Leukemia Research Reports 18 (2022) 100351

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

A rare case of complex variant translocation of t(9;22;16)(q34;q11.2;q24) in a newly diagnosed patient with chronic myeloid leukemia

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ARTICLE INFO

Keywords:
Chronic myeloid leukemia
Philadelphia chromosome
Complex variant translocation of chromosomes

ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with the dysregulated production of myeloid cells. The Philadelphia chromosome (Ph), t(9;22)(q34;q11), is a hallmark of the disease and found in 90–95% of diagnosed CML patients. The balanced, reciprocal translocation places the genes *BCR* and *ABL1*, next to each other, resulting in an increase of kinase activity. Additional cases involve complex variants, including translocation events involving an additional chromosome with the creation of the Ph chromosome. A rare three-way Ph chromosome complex variant, t(9;22;16)(q34;q11.2;q24), was identified in a 40-year-old female who presented with visual changes and leukocytosis. Cytogenetic analysis by G-banding revealed the presence of a three-way translocation involving the long arms of chromosomes 9, 22, and 16. Fluorescence in situ hybridization with a dual-color fusion probe confirmed the presence of the *BCR::ABL1* fusion.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm of hematologic stem cells with the key translocation of t(9;22)(q34.1;q11.2). This cytogenetic change results in what has come to be known as the Philadelphia chromosome (Ph), a truncated and modified chromosome 22, and a modified chromosome 9. This structural alteration is significant because it results in the Abelson murine leukemia virus (*ABL1*) gene (originally on chromosome 9) to translocate in a balanced, reciprocal manner next to the breakpoint cluster region (*BCR*) gene (located on chromosome 22) thereby forming the fusion gene of *BCR::ABL1*. The classic Ph chromosome is present in approximately 90–95% cases of diagnosed CML, with the remaining diagnosed cases having more complex translocation events [1]. Many of these complex variants involve additional chromosomes but all result in the creation of the *BCR::ABL1* fusion. Thus, 9q34.1 translocates to chromosome 22, thereby forming the *BCR::ABL1* fusion, but 22q11.2 translocates to a third chromosome with the third chromosome's contribution to this exchange translocated to chromosome 9. This case involves a third chromosome thereby creating a three-way complex translocation variant with translocation 46,XX,t(9;22;16)(q34;q11.2;q24) in a 40-year-old female with minimal prior medical history.

2. Case presentation and results

A 40-year-old female patient presented to optometrist clinic due to concerns for visual changes. During her eye exam, bilateral Roth spots were found leading to a referral to her primary care provider. At her primary care appointment, a complete blood count (CBC) was ordered due to no recent blood studies. Her hematologic values were: white blood cells 253.7 K/ul, red blood cells 3.43 M/ul, hemoglobin 10.0 g/dl, hematocrit 33.7%, and platelets 391 K/ul. A peripheral blood smear revealed leukocytosis due to neutrophils at different stages of maturation. The manual differential count found 7% blasts, 3% promyelocytes, 10% myelocytes, 5% metamyelocytes, 12% neutrophil bands, 50% segmented neutrophils, 3% eosinophils, 3% basophils, 5% lymphocytes, and 2% monocytes.

The bone marrow aspirate and biopsy showed hypercellular particles with increased amount of immature myeloid cells with relatively decreased erythroid precursors (Fig. 1). Flow cytometry identified a

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https://doi.org/10.1016/j.lrr.2022.100351
Received 18 July 2022; Accepted 19 September 2022
Available online 21 September 2022

small population of CD34, CD117, and dim CD45 positive blasts. The aberrant population of cells accounted for approximately 1% of the total events. Chromosome microarray analysis (CMA) did not detect genomic abnormalities. Fluorescent in situ hybridization (FISH) results were positive for *BCR::ABL1* fusion (Fig. 2), consistent with t(9;22) and negative for *FIP1L1::PDGFRA* fusion. Cytogenetic examination of peripheral blood cells revealed a three way translocation, t(9;22;16), in all cells examined [20] (Fig. 3). These results led to the diagnosis of CML.

Consequently, testing for *BCR::ABL1* (RT-PCR) identified co-expression of e13a2 and e14a2 *BCR::ABL1* fusion transcripts. The percentage of *BCR::ABL1* to *AB1L* transcripts was 75.66% by international standards.

