Myelodysplastic/ myeloproliferative neoplasms (MDS/MPN)

MDS/MPN Diseases

- Chronic Myelomonocytic Leukemia
- Atypical Chronic Myeloid Leukemia, bcr/abl1 neg
- Juvenile Myelomonocytic Leukemia
- MDS / MPN, Unclassified

MDS/MPN: WHO Classification

- Monoclonal hematopoietic neoplasms with clinical, laboratory or morphologic findings of both myelodysplastic syndromes and chronic myeloproliferative diseases

MDS/MPD: General features

- Hypercellular bone marrow
  - Proliferation of one or more myeloid lineages
    - May be effective and functional with increased circulating cells
    - Or morphologically and functionally dysplastic
- Cytopenias
  - Ineffective proliferation of other lineages
- Blasts < 20%
- Splenomegaly and hepatomegaly

MDS/MPD: Exclusion criteria

- Patients with well-defined myeloproliferative diseases who develop dysplasia and ineffective hematopoiesis
- Ph or Bcr/Abl

Chronic Myelomonocytic Leukemia (CMML)

CMML: Definition

- Monoclonal hematopoietic disorder of bone marrow stem cells in which monocytosis is a major defining feature.

CMML: Etiology/Epidemiology

- Unknown
- Occupational or environmental carcinogens, ionizing irradiation and cytotoxic agents

- 3/100,000 over the age of 60, annually
- Median age at diagnosis: 65-75 years
- Male predominance, M:F= 1.5-3:1

CMML: Diagnostic criteria

- Persistent monocytosis (>1 x 10^9/L, or > 1 x 10^3/uL) in PB, Monocytes >10% of WBCs
- 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

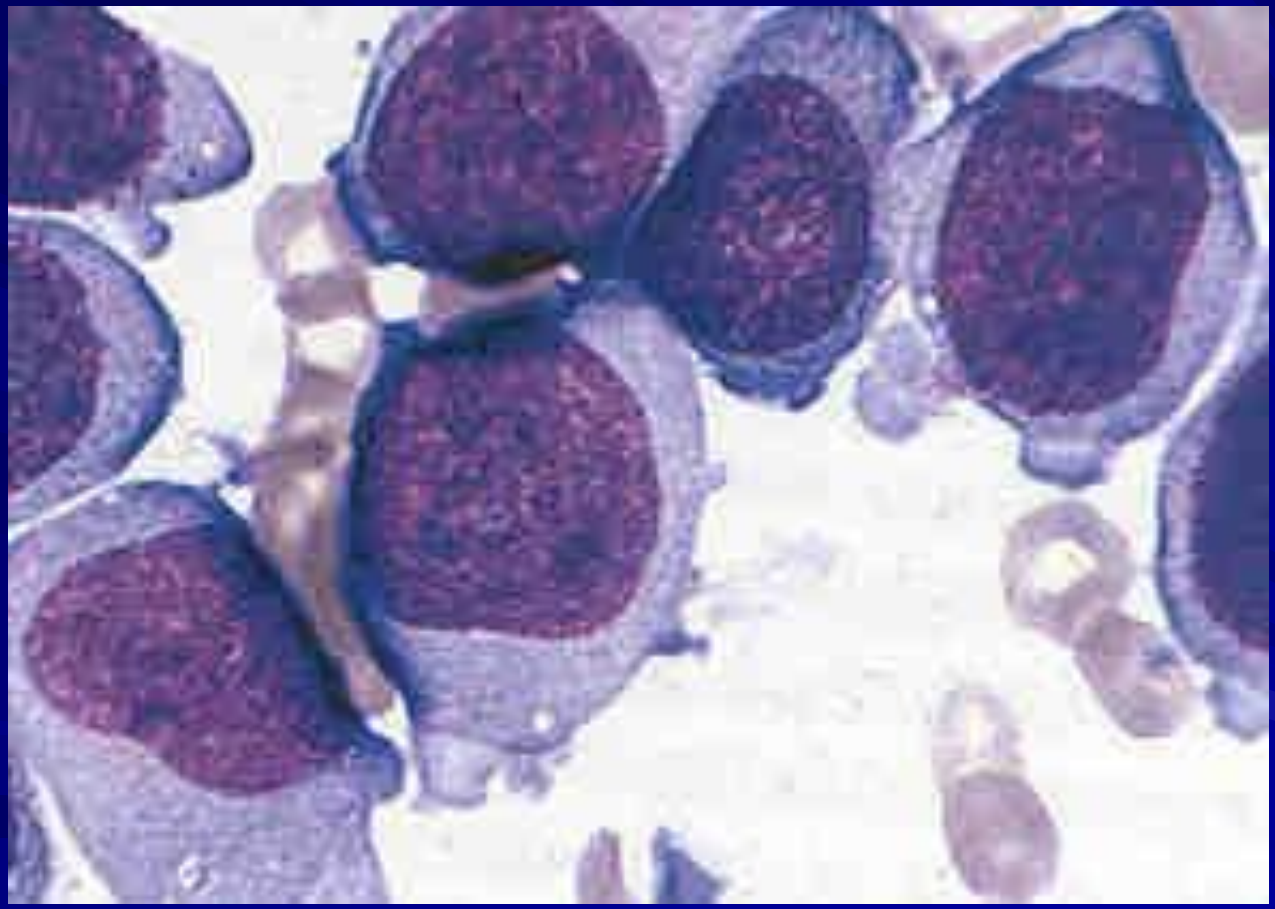
CMML: Diagnostic criteria

- Dysgranulopoiesis present in most cases, and may be more prominent in cases with normal or low WBC count
  - Neutrophils with nuclear hypolobation
  - Neutrophils with abnormal cytoplasmic granulation
- Mild anemia
- Moderate thrombocytopenia with atypical platelets

