Case Report

Juvenile myelomonocytic leukemia

N V Naren[1], K P Rashmi[2*]

{[1]Associate Professor, Department of General Medicine} {[2]Associate Professor, Department of Pathology}
Belagavi Institute of medical sciences, Belagavi-590001, Karnataka, INDIA.
Email: narennimbal@rediffmail.com, rashminimbal@rediffmail.com

Abstract

Juvenile myelomonocytic leukemia (JMML) is a rare pediatric malignancy, which presents in infancy or early childhood with myeloproliferative features and hepatosplenomegaly. JMML is Philadelphia chromosome negative with aggressive clinical course. We report a case of JMML in a three year old female child with recurrent fever, anemia and hepatosplenomegaly. Her blood examination showed leucocytosis, monocytosis and elevated HbF without increase in blasts. Philadelphia chromosome was negative. The disease progressed with worsening anemia, leucocytosis and thrombocytopenia and patient expired due to intracranial bleed within two months of diagnosis.
Key words: Juvenile myelomonocytic leukemia,Philadelphia chromosome, monocytosis.

[*]**Address for Correspondence:**
Dr. Rashmi K. Patil, H.No.201, First Stage, Rani Channamma Nagar, Belagavi-590006, Karnataka, INDIA.
Email: narennimbal@rediffmail.com
Received Date: 23/01/2015 Revised Date: 29/01/2015 Accepted Date: 02/02/2015

Access this article online

Quick Response Code:

Website: www.statperson.com

DOI: 04 February 2015

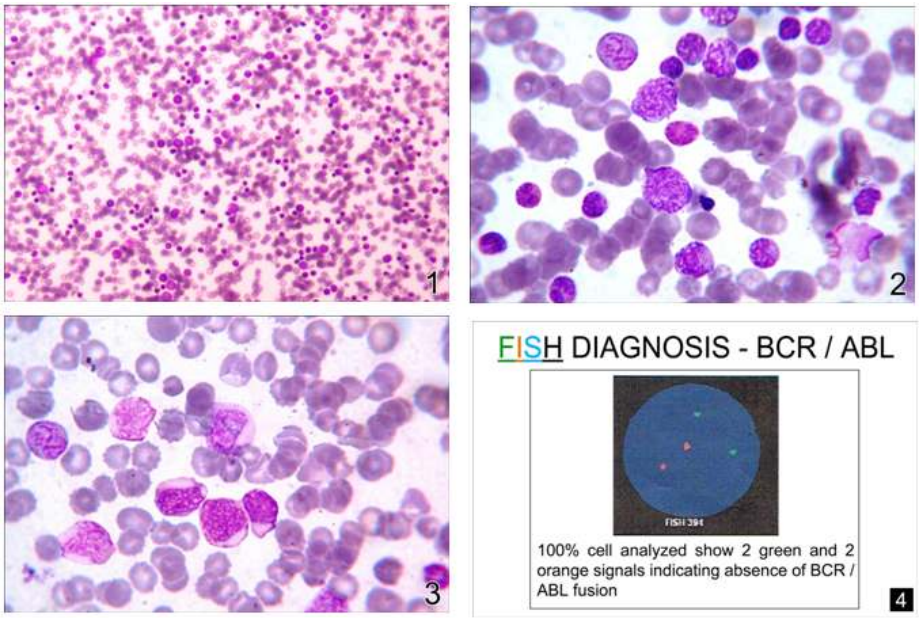
INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is a rare early childhood clonal hematopoietic disease characterized by excessive proliferation of monocytic and granulocytic cells. [1] It represents two to three percent of all pediatric leukemias. [2] The incidence of JMML in patients with Neurofibromatosis (NF 1) is approximately 14%.[3, 4] Patients with JMML present with monocytosis, leucocytosis, anemia, and thrombocytopenia as well as with spleen and liver enlargement. Progression of the disease is often rapid with infiltration of the bone marrow and other tissues by monocytic and myeloid cells. JMML usually runs an aggressive clinical course with median duration of survival of children left untreated being less than 12 months from diagnosis. [4, 5] This case is described for its extreme rarity.

CASE REPORT

Three year female child was admitted with complaints of abdominal distension, cough and fever of six months duration. Child was treated by different medications but symptoms used to subside temporarily only to recur with gradually increasing pallor. On examination, her general condition was stable with temperature of 99 deg F, pulse rate- 99/min, respiratory rate- 29/min, pallor and generalized edema. There was no cyanosis, jaundice or lymphadenopathy. Few petechial hemorrhagic spots over the leg and thigh were seen. Palpable spleen of nine centimetre and liver of four centimetre was noted. Routine hemogram revealed hemoglobin-8.5 g/dl and total leucocyte count (TLC) - 1,17000/cubic mm. A peripheral smear showed mild anisocytosis, poilkilocytosis and occasional nucleated RBCs. Differential count revealed shift to left with myeloid series upto myeloblasts (neutrophils+band forms 45%, lymphocytes 10%, monocytes 18%, metamyelocytes 14%, myelocytes 10%, promyelocytes 2%, blasts 1%) (Fig.1,2 and 3). Platelet count was 15000/cubic mm. Hemoglobin electrophoresis revealed elevated levels of hemoglobin F (HbF-6%). Chest Xray was normal. Ultrasound abdomen showed hepatosplenomegaly. Fluorescence in situ hybridization (FISH) technique based cytogenetic study for Philadelphia chromosome (Ph-BCR-ABL) was negative (Fig.4). Thus with findings of leucocytosis, monocytosis, increased HbF and negative Ph chromosome, a final diagnosis of JMML was made which fulfilled the required WHO diagnostic criteria of

JMML. Family history in father was significant. On examination of patient's father, numerous subcutaneous swellings of varying sizes were seen all over the body which suggested diagnosis of neurbromatosis type 1 (NF1) in father. On follow up unfortunately patient expired due to intracranial bleed within two months of diagnosis.



