International Journal of Enhanced Research in Medicines & Dental Care (IJERMDC),
ISSN: 2349-1590, Vol. 6 Issue 7, July-2019, Impact Factor: 3.015

Asymptomatic CML patient with positive (BCR-ABL)

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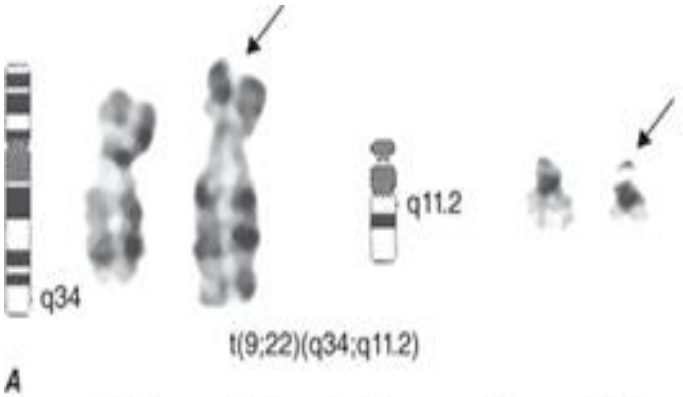
ABSTRACT

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder characterized by the presence of the Philadelphia chromosome, t(9;22), which is a constitutively active tyrosine kinase that causes excessive proliferation and differentiation of myeloid cells in the bone marrow. Most patients are either asymptomatic or present with fatigue, abdominal fullness, and splenomegaly. We report a rare case of 35yr/female admitted with complaints of mild fever, nausea, vomiting and decrease oral intake since 2-3 days, admitted for routine tests. Investigation revealed persistent leucocytosis, LAP score decreased, BCR-ABL gene positive, Peripheral smear suggestive of predominance of neutrophils with few myelocytes, HbA1C-7.1. Thus, it is important to have a high clinical index of suspicion for CML in patients with leukocytosis and concurrent symptomatology that is unusual for leukemia.

INTRODUCTION

Chronic myelogenous leukemia (CML) accounts for 15% of adult leukemias with the median age of diagnosis being 67 years[1]. CML is a clonal myeloproliferative disorder characterized by the presence of the Philadelphia chromosome, a balanced genetic translocation of chromosomes 22 and 9 known as the BCR-ABL fusion oncogene. The BCR-ABL fusion oncogene results in a constitutively active tyrosine kinase that causes excessive proliferation and differentiation of myeloid cells in the bone marrow[2]. Most patients are diagnosed during the chronic phase of CML, which is usually asymptomatic and diagnosed solely based on abnormal blood count, such as severe leukocytosis [3]. However, patients who do experience symptoms usually have fatigue, weight loss, early satiety, left upper quadrant pain with fullness and splenomegaly. However, there have been prior cases of atypical presentations of CML described. For example, there were two noted cases of recurrent painful priapism as initial presentation of CML [4]. Additionally, another patient with CML presented with syncope and myocardial infarction.[5]



