CASE REPORT

Chronic myeloid leukaemia with extreme thrombocytosis

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SUMMARY

We report two cases of chronic myeloid leukaemia (CML) with extreme thrombocytosis. The first patient was a 65-year-old man who presented with prolonged history of upper abdominal discomfort, anorexia and two episodes of recent gum bleeds without fever or other bleeding manifestations. He was a chronic smoker with no other comorbidities. Examination revealed moderate hepatosplenomegaly. On investigation, he was found to have extreme thrombocytosis ($3\,500\,000/\text{mm}^3$) and leucocytosis with moderate anaemia. In view of the leucocytosis, he was investigated for CML and found to be positive for BCR-ABL by reverse transcription PCR (RT-PCR). He received imatinib 400 mg/day and achieved complete haematological response at the end of 3 months. The second patient was a 7-year-old boy who presented with fever, cough and cold of 2-week duration. Examination revealed mild hepatomegaly with palpable spleen tip. Haemogram and peripheral smear revealed moderate leucocytosis with extreme thrombocytosis ($2\,800\,000/\text{mm}^3$). On evaluation, he was found to be BCR-ABL positive and responded well to imatinib treatment. In both these cases, massive thrombocytosis was an unusual presentation of a well-known entity, namely, CML. This degree of thrombocytosis is usually seen only in essential thrombocytosis.

BACKGROUND

Myeloproliferative neoplasms (MPNs) are relatively rare haematological malignancies. Chronic myeloid leukaemia (CML) is the commonest MPN and characterised by extreme leucocytosis, myelocyte bulge, basophilia, eosinophilia in peripheral blood and presence of underlying Philadelphia chromosome as a cytogenetic abnormality or BCR-ABL transcript as a molecular abnormality. Some patients of CML can have mild to moderate thrombocytosis. Essential thrombocytosis (ET) is characterised by moderate to severe thrombocytosis with underlying JAK2V617F mutation in about 50% of cases. We report two unusual cases of patients who presented with extreme thrombocytosis and mild to moderate leucocytosis, which, on further investigations, turned out to be CML (BCR-ABL+, p210 transcript by reverse transcription PCR (RT-PCR)). Extreme thrombocytosis in a case of CML has very rarely been reported. Both patients responded to treatment with the tyrosine kinase inhibitor drug, imatinib, with complete haematological recovery at 3 months.

Figure 1 Peripheral smear of patient 1 showing marked tailing of platelets with platelet clumps (Leishman, $\times 100$).

CASE PRESENTATION

Patient 1: A 65-year-old man, a chronic smoker, presented with a history of upper abdominal discomfort, loss of appetite, significant lethargy and progressive weight loss of 1 year duration. He also had a cough with scant mucoid expectoration and progressive exertional breathlessness for a duration of 2 years. He reported exacerbation of respiratory symptoms during change of seasons. There was no history of fever, chest pain, haemoptysis, orthopnoea, paroxysmal nocturnal dyspnoea or wheezing. The patient also reported two episodes of gum bleeding over the last 2 months, which resolved spontaneously. There was no history of any other bleeding manifestation, swellings, or night sweats. The patient did not have any bleeding during his

Figure 2 Bone marrow aspirate of patient 1 showing myeloid hyperplasia with increase in megakaryocytes, a few of them showing monolobated forms (Leishman, $\times 100$).

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Figure 3 Bone marrow biopsy of patient 1 showing megakaryocytic hyperplasia with dwarf forms and monolobated forms (H&E, ×40).

hospital stay. He was not a diabetic or hypertensive and there was no history of contact with tuberculosis. He was diagnosed at another facility as a case of chronic obstructive pulmonary disease and received irregular treatment.

On examination, the patient's blood pressure was 140/90 mm Hg and his pulse rate was regular, at 88/min. He was afebrile with respiratory rate of 20/min. General examination revealed normal oral hygiene, mild pallor and mild pedal oedema. Abdominal examination revealed moderate hepatosplenomegaly and respiratory system showed bilateral diffuse rhonchi (figures 1–3).

Patient 2: A 7-year-old child presented with a history of fever with cough and cold for a duration of 2 weeks. He did not have any bleeding manifestations or weight loss. Physical examination revealed normal oral cavity and mild pallor without any lymphadenopathy or sternal tenderness. Abdominal examination revealed mild hepatomegaly with palpable spleen tip. Table 1 shows the laboratory work up of both these patients (figure 4).

DIFFERENTIAL DIAGNOSIS

In view of the patient's markedly raised platelet count and leucocytosis, the possibility of MPN was considered. ET and CML were the most likely possibilities. Reactive causes were very less likely due to extreme thrombocytosis and associated leucocytosis.

TREATMENT

Awaiting reports of BCR-ABL and in view of marked leucocytosis and thrombocytosis, patient 1 was started on hydroxyurea. Day 5 after availability of BCR-ABL, imatinib was added. On day 10, his platelet count reduced to 1 500 000/mm³; aspirin was added to the treatment and hydroxyurea was stopped.

Patient 2 was started on imatinib after availability of confirmatory reports.

OUTCOME AND FOLLOW-UP

Patient 1: At the end of 3 months, hepatosplenomegaly clinically subsided and anaemia improved. The patient achieved haemoglobin of 13.8 g/dL, total leucocyte count of 8100/mm³ with normal differential counts and platelet count of 149 000/mm³. He achieved a complete haematological response.

