Leukaemia Section
Short Communication

Juvenile myelomonocytic leukemia (JMML)

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Abstract

Review on juvenile myelomonocytic leukemia, with data on clinics, pathology, and involved genes.

Keywords
Juvenile myelomonocytic Leukemia, Myelodysplastic syndrome, Myeloproliferative disorder, Pediatric

Identity

Other names
Juvenile chronic myelogenous leukemia (JCML);
Juvenile chronic myelomonocytic leukemia

Note
This current topic of JMML does not include discussion on Ras-associated autoimmune leukoproliferative disorder (RALD), which is a nonmalignant disorder with myelomonocytic hyperplasia and somatic mutations in KRAS or NRAS, often showing clinical overlap with JMML (Calvo et al., 2015)

Clinics and pathology

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

Phenotype/cell stem origin
JMML arises from pluripotent hematopoietic stem cells (Cooper et al., 2000). Clonal proliferations of myeloid, monocyte-macrophages, erythroid, and sometimes lymphoid progenitor cells are seen.

Figure 1. A 21 month old boy presented with peripheral monocytosis, increased fetal hemoglobin. His bone marrow aspirate showed <20% blasts. Cytogenetics identified monosomy 7, and genetic testing identified a PTPN11 mutation. This bone marrow core biopsy demonstrates a hypercellular marrow with decreased megakaryocytes.
Epidemiology
The annual incidence of JMML is estimated to be roughly 0.67/million (Passmore et al, 2003). The median age is 1.1-1.8 years with a male to female ratio of 2-3:1. (Hasle et al., 1999; Niemeyer et al., 1997; Passmore et al., 2003). Those with neurofibromatosis type 1 (NF-1) have a 200-fold increased risk of JMML (Stiller et al., 1994).

Clinics
Children with JMML commonly have splenomegaly, lymphadenopathy, and skin rashes (Hess et al., 1996). Involvement of the liver, lung, and GI tract can also occur. The diagnostic criteria for JMML are:

<table>
<thead>
<tr>
<th>Clinical and hematologic features (all 4 required)</th>
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<tr>
<td>- Peripheral blood monocyte count ≥1 x 10^9/L</td>
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<tr>
<td>- Peripheral blood and bone marrow blast percentages &lt;20%</td>
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<td>- Splenomegaly</td>
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<td>- No Philadelphia (Ph) chromosome or BCR-ABL1 fusion</td>
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<th>Genetic criteria (1 finding is sufficient)</th>
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<td>- Somatic mutation in PTPN11, KRAS, or NRAS</td>
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<td>- Clinical diagnosis of neurofibromatosis type 1 or NF1 mutation</td>
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<td>- Germine CBL mutation and loss of heterozygosity of CBL</td>
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<th>Other criteria*</th>
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<td>- Monosomy 7 or any other chromosomal abnormality</td>
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<td>or ≥ 2 of the following:</td>
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<td>- Increased hemoglobin F (HbF) for age</td>
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<td>- Myeloid or erythroid precursors on peripheral blood smear</td>
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<td>- Granulocyte-macrophages colony-stimulating factor (GM-CSF) hypersensitivity in colony assay</td>
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<td>- Hyperphosphorylation of STAT5</td>
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* (those not meeting genetic criteria but having clinical and hematologic criteria must also have). (Locatelli and Neimeyer, 2015; Baumann, et al., 2017)

Cytology
Typical peripheral blood findings include leukocytosis (usually less than 100 x 10^9/L) with variable degree of left shift, monocytosis, and thrombocytopenia. Nucleated red blood cells are often identified in the peripheral blood. Myeloblasts average about 1-5% of total nucleated cells, and by definition, blasts account for <20% of cells. (Hess et al., 1996; Niemeyer et al., 1997)

Pathology
Bone marrow findings are not specific. The marrow is usually hypercellular with a mildly increased M:E ratio (typically 3-5:1), dispersed erythroid elements, and decreased numbers of megakaryocytes. Dysplasia is usually not prominent. Blasts are required to be less than 20%; monocytes are less prominent in the marrow than in the peripheral blood, and are usually enumerated at 5-10% (Hess et al., 1996; Niemeyer et al., 1997).

Treatment
Curative therapy involves an allogeneic hematopoietic stem cell transplant (HSCT). Locatelli and Neimeyer (2015) recommend swift HSCT for those with germline NF1 mutations, somatic PTPN11 mutations, somatic KRAS mutations, and most children with somatic NRAS mutations. Most children with germline CBL mutations demonstrate spontaneous regression, though if there is disease progression, a HSCT should be considered. In children with Noonan syndrome (germline mutations of PTPN11, KRAS, and/or NRAS), the disease may be transient, and hence one can consider a 'watch and wait' scenario, with mild cytoreductive therapy for symptoms, usually 6-mercaptopruine.
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In the rare patients with tyrosine kinase fusions, ALK/ROS1 inhibitors, such as crizotinib, may be beneficial (Murakami et al., 2018).

