A Dramatic Twist of Events Starting with Flank Pain

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Polycythemia vera (PV) is a chronic, Philadelphia chromosome-negative myeloproliferative neoplasm primarily driven by the Janus kinase 2 (JAK2) V617F mutation. PV leads to clonal erythrocytosis and is frequently accompanied in laboratory blood tests with leukocytosis and thrombocytosis. The diagnostic approach to PV is based on increased red cell volume and the presence of a JAK2 mutation [1]. PV should not be defined solely by hemoglobin or hematocrit values. In a large study of the genomic landscape of myeloproliferative neoplasms, approximately 65% of patients with PV had at least one additional mutation in addition to the driver mutation, most commonly in *TET2*, *DNMT3A*, and *ASXL1* genes [2].

The disease is characterized by a pro-inflammatory and thrombotic state, which contributes significantly to the leading cause of morbidity and mortality in PV. Thrombotic and bleeding complications accounted for 45% of mortality in patients with PV, while only 13% of mortality was attributed to disease progression to myelofibrosis and or acute leukemia [3].

Arterial and venous thrombosis manifestations can be highly variable ranging from acute coronary syndrome, cerebrovascular events, and venous thromboembolism to less common but significant vascular complications including digital ischemia, splenic vein thrombosis, cerebral venous thrombosis, and retinal vein thrombosis [4].

We present a case of a patient diagnosed with positive JAK2 PV who presented with splenic infarction and developed a rare manifestation of PV with rapidly progressive bilateral microvascular limb ischemia.

PATIENT DESCRIPTION

A 79-year-old male with a medical history of non-Hodgkin lymphoma in remission, neuroendocrine tumor treated surgically, hypertension, dyslipidemia, type 2 diabetes mellitus, chronic kidney disease, and a prior transient ischemic attack was first admitted to the hospital due to worsening left flank pain. On physical examination vital signs were normal, the abdomen was soft, non-tender, without hepato-splenomegaly. Flank pain was not reproduced on palpation. Laboratory blood tests revealed leukocytes 12.7 × 10^3/μL (normal range 4–10 × 10^3/μL), hemoglobin 11.4 g/dl (normal range 13.5–17.5 g/dl), MCV 72 (normal range 80–100), platelet 311 μL (normal range 150–450/μL), and elevated C-reactive protein (CRP) 12 mg/L (normal range < 0.5 mg/L). Nephrolithiasis was suspected; therefore, an abdominal computed tomography scan was performed. It revealed a non-obstructive renal stone and a sharply demarcated large splenic infarction measuring 9.3 cm with mild splenomegaly.

An abdominal ultrasound confirmed a hypoechoic, avascular splenic lesion compatible with a splenic infarct [Figure 1A]. Further investigations regarding splenic infarction included blood tests such as antiphospholipid antibodies (beta 2 glycoprotein, anti-cardiolipin) and lupus anticoagulant that were normal. To assess a potential embolic source, a Holter monitor was conducted and was negative for occult arrhythmias. Transthoracic echocardiography demonstrated normal global and regional systolic function with a preserved ejection fraction of 65%, no significant valvular abnormalities, and no evidence of vegetations or intracardiac thrombus. The patient was discharged with a recommendation follow-up with a hematologist.

One month later, the patient presented with non-exertional leg pain and bilateral foot ulcers. Physical examination noted bilateral leg edema. Both feet were warm to touch with painful sores spread on the feet with local redness. Dorsalis pedis pulses were weak bilaterally while femoral and popliteal pulses were preserved. Laboratory blood tests revealed leukocytes 11.8 × 10^3/μL, hemo-

globin 10.3 g/dl, MCV 72, platelets 881,000/µL, elevated creatinine 2.0 mg/dl, iron × 10 µg/dl (normal range < 60 to 160 µg/dl), transferrin saturation 4.9% (normal range 20–50%), ferritin 144 ng/ml (normal range 30–400 ng/ml), and CRP 2.75 mg/L. Repeated antiphospholipid antibodies testing remained negative.

The vascular and orthopedic surgery consultations suggested the ulcerations could be secondary to microemboli or microvascular ischemia. A vascular doppler test showed normal blood flow to the lower extremities. A lower extremity computed tomography angiography revealed extensive splanchnic thrombosis, including thrombus in the portal vein, splenic vein, and superior mesenteric vein [Figure 1B]. The spleen appeared enlarged (14 cm) with areas of infarction. Heterogeneous hepatic perfusion suggested ongoing vascular compromise. The right tibialis anterior artery was obstructed on its caudal third. The left dorsalis pedis artery had severe stenosis on alternate locations [Figure 1C].

No clear evidence of malignancy was noted. At this point the working diagnosis was of an underlying hypercoagulable hematologic disorder. A hematology consultation based on the presence of marked thrombocytosis (intermittent from 2022) combined with a thrombotic state suggested a myeloproliferative disorder such as PV, potentially masked by iron deficiency anemia.

