Chronic Myelogenous Leukemia

Chronic Myeloproliferative Neoplasms

Chronic myelogenous leukemia (CML), BCR-ABL1 positive

Chronic neutrophilic leukemia

Chronic eosinophilic leukemia, NOS

Polycythemia vera

Primary myelofibrosis

Essential thrombocythemia

Mastocytosis

CMPN, unclassifiable

CML: Definition

- Clonal
- Abnormal pluripotent stem cell
- a/w BCR-ABL1 fusion gene in Ph chromosome (all myeloid lineages and some lymphocytes)
- Chronic phase, accelerated phase, blast phase

Epidemiology

- Most common MPN
- 15-20% of all leukemias
- 1-2/100,000 annually world wide
- Any age, most common in 5^{th}-6^{th} decades
- Slightly male predominance

Site of Involvement

- Chronic phase: limited to hematopoietic sites (BM. PB, spleen)
- Blast phase: can infiltrate extrahematopoietic sites (incl LN, skin, soft tissue)

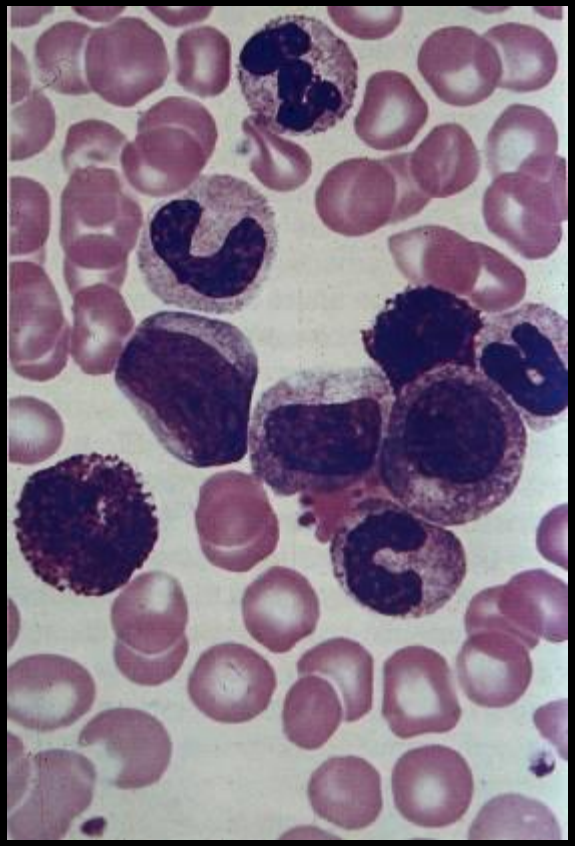
Clinical Features

- 20-40%, incidental findings
- Non-specific symptoms
- Blast phase can be initial presentation (severe anemia, thrombocytopenia, marked splenomegaly)

