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Identification of Additional Cytogenetic Abnormalities in Chronic Myeloid Leukemia Cases with t (9;22) Chromosome Translocations

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ABSTRACT

Objective: The objective of this study is to detect additional simple and complex variant translocations with t(9;22) in chronic myeloid leukemia patients.

Methodology: This retrospective cross-sectional study was conducted at the hem-oncology department of Dr. Ruth K. M. Pfau Hospital in Karachi. It comprised data from patients between 2015 and 2023. Criteria for the study involved patients diagnosed with CML through blood count, bone marrow biopsy, and cytogenetic or molecular biology, showing additional chromosomal abnormalities, whether they are inpatients or outpatients of chronic myeloid leukemia.

Results: A total of 88 patients were Philadelphia-positive CML, out of which 53 (60.2%) were males & 35 (39.7%) were females. The mean age was 48 yrs ± 11.43. The group of 9 (10.2%) patients who harbor these complex variant translocations are comprised of 4 males and 5 females; the age range of these patients at diagnosis is from 32 to 66 yrs. All the patients were in the chronic phase at presentation. Chromosomal study in CML patients reveals 9 variant translocations with t(9;22)(q34;q11). These three-way variant defects/translocations were observed as 1p13, 1q21, 1p22, 2q31, 3q21, 3p21, 11q13, 15q24, and Xp11.2.

Conclusion: In our study, 9 patients had complex variants of t (9;22). These complex variants at diagnosis and during the TKI treatment may announce treatment failure and/or transformation into an advanced stage (accelerated or blast).

Keywords: Philadelphia chromosome**,** Three-way variant translocations, t(9;22)(q34;q11)

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [3,4]Critical analysis and manuscript review; [3,4]Data analysis; Manuscript Editing.

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Introduction

Chronic myelogenous leukemia (CML) is the most frequently observed clonal disorder among myeloid disorders. It is characterized by abnormal myeloid proliferation, with all stages of maturation and differentiation visible on the smears of blood and marrow smears. The hallmark of diagnosis in CML is the Philadelphia chromosome. Philadelphia chromosome is formed with fusion by chromosome translocation which is known as the BCR-ABL fusion protein involving chromosomes 9 &22. This abnormal fusion protein causes tyrosine kinase activation, this activation leading to the abnormal increased growth of all stages of myeloid cell

lineage.[1,2] Most of the cases of CML harbour the Philadelphia chromosome. According to previously reported literature t(9;22) is reported in >90% of CML subjects, but around 5-10% of cases of CML may express the variant translocations, either simple or complex, involving the different breakpoints along with 9q34 and 22q11.[3-5]

The fusion protein BCR-ABL1 encodes the tyrosine kinase receptors and responsible for abnormal and increased proliferation of myeloid lineage cells, and this fusion protein also causes inadequate differentiation and decreased apoptosis.[7] The targeted therapy of tyrosine kinase inhibitors can decrease BCR-ABL1 abnormal activity and can decrease the progression of disease into blast phase and is also beneficial in the better outcome of the patient.

WHO classified the CML into 3 phases according to clinical and laboratory criteria. These phases are divided into 3 phases, including chronic, accelerated, and blast phases.[6] Most of the patient of CML at the time of presentation, diagnosed in the chronic phase. Patient with blast phase of CML, mostly associated with worse outcome and needs to be monitored with deep molecular response. When patients present with 1-19% blasts and marked basophilia, those patients are in accelerated phase. Some CML patients present with >20% blast in the peripheral smear or on bone marrow aspirate, and they are diagnosed as a blast crisis. In some cases of CML, patient may present with denovo blast phase at presentation without an accelerated phase of CML. Blast phase (de novo) may present as a case of acute leukemia as a separate clinical diagnosis and these cases may be resistant to conventional therapy. In the tyrosine kinase inhibitors era, chronic phase of CML transformation into blast phase has markedly decreased around 1-2%/year. In some studies, data showed frequency of additional cytogenetic alterations increases from less than 5% in chronic phase to 30% in accelerated and up to 80% in blast crisis.[8]

The Original ACAs are defined as trisomy 8, additional Ph translocation, Isochromosome 17q, and trisomy 19. Additional high-risk Cytogenetic lesions, including trisomy 21, 3q26.2, monosomy 7/7q-, 11q23, and a complex karyotype

The best-known additional chromosomal abnormalities include trisomy 8, double Philadelphia chromosomes and loss of tumour suppressor gene (p53).[9]These additional chromosomal translocations or cytogenetic aberrations may affect the different phases of CML. There is also a some role of Additional cytogenetic abnormalities (ACAs), such as major changes are trisomy 8, trisomy 19, double ph chromosome, and isochromsome 17q and minor abnormalities including numerical abnormalities (–7, –17, 117, 121, and –Y) and structural aberration t(3;21)(q26;q22)) may have negative impact on survival.[10] In some advanced cases of CML with myeloid phenotype may harbor the mutations in ASXL1, TET2, IDH and CBL family, may be associated with aggressive behavior of the disease.

