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Case Report

Chronic myeloid leukemia with variation of translocation at (Ph) [ins (22;9) (q11;q21q34)]: a case report

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Abstract: Chronic myeloid leukemia (CML) is most frequently observed in middle-aged individuals. In most patients, normal marrow cells are replaced by cells with an abnormal G-group chromosome, the Philadelphia (Ph) chromosome. The Ph chromosome that is characterized by the translocation (9;22) (q34;q11) is noted in 90-95% of patients diagnosed with CML. Studies have also shown that CML can be associated with various other cytogenetic abnormalities, with 5-10% of these cases showing complex translocation involving another chromosome in addition to the Ph chromosome. Here, we report the case of a Ph(+) CML patient with an inserted karyotype who presented clinically in the chronic phase but with atypical features. This case highlights the significance of cytogenetic abnormalities on the prognosis in CML.

Keywords: Chronic myeloid leukemia, case report, translocation, Philadelphia chromosome, cytogenetic abnormalities

Introduction

In the chronic phase, chronic myeloid leukemia (CML) is often suspected following a complete blood count (CBC) showing increased granulocytes that are mostly mature and including an increase in myelocytes. Basophils are often prominent, and the levels of myelocytes, metamyelocytes, and neutrophils often exceed those of the more primitive blast cells and promyelocytes. CML is also a clonal malignant disorder of a pluripotent hematopoietic stem cell characterized by the classical chromosomal translocation of the Philadelphia (Ph) chromosome that occurs in more than 90% of patients [1]. This abnormality is a result of the reciprocal translocation between chromosome 9 band q34 and chromosome 22 band q11. The cellular oncogene c-bal, which codes for a tyrosine protein kinase, is translocated to a specific breakpoint cluster region (bcr) of chromosome 22, resulting in the translocation of the 3' portion of the Abelson gene (abl) oncogene from 9q34 to the 5' portion of the breakpoint cluster region (bcr) gene on 22q11.2 [2]. As a result of the translocation onto chromosome 22, a chimeric BCL/ABL gene is produced, resulting in the synthesis of a 210 kD protein with considerably enhanced tyrosine protein kinase activity compared to the normal 145 kD c-abl oncogene product. This chimeric BCL/ABL gene plays an important role in the pathogenesis of CML [3].

The Ph chromosome in 10% of cases is due to a variant translocation in which the deleted segment on chromosome 22 is translocated to a chromosome other than chromosome 9; alternatively, there can also be a complex translocation involving a different chromosome [2, 4].

Here, we report a Ph(+) CML patient with an inserted karyotype who presented clinically in the chronic phase but displayed atypical clinical features.

Case presentation

The patient was a 28-year-young woman without a remarkable past medical history. The

Table 1. Routine blood test of this patient

Laboratory parameters	Date	
	11/2/2015	16/2/2015
WBC (10^9/L)	32.87	15.97
Neutrophil	27.02	9.7
Lymphocyte	1.91	4
Monocyte	3.57	1.8
Eosinophil	0.02	0.27
Basophil	0.35	0.17
RBC (10^{12}/L)	3.7	3.46
Hemoglobin (g/l)	112	105
PLT (10^9/L)	244	244

patient denied night sweats, lassitude, anorexia, unintentional weight loss, and tobacco or alcohol use. However, a brother had previously had leukemia. She presented with a fever and a sore throat, which prompted her to come to our hospital for treatment. The general physical examination revealed a normal bacterial infection, but was otherwise unremarkable. A cardiac examination revealed a regular rhythm. An abdominal examination revealed no tenderness or hepatosplenomegaly. A CBC revealed abnormalities as detailed in **Table 1**.

Evaluation of the peripheral blood smear revealed basophils (0%), myelocytes (5%), and metamyelocytes (1%). A hematology consultation was requested for evaluation. Bone marrow aspiration and biopsy were performed on February 12. Examination of the marrow revealed a slightly hypercellular marrow with granulocytic hyperplasia. Eosinophils and basophils were not prominent (**Figure 1A**, **1B**). Immunohistochemical staining demonstrated increased blast cells. Some CD34(+), CD117(+), CD61(+), and rare monolobated megakaryocytes were present (**Figure 1C**, **1D**). Flow cytometry demonstrated CD34(+), CD117(+) blast cells (0.24%). Basophils and eosinophils did not exceed these levels. Karyotype analysis revealed 46, XX, ins (22;9) (q11;q21q34) in 20 cells analyzed, with only one observed abnormality (**Figure 2**). Quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) analysis revealed the presence of the BCR/ABL transcript (p210 form) 187% IS 71.04% in bone marrow and 152% IS 57.75% in peripheral blood.

