



## Juvenile Myelomonocytic Leukaemia in a Young Child– A Case Report

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### ABSTRACT

*Juvenile myelomonocytic leukaemia (JMML) is a unique paediatric disorders previously referred to as Juvenile Chronic Myeloid Leukemia. It is a clonal haematopoietic disorders of children that is characterized by proliferation principally of the granulocytic and monocytic lineage.*

*It is clinically aggressive and more similar in its course to acute myeloid leukemia.*

*We report a very rare case of JMML in a 8 year young child.*

**Keywords:** *JMML (Juvenile myelomonocytic leukemia), CMML (Chronic myelomonocytic leukemia), Neurofibromatosis, Philadelphia chromosome, Noonan syndrome*

### INTRODUCTION

**Juvenile myelomonocytic leukemia (JMML)** is a serious chronic leukemia (cancer of the blood) that affects children mostly aged 4 and younger. The name JMML now encompasses all diagnoses formerly referred to as juvenile chronic myeloid leukemia (JCML), chronic myelomonocytic leukemia of infancy. The average age of patients at

diagnosis is 2 years old. The World Health Organization has included JMML in the category of Myelodysplastic and Myeloproliferative disorders. Since about 10% of patients are diagnosed before 3 months of age, it is thought that JMML is a congenital condition in these infants. Genetics studies showed about 80% of JMML patients have some sort of genetic abnormality.

JMML accounts for 1-2% of childhood leukemias each year; in the United States, an estimated 25-50 new cases are diagnosed that can be identified with laboratory testing. This includes:

- 15-20% of patients with neurofibromatosis 1 (NF1)
- 25% of patients with mutations in one of the RAS family of oncogenes (only in their leukemia cells)
- Another 35% of patients with a mutation in a gene called PTPN11 (again, only in their leukemia cells).

Juvenile myelomonocytic leukemia is an aggressive pediatric myelodysplastic syndrome (MDS)/myeloproliferative disorder (MPD) characterized by malignant transformation in the hematopoietic stem cell compartment with proliferation of differentiated progeny[1]. JMML constitutes approximately 30% of childhood cases of myelodysplastic syndrome and 2% of leukemia [2]. Although JMML is a progressive and often rapidly fatal disease without hematopoietic stem cell transplantation (HSCT), some patients have been shown to have a prolonged and stable clinical course without HSCT[3]. Chronic myelomonocytic leukemia (CMML) is a similar disorder with later onset. Both JMML and CMML have a high frequency of mutations affecting the RAS signaling pathway and show hypersensitivity to stimulation with GM-CSF, which causes STAT5 hyperphosphorylation[1]. In up to 60% of cases of JMML, the RAS/MAPK pathway is deregulated due to somatic mutations in the PTPN11, KRAS, and NRAS genes. Additionally, both germline and somatic mutations in the CBL gene have been found in patients with

JMML, indicating a frequency of 10 to 15% of JMML patients overall [1].

About 10 to 15% of JMML cases arise in children with neurofibromatosis type I (NF1; ) due to germline mutations in the NF1 gene. In addition, patients with Noonan syndrome-like disorder (NSLL;) due to germline mutations in the PTPN11, KRAS2, and CBL genes, respectively, also have an increased risk of developing JMML.

Germline mutations in PTPN11 lead to Noonan syndrome-1 associated with JMML and that somatic mutations in PTPN11 are associated with isolated JMML[4]. Jongmans et al. (2005) described a patient with Noonan syndrome and mild JMML who carried a mutation in the PTPN11 gene[5]. Schubert et al. (2006) described a 3-month-old female with Noonan syndrome-3 and a severe clinical phenotype who presented with a JMML-like myeloproliferative disorder. The patient was heterozygous for a mutation in the KRAS gene. This mutation was also present in her buccal cells, but was absent in parental DNA[6]. De Filippi et al. (2009) reported a boy who presented in infancy with JMML but was later noted to have dysmorphic features suggestive of, but not diagnostic of, Noonan syndrome [7]