PCR-based DNA sequencing of the *BCR::ABL1* fusion transcript was performed to detect mutations in codons 221 to 500 of the *ABL1* kinase domain, including codon 315. The sequencing results showed no definite mutation detected in the coding sequence of the *ABL1* kinase domain.

The patient's diagnosis was further categorized by placing her in the chronic phase of disease, which led to her initial treatment with cytoreductive hydrea before switching to dasatinib. Patient is three months since her diagnosis with no reported side effects from her medication and is following with oncology.

Following treatment quantitative testing for *BCR::ABL1* (RT-PCR) identified co-expression of e13a2 and e14a2 *BCR::ABL1* fusion transcripts. The percentage of *BCR::ABL1* to *ABL1* transcripts was 44.28% by international standards.

3. Methods

Eight-color flow cytometric analysis (BD FACS Canto II, San Jose, California) was performed on the peripheral blood, BD FACS Diva software (San Jose, California) according to standard procedures at the University of Texas Medical Branch. T-, B-, and myeloid lineage antigens were analyzed, using a comprehensive panel of monoclonal antibodies.

Probes specific for *BCR::ABL1* were used in FISH analysis (Abbott Molecular/Vysis and Cytocell) at the reference laboratory and MD Anderson Cancer Center on bone marrow biopsy.

Quantitative real time polymerase chain reaction (RT-PCR) was performed at The University of Texas MD Anderson Cancer Center.

Chromosomal microarray analysis (CMA) was performed using Affymetrix CytoScan HD microarray. This microarray and associated software (Chromosome Analysis Suite) are manufactured by Affymetrix (Santa Clara, CA) and used by University of Texas Medical Branch Molecular Diagnostics Laboratory (MDL) for the purpose of identifying DNA copy number gains and losses associated with large chromosomal imbalances.

The systemic literature search was performed via PubMed database with specific keywords: "Chronic Myelocytic Leukemia" and "t(9;22;16)(q34;q11.2;q24)," the search identified only one report of CML with t(9;22;16)(q34;q11.2;q24) involvement [2].

4. Discussion

The translocation between chromosomes 9 and 22 and creation of the Ph chromosome is key in the diagnosis of CML. However, the presence of the Ph chromosome alone is not specific for CML as it may be found in other malignancies, such as acute lymphoblastic leukemia, acute myeloid leukemia, or mixed-phenotype acute leukemia [1].

The Ph chromosome is significant because it contains the *BCR::ABL1* fusion. This gene leads to an increase in tyrosine kinase activity of the cell and ultimately disrupts regulation of the cell cycle. In addition to the disruption of the cell cycle, the fusion gene has been linked to the disruption of the function of white blood cells in the body, increasing the patient's susceptibility to infection [3].

The Ph chromosome is found in 90–95% of CML patients; however, 5–8% of CML patients have a complex variant that involves at least a third chromosome [1]. A consensus of the pathologic process leading to the creation of these Ph variants has yet to be reached. Two processes have been proposed.

The first is based on work by Morel et al and Emberger et al, which proposes that the complex variant occurs as a single event, with the simultaneous breaking of the chromosomal regions involved, followed by a mismatched rejoining of the broken ends [4,5]. This process is called concerted genomic rearrangement.

The second is based on work by Sessarego et al and Reedy and Sulcova which proposes that the complex variant occurs in a two-step process [6,7]. The first step includes the formation of the Ph chromosome as seen in the majority of cases followed by a second translocation event whereby a third chromosome swaps material with chromosome 9, thereby leaving the important *BCL-ABL1* fusion for propagation of symptoms associated with CML.

Other three-way complex CML variants have been reported in the literature, with prognosis ranging from good to poor, but no prognostic data currently exists in the literature for this patient's translocation variant [8].

