CASE REPORT

Chronic Myeloid Leukemia with an Atypical b2a3 (e13a3) BCR::ABL1 Transcript: A Case Report

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ABSTRACT

Chronic Myeloid leukemia (CML) is a treatable disorder that is associated with an acquired cytogenetic abnormality resulting in reciprocal translocation between the long arm of chromosome 9 and 22, which generates the BCR::ABL1oncoprotein. In Classic CML, two transcript variants are seen, b2a2 & b3a2. This case study features a 23-year-old Asian female diagnosed with CML exhibiting the rare variant b2a3 (e13a3), which encodes the p203 protein. The diagnosis of this case remained consistent with CML after receiving the patient's complete medical history, peripheral smear findings, bone marrow biopsy, and Philadelphia-positive result on cytogenetics, but the identification of an unknown band on gel other than p210 by real-time PCR did not favor the results. Further molecular analysis was carried out by using the Seeplex BCR::ABL1kit by PCR, on which this infrequent variant b2a3 was detected. This unusual variant is significant because it lacks the a2 exon, which partially encodes the SH3 domain responsible for regulating the STAT pathway. Globally, as the number of these rare cases is escalating, it demands a need for quantitative analysis to measure the disease prognosis and outcome.

Keywords: *Chronic myeloid leukemia, atypical transcript, b2a3 (e13a3), P203 protein, imatinib.*

BACKGROUND

Chronic Myeloid Leukemia (CML) is a type of myeloproliferative disorder, which is identified by the presence of translocation (q34.1;q11.2) recognized as the hallmark of chronic myeloid leukemia, accountable for producing the Philadelphia Chromosome. The relocation of the ABL gene from chromosome 9q34.1 to the BCR gene on chromosome 22q11.2 develops the BCR::ABL1 fusion protein, which has a greater tyrosine kinase activity than the normal ABL gene [1-4]. Multiple variants of BCR::ABL1 fusion transcript have been reported in the literature. The most recurrent variants are b2a2 (e13a2) and b3a2 (e14a2), which encode the p210 protein and account for 95% of CML patients. An unusual variant of BCR-ABL1 is the b2a3 transcript, which occurs due to the fusion of major-BCR at exon 13 along with ABL at exon 3, *i.e.*, e13a3, which is responsible for encoding p203 protein [1, 5, 6]. Worldwide, only 16 cases of BCR-ABL1 with a b2a3 transcript (p203) have been reported, and it is generally anticipated that this rare variant has a better treatment outcome and a decreased mortality rate [2, 7-13].

CASE PRESENTATION

A 23-year-old Asian female with noticeable leukocytosis presented to NIBD Hospital Karachi. She had a history of recurrent fever, shortness of breath, and fatigue for the last 1 year; her history was insignificant. General examination revealed mild pallor. Abdominal examination demonstrated a massive spleen crossing the umbilicus with mild hepatomegaly. Haemogram showed a white blood cell (WBC) count of 41.70×10^9/L with blast cells 1%, absolute neutrophil count 36.06×10^9/L, as well as hemoglobin concentration of 4.1g/dl, and a platelet count of 140×10^9/L/L. Peripheral blood smear analysis indicated normochromic, anisocytosis, tear-drop cells, macrocytes, elliptocytes, polychromatic cells, leukoerythroblastic picture, and platelet anisocytosis. Patient's renal and liver profiles were normal, while LDH was 522U/L(the normal ranges are provided in Supplementary Table **S1**). A bone marrow biopsy was performed. Given marked leukocytosis and awaited reports of bone marrow biopsy and BCR::ABL1 (qualitative), cytoreduction therapy was started. She received one unit of packed red blood cells and oral iron repletion for profound anemia. Bone marrow aspirate illustrated relatively suppressed erythropoiesis, hyperplastic myelopoiesis showing a bimodal peak at the level of neutrophils and myelocytes. Megakaryocytes were exhibiting pleomorphism, and a few of them were dwarf megakaryocytes. Bone marrow trephine exhibited cellularity of 100% without any marrow fibrosis. The overall marrow findings of the patient were consistent with Chronic Myeloid leukemia in chronic phase. Cytogenetic analysis showed a translocation between chromosome 9q34.1 and 22q11.2 resulting in the Philadelphia chromosome, as shown in Fig. (**1**).

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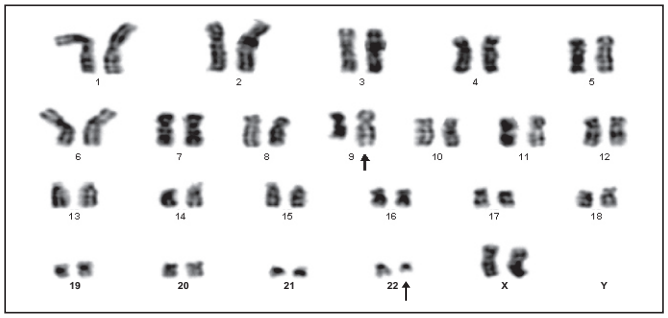

Fig. (1): 46XX,t(9;22)(q34;q11.2) [20]. 20 cells were counted all cells were positive for Philadelphia chromosome. All cells showed translocation between chromosome 9q34 and 11q11.2, resulting in Philadelphia chromosome.