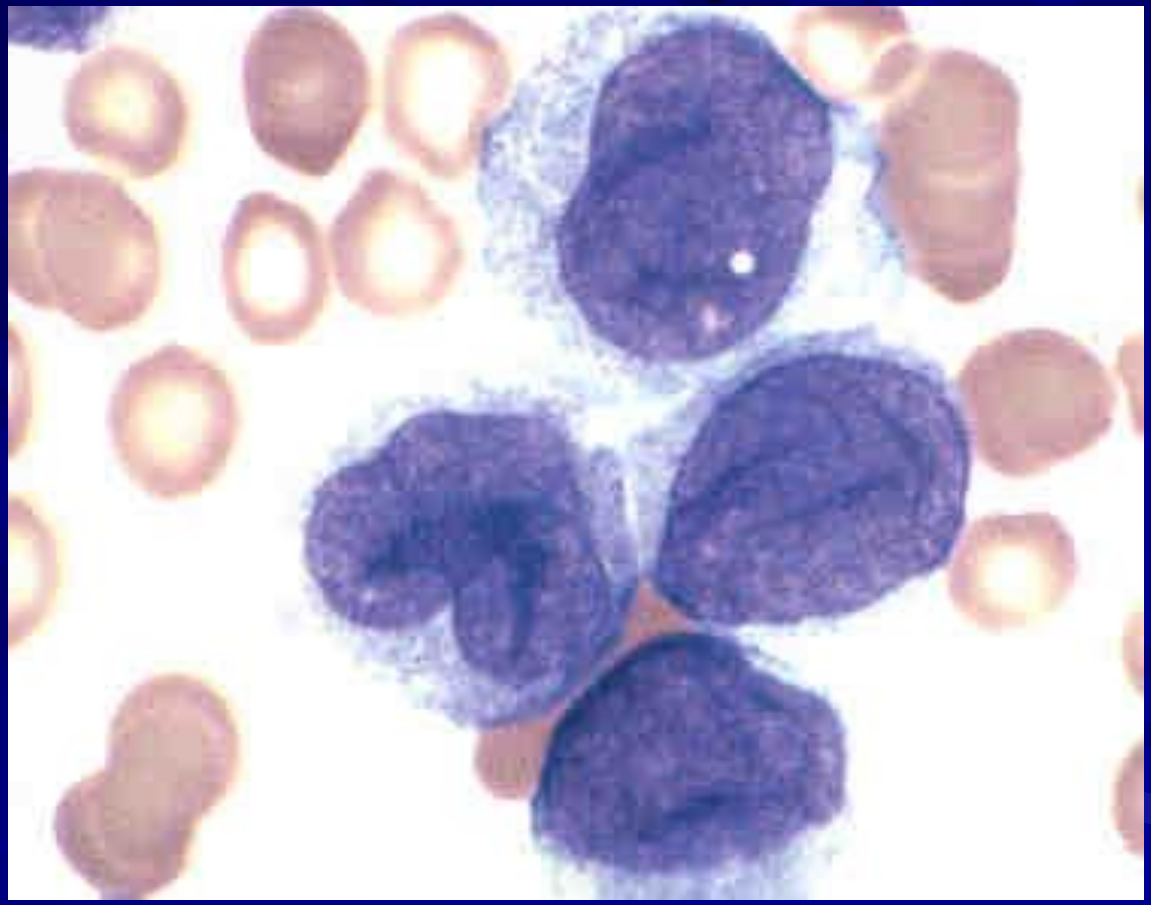
CMML: Clinical features

- Symptoms: fatigue,weight loss, fever, night sweats, infection, bleeding
- Sites of involvement
  - PB and BM always involved
  - Most common sites of extramedullary leukemic infiltration
    - Spleen
    - Liver
    - Skin
    - LNs

