

Pearls & Oysters: Polycythemia vera presenting with ischemic strokes in multiple arterial territories

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PEARLS

- Thrombosis is the presenting symptom in 20% of patients with polycythemia vera (PV); 70% of these thrombotic events are TIAs or strokes.
- JAK2 V617F mutation occurs in 95% of cases of PV; the 25%–30% of patients who are homozygous for the mutation are more likely to be symptomatic.
- Erythromelalgia can occur in 28% of patients with PV and is usually reversible with PV treatment.
- Thrombotic events in PV can be prevented with aspirin, phlebotomy (hematocrit <45 L/L), and hydroxyurea.

OY-STERS

- Recurrent thrombosis can occur in up to 33% of patients with PV and is related to age (>60 years) or increased leukocyte count (in patients <60 years).
- The diagnosis of PV can be missed if a complete blood count (CBC) is not included as part of the stroke evaluation.

CASE REPORT A 65-year-old right-handed man with a history of prostate cancer treated with radiation therapy, hyperlipidemia, hypertension, and remote cigarette smoking presented with recurrent episodes of right arm weakness and “heaviness” over 6 months. Over the preceding month, he noticed progressive imbalance, slower gait, dysarthria, and 3 episodes of syncope.

Evaluation included a normal carotid ultrasound, thyroid function tests, vitamin B₁₂, and folic acid levels. A CBC was not obtained. A brain MRI with and without contrast at that time showed multiple confluent areas of T2 hyperintensities in the left centrum semi-ovale in a watershed distribution (figure, A).

A few months later, the patient presented to the emergency room with worsening weakness of the right upper extremity. Examination was notable for facial plethora, moderate weakness of the extensor

muscle groups, length-dependent decrease in sensation in the right upper extremity, and a moderate gait apraxia. The remainder of the examination was normal. MRI of the brain with and without contrast showed acute infarction involving the high left frontal and parietal lobes as well as the left occipital lobe (figure, B–E). A CT angiogram of the head and neck showed minimal stenosis of the origin of the right vertebral artery but normal carotid arteries and intracranial vessels (figure, F). Transesophageal echocardiogram showed a normal ejection fraction without an intracardiac shunt or thrombus. Forty-eight hours of Holter monitoring revealed no arrhythmia. Laboratory values were significant for low-density lipoprotein cholesterol of 150 mg/dL, hemoglobin A1c of 6.2%, hemoglobin of 19.2 g/dL, leukocyte count of 11.3×10^9 , and platelet count of 541×10^9 . Erythropoietin (EPO) levels were within normal range at 12 mIU/mL (ref 2–15). A JAK2 V617F mutation was detected in fewer than 50% of cells, indicating heterozygosity for the mutation, and bone marrow biopsy revealed hypercellularity. The patient was diagnosed with PV and started on hydroxyurea, phlebotomy (goal hematocrit <45 L/L), aspirin 81 mg daily, and a statin. His symptoms improved and he had no recurrent events over the ensuing 9 months.

