

CLINICAL PROBLEM-SOLVING

Heading Down the Wrong Path

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

A 52-year-old woman who had undergone renal transplantation 13 years earlier was brought by her family to the emergency department of a community hospital. Five days earlier, she had suddenly begun to have tingling and numbness of her arms and she noted that the words on her computer screen appeared "mixed up." Her condition improved during the next 24 hours, but difficulty swallowing and slurred speech developed and worsened during the next three days until she was unable to speak. The day before presentation, bilateral impairment of the left visual field developed and she became lethargic. Her family sought medical care for her.

My approach begins with two questions: Where is the lesion? What is the lesion? This patient presented with a stuttering course of discrete and multifocal neurologic deficits, including bilateral sensory symptoms of the arms, alexia, dysarthria, and impaired peripheral vision consistent with central nervous system (CNS) involvement. Although some symptoms, such as dysphagia and dysarthria, suggest a brain-stem localization, left-sided visual difficulty suggests a cortical lesion. The lethargy could be due to either diffuse involvement of the brain-stem reticular activating system or widespread cortical dysfunction. Potential causes include vascular, inflammatory, infectious, and malignant processes. The patient's history of renal transplantation raises the possibility of conditions related to her immunosuppressive regimen, including opportunistic infections such as progressive multifocal leukoencephalopathy, malignant CNS tumors such as lymphoma, and reversible posterior leukoencephalopathy, which is typically accompanied by visual and neuropsychiatric symptoms. At this point she needs to undergo a detailed neurologic examination and neuroimaging.

A chest x-ray film revealed no abnormalities. Blood studies, including a complete blood count, measurement of electrolytes and prothrombin and partial-thromboplastin times, were within normal limits. Computed tomography (CT) of the brain showed no obvious lesions. The presumed diagnosis was a vascular event. The patient's condition was considered stable, and she was sent home, with a plan for prompt outpatient follow-up with a neurologist.

She had undergone cadaveric renal transplantation 13 years earlier for end-stage renal disease attributed to IgA nephropathy. Her postoperative course was complicated by tuberculous peritonitis, for which she was treated with a "full course" of isoniazid, rifampin, pyrazinamide, and ethambutol. She had hypertension and hyperlipidemia but no history of cardiovascular disease. Her current medications included cyclosporine (75 mg daily), atorvastatin (10 mg daily), nifedipine (30 mg daily, for hypertension), and levothyroxine. She had never smoked and had never drunk alcohol.

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The patient has several risk factors for stroke, including hypertension, hypercholesterolemia, and a history of renal failure. However, the neurologic manifestations are inconsistent with the presence of a single vascular lesion, and the progressive course and the negative findings on CT despite a several-day history of neurologic deficits appear inconsistent with this diagnosis. Her history of tuberculosis raises the question of CNS tuberculosis, although this diagnosis is unlikely if she received a full course of therapy. The present illness may also represent a recurrence of the disease that caused her renal failure, such as a vasculitis.

Her blood pressure was 120/80 mm Hg. The cardiovascular examination was normal; no carotid or orbital bruits were noted, and the peripheral pulses were intact. The patient was alert and oriented, with fluent speech. Testing of higher cognitive function showed that she was unable to copy intersecting pentagons or to draw a clock face or daisies, and she had difficulty dressing herself. There was also evidence of visuospatial impairment; she was unable to describe her route from home to the clinic. She had mild dysarthria. There was an incongruous left hemianopia. The remainder of the cranial-nerve examination was normal. There was a mild pronator drift of the left arm and mild weakness of the left wrist and finger extension. She had dysmetria of the left arm on finger-to-nose testing. The rest of the physical examination, including that of the skin, joints, and lymph nodes, was unremarkable.

The neurologic examination reveals a number of abnormalities that suggest the presence of lesions in the cerebellum and right hemisphere, again in a multifocal distribution. CT provides poor visualization of the brain stem and cerebellum and has a relatively low diagnostic sensitivity for disorders affecting the cerebral white matter. Magnetic resonance imaging (MRI) is indicated at this point to look for subcortical white-matter lesions or brain-stem disease.