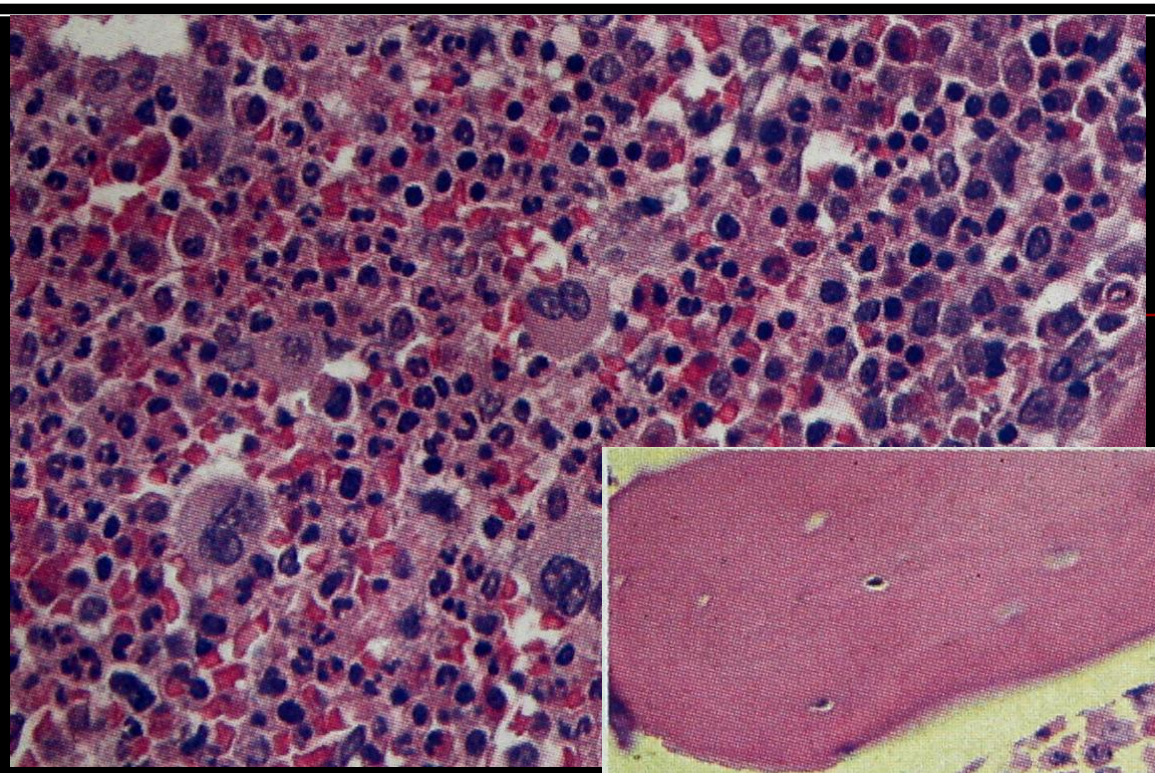
Morphology-Chronic Phase

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

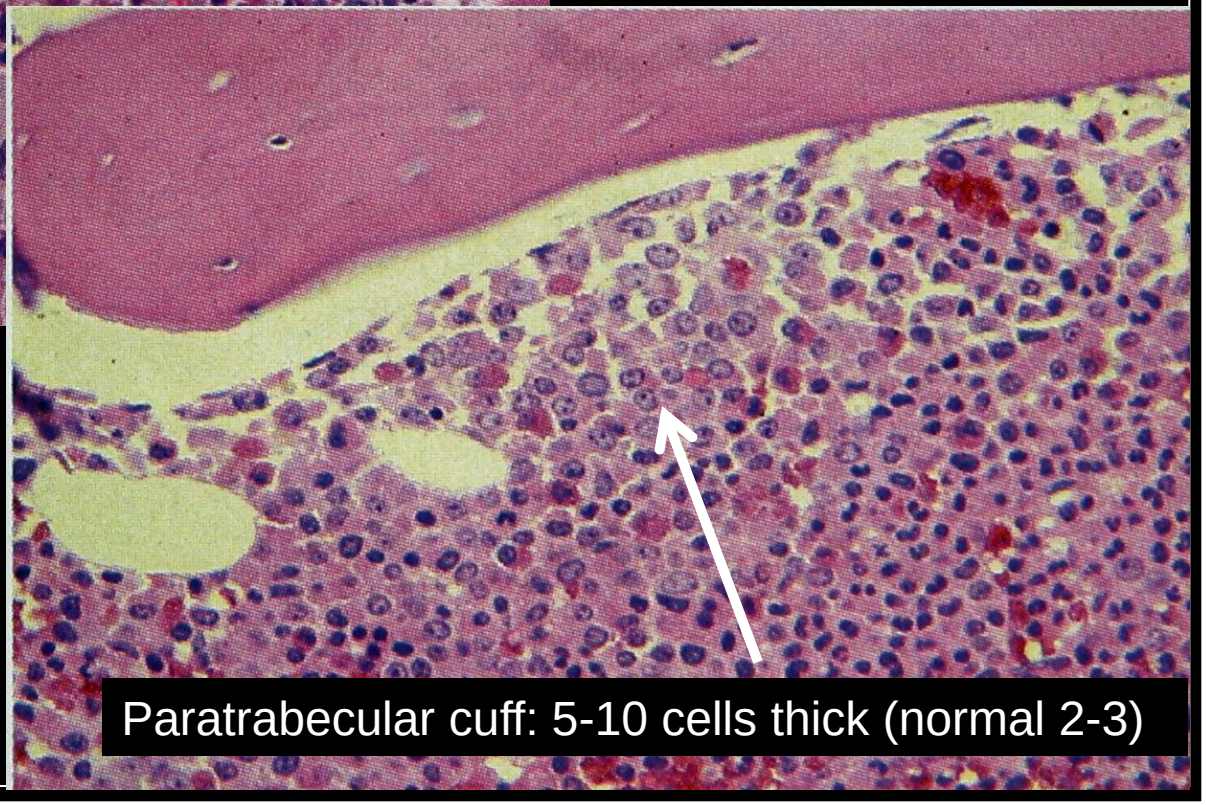


Peripheral Blood

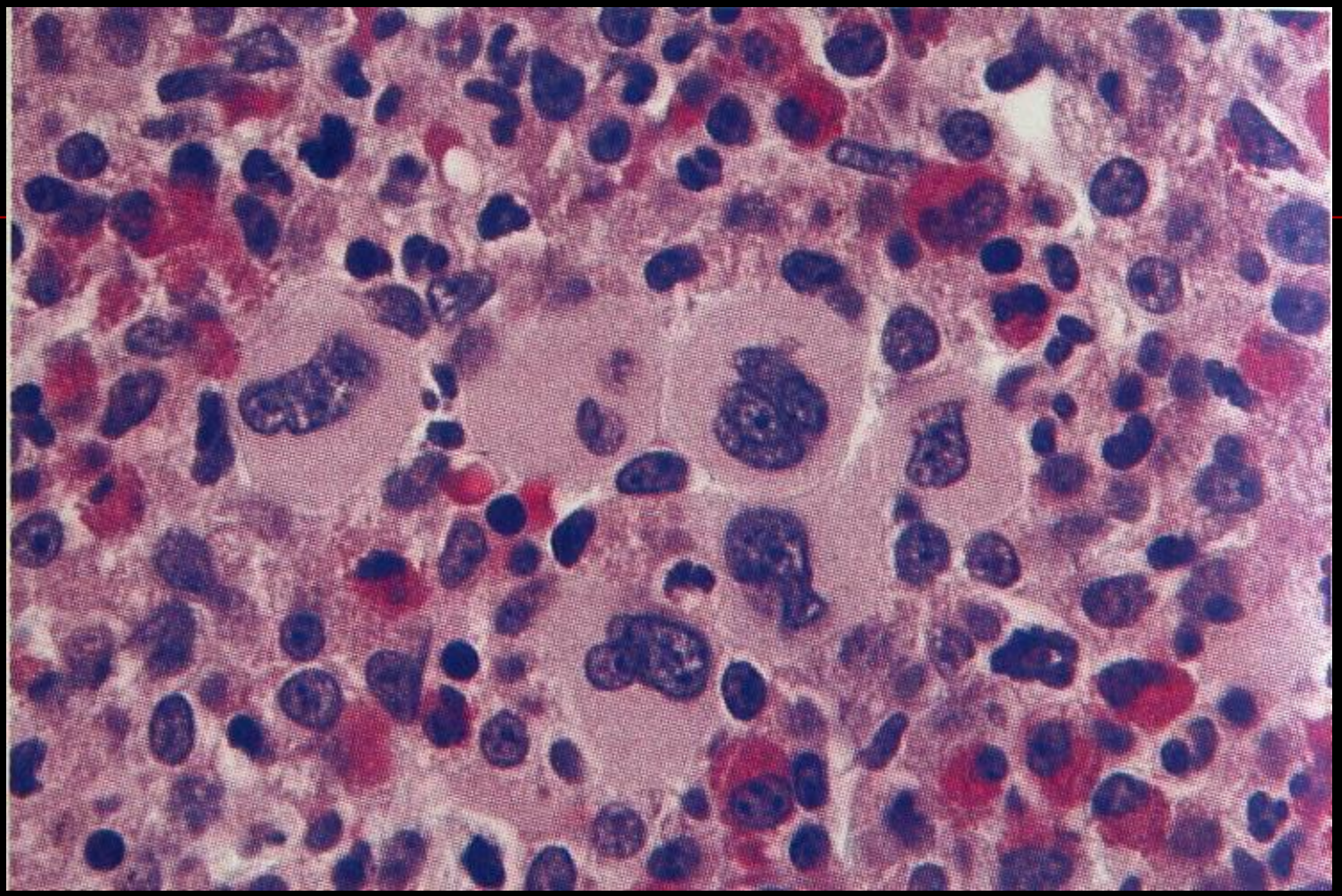


BM: hypercellular

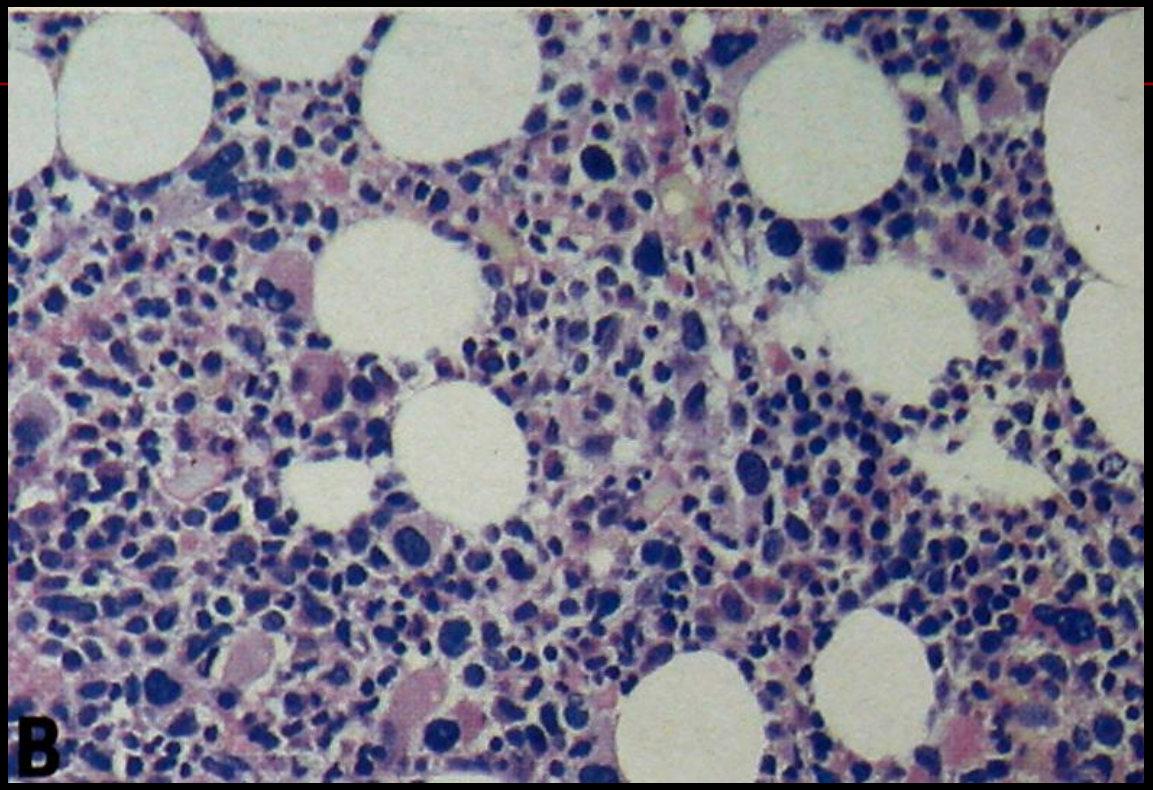
BM: increased immature cells



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

