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Case report 2

A woman with unilateral thigh pain, moderate leukocytosis and extreme thrombocytosis

MN Dilhani[1], WMNM Jayaweera[1], HSA Williams[2], AP Premawhardhena[3]

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) of hematopoietic stem cells characterized by the presence of the Philadelphia (Ph) chromosome (t (9;22) (q34.1;q11.2), in which granulocytes are the major proliferative component. Atypical presentations of chronic phase CML reported include extreme thrombocytosis with or without leukocytosis, marked megakaryocytic proliferation or significant marrow fibrosis. We describe a middle-aged woman who presented with nonspecific leg pain and abnormal FBC parameters. Moderate leukocytosis (WBC 55 x 10^3/µl), mild anemia and marked thrombocytosis (1,615 x10^3/µl) were noted without clinical or laboratory features of ongoing infection or inflammation. Clinical examination revealed mild pallor only. A prominent spleen was noted ultrasonically (13.5 cm). A leucoerythroblastic blood picture was seen with moderate neutrophil leukocytosis, tear drop poikilocytes and one percent blast cells. No characteristic myelocytes and neutrophil peaks were present, and dysplasia was absent. Mild eosinophilia was observed however basophilia was absent. Platelets were markedly increased with anisocytosis. An underlying MPN suspected. JAK2V617 F mutation was absent and BCR-ABL (transcript type- b3a2) mutation detected. Her bone marrow biopsy revealed markedly hypercellular fragments with suppressed erythropoiesis, markedly hypercellular granulopoiesis (blasts <5%) with prominent eosinophil precursors. Megakaryocyte numbers were markedly increased with numerous micro megakaryocytes. The trephine biopsy displayed a few loose clusters of megakaryocytes. A marked background fibrosis noted (Grade (3/3). The diagnosis of chronic phase-CML was made. She was commenced on Imatinib 400mg daily and she achieved and maintained all the desired milestones since diagnosis.

Introduction

Chronic myeloid leukemia (CML) accounts for 15% of newly diagnosed cases of leukemia in adults with a reported annual incidence of 1-2 affected adults per 100,000[1]. Following the initiation of molecularly targeted therapy, Tyrosine Kinase Inhibitors (TKI) survival of these patients has revolutionized to near normal life expectancy at least in the developed world[2].

Majority of patients with CML who present in chronic phase of the disease are asymptomatic and are diagnosed incidentally when investigated further. However, some may have constitutional symptoms such as fatigue, malaise, loss of weight, night sweats and anemia at presentation. Only 50% of patients have clinically palpable splenomegaly at presentation. A significant minority (5%) are diagnosed in de novo accelerated or blast phase. These patients have more marked constitutional symptoms than patients presenting with chronic phase disease. Notable symptoms are those of severe anemia, worsening thrombocytopenia, symptoms secondary to leukocytosis and a rapidly enlarging spleen[3]. A careful correlation of clinicopathological information is of paramount importance taking into consideration cytogenetics and molecular genetics to diagnose and differentiate even an atypical CML from other BCR ABL negative MPNs. This is because a patient with

[1] *Registrar in Haematology, Department of Pathology, Faculty of Medicine,* [2]*Professor, Department of Pathology, Faculty of Medicine,* [3]*Professor, Department of Medicine, Faculty of Medicine, University of Kelaniya, Sri Lanka.*

CML would benefit from TKIs, and will have a better survival advantage.

Case report

A 58-year-old woman diagnosed with type 2 diabetes mellitus and dyslipidemia for five years, presented with pain and heaviness of her right upper thigh for a few days duration. She had no history of fever or joint pains. She denied any history of trauma, previous wounds, insect bites or prolonged immobilization. Her physical examination, including bilateral lower limbs and hip joint examination was unremarkable except for the presence of mild pallor. There was no peripheral lymphadenopathy or hepatosplenomegaly. An urgent lower limb duplex ultrasonography excluded lower limb deep vein thrombosis. There were no soft tissue swelling or tumors detected ultrasonically.

Her FBC showed mild anemia with low red cell indices (Hb-10.3g/dl, MCV 77 fl, MCH 26 pg, MCHC 30g/dl), leukocytosis (WBC $55x10^9$/L) and severe thrombocytosis (Platelets- $1,615x10^9$/L). CRP (6 ng/ml) and ESR (22 mm/1st hour) were normal. Serum ferritin was normal (127 ng/ml). LDH was elevated (1297 U/L). Ultrasound scan of the abdo-men showed mild hepatomegaly and a prominent spleen (13.5 cm).

Peripheral blood showed a leucoerythroblastic blood picture with hypochromic microcytic red cells with pencil cells, few teardrop poikilocytes and occasional nucleated red cells. A marked neutrophil leukocytosis was seen with a slight left shifted maturation with occasional circulating blast cells (1% of total WBC count). There were no myelocyte and neutrophil peaks and no dysplasia was noted. A mild eosinophilia was observed but there was no basophilia. The platelet count was markedly increased with anisocytosis. However, megakaryocyte fragments were absent. The JAK2V617 F mutation opted as the first option due to the thrombocytosis. As it was absent, on further evaluation a BCR-ABL qualitative test was performed. BCR-ABL mutation was detected with the transcript type- $b3a^2$.

