In this context, we describe a unique case of one hematological condition (chronic myelogenous leukemia; CML) masquerading as another (essential thrombocytosis; ET) wherein the former presented to us with the clinical features of the latter.

**Case Report**

A 55 years old hitherto healthy lady was brought in with complaints of acute abdominal pain and burning pain in her lower limbs since a fortnight and blackish discoloration of both feet noticed five days prior to reporting to our hospital. The abdominal pain was diffuse, dull-aching in nature with no particular aggravating factors food intake (abdominal angina) nor was it associated with bloody stools. Around the same time, she also developed severe burning pain in both feet and legs; this was soon followed by mottled appearance of both feet and then, blackish discoloration suggestive of impending gangrene. Suspecting an underlying thrombo-embolic phenomenon we questioned her regarding symptoms of cardiac illness, infections, malignancy, recurrent episodes, prolonged drug intake, recent febrile illness and all these were negated by her. Apart from the pain and limb discoloration, there were no complaints of limb weakness or bowel-bladder disturbance.

On examination she was afebrile. The upper limb blood pressure was normal. Arterial pulsations were found to be diminished and unequal in the lower limbs (Table 1).

Mild pallor was noted. There was no palpable lump or lymphadenopathy. Gangrenous changes were noted in the right foot up to mid-tarsal joint and left foot involving the toes (Figure 1). Decreased local temperature and tenderness was noted but there was no crepitus.

On abdominal examination, spleen was marginally enlarged and firm. No renal bruit was heard. Cardiopulmonary

**Table 1: Unequal and diminished arterial pulsations in the lower limb**

<table>
<thead>
<tr>
<th>Arterial pulsation</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>Feeble</td>
<td>Feeble</td>
</tr>
<tr>
<td>Popliteal</td>
<td>Feeble</td>
<td>Feeble</td>
</tr>
<tr>
<td>Anterior tibial</td>
<td>Absent</td>
<td>Feeble</td>
</tr>
<tr>
<td>Posterior tibial</td>
<td>Absent</td>
<td>Feeble</td>
</tr>
<tr>
<td>Dorsalis pedis</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**Abstract**

A 55 years old female presented with hitherto abdominal pain and gangrenous changes of lower limbs. Patient was found to have extreme thrombocytosis. Approach to thrombocytosis is discussed here.

**Introduction**

Thrombocytosis or thrombocythemia is a condition characterized by the presence of elevated platelet counts (>450 x 10⁹/L) in the blood. In most cases (>80%) its likely to be reactive or spurious but those cases in which it is not, one needs to look for underlying clonal mechanisms that lead to thrombocytosis. Clonal thrombocytosis is often associated with thrombotic as well as bleeding complications.

In this context, we describe a unique case of one hematological condition (chronic myelogenous leukemia; CML) masquerading as another (essential thrombocytosis; ET) wherein the former presented to us with the clinical features of the latter.

**Fig 1:** Gangrenous changes noted in both the feet, more on the right side

**Fig 2:** Peripheral smear showed marked increase in the platelet count (>10 lacs/mm³). Also seen is a basophil with prominent purple granules and a neutrophil with lobes and fine granules. Red blood cell morphology is unremarkable. (Wright stained, 1000X)

**Fig 3:** Contrast-enhanced CT abdomen showing a massive splenic infarction

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and neurological examination was normal.

Complete hemogram showed the presence of normocytic normochromic anemia (Hemoglobin 9.7 g/dl), leucocytosis (27,900 cells/mm³) and markedly elevated platelet counts i.e. more than 100x10⁹/L (Figure 2). There were few giant platelets but not much of clustering seen. There was also presence of basophilia (5%) in the peripheral smear (Figure 2). Platelet counts, when rechecked manually, was found to be 20.82 x10⁹/L.

To look into the cause of abdominal pain, we performed a computed tomography of the abdomen which disclosed the presence of a massive infarction of the spleen (Figure 3) and patchy infarcts in the upper pole of left kidney. Furthermore, CT aortogram and lower limb angiogram showed a 1.5 cm x 7 cm size mural thrombus in the descending thoracic aorta as well as occlusion of bilateral infrapopliteal arteries, most likely of embolic origin (Figure 4a and b).

Thus, we had patient with a thrombotic disorder and impressive thrombocytosis.

### Approach to a Case of Thrombocytosis

Thrombocytosis is a common finding and frequent cause of referrals for further investigations. The incidental discovery of an elevated platelet count in an otherwise asymptomatic subject, in the absence of any other hematologic abnormalities, represents an important diagnostic challenge. In managing the patient with thrombocytosis, one must first distinguish reactive from primary thrombocytosis. The presence of acute or subacute infection, a connective tissue disorder, vasculitis, hemolysis, active bleeding, recent surgery, history of splenectomy, or iron deficiency anemia favors the diagnosis of reactive thrombocytosis. The presence of chronic thrombocytosis, thrombohemorrhagic complications, microvascular symptoms, or splenomegaly favors the diagnosis of primary thrombocytosis (Table 2).

### Defining Primary and Secondary Thrombocytosis

**Primary thrombocytosis** (also referred to as essential thrombocytosis, essential thrombocythaemia and primary thrombocythaemia) is due to a failure to regulate the production of platelets i.e. autonomous production and is a feature of a number of myeloproliferative disorders. Features include a platelet count greater than 600 x 10⁹/L, megakaryocyte hyperplasia, splenomegaly and a tendency to both thrombosis and haemorrhage. Platelet survival is normal but function is not. Other haematological diseases which cause thrombocytosis are myeloproliferative, myelodysplastic or a combination of both. It includes some leukaemias as well.

