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Case Report

Atypical presentation of chronic myeloid leukemia with e13a2 BCR-ABL1 fusion transcript in a young male

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ABSTRACT

Chronic myeloid leukemia (CML) is usually a disease of the elderly population characterized by a clonal hematopoietic progenitor cell disorder propelled by the product of the breakpoint cluster region-Abelson murine leukemia (BCR-ABL) chimeric gene, known as the Philadelphia chromosome. It occurs due to a balanced reciprocal translocation between the long arms of chromosomes 9 and 22, which codes for tyrosine kinase. The incidence of CML increases with age, and the median age of diagnosis in Western countries is 64 years. The most common finding at presentation is abdominal pain due to splenomegaly which is present in about half of the patients. We present a rare case of CML in the chronic phase where a young 23-year-old male presented with complaints of severe bilateral lower limb bone pain restricting mobility at the hip joint for 1 year. The upper end of the femur showed heterogeneous areas of bone infarct on the technetium 99 m-methylene diphosphonate bone scan. He was treated with imatinib mesylate, and he entered remission within 5 months of starting therapy. This case highlights the atypical presentation of the chronic phase of CML with the e13a2 BCR-ABL fusion transcript in a young patient and the complete recovery achieved with standard therapy.

Keywords: Chronic myeloid leukemia, e13a2 BCR-ABL fusion transcript, Imatinib, Philadelphia chromosome

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal disorder of the hematopoietic progenitors that account for 15% of all cases of leukemia with a slight predominance in males (Male: Female ratio 1.6:1). Most patients are diagnosed between the age of 55 and 65 years. CML is uncommon in children, with only 3% of patients being under 20 years of age. The Philadelphia (Ph) Chromosome, a specific translocation (9;22) (q34;q11), is present in approximately 99% of cases, resulting in the formation of the breakpoint cluster region-Abelson murine leukemia (BCR-ABL) fusion protein.[1] Splenomegaly is a common finding on physical examination in up to half of CML patients. Over the period of 3–5 years, CML progresses rapidly from a chronic benign phase to a terminal blast crisis, which represents the natural course of the disease. Before a blast crisis, there is often an accelerated phase where reducing the neutrophil count is crucial, typically achieved with high doses of busulfan or hydroxyurea. In the blast crisis of CML, cells fail to mature and resemble lymphoblasts or myeloblasts seen in acute leukemia, in contrast to the maturation of cells in the chronic phase of CML.[2]

Here, we present a case of a 23-year-old male patient in the chronic phase of CML, who visited our hospital with severe debilitating pain caused by infarcts in the upper end of the femur as

confirmed by the bone scan. Typically, the aggressive course of CML is more common in younger patients, with the blast or accelerated phase being the typical presentation. However, the prognosis of young patients with e13a2 BCR-ABL fusion remains unchanged, and similar to this patient, they show an excellent response to tyrosine kinase inhibitors (TKIs) like Imatinib.

CASE REPORT

A 23-year-old man with no significant prior medical history presented to our hospital with complaints of bone pain in both lower limbs and fatigue persisting for 1 year. The symptoms had become debilitating, interfering with his daily activities. He did not report any pain in other joints, abdominal pain, chest pain, fever, night sweats, decreased appetite, or bleeding from any sites. During the physical examination, the patient exhibited mild pallor and moderate splenomegaly (Hackett's grade 2). Hematological parameters revealed a hemoglobin level of 8.1 g/dL, a platelet count of 385,000/cu mm, and a white blood cell count of 276,700/cu mm. Differential counts showed 25% myelocytes, 13% metamyelocytes, 5% promyelocytes, 3% blasts, 35% neutrophils, 4% monocytes, 4% eosinophils, and 3% lymphocytes [Table 1].

His biochemical profile showed a creatinine level of 1.1 mg/dL, lactate dehydrogenase level of 1849 U/L, bilirubin level of 0.8 mg/dL, calcium level of 8.6 mg/dL, and uric acid level of 8.9 mg/dL. Tests for human immunodeficiency virus, hepatitis B surface antigen, hepatitis C virus, and sickling were negative. The leukocyte alkaline phosphatase score was lower than normal. A real-time reverse transcription-polymerase chain reaction (RT-PCR) was performed to detect the BCR-ABL1 fusion transcript gene, which revealed the presence of the e13a2 type BCR-ABL1 fusion gene at approximately 6.2% [Table 2]. The peripheral smear showed a range of granulocytic cells with fewer than 3% blasts. Splenomegaly was confirmed through ultrasonography. Fluorescence *in situ* hybridization confirmed the presence of BCR/ABL1 fusion genes. Morphological examination of bone marrow aspirate and core biopsy specimens showed characteristic features consistent with CML, including marked hypercellularity, myeloid hyperplasia, and prominent granulocytic lineage, without evidence of increased blasts.

He was diagnosed with a case of the chronic phase of CML. Radiographs of the lower limbs did not show any significant findings. However, on the technetium-99 m methylene diphosphonate bone scan, increased radiotracer uptake was observed in a heterogeneous manner at the upper end of the femur. This finding is suggestive of multiple bone infarcts. The rest of the bone scan appeared normal.