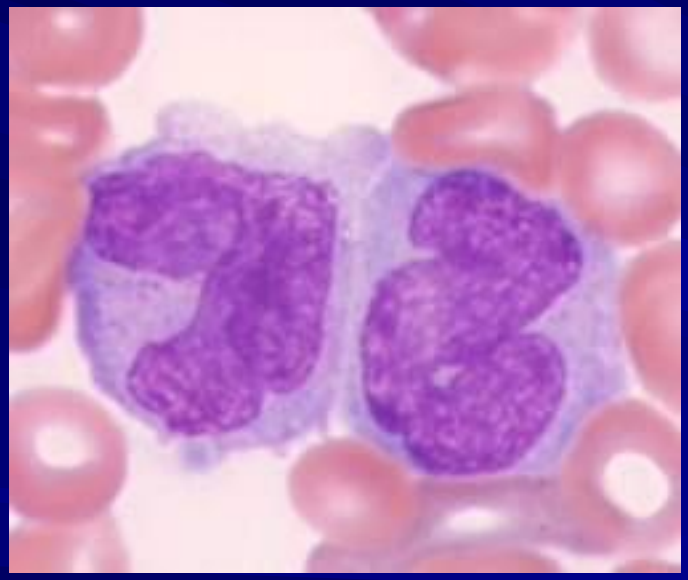
Monoblasts

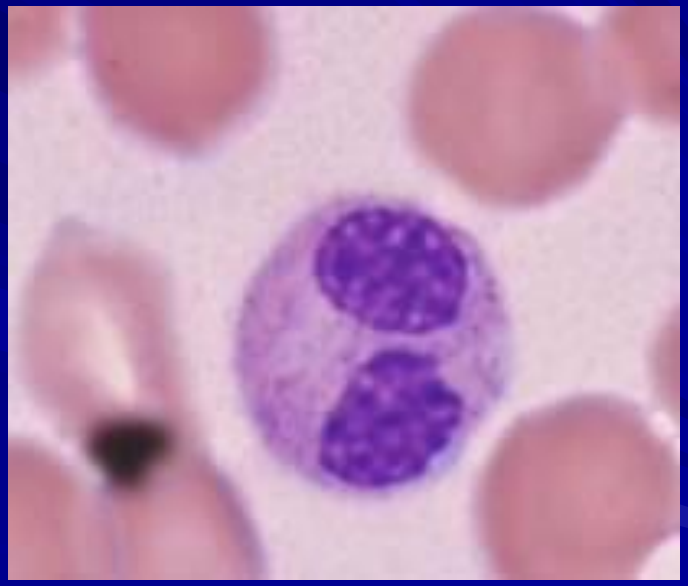


Promonocytes



CMML: PB morphology



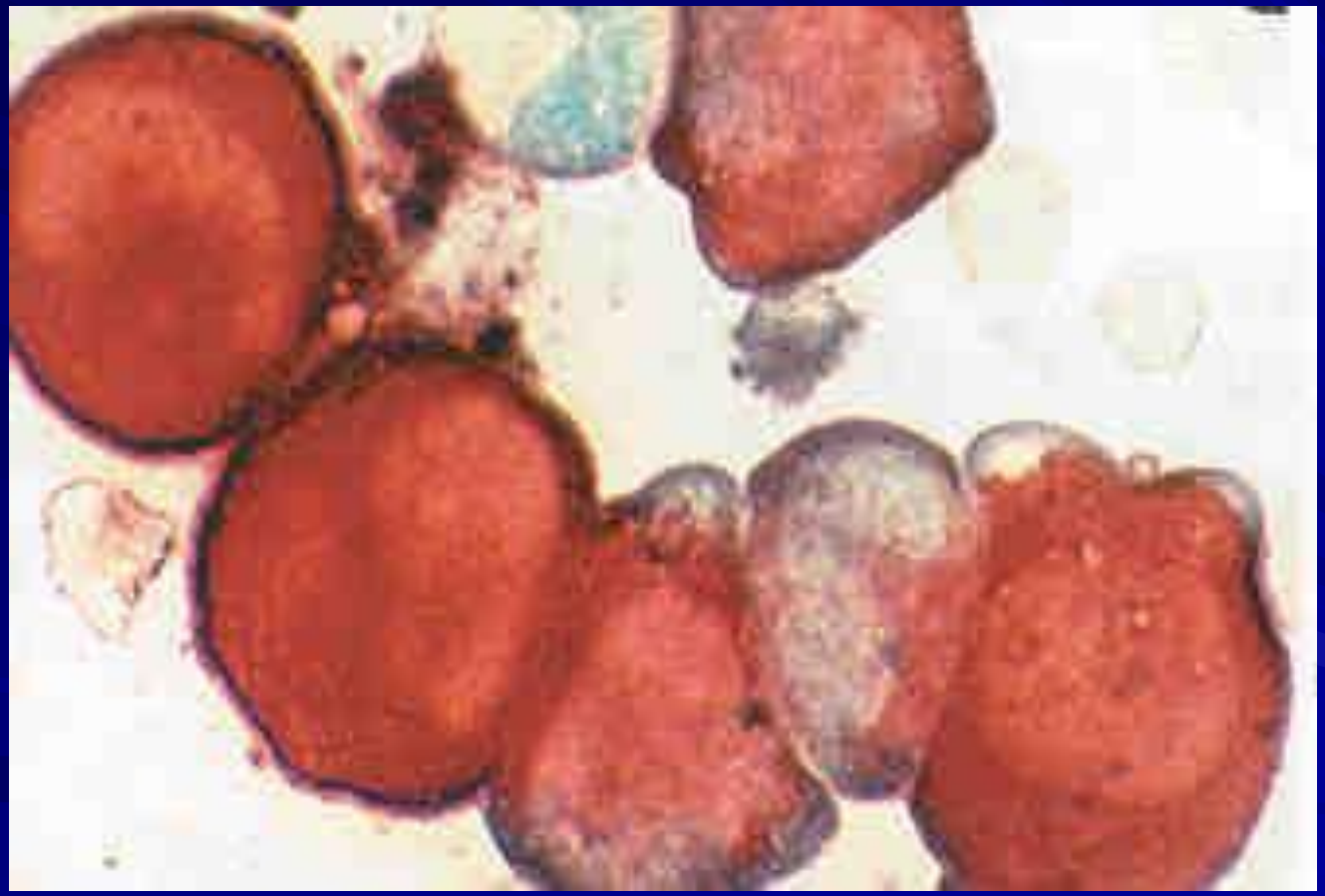


Monocytosis, dysplastic PMNs

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

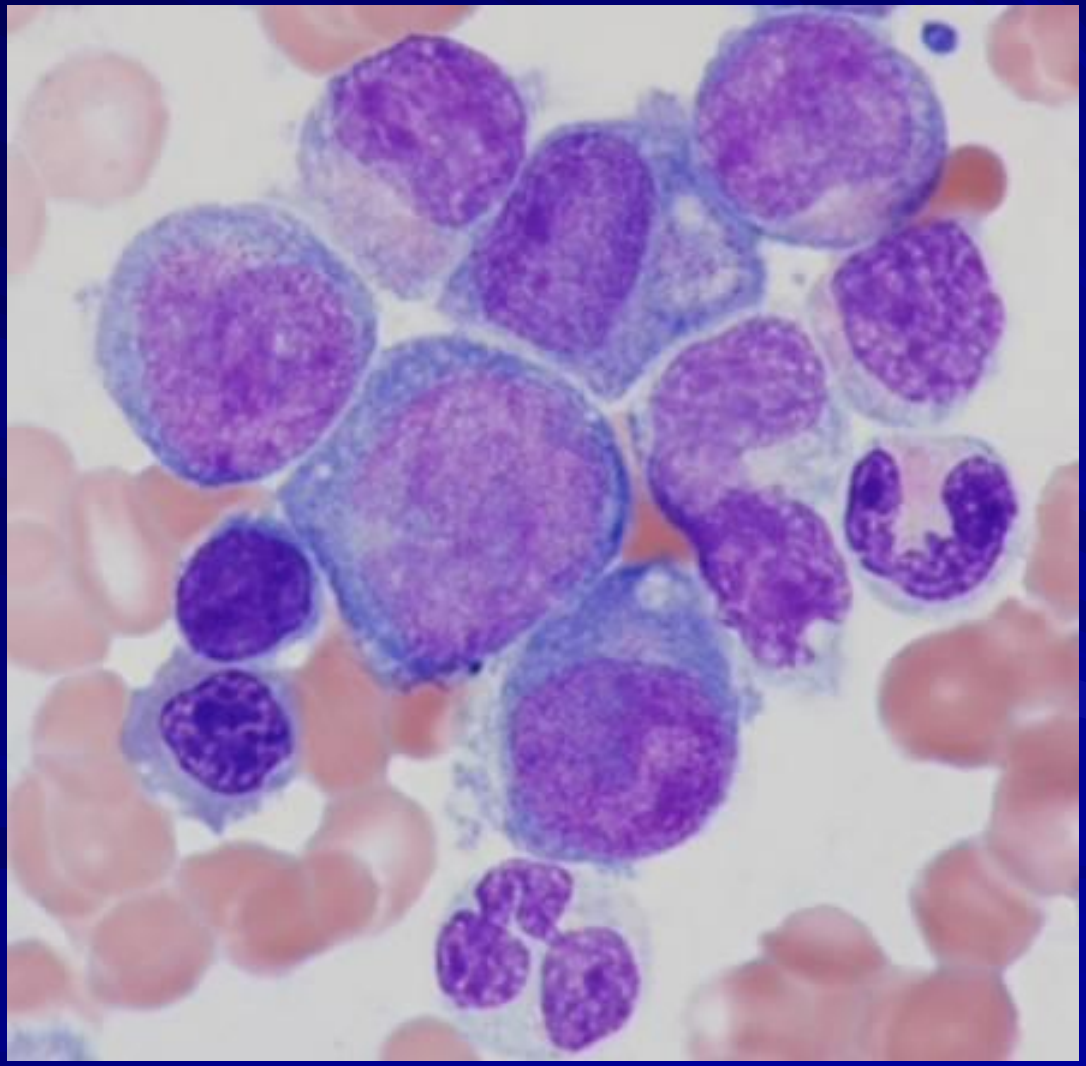
Butyrate



CMML: BM Morphology

- Dysgranulopoiesis in most cases
- Dyserythropoiesis (> 50%)
  - Megaloblastic changes, abnormal nuclear contours, ringed-sideroblasts
- Megakaryocytic dysplasia (80%)
  - Abnormal nuclear lobation and micromegs
- Variable degree of fibrosis (30%)

CMML: BM Morphology



CMML: Clinical features

- In about 50%
  - WBC count normal or slightly decreased
  - “MDS-like” picture
- In about 50%
  - WBC count increased
  - “MPD-like” picture

CMML: Clinical features

- "MDS-CMML" and "MPD-CMML"
  - Arbitrary cut-off for leukocyte count (13,000/µl)
    - Little evidence of clinical relevance
    - Duration of survival times similar
    - No cytogenetic or molecular differences
    - MDS-type may become more proliferative

