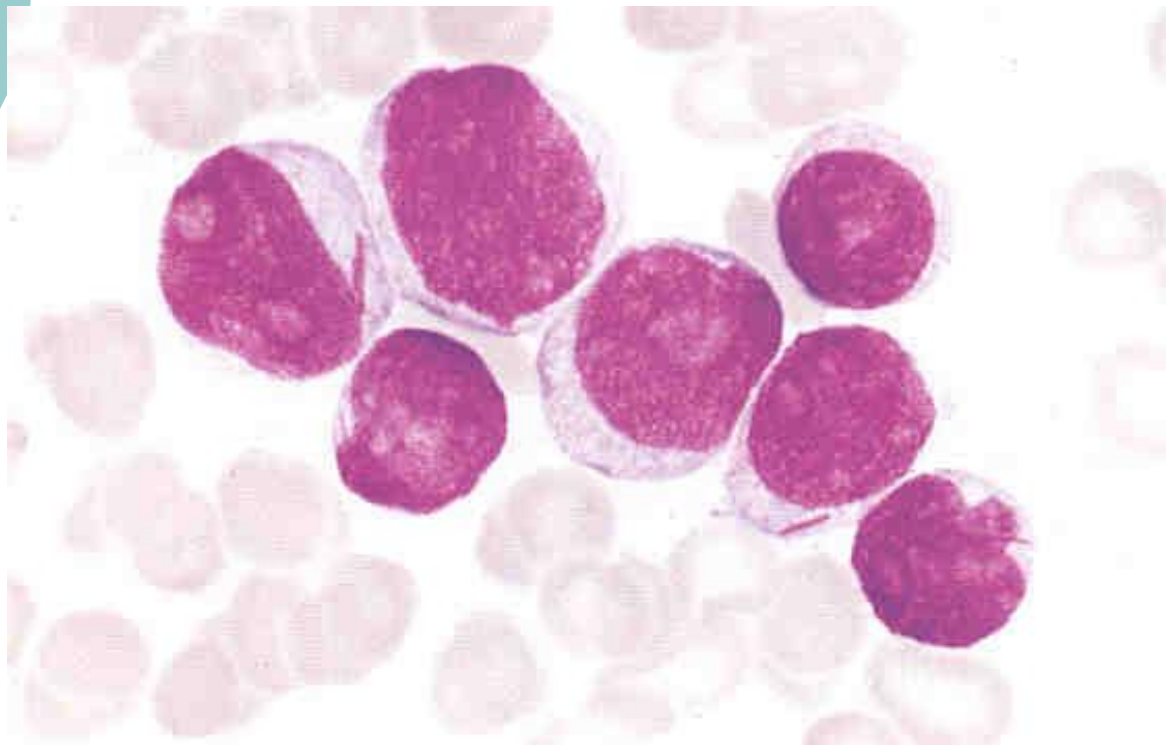
Morphology

- Bone marrow usually hypercellular
- Azurophilic granules and/or Auer rods
- (Some blasts may resemble lymphoblasts)

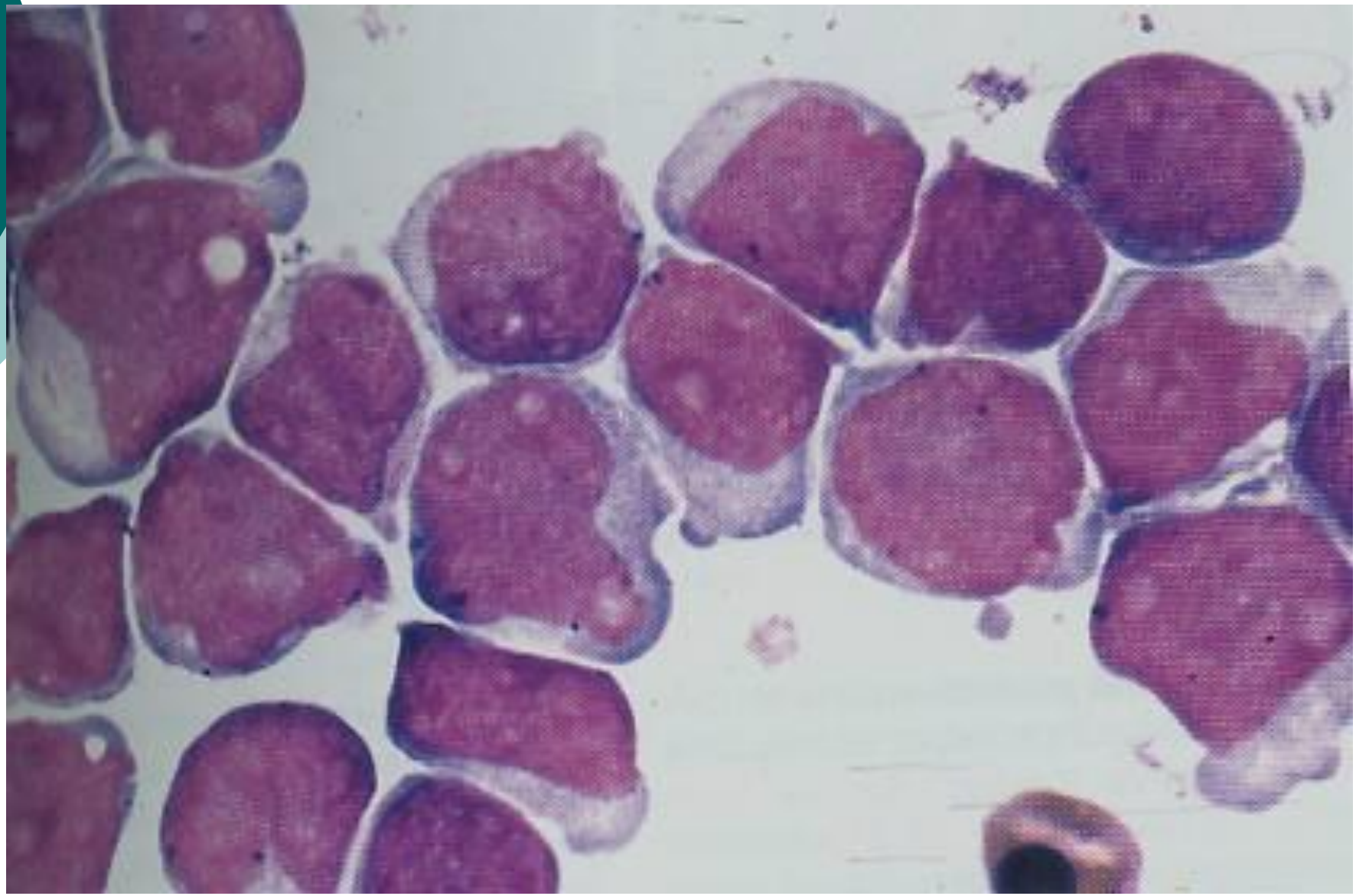
AML M1



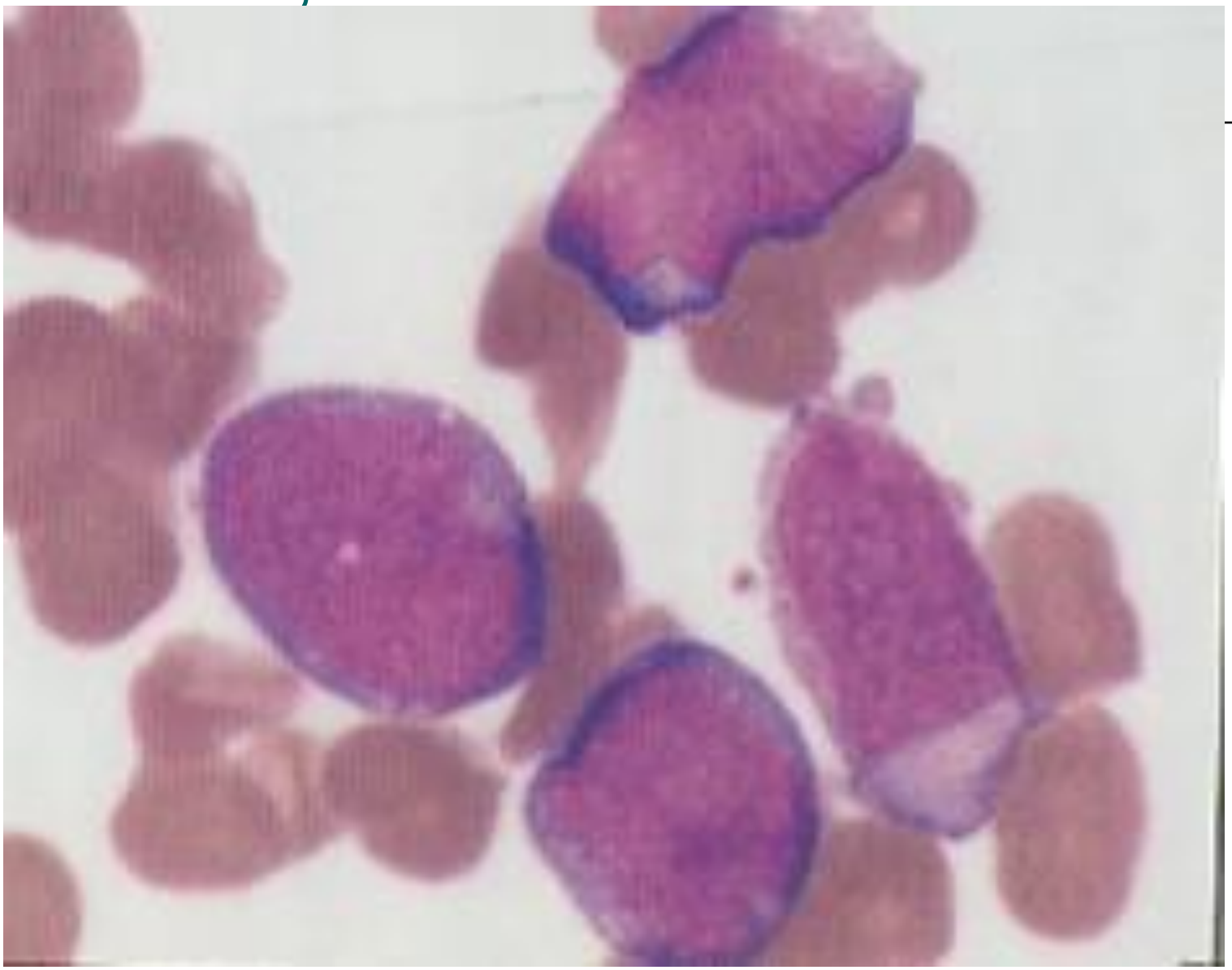
AML M1



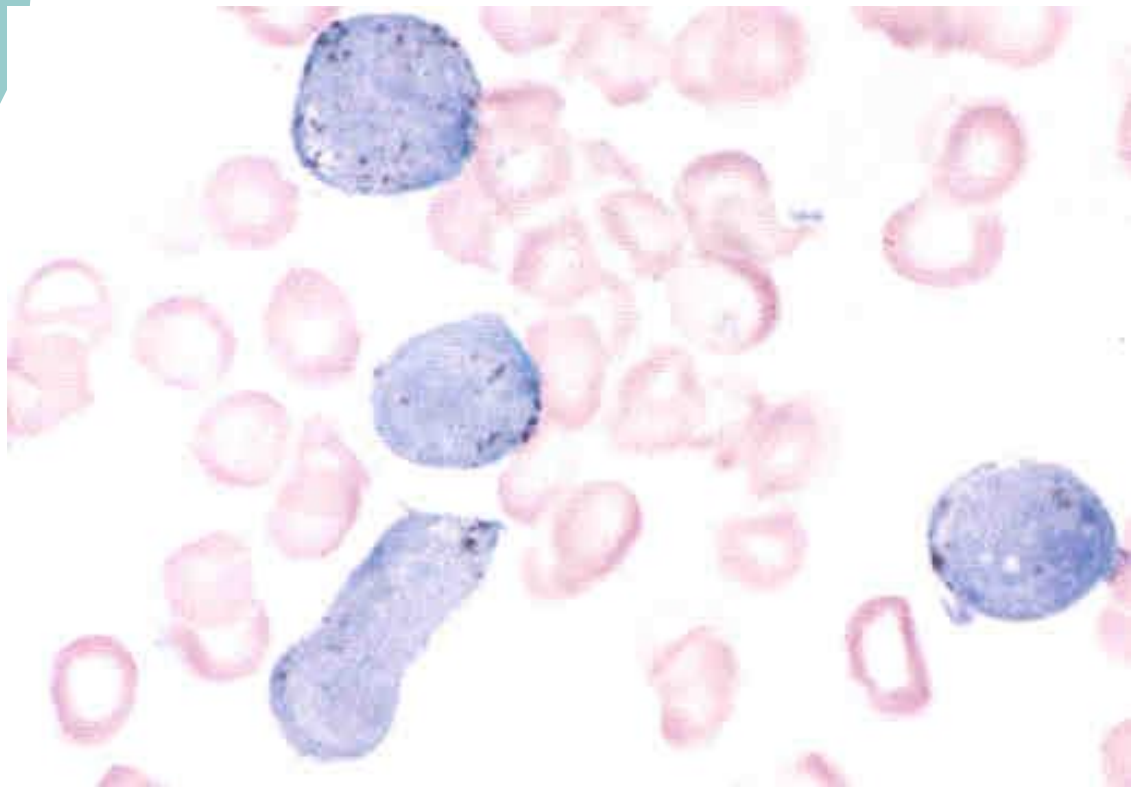
AML, M1



AML, M1



AML M1



MPO

Acute Myeloblastic Leukemia without Maturation

Differential Diagnoses

- ALL when granules are absent and MPO+ is low (but at least 3%)
- AML with maturation (when blasts are high)

Acute Myeloblastic Leukemia without Maturation

Immunophenotype

- CD13+, CD33+, CD117+, MPO+ (at least 2 of these myelomonocytic markers)
- CD11b-, CD14- (monocytic markers)
- CD3-, CD20-, CD79a- (lymphoid markers)

