Summary: A 9.5-year-old girl with malaise, fever, massive hepatosplenomegaly, anemia, leukocytosis (37.9 x 10^9/L), monocytes (1.48 x 10^9/L), and thrombocytopenia is presented. Hemoglobin F was increased (18%). Bone marrow erythroid/myeloid ratio was 40/1 with 7% myeloblast and 5% monocye suggesting erythroleukemia or juvenile myelomonocytic leukemia (JMML). The patient had a fulminating course with respiratory compromise and died in 2 weeks before heterozygous somatic mutation in the PTPN11 gene was shown. JMML must be considered also in the patients older than 6 years. A cytopenic phase may precede JMML. Leucocytosis may be transient and there may be predominance of erythroid precursors in the bone marrow.

Key Words: JMML, PTPN11 gene, child

Nonsyndromic Juvenile Myelomonocytic Leukemia With PTPN11 Mutation in a 9-Year-Old Girl

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CASE REPORT

An 8.5-year-old female patient was referred to our hematology outpatient unit with mild thrombocytopenia, monocytosis, and neutropenia (Hgb = 119 g/dL, white blood cells [WBC] = 4.89 x 10^9/L, absolute neutrophil count (ANC) = 0.74 x 10^9/L, monocytes = 1.48 x 10^9/L, platelets (PLT) = 93.5 x 10^9/L, and mean corpuscular volume = 75 FL). Physical examination was normal. She had no hepatosplenomegaly. At that time parents refused any further investigation including bone marrow aspiration/biopsy and never followed up.

Eleven months later, she was admitted to the hospital when she presented with malaise, fever, and abdominal enlargement. Physical examination was significant with enlarged liver and spleen, 10 and 11 cm palpable below costal margin, respectively. Laboratory workup revealed anemia, leukocytosis, monocytosis, and thrombocytopenia (Hgb = 9.6 g/dL, WBC = 37.9 x 10^9/L, ANC = 21.8 x 10^9/L, monocytes = 1.89 x 10^9/L, PLT = 29.1 x 10^9/L, and mean corpuscular volume = 74 FL, reticulocyte count = 40 x 10^9/L). Peripheral blood smear revealed basophilic stippling, cabot rings, polychromasia, anisocytosis, and megaloblastic changes in red blood cells. There were large platelets, some lobulation defects of neutrophils, and large basophilic granules in some lymphocytes. Differential count showed 22% band, 22% lymphocyte, 21% neutrophil, 9% late monoblast, 9% early monoblast, 7% myeloblast, 5% monocyte, 1% metamyelocyte, 3% eosinophil, 3% basophil, and 1% promyelocyte. Total bilirubin was 3.3 mg/dL, direct bilirubin was 1 mg/dL, haptoglobin was 8 mg/dL, lactate dehydrogenase was 650 U/L. D. Coombs test was negative, fetal hemoglobin (HbF) was 18%, and serum vitamin B12 and folic acid levels were normal. Urinalysis was normal. Acute viral infection was excluded with negative serology of Ebstein Barr virus, parvovirus, cytomegalovirus, hepatitis A, hepatitis B, and hepatitis C. Bone marrow aspiration was hypercellular and there were no megakaryocytes; erythroid/myeloid ratio was 40/1. Almost all cells were erythroid precursors and very few promyelocytes, lymphocytes, and neutrophils were seen. Marrow biopsy showed 85% cellularity with normal megakaryocytes in morphology and number. There was erythroid hyperplasia with increased glycophrin-positive young cells, some cytoplasmic CD68+ monocytes. There were few myeloid elements with normal maturation in patchy areas with eosinophilic predominance. Monocytes were increased; erythroid/myeloid ratio was 3/1. Cytogenetic analysis in 30 metaphases showed 46XY, 9%, 45XY, 9% trisomy 8/16, 7.5% monosomy deletion of 8q22. Bcr/abl was negative with polymerase chain reaction. Family donor search for hematopoietic stem cell transplantation (HSCT) was initiated with possible diagnosis of JMML, myelodysplastic syndrome (MDS), or erythroleukemia. Bone marrow and hair samples were sent to EWOG-MDS group for evaluation and genetic study of JMML.

