

# Juvenile Myelomonocytic Leukemia

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## Abstract:

Juvenile Myelomonocytic Leukemia (JMML), which comes under the WHO category of Myelodysplastic/Myeloproliferative Neoplasms, is a rare aggressive hematological malignancy of early childhood caused by excessive proliferation of cells of monocytic and granulocytic lineages. The peripheral blood shows leukocytosis, thrombocytopenia and anemia. The majority of patients present with infection. Hematopoietic Stem Cell Transplantation (HSCT) is the best treatment option available. Here we present a case of a one year old female child who presented with complaints of fever, cough and progressive pallor for the last six months and abdominal distention associated with vomiting, diarrhea and sub-conjunctival hemorrhages for past 2 months. The fever did not respond to medication. She developed sepsis and intracranial bleed and expired on the 10<sup>th</sup> day of hospitalization.

**Key words:** Juvenile Myelomonocytic Leukaemia, Hematopoietic Stem Cell Transplantation.

## Introduction

Juvenile Myelomonocytic Leukemia (JMML) is a rare hematological malignancy of early childhood, representing 2 to 3% of all childhood leukemia. It usually has an aggressive clinical course, with median duration of survival for untreated children being less than 1 year from diagnosis. Following the rigorous therapy of Allogeneic Hematopoietic Stem Cell Transplantation, the probability of event-free survival at five years is only 50% and the main cause of treatment failure continues to be disease relapse.<sup>1</sup>

JMML has features of both myelodysplastic and myeloproliferative disorders.<sup>2</sup> It has a unique clinical presentation in children and infants. It arises from dysregulation of signal transduction through the RAS pathway. At the molecular level, 35% of patients have gain-of-function mutations in *PTPN11* and 35% gain-of-function mutations in *NRAS* or *KRAS* signaling pathway.<sup>3</sup> Children with neurofibromatosis type 1 (NF-1), being constitutionally deficient for one allele of the NF1 gene, are at greatly increased risk of JMML. NF1 is a negative regulator of RAS pathway activity, which has a central role in JMML.<sup>4</sup> Patients less than one year of age at diagnosis have significantly better survival than older children.

Low platelet count, age over two years at diagnosis and high HbF at diagnosis are the main predictors of short survival.<sup>5</sup>

## Case Report

A one year old female child, resident of district Swabi, Khyber Pakhtunkhwa, was admitted with complaints of fever, cough and progressive pallor for the last 6 months. She was well up to the age of six months when she developed pallor and fever associated with cough. She was given broad spectrum antibiotics which showed only temporary relief of symptoms. Increasing pallor was noted by the parents.

The prenatal, natal and postnatal history was uneventful. There was no history of maternal fever, rash, lymphadenopathy or past history of pre-mature birth/abortion indicative of TORCH infections. There was no history of fits and regression of milestones. She had two previous admissions in hospital due to pneumonia and pallor. She got transfused for the first time at 6 months of age. After that, she was transfused multiple times.

On physical examination, she had a temperature of 100°F, pulse rate of 104/min, respiratory rate of 28/min and a moderate degree of pallor. Her cervical, axillary and sub mandibular lymph nodes of right side were palpable. Sub conjunctival hemorrhage was present in the left eye. Her weight was 9 Kg, length was 75cm and head circumference was 46cm. Spleen was palpable 4cm along its long axis below left sub costal margin; it was firm in consistency with well-defined border. Liver was 2cm palpable below the right costal margin, firm in consistency with sharp borders and smooth surface. Rest of the systemic examination was unremarkable.

