CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 6-2023: A 68-Year-Old Man with Recurrent Strokes

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PRESENTATION OF CASE

Dr. Scott B. Silverman: A 68-year-old man was admitted to this hospital because of worsening confusion.

The patient had a history of hypertension and coronary artery disease. A myocardial infarction had occurred 18 years before the current admission; atrial fibrillation had also been diagnosed at that time. He had taken warfarin for many years but had stopped taking it 10 years before this admission.

Seven and a half weeks before the current admission, the patient presented to another hospital with aphasia. His score on the National Institutes of Health Stroke Scale was 3, with scores ranging from 0 to 42 and higher scores indicating greater severity. The score of 3 was due to partial loss of the right visual field and mild-to-moderate aphasia and dysarthria.

Computed tomography (CT) of the head, performed without the administration of intravenous contrast material, revealed no abnormalities. CT angiography of the head and neck revealed calcified atherosclerosis along the arch of the aorta, the origin of the left vertebral artery, the intracranial portion of the left vertebral artery, the carotid bifurcations, and the cavernous portions of both internal carotid arteries; there was no hemodynamically significant stenosis. Treatment with aspirin and clopidogrel was initiated. The patient was admitted to the hospital, and the aphasia resolved on the second hospital day.

Magnetic resonance imaging (MRI) of the head, performed without the administration of intravenous contrast material, revealed a few small foci of acute infarction involving the frontal lobes, the posterior limb of the right internal capsule, and the right middle cerebellar peduncle. There was also a small focus of remote petechial hemorrhage in the subcortical white matter of the left parietal lobe.

Although continuous telemetry revealed no evidence of atrial fibrillation, the patient's strokes were thought to be cardioembolic, resulting from atrial fibrillation. Treatment with aspirin was continued, clopidogrel was discontinued, and apixaban was started; previously prescribed antihypertensive therapy with amlodipine

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N Engl J Med 2023;388:747-57.
DOI: 10.1056/NEJMcpc2211368

CME at NEJM.org

and lisinopril was resumed. The patient was discharged home on the second hospital day.

Four days after discharge, and 7 weeks before the current admission, the patient presented to the other hospital with transient mild aphasia. Results of CT of the head (performed without the administration of intravenous contrast material) and MRI of the head (performed with and without the administration of intravenous contrast material) were reportedly unchanged from the studies obtained 6 days earlier. The patient's systolic blood pressure was less than 100 mm Hg, and his symptoms were thought to be due to hypoperfusion or recrudescence of symptoms from previous stroke. Treatment with amlodipine and lisinopril was stopped, and the systolic blood pressure increased. The patient was discharged home on the fourth hospital day.

Three weeks after discharge, and 3.5 weeks before the current admission, the patient's daughter noticed that the patient had confusion and lethargy, and she took him to the other hospital for evaluation. She reported that he had new urinary incontinence, unsteady gait, and withdrawn affect. MRI of the head, performed without the administration of intravenous contrast material, revealed new foci of acute infarction involving the centrum semiovale and corona radiata bilaterally.

Dr. Javier M. Romero: CT of the chest (Fig. 1A) revealed diffuse emphysematous changes, including a spiculated mass (1.7 cm in diameter) with perilesional rectilinear markings in the lower lobe of the left lung. CT of the abdomen (Fig. 1B) revealed an exophytic hyperdense mass (1.6 cm in diameter) arising from the anterior cortex of the left kidney.

Dr. Silverman: On the fourth hospital day, the patient was transferred to a rehabilitation facility with plans for an oncology evaluation after discharge. After 10 days at the rehabilitation center, he was discharged home.

Three days after discharge from the rehabilitation center, and 1 week before the current admission, numbness and tingling in the right hand and forearm developed, and the patient's daughter again took the patient to the other hospital. On examination, he had pronator drift of the right arm and dysmetria on finger-to-nose testing. MRI of the head revealed new foci of acute infarction involving the left thalamus, the subcortical white matter of the right frontal lobe, and the periventricular white matter on the left side, but there was no hemorrhage. Treatment with apixaban was stopped, and enoxaparin was started. The patient was discharged home on the third hospital day.

Five days after discharge, the patient's daughter noticed that the patient had new difficulty with swallowing pills and worsening confusion, and she brought him to the emergency department of this hospital for evaluation. The patient was not able to provide additional history, but his daughter reported that his aphasia and difficulty with balance had worsened since discharge from the other hospital. Other medical history included hypertension, hyperlipidemia, diabetes mellitus, and obesity. Medications included enoxaparin, aspirin, atorvastatin, and metformin. There were no known drug allergies. The patient lived alone in a suburb of Boston and was retired. He had smoked cigarettes for 40 years, but he had recently decreased tobacco use from one pack per day to three cigarettes per day. He smoked marijuana occasionally, and he drank alcohol rarely. His father had had coronary artery disease with a myocardial infarction in the fourth decade of life.