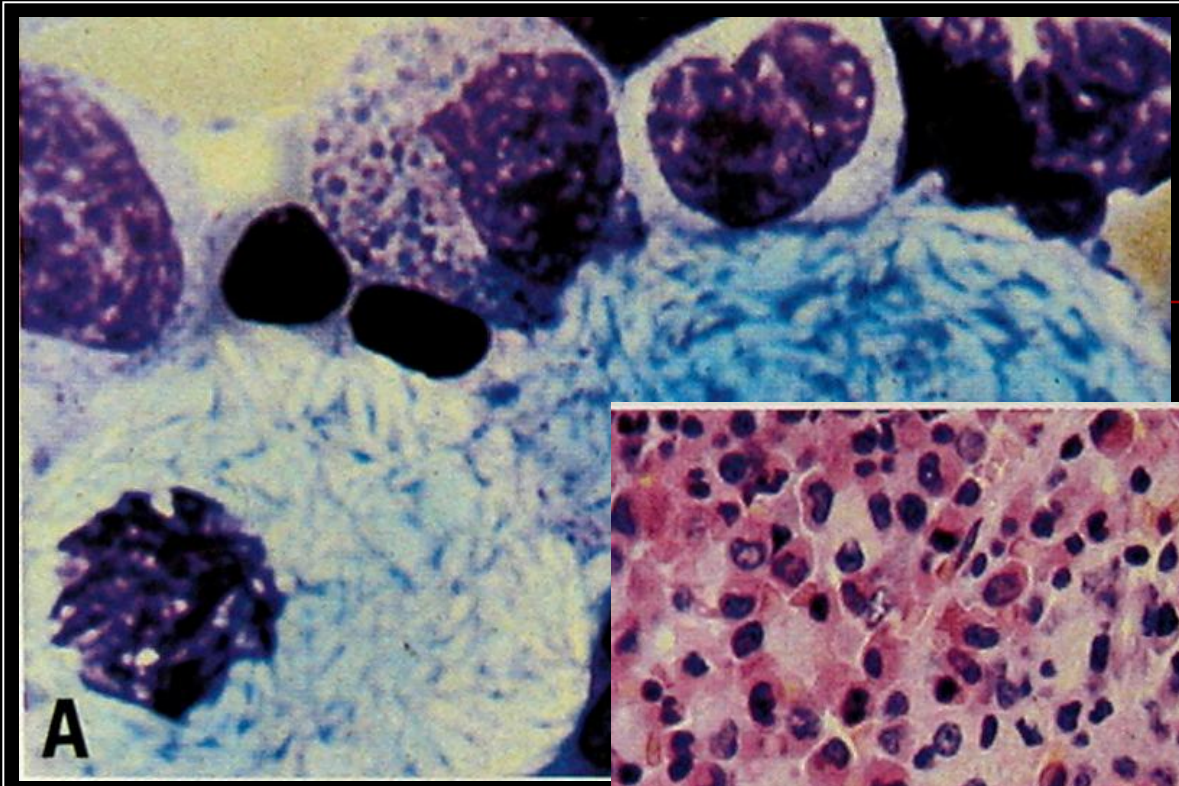


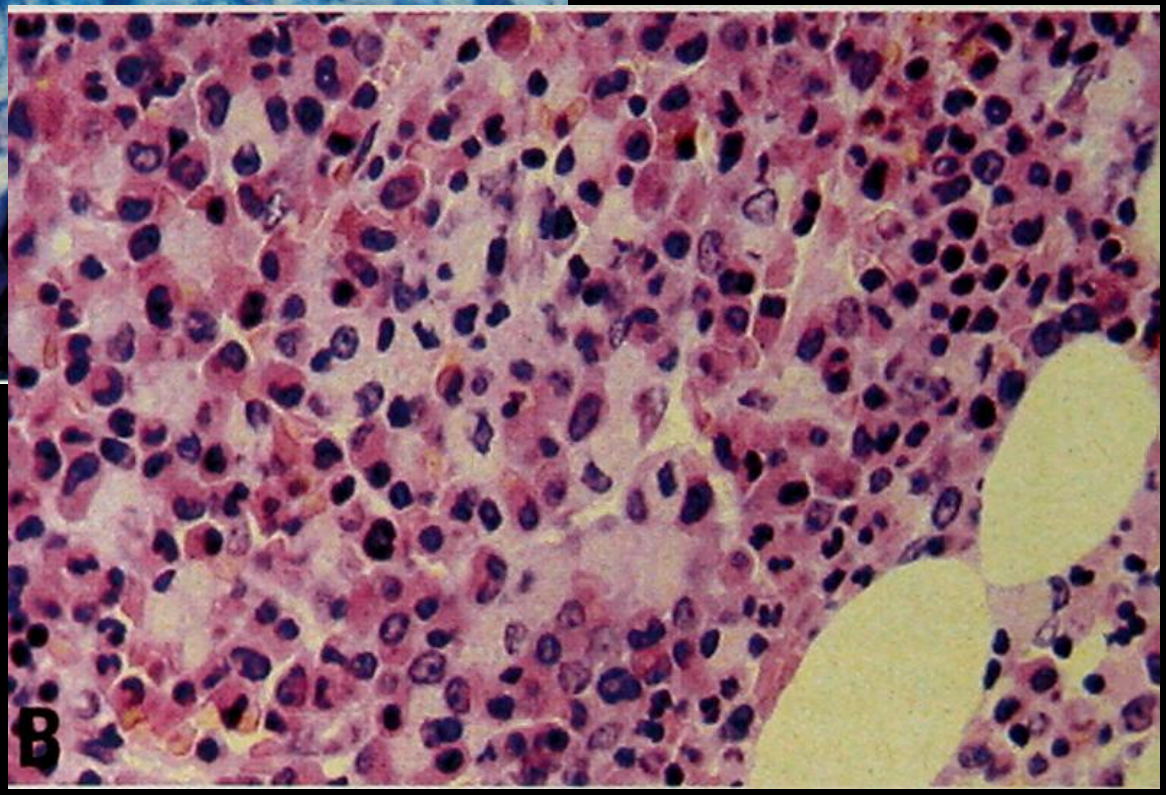
BM: small megakaryocytes

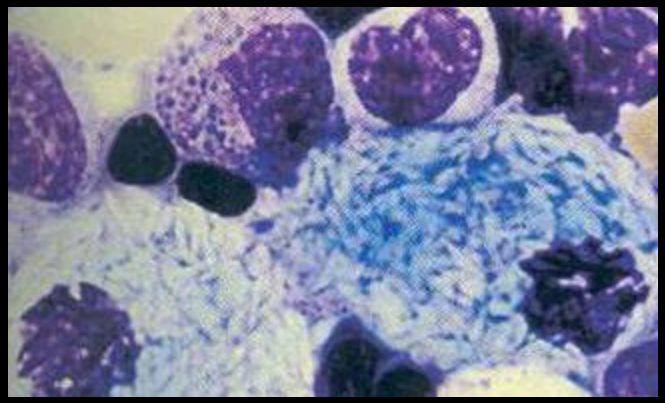


BM: increased megakaryocytes

BM: pseudo-Gaucher cells

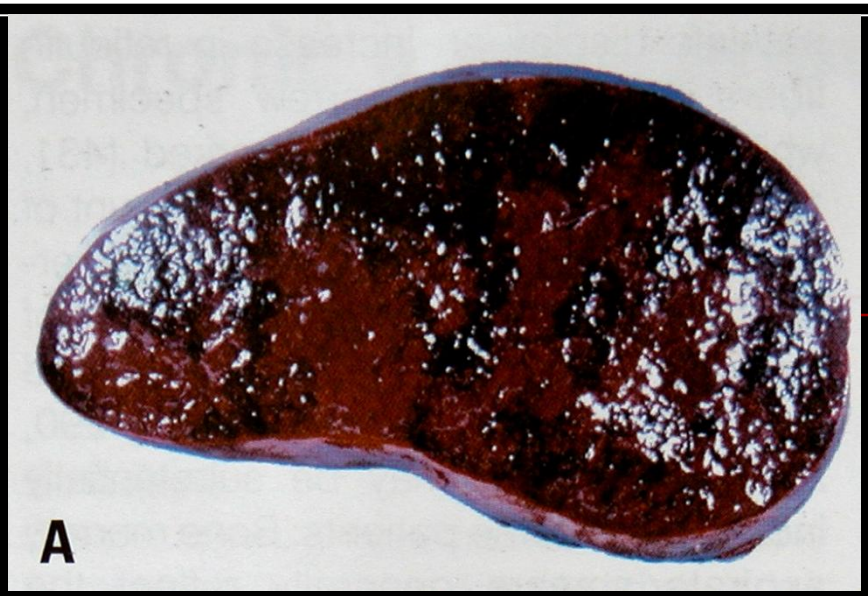


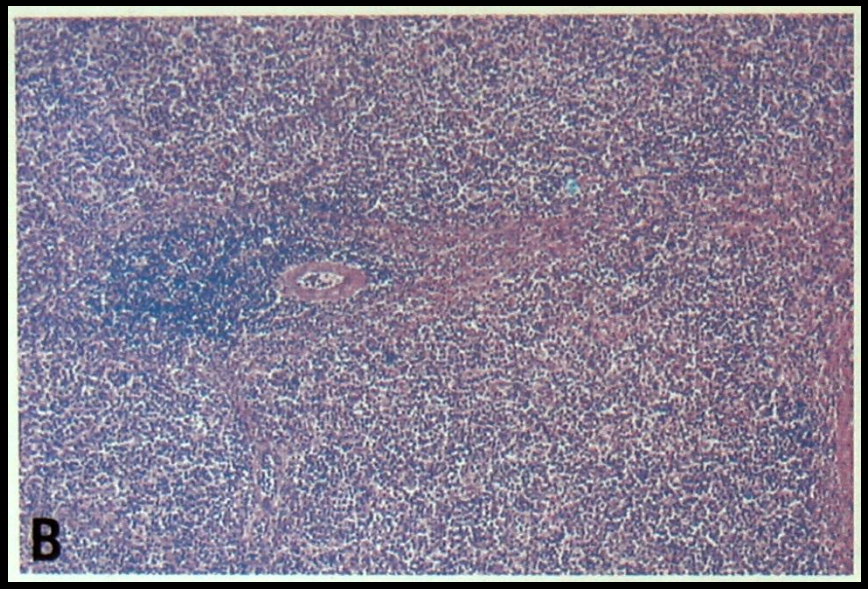


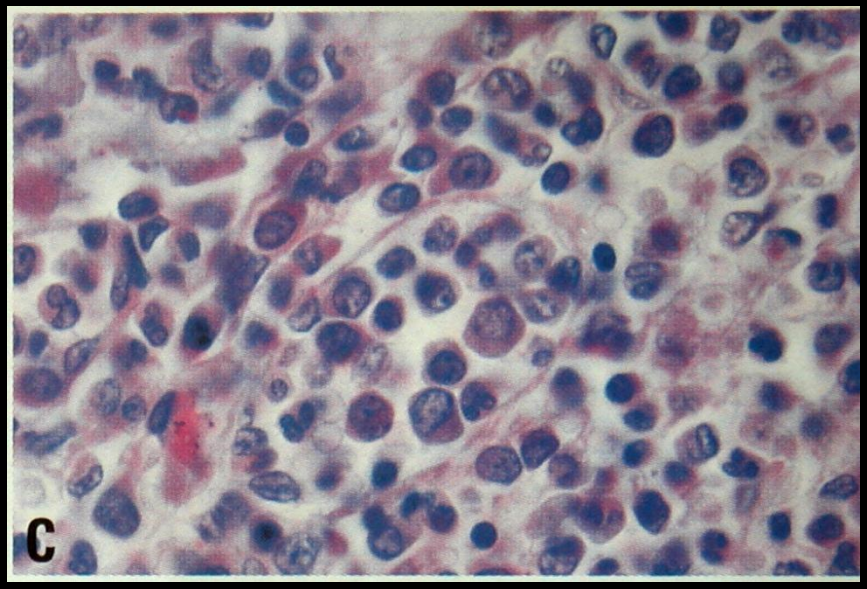


