Heme 9
Myeloid neoplasms

- The minimum number of blasts to diagnose acute myeloid leukemia is
  - 5%
  - 10%
  - 20%
  - 50%
  - 80%

- AML with the best prognosis is
  - AML with recurrent cytogenetic abnormality
  - AML with myelodysplasia
  - Therapy related AML
  - AML, NOS

- Myelodysplasia is associated with all the following, except:
  - Anemia
  - Thrombocytopenia
  - Leukopenia
  - Thrombocytosis
  - Risk of AML transformation

- Which MPN is associated with BCR/ABL fusion
  - CML
  - ET
  - PV
  - PMF

- Leukoerythroblastosis is associated with
  - CML
  - ET
  - PV
  - PMF

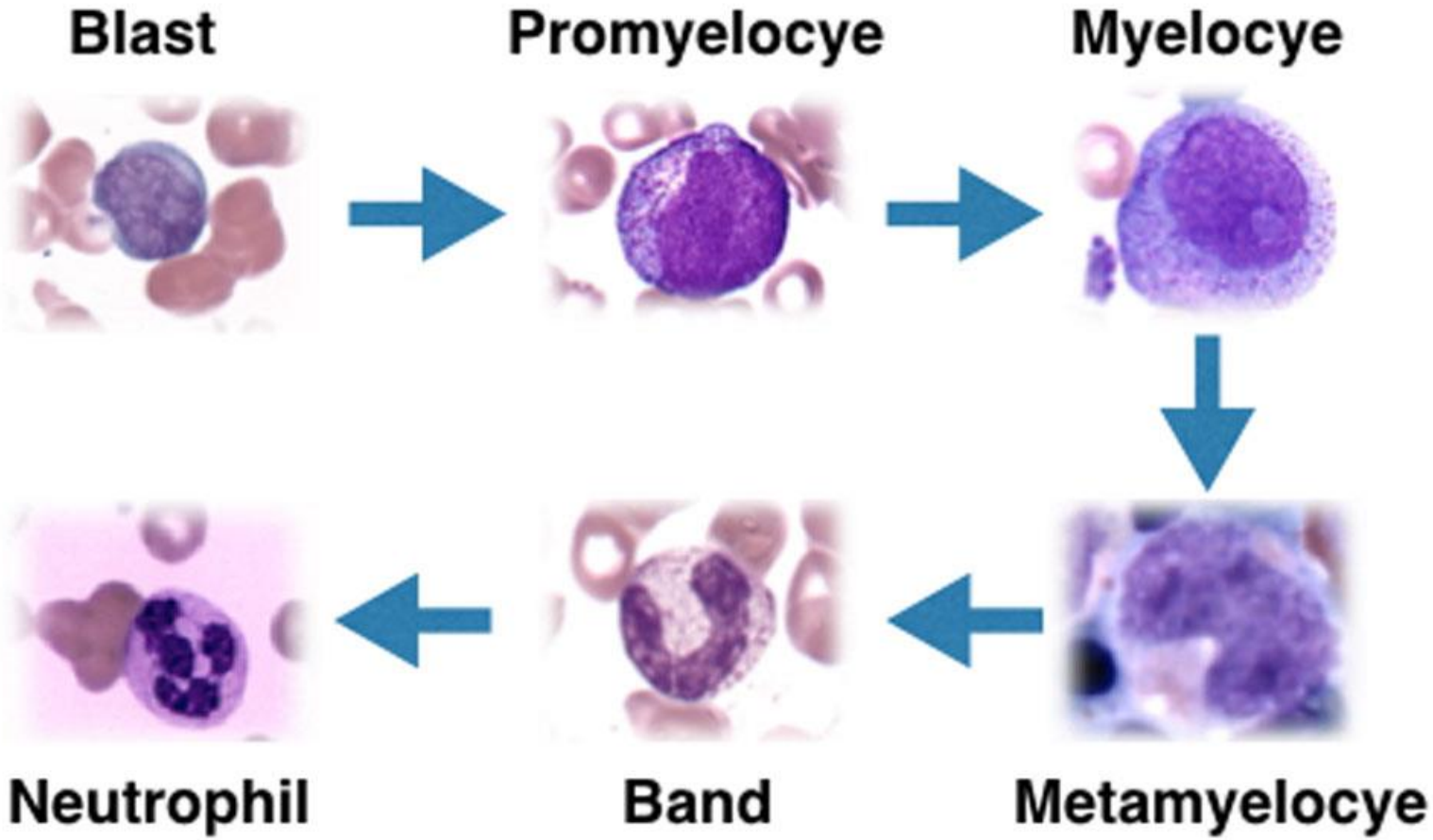
3 major categories

- Acute myeloid leukemia
- Myeloproliferative neoplasms
- Myelodysplastic syndromes

AML

- Age of presentation is around 50
  - Again can happen at any age
- Stigmata of pancytopenia
- Splenomegaly can occur
- Rarely as discrete mases
  - Called myeloid sarcoma

- Diagnosis depends on
  - Morphology
  - Immuneophenotype
  - Karyotype
    - Predictive of prognosis

