Case Report

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A rare presentation of chronic myeloid leukemia blast crisis

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Abstract:

Chronic myeloid leukemia (CML), as the name suggests, is a chronic disorder in which granulocytes undergo dysregulated production and uncontrolled proliferation. Majority of CML patients present during the chronic phase (CP) of the disease. The interval from CP to onset of blastic transformation and acute leukemia can vary from days to several years. The biological basis of blast phase is poorly understood. Most common blast crisis is myeloid type and less frequently lymphoid or promyelocytic. The transformation of CML to promyelocytic blast crisis is a rare form. These findings suggest that BCR-ABL1 gene arises from leukemic stem cell (LSC) which is still not committed to myeloid or lymphoid differentiation. The blastic clone may originate either at the multipotent LSC or at committed leukemia progenitor cell. Here, we report a case of promyelocytic blast crisis with t(15;17) in addition to t(9;22).

Keywords:

Acute promyelocytic leukemia, BCR/ABL, chronic myeloid leukemia, imatinib, PML/RARa

Introduction

Chronic myeloid leukemia (CML) is a clonal disorder of pluripotent hematopoietic stem cell characterized by dysregulated and uncontrolled proliferation of myeloid series. It shows chromosomal translocation t(9,22) that is Philadelphia (Ph) chromosome. In CML, >90% of cases are characterized by the presence of Ph chromosome, which is due to fusion of two genes, *BCR* (on chromosome 22) and *ABL1* (on chromosome 9) resulting in the *BCR-ABL1* fusion gene.[1,2]

The annual incidence of CML was reported to be 0.8–2.2/100,000 Indian population. A study was conducted by the Mumbai Cancer Registry which reported an age-adjusted rate (AAR; per 100,000) of 0.71 in males and 0.53 in females.[3] The study showed that incidence is high in older individuals, which is like West. CML is a rare phenotype in children.[4] More than 90% of CML patients are diagnosed when the disease is in chronic phase (CP) that is early phase of the disease. The interval from CP to onset of blastic transformation (BT) and acute leukemia can vary from days to several years.[4] CML blast crisis can be classified as myeloid, lymphoid, or mixed (myeloid and lymphoid) based on the immunophenotype.[5]

The transformation of CML to promyelocytic blast crisis is a rare entity. The morphology and immunophenotype of these cells are like those seen in acute promyelocytic leukemia (APML).

Case Report

A 58-year-old gentleman visited the hematology section with complaints of generalized rashes and oral bleeding for 2 days. He was diagnosed with CML-CP since June 2018 and was administered

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Imatinib mesylate for 6 months. The reverse transcriptase-polymerase chain reaction (RT-PCR) ratio for *BCR/ABL* in blood was 15% at 5 months with complete hematological response. At 6 months, the patient developed oral bleeding and generalized petechial rashes for which he was admitted to the hospital. Based on his clinical presentation, possibility of CML in blast crisis was considered. In addition to it, drug-induced cytopenia was considered as another possible differential. Complete blood count showed Hb of 10 g/dl (13–15 g/dl), platelet count of 4000 (1.50–400,000), and total count of 3700 (4000–11,000/mm^3). The patient had evidence of coagulopathy in the form of low fibrinogen levels and increased prothrombin time (PT), activated partial thromboplastin time and INR at the time of diagnosis. Bone marrow aspiration/biopsy was done to rule out transformation; it revealed cellular marrow with the presence of abnormal promyelocytes, binucleate forms, and buttock-shaped cells with hypergranular cytoplasm. Myeloperoxidase (MPO) by cytochemistry was strongly positive. Bone marrow biopsy also showed acute leukemia with myeloid differentiation. Hence, APML was suspected, and the patient was initiated on all trans retinoic acid (ATRA) followed by arsenic trioxide.

Marrow sample was subjected to immunophenotypic study, in which more than 70% of them were blasts/abnormal promyelocytes which showed positivity for immunophenotypic markers CD13, CD33, CD117, and MPO and negative for CD34, HLA-DR, CD45, and CD15 expression [Figure 1]. FISH revealed *PML/RARA* fusion in100% of cells [Figure 2], and RT-PCR showed *BCR-ABL1* major transcript. Karyotyping showed coexistent t (9;22) and t (15;17). This is consistent with CML with APML. The inv (7) was also seen which is a secondary abnormality [Figure 3].

A diagnosis of chronic myelocytic leukemia with promyelocytic BT was made. Imatinib resistance mutation gene analysis was done which was negative. Subsequently, he developed increasing WBC count with deranged coagulation parameters (increased PT, PTT, and INR) with hypofibrinogemia. He was supported with FFP, cryoprecipitate, and platelets; but subsequently, his course was complicated by hypotension warranting intensive care unit (ICU) support. In ICU, he developed differentiation syndrome, culture-negative sepsis, coagulopathy, subacute intestinal obstruction, and dyselectrolytemia. He is still hemodynamically unstable, requiring oxygen support with deranged coagulation parameters. He had a bad clinical course during the hospital stay.