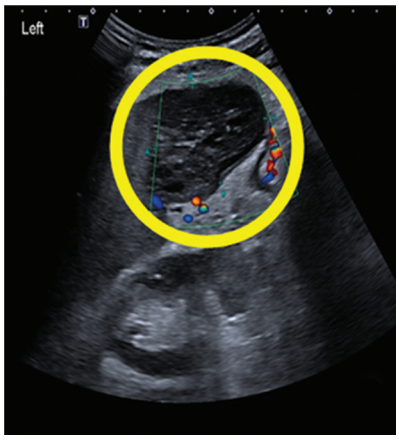
Molecular testing confirmed the presence of a JAK2 V617F mutation and low erythropoietin levels supported the diagnosis of PV. The patient was considered at high risk for thrombotic complications and required cytoreductive therapy. Hydroxyurea was contraindicated due to active leg ulcers and ruxolitinib (a targeted JAK1 and JAK2 inhibitor)10 mg orally twice daily. Despite chronic kidney disease, apixaban was advised at the full dose of 5 mg twice daily. The patient was discharged.

Four weeks later, the patient presented for the third time with rapidly progressive bilateral foot pain. On physical examination new findings included a diffuse purplish-erythematous rash on both feet, bilateral second and third necrotic toes at the distal end, deep erosive lesions affecting the distal third of both feet, and profuse foul-smelling greenish discharge from the right foot with marked necrosis [Figure 1D]. Both feet were cold with

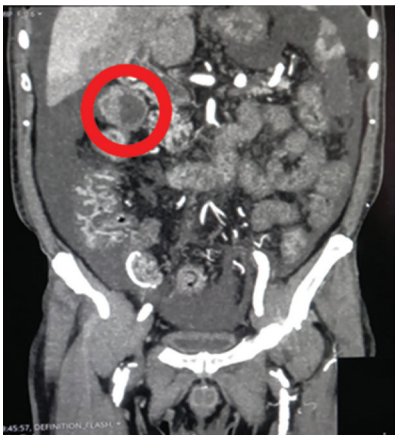
Figure 1. Polycythemia vera clinical and imaging findings with the rare presentation of micro-emboli

CT = computed tomography, CTA = computed tomography angiography (CTA)

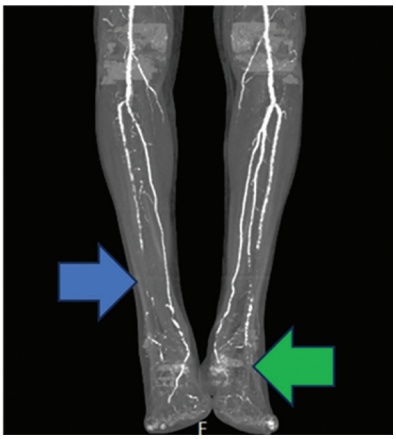
[A] Abdominal ultrasound shows a hypoechoic, avascular splenic lesion consistent with splenic infarction (yellow circle)



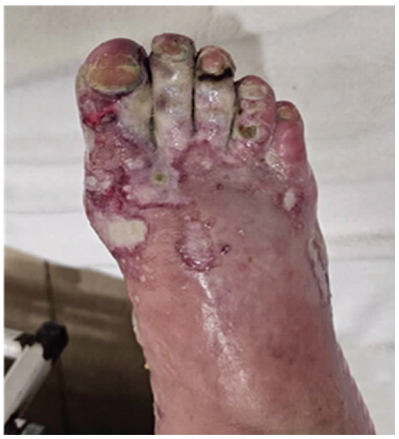
[B] Contrast-enhanced abdominal CT, coronal view, show superior mesenteric veins thrombosis (red circle)



[C] Lower extremity CTA, coronal view, show distal occlusion of the right anterior tibial artery (blue arrow) and severe segmental stenosis of the left dorsalis pedis artery (green arrow)



[D] Clinical exam show distal foot necrosis, distal foot ulcer, and discharge from the right foot



no dorsalis pedis or tibial posterior pulses. Wound cultures were positive for *Pseudomonas aeruginosa*. Blood cultures were negative. Empiric therapy with cefazolin and ciprofloxacin was initiated and later escalated to piperacillin-tazobactam because of deteriorating clinical status and progression of the infected ischemic lesions. Ruxolitinib was discontinued according to the hematology consultation due to the active infection.

Repeated arterial doppler ultrasound showed absence of distal pulses in the right foot and diminished pulse on the left suggested severe microvascular ischemia. Surgical revascularization was not an option. As a complementary therapy for vascular ischemia, a course of intravenous iloprost was initiated, but ischemia progressed and the right foot developed gangrenous changes with superimposed infection. The patient underwent a right above-knee amputation.

Postoperatively, despite treatment with broad-spectrum antibiotics and a second course of iloprost, ischemia progressed to involve the left leg, including new necrotic areas. Clinical improvement was not achieved, and left-sided amputation was considered but deferred due to hemodynamic instability. Subsequently the patient deteriorated with in-hospital complications including rhinovirus bilateral pneumonia with bacterial superinfection and oliguric progressive renal failure requiring hemodialysis. Despite combined therapy, the patient experienced acute respiratory distress syndrome. After discussion with the patient and his family, the patient declined intubation and resuscitation and was treated with supportive care including proper pain management. The patient died of septic shock and multiorgan failure.