Therefore, the patient was initiated on allopurinol 300 mg and imatinib mesylate, a TKI, at a dose of 400 mg once daily. Monthly monitoring was performed to assess the patient's progress. For the management of bone pain, tramadol and paracetamol were administered as analgesics. Clinically, the patient showed improvement and achieved a complete hematological response after 4 months of imatinib therapy [Table 1]. Subsequently, bone pain completely subsided 5 months later, and a repeat bone scan conducted at that time showed no abnormalities. In addition, a repeat RT-PCR for quantification of BCR-ABL1 fusion transcript demonstrated a major molecular response, indicating a significant reduction in the gene product to 0.073% at 10 months and complete absence at 15 months [Table 2]. According to National Comprehensive Cancer Network Guidelines for CML patients (Version-2, 2022), the patient successfully achieved the treatment milestones (Green Zone) throughout the course of his treatment.[3] The patient was advised to continue monthly follow-ups in the outpatient hematology clinic.

Provided that he presented in the chronic phase of CML and had a European Treatment and Outcome Study (EUTOS) Long-Term Survival Score of 1.5316 (low risk), he is expected to have a good prognosis. With a Sokal scale score of 0.8, the patient is classified as Intermediate risk. The EUTOS score, which is 67 (low risk) in this case, predicts complete

Table 1: Serial hematological investigations at the time of presentation, 4, 6, and 10 months of therapy.

Parameters	Normal reference value	Duration after treatment				
		At the time of presentation	After 4 months	After 6 months	After 10 months	After 15 months
White blood count (per cu mm)	4000–11000	276700	8600	7400	7300	6700
Platelets (per cu mm)	150000–400000	385000	136000	103000	141000	159000
Hemoglobin (g%)	11.5–16.5	8.1	13.4	13.9	13.7	13.6
Basophils (%)	0–1	6	0	0	0	0
Eosinophils (%)	1–3	4	10	19	8	5
Blasts (%)	-	3	0	0	0	0
Promyelocytes (%)	-	5	0	0	0	0
Myelocytes (%)	-	25	0	0	0	0
Metamyelocytes (%)	-	13	0	0	0	0
Bandforms (%)	-	2	0	0	0	0

Table 2: Serial quantitative PCR for BCL-ABL1 fusion transcript after 4, 6, and 10 months of treatment.

Duration of after treatment	Results		
	Mean BCR-ABL1 copies	Mean ABL1 copies	(BCR-ABL1/ABL1 [%])
After 4 months	2369	58991	6.224
After 6 months	68	48781	0.216
After 10 months	15	30843	0.073
After 15 months	0	-	0

PCR: Polymerase chain reaction, BCR-ABL1: Breakpoint cluster region protein-Abelson murine leukemia 1

cytogenetic remission (CCgR) within 18 months of therapy. However, it is noteworthy that our patient showed complete molecular remission after 15 months of treatment, which is even earlier than the predicted CCgR timeline. This indicates an excellent response to the treatment and suggests a more favorable prognosis than initially anticipated.

DISCUSSION

In most cases, CML is characterized by t(9;22) (q34;q11.2) genetic translocation, leading to the fusion of the ABL1 gene with the BCR gene. This fusion leads to the production of the BCR-ABL1 fusion protein, a tyrosine kinase that exhibits uncontrolled activity.[4] The increased activity of the BCR-ABL protein leads to the phosphorylation of various substrates, activating numerous signal-transduction cascades involved in the differentiation and growth of cells. Recent research suggests that both the BCR-ABL protein and the cytokines activate the same signaling pathways that regulate the differentiation and growth of normal hematopoietic cells. Due to the constitutive nature of the BCR-ABL protein, these cells evade normal growth inhibition and become leukemic.[2]

CML has classically been considered a disease of the elderly population. However, recent data emphasize that young adults are also susceptible to CML, and there is inadequate knowledge of the disease survival outcomes in this specific patient population.[4] Certain characteristics indicating a more aggressive disease course, such as splenomegaly (enlarged spleen), organomegaly (enlarged organs), an increased frequency of associated symptoms, elevated white blood cell count, a higher percentage of peripheral blasts, and lower hemoglobin levels are more commonly observed in young adults with CML compared to older patients.[1,5] According to one study, a greater number of young adults with CML have BCR-ABL transcript levels of more than 10% on the international scale compared to older patients.[1] In this context, we present an intriguing case of chronic phase CML in a 23-year-old young male who experienced bilateral lower limb bone pain attributed to bone infarctions associated with CML. The patient presented in the chronic phase of the disease and no aggressive features were observed at the time of diagnosis.

CML has a triphasic nature with the chronic phase being the most prevalent, accounting for up to 90% of cases with a potential progression into accelerated and blast phases. Hence, it exhibits a huge diversity in clinical prognosis which, as per statistics, remains highly unclear for young patients. Age is considered to be an important prognostic factor; however, the scoring system yet fails to take into account this subset of young patients.[4]

Management and outcome

The therapy goals for CML are mentioned as the following: (1) Hematologic remission (complete blood count and physical examination are normal without organomegaly), (2) cytogenetic remission (chromosome returns to normal with Ph1-positive cells being 0%), and (3) molecular remission (PCR result turns negative for BCR/ABL messenger ribonucleic acid.[5]

In our case, the patient demonstrated an excellent response to treatment with imatinib mesylate. Complete hematological remission was achieved within 4 months, followed by the major molecular response at 10 months and complete molecular remission at 15 months. These findings are contrary to previous studies suggesting a less favorable response to imatinib in patients with e13a2 BCR-ABL fusion.[6]

CONCLUSION

CML is classically considered a disease of adults; however, recent data showed that the young population is also affected. Little is known about the outcome of CML in the young population, although it is believed to be improved with TKIs. Based on our case, we conclude that the presentation and type of fusion transcript of CML in young adults can be myriad; however, it does not significantly impact the outcome of the patient.

Ethical approval

The research/study complied with the Helsinki Declaration of 1964.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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