Board Review- Part 2A: Malignant HemePath

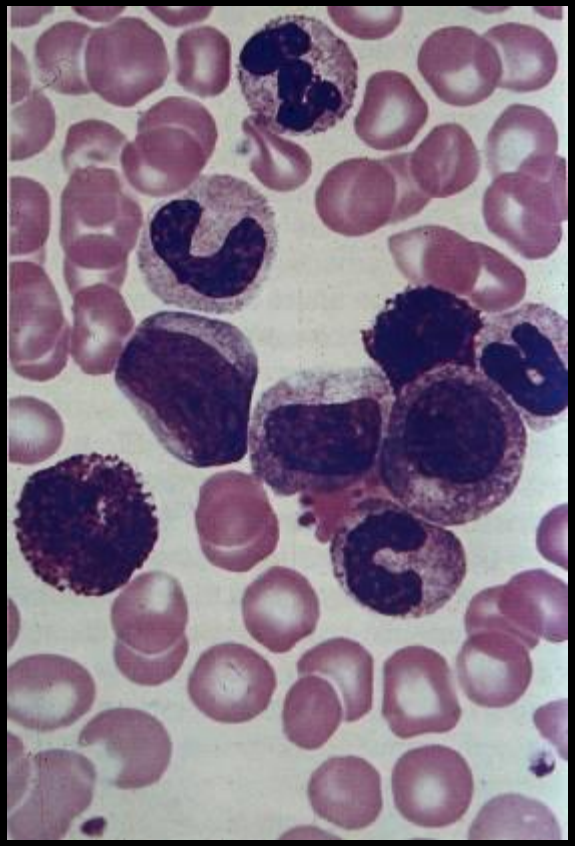
4/25/2018

Chronic Myelogenous Leukemia, bcr/abl1 pos

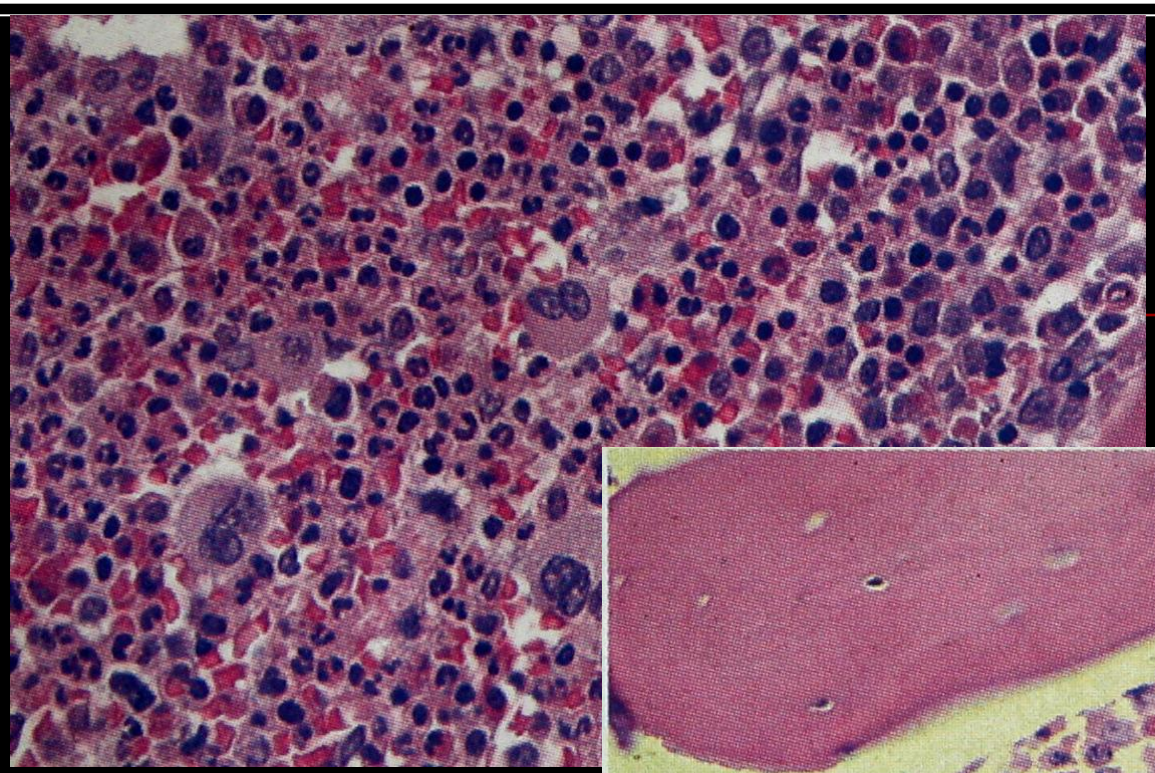
Morphology-Chronic Phase

Peripheral blood

- Leukocytosis (median 100k/μL), due mainly to neutrophils (peak in myelocytes and PMNs); no significant dysplasia; blasts <2%
- Basophilia: invariably present; and eosinophilia
- Monocytes: can be increased in absolute numbers, but usually <3%
- Thrombocytosis common, thrombocytopenia rare

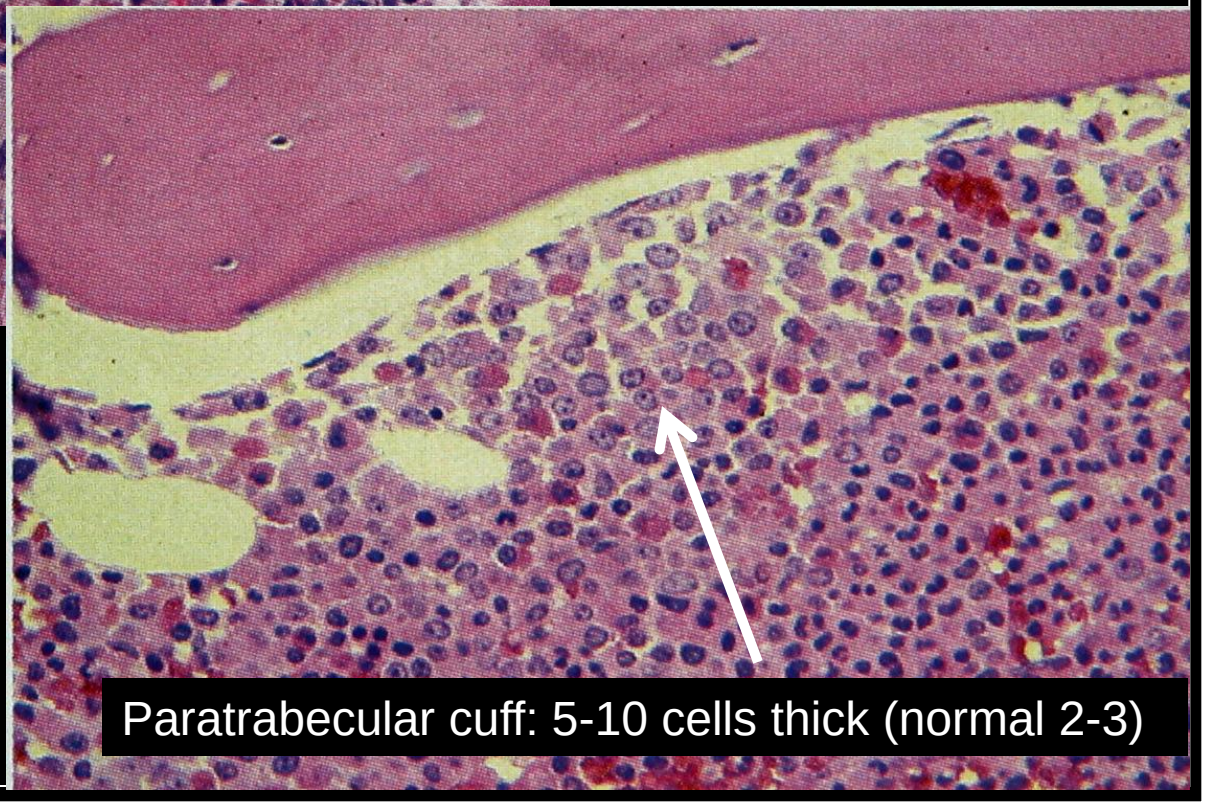


Peripheral Blood

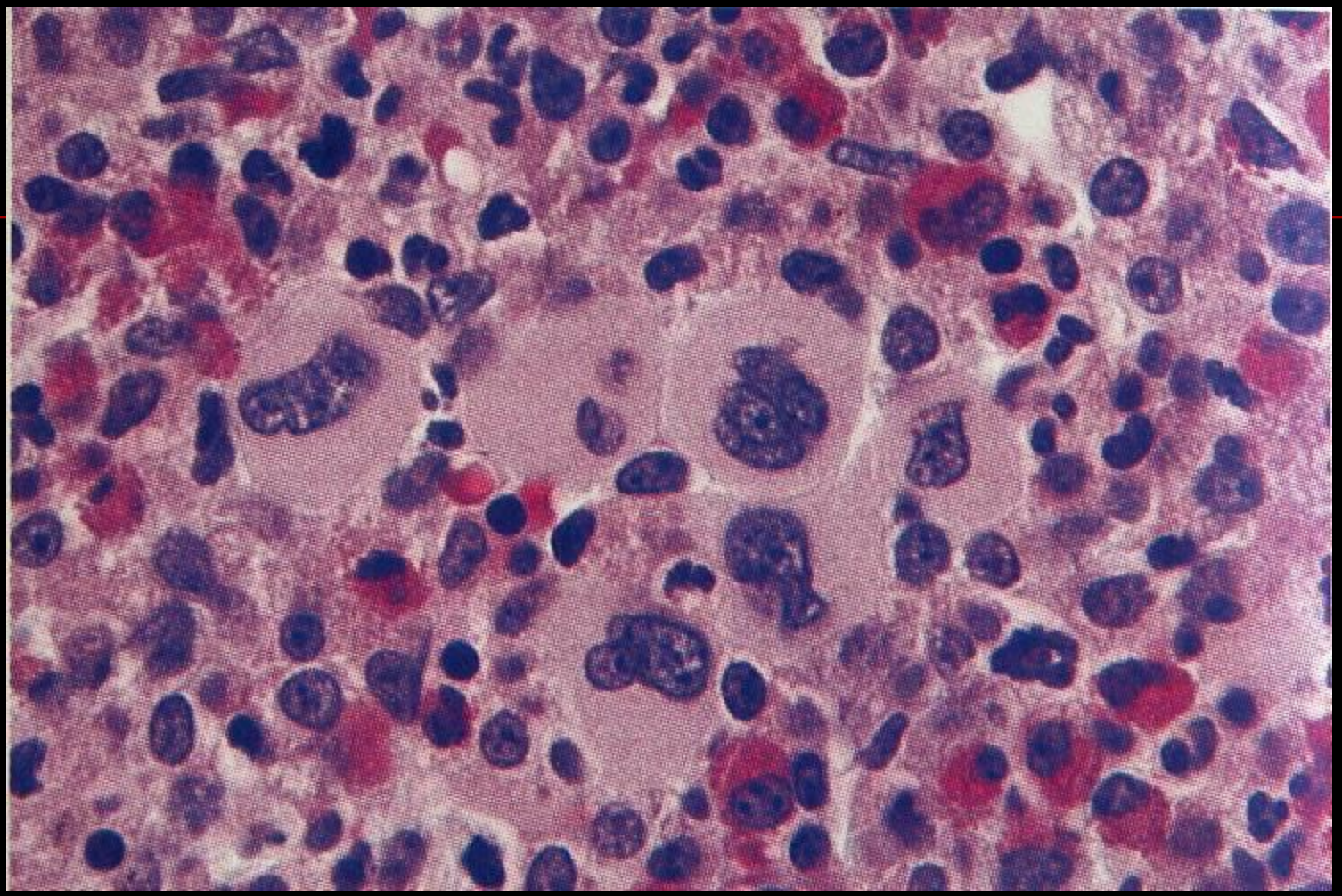


BM: hypercellular

BM: increased immature cells

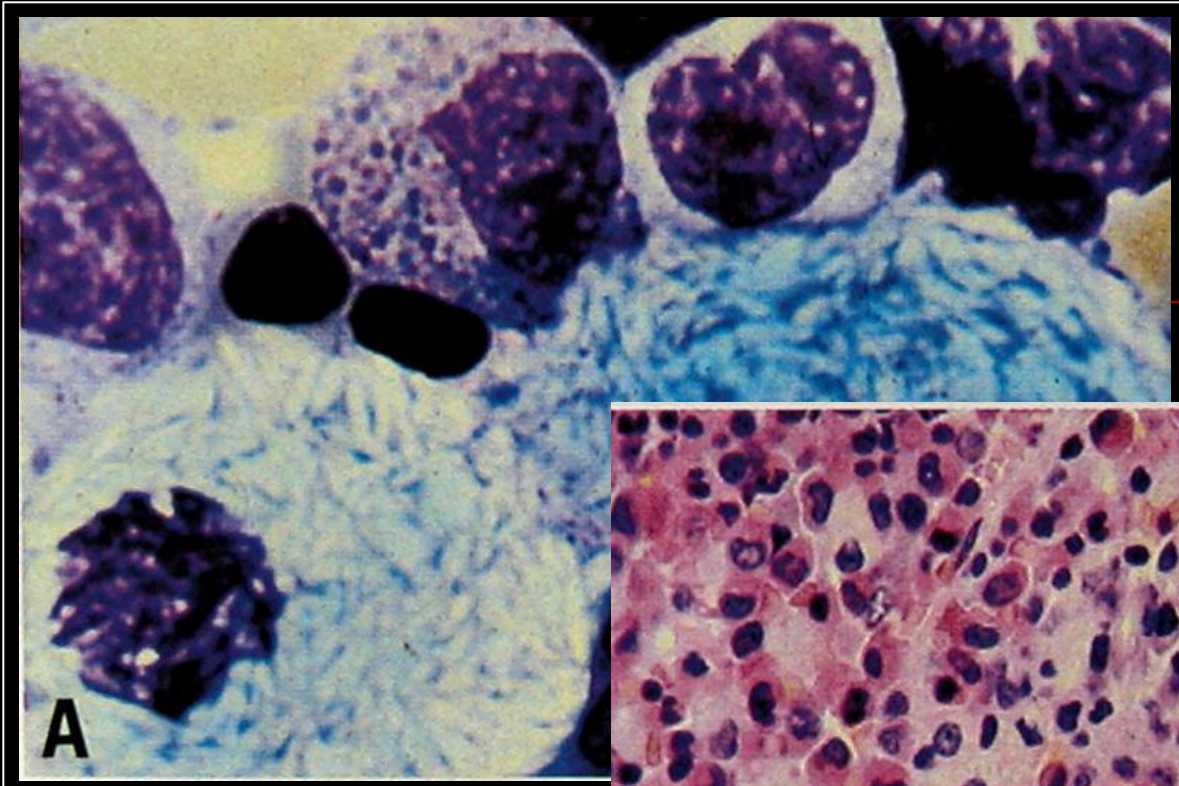


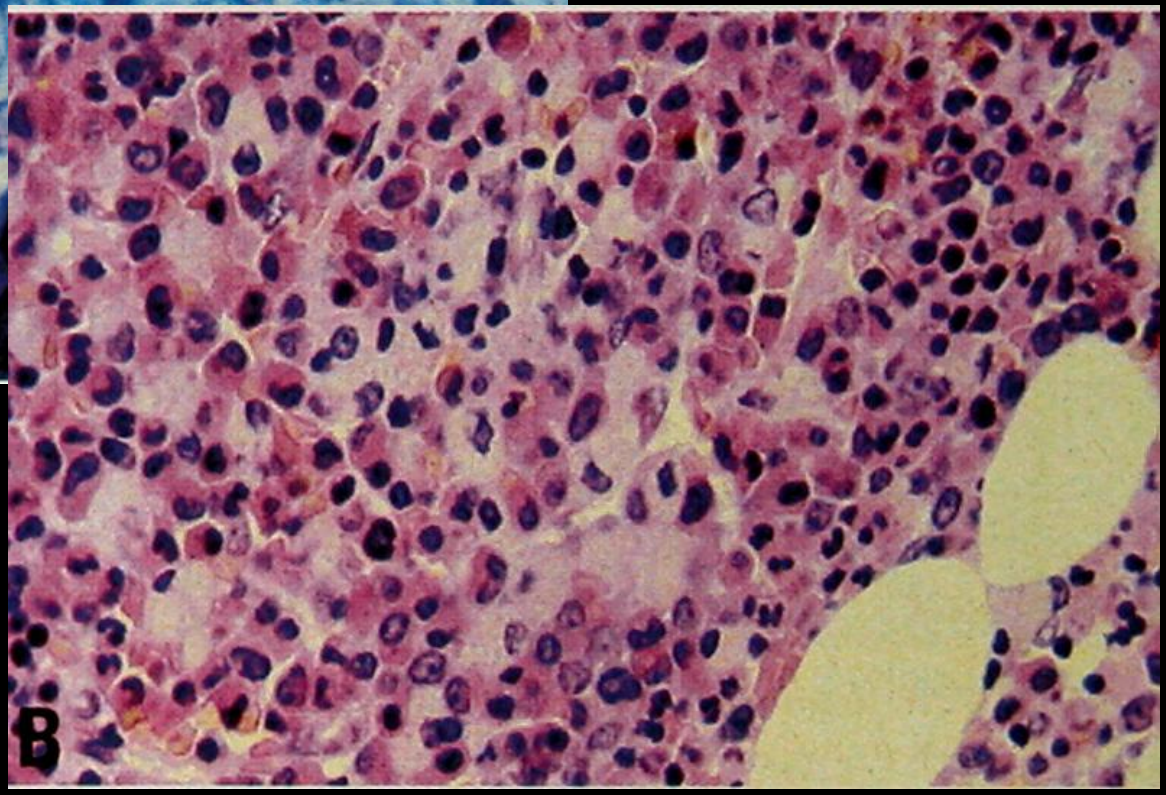
Paratrabecular cuff: 5-10 cells thick (normal 2-3)



BM: small megakaryocytes

BM: pseudo-Gaucher cells

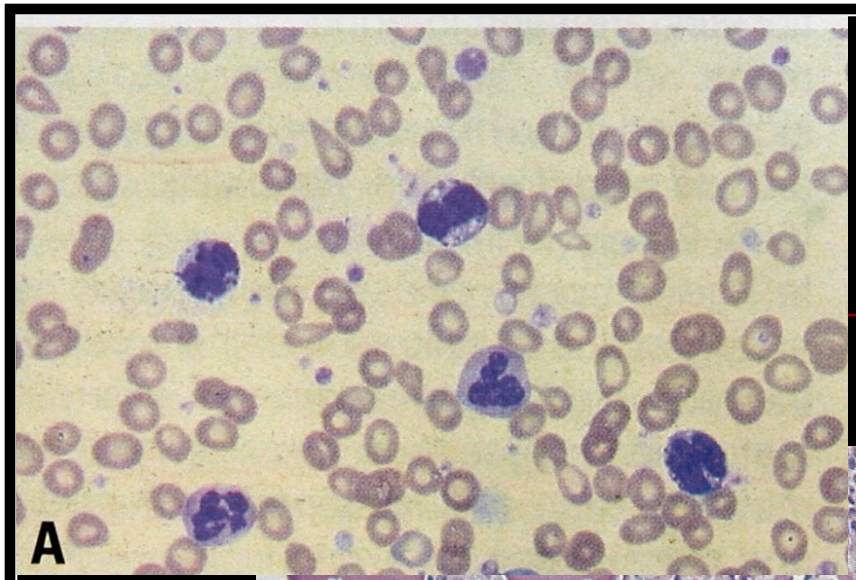


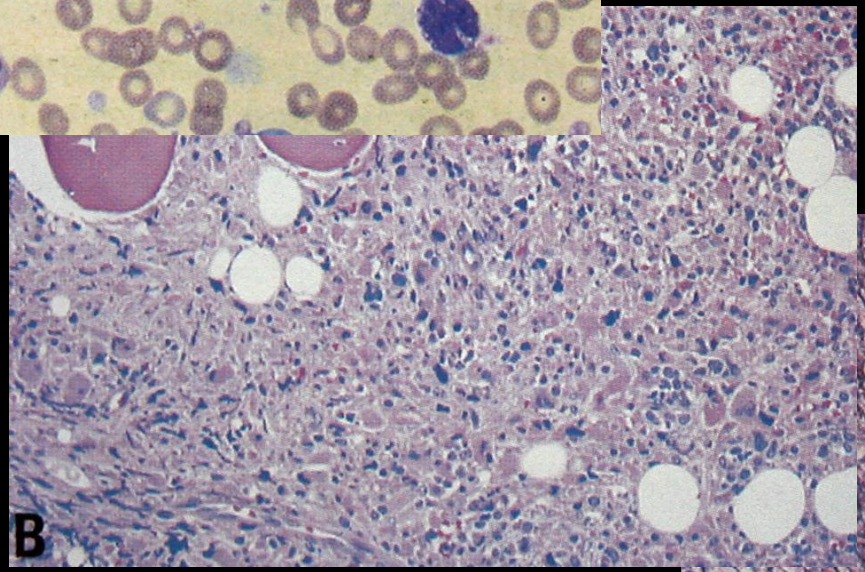


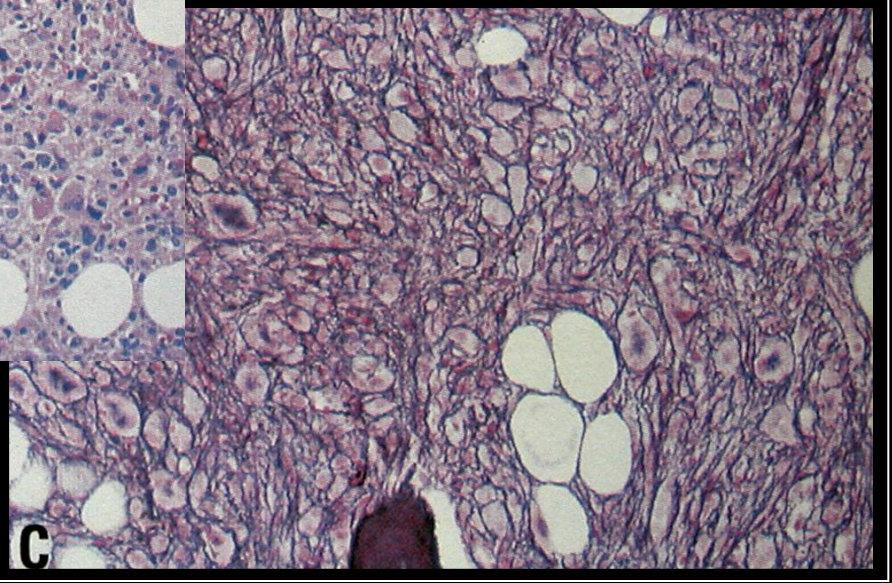
Morphology-Accelerated Phase (any one of these criteria)

- Blasts 10-19% in PB or BM
- Basophils ≥20% in PB
- Plt <100k, unrelated to therapy
- Plt >1,000k, despite therapy
- Increasing WBC count and spleen size, unresponsive to therapy
- Evidence of clonal evolution (extra Ph, +8, +19, or i(17q)