Legends of Photos

Figure 1: Blood smear showing increased leucocyte count (Leishman's stain, x 100)

Figure 2: Blood smear showing mild anisopoikilocytosis of RBCs, increased WBCs with shift to left in myeloid series cells and decreased platelet count (Leishman's stain, x 1000)

Figure 3: Blood smear showing increased monocytic cells (Leishman's stain, x 1000)

Figure 4: FISH technique based cytogenetic study for Philadelphia chromosome showing absence of BCR/ABL fusion signal

DISCUSSION

Juvenile myelomonocytic leukemia (JMML) is a clonal stem cell disorder bridging between myelodysplastic syndrome and myeloproliferative diseases. [2, 5] More than 95% of JMML patients are diagnosed under the age of 6 years with median age at diagnosis of 2 years. It is prevalent in males than females in a ratio of 2.5 to 1.[2,6] Children with JMML mostly presents with hepatosplenomegaly, lymphadenopathy, recurrent infections and bleeding.[7] Characteristic diagnostic criteria are persistent elevated absolute monocyte count in the blood (greater than 1000/microlitre of blood), absence of philadelphia chromosome (Ph chromosome) and less than 20% blasts in blood or bone marrow. JMML needs to be differentiated from other forms of myeloproliferative disorders like chronic myeloid leukemia (CML). Childhood CML is extremely rare in infants and presents with positive Ph chromosome without monocytosis in peripheral smear. The cause of JMML remains largely unknown. Upto 14% of cases occur in children with neurofibromatosis type 1(NF1), an autosomal dominant disorder caused by germline inactivation of one allele of the NF 1 gene on chromosome 17. [3, 4, 8] Children with NF 1 gene mutation are strongly predisposed to myeloid malignancies particularly JMML. NF 1 functions as a tumor suppressor gene in immature myeloid cells by neagatively regulating Ras. Inactivation of NF 1 is associated with constitutive activation of Ras signaling resulting in hyperactivation of cells in response to stem cell factor, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF). [8] Thus these data suggest the pathogenesis of JMML caused by deregulated Ras signaling in respone to GM-CSF and other myeloid growth factors. JMML is Ph chromosome negative with aggressive clinical course. Without treatment, JMML progresses rapidly. Stem cell transplantation (SCT) is the only effective therapy for producing sustained remission in JMML. [9] Chemotherapy by itself has proven unable to bring about long term survival in JMML. In some patients, splenectomy has been performed as palliative treatment. Children older than 2 years at diagnosis with low platelets, elevated HbF and monosomy 7 cytogenetic abnormalities are associated with unfavorable prognosis. [10] Our patient had presented with he, gpatospenomegaly generalized edema and patient's father had numerous

subcutaneous neurofibromas. Routine hemogram, peripheral smear and negative Ph chromosome (BCR-ABL) confirmed JMML fulfilling the criteria required for diagnosis of JMML. We were able to establish diagnosis of neurofibroma in father providing most likely explanation of JMML in child due to germ line NF 1 mutation.

CONCLUSION

We have diagnosed JMML on peripheral smear examination and cytogentic study. This case is presented for its extremely uncommon incidence in childhood.

REFERENCES

1. Arico M, Biondi A, Pui C-H. Juvenile myelomonocytic leukemia. *Blood* 1997;90:479-88.
2. Franco L, Peter N, Marco Z, Elizabeth K, Edoardo L, Christine P, et al. Hematopoietic stem cell transplantation in children with Juvenile Myelomonocytic Leukemia. *Blood* 2005;1:410-19.
3. Shannon KM, O' Connell P, Martin GA, Paderanga D, Olson K, Dinndorf P, McCormick F: Loss of the normal *NF1* allele from the bone marrow of children with type I neufibomatosis and malignant myeloid disorders. *N Engl J Med* 1994;330:597-601.
4. Stiller CA, Chessells JM, Fitchett M. Neurofibromatosis and childhood leukemia/lymphoma: a population-based UKCCSG study. *Br J Cancer*1994;70:969-972.
5. Hasle H, Niemeyer CM, Chessells JM, et al. A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. *Leukemia* 2003;17:277-82.
6. Vardiman JW, Pierre R, Imbert M, et al. Juvenile myelomonocytic leukemia. In: Jaffe ES, Harris NL, Stein H *et al*. Pathology and Genetics of Haematopoitic and Lymphoid Tissues. World Health Organisation Classification of Tumors. Lyon, France: IARC Press; 2001:55-57.
7. Emanuel PD. Myelodysplasia and Myeloproliferative disorders in childhood:An update. *Br J hematol* 1999; 105:852-63.
8. Cooper JN, Shannon KM, Loken MR, Weaver M, Staphens K, Sievers EL.Evidence that juvenile myelomonocytic leukemia can arise from a pluripotential stem cell. *Blood* 2000;96(6):2310-13.
9. Donadieu J, Stephan JL, Blanche S, et al. Treatment of juvenile chronic myelomonocytic leukemia by allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1994;13:777-82.
10. Locatelli F, Nolleke P, Zecca M, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. *Blood* 2005;105:410-19

Source of Support: None Declared
Conflict of Interest: None Declared