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Clinical Reasoning:
# A 66-year-old man with recurrent multi-territory infarcts

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SECTION 1

A 66-year-old man was referred to our center for evaluation of recurrent infarcts in multiple vascular territories over the preceding 6 months (figure 1). The patient first presented with a 3-month, stuttering course of transient neurologic deficits, including right arm and leg hemiparesis, expressive aphasia, and right homonymous hemianopia. He was initially evaluated at a community Stroke Prevention Clinic. His medical history was significant for several classic vascular risk factors: coronary

Figure 1   Serial MRI of multifocal infarctions
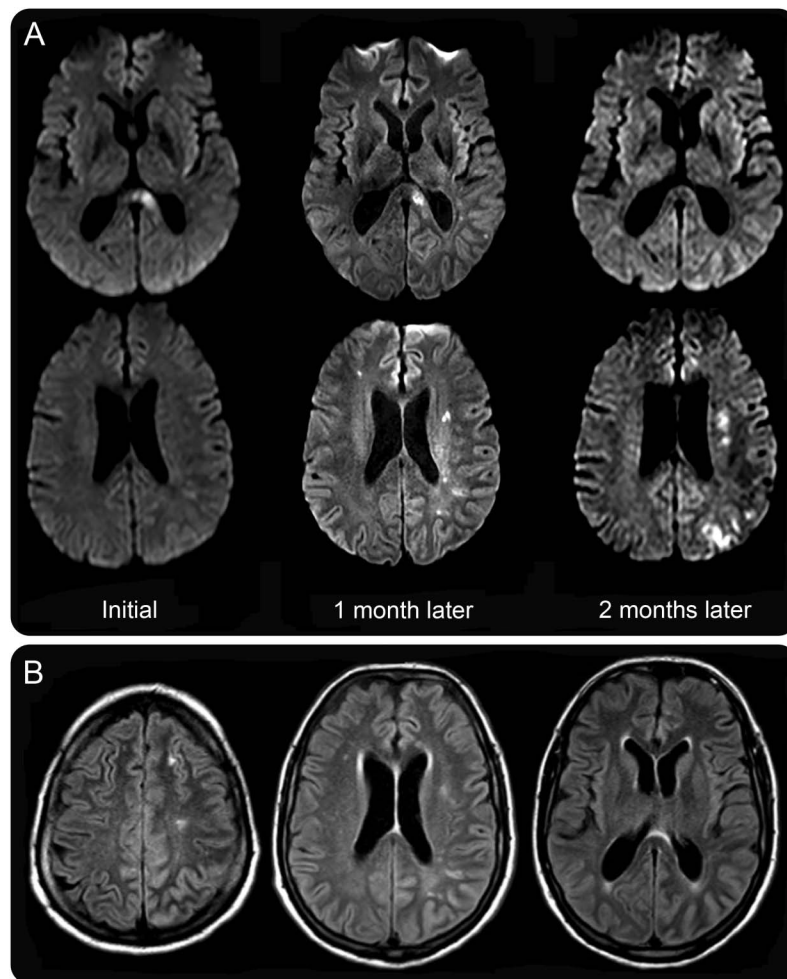
(A) Axial diffusion-weighted imaging (DWI) from January (initial), February (1 month later), and March 2014 (2 months later) shows a dynamic pattern of MRI lesions with resolution of some DWI lesions and new appearance of others, predominantly in the left hemisphere. (B) T2 fluid-attenuated inversion recovery at the time of initial presentation depicts subcortical and deep white matter hyperintensities.

artery disease requiring a coronary artery bypass graft, dyslipidemia for which he was taking atorvastatin 20 mg daily, and obstructive sleep apnea with noncompliance to his continuous positive airway pressure mask. In addition, he had atrial fibrillation for which he had undergone a cardiac ablation procedure 2 years prior. He was a nonsmoker and was normotensive. He had a distant history of left nephrectomy for biopsy-proven renal cell carcinoma, with several subsequent normal abdominal ultrasounds.

