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CASE REPORT

Transient monosomy 7 in a chronic myelogenous leukemia patient during nilotinib therapy: a case report

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Key Clinical Message

Tyrosine kinase inhibitor treated chronic myelogenous leukemia patients with monosomy 7 arising in Philadelphia chromosome negative (Ph−) cells tend to evolve into MDS/AML. However, monosomy 7 in Ph− cells can be a transient finding, and it is not an absolute indication of the emergence of a new myeloid malignancy.

Keywords

chronic myelogenous leukemia, monosomy 7.

Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm that is always associated with a *BCR-ABL1* fusion gene. Most often, the BCR-ABL1 fusion is the result of a reciprocal translocation involving chromosomes 9 and 22 with the derivative chromosome 22 harboring the active abnormal fusion. The derivative chromosome 22 is also known as the Philadelphia chromosome. The *BCR-ABL1* fusion gene results in an unregulated tyrosine kinase activity, responsible for the expansion of myeloid elements in CML [1]. Tyrosine kinase inhibitors (TKIs) block the initiation of the BCR-ABL1 pathway, and are currently used as a first-line treatment for CML patients. However, it has been reported that after treatment with TKIs, Philadelphia chromosome negative (Ph-negative) clones can emerge with various cytogenetic abnormalities associated with different outcomes [2–22]. Most abnormalities are similar to those associated with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), including trisomy 8, monosomy 7 and 20q-. Based on published data, CML patients that develop chromosome 7 abnormalities in Ph− cells, particularly monosomy 7, appear to have the greatest risk of developing MDS/AML [6, 12, 13]. We report a case of a CML patient who achieved complete hematologic, cytogenetic, and molecular remission on nilotinib as a first-line treatment, but was found to develop monosomy 7 in Ph− cells. The monosomy 7 clone was transient and disappeared after one year follow-up while maintaining Nilotinib and without the initiation of additional therapy. The patient has not shown any morphologic or clinical progression to MDS/AML.

Case Report

The patient is a 54-year-old Caucasian male with no significant past medical history who presented with splenomegaly. The complete blood cell count (CBC) showed a hemoglobin (Hb) of 7.2 g/dL (reference range, 13.5–17.5 g/dL), white blood cells (WBCs) of 244.1 × 10^9/L (reference range, 3.5–10.5 × 10^9/L), and platelets (PLTs) of 1706 × 10^9/L (reference range, 150–450 × 10^9/L). A bone marrow (BM) biopsy, in conjunction with

