Juvenile Myelomonocytic Leukemia

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Abstract Juvenile myelomonocytic leukemia (JMML) is a rare fatal hematopoietic disorder of early childhood. We are presenting a case of 9-month-old female child who was admitted with abdominal distension, irritability, and hepatosplenomegaly. Peripheral blood film examination showed leukoerythroblastosis with leukocytosis, absolute monocytosis, microcytic hypo chromic anemia, and thrombocytopenia. Bone marrow examination showed myeloid hyperplasia, Hb HPLC revealed normal HbF (1.3 %) and HbA2 (2.9 %). There was absolute gamma globulinemia and DCT positivity. Cytogenetic studies revealed a normal karyotype with absence of Philadelphia (Ph) chromosome, monosomy 7 or any other chromosomal abnormality. Diagnosis of JMML was rendered according to the diagnostic criteria laid down by WHO classification 2008 with presence of peripheral blood monocytosis $>1 \times 10^9/L$, blasts <20 % of leucocytes in blood or nucleated cells in bone marrow, absence of Ph chromosome, presence of immature granulocytes in the blood and WBC count $>10 \times 10^9/L$. The patient was then started on a regimen of chemotherapy to which she gave a promising response.

Keywords JMML · HbF · Ph chromosome

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Introduction

Juvenile myelomonocytic leukemia (JMML) is a rare fatal hematopoietic disorder of early childhood. It represents about 2–3 % of childhood leukemia's with about 75 % cases occurring below 3 years of age [1, 2]. The course of JMML is quite variable with 1/3rd of patients having rapidly progressive course, 1/3rd having relatively indolent course while remaining 1/3rd have intermediate prognosis [2].

Case History

A 9-month-old female child was admitted with complaints of abdominal distension and irritability since 4 months. The child was developmentally normal. Physical examination revealed petechiae, pallor, hepatomegaly (4 cm below costal margin), and splenomegaly (8 cm below costal margin).

Peripheral blood film examination showed leukoerythroblastic blood picture with leukocytosis, absolute monocytosis, microcytic hypo chromic anemia, and thrombocytopenia (Fig. 1). TLC was $31.9 \times 10^3/\mu L$, Hb 4.9 gm/dL, platelet count $10 \times 10^6/\mu L$ and absolute monocyte count $3.83 \times 10^9/L$ (DLC: N42L34E1M12Stab 05Myelo3Metamyelo3). Reticulocyte count was 1.9 %. Bone marrow examination revealed cellular smears with myeloid hyperplasia, features of dysmyelopoiesis and presence of 10 % blasts.

The peripheral blood leukocytosis with absolute monocytosis persisted for more than 3 months which pointed towards a strong suspicion of JMML. Hemoglobin high performance liquid chromatography (Hb-HPLC) revealed normal HbF values (1.3 %) and HbA2 values (2.9 %).

Fig. 1 Leukocytosis with immature forms and increased monocytes. H/E, $\times 100$

There was absolute serum gamma globulinemia (3.6 mg/dL) with reversed A/G ratio (0.88) and positive direct antiglobulin test (DAT). To rule out infection associated monocytosis, serological tests for Cytomegalo virus (CMV), Herpes virus (HSV), and Epstein barr virus (EBV) were done and found negative.

Cytogenetic studies of the patient revealed a normal karyotype with absence of Philadelphia (Ph) chromosome, monosomy 7 or any other chromosomal abnormality.

Diagnosis of JMML was rendered according to the diagnostic criteria laid down by WHO classification 2008 with presence of all major criteria like peripheral blood monocytosis $>1 \times 10^9/L$, blasts $<20\%$ of leukocytes in blood or nucleated cells in bone marrow, absence of Ph chromosome and two minor criteria like presence of immature granulocytes in the blood and WBC count $>10 \times 10^9/L$ [3].

Stem cell transplantation was not possible due to financial reasons. The patient was started on a novel regimen of chemotherapy consisting of Cytosine arabinoside, etoposide, vincristine, and isotretinoin. During the first cycle of chemotherapy, her TLC decreased to $0.8 \times 10^3/\mu L$ and then it started increasing to reach $2.4 \times 10^3/\mu L$. There was disappearance of immature myeloid forms from peripheral blood film as well as reduction in monocyte count. There was mild regression of spleen size (about 1 cm decrease). However, the patient left the hospital against medical advice without completing the treatment.

Discussion

JMML is a myelodysplastic and myeloproliferative disorder whose diagnostic criteria were laid down by Neimeyer

et al. in 1998 and were incorporated in the WHO classification 2008 [3, 4].

JMML accounts for about 3 % of all pediatric hematological malignancies and 18 % of all cases of myelodysplastic syndromes (MDS) in children less than 15 years of age. Children typically present at young age (median age at diagnosis = 2 years) with hepatosplenomegaly, monocytosis, anemia, thrombocytopenia, and elevated HbF. About 40 % cases occur before 1 year. Boys are affected more often than girls (M:F = 2.5) [5].

Bone marrow aspirates are usually hypercellular with granulocytic proliferation as was seen in the present case, although in some patients of JMML, erythroid precursors may predominate especially in cases of monosomy 7 [1].

There is reversion in JMML to fetal erythropoiesis resulting in increased HbF levels; however, normal levels can be seen in about 1/3rd of patients. One study showed that patients with normal karyotype have wide range of HbF levels with about 25.4 % of patients having normal HbF levels [1].

Polyclonal hypergammaglobulinemia is commonly found in the patients of JMML; however, its significance remains unclear [6]. Autoantibodies with no apparent clinical relevance have been observed in less than 1/4th of the patients of JMML [1]. The present case showed both increased serum globulins levels and positive DCT.

Many viral infections like CMV, EBV, and HSV show similarity in clinical and laboratory findings with JMML [7]. Various serological and cytogenetic analyses are required to discriminate between the two conditions.

Karyotyping studies show normal karyotype in about 64.3 % of children, monosomy 7 in about 25.5 %, and other aberrations in 10.2 % of cases [1]. Molecular studies reveal presence of mutations involving genes of RAS/MAPK pathways, PTPN11, KRAS, and NF-1 in about 80 % of cases [8]. Ph chromosome is always absent in JMML. However, chromosomal abnormalities influence neither the natural course of the disease nor the patient's clinical outcome with various treatments [9]. The present case did not show any abnormality on karyotyping. However, molecular studies could not be undertaken due to financial constraints.

Bone marrow transplantation is the treatment of choice in JMML. However, many non transplant treatments of JMML were tried with variable degrees of success. Hyung Jin Kang et al. [10] in their study used a novel regimen of chemotherapy which showed effective results on JMML patients. Same treatment was used in this patient to which she showed a promising initial response. However, the patient did not complete the treatment and was lost to follow up.

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