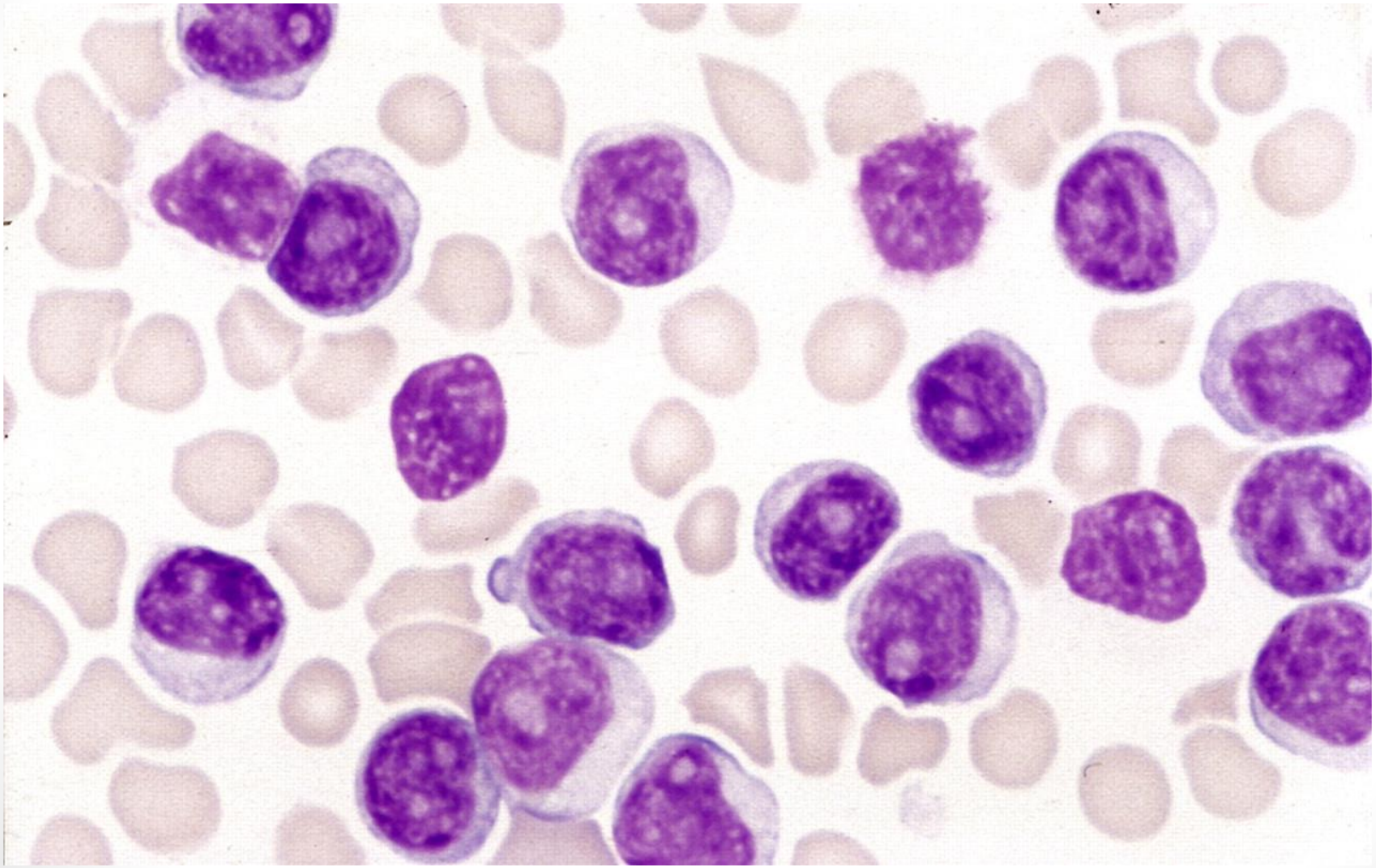

Blast
Promyelocye
Myelocye
Neutrophil
Band
Metamyelocye

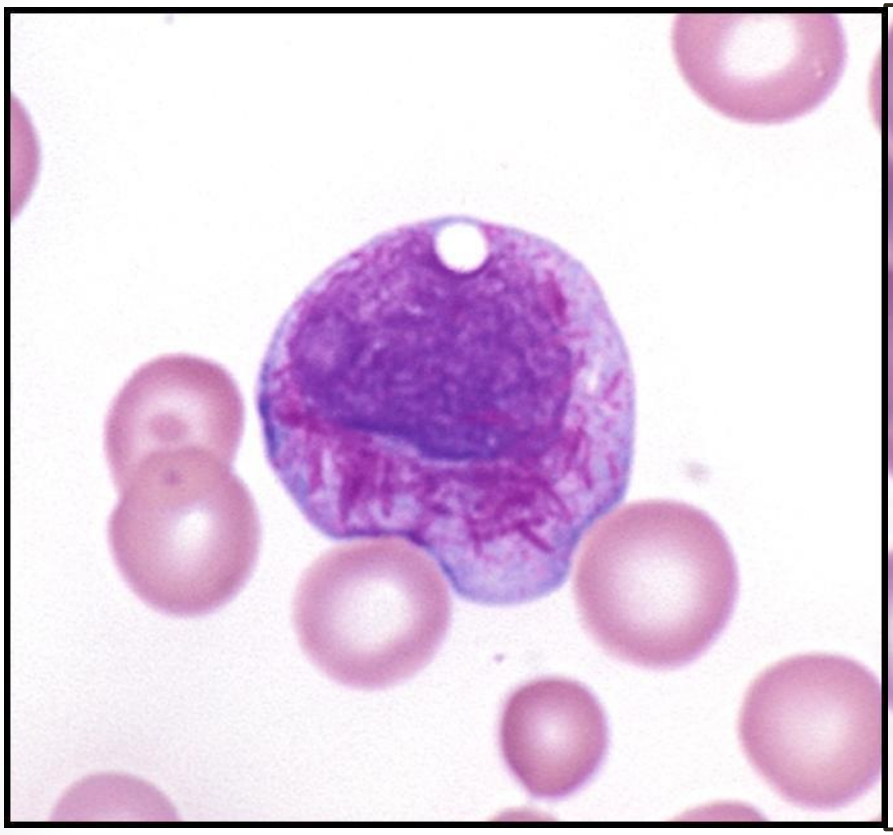
Pathogenesis

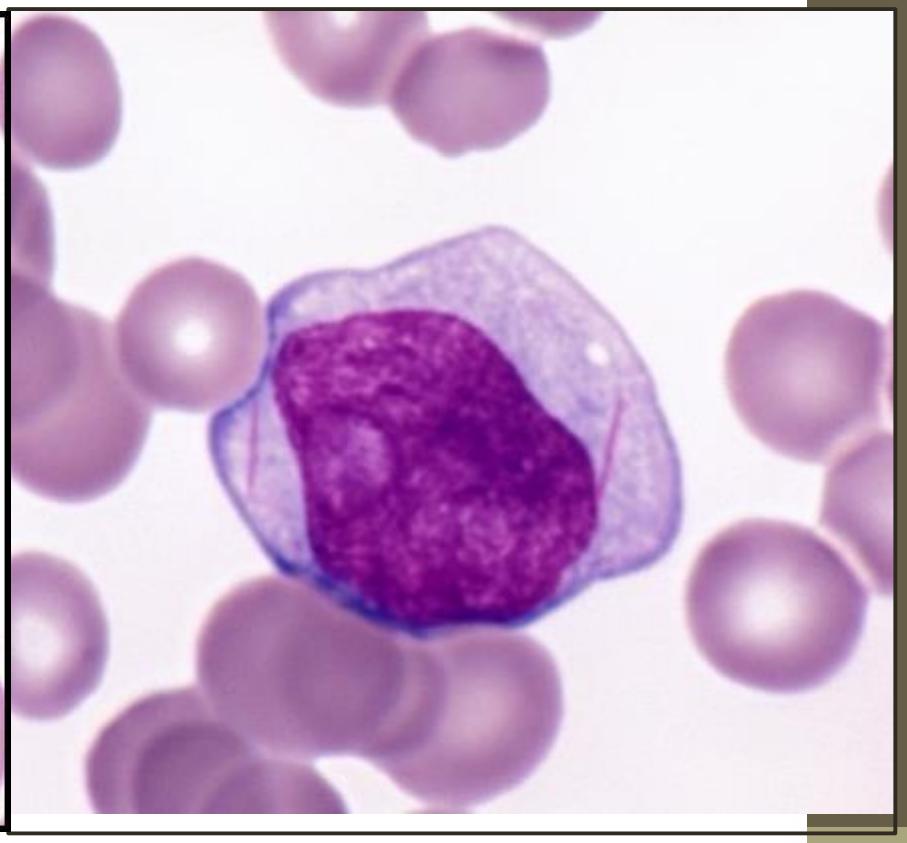
- Mutations that result in arresting myeloid cells at an early stage of differentiation
- One example is acute promyelocytic leukemia
  - t(15;17) resulting in fusion of RARA with PML
  - The resulting fusion gene arrests myeloid cells at the promyelocyte stage
  - Treatment with all-trans retinoic acid overcomes this protein and forces the cells to differentiate into neutrophils
  - Cure rate of ~80%

