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CASE REPORT

A Case of Chronic Myeloid Leukemia Following Tyrosine Kinase Inhibitors (TKI) Exhibiting Trisomy 8 and a Double Philadelphia (Ph) Chromosome, with No Signs of Disease Progression

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Abstract

Ever since secondary chromosomal changes were first identified in patients with chronic myeloid leukemia (CML), questions as to whether these cytogenetic evolution patterns seen correlate with type of therapy given during chronic phase (CP) have been raised. Patients who received treatment such as hydroxyurea or busulfan have shown to have increased incidence of trisomy 8 (+8), double Philadelphia (Ph) chromosome, isochromosome i(17q) or other secondary chromosomal abnormalities. Karyotypic abnormalities were also have been reported in some of the patients who developed cytogenetic response to imatinib. In this case report, we described a case of CML in chronic phase developed complex chromosomal abnormality with +8 and an additional Ph chromosome after receiving treatment with hydroxyurea and imatinib.

Keywords: Chronic myeloid leukemia, double Philadelphia chromosome, trisomy 8

Introduction

Chronic myeloid leukemia is a malignant disorder caused by reciprocal translocation between the long arms of one chromosome 9 at band 9q34 and one chromosome 22 at band 22q11.2 forming Philadelphia (Ph) chromosome. This translocation results in BCR-ABL1 fusion gene that encodes for BCR-ABL1 oncogenic protein that persistently enhanced tyrosine kinase activity and thus proliferate uncontrollably.

Some patients acquire additional cytogenetic abnormalities (ACAs) during the course of the disease as a result of genetic instability or due to disease progression (Wang et al, 2016). Among the commonest seen are trisomy 8, isochromosome i(17q) and double Ph chromosome. These new clones (other than iso-17q) may remain clinically insignificant except when there is accelerated or blastic transformation. Studies showed that 10% to 20% of patients developed clonal cytogenetic changes in addition to the Ph translocation during chronic phase (Raquel et al, 2018).

The role of double Ph chromosome in disease progression has been hypothesized that the presence of a double *BCR::ABL1* chimeric gene induces more kinase activity and lead to more aggressive proliferation of blast cells (Otero et al, 2008).

Trisomy 8 is a common feature of cases of clonal evolution in patients with CML treated with imatinib who are in cytogenetic remission (Abdou et al, 2013). There are studies shows that a small group of patients with CML who was on imatinib mesylate does not progress into advance phase of CML when the new clone of trisomy 8 was detected. Most of them showed suppression of Ph chromosome, which suggest that the emergence of trisomy 8 cells may due to the treatment (Eric et al, 2003). Other studies however reported that the emergence of trisomy 8 in Ph negative patients during the course of imatinib treatment is transient and not related to therapy or progression of the disease (Kim et al, 2008).

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Case Report

This was a case of 29-year-old man presented with intermittent history of prolonged fever for six months associated with loss of weight and loss of appetite.

On physical examination, he had pallor with moderate hepatosplenomegaly. Laboratory investigations revealed low hemoglobin (10.8 g/dL), marked hyperleukocytosis (206.4 x 10^9/L) and thrombocytosis (947 x 10^9/L). Peripheral blood film showed hyperleukocytosis with presence of 4% blast cells (Figure 1). NAP score was low (11/100 neutrophils).

Bone marrow aspirate smear was markedly hypercellular with findings that were similar with his peripheral blood film. Trephine biopsy showed hypercellular marrow with granulocytic hyperplasia. Molecular analysis showed that this patient was positive for *BCR::ABL1* transcripts (major fragment p210). Karyotyping analysis was performed on cultured bone marrow cells which showed normal male karyotype with no Philadelphia chromosome observed in all 12 metaphase spread. Fluorescence in situ hybridisation (FISH) was then performed on 200 nuclei and metaphase spreads using Vysis LSI BCR/ABL Dual Colour Dual Fusion Translocation Probe. The probe consists of two colours, the SpectrumOrange probe and SpectrumGreen probe. FISH analysis demonstrates presence of one green, one orange and two fused green/orange (yellow) signal pattern in 161 nuclei and metaphase spreads analysed which is about 80.5% detection indicating presence of *BCR::ABL1* fusion gene (Figure 2).

He was diagnosed as chronic myeloid leukemia in chronic phase. He was given hydroxyurea and arabinosine cytarabine for cytoreduction and was started on imatinib two months after the diagnosis being made. The patient had achieved complete cytogenetic response and major molecular response within 10 months of starting imatinib therapy.

Unfortunately, two years later due to poor compliance to imatinib, he developed cytogenetic relapse. Chromosome analysis showed presence of trisomy 8, t(9:22) and an additional der(22) chromosome derived from t(9:22) in seven metaphase spread seen at 400 band resolution (G-banding) (Figure 3). FISH analysis done on 200 nuclei using Vysis LSI BCR/ABL Dual Colour Dual Fusion translocation probe demonstrate presence of two *BCR::ABL1* fusion gene in 32.5% of cells analyzed with additional *BCR::ABL1* fusion gene (three fusion signals) in 67.5% the cells analyzed which indicates double Ph chromosome (Figure 4). FISH analysis done on 10 metaphase spreads using telomere probe 8p/8q Vysis ToTelVysion DNA Probe showed presence of three orange and three green signal patterns in all metaphase spreads which is consistent with trisomy of chromosome 8 (Figure 5). The repeat bone marrow aspirate smear and trephine biopsy findings were consistent with CML in chronic phase with no other accelerated features or blastic transformation.