Accelerated phase



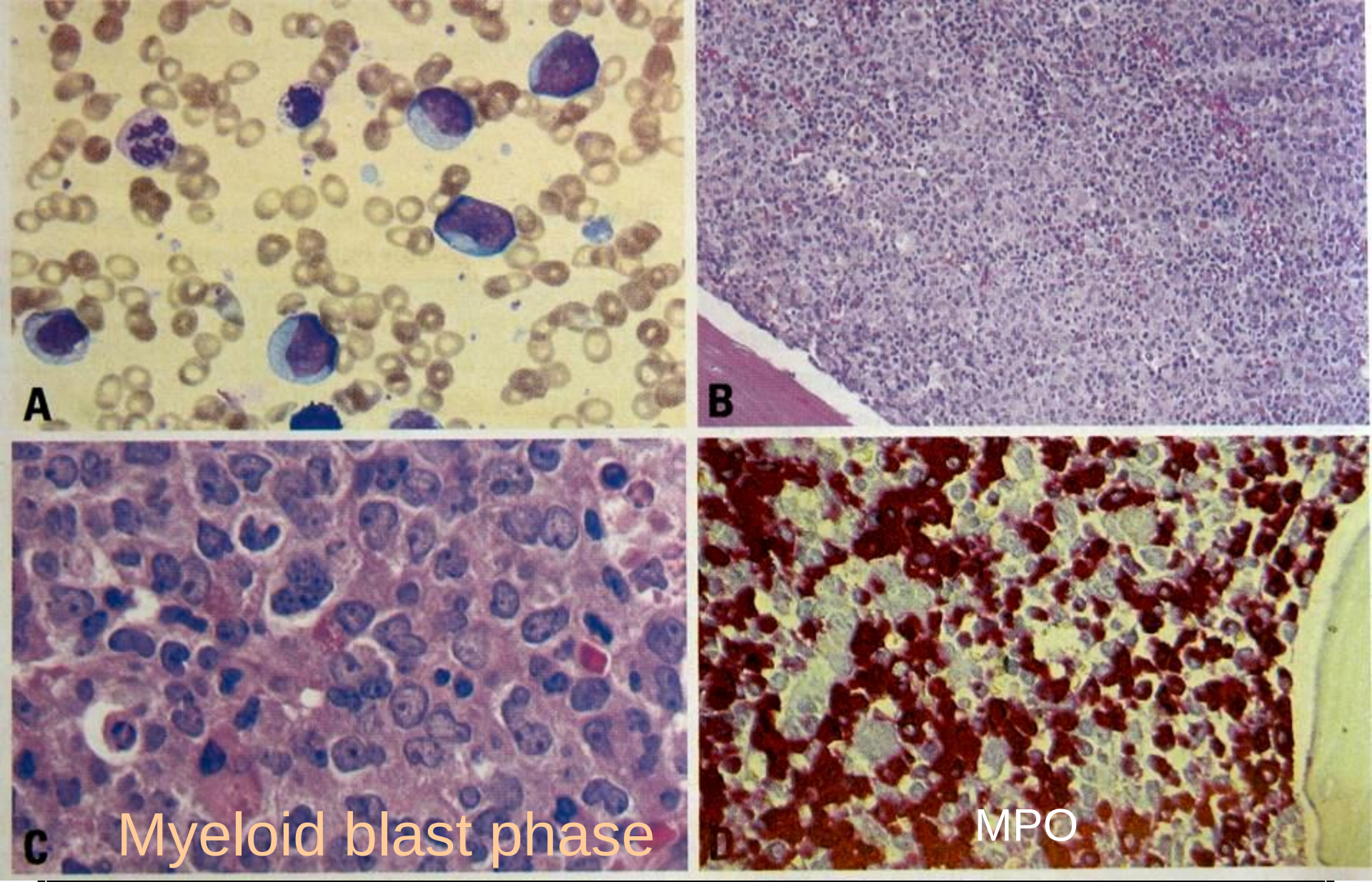




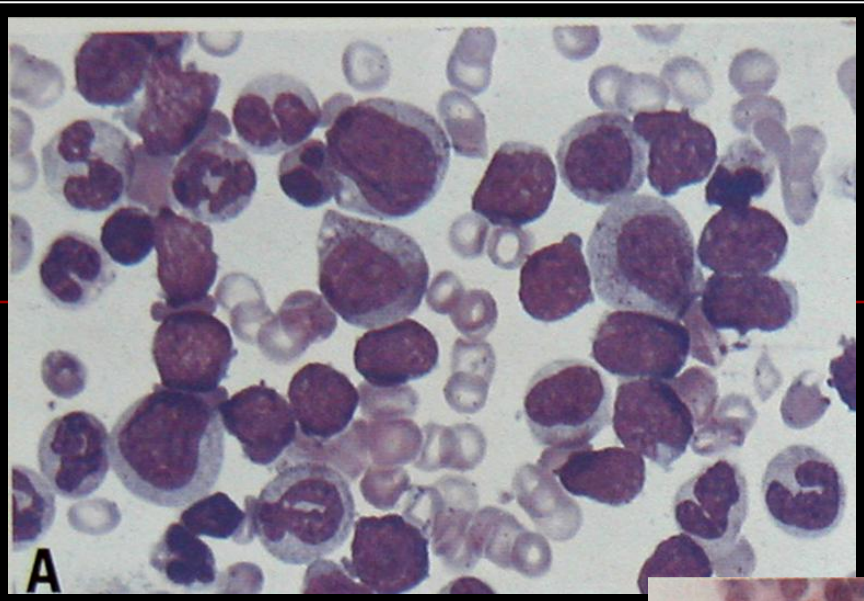
Morphology- Blast Phase

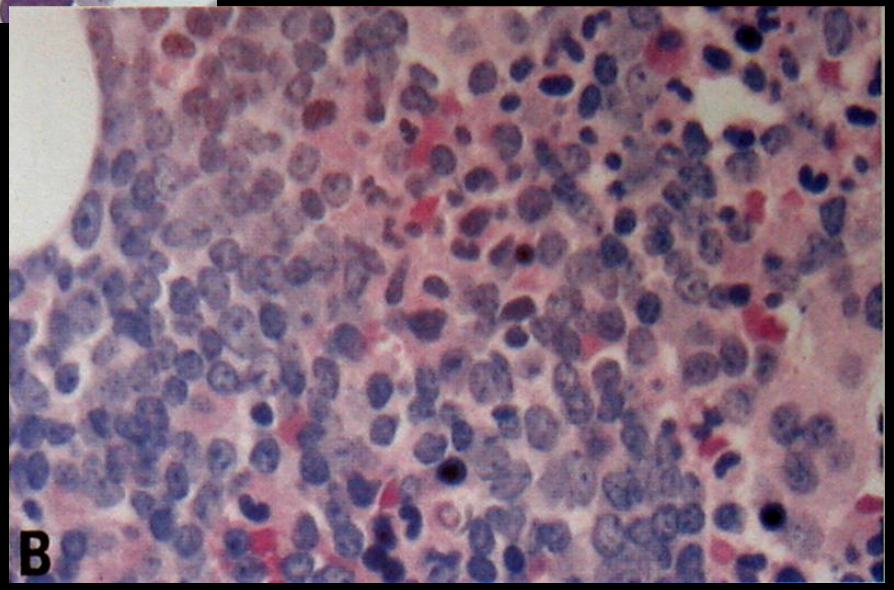
- >20% blasts in PB or BM
- Extramedullary proliferation of blasts
- Large aggregates and clusters in BM bx

(acute leukemia: myeloid: 70%; lymphoid: 20-30%)


A
B
C
Myeloid blast phase
D
MPO

Lymphoid blast phase





Genetics/Molecular

- Ph: 90-95%
- Cryptic t(9:22)-> use PCR, RT-PCR, FISH
- BCR/ABL

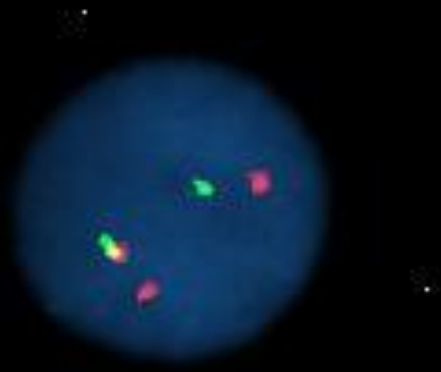
  M-bcr, p210, CML (almost always)

  μ-bcr, p230, CML (rare), prominent neutrophilic maturation

  m-bcr, p190, ALL, CML (rare)

  (p190: small amount in >90% of CML due to alternative splicing)
- AP or BP: additional cytogenetic changes in 80%: extra Ph, +8, or i(17q)

FISH for bcr-abl1



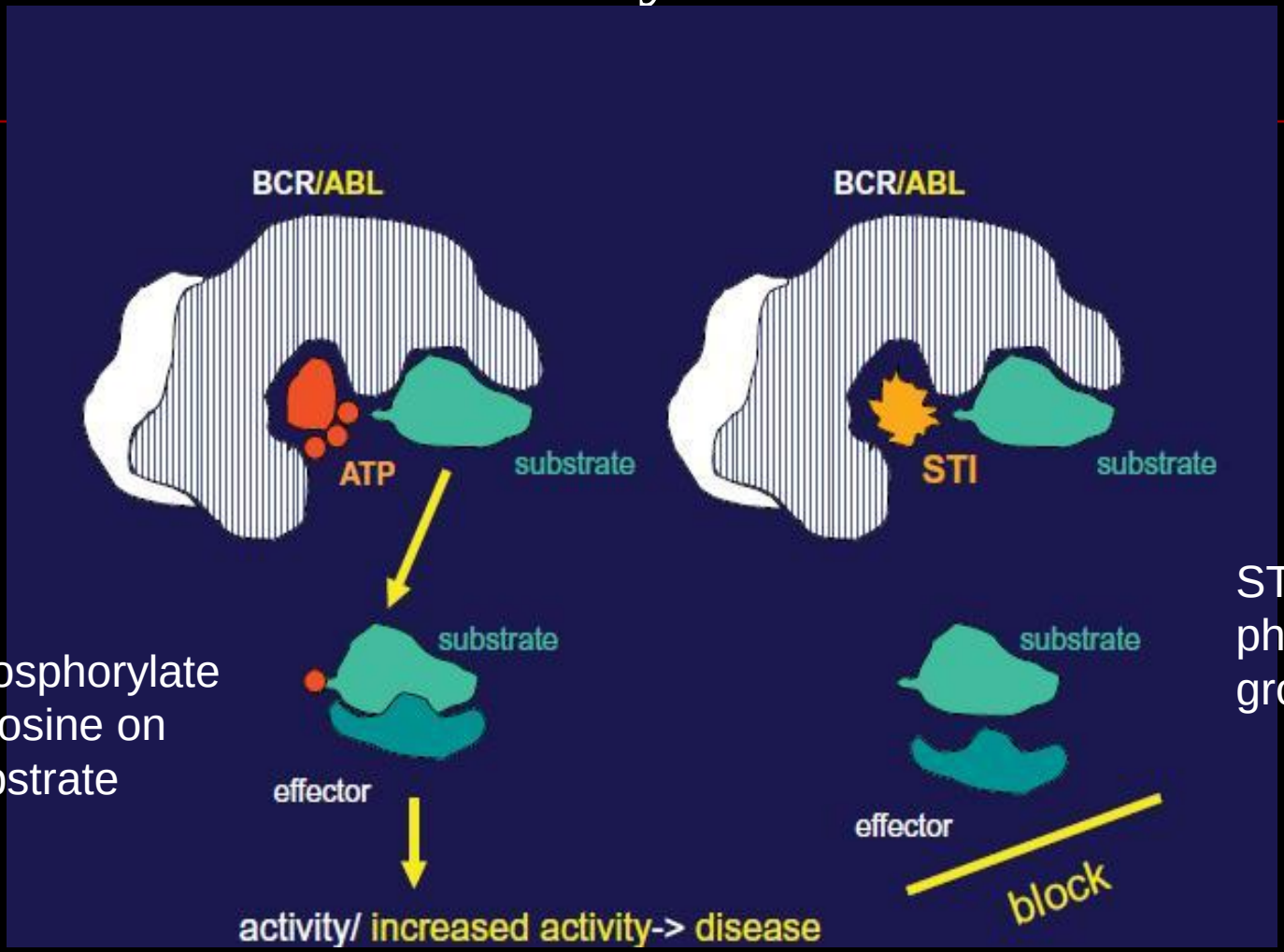
Bcr probe: green
Abl1 probe: red

Bcr-abl1 fusion: green + red -> yellow

Prognosis and Predictive Features

- Natural history: chronic phase -> AP and/or BP
- Median survival: 6 yrs with previous conventional therapy
- Prognostic parameters: age, spleen, blasts, basophil count, fibrosis
- STI517 (Gleevec): tyrosine kinase inhibitor yields 89-95% progression free survival in 5 yrs. Complete cytogenetic response of 70-90%

Gleevec: inhibitor of Tyrosin Kinase bcr-abl1



Phosphorylate Tyrosine on substrate

STI lacks phosphate groups

Loss of response/resistance to Imatinib

- Due to emergence of subclones of leukemic cells with point mutations that prevent binding of Imatinib to bcr-abl1
- Increase dose
- Consider alternate treatment:
  Desatinib
  Nilotinib
- Consider stem cell transplant

Polycthemia Vera

WHO MAJOR CRITERIA

- 1. Hb >16.5 g/dL in men and >16.0 g/dL in women
- 2. Hypercellular bone marrow with panmyelosis (erythroid, granulocytic, and megakaryocytic hyperplasia)
- 3. Presence of JAK2 V617F or JAK2 Exon 12 mutation

WHO MINOR CRITERIA

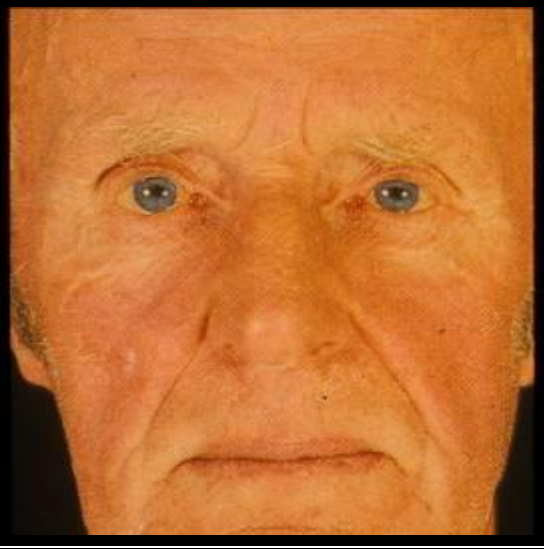
- Low serum erythropoietin level

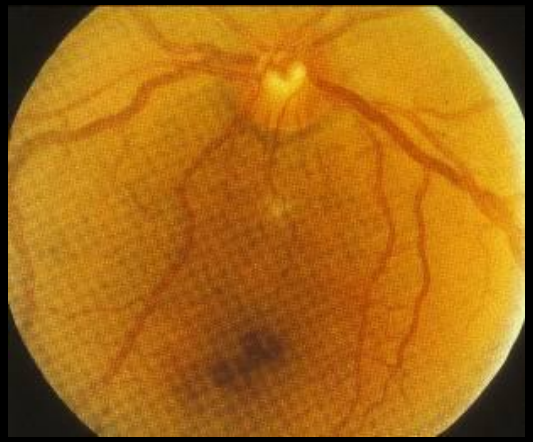
Diagnosis of Polycythemia Vera

- Three majors, or
- First 2 majors + minor.

Polycythemia Vera
Clinical Signs and Symptoms

- **Plethora, headache, dyspnea or orthopnea, eye complaints**
- **Epigastric discomfort – risk of Budd-Chiari syndrome**
- **Abnormal blood flow: MI, stroke**





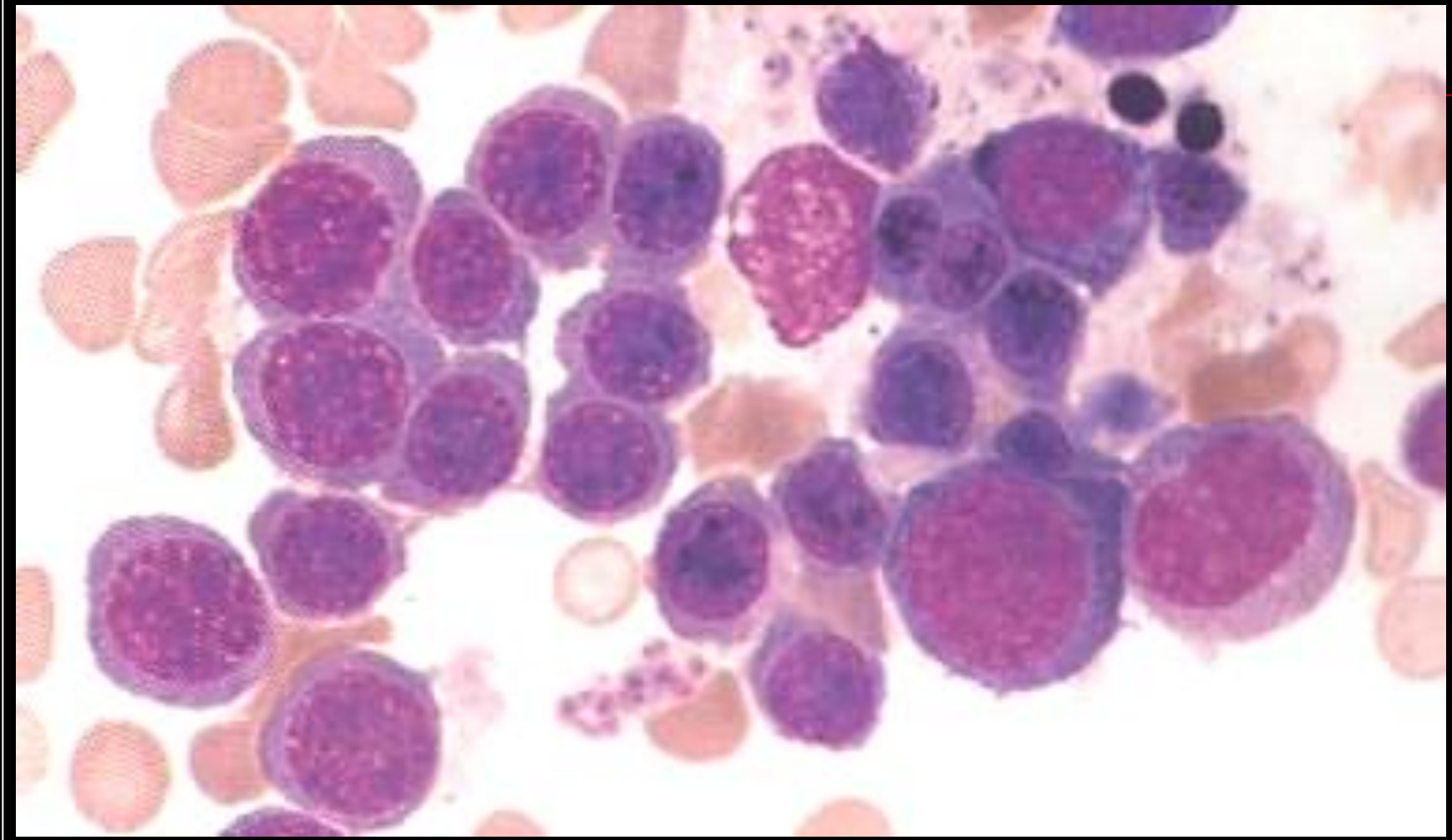
Polycythemia Stage

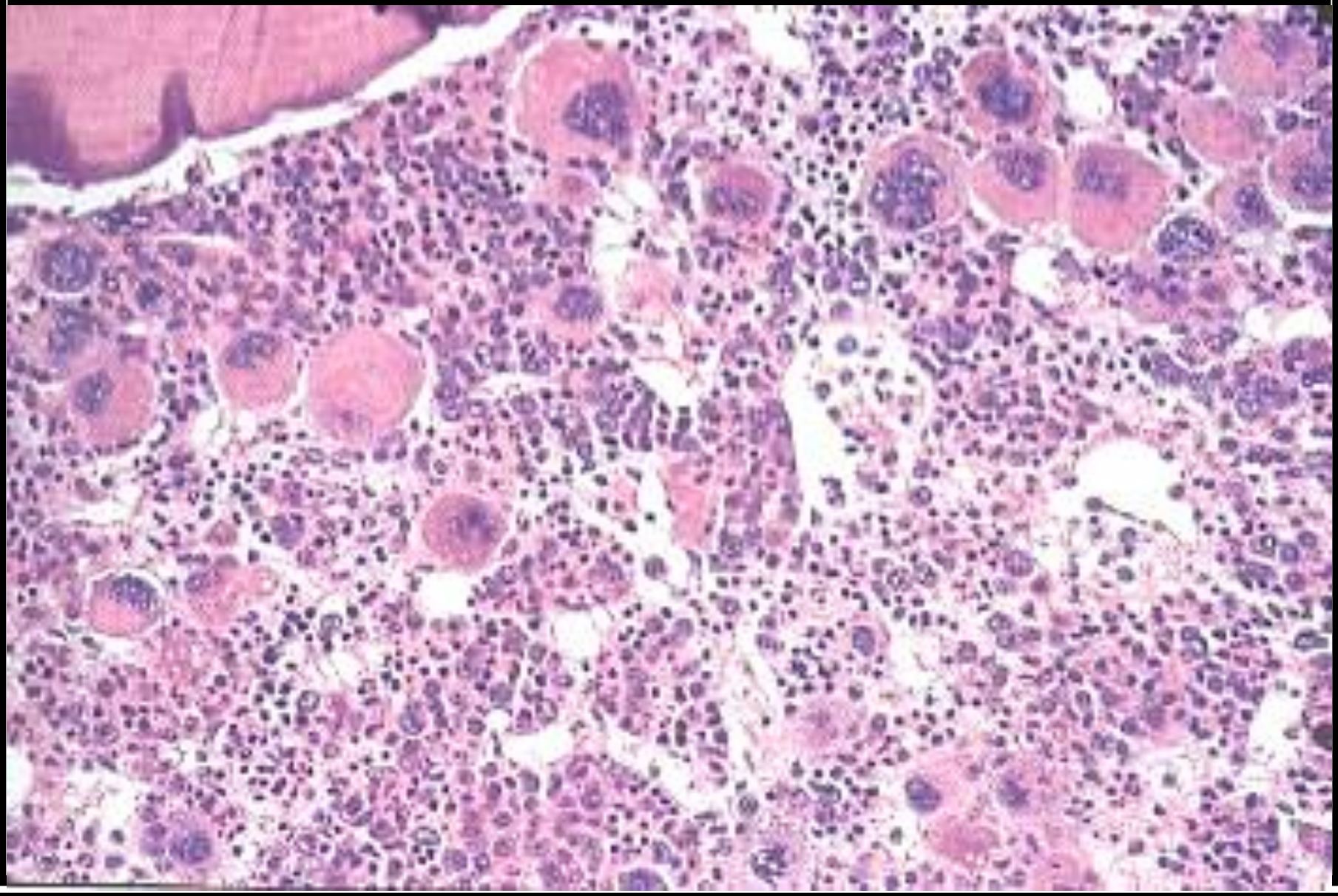
- Normoblastic erythroid proliferation in BM
- Normochromic, normocytic RBCs in PB
- If bleeding or phlebotomy-> RBCs hypochromic and microcytic
- Neutrophilia
- Basophilia
- Thrombocytosis (50%)

Polycythemia Stage

Megakaryocytes

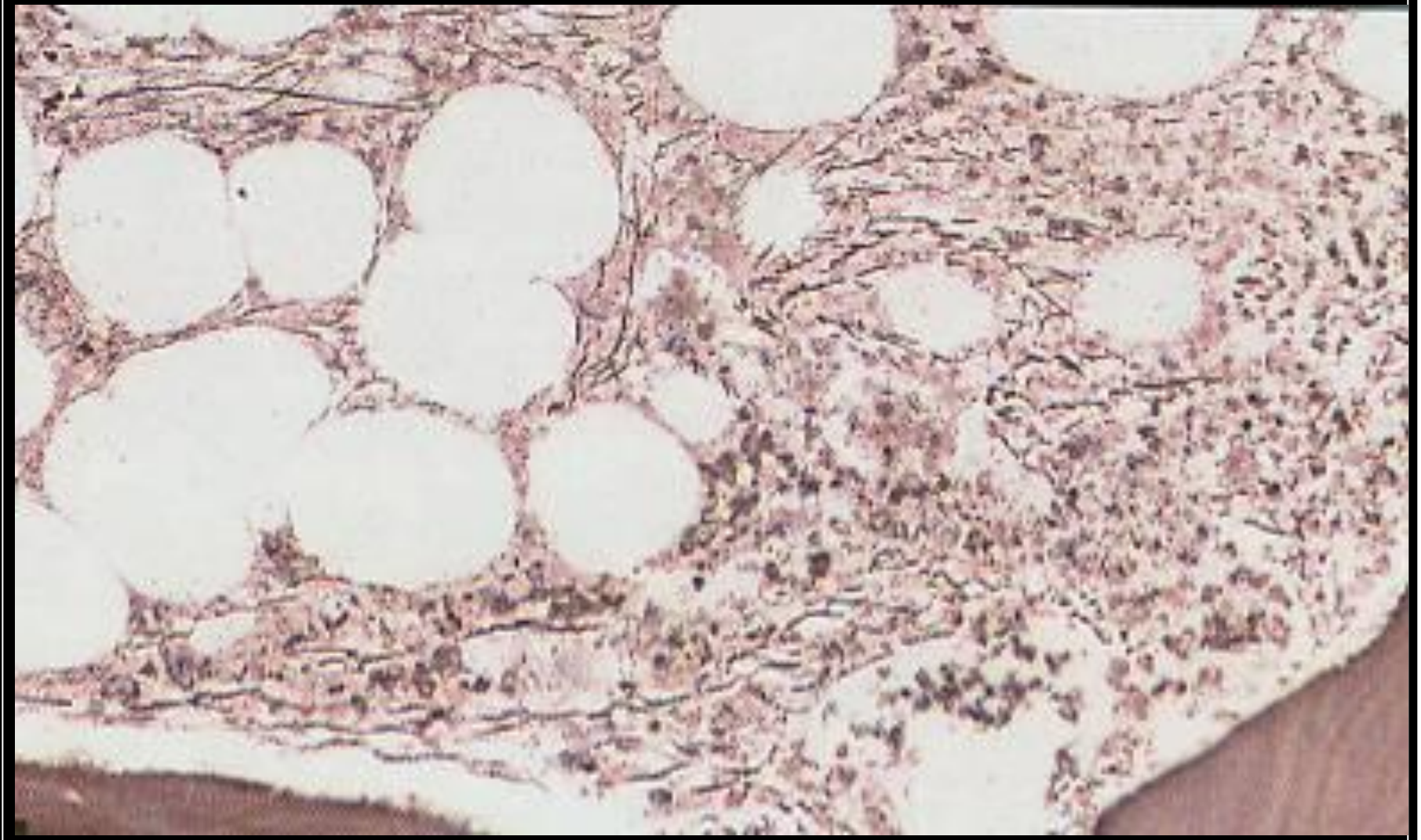
- Increased, clustered (parasinusoidal and paratrabecular); sinusoids dilated
- Pleomorphic, nuclear hyperlobulation but not dysplastic
- No stainable iron in 95%





Spent Phase - Post-Polycythemic Myelofibrosis and Myeloid Metaplasia

- Red cell mass decreases
- BM cellularity decreases
- BM fibrosis (reticulin and collagen increased)
- Splenomegaly – with extramedullary hematopoiesis



Reticulin

Genetics

- Specific defects in only 20%
- +8, +9, del 20q, del 13q, del 1p
- No Philadelphia chromosome or BCR/ABL fusion gene
- Genetic defects increase during progression to MDS or AML

Prognosis

- Without therapy-> survival a few months
- With therapy survival-> survival >10 years
- Death due to thrombosis or hemorrhage
- MDS or AML in only 2% treated with non-cytotoxic agents
- MDS or AML in 10-20% treated with cytotoxic agents