The temporal temperature was 36.6°C, the blood pressure 158/75 mm Hg, the pulse 70 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 25.1. The patient was alert and interactive. He was able to answer orientation questions correctly, although he was slow to respond. His speech was fluent, with no paraphasic errors. He had some difficulty with following simple commands and was unable to follow complex commands. There was decreased activation of the right nasolabial fold with preserved wrinkling of the forehead. Pronator drift of the right arm was present, and there was mild hemiparesis on the right side. The remainder of the examination was normal.

Blood levels of electrolytes and rheumatoid factor were normal, as were results of liver-function and kidney-function tests. The hemoglobin level was 12.7 g per deciliter (reference range, 13.5 to 17.5); the remainder of the complete blood count with differential count was

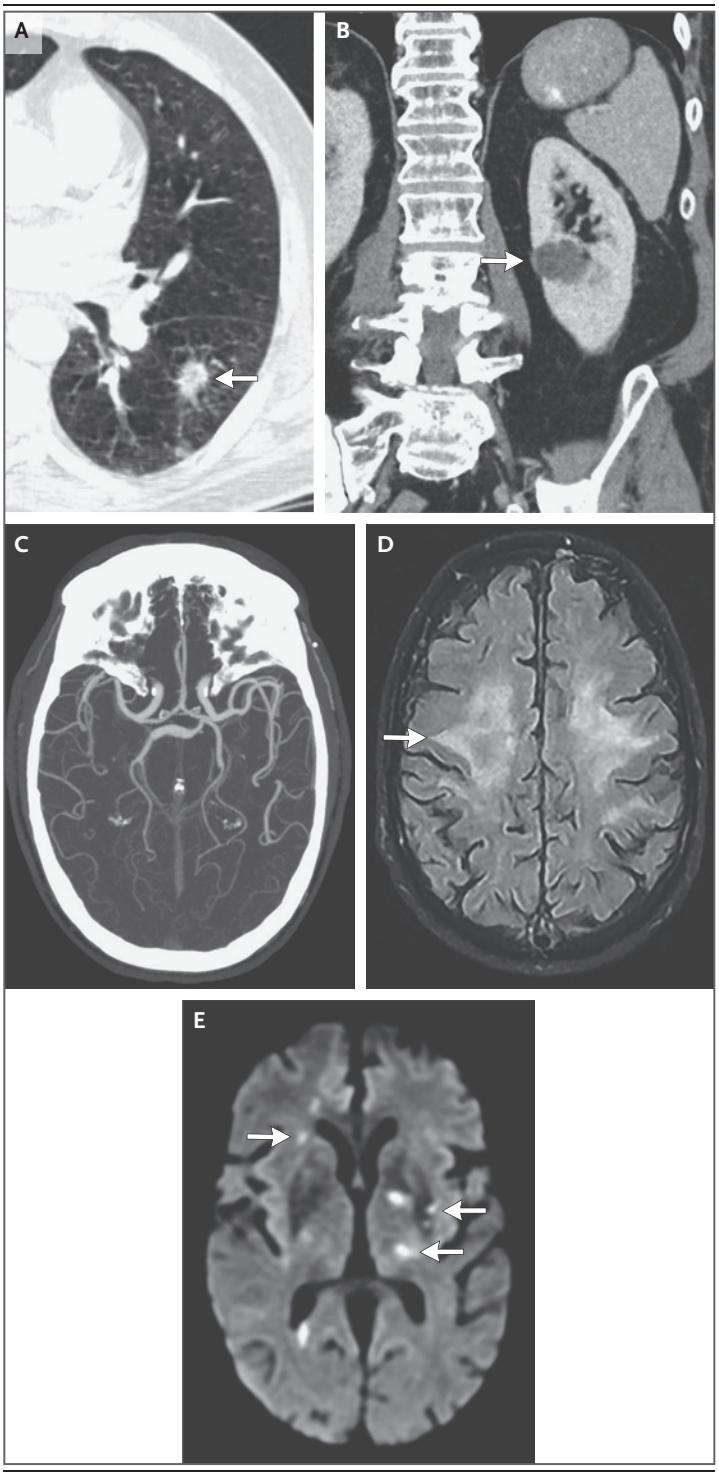

Figure 1. Initial Imaging Studies.

Two weeks before the current admission, CT of the chest and abdomen was performed with the administration of contrast material. An axial image from CT of the chest (Panel A) shows a mass (1.7 cm in diameter) with perilesional rectilinear markings in the lower lobe of the left lung (arrow). A coronal image from CT of the abdomen (Panel B) shows an exophytic hypodense mass (1.6 cm in diameter) arising from the anterior cortex of the left kidney (arrow). On the current admission, CT angiography and MRI of the head were performed. A maximum-intensity-projection image from CT angiography (Panel C) shows calcification of the carotid siphons but no radiologically significant stenosis. An axial fluid-attenuated inversion recovery image from MRI (Panel D) shows confluent low attenuation of the periventricular white matter and corona radiata (arrow). An axial diffusion-weighted image from MRI (Panel E) shows multiple new foci of acute infarction involving the left thalamus, the left lentiform nucleus, and the right frontal white matter (arrows).

normal. The erythrocyte sedimentation rate was 15 mm per hour (reference range, 0 to 13). The D-dimer level was 912 ng per milliliter (reference value, <500). Urinalysis showed more than 100 white cells per high-power field (reference value, <10). A test for lupus anticoagulant was negative, as were tests for antibodies against cardiolipin and β_2-glycoprotein 1. Antinuclear antibodies were present at a titer of 1:160 in a speckled pattern. Blood specimens were obtained for culture. Imaging studies were obtained.

