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Teaching cases

Transformation of primary myelofibrosis with 20q− in Philadelphia-positive acute lymphoblastic leukemia: Case report and review of literature

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ABSTRACT

A 56-year-old male with chronic idiopathic myelofibrosis and cytogenetic finding of 20q− after a period of 10 months developed acute Philadelphia-positive lymphoblastic leukemia. Immunophenotyping of peripheral blood by flow cytometry showed HLA-DR, CD34, CD19, CD22, CD10, CD33, and CD11b positivity. Cytogenetic analysis revealed the presence of 20q− and Philadelphia chromosome t(9;22)(q34:q11) at the time of disease transformation to ALL. The JAK2V617F mutation was not found. This is a very rare case of simultaneous presence of two cytogenetics abnormalities and evolution of primary idiopathic myelofibrosis to Philadelphia-positive acute lymphoblastic leukemia.

Introduction

Primary myelofibrosis (PMF) or agnogenic myelofibrosis with myeloid metaplasia is a myeloid disorder that results from abnormal clone proliferation of stem cells with multilineage potential and is characterized by myelofibrosis and extramedullary hematopoiesis.

PMF can progress to acute leukemia in 14–20% of the cases. Usually, the disease terminates as acute myeloid leukemia (AML), but transformation to acute lymphoblastic leukemia (ALL) is extremely rare. There are only several cases reported so far, including 2 pediatric cases and 4 adults [1]. Leukemic transformation has been attributed to gene loss or/and inactivation without clear explanation, based on the possibility that the malignant cell clone is unstable.

We here report a very rare case of PMF transformation to Philadelphia-positive ALL confirmed by cytogenetic and RT-PCR analyses.

Case report

A 56-year-old male developed malaise and fatigue in April 2004. Physical examination disclosed splenomegaly (160 mm in diameter). The laboratory analyses showed hemoglobin (Hb) 80 g/l, platelets 1058×10^9/l, white blood cell count (WBC) 8.7×10^9/l, with 2% myelocytes, 4% metamyelocytes, 7% bands, 65% segmented neutrophils, 2% monocytes, and 22% lymphocytes in the differential leukocyte formula, leukocyte alkaline phosphatase (LAP) score of 43 (normal 20–80). Peripheral blood smear showed anisocytosis, polychromasia, dacryocytes and immature granulocytes. Bone marrow cytology disclosed hypocellularity with the persistence of all cell lines and without increased blasts. Cytogenetic studies (Fig. 1I) revealed the following karyotype: 46,XY,del(20)(q11)(3)/46,XY(17). The RT-PCR analysis showed that JAK2 mutation was negative. The growth of cell colonies *in vitro* showed the presence of spontaneous growth of erythroid and granulocyte cell colonies (CFU-GM and BFU-E). The histological examination of the bone marrow trephine biopsy revealed hypercellularity with presence all three hematopoietic cell lines (Fig. 2a). The myeloid series was abundant and showed no dysplastic cytological features; however, there were immature myeloid precursors localized centrally in the medullar space. There was megakaryocyte hyperplasia with pleomorphic morphology, and there was emperipolesis of other hematopoietic cells within megakaryocytes. There was reticulin and collagen fibrosis (Grades

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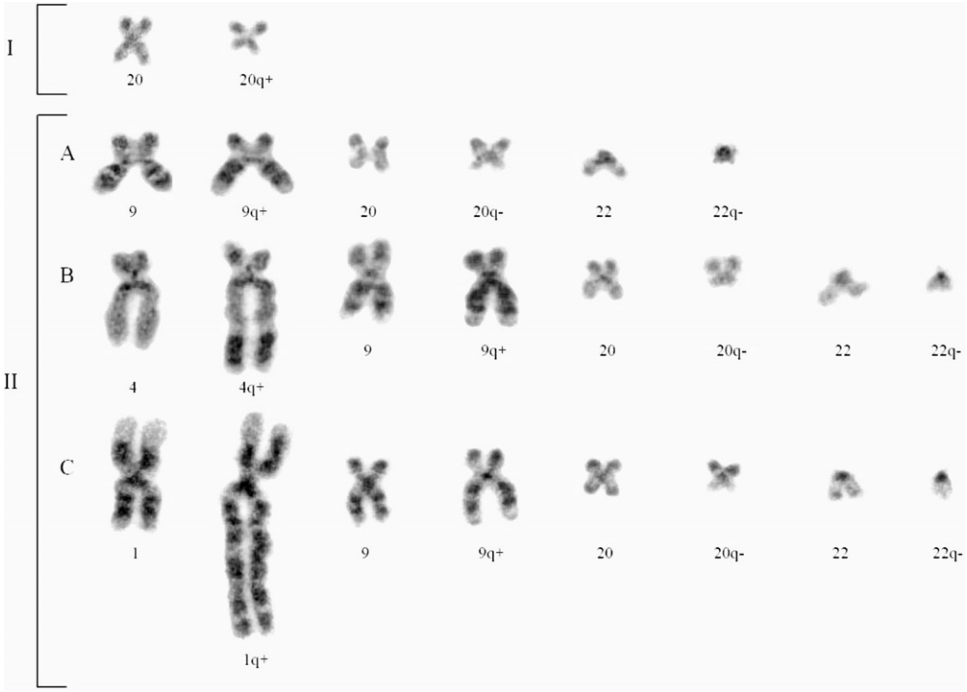

