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Case Report Open Access

A Rare Presentation of ph Chromosome: idic der (22q11) in Blast Crisis Chronic Myeloid Leukemia

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Abstract

The ider(22)t(9;22)(q34;q11) is a rare secondary karyotypic abnormality of Ph chromosome positive chronic myeloid leukemia associated with disease progression, poor clinical outcome and short survival in most of the previously reported cases. The present case of CML with idic der(22)t(9;22)(q34;q11) or idic der Ph with hybrid transcript ratio of BCR-ABL being 97% showed a complex karyotype: 48,XY,+8,t(9;22)(q34;q11)i dic(22)(q11),+idic der(22)t(9;22)(q34;q11). On treatment with Imatinib the initial transcript ratio was reduced to 12.125%, 0.932% but later increased to 93%. The patient developed extra medullary myeloid cell tumor of testis after a year of treatment followed by the detection of *T3151* mutation. Cytogenetics provides an evidence for progression of disease at an earlier phase than other markers in this case.

Keywords: Chronic myeloid Leukemia; idic der Ph; Imatinib; Karyotype; Prognosis

Introduction

Chronic myeloid leukemia (CML) is genetically characterized by the presence of the reciprocal translocation t(9;22)(q34;q11), resulting in a BCR-ABL gene fusion on the derivative chromosome 22 called Philadelphia chromosome (Ph) in 90%-95% of patients. [1] In 5%-10% of patients, variant translocation and masked Ph chromosome were reported [2-7] Furthermore, rearrangements in Ph chromosome like iso, dicentric and amplified or multiple Ph chromosomes are rarely reported in literature [8-11]. we present a case of CML with idic der Ph chromosome from a young male. The genesis and clinical outcome of the same is discussed in detail with reference to the available literature.

Case History

A 36-year-old male patient presented in December 2006 with a past history of being treated elsewhere as CML, with hydroxyurea for four years. Clinically patient was asymptomatic. Detailed investigations done in our centre revealed: Hb of 125 grams/L, raised WBC count of 100 x 10^9/L and platelet count of 23.6 x 10^9/L. The differential count of blood and Bone Marrow Aspirate (BMA) findings were suggestive of CML in Chronic Phase. The cytogenetic analysis from BMA revealed two abnormal clones with karyotypes :46,XY,t(9;22)(q34;q11) [2] and 47,XY,t(9;22)(q34;q11),+idic der(22)t(9;22)(q34;q11) [12-15] suggesting CML in Blast Crisis. The ratio of Bcr-Abl/Abl transcript by RT-PCR was detected to be 97% in leukocytes of the peripheral blood. The patient was treated with Imatanib mesylate (Glivec) 400 mg. Initially he responded to therapy, the ratio of Bcr-Abl/Abl transcript was gradually reduced to 12.125% and 0.932% in the interval of 3 and 5 months respectively. Qualitative analysis of Imatinib Resistance mutations screened in Abl kinase domain of Bcr-Abl transcript revealed no mutations.

In December 2007, he developed left testicular swelling, the biopsy showed perivascular infiltration by population of cells having round vesicular nuclei, moderate cytoplasm and prominent nucleolus. A few eosinophils were also noted. Immunohistochemistry was performed on the testicular biopsy, revealed the neoplastic cells to be positive for *CD68, MPO* and negative for *CD34, CD117*. A diagnosis of extra medullary Myeloid cell tumor of testis -Blastic type was made. Then the dosage of imatinib was increased to 600 mg.

In August 2008 his Hb was 119 grams/L, WBC 57.7 x 10 9/L and platelates 19.4 x 10 9/L. Hypercellular marrow with marked myeloid hyperplasia, with increase in early myeloid precursors, increase in basophiles (4%) and micromegakarycytes were noted. It was reported as CML not in remission. The karyotype: 47,XY,t(9;22)(q34;q11)idic der(22)(q11),+idic der(22)t(9;22)(q34;q11) (32) was observed without standard ph chromosome (Figure 1). The Abl/Abl transcript was found to be 97% and mutation was not detected. Patient was shifted to tablet Dasatinib 100 mg OD. His tolerance to this drug was not good, he had intolerable diarrhea and did not wanted to continue the same. Patient was shifted back to hydroxyurea and Imatinib 600 mg.