Acute Myeloblastic Leukemia without Maturation

Genetics

- No specific recurrent chromosome abnormalities

Acute Myeloblastic Leukemia without Maturation

- Aggressive course and poor prognosis

Acute Myeloblastic Leukemia with Maturation

Acute Myeloblastic Leukemia with Maturation

Synonym

- FAB: Acute myeloid leukemia, M2

Acute Myeloblastic Leukemia with Maturation

- At least 20% blasts in bone marrow or blood (but less than 90%)
- Granulocytic elements at least 10% of non-erythroid cells
- Monocytic elements <20% of non-erythroid cells

Acute Myeloblastic Leukemia with Maturation

- 30-45% of all AMLs
- All ages
- 20% < 25 years
- 40% are 60 years or older

Acute Myeloblastic Leukemia with Maturation

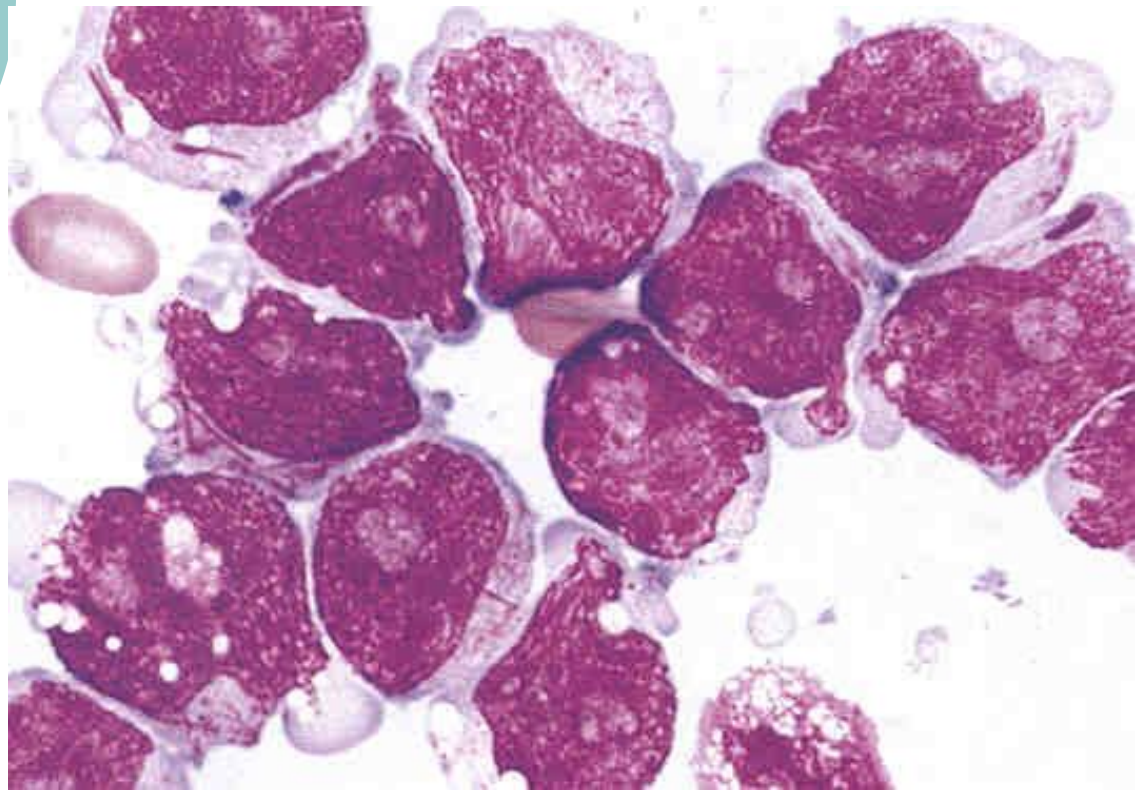
- Anemia
- Thrombocytopenia
- Neutropenia
- Variable number of blasts in blood

Acute Myeloblastic Leukemia with Maturation

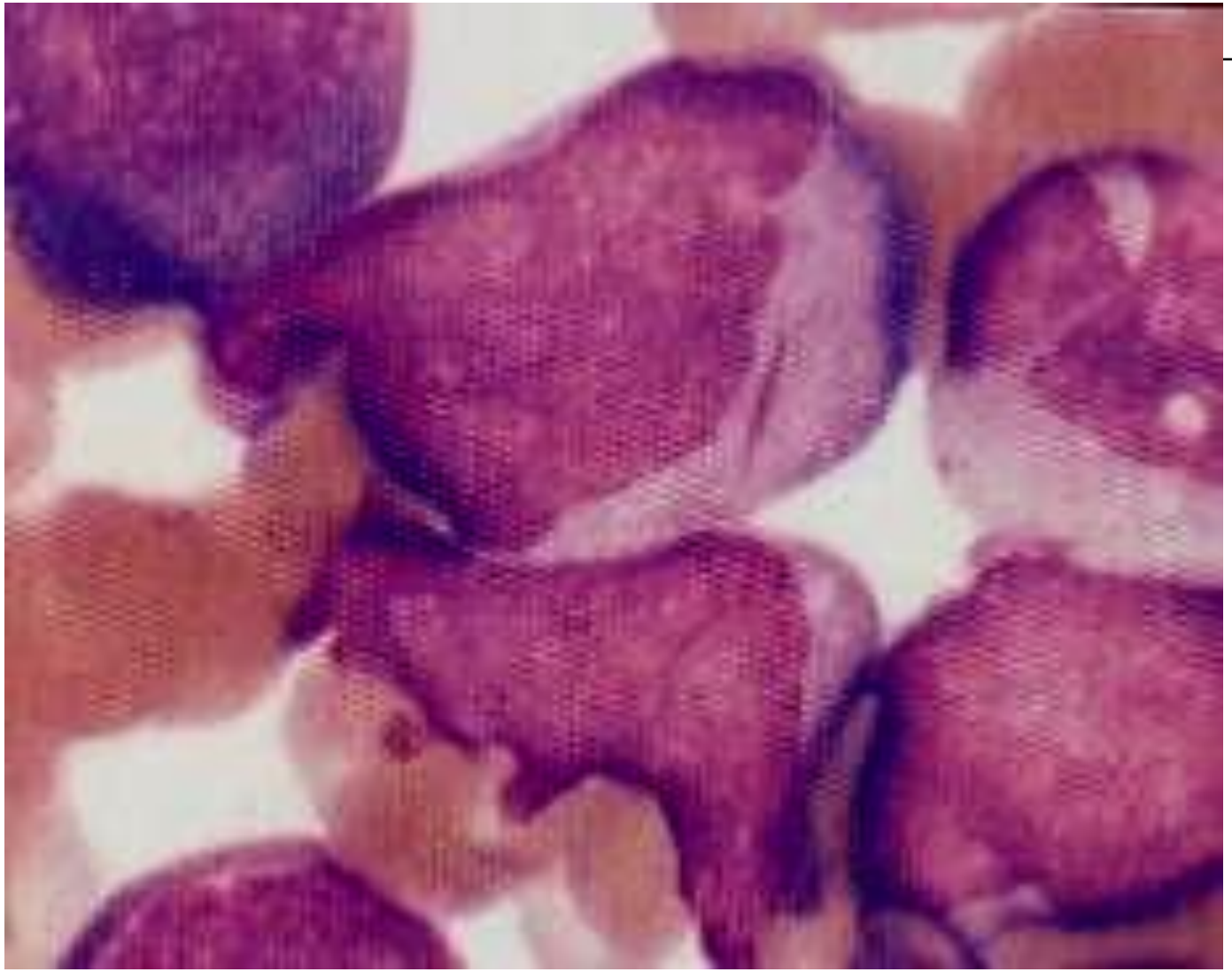
Morphology

- Bone marrow hypercellular
- Blasts with or without granules
- Auer rods frequent
- Various degrees of dysplasia
- Eosinophils and basophils may be increased

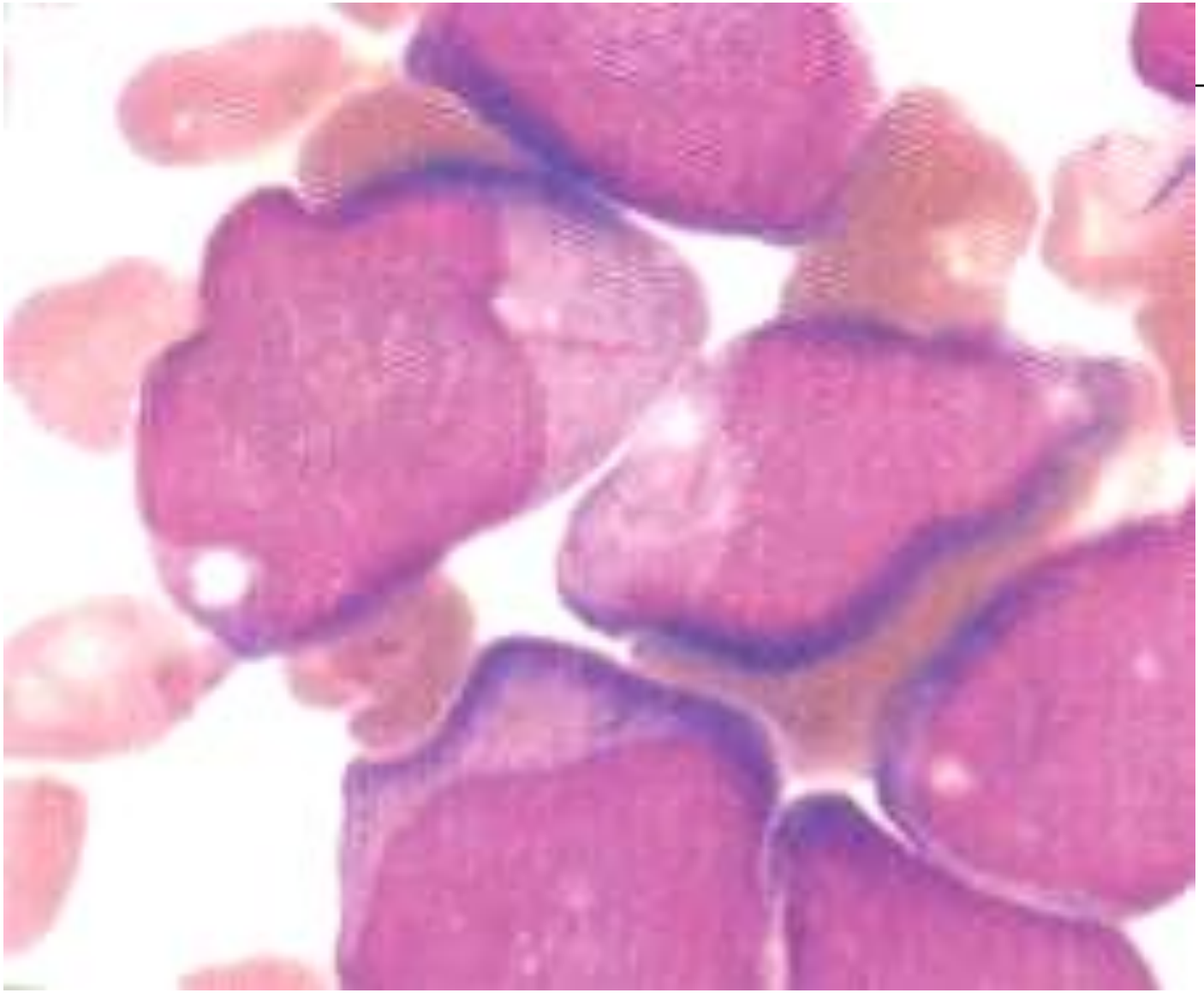
M2 morphology



AML, M2



AML, M2



Acute Myeloblastic Leukemia with Maturation

Differential Diagnoses

- RAEB (if blast numbers are at lower limit)
- AML without maturation (if blast numbers are at upper limit)
- AMML (when monocytes are increased)

Acute Myeloblastic Leukemia with Maturation

Immunophenotype

- CD13+, CD33+, CD15+
- Often CD34+, CD117+, HLA-DR+

Acute Myeloblastic Leukemia with Maturation

Genetics

- del(12)(p11-p13) associated with increased basophils
- t(6;9)(p23;q34) (DEK/CAN fusion gene)
- t(8;16)(p11;p13) associated with erythrophagocytosis

Acute Myeloblastic Leukemia with Maturation

- Responds frequently to aggressive therapy
- t(6;9)(p23;q34) have poorer prognosis

Acute Myelomonocytic Leukemia (AMML)

Acute Myelomonocytic Leukemia (AMML)

Synonym

- FAB: Acute myeloid leukemia, M4

AMML

- Blasts at least 20%
- Granulocytic elements at least 20% of non-erythroid cells in bone marrow
- Monocytic elements at least 20% of non-erythroid cells in bone marrow (if <20% but circulating monocytes at least 5 x 10^9/L, Dx still AMML)

AMML

- Anemia
- Thrombocytopenia
- Fever
- Fatigue
- Variable circulating blasts

AMML

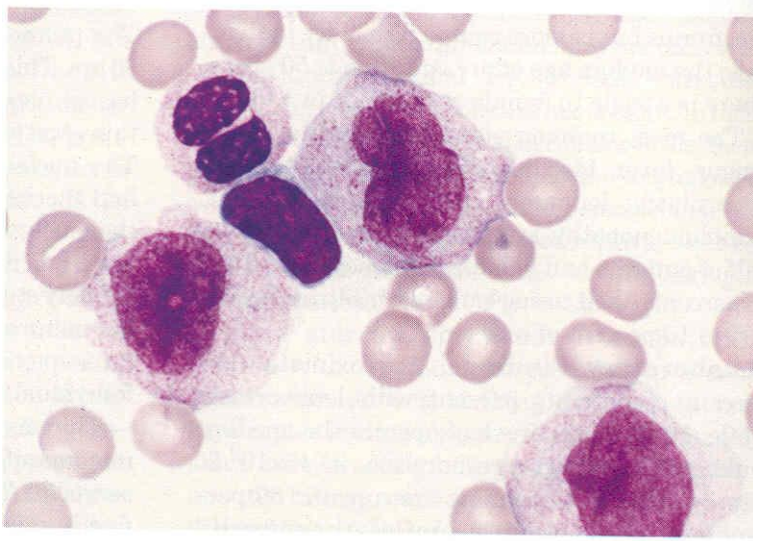
- 15-25% of all AMLs
- Older individuals
- Median age: 50 years
- Male-to-female ratio 1.4:1

