A rare presentation of essential thrombocytosis masked as vasculitis

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Abstract

This case study presents the clinical journey of a 37-year-old woman who previously experienced gangrene in her fingers and toes. Initial assessments revealed elevated total white blood cell count and platelets, coupled with low hemoglobin levels. Despite normal inflammatory markers and negative results for antiphospholipid syndrome, antinuclear antibodies, and anti-neutrophil cytoplasmic antibodies, arterial Doppler imaging displayed no abnormalities. Suspecting vasculitis, the patient was initially treated with steroids and aspirin. However, subsequent investigations revealed essential thrombocytosis, a myeloproliferative disorder, confirmed by a positive JAK2 gene mutation. This case underscores the complexity of diagnosing rare hematological disorders and the importance of comprehensive evaluations for accurate treatment strategies.

Keywords: Essential thrombocythemia, Myeloproliferative neoplasms, White blood cells, Platelets

Introduction

Essential thrombocythemia (ET) is a rare, but chronic blood disorder characterized by an abnormal increase in the number of platelets in the blood. Platelets are crucial for blood clotting, but an excess of these cells in ET can lead to various complications. This condition falls under the broader category of myeloproliferative neoplasms (MPN). The prevalence of ET in the general population is approximately 30 per 100,000. It typically affects adults, with a higher incidence in individuals aged 65 to 70 years, but the disease may occur at any age. It is more predominant in females than males at a ratio of about 2:1.1

Predisposition to vascular occlusive events, involving cerebrovascular, coronary, and peripheral circulation, as well as hemorrhages has been noted in affected subjects. Some patients with ET are asymptomatic, while others may experience vasomotor symptoms such as headaches, visual disturbances, lightheadedness, atypical chest pain, distal paresthesia, and erythromelalgia. Thrombotic or hemorrhagic disturbances are also possibilities. Arterial and venous thromboses, as well as platelet-mediated transient occlusions of the microcirculation and bleeding, represent the main risks for ET patients.2 MPN include polycythemia vera, primary myelofibrosis, and essential thrombocythemia. These three types share the same mutations. Around 55% of ET patients have a mutation of the Janus kinase 2 (JAK2) gene in their blood cells.3

According to the World Health Organization (WHO), ET occurs when the platelet count is higher than a specific number (referred to as 450000/µL) with the presence of JAK2, calreticulin (CALR), or myeloproliferative leukemia virus oncogene (MPL) mutation, while also lacking clonal or reactive causes. JAK2 is a non-receptor tyrosine kinase found in the cytoplasm, playing a pivotal role in hematopoiesis. Its mutation leads to the gain of function, resulting in the activation of intracellular signaling pathways associated with the receptors of hematopoietic cytokines, including erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor.3,4

Case presentation

A 37-year-old female presented with a three-week history of gangrene in both toes (Fig. 1a) and roughening of the skin surfaces (Fig. 1b). The patient did not show any other signs of a connective tissue disorder, such as a malar rash, oral ulcer, alopecia, recurrent abortions, Raynaud’s disease, or similar episodes of gangrene in the past. However, the patient did experience some vague, nonspecific aches
and pains that were overlooked. Initial laboratory reports showed an increased total white blood cell (WBC) count and platelets, and low hemoglobin levels. Inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were unremarkable. Antiphospholipid (APL), antinuclear antibody (ANA), and antineutrophil cytoplasmatic (ANCA) tests were negative, and arterial Doppler imaging revealed no abnormalities. She was initially treated with steroids and aspirin (Ecosprin) for suspected vasculitis. The patient responded well to the initial treatment. However, routine follow-up investigations presented a new set of challenges. Hemoglobin levels were 9.2 gm/dl, with an increased total WBC count of 25300 cells/cmm and a platelet count of 15.9 lakhs/cmm.

Given the atypical presentation and inconclusive initial investigations, a more thorough examination was initiated. JAK2 gene mutation testing was carried out, and polymerase chain reaction (PCR) qualitative tests yielded positive results. The patient was referred to a hematologist for further treatment and was prescribed JAK inhibitors. Based on the clinical investigations and lab findings, the diagnosis was concluded as Essential Thrombocythemia (ET), a myeloproliferative disorder characterized by the clonal proliferation of megakaryocytes in the bone marrow, leading to increased platelet production.

Discussion
This case emphasizes the challenges of diagnosing patients who present with atypical symptoms, highlighting the importance of a comprehensive diagnostic approach. Initially, the patient was presented with gangrene in the

Fig 1a: Gangrene in the toes

Fig 1b: Roughening of the hand skin
toes, along with elevated white blood cell count, platelets, and low hemoglobin levels. The initial suspicion of vasculitis developed from the clinical presentation of gangrene in a young female with a normal arterial Doppler. Despite this, her inflammatory parameters, including CRP and ESR, were within normal ranges. Additionally, the negative results from APL, ANA, and ANCA tests, along with the normal arterial Doppler, led to the decision to conduct further investigations. The case highlights the critical consideration of myeloproliferative neoplasms as a differential diagnosis in cases of atypical thrombosis.

A similar study by Alayyuan et al. reported the case of a 52-year-old woman who initially presented with painful toe swelling and discoloration. She underwent repeated unsuccessful treatments including abscess drainage and toe amputation. Two years later, she was diagnosed with essential thrombocythemia, emphasizing the importance of considering myeloproliferative neoplasms as a differential diagnosis in cases of atypical thrombosis.