She underwent a bone marrow biopsy. It showed, marked hypercellularity with relatively suppressed erythropoiesis and markedly hypercellular granulopoiesis, increased eosinophil precursors arranged in sheets. Blasts were <5%. Megakaryocytes were markedly increased in number with numerous micro megakaryocytes arranged in loose clusters. There was marked background fibrosis with reticulin stain of MF grade 3.

A diagnosis of chronic phase Chronic Myeloid Leukemia (CML) was made. She was commenced on standard dose of first generation TKI (Imatinib mesylate) according to established recommendations[4], patient preference and availability. Until the BCR-ABL1 results were made available, doses of Aspirin 75 mg and Hydroxyurea 500 mg daily were administered. She experienced mild dyspeptic symptoms and myalgia with Imatinib mesylate which responded well to antacids and simple analgesics. She achieved a complete hematological response by 1 month. Her molecular response at three months (BCR-ABL1 - 3.7% IS) and six months (BCR-ABL1 - 0.12% IS) after commencing treatment is at optimal level. Currently she continues to be on Imatinib mesylate and maintains the major molecular remission with hematologic response and normal platelet count.

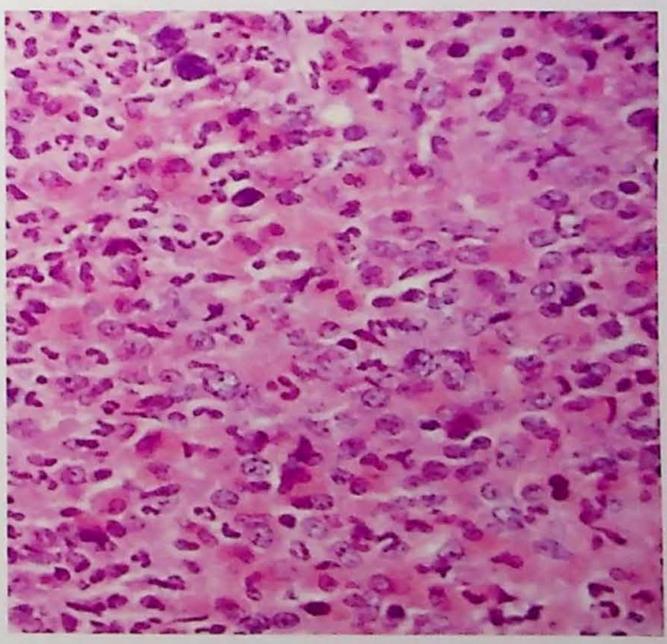

Figure 1. Trephine biopsy H and E stain x 40: Marked granulocytic and megakaryocytic hyperplasia. Numerous micro megakaryocytes and sheets of eosinophil precursors noted.

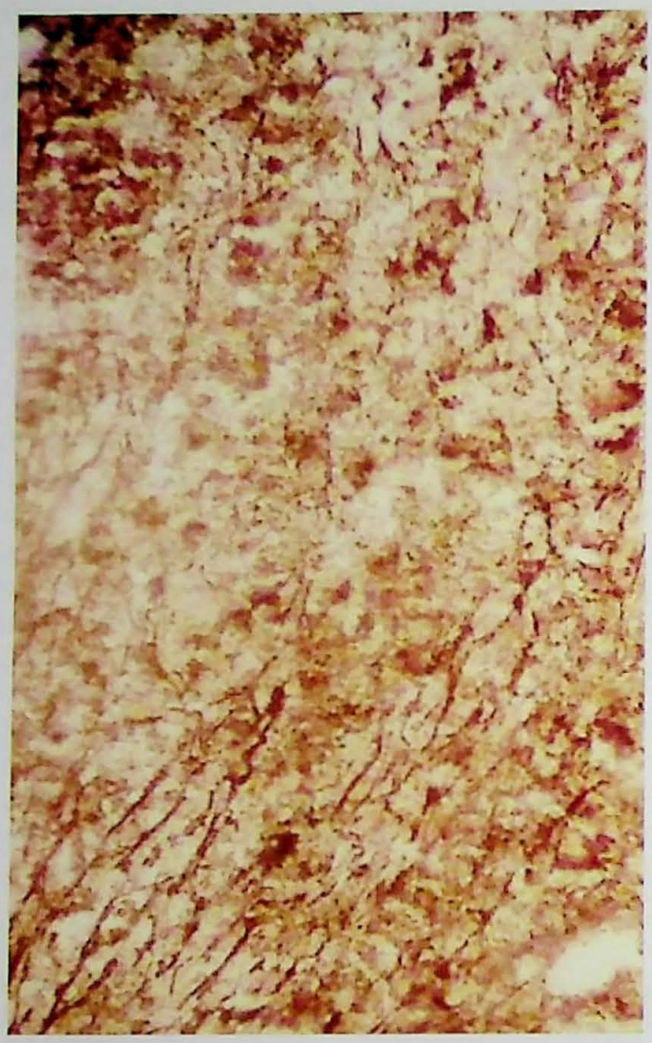

Figure 2. Reticulin stain x 40; show marked (Grade3/3) fibrosis.

