Genetics and Molecular Biology, 31, 1, 36-38 (2008)

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Short Communication

Myeloproliferative syndrome of monosomy 7: A brief report

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Abstract

We report the case of a five-month-old black male infant who had recurrent episodes of respiratory infections and also presented anemia and enlargements of the spleen, liver and lymphnodes. Hematological analysis revealed morphological abnormalities with megaloblastic dyserythropoiesis, while fetal hemoglobin assaying showed normal levels. Conventional and molecular cytogenetic analysis revealed monosomy of chromosome 7. Despite all therapeutic efforts during allogenic bone marrow transplantation, the child died due to generalized infection. The clinical and genetic distinctions between monosomy 7 syndrome and myelodysplastic disorders in childhood are discussed.

Key words: leukemia, monosomy 7, myeloproliferative syndrome.

Received: July 23, 2007; Accepted: October 1, 2007.

Monosomy 7 is the most common cytogenetic abnormality among myeloid disorders during childhood. It can be found in both preleukemic myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). In patients with AML, monosomy suggests involvement of pluripotent hematopoietic stem cells in the leukemic process. Monosomy 7 also occurs in some patients who are reported as having juvenile myelomonocytic leukemia (JMML) (Johnson and Cotter, 1997; Hasle *et al.*, 1999).

JMML is a rare malignant disease, representing less than 5% of childhood leukemia. Because of the heterogeneity of its clinical features, JMML can be misdiagnosed as other myeloproliferative disorders. However, most JMML cases present splenomegaly, pallor, hepatomegaly, lymphadenopathy and facial eczematous rash. The hematological profile includes high white blood cell (WBC) counts (< 100,000/mm^3), monocytes, anemia with variable normoblastemia, thrombocytopenia and autoantibodies. Fetal hemoglobin (HbF) and immunoglobulin levels are usually elevated, whereas leukocyte alkaline phosphatase levels are lowered and the Philadelphia chromosome is always absent (Niemeyer *et al.*, 1997; Hasle *et al.*, 1999, 2003; Lopes *et al.*, 2006; Hasle, 2007).

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A 5-month-old black male infant was hospitalized in CEONHPE, city of Recife, in June 2002, with intense pallor, fever and persistent diarrhea. At physical examination, he presented abnormal abdominal features due to a huge hepatosplenomegaly (which had first been noticed two months earlier). No congenital stigmata signs were found. He was treated with antibiotics, antifungals and blood transfusions. He was investigated for acute leukemia (AL), thalassemia syndromes, congenital dyserythropoietic anemia (CDA) and myelodysplastic syndrome (MDS). The hematological findings were: hemoglobin 3.9 g; hematocrit 17%; median corpuscular volume and reticulocyte count 60%; WBC 24,000/mm^3; elevated circulating monocytes (5,320/mm^3); and platelet count 23,000/mm^3. Biochemical tests showed very high levels of LDH (more than 20,000/mm^3) and the uric acid concentration was 13 mg/dL. Bone marrow (BM) aspirates were morphologically characterized by erythroid hyperplasia with dyserythropoiesis. The erythroid cells were either binucleated or multinucleated with asynchronous nucleus-cytoplasm ratio. The neutrophil compartment showed moderated hyperplasia and 6% blast cells. Hemoglobin assaying showed HbA 95%, HbA_2 2.5% and HbF 2%; positive serology for herpes virus; negative findings for HIV, HTLV-1/2 and CMV (IgG and IgM); unreactive quantitative and qualitative VDRL and antinuclear antibodies (FAN); and anti-I positive cold antibodies. Cytogenetic analysis was per-

formed on BM aspirates, following the standard G-banding procedure, and chromosomes were identified and arranged in accordance with ISCN (2005). Karyotyping revealed 45,XY,-7[15]/46,XY[5]. Fluorescence *in situ* hybridization (FISH), performed with spectrum orange whole chromosome painting [WCP7 - Vysis], confirmed monosomy 7. Molecular analysis to investigate *N-ras* mutations produced normal results.

The child evolved with serious recurrent episodes of respiratory infections due to bacterial and fungal organisms, despite antibiotic therapy. The refractory disease was characterized by episodes of opportunistic infectious, spleen enlargement and persistent anemia, thrombocytopenia and circulating erythroblast cells. He was treated with cytarabin, α-interferon and blood transfusions. Because of severe weight loss, daily fever and worsening of the infectious process, a new treatment with 6-mercaptopurine and ara-C in low doses was started. He presented partial clinical improvement and reduction of the splenomegaly, but the infectious episodes persisted. He underwent a splenectomy procedure, and allogeneic bone marrow transplantation was performed. Despite all the therapeutic efforts, he died of generalized infection.