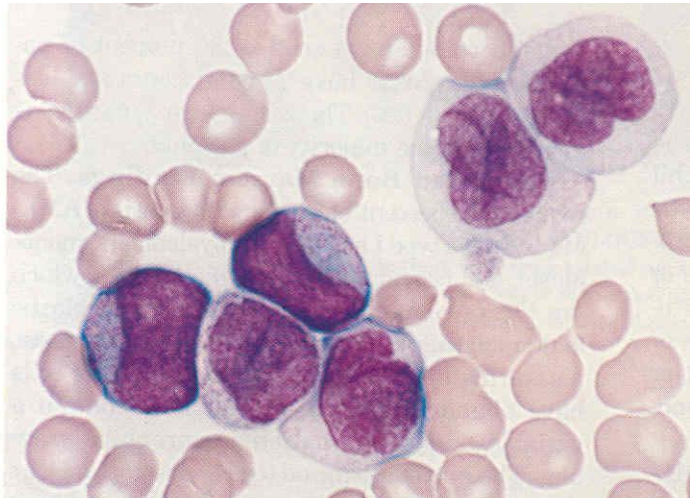
AMML

Morphology

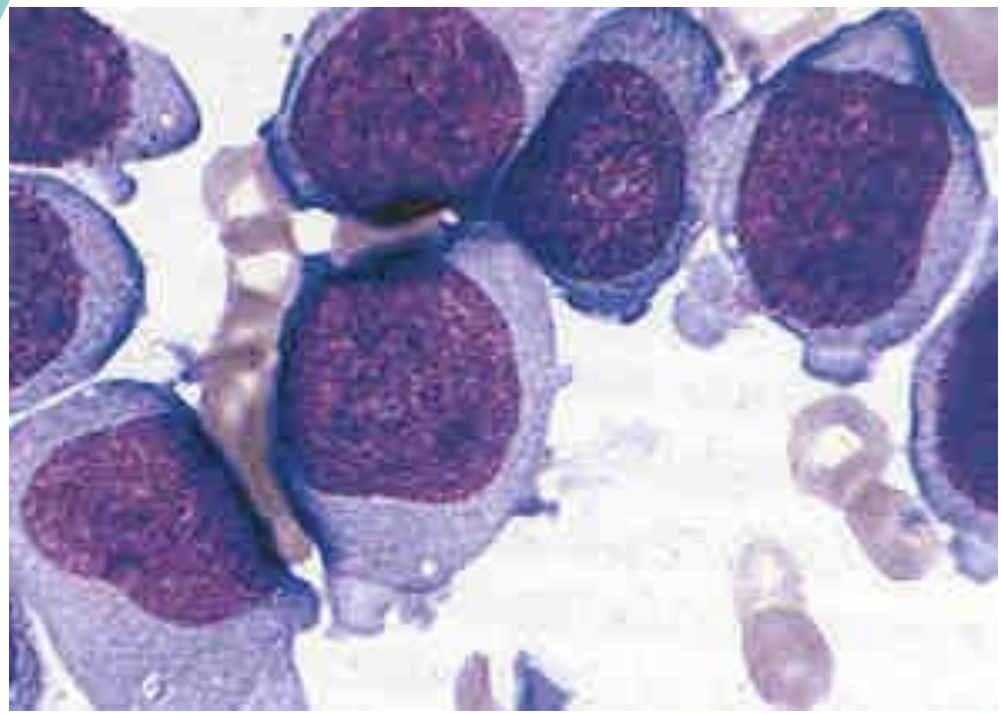
- Monoblasts – round nuclei, lacy chromatin, one or more prominent nuclei. Abundant basophilic cytoplasm. Pseudopods. Some granules and vacuoles.
- Promonocytes – blast equivalent. More irregular nucleus. Less basophilic. More granules

Monoblasts, promonocytes

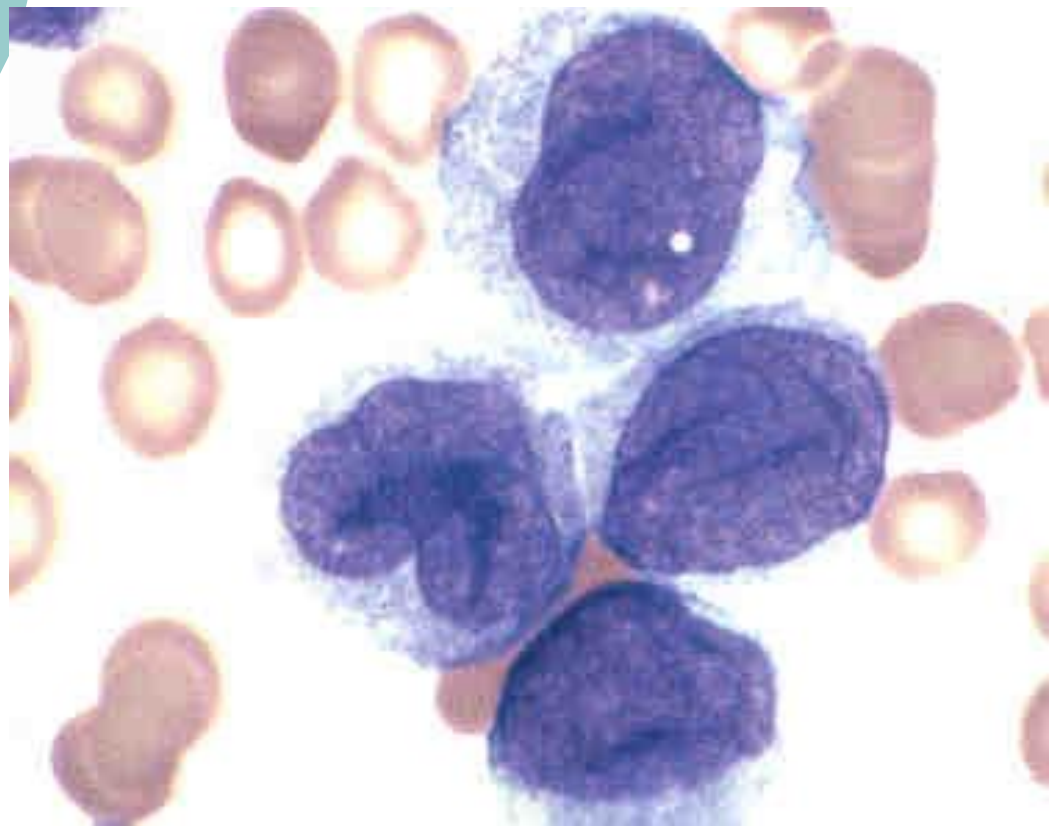




Monoblasts



Promonocytes

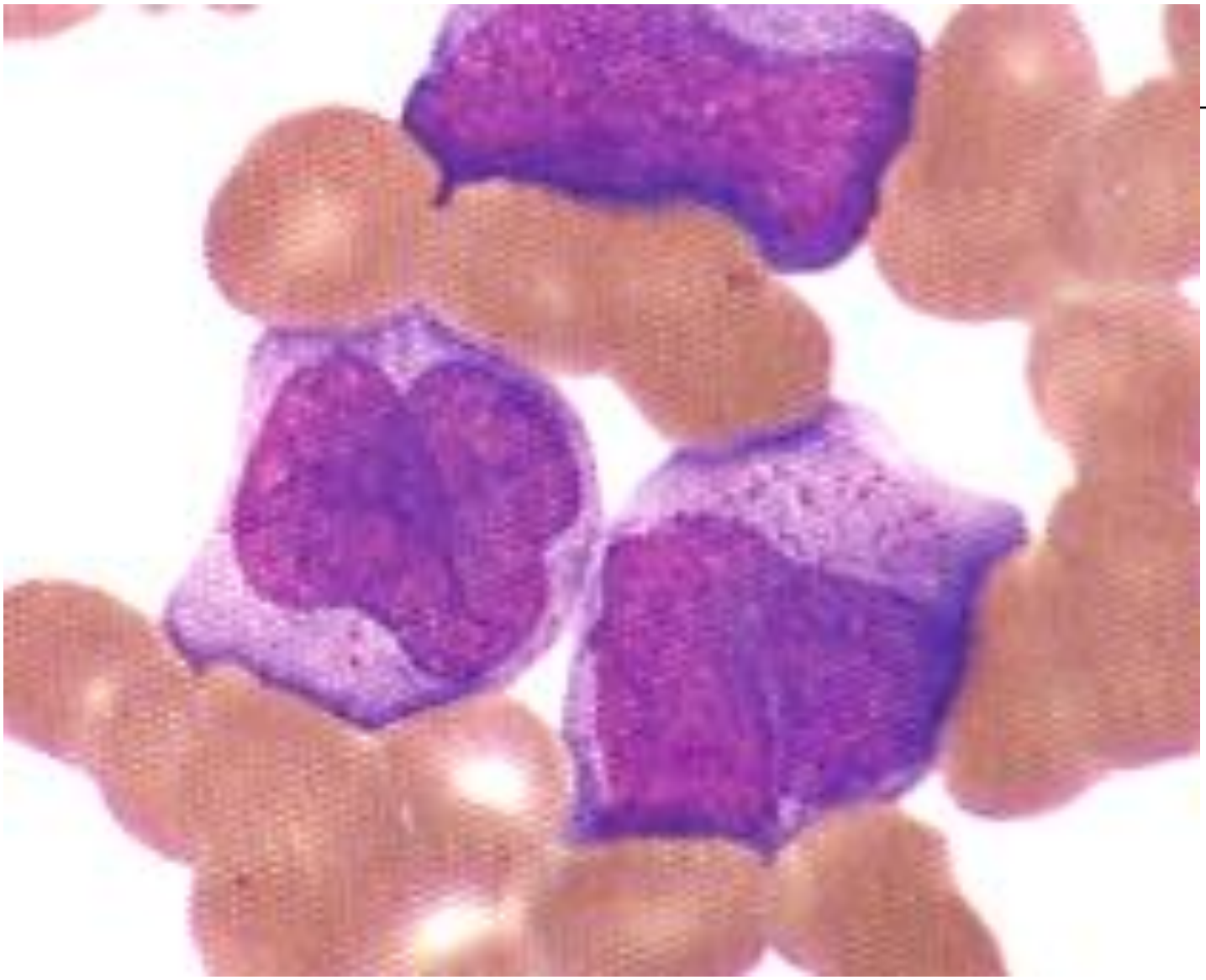


AMML

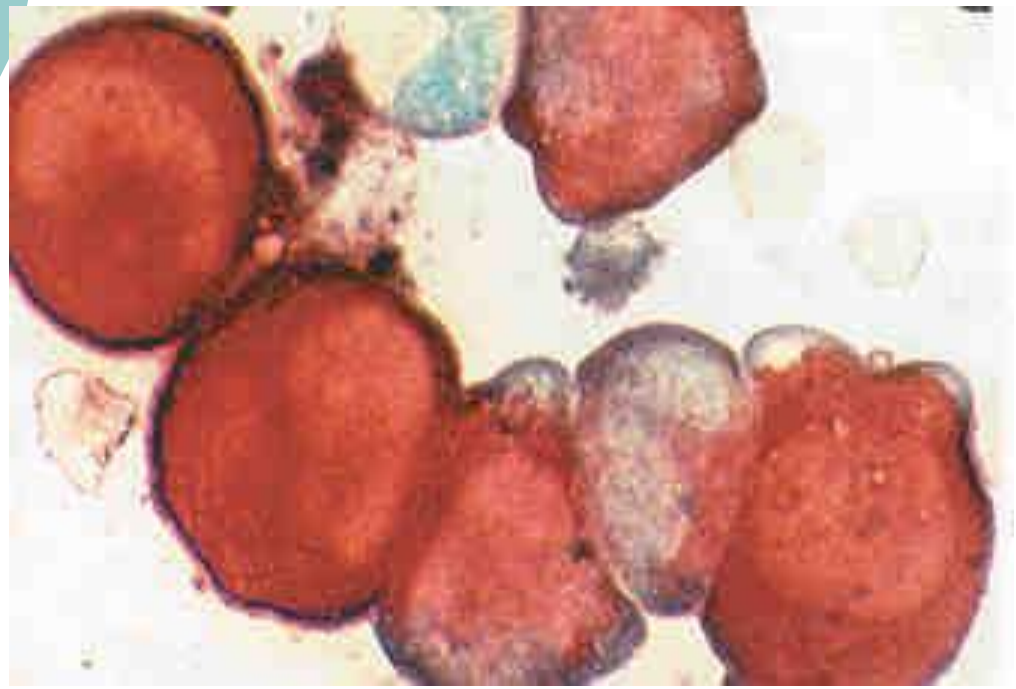
Morphology

- MPO+ (at least 3% of blasts)
- Monocytic elements non-specific esterase +
- Morphology sufficient criterion for monocytic cells (even if esterase negative)
- Double staining for MPO and esterase can be present

AMML



Butyrate



AMML

Differential Diagnoses

- AML with maturation
- Acute monocytic leukemia

AMML

Immunophenotype

- CD13+, CD33+ (myeloid)
- CD14+, CD4+, CD11b+, CD11c+, CD64+, CD36+, lysozyme+ (monocytic)
- [CD34+ (residual cells)]

AMML

Genetics

- Non-specific
- Specific abnormalities are under AML with recurrent genetic abnormalities, such as (inv)16 or 11q23

AMML

- Frequently responds to aggressive therapy
- Variable survival rates

Acute Monoblastic/Monocytic Leukemia

Acute Monoblastic/Monocytic Leukemia

Synonyms

- FAB: Acute monoblastic leukemia, M5a
- FAB: Acute monocytic leukemia, M5b

Acute Monoblastic/Monocytic Leukemia

- At least 80% of non-erythroid cells are monoblasts, promonocytes, and monocytes
- Promonocytes are blast equivalents
- Granulocytic elements <20%