Treatment with clopidogrel was initiated. The complete blood count, prothrombin and partial-thromboplastin times, and serum levels of creatinine, electrolytes, glucose, alanine aminotransferase, aspartate aminotransferase, triglycerides, cholesterol, albumin, and vitamin B₁₂ were all normal. Cyclosporine levels were in the low therapeutic

range. Blood and urine cultures were negative. An echocardiographic examination and 48-hour Holter monitoring were normal. Ultrasonography of the carotid arteries revealed narrowing to less than 50 percent at the carotid bifurcations.

During the next three weeks, the patient's dysarthria and incoordination of the left arm improved; however, she continued to have marked constructional apraxia (the inability to assemble different parts of a spatial array despite intact primary motor and sensory modalities), difficulty dressing (which was believed to be due to a combination of tactile and visuospatial incoordination and hemineglect to the left side), and a left hemianopia. Her family noticed that she had difficulties with memory and negotiating her way around the house. She had headaches, for which her husband had brought her to the emergency department of three hospitals. CT was performed during these visits, and she was referred back to the original neurologist. On review by the neurologist, the first scan showed a small hypodensity in the right periventricular white matter; subsequent scans showed a progression of abnormalities, with increasing nonspecific hypodensities in the subcortical white matter bilaterally.

The evolving symptoms and CT changes confirm a progressive and multifocal process, primarily involving the subcortical regions. The CT findings are nondiagnostic, but they may indicate small subcortical infarcts or areas of inflammation or demyelination. The differential diagnosis remains broad inflammatory and noninflammatory vasculopathy, multiple emboli, opportunistic infections such as progressive multifocal leukoencephalopathy or toxoplasmosis, a malignant tumor such as multifocal lymphoma, and autoimmune conditions such as systemic lupus erythematosus, progressive systemic sclerosis, or multiple sclerosis. MRI is indicated.

MRI of the brain performed before the administration of gadolinium demonstrated multiple hyperintense lesions on T₂-weighted and fluid-attenuated inversion recovery images. The lesions involved the left cerebellar hemisphere, middle cerebellar peduncle, midline cerebellum, subcortical white matter bilaterally, and parietal white-matter regions, with one lesion abutting the cortical gray matter. After the administration of gadolinium, there was enhancement of three of the lesions in the subcortical white matter. Gyrus enhancement

was seen on several images. On T₂-weighted images, foci of increased signal were seen in the genu and body of the corpus callosum.

MRI confirmed the presence of multifocal disease involving primarily the cerebral white matter, brain stem, cerebellum, and corpus callosum. The observation that the lesions enhance essentially rules out the diagnosis of progressive multifocal leukoencephalopathy, since it typically produces coalescing but nonenhancing white-matter lesions.

Severe hypoxic injury and severe hypoglycemia are associated with gyral enhancement; neither of these diagnoses is tenable in this case. Cortical involvement and gyral enhancement in association with occipital-lobe disease have also been described with cyclosporine neurotoxicity. However, this patient had neither elevated cyclosporine levels nor the occipital distribution of lesions on MRI that is characteristic of this condition.

Gadolinium-enhancing lesions can also suggest an inflammatory demyelinating condition such as multiple sclerosis. However, the gyral enhancement seen in this case is not typical of that seen in multiple sclerosis, and the patient's age, persistent headaches, and presentation would be unusual for the initial presentation of multiple sclerosis. Malignant tumors, inflammatory vasculitis, and other types of vasculopathy (including infectious forms) continue to be concerns. Analysis of the cerebrospinal fluid in a case such as this is warranted, and it should include an assessment for oligoclonal bands and cytologic examination.

The neurologist noted that the level of thyrotropin was "grossly elevated," with low levels of triiodothyronine and thyroxine. The white-cell count in the cerebrospinal fluid was 8 per cubic millimeter (85 percent lymphocytes, 2 percent neutrophils, and 9 percent monocytes), the glucose level was 57 mg per deciliter (3.2 mmol per liter), and the protein level was 0.90 g per liter (normal range, 0.12 to 0.60). The cytologic examination was negative for malignant tumor cells. Oligoclonal banding was present. The patient continued to receive cyclosporine, and her thyroxine dose was increased.

