Clinical Reasoning: A 65-Year-Old Woman With New Headache, Pulsatile Tinnitus, and Visual Disturbances

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Section 1

A 65-year-old previously healthy woman noticed new-onset, gradual, blurry vision in her left eye with perceived loss of peripheral vision and pulsatile tinnitus in the left ear for the past 2 weeks. In the past year, she visited 3 different emergency departments for new nonpulsatile and nonthunderclap headaches, which she described as “searing” pain. The headaches were accompanied by nausea without phonophobia or photophobia, were not worsened or triggered by recumbency and Valsalva, and did not wake her from sleep. There were no associated neurologic or systemic symptoms. A noncontrast CT scan of the brain was interpreted as normal. Visual acuity was 20/25 bilaterally. There was no relative afferent pupillary defect. On ophthalmoscopy, she had bilateral severe optic nerve head edema (Figure, A). Formal visual field testing (Humphrey 24-2) showed enlargement of the blind spots in each eye (Figure, B). The remaining neurologic examination was normal.

Questions for Consideration:

1. What are the red flags in this patient’s headache history?
2. What is the differential diagnosis and next most appropriate imaging study to order?

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(A) Fundus photographs demonstrating bilateral optic disc edema. (B) Humphrey visual fields (24-2 algorithm) demonstrating blind spot enlargement in the right eye. (C) Coronal contrast-enhanced CT of the head showing compression of the left internal jugular vein by the elongated styloid process (black arrow). (D) MR venography, coronal view demonstrating nonvisualization of the right distal transverse sinus, sigmoid sinus, and internal jugular vein (white arrowheads) with filling defect due to thrombus within the left internal jugular vein (white arrow). (E) Sagittal MR venography image demonstrating the barely visible right internal jugular vein (white arrow). (F) Sagittal MR venography image demonstrating thin, nonocclusive thrombus in the left internal jugular vein (white arrow). MR = magnetic resonance.

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Section 2

This patient's presentation with new headaches at an older age, accompanied by blurred vision and pulse-synchronous tinnitus, raises suspicion for increased intracranial pressure (ICP). Ophthalmoscopy can confirm the presence of ICP by identifying optic disc edema. In addition, even when performed correctly, ophthalmoscopy can be difficult to interpret because common and benign etiologies can mimic optic disc edema, including optic disc drusen and small, crowded, or anomalous optic nerves.¹

Bilateral optic disc edema with normal visual function in this patient is consistent with papilledema. The differential diagnosis for papilledema is broad, including idiopathic intracranial hypertension (IIH), cerebral venous sinus thrombosis (CVST), hydrocephalus, intracranial space-occupying lesions, and meningoencephalitis. Brain parenchymal imaging with MRI or CT including venography should be performed in all patients with suspected papilledema.

Our patient's CT scan revealed an elongated left styloid process, possibly compressing the left internal jugular vein (Figure, C). An elongated styloid process can rarely cause compression of adjacent structures including the carotid artery or jugular vein as it passes between the styloid process and the transverse process of the first cervical vertebrae and can be associated with ischemic events and tinnitus (vascular Eagle syndrome).²

Magnetic resonance venography revealed complete opacification of right transverse and sigmoid sinuses with high T2/FLAIR hyperintense signal within opacified areas without corresponding high signal on T1, consistent with extensive chronic thrombosis. There was also a nonocclusive filling defect in left sigmoid sinus and jugular vein (Figure, D–F). A lumbar puncture to measure the ICP demonstrated an opening pressure of 47 cm of water with normal CSF composition. No infectious etiology was identified. Her remaining blood work revealed an elevated hemoglobin of 168 g/L (120–160 g/L) and hematocrit of 0.52 (0.38–0.50).

Digital subtraction angiography (DSA) was performed to assess the degree of stenosis and pressure gradient across dural venous sinuses, to exclude the presence of dural arteriovenous fistula, and, given her elongated styloid process, to assess the effect of provocative maneuvers (head turning) on venous outflow. DSA demonstrated severe stenosis of left jugular bulb and both right transverse and sigmoid sinuses, resulting in severe venous hypertension. Head turning decreased venous outflow although the area of worst stenosis was located above the level of the styloid process.

Treatment with oral anticoagulation was initiated, and to decrease ICP, acetazolamide was initiated, with close neuro-ophthalmic follow-up.

Questions for Consideration:

1. Do you think the elongated styloid process is causative?
2. What additional investigations would you order?

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Section 3

One possible interpretation of our patient's presentation is that jugular vein compression by an elongated styloid process could promote venous stasis, predisposing to thrombosis formation. Although imaging demonstrated an elongated left styloid process, the evidence for it being the culprit for CVST was not definitive on DSA. In addition, thrombosis was more extensive on the right side and the measured styloid length was near the upper limit of normal. Therefore, an alternate diagnosis was pursued.

The recent European guidelines do not recommend screening for occult malignancy or thrombophilia in patients with CVST.³

However, given her extensive unprovoked thrombosis and elevated hemoglobin/hematocrit, hypercoagulability screening was performed, including Factor V Leiden, protein C/S, homocysteine, antiphospholipid and anticardiolipin antibodies, and prothrombin and Janus kinase 2 (*JAK2*) mutations.