Pseudo-Gaucher and sea blue histiocytes seen in 30%; they are derived from the neoplastic clone

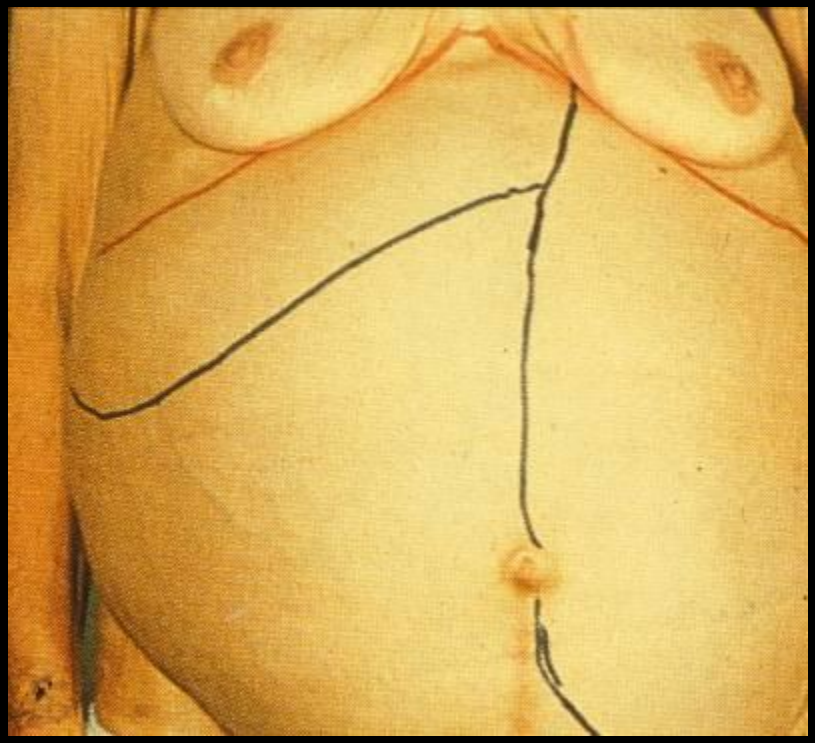
Spleen





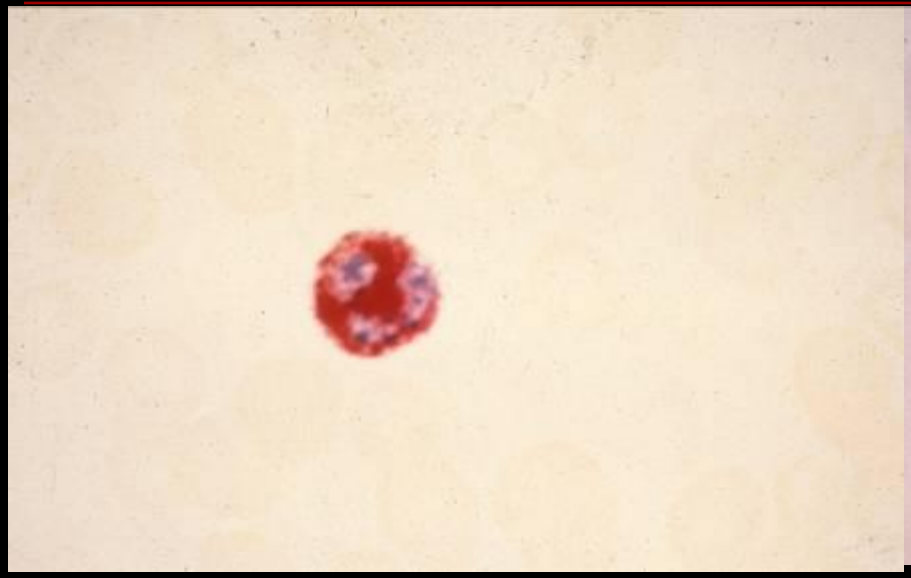


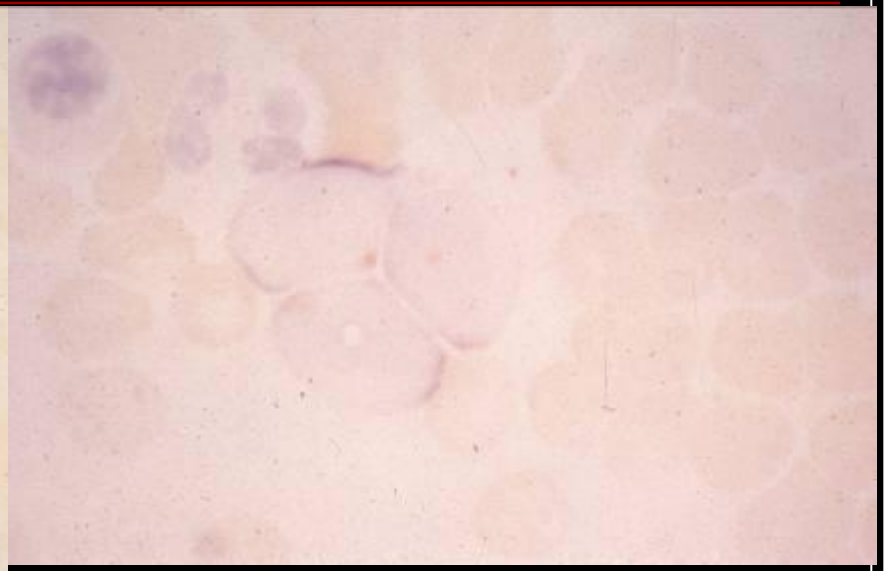
Chronic Myelogenous Leukemia



Hepatosplenomegaly

Leukocyte Alkaline Phosphatase (LAP)





