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Case Report RRJoOH

Extra Philadelphia in CML Due to Isodicentric 22: A Case Report

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Abstract

Introduction: Chronic Myelogenous Leukemia is a malignancy that affects the hematopoietic stems cells (HSC) of the bone marrow, leading to the rapid and continual proliferation of granulocytes and precursor blast cells. This is caused due to a reciprocal translocation that occurs between chromosomes 9 and 22, leading to the formation of derivative 22 also called as Philadelphia (Ph) chromosome. The Ph chromosome then encodes a fusion oncoprotein that functions as a tyrosine kinase activator encouraging cellular functions such as cell proliferation and rapid division and providing resistance to apoptosis. CML has been classified into different phases, based on the blast percentage, with symptoms becoming severe as the condition progresses to advanced phases. While the primary marker for this condition tends to be the Philadelphia chromosome, it has been observed that additional Ph observed in accelerated phase is a very important prognostic marker and we present a single case report with isodicentric Ph chromosome. Additional Ph presented as isodicentric is a rare cytogenetic phenomenon associated with CML and the clinical outcome is discussed.

Keywords: Philadelphia-Chromosomes, translocation, Chronic Myeloid Leukemia, Isodicentric, Prognostic Marker

INTRODUCTION

Chronic Myelogenous Leukemia (CML) is a malignancy that primarily affects the granulocytes. It is a condition that has an incidence rate of about 1–2 cases per 100,000 individuals. Statistics show that CML cases make up around 15% of newly diagnosed cases of adult leukemia, with incidence rates increasing with an increase in age [1]. This abnormality was discovered by Peter Nowell in 1960 [2]. Initial records of patients with CML come from the year 1845. But it was only in 1973 when Janet Rowell was able to link a cytogenetic abnormality as the cause for this condition [3]. This was the first time chromosomes were linked with the cause of cancer. The cytogenetic abnormality that leads to CML involves the reciprocal balanced translocation between chromosomes 9 and 22, leading to the formation of the "minute" Philadelphia chromosome, which is the major marker for this condition [4]. The formation of the Philadelphia chromosome involves the genes breakpoint cluster region (*BCR*) and Ableson Murine Leukaemia1 (*ABL1*), present on chromosomes 22q11 and 9q34, respectively. The translocation forms the *BCR/ABL1* oncogene, which encodes the BCR/ABL1 oncoprotein. This fusion oncoprotein acts as a chimeric tyrosine kinase, which remains active over a prolonged period (Nowell and Hungerford, 1960) [2]. This causes cells to gain traits, such as rapid and continual proliferation,

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differentiation, and resistance to apoptosis, leading to the development of CML [4]. Additionally, the Philadelphia chromosome causes further genetic instability through different mechanisms, which can lead to the accumulation of additional mutations and chromosomal abnormalities [5]. While studies are limited, the type and number of additional abnormalities act as crucial prognostic markers, as they indicate the progression of CML to advanced stages [6]. These ACAs are also conducive in deciding a suitable treatment plan, since certain abnormalities respond better to a specific type of tyrosine kinase inhibitor compared to other inhibitors [7].

CASE PRESENTATION

A 43-year-old male was diagnosed with Chronic Phase CML (CML CP) in 2020. He had no ACAs at diagnosis and was started on imatinib. In view of lack of hematological response and rising WBC count, he was advised to change to Dasatinib while awaiting Imatinib Resistance Mutation Analysis (IRMA) by Sanger sequencing. This showed a concomitant T315I mutation along with E255L Kinase domain mutations that rendered the patient nonresponsive to these TKIs. Therapy was changed and ponatinib commenced, after which the patient had a complete hematological response. However, owing to cost, the patient was not compliant with medication. He was taken to an allogeneic haploidentical stem cell transplant which they opted for over long term ponatinib. He underwent a repeat bone marrow to establish the stage of CML prior to transplant. At this juncture, ponatinib had been withdrawn for 15 days in view of cardiac side effects. He had leucocytosis and mild splenomegaly but was otherwise well. Bone marrow aspiration showed marked increase in myeloid series and with many myelocytes, few metamyelocytes and 5% blasts which was suggestive of Chronic Myeloid Leukemia in CP [8–12].

METHODS

Cytogenetics and FISH analysis was carried out at the Division of Molecular Biology and Genetics. Short term culture was set-up using RPMI1640 culture media and cultures were harvested using standardized protocol [13]. Karyotype was performed on GTG banded slides and were scanned under BX53 Olympus automated Metaphase scanner with chromosome analysis software from ASI version 8.1.2 Israel. 20 metaphases were analyzed [14].