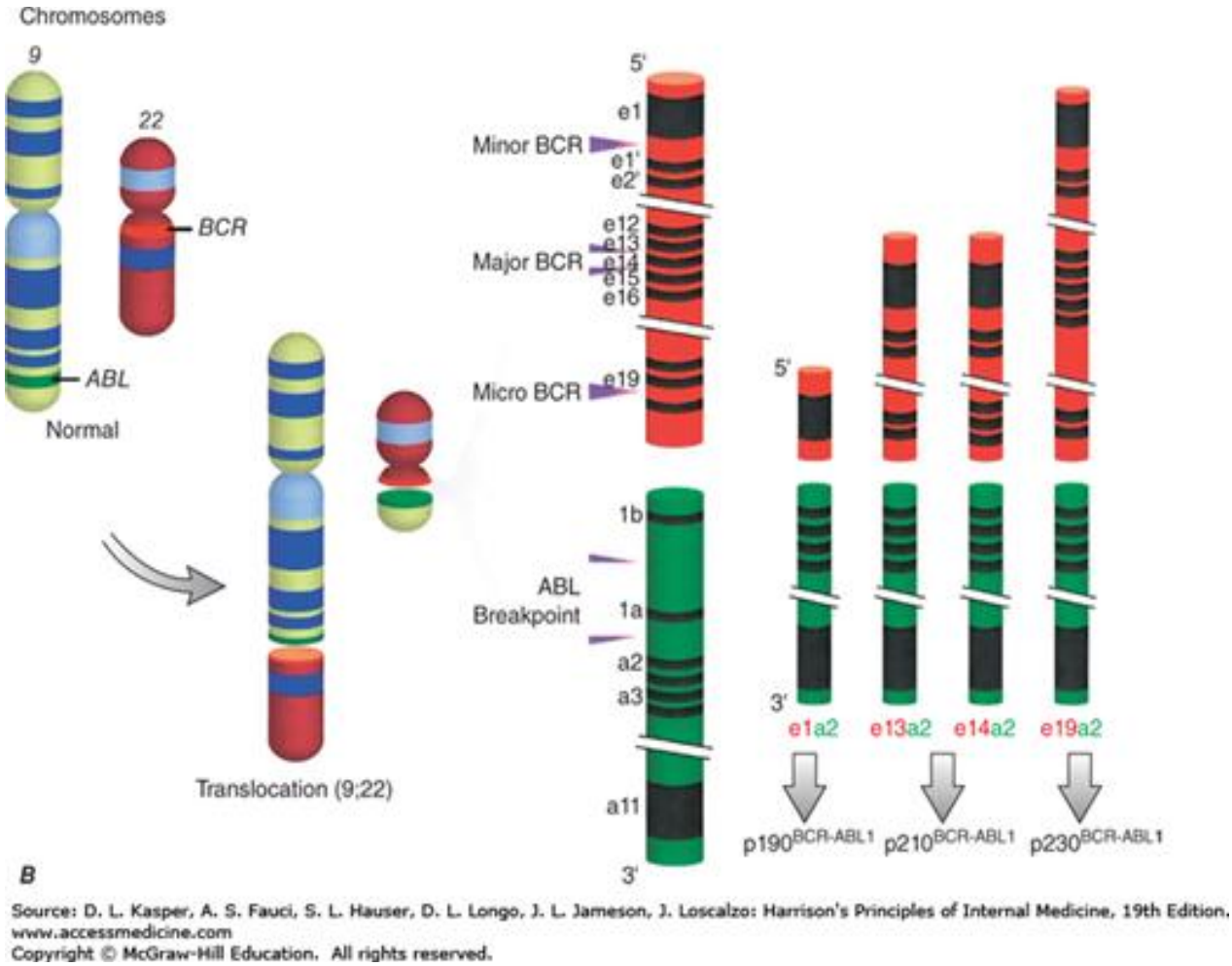


Figure 1: The Philadelphia (Ph) chromosome cytogenetic abnormality.

B- Breakpoints in the long arms of chromosome 9 (*ABL* locus) and chromosome 22 (*BCR* regions) result in three different BCR-ABL oncoprotein messages, $p210^{BCR-ABL1}$ (most common message in chronic myeloid leukemia [CML]), $p190^{BCR-ABL1}$ (present in two-thirds of patients with Ph-positive acute lymphocytic leukemia; rare in CML), and $p230^{BCR-ABL1}$ (rare in CML and associated with an indolent course). *(© 2013 The University of Texas MD Anderson Cancer Center.)*

INCIDENCE AND EPIDEMIOLOGY

CML accounts for 15% of all cases of leukemia. There is a slight male preponderance (male:female ratio 1.6:1). The median age at diagnosis is 55–65 years. It is uncommon in children; only 3% of patients with CML are younger than 20 years. CML incidence increases slowly with age, with a steeper increase after the age of 40–50 years. The annual incidence of CML is 1.5 cases per 100,000 individuals. In the United States, this translates into 4500–5000 new cases per year. The incidence of CML has not changed over several decades. By extrapolation, the worldwide annual incidence of CML is about 100,000 cases. With a median survival of 6 years before 2000, the disease prevalence in the United States was 20,000–30,000 cases. With TKI therapy, the annual mortality has been reduced from 10–20% to about 2%. Therefore, the prevalence of CML in the United States is expected to continue to increase (about 80,000 in 2013) and reach a plateau of approximately 180,000 cases around 2030. The worldwide prevalence will depend on the treatment penetration of TKIs and their effect on reduction of worldwide annual mortality. Ideally, with full TKI treatment penetration, the worldwide prevalence should plateau at 35 times the incidence, or around 3 million patients.

CASE REPORT

A 35yr old female presented with complaints of mild fever, nausea, vomiting, decrease oral intake since 2-3 days. General examination revealed no icterus, no pallor, no cyanosis. Pulse rate-60bpm,BP-130/80mmhg on right arm on sitting position,RR-18/min, temp-normal.

Systemic Examination revealed Per Abdomen- soft, non tender, spleen-not palpable, liver – not palpable. Heart sounds were normally heard and no murmur. there was no sign of meningeal irritation, no focal neurological deficit and normal fundus. Chest examination was normal.