LAP stain: 4+ cell

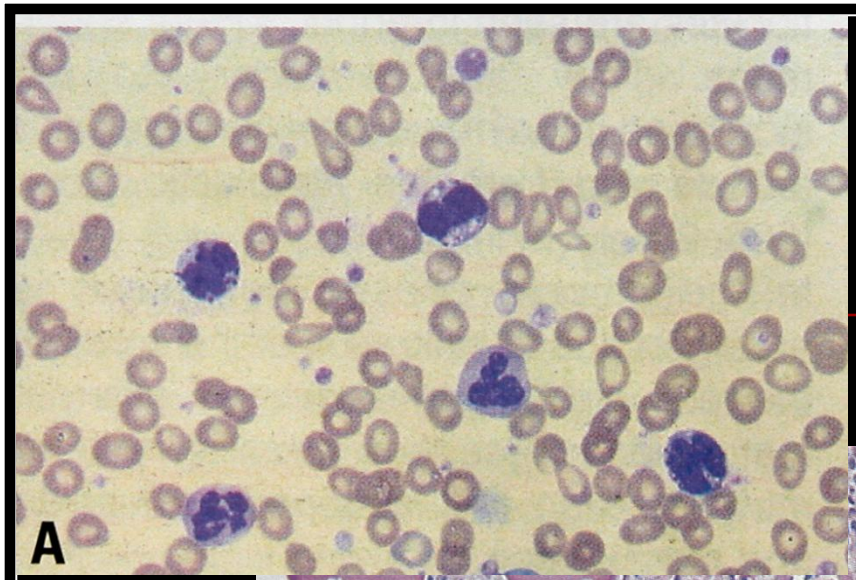
LAP stain: 0+ cell

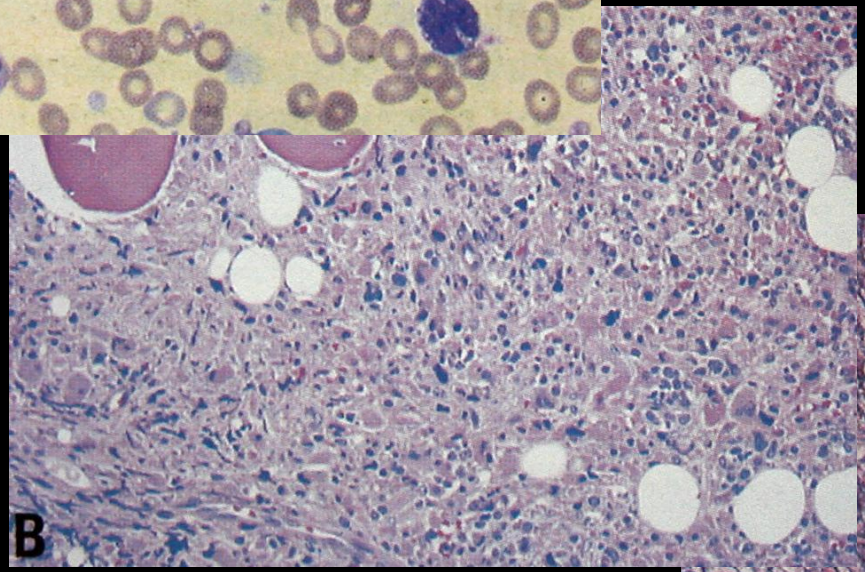
CML typically has a very low LAP score (less than 10, normal 10-90)

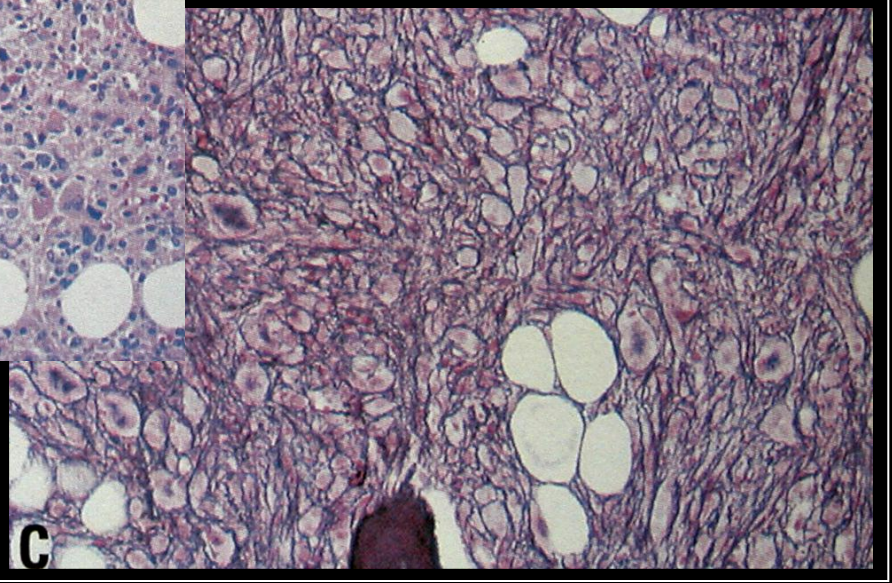
Morphology-Accelerated Phase (any one of these criteria)

