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Leukaemia Section

Mini Review

Juvenile Chronic Myelogenous Leukemia (JCML)

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Identity

Alias

Juvenile myelomonocytic leukemia (JMML)
Juvenile myelomonocytic leukemia syndrome (JMML syndrome)

Note

The proper terminology of this disorder is controversial; many authors, including the European Working Group on MDS in Childhood favor the term JMML; another working group suggests using the term JMML syndrome with a qualifier with or without monosomy 7 or 7q-.

Clinics and pathology

Disease

JCML is a chronic myeloproliferative disorder that typically affects young children: more than 95% of cases are diagnosed before age 4.

Phenotype/cell stem origin

Evidence exists for leukemic involvement of CD34-positive stem cells and monocyte-macrophage, erythroid, and B-lymphoid lineages in cases with cytogenetic abnormalities.

Epidemiology

Annual incidence is estimated to be roughly 4/million; median age 1-4 yrs; sex ratio: 1.4M/1F.

Clinics

Splenomegaly, lymphadenopathy, and skin rash are common; typical peripheral blood findings include leukocytosis (usually less than 100 x 10^9/L), monocytosis, and thrombocytosis with variable degree of left shift; myeloblasts average about 5% of total nucleated cells; elevation of fetal hemoglobin (hbF) very common; absence of the Philadelphia chromosome in all cases.

Proposed clinical criteria from the International Juvenile Myelomonocytic Leukemia Working Group includes:

1. White blood cell count > 13 x 10^9/L (corrected for nucleated red blood cells).
2. Absolute monocyte count >1 x 10^9/L (corrected).
3. Presence of immature myeloid precursors (myelocytes, promyelocytes, and myeloblasts) in the peripheral blood.
4. Bone marrow aspirate revealing < 30% blasts
5. No Ph chromosome on cytogenetic assessment.

About 15% of cases are associated with neurofibromatosis type 1 (NF-1 mutation).

Pathology

Blood: leukocytosis, monocytosis, left shift in myeloid maturation, circulating mucleated red blood cells.

Bone marrow: hypercellular marrow with mildly increased M:E ratio (typically 5:1), dispersed erythroid elements, and decreased numbers of megakaryocytes; dyplasia is usually not prominent.

Treatment

Intensive chemotherapy and all trans retinoic have not been shown to induce durable remissions; complete remissions have been achieved with stem cell transplantation.

Prognosis

The disease is uniformly fatal when treated with conventional chemotherapy; among those who undergo bone marrow transplantations, the majority ultimately relapse, with an overall survival rate of 25%.

Cytogenetics

Cytogenetics morphological

Other than the frequent association with monosomy 7, no consistent cytogenetic abnormalities have been identified; whether the infantile monosomy 7 syndrome is distinct from JCML is controversial.

Genes involved and proteins

Note

Mechanisms of Oncogenesis:

JCML patients show spontaneous growth of granulocyte-macrophage colony forming units (CFU-GM) from peripheral blood, which appears to be the result of hypersensitivity to GM-CSF, IL-3, or SCF; cases associated with NF-1 are likely to be the result of constitutive activation of the Ras pathway as a result of decreased GT Pase activity although there is also evidence of a GAP independent function; up to 30% of cases show mutations in K-ras and N-ras; the importance of the RAS pathway has been confirmed in mouse models with targeted disrupted of Nf-1; recently data suggest that TNFa produced by neoplastic cells may prevent expansion of hematopoietic progenitors.

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