At the time of admission investigation revealed TLC-29900/cumm, HBA1C-7.1(first time diagnosed DMT2), Fasting blood sugar-128mg/dl. On next day TLC-34300cu/mm, DLC of N/L/M-86/5/6. Initially treatment was started with higher antibiotics (inj meropenem and inj targocid), i/v antipyeretics, i/v antiemetic,i/v antacid, inj human actrapid for DMT2.

Chest Xray, USG, KFT, LFT did not show any abnormality, Serum procalcitonin and serum lactate was normal. Patient was further investigated blood culture and urine culture was send which was sterile. Urine for ketones negative.

Patients peripheral smear of blood suggested predominant neutrophils with few myelocytes. Relevent Reference was sended to hematologist in view of persistent leucocytosis and patient was further investigated as advised for PCR for BCR/ABL (quantitative) which came positive, and LAP score was sent which was decreased(LAP score-4).

DISCUSSION

CML is classified into three different phases: chronic, accelerated, and blast .The natural history of CML is a chronic phase for three to five years followed by rapid progression to the fatal blast phase. In two-thirds of patients, the blast phase is proceeded by an accelerated phase.

Approximately 85% of patients with CML are diagnosed in the chronic phase.[6] Forty percent of patients with chronic phase CML are asymptomatic with the diagnosis made solely based on an abnormal blood count. Among the patients who have symptoms, complaints are usually related to anemia and splenomegaly; these include fatigue, weight loss, anorexia, early satiety, and left upper quadrant pain or fullness. Other less common symptoms include thrombosis or bleeding from thrombocytopenia or platelet dysfunction. Splenomegaly is the most common finding on physical exam and is present in over half of patients.7

DIAGNOSIS

Unexplained leukocytosis with left shift (immature myeloid cells including myelocytes, promyelocytes or blasts), basophilia, and splenomegaly are suggestive of CML. The differential diagnosis includes leukemoid reaction (due to infection or inflammation), Ph negative myeloproliferative disorder, chronic myelomonocytic leukemia, and proliferative myelodysplastic syndrome. On occasion, CML may present as an isolated thrombocytosis. The diagnosis of CML may be confirmed with fluorescence *in situ* hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) for BCR-ABL performed on the peripheral blood. However, bone marrow aspiration with cytogenetic analysis (karyotype) is required to appropriately stage as the chronic phase, accelerated phase, or blast phase and to identify chromosomal abnormalities that are not detectable with FISH for BCR-ABL.

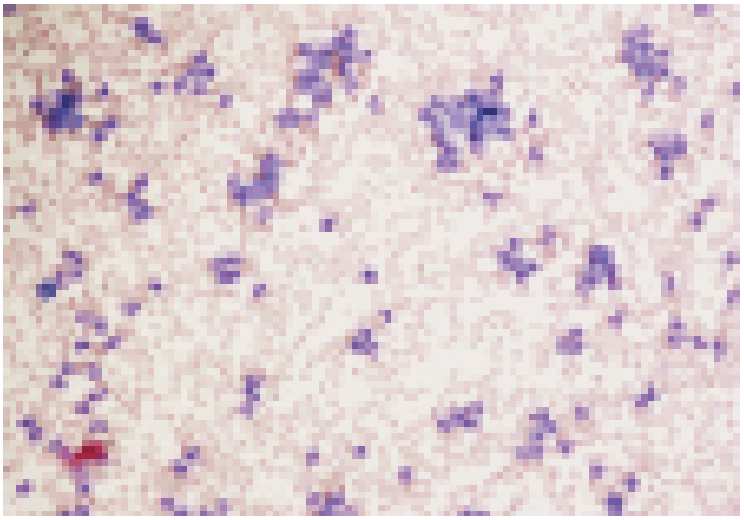


Figure 2: Peripheral blood of chronic phase chronic myeloid leukemia showing leukocytosis with circulating immature myeloid cells (Wright-Giemsa stain, ×4).