- 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







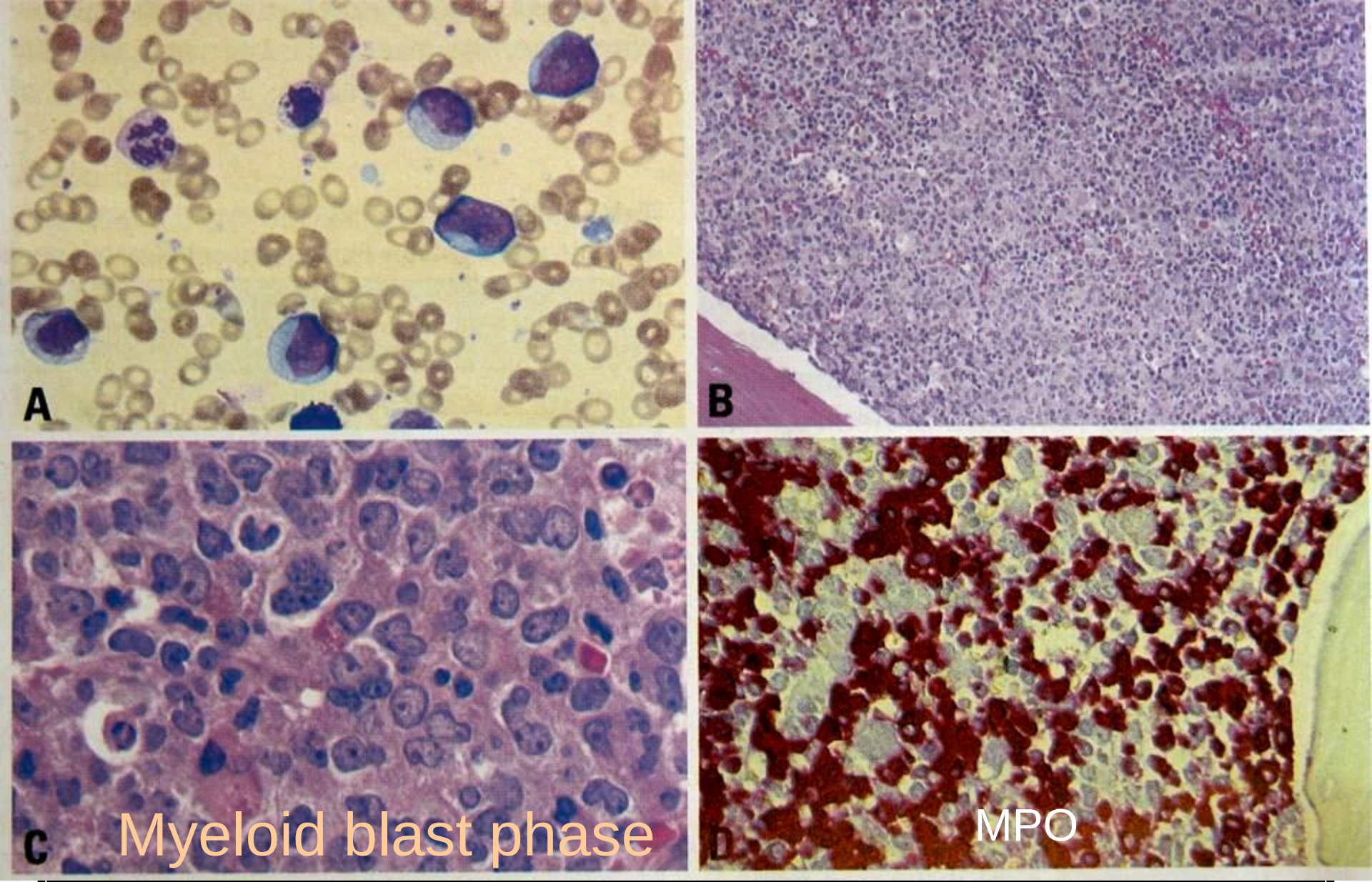
Morphology- Blast Phase

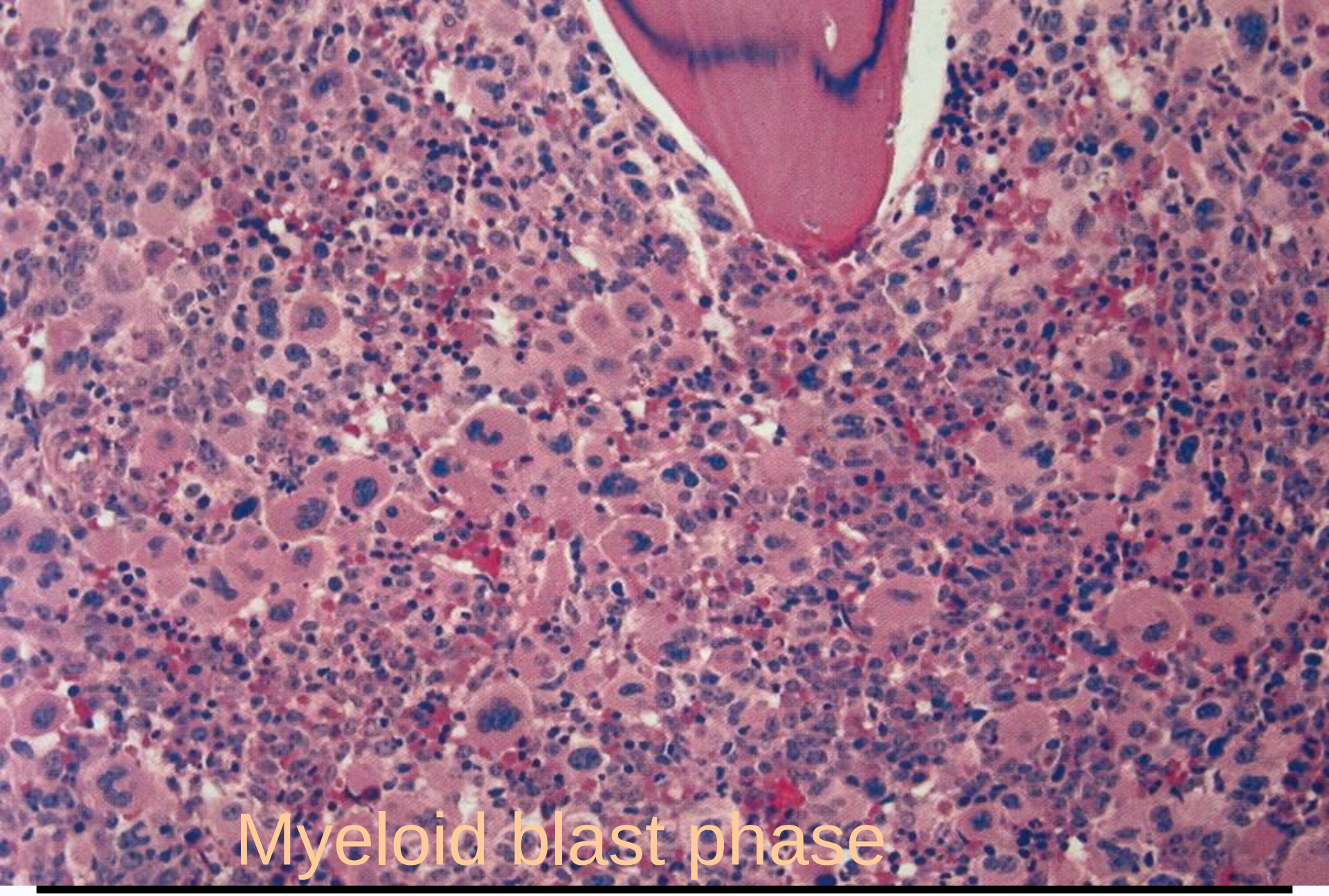
- >20% blasts in PB or BM
- Extramedullary proliferation of blasts
- Large aggregates and clusters in BM bx

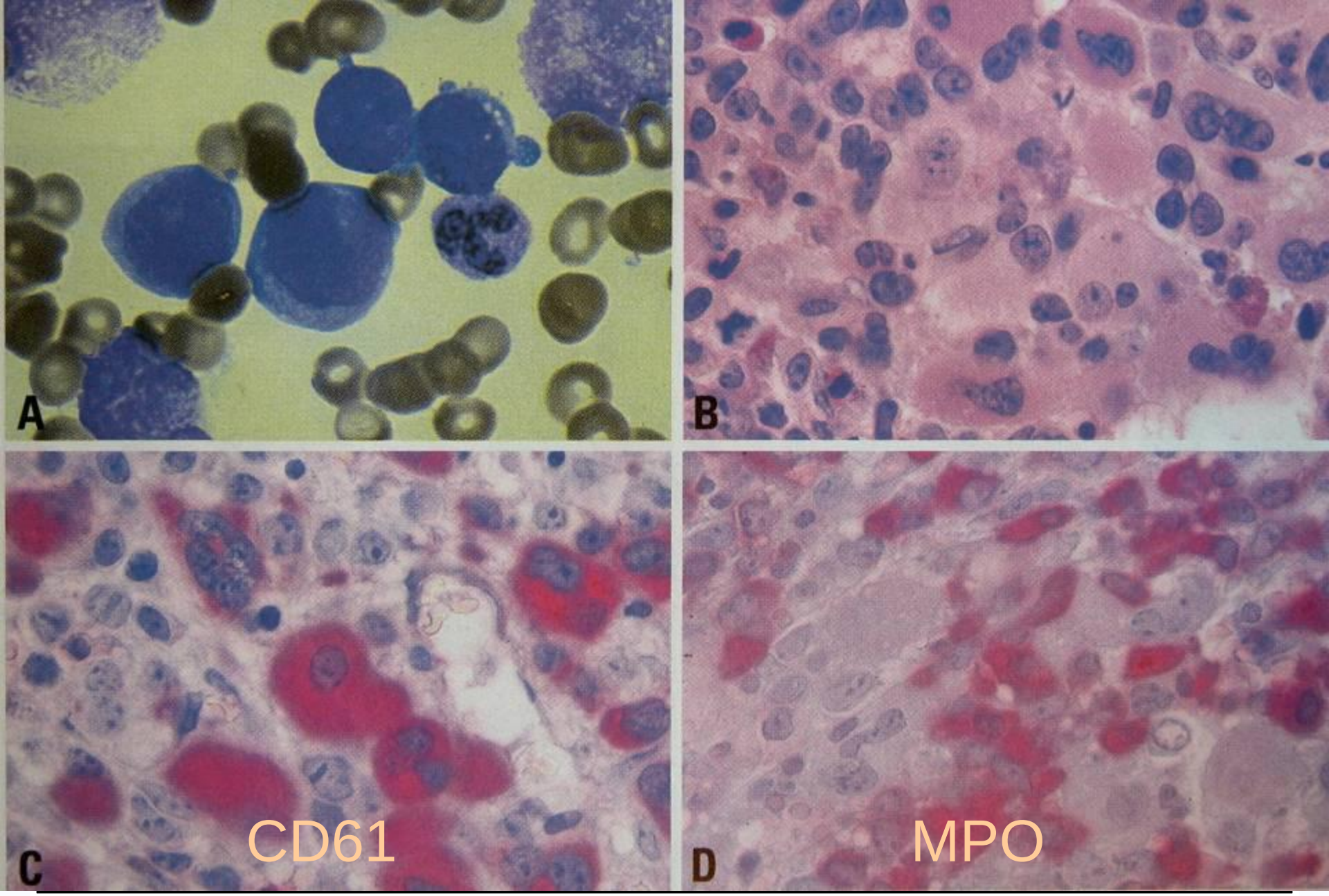
(acute leukemia: myeloid: 70%; lymphoid: 20-30%)

Cytochemistry/Immunophenotype

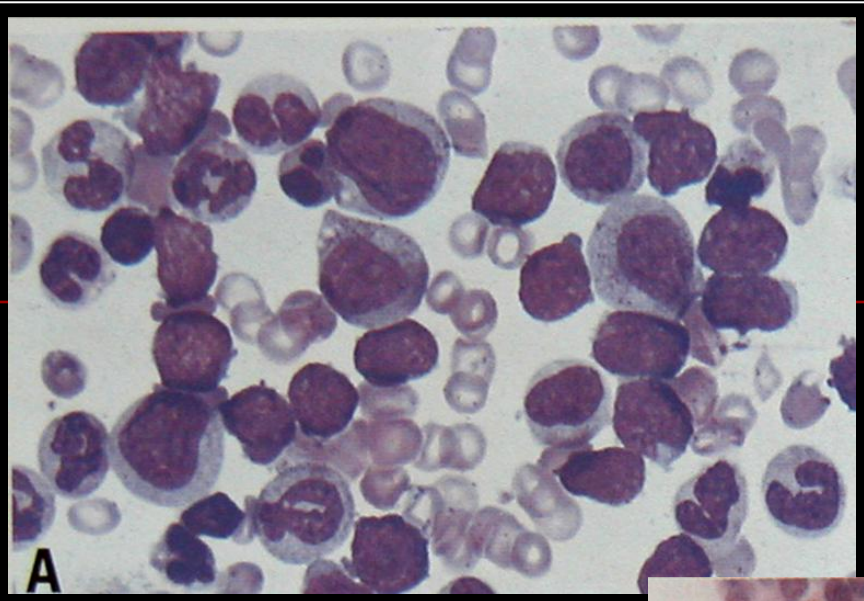
- Chronic phase: decreased LAP
- Blast phase: myeloid, lymphoid (precursor B)