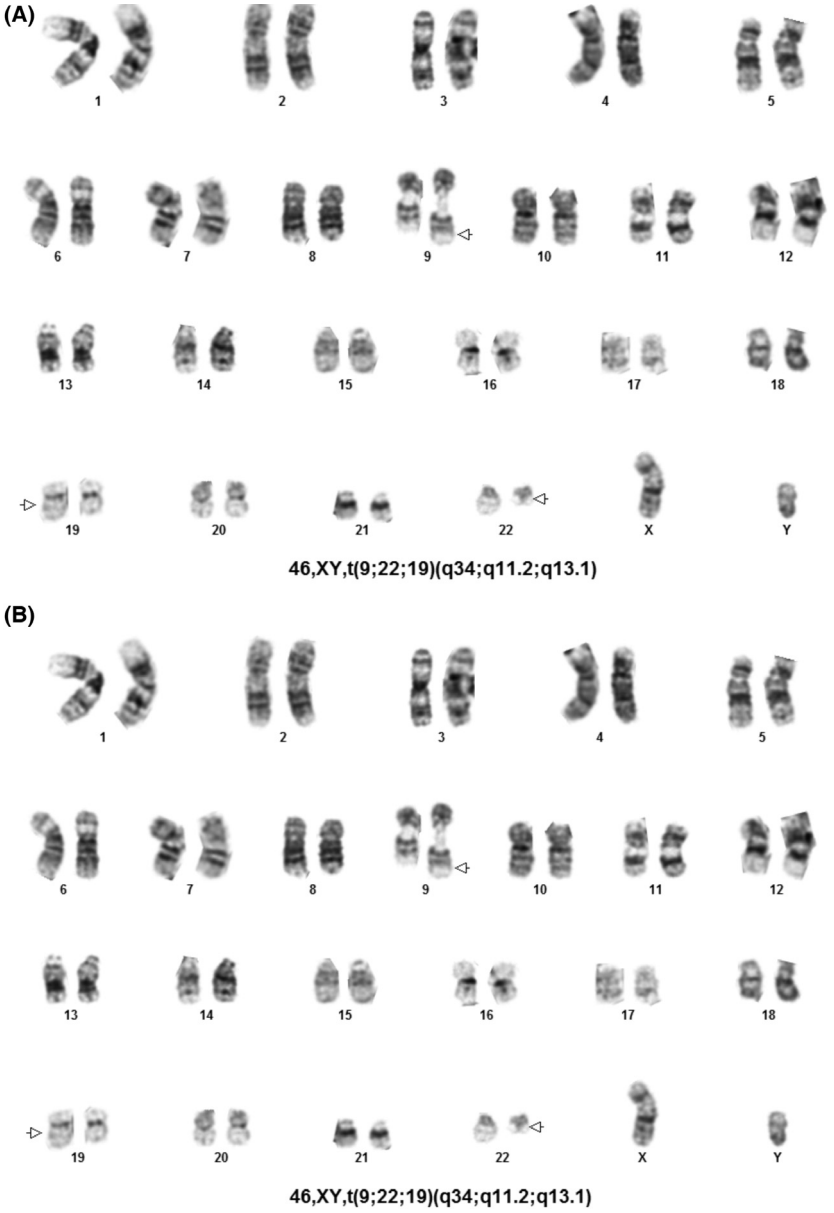

Figure 1. Bone marrow chromosome karyotypes. (A) CML diagnosis: The diagnostic cytogenetic analysis shows a three-way translocation involving chromosomes 9, 22, and 19 (highlighted by the arrow heads). (B) CML in hematologic and cytogenetic remission on Nilotinib therapy: cytogenetic analysis shows monosomy 7 and absence of the complex 9;22;19 translocation (Ph-negative metaphase).

cytogenetics, was diagnostic of CML, accelerated phase (10% myeloblasts). The conventional karyotype showed t(9;22;19)(q34;q11.2;q13.1) in 20 metaphases and no other cytogenetic abnormalities (Fig. 1). Fluorescence in situ hybridization (FISH) revealed BCR/ABL1 fusion in 94.2% of nuclei. The morphological, cytogenetic, and molecular characteristics are summarized in Table 1. The patient was started on nilotinib 400 mg P.O. twice a day. Three months after treatment, the patient developed pancytopenia (Hb of 12.4 g/dL, WBC of 2.2×10^9/L, PLTs of 112×10^9/L); thus, the nilotinib dose was decreased to 600 mg P.O. daily. The patient tolerated the treatment with no significant symptoms. After 6 months, he achieved complete hematologic, major cytogenetic, and major molecular remission (Table 1). Repeat BM biopsy 13 months after diagnosis showed no evidence of residual CML or overt dysplasia except the presence of occasional small megakaryocytes. Interest-

Table 1. Summary of the morphological, cytogenetic, and molecular data of the patient.