There are few reports in the literature on childhood MDS. Thus, in order to standardize the diversity of classification and establish the incidence of MDS in children, a group of specialists have gathered together the clinical, laboratory, cytogenetic and molecular biological characteristics of this rare disease and have proposed criteria for diagnosing and treating childhood MDS (Lopes *et al.*, 2006; Hasle, 2007).

The first systematic attempt at morphological classification of MDS was provided by the French-American-British group (Bennett *et al.*, 1982). Soon afterwards, controversies regarding MDS arose from reports on patients with JMML. This pathological entity, like myeloproliferative syndrome, resembles MDS in several overlapping features. To try to solve this problem the World Health Organization (WHO) proposed that cases with WBC count less than 13,000/mm^3 should be classified as MDS, whereas those with WBC more than 13,000/mm^3 should be classified as a hybrid group of so-called MDS/myeloproliferative disease, in which JMML is included. This current approach includes all the cases previously classified as JCML, chronic myelomonocytic leukemia (LMMC) and monosomy 7 syndrome (Hasle *et al.*, 1999; Luna-Fineman *et al.*, 1999; Nosslinger *et al.*, 2001; Hasle, 2007).

Therefore, the patient analyzed in the present report had a diagnosis of JMML, because he presented intense pallor, huge splenomegaly and recurrent infections at the age of five months. The laboratory analyses consisted of cytogenetic and molecular analysis and showed monosomy 7 without additional *N-Ras* mutations. It is worth mentioning the importance of the viral serology tests performed in this case, because some infectious diseases can also mimic JMML; for example, neonatal cytomegalovirus and human herpes virus (HHV) (Lorenzana *et al.*, 1997; Pinkel, 1998).

It is well recognized that there is a close association between neurofibromatosis type 1 (NF1), monosomy 7 and JMML. The proposed pathway mechanism for this association is based on the activation of the *Ras* gene by point mutation, which is found in approximately 40% of the patients with MDS (Miyauchi *et al.*, 1994). Loss of the normal *NF1* allele is a common finding in children with NF1 who have JMML and monosomy 7 (Bollag *et al.*, 1996). Furthermore, the somatic *PTPN11* mutation is also observed in 35% of the children with JMML, thus making molecular genetics very helpful in diagnosing JMML with mutually exclusive abnormalities or an association with clinical features (Lauchle *et al.*, 2006).

JMML has been described as an aggressive illness, with overall survival of approximately nine months. Patients often present repeated bacterial infectious episodes, and most untreated patient die from organ failure due to infiltration of leukemic cells or infectious processes (Niemeyer *et al.*, 1997). Blast crises and/or transformation seldom occur.

So far, no therapeutically specific and consensual approach to treatment has been found. Single agent or combination therapies using mercaptopurine, ara-C, 6-thioguanine, interferon-alpha and vepesid have been applied, but the clinical benefits remain controversial. Currently, allogenic hematopoietic stem cell transplantation (HSCT) represents best choice for curative treatment, for younger patients with a compatible donor (Lilleyman *et al.*, 1977; Locatelli *et al.*, 2005; Bergstraesser *et al.*, 2007). However, about 50% of the patients become ill again at a mean age of four months, which gives rise to the need for complementary treatment to prevent the return of the disease (Locatelli *et al.*, 2005). Retinoic acid (isotretinoin) has been shown to have *in-vitro* and *in-vivo* activity in JMML and the drug is included both before and after HSCT, but still with uncertain results. More recently, novel agents directed towards molecular targets have been evaluated. Farnesyltransferase inhibitors were tested in a phase II window study as part of the Children's Oncology Group study on patients with JMML, and showed complete or partial response in 58% of the cases, thereby demonstrating the opening of new therapeutic possibilities for this specific disease (Castleberry *et al.*, 2005).

Cooperative groups gathering significant numbers of children with MDS will be important for enabling evaluation of the clinical response to current treatments, thereby providing new therapeutic strategies for this rare malignancy.

Acknowledgment

This work was partially supported by grants from Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco (FACEPE). The authors are grateful to Pro-

grama Criança e Vida for the helpful support within the childhood cancer care network.

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Associate Editor: Emmanuel Dias Neto