Prognosis and treatment for CML are based largely on the phase of the disease at the time of diagnosis, with patients diagnosed in the chronic phase often presenting with fewer symptoms than those diagnosed in either accelerated or blast phases [9]. The patient in this study is in the chronic phase and is currently being treated with 50 mg dasatinib daily. Dasatinib is an orally designed adenosine triphosphate (ATP)-competitive protein tyrosine kinase inhibitor (TKI) with strong action against the BCR::ABL protein. Originally approved for use in the United States of America in 2006, dasatinib is included in

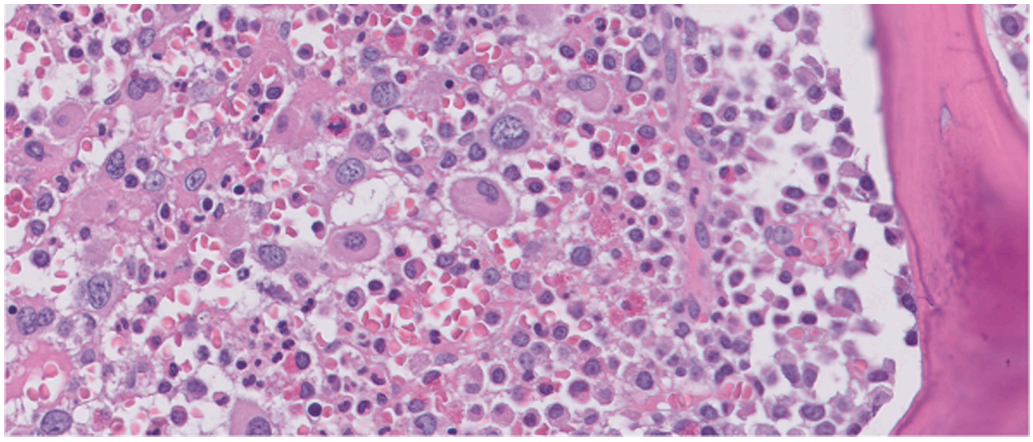

Fig. 1. Hypercellular bone marrow biopsy with increased myeloid/erythroid ratio.

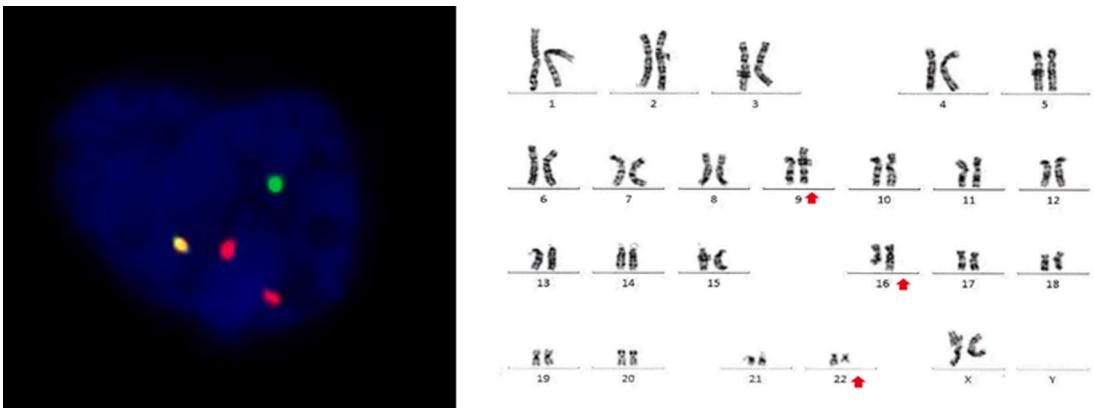

Fig. 2. (A) Fluorescence in situ hybridization was used for the detection of t(9;22)(q34;q11). (B) Cytogenetic analysis shows a complex variant three-way translocation 46,XX,t(9;22;16)(q34;q11.2;q24). Arrowheads designate all derivative chromosomes.

second-generation TKIs which overall produce faster and deeper responses than the first-generation TKI imatinib [10].

To conclude, this study reports a rare case of a CML patient, who presents with the *BCR::ABL1* fusion involving a complex three-way translocation variant 46,XX,t(9;22;16)(q34;q11.2;q24).

Role of the funding source

None.

Informed consent

The patient reported in the manuscript signed the informed consent/authorization for participation in research (MD Anderson Cancer Center protocol LAB01–473) which includes the permission to use data collected in future research projects. A copy of the signed consent is kept on file in the patient electronic records

Declaration of Competing Interest

The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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