A rare case of Acute Lymphocytic Leukemia (ALL) presenting with double Philadelphia chromosome - relapse or secondary leukemia?

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Abstract

The Philadelphia chromosome is observed in 5% of pediatric acute lymphocytic leukemia (ALL) and in 25% to 50% of adult ALL cases, and is associated with poor prognosis. Double Ph in a hyperdiploid karyotype is common in chronic myeloid leukemia (CML), but rarely found in ALL. We report here the case of a girl diagnosed with ALL at 7 years of age. After treatment with the pediatric protocol BFM 83 for ALL, she stayed in continuous complete remission for nine years. At age 19, she was re-admitted with a white blood cell count of 6.8 x 10^9/L with 3% blasts, and a platelet count of 65 x 10^9/L. Bone marrow aspirate showed 92.6% lymphoid blast cells, and chromosome analysis after G-banding revealed the karyotype 51,XX,+?5,t(9;22)(q34.1;q11.2),+16,+20,+21,+der(22)t(9;22)(q34.1;q11.2)[10]/46,XX[1]. FISH analysis for the BCR/ABL fusion showed 56% of interphase cells with two fusion signals, 30% with one, and 6% with three. Double Ph is rare in relapsed leukemia, and the possibility of secondary leukemia cannot be ruled out.

Key words: relapsed acute lymphocytic leukemia, double Philadelphia chromosome.

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Introduction

The Philadelphia (Ph) chromosome, the hallmark genetic lesion of chronic myeloid leukemia (CML), is less frequently found in acute lymphocytic leukemia (ALL) and rarely in acute myelogenous leukemia (AML). It is present in only 5% of the pediatric and 25% to 50% of the adult ALL cases, and is associated with poor prognosis (Secker-Walker et al., 1991). Additional cytogenetic aberrations are described in 41% to 86% of patients with Ph+ ALL. A hyperdiploid karyotype, defined by the presence of more than 50 chromosomes, is detected in 2% to 9% of adult ALL patients and in 29% of pediatric patients (Ritterbach et al., 1998; Wetzler et al., 2000). Translocation t(9;22) is a common structural aberration found in patients with hyperdiploidy (37% and 64%, respectively) (The Groupe Français de Cytogénétique Hématologique, 1996; Faderl et al., 2000).

The BCR/ABL breakpoint varies according to the type of leukemia. CML is almost always associated with the p210BCR/ABL variant. In pediatric Ph+ ALL, nearly 90% of cases have the p190 variant, but in adult ALL approximately 25% to 50% of cases are p210BCR/ABL (Secker-Walker et al., 1991). In fact, the so-called Ph+ ALL seems to be a heterogeneous disease including: (1) lymphoid lineage-restricted ALL that can be either p190 or p210BCR/ABL, although most cases have been p190BCR/ABL, (2) stem cell ALL, with evidence of disease in both lymphoid and myeloid lineages, that can either be p190 or p210BCR/ABL, (3) misclassified CML in lymphoid blast crisis, which is a stem cell disease and mainly p210BCR/ABL (Radich et al., 2001).

We report a case of relapsed ALL associated with double Philadelphia chromosome in a patient who had been diagnosed with ALL at 7 years of age and had stayed in remission for nine years.

Case Report

A 7-year-old girl was admitted to HSP/UNIFESP in October 1989 with widespread adenopathy and weight loss. On physical exam she showed submandibular, cervical, axilar and inguinal adenopathies, besides splenomegaly. Peripheral blood tests revealed 8.4 g/dL of hemoglobin, a white blood cell count of 28.6 x 10^9/L with 78% blast cells, and a platelet count of 90 x 10^9/L. Bone marrow aspirate was hypercellular, with 90% blast cells of the FAB L2 subtype, and peroxidase-negative. Immunophenotyping showed CD19+, CD10+, CD13- and CD33-. The patient was treated according to the children ALL BFM 83 protocol (Riehn. et al., 1990), and achieved complete remission...
after induction. She completed the whole protocol by May 1992 and stayed nine years out of treatment. In November 2001, at the age of 19, she was admitted complaining of leg pain, ecchimosis, fever, and anorexia. There were no abnormal physical findings other than ecchimosis. Peripheral blood tests revealed 12.3 g/dL of hemoglobin, a white blood cell count of 6.8 x 10^9/L with 3% blasts, and a platelet count of 65 x 10^9/L. Bone marrow aspirate was hypercellular, with 92.6% lymphoblasts, which were morphologically similar to those observed at the first diagnosis, and were peroxidase-negative. Flow cytometry immunophenotyping showed: CD10+, CD19+, CD13+, CD33+. Cytoplasm and surface immunoglobulins were negative. Chromosome analysis revealed a 51,XX,+?5,t(9;22)(q34.1;q11.2),+16,+20,+21,+der(22)t(9;22)(q34.1;q11.2)[10]/46,XX[1] karyotype. RT-PCR showed the p190BCR/ABL variant. FISH performed on the BCR/ABL rearrangement showed 56% of cells with two BCR/ABL fusion signals, 30% with one signal, and 6% with three signals (200 interphase cells were counted by each of two observers). The patient was treated with Prednisone (D1-21), Vincristine (D1, 8, 15), Daunorubicine (D1, 8, 15), and L-asparaginase (D7-8, D14-15). A bone marrow aspirate performed on day 14 after induction had 71% blasts, and she was scheduled for the Hyper-CVAD regimen (Garcia-Manero et al., 2000). In spite of the treatment, she developed hepatosplenic candidiasis and cerebellar toxicity probably due to cytarabine, and died in sepsis without remission in February 2002.

