# Juvenile Myelomonocytic Leukemia (JMML)

# JMML: Definition

- Monoclonal hematopoietic disorder of childhood characterized by proliferation of the granulocytic and monocytic lineages
- Erythroid and megakaryocytic abnormalities common
- Bone marrow stem cell with multilineage potential in the myeloid series

# JMML: Diagnostic Criteria

- PB monocytosis > 1 x $10^9$/L (1 x $10^3$/uL)
- Blasts < 20% of WBCs in the blood and of the nucleated bone marrow cells
- No Ph chromosome or BCR/ABL

# JMML: Diagnostic Criteria

- Two or more of the following:
  - Hemoglobin F increased for age
  - Immature granulocytes in PB
  - WBC>10 x $10^9$/L
  - Clonal chromosomal abnormality (monosomy 7)
  - GM-CSF hypersensitivity of myeloid progenitors *in vitro*

# JMML: Epidemiology

- 1.3 per million children ages 0-14, annually
- 2-3% of all childhood leukemias
- 20-30% of all cases of myeloproliferative and myelodysplastic diseases in patients less than 14-years-old.

# JMML: Epidemiology

- 75% occur in children <3 years old
- Male predominance of ~ 2:1
- 10% of patients have neurofibromatosis type 1 (NF-1, with 200-500 fold increased risks)

# JMML: Sites of Involvement

- PB and BM always involved
- Leukemic infiltration
  - Liver
  - Spleen
  - LN
  - Skin
  - Respiratory tract

# JMML: Clinical Features

- Constitutional symptoms
- Bleeding
- Bronchitis or tonsillitis in (50%)
- Maculopapular skin rash (40-50%)
- Café-au-lait
- Hepatosplenomegaly (~100%)

