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Acute Leukemia

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Acute leukemia

- Classified into two types
  - Acute lymphoblastic leukemia
  - Acute myeloblastic leukemia

Acute lymphoblastic leukemia

Acute Lymphoblastic Leukemia

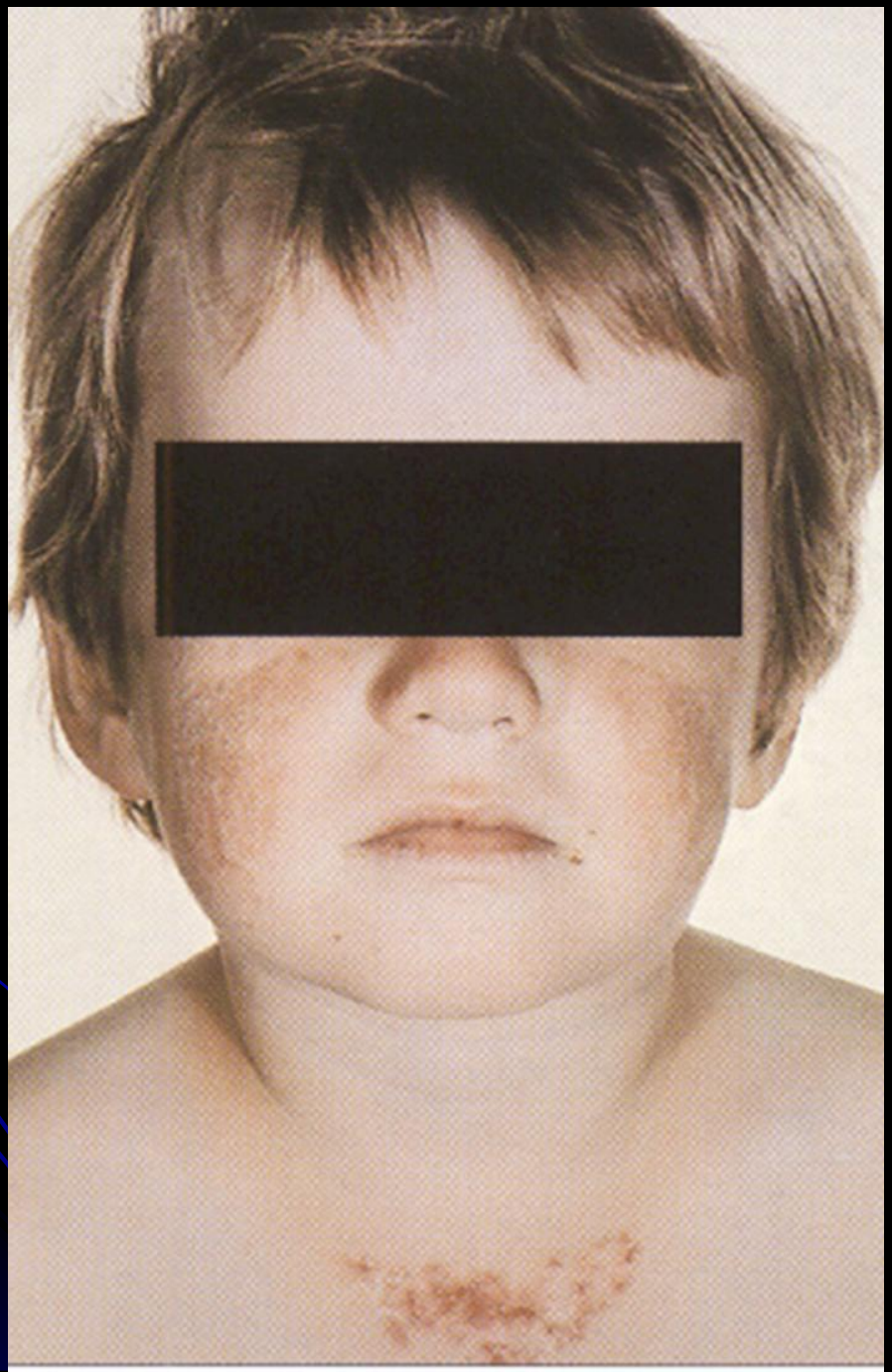
- Neoplastic proliferation of lymphoblasts which have their origin in a lymphocyte progenitor cell
- 80% in children, peaks at age 4
- Higher incidence in developed countries

Risk factors

- Environmental factors
  - Ionizing radiation (especially in utero)
- Chromosome instability syndromes
  - Down's syndrome
  - Ataxia telangiectasia
  - Bloom's syndrome
- Idiopathic

Clinical presentation

- Abrupt onset
- Symptoms related to bone marrow depression
- May present with infection, joint pain, bleeding, and fatigue

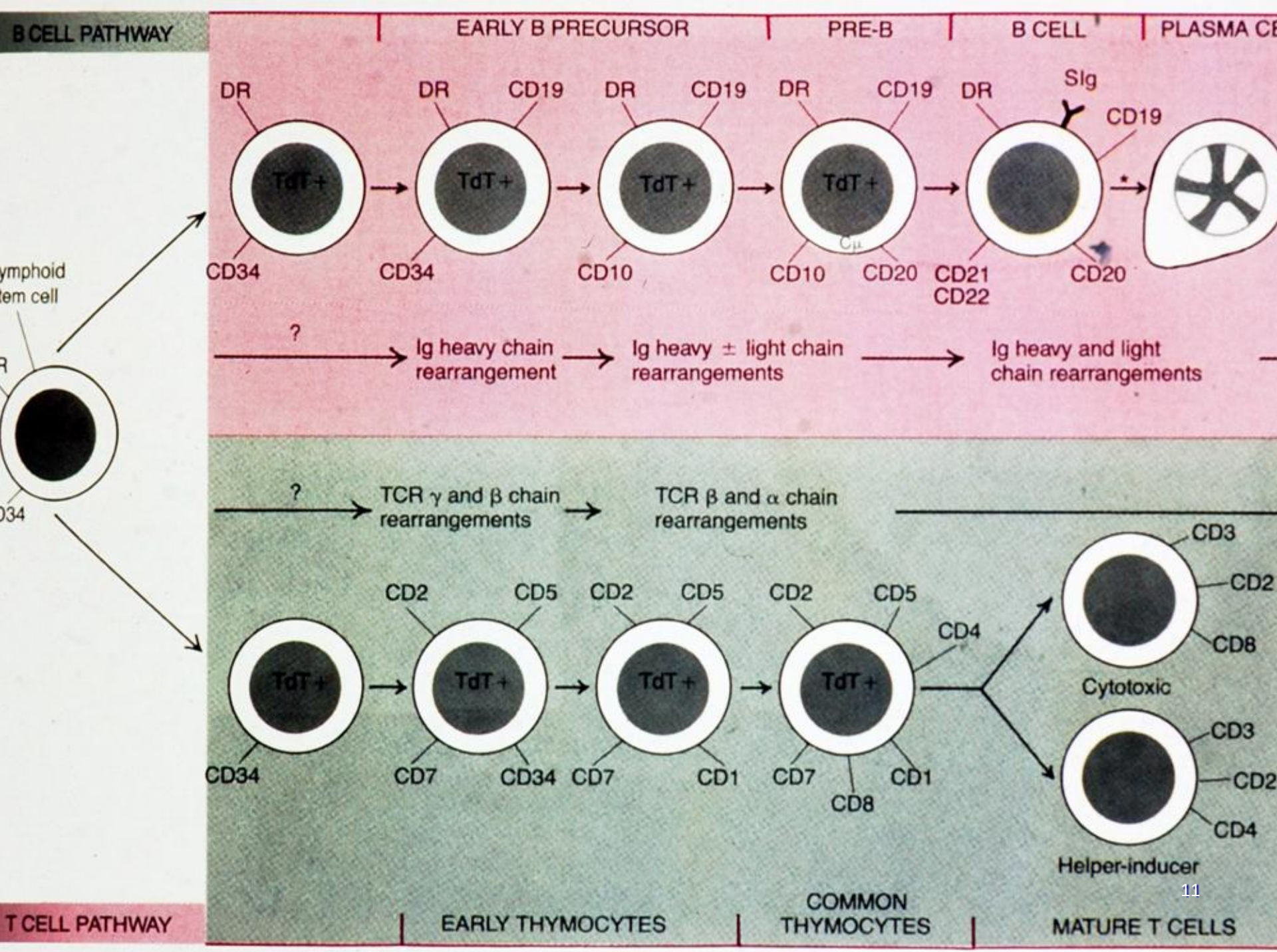


Peripheral blood findings

- Anemia
- Thrombocytopenia (<100K)
- Leukopenia or leukocytosis

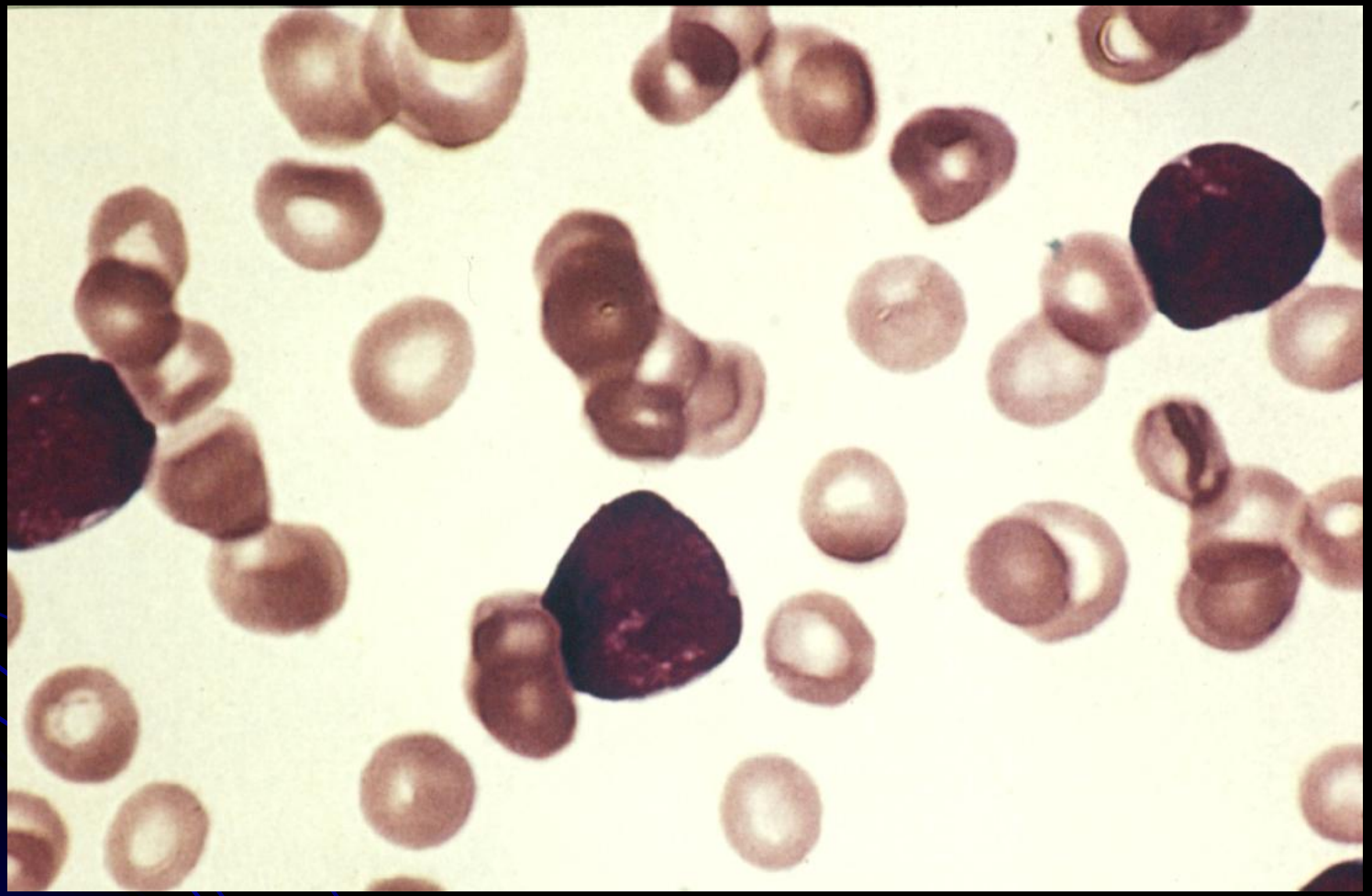
Classification

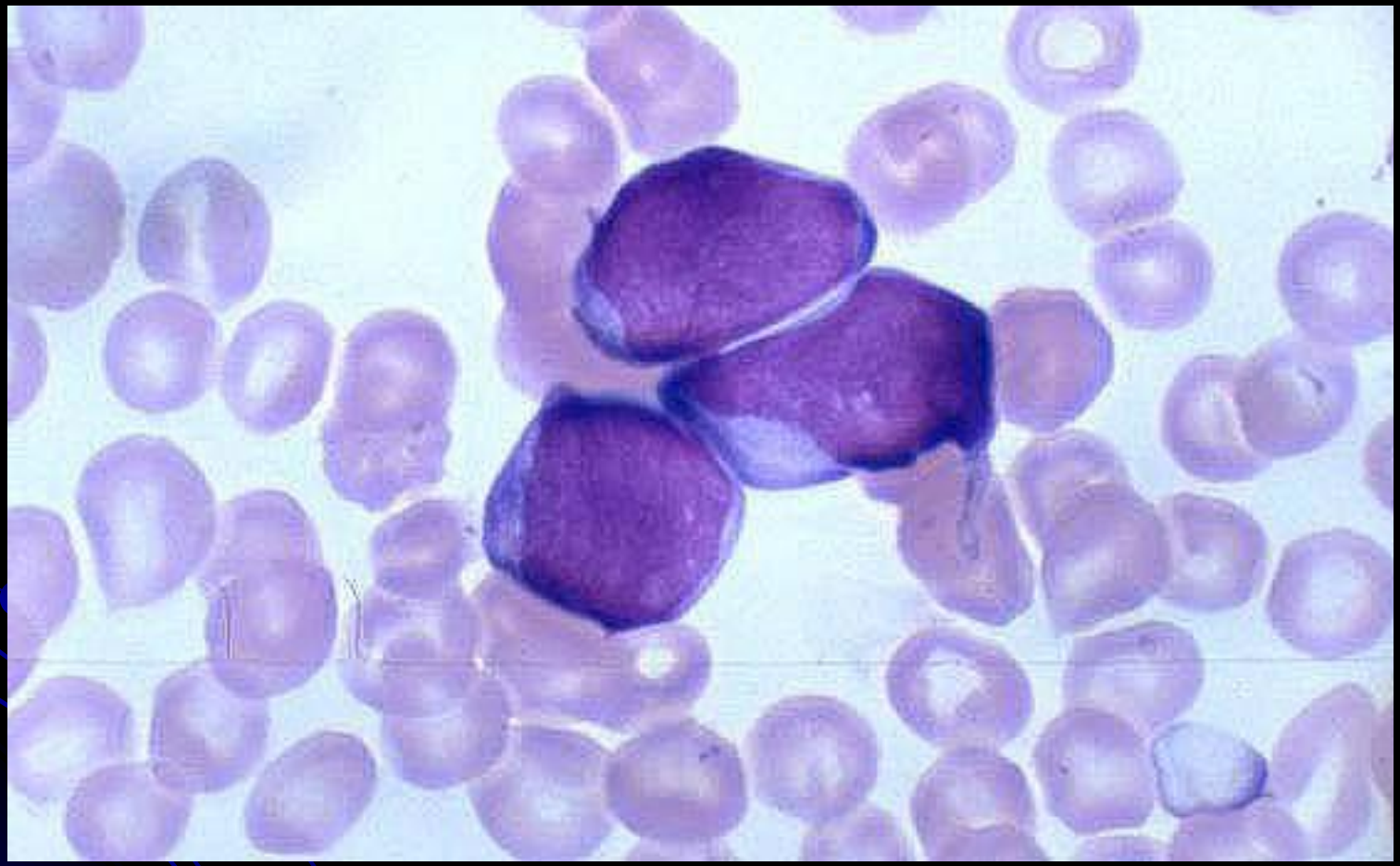
- WHO Classification (2001) divides into B or T-cell ALL
- Incorporates cytogenetic information into diagnosis
- ≥20% blasts required


B CELL PATHWAY
EARLY B PRECURSOR
PRE-B
B CELL
PLASMA CE
DR
CD19
Sig
TdT +
CD34
CD10
Cμ
CD20
CD21
CD22
?
Ig heavy chain rearrangement
Ig heavy ± light chain rearrangements
Ig heavy and light chain rearrangements
ymphoid
tem cell
034
TCR γ and β chain rearrangements
TCR β and α chain rearrangements
CD2
CD5
CD4
CD7
CD1
CD8
CD3
Cytotoxic
Helper-inducer
T CELL PATHWAY
EARLY THYMOCYTES
COMMON THYMOCYTES
MATURE T CELLS