Essential Thrombocythemia

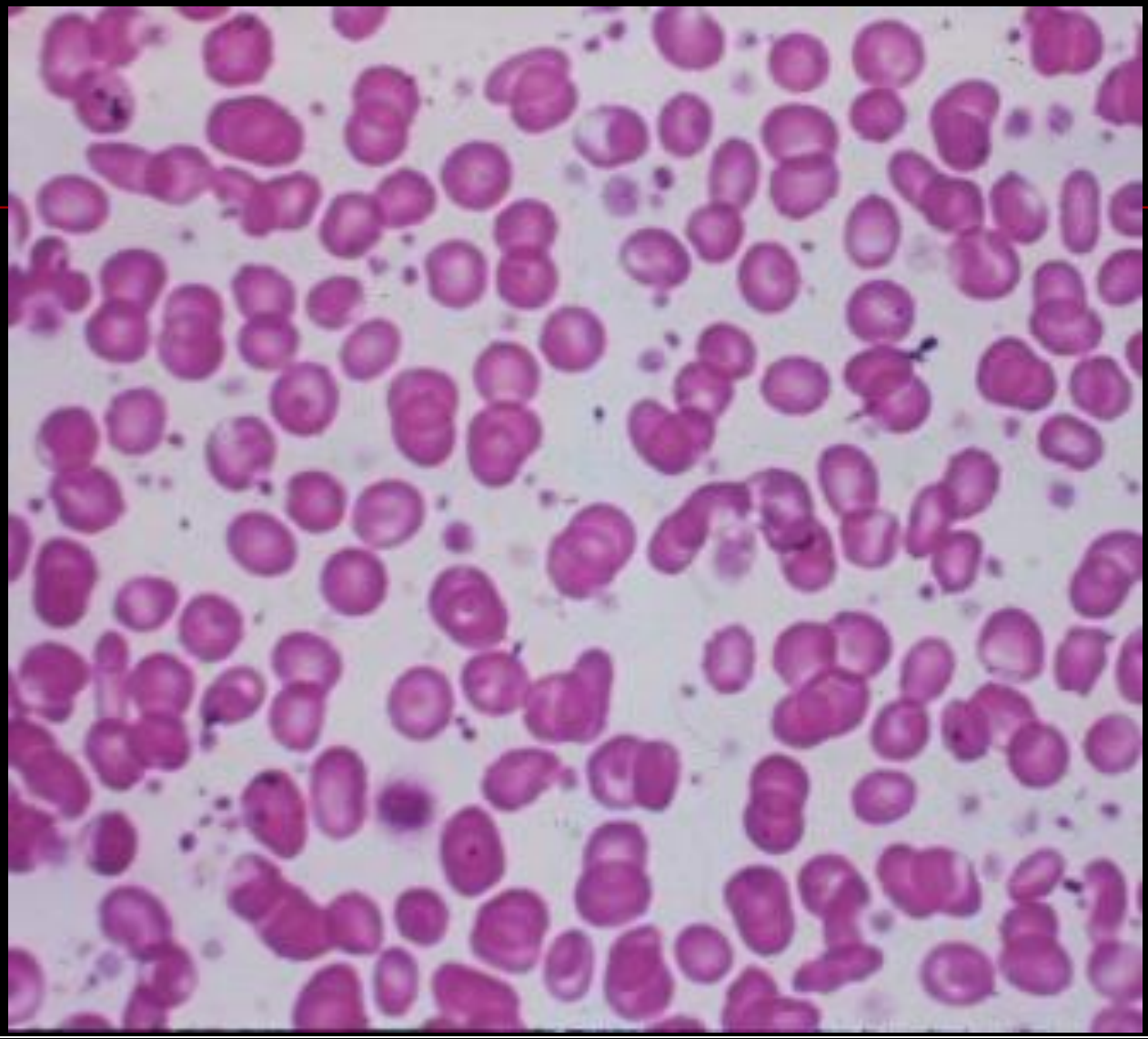
Diagnostic criteria:
4 majors or (3 first minors +2 minors)

Major criteria:

- Platelets >450 x 10^9/L
- BM: proliferation of enlarged, mature megakaryocytes
- Not meeting criteria for: PV, primary myelofibrosis, CML, MDS, or other myeloid neoplasms
- JAK2 V617F, CALR, or MPL mutations

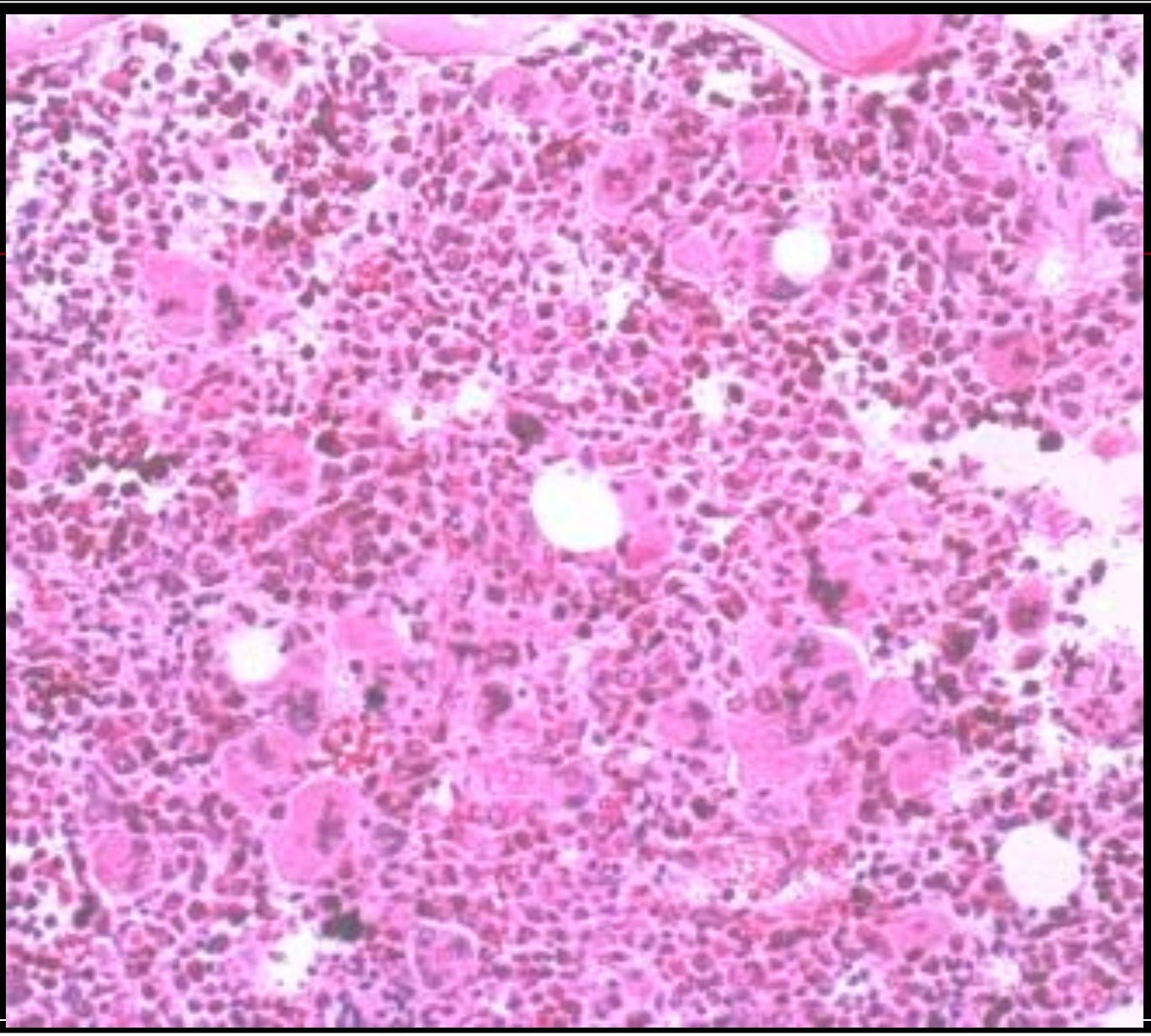
Minor criteria:

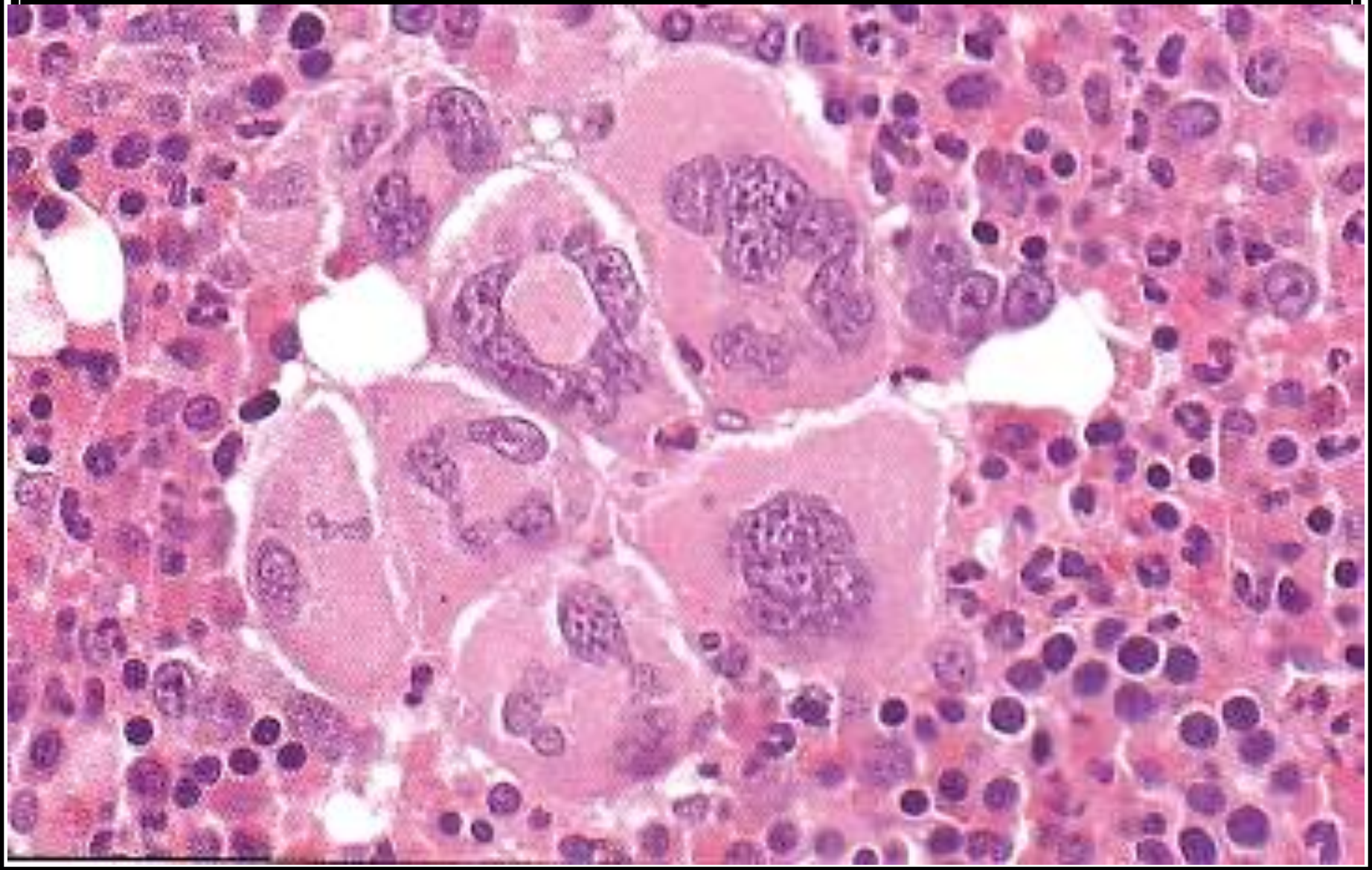
- Presence of a clonal marker (other myeloid mutation)
- Absence of reactive thrombocytosis



Morphology Bone Marrow

- Normocellular or mildly hypercellular
- Giant megakaryocytes, clustered or scattered, with abundant mature cytoplasm, hyperlobulated nuclei
- Reticulin not increased





Genetics

- Only 5-10% with abnormal karyotype
- del (13q22), +8, +9

Prognosis and Predictive Factors

- 10-15 year survival common
- Splenectomy worsens survival (sequestration reservoir is eliminated and Plts increase)
- Transformation to MDS and AML in <5% and usually therapy-related
- Fibrosis may increase (DDX: Primary myelofibrosis)

Primary Myelofibrosis

PM

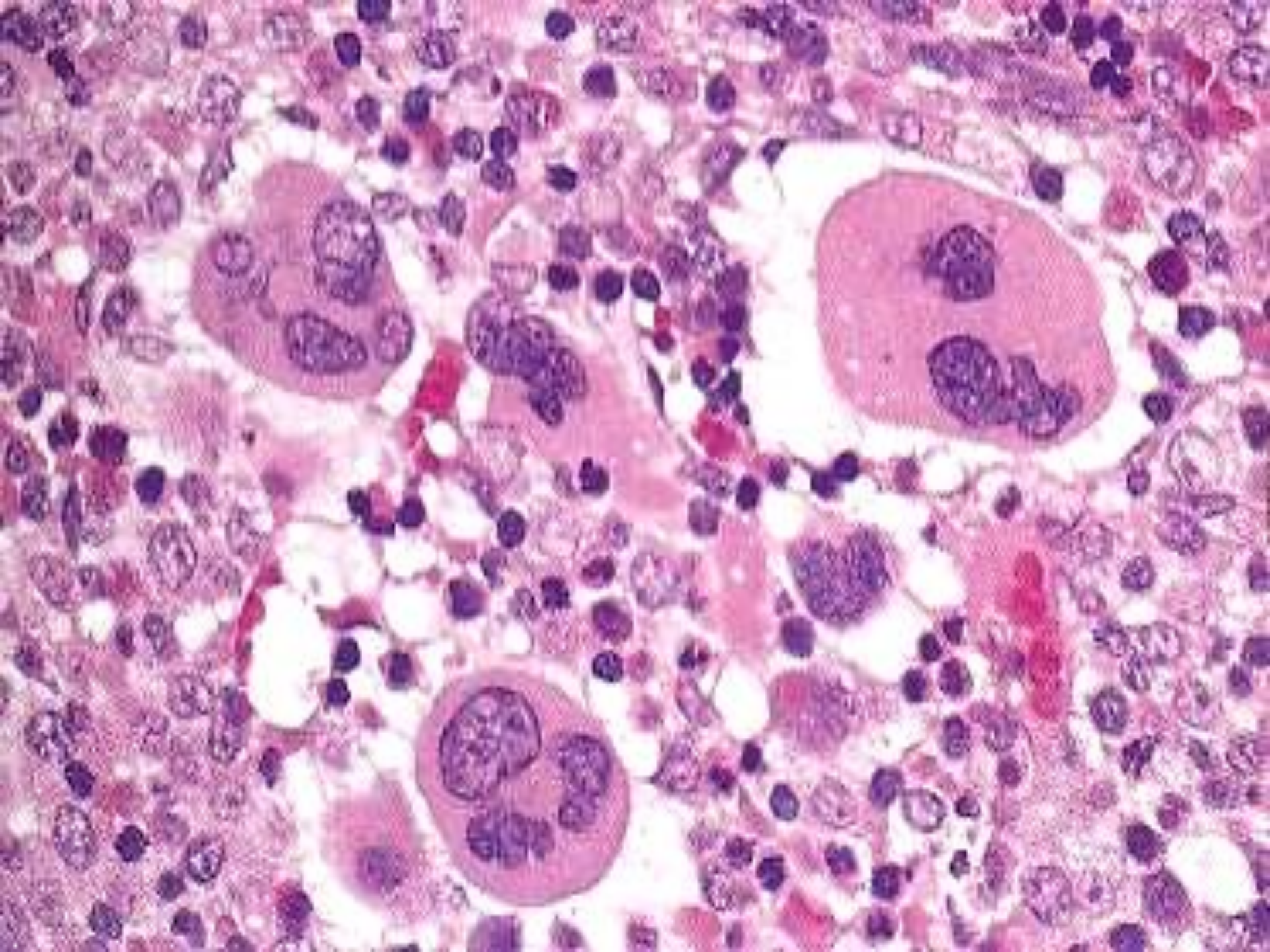
- Megakaryocytic proliferation with atypia, with bone marrow fibrosis (reticulin and/or collagen)
- Not meeting criteria for P. vera, CML, MDS, or other myeloid neoplasms
- JAK2 V617F, MPL, or CALR mutations; in the absence of these mutations-> presence of a clonal marker (other myeloid mutation), no evidence of myelofibrosis due to other etiologies

PM

- Initial prefibrotic stage - hypercellular bone marrow
- Fibrotic stage with leukoerythroblastic peripheral blood
- Hepatosplenomegaly with extramedullary hematopoiesis

Prefibrotic (Cellular) Stage

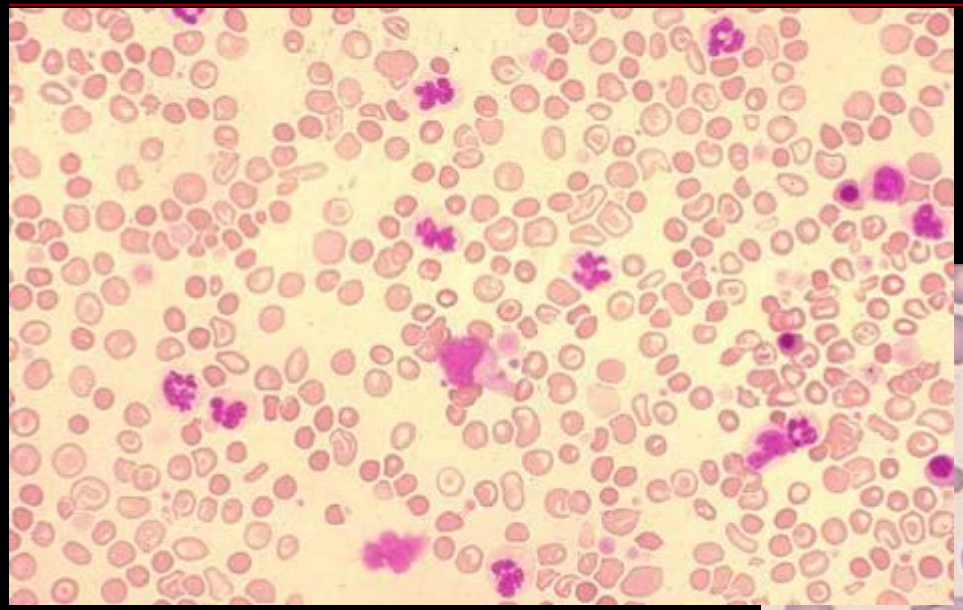
- Megakaryocytes large and dysplastic: “Cloud-like” or “balloon-like” lobulation of megakaryocytic nuclei
- Reticulin minimal or variable
- Blasts not increased



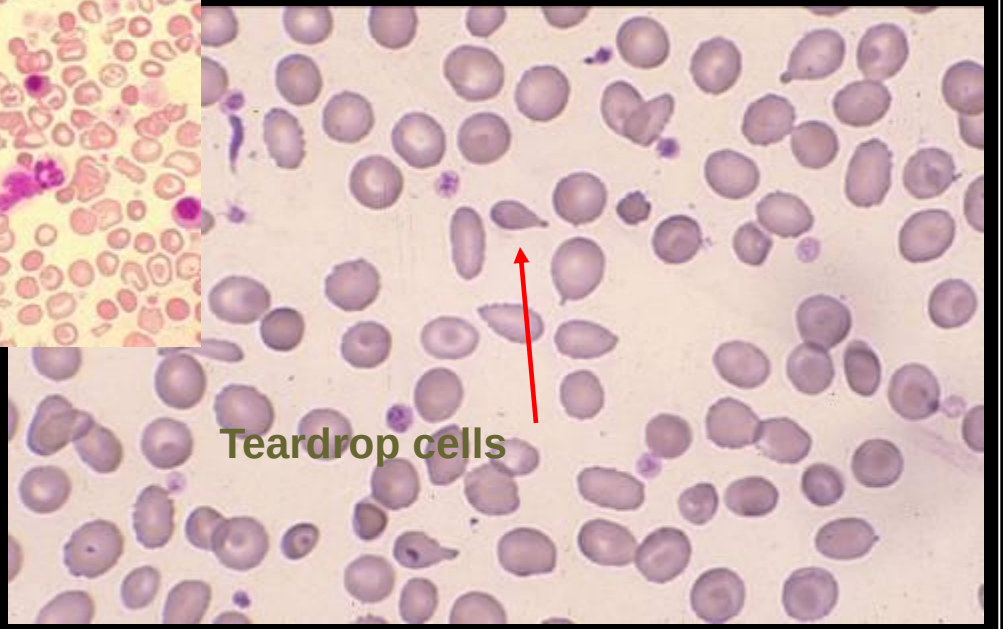
Fibrotic Stage

- Most diagnosed in this stage (70-80%)
- Splenomegaly and hepatomegaly
- Extramedullary hematopoiesis
- Leukoerythroblastic peripheral blood smear with ‘tear-drop” RBCs and nucleated RBCs; later leukopenia
- Bone marrow fibrosis (reticulin increased)
- Dilatated marrow sinuses with intrasinusoidal hematopoiesis

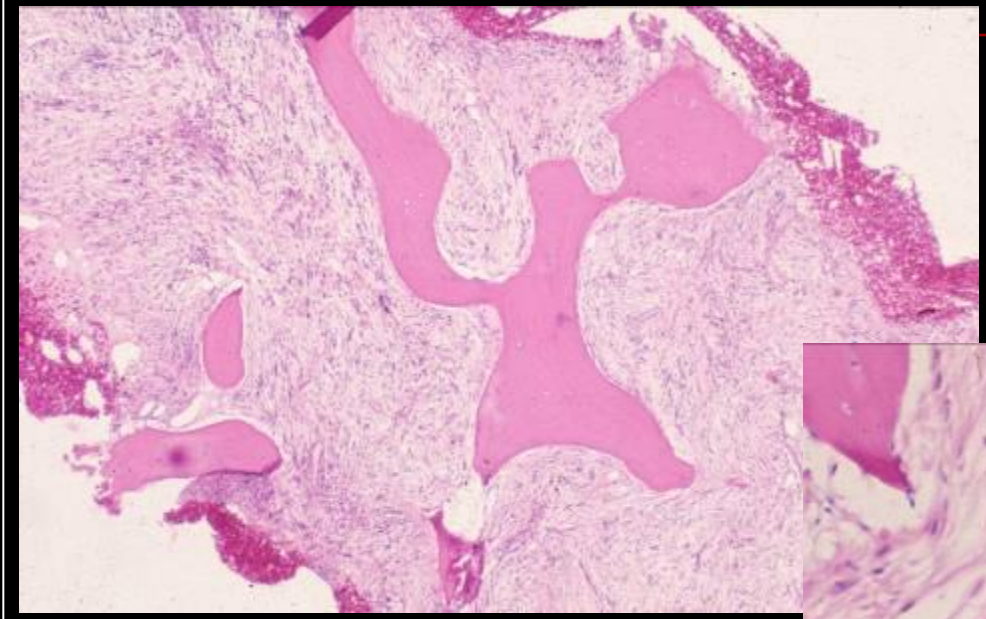
Primary Myelofibrosis



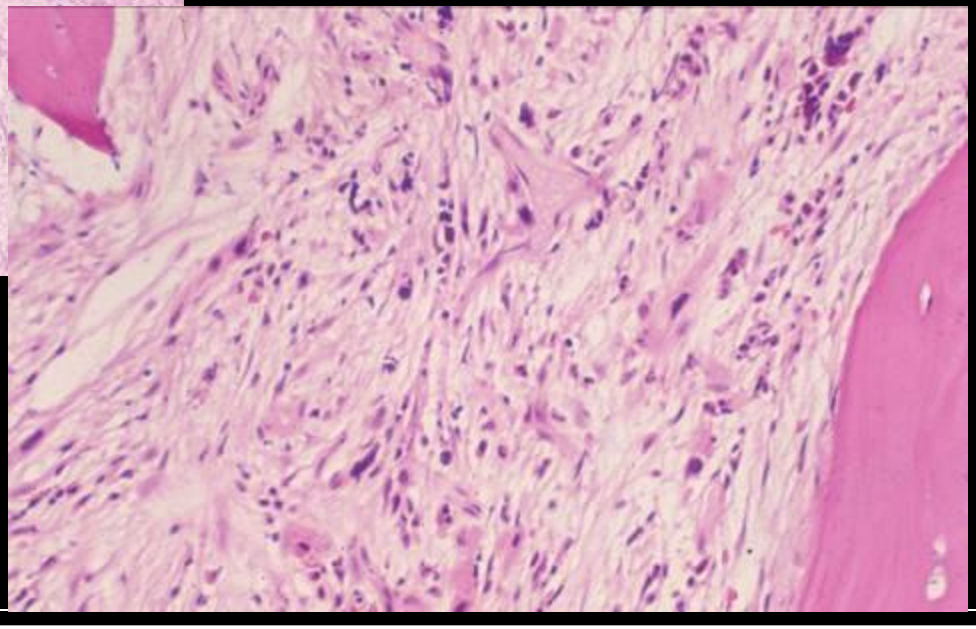
Peripheral blood smear

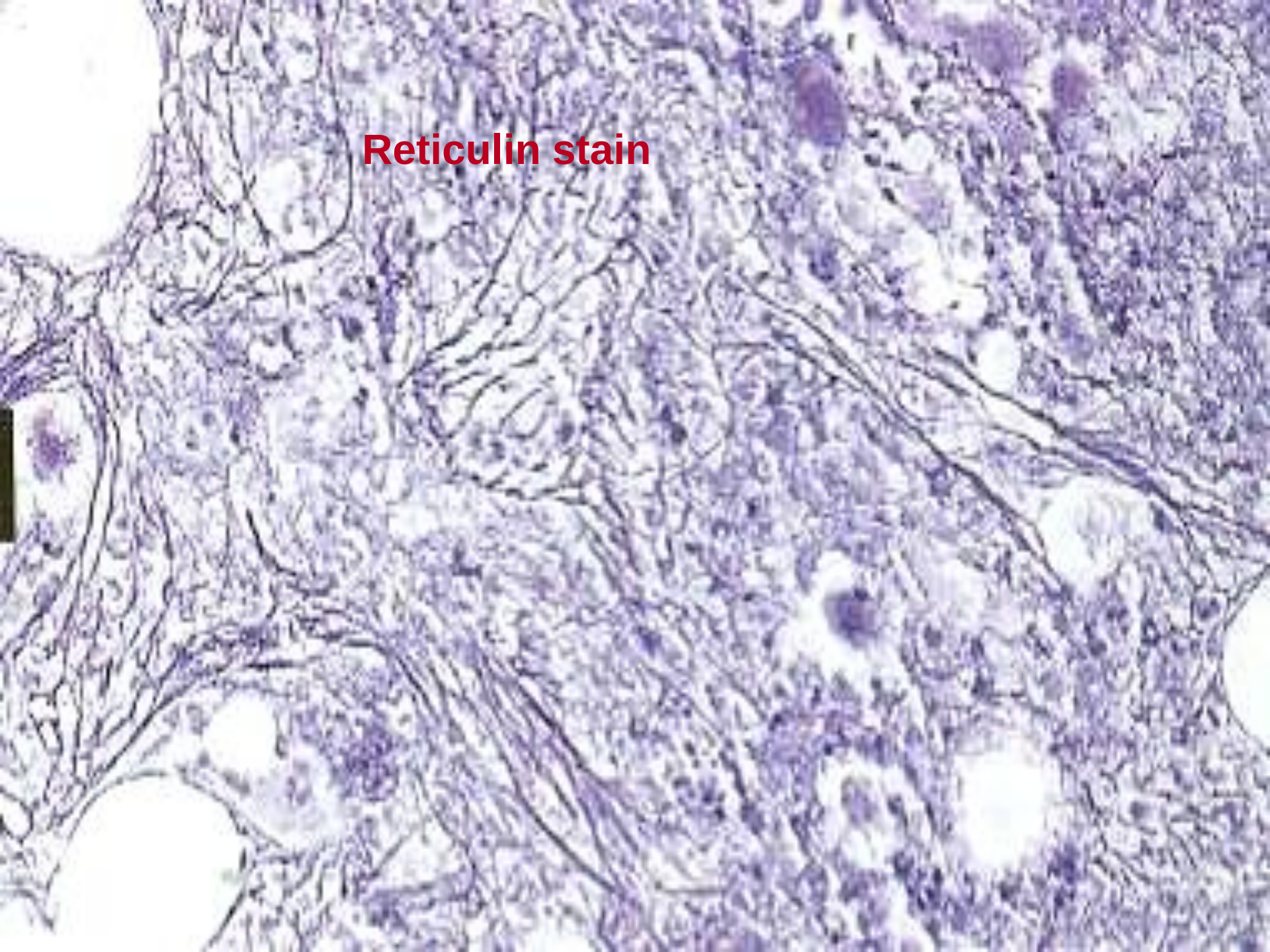


PM



Bone marrow biopsy




Reticulin stain

Genetics

- Cytogenetic abnormalities in 60%
- None specific for PM
- No Philadelphia chromosome or BCR/ABL fusion gene
- 13q, del(20q), partial trisomy 1q most common