The symptoms are typical ones which lead to testing for JMML, though children with JMML may exhibit any combination of them: pallor, fever, infection, bleeding, cough, poor weight gain, a maculopapular rashes (discolored but not raised, or small and raised but not containing pus), lymphadenopathy (enlarged lymph nodes), moderate hepatomegaly (enlarged liver), marked splenomegaly (enlarged spleen), leukocytosis (high

white blood cell count in blood), absolute monocytosis (high monocyte count in blood), anemia (low red blood cell count in blood), and thrombocytopenia (low platelet count in blood). Most of these conditions are common, nonspecific signs and symptoms.

Children with JMML and Neurofibromatosis 1 (NF1) (about 14% of children with JMML are also clinically diagnosed with NF1, though up to 30% carry the NF1 gene mutation) may also exhibit any of the following symptoms associated with NF1 (in general, only young children with NF1 are at an increased risk of developing JMML):

- 6 or more café-au-lait spots on the skin
- 2 or more neurofibromas on or under the skin
- Plexiform neurofibromas.
- Optic glioma.
- Freckles under the arms or in the groin
- 2 or more Lisch nodules (tiny tan or brown-colored spots on the iris of the eye)
- Various bone deformations including bowing of the legs below the knee, scoliosis, or thinning of the shin bone

Children with JMML and Noonan's Syndrome may also exhibit any of the following most-common symptoms associated with Noonan's Syndrome:

- Congenital heart defects
- Undescended testicles in males
- Excess skin and low hair line on back of neck
- Widely set eyes
- Diamond-shaped eyebrows
- Ears that are low-set, backward-rotated, thick outer rim

- Deeply grooved philtrum.

**Differential diagnosis list includes infectious diseases like -**

- Epstein-Barr virus,
- cytomegalovirus,
- herpesvirus 6,
- histoplasma,
- mycobacteria,
- toxoplasma,
- Which can produce similar symptoms.

Role of splenectomy is that in JMML, the spleen acts as a trap for leukemic cells, which leads to their enlarged size. The fear is that since radiation therapy and chemotherapy attack active leukemia cells rather than dormant ones, if the spleen is not removed it may harbor JMML cells that can later lead to relapse. The impact of splenectomy for post-transplant relapse, though, is unknown.

The role of chemotherapy against JMML before bone marrow transplant has not been studied and is still unknown. Chemotherapy by itself has proven unable to bring about long-term survival in JMML.

Radiation to the spleen does not generally result in a decrease in spleen size or reduction of platelet transfusion requirement.

The only treatment that has resulted in cures for JMML is a bone marrow transplant [Stem cell transplantation], with about a 50% survival rate. The risk of relapsing after transplant is high, and has been recorded as high as 50%. Generally, JMML clinical researchers recommend that a patient have a bone marrow transplant scheduled as soon as possible after diagnosis. A younger age at bone

marrow transplant appears to predict a better outcome.

Prognosis refers to how well a patient is expected to respond to treatment based on their individual characteristics at time of diagnosis. In JMML, three characteristic areas have been identified as significant in the prognosis of patients.

Characteristic	Values indicating a more favorable prognosis
Sex	Male
Age at diagnosis	< 2 years old
Other existing conditions	Diagnosis of Noonan syndrome

Without treatment, the survival [5 years?] of children with JMML is approximately 5%. Only Hematopoietic Stem Cell Transplantation (HSCT), commonly referred to as a bone marrow or (umbilical) cord blood transplant, has been shown to be successful in curing a child of JMML.

### CASE REPORT

Our patient was a 8 years old male child who had first presented with complaints of fever with ear discharge for last 4 months. He was treated with antibiotics. Subsequently on a follow up examination, the Child's haemogram result showed an elevated total leucocyte count, for which the patient was brought to our hospital.

