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**Case Report**

# Rare Coexistence of Inv(16) and T(9;22) in Patient with Chronic Myeloid Leukaemia Presenting as Blast Crisis

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## Abstract

Chronic myeloid leukemia (CML) is associated with BCR-ABL1 fusion gene located on chromosome 22 as a result of a t(9;22)(q34;q11.2) translocation in about 90% of the patients. Also, coexistence of the t(9;22) and inv(16) chromosomal aberrations is a rare occurrence that has been described in CML (mainly the myeloid blast phase [CML-BP]), de novo AML, and a few cases of therapy-related AML (t-AML). We describe a 22 years old male in primary blast crisis of CML as initial presentation with coexistence of the t(9;22) and inv(16). Majority of cases, in which these abnormalities coexist are CML-BP, which is typically characterized by an aggressive clinical course rapid disease progression and resistance to chemotherapy.

**Keywords:** ***CML, inv(16), blast crisis, t(9;22), leukaemia***

## Introduction

Chromosomal abnormalities, such as inv(16)(p13q22) and its variant-t(16;16)(p13;q22), in acute myeloid leukemia (AML) is considered to be commo as it can occur in about 10%-12% of all AML cases [1]. The BCR/ABL1 rearrangement, created by t(9;22)(q34;q11.2), is highly associated with chronic myelogenous leukemia (CML) and to lesser extend in precursor lymphoid neoplasm and AML.. Coexistence of the inv(16) and t(9;22) chromosomal aberrations is uncommon occurrence that has been reported in CML (mainly the myeloid blast phase [CML-BP]), de novo AML, and some cases of therapy-related AML (t-AML) [2]. Few cases have been reported in literature with coexistence of inv(16) and t(9;22). Majority of the cases, in which these two abnormalities coexist are CML-BP, which is known to have aggressive clinical course with fast disease progression and reported resistance to multiple chemotherapy regimens [3].

## Case report

A previously healthy 22 years old Asian male, presented to the emergency department with headache, generalized abdominal pain, intermittent fever, fatigue and malaise for few days. It was associated with significant weight loss more than 12 Kilograms in few months, night sweats and lower back pain. Upon evaluation, the patient had a temperature of 36.2 Celsius, pulse of 74 beats/minutes, respiratory rate of 18 breath/minutes, blood pressure of 109/72 mmHg, pulse oximetry showed 99% saturation on room air. Physical examination revealed hepatosplenomegaly and was negative for lymphadenopathy. Initial laboratory data was significant for hyperleukocytosis with WBC (White Blood Cells) count of 570.11 × 10^9/ L, monocytosis of 43.80 × 10^9/ L , eosinophilia of 18.85 × 10^9/ L , blast of 53% (273.36 x10^9/ L), platelets of 219 x10^9/ L, and haemoglobin of 69 g/L. Abdominal Computed Tomography scan showed massive splenomegaly with the spleen extending up to the upper pelvis with a craniocaudal dimension of 32 cm, moderate hepatomegaly with a craniocaudal length of about 24.6 cm, and skeletal sclerosis. Patient was admitted to haematology ward and underwent urgent daily leukocytapheresis for three days.

Subsequent bone marrow biopsy was markedly hypercellular with overall cellularity of 100%. The normal marrow elements were replaced by sheets of myeloid cells (myeloperoxidase positive), a subset of which show CD117 and CD34 expression (~20%). Also, there was scattered normal appearing and small hypolobated megakaryocytes are which made prominent by Factor VIII immunostaining and scattered small mature lymphocytes mostly CD3+ T cells and a small population of CD20+ B cells. CD68 immunostaining highlights scattered monocytes. Lymphoid aggregates, granulomata, and cells foreign to the bone marrow are absent. Reticulin stain shows no increase in reticulin meshwork. (**Figure 1**)