The investigations showed Hemoglobin 7gm/dl,

## Correspondence

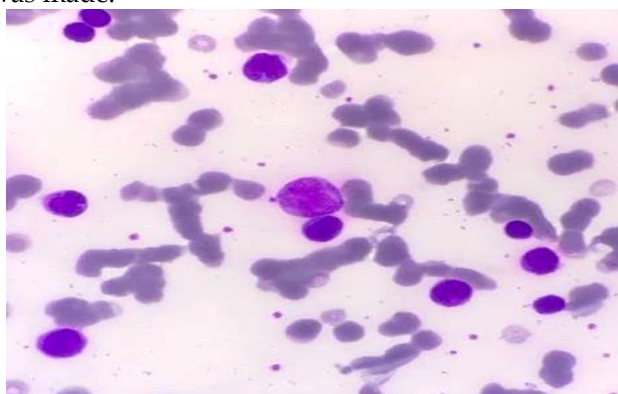
Dr. Amna Imtiaz

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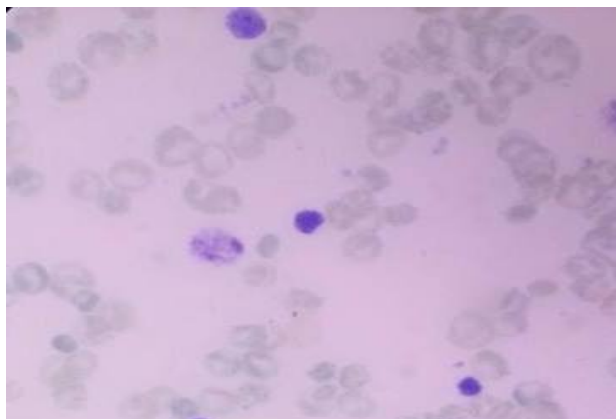
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Platelet count 143,000/ $\mu$ l, and TLC 66,900/ $\mu$ l. The differential counts showed Neutrophils 43%, Lymphocytes 22%, Eosinophils 4%, Monocytes 8%, Myelocytes 5%, Metamyelocytes 5% and Atypical cells 13%. 5 nucleated RBCs were seen per 100 WBCs (Figure-1). Peripheral smear showed anisocytosis, poikilocytosis, and leukocytosis with left shift. Reticulocytes were 0.3%(Figure 2 ). Blood culture showed no growth. Chest X-ray was normal, Ultrasound Abdomen showed hepatosplenomegaly. Bone marrow examination showed a hypercellular aspirate with hyperplastic and moderately dysplastic myelopoiesis (Figure-3). Erythropoiesis was moderately cellular showing normoblastic maturation with mild dysplasia. Dysmegakaryocytopoiesis was noted with few hypolobated forms. Blast were 18%, M:E ratio was 4:1, lymphocytes and plasma cells were normal Figure 4). Increase in monocytes and its precursors was noted.

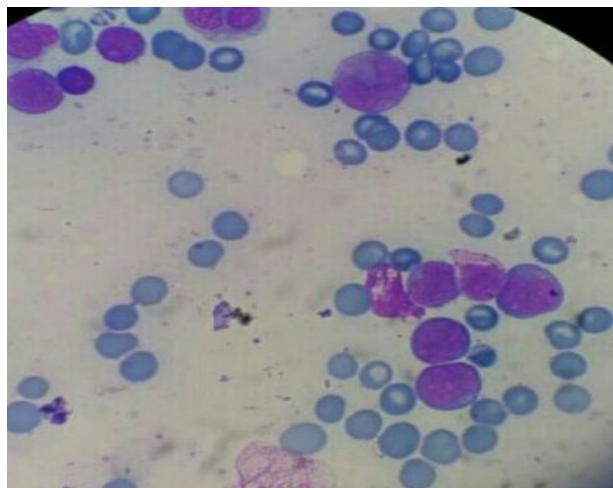
Based on these findings, a final diagnosis of Myelodysplastic/ Myeloproliferative Neoplasm, most likely Juvenile Myelomonocytic Leukemia (JMML) was made.



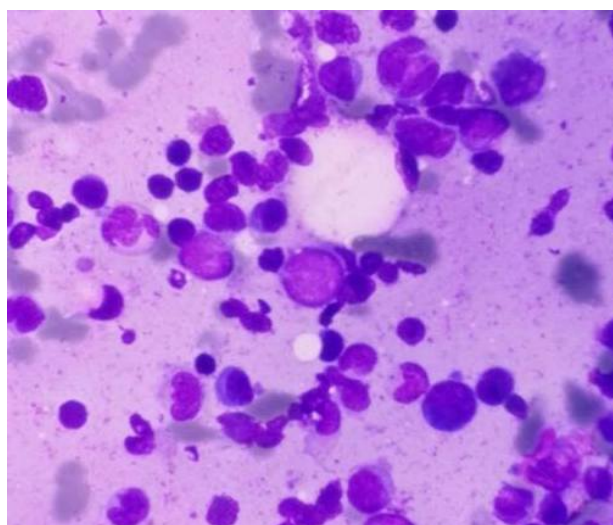
**Figure 1: Peripheral smear showing Dysplasia) (Wright X 1000)**