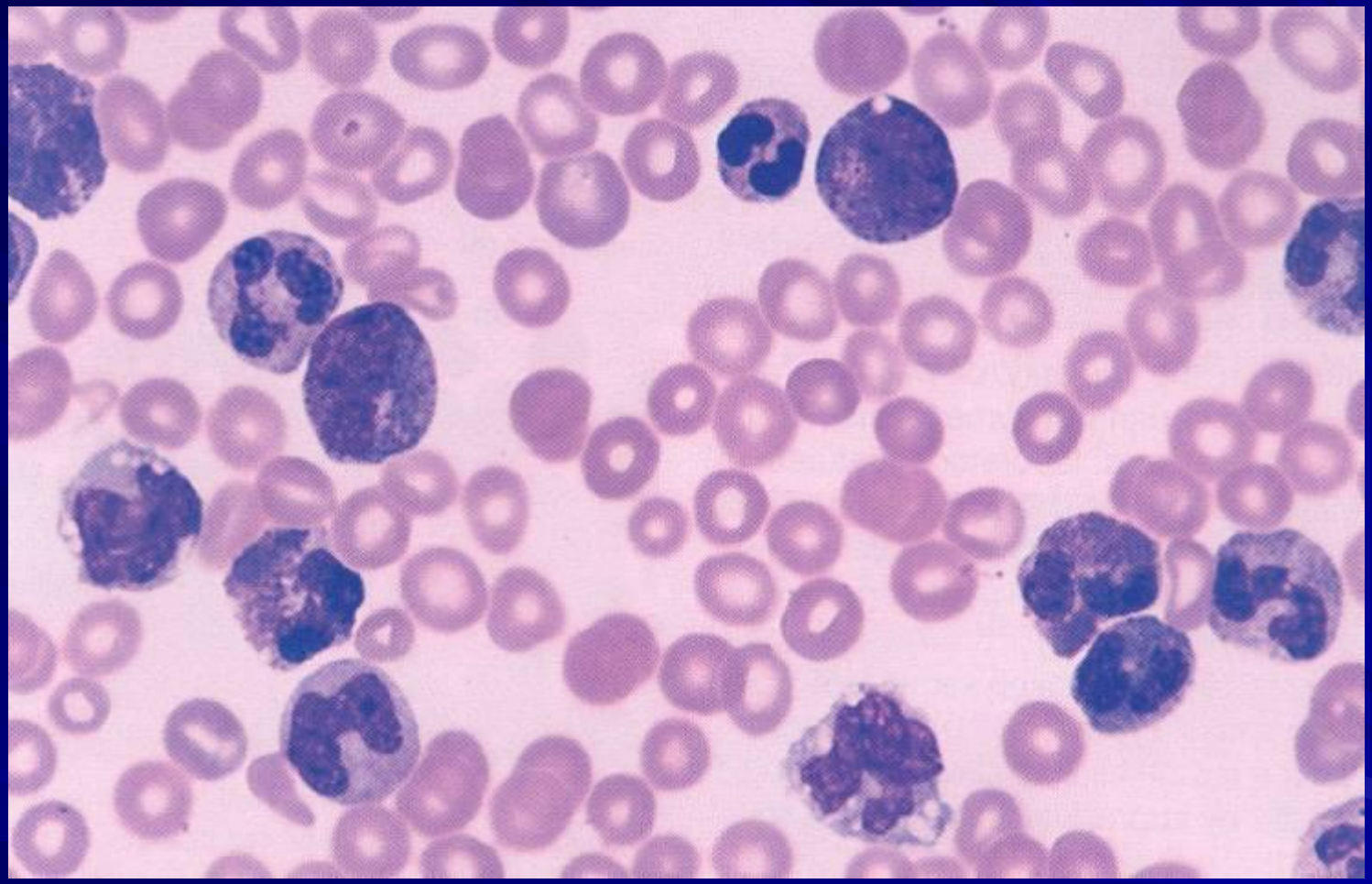
# JMML: PB Morphology

- Leukocytosis
  - WBC 25-35 x $10^9$/L
  - > 100 x $10^9$/L in 5-10%
  - Neutrophils (including Promyelocytes and myelocytes) and monocytes
  - Blasts usually < 5%, always < 20%
  - Eosinophilia and basophilia in minority

# JMML: PB Morphology

- Anemia
  - NRBCs frequent
  - RBCs typically normocytic, but may be microcytic, or macrocytic (a/w monosomy 7)
- Thrombocytopenia (may be severe)

# JMML: PB Morphology

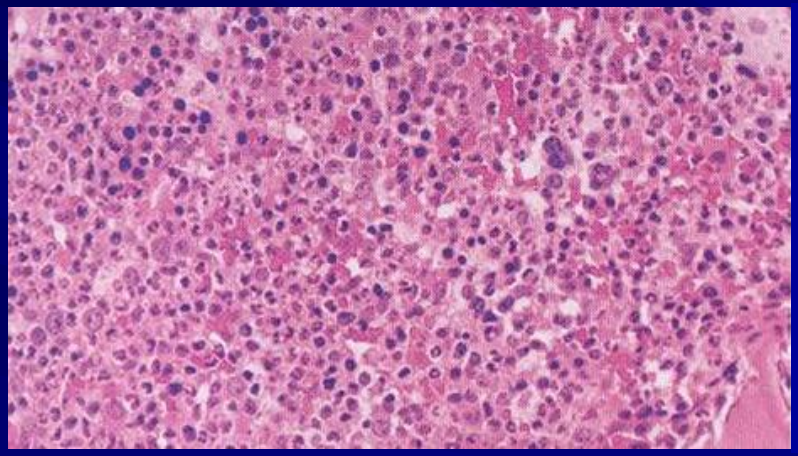


- Leukocytosis: ↑ monocytes, neutrophils (including immature forms). Thrombocytopenia.

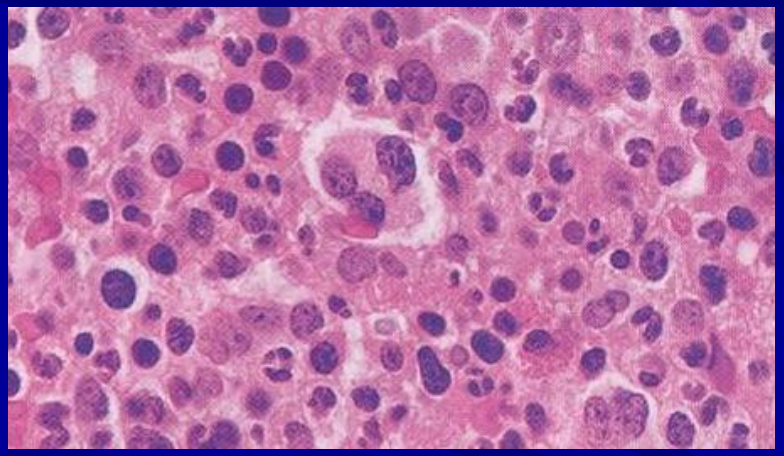
# JMML: BM Morphology

- Hypercellular bone marrow
  - -Granulocytic proliferation
  - -Monocytes usually 5-10%
  - -Blasts < 20%
- Dyspoiesis/dysplasia usually minimal
  - – Pseudo-Pelger-Huet neutrophils
  - – Hypogranularity of neutrophil cytoplasm
  - – Megaloblastic changes in erythroid precursors

# JMML: BM Morphology



- Hypercellular bone marrow with granulocyte proliferation.