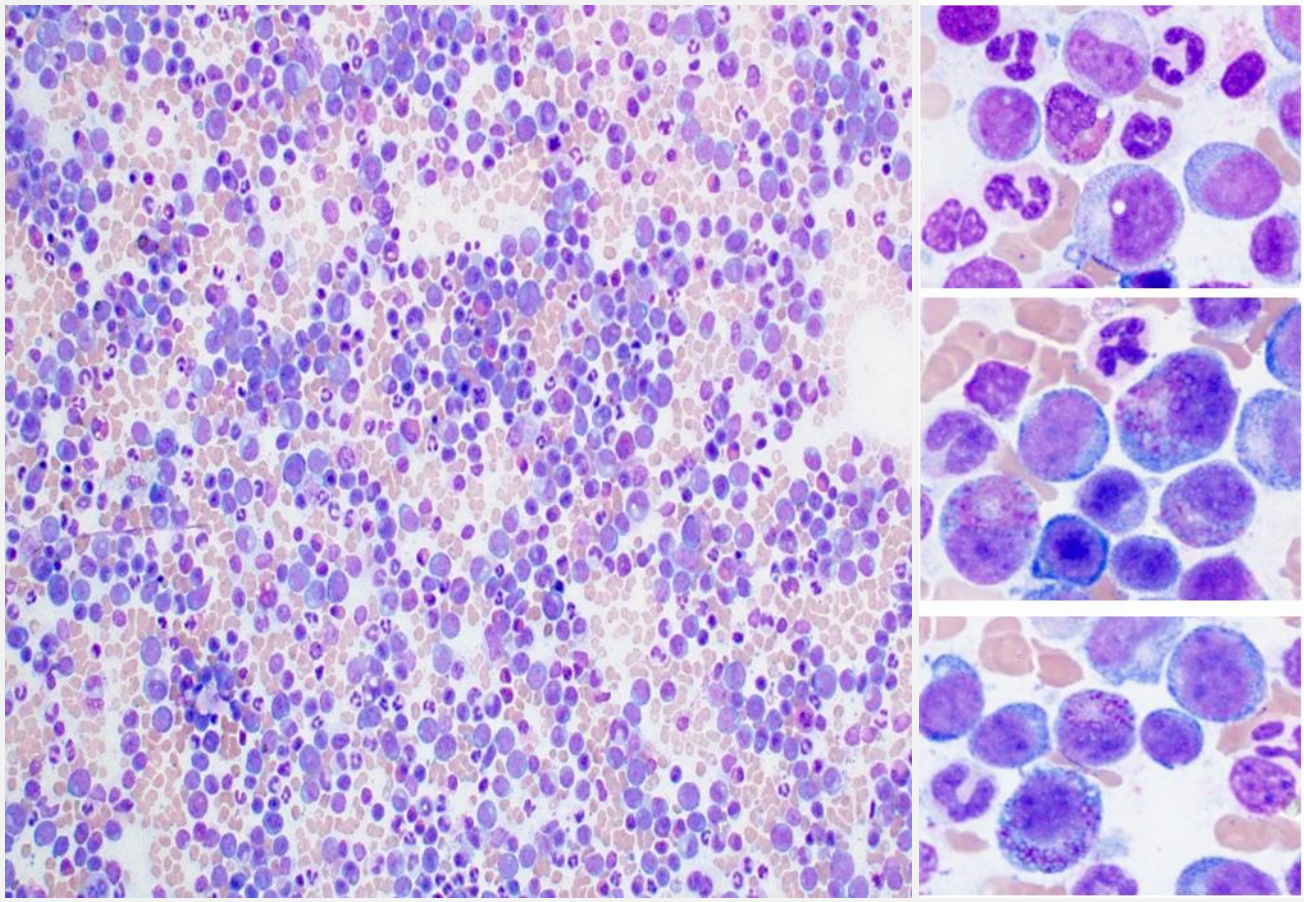

**Figure 1: Chronic myeloid leukemia, blast phase (Wright-Giemsa stained bone marrow aspirate smear, 200X magnification). Eosinophils and their precursors with basophilic granules are apparent (insets; 1000X magnification).**

Bone marrow flow showed approximately 26% CD34-positive cells that are positive for MPO, CD13, CD33, CD36 (partial), CD38, CD64 (partial), CD117, CD123, and HLA-DR. Monocytes account for 30% of the events, a small lymphocyte population (1.4%) is present and comprised mostly of T cells.