Patient 2: This patient also responded very well to treatment with normalisation of platelet count at 3 weeks and complete haematological response at the end of 3 months.

DISCUSSION

CML is a MPN characterised by the presence of Philadelphia chromosome t(9;22). CML is characterised by marked leucocytosis, myelocyte bulge, basophilia, eosinophilia and normal to mild thrombocytosis in peripheral blood. A fair number of patients may have mild thrombocytosis. Jameel and Jamil¹ studied the clinicopathological profiles of 59 patients of CML and found that about 10% of patients had a platelet count of >500 000/mm³. Case reports of extreme thrombocytosis in CML are rare. Langabeer *et al* described an 80-year-old patient of CML with thrombocytosis (platelet count of 1 400 000/mm³). On RT-PCR, that patient was found to have a variant e19a2 BCR-ABL1 transcript. Treatment response could not be assessed well due to multiple treatment interruptions.² Yamagata reported a case of CML with variant BCR-ABL transcript c3-e2. The patient had severe thrombocytosis and clinical features suggestive of essential thrombocytosis (ET) rather than that of a typical CML. The patient had poor response to interferon α.³ Kim *et al*⁴ also reported a 51-year-old man who presented with extreme thrombocytosis (platelet count of 1 594 000/mm³) and leucocytosis. RT-PCR analysis for BCR-ABL arrangement showed presence of a b3a2 fusion gene. The patient responded to imatinib treatment.

Table 1 Relevant investigations performed during hospital stay

Investigation	Patient 1	Patient 2
Haemogram	Hb: 9.9 g/dL, total WCC: 66 400/mm ³ , differential count: N88 L2, platelet count: 3 500 000/mm ³	Hb: 11.4 g/dL, total WCC: 21 200/mm ³ , differential count: N52 L32 E4 B10, platelet count: 2 800 000/mm ³
Peripheral smear	Normocytic normochromic RBC, marked neutrophilic leucocytosis with severe thrombocytosis (figure 1)	Normocytic normochromic RBC, moderate leucocytosis with mild basophilia and severe thrombocytosis (figure 4)
LAP score	50 (control: 324)	0 (control: 286)
Bone marrow aspiration	Hypercellular marrow with basophilia, eosinophilia and mild increase in megakaryocyte number with monolobated and multilobated forms and occasional dwarf forms (figure 2)	Hypercellular marrow with myeloid hyperplasia and increase in number of megakaryocytes with clustering, hyperlobated as well as dwarf forms, were seen
Bone marrow biopsy	Hypercellular marrow with features suggestive of MPN (figure 3)	Hypercellular marrow with features suggestive of MPN/CML
Serum LDH	616.8 IU/L	Not done
USG of the abdomen	Moderate hepatosplenomegaly with mild prostatomegaly	Mild hepatosplenomegaly
RT-PCR for BCR-ABL	Positive for p210 transcript	Positive for p210 transcript
JAK-2 V617F mutation	Negative	Not performed
CECT of the thorax	Emphysematous lungs, no lymphadenopathy	

CECT, contrast-enhanced CT; CML, chronic myeloid leukaemia; Hb, haemoglobin; LAP, leucocyte alkaline phosphatase; LDH, lactate dehydrogenase; RBC, red blood cell; RT-PCR, reverse transcription PCR; MPN, myeloproliferative neoplasm; USG, ultrasonography; WCC, white cell count.

Figure 4 Peripheral smear of patient 2 showing marked thrombocytosis (Leishman, ×100).

Shen *et al* also reported a case of CML mimicking ET. Fluorescence in situ hybridisation (FISH) and RT-PCR confirmed the diagnosis. Morphologically, bone marrow aspiration and biopsy revealed megakaryocytes that were smaller than normal and had a typical hyperlobated round nuclei.⁵ At times,

leucocytosis, basophilia, peripheral immature cells and splenomegaly may be absent at the onset of disease or at the initial presentation to clinic, but may develop in later years. Rice and Popat reported two cases of women who initially presented with only severe thrombocytosis and vascular events (stroke, myocardial infarction) and later developed typical features of CML. The authors concluded that every case of ET should be tested for the Philadelphia chromosome.⁶ The literature also reveals case reports of Philadelphia positive (Ph+) ET without features of CML in peripheral blood. These cases were ultimately diagnosed as CML and thrombocytosis was considered as an early manifestation of the chronic phase of CML.⁷

In our cases, transcript analyses revealed a p210 transcript, confirmed by RT-PCR, and the patients responded extremely well to imatinib therapy.

Contributors SPV thoroughly evaluated the clinical history and physical findings, and worked up the case along with reviewing the literature. AS helped in collecting the clinical history and planning work up of the patients. SEJ and DB helped in haematological work up of the patients and review of the literature.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Chronic myeloid leukaemia (CML) can rarely present with extreme thrombocytosis.
- ▶ Essential thrombocythemia becomes a close differential diagnosis.
- ▶ Sometimes thrombocythaemia may be the only peripheral blood finding in the chronic phase of CML.
- ▶ Variant BCR-ABL transcripts may be associated with extreme thrombocytosis in CML, which can have a different response to drugs in comparison to typical CML.
- ▶ All patients with thrombocythaemia should be investigated for BCR-ABL translocation.

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