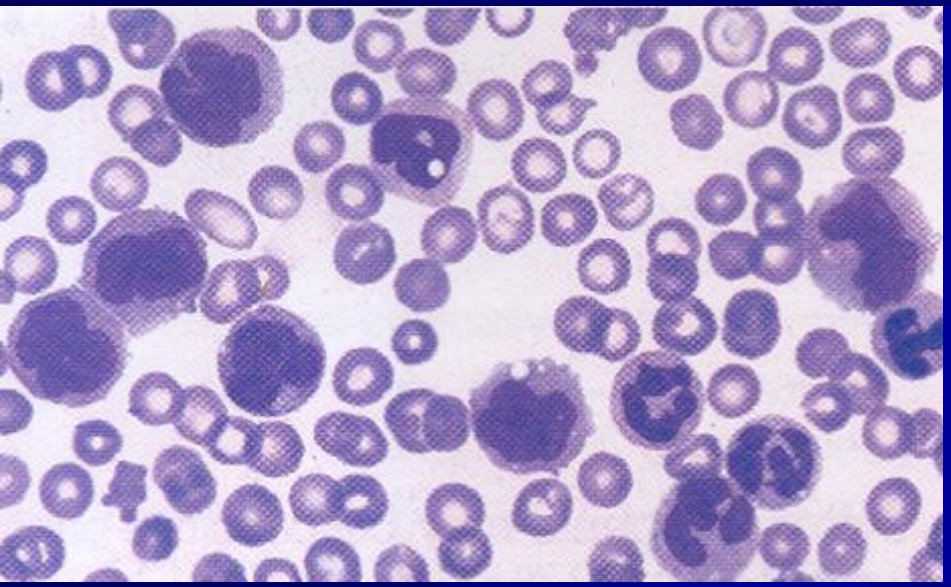
CMML: Morphology; other organ systems

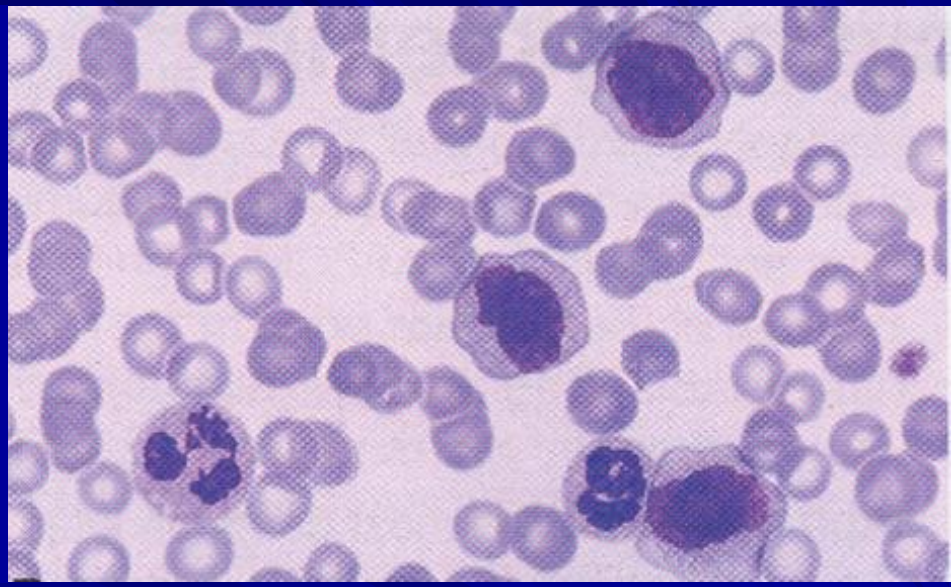
- Spleen
  - Red pulp infiltration by leukemic cells
- Lymph node involvement
  - Uncommon
  - Sign of transformation to a more acute phase
  - LN may be diffusely infiltrated by myeloid blasts

CMML: Classification

- CMML-1
  - PB blasts <5% of WBC and <10% of nucleated BM cells
- 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
- AML
  - PB and/or BM blasts 20% or more

CMML-1

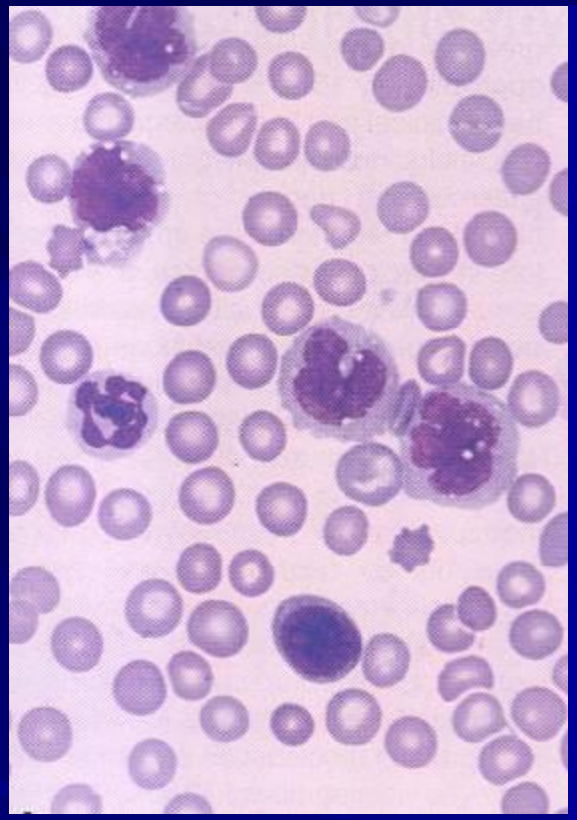
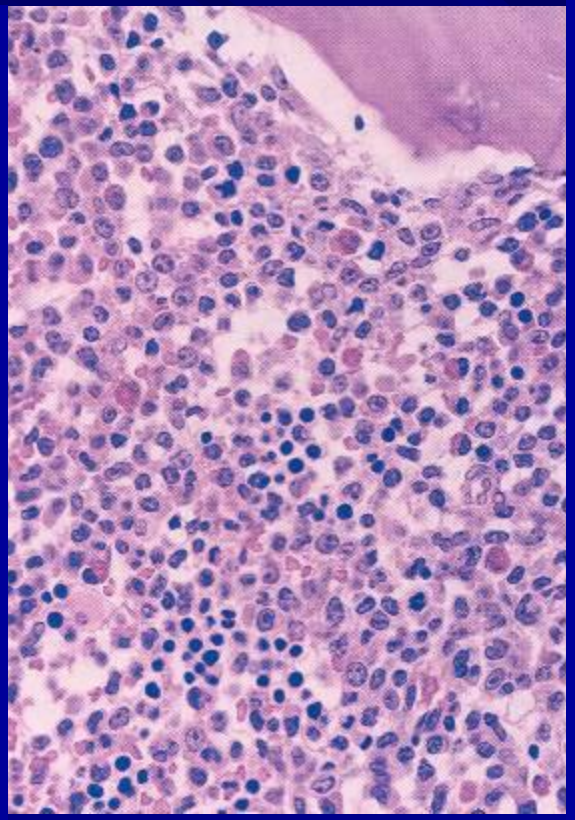
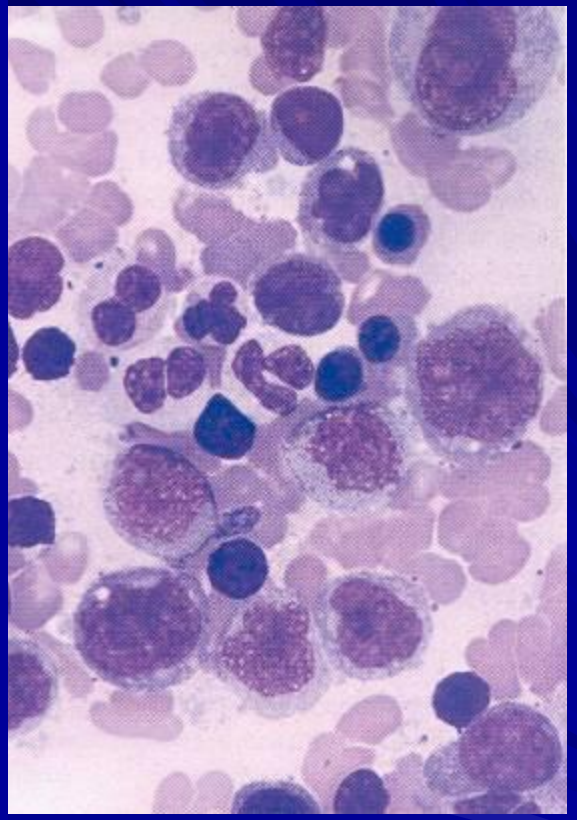