Discussion

CML is a clonal stem cell disorder characterized by uncontrolled and dysregulated proliferation of granulocytes. The symptoms during presentation include weakness, loss of weight, anemia, and splenomegaly; but most of the times, more than 50% of patients are asymptomatic and are diagnosed on routine blood tests performed. Most of the CML patients are diagnosed during the early phase known as the CP.[4]

Most of the CML cases have the characteristic t(9,22) that is Philadelphia (Ph) chromosome. This reciprocal translocation juxtaposes the c-abl oncogene 1 (ABL1) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22, generating the BCR-ABL1 fusion oncogene. The phenomenon of acquisition of the Ph chromosome harboring the BCR-ABL1 oncogene is known to be the instigating event in the onset of CML-CP. However, there is another argument that clonal evolution of hematopoiesis may be initiated even before the acquisition of the Ph chromosome. Evidence suggests that this acquisition of BCR-ABL1 oncogene bestows the single HSC that harbors the Ph chromosome with a proliferative advantage leading to aberrant gene expression and cellular differentiation as against the normal cells, thereby steering the expansion of the myeloid compartment.[2]

Most CML-CP patients are receiving tyrosine kinase inhibitors as the treatment. The first drug to be developed

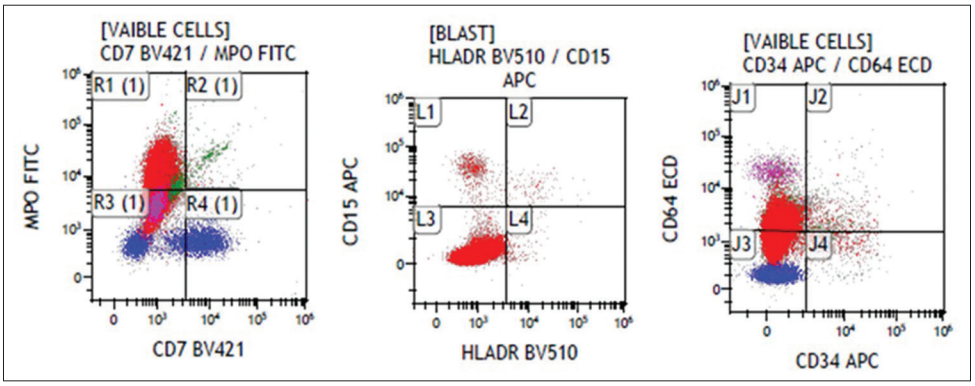

Figure 1: Histogram plots show myeloperoxidase positive with CD15, CD34, and HLA-DR negative

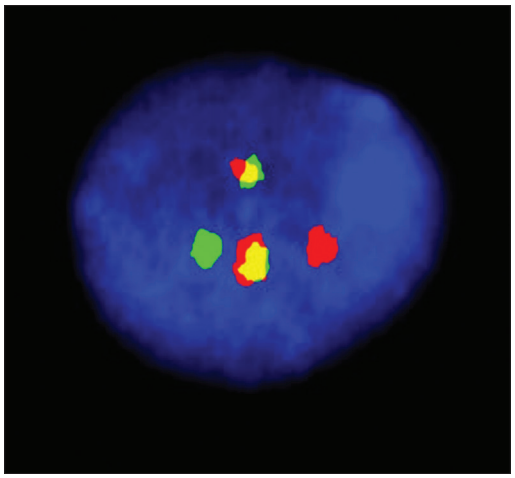

Figure 2: Fluorescence *in situ* hybridization analysis of 200 interphase cells is POSITIVE for the PML/RARA fusion in 100% of cells, indicating that the t(15;17) is present

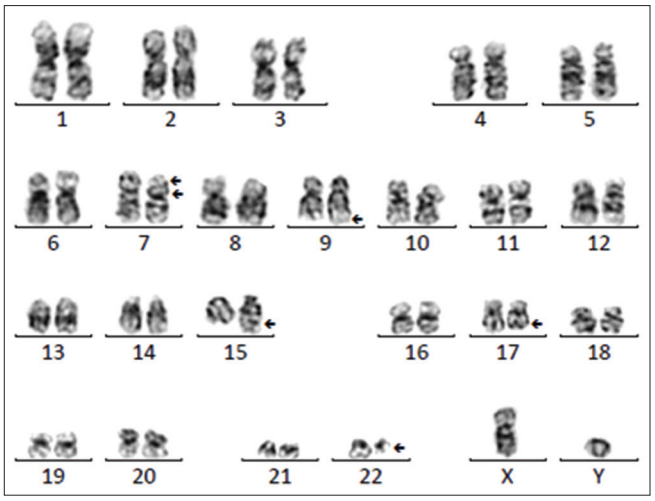

Figure 3: All the 15 metaphases analyzed from this bone marrow aspirate, with a low mitotic index, are abnormal and show a co-existent t(9;22) and t(15;17). This is consistent with chronic myeloid leukemia with acute promyelocytic leukemia. The inv (7) is a secondary abnormality