Precursor B ALL

- Presents usually in children
- Pancytopenia due to extensive marrow involvement (dry tap)
- 85% of ALL
- Can occasionally present with lymph node involvement but no marrow involvement (acute lymphoblastic lymphoma)



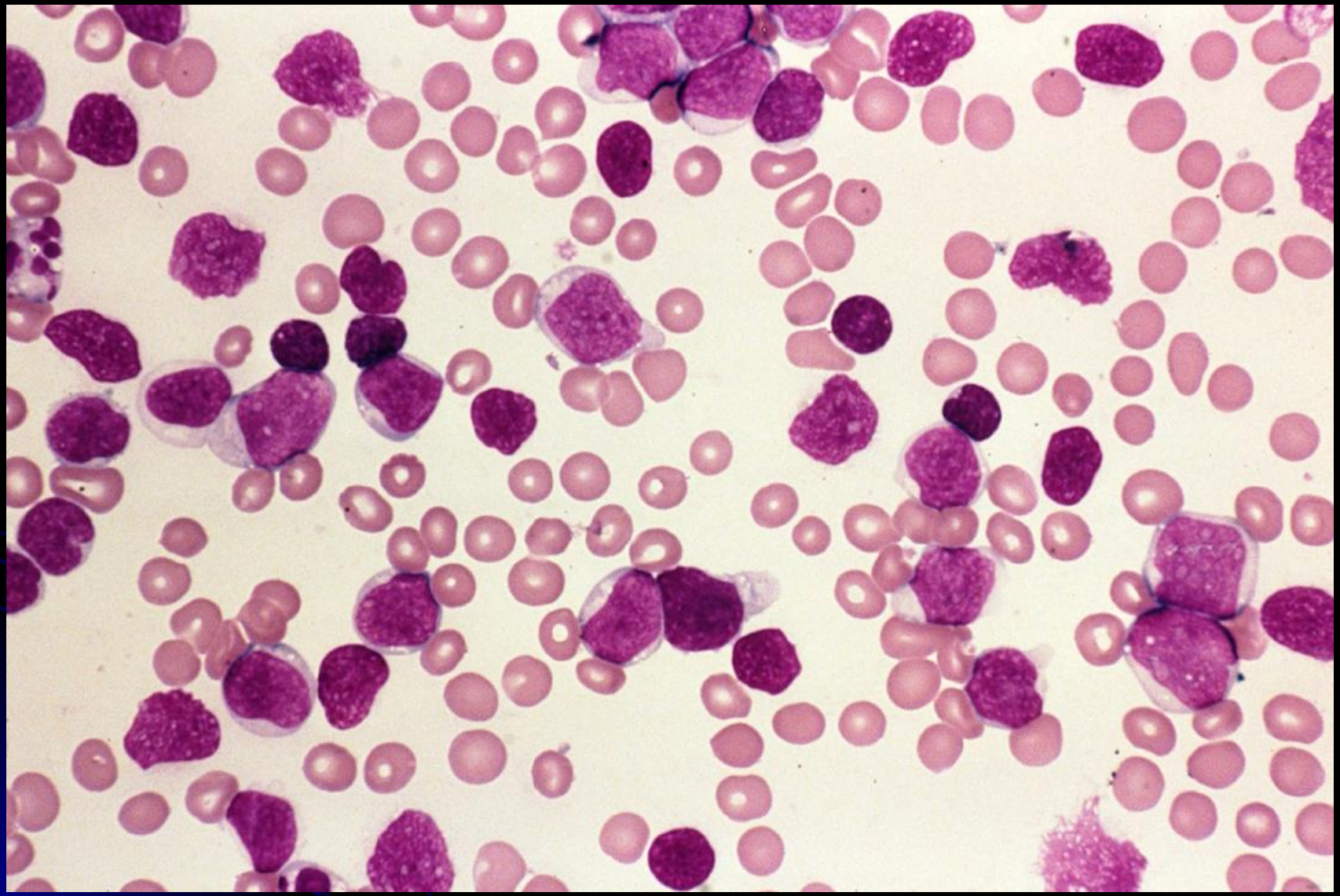


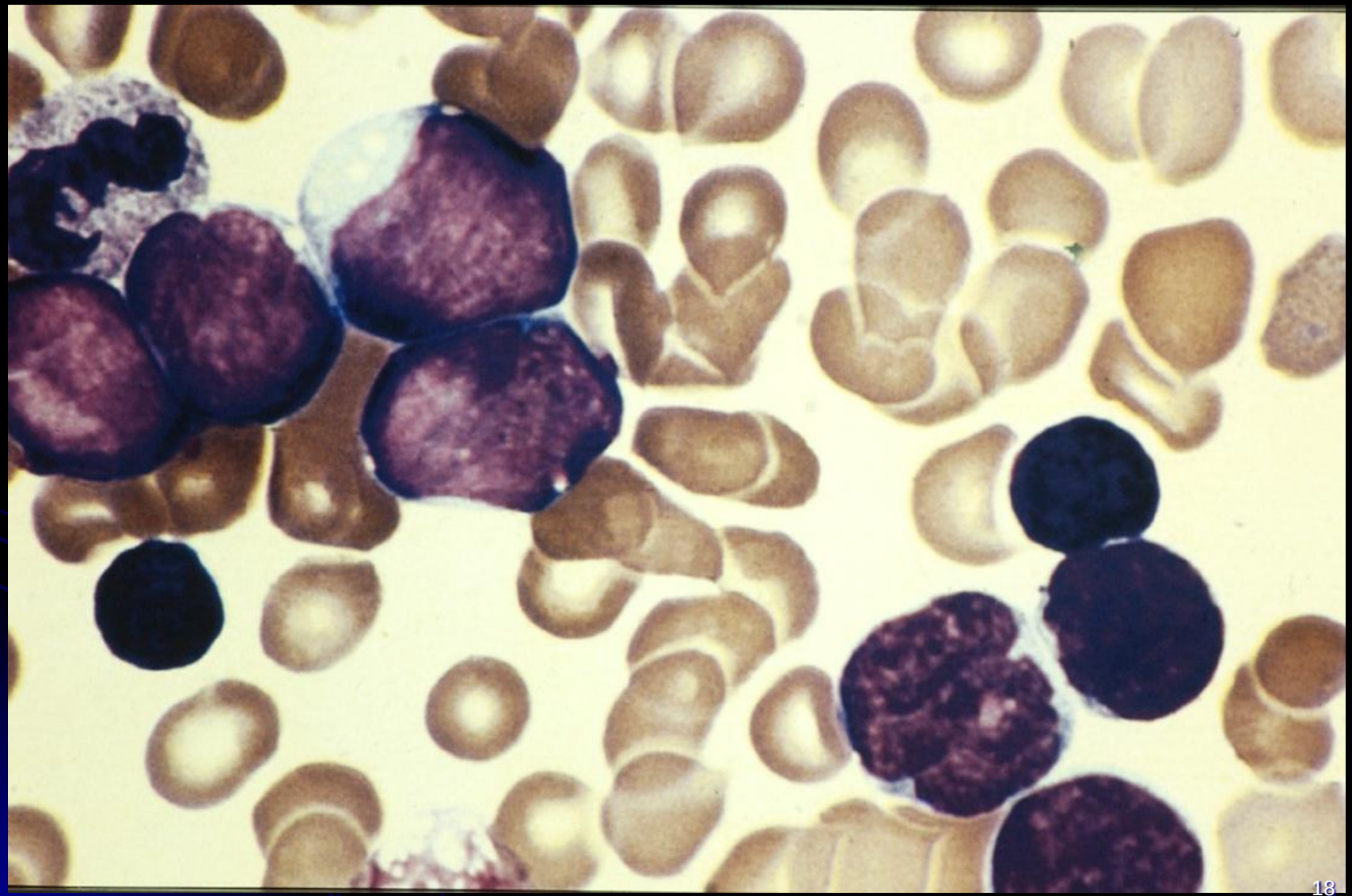
Precursor B ALL

- Flow cytometry
  - CD19+,CD10+,TdT+,Ig-
- Cytogenetics
  - t(4;11) – poor prognosis
  - t(9;22) – poor prognosis
  - Hypodiploidy – poor prognosis
  - Hyperdiploidy – Favorable prognosis

Precursor T ALL

- Presents in teens and young adults. M>F
- Often presents with mediastinal mass, hyperleukocytosis, CNS involvement
- Rapidly progressive





Precursor T-ALL

- Flow cytometry
  - Common thymocyte CD1+CD2+CD3±CD4+CD5+CD7+CD8+Tdt+
- Cytogenetics
  - Various abnormalities

ALL

- Therapy
  - Multiagent chemotherapy
    - Prednisone, vincristine, methotrexate, cyclophosphamide, daunorubicin, l-asparaginase
  - G-CSF
  - Bone marrow transplantation

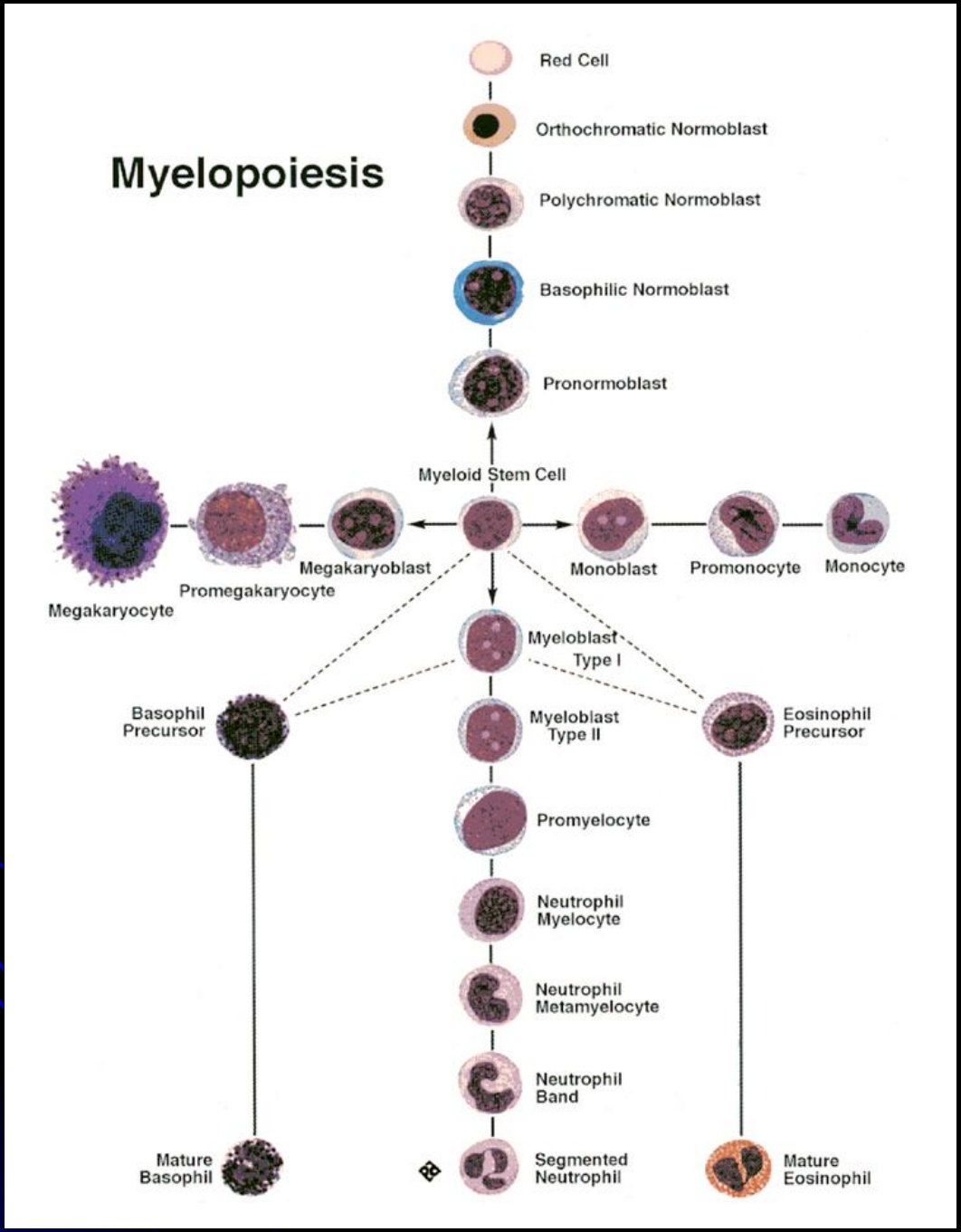
Factors for good prognosis

- Age <10 years
- WBC <10K
- Precursor B-ALL phenotype, CD10+
- Disease free at 14 day marrow
- Hyperdiploidy

Acute myeloblastic leukemia

Definition

- Neoplastic proliferation of hematopoietic precursor cells (myeloblasts and/or promyelocytes)


Myelopoiesis
Red Cell
Orthochromatic Normoblast
Polychromatic Normoblast
Basophilic Normoblast
Pronormoblast
Myeloid Stem Cell
Megakaryocyte
Promegakaryocyte
Megakaryoblast
Monoblast
Promonocyte
Monocyte
Myeloblast Type I
Basophil Precursor
Myeloblast Type II
Eosinophil Precursor
Promyelocyte
Neutrophil Myelocyte
Neutrophil Metamyelocyte
Neutrophil Band
Mature Basophil
Segmented Neutrophil
Mature Eosinophil

Epidemiology

- 80% of adult leukemias, 20% of childhood leukemias
- Blasts do not have increased proliferative rates but decreased maturation rates

Risk Factors

- Congenital disorders
  - Downs Syndrome
  - Fanconi's anemia
  - Neurofibromatosis
- Environmental exposures
  - Benzene
  - Ionizing radiation
  - Alkylating agents
- Idiopathic

Clinical Presentation

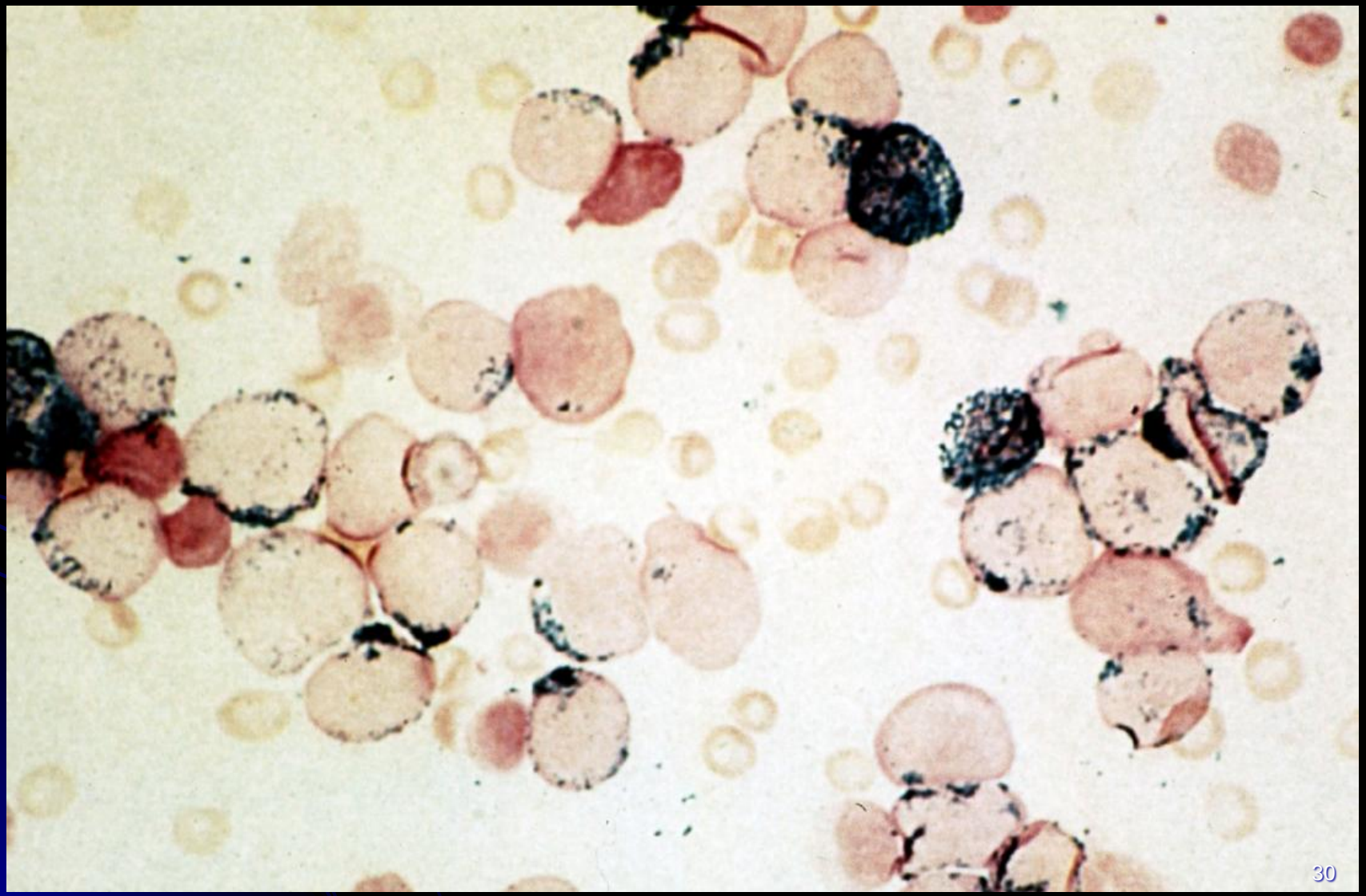
- Symptoms due to replacement of marrow by blasts
  - Fatigue, infection, bleeding, sternal tenderness, gingival hyperplasia