Further evaluation in the current case showed that there was a decrease in hemoglobin levels, an increase in total WBC count, and elevated platelet count. The subsequent positive findings in JAK2 gene mutation and PCR qualitative tests shifted the diagnosis towards ET, a condition that can mimic vasculitis due to its potential to cause thrombotic complications. Pedersen et al. reported that patients with ET have more reticulated platelets and higher potential for aggregation compared to healthy individuals. These results might partially explain why patients with ET have a higher risk of thromboembolism.

The WHO diagnostic criteria for ET stipulate that the presence of all four major criteria or the satisfaction of the first three major criteria, along with the minor ones, is essential for diagnosis. The major criteria include a platelet count of $\geq 450,000/\mu L$, a bone marrow biopsy revealing proliferation primarily in the megakaryocytic lineage, characterized by an increase in enlarged, mature megakaryocytes with hyperlobulated nuclei, and the absence of significant rise or left shift in neutrophil granulopoiesis or erythropoiesis, with only a minor increase in reticulin fibers. The presentation should not align with WHO criteria for BCR-ABL1 positive chronic myeloid leukemia (CML), polycythemia vera (PCV), myelofibrosis, myelodysplastic syndromes (MDS), or other myeloid neoplasms. Additionally, the presence of JAK2, CALR, or MPL mutations is considered a major criterion. Minor criteria include the presence of a clonal marker or lack of evidence of reactive thrombocytosis. The evaluation of patients with suspected ET involves conducting a complete blood count, a bone marrow biopsy, and genetic testing to assess for relevant gene mutations. These comprehensive criteria provide a structured approach for accurate diagnosis and classification of ET cases.

The elevated platelet count observed in the case serves as a clear indication, meeting one of the major criteria. Although the case does not explicitly conduct a bone marrow biopsy, the presented characteristics strongly suggest megakaryocytic proliferation, aligning with another major criterion. Furthermore, the exclusion of vasculitis based on negative results in APL, ANA, and ANCA tests corresponds to the criteria specifying the absence of other conditions like CML, PCV, myelofibrosis, MDS, or other myeloid neoplasms. Finally, the positive results in the JAK2 gene mutation test contribute to satisfying the major criterion associated with the presence of specific mutations in ET diagnosis.

Certain conditions associated with digital gangrene include APLA, medium vessel vasculitis, SSC, and ET, with other causes being even rarer. With a platelet count of 15.9 lakhs/cmm, normal ESR and CRP, and a very high TLC (>25,000 cells/cmm), ET should have been the first diagnosis, with CML a close second. JAK2 kinase testing was done to confirm the diagnosis. JAK2 is a non-receptor tyrosine kinase that plays a crucial role in the formation of blood cells. Patients with ET have a JAK2 mutation in about half of the cases. The JAK2 V617F is the most frequently observed mutation, occurring in 50% to 60% of patients with ET, according to Babakhanlou et al.

ET is typically a slow-progressing condition with a median survival of 18 years. In patients under 60, reported life expectancy can extend up to 33 years, surpassing that of polycythemia vera. Despite its indolent nature, ET carries a lower life expectancy compared to the general population due to the heightened risk of thrombotic complications that complicate disease progression. Thrombosis is the leading cause of morbidity and mortality in ET, occurring in approximately 20% of cases, followed by hemorrhage at 10%. There is <1% risk of progression to myelofibrosis. Complications include cerebral vessel thrombosis leading to strokes, coronary artery involvement causing acute coronary syndrome, and hepatic vein thrombosis leading to Budd-Chiari syndrome.
ET often poses a diagnostic challenge due to its ability to mimic other conditions, particularly vasculitis, through its thrombotic complications. The absence of specific clinical or laboratory markers for ET further complicates its recognition. This case underscores the importance of considering myeloproliferative disorders in the differential diagnosis of patients presenting with vascular complications. The initial use of steroids and antiplatelet therapy might have contributed to the improvement of symptoms, as these interventions can have a nonspecific anti-inflammatory effect. However, the definitive diagnosis of ET led to a more targeted and appropriate management plan, addressing the underlying hematologic disorder.

In the current patient with digital gangrene, the differential diagnosis to be considered includes APLA, medium vessel vasculitis, SSc, and ET, among others, although less common. Given a platelet count of 15.9 lakhs, normal ESR and CRP levels, and markedly elevated TLC (>25,000 cells/mm³), ET would reasonably be the primary diagnosis, with CML as a secondary consideration. Treatment should be coordinated by a hematologist, especially considering the complexity of ET. Hematinics may be prescribed to manage concurrent deficiencies, with careful monitoring to avoid complications.11

**Conclusion**

The case highlights the significance of including myeloproliferative disorders, particularly ET, within the differential diagnosis when confronted with clinical presentations resembling vasculitis. Positive JAK2 gene mutation and PCR qualitative tests are pivotal in accurate diagnosis, and guiding appropriate management strategies, thereby contributing to enhanced patient outcomes.

**Patient declaration statement**

The authors certify that the patient had given her consent for images and other clinical information to be reported in the journal. The patient understood that her names and initials will not be published and due efforts will be made to conceal her identity.

**Citation**

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