Prognosis

- Survival range: months to decades
- Median survival: 3 to 5 years from Dx
- Adverse factors: >70 years, Hb <10g/dL, platelets <100 x 10^6/L, granulocytic immaturity, abnormal karyotypes
- Acute leukemia: 5-30% (some, but not all, may be cytotoxic therapy-related)

Prognosis

- Acute leukemia: 5-30%
- Some, but not all, may be cytotoxic therapy-related

Chronic Myelomonocytic Leukemia (CMML)

CMML: Diagnostic criteria

- Persistent monocytosis (>1 x 10^9/L) in PB
- No Ph or Bcr/Abl
- <20% blasts in PB or BM, 20% may include:
  - Myeloblasts
  - Monoblasts
  - Promonocytes
- May have dysplasia in one or more myeloid lineages (not necessary)

CMML: Diagnostic criteria

- If dysplasia is minimal or absent, CMML can be diagnosed if:
  - Monoclonal cytogenetic abnormality in marrow cells, *or*
  - Monocytosis persistent for at least 3 mo, *and*
  - All other causes of monocytosis are excluded

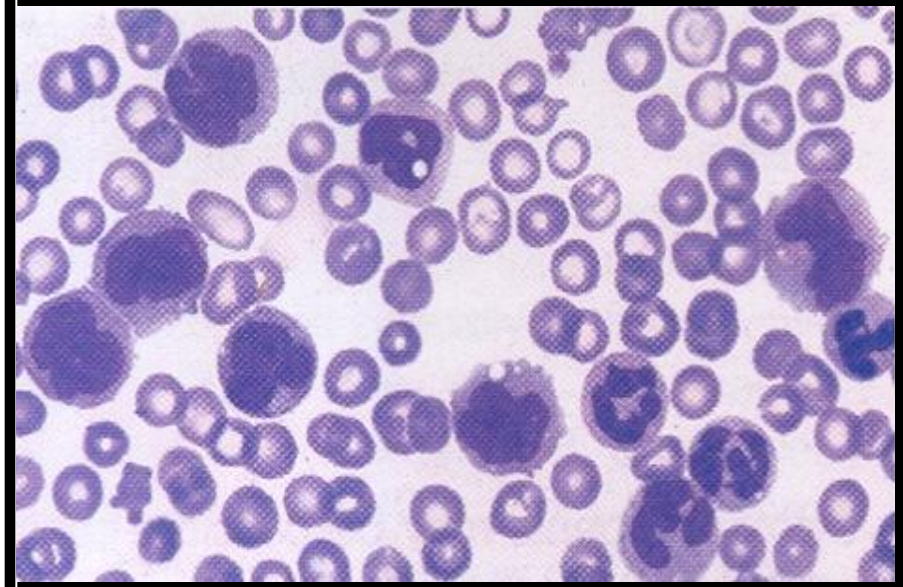
CMML: Subtypes

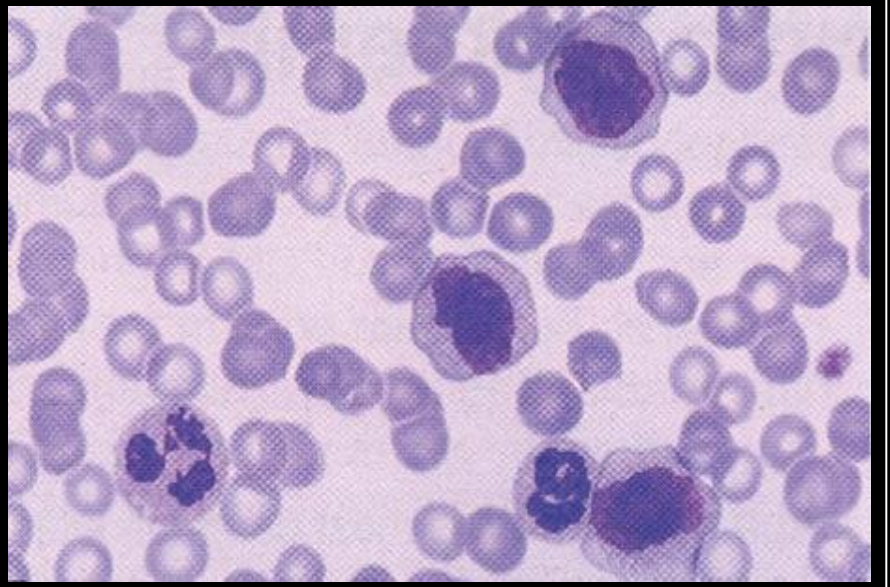
- In about 50%
  - WBC <13k
  - MDS-like picture (dysplastic)
- In about 50%
  - WBC $\geq$ 13k
  - MPN-like picture (proliferative)

CMML: Classification

- CMML-0
  - PB blasts 0-1% of WBC and 0-4% of nucleated BM cells
- CMML-1
  - PB blasts 2-4% of WBC and 5-9% of nucleated BM cells, no Auer rods
- CMML-2
  - PB blasts 5-19% or BM blasts 10-19% or with Auer rods
  - May be at risk of rapid transformation to acute leukemia and poor prognosis

CMML





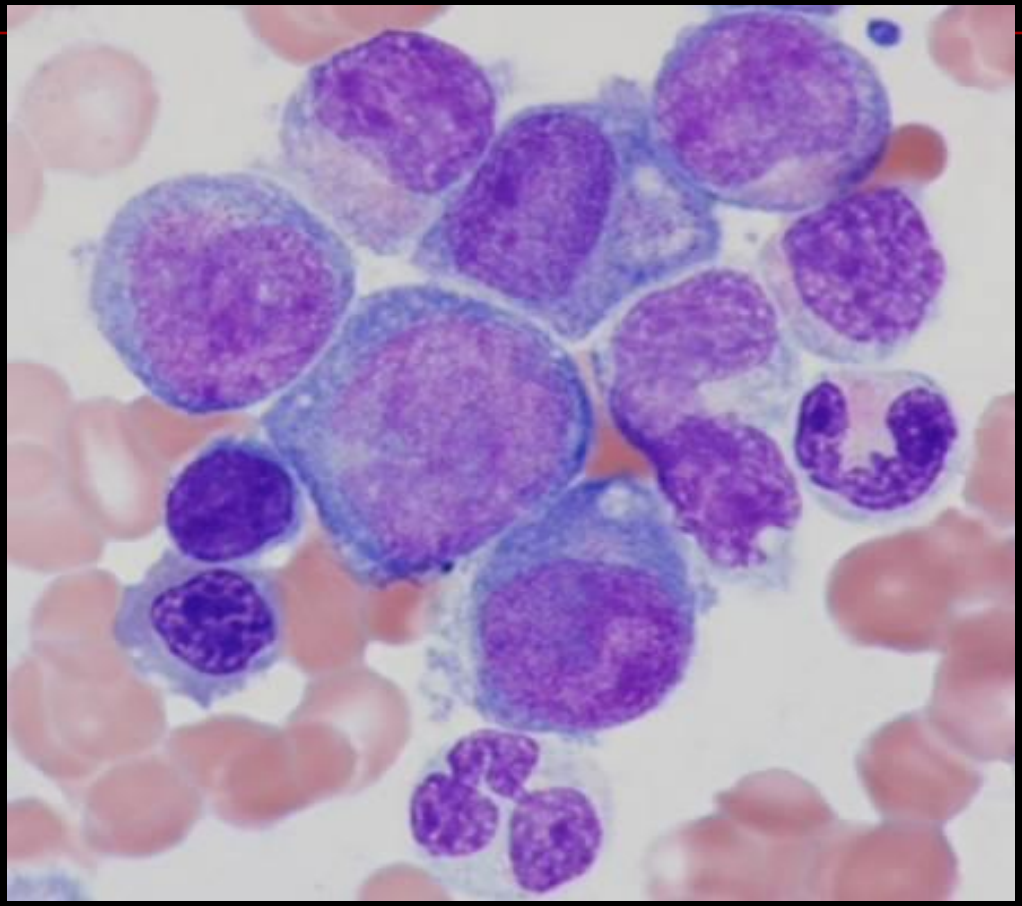
- 50% of cases:↑ WBC with minimal dysgranulopoeisis
- 50% of cases: Normal WBC with absolute monocytosis, neutropenia and dysgranulopoiesis.

- Degree of leukocytosis, neutrophilia and dysplasia is variable.

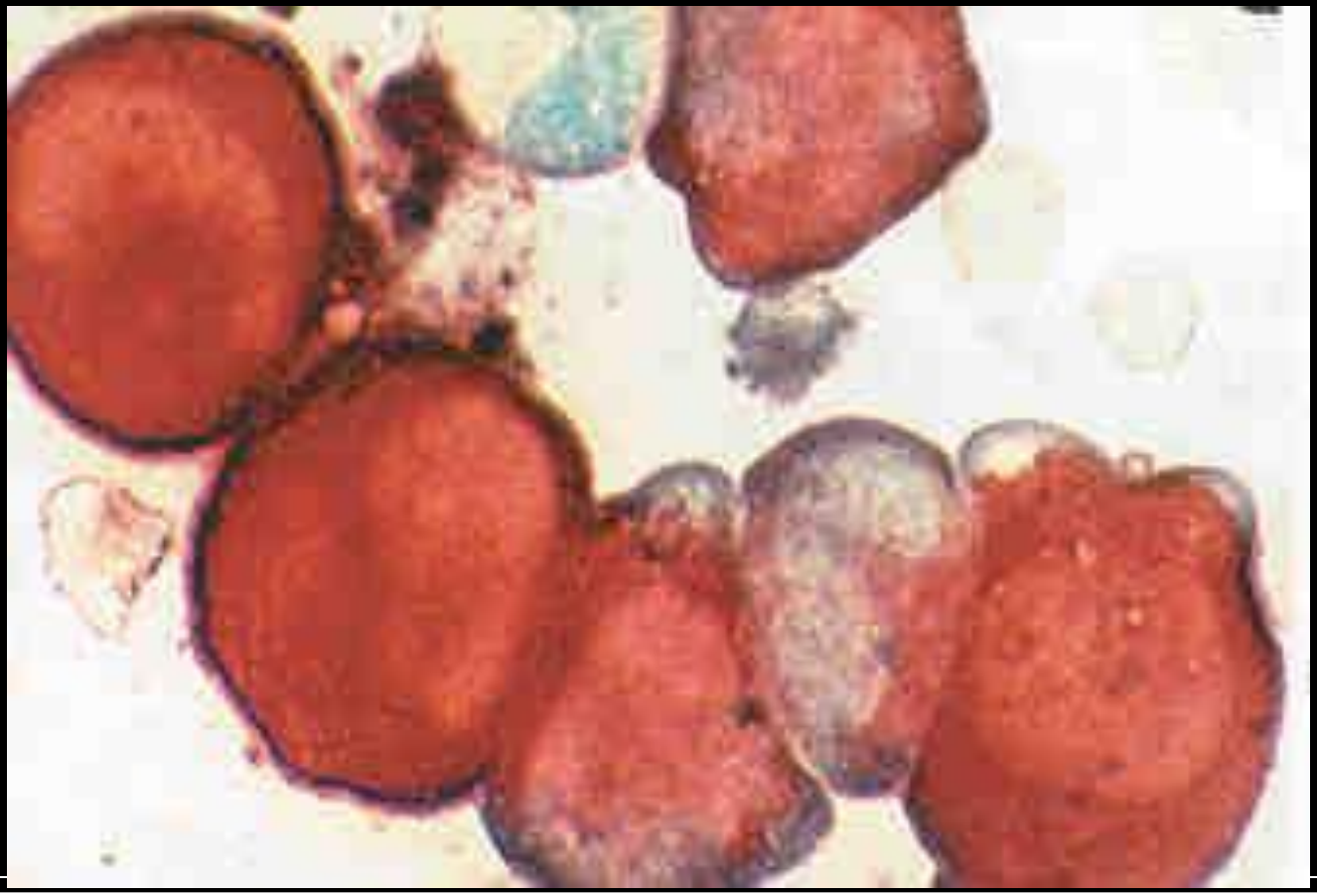
CMML: BM Morphology

- Hypercellular in >75% of cases
- Granulocytic proliferation
- Monocytic proliferation: positive for these non-specific esterases (NSE)
  - Alpha naphthyl acetate esterase
  - Alpha naphthyl butyrate esterase

CMML: BM Morphology



Butyrate



CMML: Immunophenotype

- CD33/13 (+), variable CD14/64/68
- Increased percentage of CD34(+) cells may be associated with early transformation to acute leukemia
- Plasmacytoid dendritic cells present
  - Characteristic phenotype: CD123/4/56/14/43/68
  - CD2/5 often present

CMML: Genetics

- Nonspecific cytogenetic abnormalities in 20-40%
  - +8
  - -7/del (7q)
  - Structural abnormalities of 12p
  - Abnormalities of 11q23 uncommon -> suggest acute leukemia
- i(17q)
  - More aggressive course
- RAS point mutations (40%)

CMML: prognosis/predictive factors

- Prognosis
  - Median survival 20-40 months
  - 15-30% progress to acute leukemia
- Predictive factors
  - PB and BM blast percentage (most important factor)
  - Splenomegaly
  - Severity of anemia
  - Degree of leukocytosis

Myelodysplastic Syndromes

Introduction

General:

-Stem cell disorder

-Dysplasia

-Ineffective hematopoiesis

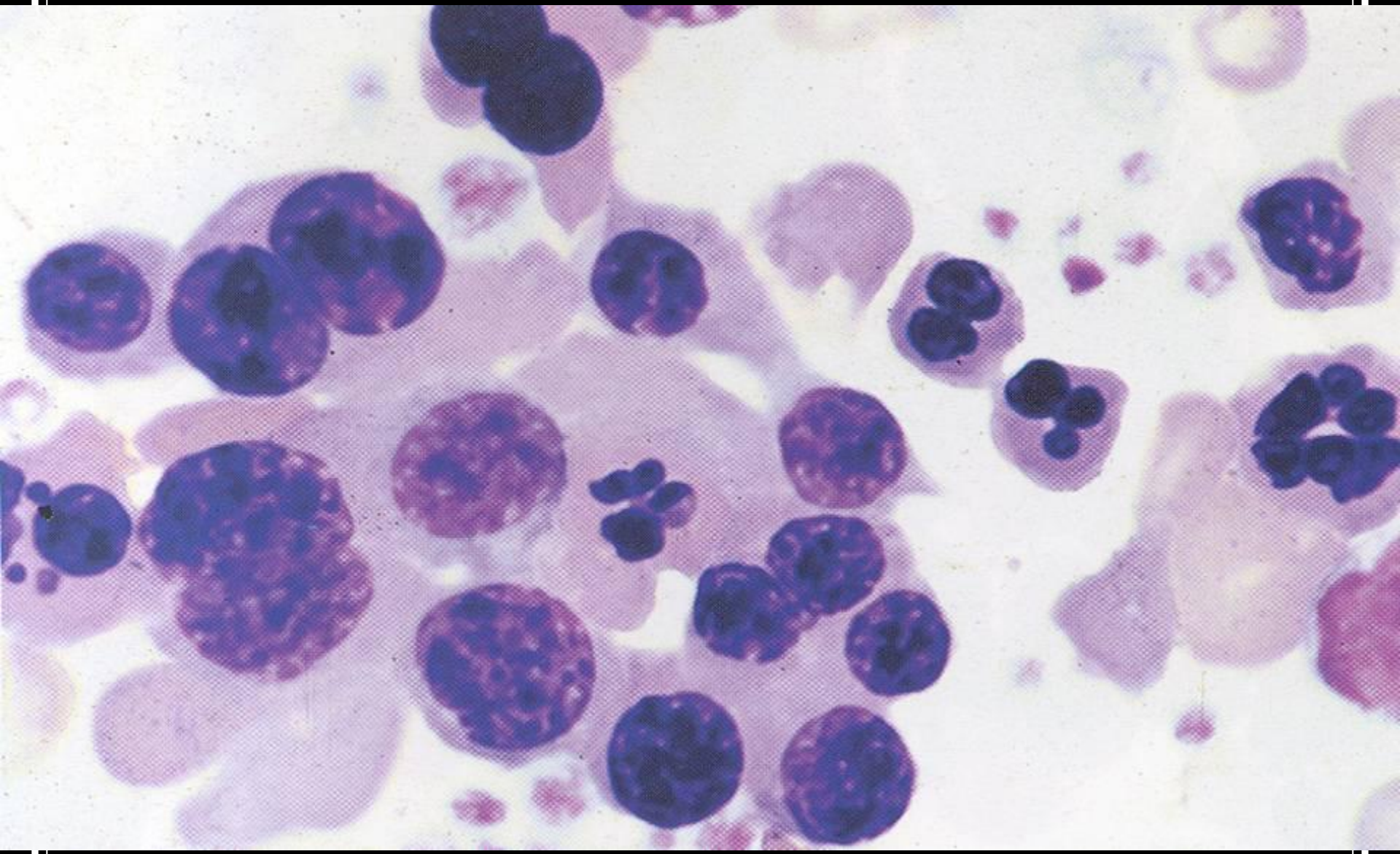
-Blasts <20% in blood and BM

- Median age: 70 y/o

- Incidence: 3-5/100,000

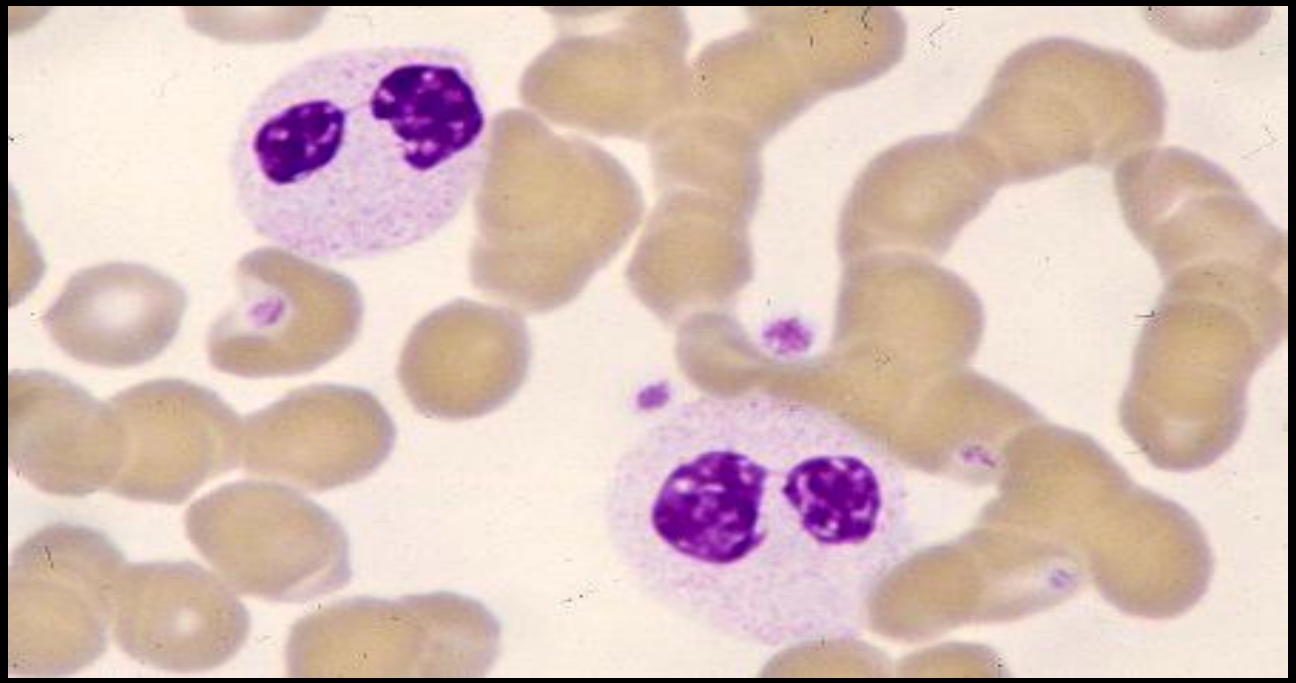
Morphology

- Dyserythropoiesis
- Dysgranulopoiesis
- Megakaryocyte dysplasia
- BM: hypercellular (sometines normal, or hypocellular)
- BM bx may have abnormal localization of immature precursors (ALIP): 5-8 immature cell cluster, 3 or more ALIPs per section-> (+); recheck smear and BM, note in report.

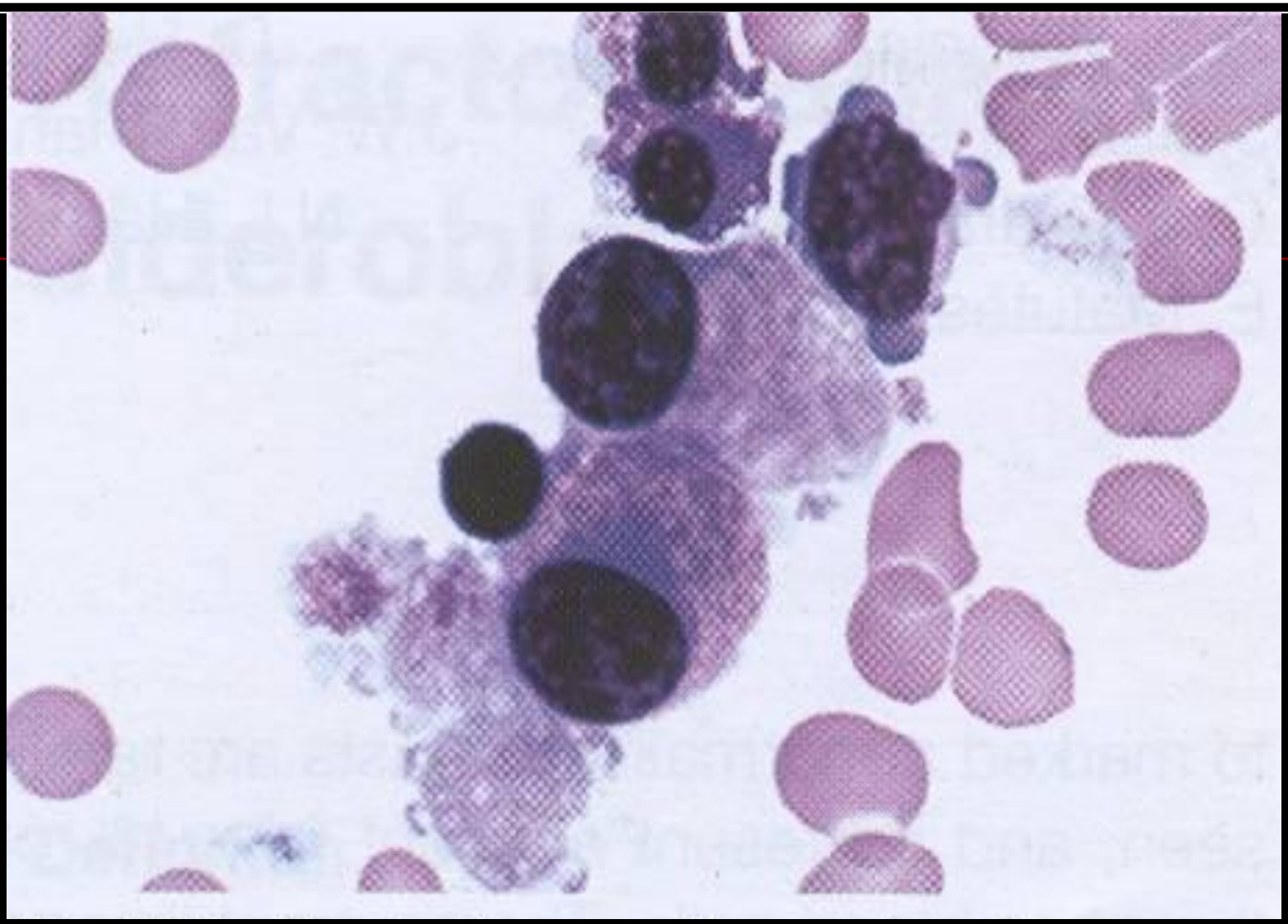


Dyserythropoiesis, Bone marrow aspirate

Dysgranulopoiesis



Circulating pseudo-Pelger-Huet neutrophils, with hypogranular cytoplasm, bilobed 'spectacle' nuclei, Blood smear



Dysplastic megakaryocytes, Bone marrow aspirate

International Prognostic Scoring System for MDS
(International MDS Working Group)

- **Blast count**
- **Karyotype**:
  good: normal, -Y,-5q, -20q
  poor:>=3 chromosal abnormalities, chromosome 7
  intermediate: others
- **Cytopenias**: Hb<10 g/dL; N<1,800 /mL; Plt <100k /mL
- **Scores** (high means worse prognosis):
  - Low: 0
  - Int-1: 0.5-1
  - Int-2: 1.5-2
  - High: >=2.5

Recurrent Chromosomal Abnormalities in MDS

Unbalanced

- -7 or del(7q)
- -5 or del(5q)
- i(17q) or t(17p)
- -13 or del(13q)
- del(11q)
- del(12p) or t(12p)
- del(9q)
- idic(X)(q13)

Balanced

- t(11;16)
- t(3;21)
- t(1;3)
- t(2;11)
- inv(3)
- t(6;9)

Chromosomal Abnormalities Not Considered as Definitive in MDS

- +8
- del(20q)
- -Y

Mutations in MDS

- Mutations in 80% to 90% of MDS patients; the most common are SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2.
- These clonal mutations are also seen in apparently healthy older individuals without MDS, so-called “clonal hematopoiesis of indeterminate potential” (CHIP). Thus, these somatic mutations alone are not considered diagnostic of MDS even in a patient with unexplained cytopenia.