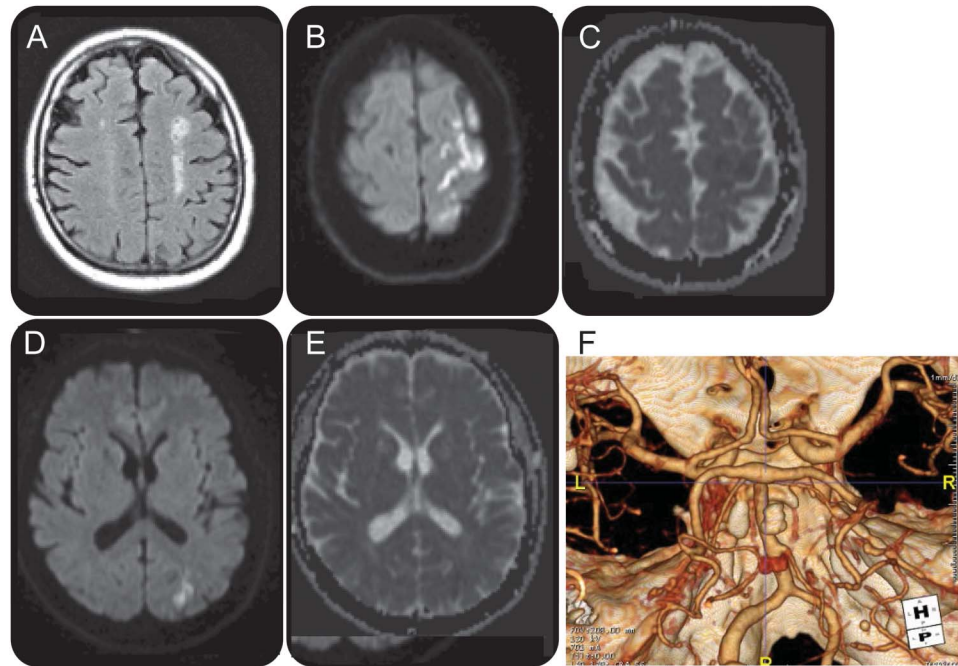
Of interest, the patient had presented to a wound care clinic months prior for a nonhealing left toe ulcer with paresthesia and dusky discoloration. Ankle brachial index was without significant arterial insufficiency. Venous duplex revealed normal venous system without deep vein thrombosis. Management with pregabalin was initiated for a presumed neuropathy. Nerve conduction studies were not pursued. After initiation of the treatment for PV, his ulcer healed and he had no further complaints of paresthesia, leading to discontinuation of pregabalin. He was diagnosed with erythromelalgia associated with PV.

DISCUSSION Our patient presented with dysarthria, dysphasia, gait apraxia, dizziness, and headache, which are often the presenting manifestations of thrombocytosis in PV.¹ He met the World Health

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(A) Fluid-attenuated inversion recovery sequence of MRI brain obtained on first evaluation shows chronic left watershed ischemic changes. (B) Diffusion-weighted sequence of MRI brain obtained 2 months following the initial scan shows acute ischemic stroke in left frontoparietal distribution. (C) Apparent diffusion coefficient (ADC) maps correspond to the diffusion changes seen in B. (D) Diffusion-weighted sequence of MRI brain shows left occipital ischemic stroke. (E) ADC maps correspond to the diffusion changes seen in D. (F) CT angiogram of intracranial vasculature demonstrates absence of intracranial stenosis.

Organization (WHO) criteria of PV with fulfillment of the 2 major criteria (hemoglobin >18.5 g/dL, JAK2 617V mutation) and 1 minor criterion (low or normal serum EPO level).² In the absence of cardioembolic etiology or steno-occlusive vascular disease, his stroke was attributed to PV in the setting of other vascular risk factors including age, prediabetes, hypercholesterolemia, hypertension, and remote smoking history.

PV is a myeloproliferative disorder characterized by excessive proliferation of the myeloid cell lines. It is estimated to occur in 1 in 100,000 people each year in the United States, with median age at diagnosis of 60 years and men accounting for more than half (58%) of the cases.³ In a retrospective study of more than 1,200 patients with PV, stroke and TIA accounted for approximately 70% of arterial thrombotic events at diagnosis.³ In a separate study, approximately 33.6% of patients with thrombosis (arterial or venous) had thrombotic recurrence, with increased risk associated with increased age (≥ 60 years) or increased leukocyte count ($>12.4 \times 10^9/L$) in patients ≤ 60 years.⁴

Thrombosis in PV is attributed to several factors, including endothelial damage and its subsequent interaction with activated platelets.⁵ In addition to the platelet-related factors, high volume of erythrocytes may increase blood viscosity and lead to an

impairment of blood flow resulting in vascular complications such as erythromelalgia, peripheral ischemia, and atypical TIAs.⁵ This could explain the watershed-distribution infarctions noted on our patient's brain MRI as well as his syncopal episodes. Erythromelalgia, defined as acral paresthesia accompanied by erythema, pallor, or cyanosis in the presence of palpable pulses, has been described in approximately 28% of WHO-defined PV cases.¹ It is thought to be the result of microvascular thrombotic complications in thrombocythemia ($>400,000/\mu L$). Our patient's symptoms resolved after normalization of his platelet count.

