Philadelphia positive acute lymphoblastic leukemia 16 years after the apparent cure of acute lymphoblastic leukemia. New leukemia or late relapse?

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A Philadelphia-positive ALL in an adult occurring 21 years after the initial diagnosis is reported here. This case raises the question as to whether or not this event is a relapse or a new leukemia. A possible role of interferon-α previously administered to the patient for a chronic viral hepatitis is discussed too.

Acute lymphoblastic leukemia (ALL) relapses occurring more than five years after achieving complete remission (CR) are unusual[1] and raise the possibility of a new neoplasm.[2]

We report a second leukemia 16 years after the cure of a childhood ALL. This second leukemia was Philadelphia chromosome (Ph1) positive, a poor prognostic factor. In addition, we discuss herein the possible role played by interferon-α (IF-α) in the etiopathogenesis of this new leukemia.

Case Report

A three-year-old child affected by ALL in 1974 received induction treatment, holocranial radiotherapy and intrathecal methotrexate and he achieved CR. Maintenance treatment was given until June 1977. After therapy for testicular relapse treatment was stopped in 1979.

In December 1990 a chronic viral C hepatitis was diagnosed and IF-α was given for three years, but was subsequently discontinued as it was ineffective.

In 1995, 21 years after the first diagnosis the patient presented with clinical and analytical signs of an apparent ALL *relapse*. Immunophenotyping revealed a B lineage *common* ALL. Reverse-transcription polymerase chain reaction (RT-PCR) with nested primers specific for *minor breakpoint* rearrangements (primers supplied by Oncogen RP, Cambridge, MA, USA) was positive giving rise to the expected bands in *bcr/abl* e1a2 rearrangements. No amplification was noted when transcripts from the patient were assayed with primers specific for *mayor breakpoint* rearrangements.

After receiving a single chemotherapy course, he died of septic abdominal infection.

In patients achieving long-lasting CR, late relapses are unusual and raise a controversial issue: relapse versus new leukemia.

Pagano *et al*.[3] revealed that the actuarial estimated cumulative proportion of ALL patients with a secondary haematologic neoplasm at 5 and 10 years were 0.59% and 3.63%, respectively.

In our case, the lack of immunologic and molecular data from the first leukemia hampers understanding of whether we are facing a genuine relapse or a distinct ALL. The hypothesis of a different neoplasm is supported by two facts. Firstly, the strikingly long duration of our patient's relapse-free survival (therefore, a drug-induced leukemia cannot fully discarded). Secondly, although in pediatric ALL, Ph1 can be absent at diagnosis, subsequently emerging as a consequence of clonal evolution,[4] and a subset of good prognosis Ph1 ALL could exist,[5] Ph1 is usually associated with aggressive disease, poor prognosis and no short term remissions.[6]

Nevertheless, a relapse cannot be completely ruled out. In this case IF-α, as an immune modulator, administered to the patient in previous years may have prompted the leukemia relapse.

IF-α can activate B-cells in malignant and non-malignant lymph nodes to proliferation and blast transformation.[7] IF-α has been shown to regulate B-cell differentiation and to act as a natural regulator of B-cell functions. In some neoplasms of B-cell origin, especially myeloma, IF-α is able to stimulate the proliferation of Interkeukin-6 dependent cells of clonogenic tumor cells *in vitro*[8] as well as *in vivo*.[9]

Key words

Acute lymphoblastic leukemia, late relapse, Philadelphia chromosome, interferon-α.

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bcr-abl rearrangement in adult T-lineage acute lymphoblastic leukemia

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The *bcr-abl* rearrangement in T-lineage ALL has been rarely described. In the last three years we studied all new patients with ALL at diagnosis by cytogenetic and molecular analysis. Three out of eleven T-lineage ALL patients presented the rearrangement and only one was Philadelphia positive.