MDS-singlelineage dysplasia (MDS-SLD)

- Definition: unequivocal dyplasia in 1 lineage (at least 10% of cells in this lineage)
- Exclude: drug, toxin, viral, immunologic, congenital disorders, Vitamin (B12, folate) deficiency
- Blasts:
  - Blood<1%
  - BM<5%

MDS-SLD

- Genetics: up to 50% (-20q, +8, abnormality 5, 7)
- Median survival: 66 months, 10% transformed to AML in 5 yrs

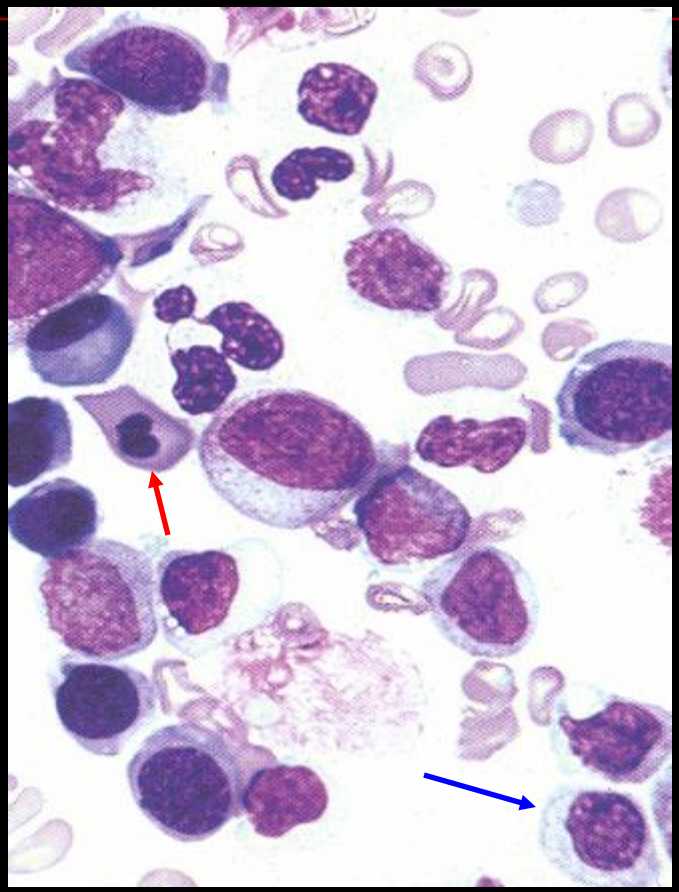
MDS-multilineage dysplasia (MDS-MLD)

- Morphology
  - Dysplastic changes in ≥10% of the cells in ≥2 myeloid cell lines
  - Neutrophils may show
    - Hypogranulation and/or hyposegmentation
  - Erythroids may show
    - Cytoplasmic vacuoles
    - Marked nuclear irregularity
  - Blasts <5%

MDS-MLD

- Genetics: up to 50% (-20q, +8, abnormality 5, 7, complex karyotypes)
- Median survival: 36 months, 15% transformed to AML in 2 yrs

MDS-MLD: Bone marrow aspirate



Multilineage dysplasia:
Erythroid dysplasia
Neutrophils with hypolobulated nuclei

MDS with ring sideroblasts (MDS-RS)

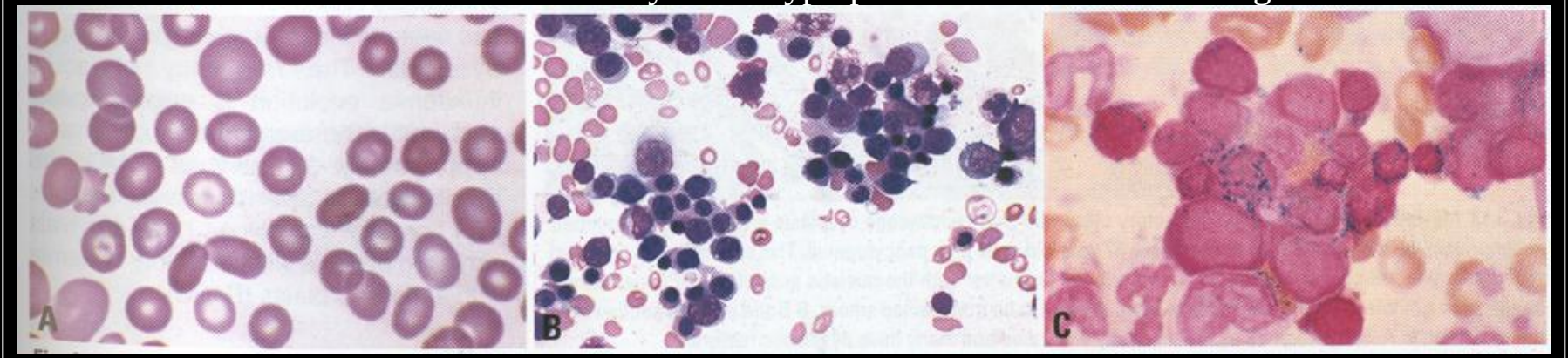
- **Definition:**
- MDS plus presence of ring-sideroblasts (RS) in >15% of erythroid precursors
- RS:
  - >=5 siderotic granules;
  - >=1/3 of nuclear circumference
- Blasts in BM <5%
- Include MDS-RS-SLD and MDS-RS-MLD
- Rule out: antituberculosis (Isoniazid), alcoholism, congenital disorder (sideroblastic anemia), chemical exposure (lead, benzene)

MDS-RS-SLD

PB: Dimorphic RBCs

BM: Erythroid hyperplasia

BM: Ring-sideroblasts



MDS-RS and SF3B1 mutation

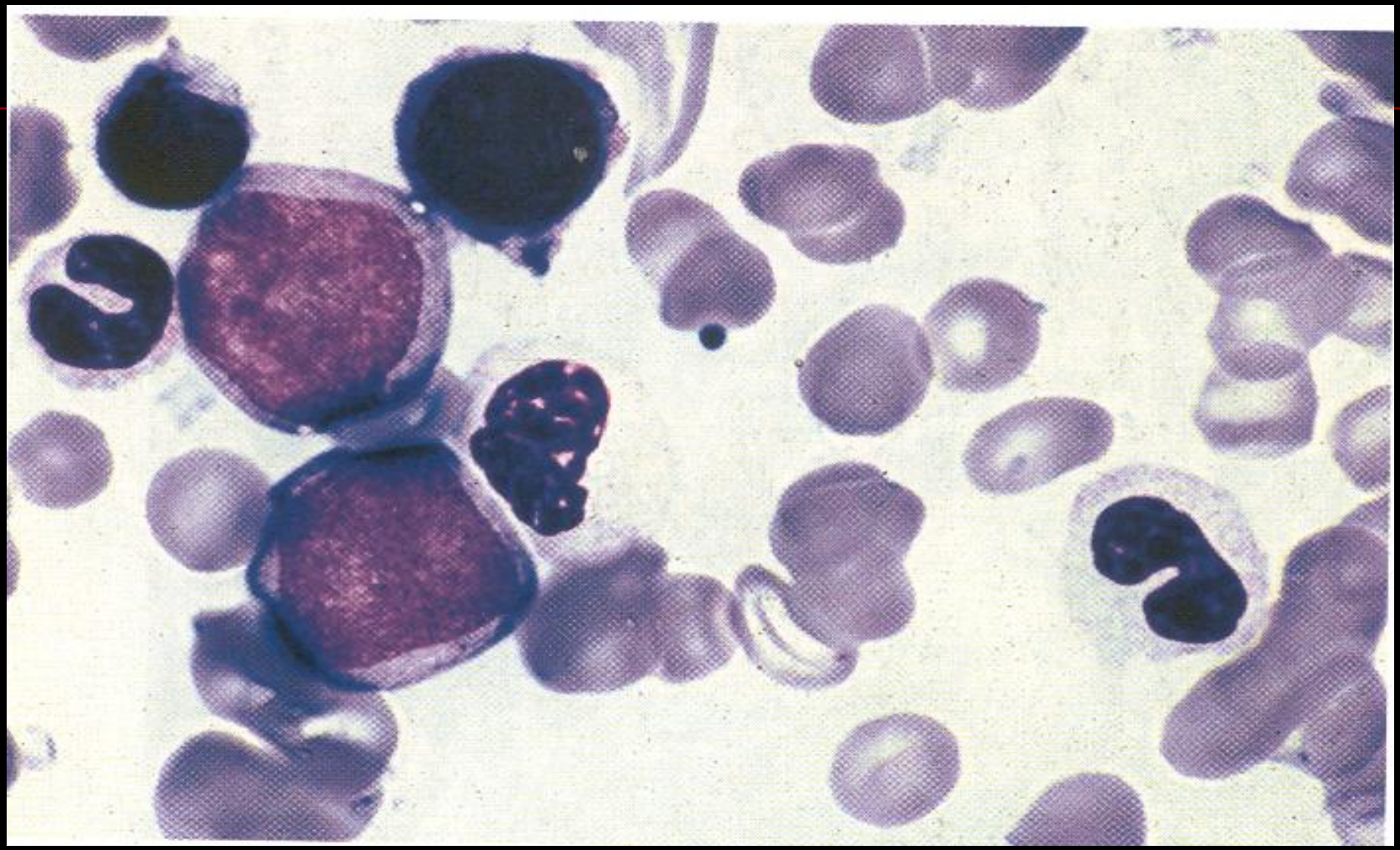
- If an SF3B1 mutation is identified, a diagnosis of MDS-RS may be made if ring sideroblasts comprise 5-14% of nucleated erythroid cells,
- At least 15% ring sideroblasts are still required in cases lacking a demonstrable SF3B1 mutation.
- If ring-sideroblasts are less than 5%, even with SF3B1 mutation the DX is still MDS-SLD or MDS-MLD.

MDS with Excess Blasts (MDS-EB)

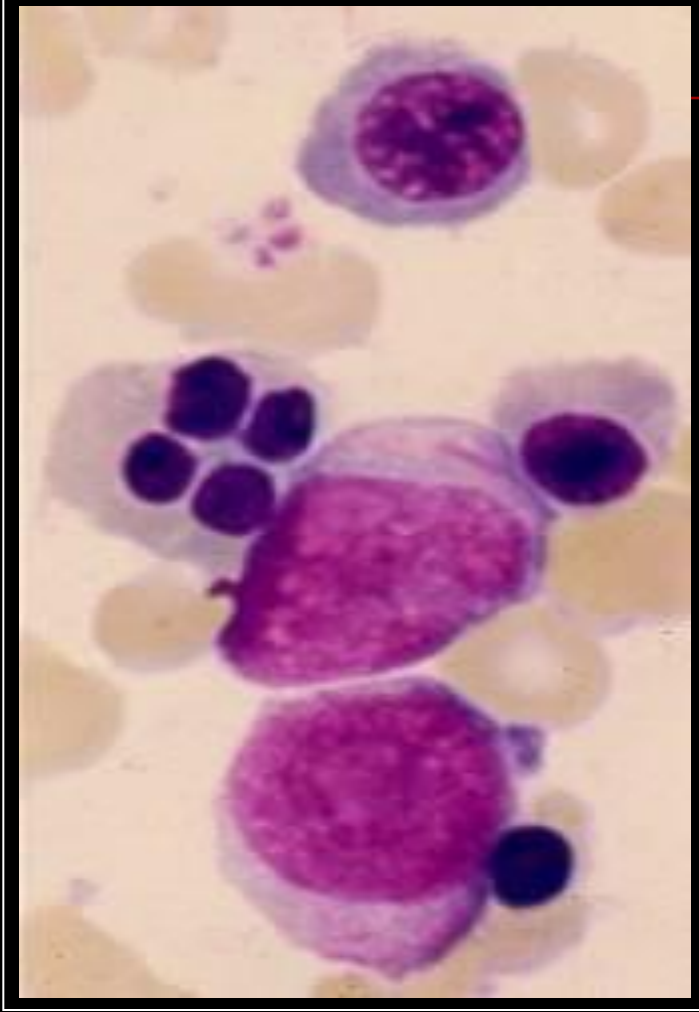
- Subtypes:
  - MDS-EB-1, Blasts: 2-4% (blood) or 5-9% (BM)
  - MDS-EB-2, Blasts: 5-19%(blood) or 10-19% (BM)

***MDS-EB-1 and myeloblasts with Auer rods should be upgraded to MDS-EB-2

MDS-EB-1, bone marrow

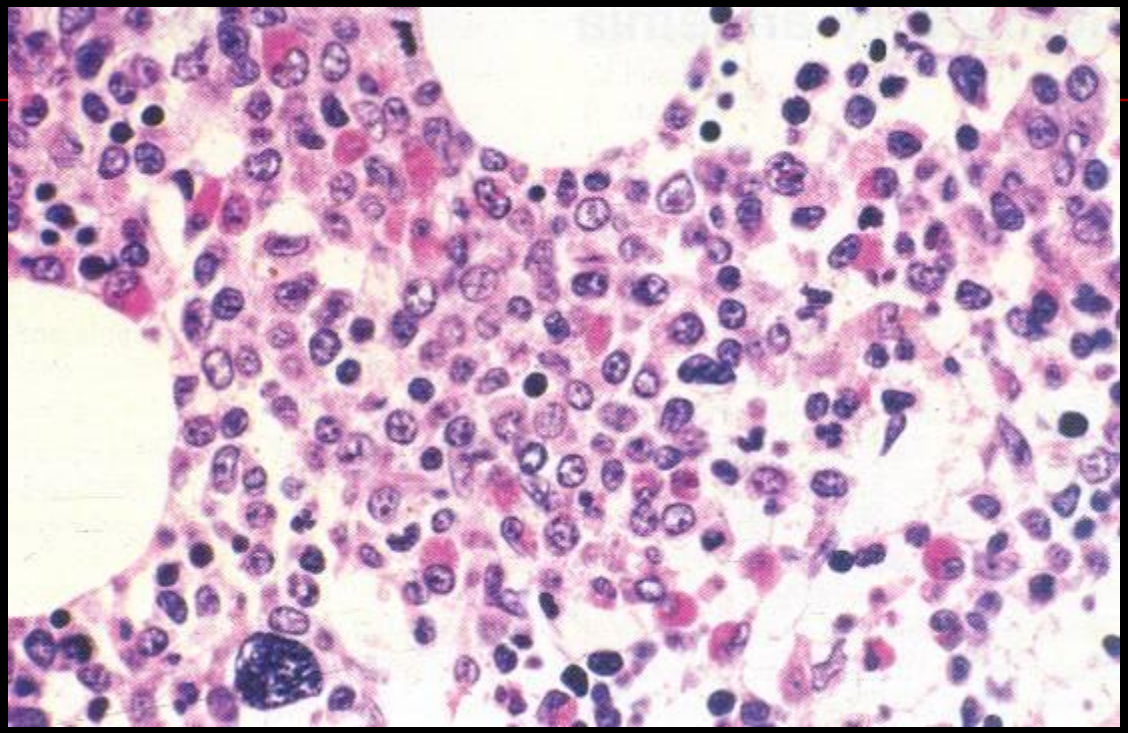


MDS-EB-2



Two myeloblasts,
one with an Auer rod,
and a quadrinucleate normoblast

ALIP



Abnormal localization of immature precursors (ALIP):
Immature myeloid cell clusters (5-8 cells) present in central portion of marrow away from usual locations (paratrabecular or perivascular) three or more clusters/ section

ALIP

- Frequently present in RAEB
- Associated with rapid evolution to AML
- If found in other subtypes, blast count in aspirate may have been inaccurate
  - Re-evaluate
    - Peripheral blood smear
    - Bone marrow aspirate smear

MDS-EB

- Genetics: 30-50%, including +8, -5, del(5q), -7, del(7q), del(20q), or complex karyotypes
- Median survival:
  - MDS-AEB-1: 16 months
  - MDS-EB-2: 9 months

Myelodysplastic syndrome with isolated del (5q)

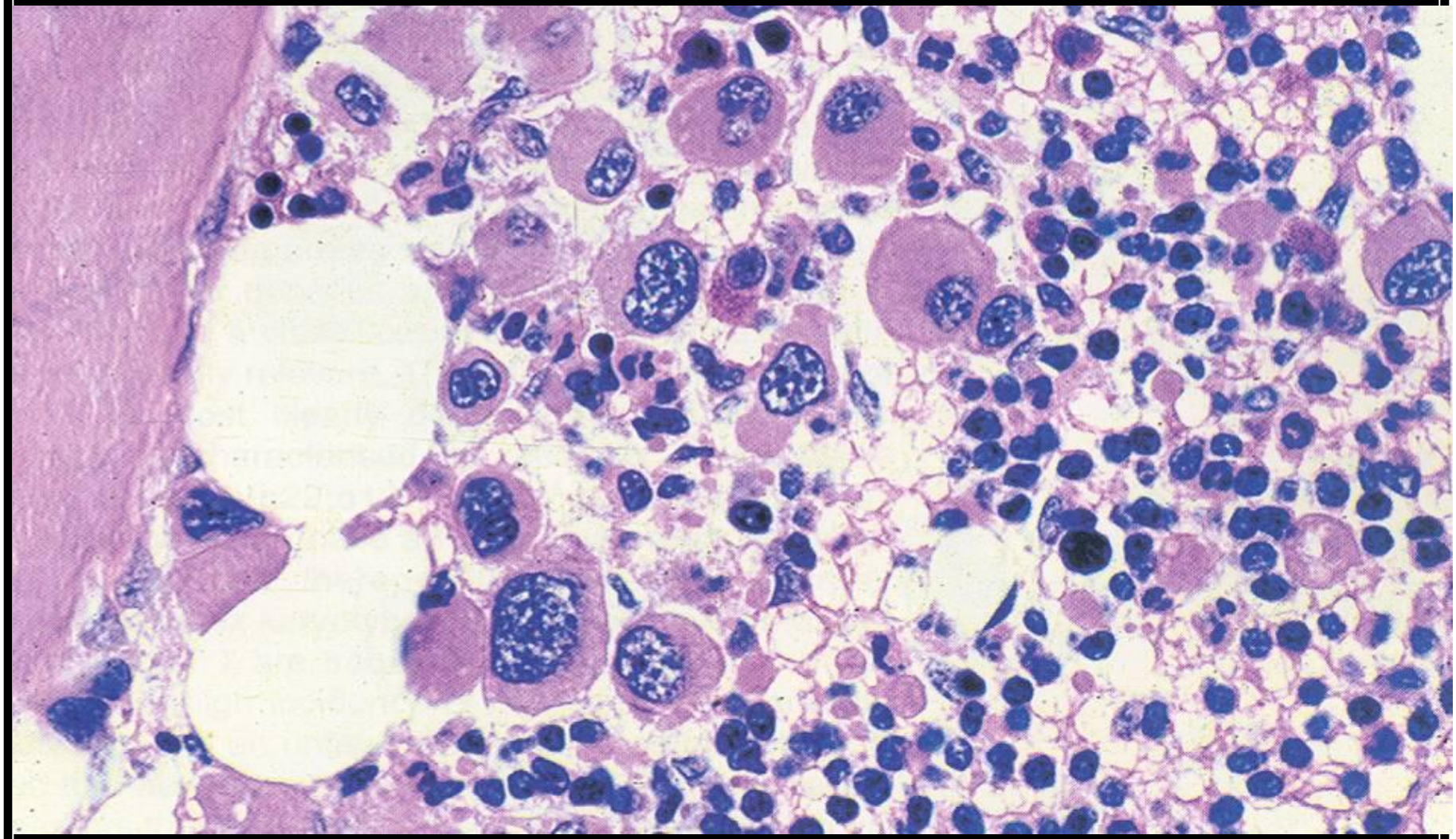
- A myelodysplastic syndrome a/w an isolated del(5q)
- <5% blasts in PB and BM

Myelodysplastic syndrome with isolated del (5q)

- Clinical features
  - Refractory anemia, severe (accounts for most common symptoms)
  - Significant increase in platelet count, occasionally normal

Myelodysplastic syndrome with isolated del (5q)

- BM Morphology
  - Normocellular or hypercellular
  - Megakaryocyte number increase (or normal), many hypolobated
  - Variable degree of erythroid dysplasia
  - <5% blasts
  - Scattered aggregates of small lymphocytes



Numerous megakaryocytes of varying sizes with hypolobulated nuclei, bone marrow biopsy

Myelodysplastic syndrome with isolated del (5q)

- Genetics:
  - Del(5q), between bands q31 and q33
  - Break points and size of deletion are variable
- 1 additional cytogenetic abnormality besides the del(5q) is allowed, unless that abnormality is monosomy 7 or del(7q).
- TP53 mutation identifies an adverse prognostic subgroup in this generally favorable prognosis MDS entity.
- A subset of cases have JAK2, MPL, or SF3B1 mutations.