Previous description of the cerebral vasculature in the setting of arterial thrombosis in PV is sparse. In our patient, with multiple large-artery involvement and recurrent strokes, there was only minimal narrowing in the intracranial and extracranial vasculature, indicating that factors other than vascular narrowing play a role in PV-related stroke.⁶

The etiology of PV is attributed to a gain-of-function mutation of the JAK2 domain (JAK2 V617F mutation) found in more than 95% of patients, with the remaining 5% harboring other JAK2 mutations with similar functional consequences. Homozygosity is displayed by approximately 25%–30% of patients with PV, with those patients more likely to have symptomatic disease.⁷ The

number of cells expressing the JAK2 V617F mutation (the allele burden) typically correlates with the clinical phenotype and resultant myelopoiesis.⁸ JAK2 V617F is also seen in other myeloproliferative disorders, including essential thrombocythemia and primary myelofibrosis, but its presence is not diagnostic of any one of these diseases. To make a specific diagnosis, correlation with other clinical and laboratory findings is required. Similarly, the absence of the JAK2 V617 mutations does not exclude the diagnosis. The tyrosine kinase JAK2 acts in the signaling pathways of the EPO receptor and the mutation increases sensitivity to the EPO hormone. For this reason, and similar to our patient, primary PV is associated with a low or normal serum level of EPO, as opposed to secondary PV, in which EPO levels are high.

Several laboratory techniques have been developed for JAK2 V617F genotypic analysis. Different sensitivity of various assay methods partially accounts for the wide range of mutation frequencies: re-evaluation of the same cases with a more sensitive technique has increased the detection rate from 73% to 97% in patients with PV.⁸

Treatment of PV is focused on cytoreduction to reduce future thrombotic events. A hematocrit <45 L/L is associated with lower rate of cardiovascular death and major thrombosis.⁹ Chemotherapy with hydroxyurea and use of anagrelide, a medication that inhibits the maturation of platelets, may also be used in conjunction with phlebotomy. In addition to these therapeutic strategies, an antiplatelet drug is often used to reduce thrombotic risk. A randomized controlled trial in 2004 enrolled 518 patients with PV to assess the safety and efficacy of prophylaxis with low-dose aspirin (100 mg daily). Treatment with aspirin in conjunction with hydroxyurea and cytoreduction reduced the risk of nonfatal stroke, major venous thrombosis, and stroke-related death.⁹ In addition, in a review of 630 individuals with PV with no clear indication or contraindication to aspirin therapy, low-dose aspirin in conjunction with cytoreduction reduced the risk of thrombotic and all-cause mortality.¹⁰

This case highlights the occurrence of multiple and recurrent ischemic strokes as an initial presentation of PV with JAK2 heterozygosity in the setting of normal vasculature, cardiac imaging, and cardiac monitoring. Although the exact mechanism of this phenomenon in the setting of PV has not been established, we postulate that the microenvironment of a particular vessel (narrowing not well visualized on current imaging modalities, turbulence, endothelial dysfunction) or predisposition to thrombosis in an area with increased susceptibility such as in a watershed territory may have increased the risk of recurrent strokes in the same vascular distribution. The

diagnosis was primarily made by obtaining careful history and examination, excluding alternative etiologies, and obtaining a CBC with subsequent targeted genetic testing. Clinical clues that would lead one to suspect PV in a stroke patient include symptoms such as chronic headache, single limb weakness, blurred vision, dysarthria, dysphasia, gait instability, and dizziness as well as peripheral symptoms such as erythromelalgia. A CBC is critical for the diagnosis and typically leads to further investigations. Avoiding diagnostic delays in patients with PV is critical to prevent thrombotic recurrence as treatment differs from that of typical ischemic stroke.

AUTHOR CONTRIBUTIONS

Dr. Santoshi Billakota: manuscript writing and production. Dr. El Husseini: manuscript revisions, figures, study supervision.

ACKNOWLEDGMENT

The authors thank Larry Goldstein, MD, and Ellen Bennett, PhD, for critical review of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology 2014;82:e168-e170

DOI 10.1212/WNL.0000000000000430

This information is current as of May 19, 2014

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