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Transient Myeloproliferative Syndrome/Transient Acute Myeloid Leukemia in a Newborn with Down Syndrome: A Case Report and Literature Review

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ABSTRACT

We report the case of a newborn with Down syndrome (DS) associated with transient acute myeloid leukemia (AML). The leukemic presentation resolved spontaneously without treatment just 4 weeks after birth. An abnormal hematopoietic function is a well-known characteristic of DS; however, acute leukemia is rare in newborns with this genetic disorder. The presence of peripheral blast cells matched generally by an equivalent quantity in the bone marrow may be considered a true leukemia that, although transient, may predict the development of a generally megakaryoblastic AML within the first few years of life. This leukemia is not transient and must be treated accordingly. The cytogenetic and molecular abnormalities involving DS chromosome 21 in leukemogenesis in these patients are not well understood. In DS, AML, transient or not, generally shows cytogenetic and molecular aspects that differ from those of adult acute leukemias. *Lab Hematol.* **2003;9:38-41.**

KEY WORDS: **Down syndrome · Transient myeloproliferative disease · Transient leukemia**

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INTRODUCTION

Down syndrome (DS) is a genetic disorder characterized by a numerical chromosomal abnormality. Ninety-five percent of all DS patients have the karyotype 47,XX or XY,+21, and the remaining 5% have a normal number of chromosomes with the extra chromosome 21 translocated to another chromosome, usually 22, 13, 14, or 15.

Children with DS account for 1 of every 700 live births, and the risk is correlated with maternal age. The father's age is less relevant, although 20% of all +21 cases are due to paternal nondisjunction.

Other than showing the various typical clinical features, infants with DS may infrequently develop a condition called transient myeloproliferative disease, which is characterized by acute leukemia and a high number of circulating blast cells. There is also a marked increase in peripheral white blood cells (WBC), and anemia and thrombocytopenia may be absent.

A CASE REPORT

A male baby was born April 15, 2002, after 37 weeks of pregnancy to a 40-year-old mother. The neonate was not a firstborn. At birth, he had the specific physical features suggestive of DS. The presence of trisomy 21 without other abnormalities was confirmed by karyotype analysis (Figure 1).

There were no cardiovascular disturbances, and the baby was generally doing well. The blood count at birth showed leukocytosis (WBC, $25 \times 10^3/\mu L$) and thrombocytopenia (platelets, $65 \times 10^3/\mu L$) with no evidence of hemorrhage or anemia (hemoglobin, 19 g/dL). At the peripheral level, the percentages of segmented neutrophils, lymphocytes, and monocytes reached 30%, 35%, and 5%, respectively. Furthermore,

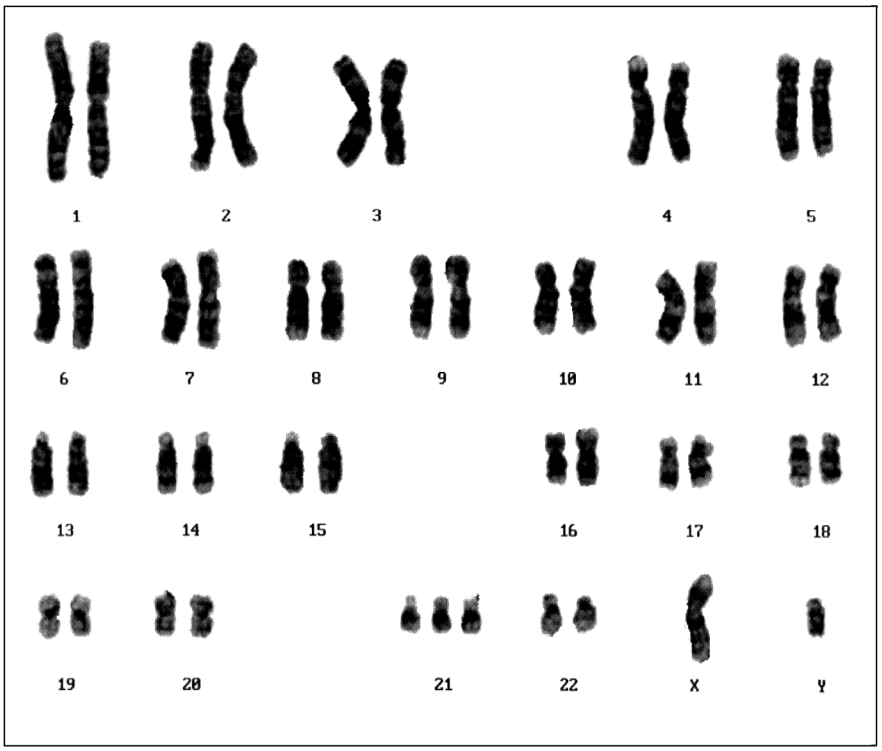

FIGURE 1. Karyotype 47,XY,+21.

the level of mononucleate blast cells was 30%. May-Grünwald-Giemsa staining detected blast cells with an elevated nucleus/cytoplasm ratio, an agranular cytoplasm, no Auer rods, and nuclei that sometimes included 1 or 2 nucleoli (Figure 2). The results of Sudan black B and periodic acid–Schiff staining and staining for myeloperoxidase and naphthylbutyrate esterase were negative. Analysis of bone marrow aspirate indicated that 30% of blast cells possessed morphologic characteristics similar to those seen at the peripheral level. There were no morphologic abnormalities in the remaining cell populations of both the bone marrow and the peripheral blood.