Myelodysplastic syndrome with isolated del (5q)

- Prognosis and predictive factors
  - Long survival: median 145 months
  - Karyotypic evolution is uncommon (if additional cytogenetic abnormalities are found subsequently -> evolution to AML or higher grade MDS)
  - Significance of isolated del(5q) and >5% blasts is not clear

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

AML: Approach to Diagnosis

- Peripheral blood smear or bone marrow aspirate show leukemic promyelocytes -> acute promyelocytic leukemia (urgent treatment with ATRA)
- ≥ 20% myeloblasts in BM (by flow cytometry) -> AML, NOS pending cytogenetics, FISH, and molecular studies
- Results of cytogenetics, FISH, and molecular studies at a later time -> may modify the AML diagnosis (AML with recurrent chromosmal abnormalities, AML with specific mutations)

AML,

Not Otherwise Specified (NOS)

Acute Myeloblastic Leukemia, Minimally Differentiated (M0)

- 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 (M0)

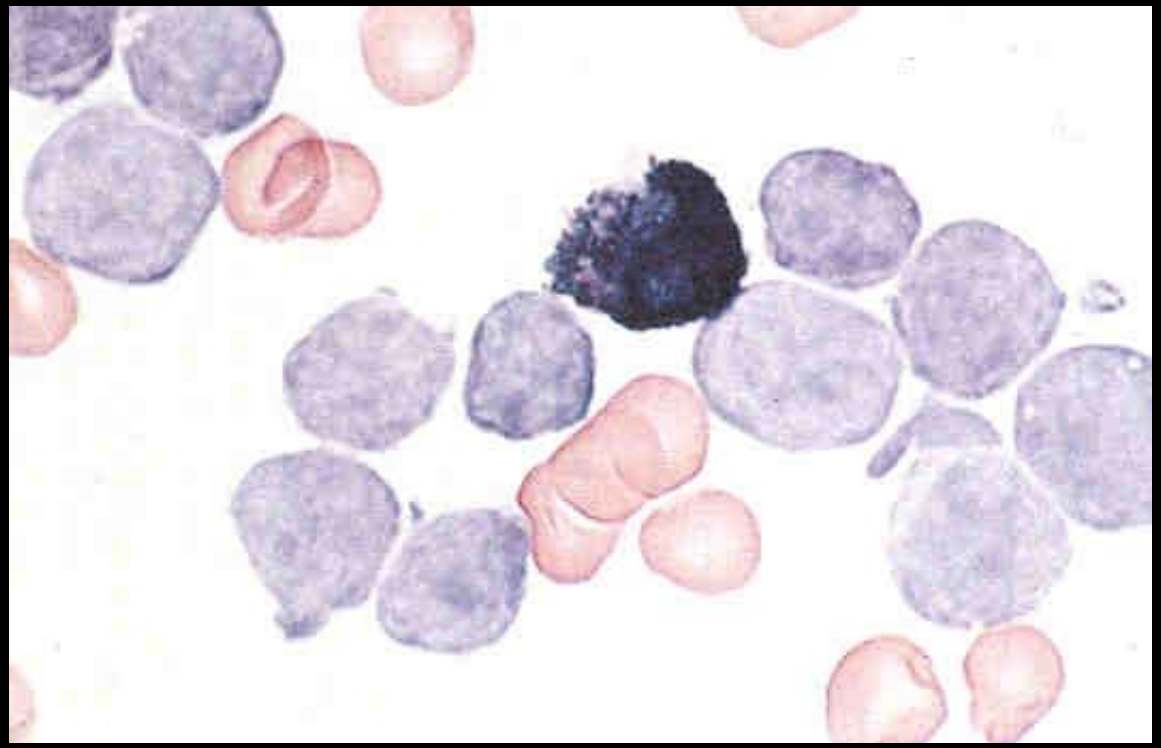
- No evidence of myeloid differentiation by morphology or light microscopy cytochemistry
- Myeloblast nature determined by immunologic markers and ultrastructural studies (ultrastructural cytochemistry)
- Not typically seen with current flow cytometry availability

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)

AML M0



Negative MPO

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

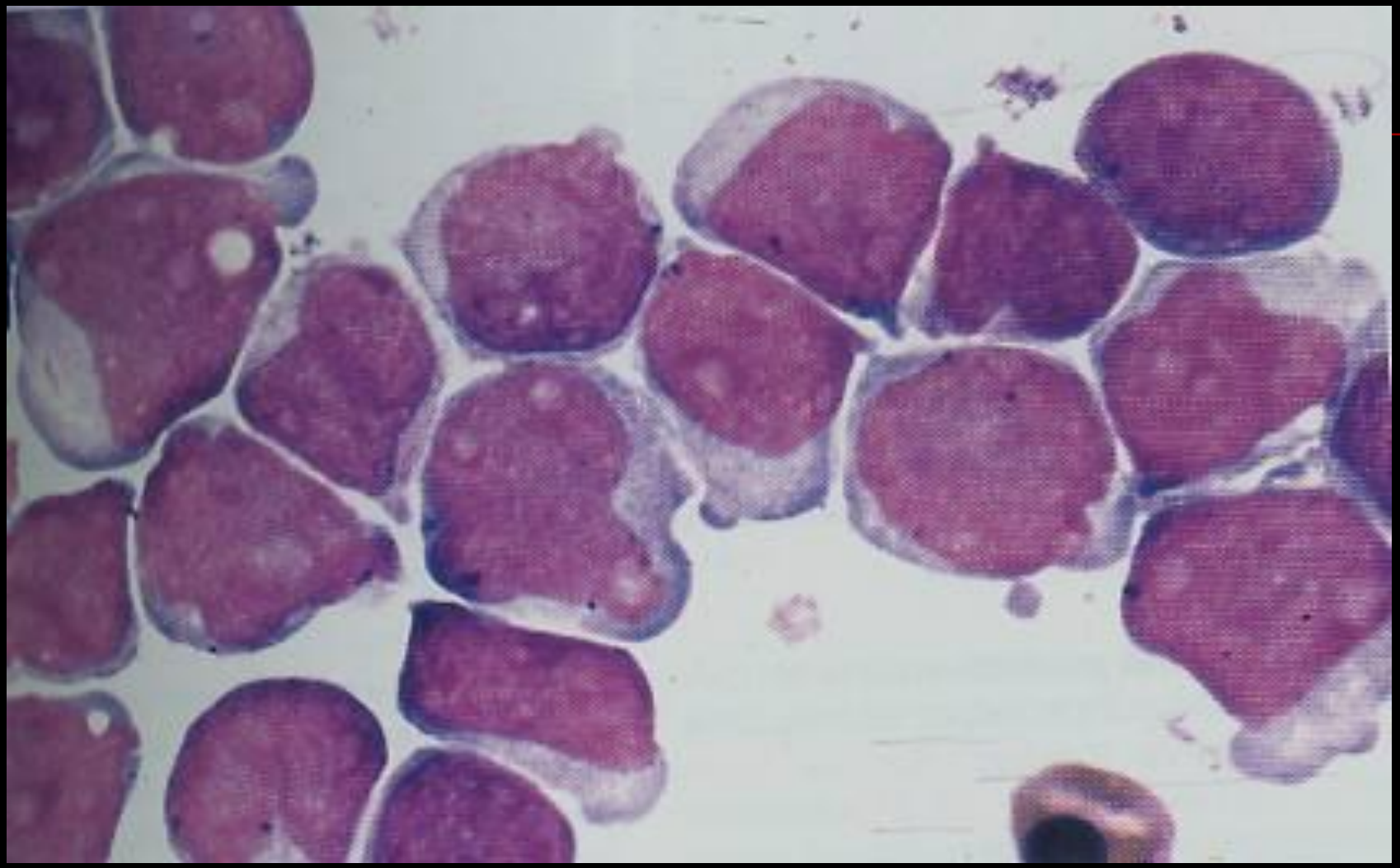
Genetics

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

Acute Myeloblastic Leukemia without Maturation (M1)

- No maturation (<10% granulocytic elements beyond myeloblasts)
- MPO or SBB positivity >3% of blasts
- Auer rods may be present

AML, M1



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

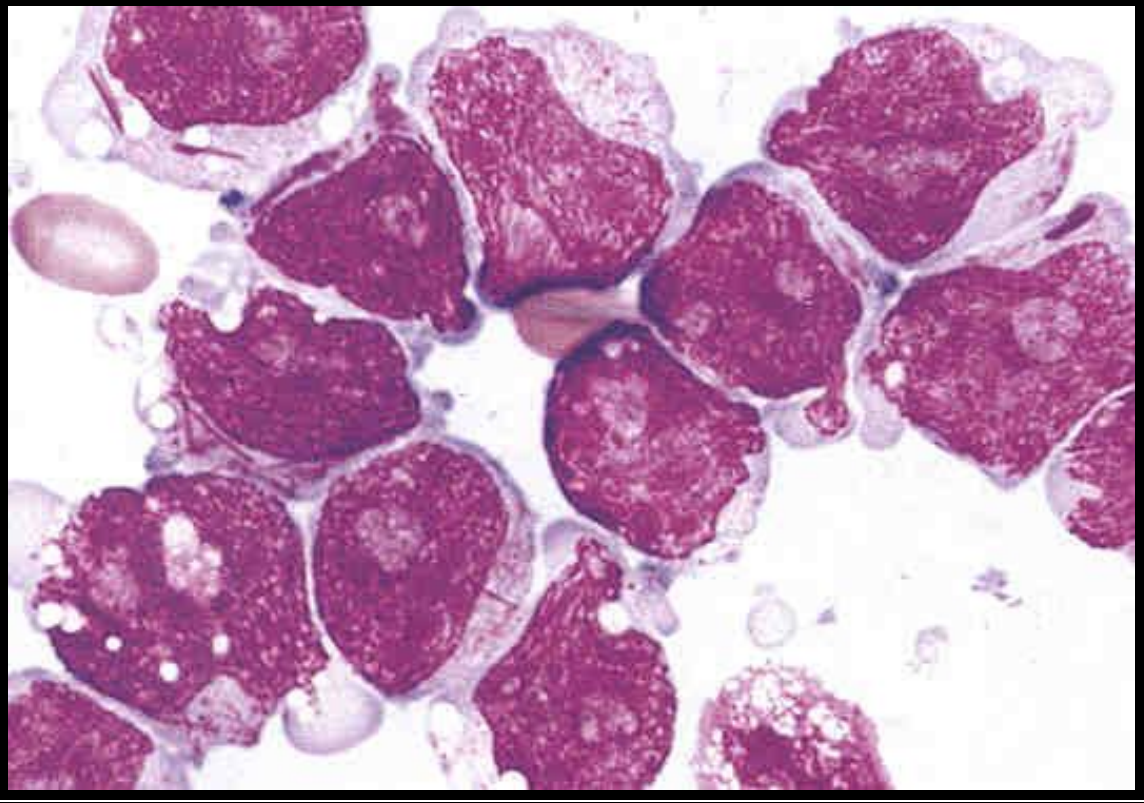
Genetics

- No specific chromosome abnormalities

Acute Myeloblastic Leukemia with Maturation (M2)

- Granulocytic elements (beyond myeloblasts) at least 10% of bone marrow cells
- Monocytic elements <20% of bone marrow cells

M2 morphology



Acute Myeloblastic Leukemia with Maturation

Immunophenotype

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

Acute Myeloblastic Leukemia with Maturation

Genetics

- No specific findings
- t(8;16)(p11;p13) associated with erythrophagocytosis [may be also in M5]

Acute myelomonocytic leukemia, AMML (M4)

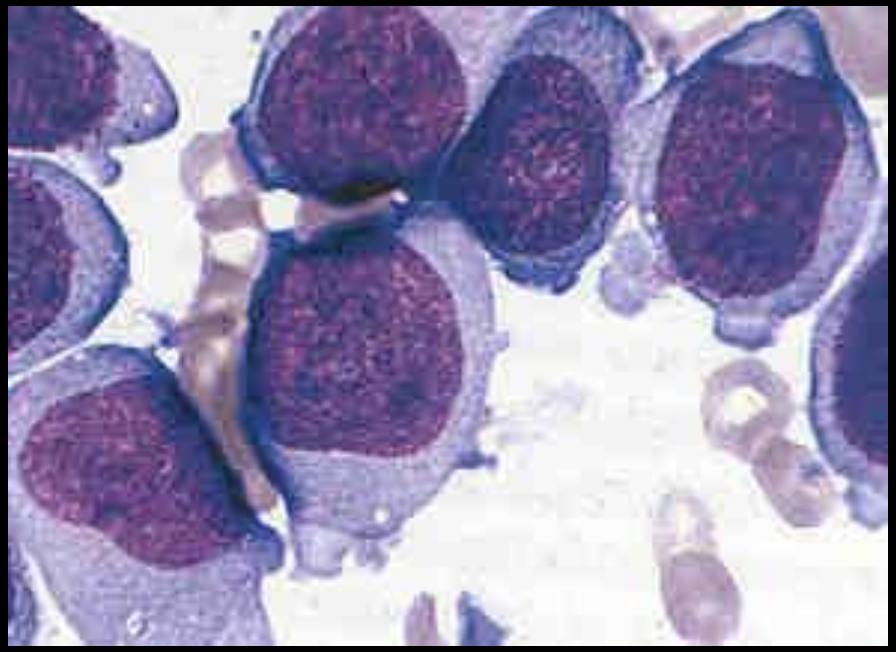
- Blasts at least 20% (incl promonocytes)
- Monocytic elements 20%-80% of non-erythroid cells in bone marrow (if <20% but circulating monocytes at least 5 x 10^9/L, diagnosis is still AMML)

AMML

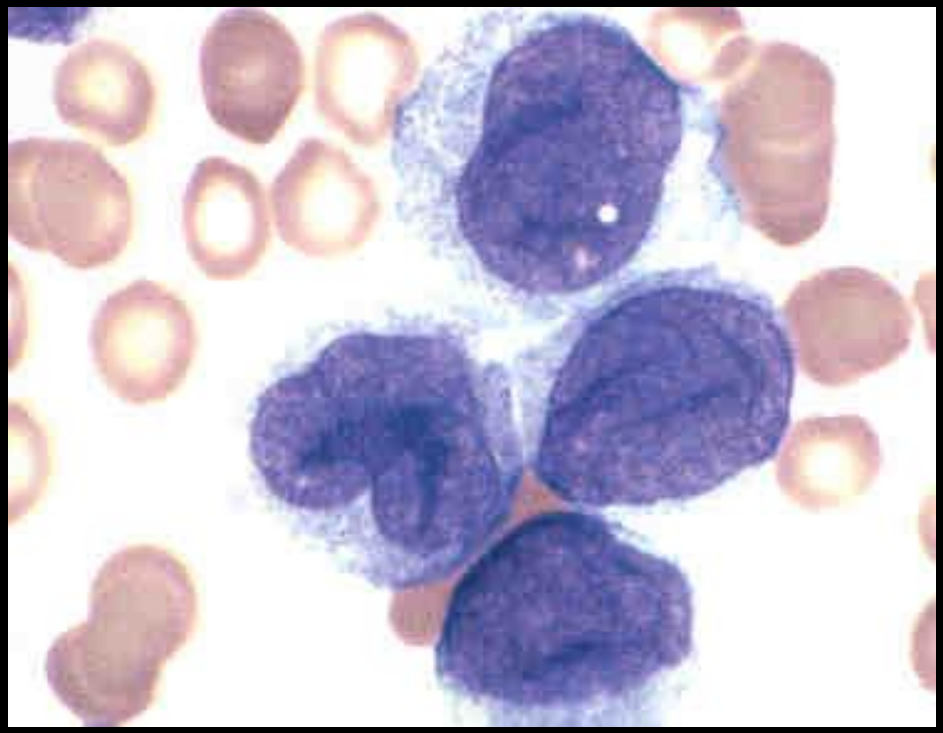
Morphology

- 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 cytoplasm. More granules

Monoblasts



Promonocytes

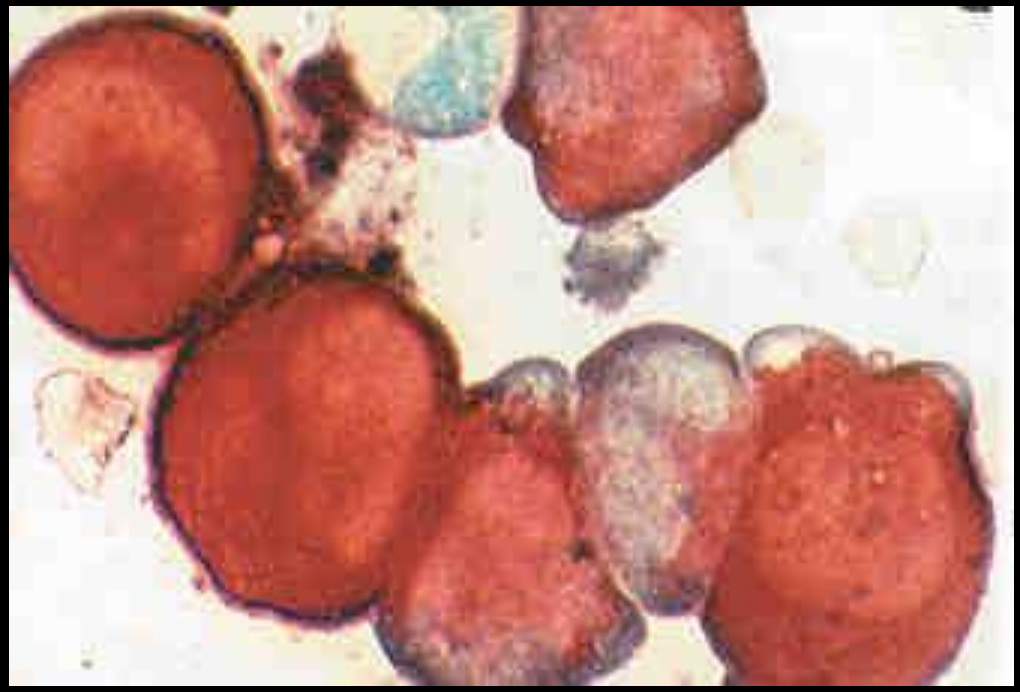


AMML

Morphology

- MPO+ (at least 3% of blasts)
- Monocytic elements: positive non-specific esterase

Butyrate
(non-specific esterase)



AMML

Immunophenotype

- CD13+, CD33+ (myeloid)
- CD14+, CD4+, CD11b+, CD11c+, CD64+, CD36+, lysozyme+ (monocytic)

AMML

Genetics

- Non-specific
- [Specific abnormalities are under AML with recurrent genetic abnormalities, such as inv(16)]

Acute Monoblastic/Monocytic Leukemia (M5a/M5b)

- 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

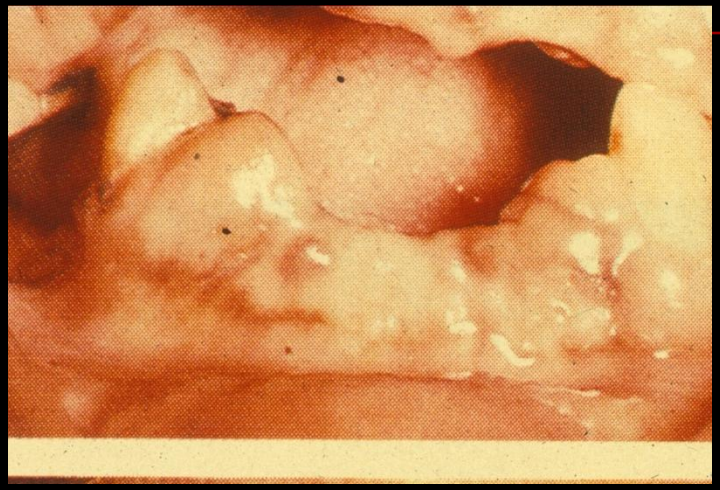
Acute Monoblastic/Monocytic Leukemia

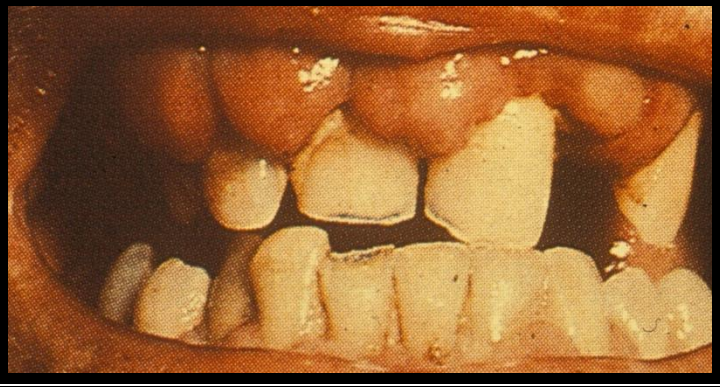
- Bleeding disorders most common presentation
- Cutaneous and gingival infiltration
- CNS involvement
- Extramedullary masses

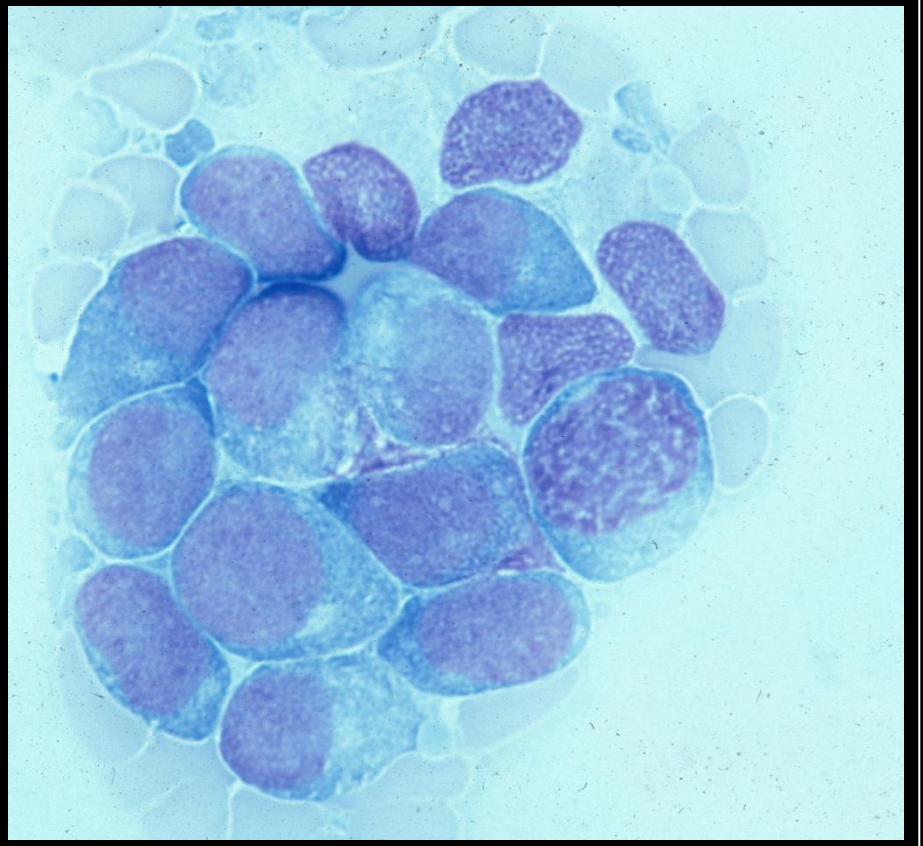
Acute Monoblastic/Monocytic Leukemia

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

Acute Monoblastic Leukemia







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

- No specific finding
- [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 [may be also in AML-M2]

Acute Erythroid Leukemia (M6)
aka Pure Erythoid Leukemia

- Definition
  - Acute leukemia characterized by predominant erythroid population
- ≥80% immature erythroid precursors with ≥30% promonoblasts

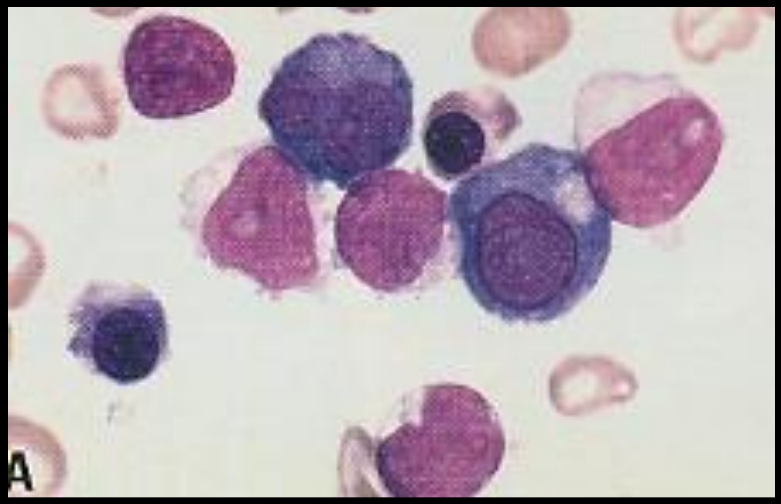
Acute Erythroid Leukemia do not include:

- AML, NOS
  - ≥50% erythroid precursors in BM
  - ≥20% myeloblasts in BM
- MDS
  - ≥50% erythroid precursors in BM
  - <20% myeloblasts in BM

[These cases may have been included under WHO 2008 as AML-M6, with myeloblasts as % of non-erythroid cells]

Acute Erythroleukemia

- Morphology
  - BM
    - Hypercellular
    - Megakaryocytic dysplasia
  - Erythroid
    - All stages with left shift
    - Frequent dysplasia
      - megaloblastoid nuclei
      - multinucleated forms
    - Cytoplasmic vacuoles
  - Myeloblasts (very few)
    - Similar to those in AML M1 or M2

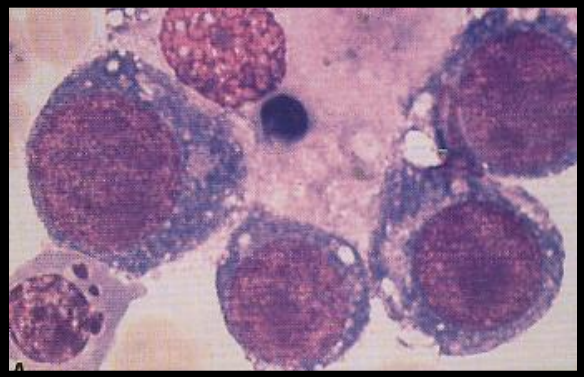


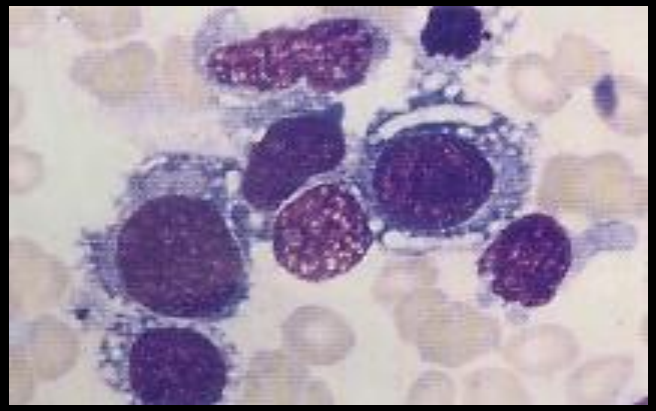
Acute Erythroleukemia

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

Acute 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



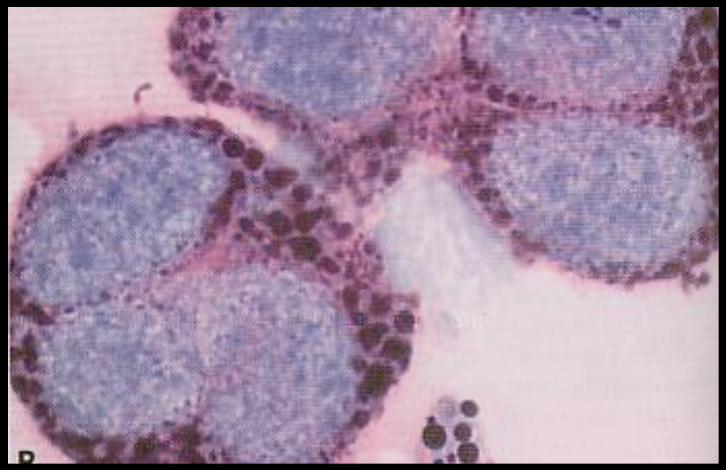


Acute Erythroid Leukemia

Cytochemistry

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

- EM
  - Free ferritin particles or siderosomes (heavily iron-laden lysosomes)



