AN UNUSUAL PRESENTATION OF CHRONIC MYELOID LEUKEMIA

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Abstract:
Chronic Myeloid Leukemia is a clonal myeloproliferative disorder of the primitive hematopoietic stem cell that is characterized by overproduction of cells of the myeloid series, which results in marked splenomegaly, leukocytosis, basophilia and thrombocytosis. Usual presentation is patients with easy fatigability, weight loss and massive splenomegaly. We present here a elderly female with an unusual presentation of Chronic Myeloid Leukemia

Keyword: chronic myeloid leukemia (CML), massive hepatomegaly, bleeding tendency

Introduction
Chronic myeloid leukemia is predominantly a disease of the elderly. Classically patients present with easy fatigability, weight loss and massive splenomegaly. Bleeding manifestations are a presentation of blast crisis in the natural history of the disease course. Here we present an elderly female with massive hepatomegaly and bleeding tendency in the chronic phase as the initial presentation.

CASE REPORT
52 yr old post menopausal female – house wife was admitted on 25/7/2011 with Chief complaints of Swelling over both the forearms for the past 7 days which was spontaneous in origin, not painful and not associated with fever and trauma. On elaborating the history she also had swelling of legs & abdominal distension of one month duration. She experienced easy fatigability over the last three months. She had reduced appetite and had lost approximately 4 kgs in 3 months. She had grade II dyspnoea with no chest pain, palpitation or syncope. She never had malena/ hematemesis or bleeding tendencies. Her past history was nil contributory for any systemic illness, jaundice, malignancy, chemotherapy, or radiation exposure. She was earlier treated by a local practitioner as abscess right upper limb, Incision done and red blood clots drained 3 days back.

On examination
Patient moderately built, pallor+, bl pitting pedal oedema+, bilateral, firm, mobile non tender axillary nodes of size 1.5x1cms present. Two on left axilla and one on right axilla. Bony tenderness present.
No ecchymoses or purpuric spots. Jvp not elevated. Rt upper limb - 10 x 6 cms swelling with firm to cystic consistency, mild tenderness and reddish bluediscolouration over the surface seen below the elbow. Plane of the swelling subcutaneous. No distal neurovascular deficit. Lt upper limb – healed linear incision marks seen below the elbow (I&D) Her Vitals were stable.

I&D MARK LT FOREARM

SKIN MARKING OVER THE ABDOMINAL WALL SHOWING LIVER & SPLEEN
P/A – LIVER Palpable 14cms from RCM, firm in consistency, surface smooth, borders sharp, not tender, no rub, no bruit SPLEEN Palpable 6 cms from the LCM, firm in consistency, surface smooth, borders sharp, not tender, notch not palpable. No rub

no bruit No other mass palpable, no free fluid Other system examination - unremarkable.

INVESTIGATIONS
Hb-8.4gm/dl, TC- >1,00,000, Platelet count-3,25,000 Urine albumin-nil sugar-nil deposits-4 to 6 epithelial cells, 1 to 2 pus cells ESR-16/32, Uric acid-8.2 Liver function test and Renal function tests were within normal limits. Peripheral smear study – RBCs appear microcytic and hypochromic WBCs appear increased in number and shows varying stages of maturation from myeloblasts, promyelocytes, myelocytes to mature WBC series Platelets appear increased in number and normal in morphology Differential count - Myeloblast – 02%
- Promyelocyte – 04%
- Myelocyte – 07%
- Metamyelocyte – 04%
- Band form – 02%
- Mature neutrophil – 52%
- Eosinophils – 04%
- Basophils – 06%
- Lymphocyte – 18%
- Monocyte – 01% features suggestive of Chronic Myeloid Leukemia CHRONIC PHASE
PERIPHERAL SMEAR STUDY SHOWING INCREASED WBC COUNT AND VARIOUS STAGES OF GRANULOCYTE MATURATION

Stool routine- No Ova, No Cyst, No Occult blood Ultrasound Abdomen- Hepatosplenomegaly, no intra abdominal nodes seen, no ascites.

Chest x ray: CT ratio 50%, lung fields normal, costophrenic angles free. CT Abdomen( P&C)- Hepatosplenomegaly, no para aortic nodes seen, no ascites.

BT- 9 mins 20 secs CT-7 mins 50 secs PT-16 secs, control- 14 secs , aPTT-28 secsINR – 1.2FNAC of swelling over rt upper limb-few neutrophils and macrophages seen in the background of plenty RBCs

Rpt peripheral smear study-RBCS –Microcytic hypochromic anemia, Platelets-normal & increased Wbcs – increased and as follows

- Myeloblast – 02%
- Promyelocyte – 06%
- Myelocyte – 05%
- Metamyelocyte – 04%
- Band form – 02%
- Mature neutrophil – 55%
- Eosinophils – 03%
- Basophils – 04%
- Lymphocyte – 18%

Monocyte – 01% features suggestive of chronic myeloid leukemia - chronic phase.