COMMENT

PV is a JAK2-mutated myeloproliferative neoplasm in which thrombotic complications remain the leading cause of morbidity and mortality. Thrombosis in PV is not solely driven by erythrocytosis, but by a complex thrombo-inflammatory milieu involving activated platelets, leukocytes, and erythrocytes as well as endothelial dysfunction, microparticle generation, increased inflammatory cytokine production from aberrantly activated T and NK cells, and upregulation of adhesion molecules and coagulation pathways. Together, these mechanisms create a persistent prothrombotic state that predisposes patients to both arterial and venous thromboses, including events at unusual anatomical sites [1,2]. This pathophysiological framework is central to understanding the severe and multi-territorial thrombotic manifestations observed in our patient. Although the patient had a history of non-Hodgkin lymphoma and a neuroendocrine tumor, both potential contributors to hypercoagulability, extensive evaluation excluded active malignancy as a driving factor. A key diagnostic feature was the presence of chronic microcytic anemia with marked thrombocytosis, consistent with masked or occult PV. Iron deficiency can limit erythroid proliferation, thereby preventing the typical elevation in hemoglobin and hematocrit despite underlying polycythemia [1].

The splenic infarction observed early in the patient's disease course likely represented the first clinical manifestation of an unrecognized myeloproliferative neoplasm. Thromboembolic events may precede hematologic diagnosis in PV, and although rare, PV has been described as an underlying etiology of splenic infarction caused by thromboembolic disease [3]. The most striking aspect of this case was the rapid and fulminant disease progression, culminating in bilateral distal microvascular ischemia and tissue necrosis requiring limb amputation. While microvascular symptoms such as erythromelalgia are relatively common in PV, limb-threatening ischemia and digital necrosis are uncommon manifestations. Similar cases of acute limb ischemia and digital necrosis associated with myeloproliferative disorders have been reported. A previously published case report described digital necrosis as a rare manifestation of underlying polycythemia in a patient with preserved proximal arterial pulsations. After diagnosis and cytoreductive management with phlebotomy, surgical amputation was performed with favorable wound healing and outcome [4]. These reports underscore the potential severity of microvascular complications in PV.

The primary therapeutic goal in PV is prevention of thrombotic events while minimizing treatment-related toxicity. In low-risk patients, this is typically achieved with low-dose aspirin and phlebotomy to maintain hematocrit below 45%. Cytoreductive therapy is reserved for high-risk patients or those requiring frequent phlebotomy. In the present case, treatment options were constrained by clinical factors. Hydroxyurea, the standard first-line cytoreductive agent, was contraindicated due to active ischemic leg ulcers. Consequently, the JAK1/2 inhibitor ruxolitinib was selected as an alternative cytoreductive therapy. In the phase 3 RE-

SPONSE trial, ruxolitinib demonstrated superior efficacy compared with standard therapy in patients with PV who were resistant or intolerant to hydroxyurea, including improved hematocrit control, spleen volume reduction, symptom burden improvement, and fewer thromboembolic events [5].

CONCLUSIONS

Hypercoagulability due to PV is a rare clinical manifestation. This case highlights a rare and devastating presentation of masked PV, which began with nonspecific flank pain due to splenic infarction and rapidly evolving into catastrophic thrombi, including splenic infarction, extensive visceral venous thrombosis, as well as rapidly developing microvascular ischemia in the extremities. Spleen ischemia should always raise suspicion for an underlying hematological disease, and further investigation is crucial. Early diagnosis and treatment of PV is imperative to improve prognosis.

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Capsule

Low-plastic diet and urinary levels of plastic-associated phthalates and bisphenols: the randomized controlled PERTH Trial

Harray and co-authors investigated whether a low-plastic diet could reduce human exposure to plastic-associated chemicals, particularly phthalates and bisphenols. In the randomized controlled PERTH trial, participants followed either a conventional diet or a diet specifically designed to minimize contact with plastic packaging, storage containers, and food-processing materials. The intervention resulted in significant reductions in urinary concentrations of several phthalates and bisphenol compounds, demonstrating that dietary exposure is a major contributor to the body burden of these chemicals. The findings highlight the feasibility of exposure reduction through lifestyle modifications and raise important public health considerations regarding chronic exposure to endocrine-disrupting compounds.

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Capsule

Diet–microbiome associations in 10,068 individuals from the Human Phenotype Project to guide personalized nutrition

Segev and colleagues analyzed diet–microbiome interactions in more than 10,000 participants enrolled in the Human Phenotype Project to better understand how dietary patterns shape the gut microbiome and influence metabolic health. The study identified strong associations between specific dietary components and microbial taxa, as well as considerable interpersonal variability in microbiome responses to similar foods. Machine-learning models integrating dietary, microbiome, and clinical data enabled improved prediction of personalized metabolic responses. The findings support the development of individualized nutritional recommendations based on microbiome composition and host characteristics.

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