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CASE REPORT

Isodicentric Philadelphia chromosome: an uncommon chromosomal abnormality in the chronic phase of chronic myeloid leukemia (CML)

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Key Clinical Message

An isodicentric Philadelphia chromosome is an uncommon finding previously described as a secondary chromosomal abnormality in accelerated- or blast-phase of chronic myeloid leukemia (CML) with resistance to imatinib mesylate or dasatinib. Here, we present a case with idic(Ph) chromosome identified at initial diagnosis in a patient with chronic-phase CML.

Keywords

CML, cytogenetics, isodicentric, philadelphia chromosome.

Introduction

The presence of an idic(Ph) chromosome(s) represents a mechanism for genomic *BCR-ABL1* amplification and may contribute to resistance against targeted therapies based on imatinib or dasatinib. A 52-year-old, previously healthy man presented to his local ED with worsening right groin pain of 2-months duration, which began after a traumatic fall with direct trauma to that site. At that time, he was discharged home from the ED with a diagnosis of rectus sheath hematoma. His pain continued to progress, and he returned to the ED where repeat CT demonstrated worsening hematoma size and a CBC showed significant leukocytosis. The patient was transferred to our hospital with a concern for leukemia. At our institution, the admission white blood cell count (WBC) was 116.4 $\times$ 10^9/L with a differential consisting of 70% neutrophils, 3% metamyelocytes, 6% myelocytes, 2% promyelocytes, 7% lymphocytes, 5% eosinophils, 4% basophils, and 3% blasts (Fig. 1A). The platelet count was 506 $\times$ 10^9/L and the hemoglobin level was 10.5 g/dL. The serum lactate dehydrogenase (LDH) level was 725 U/L (normal level up to 214 U/L).

Peripheral blood flow cytometry showed an increased granulocyte population with left-shifted maturation and myeloblasts accounting for about 2.5% of the total events. A bone marrow biopsy showed findings consistent with CML including marked marrow hypercellularity with left-shifted granulocytic preponderance, numerous "dwarf" megakaryocytes, and 3% blasts (Fig. 1B). Fluorescence hybridization (FISH) analysis on the bone marrow with *BCR-ABL1* dual-color, dual-fusion probes revealed three distinct *BCR/ABL1* fusion patterns. The typical *BCR/ABL1* fusion pattern was observed in 31% of interphase nuclei analyzed. A variant *BCR/ABL1* fusion pattern (3 fusions; 1 orange; 1 green) was observed in 62.5% of nuclei (Fig. 1C) and 2.5% of nuclei showed 4 fusions; 1 orange; and 1 green pattern. Karyotyping studies revealed the presence of an isodicentric Philadelphia chromosome, 46, XY,der(9)t(9;22)(q34;q11.2),-22,+ider(22)(q10)t(9;22)(q34; q11.2), in all 20 analyzed metaphases (Fig. 1D). Additional metaphase FISH studies with *BCR/ABL1* probes showed

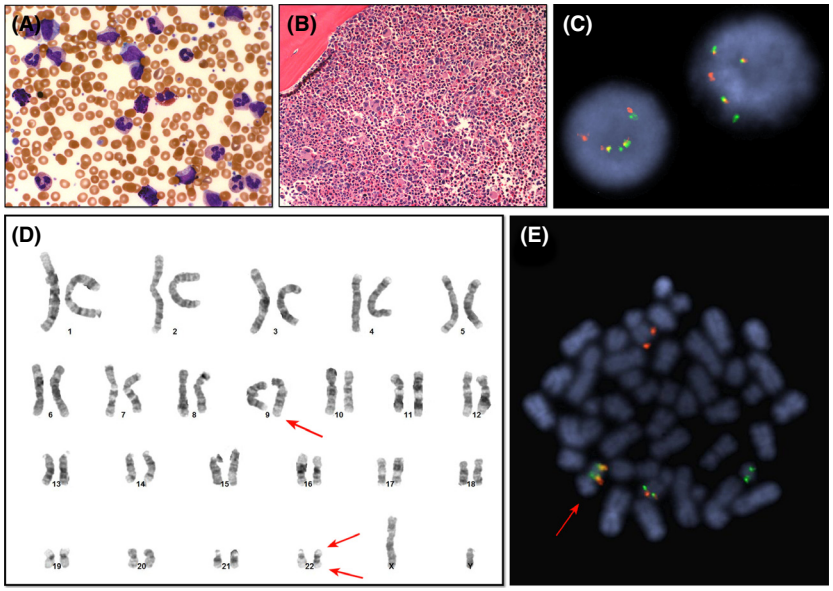

Figure 1. Pathologic and cytogenetic findings in the peripheral blood and bone marrow biopsies. (A) The peripheral blood smear shows a leukocytosis with neutrophils at various stages of maturation, a basophilia (<20%), and 3% blasts; (B) The marrow is hypercellular with diffuse granulocytic proliferation and numerous "dwarf" megakaryocytes; (C) BCR-ABL1 FISH showed a variant fusion pattern (3 fusions; 1 orange; 1 green); (D) Chromosome analysis revealed an abnormal male karyotype with an isodicentric Philadelphia chromosome; (E) Metaphase FISH studies show the presence of two BCR/ABL1 fusion signals on the idic(Ph) chromosome.

the localization of two fusion signals on the isodicentric Philadelphia chromosome and another fusion signal on the derivative chromosome 9 (Fig. 1E). *BCR-ABL1* fusion transcripts were at the level of 100% on the International Scale (IS). The patient was initiated on imatinib mesylate at 400 mg/day. Two weeks later, the WBC trended down to 40×10^9/L and LDH level was 299 U/L. No peripheral blasts were observed. The 3-month follow-up visit showed complete hematological response, with the bone marrow showing morphologic remission and a normal karyotype (46,XY) by unstimulated bone marrow culture. However, PCR studies for the mutant transcript showed that there was lack of a major molecular response (MMR, defined as <0.1% on the IS) with *BCR-ABL1* transcripts at 6.12% on the IS. The patient is clinically well and continues to be followed closely in the clinic at this time.

Chronic myeloid leukemia (CML) is linked to the Philadelphia chromosome t(9;22)(q34;q11.2), which results in the formation of a chimeric *BCR-ABL1* gene fusion. By binding to the kinase domain of *ABL1*, imatinib mesylate inhibits the function of the fusion gene and is a highly effective therapy. However, resistance to therapy is not uncommon and multiple etiologic mechanisms have been described. Mechanisms of resistance against imatinib treatment may include mutations within the *ABL1* kinase domain, genomic *BCR-ABL1* amplification and clonal evolution [1].

Very few cases of CML with the presence of idic(Ph) chromosome(s) have been reported in the literature. The idic(Ph) chromosome has generally been observed in accelerated phase or in blast phase of CML [2, 3]. In other cases, idic(Ph) chromosome(s) were observed as a secondary chromosomal abnormality in patients resistant to imatinib mesylate or dasatinib [1, 4–6]. In our patient, the idic(Ph) chromosome was observed at diagnosis with 3% blasts, suggesting the presence of idic(Ph) in chronic phase. Additional studies will help in clarifying the prognostic significance of the presence of idic(Ph) chromosome during the chronic phase of CML. To date, only one other study reported the occurrence of idic(Ph) chromosome during chronic phase CML, and this case was associated with lack of hematological and cytogenetic response despite administering higher doses of imatinib [7].

Conflict of Interest

None declared.

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