Dr. Romero: CT angiography of the head and neck (Fig. 1C), performed with and without the administration of intravenous contrast material, revealed focal encephalomalacia within the left frontal corona radiata and right cerebral peduncle. Atheromatous changes had resulted in multifocal mild narrowing of the cervical and intracranial arteries. MRI of the head (Fig. 1D and 1E), performed without the administration of intravenous contrast material, revealed numerous new small foci of acute infarction involving the centrum semiovale and corona radiata bilaterally, the left thalamus, the left internal capsule and lentiform nucleus, the left subinsular region, the medial right precentral gyrus, the anterior right frontal lobe, the superior frontal gyri, and the right temporal lobe. There were also several scattered patches of increased signal intensity in the periventricular and subcortical white matter on fluid-attenuated inversion recovery imaging and T2-weighted imaging, findings that are indicative of moderate small-vessel disease.

Dr. Silverman: The patient was admitted to the

hospital, and intravenous heparin was administered. Transthoracic echocardiography performed on the second hospital day revealed a normal ejection fraction and no valvular vegetations or patent foramen ovale. Blood cultures showed no growth. A diagnosis and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Aneesh B. Singhal: In this 68-year-old man, multiple focal and nonfocal neurologic deficits developed over a period of 7 weeks, along with cognitive decline. Imaging revealed accumulating multifocal small ischemic lesions and white-matter lesions. In addition, lung and kidney masses that were suggestive of cancer were identified. Determining the cause of the strokes in this patient is important to assess the risk of recurrence and initiate appropriate preventive therapy. The correlation between clinical and imaging findings provides important diagnostic clues, as does the distribution of the ischemic lesions. Stroke classification schemas[1,2] can be helpful in considering potential mechanisms of the strokes in this patient.

MECHANISMS OF STROKE

Small-Vessel Disease

Although this patient had small infarcts, small-vessel disease can be ruled out as the cause of his strokes because he did not have a lacunar syndrome. Patients with stroke that is caused by small-vessel disease typically have single infarcts in the distribution of penetrating cerebral arteries, which have been affected by lipohyalinosis associated with chronic hypertension and have become occluded.[3]

Cardioembolism

This patient had longstanding atrial fibrillation, which is the most frequent cause of stroke in the United States. At the time of his initial presentation, 7.5 weeks before the current admission, he was not receiving therapeutic anticoagulation, which reduces the risk of stroke by approximately 60%. He had aphasia and hemianopia, which are typical of cardioembolism to the left middle cerebral artery. However, imaging revealed scattered small infarcts in deep regions of the brain and not the wedge-shaped larger infarcts that are more typical of atrial fibrillation–related stroke.

Aphasia recurred a few days later, but imaging revealed no new brain lesions. The aphasia was attributed to poststroke recrudescence, which is a consequence of previous stroke that has been characterized within the past decade.[4] This patient's third and fourth hospital admissions were due to confusion and changes in his affect and gait, which do not fit into typical clinical stroke syndromes.[5] Instead, he probably had embolic encephalopathy.[6]

The rapidly progressive clinical presentation and the infarct distribution suggest the possibility of embolism that is caused by a condition other than atrial fibrillation, such as thrombotic thrombocytopenic purpura, aortic arch atheroma (cholesterol embolism), infective endocarditis, nonbacterial thrombotic endocarditis, cardiac tumor, or cardiomyopathy. However, the patient had a normal platelet count, negative blood cultures, and no abnormalities on echocardiography, and he did not have symptoms of systemic infection. Nonbacterial thrombotic endocarditis remains a possibility, given the likelihood of underlying cancer. However, this condition invariably results in much larger multifocal infarcts, which are presumably due to the embolic burden associated with underlying cancer-related hypercoagulability and friable valvular vegetations.[6]

Large-Artery Atherosclerosis

This patient had several risk factors for atherosclerosis: older age, untreated atrial fibrillation, coronary artery disease, chronic hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking, marijuana use, and a family history of early-onset coronary artery disease. It was not surprising that imaging showed atherosclerosis in the extracranial and intracranial arteries, as well as white-matter lesions, which were possibly due to chronic microvascular ischemia. However, he had frequent episodes within a 4-week period, which would not be typical of stroke that is caused by atherosclerosis, especially in the context of treatment with antiplatelet agents and anticoagulants.[7] It is possible that underlying atherosclerosis and chronic microvascular ischemia lowered the threshold for stroke associated with other mechanisms.