For molecular analysis, a qualitative conventional PCR was requested for BCR-ABL1 translocation, but an unknown band was found on the gel (**Fig. 2**);

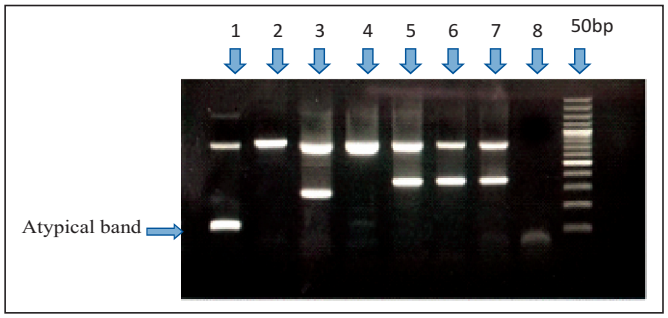

Fig. (2): Qualitative analysis of BCR-ABL transcripts on agarose gel by operating conventional PCR.Lane 1: It shows an atypical band appeared on 220 base pair indicating b2a3 variant of CML, lane 2: negative patient sample, lane 3: positive sample for p210 variant, lane 4: negative patient sample, lane 5: positive sample for p210 variant, lane 6: positive sample for p210 variant, lane 7: positive control sample, lane 8: negative control sample.

p210 and p190 showed a negative result. Therefore, a qualitative test was repeated on a different test by using Seeplex BCR-ABL1kit (Seegene, Korea), on which b2a3, a rare type of fusion transcript reported in <1% of CML cases, was revealed. The primers used for amplification are listed in Supplementary Table **S2**. After receiving cytoreduction therapy (hydroxyurea 1000 mg/day) for two weeks, the counts returned to normal, and the patient was advised to start imatinib 400 mg/day. After three months of administering imatinib therapy, we conducted a follow-up qualitative analysis using PCR for this rare variant, as quantitative analysis was not feasible. The result of the transcript test was negative after receiving treatment for 2.5 years. It is worth noting that the patient has responded well to treatment, as the clinical symptoms subsided with complete regression of the spleen and liver, and also achieved hematological remission. The unavailability of quantitative analysis for this infrequent variant precludes the documentation of deep molecular response. Nevertheless, the patient is undergoing assessments every three months to monitor molecular remission status, relying on negative results obtained through qualitative PCR.

DISCUSSION AND CONCLUSION

In the above case, we are delineating an infrequent variant b2a3 and its clinical significance in CML. The Philadelphia chromosome, obtained from the BCR::ABL1 fusion protein (p203), is responsible for encoding an active tyrosine kinase. The BCR gene is divided into 3 segments: minor-BCR, major-BCR, and micro-BCR from 3' to 5'. Frequently, 95% of cases of CML have p210 fusion protein arising from major-BCR breakpoint a2 through a11 of ABL1 protein (**Fig. 3**) [14, 15]. The first case of this rare atypical variant b2a3 (e13a3) was reported in 2003, and so far 16 cases have been reported [2, 5]. The usual ABL1 protein contains an SH3 domain that is followed by an SH2 domain, which is involved in the activation of pro-oncogenic pathways in this myeloproliferative neoplasm [16,17]. Absence of A2 in this atypical BCR-a3 variant makes it substantial.

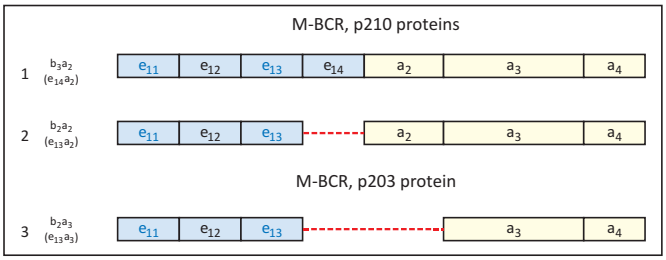

Fig. (3): Arrangement of BCR/ABL transcript associated with Chronic Myeloid Leukemia.

(1) Fusion of M-BCR at exon 14 along with ABL at exon 2 resulting in b3a2 transcript.
(2) Fusion of M-BCR at exon 13 along with ABL at exon 2 resulting in b2a2 transcript.
(3) Fusion of M-BCR at exon 13 along with ABL at exon 3 resulting in b2a3 transcript.

The a2 exon partly encodes the SH3 domain, which is a contributing factor to induce STAT activity that is associated with the regulation of proliferation and resistance to apoptosis [8, 11, 13]. Available data and *in vivo* studies suggest that the SH3 deletion, which may lead to reduced activation of STAT5 by BCR::ABL1 protein, demonstrates a delay in disease development and a good response to the tyrosine kinase inhibitor (TKI). Imatinib was the preferred TKI for treating this variant based on the available limited data. Furthermore, in previously reported cases, most individuals with the b2a3 (e13a3) transcript responded well to first-line tyrosine kinase inhibitor (TKI) therapy, particularly imatinib. Relying on this evidence, imatinib was favored as the treatment of choice for our patient, who also demonstrated a favorable response [2, 6-8, 11, 13, 14, 18]. Moreover, quantitative analysis for rare variants is currently not widely available in low- and middle-income countries, making it challenging to monitor disease progression and treatment response.

The increasing number of reported cases globally emphasizes the need for the development of kits in limited-resource settings that can quantify this infrequent variant [6, 13].

LIST OF ABBREVIATIONS

ABL: Abelson
BCR: Breakpoint Cluster Region
CML: Chronic Myeloid Leukemia
PCR: Polymerase Chain Reaction
STAT: Signal Transducers and Activators of Transcription

CONSENT FOR PUBLICATION

Informed consent was taken from the patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the journal's website.

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