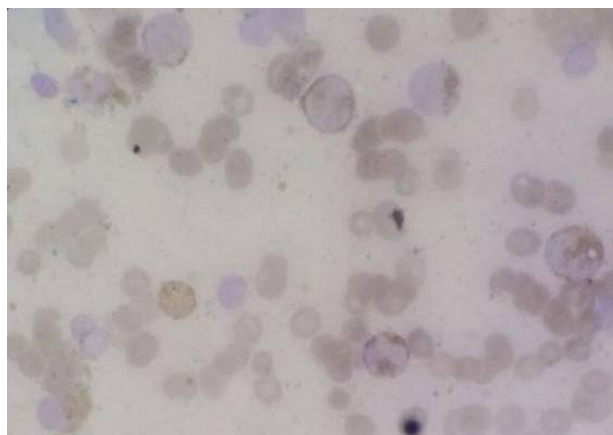
**Figure-2: Reticulocytes**



**Figure 3: Aspirate Dysplasia (Wright X 1000)**



**Figure 4: Aspirate showing blasts (Wright X 1000)**



**Figure-5: Sudan Black-B Stain positivity X 1000**

## Discussion

In 1982, the French - American - British (FAB) group introduced a classification for the Myelodysplastic Syndromes (MDS), a heterogenous group of diseases that prior to the FAB scheme was often referred to only as "preleukemia".<sup>6</sup>

According to the 2008 WHO classification, the category of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) includes atypical chronic myeloid leukaemia (aCML), chronic myelomonocytic leukaemia (CMML), MDS/MPN-unclassifiable (MDS/MPN-U), juvenile myelomonocytic leukaemia (JMML) and a "provisional" entity, refractory anaemia with ring sideroblasts and thrombocytosis (RARS-T).<sup>7</sup>

Juvenile myelomonocytic leukemia (JMML) is a rare but frequently lethal clonal myeloproliferative neoplasm of early childhood characterized by the overproduction of myelomonocytic cells that infiltrate the spleen, lung, and intestines. It occurs with an estimated incidence of 1.2 cases per million annually, with a median age of diagnosis of 2 years. Patients usually present with fever, thrombocytopenia, failure to thrive, and splenomegaly.<sup>8</sup>

Morphologic evaluation of peripheral blood smear is the most important step in establishing the diagnosis. Immature monocytes, along with myelocytes, metamyelocytes, and erythroblasts, are usually found. Almost all cases show striking monocytosis, with dysplastic cells; an absolute monocyte count  $>1 \times 10^9/L$  is required for diagnosis of JMML. A remarkable feature of many JMML cases with normal karyotype is a markedly increased synthesis of fetal hemoglobin (HbF). BM findings in JMML are not solely diagnostic, but are rather consistent with the diagnosis. BM aspirate shows hypercellularity with predominance of granulocytic cells at all stages of maturation, although sometimes erythroid series predominates: blast percentage is moderately elevated but never reaches the level seen in acute leukemia.<sup>9</sup>

Cytogenetic analysis, in vitro bone marrow progenitor cultures, trephine biopsies, flow cytometry and immunohistochemical studies may be helpful, only in those cases where the morphology of the white cells is difficult to appreciate or differentiate as opposed to this case in which history, clinical finding and smear of blood and bone marrow were clear enough to make the diagnosis.

In 25% of all JMML, activating point mutations are found in codon 12, 13 and 61 of *NRAS* and *KRAS* resulting in a continuous activation of the *RAS* pathway. Niemeyer *et al.* reported that 11% of

the JMML patients have clinical signs of neurofibromatosis type 1. Thereafter, Side *et al.* found *NF1* gene mutations in 15% of the JMML patients without clinical signs of NF1. Children with Noonan syndrome are at increased risk for developing JMML.<sup>10</sup>

We treated our patient with antibiotics for infections, packed red cell (filtered) and platelet transfusions for symptomatic anemia and thrombocytopenia. The use of pre-storage leukoreduced transfusion products is recommended. Along with the management of the symptoms and complications, we planned to start the recommended treatment protocol but her fever did not subside rather she developed sepsis and intracranial bleed and expired on the 10<sup>th</sup> day of admission.

Allo-Stem Cell Transplant remains the principal treatment for JMML, with an event-free 5-year survival of 52%. The principal cause for failure is relapse, which approaches 50%, though 50% of these patients can be rescued with a second allograft.<sup>11</sup> Recently, azacytidine, a hypomethylating agent, was reported to induce hematologic/molecular remissions in some children with JMML, and its role in both reducing leukemia burden before HSCT and in non-transplant settings requires further studies.<sup>9</sup>

## Recommendations

Other than hematopoietic stem cell transplantation (HSCT), all treatments in JMML are experimental. However infection, bleeding and anemia should be treated using broad spectrum antibiotics and blood transfusions.

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- B. Experimentation/Study Conduction
- C. Analysis/Interpretation/Discussion
- D. Manuscript Writing
- E. Critical Review
- F. Facilitated for Reagents/Material/Analysis