Morphology

- At least 20% blasts by definition
- Auer rods







Class	Prognosis
I. AML With Recurrent Chromosomal Translocations	
AML with t(8;21)(q22;q22); *RUNXT1/RUNX1* fusion gene	Favorable
AML with inv(16)(p13;q22); *CBFB/MYH11* fusion gene	Favorable
AML with t(15;17)(q22;q21.1); *PML/RARA* fusion gene	Favorable
AML with t(11q23;variant); *MLL* fusion genes	Poor
AML with mutated *NPM1*	Variable
II. AML With Multilineage Dysplasia	
With previous MDS	Very poor
Without previous MDS	Poor
III. AML, Therapy-Related	
Alkylating agent–related	Very poor
Epipodophyllotoxin-related	Very poor
IV. AML, Not Otherwise Classified	
Subclasses defined by extent and type of differentiation (e.g., myelocytic, monocytic)	Intermediate

Immunophenotype

- CD34
- Myeloid markers
  - MPO, CD33, CD13, CD117, CD15
  - MPO is the most specific

Clinical manifestations

- Very similar to ALL
  - Stigmata of pancytopenia
- CNS manifestations are less frequent than ALL
- Treatment with chemotherapy and possibly SCT
- Prognosis is variable but oveall 5-year survival is~15-30%.