Fig. 1. Cytogenetic findings: (I) at diagnosis: deletion of chromosome (20)(q11) (3 cell); (II) in transformation of disease: (A) cell line with t(9:22) Philadelphia chromosome and del(20)(q11) (2 cells). (B) Cells with addition of chromosome (4)(q31), t(9;22) and del(20)(q11) (4 cells). (C) Cells with addition on chromosome (1)(q42), t(9;22) and del(20)(q11) (3 cells).
(I) Cytogenetic result at diagnosis: 46,XY,del(20)(q11)[3]/46,XY[17];
(II) Cytogenetic result in transformation of disease: 46,XY,t(9;22)(q34;q11),del(20)(q11)[2]/46,XY,add(4)(q31),t(9;22)(q34;q11),del(20)(q11)[4]/46,XY,add(1)(q42),t(9;22)(q34;q11),del(20)(q11)[3].

2 and 3) and increased fibroblasts (Fig. 2b). The photo looks more like Grades 1 and 2, which also goes along with the high peripheral platelet count.

Based on splenomegaly, dacryocytes in peripheral blood, bone marrow fibrosis, cytogenetic finding, spontaneous growth of erythroid and granulocytic cell colonies, a diagnosis of myelofibrosis was established. On ultrasonography, the spleen was 155 mm in diameter. Serum LDH was elevated, 617 UI/l. The patient was treated with hydroxyurea 1.0 g daily.

The patient's condition deteriorated 10 months later when he started feeling fatigue, malaise and pain in both knee and elbow joints. He was pale, afebrile, with splenomegaly of 170 mm. The laboratory analyses showed Hb 113 g platelets 99×10^9/l, WBC 67×10^9/l with 65% of lymphoblasts, 2% bands, 24% segmented, 6% lymphocytes and 3% monocytes, LDH 548 UI/l. Immunophenotyping of peripheral blood by flow cytometry showed that the blasts were positive for HLA-DR (96.45%) CD34 (93.62%), CD19 (92.76%), CD22 (72.26%), CD10 (93.99%), CD33 (61.03%), and CD11b (41.22%). The diagnosis of transformation of PMF to precursor B-ALL with coexpression of CD33+, CD11b+ was established. Biopsy and histopathology revealed the infiltration of bone marrow with lymphoblasts. Cytogenetic examination (Fig. 1II) of bone marrow cells showed the following karyotype: 46,XY,(q34;q11),del(20)(q11)[2]/46XY,add(4q),t(9;22)(q34:q11), del(20)(q11)[4]/46XY,add(1q),t(9;22)(q34:q11),del(20)(q11) [2,3]. In all analyzed mitoses there was del(20)(q11), and t(9;22)(q34:q11) was present in 7 mitoses. The diagnosis of PMF transformed into Ph-positive ALL was established (Fig. 2c). The RT-PCR analysis disclosed rearrangement of BCR-ABL, t(9;22)(p210).

The patient was treated according to protocol LALA94 with the following drugs: cyclophosphamide 1000 mg i.v., vincristine 2 mg i.v., doxorubicine 50 mg i.v. on days 1, 2, 3, prednisone 60 mg daily per os. In the period of aplasia, he was treated with packed red blood cells, platelet transfusions and antibiotics, but unfortunately, 21 days after starting treatment, the patient died.

Discussion

We report a patient with 20q− chromosome abnormality who presented as PMF with low hemoglobin, thrombocytosis, normal WBC and LAP score, and bone marrow collagen fibrosis.

PMF is a clonal myeloproliferative disorder characterized by an abnormal deposition of collagen in the bone marrow, extramedullary hematopoiesis, splenomegaly, and the leukoerythroblastic blood smear [1–3]. The diagnosis of PMF in our patient was established by excluding causes of secondary myelofibrosis and on clinical and morphological grounds. Our patient had splenomegaly and anemia, tear drop erythrocytes, marrow hypercellularity with granulocytic dysplasia, significant marrow fibrosis and negative *JAK2V617F* mutation. Absence of JAK2 mutation does not exclude the presence of CIMF nor does it predict the development of secondary AML [5].

Leukamogenesis is a complex process caused by one or multiple gene alterations, which perturbs the regulation of development and maturation of the multipotent hemopoietic progenitor cells gradually leading to acute leukemia [6].

The loss of genetic material is variable in size and responsible for the pathogenesis of different hematological disorders. Several pieces of evidence suggest that del(20q) is an early event in the development of myeloid neoplasia and that loss of L3MBTL1 can contribute to the development of 20q(−) hematopoietic malignancies by inducing replicative stress, DNA damage, and genomic instability [6–8].

Deletions of long arm of chromosome 20 [del(20q)] are associated with myeloproliferative disorder and myelodysplastic syndromes [2–4]. The deletion 20 q can arise in early hematopoietic