Acute Monoblastic/Monocytic Leukemia

- Acute monoblastic leukemia – at least 80% monoblasts
- Acute monocytic leukemia – less than 80% monoblasts

Acute Monoblastic/Monocytic Leukemia

Acute Monoblastic Leukemia

- 5-8% of all AMLs
- Young individuals (but at any age)
- In infancy often with 11q23
- Extramedullary lesions possible

Acute Monoblastic/Monocytic Leukemia

Acute Monocytic Leukemia

- 3-6% of all AMLs
- Adults
- Median age: 49 years
- Male-to-female ratio 1.8:1

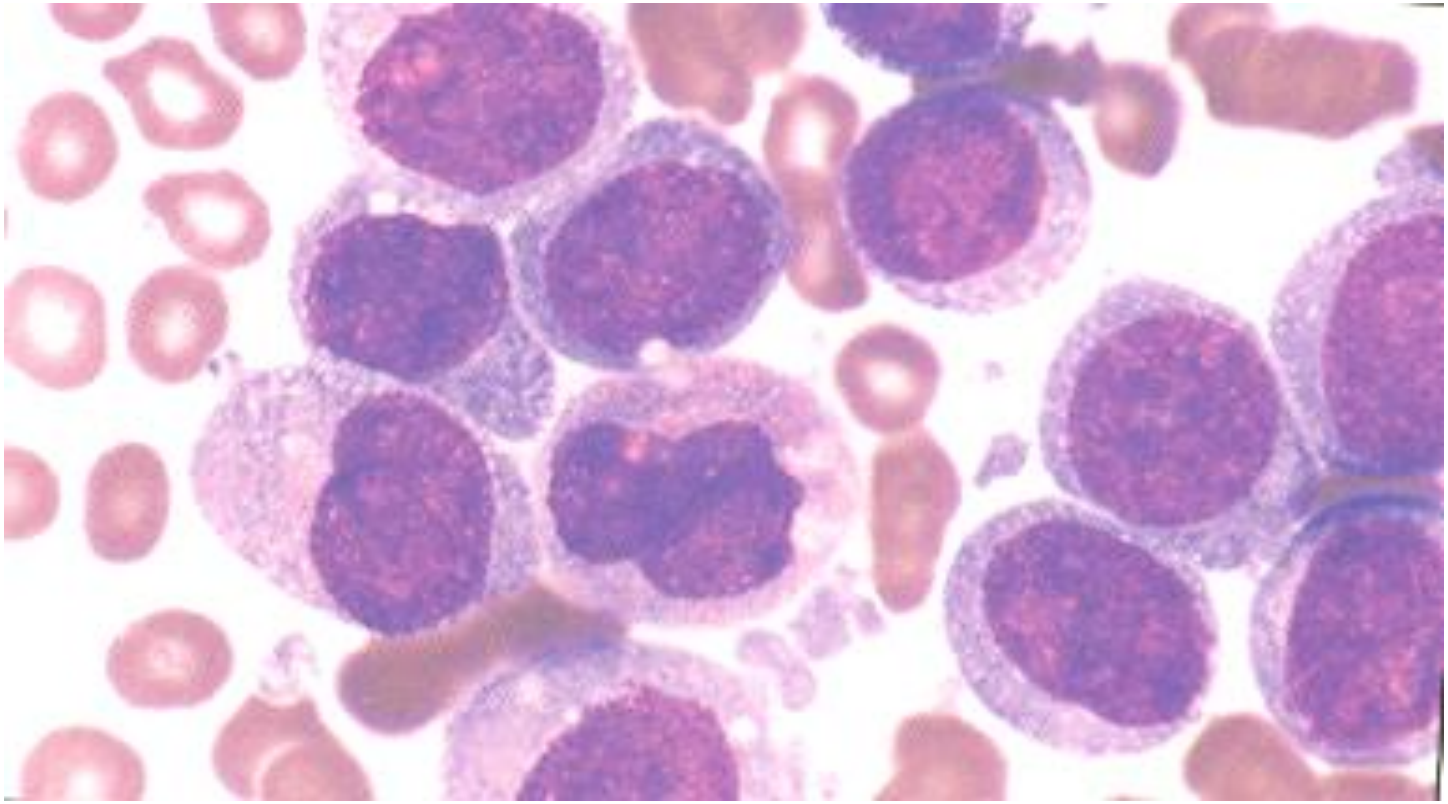
Acute Monoblastic/Monocytic Leukemia

- Bleeding disorders most common presentation
- Cutaneous and gingival infiltration
- CNS involvement
- Extramedullary masses

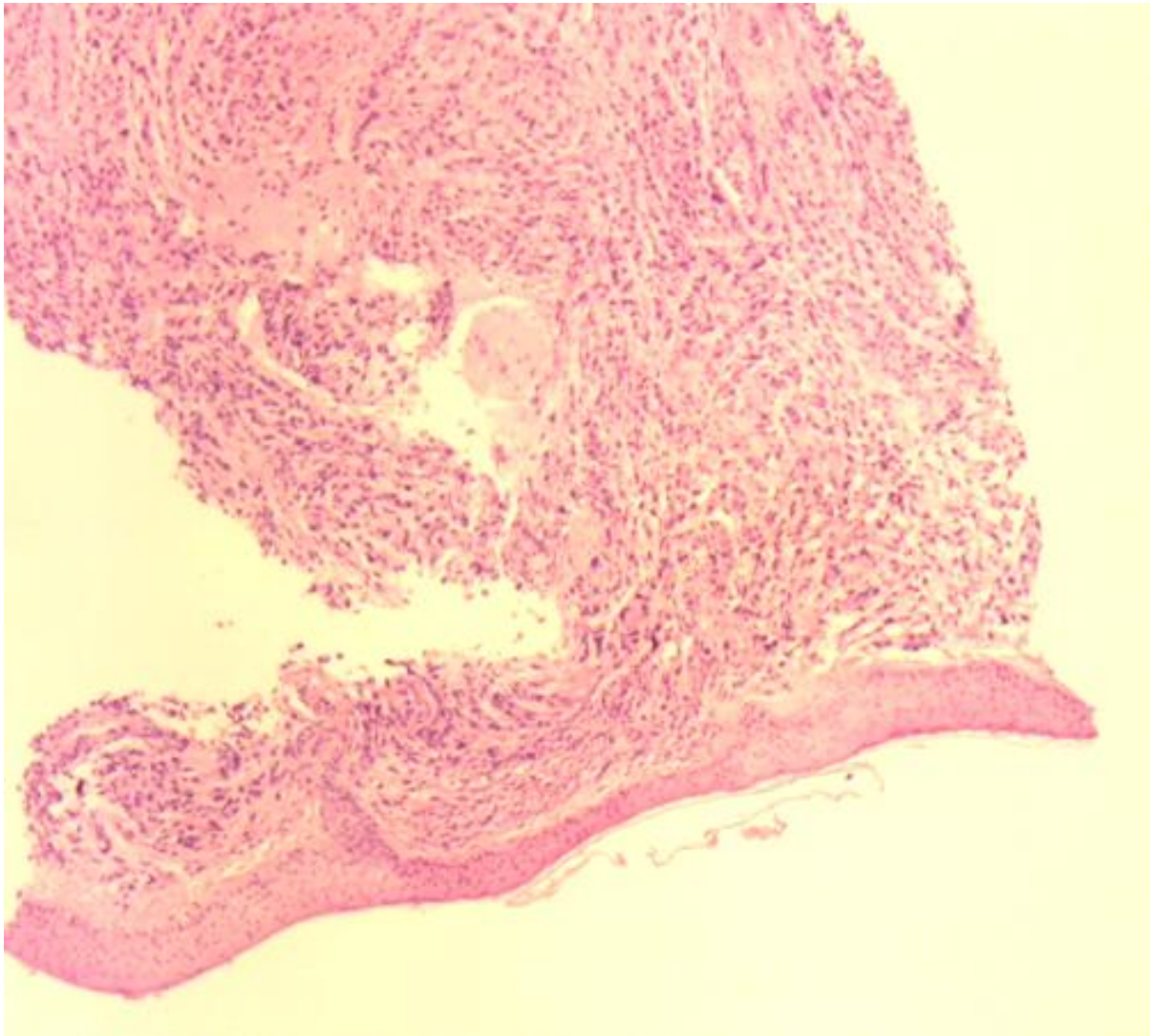
Acute Monoblastic/Monocytic Leukemia

- Non-specific esterase activity strongly positive (but weak or even negative in 20%)
- MPO negative (promonocytes may have some positivity)