Undetermined and Other Causes

This patient could have had a condition known as cryptogenic embolic stroke of undetermined source. Recent studies have elucidated occult causes of this condition that can be identified with focused testing.[8]

In this patient, the overall differential diagnosis can be narrowed on the basis of the rapid clinical progression, the infarct distribution, and the absence of nonatherosclerotic arteriopathy on CT angiography. It is important to note the location of the infarcts in the deep regions of the brain (e.g., the cerebral peduncle and forceps minor). Embolic showers from a central embolic source (e.g., a thrombus in the left atrial appendage in a patient with atrial fibrillation who is not receiving anticoagulation) usually travel to distal cortical regions. In contrast, the deep location of the infarcts in this patient favors arterial thrombosis as the cause of his strokes.

Table 1. Causes of Small-Vessel Cerebral Arteriopathy.

Category	Possible Causes
Infection	Mycobacterial or bacterial infection (e.g., tuberculosis, syphilis, neuroborreliosis, or pneumococcal infection) Viral infection (e.g., coronavirus disease 2019, varicella–zoster virus infection, or human immunodeficiency virus infection) Fungal infection (e.g., aspergillosis, nocardiosis, cryptococcal infection, or histoplasmosis)
Inflammatory disease	Primary angiitis of the central nervous system Rheumatologic condition with cerebral involvement (e.g., polyarteritis nodosa, sarcoidosis, neuro-Behçet's disease, scleroderma, Sjögren's syndrome, Susac's syndrome, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, systemic lupus erythematosus, Crohn's disease, Kohlmeier–Degos disease, Cogan's syndrome, or Churg–Strauss syndrome)
Brain cancer	Intravascular lymphoma Gliomatosis cerebri
Other cancer with paraneoplastic syndrome	Gastrointestinal or lung cancer Lymphoma Leukemia Myelodysplastic syndrome
Monogenic condition	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (*NOTCH3* mutation) Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (*TREX1* mutation)
Other cause	Exposure to radiation Use of vasoconstrictive drugs

SMALL-VESSEL CEREBRAL ARTERIOPATHIES

Approach to Diagnosis

This patient probably had small-vessel cerebral arteriopathy. The differential diagnosis for small-vessel cerebral arteriopathy is broad (Table 1). Diagnosis of a specific arteriopathy relies on factors such as the patient's age, the family history, the tempo of progression, the presence of systemic signs (e.g., skin and retinal lesions) and extracerebral neurologic deficits (e.g., neuropathy), the features observed on imaging of the brain and vasculature, and the results of diagnostic tests, including tests for inflammatory and cancer biomarkers, genetic tests, cerebrospinal fluid (CSF) analysis, and biopsy of the skin, temporal artery, and brain.[9]

Infections, Inflammation, Radiation, and Drugs

In this patient, infectious and rheumatologic causes of small-vessel cerebral arteriopathy are unlikely owing to the absence of fever, constitutional symptoms, skin lesions, and signs of meningeal irritation. Nevertheless, CSF analysis and additional studies would be needed to rule out these conditions. Arteriopathy induced by radiation or drugs can be ruled out because the patient had no history of exposure to radiation or use of vasoconstrictive drugs. Although he had smoked marijuana, this drug has only weak vasoconstrictive properties and would be unlikely to cause recurrent multifocal infarcts.[10]

Monogenic Conditions

Could this patient have a genetic arteriopathy? Patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is caused by a *NOTCH3* mutation on chromosome 19p, can have mood disturbances, migraines, and small-vessel strokes.[11] The expected MRI findings are small infarcts and white-matter changes affecting the external capsule and anterior temporal lobe. Patients with retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S), which is caused by a *TREX1* mutation, can have vision symptoms, retinal and small cerebral infarcts, and mild liver and kidney dysfunction.[12] CADASIL, RCVL-S, and other genetic arteriopathies are rare, collectively causing less than 1% of all strokes. In addition,

symptoms typically develop when the patient is 25 to 50 years age, and disease progression is much slower than that observed in this patient.[13] Therefore, monogenic arteriopathy is unlikely.

Primary Angiitis of the Central Nervous System

This patient's presentation is consistent with primary angiitis of the central nervous system (PACNS), a rare vasculitis that is restricted to the small and medium arteries and veins of the brain, spinal cord, and leptomeninges.[14-16] PACNS is most likely to occur in patients 40 to 60 years of age. It occurs twice as frequently in men as in women. The acute-to-subacute encephalopathy and multifocal neurologic deficits that were observed in this patient are consistent with the diagnosis of PACNS. Headache was not reported by this patient but is also common.