- 50% of cases:↑ WBC with minimal dysgranulopoiesis
- 50% of cases: Normal WBC with absolute monocytosis, neutropenia and dysgranulopoiesis.

- Degree of leukocytosis, neutrophilia and dysplasia is variable.

CMML-2

- Blasts 5-19% in the blood
- Blasts <20% in BM
- Auer rods present

CMML: Immunophenotype

- CD33/13 (+), variable CD14/64/68
- Increased percentage of CD34(+) cells may be associated with early transformation to acute leukemia

CMML: Genetics

- Nonspecific cytogenetic abnormalities in 20-40%
  - Trisomy 8
  - del (7q)
  - Structural abnormalities of 12p
  - JAK2 V617F uncommon
  - Abnormalities of 11q23 uncommon -> suggest acute leukemia

CMML: Genetics

- RAS point mutations (40%)
- i(17q)
  - More aggressive course
- Cases that may resemble CMML with marked eosinophilia:
  -t(5;12)(q31;p12) resulting in ETV6/PDGFRB abnormal fusion gene -> MPN with eosinophilia and ETV6/PDGFRB mutation
  -del(4)(q12) resulting in FIP1L1/PDGFRA abnormal fusion gene -> MPN with eosinophilia and FIP1L1/PDGFRA mutation

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

Atypical Chronic Myeloid Leukemia (aCML), bcr/abl1 negative

aCML: Characteristic features

- Leukocytosis with dysplastic immature and mature neutrophils
- Multilineage dysplasia
- No Ph or Bcr/Abl

aCML: Epidemiology

- Unknown incidence
- Estimated 1-2 cases for every 100 Ph(+) CML
- Median age: 7^{th}-8^{th} decades
- M:F = 1-2.5:1

aCML: Diagnostic criteria

- PB leukocytosis (mature and immature neutrophils), WBC >13 $x10^9$/L (13 $x10^3$/uL)
- Prominent dysgranulopoiesis (major characteristics)
- No Ph or Bcr/Abl
- No rearrangement of PDGFRA or PDGFRB
- Neutrophil precursors (promyelocytes, myelocytes, metamyelocytes) >10% of WBCs
- Basophils <2% of WBCs

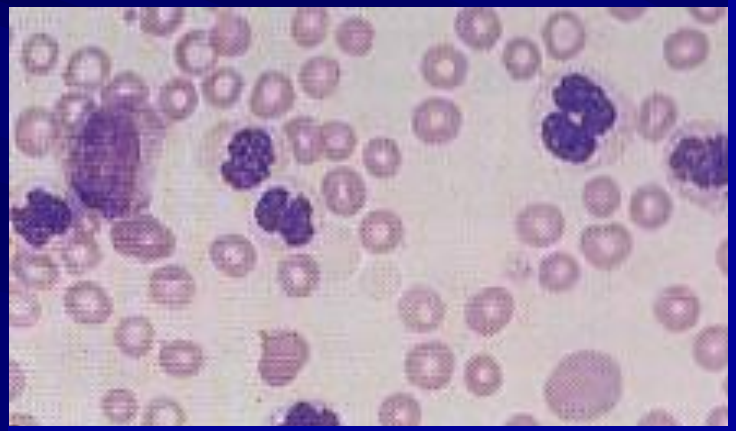
aCML: Diagnostic criteria

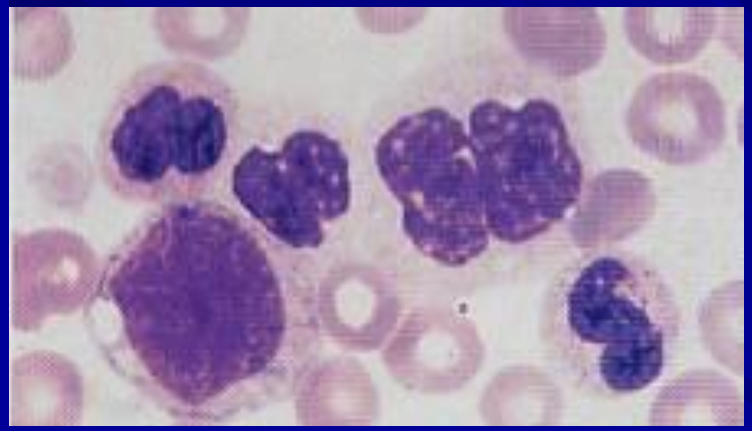
- Monocytes < 10% of WBC
- Hypercellular BM with granulocytic proliferation and dysplasia, with or without erythroid and megakaryocytic dysplasia
- Some cases may have megakaryocytes similar to those in CML
- <20% blasts in PB and BM

