



Case Report

Juvenile Myelomonocytic Leukemia (JMML) presenting as bilateral periorbital swelling in a ten year old - A case report

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ABSTRACT

Juvenile Myelomonocytic Leukemia (JMML) is an infrequent pediatric myelodysplastic – myeloproliferative neoplasm characterized by the proliferation of myelomonocytic cells. The incidence of JMML is estimated to be 0.13 cases annually per 100000 children aged from 0-14 years. JMML is difficult to diagnose due to its similar clinical and bone marrow findings with that of other myeloproliferative neoplasms such as Chronic Myeloid Leukemia. Some characteristic features that establish the diagnosis of JMML are the presence of monocytosis ($\geq 1 \times 10^9/L$), blast percentage in blood and bone marrow of $< 20\%$, splenomegaly, absence of Philadelphia (Ph) chromosome or BCR-ABL1 fusion and raised fetal hemoglobin. Leukemic infiltration to any hematopoietic organ is also seen in JMML but orbital tissue infiltration is unusual. Here in, we report an unusual case of JMML in a ten year old child with emphasis on the distinguishing features for appropriate diagnosis and management plan.

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1. Introduction

Juvenile Myelomonocytic Leukemia (JMML) is an aggressive clonal hematopoietic disorder of childhood, characterized by the overgrowth of predominantly granulocytic and monocytic cell lineages.¹ It is an uncommon form of myelodysplastic and myeloproliferative neoplasm with an annual incidence estimated to be around 0.13 cases per 100000 children aged from 0-14 years.² It nearly accounts for less than 2-3% of all leukemias, usually affecting children below 3 years.³ The male to female ratio of affected children is 2:1.

The diagnosis of JMML requires the presence of monocytosis ($\geq 1 \times 10^9/L$), blast percentage in peripheral blood and bone marrow of $< 20\%$, splenomegaly and absence of Philadelphia (Ph) chromosome or BCR-ABL1 fusion. Genetic association with somatic mutation in PTPN11, KRAS, NRAS or NF1 mutation and germline CBL mutation (activation of RAS-MAPK

pathway) may also be seen. Other criteria include Monosomy 7 or presence of ≥ 2 of the following i) increased Fetal Hemoglobin (Hemoglobin F) for age, ii) myeloid and erythroid precursors on a peripheral blood smear, iii) granulocyte–macrophage colony stimulating factor hypersensitivity in colony assay or iv) hyperphosphorylation of STAT 5.⁴

Leukemic infiltration of mostly liver and spleen is seen with other non-hematopoietic organs like lymph nodes, skin, respiratory system and gut, although any tissue can be infiltrated.⁵ Patients generally present with hepatosplenomegaly, lymphadenopathy, infection and skin disease. Conventional chemotherapy is rarely beneficial, with a median survival of less than two years. However, long term survival has been reported after allogeneic bone marrow transplantation.⁶

JMML patients may transform into a blast crisis, and death is usually due to infection or organ failure as a result of infiltration by monocytes and macrophages.⁷ The worst prognosis group is those patients over the age of two years,

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with a low platelet count and an increased Hemoglobin F level.²

The purpose of the case report is to highlight a rare presentation of JMML as bilateral periorbital swelling in a ten year old girl with its unique clinical and laboratory findings.