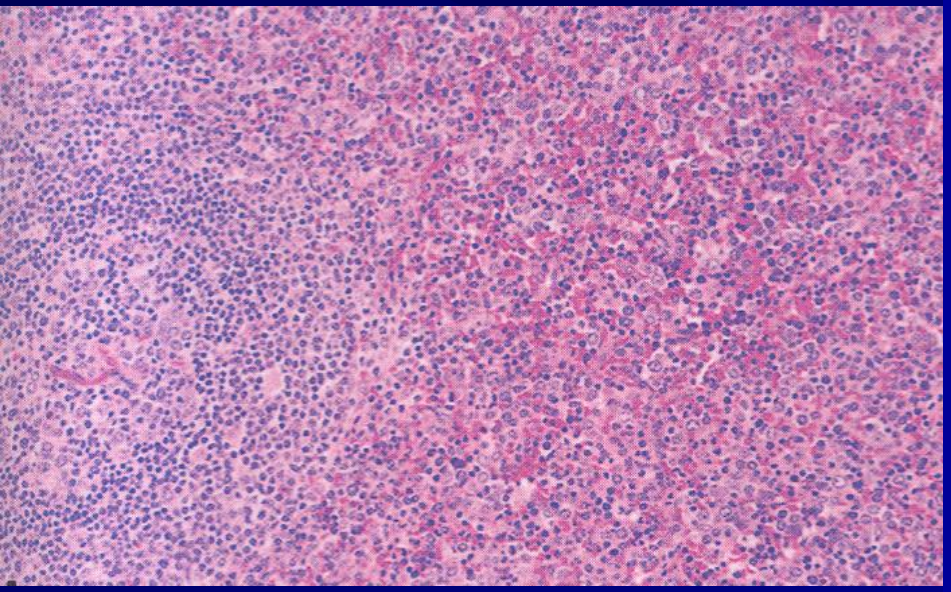


- Megakaryocytes are reduced but are morphologically normal, blasts are not substantially increased.

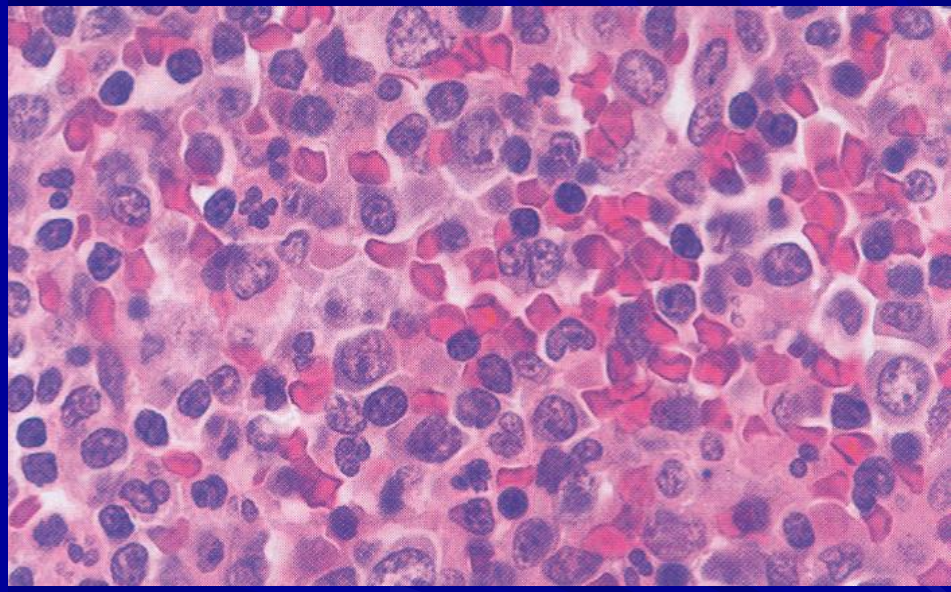
# JMML: Morphology of Other Organs

- Leukemic infiltration
  - Skin
    - Superficial and deep dermis
  - Lung
    - Peribronchial lymphatics into alveolar septae
  - Spleen
    - Red pulp
    - Predilection for trabecular and central arteries
  - Liver
    - Sinusoids and portal tracts