Objectives

1. To identify and characterize additional cytogenetic abnormalities present in Chronic Myeloid Leukemia (CML) patients with the t(9;22)(q34;q11)
2. To determine the frequency and spectrum of secondary chromosomal abnormalities accompanying t(9;22)
3. To evaluate the clinical significance of additional cytogenetic abnormalities**,** including their association with disease progression and treatment response

Methodology

This cross-sectional observational study was conducted at the Department of Hematology/Oncology, Dr. Ruth KM Pfau Civil Hospital, Karachi, utilizing data from patients treated between January 1, 2015, and December 31, 2023. The study included patients with a confirmed diagnosis of chronic myeloid leukemia (CML) based on blood count, bone marrow biopsy, and

cytogenetic or molecular analysis demonstrating the presence of the Philadelphia chromosome (t(9;22)). Only de novo CML cases were included, while relapse cases were excluded. For cytogenetic evaluation, bone marrow aspirate samples underwent unstimulated culture for 24 hours. Chromosomal abnormalities were classified according to the International System of Human Cytogenetic Nomenclature (ISCN 2005), which facilitated the identification of both simple and complex numerical and structural aberrations.

Ethical approval was obtained from the Ethical Board of Dow University of Health Sciences (IRB-3614/DUHS/EXEMPTION/2024/257), and informed consent was secured from all participants

Results

Among the all CML (88) patients of with Philadelphia-positive CML, male female ratio was 1.5:1, as shown in Figure 1. The mean age was 48 yrs±11.43. The group of 9 (10.2%) patients who harbor these complex variant translocations including 1p13, 1q21, 1p22, 2q31, 3q21, 3p21, 11q13, 15q24, and Xp11.2, this group consisted of 5 females and 4 males, the age of these patients at diagnosis ranged of these patients from 32 to 66 years.

Table I: The karyotype at diagnosis.

SNO.	AGE (yrs.)	Sex	Karyotype at diagnosis (complex variants)
1	53	F	46XX, t(1;9;22)
2	38	F	46XX, t(9;22;15)
3	48	F	46XX, t(1;9;22)
4	33	F	46XX, t(2;9;22)
5	43	F	46XX, t(X;9;22), 48X, +8, t(X;9;22), +19
6	66	M	46XY, t(1;9;22)
7	43	M	46XY, t(3;9;22)
8	32	M	46XY, t(3;9;22)
9	56	M	46XY, t(9;11;22), del(12)

Table II: The phases at diagnosis and treatment and follow-up

Age/sex	WBCs	Platelet	Blast	Phase at diagnosis	Treatment	Follow up after 1 year
53/F	213	355	2	Chronic	Hydroxyurea Imatinib	Alive
38/F	110	300	1	Chronic	Nilotinib	Alive
43/F	255	172	2	Chronic	Hydroxyurea Imatinib	Alive
33/F	125	178	0	Chronic	Imatinib	Loss of follow-up
43/F	250	457	2	Chronic	Imatinib	Alive
66/M	103	250	0	Chronic	Imatinib	Passed Away within 5 months
43/M	115	200	2	Chronic	Hydroxyurea Imatinib	Alive
32/M	350	525	3	Chronic	Imatinib	Alive
56/M	371	352	0	Chronic	Imatinib	Alive

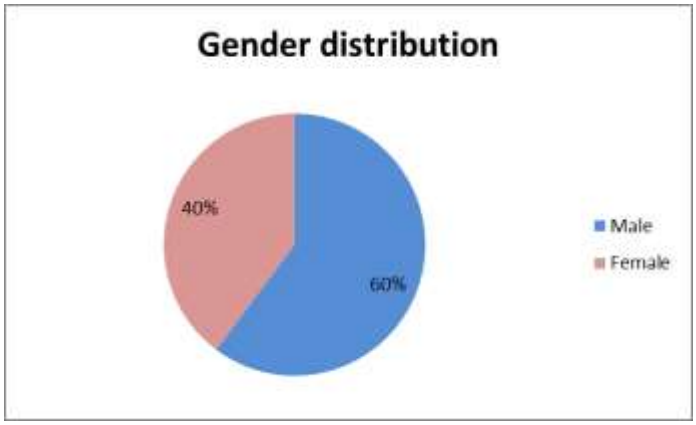

Figure 1: Gender distribution.