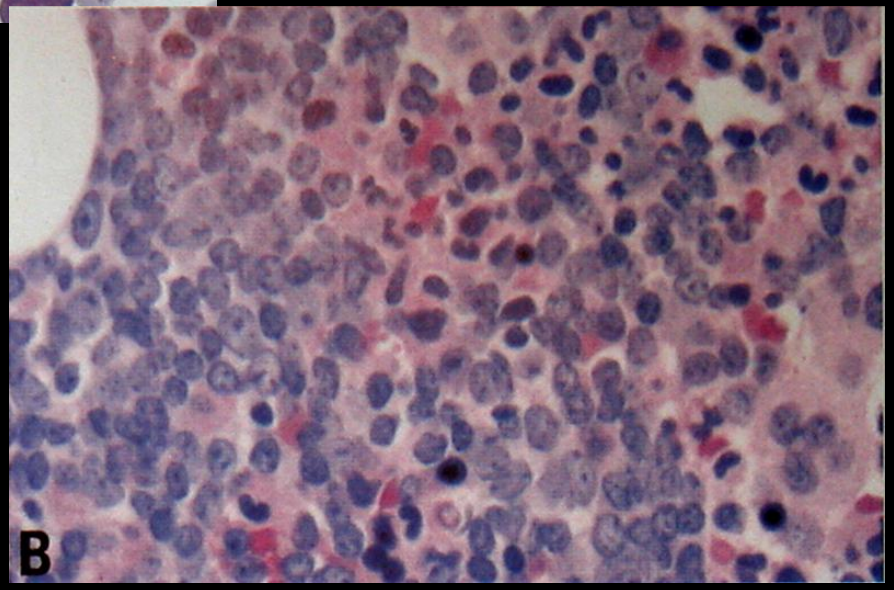

A
B
C
Myeloid blast phase
D
MPO


Myeloid blast phase

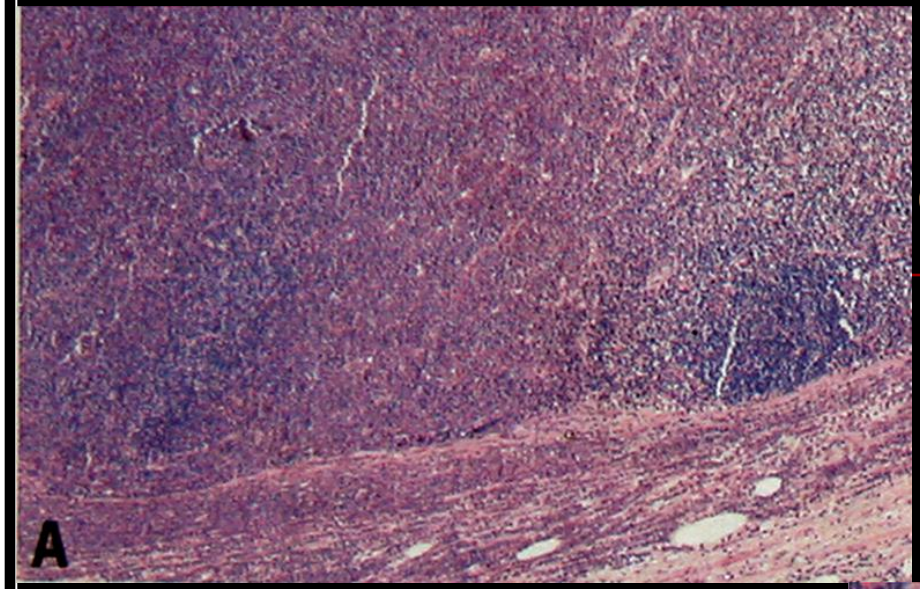

A
B
CD61
C
MPO
D

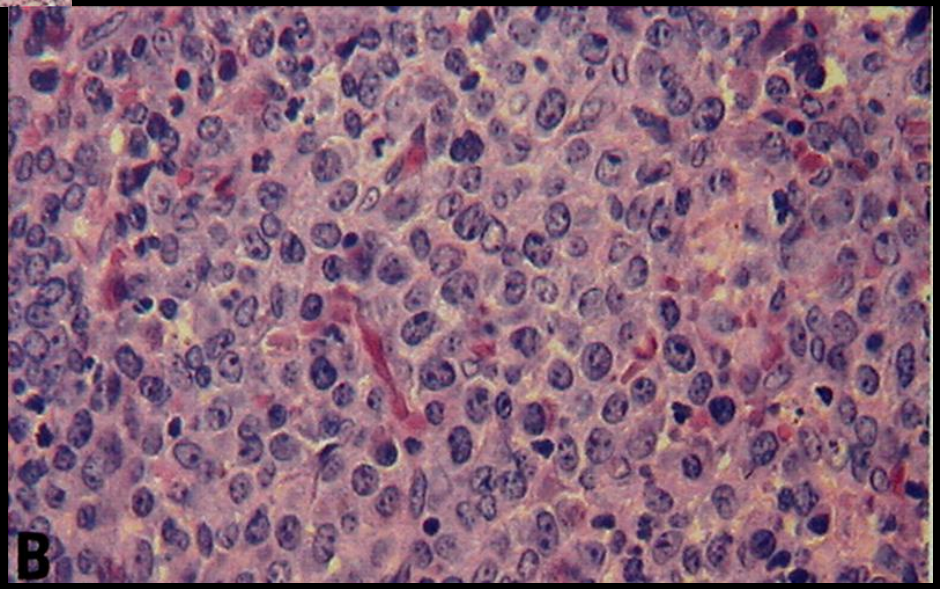
Lymphoid blast phase





Myeloid blast phase, extramedullary (LN)





Genetics/Molecular

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

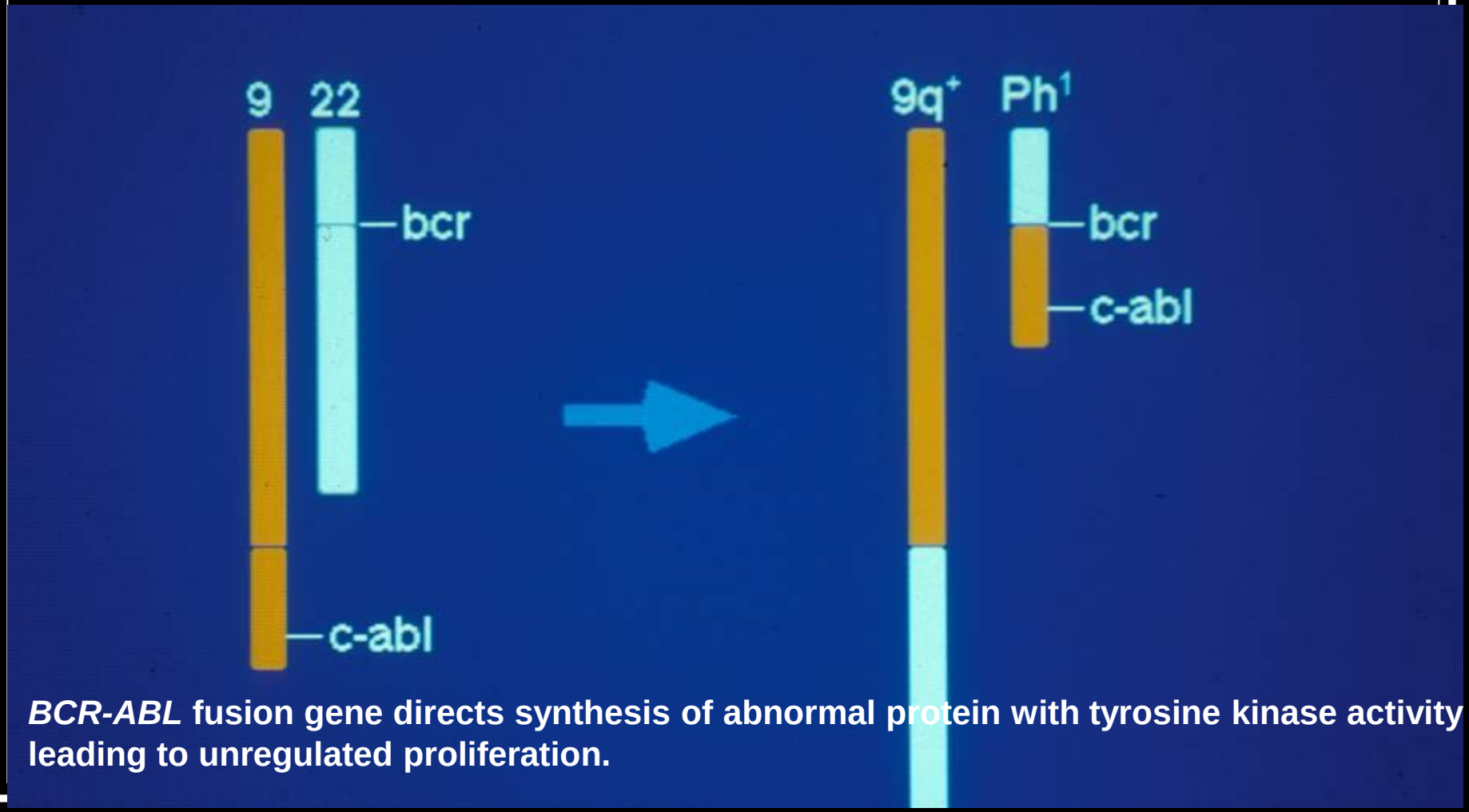
  M-bcr, p210, CML (almost always)