The white-cell and protein levels in the cerebrospinal fluid are minimally elevated; one would expect a low glucose level and a more profound

leukocytosis with more marked neutrophilia in the presence of an active bacterial or fungal infection. Viral infection would also be expected to produce a much more pronounced lymphocytosis. The results of the analysis of the cerebrospinal fluid cannot be used to confirm a diagnosis. The oligoclonal banding and slight elevation of white-cell count and protein are consistent with a diagnosis of multiple sclerosis, but not specific for it. These findings can be seen in a range of inflammatory and infectious CNS disorders, including connective-tissue diseases, paraneoplastic syndromes, and infection with human immunodeficiency virus (HIV). The patient had laboratory evidence of hypothyroidism, which may have contributed to symptoms such as slowness of thought and sluggish reflexes. A condition such as this should be treated, but it cannot explain the MRI abnormalities in this case, since these have only very rarely been reported with severe thyroid dysfunction. The clinical presentation in this case is relapsing, progressive, and protracted, and periods of relative improvement and worsening would not be expected with severe hypothyroidism. A diagnosis of multifocal small-vessel infarction is possible, with a vasculitic or noninflammatory type of vasculopathy the most likely underlying cause.

At this point, I would repeat the physical examination and order additional laboratory tests, including tests for antinuclear antibody, extractable nuclear antibody, and antiphospholipid antibody, to look for evidence of a rheumatologic disease that is associated with vasculitis or cerebritis.

After the thyroxine dose was increased, the patient's family noted mild improvement in some of her symptoms, including cognition and mood, which lasted several weeks. However, her apraxia progressed; she was observed putting skirts on upside down and sweaters on backward. Her family subsequently noted that she became increasingly anxious and sad. She had persecutory ideation that her mother-in-law had caused her illness. She had impaired short-term memory with preserved long-term memory. At this time (seven months after her initial presentation), she was referred to a tertiary care center with a suspected diagnosis of multiple sclerosis.

Despite thyroid-hormone-replacement therapy and initial improvement, her condition again deteriorated.

rated during a period of several weeks, confirming that hypothyroidism was not the cause of this constellation of findings. The relentless cognitive clinical deterioration, without signs of pyramidal, optic-nerve, or spinal-cord involvement, is unusual for multiple sclerosis. Her symptoms suggest that she now has widespread involvement of the cortex. She has a mood disturbance, impaired executive function and initiative typical of a frontal-lobe impairment, and memory impairment and apraxias consistent with the presence of temporoparietal disease. The differential diagnosis continues to include demyelinating disease, autoimmune inflammatory diseases, vasculitis, and cancer. I would assess autoimmune serologic markers, repeat neuroimaging studies, and consider a trial of treatment with high-dose corticosteroids.

A repeated MRI showed resolution of some of the lesions and a decrease in the size of others. The lesion in the right parietal region involved both cortical gray-matter and subcortical white-matter areas (Fig. 1). The erythrocyte sedimentation rate was 37 mm per hour, the C-reactive protein 1.5 mg per deciliter, and the rheumatoid factor 34 IU per milliliter; serum immunoelectrophoresis showed a subtle polyclonal increase in IgG only; and a test for antinuclear antibodies was positive (titer, 1:640), with a speckled pattern. Tests for anti-Ro antibodies were positive. Tests for hepatitis B virus, hepatitis C virus, HIV, double-stranded DNA, and antineutrophil cytoplasmic antibodies were negative. Levels of proteins C and S, factor V Leiden, fibrinogen, antithrombin III, homocysteine, and C3 and C4 were normal. Tests for prothrombin variant and antiphospholipid and anticardiolipin antibodies were negative.

Although there is apparent resolution of some lesions, progression of others is evident elsewhere, indicating active disease. Diffusion-weighted MRI is indicated in such circumstances to search for ischemic changes associated with vasculitis. The antiphospholipid antibody syndrome may cause multifocal infarction in the CNS, but negative tests for antiphospholipid antibodies and anticardiolipin antibodies argue against this diagnosis.