**Evolution**

As stated above, those with Noonan syndrome with germline mutations in PTPN11, KRAS, and/or NRAS as well as those with germline CBL mutations have disease that may spontaneously regress without therapy (Locatelli and Neimeyer, 2015). However, in other cases, in those who did not receive an allogeneic hematopoietic stem cell transplant (HSCT), the median survival after diagnosis is <12 months (Niemeyer et al., 1997). In those who receive HSCT, the 5-year overall survival rate is 64%, with an event free survival of 52% (Locatelli et al., 2005). The 5-year cumulative incidence of relapse is 35%, while the 5-year cumulative incidence of transplantation-related mortality is 13% (Locatelli et al., 2005)

**Prognosis**

High risk features include older age (>1.4-4 years), PTPN11 mutation, monosomy 7, HbF >40%, low platelets (20% bone marrow blasts (Dvorak and Loh, 2014; Locatelli et al., 2005; Niemeyer et al., 1997; Novitzky et al., 2000; Passmore et al., 2003). In genetic studies, patients with ≤2 somatic alterations have improved outcomes compared to those with ≥2 alterations (Stiegliz et al., 2015). DNA methylation studies have also been done, showing three clusters of methylation in JMML; those with the highest levels of methylation have been found to have poorer clinical outcomes (Lipka et al., 2017; Stieglitz et al., 2017).

**Genetics**

Note

Approximately 85-90% of children with JMML have identified mutations, either germline and/or somatic. Somatic, gain-of-function mutations occur in PTPN11, KRAS, and NRAS, in 35-38%, 18%, and 14% of cases respectively. NF1 germline mutations with acquired loss of the normal allele are seen in 5-15% of patients, and CBL germline mutations with acquired loss of the normal allele and duplication of the mutant allele (acquired uniparental disomy) are seen in 9-18% of patients. (Chan et al., 2009; Niemeyer and Flotho, 2019). Rare cases without any of the above mutations have been found to harbor RRAS or RRAS2 somatic mutations (Stieglitz et al., 2015).

Secondary mutations in SETBP1, JAK3, ASXL1, and SH2B3 are also identified and are often subclonal. Additional mutations in the RAS pathway genes are also sometimes detected, coined 'Ras double mutants' (Caye et al., 2015; Stieglitz et al., 2015).

A recent study reported receptor tyrosine kinase fusions (DCTN1 /ALK, RANBP2 /ALK, and TBL1XR1 / ROS1) in patients without identified RAS pathway mutations (Murakami et al., 2018).

**Cytogenetics**

Normal karyotypes are present in most cases of JMML (~68%). Another 16-25% of cases have monosomy 7 or deletion 7q (Aricò et al, 1997; Niemeyer et al., 1997).

**Genes involved and proteins**

**CBL**

**Location** 11q23.3

**Note**

There is a high rate of spontaneous resolution of disease without stem cell transplant in those with homozygous mutations including a germline mutation (Chang et al., 2014).

**DNA/RNA** 16 exons.

**Protein**

This oncogene encodes a RING finger E3 ubiquitin ligase which marks activated receptor and nonreceptor tyrosine kinases and other proteins for degradation by ubiquitination.

Homozygous mutations lead to continuous activation of RAS. (Chang et al., 2014).

**Germinal mutations**

Germ line heterozygous mutations (autosomal dominant) lead to a Noonan syndrome-like disorder. The most common mutation is c.1111T>C (Y371H); other common mutations are missense mutations in exons 8 and 9 or in introns 7 or 8 (Loh et al., 2009).

**Somatic mutations**

Loss of wild-type allele with duplication of mutant allele.

**KRAS**

**Location** 12p12.1

**Note**

Somatic mutations also occur in RALD (Ras-associated lymphoproliferative disease).

**DNA/RNA** 6 exons.

**Protein**

A Ras oncogene which encodes a member of the small GTPase superfamily. Mutations lead to activation.

**Germinal mutations**

Germ line heterozygous mutations (autosomal dominant) lead to Noonan syndrome.

**Somatic mutations**
Somatic mutations are usually point mutations at codons G12, G13, and Q61 (exons 2 and 3) leading to amino acid substitutions (Chan et al., 2009; Chang et al., 2014).

**NF1 (neurofibromin 1)**

**Location** 17q11.2

**DNA/RNA** 57-58 exons (depending on transcript variant).

**Protein**

GTPase activating protein for Ras. Normally acts as tumor suppressor by inhibiting Ras signaling

**Germinal mutations**

Germine mutations cause neurofibromatosis type 1 (NF1) characterized by café-au-lait spots, Lisch nodules, neurofibromas, optic pathway gliomas.

**Somatic mutations**

Somatic mutations are usually deletions leading to loss of heterozygosity with duplication of the mutated germine allele.

**NRAS**

**Location** 1p13.2

**Note**

Somatic mutations also occur in RALD (Ras-associated lymphoproliferative disease).

**DNA/RNA** 7 exons.

**Protein**

A Ras oncogene which encodes a membrane protein with intrinsic GTPase activity that shuttles between the Golgi apparatus and the plasma membrane.

**Germinal mutations**

Germine heterozygous mutations (autosomal dominant) lead to Noonan syndrome.

**Somatic mutations**

Somatic mutations are usually point mutations at codons G12, G13, and Q61 (exons 2 and 3) leading to amino acid substitutions (Chan et al., 2014).

**PTPN11**

**Location** 12q24.13

**DNA/RNA** 16 exons

**Protein**

A member of the protein tyrosine phosphatase family which relays signals from activated GM-CSF receptor complexes, regulating proliferation, differentiation, and migration.

**Germinal mutations**

Germine mutations (autosomal dominant) lead to Noonan syndrome, usually within exons 3, 4, and 13.

**Somatic mutations**

Somatic mutations usually involve exons 3, 4, and 13, with most common mutations being: c.226G>A (E76K), c.214G>A, c.227A>G, c.1508G>C. (Chan et al., 2009; Chang et al., 2014).

**References**


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