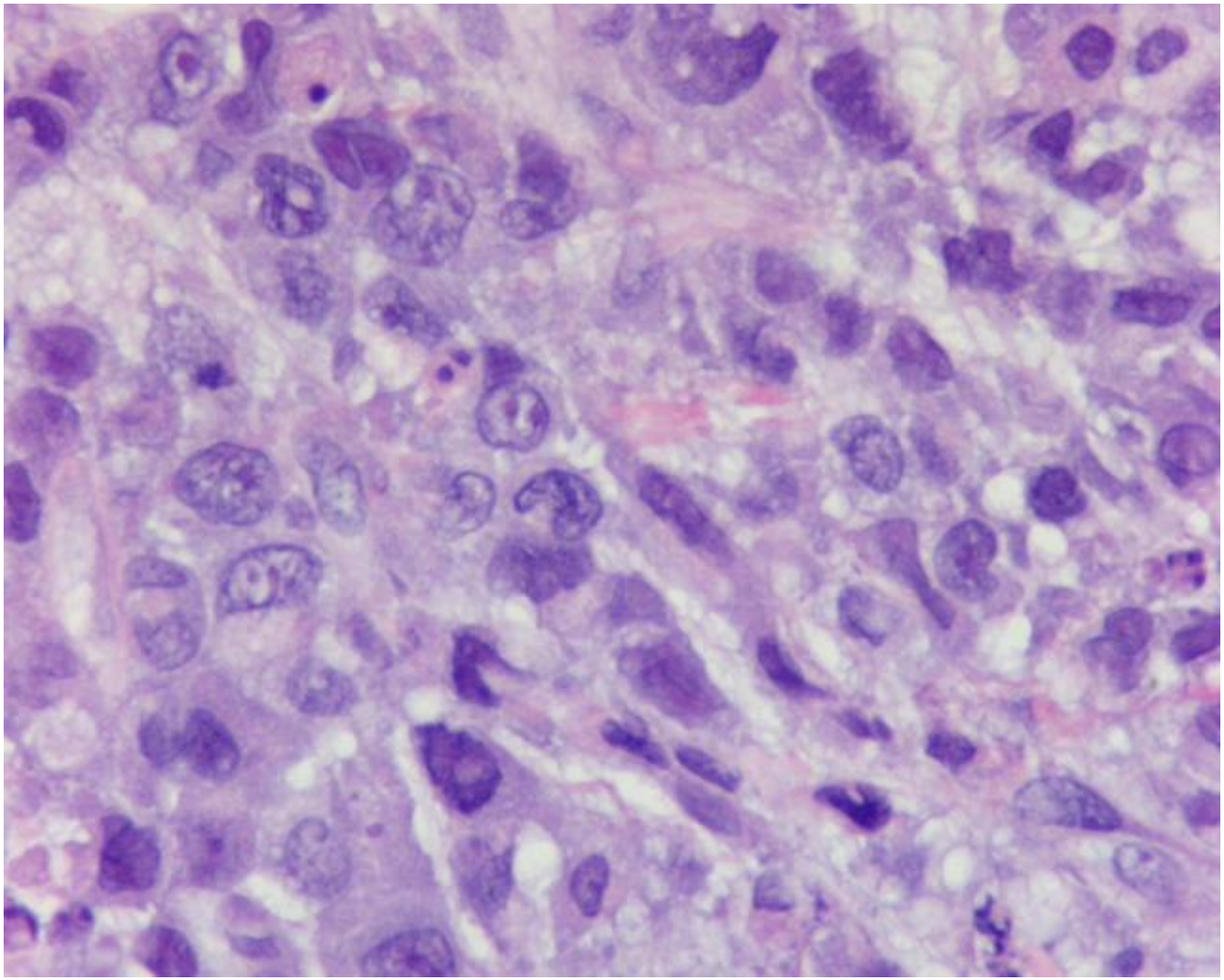
AML, M5



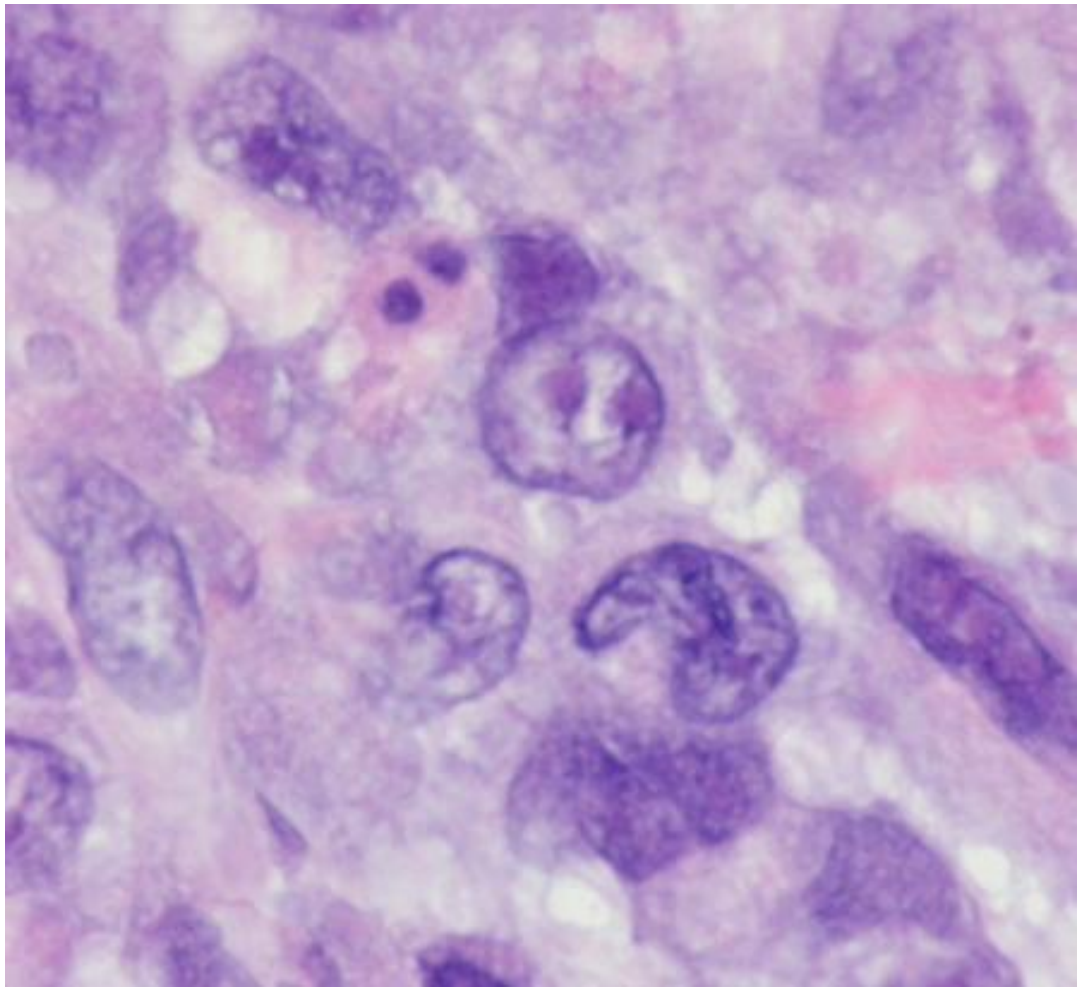
AML, M5



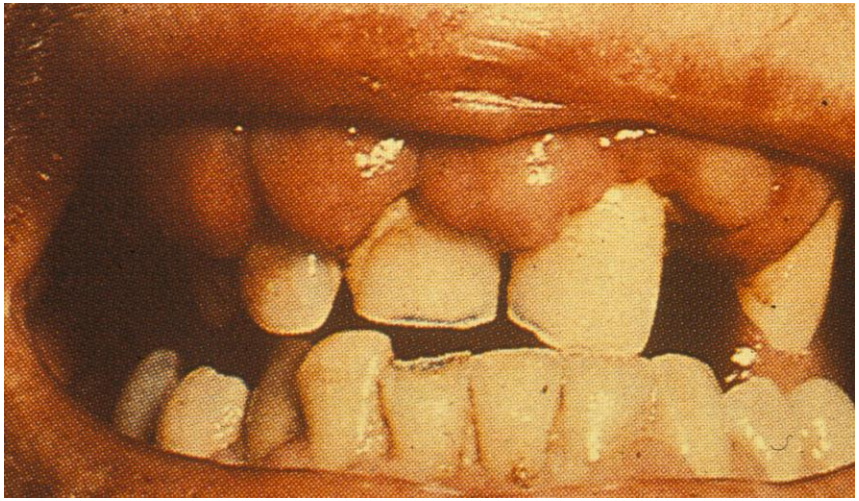
AML, M5

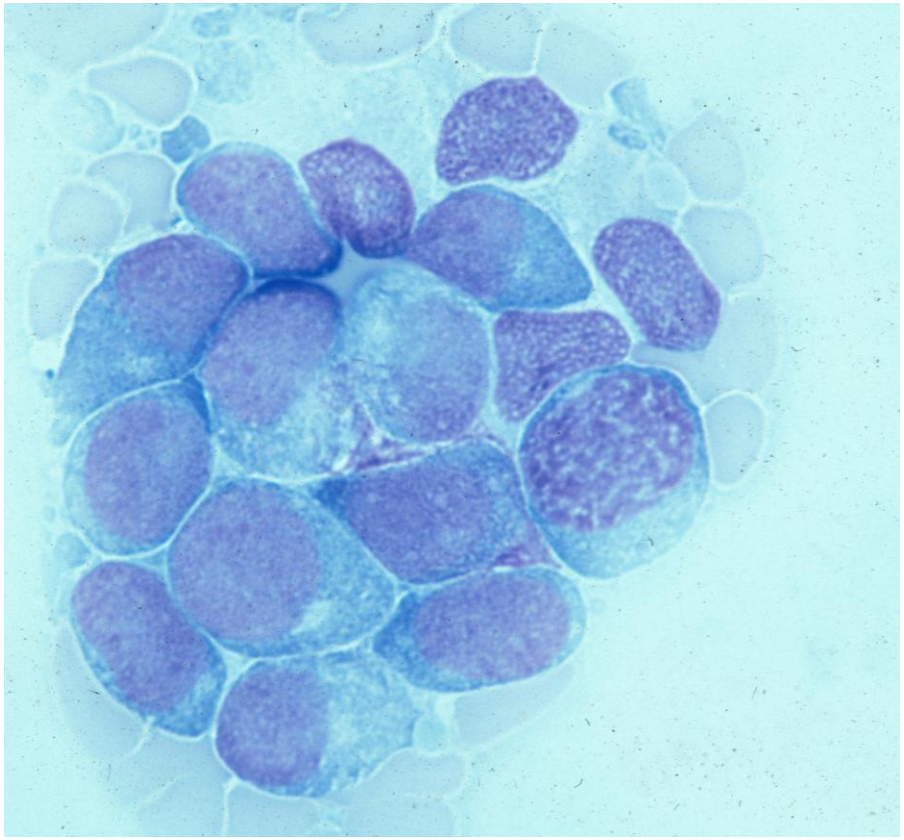


AML, M5



Acute Monoblastic Leukemia





Acute Monoblastic/Monocytic Leukemia

DDx: Acute Monoblastic Leukemia

- AML, minimally differentiated
- AML, without maturation
- Acute megakaryoblastic leukemia
- Soft tissue sarcomas
- Lymphomas

Acute Monoblastic/Monocytic Leukemia

DDx: Acute Monocytic Leukemia

- AMML
- Microgranular variant of acute promyelocytic leukemia (MPO++)

Acute Monoblastic/Monocytic Leukemia

Immunophenotype

- CD13+, CD33+, CD117+, (variable myeloid)
- CD14+, CD4+, CD11b+, CD11c+, CD64+, CD68+, CD36+, lysozyme+ (monocytic)
- CD34 usually negative

Acute Monoblastic/Monocytic Leukemia

Genetics

- Abnormalities of 11q23 with acute monoblastic leukemia (included in AML with recurrent genetic abnormalities)

Acute Monoblastic/Monocytic Leukemia

Genetics

- t(8;16)(p11;p13) associated with acute monocytic leukemia
- Erythrophagocytosis by leukemic cells

Acute Monoblastic/Monocytic Leukemia

- Both acute monoblastic and monocytic leukemia follow aggressive course

Acute Erythroid Leukemia

Acute Erythroid Leukemia

- Definition
  - Acute leukemia characterized by predominant erythroid population
- Two subtypes based on presence or absence of a significant myeloid component

Acute Erythroid Leukemia

- Erythroleukemia (erythroid/myeloid)-M6a
  - ≥50% erythroid precursors in BM
  - ≥20% myeloblasts of non-erythroid cells in BM
- Pure erythroid leukemia-M6b
  - ≥80% immature erythroids in BM
  - No significant myeloblastic component

Acute Erythroid Leukemia

- Clinical features
  - Profound anemia
  - Normoblastemia
  - May evolve from MDS, either RAEB or RCMD with or without RS
  - Some CML can undergo erythroblastic transformation

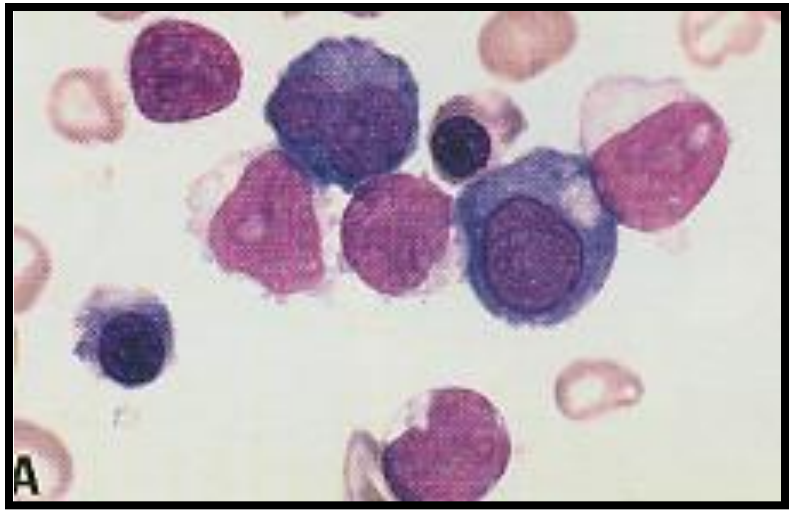
Erythroleukemia (erythroid/myeloid)

- Epidemiology
  - Adults
  - 5-6% of AML

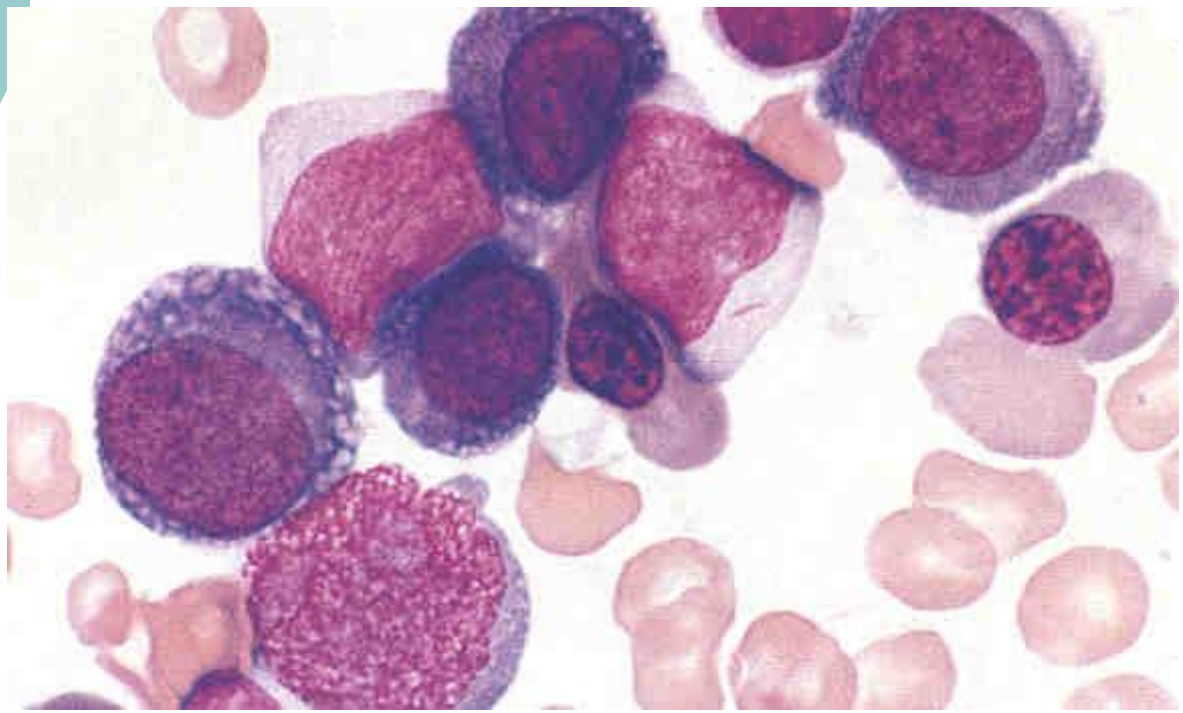
Erythroleukemia (erythroid/myeloid)

Morphology

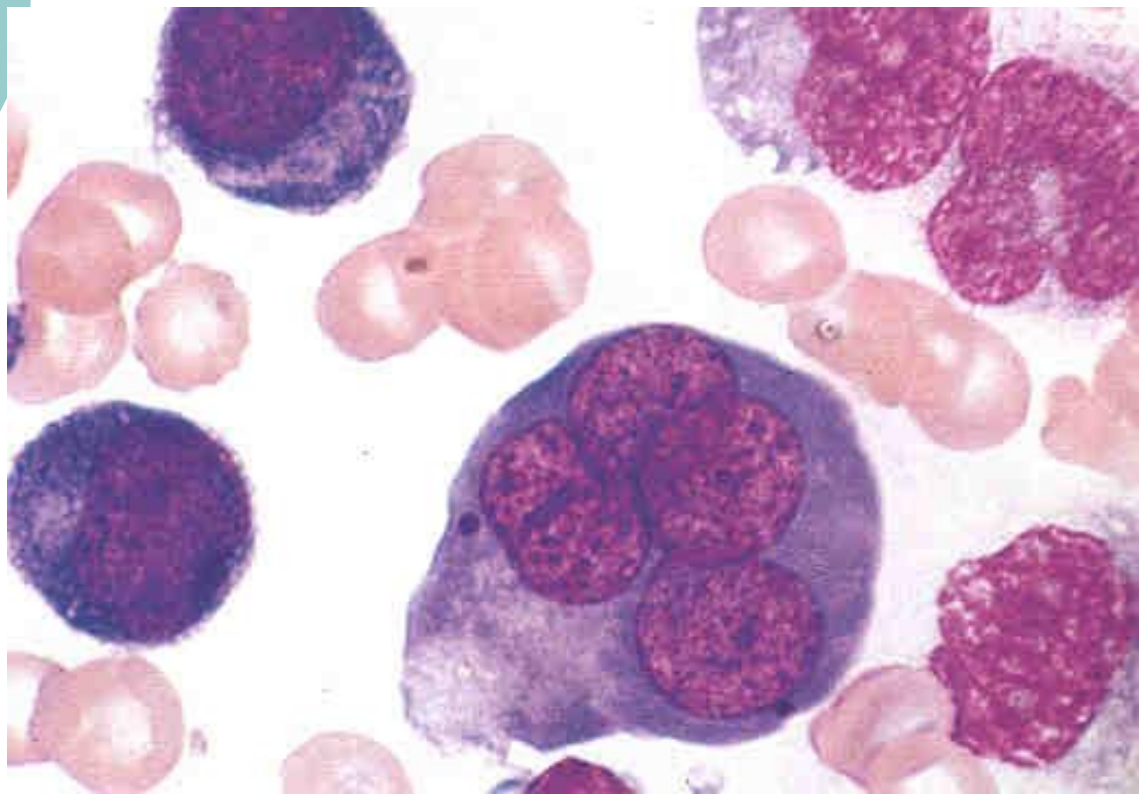
- BM
  - Hypercellular
  - Megakaryocytic dysplasia
- Erythroid
  - All stages
  - Frequent dysplasia
    - megaloblastoid nuclei
    - multinucleated forms
  - Cytoplasmic vacuoles
- Myeloid
  - Blasts similar to those in AML M1 or M2