Classification

- WHO Classification (2001)
  - Relies upon morphology, cytochemistry, flow cytometry, cytogenetics, and molecular studies
  - Requires ≥ 20% blasts

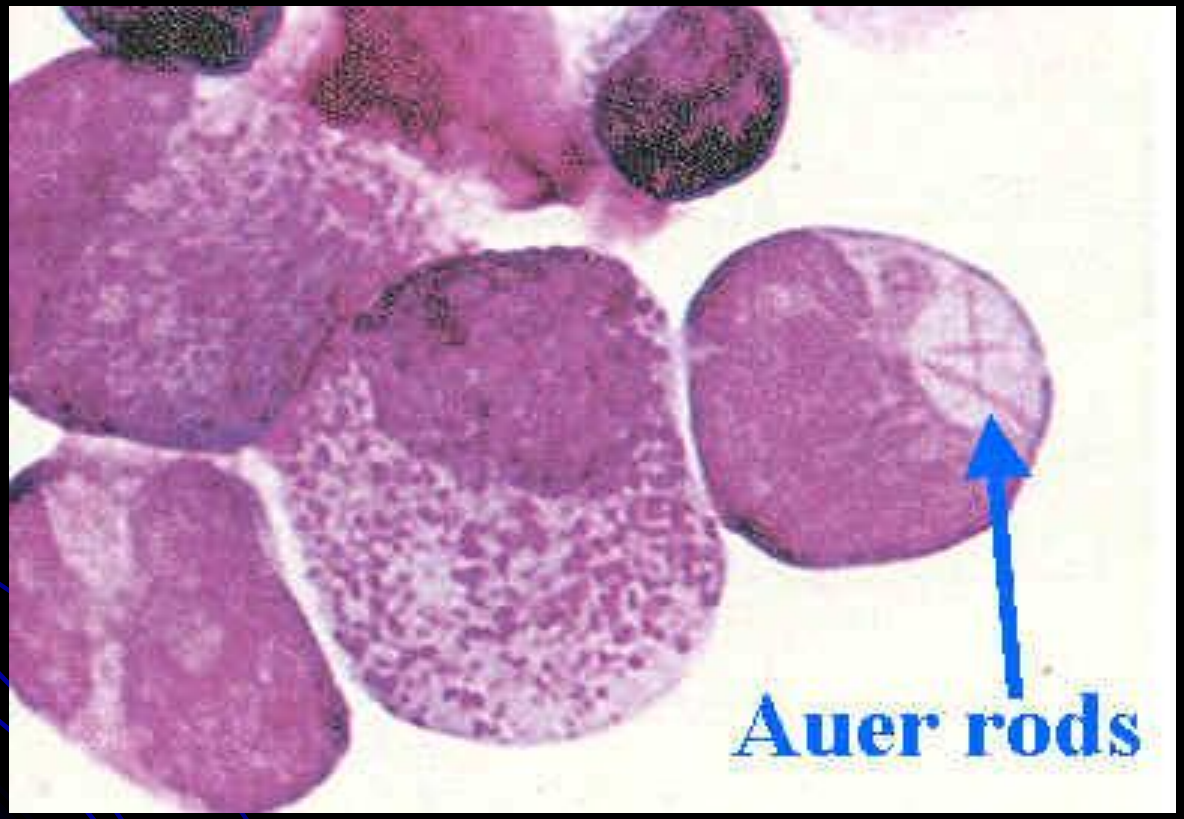
Myeloid versus lymphoid blasts

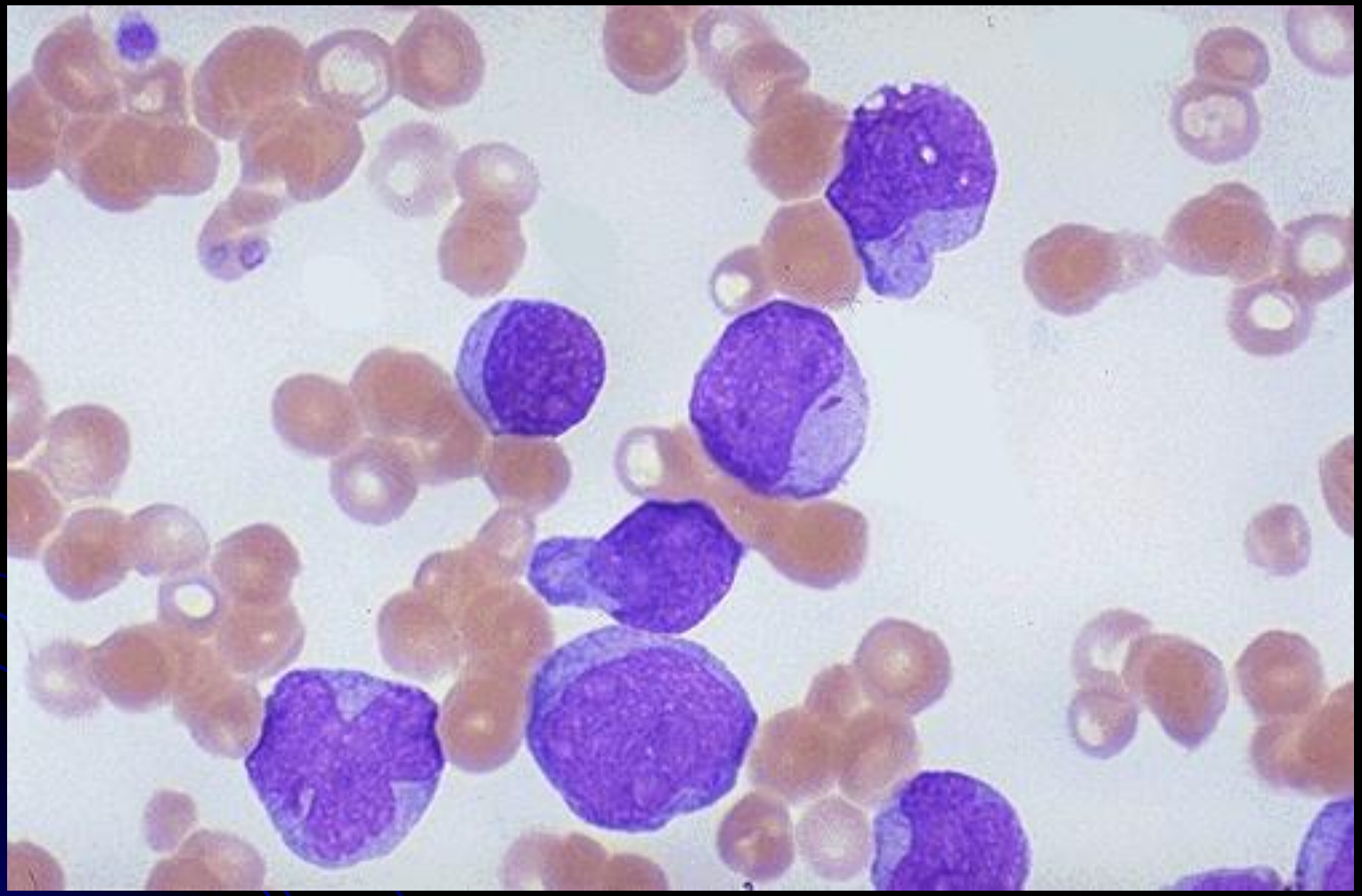
- Myeloid blasts are:
  - Usually larger and exhibits more cytoplasm than lymphoid blasts
  - Often have cytoplasmic vacuoles or Auer rods
  - Are usually myeloperoxidase positive
  - Are positive for myeloid associated antigens by flow cytometry
    - CD13, CD33, CD15



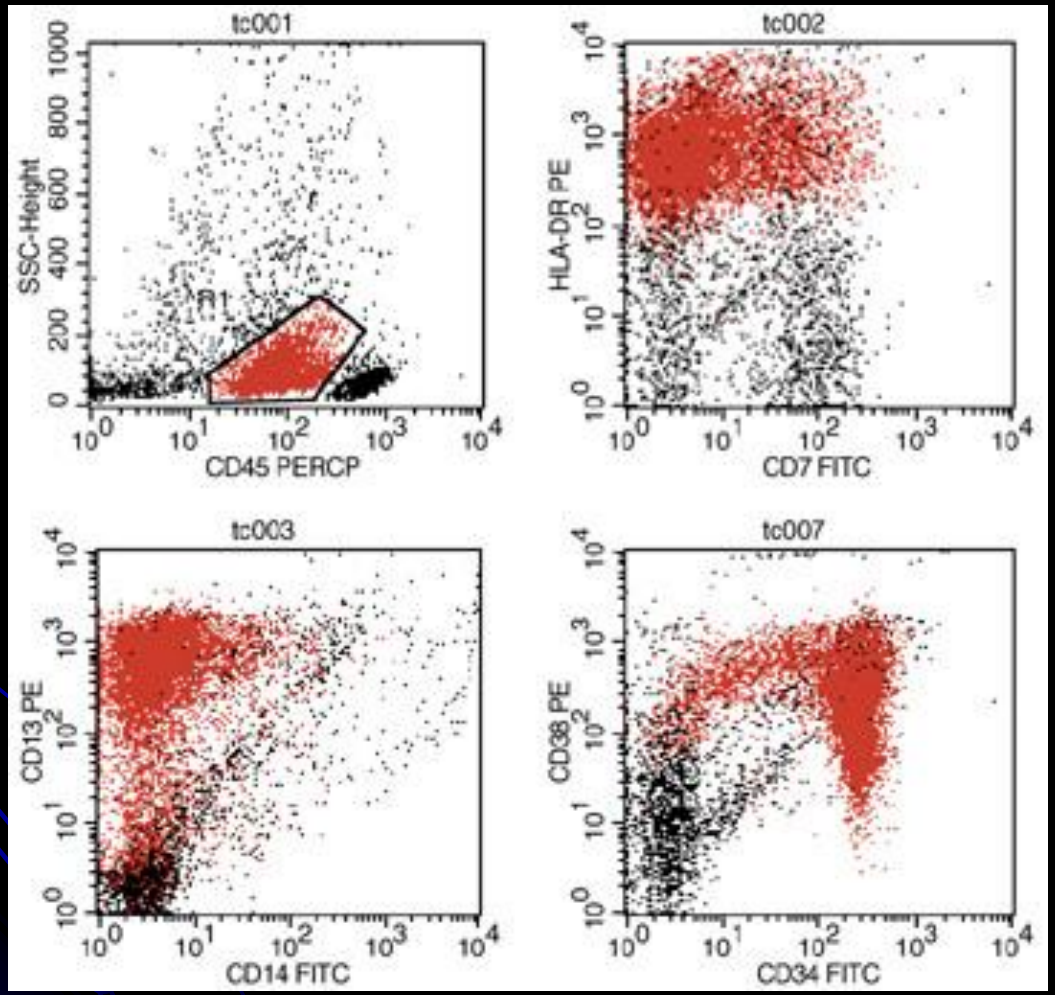
Auer rods

- Fusion of primary granules creating azurophilic rod
- Found in many AMLs, **NEVER** in ALL