All the patients who acquire the complex variant are in the chronic stage of chronic myeloid leukemia at the initial presentation.

The cytogenetic analysis identified three-way variant translocations involving an additional chromosome along with t(9;22) (q34;q11). Table 1 summarizes the data on variant translocations

involving chromosomes 1p13, 1q21, 1p22, 2q31, 3q21, 3p21, 11q13, 15q24, and Xp11.2 observed in nine patients. In this study, two patients, labeled as 5 and 9 in Table I, exhibited additional chromosomal abnormalities along with complex variant translocations. Patient 5 displayed an abnormality on the X chromosome, while patient 9 had a numerical abnormality involving chromosome 12. Table II presents the available treatment options, including imatinib, nilotinib, interferon-α, and hydroxyurea.

Discussion

The role of additional cytogenetic abnormalities (ACAs) in defining accelerated phase of CML is still a matter of debate and one study showed prognosis with single changes (+8, +Ph) is controversial.[12] In our study, 9 (10%) patients, additional cytogenetic abnormalities at baseline were detected, aligning with previously reported local data.[1] A study from Pakistan reported ACAs in 2.2% of patients at diagnosis.[14] In contrast , studies from Italy and Romanian found ACAs in 5% of patients at diagnosis.[15] Another study from Taiwan reported ACAs in higher number of patients which was around 10.7%.[16] In current research, we reported nine CML patients acquiring the variant cytogenetic abnormalities involving breakpoints of many chromosomes by karyotyping analysis. Each case contains classical Ph chromosome t (9;22) bcr-abl fusion protein. These 9 patients acquire another chromosome in each of these complex variants. The Philadelphia chromosome or t(9;22) is found in the majority of CML patients (>90%), though roughly 5%have variant translocation in which third chromosome is also involved. Kockerols et al.[17] observed that high-risk ACAs at diagnosis were associated with poor response to treatment, an increased chances of disease progression to blast crisis. A study involving 210 patients from the TIDEL-II trial who were treated with imatinib as first-line therapy revealed through multivariable analysis that the simultaneous presence of additional genetic abnormalities can led to lower molecular response rates and increase treatment failure rates.[18] Within this observational study, we reported 9 patients with CML carrying complicated Ph1 translocations related to numerous associate chromosomes by way of cytogenetic evaluation. The involvement of the third chromosome in these complex translocations is in Ph-positive CML cases. However, reporting the spectrum of cases with these complex translocations is challenging due to considerable variability in cytogenetic nomenclature prior to ISCN guidelines 2005. The clinical and prognostic implications of these variant translocation continue to be debated in the previous case reports. Previous studies indicate similar outcomes between patients with complex variant translocation and those with classical ph chromosomes when treated with imatinib mesylate [19]The literature review found that the studied translocation is a rare rearrangement, sixteen cases related to chromosome X have been defined to date. Moreover, it does not offer enough information to permit drawing definitive conclusions in the analysis of sufferers with variant translocations concerning the X chromosome. The clinical significance of variant Philadelphia chromosomes remains controversial. Some previous studies have suggested that the presence of additional cytogenetic abnormalities may be associated with worse prognosis; however, the European Leukemia Net recommendations do not provide specific guidelines for patients harboring additional variant translocations.[20]

Conclusion

In conclusion, we identified a low frequency complex variant involving t(9;22) translocations, accounting for approximately 10% of CML cases diagnosed at our department over the seven years. Early detection of these cytogenetic abnormalities may therefore assist in optimizing therapeutic strategies.

Limitations: A potential limitation of this study is selection bias, as conventional methods were applied only to a subset of samples. We need to do large sample-size studies in the future. Despite the limited sample size, our experience suggests that patients harboring complex Philadelphia chromosome translocations do not exhibit significant differences in hematological or clinical characteristic compared with those carrying the classical translocation.

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