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# Juvenile Myelomonocytic Leukemia: A Case Report

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**Abstract** **Case Report**

Juvenile myelomonocytic leukemia (JMML) is a rare pathology affecting the hematopoietic stem cell. Its pathophysiology is linked to deregulation of the RAS signal transduction pathway. It is a rare, myelodysplastic-myeloproliferative disease typically presenting in early childhood. This disorder is difficult to distinguish from other myeloproliferative syndromes such as chronic myeloid leukemia (CML) because of the similarities in their clinical and bone marrow findings. However, because of its unique biological characteristics such as absolute monocytosis with dysplasia, absence of Philadelphia chromosome or BCR-ABL fusion protein, hypergammaglobulinemia, and raised fetal hemoglobin level, this disorder does not satisfy the criteria for inclusion in the CML or chronic myelomonocytic leukemia (CMML) group, as seen in adult patients. We report the case of a male infant aged 15 months who was hospitalized for prolonged fever associated with tumor syndrome. This case has been reported in line with The 2016 iteration of the World Health Organization classification of myeloid neoplasms. The interest of this observation is to describe a rare case of JMML.

**Keywords:** Juvenile myelomonocytic leukemia, monocytosis, myelodysplastic, myeloproliferative, dysmyelopoiesis, monosomy 7.



## INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is characterized by excessive growth of exclusively myelomonocytic cells in both mature and immature forms.

Patients with JMML usually present before the age of 2 years with hepatosplenomegaly, lymphadenopathy, infection and skin disease.

The diagnosis requires the absence of the Philadelphia chromosome or BCR-ABL fusion protein, monocytes of more than 1 x 109/l on peripheral blood and bone marrow blast count of less than 20%. Further evidence includes an elevated fetal hemoglobin level, white cell count of more than 10 x 109/l, myeloid precursors on peripheral blood, hypergammaglobulinemia, detection of clonal abnormality and in vivo hypersensitivity to granulocyte colony stimulating factor (GM-CSF). Other pathological findings include infiltration of various non-haemopoietic organs (skin, lungs, intestines) with leukemic monocytic cells. There is also increased incidence of monosomy 7 as well as neurofibromatosis type 1 abnormalities [1].

## CASE REPORT

We present the case of a 15-month-old male infant with 4-day history of abdominal pain, fever and fatigue.

Clinical examination revealed a conscious child, haemodynamically stable, febrile to 39°C, with mucocutaneous pallor and a tumor syndrome consisting of hepatomegaly, splenomegaly and adenopathy. A complete blood count on admission showed leukocytosis (39.5 G/dl), anaemia (6.7 G/dl), and thrombocytopenia (26 G/dl).

Peripheral blood smear showed immature granulocytes, atypia in neutrophils, monocytosis with 14% circulating blasts (Figure 1).

The bone marrow is rich with granular hyperplasia and signs of dysmyelopoiesis. The blasts are increased and make up about 7% of the nucleated cells in the bone marrow, while the monocytes make up 12% (Figure 2).

Cytogenetic analysis revealed the presence of monosomy 7, while JAK2 mutation analysis was negative. BCR-ABL transcript testing was not performed due to lack of resources.

Given the presentation of the disease (myeloproliferative variant), the patient was started on cytoreductive therapy.

Bone marrow was performed and revealed hyper cellular marrow for patient`s age with around 80% cellularity, adequate trilineage hematopoiesis with dysplasia mainly noted in erythroid precursors in the form of signi□cant megaloblastoid changes and basophilic stippling. Some small and hypolobated megakaryocytes (small and hypolobated) precursors. The blasts are increased and account for around 12% of marrow nucleated cells, while the monocytes account for 1.2%