Auer rods



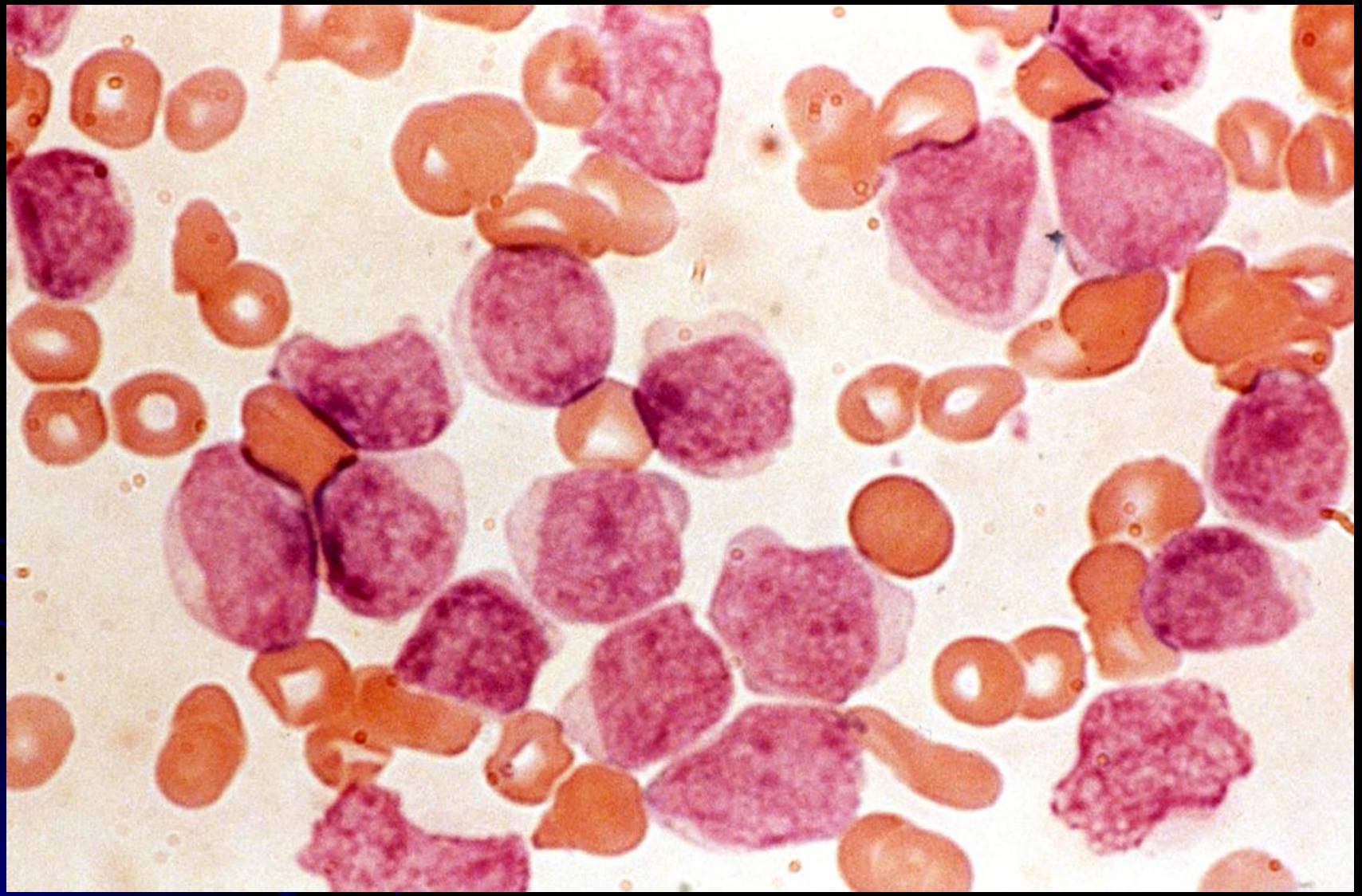
Flow cytometry



Subclassification of acute myeloid leukemias

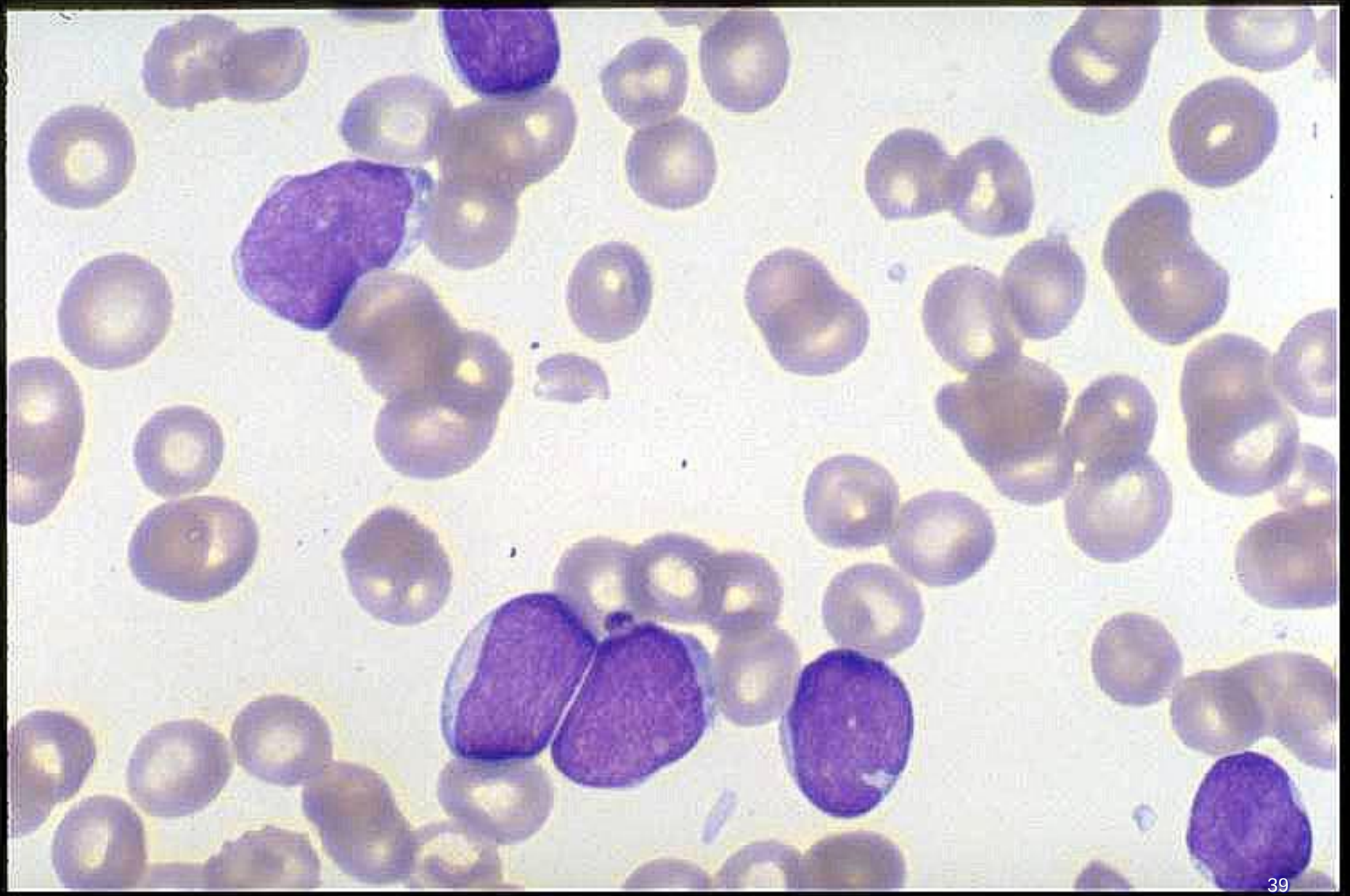
Acute myeloblastic leukemia, minimally differentiated

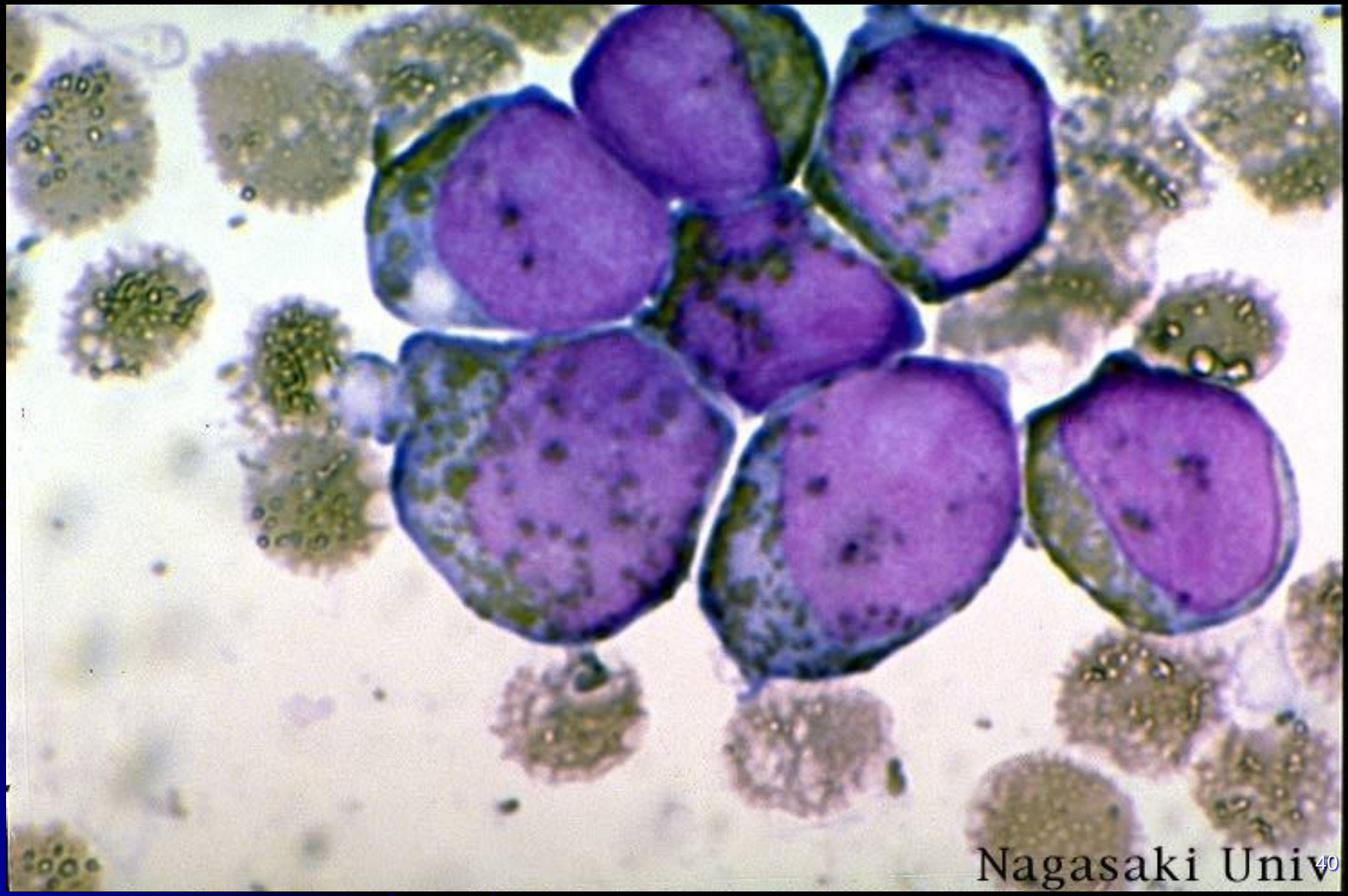
- 2% of AML cases, often older men
- Nongranular blasts are present
- <3% are myeloperoxidase positive
- Express myeloid antigens (CD13, CD33) by flow cytometry



Acute myeloblastic leukemia without maturation

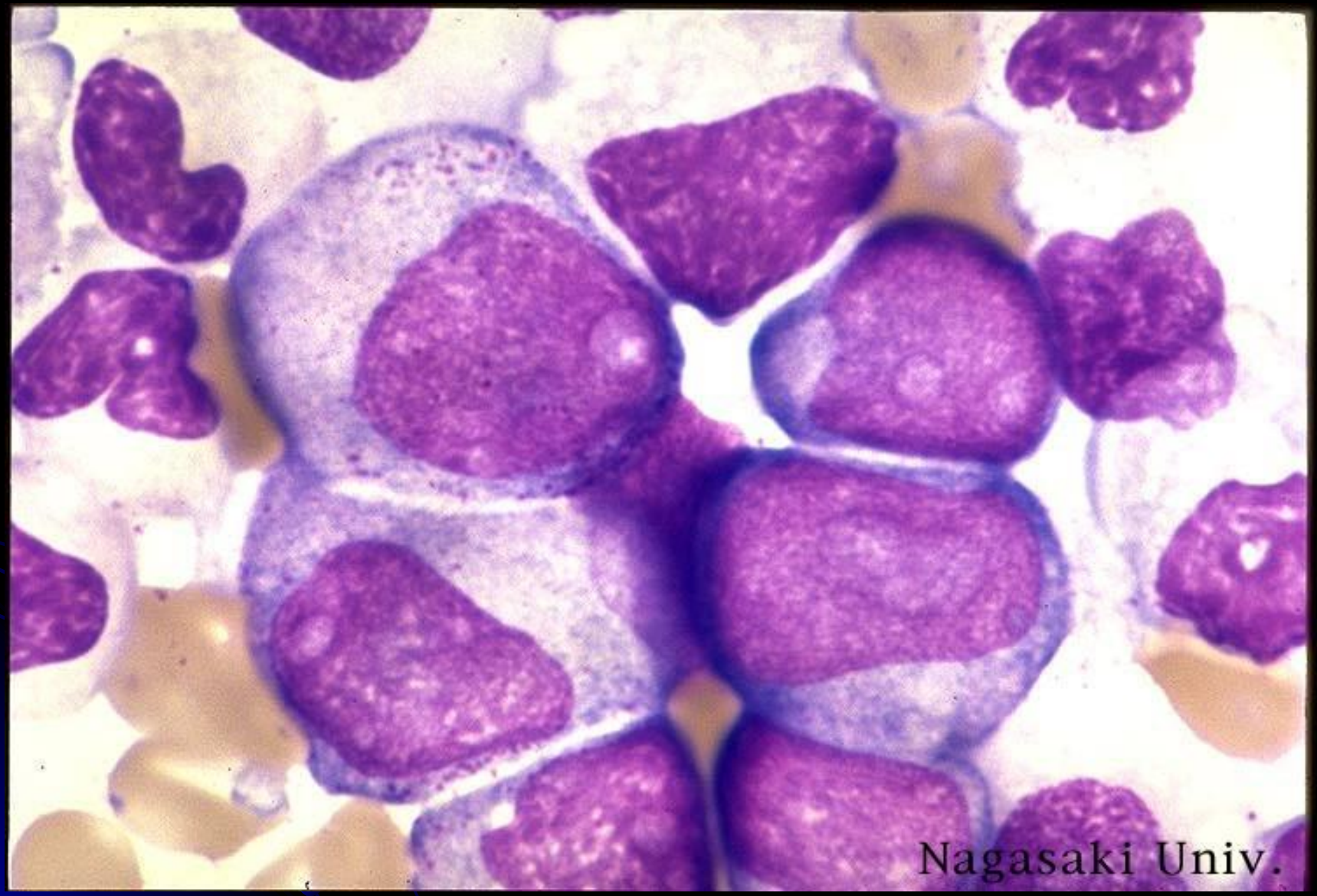
- 10-20% of AML cases
- >90% of nonerythroid cells are myeloblasts
- Remaining cells are maturing granulocytes
- >3% of blasts are myeloperoxidase positive