The combination of positive tests for antinu-

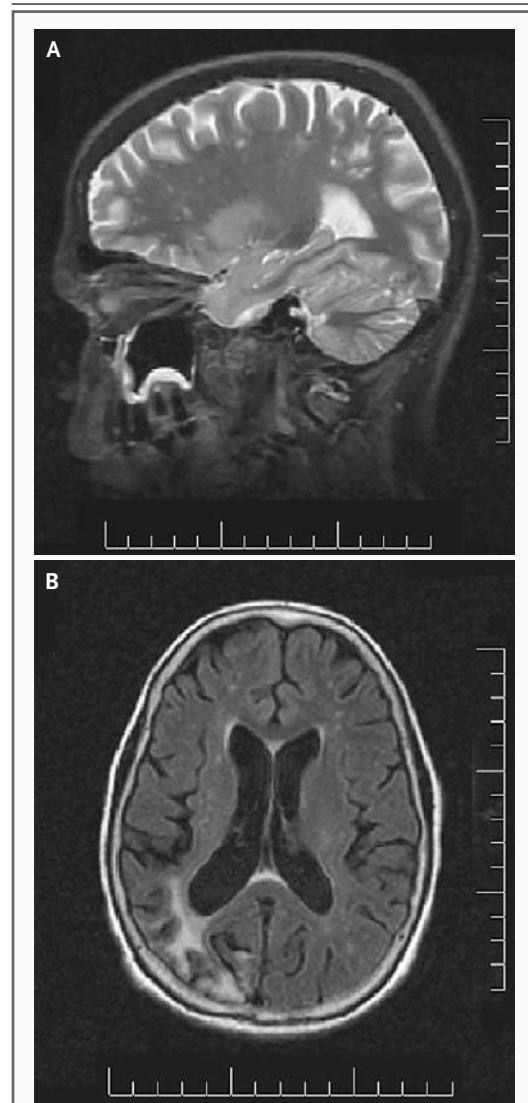


Figure 1. MRI of the Brain Obtained Seven Months after the Patient's Initial Presentation.

A T₂-weighted sagittal image of the brain (Panel A) demonstrates tiny foci of increased signal intensity in juxtacortical and subcortical white matter. None of the lesions have the typical appearance of "Dawson's fingers" (ovoid lesions that are oriented perpendicular to the ependymal surface of the lateral ventricles and resemble fingers stretching radially outward into the periventricular white matter) characteristic of demyelinating diseases such as multiple sclerosis. A fluid-attenuated inversion recovery axial image (Panel B) shows increased signal in the right posterior parietal and occipital lobes, which involves both cortical gray matter and subcortical white matter.

clear antibodies and anti-Ro antibodies and a negative test for double-stranded DNA suggests the possibility of Sjögren's syndrome. Although neurologic manifestations of Sjögren's syndrome generally involve the peripheral nervous system, the syndrome can present as neuropsychiatric manifestations and focal neurologic findings and may mimic multiple sclerosis clinically and radiologically. However, the positive tests for antinuclear antibodies and anti-Ro antibodies are of low specificity. I would look carefully for clinical evidence of Sjögren's syndrome, such as sicca syndrome and cutaneous signs of vasculitis, because they are often associated with CNS vasculitis in patients with Sjögren's syndrome.

In the absence of clinical findings of disease outside the CNS, I would consider the possibility of vasculitis restricted to the brain. With the patient's condition continuing to deteriorate in the absence of a clear diagnosis, I would order cerebral angiography and strongly consider ordering a brain biopsy.

The patient had no signs of sicca syndrome or cutaneous vasculitis. A cerebral angiogram showed focal irregularities of the right and distal middle cerebral arteries (Fig. 2), interpreted as "subtle abnormalities consistent with vasculitis." She was treated with high-dose corticosteroids (a pulse of 1 g of methylprednisolone daily for three days and 60 mg of prednisone daily thereafter). However, her condition continued to deteriorate. Within 10 days after the initiation of corticosteroids, incontinence and truncal ataxia developed. The patient became unable to walk, and her apraxia, confusion, and lethargy worsened. Diffusion-weighted MRI (Fig. 3) showed evidence of evolving new infarcts of the right frontal lobe with new juxtacortical and subcortical lesions. Cyclophosphamide was added to the treatment regimen.