The multifocal punctate infarcts that were seen on this patient's MRI are typical of PACNS. Other potential MRI findings include diffuse bihemispheric white-matter hyperintensities, leptomeningeal enhancement, and mass lesions that mimic tumors.[17] CSF analysis reveals an elevated protein level and lymphocytic pleocytosis. Cerebral angiography, when positive, reveals multifocal nonconcentric arterial irregularities, usually in the distal branches. However, the sensitivity of cerebral angiography for the diagnosis of PACNS is only 10 to 20% because PACNS predominantly affects small-caliber arteries, which cannot be visualized. Intracranial vessel-wall MRI may show concentric wall thickening and contrast enhancement, features that may distinguish PACNS from other inflammatory as well as noninflammatory arteriopathies. However, brain biopsy is needed for the definitive diagnosis of PACNS.[18]

The clinical course of PACNS is typically progressive.[19] Treatment strategies include induction therapy with glucocorticoids and intravenous cyclophosphamide, followed by maintenance therapy with immunomodulatory agents such as oral cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab, or methotrexate. An important mimic of PACNS is intravascular lymphoma of the central nervous system (CNS); CSF analysis for malignant cells and brain biopsy are needed to rule out this entity.

Paraneoplastic Vasculitis

Although PACNS is a possibility in this case, the findings on imaging of the chest and abdomen were indicative of probable cancer. Lung, gastrointestinal, and other cancers are identified in up to 10% of patients with stroke, and stroke is the first manifestation of cancer in approximately 5% of cases.[20] Common mechanisms of cancer-related stroke include hypercoagulability as well as nonbacterial (marantic) thrombotic endocarditis, which usually causes multifocal, widely distributed large and small infarcts.[6] In rare cases, a paraneoplastic vasculitis that is similar to PACNS can result from one of the following processes: an immunologic reaction against vascular endothelium (molecular mimicry), endothelial injury due to the release of proinflammatory cytokines by tumor cells, or hypersensitivity to deposits of tumor protein or circulating immune complexes that contain tumor antigens on the vessel wall.[21,22]

SUMMARY

This patient most likely had multifocal small-vessel thrombotic strokes due to paraneoplastic cerebral vasculitis in the context of lung cancer. I suspect that, in addition to biopsy of the lung, kidney, and brain, diagnostic testing included CSF analysis and intracranial vessel-wall MRI as adjunctive studies to assess for CNS vasculitis and to rule out diagnoses that mimic this condition.

CLINICAL IMPRESSION

Dr. Silverman: The patient presented with multiple recurrent strokes, despite receiving therapeutic anticoagulation. On the basis of the subcortical cerebral infarcts and progressive leukoencephalopathy, a small-vessel vasculopathy was suspected. More specifically, a small-vessel vasculitis associated with an underlying cancer was suspected, given the masses identified in his lung and kidney. The next steps in diagnostic testing included intracranial vessel-wall MRI, CSF analysis, and biopsy of the lung and kidney masses.

CLINICAL DIAGNOSIS

Recurrent subcortical infarcts with progressive leukoencephalopathy.

DR. ANEESH B. SINGHAL'S DIAGNOSIS

Multifocal thrombotic cerebral infarcts due to paraneoplastic vasculitis of the central nervous system in the context of lung cancer.

IMAGING STUDIES

Dr. Romero: High-resolution, contrast-enhanced vessel-wall MRI is an imaging technique that has been implemented relatively recently. This method highlights features of the arterial and venous vessel walls, such as inflammation, wall thickening, hemorrhage, and calcification. In this patient, intracranial vessel-wall MRI (Fig. 2) revealed segmental concentric enhancement of the internal carotid arteries and middle cerebral arteries bilaterally, findings that possibly indicated a nonspecific inflammatory process, such as vasculitis of undetermined cause.

DIAGNOSTIC TESTING

Dr. Melanie Lang-Orsini: CSF analysis revealed a normal glucose level (50 mg per deciliter; reference range, 5 to 55) and a mildly elevated protein level (80 mg per deciliter; reference range, 50 to 75), as well as a nucleated cell count of 31 cells (with 97% lymphocytes). Microbiologic studies were negative.

Core-biopsy specimens of the lung mass and mediastinal lymph nodes (Fig. 3A and 3B) showed adenocarcinoma that was composed of clusters of atypical cells with enlarged irregular nuclei and scant cytoplasm. The tumor cells were positive for TTF1 on immunohistochemical staining; this finding is consistent with primary lung adenocarcinoma. A biopsy specimen of the kidney mass (Fig. 3C, 3D, and 3E) showed bland polygonal cells that were forming tubular structures. The tumor cells were positive for PAX8; this finding is consistent with primary renal neoplasm, rather than metastasis from the lung adenocarcinoma. The tumor cells also expressed AMACR and CD117. The morphologic features and immunophenotype were consistent with low-grade papillary renal neoplasm, which has a differential diagnosis of papillary adenoma and papillary renal cell carcinoma. To distinguish between these two entities, the pathological findings would need to be correlated with the results on imaging studies. However, overall, this low-grade lesion was unlikely to be the cause of the patient's symptoms.