Nagasaki Univ

Acute myeloblastic leukemia with maturation

- 30-45% of AML cases
- 20-89% of nonerythroid cells are myeloblasts
- Monocytic precursors <20%
- Granulocytes are >10% of cells
- Most blasts are MPO positive, Auer rods often present
- May be associated with t(8;21)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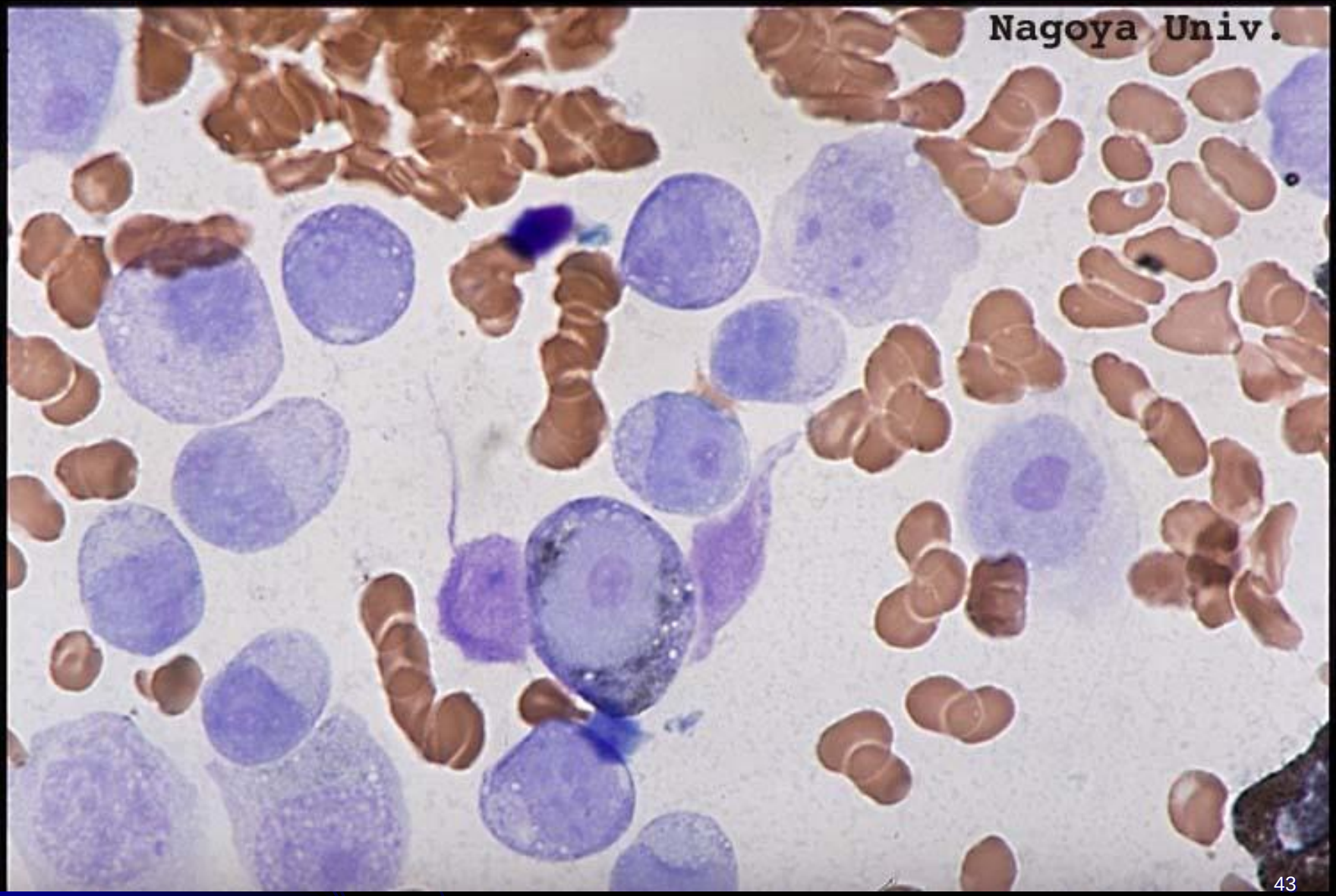
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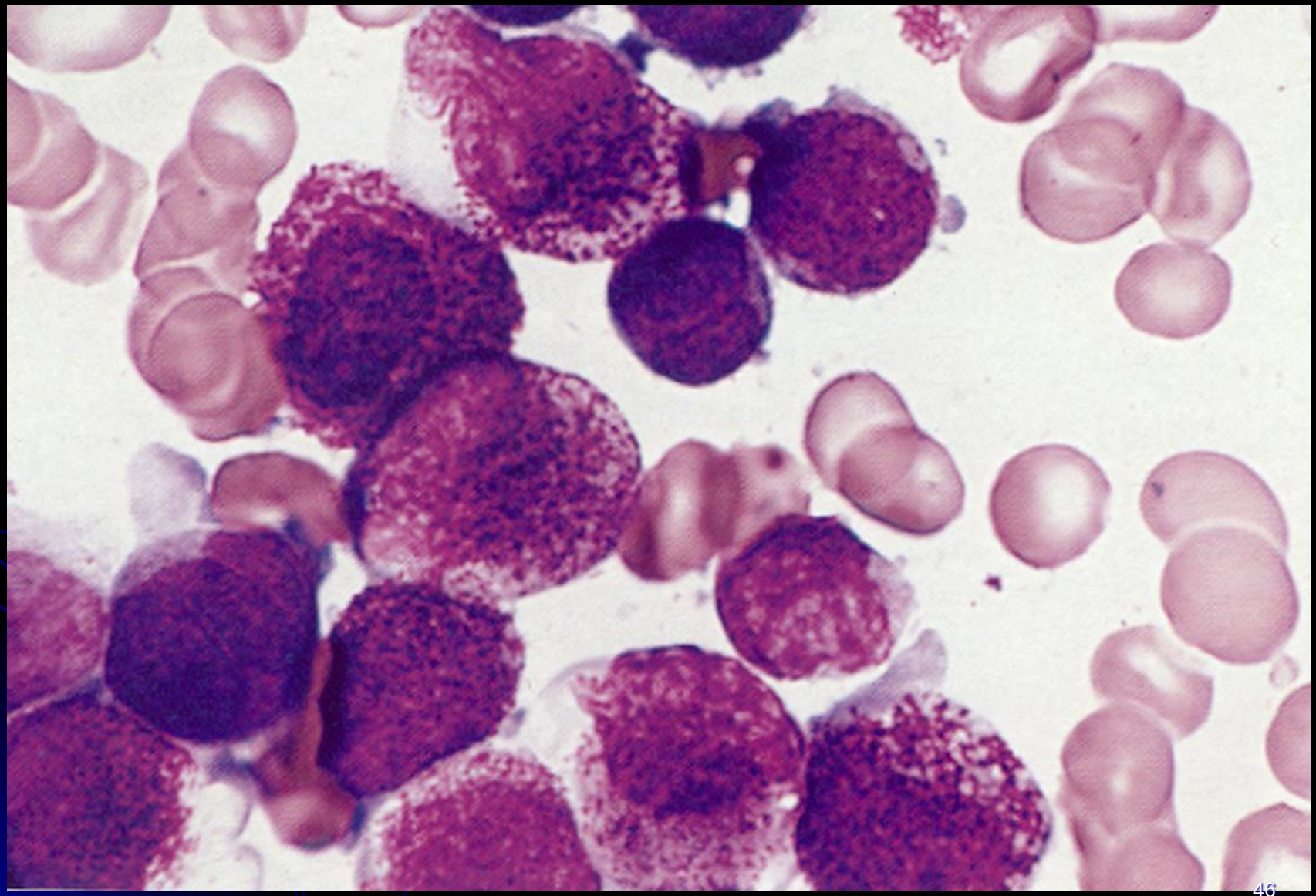
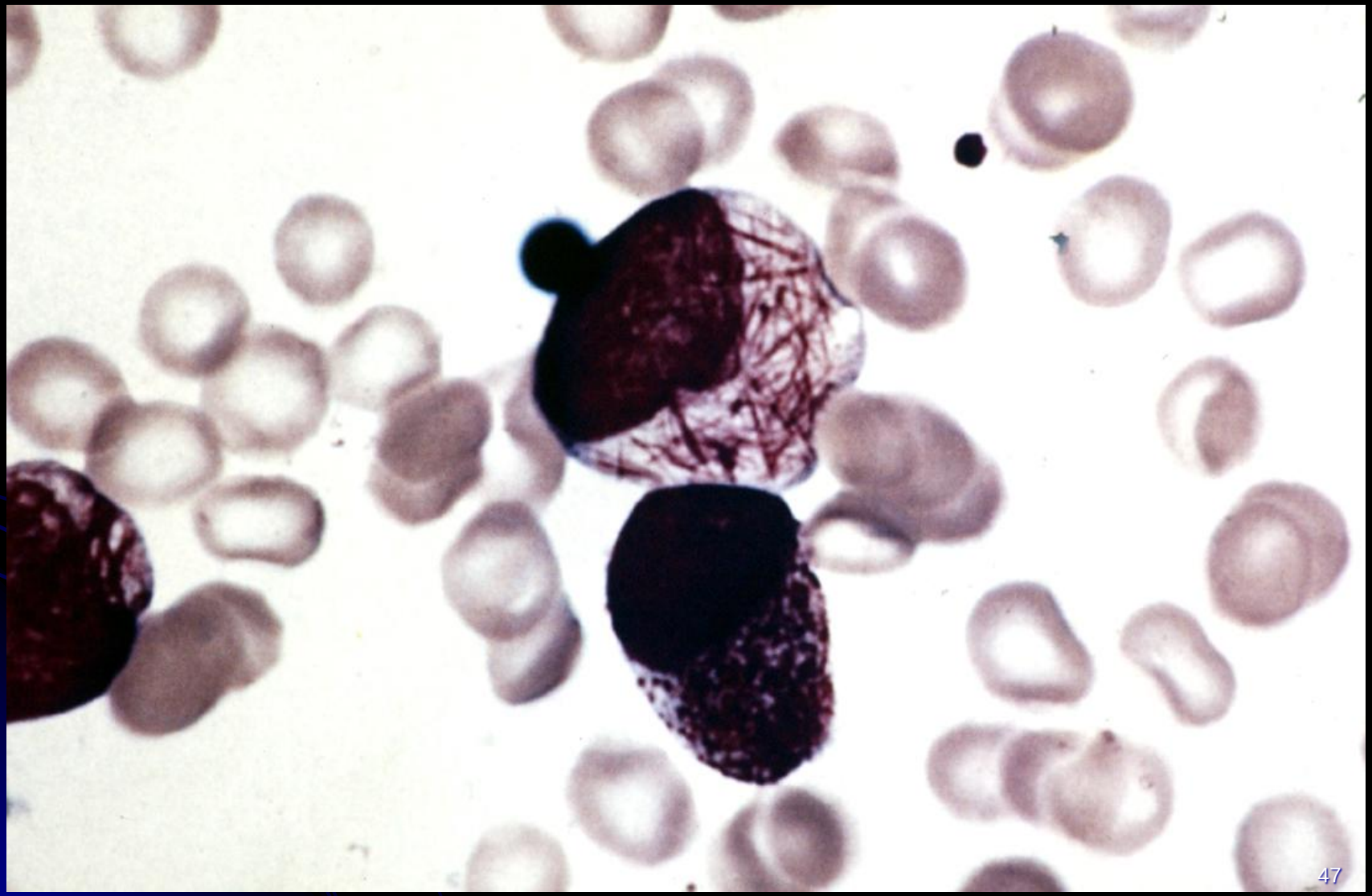
Acute promyelocytic leukemia

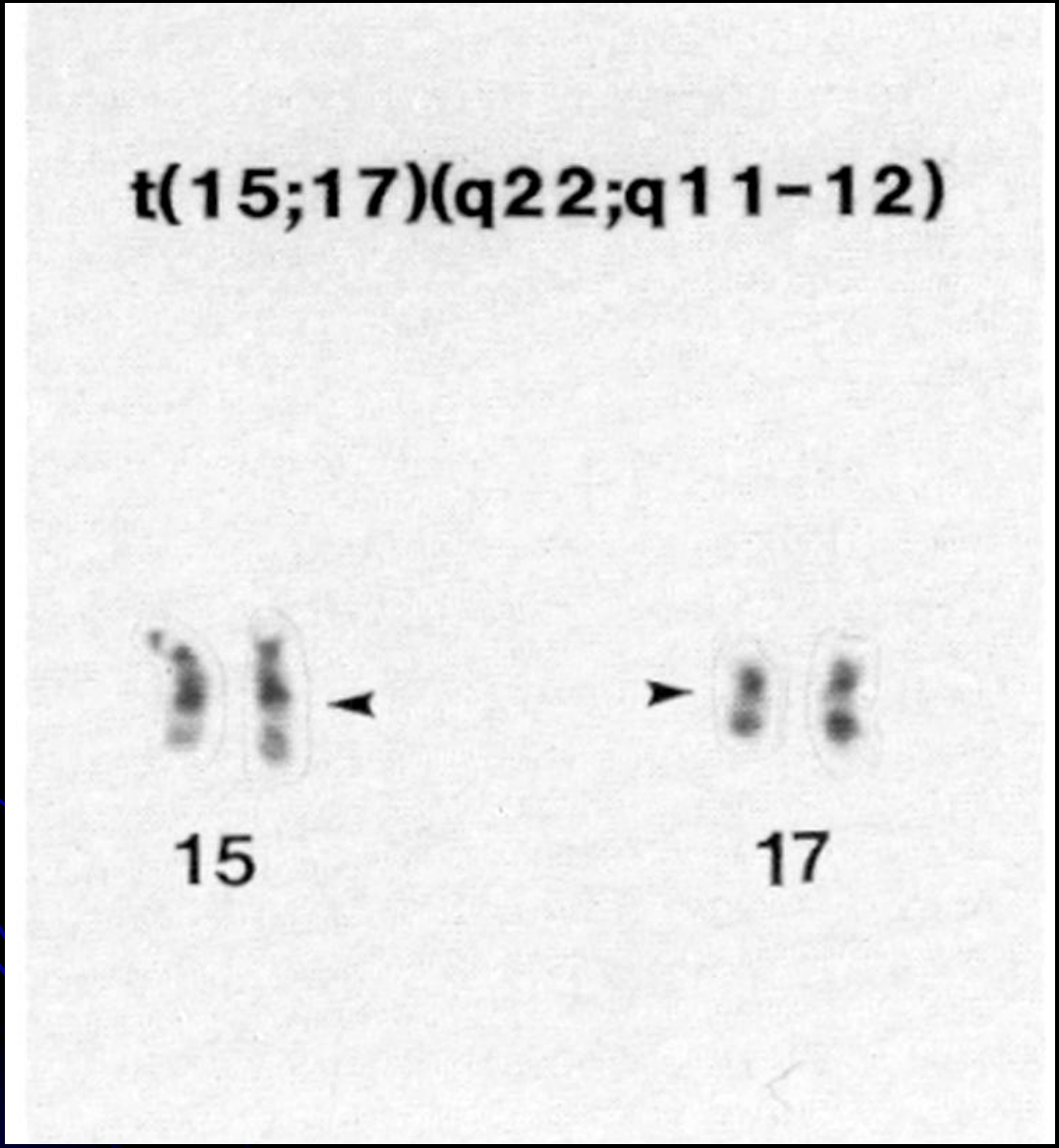
- 10-15% of AML cases
- Most cells (>50%) are abnormal promyelocytes
- Often presents with leukopenia, disseminated intravascular coagulation (DIC)

Acute promyelocytic leukemia

- **Defined by t(15;17)**
- Breakpoints at PML gene and RARA gene
- Gene product produces abnormal retinoic acid receptor that BLOCKS myeloid differentiation
- Treated with ATRA
  - Neoplastic promyelocytes differentiate into neutrophils

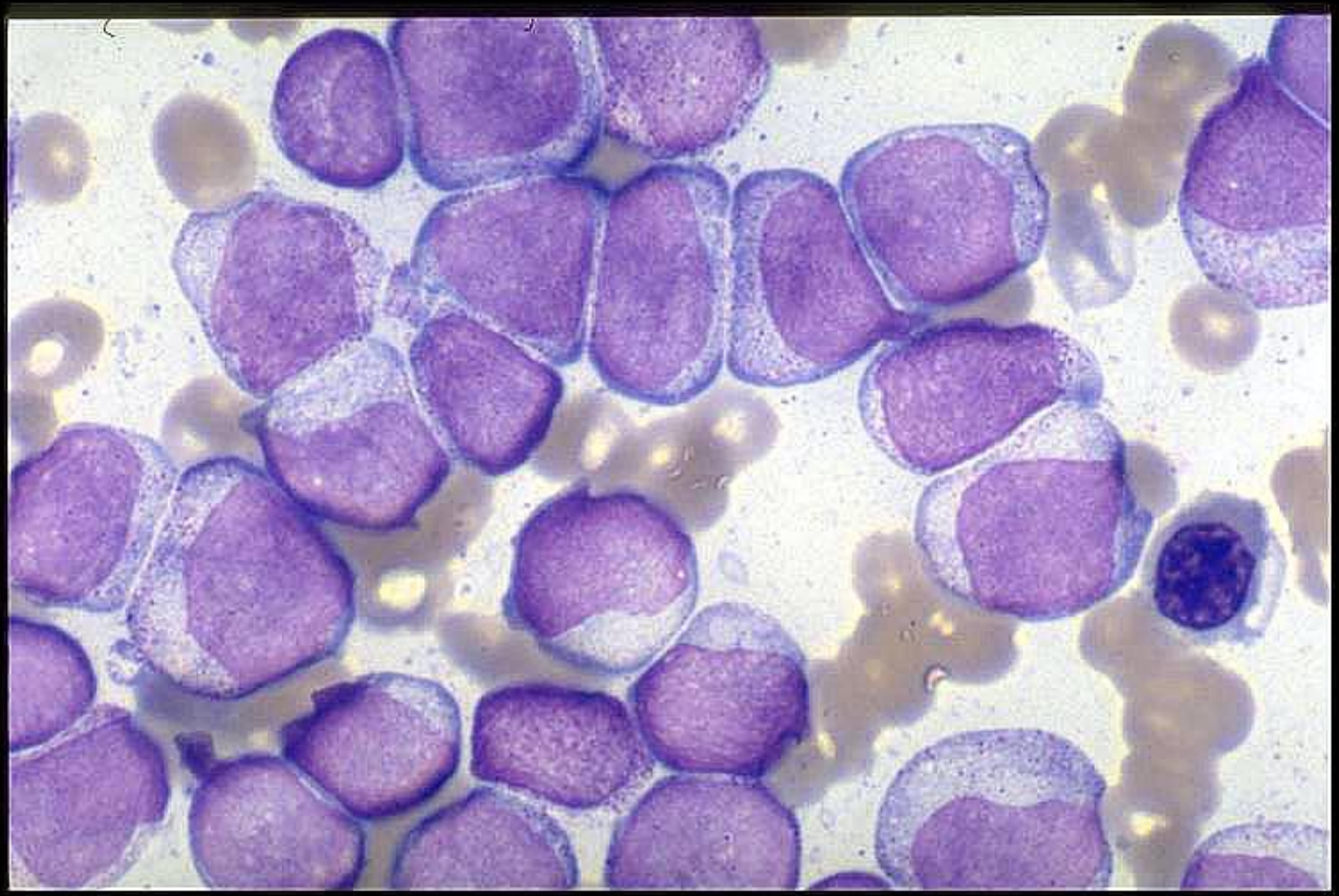


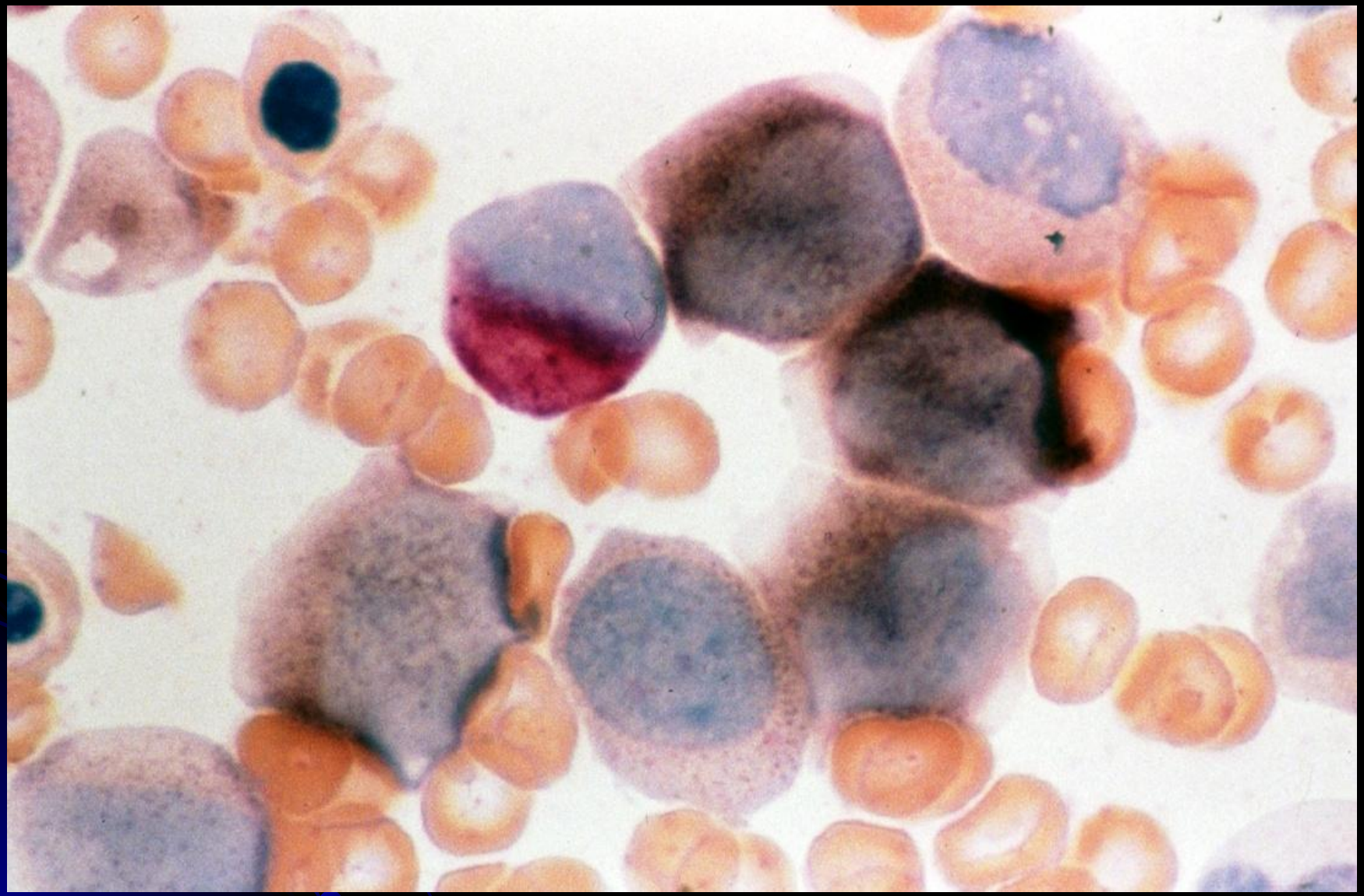



t(15;17)(q22;q11-12)
15
17

Acute myelomonocytic leukemia

- 15-20% of AMLs
- Often presents with hyperleukcocytosis, hepatosplenomegaly, tissue infiltrates
- Myeloblasts and monoblasts>20% of nonerythroid cells
- Monocytes and precursors 20-79% of nonerythroid cells
- Monocytic cells positive for NSE