Peripheral blood analysis for BCR-ABL1 by PCR (Polymerase chain reaction) revealed the presence of e13/14a2 (p210) transcript at >10%, and absence of e1a2 (p190). Bone marrow FISH (Fluorescent in situ hybridization) analysis showed inv(16)(p13;q22) - CBFB::MYH11 and t(9;22)(q34;q11) - BCR::ABL1 fusion in blast cells. NGS (Next Generation Study) didn't show further pathological gene alteration and karyotyping unfortunately was failed.

Based on the immunomorphological study, FISH (Fluorescent in situ hybridization) analysis, cytogenetics, and molecular analyses of the specimens, the diagnosis of chronic myeloid leukemia in severe primary myeloid blast crisis (CML BC) was made.

## Discussion

The coexistence of inv(16) and t(9;22) is rare in hematological malignancies. There were few reported cases in which both of these cytogenetic abnormalities had a CML phenotype. Although the prevalence of both cytogenetic abnormalities coexistence has not been evaluated fully yet, only one previous study has shown that AML with the occurrence of inv(16) with t(9;22) is below 1%. [2].

We describe a case of a rare occurrence with coexistence of t(9;22 )and inv(16) in chronic myeloid leukaemia. This study noted a CML patient with inv(16) who showed a small fraction of rearranged clone involving CBFB/MYH11 in comparison to the rearrangmenet of BCR/ABL1. In this case, the blasts were of myeloid lineage and peripheral blood showed monocytosis and abnormal eosinophils. According to several previous reported cases, showed that CML with inv(16) is usually observed during the plastic phase and had an aggressive disease course. The expected period of progression in CML chronic phase to the advanced stage ranged between 3 - 5 years. On the other hand, the occurrence of the inv(16) and the beginning of the blastic phase seem to be evident at the early course of the disease among CML patients [3].

Upon literature review, Eunhee et al. reported 7 cases of CML with the coexistence of cytogenetic abnormalities [2]. Yaping Wu et al. reported 5 cases of chronic myelogenous leukemia (CML) and 1 case of acute myeloid leukemia (AML) with inv(16) and t(9;22) coexistence. 4 out of 5 patient with CML had a rapid transformation to myeloid accelerated phase of blast crisis [4]. Carlos et al. have also previously reported rare chromosomal aberration of Coexistence of inv(16) and t(9;22) in a 13 year old male which is very rare [5].

In this case, patient was started on AML (Acute Myeloid Leukemia) induction chemotherapy with 7+3 protocol plus TKI (Tyrosine Kinase Inhibitor) with Dasatinib for three days then switched to Ponatinib aiming toward complete remission to proceed with allogenic stem cell transplantation. The results show that patients with CML in blastic phase have a better clinical courses in this era of therapy.

## Conclusion and recommendation

Despite the era of bone marrow transplant and tyrosine kinase inhibitors, patients with coexistence of inv(16) and t(9;22) in chronic myeloid leukaemia usually have poor prognosis. We are reporting this case to raise awareness among physicians about this rare occurrence of and its highly aggressive nature and unfavourable prognosis. Further studies need to be done in this specific subgroup of patients and continued monitoring of disease course is of value.

## Ethics approval and consent to participate

Consent was obtained or waived by all participants in this study.

## List of abbreviations

CML: Chronic myeloid leukaemia
AML: Acute myeloid leukaemia
BP: Blastic Phase
FISH: Fluorescent in situ hybridization
TKI: Tyrosine Kinase Inhibitor
PCR: Polymerase chain reaction

## Data Availability

Not applicable

## Conflicts of Interest

The authors declare that they have no conflict of interests.

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## Authors' contributions

Aymen Abbas contributed in introduction, case presentation, consent and literature review.
Mutaz Kalas contributed in the discussion, citation, reviewing, creating tables and figures.
Emadullah Raidullah contributed in the abstract, conclusion and helped editing the article.

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Not applicable

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