Ultimately, testing for prothrombotic *JAK2* V617F mutation was positive.

Questions for Consideration:

1. Given this result, what further investigations should now be performed?
2. What should the patient be told regarding her future risk of thrombotic events?

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Section 4

The *JAK2* V617F substitution is a driver mutation in myeloproliferative neoplasms and is present in nearly all cases of polycythemia vera (PV) and 50%–60% of cases of primary myelofibrosis and essential thrombocytosis.⁴ Our patient had a hemoglobin of 168 g/L, which had increased from 139 g/L 1 year earlier. There was also mild thrombocytosis with platelet count 435 (150–400) compared with her previous count of 337. A bone marrow biopsy demonstrated hypercellularity with panmyelosis and atypical cells, which was diagnostic of PV. Treatment with hydroxyurea was recommended but was declined by the patient; thus, serial phlebotomies were used as an alternate treatment strategy.

JAK2 V617F is associated with an increased risk of thrombotic events both in carriers and in patients with myeloproliferative neoplasms,⁵ thus necessitating long-term treatment with direct oral anticoagulation. Over the next year, her papilledema resolved and follow-up venography demonstrated recanalization at the site of previous CVST.

Discussion

This clinical reasoning case is one of the few reports of CVST arising because of *JAK2* V617F mutation—an underappreciated etiology and diagnostic consideration of CVST. Testing for *JAK2* mutation must be performed in all CVST patients with elevated hemoglobin and should be considered even in those with normal CBC.⁶

Although well-appearing patients with papilledema are often presumed to have IIH, it is a diagnosis of exclusion and requires normal neuroimaging with venography (excluding indirect signs of raised ICP), normal CSF analysis, and no neurologic deficits beyond a sixth nerve palsy.⁷ This patient was not in the typical demographic group for IIH because only approximately 5% of patients are older than 50 years at diagnosis.⁸ Venography should be performed in all patients with papilledema who are not in a typical group for IIH (and some would argue it should be performed in all) because CVST is a relatively common secondary cause of raised ICP.⁹

Venous stasis, vessel wall injury, and hypercoagulability (Virchow triad) are responsible for development of venous thrombosis. Although CVST is not commonly seen in Eagle syndrome, it has been reported in some with styloid-jugular compression with high pressure gradients across the region of venous compression with resolution poststyloidectomy.^{8,10,11} Styloidectomy was considered in this case; however, when the *JAK2* mutation and bone marrow biopsy confirmed PV, non-invasive treatment with anticoagulation and serial phlebotomies commenced. Although it is unclear whether the elongated styloid process contributed to CVST in our patient, we hypothesize that the combination of her underlying hypercoagulable state and venous stasis produced by an elongated styloid process together increased her risk of developing CVST.

The pathophysiology of hypercoagulable states in patients with *JAK2* V617F mutation is multifactorial. In patients with overt myeloproliferative neoplasms, hyperviscosity is a probable contributor. However, the mutation alone carries an increased risk of thrombosis.⁵ One additional mechanism for thrombus formation is abnormal neutrophil activation leading to altered cell adhesion and binding of platelets and leukocytes to vascular endothelium.¹²

The evidence regarding optimal duration of anticoagulation after the initial treatment of CVST with low-molecular-weight heparin is not clear, and the general recommendation is between 3 and 12 months.³ In patients with PV, the risk of recurrent thrombosis must be managed and cytoreductive therapy such as hydroxyurea is recommended in older patients with PV or in those with a previous thrombotic event.¹³ Because our patient declined hydroxyurea, phlebotomy and long-term anticoagulation with apixaban were chosen. Although comparative safety and efficacy of direct oral anticoagulants (DOACs) vs warfarin have not yet been established in randomized control trials for patients with chronic CVST, emerging evidence suggests that both are effective in preventing recurrence.¹⁴ DOACs are increasingly used because of their convenience and favorable pharmacologic properties.

This clinical reasoning case is unique because it highlights an underappreciated diagnostic etiology of CVST: *JAK2* mutation. We underline unique clinical characteristics of patients with *JAK2* mutation and describe the clinical reasoning that led to a correct diagnosis and management of the disease in our patient. Recognition of optic disc edema was paramount in this case, highlighting the importance of ophthalmoscopy in evaluating patients with headaches and underpinning the importance of collaborative relationships between neurologists and neuro-ophthalmologists. There was some degree of unilateral jugular vein compression by an elongated styloid process that may have contributed to an upstream vulnerable milieu of cerebral venous stasis. While this was a tempting initial explanation for thrombosis, a hypercoagulable workup revealed that a prothrombotic mutation in *JAK2* was the most likely underlying cause of CVST.

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Appendix Authors

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Laura Donaldson, MD, PhD	Department of Ophthalmology and Vision Science, University of Toronto	Wrote the article

Continued

Appendix (continued)

Name	Location	Contribution
Ryan T. Muir, MD	Department of Medicine, Division of Neurology, University of Toronto	Revised the article for intellectual contribution
Joanna D Schaafsma, MD, PhD	Department of Medicine, Division of Neurology, University of Toronto	Revised the article for intellectual contribution
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