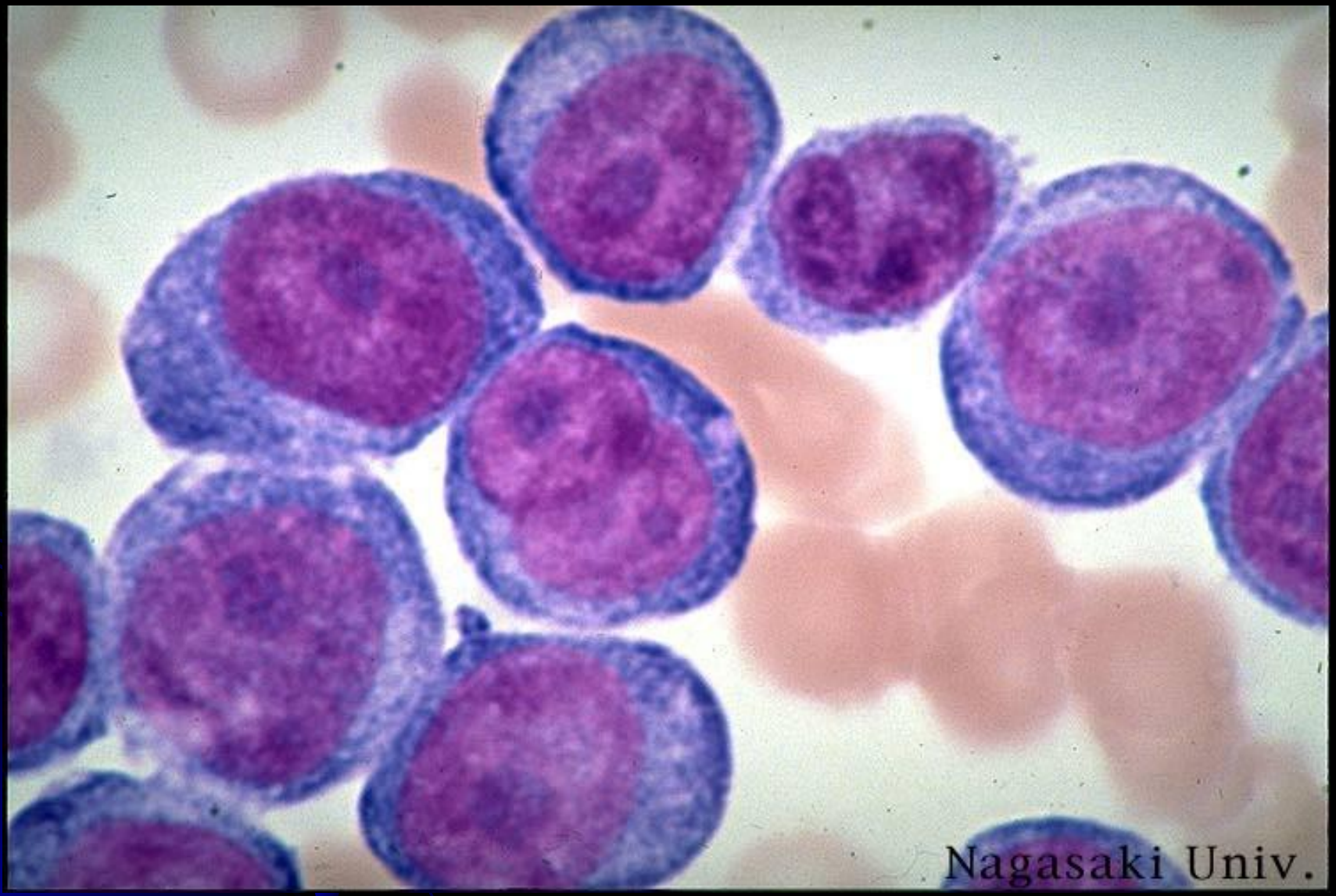


Leukemias with monocytic differentiation

- 10-12% of AML cases
- Can present with DIC and extramedullary myeloid tumor

Leukemias with monocytic differentiation

- Acute monoblastic leukemia
  - >80% of cells are monoblasts
- Acute monocytic leukemia
  - >80% of cells are of monocytic lineage (monoblasts+promonocytes+monocytes)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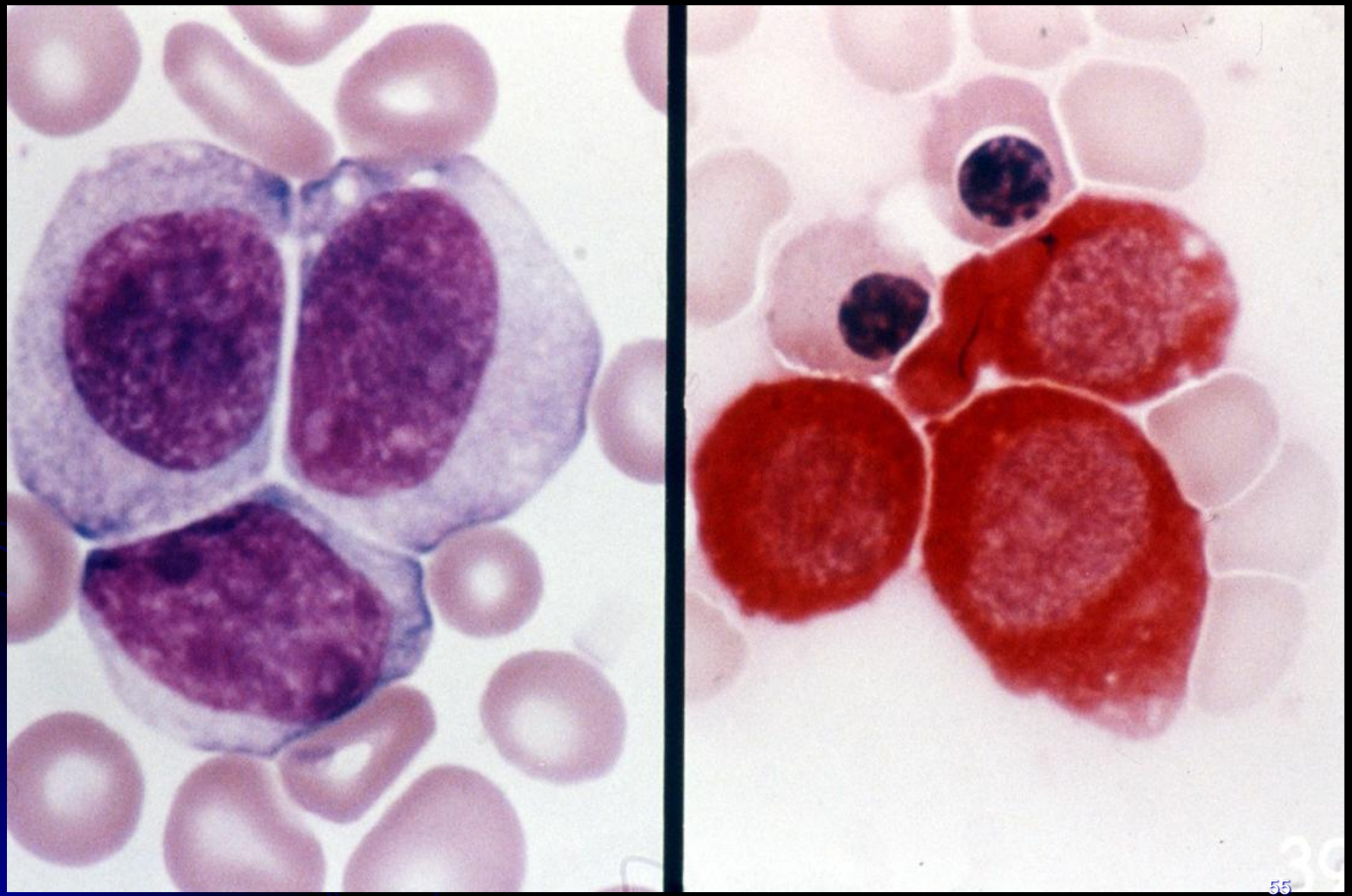
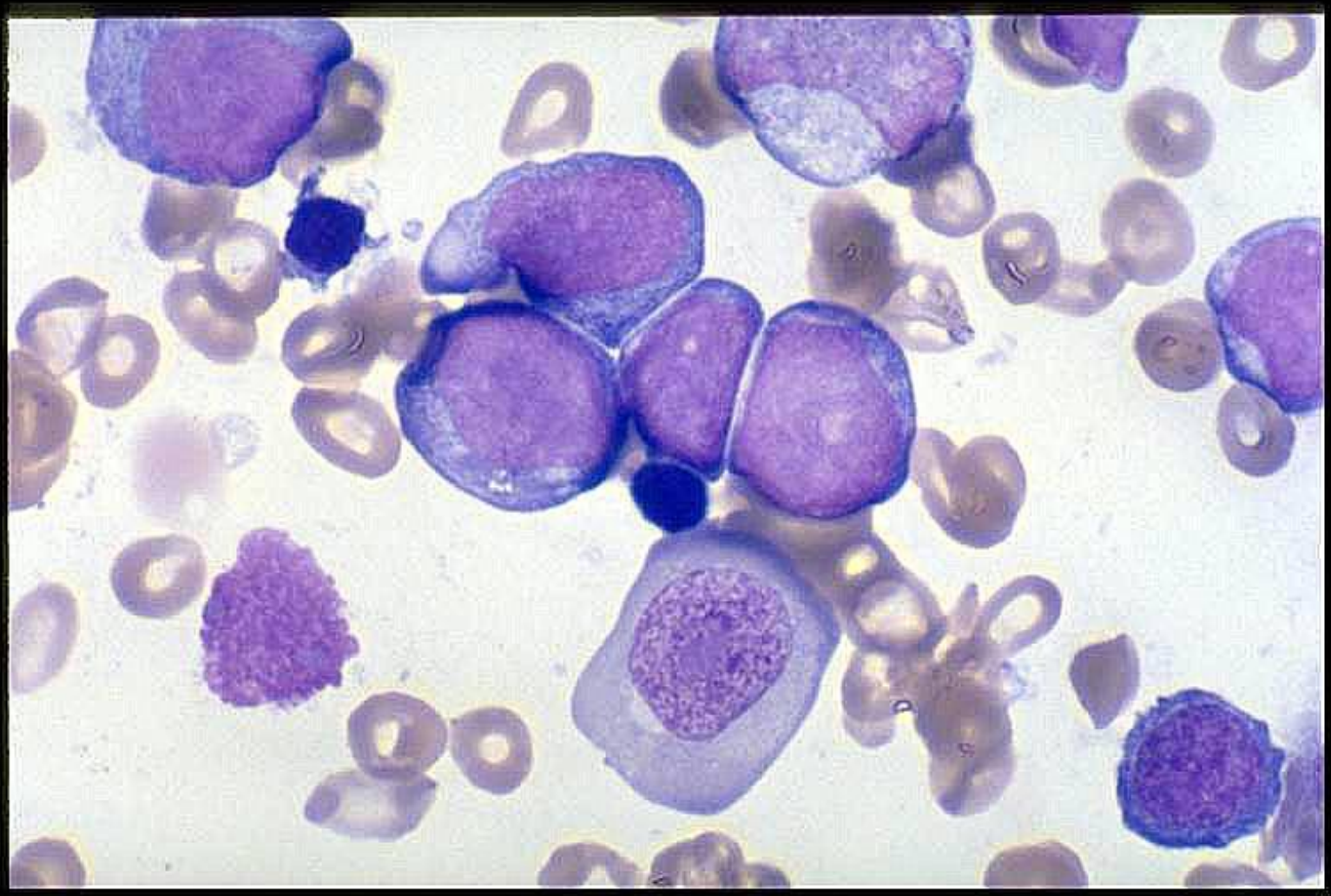
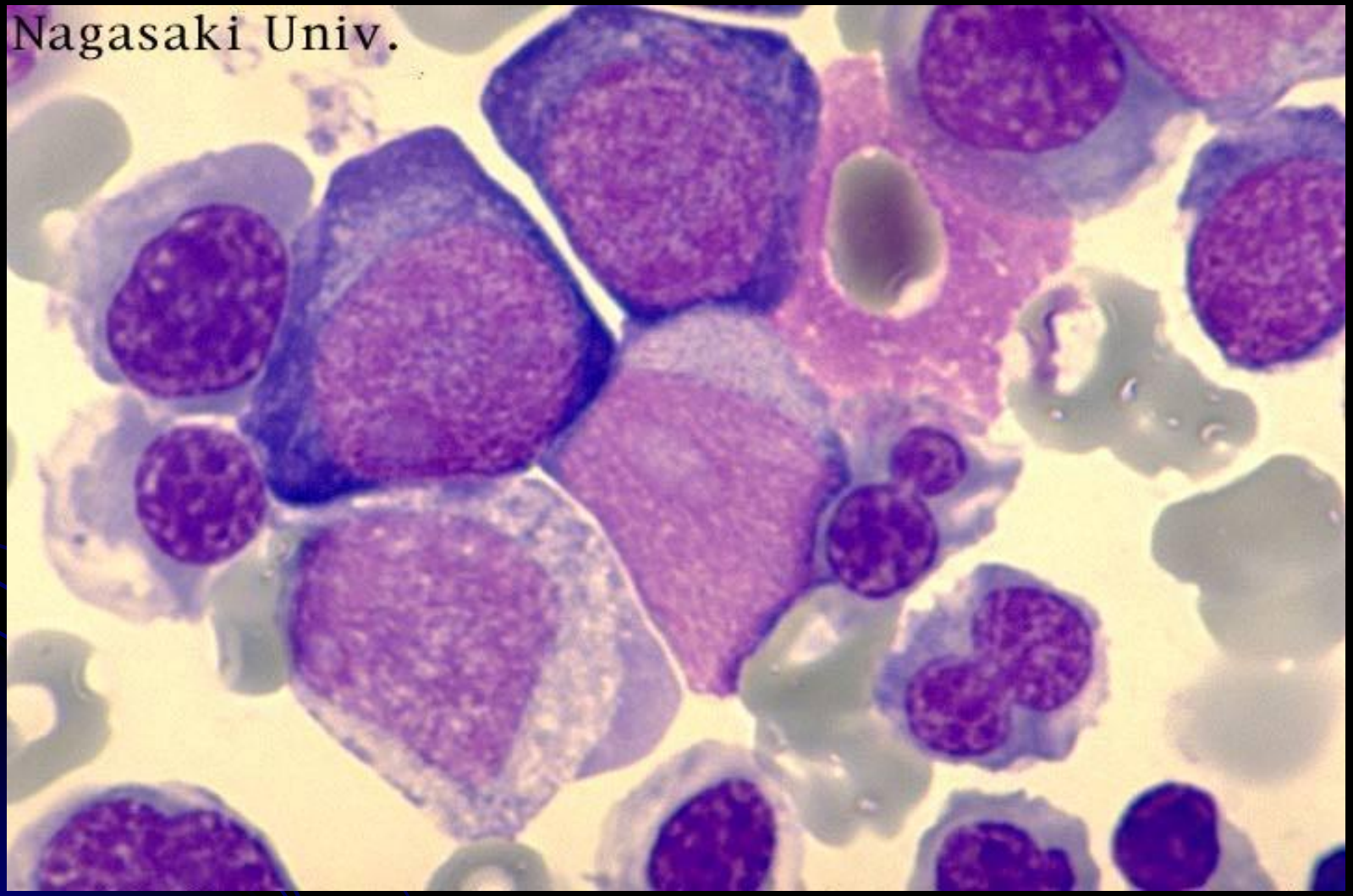