aCML: Clinical features

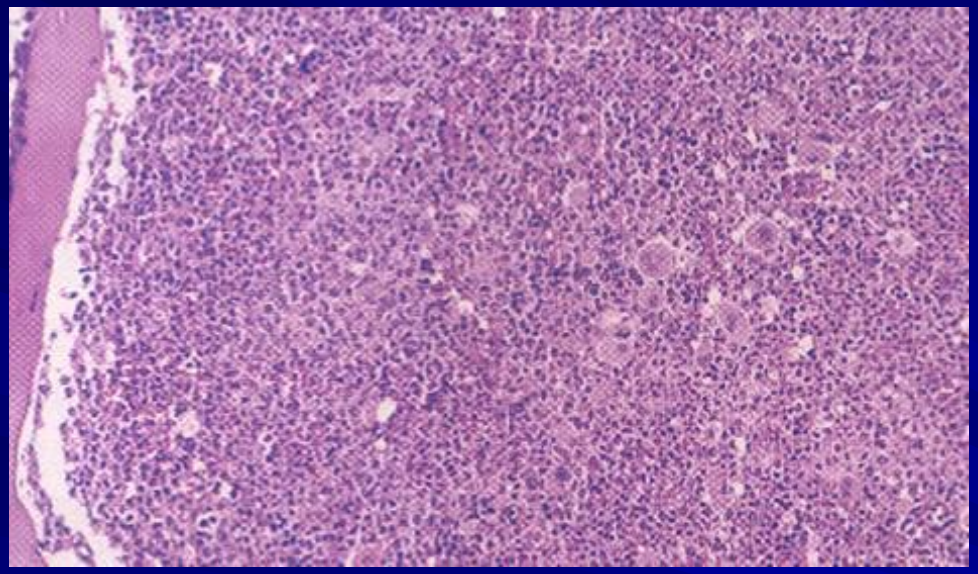
- PB and BM always involved
- Spleen and liver involvement: common
- Most patients have symptoms related to
  - Anemia
  - Thrombocytopenia
  - Splenomegaly

aCML: PB morphology





aCML, BM



- Hypercellularity due granulocytic proliferation. Bone marrow biopsy.

aCML: BM morphology

- BM megakaryopoiesis and erythropoiesis are variable in quantity
- M:E >10:1
- Increased reticulin fibers at diagnosis or later in course of disease

aCML: Cytochemistry/Immunophenotype

- No specific abnormalities

aCML: Genetics

- +8, +13, del(20q), i(17q), del(12p)
  - 80% of cases
  - Not specific
  - No Ph or Bcr/Abl1
  - Some cases with JAK2 V617F
  - 30% of cases with NRAS or KRAS

aCML: Course and prognosis

- Median survival < 20 months
- Poor prognostic factors
  - Thrombocytopenia
  - Marked anemia
- 25-40% evolve to acute leukemia
- The remaining patients die of marrow failure