Discussion

CML is classically diagnosed on characteristic morphological findings of peripheral blood along with the presence of the Ph chromosome by cytogenetic analysis and/or assessment of translocation BCR-ABL1 by RT-PCR. Patients who present in chronic phase CML have leukocytosis (12 – 1000 x10^9/L, median: ~ 80x10^9/L) with prominent peaks of myelocytes and segmented neutrophils. Although a bone marrow aspiration is essential to establish the phase of the disease and to ensure material for karyotyping a trephine biopsy is not mandatory in all cases but, should be reserved for those who have an atypical peripheral blood smear finding, or a dry aspirate[3].

We describe a patient who was incidentally found to have marked leukocytosis and thrombocytosis when investigated for a nonspecific leg pain in whom the typical morphological features of chronic phase CML were absent in the peripheral blood film. In view of the presence of mild anemia, marked leukocytosis and thrombocytosis along with the leucoerythroblastic blood film with teardrop poikilocytes and high LDH, a diagnosis of Philadelphia negative myeloproliferative neoplasm was suspected in first instance and only the analysis of JAK2V617F mutation was done initially. CALR or MPL mutations were not deemed necessary due to economical constrains. Adhering to the 2016 WHO classification, it is mandatory to exclude a BCR-ABL translocation when a Philadelphia negative MPN is to be diagnosed. BCR-ABL mutation was tested and it yielded positive in this patient. Bone marrow aspiration and trephine biopsy further established that she had chronic phase CML. Her excellent response to TKI therapy confirmed her diagnosis.

Thrombocytosis, defined as a platelet count of >450×10^9/L, is common in chronic myeloproliferative neoplasms. It has been reported that ~30%-50% of CML patients had thrombocytosis at diagnosis. But, extreme thrombocytosis, defined as a platelet count >1,000×10^9/L, is rare in CML at diagnosis[5]. This patient we described had asymptomatic thrombocytosis with a platelet count of 1,615x10^9/L. In an Italian multicenter study conducted among CML patients with extreme thrombocytosis the median platelet count was 1,466x10^9/L. This subset of patients showed the following peculiarities: female predominance, an e14a2 break-point subtype, high or intermediate risk according to Sokal and/or Euro scores, with a favorable outcome in terms of both cumulative cytogenetics and molecular response rate and survival, associated with a low incidence of thrombo-hemorrhagic complications. In line with this data, our patient also achieved the timely desired molecular milestones, showed an excellent response to first generation TKI and never experienced thrombocytosis induced thrombotic or hemorrhagic complications.

The typical bone marrow morphology in chronic phase CML is characterized by markedly hyper-

cellular marrow spaces with total obliteration of intervening fat spaces, relative suppression of erythropoiesis and predominant granulopoiesis with expansion at myelocyte stage. An increase of eosinophils and basophil precursors may be noted. The megakaryocytes may be normal or increased in number. In 40-50% of cases moderate to marked megakaryocyte proliferation is noted. Megakaryocytes are characteristically described to be of a relatively smaller size than their normal counterparts so named as dwarf megakaryocytes. They display a more roundish shape and have scanty cytoplasm. Megakaryocyte nuclei are shrunken with reduced segmentation or lobe numbers. This characteristic morphology is said to be a diagnostic hallmark, facilitating CML to be distinguished from other, Ph-negative MPNs. However, a significant increase in density of megakaryocytes is seen in only 30% of biopsies, and excessive increase in density of megakaryocytes is found in only a small percentage of patients (5%). A diagnostic pit fall in these cases is the presence of fibrosis of grades 2 or 3 making it difficult to be distinguished from primary myelofibrosis, especially in inexperienced hands[3,6].

Patients with chronic phase CML, with higher grades of reticulin fibrosis at initial diagnosis in the pre-imatinib era were associated with a worse outcome[7]. In contrast, advent of TKIs have revolutionized and changed the outlook favorably for this category of patients[8]. Kantarjian et al studied one hundred and ten patients with Ph-positive chronic phase CML receiving imatinib mesylate following interferon failure, looking specifically for the presence of any prognostic significance correlating with the degree of marrow reticulin fibrosis. A total of 67 patients (61%) had severe grade 3-4 reticulin fibrosis. Remarkably they had similar complete cytogenetic response rates, estimated 4-year survival rates and failure-free survival rates with imatinib therapy when compared with those who had lower grades of fibrosis. This study has demonstrated that the previously reported poor prognostic significance of marrow fibrosis in chronic phase CML has been overcome with imatinib therapy. Our patient described here has also shown an excellent response to imatinib therapy with timely attainment of milestones with maintenance of optimal BCR ABL targets.

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