

Minor p190 Fusion Transcript in CML- A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Author LN designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author FA performed the statistical analysis, wrote the protocol, critical revision of manuscript. Authors MM and RK managed the literature searches. Authors GSD, SSM and SJR helped in terms of technical support, supervision and clinical details respectively. All authors have read and approved the final manuscript.

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Case Report

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ABSTRACT

Objective: Detection of minor (p190) BCR-ABL fusion protein in a CML patients.

Case Report: A 26-year-old female presented with complaints of pain abdomen and episodes of vomiting. On examination her vitals were stable and there was moderate splenomegaly. The peripheral blood and bone marrow cytological features were consistent with myeloproliferative neoplasm. Fluorescent in situ hybridization (FISH) for BCR ABL was positive, with 87% of cells showing fusion transcript. However, Real Time Polymerase chain reaction (RT-PCR) for p210 BCR-ABL was found to be negative. In view of high morphologic index of suspicion for CML, further molecular analysis was carried out for BCR/ABL fusion transcript variants along with JAK2 V617F mutations.

Conclusion: The patient was found to be positive for BCR/ABL p190 e1a2 fusion transcript, while BCR/ABL p210 fusion transcript was negative.

Keywords: Minor (p190); BCR-ABL fusion transcript; chronic myeloid leukemia; real time polymerase chain reaction.

1. INTRODUCTION

Chronic myeloid leukemia (CML) is characterized by the Philadelphia (Ph) chromosome which exists in three principal forms (P190, P210, and P230) that arise from distinct breakpoints in the BCR gene on chromosome 22, resulting in translocation of BCR exon 1, exons 1–12/13, or exons 1–19, respectively, to the c-ABL gene on chromosome 9 [1]. The majority of patients (>90%) with CML express a 210-kDa BCR-ABL (t (9; 22) (q34;q11) protein, while patients with Ph⁺ ALL commonly express a 190-kDa BCR-ABL protein 9 [2]. Only a subgroup of patients with CML express 190 kDa BCR-ABL fusion protein and its presence indicates poor response to treatment [3]. We report a patient with CML expressing minor BCR ABL transcript (p190) due to its rarity and prognostic implications.

2. CASE REPORT

A 26-year-old female presented with complaints of pain abdomen and episodes of vomitings. On examination her vitals were stable and there was moderate splenomegaly. Laboratory investigations showed leukocytosis of $234 \times 10^9/L$, hemoglobin (Hb) level of 10.7g/dL and platelet count of $2.25 \times 10^9/L$. Bone marrow evaluation showed promyelocytes (03%), myelocytes (13%), metamyelocytes (09%), eosinophils (08%), basophils (12%), blasts (06%), neutrophils (43%) and lymphocytes (03%) (Fig. 1). The peripheral blood and bone marrow cytological features were consistent with myeloproliferative neoplasm. Cytogenetic analysis failed due to non availability of analyzable metaphases. Fluorescent in situ hybridization (FISH) for BCR ABL was positive, with 87% of cells showing fusion transcript

(Fig. 2). However, Real Time Polymerase chain reaction (RT-PCR) for p210 BCR-ABL was found to be negative. In view of high morphologic index of suspicion for CML, further molecular analysis was carried out for BCR/ABL fusion transcript variants along with JAK2 V617F mutations (GeneLab). The patient was found to be positive for BCR/ABL p190 e1a2 fusion transcript, while BCR/ABL p210 fusion transcript was negative. The Jak2V617F mutation analysis was also tested negative (Table 1).

Transcript expression load for BCR-ABL p190 e1a2 (m-bcr) was found to be 63.4% by quantitative RT-PCR. She was started on Veenat 400 mg/day. On follow-up at 3 months, her copy number for the e1a2 transcript by qRT-PCR (Genelab) was found to be 15.44%. The dosage of Veenat was escalated to 600mg/day. At 6 months follow-up her e1a2 transcript load decreased to 6.5% estimated by qRT-PCR (Genelab), continued on treatment with same dosage. There was reduction in transcript load at 9 months follow-up with 3.72% of p190 e1a2 transcript levels. She was evaluated for imatinib resistance (Oncquest) and the results were positive for E255V in P-loop of ABL1 kinase domain of BCR/ABL1 transcript.