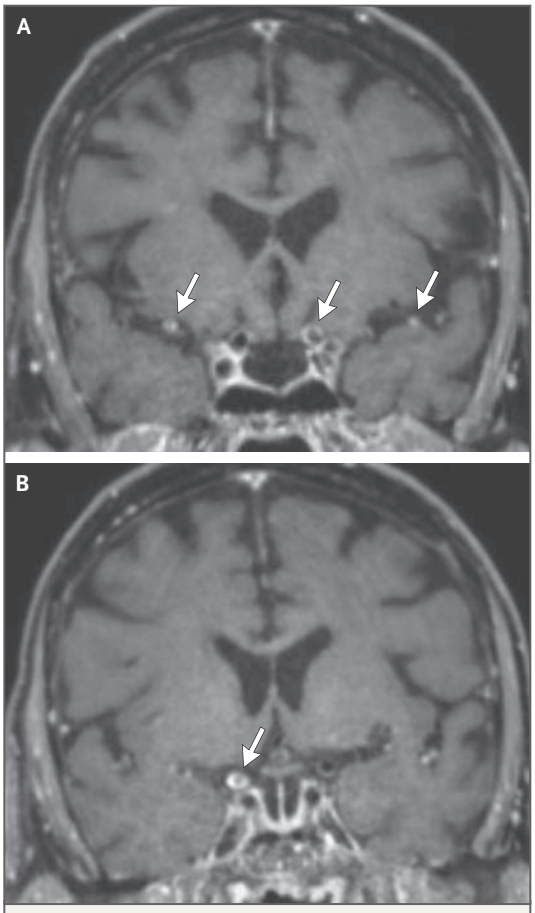

Figure 2. Intracranial Vessel-Wall MRI.
High-resolution, contrast-enhanced vessel-wall MRI was performed. Coronal images show concentric enhancement of the M1 segments of the middle cerebral arteries bilaterally (Panel A, arrows) and of the terminus of the right carotid artery (Panel B, arrow).

PATHOLOGICAL DIAGNOSIS

Primary lung adenocarcinoma with metastasis involving the mediastinal lymph nodes.

DISCUSSION OF MANAGEMENT AND FOLLOW-UP

Dr. Silverman: The CSF lymphocytic pleocytosis and the findings on intracranial vessel-wall MRI