FISH

FISH was performed on overnight cultured cells, probes specific for ABL1 gene on region 9q34.1 in Orange and BCR gene region at 22q11.2 in Green were procured from Metasystems (Cat Lot No. D-5082-100-TC). Probe and specimen were hybridized using Euroclone Hybridization chamber. Co-denaturation at 750C for 2 minutes and hybridization at 370C for 6 hrs. following post hybridization washes [15].

FISH analysis was conducted on BX53 fluorescence Olympus microscope with 100W mercury lamp and triple band pass filter. 200 nuclei were screened and all the cells showed extra copy of BCR::ABL1 fusion.

RESULTS

Karyotype showed clonal evolution. With majority of cells showing loss of Y chromosome and two copies of Philadelphia chromosome and second clone showed iso dicentric 22 with t (9;22).

FISH analysis showed that three copies of BCR::ABL1 gene fusion. Figure 1 shows the idic22 with t(9;22). Using reverse DAPI in Figure 2 confirms the presence of isodicentric 22. Isodicentric 22 is a structural chromosomal abnormality. It results due to centric fusion of two derivative 22 with t(9;22) the Isoform of derivative 22 t(9;22)(q34.1;q11.2) has resulted in extra fusion for BCR::ABL1 gene.

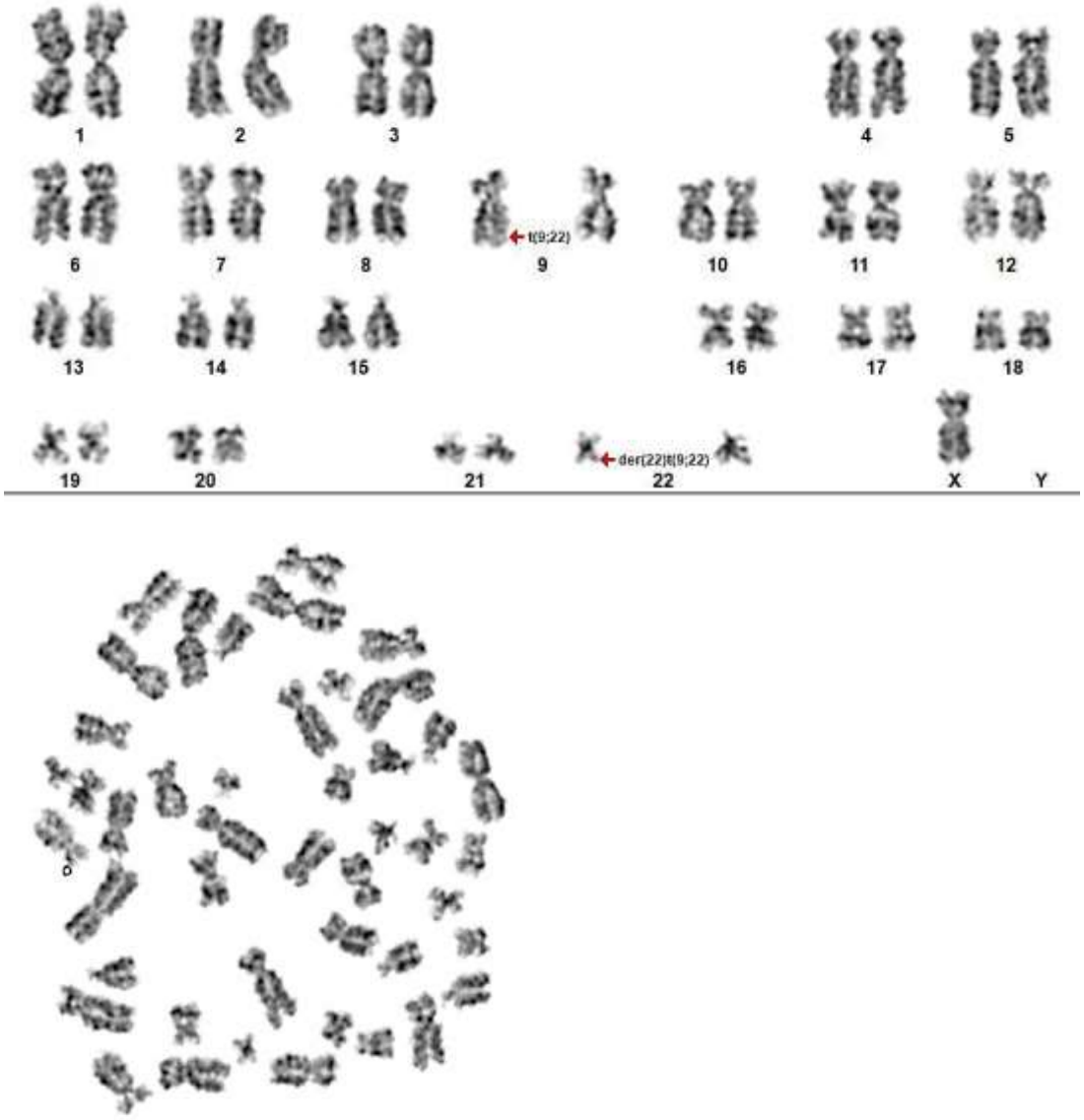

Figure 1. Cytogenetic findings. (A) Chromosome analysis revealed an abnormal male karyotype with anisodi centric Philadelphia chromosome and loss of Y chromosome.