On examination child had marked pallor and high temperature. There was no skin rash and jaundice and bilateral upper cervical lymph node was palpable. He had marked hepatosplenomegaly with liver 4 cm and spleen 6 cm below the costal margin

### Haematological Findings

• Hemoglobin	3.8g/dl
• TLC	1.3 lakhs/cmm
• Platelet count	55,000/cmm
• DLC	
• Blast	7%
• Promyelocyte	3%
• Myelocyte	21%
• Metamyelocyte	2%
• Neutrophil	37%
• Lymphocyte	11%
• Monocyte	17%
• Eosinophil	2%
• The Absolute monocyte count is	17,000/cmm
• Nucleated red cells	5/100 WBCs

### BONE MARROW EXAMINATION

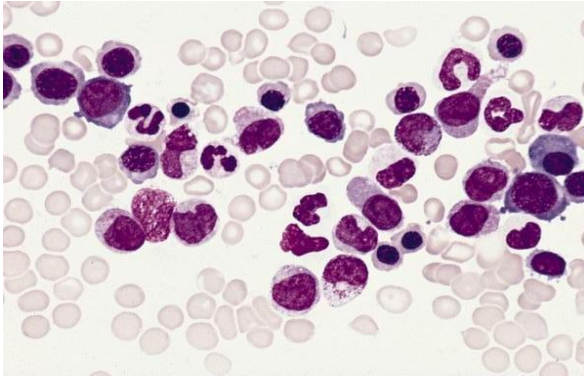
• Hypercellular with marked proliferation of myeloid lineage cells with M:E ratio 20:1	
• Blast	14%
• Promyelocyte	10%
• Myelocyte	16%
• Metamyelocyte	2%
• Band	9%
• Neutrophil	26%
• Lymphocyte	7%
• Monocyte	15%
• Eosinophil	1%
• Megakaryocytes	occasional

There were no ring sideroblast

Fetal Hb 20%

LAP score 32 (control 180)

- Cytogenetic analysis reveal normal karyotypes.
- There was neither monosomy 7 nor Ph chromosome.



Peripheral Blood Smears of Juvenile Myelomonocytic Leukemia

## DISCUSSION

JMML is a bridging disorder between MDS and MPD and included into the WHO category of MDS/MPD.

WHO diagnostic criteria of JMML

1. Peripheral blood monocytes  $>1 \times 10^9 /L$
2. Blasts(including promonocytes) are  $< 20\%$
3. No Ph chromosome

Plus 2 or more of the following

- A. Hemoglobin F increased for age
- B. Immature granulocytes in the peripheral blood
- C. White blood cell count  $>10 \times 10^9 /L$ .

D. Clonal chromosomal abnormality (e.g., monosomy 7).

E. Granulocyte-macrophage colony-stimulating factor (GM-CSF)

F. hypersensitivity of myeloid progenitors in vitro

These criteria are identified through blood tests and bone marrow tests.

**Blood tests:** A complete blood count (CBC) will be performed on a child suspected of having JMML and throughout the treatment and recovery of a child diagnosed with JMML.

The present case fulfilled the required criterias for diagnosis of JMML, such as neutrophilia , anaemia, thrombocytopenia, prominent monocytosis, immature circulating granulocytes including few blast and nucleated red cells and lacked Ph chromosome.

- When a picture of leukemia presents itself within the first four weeks of life, possibility of congenital leukemia should be considered.
- Occasionally the clinical and morphological picture of JMML mimicked by a variety of infectious organism e.g. EBV, CMV and. Careful investigation is mandatory in all children suspected JMML.
- The outcome of children with MDS is poor in most reports. Bone marrow transplant is the only therapy that has been demonstrated to clearly improve survival time



**CONCLUSION**

Juvenile myelomonocytic leukaemia (JMML) is a clonal haematopoietic disorders of children that is characterized by proliferation principally of the granulocytic and monocytic lineage. . Bone marrow transplant is the only therapy that has been demonstrated to clearly improve survival time

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