3. DISCUSSION

Majority of CML patients express 210-kDa BCR-ABL (t (9; 22) (q34;q11) protein and minor transcript positivity is rare. In our institute, which is a tertiary care cancer center, minor transcript constituted 1.78% (1/56) of newly diagnosed CML patients tested by Real Time PCR. This finding was in agreement with the reported frequency in literature [3-8].

Table 1. Chromosomal alterations for t (9;22) in Chronic myeloid leukemia and Jak2 Mutation

No.	Chromosomal alteration	Genes involved	Fusion gene	Result
1	t(9;22)(q34;q11)	MAJOR (p210) BCR(22q11) and ABL (9q34)	b2a2	Not detected
			b2a3	Not detected
			b3a2	Not detected
			b3a3	Not detected
2	t(9;22)(q34;q11)	MINOR (p190) BCR(22q11) and ABL (9q34)	e1a2	Detected
			e1a3	Not detected
3	t(9;22)(q34;q11)	MICRO (p230) BCR(22q11) and ABL (9q34)	e19a2	Not detected
			Jak2	V617F

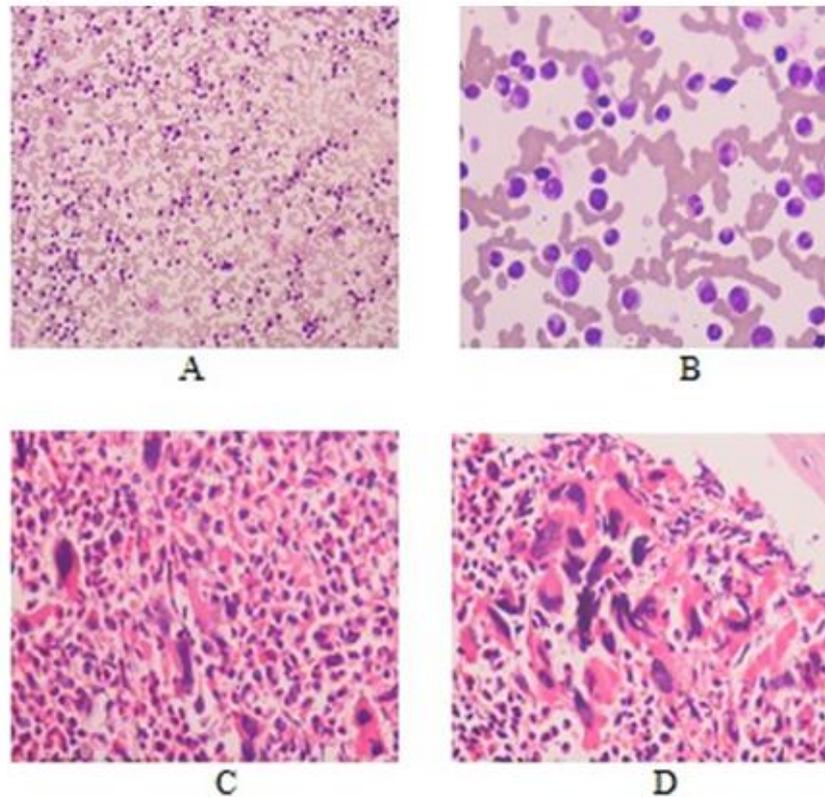


Fig. 1. A - Peripheral smear showing overwhelming leukocytosis (Leishman 4X); B - Peripheral smear showing shift to left and basophilia (Leishman 40X); C - Bone marrow biopsy: Myeloid hyperplasia(H&E stain 40X); D - Bone marrow biopsy: Focal clustering of megakaryocytes (H&E 40X)