# JMML

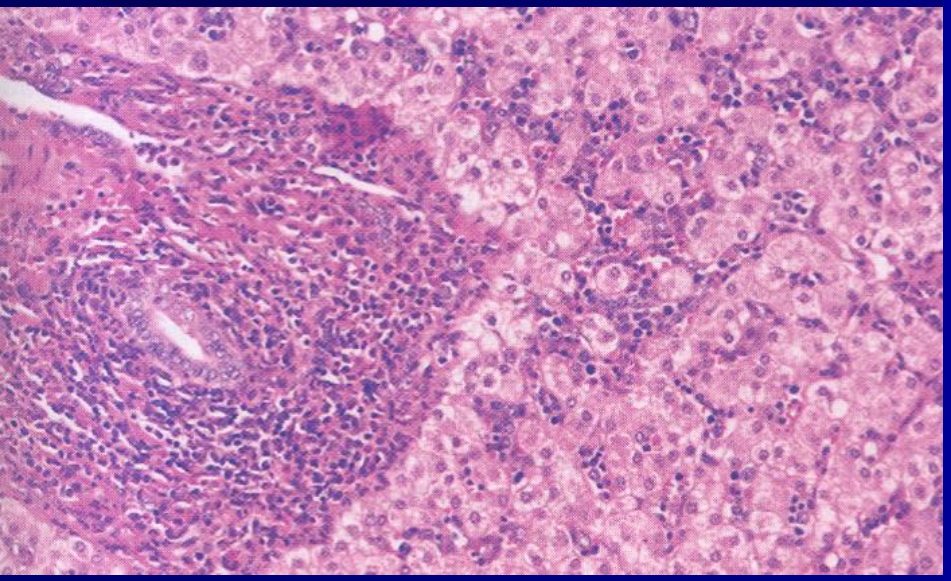


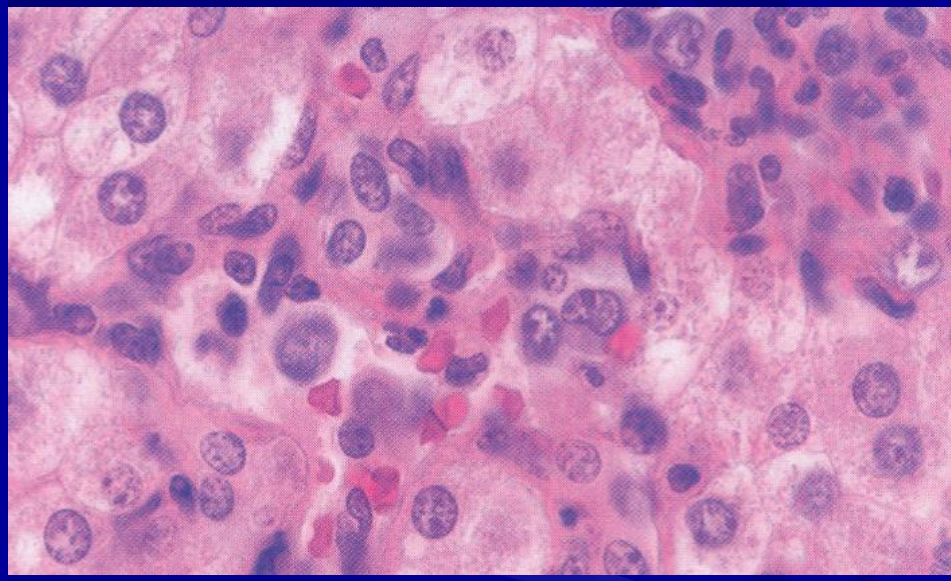
- Spleen: leukemic infiltrate in red pulp region of spleen spares the germinal center.



- Comprised mainly of immature and mature neutrophils and monocytes.

# JMML





- Liver: leukemic infiltrate in the portal regions as well as the hepatic sinusoids.