Bone marrow aspiration cytology, marrow is hypercellular, Granulocytic hyperplasia with a increased granulocytic to erythroid ratio . megakaryocytes are increased in number. Blast cells less than 5%. Features suggestive of chronic myeloid leukemia – chronic phase.

During the course of the hospital stay, on attempted intravenous cannulation patient developed swelling over the forearm extending upto the arm, subcutaneous bleeding was controlled with tight compression. But the patient developed features of compartmental syndrome, hence decompression faciotomy along with removal of blood clots from the rt upper limb done. Whole fresh blood transfused. Patient recovered well with supportive medications and discharged later.
She is currently on outpatient medications for CML from a specialised tertiary care centre.

**Discussion**

Our patient was diagnosed as Chronic Myeloid Leukemia based on clinical history, peripheral study and bone marrow study. CML is characterised by a specific chromosomal abnormality and specific molecular abnormality. The Philadelphia chromosome is a reciprocal translocation between the long arm of chromosome 9 & 22. The larger part of 22q is translocated to 9q and a smaller portion of 9q is moved to 22q, the portion of 9q that is translocated contain abl, a protooncogene, that is the cellular homolog of the Abelson Murine Leukemia Virus. The abl gene is received at a specific site on 22q, the breakpoint cluster region(bcr). The fusion gene bcr/abl produces a novel protein that differs from the novel transcript of the abl gene in that it possesses tyrosine kinase activity, which is crucial for pathogenesis of CML.

The natural history of the disease is divided into 3 phases

- **Chronic phase**
- **Accelerated phase**
- **Blast crisis**

Chronic phase does not behave like a malignant disease. It consists of elevated white blood cells with increase in both immature and mature granulocytes usually <5% circulating blasts and 10% marrow blasts and promyelocytes majority of them myelocytes, metamyelocytes and band cells. Platelet cells are almost always elevated. Leucocyte alkaline phosphatase is reduced.

Disease acceleration is characterised by worsening of anaemia, blood or marrow blasts between 10 – 19%, blood or marrow basophils more than 20% or platelets < 100,000 per cu mm.

Blast crisis is defined as acute leukemia where blood and marrow blasts above 20% bleeding manifestation is usually seen in blast crisis.

Our patient was diagnosed to be CML-chronic phase by peripheral smear study and confirmed by repeat smear and bone marrow study. Cytogenetic study could not be done.

CML patients in chronic phase presenting with bleeding tendency such as hemorrhage, ecchymoses, haematomas or thromboembolic manifestations are quite rare (10). One such rare presentation of massive subcutaneous bleeding as the first presentation of CML -chronic phase has been reported in Croatia.(12). Though Platelet count was high, Platelet dysfunction appears to be the primary cause of bleeding. In patients with CML and thrombocytosis platelet function studies showed 'abnormal platelet aggregation' to be the commonest abnormality followed by defective platelet adhesiveness, factor 3 release, reduced dendrite formation and abnormal fragility all contributing to defective platelet fibrin network and bleeding diathesis(6,7,8,9). Platelet morphology was abnormal in patients
with CML, both small and giant platelets – bizarrely formed with reduced granulations are often seen by light microscopy. Ultra structural platelet abnormalities are often seen in these patients including disorganisation and scarcity of microtubules, hypertrophy of dense tubular and open canalicular system with reduced granulations. CML patients were also found to have reduced platelet content of ADP and Serotonin. In addition the serotonin carrying capacity of platelets are reduced with the hemostatic process of vasoconstriction. One another platelet defects in CML is a reduced responsiveness to epinephrine all leading to bleeding tendencies. (11)

Other unusual presentation in this patient is the massive hepatomegaly. Classically patients with CML have moderate to massive splenomegaly, Liver may or may not be enlarged. In a study of Clinical features at diagnosis in 430 pts with CML seen in Dept of Haematology, Royal Postgraduate Medical School, London over a 16 year period, only 2.2% of patients had hepatomegaly.(5). In a large study by M D Anderson Cancer Centre, Texas among patients presenting with Chronic Myeloid Leukemia from 1980 to 2005 hepatomegaly was seen in 10 – 20% and was only minor ranging from 1 – 3cm from right costal margin.(2).

The aim of this report is to make the readers aware of this unusual presentation. We also want to emphasise the irony that bleeding tendency in CML may also be due to platelet dysfunction in chronic phase even though the platelet count may be high.

Conclusion
CML should be suspected in all middle and elderly patients presenting with easy fatiguability, weight loss, bleeding manifestation with splenomegaly/hepatomegaly. Peripheral smear study, Bone marrow study and cytogenetics are confirmatory.

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