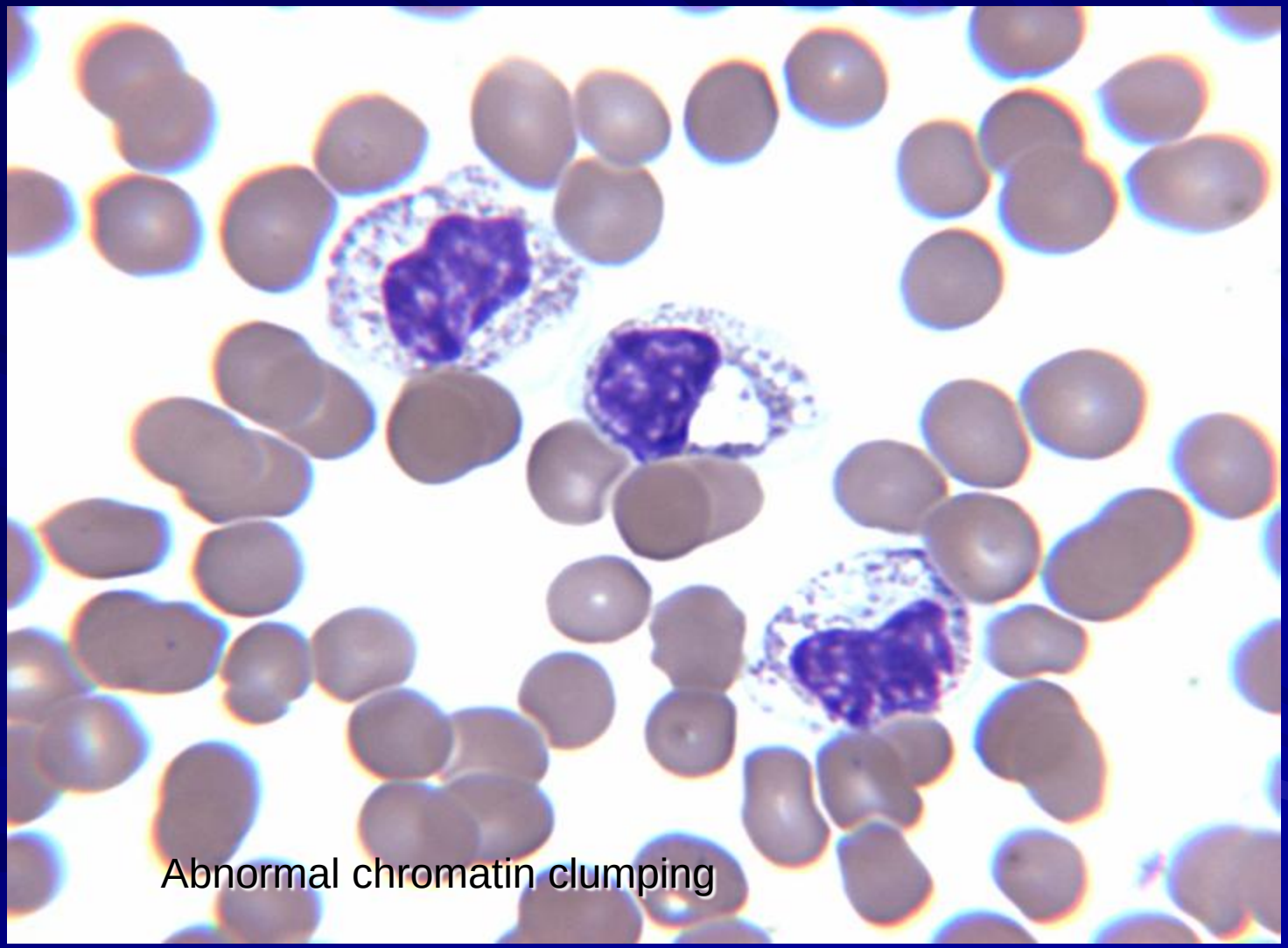
aCML: Variant

- Syndrome of abnormal chromatin clumping
  - PB morphology
    - high percentage of immature and mature neutrophils with exaggerated clumping of chromatin (“chromatin condensation”)
    - nuclear hypolobation and cytoplasmic hypogranularity are common
    - WBC count usually increased
    - Severe anemia and thrombocytopenia

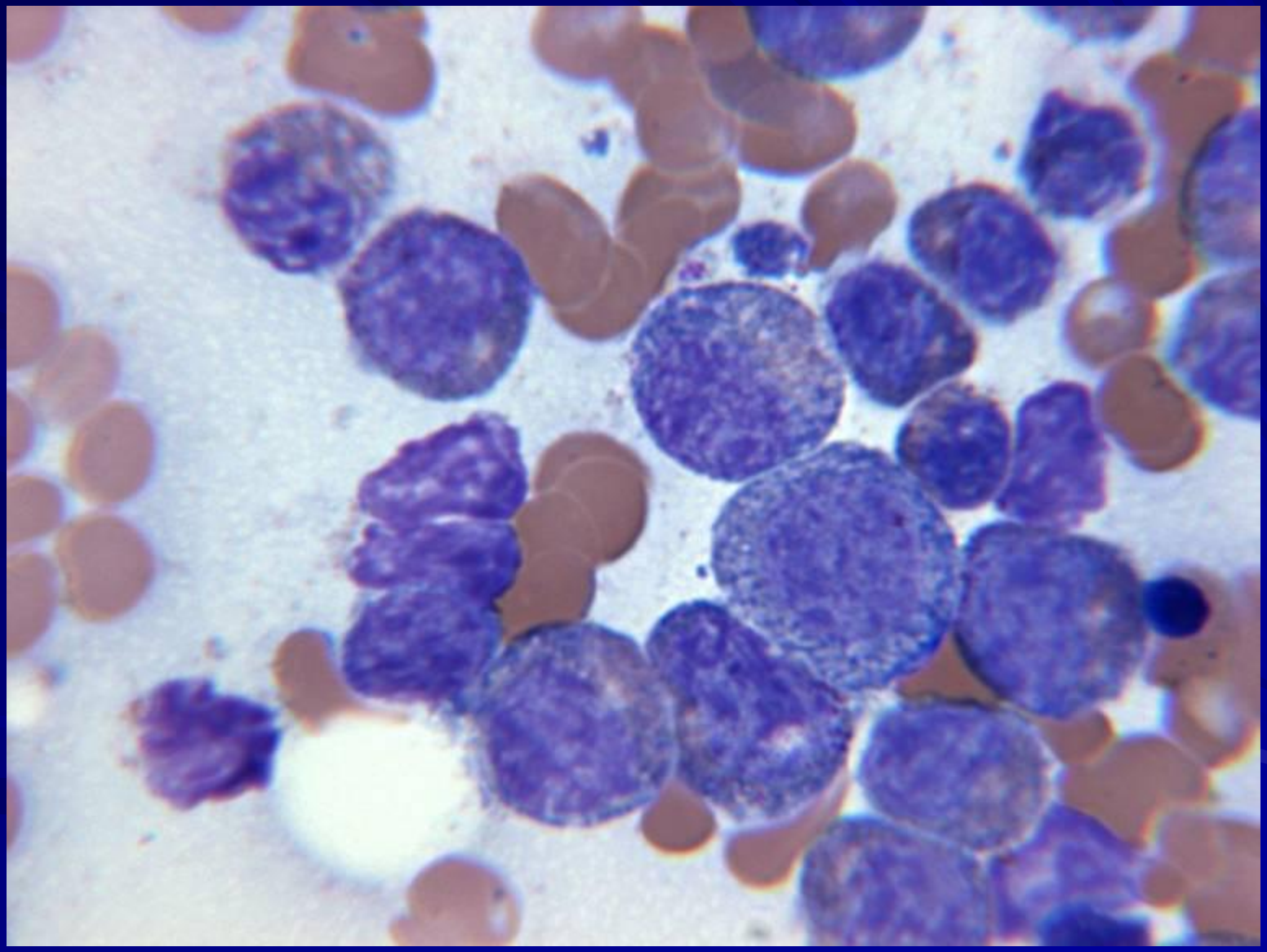
aCML

- Syndrome of abnormal chromatin clumping
  - BM morphology
    - hypercellular
    - granulocytic proliferation with nuclear abnormalities similar to PB
    - Moderate dysplasia in erythroblastic and megakaryocytic lineages
  - Survival is similar to aCML

aCML: Peripheral Blood Smear



aCML: Aspirate Smear



aCML: Aspirate Smear