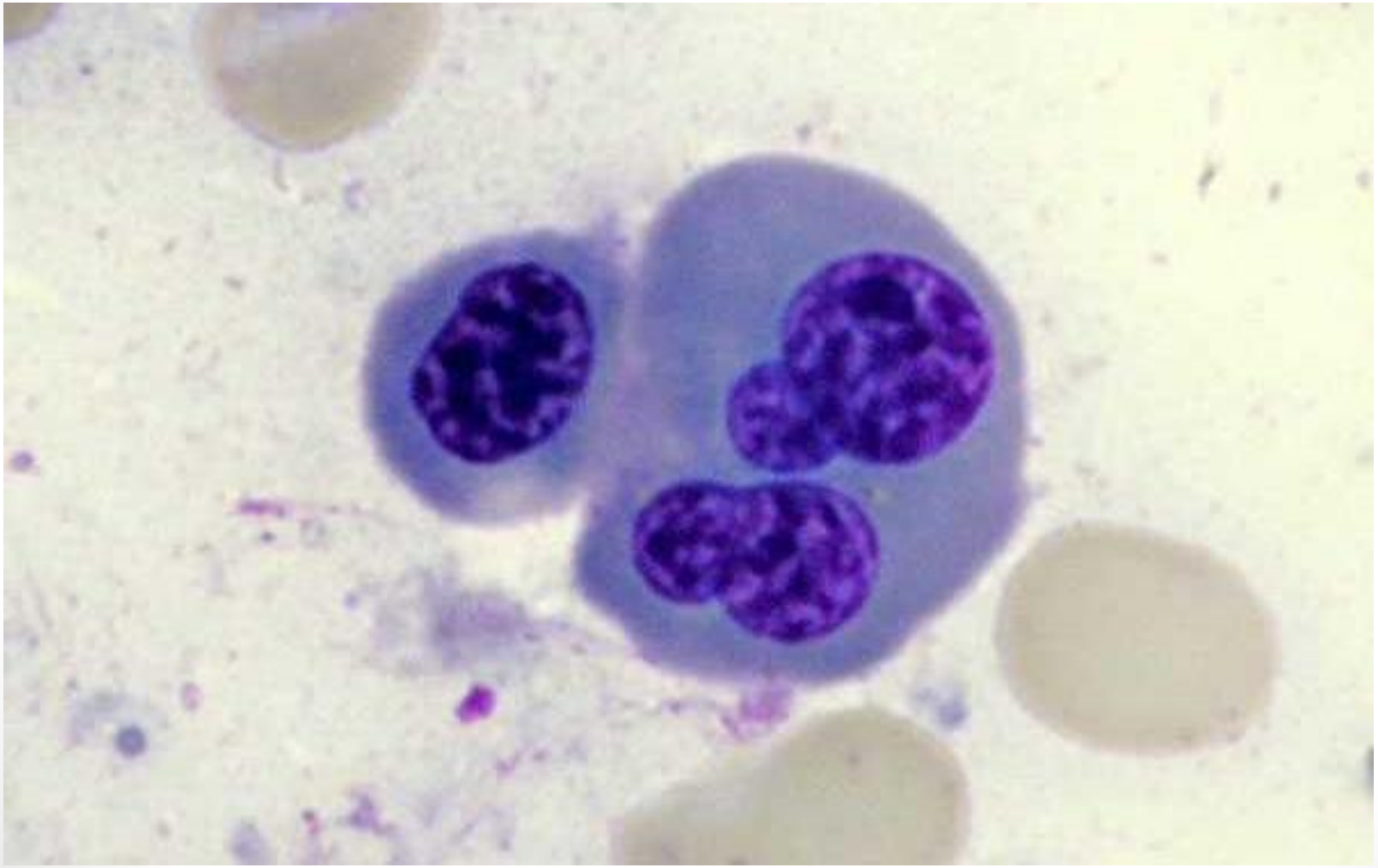
Myelodysplastic syndrome

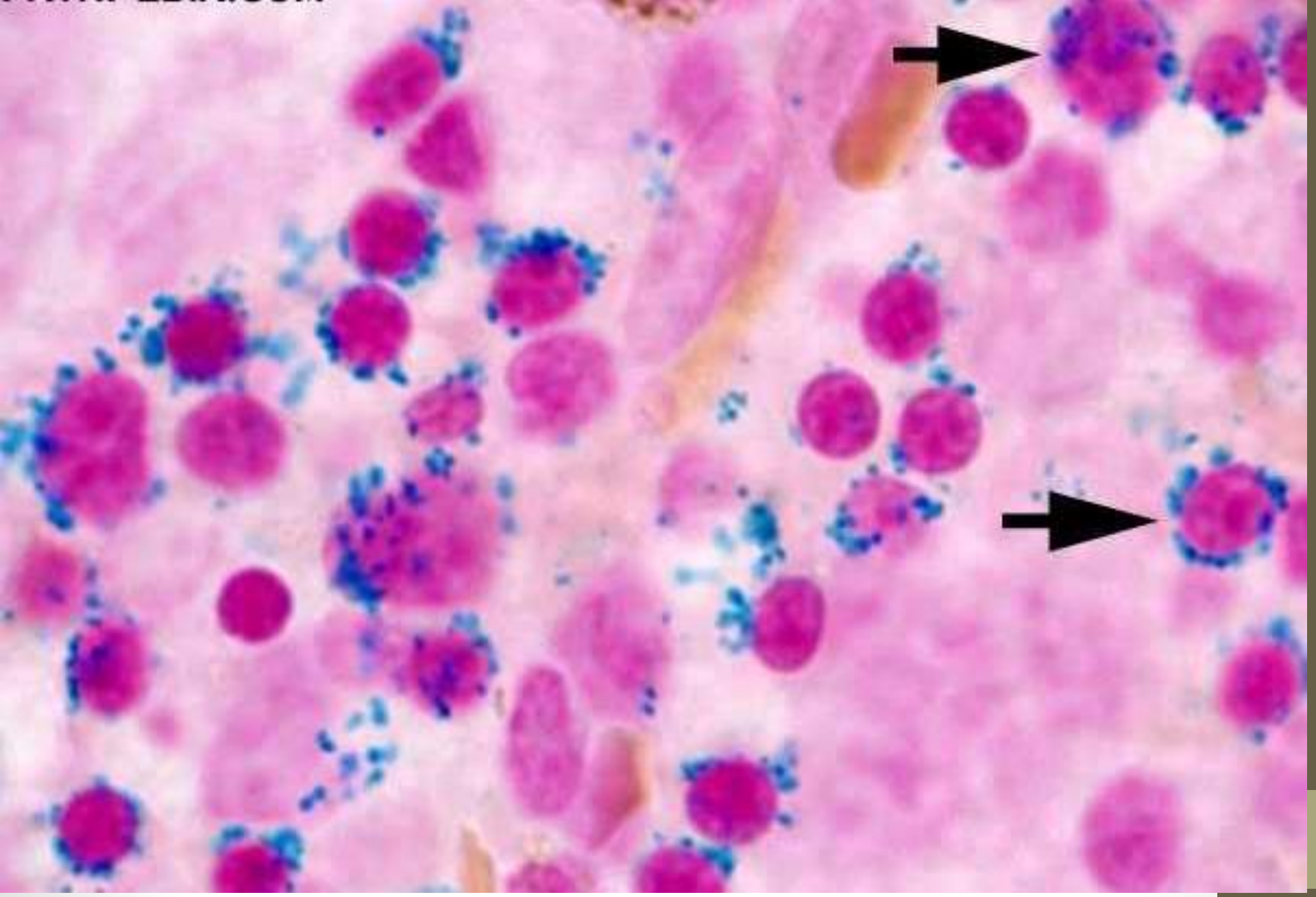
- **The term *myelodysplastic syndrome* (MDS) refers to a group of clonal stem cell disorders characterized by maturation defects that are associated with ineffective hematopoiesis with cytopenias and a high risk of transformation to AML**
- **Cytosis rules out MDS!!!**

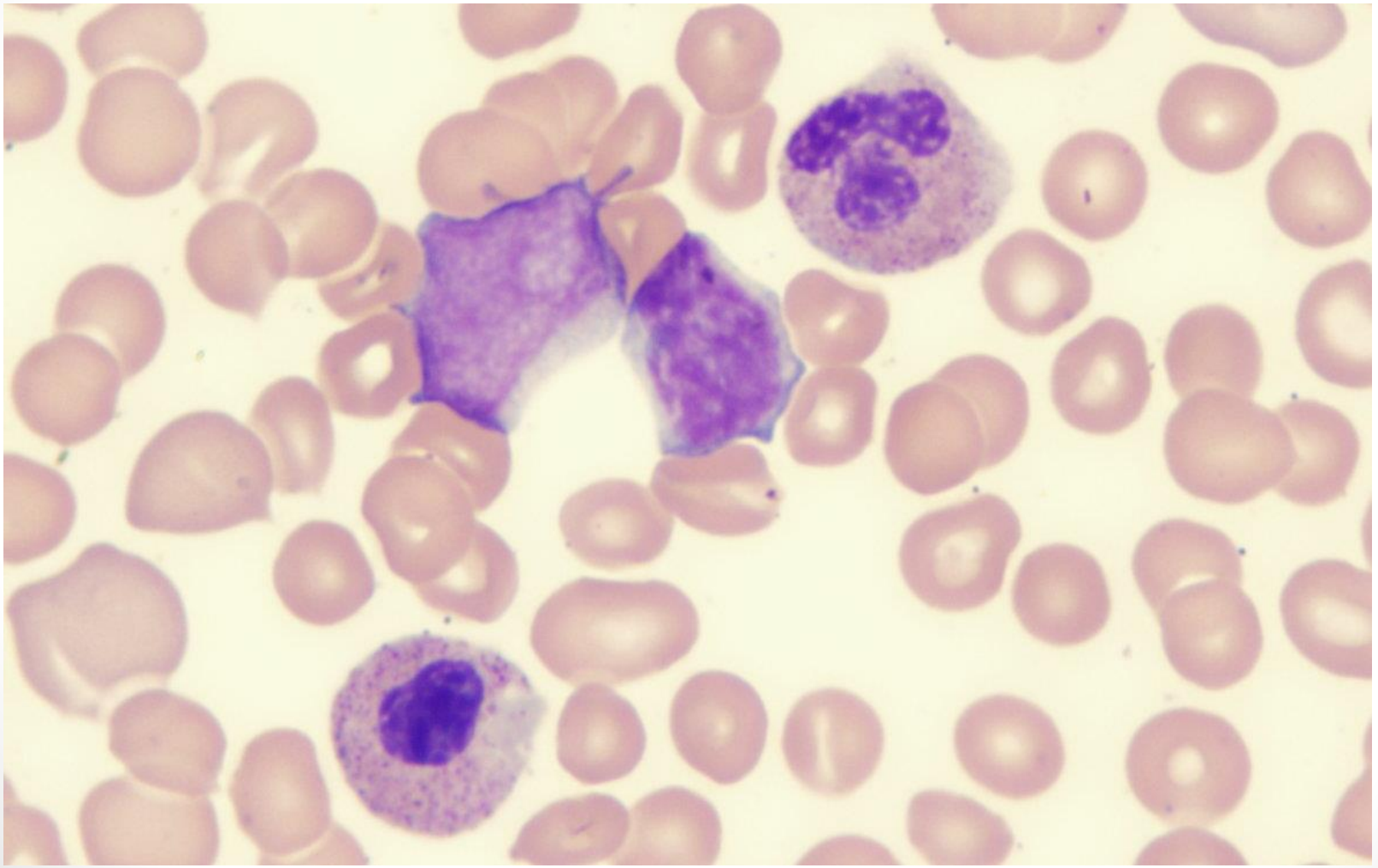
- Most cases are idiopathic
  - Some cases are induced by exposure to alkylating agents or ionizing radiation
- Pathogenesis involves genetic and epigenetic mutations that result in inability of the stem cells to have effective poeisis
  - Still able to proliferate and differentiate but in a disorderly manner!