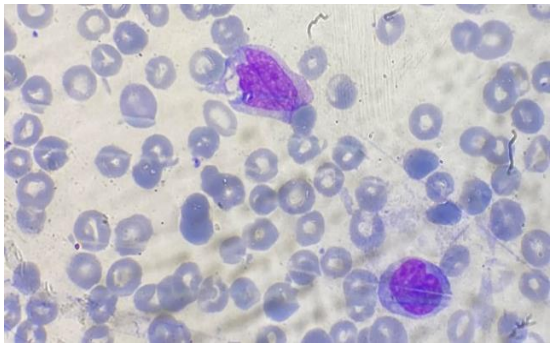

**Fig 1: Peripheral blood smear showing immature granulocytes (G) and monocytes**

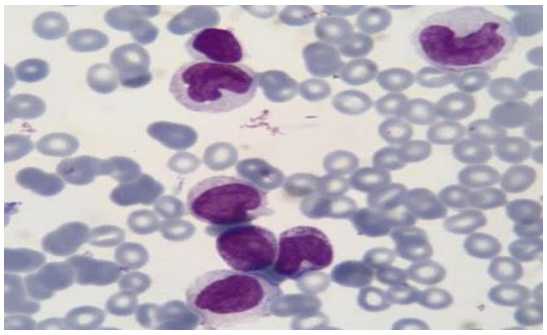

**Fig 2: Bone marrow shows a rich marrow with granular hyperplasia and signs of dysmyelopoiesis and blasts**

## DISCUSSION

Juvenile myelomonocytic leukemia (JMML) is a myelodysplastic (MDS)/myeloproliferative neoplasm (MPN) overlap syndrome of the pediatric age group characterized by sustained, abnormal, and excessive production of myeloid progenitors and monocytes, aggressive clinical course, and poor outcomes.

The differentiation pathway is shunted towards the monocytic differentiation and the progenitor colonies of JMML cells show a spectrum of differentiation, including blasts, pro-monocytes, monocytes, and macrophages [2]. The overproduction of the myeloid lineage cells leads to a suppression of other cell lines; consequently, these patients can present with anemia and thrombocytopenia [3]. JMML is very rare and the diagnosis is often difficult to establish. The criteria for the diagnosis of JMML have been recently updated in 2016 [4].

In children, it accounts for 3% of malignant haemopathies and 18% of MDS. It usually affects young children, with 75% of cases occurring before the age of 3 years [5, 6].

In a retrospective analysis of 110 patients realized by Niemeyer *et al*., the median age at diagnosis was 1.8 years compared with 1.1 years in the UK series [5]. Azma *et al*., reported three cases of LMMJ, all aged over 3 years. A clear male predominance was reported in this study.

The sex ratio was 2.5, 2.1, 1.7, and 4.8 respectively, according to the European working group and the sequences of Niemeyer *et al*., and the French and British sequences [8, 12, 13].

In the series by Niemeyer *et al*., the most frequent clinical signs were splenomegaly (97%), hepatomegaly (97%), adenopathy (76%), pallor (65%), fever (54%), and cutaneous hemorrhages (46%) [7]. Skin lesions may include xanthomas, eczema, and purpuric erythematous nodules [8]. Respiratory and digestive symptoms have also been documented in the literature. Our patient presented with anemia, tumor syndrome and

abdominal pain without symptoms of respiratory distress.

Many conditions have been identified as predisposing factors for JMML. These include Down syndrome, Kostmann syndrome, Noonan syndrome, Fanconi anemia, trisomy 8 mosaicism, neurofibromatosis, Schwachmann syndrome, immunodeficiency and familial, leukemia. In addition, previous chemotherapy administered to children for other disorders can also be a predisposing factor for the subsequent development of childhood MDS and MPDs. In this case series, there was no risk factor identified [10].

Most JMML patients have hepatosplenomegaly and lymphadenopathy, as seen in this case report. Busque L *et al*., showed that most cases had a leucocyte count of less than 50 x 109 /l which is seen in our patient, less than 8% of cases have counts greater than 100 x 109 /l [11].

Allogeneic hematopoietic cell transplantation (HCT) is the standard of care for most patients with JMML, with a cure rate of approximately 50% [14, 15]. However, to date, no standard chemotherapy regimen prior to HCT has demonstrated effects on post-transplantation outcomes. The role of conventional chemotherapy is limited to achieving transient cytoreduction or symptom relief [16].

Standardized response criteria are essential for demonstrating the efficacy of a particular treatment strategy in patients. The lack of established and universally accepted criteria to assess the response to non-transplant therapies makes it difficult to demonstrate the efficacy of chemotherapy. Most studies on chemotherapeutic response in JMML were published more than a decade ago, and the definition of the response varied among the studies [16-18]. However, reports on the differences in response-based clinical outcomes to prove the validity of the criteria are limited. Additionally, while prognostic factors predicting post-transplantation relapse or survival have often been reported [19], data predicting chemotherapeutic response are lacking.

Further, the role of azacitidine, a hypomethylating agent has shown promise as a single agent in the pre-HSCT management of JMML [5]. Lately, a lot of agents targeting the molecular pathways are being explored as treatment options for JMML.

## CONCLUSION

Juvenile myelomonocytic leukemia (JMML) is a rare hematological malignancy... Early diagnosis of JMML can be difficult because of the overlap in some of the clinical and laboratory features with other types of myelodysplasia or myeloproliferative disease. Genetic studies are now required for all patients with JMML. The prognosis is often poor, and the mortality rate remains high. Current molecular studies are aimed at the use of targeted therapies aimed at deregulated signaling pathways. A correct diagnosis is however important since intensive chemotherapy and early stem cell transplantation will help improve the survival of these patients

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