Acute erythroid leukemia

- 3-5% of AML cases, generally in elderly
- Present with pancytopenia
- >50% of nucleated bone marrow cells are erythroid precursors
- 20% or more of nonerythroid cells are myeloblasts
- Prominent dyserythropoiesis

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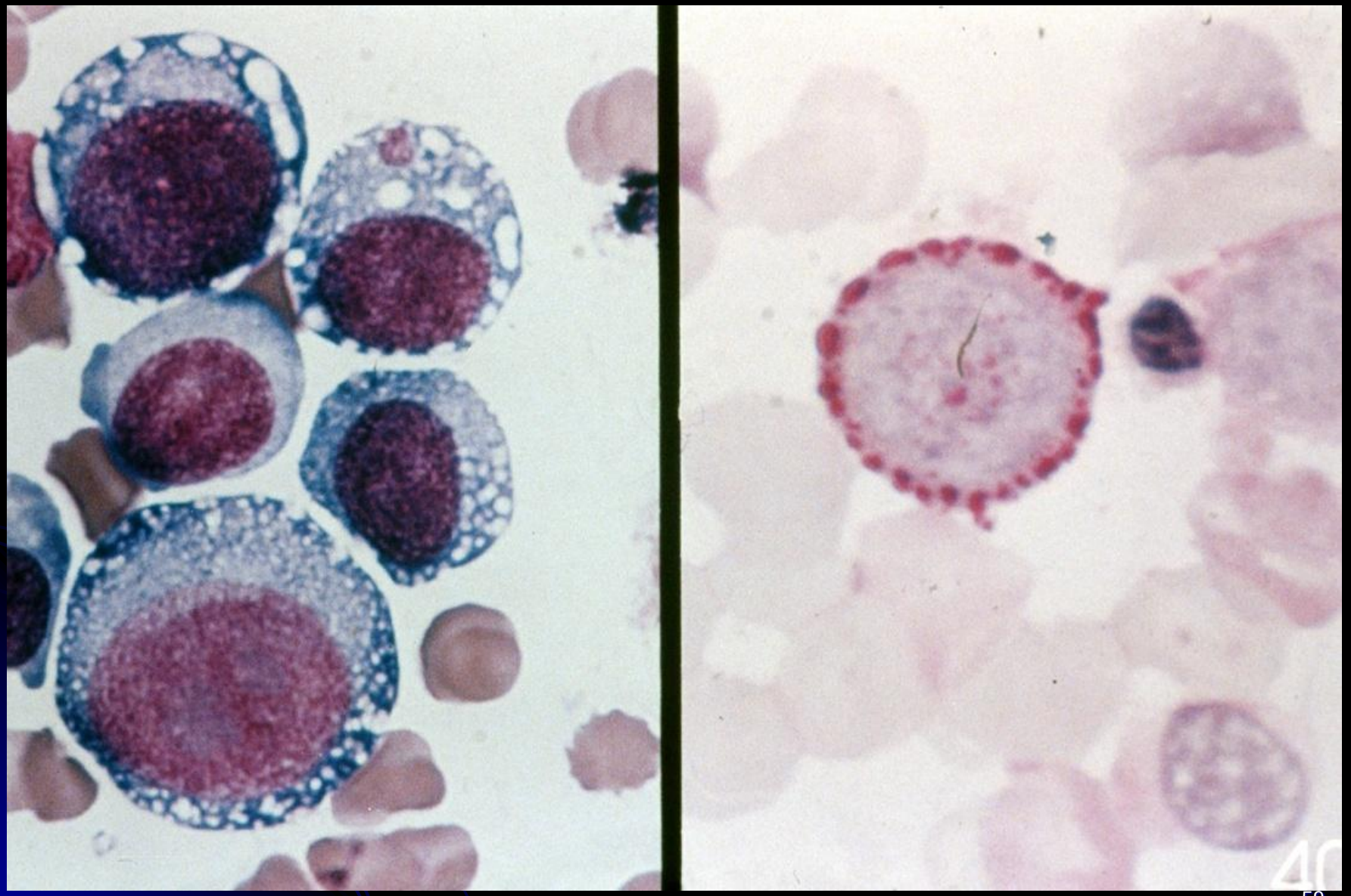
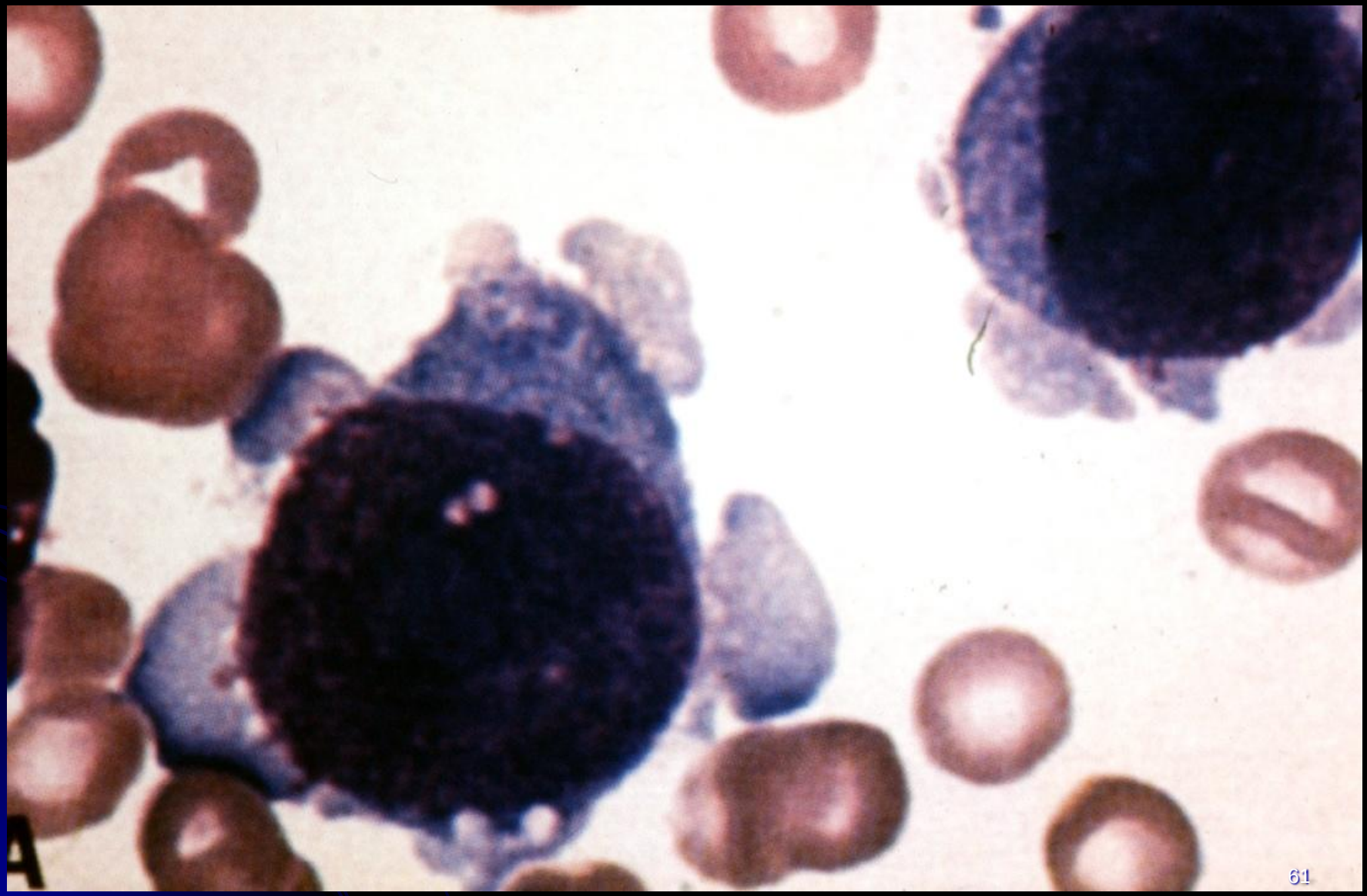
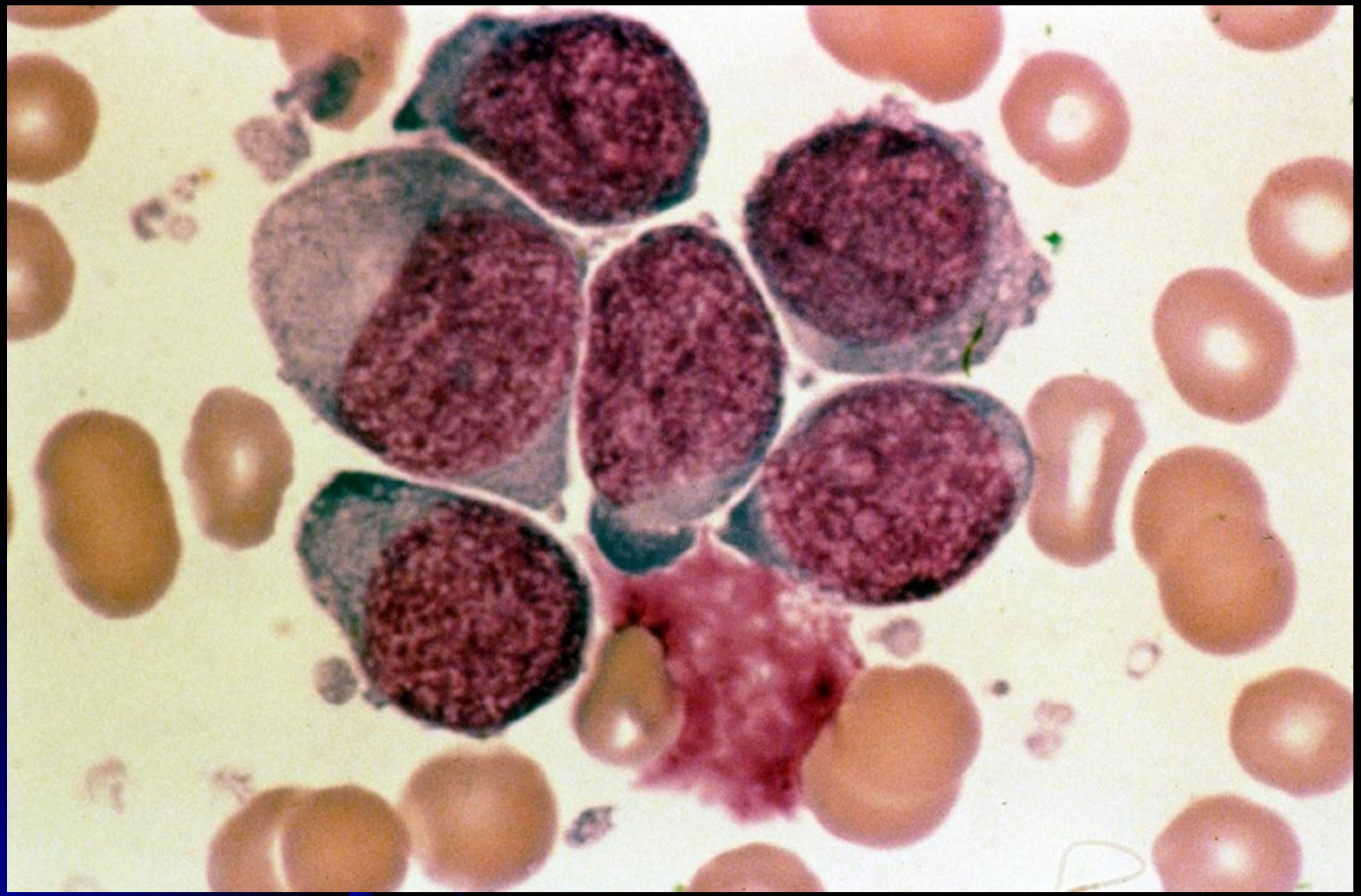


Acute megakaryocytic leukemia

- Up to 10% of AML in children (especially in Down's Syndrome)
- Peripheral blood often contains micromegakaryocytes and abnormal platelets
- >20% blasts in bone marrow
- Blasts express megakaryocytic antigens (CD61, CD41)





Cytogenetics and prognosis

- t(15;17) - favorable
- t(8;21) - favorable
- t(9;22) - poor
- inv(16) - favorable

Prognostic factors

- Cytogenetics
- Morphologic subtype
- Antecedent myelodysplastic syndrome
- Initial response to chemotherapy
- WBC count > 100K
- Age
- Comorbid conditions

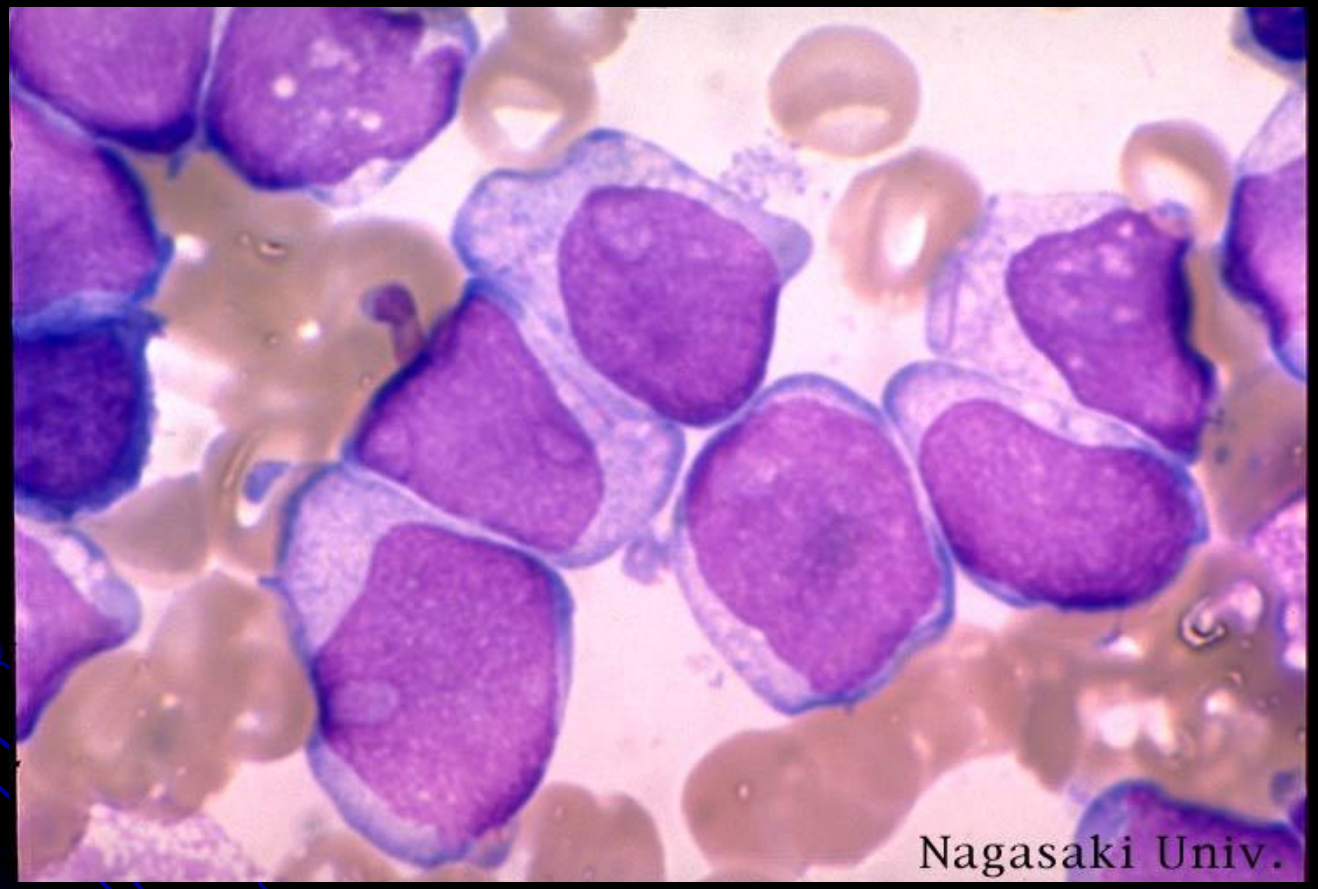
Treatment

- Chemotherapy
  - Induction
  - Postremission maintenance therapy
- Bone marrow transplantation
  - Sibling HLA matched
  - Matched unrelated donor

Case Studies

Case #1

- 45 year old male presents with malaise and gingival bleeding.
- CBC: Hb: 8.7, WBC: 122K, Platelets: 54K


Nagasaki Univ.