Question for consideration:

1. What potential stroke mechanisms need to be considered?

SECTION 2

There are multiple common etiologies of ischemic stroke that need to be considered at the outset, including large-artery atherosclerosis, cardioembolism, and small-vessel occlusion.[1] Other potential yet uncommon etiologies include infectious and inflammatory arteriopathies, genetic syndromes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, systemic disorders that also involve the cerebrovascular system such as systemic lupus erythematosus, noninflammatory disorders of the arterial wall such as Moyamoya disease, thrombophilias, and vasospasm-related disorders.[2]

A cardioembolic mechanism was first considered given the patient's history of atrial fibrillation and multifocal infarcts, but a transesophageal echocardiogram was negative for any intracardiac thrombus. Given the history of atrial fibrillation, his community neurologist started him on apixaban 5 mg daily. Despite this, he continued to have ischemic events. Serial MRIs (figure 1) showed multiple small acute to subacute infarcts in the left hemisphere, in the anterior cerebral artery, middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories, without areas of hemorrhage on susceptibility-weighted sequences. His initial magnetic resonance angiography (MRA) did not reveal any evidence of atherosclerosis or stenosis of the intracranial or extracranial vessels of the head and neck. As a result, large-vessel atherosclerosis etiology was largely ruled out. The location and appearance of ischemic strokes was not consistent with small-vessel atherosclerosis, given the involvement of both white and gray matter, with some infarcts following the boundaries of the large arterial vascular territories. In addition, there was lack of risk factors commonly predisposing to small-vessel disease, such as hypertension and diabetes.

Question for consideration:

1. What further investigations are needed to elucidate the stroke etiology?

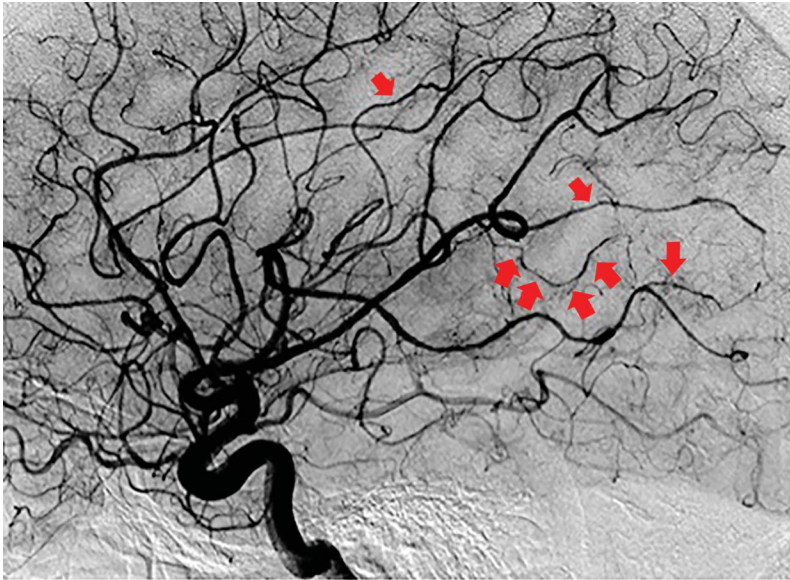**Figure 2   Cerebral catheter angiogram, left internal carotid artery injection, lateral projection**

Image depicts narrowing and irregularity of multiple distal arterial branches.

SECTION 3

Other, less common, stroke mechanisms such as infectious and inflammatory arteriopathies and malignant processes were considered. A basic autoimmune screen including erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and complements were within normal limits, along with an infectious workup including hepatitis serologies and HIV testing. A lumbar puncture showed 2 leukocytes (52% lymphocytes, 22% neutrophils), 248 erythrocytes, glucose of 4.1 mmol/L (reference range 2.2–4.4 mmol/L), and a slightly elevated protein of 0.85 g/L (reference range 0.15–0.45 g/L). CSF cytology showed no malignant cells and flow cytometry demonstrated a benign reactive T-lymphoid population. Microbiological studies, including varicella-zoster virus, were negative.

Despite anticoagulation, the patient continued to have TIAs with corresponding new acute infarcts in the left hemisphere, again in multiple territories. A repeat MRA was not diagnostic. Due to persistent clinical suspicion of an inflammatory arteriopathy, the patient underwent a cerebral angiogram, the gold standard for intraluminal imaging, which showed multiple abnormalities including concentric vessel wall narrowing and irregularities of the distal arterial branches of the MCA, PCA, superior cerebellar artery, and posterior inferior cerebellar artery on the left side (figure 2). As a result, he was given a presumed diagnosis of primary CNS vasculitis, given the acquired neurologic deficits combined with multifocal CNS lesions and typical angiographic findings. He was empirically started on prednisone at 1 mg/kg/day.

A month later, the patient returned to our center with worsening right hemiparesis despite high-dose steroids, accompanied by right-sided intermittent rhythmic movements of the arm with no associated impairment of awareness, which were thought to be either focal motor seizures or limb-shaking TIAs. He did not endorse headaches or other systemic features. His cognitive deficits were also progressively worsening, with Montreal Cognitive Assessment score of 16/30 on admission.