# JMML: Cytochemistry/Immunophenotype

- No specific abnormalities
- Lysozyme should be used for detection
  - Myelo-peroxidase may be weakly expressed
- Alpha naphthyl acetate esterase (+)
- Butyrate esterase (+)
- LAP scores decreased (50%), not helpful

# JMML: Genetics

- No Ph or BCR/ABL1
- Monosomy 7 (30-40%)
- Point mutations in RAS (20%)-> enhance RAS signaling
- NF-1 mutation -> loss of Neurofibromin (a negative RAS modulator)-> RAS hyperactivity

# JMML: Predictive Factors

- Better Prognosis:
  - < 1 year of age
- Worse prognosis:
  - > 2 years old
  - PLT < 33 x 109/L
  - Hbg F > 15%

# JMML: Prognosis

- Overall poor prognosis
- Untreated, 30% die in one year
- Median survival from 5 months to 4 years
- Most die from organ failure (leukemic infiltration)
- 10-20% evolve to acute leukemia
- Response to chemotherapy often poor
- HSCT may cure 50% of patients

# Myelodysplastic/ myeloproliferative disease, unclassifiable

# MDS/MPD, U: Definition

- Cases with clinical, laboratory and morphologic features that support a diagnosis of both MDS and MPD, but do not meet criteria for other entities in the MDS/MPD category

# MDS/MPD, U: Characterization

- Proliferation of one or more myeloid lineages that is ineffective and/or dysplastic

*and, simultaneously:*

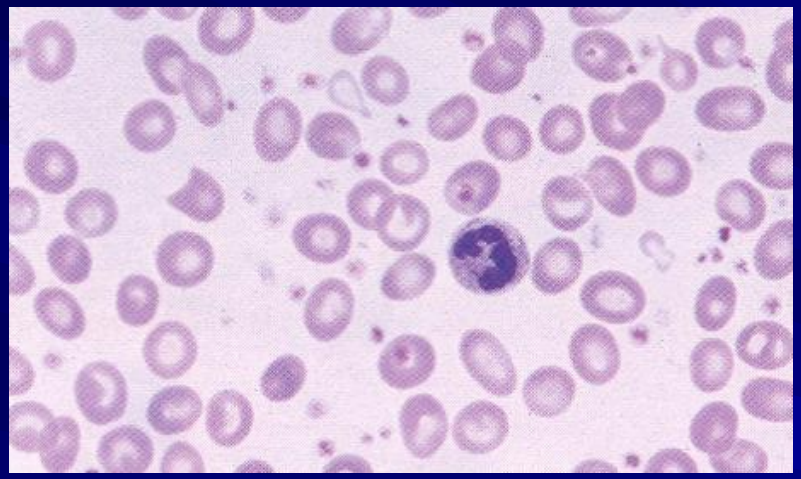
- Effective proliferation +/- dysplasia in one or more of the other lineages

# MDS/MPD, U: Exclusion Criteria

- Patients with a previous, well-defined myeloproliferative disease who develop dysplastic features associated with transformation to a more aggressive phase
- Ph, BCR/ABL

# Refractory anemia with ring-sideroblasts associated with marked thrombocytosis (RARS-T)
# [a provisional entity under MDS/MPN-U]

# RARS associated with marked thrombocytosis

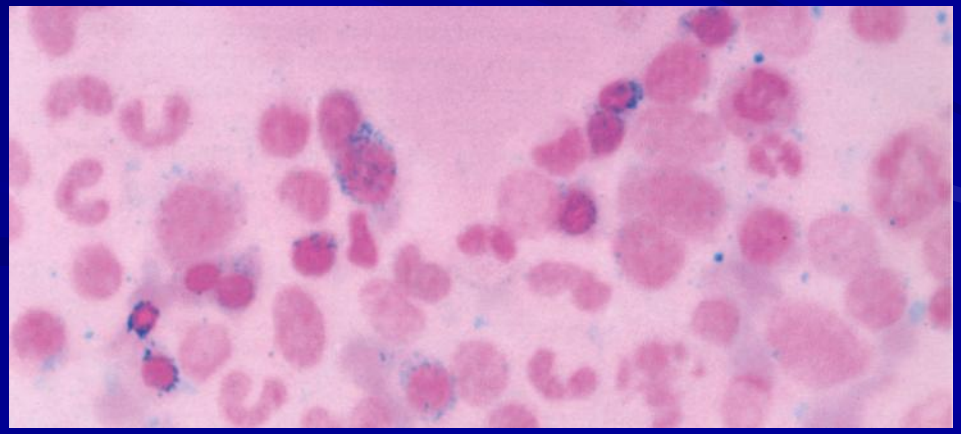


- Marked thrombocytosis & RBC abnormalities, including hypochromasia.