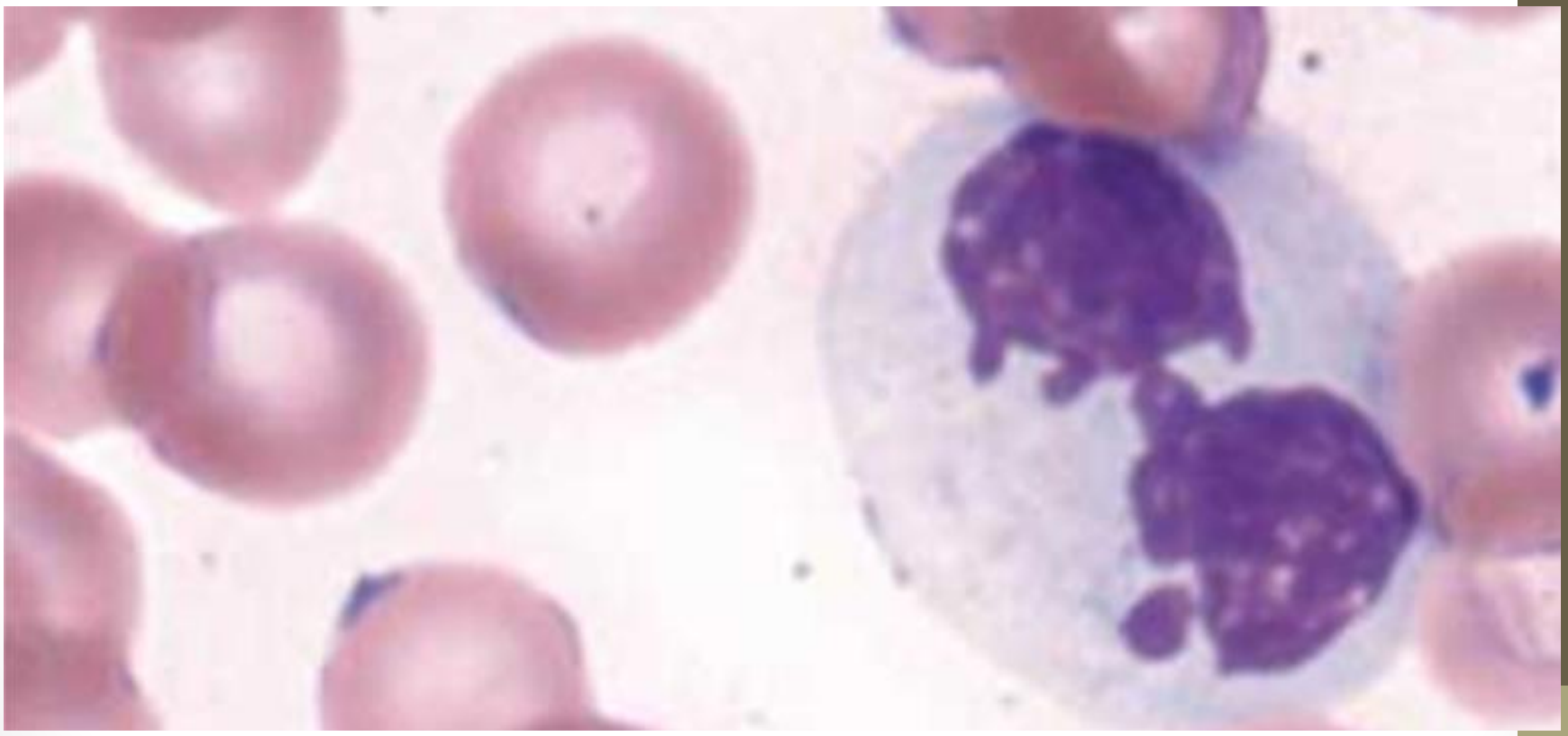
Morphology

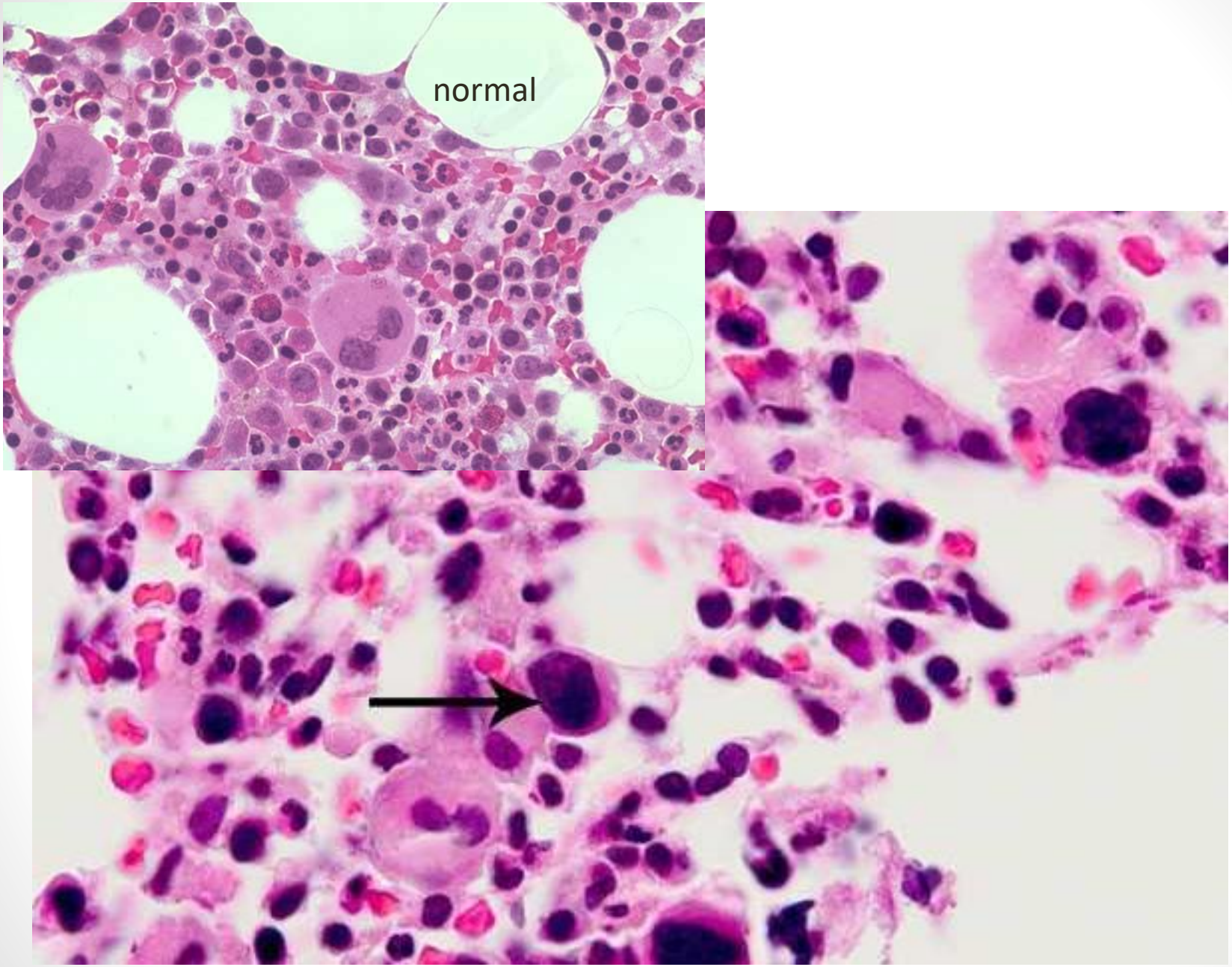
- Hypercellular bone marrow
- Dysplastic changes
  - Erythroid: Abnormal nuclear contour and iron deposits (ring sideroblasts)
  - Myeloid: abnormal segmentation and grnaulation
  - Megakaryocyte: small and monolobed