The Philadelphia (Ph) chromosome, t(9;22)(q34;q11), is present in more than 95% of patients with chronic myelogenous leukemia (CML) and in 15-25% of adults with acute B-lineage lymphoblastic leukemia (ALL).[1,2] In T-lineage ALL it has rarely been reported[3,4] and singular cases of T-lineage adult ALL carrying the *bcr-abl* rearrangement have been recently described.[5-8] *bcr-abl* rearrangement in T lineage ALL is thus a rare event and the clinical relevance of this translocation is currently unknown.

In the last three years we studied 25 new consecutive cases of ALL (14 B-lineage and 11 T-lineage). We present here the clinical, immunologic, cytogenetic and molecular features of three out of the eleven T-lineage ALL patients presenting *bcr-abl* rearrangement at diagnosis.

Patient #1. A 15-year-old male was referred with a recent history of cough and fatigue. He was treated with daunomicin, vincristine, asparaginase, and prednisone and obtained a complete remission. He relapsed 7 months later, did not obtained a second remission and died 4 months later.

Patient #2. A 32-year-old male was admitted with acute leukemia. He was treated with idarubicin, cytarabine, vincristine and prednisone and obtained complete remission. He was later submitted to allogeneic peripheral blood transplantation from his HLA-identical sister while in first CR. The patient developed acute but not chronic GVHD. He relapsed 18 months later. He is actually in second CR after reinduction treatment.

Table 1. Clinical and biological characteristics of the patients.

Patients	*#1*	*#2*	*#3*
Age/Sex	15/M	32/M	47/M
Hb g/dL	13.7	6.9	12.9
WBC x 10^9/L	59.4	19.6	9.6
Plt x 10^9/L	329.	39.	436.
LDH U/L	1575	2290	711
Splenomegaly	–	+	–
Mediastinal enlargement	++	–	+++
Lymph–node enlargement	+	+	–
Phenotype	TdT,CD34,cCD3, CD4,CD5,CD7, CD13	TdT,cCD3,CD1, CD2,CD4,CD5, CD7,CD8	TdT,CD1,CD2, CD4,CD5,CD7, CD8
Karyotype	46,XY,t(9;22) (q34;q11)	46,XY	46,XY,6q–, –7,–9, +2mar
BCR type	M	M	M
Response to induction	CR	CR	CR
Survival (months)	11	24+	5

Patient #3. A 47 year-old male was admitted with acute pericarditis. The chest X-ray and chest CT scan showed massive mediastinal enlargement and pleural and pericardial effusion. Blood counts were normal, but differential counts showed 20% blast cells. Bone marrow aspiration revealed 50% blast cells with cerebroid nucleus. Pleural fluid contained 117.0×10^9/L blast cells. The patient was treated with daunoblastin, vincristine, asparaginase and prednisone and obtained complete remission. He was submitted to autologous peripheral staminal cell transplantation, but died of adult respiratory distress syndrome two weeks later.

Clinical and biological data are shown in Table 1. *bcr-abl* transcript was detected by RT-PCR and the rearrangements occur in all patients within the 5.8-kb M-bcr region associated with P210 *bcr-abl* expression; monoclonal rearrangement of the TCRg gene, but not of the IGH locus was also detected by PCR (Figure 1).

Ph+ CML is known to arise in a multipotent hematopoietic stem cell.[9] This is also shown by the fact that Ph translocation and/or *bcr-abl* expression can be simultaneously found in cells of myeloid and lymphoid lineage. Occasional reports of Ph+ T-cell blast crisis of CML provide evidence that T-cell precursors can be involved in Ph+ leukemic transformation.[10] Single cases of T-lineage ALL with Ph translocation or *bcr-abl* rearrangement have also been reported.[3-8]

The characteristics of our three *bcr-abl* T-ALL cases are indistinguishable from other T-lineage ALL. Two presented with mediastinal enlargement and one patient had intermediate characteristics between T-ALL and T mediastinal lymphoblastic lymphoma.

We do not know whether the presence of *bcr-abl* gene rearrangement makes the prognosis of T-lineage ALL worse, but two out of three patients had bad prognosis characteristics such as early T phenotype,