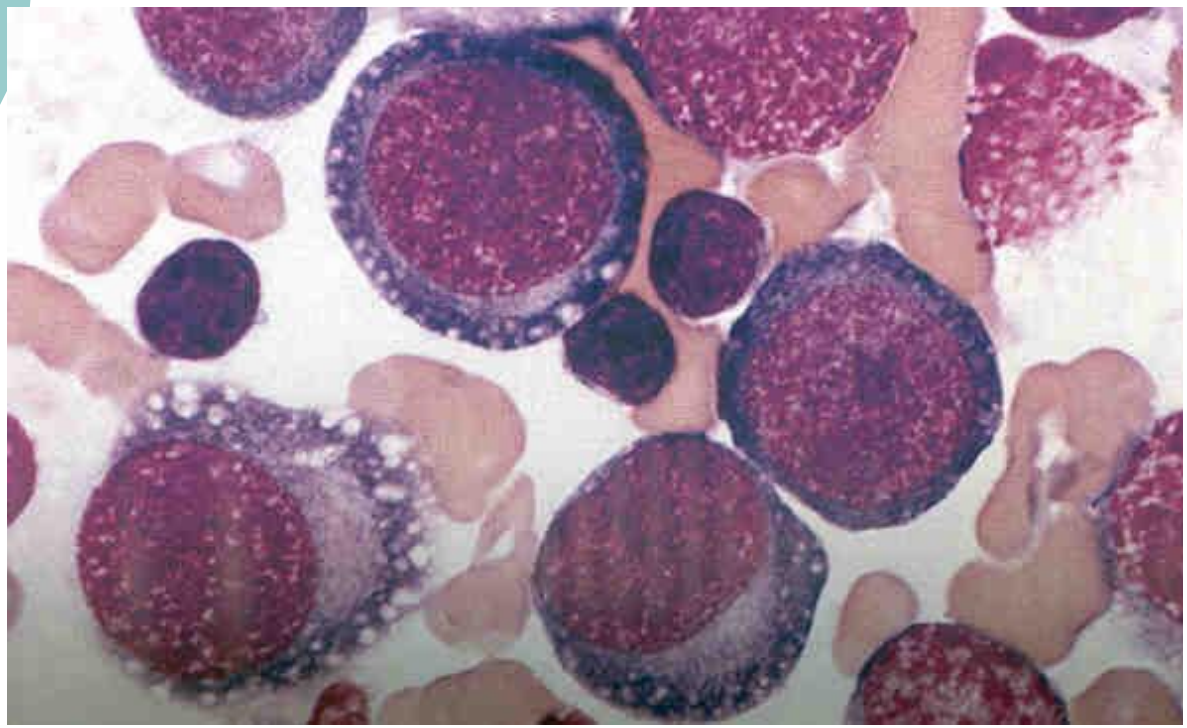
Erythroleukemia (erythroid/myeloid)



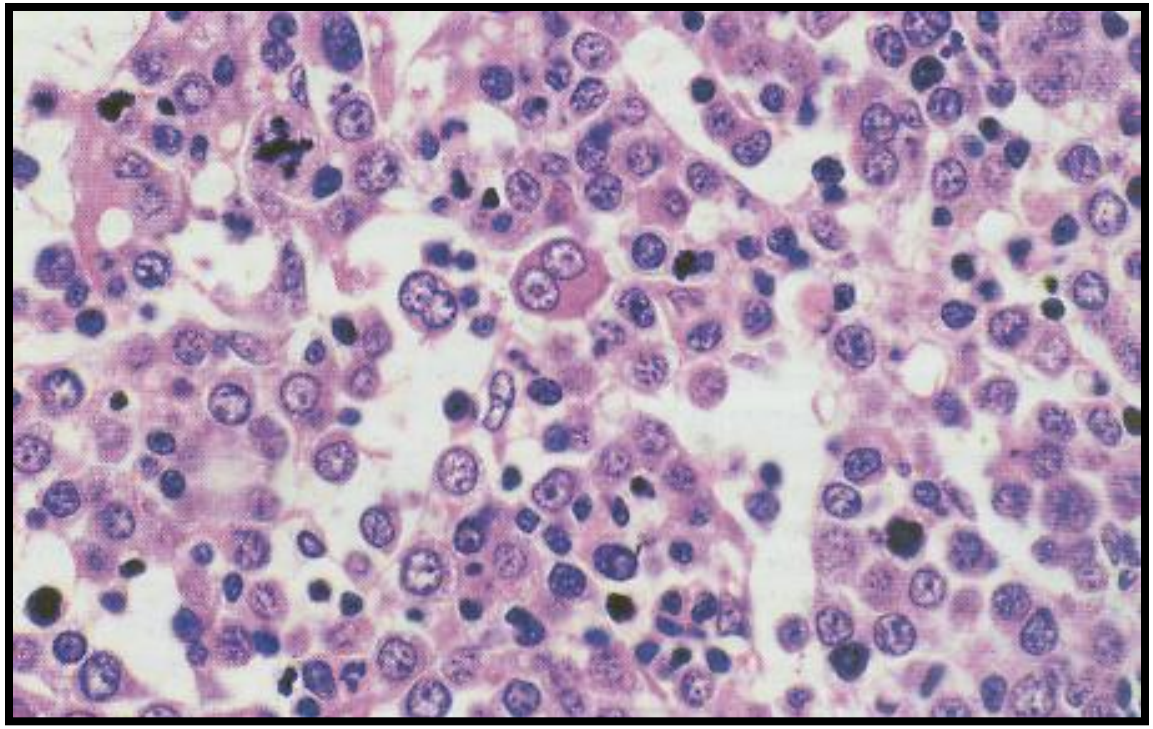
Erythroleukemia (erythroid/myeloid)



Erythroleukemia (erythroid/myeloid)

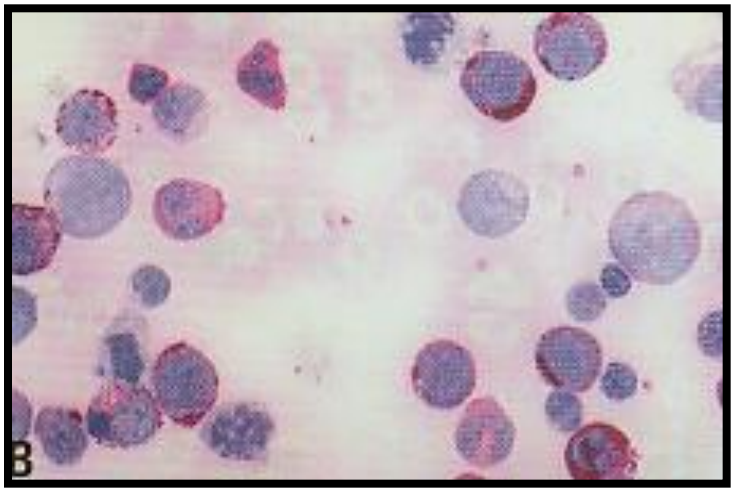


Erythroleukemia (erythroid/myeloid)



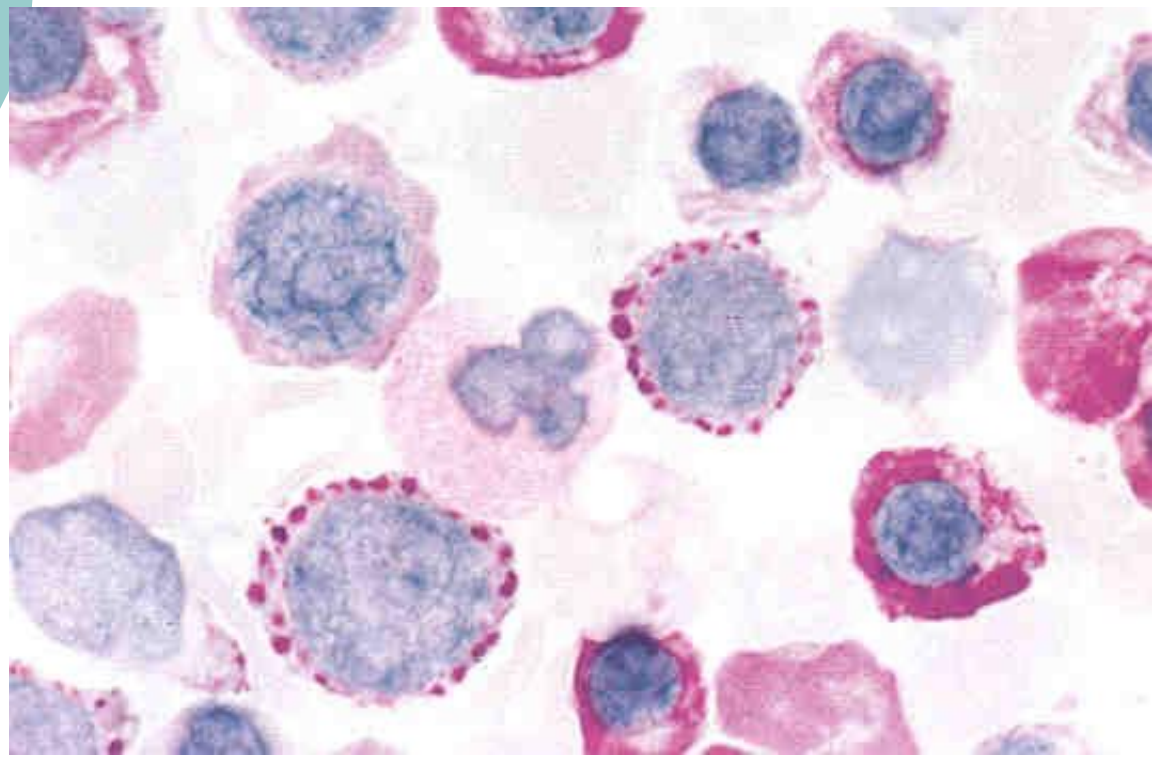
Erythroleukemia (erythroid/myeloid)

- Cytochemistry
  - Iron: Ringed sideroblasts
  - PAS: Globular or diffuse cytoplasmic staining
  - MPO: Myeloblasts



PAS

Erythroleukemia (erythroid/myeloid)



PAS

Erythroleukemia (erythroid/myeloid)

- Immunophenotype
  - Erythroid
    - MPO negative
    - Glycophorin A, hemoglobin A positive
  - Myeloblasts
    - CD13, CD33, CD117, MPO, +/-CD34 and HLA-DR

Erythroleukemia (erythroid/myeloid)

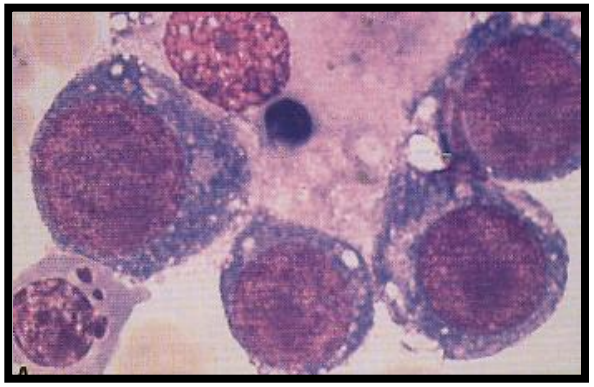
- Differential diagnosis
  - RAEB
  - AML with maturation and increased erythroid precursors
  - AML with multilineage dysplasia
    - Dysplasia involving $\geq$50 of the myeloid or megakaryocyte-lineage cells.