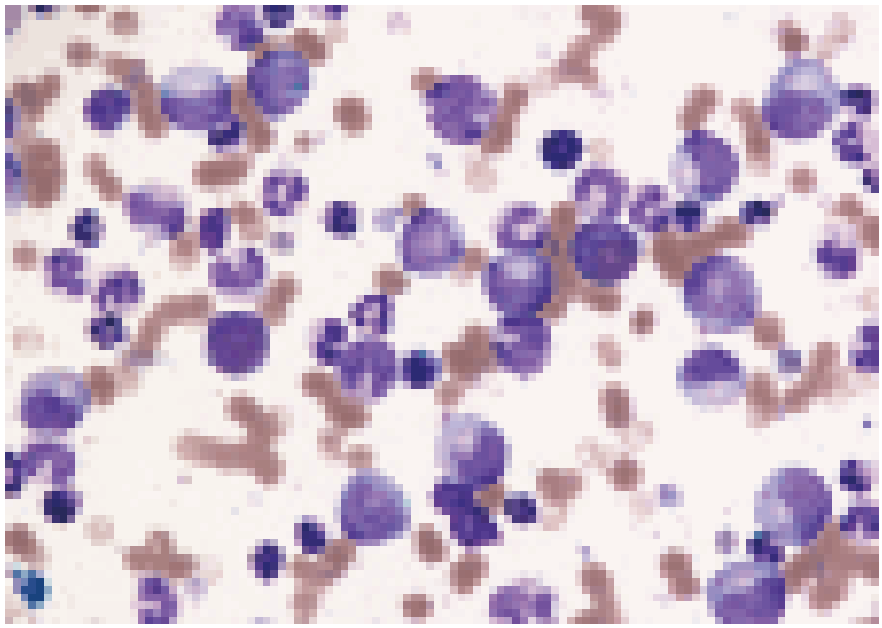


Figure 3: Bone marrow aspirate of chronic phase chronic myeloid leukemia showing a spectrum of immature myeloid cells including blasts and promyelocytes (Wright-Giemsa stain, ×20).

TREATMENT

TKI therapy has transformed the outcomes of patients with CML over the last 15 years. TKIs interfere with the interaction between the BCR-ABL oncoprotein and adenosine triphosphate, thereby blocking proliferation of the malignant clone. There are currently three TKIs approved by the Food and Drug Administration for the first-line treatment of chronic phase CML: imatinib, dasatinib, and nilotinib. Imatinib was the first TKI to be approved in 2001. In the landmark study comparing imatinib to combination interferon and cytarabine therapy, imatinib had superior tolerability, hematologic and cytogenetic responses, and decreased likelihood of progression to accelerated phase or blast phase CML.[8] The choice of first-line therapy depends on the Sokal or Hasford risk stratification score, patient age, ability to tolerate therapy, and medical comorbidities. The Sokal score includes age, spleen size, platelet count, and blast percentage.[9] The Hasford score also incorporates the percent of eosinophils and basophils.[10] Compared to imatinib, dasatinib and nilotinib have improved efficacy and may be preferred in intermediate- and high-risk patients based on the Sokal or Hasford risk stratification scores.[11-14]

The response to therapy is classified based on hematological, cytogenetic, and molecular responses. Optimal responses to first-line TKI therapy include complete hematologic response with *BCR-ABL1*transcript ≤10% (RT-PCR) and/or Ph positive cells ≤35% (bone marrow cytogenetics) at 3 months, *BCR-ABL1*transcript <1% and/or no detectable Ph positive cells at 6 months, and *BCR-ABL1* transcript ≤0.1% at 12 months. Failure of first-line TKI therapy is defined as failure to achieve a complete hematologic response and/or Ph positive cells >95% at 3 months, *BCR-ABL1* transcript >10% and/or Ph positive cells >35% at 6 months, and *BCR-ABL1* transcript >1% and/or Ph positive cells at 12 months. Loss of complete hematologic response, complete cytogenetic response, or major molecular response or presence of mutations or clonal evolution are also considered as treatment failure.

Administration of the protein synthesis inhibitor omacetaxine is a treatment option for patients who have failure or intolerance to two or more TKIs, including patients who harbor the T315I mutation. The accelerated or blast phases may be treated with an alternative TKI as a bridge to HSCT. HSCT is a potentially curative treatment in patients with CML, and HSCT evaluation is recommended for patients with the T315I mutation, failure or intolerance to two or more TKIs, or those with accelerated or blast phase CML

The presented case illustrates the asymptomatic chronic myelogenous leukemia in this patient and the complexities in diagnosis of CML. Upon initial presentation, the patient's white blood cell count was elevated approximately 30000/cumm without any foci for sepsis. At the time of admission, CML was a differential diagnosis. However, it is not uncommon for patients in an immune compromised state, such as leukemia, to develop recurrent infections.15 Thus, in this patient the

differential diagnoses is myeloproliferative disorder, leukemia, or sepsis. Our patient took leave against medical advice after 2 days of admission

Therefore we could not follow up and could not see the progression of disease or future required line of treatment.

CONCLUSION

- This case emphasizes the importance of high clinical suspicion for myeloproliferative disorders in patients with persistent elevated white blood counts without any foci for sepsis and non palpable spleen along with the importance for physicians to follow-up their patients in order to prevent significant complications of undiagnosed disease.

- Without careful tracking of her white blood cell count and further clinical investigation, the diagnosis of CML could have been missed.

- Treatment should be aggressive as the disease progression is fast.

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