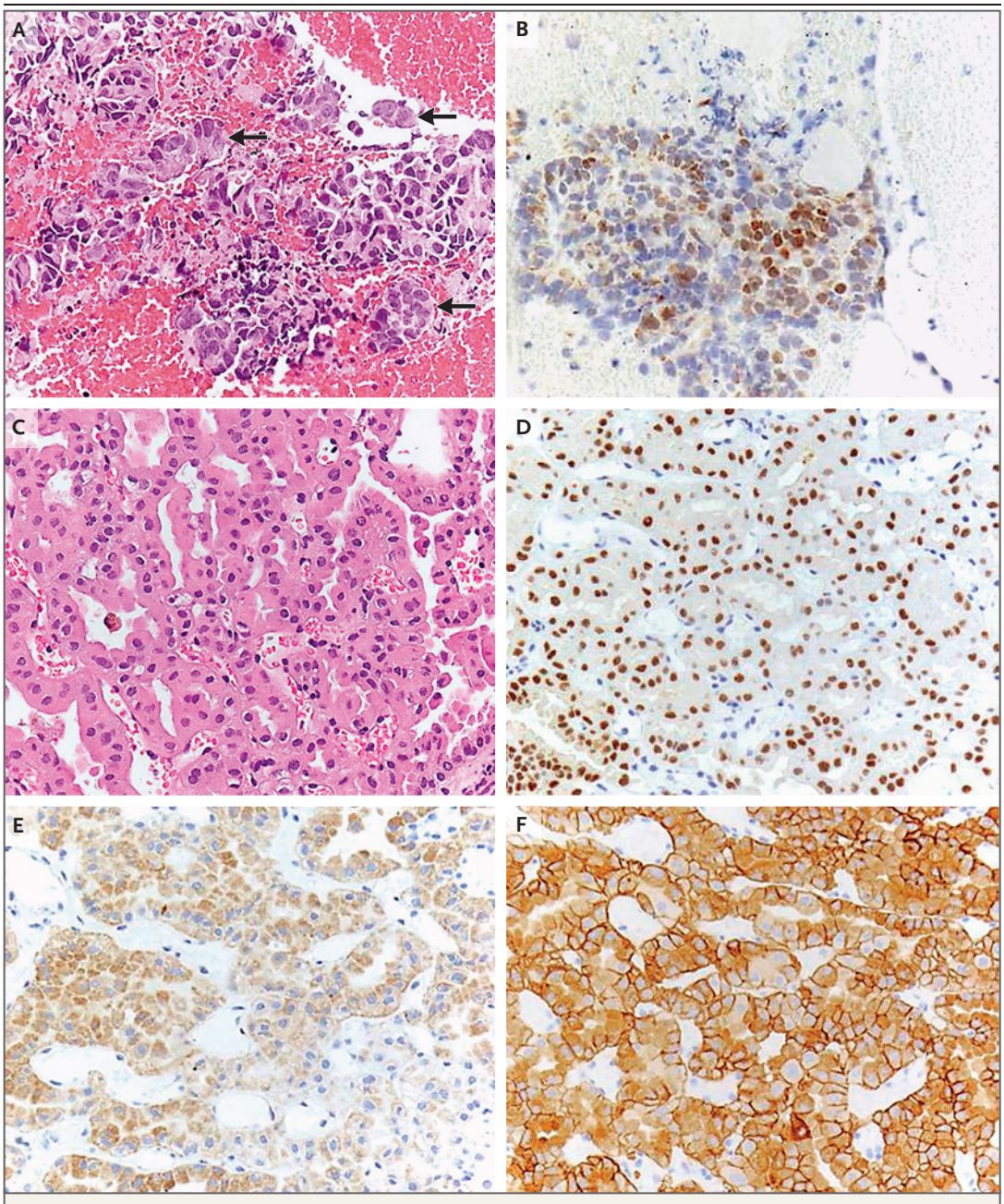

Figure 3. Biopsy Specimens from the Lung and Kidney.

A core-biopsy specimen of a mediastinal lymph node was obtained. Hematoxylin and eosin staining shows metastatic adenocarcinoma that is composed of clusters of atypical cells with enlarged irregular nuclei and scant cytoplasm (Panel A, arrows). Immunohistochemical staining shows expression of TTF1 in the neoplastic cell nuclei (Panel B), a finding consistent with metastatic adenocarcinoma of the lung. A biopsy specimen of the kidney mass was also obtained. Hematoxylin and eosin staining shows bland polygonal cells with granular pink cytoplasm and round nuclei that are forming tubular structures (Panel C). Immunohistochemical staining shows nuclear expression of PAX8 (Panel D), AMACR (Panel E), and CD117 (Panel F).

were consistent with a diagnosis of vasculitis. Taken together with the results on lung biopsy, the findings were most consistent with a clinical diagnosis of paraneoplastic CNS vasculitis that was associated with lung adenocarcinoma. A brain biopsy was not performed because of our

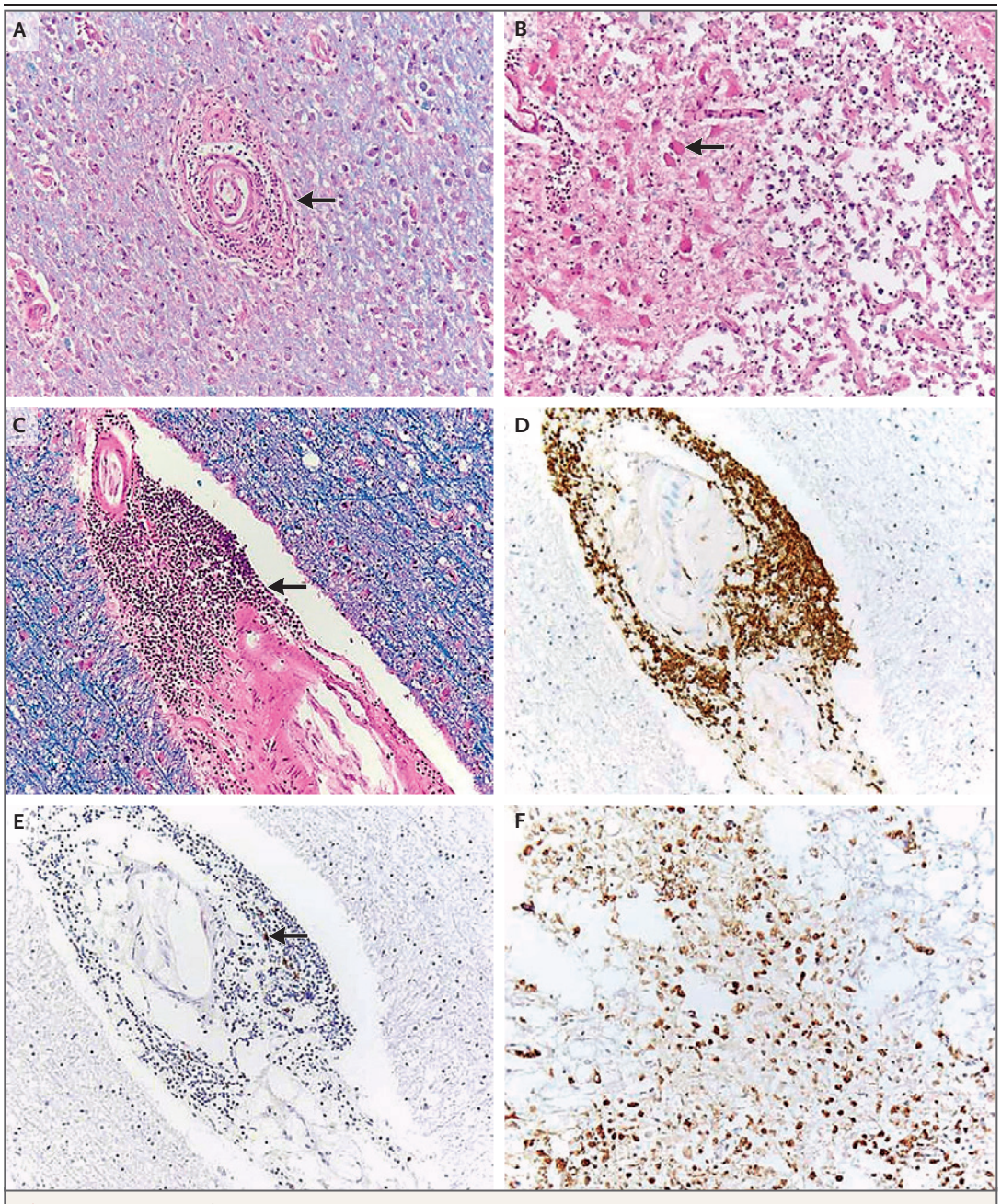

Figure 4. Autopsy Specimens.