normal

Clinical manifestations

- Age 50-70
- Cytopenia and its effects
  - Does not have to be PANcytopenia
    - Patients may present with only anemia or only thrombocytopenia
- transforms to AML in 10-40% of the cases
- Survival between 9-29 months

Myeloproliferative Neoplasms

- Four major neoplasms
  - Chronic myelogenous leukemia
  - Polycythemia vera
  - Essential thrombocythemia
  - Primary myelofibrosis

- **The common pathogenic feature of myeloproliferative neoplasms is the presence of mutated, constitutively activated tyrosine kinases or other acquired aberrations in signaling pathways that lead to growth factor independence (uncontrolled growth).**

- They can transform into
  - Spent phase: fibrosis
  - Blast phase: acute leukemia

CML

- Pathogenesis
- BCR-ABL translocation t(9;22)
  - The same as in B-ALL
  - Present in all cells (B, T, myeloid)
  - It is a tyrosine kinase that results in uncontrolled proliferation
  - **Does NOT inhibit differentiation**

- Disease course is marked by excessive production of relatively normal blood cells, particularly granulocytes and platelets.

morphology

- Hypercellular bone marrow
- Splenomegaly with extensive extramedullary hematopoiesis
- High WBC count, often exceeding 100000

Clinical manifestations

- Age 50-70
- Nonspecific symptoms of fatigue, weakness
- Dragging sensation in the abdomen due to splenomegaly
- Must be distinguished from “leukemoid reaction”
  - High WBC count secondary to infection or infarction
  - Best done by molecular testing for BCR-ABL

- Slowly progressive disease
  - Median survival is 3 years without treatment
- Can progress to accelerated phase
  - Anemia, thombocytopenia and additional genetic mutations
- Progress to blast phase
  - 70% AML
  - 30% ALL
- Rarely progresses to spent phase with fibrosis

PV

- Discussed previously

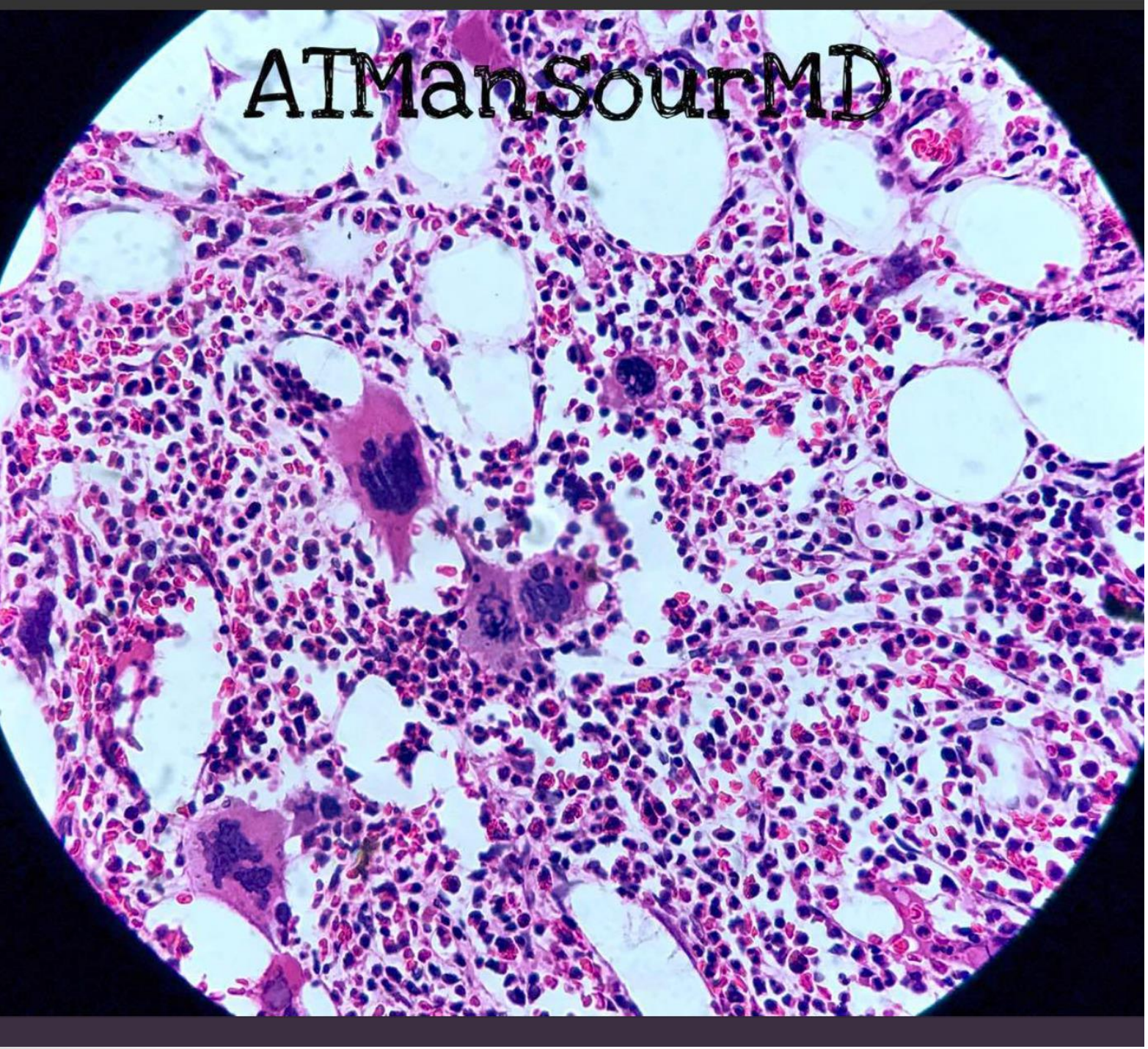
Primary myelofibrosis

- **The hallmark of primary myelofibrosis is the development of obliterative marrow fibrosis, which reduces bone marrow hematopoiesis and leads to cytopenias and extensive extramedullary hematopoiesis**