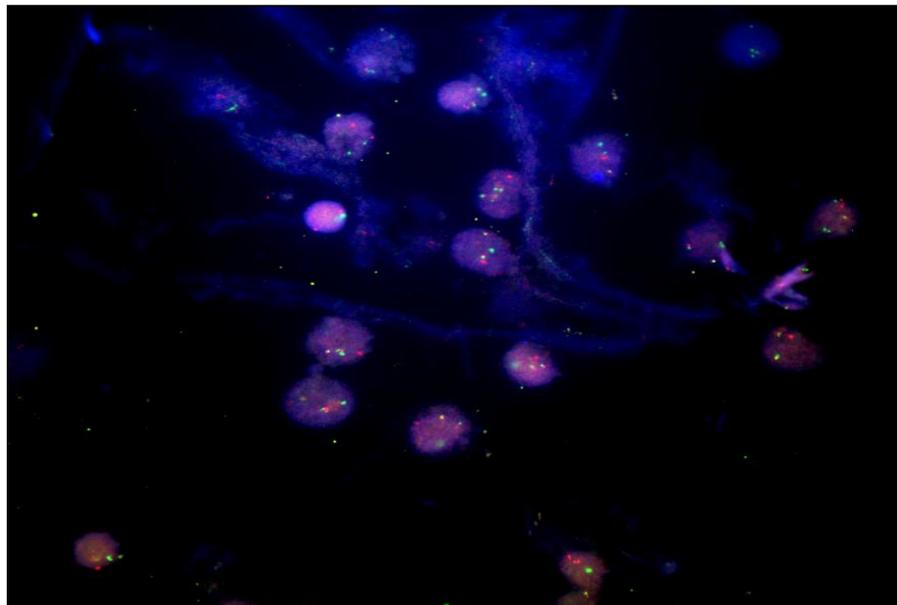


Fig. 2. ZytoLight® SPEC BCR/ABL1 Dual Color Dual Fusion Probes were used for detection of BCR-ABL 1 rearrangements. Bone marrow biopsy tissue section with translocation affecting the BCR/ABL1 loci as indicated by one separate orange signal, one separate green signal and two orange/green fusion signals

In translocation of t(9;22), ABL part in the chimeric protein is constant while the BCR portion varies greatly, resulting in different sizes of the BCR sequence, hence it is not only a reflection of the site of breakage but may also be a result of alternative splicing [9]. Blast phenotype can be predicted by BCR-ABL transcript type and levels in association with pattern of secondary genetic changes. CML or B cell acute lymphoblastic leukemia can arise from p210 and p190 based on transduction of stem cells or progenitor cells, supported by *in vivo* studies. Higher frequency of p190 in acute lymphoblastic leukemia might be due to BCR intron 1 breaks formed by a lymphoid specific mechanism, so its rare in CML. Genomic breakpoints in p190 and p210 BCR-ABL indicate distinct mechanisms of action [10,11].

E255V in P-loop of ABL1 kinase domain of BCR/ABL1 transcript being positive in our patient is a clinically relevant mutation and has been previously reported in patients who develop resistance to imatinib mesylate [12]. Poor prognosis of CML patients expressing minor BCR ABL transcript, with survival ranging from 3 months to 9 years was reported [13]. Treatment with imatinib, as frontline therapy, achieved complete hematological response showing no molecular remission in our patient similar to other studies [3,5,6,14]. In contrast Radojkovic et al., reported response to imatinib treatment in a patient with Philadelphia negative, p190 BCR-ABL positive CML [15].

A higher number of patients need to be evaluated along with the monitoring of response to tyrosine kinase inhibitors with high end techniques and understand the resistance to therapy, to determine the prognostic significance.

4. CONCLUSION

In CML patients BCR-ABL t(9;22) translocations variants need to be tested, as these variants would help in quantitative analysis at follow up. The rare variants would aid in determining the prognostic significance, as the presence of p190 BCR ABL indicates resistance to imatinib therapy.

CONSENT

As per international standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was approved by the institutional ethics committee (EC Reference No: IEC/2019/162).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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