The patient was diagnosed with chronic phase CML. The initial hematology opinion recommended initiating tyrosine kinase inhibitor therapy. The patient subsequently joined a clinical trial of flumatinib, a tyrosine kinase inhibitor, administered at 400 mg/d. She achieved complete molecular remission after 3 months. After a 6-month follow-up, the patient returned to normal life with persistent molecular remission.

Discussion

CML is a common malignancy of adults and accounts for 20% of all cases of leukemia. CML was also the first malignancy to be linked to a clear genetic abnormality, the Ph chromosome. This genetic abnormality is so named because of the city in which it was first discovered and described in 1960 by Peter Nowell and David Hungerford [5]. CML is confirmed by detecting the characteristic (Ph) [t(9;22) q34;q11.2)] translocation by routine cytogenetics, fluorescent in situ hybridization, or molecular studies (RT-PCR) for the BCR-ABL fusion gene. In most studies of patients diagnosed with CML, the complete blood counts are elevated [6]. In the chronic phase, CML is discovered in some patients only during routine blood counting; the white cell count is usually between 50 and 500 × 10^9/L, and a complete spectrum of granulocytic cells is typically seen in the blood film. In one recent series [7], 245 patients were analyzed, and 178 of these (72.8%) were in the chronic phase of CML, with a mean total white cell count of 168 × 10^9/L. However, the current case had a count of only 32.87 × 10^9/L. After treatment with an anti-inflammatory agent, her CBC was reduced, and symptoms improved. This may have been a case of "preleukemic" or "smoldering" CML.

With flumatinib treatment, the patient achieved complete molecular remission after 3 months and remission was sustained for at least 6 additional months of follow-up. In one recent case report [8], an elderly man was diagnosed with chronic phase CML but was not treated with tyrosine kinase inhibitor therapy, although he was followed-up with periodic CBCs and differential blood counts. He remained asymptomatic with essentially stable blood counts from September 2013 to August 2014. The reasons for the "containment" of granulocyte proliferation in these patients remains a mystery.

Though the classical chromosomal abnormality is the presence of the Ph chromosome, CML