Hematoxylin and eosin staining shows multifocal infarcts in the brain. A subacute infarct is composed of sheets of macrophages, and an arteriole with a mural lymphocytic infiltrate is present at the center (Panel A, arrow). A subacute-to-remote infarct is composed of a cavity that contains macrophages and has a rim of reactive astrocytes (Panel B, arrow). There is an arteriole with a dense mural lymphocytic infiltrate that is not associated with infarction (Panel C, arrow). On immunohistochemical staining for CD3 and CD20, the lymphocytes are composed predominantly of CD3+ T cells (Panel D), with scattered B cells (Panel E, arrow). Staining for CD68 highlights macrophages in areas of infarction (Panel F).

high suspicion for CNS vasculitis in the context of cancer.

In consultation with the neuroimmunology team, we administered immunosuppressive therapy for the CNS vasculitis. The patient received a 5-day course of intravenous methylprednisolone,

followed by daily oral prednisone. He received one dose of intravenous cyclophosphamide, and there were plans for additional therapy. Anticoagulation therapy was continued because of his history of atrial fibrillation, his newly found cancer, and the possibility of an underlying hypercoagulable state. The patient was treated with intravenous heparin during his hospitalization. Before discharge, the treatment was transitioned to enoxaparin, and the factor Xa level was obtained to confirm that a therapeutic state had been established. Low-dose aspirin therapy was continued because of his history of coronary artery disease. In consultation with the oncology and radiation oncology teams, we planned to administer radiation therapy for the lung adenocarcinoma and to pursue observation only for the low-grade renal neoplasm.

The patient was transferred to a rehabilitation hospital. Four days later, he was admitted to this hospital with hypoxemia. CT of the chest revealed a pulmonary embolus and enlargement of the tumor in the left lower lobe. Treatment with an intravenous heparin infusion was initiated. The patient had large-volume hemoptysis, hypoxemic respiratory failure, and hypotension that led to treatment with vasopressors for hemodynamic support. After his health care proxy was consulted, the goals of care were transitioned to a focus on comfort, and the patient died in the hospital. An autopsy was performed.

AUTOPSY

Dr. Lang-Orsini: On autopsy, the brain weighed 1470 g and had multiple infarcts, primarily within the white matter. These ranged from subacute infarcts, which were composed of sheets of macrophages (Fig. 4A), to more remote infarcts, which were composed of cavities that contained macrophages and were surrounded by a rim of reactive gliosis (Fig. 4B). A perivascular and intramural lymphoid infiltrate was present in scattered vessels, both in areas associated with infarction and in areas not associated with infarction (Fig. 4C). Immunohistochemical staining for CD3 and CD20 revealed that the lymphocytes were composed predominantly of T cells (Fig. 4D), with scattered B cells (Fig. 4E). Staining for CD68 revealed scattered perivascular macrophages and also highlighted macrophages in the infarcts (Fig. 4F). The combination of multifocal infarcts of different ages and a perivascular T-cell infiltrate was most consistent with a previously treated vasculitis.

The vasculitis could not be further classified, given that previous treatment with glucocorticoids can alter the appearance. However, PACNS tends to be more granulomatous, and giant-cell arteritis would be associated with inflammation of larger-caliber muscular arteries in the leptomeninges or cerebral cortex. In addition, there was no evidence of CNS involvement by metastatic carcinoma.

Pathological examination of the lungs confirmed the diagnosis of adenocarcinoma involving two left hilar lymph nodes. Examination of the left kidney was notable for a well-circumscribed nodule (1.5 cm in diameter), a finding compatible with low-grade papillary renal neoplasm and most consistent with papillary adenoma.

Dr. Silverman: The autopsy findings were consistent with CNS vasculitis with treatment-related changes. Although glucocorticoid treatment limited further classification, there were no features on pathological examination that are typically seen with PACNS or with systemic vasculitis. The presence of newly diagnosed lung cancer in association with recurrent stroke due to small-vessel vasculitis made a paraneoplastic cause the most likely diagnosis.

FINAL DIAGNOSIS

Paraneoplastic vasculitis of the central nervous system.

This case was presented at Neurology Grand Rounds.

Disclosure forms provided by the authors are available at NEJM.org.

We thank Dr. Matthew Frosch for assistance with the pathology portions of the conference and article.

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