Questions for consideration:

1. What is supportive of primary CNS vasculitis?
2. What other diagnostic considerations are present?

Figure 3   MRI demonstrates leptomeningeal enhancement
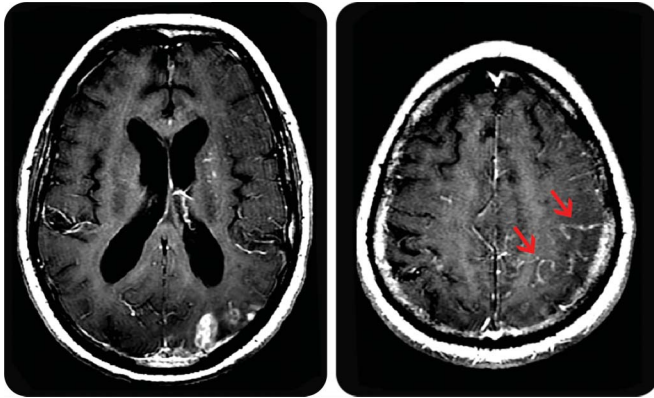
Axial contrast-enhanced T1-weighted images show leptomeningeal enhancement, predominantly in the left frontoparietal-temporal region (arrows), which signifies involvement of the vessel lumens in the subarachnoid space.

SECTION 4

The cerebral angiogram suggested a process leading to narrowing of the distal arterial branches, the most likely being an inflammatory vasculopathy such as primary CNS vasculitis. However, the clinical progression despite an adequate prednisone trial, lack of headaches or systemic features, and primarily unilateral hemispheric involvement raised the question of an alternative diagnosis. Malignant and infectious causes of arteritis needed to be reconsidered, the latter thought to be unlikely given the bland CSF and negative microbiologic studies.

Given the multiple atypical features for vasculitis and the possibility of malignancy causing the arteritis, CTs of the chest, abdomen, and pelvis were performed, but were negative for malignancy. Serum lactate dehydrogenase and peripheral blood flow cytometry were normal.

In the absence of diagnostic findings of a systemic disorder, oral cyclophosphamide 100 mg daily was added to the patient's treatment regimen. At the same time, an MRI was repeated and showed leptomeningeal enhancement, predominantly in the left frontoparietal-temporal region (figure 3), along with continued appearance of new acute infarcts in the left hemisphere. The patient showed no clinical improvement despite the addition of cyclophosphamide to his immunosuppression.

Question for consideration:

1. What further testing would you perform to clarify the diagnosis?

The patient underwent a left parieto-occipital brain biopsy that confirmed intravascular large B-cell lymphoma. Immunostaining showed that the atypical cells within the blood vessels intensely expressed CD20, identifying them as B-lymphocytes (figure 4).

The patient was started on R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy for intravascular lymphoma (IVL). He was transferred to an oncology tertiary care center for ongoing treatment.

DISCUSSION IVL has often been described as the oncologist's "great imitator."[3] It is characterized by the aggressive proliferation of clonal B-lymphocytes within small vessels, causing occlusion and ischemia, with usual sites of involvement including the skin and the CNS.[3] It is unique due to its predominant neuroectodermal tropism with relative sparing of surrounding tissue, lymph nodes, and bone marrow.[3] Symptoms of the disease depend on the tissue surrounded by the affected vessels causing a myriad of clinical presentations including focal motor, sensory, visual, and language deficits.[4,5] In contrast to IVL, where damage to surrounding tissue occurs secondary to malignant cells occluding the intraluminal space, CNS vasculitis is characterized by inflammatory damage to the blood vessel walls themselves.[4] The end result is the same—ischemic infarction of surrounding tissues. Acquired progressive neurologic deficits, accompanied by multifocal brain parenchymal infarcts on neuroimaging, are the hallmark of CNS vasculitis.[4] IVL can mimic these imaging findings. Due to its rarity, lack of clinical markers, and noninvasive diagnostic tests, the need for a brain biopsy of a suspected site of involvement is essential to establish an antemortem diagnosis.[3] Whether a less invasive, lesional skin biopsy can be performed to rule in the diagnosis remains to be answered.

There are no pathognomonic neuroradiologic findings for IVL.[3,5] The most often cited abnormalities on brain MRI are multifocal, discrete, cortical, or subcortical lesions that are hyperintense on T2-weighted and fluid-attenuated inversion recovery images and accompanying meningeal enhancement on T1-weighted postgadolinium images.[3,6,7] In contrast, CNS vasculitis lesions usually occur in the deep as opposed to subcortical white matter and lack meningeal enhancement.[4] The most common abnormalities of both disorders on cerebral angiogram are multivessel segmental narrowing in a beadlike pattern.[4,8] However, despite some subtle