2. Case History

A ten year old girl presented with painful, progressive bilateral periorbital swelling associated with bilateral proptosis and normal visual acuity. Clinically she had mild hepatosplenomegaly. Her ultrasonography findings of both orbits revealed solid mixed echogenic Space Occupying Lesion (SOL) below bilateral superior orbital rim measuring 34x33x8mm on the right side and 43x33x13mm on the left side with early cortical erosion in both inferior orbital rim. The Magnetic Resonance Imaging study of the brain was suggestive of bilateral periorbital neoplastic mass with a common differential diagnosis of orbital extension of retinoblastoma, lymphoma, or leukemic infiltrate. (Figure 1) Her complete blood count on admission showed hyperleukocytosis ($2 \times 10^9/L$) and thrombocytopenia ($30 \times 10^9/L$). Her peripheral blood smear showed 17% blasts with monocytosis ($1.3 \times 10^9/L$) and occasional nucleated red blood cells. (Figure 2) Her Serum Lactic Acid dehydrogenase (LDH) levels were raised ($652 \mu/L$) with raised Hemoglobin F of 56.4%. The ultrasonography of the abdomen also revealed metastatic soft tissue deposits in both kidneys and spleen. Later, her bone marrow findings were suggestive of hypercellular marrow with marked granulocytic hyperplasia with 5% blasts and 15% of monocytoid cells. The erythropoiesis and megakaryopoiesis was suppressed and showed mild dysplastic features. Blasts were Myeloperoxidase (MPO) positive. (Figures 3 and 4) On immunophenotyping, blasts were CD13, CD33 positive with aberrant CD19 and CD56 expression. Monocytoid cells expressed CD14, CD15, CD 64, CD11b. Cytogenetic abnormality for the BCR-ABL1 fusion gene was negative. Other chromosomal abnormalities could not be determined. Based on the above findings, diagnosis of Juvenile Myelomonocytic Leukemia was considered. The patient was then subjected to chemotherapy and further managed with supportive treatment.

3. Discussion

Myelodysplastic- myeloproliferative neoplasms of childhood are a heterogeneous group of clonal hematopoietic disorders with overlapping clinical features and evolving diagnostic criteria. World Health Organisation (WHO) has proposed a classification of the Myeloproliferative neoplasms (MPN), Myelodysplastic Syndromes (MDS) and the overlap Myelodysplastic/myeloproliferative neoplasms. The latter

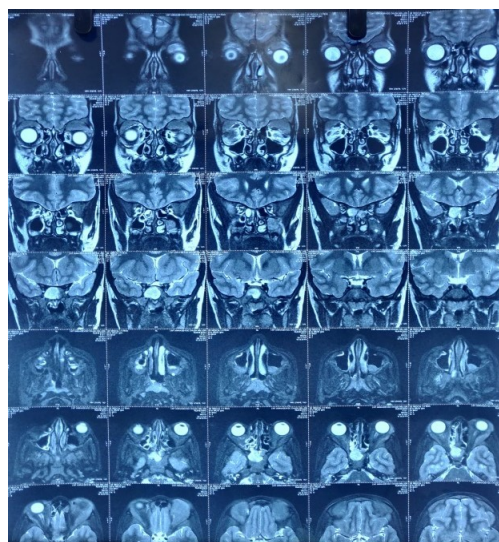


Fig. 1: Magnetic resonance imaging brain showing bilateral periorbital swelling

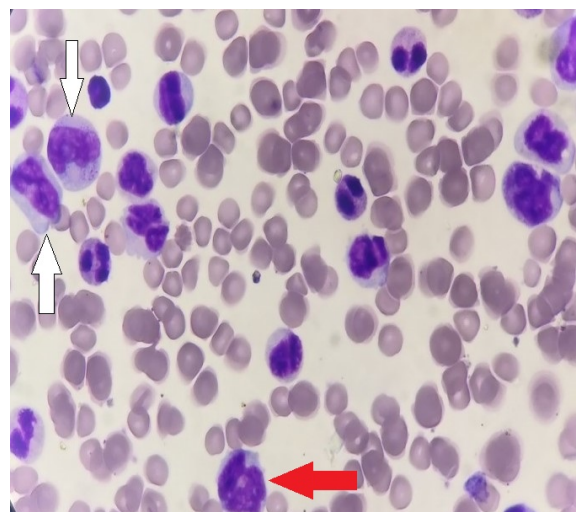


Fig. 2: Peripheral blood smear showing hyperleukocytosis with increased blasts (red arrow) and monocytoid cells (white arrows). (Geimsa stain, 400X magnification)

group includes conditions in which there are features of both myelodysplasia and myeloproliferation and thus, JMML and Chronic Myelomonocytic Leukemia (CMML) was assigned to this group rather than to the MDS.^{3,6}