If this is an inflammatory process, it is not one that responded to an aggressive form of therapy. It is possible that the diagnosis is primary CNS vasculitis, since therapy is not always effective for that disease. Additional chemotherapeutic agents such as cyclophosphamide are often necessary to induce a response. Because the angiographic findings are not specific, coagulopathies and noninflammatory vasculopathies, such as those asso-

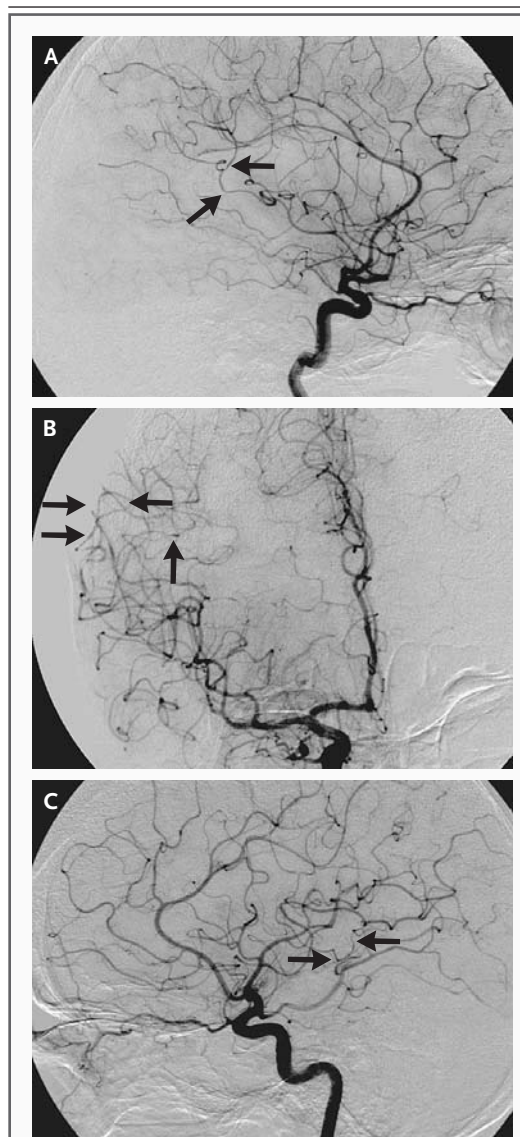


Figure 2. Cerebral Angiogram Showing Irregularities (Arrows) in the Posterior Branches of the Middle Cerebral Arteries Consistent with the Presence of Vasculitis.

The right internal carotid artery is shown in a lateral view (Panel A) and a frontal view (Panel B), and Panel C shows a lateral view of the left internal carotid artery.

ciated with CNS lymphoma or, in rare cases, with endovascular cancer, arise in the differential diagnosis. At this point, I would repeat MRI to look for clues regarding the progress of the disease. Diffusion-weighted MRI to identify ischemia should also be included.