- JAK2 mutation in ~50-60% of the cases
- Neoplastic cells involve the megakaryocytes
  - Secrete fibrogenic factors resulting in extensive fibrosis
    - PDGF and TGF-B
- Extramedullary hematopoiesis with marked splenomegaly

Morphology

- Peripheral blood:
  - leukoerythroblastosis
    - Tear drop RBCs
    - Erythroid precursor cells
    - Immature myeloid cells
    - As you recall this is also found in myelophthisic anemia
  - Abnormally large platelets
- Bone marrow:
  - severe fibrosis
  - Abnormally large and clustered megakaryocytes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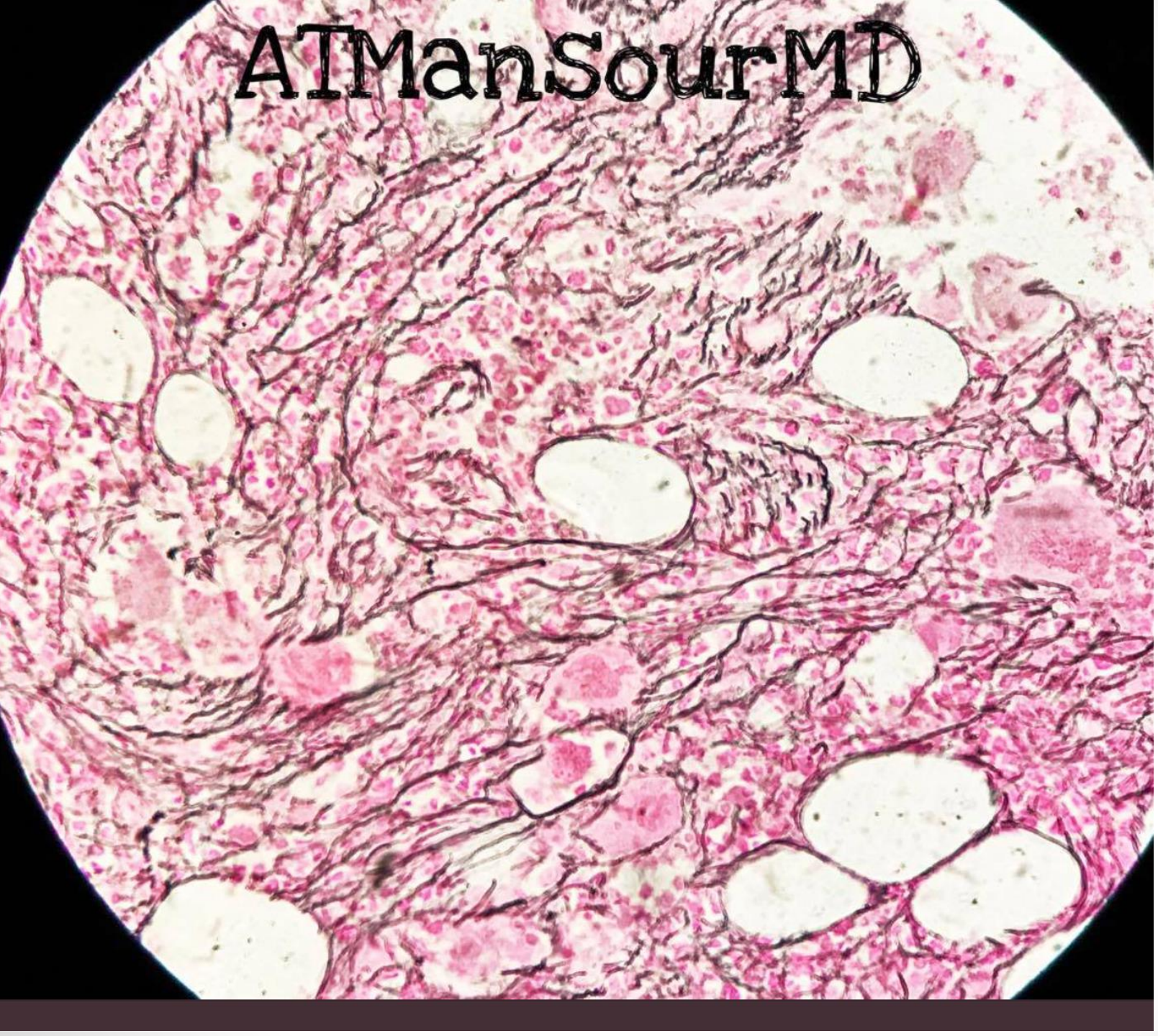
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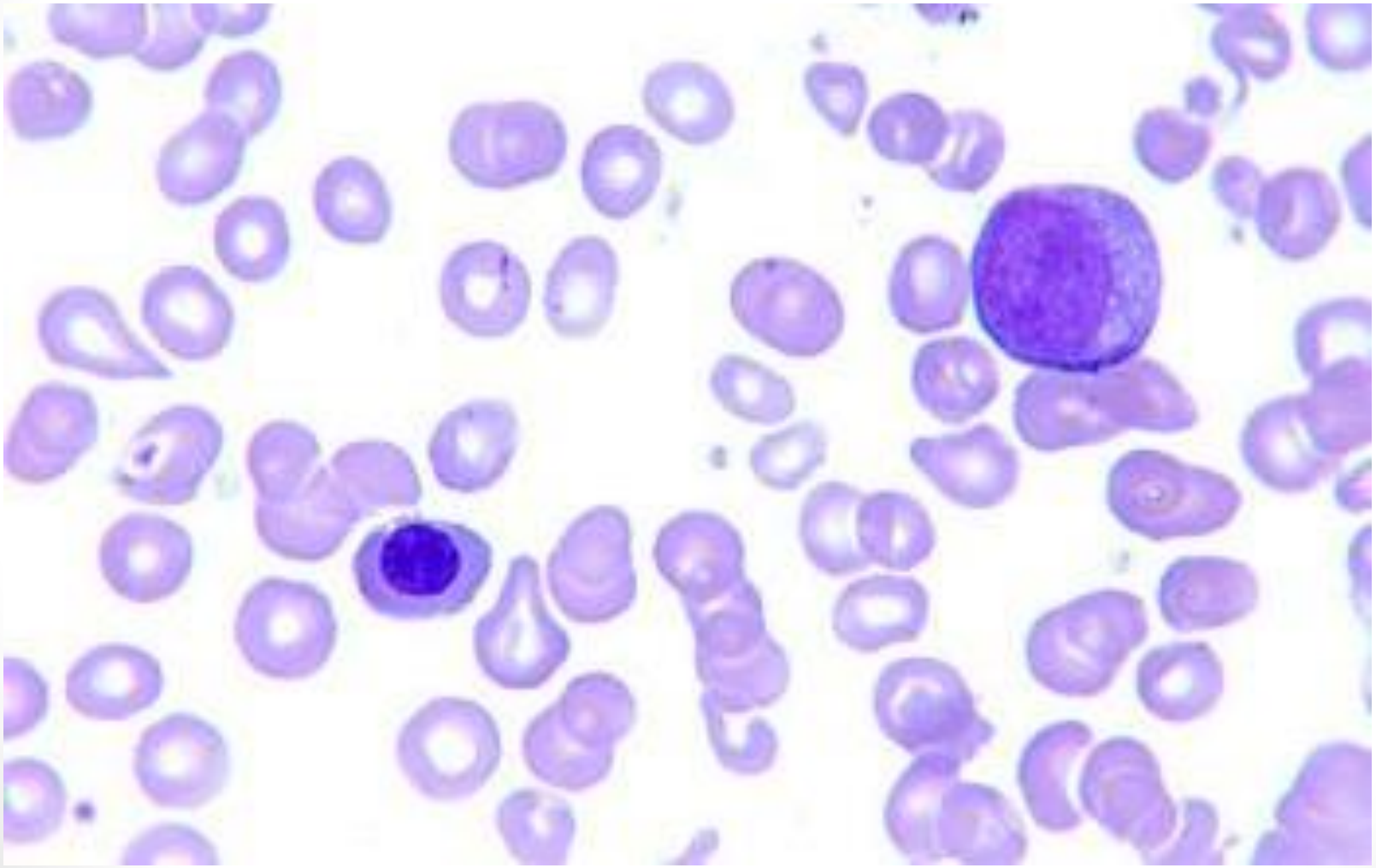