In September 2010 his Hb was 130 grams /L, WBC 30.2 x 109/L and platelates 27 x 109/L. Surprisingly marrow was in hematological remission, but complex karyotype 48,XY,+8,t(9;22)(q34;q11)idic der (22)(q11),+idic der (22)t(9;22)(q34;q11) (25) was observed. Bcr-Abl/Abl transcript was 90% and he was planned for a trail of Nilotinib. Meanwhile in October 2010 the mutation *T3151* (Thr to IIe) was detected. Based on these findings the patient was advised for Bone Marrow Transplantation, awaiting allogeneic bone marrow transplantation from his HLA-matching sibling. Later the patient was lost for follow-up.

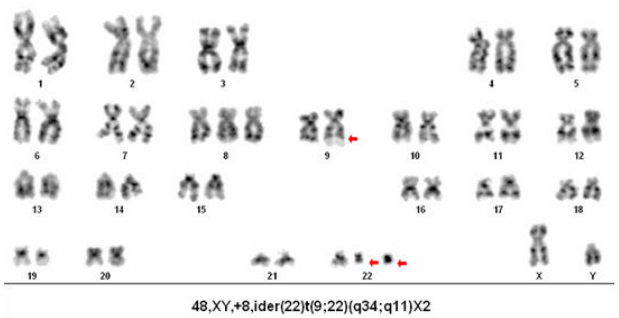

Figure 1: Karyotype-48,XY,+8,t(9;22)(q34;q11) idic(22)(q11),+ idic der (22)t(9;22)(q34;q11)

Discussion

The available literature reveals that CML with idic der Ph chromosome were failed to respond to imatinib treatment [9,14,15] Further, Patients who are not responding to Imatinb were more likely to develop additional karyotypic changes during the course of the disease [15]. As the disease evolves from chronic phase to blast crisis in CML, it is accompanied by recurring secondary chromosomal abnormalities such as +Ph,+8,+19,i(17)(q10) [7,11]. These abnormalities occur as sole or in combination. Trisomy 8 probably occurred before the transformation or it was present in chronic phase or accelerated phase predominantly in myeloid series [11] Interesting aspects of our case is the presence of classic Ph clone along with idic der ph chromosome, it accounts for four ph chromosomes and karyotype evolution. During third year of his treatment the karyotype was 48,XY,+8,t(9;22)(q34;q11)idic der(22)(q11),+ idic der(22)t(9;22)(q34;q11). In the present case, during karyotype evolution, addition of idic der Ph chromosome occurred initially followed by Trisomy 8. This patient also did not respond to Imatinib treatment.

Gargallo et al. [12] reported a case with amplification of the BCR/ABL fusion gene clustered on masked Ph chromosome associated with myeloblastic phase developed during the disease progression. Gadzicki et al. [15] gave evidence that the genomic Bcr-Abl amplification results in an increased level of Bcr-Abl transcript and karyotype evolution by acquiring ider (22) linking to two potent mechanisms of resistance against Imatinib treatment. In the present case, although the patient responded to Imatinib initially (transcript ratio reduced from 97% to 0.932 with Imatinib 400 mg), later the cytogenetics (double idic der Ph + 8) and molecular evidences of relapse (93%) were noted. The presence of the multiple gene copies of the Bcr-Abl transcript, because of multiple copies of Ph (idic der ph) seems to be the cause for resistance to Imatinib, despite increased drug dosage.

Most of the iso Ph or idic Ph chromosome reported in the literature have been described to be a fusion occurring at the p arms at band p13, resulting in multiple copies of the fusion oncogene [13,14]. Li et al. [9] described a rare case of an ider (22) formed by a fusion in the q arm at q11 in the absence of classic Ph chromosome and lack of mutation at Imatinib binding region on the fusion product with a short survival. In our case it may be of the former type.

A few studies revealed Bcr-Abl kinase domaine mutations in CML that have been detected in association with clinical resistance to Imatinib and no cytogenetic response [12,14-18]. Thus, the studies suggest that Imatinib resistant mutation should be included in the management of CML patients together with molecular, cytogenetic and clinical monitoring. In the present case, complex karyotype and high Bcr-Abl/Abl transcripts were detected from the beginning but mutation *T3151* was detected later. Cytogenetic studies often provide evidence of progression of disease at an earlier phase than other markers.

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