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 10⁹/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
JMMJ: PB Morphology

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

- Thrombocytopenia (may be severe)
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.
• 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%)\(\rightarrow\) enhance RAS signaling
- NF-1 mutation \(\rightarrow\) loss of Neurofibromin (a negative RAS modulator)\(\rightarrow\) RAS hyperactivity
JMML: Predictive Factors

Better Prognosis:
- < 1 year of age

Worse Prognosis:
- > 2 years old
- PLT < 33 x 10^9/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