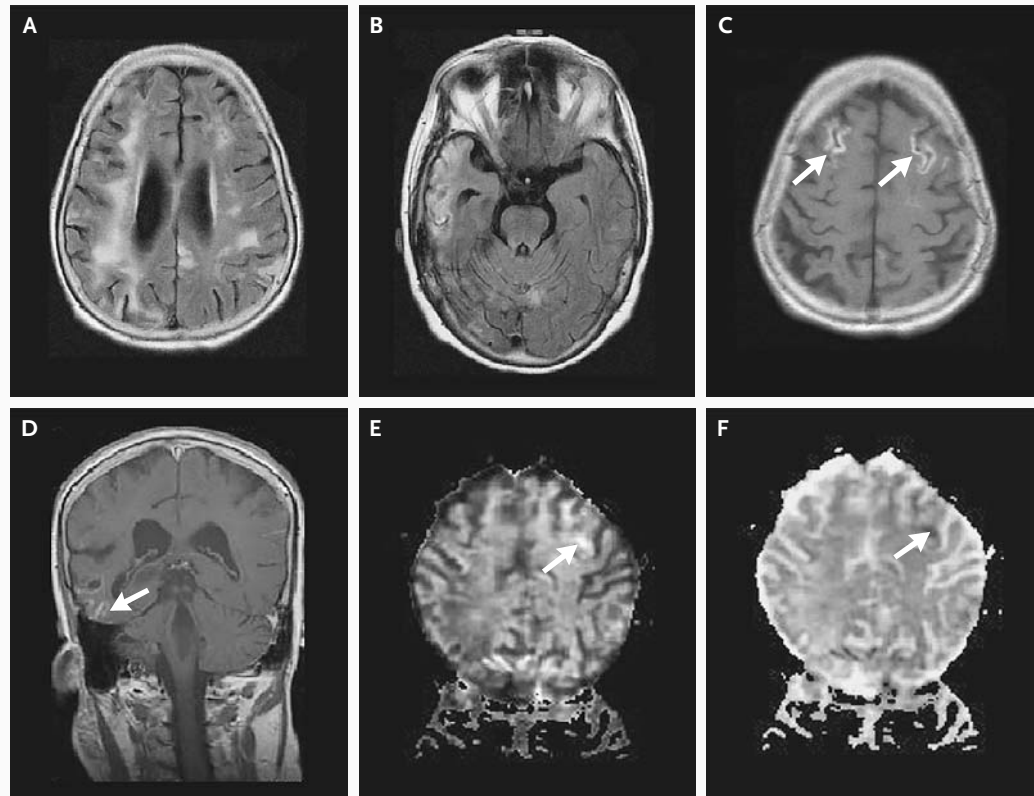


Figure 3. MRI of the Brain Showing Disease Progression.

T₂-weighted MRI and fluid-attenuated inversion recovery MRI of the brain show multiple hyperintense subcortical and cortical lesions involving the parietal and occipital lobes (Panel A). A hyperintense signal with encephalomalacia is also seen in the right temporal lobe (Panel B). Abnormal gyriform enhancement (arrows) is seen predominantly in both frontal lobes (Panel C) and peripherally in the right temporal lobe (Panel D). Diffusion-weighted imaging (Panel E) and apparent diffusion coefficient maps (Panel F) demonstrate restricted diffusion consistent with the occurrence of acute infarction (arrows).

MRI demonstrated multiple, hyperintense subcortical and cortical lesions, with encephalomalacia and volume loss in the right temporal, occipital, and parietal lobes (Fig. 3A and 3B). There were also areas of abnormal gyriform enhancement in the frontal lobes, as well as at the periphery of the right temporal lobe (Fig. 3C and 3D). These areas demonstrated restricted diffusion on diffusion-weighted imaging (Fig. 3E) and apparent diffusion coefficient maps (Fig. 3F). There was also an abnormal signal within the right cerebellar hemisphere compatible with areas of previous ischemic injury and associated with volume loss. The patient continued to be treated with methylprednisolone and cyclophosphamide. However, her clinical condition continued to deteriorate.

The evolution of the lesions seen on MRI and on the diffusion-weighted images confirms that multifocal cerebral ischemia with acute and subacute ischemic damage is the cause of this patient's illness. There are multiple progressive ischemic lesions in her brain, nonspecific serologic findings of inflammation, and evidence of vasculopathy on a cerebral angiogram. Her condition did not improve despite aggressive treatment for a possible inflammatory or autoimmune disease. Although a refractory vasculitic syndrome remains a possible diagnosis, I am increasingly concerned about the possibility of another diagnosis, such as cancer. A brain biopsy is needed.

Examination of a biopsy specimen of the brain showed eosinophilic neurons and disruption of

the neuropil consistent with the presence of ischemia. There was no evidence of vasculitis, but the vessel lumens were almost completely obliterated by large malignant cells. The cells were identified as large B cells that stained for CD20 (Fig. 4). The pathological diagnosis was intravascular lymphomatosis, with secondary ischemic damage. Despite treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone; intrathecal methotrexate; and whole-brain radiation therapy, her condition continued to deteriorate. She was transferred to a palliative care ward, where she died a few weeks after the biopsy and nine months after the onset of symptoms.

COMMENTARY

This woman's presentation began with the acute onset of several neurologic deficits. Her clinician first considered the possibility of stroke, presumably on the basis of the high prevalence of this condition as a cause of neurologic deficits and on her risk-factor profile, which included hypertension, hypercholesterolemia, and renal failure. However, the apparent involvement of several regions of the brain prompted the discussant to consider other disorders of cerebral blood vessels or brain parenchymal disease associated with inflammation, demyelination, or infiltration by tumor.

The ultimate diagnosis — intravascular lymphomatosis — was made only after a protracted course. In part, this delay is explained by the rarity of this disease and the need for a brain biopsy to establish the diagnosis. The clinicians initially focused on more common disorders: first stroke, then multiple sclerosis, and then, when the findings were clearly inconsistent with these two diseases, vasculitis. It was not until treatment for a presumed diagnosis of vasculitis failed that definitive diagnostic testing was pursued. However, the fragmented nature of the care, which was obtained in a variety of emergency rooms, and the early reliance on CT rather than MRI also appeared to contribute to the delay in making the correct diagnosis and in recognizing the progressive nature of the illness.