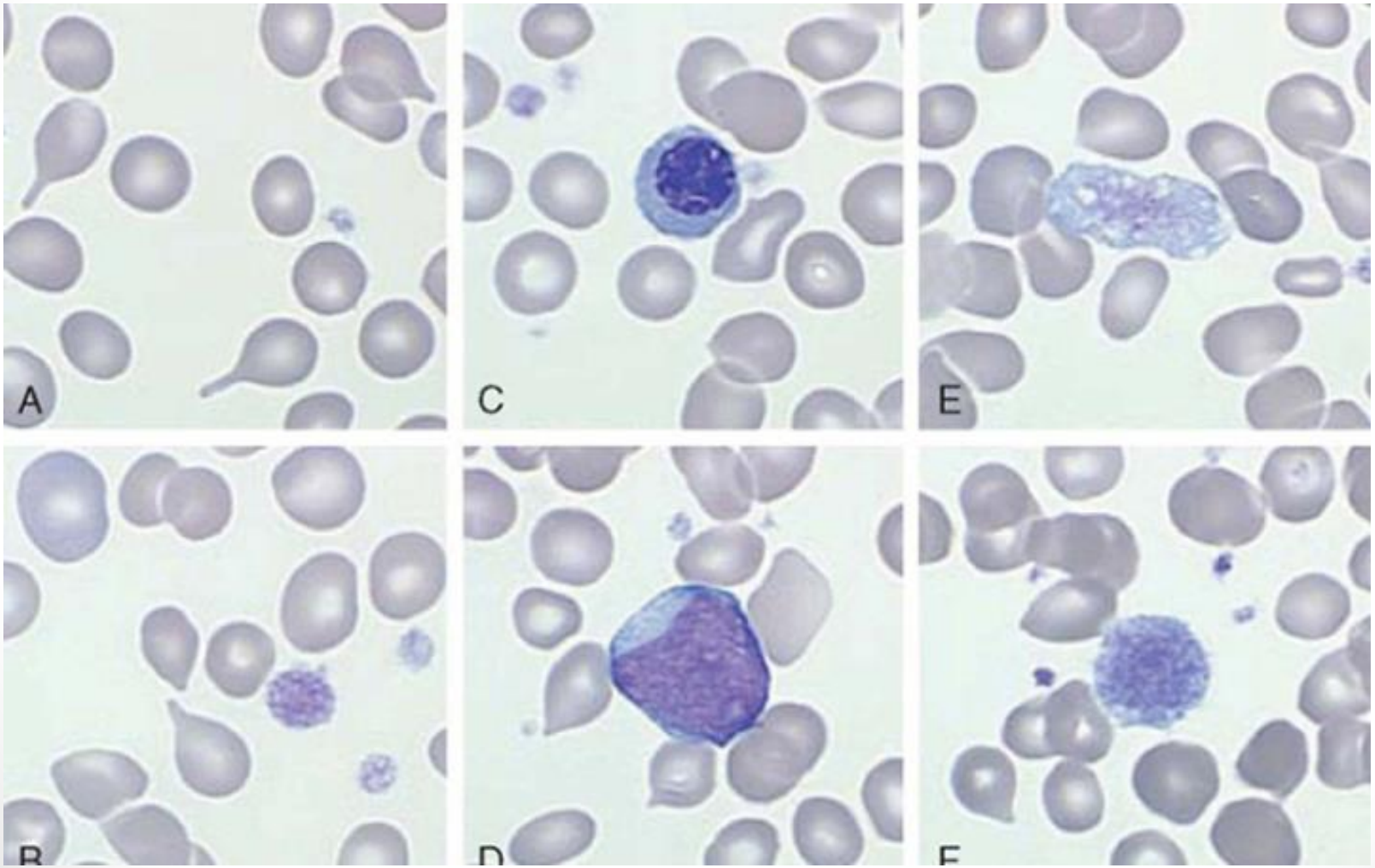
A
C
E
B
D
F

Clinical manifestations

- Age more than 60
- Anemia and splenomegaly
- Fatigue, weakness and night sweats
- Lab results
  - Anemia: normochromic and normocytic
  - Leukoerythroblatosis
- Bone marrow is a must for diagnosis

- Median survival is 4-5 years
- 5-20% transform to AML
- Treat with JAK2 inhibitors and possibly SCT

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