was imatinib. During the first 2 years progression to advanced disease is extremely low with the use of imatinib. However, we can see two types of responses for the therapy, primary resistance that is failure to respond to imatinib and few other patients respond initially and later lose response (secondary resistance). The patients in CML-CP resistance to imatinib are still not clearly understood. CML patients progress from CP to advanced phase which is divided into accelerated and blastic phase. In the accelerated phase, patients may still respond to treatment for some months or sometimes years. The median survival of patients in blastic phase is approximately 6 months. Some patients without accelerated phase can progress directly to blastic phase.[3]

The promyelocytic blast crisis is a very rare type of CML BT. We report a case of CML transforming to APML considered as promyelocytic blast crisis with t(15;17) in addition to t(9;22). The morphology and immunophenotypic findings of the blasts were like APML. The presence of BCR-ABL1/t(9,22) was confirmed by RT-PCR/FISH and t(15,17) by FISH. After initiation of ATRA, he subsequently developed increasing WBC count with deranged coagulation parameters (increased PT, PTT, and INR) with hypofibrinogemia. The duration of CP to promyelocytic blast crisis transformation was 6 months in this patient. However, usually, the BT develops in ranges from 8 months to 9 years. Genomic instability and less vulnerability of stem cell to imatinib might have caused the CML progression in short duration. Although the patient was under imatinib, there was successful reduction of BCR-ABL transcript; however, the presence of baseline leukemic clonal evolution was persistent.

The biological basis of blast phase is still not understood. Usually, most of the CML patients get transformed to have myeloblastic phenotype, approximately 25% of them transform into pre–B lymphoblastic cell phenotype. Rarely, they get transformed to T lymphoblastic cell phenotype. These findings showed tells us that BCR-ABL1 oncogene arises from a primitive cell, known as leukemic stem cell (LSC), which is not yet committed to myeloid or lymphoid differentiation. The blastic clone may originate at the level of the multipotent LSC or at the level of committed leukemia progenitor cell.[2]

CML blast crisis especially promyelocytic crisis is highly rare, which accounts for nearly 30 cases in western literature until 2007. The first case with promyelocytic blastic crisis during imatinib mesylate therapy was a 50-year-old male, published by Gozzetti *et al*.[6]

Even in this tyrosine kinase inhibitors era, the CML blastic crisis remains the main therapeutic challenge.

In a study conducted by Alimena *et al*.,[7] a series of 69 cases of blast crisis of CML was found. Of 69 cases, one case was classified as promyelocytic leukemia. Sadiq *et al*.[8] in their case study reported a 60-year-old woman with promyelocytic crisis of CML who succumbed to death within 2 weeks after starting the therapy.

During the early stages of CML CP, if there is addition of t(15,17) due to clonal evolution, it may lead to this clinical illustration. Rosenthal *et al*.[9] in their study showed 89 cases of blast crisis of CML in which 2 cases were identified to be APML. These two cases showed t (15;17) in addition to t (9;22). Both these patients developed disseminated intravascular coagulation when they were subjected to treatment.

Oku *et al*.[10] in their case study reported a 66-year-old woman who had presented with promyelocytic blast

crisis of CML, who was diagnosed based on the demonstration of both t(9,22) and t(15,17) by karyotype and FISH analysis. Authors claimed that the possibility of clonal evolution with addition of the PML/RAR alpha translocation may have occurred during the early CP of CML, during imatinib treatment.[10] In this case also, the patient was on imatinib when he was diagnosed as CML in CP. Soon within 6 months, he developed blast crisis which says probably there could be a clonal evolution during early phase which showed expansion during treatment.

Most of the patients succumbed due to disseminated intravascular coagulation within 6 months. This patient had bleeding complications, organ dysfunction, differentiation syndrome, subacute intestinal obstruction, electrolyte imbalance, and evidence of disseminated intravascular coagulation. Overall, the patient was hemodynamically unstable and was on oxygen support. In this patient, blastic progression was seen within 6 months.

The origin of coexisting of both oncogenes, BCR/ABL and PML/RARa, is still unknown. There are studies which show that Imatinib mesylate, the kinase inhibitors do not cause clonal evolution or second hit. Until now no study has shown that the drug can induce gene damage or can cause secondary cancers.[11] However, all previous studies specializing in promyelocytic blast crisis of CML discovered the coinciding presence of PML/RARa and BCR/ABL chimeral genes, implying origin from the CML clone.

Conclusion

In conclusion, CML in acute promyelocytic (APML) BC is rarely encountered in clinical practice. APML is a medical emergency which requires immediate treatment; so, prompt diagnosis and initiation of treatment is important to prevent early deaths related to APML complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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