He was then started on bulsulfan, fludarabine and cyclosporine and responded well to treatment. He managed to undergo allogenic peripheral blood stem cell transplant (PBSCT) a few months later but developed mild complications due to graft versus host reaction. Nevertheless, he has been in molecular remission ever since.

Discussion

In chronic myeloid leukemia, the exact chromosomal defect in Philadelphia chromosome is translocation, in which parts of two chromosomes, 9 and 22, swap places. The result is that a fusion gene is created by juxtapositioning the *ABL1* gene on chromosome 9 (region q34) to a part of the *BCR* ("breakpoint cluster region") gene on chromosome 22 (region q11.2). This reciprocal translocation creates an elongated chromosome 9 (der 9), and a truncated chromosome 22 (the Philadelphia chromosome) forming an oncogenic *BCR-ABL1* fusion gene that can be found on the derivative 22 chromosome. This hybrid gene encodes the *BCR::ABL1* fusion protein with its characteristic of dysregulated tyrosine kinase activity (Bruno et al, 2004).

Current evidence indicates that acquired genetic instability as a consequence of the Philadelphia (Ph) translocation and the resulting *BCR::ABL1* fusion protein causes the continuous acquisition of additional chromosomal aberrations (ACAs) and mutations. Clonal evolution in CML denotes the presence of a variety of additional, non-random chromosomal abnormalities besides the Ph chromosome. Although clonal evolution may involve any abnormality within any chromosome and regardless of whether *BCR::ABL1* has a direct or an indirect role in promoting genomic instability, 60% to 80% of patients with CML develop additional non-random chromosomal abnormalities involving chromosomes 8, 17, 19, and 22 with duplication of the Ph chromosome and trisomy of chromosome 8 being the most frequently reported (Fabarius et al, 2011). Other studies reported that patients who develop resistance to imatinib frequently develop clonal evolution as a mechanism of resistance (Meike et al, 2023).

Trisomy 8 is one of the most common chromosome abnormalities detectable in Ph positive CML patients associated with disease evolution. Early detection of cells containing an extra chromosome 8 is important for diagnostic, therapeutic, and prognostic reasons (Abdou et al, 2013). Trisomy 8 in Ph positive CML patients is frequently observed as a secondary chromosome change and is considered one of the non-random abnormalities associated with the blastic phase of the disease (Wang et al, 2016). This is because the *MYC* gene

is located at 8q24 and it may be expected that chromosome 8 trisomy is associated with *c-myc* overexpression and that this is pathogenetically involved in disease progression. The *MYC* gene encodes a transcription factor, which converts mitogenic signals to altered gene expression in various human malignancies, particularly with regards to cell cycle and apoptosis Menssen et al, 2002). Apart from *c-myc* gene, other genes with possible significance in leukomogenesis located on chromosome 8 include *c-mos* on 8q22, *MOZ* on 8p11, and *ETO* on 8q22. Some studies however suggest that trisomy 8 associated with human hematologic neoplasia is generally not related to gross rearrangements of the *c-mos* or *c-myc* genes (Sonal et al, 2012).

Apart from that, there are studies which show that intensive chemotherapy the patient received during chronic phase of the disease also plays a role in the secondary chromosomal changes as seen in this patient. In early database, approximately 12% CML patients who had received hydroxyurea therapy had developed trisomy of chromosome 8 and 29% had developed double Ph chromosome (Mitelman et al, 2001). This patient had received hydroxyurea when he was first diagnosed with CML in chronic phase.

In a study among twenty-eight CML patients who developed trisomy 8 during therapy, only 11% of them developed blastic transformation and irrespective of the clone size of trisomy 8, it has no effects on inducing treatment resistance or disease progression (Wang et al, 2016). This may indicate a secondary event due to genetic instability induced by the persistence of BCR-ABL1 (Wang et al, 2016).

Based on the 2016 update of WHO classification of tumours of hematopoietic and lymphoid tissue, ACAs emerging during therapy are defined under accelerated phase of the disease (Arber et al, 2016). However, in a recent study among 251 Malaysian CML patients undergoing TKI therapy, Siti et al. classified these ACAs into 4 groups in which trisomy 8 and double Ph chromosome were grouped together under group 1 with relatively good prognosis with no progression into accelerated or blast phase. Another study by Wang et al. also compares between two groups of ACAs in which trisomy 8, -Y and extra copies of Ph chromosome falls under the same group showing better treatment response and survival compared to the other group with have monosomy 7/del(7q) and 3q26.2 rearrangement (Wang et al, 2016). This study supports our findings of no evidence of disease progression seen particularly associated with trisomy 8 and double Ph chromosome.

In term of prognosis, considering that this patient had undergone allogenic bone marrow transplant, cytogenetic follow up is crucial as several studies have shown that cytogenetic evolution pattern do exist after allogeneic bone marrow transplantation (BMT), which is characterized by random, sometimes transient, chromosomal changes (Kim et al, 2008). Furthermore, a high incidence of translocations and deletions involving 13q was recently reported in patients with persistent or relapsed disease following BMT. It has been suggested that the unusual cytogenetic changes observed after BMT arise as a result of the pre BMT conditioning regimen, i.e., the clastogenic effect of radiotherapy and cyclophosphamide (Christian et al, 2022).

Conclusion

In conclusion, here we reported a unique case of CML in chronic phase which developed trisomy 8 and double Ph chromosome during follow-up following receiving tyrosine kinase inhibitor therapy with no evidence of disease progression which may solely be a secondary event as a result of genetic instability. Nevertheless, close monitoring is crucial to prevent risk of relapse.

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