Immunophenotyping of peripheral blood and bone marrow (Figure 3) was performed with a multicolor antibody panel of 3 to 4 colors. CD45 (leukocyte common antigen) was used as an immunologic tracer. Immunophenotyping by analysis window SSC/45 detected a medium intensity cell cluster (30% of the suspension under examination) for $CD45^+$ (forward scatter, medium/high). Antigenically, the blast cells were positive for CD34, CD117, HLA-DR, CD33, CD38, and weak coexpression of CD7 and negative for myeloperoxidase, lysozyme, terminal deoxynucleotidyl transferase, CD13, CD14, and CD15 (Figure 3). A weak expression of myeloperoxidase was seen only in bone marrow blast cells. The lymphoid and erythroid populations exhibited no antigenic aberrations or atypicality.

On the basis of mainly the blast cell immunophenotype, the presentation suggested an acute myeloid leukemia (AML) without maturation. It has been impossible to evaluate the megakaryocytic population.

The infant was followed and monitored without any specific treatment. The clinical picture was silent. The peripheral blast cells persisted for 4 weeks, after which the hemogram and the differential WBC count returned to normal (WBC, $7.2 \times 10^3/\mu L$; hemoglobin, 13.0 g/dL; platelets, $220 \times 10^3/\mu L$; neutrophils, 22%; lymphocytes, 63%; and monocytes, 7%), and the peripheral blast cells disappeared.

DISCUSSION

Hematopoiesis is abnormal in patients with DS. Polycythemia is indeed more common in newborns with DS than in unaffected babies [1], the hematocrit medium value is markedly higher in DS children than in unaffected infants [2], and the platelet medium value is lower in newborns with DS than in unaffected babies. Abnormalities are also detected in the myeloid system. The granulocyte progenitor cell number is generally lower, and the circulating neutrophil granulocytes have additional abnormalities in morphology, enzyme levels, and bactericidal activity [3].

Leukemia is more common in children with DS than in unaffected babies. In newborns with DS, there is a trend toward the development of a hematopoietic disorder consisting of an overlapping acute myeloid leukemia, generally with a megakaryoblastic phenotype.

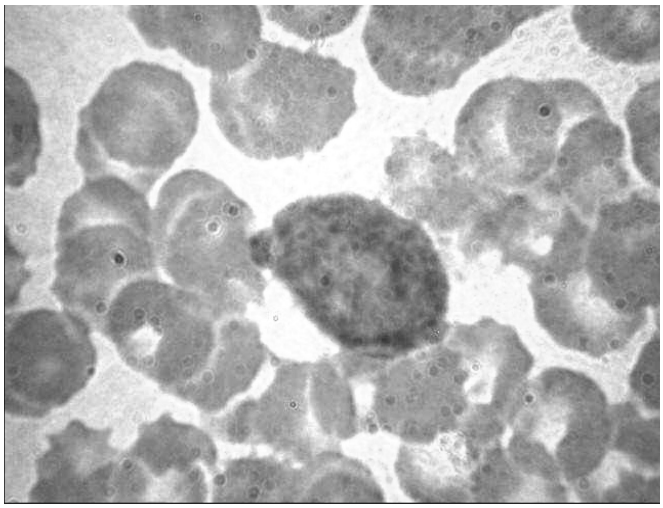

FIGURE 2. May-Grünwald-Giemsa stain of a peripheral smear. Agranular blast cell with little cytoplasm and a nucleolated nucleus.

The incidence of acute leukemia in patients with DS is 14 times higher than in unaffected children, and the disease is mainly myelogenous. Kojima et al [4] highlighted the fact that 14 of 20 cases of acute leukemia in DS patients were acute megakaryoblastic leukemias occurring in children younger than 4 years. The remaining 6 cases were acute lymphoblastic leukemias in children older than 4 years. The Canadian Down Syndrome Leukemia Registry confirmed the results of this study.

Because the leukemic picture resolves spontaneously, the disorder has been called transient myeloproliferative disorder, transient blastemia, or transient abnormal myelopoiesis. Now, the disease is commonly referred to as "transient leukemia" (TL).