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

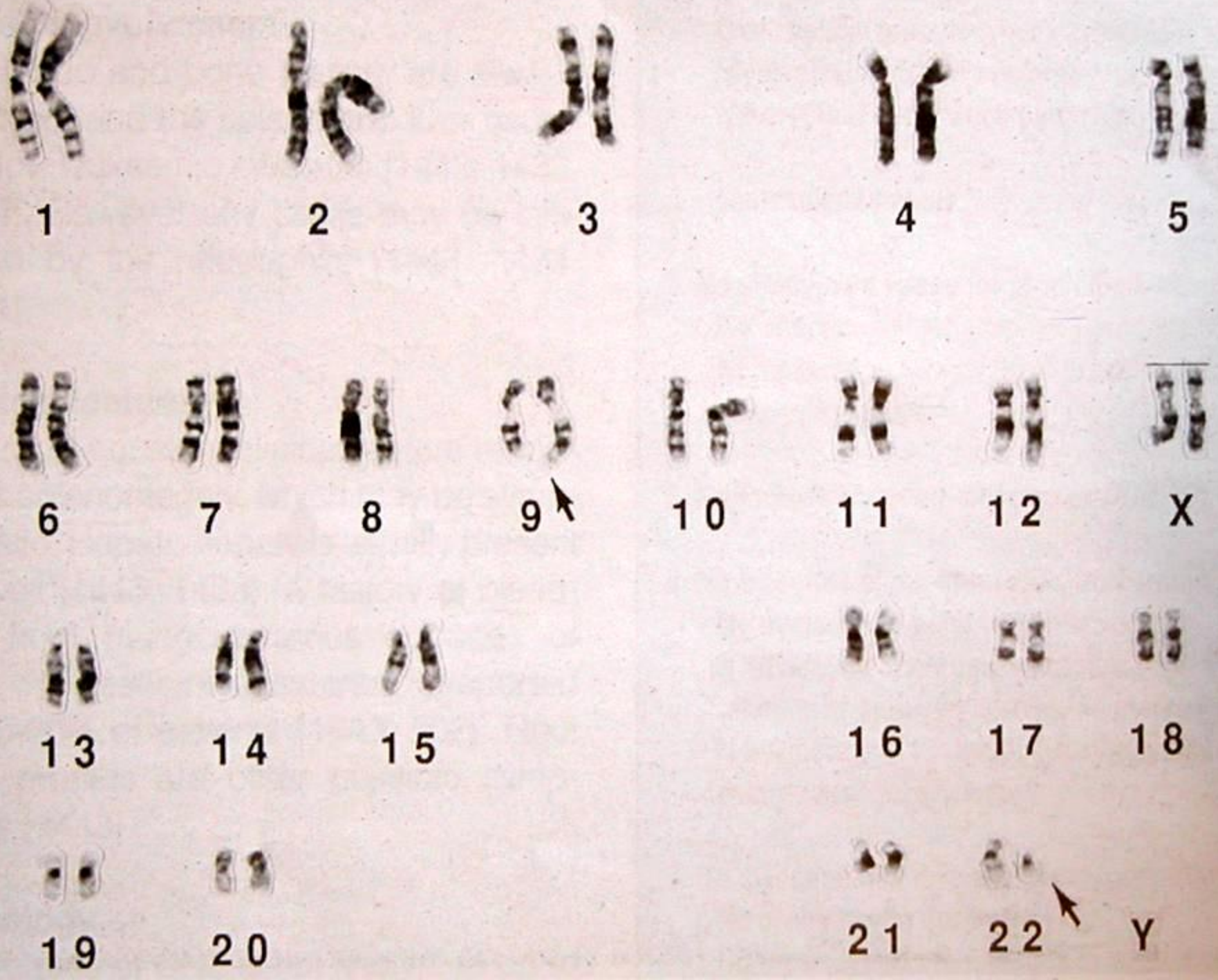
  m-bcr, p190, ALL, CML (rare)

  (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)

Philadelphia Chromosome



BCR-ABL **fusion gene directs synthesis of abnormal protein with tyrosine kinase activity leading to unregulated proliferation.**


1
2
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5
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X
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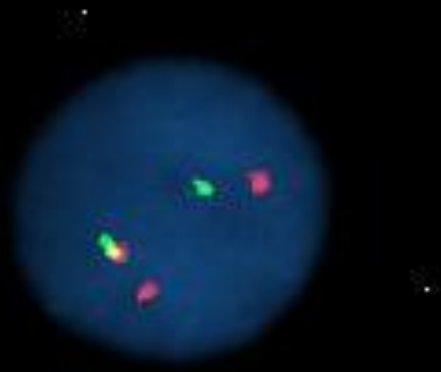
Y

FISH for bcr-abl1



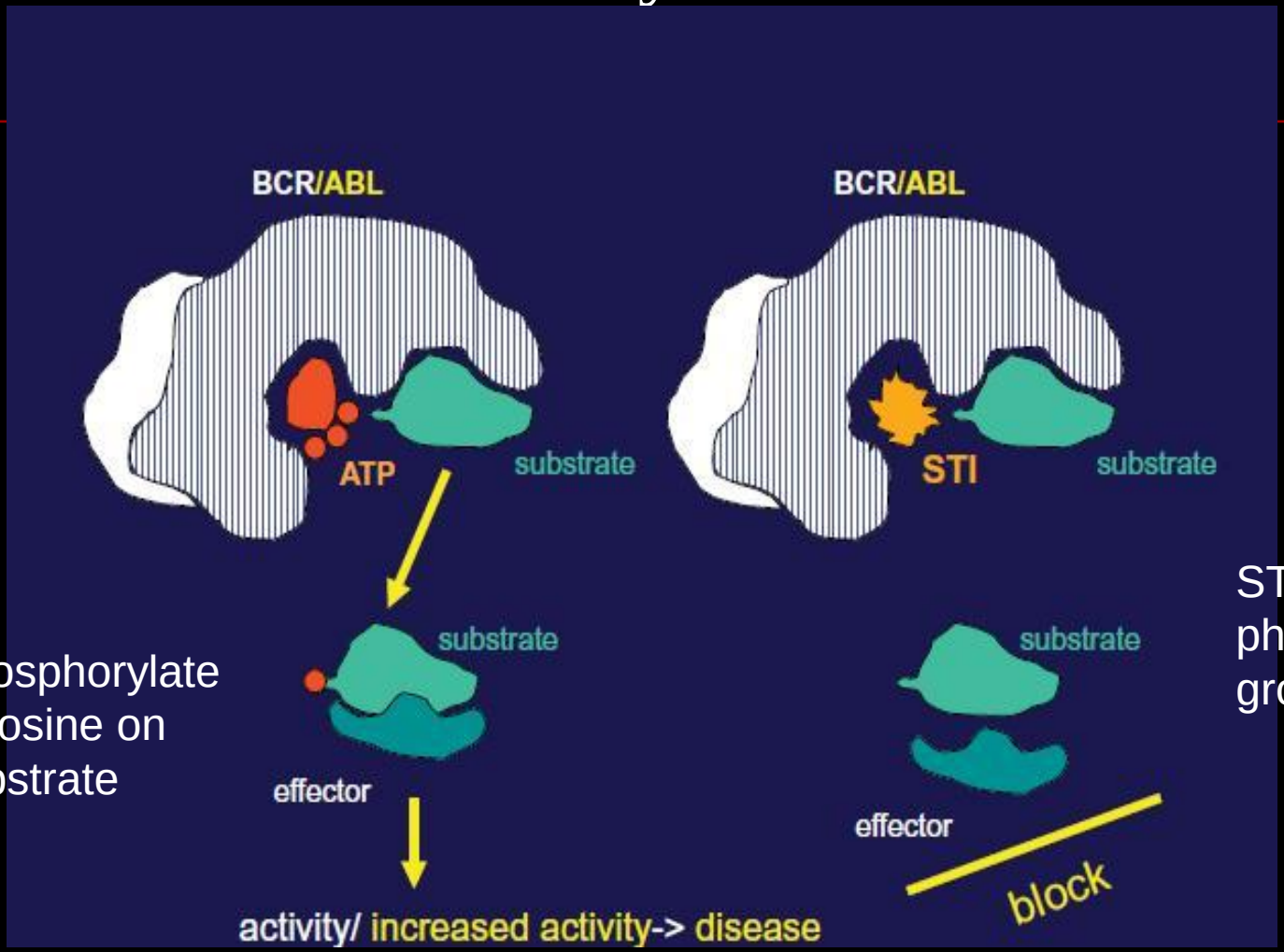
Bcr probe: green
Abl1 probe: red

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