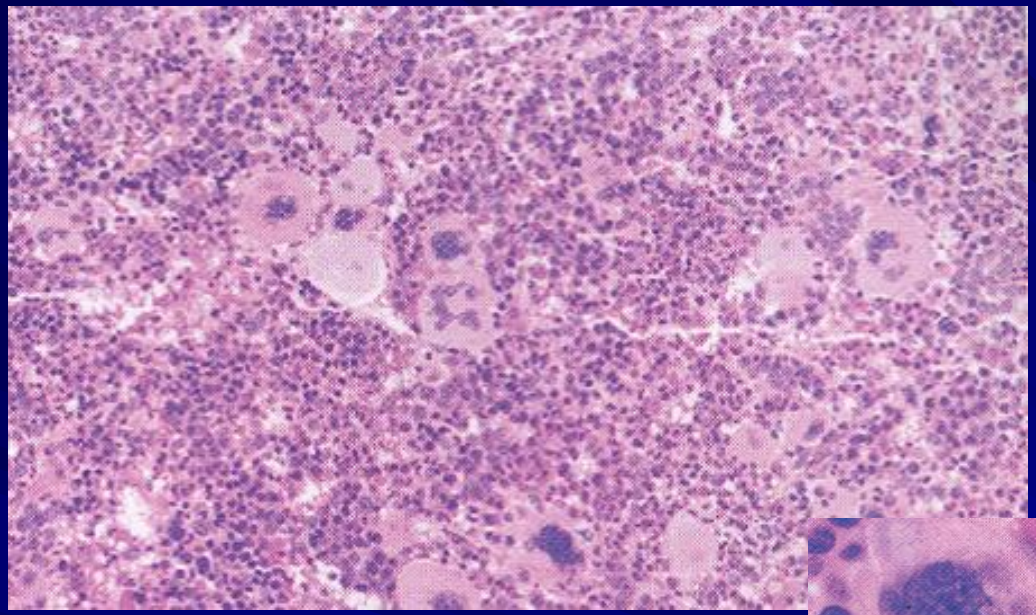
Peripheral blood smear.

- >15% of erythroid precursors are ring-sideroblasts.

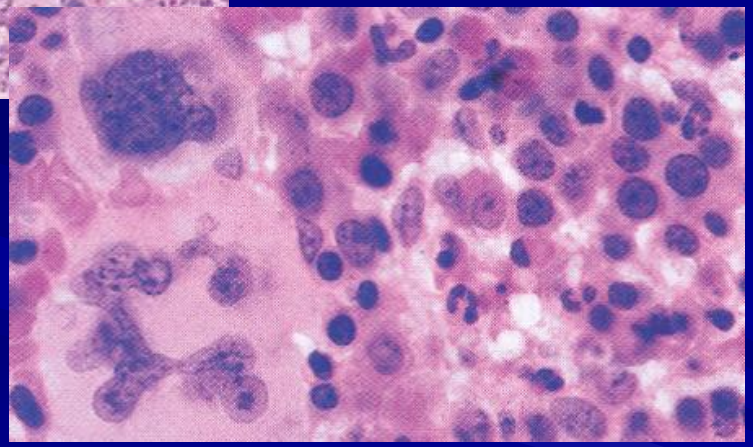
Bone marrow aspirate.

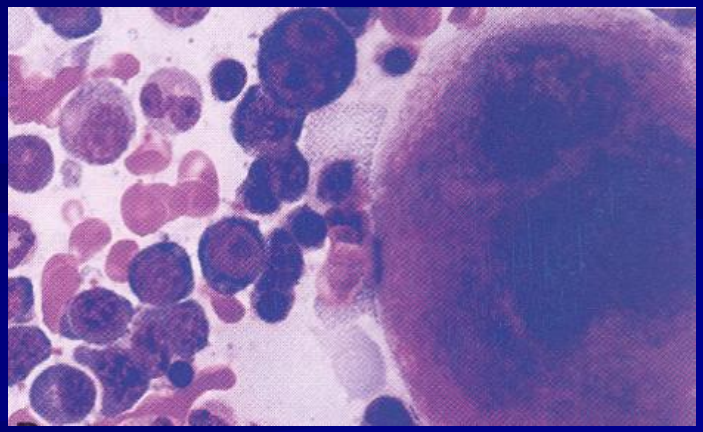


# RARS-T



- Hypercellular BM.
  marked erythroid
  & megakaryocytic proliferation.





- Enlarged megakaryocytes (similar to ET)

# MDS/MPD, U-RARS with marked thrombocytosis

- Genetics
  - Not specific
  - No Ph, BCR/ABL
  - No del(5q)
  - Many cases with JAK2 V617F mutation, less commonly JAK2 MPL W515K/L (supportive of MPN nature)
- Cell of origin
  - Unknown
- Prognosis/predictive factors
  - Unknown