Typically, TL is diagnosed in clinically normal children with DS via the casual detection of leukocytosis with circulating blast cells. The characteristic feature of transient leukemia in DS patients is that the TL disappears on its own without treatment in just a few months. The typical and persistent spontaneous remission of the leukemic presentation in 4 to 6 weeks suggests a transient disruption of the granulocytopoietic system [5]. On the other hand, several arguments support the idea that a malignant clone is expressed in these patients [5]:

- The presence of transient cytogenetic alterations in some patients;
- An abnormal growing pattern of hemopoietic precursor cells in vitro;
- The development of a clear leukemia within the first 4 years of life (in these cases the leukemia and the TL have the same phenotype [6,7]).

It is well known that the blast cells seen in TL come from a monoclonal source. TL is a preleukemic state clinically evident only at birth. TL may result from an unknown stimulation in utero involving other cell events and triggering a malignant leukemic process [3].

Chromosomal aberrations in addition to trisomy 21 have only rarely been reported, whereas additional chromosomal aberrations may occur during TL. In a case report from Granzen et al [8], the chromosome 11 abnormalities were del(11)(q23), but rearrangements of the ALL-1 (MLL, HRZ, and HTRX1) gene were not found. Ohnishi et al [9] reported a case of TL associated with DS and with spontaneous remission and the development of myelodysplastic syndrome. From a cytogenetic point of view, the blast cells were characterized by the presence of a t(7;11)(p13;p14) translocation that was absent in the TL phase. Furthermore, the gene fusion NUP98/HOXA and the NUP98 gene rearrangement were also absent, as in the case of the t(7;11)(p15;p15) translocation that is present in the AML M2 subtype in the French-American-British (FAB) classification, but rare in AML FAB subtype M4. These observations confirm that the meaning of the cytogenetic changes seen in leukemia or TL associated with DS remains poorly understood.

The number of bone marrow blast cells is directly correlated with the number of peripheral blast cells. In some cases, the number of blast cells is low, both at the bone marrow and at the peripheral blood levels, a phenomenon that is common in TL and almost never seen in other types of leukemia. Light microscopy study shows that the leukemic cells in TL are undifferentiated blast cells, and the morphology does not have a diagnostic value.

Usually, the search for surface markers shows a myeloid pattern positivity (CD13, CD33, and/or CD11b). A high frequency of blast cell positivity for the CD7 marker, commonly associated with a T-lymphoid lineage, is indicative of

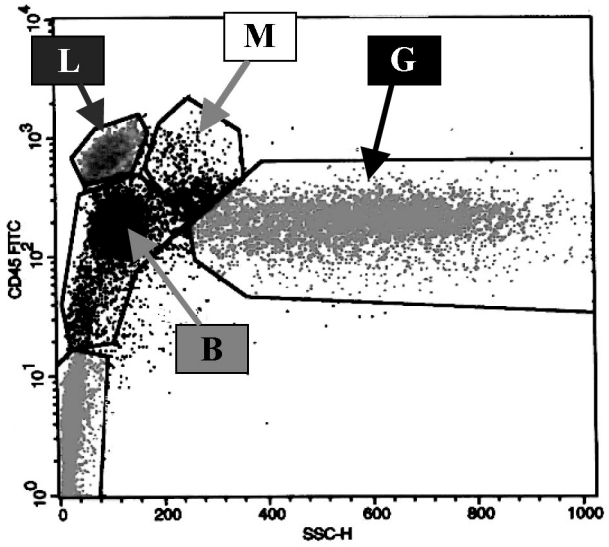

FIGURE 3. Peripheral blood immunophenotype. G indicates granulocytes; M, monocytes; L, lymphocytes; B, blast cells.

lineage infidelity. Girodon et al [10] observed a double population of blast cells in a newborn with DS and TL. The first population was immunologically characterized by normal myeloid immature precursors. In the second population, the immature blast cells expressing CD41, CD42, CD61, CD36, CD13, CD1a, and CD2 were involved in the megakaryoblastic leukemic differentiation, the most common leukemia in children with DS.

As far as therapy is concerned, Taub et al [11] carried out in vitro studies of the molecular basis of blast cell sensitivity to chemotherapeutic agents in children with DS and AML by analyzing genes located on chromosome 21. Patients with DS had higher than normal levels of superoxide dismutase and cystathionine β-synthase transcripts. The cystathionine β-synthase transcript increase was correlated with higher in vitro blast cell sensitivity to Ara-C. On the other hand, there was no correlation between superoxide dismutase transcript increase and in vitro blast cell sensitivity to Ara-C and daunorubicin.

Additional studies on the molecular mechanisms responsible for chemotherapeutic sensitivity in patients with Down syndrome are required to fully understand the treatment and cure of AML.

At the moment, DS cases associated with TL may be considered frank leukemic reactions with a high likelihood of developing nontransient leukemia within the first years of life.

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