Intravascular lymphomatosis, also known as intravascular lymphoma or malignant angioendotheliomatosis, is a rare neoplastic disease characterized by the intraluminal proliferation of malignant cells of B-cell lineage. Small and, less frequently, medium-sized blood vessels become

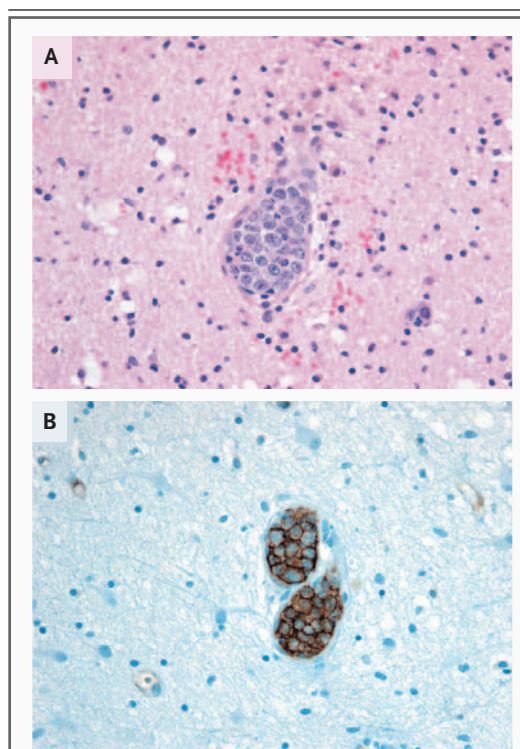


Figure 4. Biopsy Specimen of the Brain Showing Intravascular Lymphomatosis.

Panel A shows numerous large malignant lymphoid cells within the vascular space that obstruct the cerebral vasculature (hematoxylin and eosin). In Panel B, the tumor cells within the intravascular spaces show strong staining for CD20. The findings suggest the presence of an intravascular large B-cell lymphoma with subsequent ischemic damage to the brain parenchyma.

occluded, causing ischemic infarction of tissues.¹ Intravascular lymphomatosis tends to affect the CNS and skin, but involvement of other organs and the peripheral nervous system has been reported in late stages of disease.²⁻⁶ The presentation of the disease is diverse and can include a progressive or relapsing–remitting multifocal neurologic syndrome related to recurrent infarctions in different vascular territories⁷; a progressive or acute myelopathy characterized by back or radicular pain, progressive paraparesis, and bladder dysfunction^{8,9}; progressive cognitive impairment characterized by either subacute encephalopathy or a subacute dementing illness¹⁰; or progressive peripheral neuropathy and mononeuritis multiplex.^{11,12}

Both vasculitis and intravascular lymphomatosis produce infarcts affecting multiple vascular

territories. CT or MRI usually reveals the presence of both cortical gray-matter and subcortical white-matter strokes. Although there are subtle differences in the appearance of vasculitis and intravascular lymphomatosis on neuroimaging (such as the finding of more peripherally located lesions and meningeal involvement in intravascular lymphoma), neuroimaging cannot definitively distinguish between them. On cerebral angiography, both disorders are associated with alternating stenosis and dilatation (often called “beading”) of blood vessels. Such angiographic findings may be present in up to 45 percent of cases of intravascular lymphomatosis that have been confirmed by brain biopsy.^{7,13-15} Intravascular lymphoma should be considered in patients presenting with features of inflammatory vasculitis whose condition continues to deteriorate despite aggressive immunosuppressive therapy, as occurred in this case.

Knowledge of the treatment of intravascular lymphomatosis is limited by the rarity of the disease. There are no findings from randomized trials or large case series to guide therapy. A transient but dramatic response to corticosteroid administration has been reported.¹⁰ Case reports have described prolonged remissions in some patients treated with aggressive chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone.^{4,10} In general, the prognosis is poor. Given the challenges posed by this rare condition, it is not surprising that the patient's physicians headed down the wrong path before ultimately reaching the correct diagnosis.

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