Case #1

- Which of the following is true:

A) The patient' blasts will be positive for myeloperoxidase

B) The patient's blasts are likely CD33+

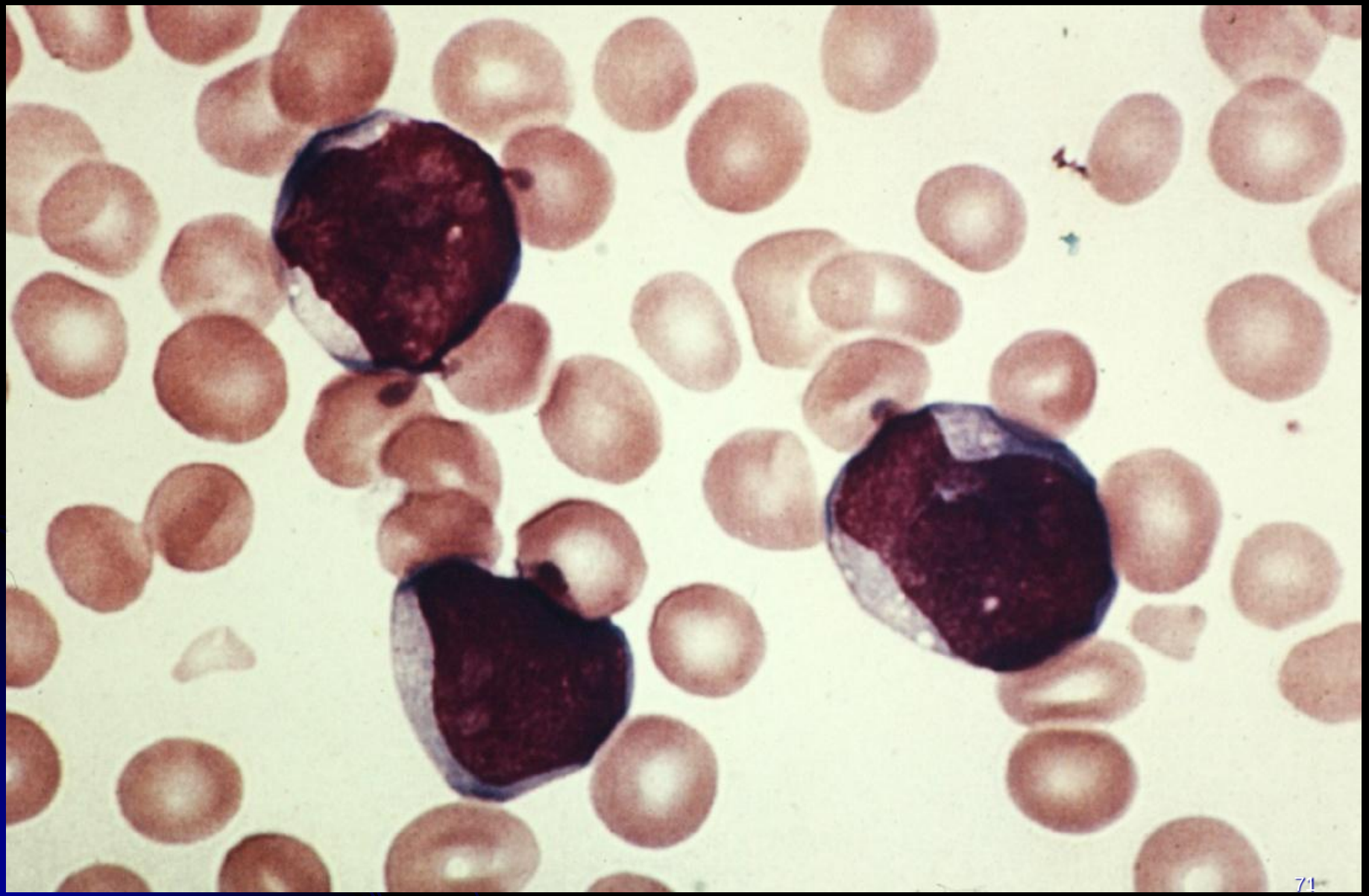
C) The patient's blasts are likely CD34+

D) All of the above

Case #2

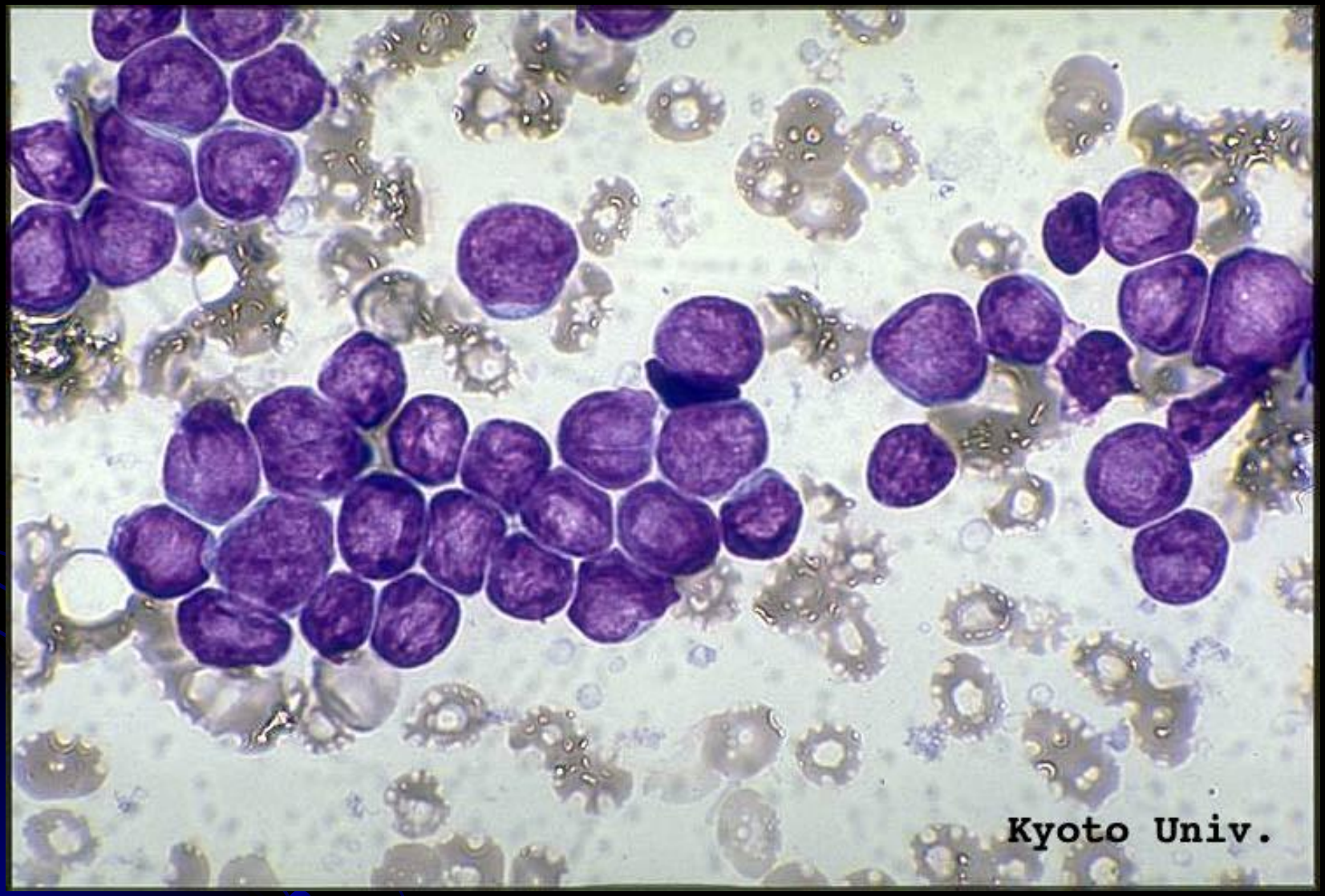
- 16 year old female complains of diffuse arthralgias, nausea, and vomiting.

- CBC: Hb: 7.4, WBC: 0.5K, Platelets: 114K



Bone marrow evaluation

- 300 cell differential reveals 97% blasts without Auer rods
- Normal hematopoiesis is markedly depressed
- Immunophenotypic studies show the blasts to be positive for CD19, CD10, and TdT and negative for CD13, CD33
- Cytogenetics reveal t(4;11)


Kyoto Univ.

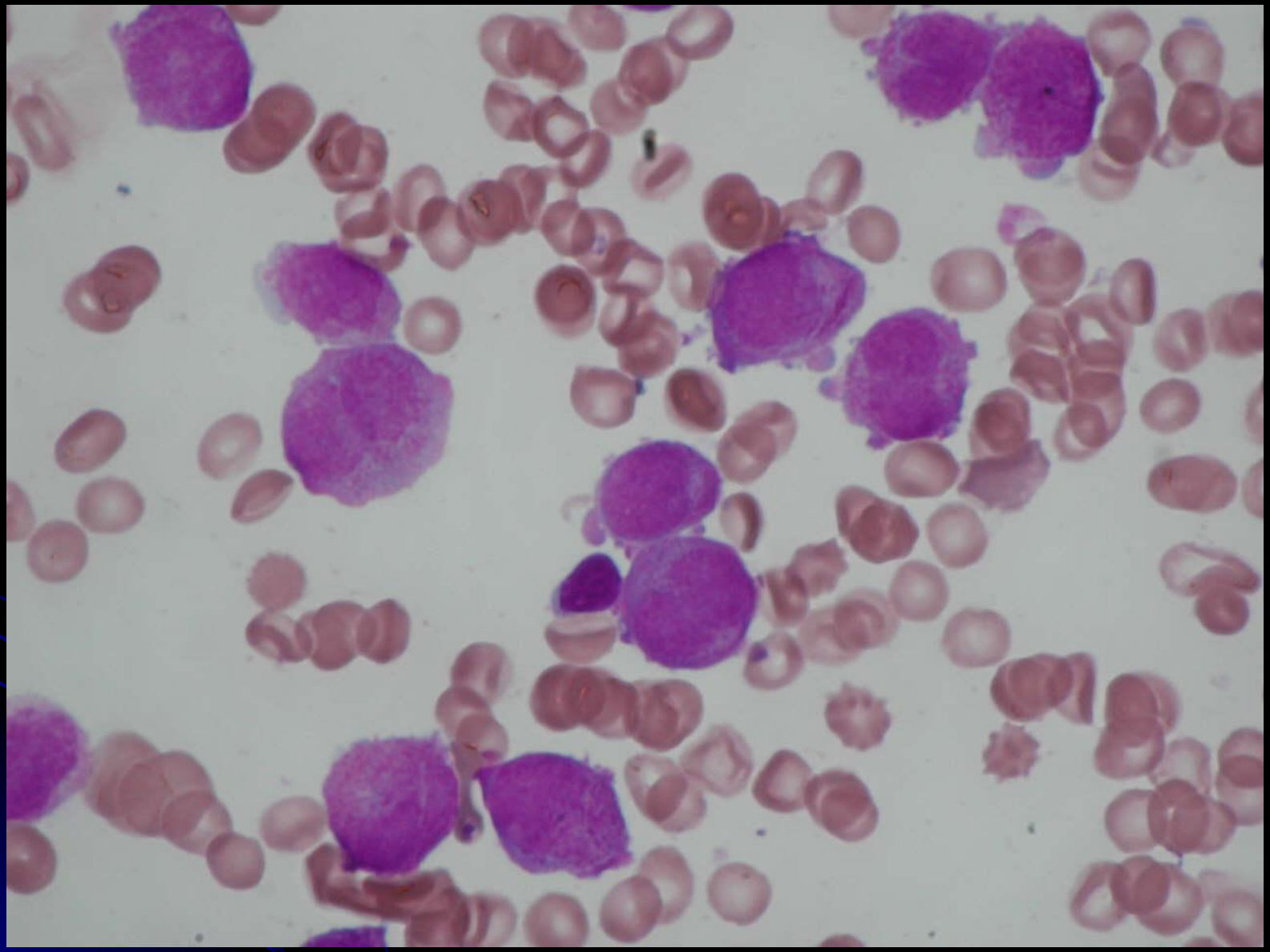
Case #2

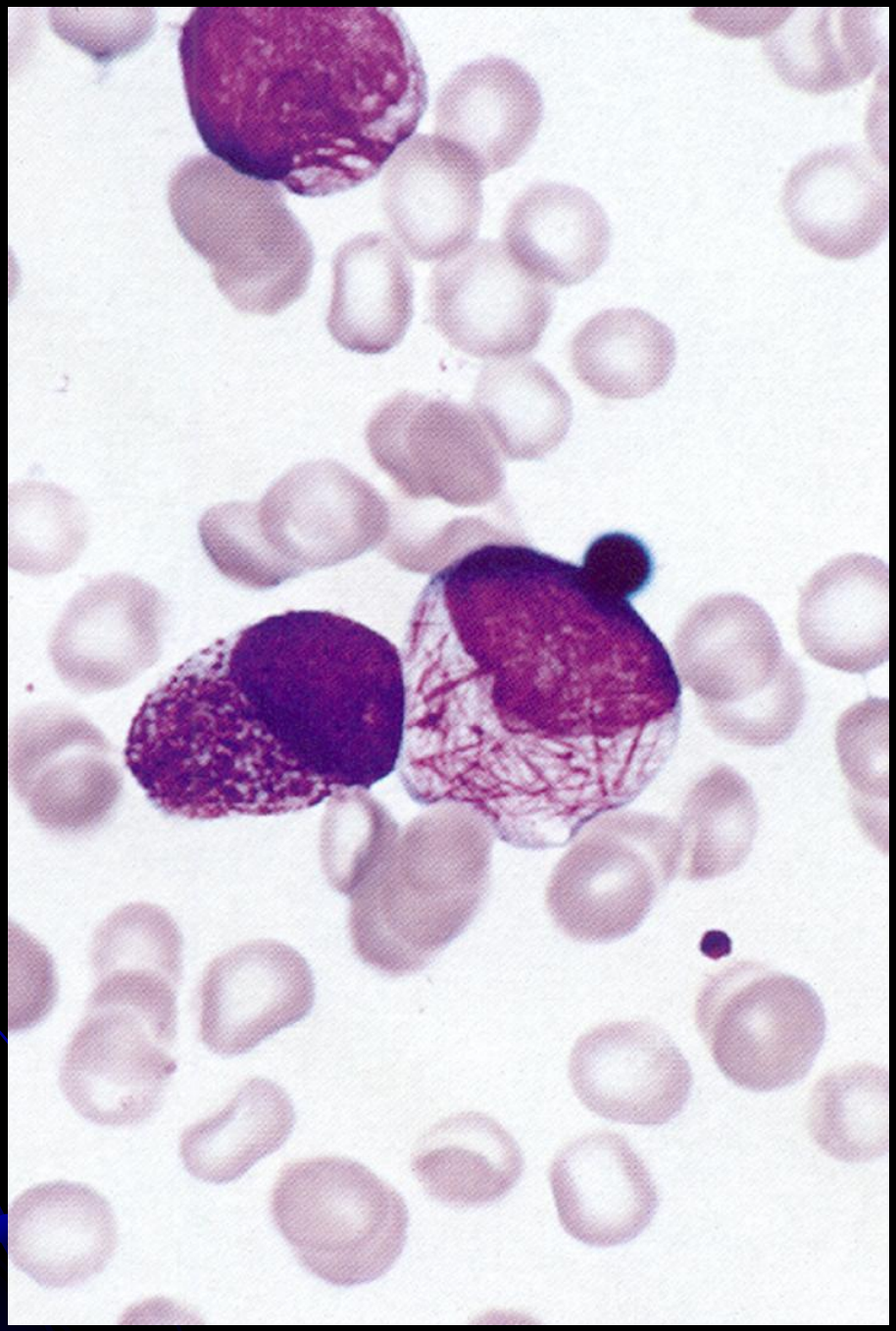
- Which of the following is true:
  - A) The patient has acute myeloblastic leukemia, poor prognosis
  - B) The patient has acute myeloblastic leukemia, good prognosis
  - C) The patient has acute lymphoblastic leukemia, good prognosis
  - D) The patient has acute lymphoblastic leukemia, poor prognosis

Case #3

- 31 year old male presents with extreme fatigue. CBC shows marked leukopenia.

- CBC: Hb: 5.8, WBC: 0.4, Platelets: 11K





Case #3

Which of the following is true:

A) The patient's prothrombin time will be elevated

B) The patient should be initially treated with all trans retinoic acid

C) The karyotype of the cells is: 46,XY,t(9;22)

D) A and B

E) A and C

Question #4

22 year old male presents with leukocytosis (WBC: 175K). Peripheral smear review reveals intermediate to large sized blasts with fine chromatin and irregularly shaped nuclei. No Auer rods are identified. Flow cytometric analysis shows a population of blasts that are positive for CD2, CD3, CD4, CD8, and TdT.

- Which of the following is true:
  - A) This disorder is most common in patients <10 years old
  - B) Patients may present with concomitant lymphadenopathy and mediastinal mass
  - C) Patients seldom have CNS involvement
  - D) t(9;22) is often seen in this disorder

Questions?