Date	Conventional karyotype	FISH BCR/ABL1	PCR BCR/ABL1	Morphology
Diagnosis	46,XY,t(9;22;19)(q34;q11.2;q13.1)[20]	94.2%	64%	CML
+6 months	46,XY,t(9;22;19)(q34;q11.2;q13.1)[4]/ 46,XY[16]	N/A	5.2%	Normal
+13 months	45,XY,-7[[15]/46,XY[5]	Normal	0.4%	Occasional small megakaryocytes
+18 months	45,XY,-7[6]/46,XY[14]	N/A	0.08%	Occasional small megakaryocytes
+30 months	46,XY[20]	N/A	0.007%	Normal

ingly, while there was no evidence of the complex 9;22;19 translocation, the karyotype showed monosomy 7 in 15 of 20 metaphases, indicating the emergence of an unrelated myeloid clone. A FISH panel for MDS was performed, using probes that recognize inv(3), -5/5q-, -7/7q-, +8, 13q-, 20q-, 11q23/MLL, and 17p-. This study confirmed the presence of monosomy 7 in 61.5% of nuclei, and did not detect any other abnormalities. He was continued on nilotinib 600 mg P.O. daily with close follow-up. Eighteen months after the initial diagnosis, the patient underwent another BM biopsy which showed no significant morphologic changes, with monosomy 7 detected in six of 20 metaphases. Repeat BM biopsy 30 months after the initial diagnosis showed a morphologically normal bone marrow with BCR/ABL1 fusion in 0.007% of total abl by RT-PCR, and a normal karyotype in 20 metaphases with complete disappearance of the monosomy 7 clone. Repeat MDS FISH study on his peripheral blood was completely normal. The patient is currently in complete remission at 40 months following diagnosis.

Discussion

Of CML patients treated with TKIs, approximately 2–10% of patients develop cytogenetic abnormalities in Ph-negative cells [12, 15, 21]. Although most remain stable, a subset of patients, especially those with monosomy 7 abnormality, are at risk of developing MDS or AML [6, 12, 13]. For those who displayed monosomy 7 without developing MDS or AML, persistent monosomy 7 has been observed [2, 4, 9]. It is uncertain whether MDS changes would became apparent in patients with persistent monosomy 7 after long-term follow-up.

The majority of reports on cytogenetic abnormalities developing in Ph-negative cells are observed in CML patients treated with Imatinib, the first generation of TKI. Very few cytogenetic abnormalities in Ph-negative cells have been reported in CML patients treated with Nilotinib [23], a new aminopyrimidine-derivative tyrosine kinase inhibitor that has been shown to be a more potent inhibitor than Imatinib and can be considered as a first-line therapy for CML [24]. Zeidan et al. [22]. reported a case of monosomy 7 in a CML patient treated with imatinib followed by nilotinib, and Larsson et al. [13] reported a CML patient on dasatinib (similar to Nilotinib) therapy developing a monosomy 7 clone. Unlike our patient, MDS and AML, respectively, developed in both of these patients. To the best of our knowledge, this is the first report of transient monosomy 7 in Ph-negative cells with nilotinib as the first-line treatment.

The mechanisms for the emergence of such clones remain unclear. Bumm et al. [5] suggests that CML patients have been exposed to genomic damage, which produces multiple abnormal clones, including the t (9;22) clone. These clones may not be apparent during the proliferative phase of the Ph-positive clone. Therefore, TKI treatment suppresses Ph-positive clone proliferation and allows the Ph-negative clones to emerge. The second suggested mechanism by O'Dwyer et al. [18] is that these clonal abnormalities are a direct consequence of TKI toxicity. The third possible mechanism is indirect toxicity of TKI by inhibiting the normal role of ABL tyrosine kinase in p53-mediated growth arrest after DNA damage [4]. However, clonal abnormalities in Ph− cells have been reported in CML patients after interferon treatment suggesting the genesis of these cytogenetic clones is not solely associated with the initiation of TKI therapy [25]. Thus, the exact etiology behind the appearance of these abnormal clones is not fully understood.

In summary, this case illustrates that monosomy 7 occurring in Ph− cells can be a transient finding in CML patients on TKI treatment, and that it is not an absolute indication of the emergence of a new myeloid malignancy. In addition, while most cytogenetic abnormal, Ph− myeloid clone have thus far been identified in CML patients treated with imatinib, with the increasing use of newer TKI such as Nilotinib, these Ph− clones may be more commonly associated with the second generation of TKI.

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