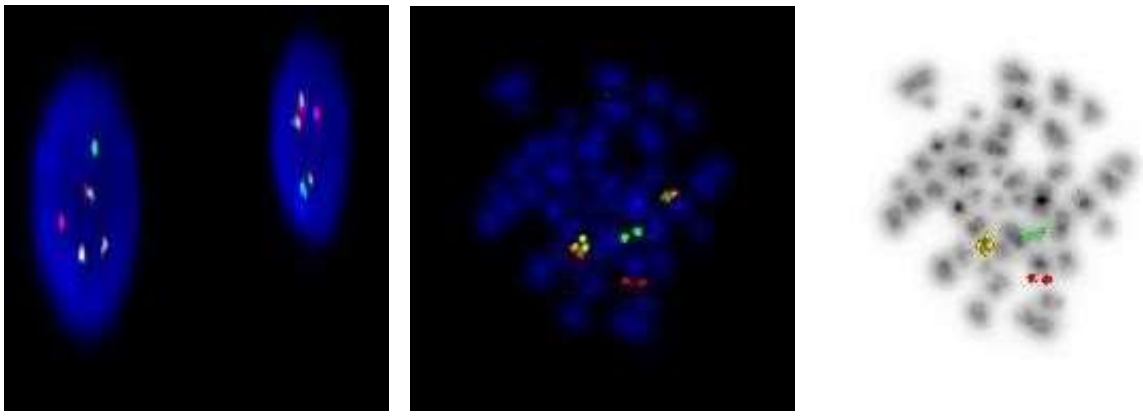

Figure 2. C) BCR::ABL1 FISH image three fusion pattern (D) Metaphase FISH studies show the presence of two BCR::ABL1 fusion signals on derivative 22 indicating idic(Ph) chromosome. (E) Reverse DAPI image of idic Ph chromosome.

CLINICAL RELEVANCE OF EXTRA PHILADELPHIA

The Ph chromosome is the "biomarker" used for the diagnosis of CML [8]. However, with improvements in technology, it was observed that chromosomal abnormalities apart from the Ph chromosome were also present in CML patients [5]. These abnormalities are referred to as additional chromosomal abnormalities (ACAs). The accumulation of ACAs in Ph positive CML cells is referred to as "clonal evolution", which is an important marker for the progression of CML to advanced stages [6]. Clonal Evolution is one of the criteria defining the accelerated phase and is associated with poor prognosis. Around 10–12% of patients with CP-CML have ACAs. This percentage increases to about 50% in AP-CML patients and around 80% in BP-CML patients [9]. It has also been observed that in some cases, a secondary ACA may also be visualized [10].

There are multiple reasons as to why these ACAs arise. Some studies suggest that CML cells are more prone to the production of reactive oxygen species (ROS). However, due to the ROS not being sufficiently quenched, it can interact with DNA, causing double strand breaks [11]. Another reason for this is the DNA repair mechanism being faulty in leukemic cells. It has been suggested that as the disease progresses, DNA repair mechanism becomes less efficient and more erroneous. Additionally, the over-activity of the BCR/ABL1 oncoprotein also leads to defects in mismatch repair and nucleotide excision repair mechanisms. Therefore, it is gradually replaced by the nonhomologous end joining repair mechanism, which is prone to more errors. This cell is, therefore, forced to rely on error-prone methods of DNA repair, ultimately resulting in further genetic instability. This not only signifies the progression of the condition and could also affect the response to treatment [5].

Loss of Y – Is It Clinically Relevant?

In a study by Eric et al. (2010) [12], poor response to imatinib was more frequent in Y patients.

CONCLUSIONS

Cytogenetic analysis plays an important role in establishing diagnosis in CML. It also highlights the importance of additional chromosomal abnormalities. Karyotype and FISH analysis together have the power to lead to a much more defined diagnosis, prognosis, identification of clonal evolution and overall, in leading to an adapted therapy for follow-up CML patients.

Conflict of Interest Statement

The authors would like to state that there are no conflicts of interest in publishing this manuscript. All co-authors agree that they have seen the contents of the manuscript and there is not any financial interest. All authors would like to agree that the manuscript is original work and is not submitted for publication elsewhere.

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