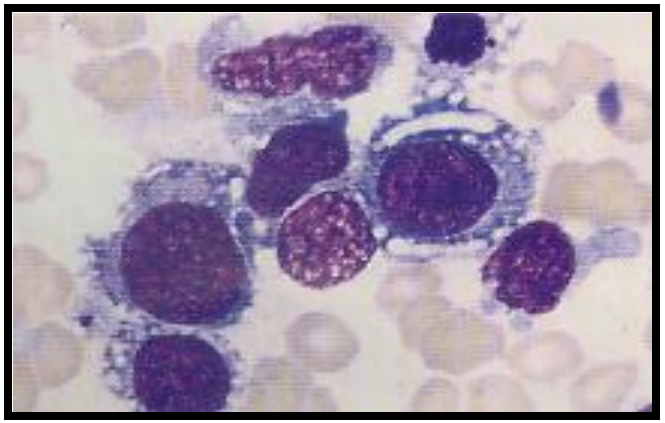
Pure Erythroid Leukemia

- Epidemiology
  - Rare
  - Any age

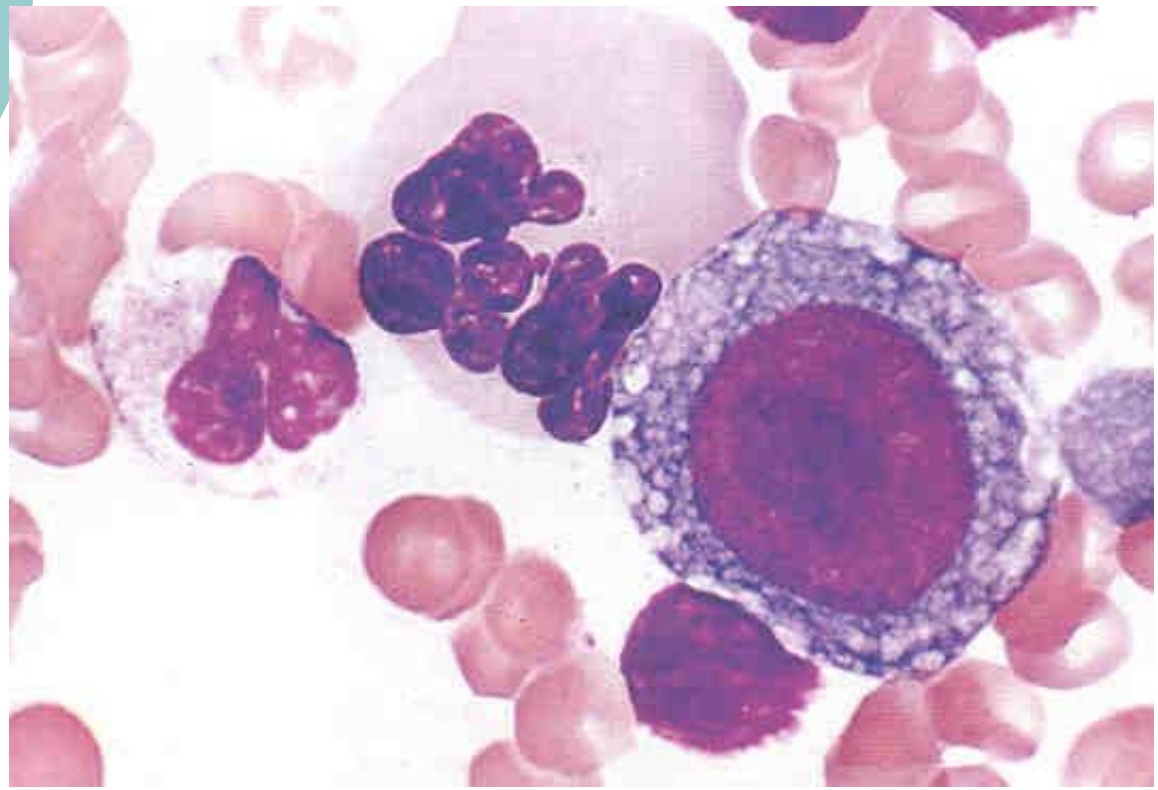
Pure Erythroid Leukemia

- Morphology
  - Medium to large-sized erythroblasts with round nuclei, fine chromatin and one or more nucleoli
  - Deeply basophilic cytoplasm, agranular and often vacuolated





Pure Erythroid Leukemia

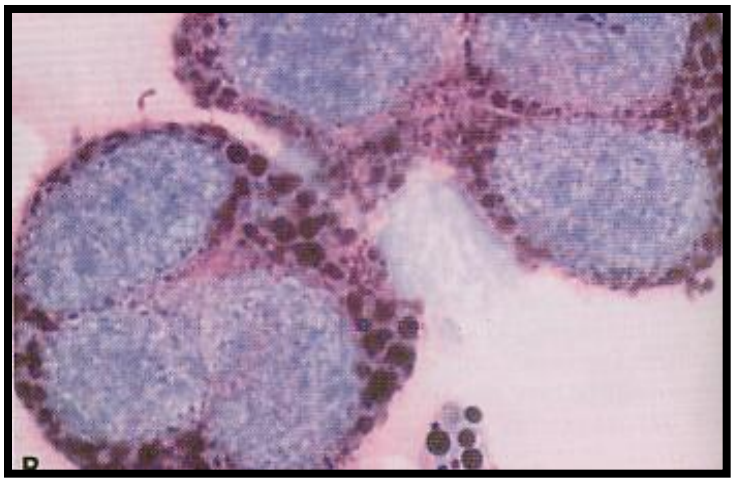


Pure Erythroid Leukemia

Cytochemistry

- PAS positive vacuoles
- MPO negative
- Alpha-naphthyl acetate esterase and acid phosphatase positive

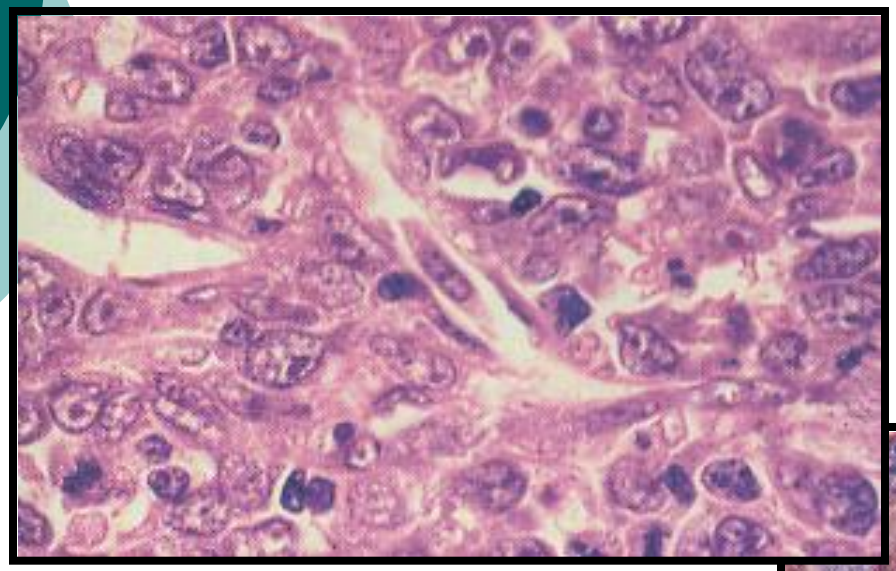
- EM
  - Free ferritin particles or siderosomes and rhopheocytosis

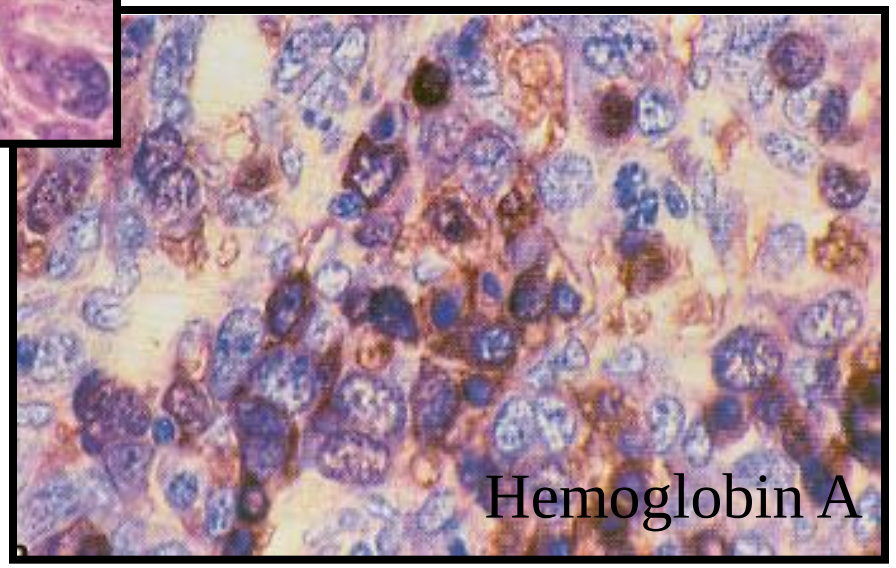


Pure Erythroid Leukemia

- Immunophenotype
  - Glycophorin A and hemoglobin A in more differentiated forms
  - Immature forms negative for glycophorin A
    - Positive for carbonic anhydrase 1, Gero antibody (against the Gerbich blood group)
    - Positive for CD36 (CD36 may be expressed in monocytes and megakaryocytes)
    - Megakaryocytic antigens CD41 and CD61 may be partially expressed
  - Negative for MPO, HLA-DR, CD34

Pure Erythroid Leukemia





Pure Erythroid Leukemia

- Differential diagnosis of pure erythroid leukemia
  - Megaloblastic anemia due to vit B12 or folate deficiency
    - Response to vitamins
    - Less dysplasia
    - Hypersegmented neutrophils
  - Other AML; especially megakaryoblastic
    - Ambiguous immunophenotype/concurrent erythroid-megakaryocytic involvement
  - ALL, lymphoma
    - Lymphoid markers

Acute Erythroid Leukemia

- Genetics
  - No specific chromosome abnormality
  - Complex karyotypes common
    - Chromosomes 5 and 7 frequently affected

Acute Erythroid Leukemia

- Cell of Origin
  - Erythroleukemia (erythroid/myeloid)
    - Multipotent stem-cell with wide myeloid potential
  - Pure erythroid leukemia
    - Primitive stem cell with some degree of commitment to the erythroid lineage

Acute Erythroid Leukemia

- Prognosis and predictive factors
  - Erythroleukemia (erythroid/myeloid)
    - Aggressive clinical course
    - May evolve to a prominent myeloblast picture
  - Pure erythroid leukemia
    - Rapid clinical course

Acute Megakaryoblastic Leukemia

Acute Megakaryoblastic Leukemia

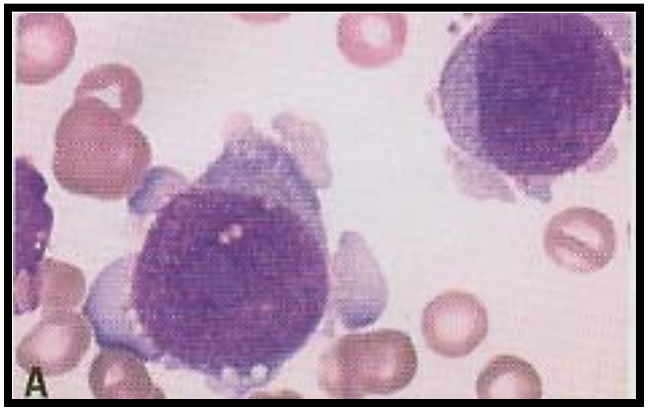
- Definition
  - Acute leukemia in which ≥50% of the blasts are megakaryocytic lineage
- Epidemiology
  - Adults and children
  - 3-5% of AML

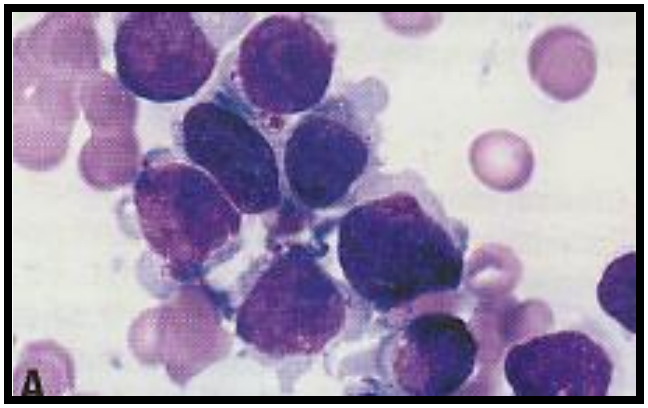
Acute Megakaryoblastic Leukemia

- Clinical features
  - Cytopenias, often thrombocytopenia
  - Dysplastic features in neutrophils and platelets
  - Organomegaly in children with t(1;22)
    - Bone lytic lesions
  - Mediastinal germ cell tumors in young adult males
  - Other types of AML and histiocytosis

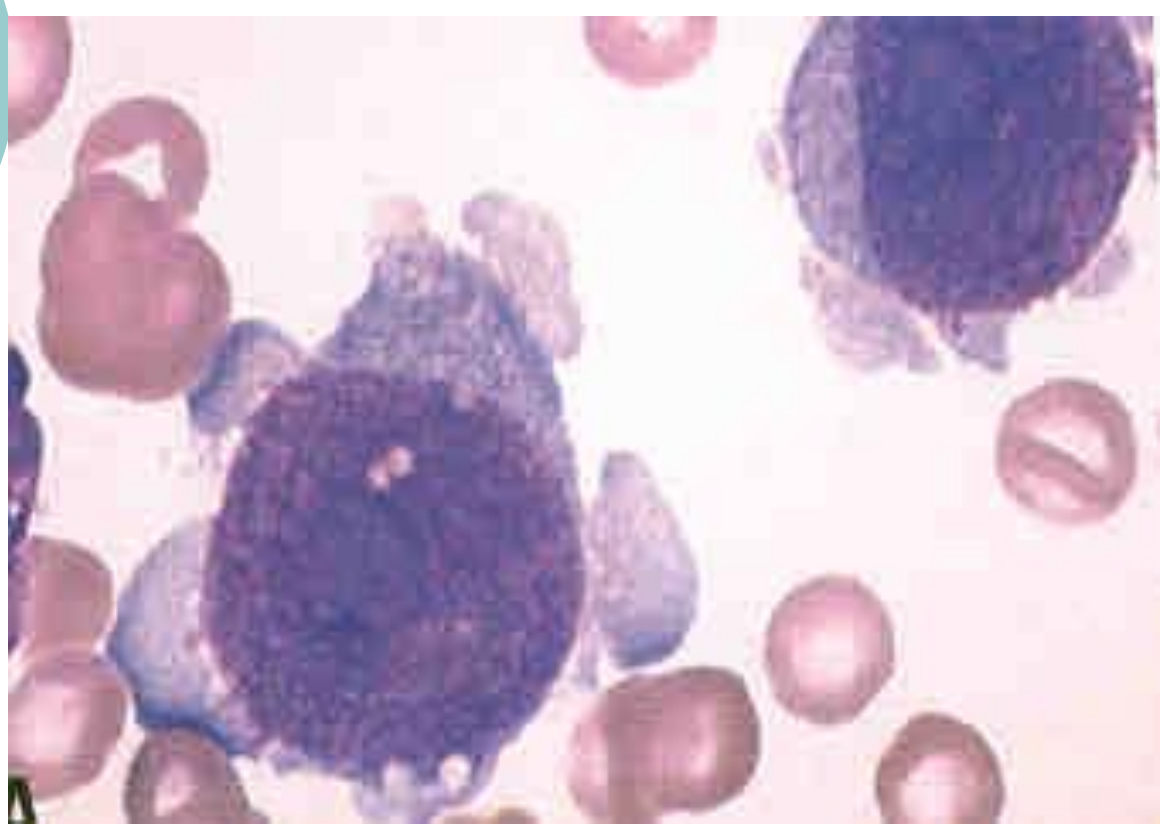
Acute Megakaryoblastic Leukemia

- Morphology
  - Megakaryoblast
    - Medium to large size
    - Round, slightly irregular nucleus
    - Fine reticular chromatin
    - One to three nucleoli
    - Basophilic cytoplasm
      - Agranular
      - Bleb or pseudopod formation
  - Blasts may occasionally be small resembling lymphoblasts