Acute Erythroid Leukemia

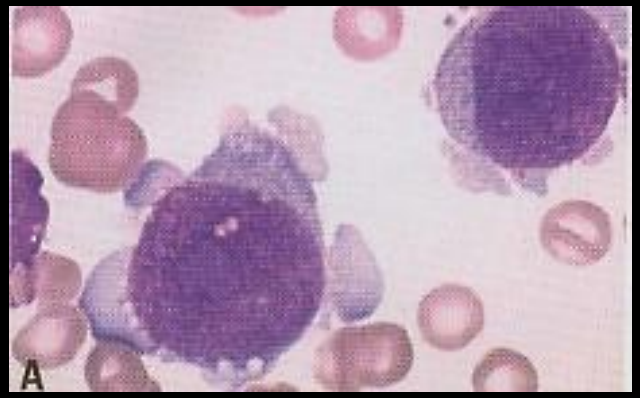
- Genetics
  - No specific chromosome abnormality
  - Complex karyotypes common
    - Chromosomes 5 and 7 frequently affected

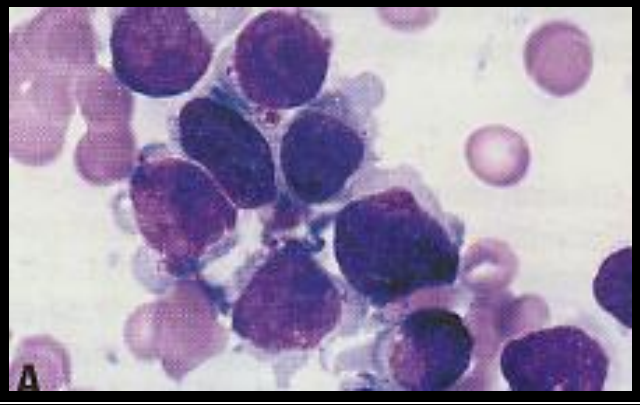
Acute Megakaryoblastic Leukemia (M7)

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

Acute Megakaryoblastic Leukemia

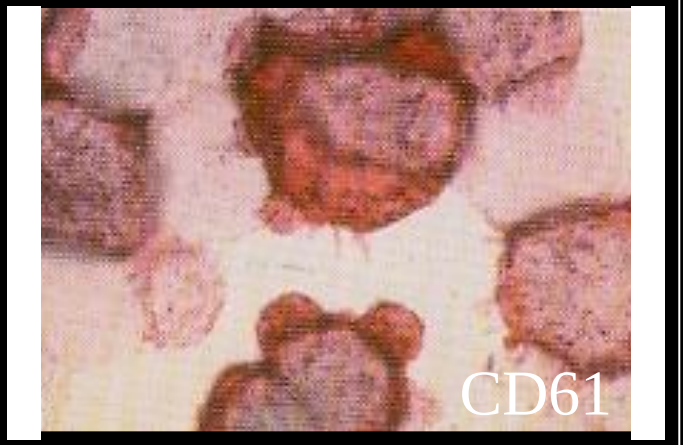
- Morphology
  - Megakaryoblast
    - Medium to large size
    - Round, slightly irregular nucleus
    - Fine reticular chromatin
    - One to three nucleoli
    - Basophilic cytoplasm
      - Agranular
      - Bleb or pseudopod formation
  - Blasts may occasionally be small resembling lymphoblasts





Acute Megakaryoblastic Leukemia

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



Acute Megakaryoblastic Leukemia

- Genetics
  - No unique chromosomal abnormality in adults
  - Young men with germ cell tumors i(12p)
- Cell of origin
  - Precursor committed to the megakaryocytic lineage

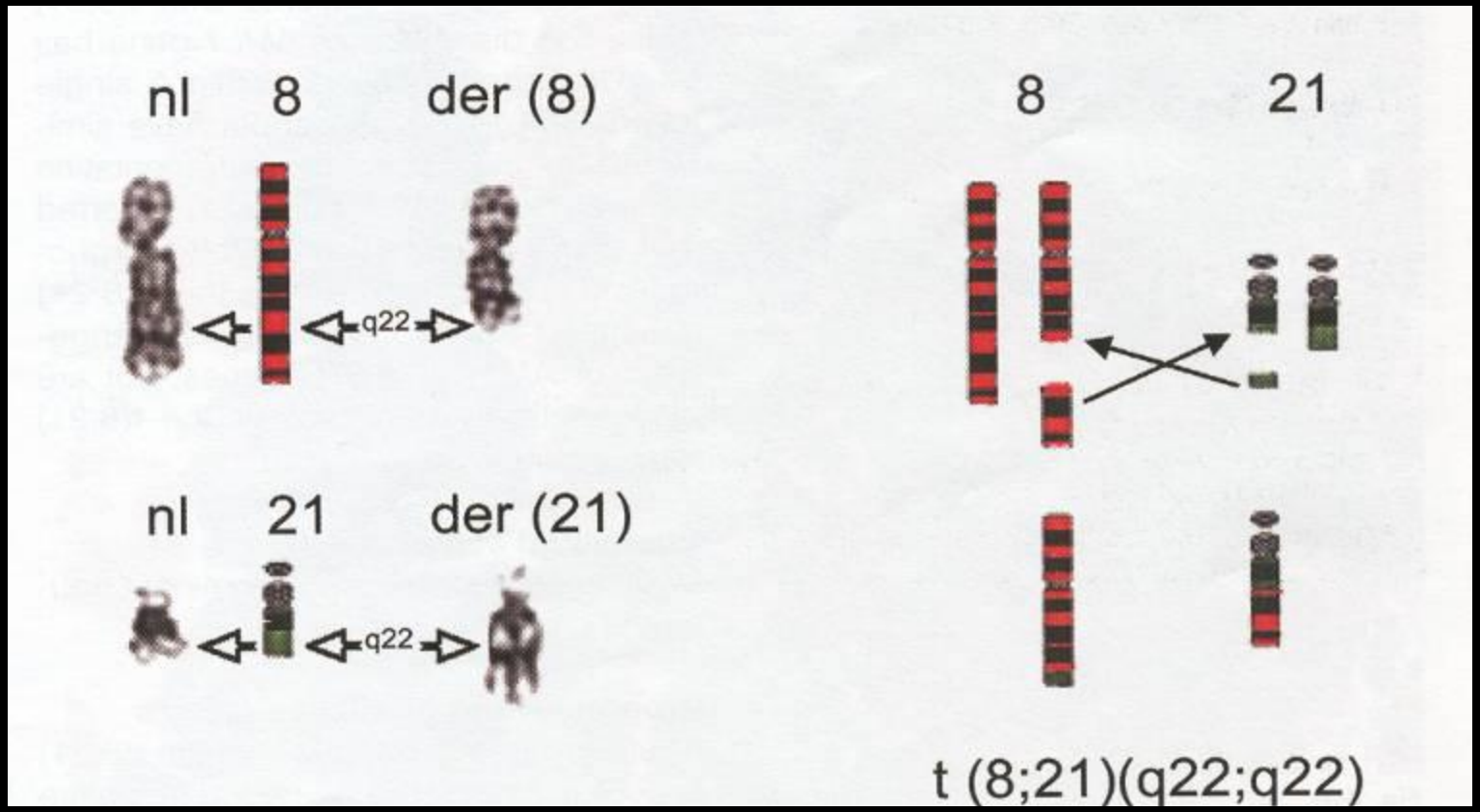
Isochromosome (12p): unbalanced structural abnormality in which the arms of the chromosome 12 are mirror images of each other (12p).

Acute Myeloid Leukemia with Recurrent Cytogenetic Abnormalities

Acute Myeloid Leukemia with recurrent cytogenetic abnormalities t(8;21)(q22;q22) RUNX1-RUNX1T1

- 5-12% of all AMLs,
  1/3 of AML-M2 cases
- May present with myeloid sarcoma
- Bone marrow blasts may be less than 20%
- Blasts may be pos for CD19 and CD56
- Good prognosis with high dose of Cytarabin (except for cases with KIT mutation)

Acute Myeloid Leukemia with recurrent cytogenetic abnormalities t(8;21)(q22;q22)



Acute Myeloid leukemia with inv(16)(p13q22) or t(16;16)(p13;q22) ; (CBFB/MYH11)

-Typically AML-M4e plus chromosome abnormality (occasional cases not AML-M4e)

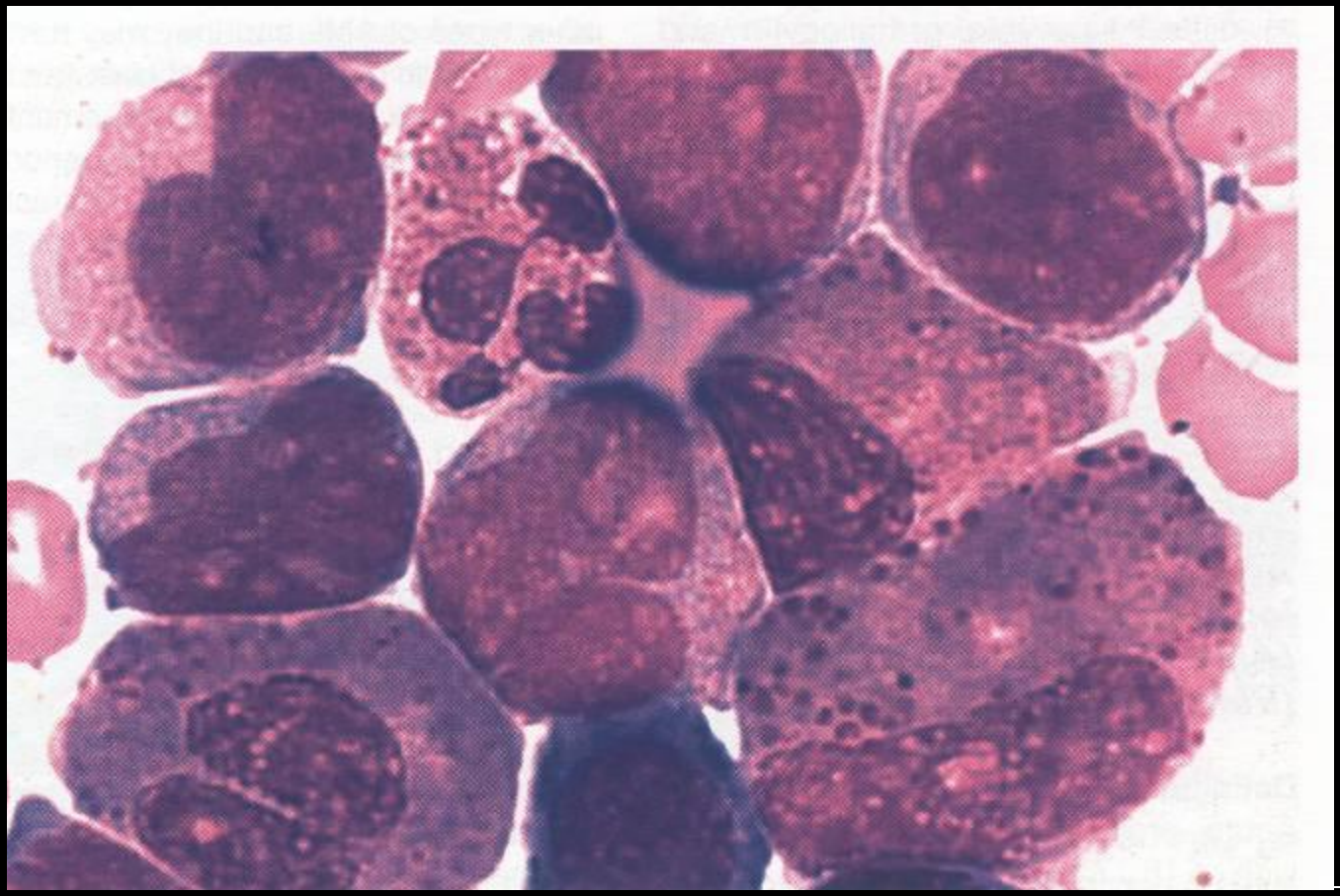
-High complete remission rate with long term disease-free survival with high dose of Cytarabin (except for cases with KIT mutation)

Acute Myeloid Leukemia with inv(16)(p13q22): Morphology and cytochemistry

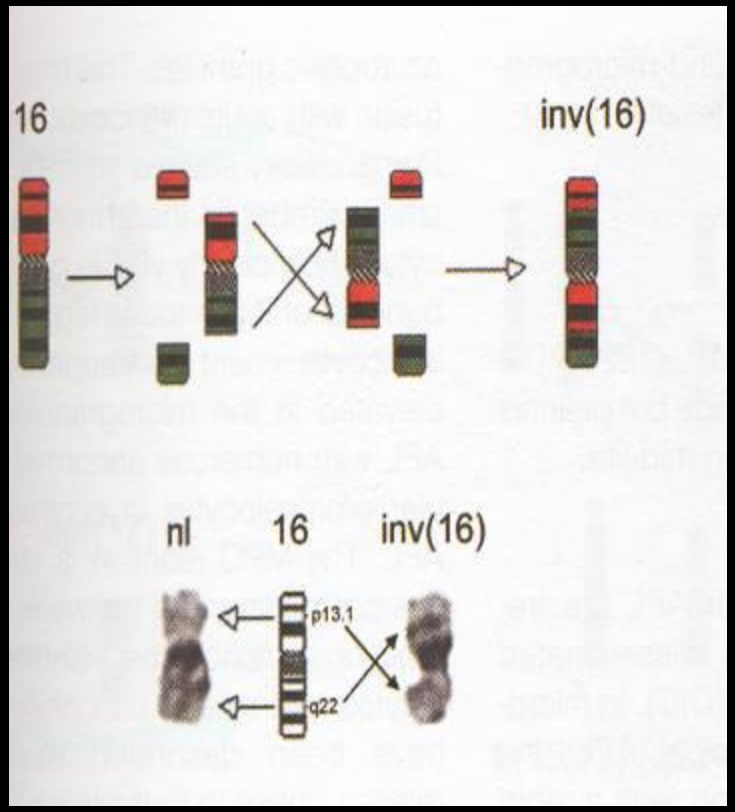
Peripheral Blood: eosinophils not increased

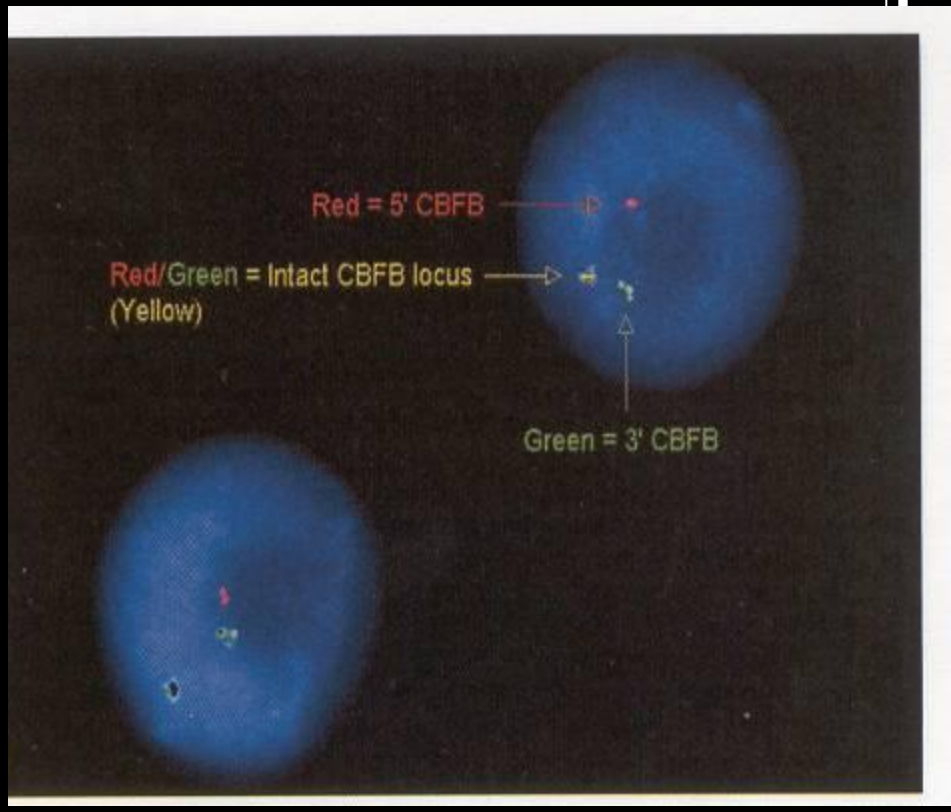
BM: hypercellular, ≥ 20% blasts
(may be lower than 20% in some cases)
-Most striking abnormality:
eosinophils: immature granules,
purple-violet in color,
obscure cell morphology
-Auer rods may be seen
-3% or more blasts with MPO+
-NSE+
-Neutrophils: sparse

Acute Myeloid Leukemia with inv(16)(p13q22)



Acute Myeloid Leukemia with inv(16)(p13q22)





FISH

Acute promyelocytic leukemia

t(15;17)(q22;q21) (PML/RARA)

Epidemiology:

-5-8%AML; age: mid life

-Typical hypergranular and microgranular (hypogranular) APL: both with high risk for DIC

-Microgranular APL: high WBC with numerous promyelocytes

-Basophilic cytoplasm of APL cells in patients previously treated with ATRA (relapse)

-Excellent response to ATRA, arsenic trioxide

-Many case are FLT3-ITD pos without adverse impact

# Acute promyelocytic leukemia,
t(15;17)(q22;q21) (PML/RARA)

Morphology and cytochemistry

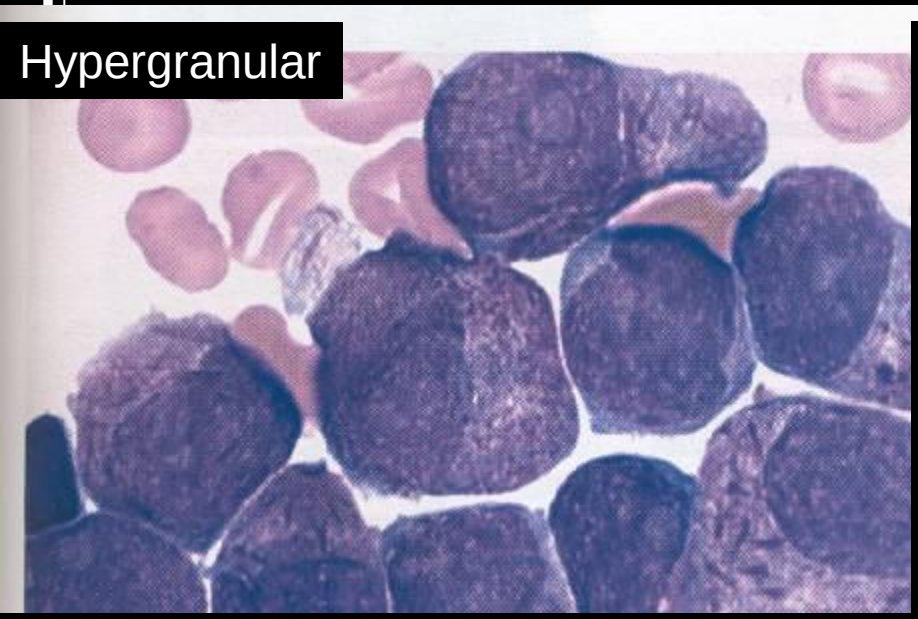
-Hypergranular APL: kidney-shaped, bilobed, dense large granules; “Faggot” cells: bundles of Auer rods MPO: (++)

-Microgranular (hypogranular): bilobed promyelocytes, MPO(++) vs (- or + in monocytes of AMML)

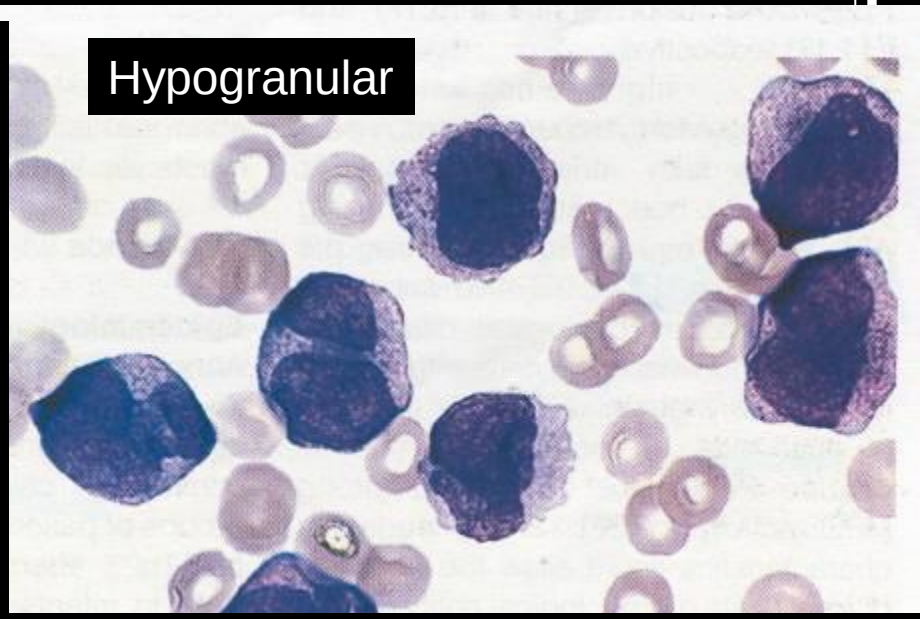
-BM: hypercellular, abundant cytoplasm, convoluted nuclei

# **Acute promyelocytic leukemia,**
t(15;17)(q22;q21) (PML/RARa)

Hypergranular



Hypogranular



# Acute promyelocytic leukemia,
t(15;17)(q22;q21) (PML/RARa)

Immunophenotype:

CD33, homogenous, bright
CD13, heterogeneous
CD34(-)
HLA-DR(-)
CD15(-)
-Frequent CD2 and CD9 co-expression
-PML Ab stain (Imunocytochemistry): nuclear multigranular vs speckled in normal promyelocytes or other blasts of AMLs

Acute promyelocytic leukemia

Variant RARA translocations

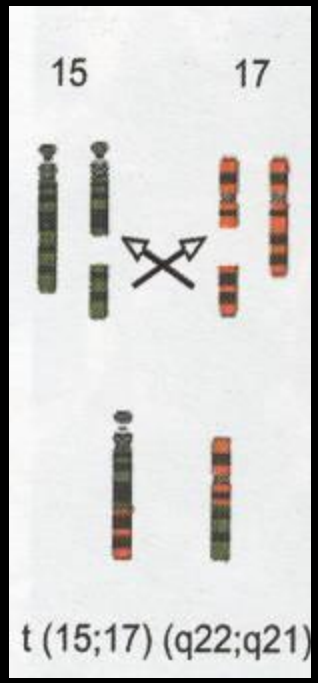
-t(11;17)(q23;q12), ZBTB16 on chr11; several cases reported, no Auer rods, regular nuclei, pseudo Pelger-Huet, resistant to ATRA

-t(5;17)(q35;q12), NPM1 on chr 5; no Auer rods, respond to ATRA

-t(11;17)(q13;q21), NUMA on chr 11

Acute promyelocytic leukemia

Genetics:



Acute myeloid leukemia with 11q23 (MLL) abnormalities

-Typically AML, with monocytic / myelomonocytic feature (M4, M5), occasionally M1, M2
-Epidemiology: 5-6% of AML, more in children

[Previous therapy, topoisomerase II inhibitors ->t-AML
Previous MDS-> AML with myelodysplasia-related changes]

Acute myeloid leukemia with 11q23 (MLL) abnormalities

Immunophenotype:

-Myeloid: CD13, CD33(+)
-Monocytic: CD14, CD4, CD11b, CD11c, CD64, CD36, Lysozyme(+)
-CD34(-)

Acute myeloid leukemia with 11q23 (MLL) abnormalities

Genetics:

-Human homolog of Drosophila trithorax gene, (MLL) at band 11q23

- More than 80 different partners for 11q,

-t(9;11): intermediate survival, superior to other 11q translocations, such as t(9;19) etc.

Acute myeloid leukemia with other recurrent chromosal abnormalities

- inv(3)(q21;q26.2) or t(3;3)(q21;q26.2), a/w thrombocytosis (22% of patients), multilineage dysplasia, poor prognosis
- t(1;22)(p13q13): megakaryoblastic, children less than 3 y/o without Down syndrome, organomegaly, aggressive disease, may respond to intensive chemotherapy
- t(6;9)(p23;q34) (DEK/NUP214 fusion gene) a/w basophilia and multilineage dysplasia, poor prognosis

AML with Gene Mutations: FLT3

- FLT3: FMS-like tyrosine kinase-3, member of the class III receptor tyrosine kinase family
- Mutated gene leads to a constitutive activation of protein (leukemic transformation)
- FLT3-ITD Found in 28–34% of cytogenetically normal AML
- Associated significantly to worse clinical outcome

AML with Gene Mutations: NPM1

- NPM1: Nucleophosmin 1, nuclear protein with oncogenic and tumour-suppressive function
- Found in 25–35% of AML and predominantly in cytogenetically normal AML
- Associated to favorable prognosis (in absence of FLT3-ITD mutations)

AML with Gene Mutations: CEBPA

- CEBPA: CCAAT/enhancer-binding protein alpha, a transcription factor for differentiation of myeloid progenitors into neutrophils
- Found predominantly in cytogenetically normal AML and in AML with 9q deletion
- Associated with higher CR rate and better DFS and OS
- Improved prognosis associated with AML with mutated CEBPA is associated with biallelic, but not single, mutations

AML with BCR-ABL1

- A new provisional category of AML with BCR-ABL1 is added to recognize these rare de-novo AML cases that may benefit from TKI therapy
- The diagnostic distinction between de novo AML with BCR-ABL1 and blast transformation of CML may be difficult without adequate clinical information.

AML with mutated RUNX1

- A provisional category of AML with mutated RUNX1 has been added to the classification for cases of de-novo AML with this mutation (i.e. not associated with MDS-related cytogenetic abnormalities).
- This new provisional disease category appears to represent a biologically distinct group with a possibly worse prognosis than other AML types.