**Secondary or reactive thrombocytosis**: This can be secondary to a number of conditions. It is an exaggerated physiological response to a primary problem, such as an infection. The trigger factor (e.g., infection) results in the release of cytokines which mediate an increase in platelet production. It is often a transient phenomenon which disappears when the underlying cause is resolved.

### Clinical Presentation of Primary versus Secondary Thrombocytosis

In primary thrombocytosis, the clinical features can relate to an increased bleeding tendency and, rather oddly, an increased tendency to thrombosis. Pathogenesis of thrombosis is multifactorial; rheologic abnormalities due to increased red cell mass in PV, abnormal function of platelets (hypo or hyperaggregation), and enhanced interaction with leukocytes and endothelial cells due to the presence of high molecular weight von Willebrand factor are all possible contributing multimers.

About a third of patients are...
asymptomatic at the time of diagnosis. Most symptomatic patients have vasomotor symptoms or symptoms related to small or large vessel thrombosis. Between 20% and 30% of patients have constitutional symptoms that usually include sweating, low-grade fever and pruritus. On examination, 40-50% of patients have splenomegaly at presentation and 20% have hepatomegaly.

Clinical features can include neurological symptoms (headache, dizziness, syncope, transient ischemic attack, paraesthesia, erythromelalgia), arterial and venous thrombosis, bleeding (GI and mucosal mainly), pregnancy complications (spontaneous abortions, intrauterine growth retardation, fetal demise, post-partal haemorrhage). Bleeding is usually not severe (only rarely requires transfusion) and it is unusual unless the platelet count exceeds 1,000 × 10⁹/L.⁷

Secondary thrombocytosis: A history of the primary condition may be elicited (eg, infection, malignancy, anemia) but sometimes the causative factor is not obvious. Symptoms prevalent in primary thrombocytosis are notably absent. There are no specific clinical findings on examination.

However, clinical impression often requires confirmation through laboratory testing, which is also necessary to distinguish among the different causes of primary thrombocytosis (including essential thrombocytopenia) (Figure 5).

In our patient, work-up for secondary causes was negative i.e. normal ferritin, LDH and CRP levels, absence of Howell Jolly bodies. Also, testing for anticardiolipin antibodies (ACLA) and anti-nuclear antibody (ANA) as well as two-dimensional echocardiogram (2D-ECHO) was normal.

We proceeded with the next step i.e. bone marrow examination. The biopsy findings revealed that the marrow was markedly cellular for age with decrease in the fat spaces. The marrow also showed trilineage haematopoiesis with increase in the myeloid series. Megakaryocytes were also increased in the number, few monolobated (dysplastic) forms were also seen. There was marked suppression of the erythroid series. Fibrosis was not seen, thus ruling out the possibility of primary myelofibrosis. This picture was suggestive of a myeloproliferative neoplasm, either essential thrombocythemia or chronic myeloid leukemia (CML) (Figure 6).

CML and Thrombocytosis

Thrombocytosis is a relatively common presenting feature of CML but platelet counts >1000 × 10⁹/L is rare.¹¹ Extreme thrombocytosis in CML could mislead to a diagnosis of ET. Although CML is easily predicted by approaches of morphologic basis, cases with extreme thrombocytosis would require molecular techniques
such as chromosome analysis, FISH and RT-PCR for a proper differential diagnosis including other disorders of MPN such as ET.12

What is Different in CML Patients Having Extreme Thrombocytosis?

Whereas e13a2 or e14a2 BCR-ABL transcripts are the common ones seen in CML, an association with e19a2 BCR-ABL1 transcripts has been documented in CML patients with pronounced thrombocytosis.13 Japanese researchers Ikeda et al describe that till 2014, only approximately 50 patients with e19a2 BCR-ABL1 have been reported in CML. Among these, 15 patients were treated with Tyrosine Kinase Inhibitors (TKIs). Of these 15 patients, 14 received imatinib as a first TKI, but in general they responded poorly to imatinib, and most of them eventually required a second-generation TKI or died. This finding highlights the utility of a modern tool like RQ-PCR (real-time quantitative polymerase chain reaction) in identifying and monitoring the BCR-ABL transcripts as mutations in the BCR-ABL kinase domain may cause or contribute to resistance to tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia patients.

Course and Outcome in Our Patient

For this lady, disease specific therapy in the form of tyrosine kinase inhibitor Imatinib 400 mg once daily has been initiated. She has been started on warfarin anticoagulation and advised a repeat CT aortogram after 3 months by our interventional vascular radiologists. The gangrenous limbs turned dry and developed a line of demarcation gradually; they await auto-amputation. She has been advised immunization against pneumococcal and influenza pathogens since she will be soon rendered asplenic as a consequence of the massive splenic infarct. At the time of discharge, i.e. after one month of Imatinib therapy, her platelet count was 800 x 10^9/l (8 lac cells/mm³). Hematological response to TKI therapy will be assessed at the end of three months.

Conclusions

This case highlights the complex pathogenesis of myeloproliferative neoplasms and wisens us up about the possibility of overlap in the clinical and laboratory features between the different MPNs. This case also unfolds the value of routine cytogenetic and molecular biological analysis in the diagnosis of chronic myeloid leukemia, which otherwise could be mistaken for essential thrombocytosis, especially in the presence of marked thrombocytosis.

References