JMML is a lethal clonal disorder characterized by proliferation of granulocytic and monocytic lineages. It accounts for 20-30% of all cases of myelodysplastic and myeloproliferative diseases in patients aged less than 14 years. Patient's age at diagnosis ranges from one month to early adolescence as described in this report. Approximately 15% of cases occur in infants with Noonan Syndrome like disorder and 10% occur in

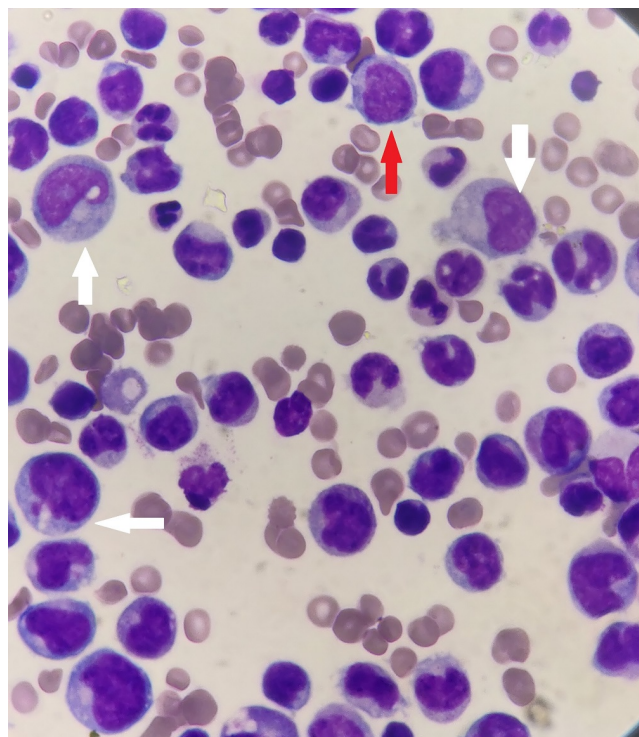


Fig. 3: Bonemarrow Aspirate showing presence of granulocytic cells with blasts (red arrow) and scattered monocytoid cells (white arrows). (Geimsa stain, 400X magnification)

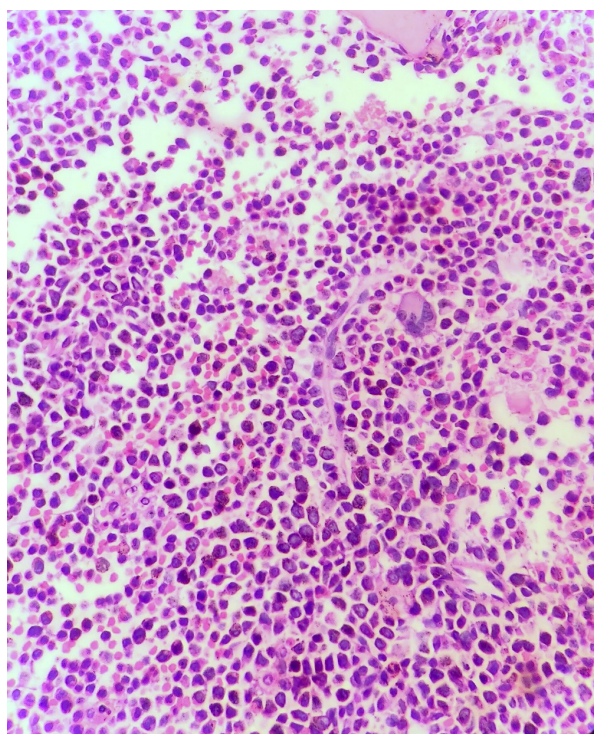


Fig. 4: Bone marrow biopsy showing hypercellular marrow with increased granulocytic and monocytic proliferation (Hematoxylin & Eosin stain, 200X magnification)

children with Neurofibromatosis type 1. Some patients may carry germline mutations in *PTPN11* or *KRAS*.⁸ In this case report, there were no associated syndrome identified clinically. Due to unavailability of advanced facilities of advanced cytogenetics and molecular studies in our institution, the specific genetic mutations were not analyzed.