Discussion

We describe here the rare case of a young female patient with double Ph chromosome and ALL diagnosed twelve years after the first ALL diagnosis, and after nine years of complete remission. The main question is whether her leukemia was secondary to the treatment received twelve years earlier or a true relapsed leukemia.

Patients with Ph chromosomes treated only with conventional chemotherapy have a poor long-term survival. Although 72% to 97% of the pediatric Ph+ cases achieve complete remission (CR) after induction therapy, the 5-year event-free survival (EFS) ranges from 10% to 20%, vs. 76% in the Ph-negative population. Failure is due mainly to recurrent disease, and the poor prognosis persists after stratification in a high-risk treatment protocol. In adult ALL, the CR rate of Ph+ patients is generally similar to that of Ph-negative patients (60% to 80%). Nevertheless, the duration of remission is usually shorter (<12 months) and forces the EFS rate towards 10%, vs. 28% to 39% for the whole group of adult ALL (Garcia-Manero et al., 2000; Radich et al., 2001). Hyperdiploid karyotypes with double Ph are common in CML, with over five hundred reported cases. In contrast, they are rare in ALL, and a total of 66 cases with double Ph are reported in Mitelman’s Catalog of Chromosome Aberrations in Cancer (http://cgap.nci.nih.gov/Chromosomes/CytSearchForm). Of those, only 23 were associated with hyperdiploidy and, interestingly, only three patients showed more than two copies of the Ph chromosome on conventional karyotyping. In a series of 66 karyotypes of Ph+ ALL patients, Rieder et al. (1996) found eight cases with double Ph (12%), but only three (9%) were hyperdiploid. Therefore, since Ph+ cases represent approximately 25% of ALL, cases with double Ph should represent a smaller percentage of adult ALL. Thomas et al. (1998) found seven cases of double Ph in 41 Ph+ ALL (17%), and the presence of an extra Ph chromosome was considered an initial parameter associated with a statistically significant worse prognosis. Uckun et al. (1998) studied 1,322 children with ALL, and found 30 Ph+ patients, four of whom had double Ph, corresponding to 13% of Ph+ ALL and to 0.03% of pediatric ALL.

It has been recognized that ALL shows significant immunophenotypic and karyotypic diversity. Moreover, ALL patients frequently undergo karyotype and immunophenotype changes at the time of relapse. Clonal evolution is not the only cytogenetic observation at relapse; some cases show entirely different karyotypes, thereby raising the possibility of secondary leukemia (Raimondi SC, 1993). Chucrallah et al. (1995) analyzed 32 relapsed adult ALL patients and found that nine (28%) had clonal evolution, 12 (37%) had a different karyotype, and 11 (34%) had an unchanged karyotype.

FISH analysis performed in the present case showed the double BCR/ABL fusion signals in the majority of interphase cells, and rare cells with three fusion signals. Unfortunately, FISH could not be performed on marrow smear from the first diagnosis stored in a common file at room temperature, and thus it was not possible to clarify if the patient was Ph+ at first diagnosis. However, this possibility is unlikely, because the patient stayed in remission and out of treatment for nine years following conventional chemotherapy, whereas the outcome of Ph+ ALL cases is highly unfavorable. Although the phenotype change (acquired CD13 and CD33) and the probably acquired Ph+ favor the hypothesis of a secondary leukemia, the doubt remains whether the second disease could be a relapsed ALL with clone evolution.

References


