Juvenile Myelomonocytic Leukemia

Prakash Satwani, MD[a,*], Justine Kahn, MD[b], Christopher C. Dvorak, MD[c]

KEYWORDS

• RAS pathways • PTPN11mutation • Allogeneic hematopoietic cell transplantation • Children • Leukemia

KEY POINTS

- Juvenile myelomonocytic leukemia (JMML) is a rare myeloid malignancy that occurs only in young children and has a variable clinical course.
- The pathogenesis of JMML involves hyperactivation of the RAS pathways.
- Significant progress has been made in understanding aspects of the molecular basis of JMML. It is now known that 85% to 90% of patients can be firmly diagnosed with the help of molecular studies.
- Allogeneic hematopoietic stem cell transplant is the only curative option for children with JMML, and unfortunately it is an option fraught with frequent relapse and significant toxicity.

INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is a rare myeloid malignancy that occurs in young children. Similar to other myeloid neoplasms, such as chronic myeloid leukemia (CML) and some cases of acute myeloid leukemia (AML), or to premalignant disorders, such as myelodysplastic syndrome (MDS), JMML is a disorder of myeloid progenitors, or stem cells.

Because of its rarity and because of its varied clinical presentations, JMML is often difficult for general pediatricians, pediatric oncologists, and even for hematopathologists to diagnose. Clinically, a child with JMML may exhibit symptoms that suggest a

Financial Disclosure Statement: None.

[a] Division of Pediatric Hematology/Oncology and Stem Cell Transplantation, Columbia University Medical Center Morgan Stanley Children's Hospital of New York-Presbyterian, 3959 Broadway, CHN-1002, New York, NY 10032, USA; [b] Division of Pediatric Hematology/Oncology and Stem Cell Transplantation, Columbia University Medical Center Morgan Stanley Children's Hospital of New York-Presbyterian, 3959 Broadway, CHN-1002, New York, NY 10032, USA; [c] Division of Pediatric Allergy, Immunology, and Bone Marrow Transplant, Benioff Children's Hospital, University of California San Francisco, 505 Parnassus Ave., M-659, San Francisco, CA, 94143-1278, USA
* Corresponding author.
E-mail address: ps2087@columbia.edu

Pediatr Clin N Am 62 (2015) 95–106
http://dx.doi.org/10.1016/j.pcl.2014.09.003 **pediatric.theclinics.com**
0031-3955/15/$ – see front matter

common viral syndrome. Blood counts and hematologic features may mimic AML. Over the last decade, however, significant progress has been made toward understanding the unique molecular mechanisms and features that render JMML distinct from similar conditions.

EPIDEMIOLOGY, NOMENCLATURE, CLINICAL PRESENTATION, AND DIFFERENTIAL DIAGNOSIS

Epidemiology

JMML is a rare pediatric disease with an annual incidence of approximately 1.2–1.8 cases per million in the United States.[1,2] More recent data suggest that this is an underestimate, because JMML is frequently misclassified and misdiagnosed. Chan and colleagues[3] suggest that based on recently established clinical, cytogenetic, and molecular characteristics, the incidence of JMML in the coming years will increase because of improved diagnostics. Certain genetic syndromes are associated with a propensity to develop JMML or JMML-like disease. The incidence of true JMML is increased 200- to 500-fold in neurofibromatosis (NF)-1.[4] Conversely, some children with Noonan syndrome (NS) display a hematologic phenotype, including a self-resolving myeloproliferative disorder in infancy, which resembles JMML and may last for 1 to 2 years.[5,6]

Clinical Presentation

JMML most often occurs in children younger than 2 years old, and almost always before puberty. Children affected with JMML usually present with fever, respiratory symptoms, skin rash, and hepatosplenomegaly. In children with high burden of disease, hepatosplenomegaly may be significant and respiratory symptoms may be severe. JMML can be associated with NF-1 and in these patients the classic café-au-lait spots may take on a slightly unusual form. Laboratory tests are significant for elevated white blood cell counts with an atypical monocytosis and associated thrombocytopenia. Immature granulocytic precursors and nucleated red cells are evident in most cases, and the peripheral blood blast cell percentage averages 2% and rarely exceeds 20%.[7] The diagnosis of JMML is supported when, in the setting of the previously mentioned symptoms, a patient has an absolute monocyte count exceeding 1×10^9/L in the peripheral blood. However, other possible causes, such as CML, must be excluded.

Bone marrow aspirate is not always required to make the diagnosis of JMML; however, it can be suggestive of the diagnosis in the right clinical setting. Unlike in AML, the bone marrow in patients with JMML demonstrates no blockage of differentiation of myeloid elements (**Fig. 1**). Rather, as is seen in CML, the bone marrow in JMML exhibits myeloid hyperplasia with granulocytic cells at varying stages of maturation. The marrow blast count may be slightly elevated but in classic JMML it does not reach the counts seen in AML. Rare cases of JMML have been described with a predominance of erythroid precursors in the marrow and mimicking acute erythroblastic leukemia. Megakaryocytes are reduced in number and this is mirrored by evidence of thrombocytopenia in the peripheral blood. Of interest, monocytosis seen in the bone marrow is less pronounced than it is in the peripheral blood.[7]

Differential Diagnosis

At initial presentation JMML is difficult to distinguish from other more common illnesses. Young infants with viral infections, such as human herpes virus-6, parvovirus, or cytomegalovirus, can present with clinical and hematologic features similar to those of JMML. Occasionally, patients with JMML may present with these viral infections in addition to their underlying hematologic malignancy. Very young boys with Wiskott-Aldrich syndrome can occasionally present with clinical features mimicking JMML.[8]