While waiting for the results of the genetic analysis, she was readmitted on the third day of discharge with fever, tachypnea, tachycardia, and edema on her legs. Respiratory rate was 28/min. Heart rate was 124/min. Axillary temperature was 38°C. Systolic/diastolic pressures were 110/80 mm Hg. Chest x-ray was normal. Hgb was 7.2 g/dL, WBC was 13 x 10^9/L, ANC was 5.1 x 10^9/L, monocytes showed 2.8 x 10^9/L, and PLT count was 34.9 x 10^9/L. Reticulocyte count was 49 x 10^9/L and haptoglobin was 8 mg/dL. D. Coombs test was negative. Urinalysis was normal. Blood culture remained negative. Piperacillin/tazobactam and supportive therapy with packed red cells, platelets, and nasal oxygen were administered. No chemotherapy was administered due to uncertainty in diagnosis and spontaneous decrease in WBC counts. On chest x-ray, perihilar vascular markings were prominent and right transverse fissure was thickened. She had a sudden loss of consciousness on day 8 of hospitalization; Hgb dropped to 5.2 g/dL, WBC increased to 37.0 x 10^9/L, PLT count was 53.9 x 10^9/L, prothrombin time and active partial thromboplastin time were prolonged (62.5 s and 61.7 s, respectively), International normalized ratio was 8.26, and thrombin time was normal (20.3 s). She had respiratory arrest and was unresponsive to resuscitation.

Genetic study was completed after her death. DNA analysis performed from bone marrow revealed a heterozygous mutation in the PTPN11 gene, exon 13 c.1508 G > T, amino acid p.503 G > V. This mutation was not expressed in hair follicles.
DISCUSSION

Although JMML is a disease of very young children, some patients present at an older age as our patient. Only 4.5% of the patients were 5 years and older in a report by Niemeyer et al. In a review it is even emphasized that “If a child is older than 6 years other potential diagnosis should be strongly considered.”

In JMML, bone marrow aspirates show hypercellularity with predominance of myeloid cells at all stages of maturation. Monocytosis is less pronounced in the marrow than in the peripheral blood. Our patient had high WBC count, > 1.0 x 10^9/L monocytes in the peripheral blood, anemia, thrombocytopenia, and elevated HbF which were diagnostic features for JMML but erythroid predominance in the bone marrow (erythroid/myeloid ratio 40/1) was an unusual finding for JMML. In a study of EWOG-MDS group comprising 110 patients with JMML only 6% showed that erythroid precursors accounted for more than half of the marrow cells. Erythroid predominance in the marrow and age of the patient were challenging for the diagnosis of JMML. Myeloid cells were only seen in patchy areas which was a feature of MDS. According to the 2nd International JMML symposium consensus criteria for JMML, our patient fulfilled the features of category 1 and 2.

Somatic PTPN11 mutations, the gene encoding the protein tyrosine phosphatase SHP2, are the most frequent molecular lesions in JMML, encountered in 35% of non-syndromic JMML cases. The mutation detected in our patient (1508 G > T, Gly503Val) was not a novel mutation and it was reported in 4 of 69 nonsyndromic cases with PTPN11 mutation.

JMML rarely converts into blast crisis, most children die because of progressive respiratory and organ failure. The median survival time without HSCT is approximately 1 year. Poor prognostic factors are reported as older age at diagnosis (> 2 y), platelet count < 33 x 10^9/L at presentation, and/or high HbF for age, and female sex in some series. Our patient had all the poor prognostic factors and a rapidly progressive clinical course with fatal outcome. Erythroid predominance, older age, and spontaneous decrease in WBC were challenging. During second hospitalization after packed red cell transfusion, monocytosis count dropped to < 0.5 x 10^9/L. Respiratory distress was probably due to the monocytic infiltration of the lungs and cerebral bleeding due to disseminated intravascular coagulation. In patients with high WBC count, respiratory compromise, and severe organomegaly, 6-mercaptopurin ± cis retinoic acid is recommended. Low-dose cytosine arabinoside could be used for severe cases or for progressive disease and if this fails, higher doses of cytosine arabinoside plus fludarabine is recommended. In asymptomatic cases a watchful waiting until donor search is considered.

EWOG-MDS/European Group for Blood and Marrow Transplantation (EBMT) JMML trial showed that the patients who received either no pre-HSCT therapy or low-dose chemotherapy in comparison to high-dose acute myeloblastic leukemia-like chemotherapy had identical event free survival (52% vs. 50%), relapse incidence (35% vs. 38%), and treatment-related mortality (13% vs. 13%). Pretransplant splenectomy had no statistical benefit in event free survival, relapse incidence, or transplant-related mortality.

In a published report, mutation of PTPN11 was associated with older age at diagnosis (> 2 y), increased HbF (> 10%), reduced overall survival, and an unfavorable factor predicting relapse after HSCT.

In summary, JMML could present at an older age and a cytopenic phase may precede JMML. WBC numbers may show fluctuations and marrow may show erythroid predominance.

ACKNOWLEDGMENTS

The authors thank Professor C. M. Niemeyer and EWOG-MDS for genetic study.

REFERENCES