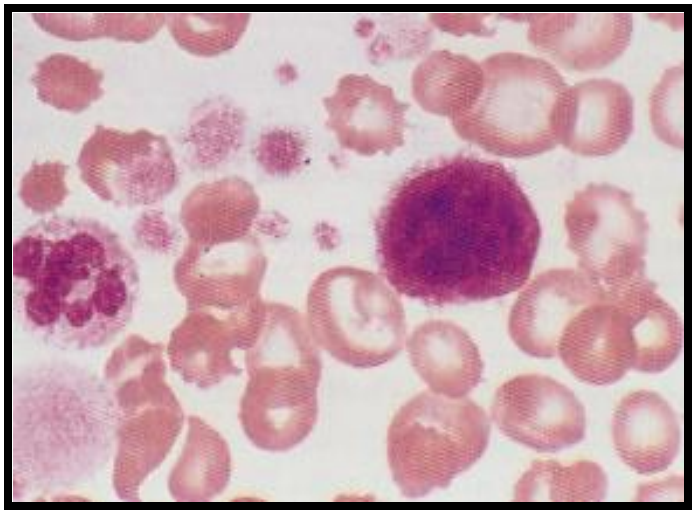


Acute Megakaryoblastic Leukemia



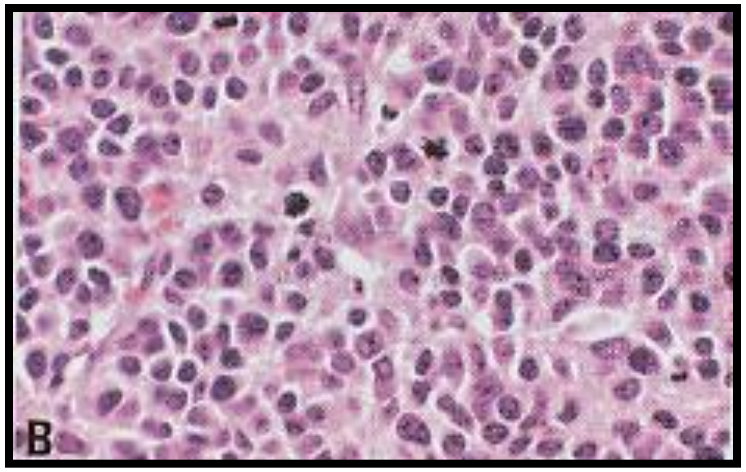
Acute Megakaryoblastic Leukemia

- PB
  - Micromegakaryocytes, megakaryoblastic fragments
  - Dysplastic large platelets
  - Hypogranular neutrophils
    - Micromegakaryocytes
      - Small cells
      - One or two round nuclei
      - Condensed chromatin
      - Mature cytoplasm
      - (Not to be counted as blasts)

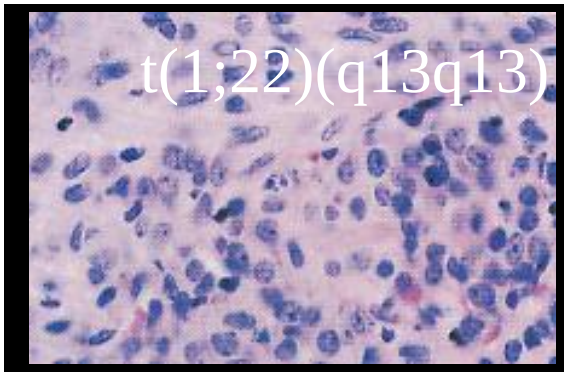


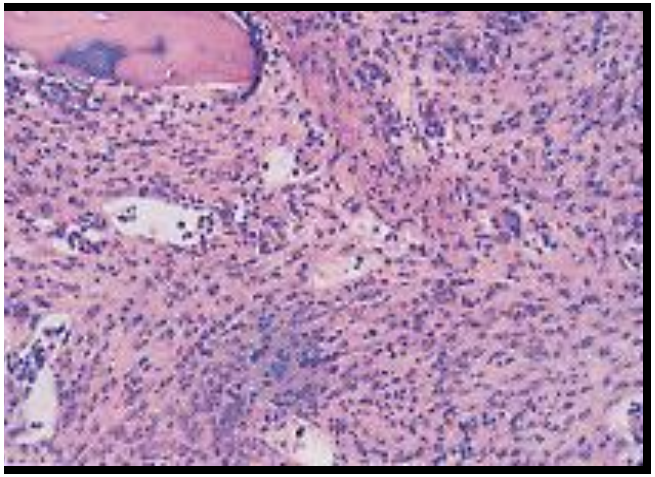
Acute Megakaryoblastic Leukemia

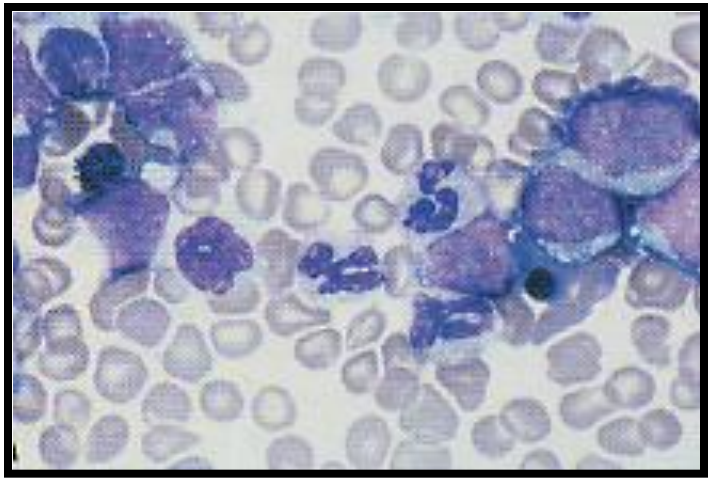
- Morphology/histopathology
  - BM
    - Uniform population of poorly differentiated blasts
    - Mixed with maturing dysplastic megakaryocytes
    - Clusters of blasts
    - Variable reticulin fibrosis



Acute Megakaryoblastic Leukemia







Acute Megakaryoblastic Leukemia

- Cytochemistry
  - SSB and MPO negative
  - PAS, acid phosphatase and punctate NSE positive
- EM
  - Peroxidase activity confined to the nuclear membranes and ER with Platelet Peroxidase (PPO) reaction

Acute Megakaryoblastic Leukemia

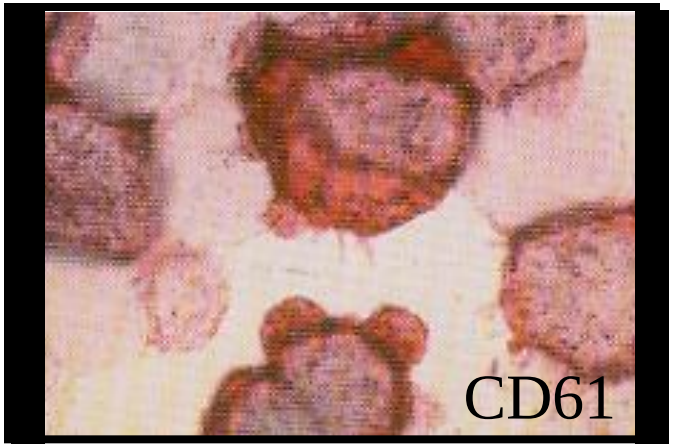
- Differential diagnosis
  - Minimally differentiated AML
  - Acute panmyelosis with myelofibrosis
    - Trilineage proliferation
  - ALL
  - Pure erythroid leukemia

Acute Megakaryoblastic Leukemia

- Differential diagnosis (cont.)
  - Blastic transformation of CML or CIMF
    - History of chronic phase
    - Splenomegaly common
    - Red cell abnormalities in CIMF
    - BCR/ABL in CML
  - Metastatic tumors in children
    - Alveolar rhabdomyosarcoma
    - Neuroblastoma

Acute Megakaryoblastic Leukemia

- Immunophenotype
  - Platelet glycoproteins
    - CD41, CD61 (cytoplasmic more sensitive)
    - CD42 less frequent
  - Factor VIII
  - Myeloid markers
    - CD13 and CD33 positive
    - MPO, CD34, CD45 and HLA-DR negative
  - CD36
  - Lymphoid marker
    - Aberrant CD7



Acute Megakaryoblastic Leukemia

- Genetics
  - No unique chromosomal abnormality in adults
  - inv(3)(q21;q26) found in other leukemias
  - Children t(1;22)(p13q13)
  - Young men with germ cell tumors i(12p)
- Cell of origin
  - Precursor committed to the megakaryocytic lineage and possibly erythroid lineage

Acute Megakaryoblastic Leukemia

- Prognosis
  - Poor
    - Particularly in infants with t(1;22)

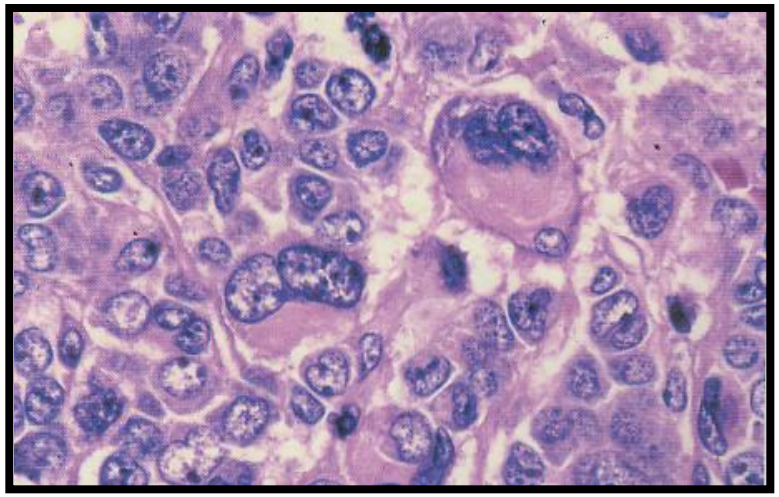
Acute Myeloid Leukemia/Transient Myeloproliferative Disorder in Down Syndrome

Acute Myeloid Leukemia/Transient Myeloproliferative Disorder in Down Syndrome

- Down Syndrome
  - Increased predisposition to acute leukemia
    - Particularly AML, megakaryoblastic subtype
  - Spontaneous remission (transient myeloproliferative disorder)

Acute Myeloid Leukemia/Transient Myeloproliferative Disorder in Down Syndrome

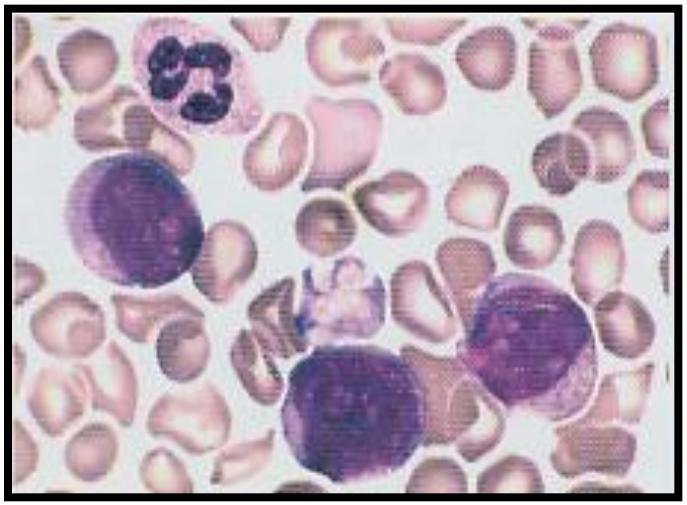
- Clinical features
  - Manifests in neonatal period
  - Marked leukocytosis
    - PB blasts usually ≥30%, often ≥50%
  - May be prominent extramedullary involvement



Acute Myeloid Leukemia/Transient Myeloproliferative Disorder in Down Syndrome

Morphology (persistent or transient leukemia)

- Unusual blasts
  - 12-15 um round to slightly irregular nuclei
  - Moderate amounts of basophilic cytoplasm
    - Cytoplasmic blebs
    - Coarse azurophilic granules
- Promegakayocytes and micromegakaryocytes frequent
- Dyserythropoiesis common
- Dysgranulopoiesis minimal
- Increased basophils



Acute Myeloid Leukemia/Transient Myeloproliferative Disorder in Down Syndrome

- Cytochemistry
  - Blasts
    - MPO, SBB, TdT negative
    - May have scattered, granular PAS positivity
- EM
  - Variable number of blasts with platelet peroxidase reactivity

Acute Myeloid Leukemia/Transient Myeloproliferative Disorder in Down Syndrome

- Genetics
  - Trisomy 21
  - Additional clonal abnormalities
    - Trisomy 8 most frequent
    - No t(1;22)
  - FISH shows cytogenetic abnormalities in megakaryocytic and erythroid precursors
  - Molecular studies in transient proliferative disease
    - Clonality by X-chromosome linked polymorphism analysis

Acute Myeloid Leukemia/Transient Myeloproliferative Disorder in Down Syndrome

- Cell of origin
  - Myeloid precursor cell with potential for megakaryocytic and erythroid differentiation
- Prognosis
  - Transient myeloproliferative disorder
    - Remits spontaneously in one to three months
      - Recurrence and 2nd remission or persistent disease may occur