Precursor B lymphoblastic leukemia/lymphoma

Precursor B lymphoblastic leukemia/lymphoma

Definition: a neoplasm of lymphoblasts committed to the B-cell lineage.

-B-LBL: lymphoma mass, without or minimal blood and BM involvement
-B-ALL: lymphoblastic leukemia, extensive BM and blood involvement (>25% BM cells)

Precursor B lymphoblastic leukemia/ lymphoblastic lymphoma

Clinical features:

-B-ALL: WBC decreased, normal or markedly elevated

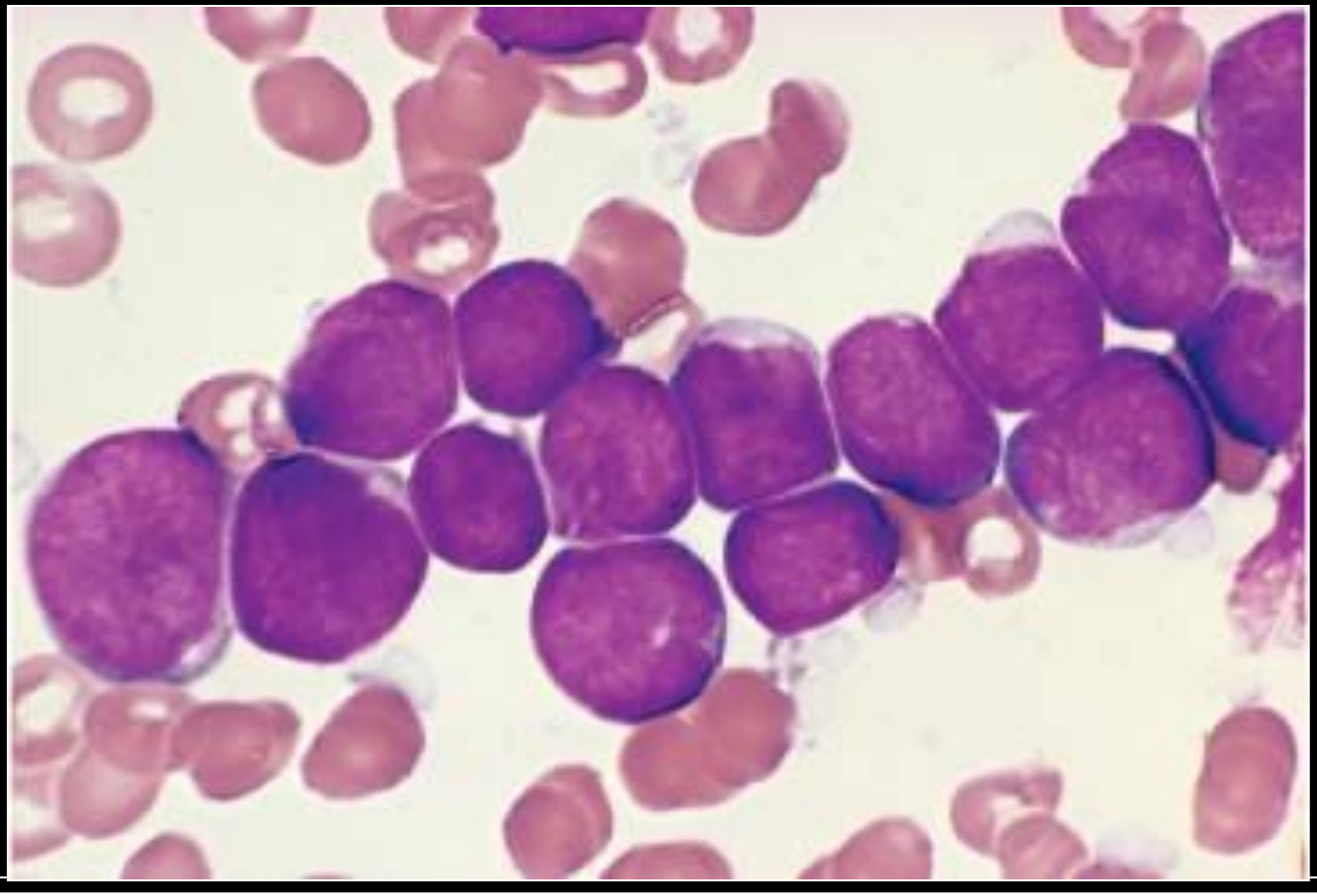
Anemia, thrombocytopenia

Lymphadenopathy, hepatosplenomegaly

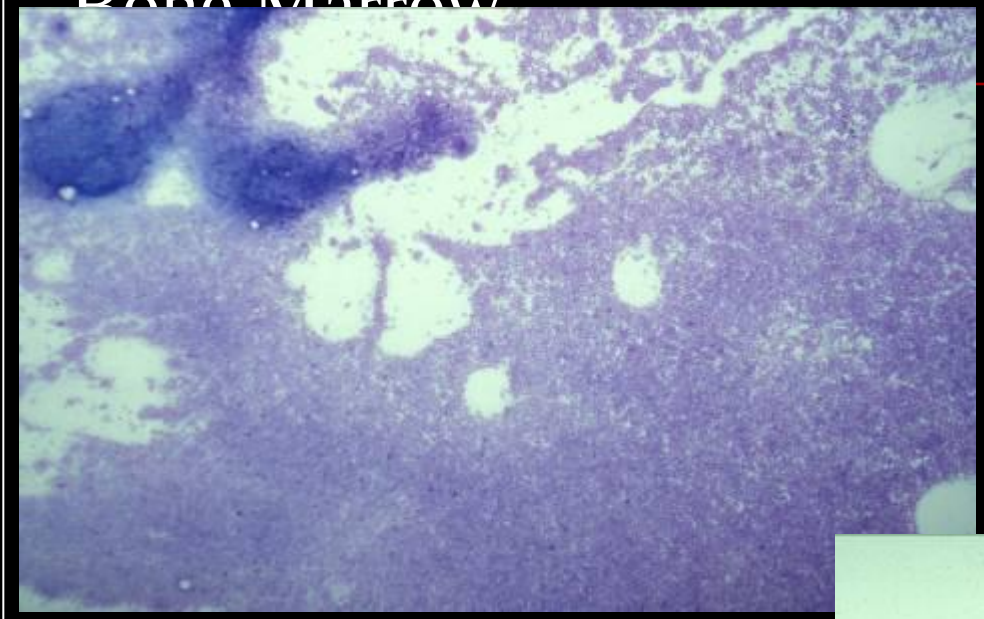
Bone pain, arthralgias

-B-LBL: skin, bone, soft tissue, and lymph node

Acute Lymphoblastic Leukemia

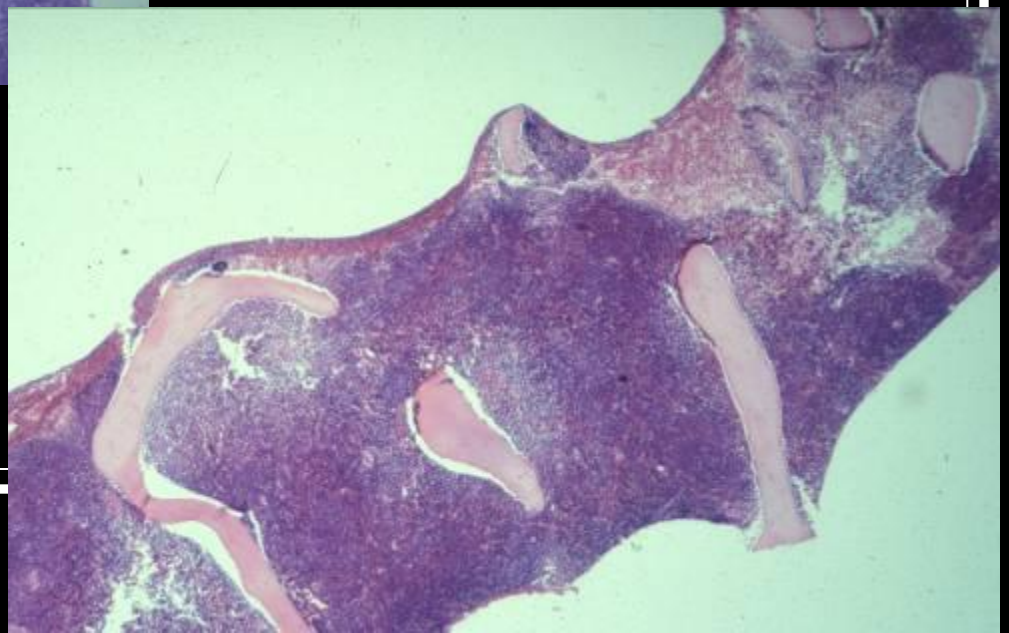


Acute Lymphoblastic Leukemia
Bone Marrow

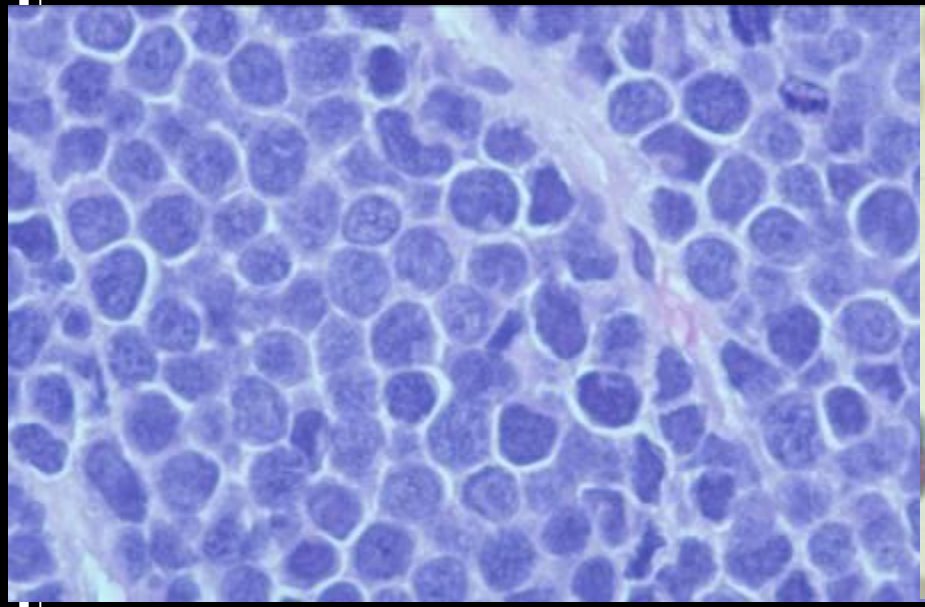


Bone marrow aspirate smear

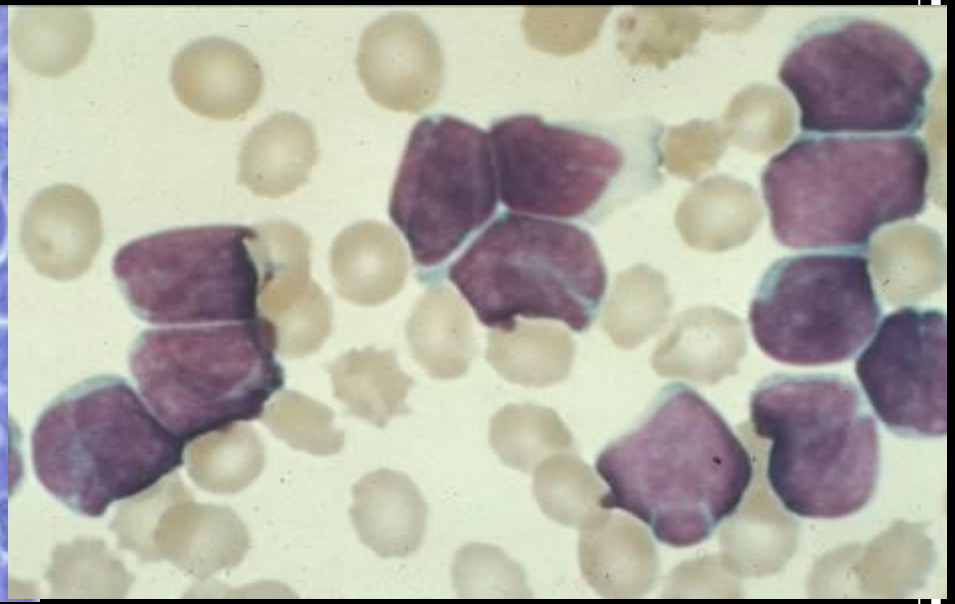
Bone marrow biopsy



Lymphoblastic Lymphoma/Leukemia



Mediastinal mass:
Lymphoblastic lymphoma



Peripheral blood:
Acute lymphoblastic leukemia

Precursor B lymphoblastic leukemia/ lymphoblastic lymphoma

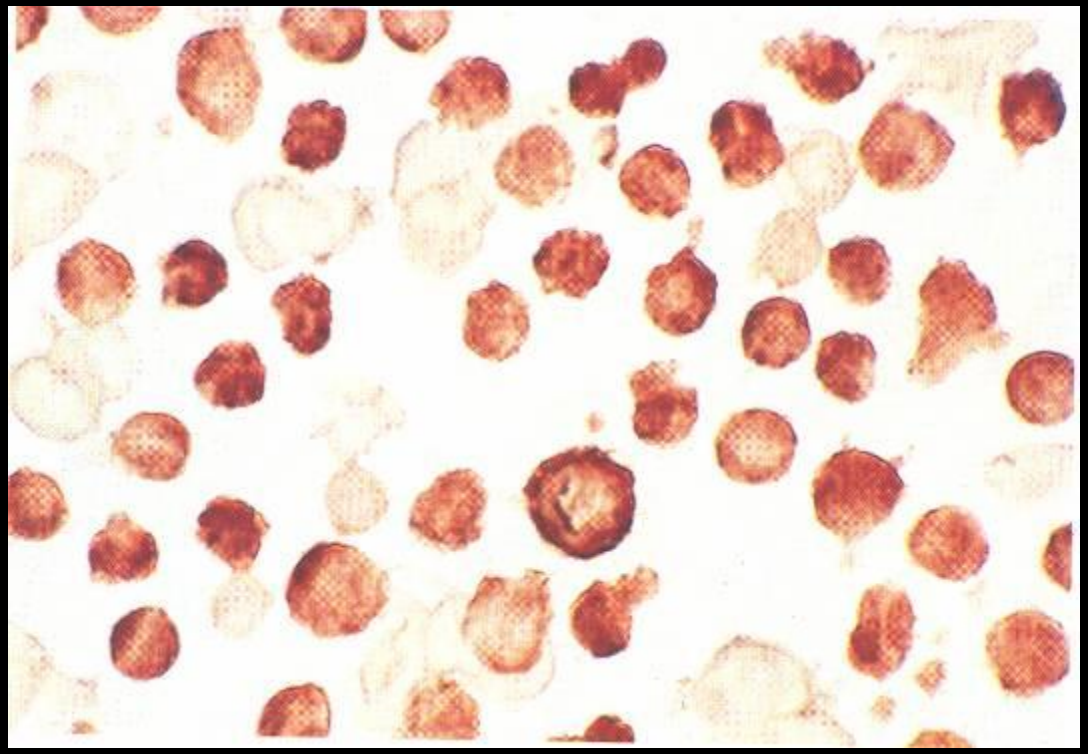
Cytochemical stains

TdT: positive

MPO, SBB: negative

PAS : nuclear is partially encircled by a rim of PAS reactivity

Precursor B-ALL



TdT

Precursor B lymphoblastic leukemia/ lymphoblastic lymphoma

Immunophenotype

TdT, HLA-DR

CD19, CD79a, CD10, CD24

[Note that t(4;11)(q21;q23) cases are typically negative for CD10 and CD24]

Variably positive for CD20 and CD22 (typically low)

CD45 often negative

Cytoplasmic Mu chain in pre-B ALL

Precursor B lymphoblastic leukemia/ lymphoblastic lymphoma

Genetics:

t(9;22)(q34;q11.2)

- 3-4% of cases
- in most childhood cases associated with a 190 kd
- BCR/ABL fusion tyrosin kinase
- unfavorable prognosis (event-free survival was increased with Gleevec)

t(4;11)(q21;q23)

- associated with AF4/MLL
- 2-3% of cases
- unfavorable prognosis

Precursor B lymphoblastic leukemia/lymphoblastic lymphoma

Genetics:

t(1;19)(q23;p11.3)
- associated with PBX/E2A
- 6% of cases (25% of pre-B ALL)
- unfavorable prognosis (better now with intensive chemo)

t(12;21)(p13;q22)
- associated with TEL/AML1
- not picked up with cytogenetics -> need FISH or PCR
- 16-29% of cases
- favorable prognosis

Precursor B lymphoblastic leukemia/lymphoblastic lymphoma

Genetics:

Hyperdiploidy (>50)
- 20-25% of cases
- favorable prognosis

Hypodiploidy (<50)
- 5% of cases
- unfavorable prognosis

Precursor B lymphoblastic leukemia/ lymphoblastic lymphoma

B-ALL:

- Good prognosis in the pediatric group, 80% of patients cured
- Poorer prognosis in adult group with more unfavorable genetic results

B-LBL: median survival of 60 months

“BCR-ABL1-like ALL”

- B-ALL with translocations involving tyrosine kinases or cytokine receptors.
- Translocations of tyrosine kinase genes involve many different genes including ABL1 (with partners other than BCR), as well as other kinases including CRLF2 (up to 50% of cases), ABL2, PDGFRB, NTRK3, TYK2, CSF1R, and JAK2.
- Over 30 different partner genes have been described. Some patients, especially those with EBF1-PDGFRB translocations, have shown remarkable responses to TKI therapy, even after failing conventional therapy.

Precursor T lymphoblastic leukemia/lymphoma

Precursor T lymphoblastic leukemia/lymphoma

Definition: a neoplasm of lymphoblasts committed to the T-cell lineage.

-lymphoma: mass, without or minimal blood and BM involvement

-lymphoblastic leukemia: extensive BM and blood involvement (>25% BM cells)

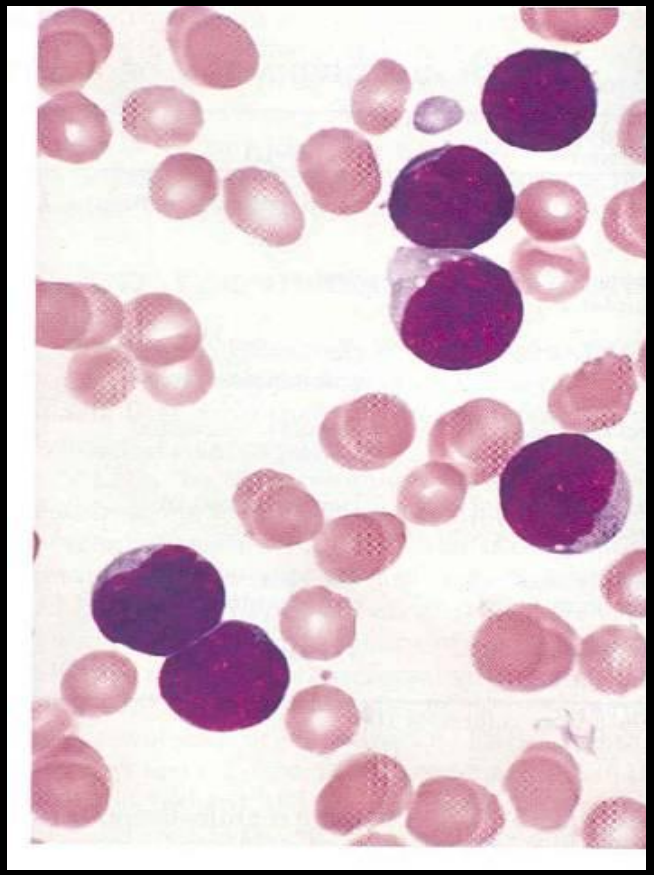
Precursor T lymphoblastic leukemia/ lymphoblastic lymphoma

Clinical features:

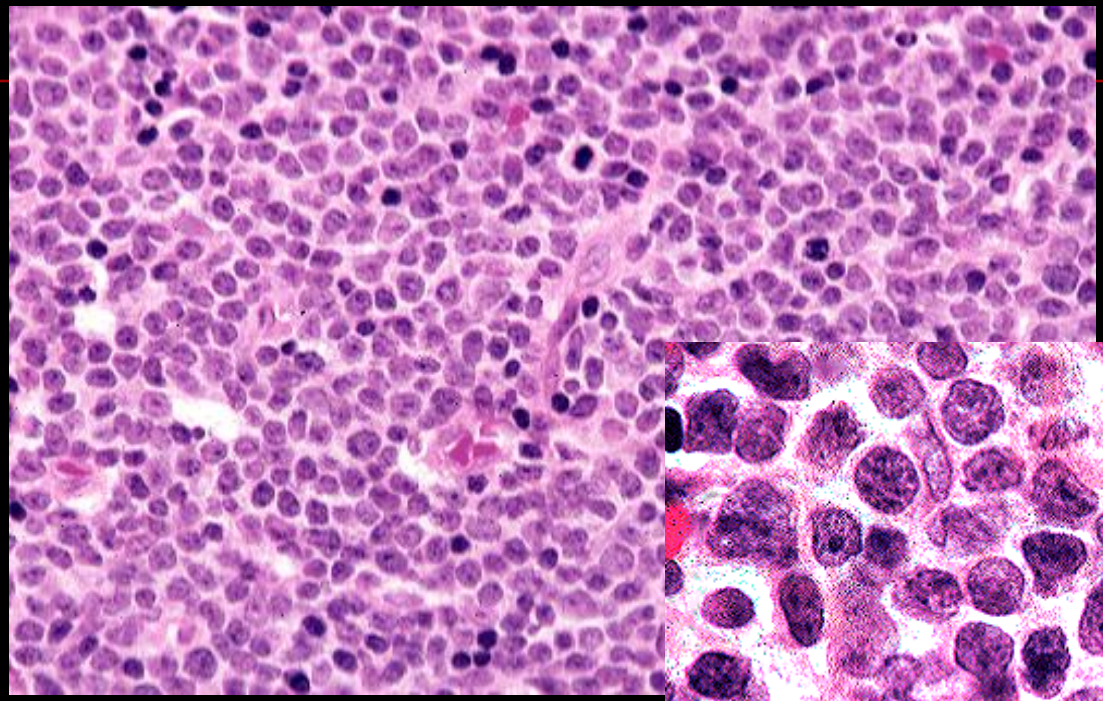
-Leukemia: high WBC

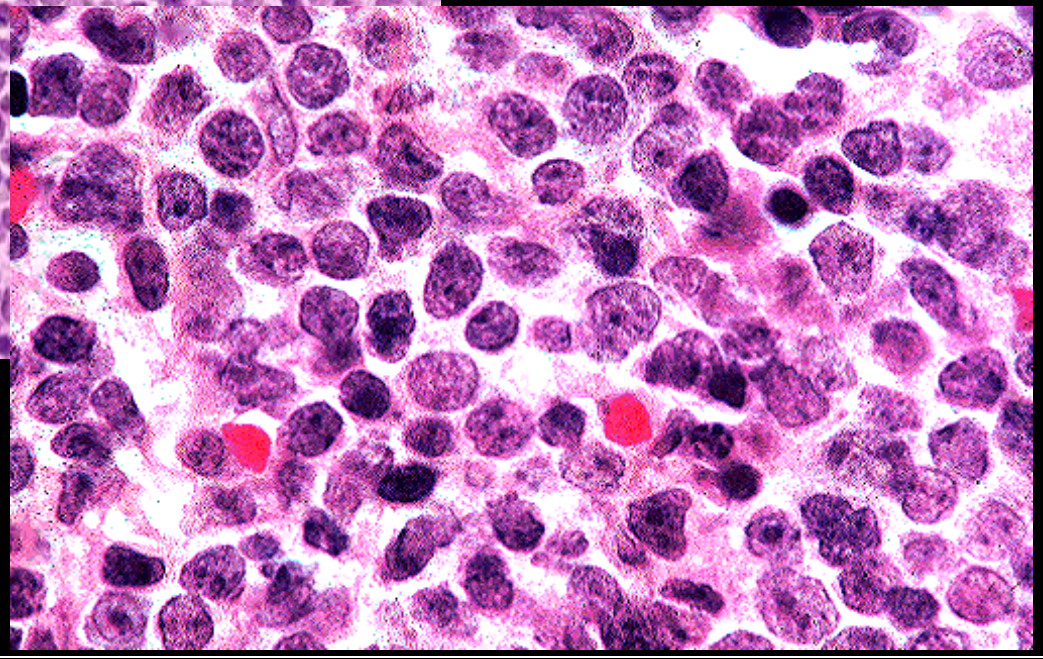
-Lymphoma: large mediastinal mass (or other tissue mass), rapid growth, pleural fluid involvement

Acute Lymphoblastic Leukemia



Precursor T Lymphoblastic Lymphoma





Precursor T lymphoblastic leukemia/ lymphoblastic lymphoma

Cytochemistry:

Acid phosphatase

TdT

PAS: nuclear

Precursor T lymphoblastic leukemia/ lymphoblastic lymphoma

Immunophenotype:
-TdT: +
-cCD3, the only lineage specific marker
-CD4,8: double – or +
-Variable surface: CD1a,2,3,5,7,10,79a,13,33,117(rare)
-TCR: may have rearrangement, not lineage specific

Precursor T lymphoblastic leukemia/lymphoblastic lymphoma

Genetics:

TCR loci(**1/3** of T-ALL):

14q11.2(alpha, delta)
7q35(beta)
7p(14-15)(gamma)

Genes: MYC(8q24.1)
TAL(1p32)
RBTN1(LMO1)(11p15)
RBTN2(LMO2)(11p13)
HOX11(10q24)
LCK(1p34.3-35)

Precursor T lymphoblastic leukemia/ lymphoblastic lymphoma

Prognosis:
-Poor in pediatric patients compared to B lympohblastic leukemia which is curable
-In adult patients: survival comparable to B-ALL with current treatment (Hyper CVAD), typically not curable