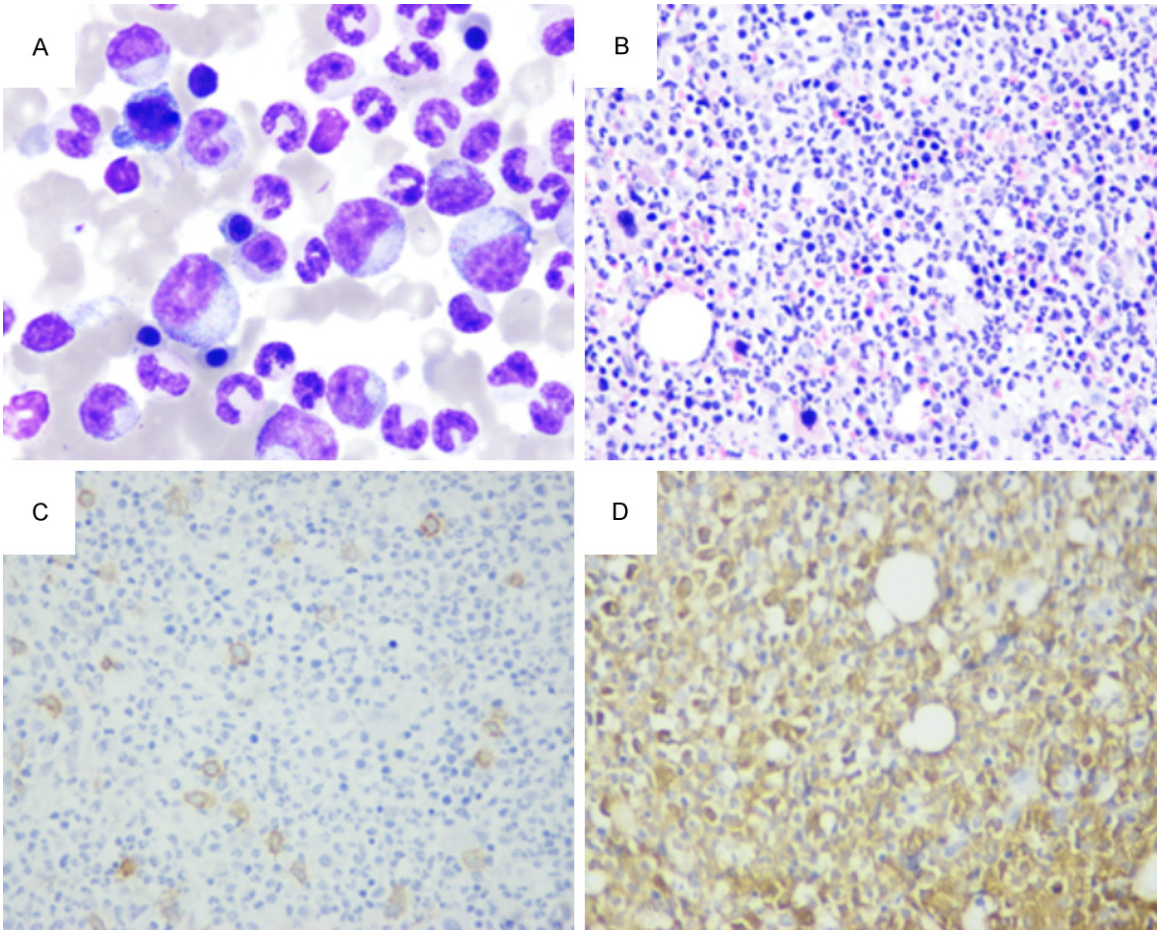

Figure 1. A. Bone marrow aspirate: numerous granulocytes without dysplasia. Wright Stain (1000 ×). B. Bone marrow biopsy: hypercellular particle with granulocytic predominance. Hematoxylin & Eosin Stain (400 ×). C. CD117 expression by Immunohistochemical staining (400 ×); D. MPO expression by Immunohistochemical staining (400 ×).

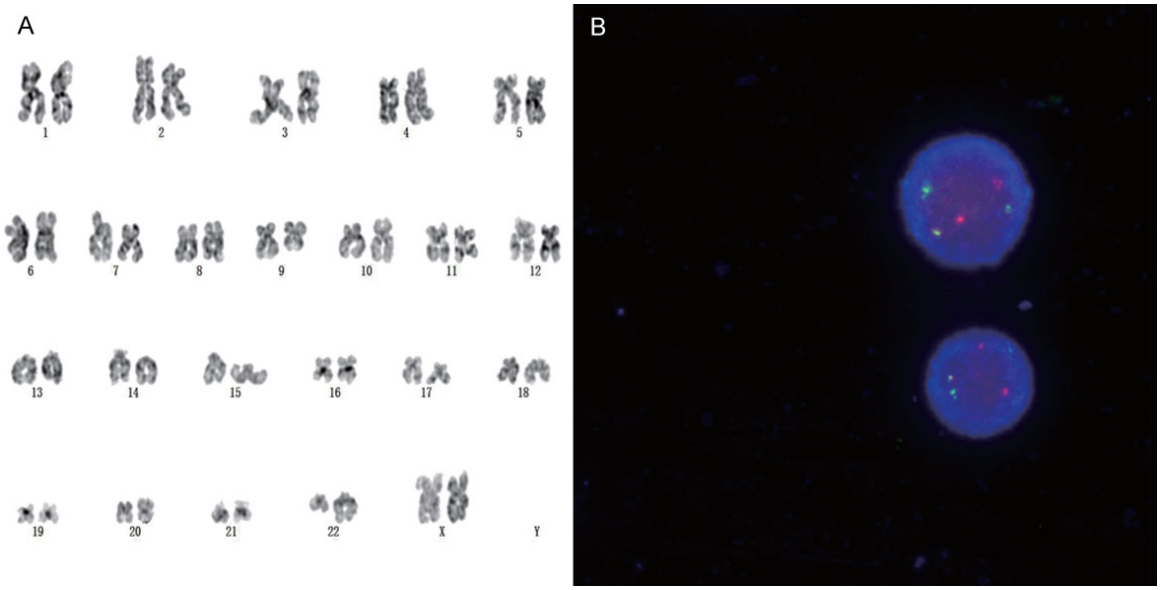

Figure 2. A. Chromosome analysis by G banding showing inserted karyotype of 46, XX, ins (22;9) (q11;q21q34) in this patient; B. The fusion signal is observed in the patient by FISH.

can also be associated with various other structural and numerical chromosomal aberrations. Walid et al. have reported a case of CML with secondary chromosomal changes including trisomy 17q21 to 17qter and partial monosomy of 16p13.3 [9]. Another study conducted in Malaysia on 256 patients with CML showed 15% of Ph chromosome-positive patients had additional chromosomal aberrations, and one patient had a hyperdiploid karyotype showing 51 chromosomes, with trisomy 6, 10, 13, 19, and the presence of two Ph chromosomes [3]. The presence of a hyperdiploid karyotype can be a poor prognostic factor [10].

Conclusion

Cytogenetic complexities play a major role in the prognostic evaluation of CML. Along with the Ph chromosome, various chromosomal aberrations can be associated with CML. Insertions are not commonly reported in CML, but may be a good prognostic factor if present.

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Disclosure of conflict of interest

None.

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