Most cases present with early constitutional symptoms or evidence of infection. There is usually a presentation with hepatosplenomegaly, as noticed in this case. Leukemic infiltration to various non-hematopoietic tissues is seen commonly to lymph nodes, lungs, gastrointestinal tract and skin (papillary and reticular dermis). JMML rarely involves the central nervous system and ocular tissues.⁶ In this case, ocular infiltration is the first clinical manifestation which is quite rare, with systemic leukemic infiltrates involving both kidneys and spleen. Busque L et al described that most cases had a leucocyte count of less than $50 \times 10^9/L$; less than 8% of cases have counts greater than $100 \times 10^9/L$, which is also seen in the present case.⁸

The leucocytosis consists mainly of neutrophils, with some promyelocytes and myelocytes and monocytes. Blast counts for less than 20% with monocytosis were observed in this case. Bone marrow aspirate and biopsy are cellular with granulocytic proliferation. Monocytes account for 5–10% of the bone marrow cells. In our case, the monocytoid cells comprised about 15% of all marrow cells. There is also an alteration in the hemoglobin pattern in patients with JMML: Hemoglobin A2 concentration is reduced, whereas the Hemoglobin F level is greater than 10% at diagnosis.⁹ In our case, Hemoglobin F was also raised with 56.4%.

In general, JMML lack cytogenetic abnormalities; 40 – 67% of patients will have normal cytogenetic analysis, 25 – 33% will have monosomy 7 and only 10 – 25% will have other chromosomal aberrations.⁹ Trisomy 8, an uncommon chromosomal abnormality which is seen in only 4% of patients in the study done by Passmore SJ et al.² In this study, the cytogenetics could not be done as it was not available in the institution.

The absence of the *t*(9;22) translocation and BCR-ABL rearrangement is one of the laboratory criteria for the diagnosis of JMML according to the International Juvenile Myelomonocytic Leukemia Working group.³ As seen in this case, the patient was negative for the BCR-ABL1 fusion gene by DNA analysis.

JMML is typically more fatal than most other chronic myeloproliferative disorders with a median survival of less than 10 months.⁶ The initial course of JMML is varied with approximately one-third of patients developing a rapidly progressive course leading to an early death. Morbidity and mortality often occur due to bleeding, infection or non-hematopoietic organ failure due to monocytic infiltration.

The worst prognosis is those of patients over the age of 2 years, with a low platelet count and a high haemoglobin F

level. In our case, the patient was above the age of 2 years with raised haemoglobin F, indicating a somewhat poor prognosis. JMML with KRAS or NRAS mutation generally has an aggressive course with early hematopoietic stem cell transplantation needed.¹⁰

The treatment of JMML is controversial and current approach depends on the genetic mechanisms underlying the disease. Recently, stem cell transplantation is the only effective therapy in the clinical management of JMML. The use of a DNA-hypomethylating agent, 5-azacytidine is reported to induce hematologic and molecular remission in some cases according to current clinical trials.¹⁰

4. Conclusion

JMML is a unique but an aggressive clonal hematopoietic neoplasm with an unusual presentation as periorbital leukemic infiltration. Early diagnosis of JMML is difficult because of the overlap in some of the clinical and laboratory features with other types of myelodysplastic or myeloproliferative disease. An accurate diagnosis is however necessary, using the advanced techniques of flowcytometry, and genetic studies for the identification of specific molecular pathways involved, since intensive chemotherapy and early stem cell transplantation will help improve the prognosis and survival of these patients.

5. Source of Funding

None.

6. Conflict of Interest

None.

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