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Figure 4   Intravascular large B-cell lymphoma
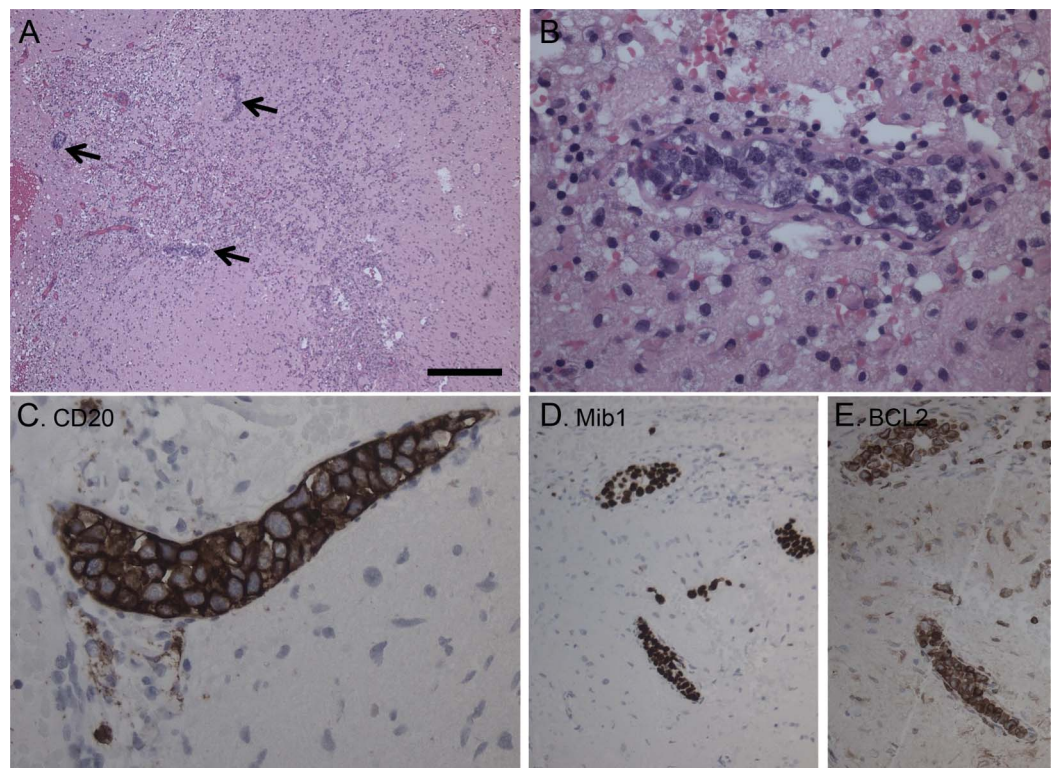
(A) Low-power image of brain parenchyma and blood vessels (arrows) with cellular infiltrate. (B) Higher power microphotograph of blood vessels shows intraluminal packing with large pleomorphic cells that are shown to be strongly positive for CD20 (C) and BCL2 (E). The proliferative index as shown by MiB1 immunohistochemistry is very high (D). Scale bar represents 450 μm in (A), 50 μm in (B), 150 μm in (C), 150 μm in (D), and 75 μm in (E).

differences, neuroimaging cannot definitively distinguish between IVL and CNS vasculitis, further underscoring the need for a biopsy. In a review of the literature, multiple reports of normal cerebral angiograms in IVL with CNS involvement exist, with up to 45% of cases of IVL having angiographic findings that have been confirmed by brain biopsy.[4,8] That means that roughly 50% of IVL cases with CNS involvement are angiography negative.[4] Unilateral presentation is not a common radiologic feature in either IVL or CNS vasculitis, as was seen in our patient.

Framing bias added to the difficulties in obtaining a diagnosis in our patient. Indeed, he was admitted to our institution carrying a presumed diagnosis of primary CNS vasculitis. Lack of response to first-line treatment led to the addition of second-line treatment rather than reconsideration of the diagnosis. In addition, the lack of prodromal malaise, fever or headache, systemic features of vasculitis, and leptomeningeal enhancement were, in retrospect, indicators of an alternative diagnosis.

IVL should be considered in the differential diagnosis in patients with presumed primary CNS vasculitis given its significant impact on prognosis and management.

AUTHOR CONTRIBUTIONS

Dr. Elizabeth Kouzmitcheva: drafting/revising the manuscript, interpretation of data. Dr. Claude Steriade: drafting/revising the manuscript, interpretation of data. Dr. Anca Prica: revising the manuscript, analysis and interpretation of data. Dr. Lili-Naz Hazrati: revising the manuscript, analysis and interpretation of data. Dr. Daniel M. Mandell: revising the manuscript, analysis and interpretation of data.

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