

Case Records of the Massachusetts General Hospital

*Weekly Clinicopathological Exercises*

FOUNDED BY RICHARD C. CABOT

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Case 10-2000**PRESENTATION OF CASE**

A 63-year-old man was admitted to the hospital in early July because of rapidly progressive changes in behavior and ataxia.

The patient had been well until 13 days earlier, when he began to have bifrontal headaches, with low-grade fever. Ibuprofen and acetaminophen were prescribed. Two days later, he was found to be disoriented and confused, with a stumbling gait, and was brought to another hospital. The white-cell count was 12,600 per cubic millimeter, with 88 percent neutrophils; the erythrocyte sedimentation rate was 55 mm per hour. The aspartate aminotransferase level was 91 U per liter, and the alanine aminotransferase level was 31 U per liter. Other chemical values, including the osmolality and ammonia level, were normal. A computed tomographic (CT) scan of the brain showed no abnormalities. A lumbar puncture was performed (Table 1).

Haloperidol, ceftriaxone, and acyclovir were administered, and pulsed doses of dexamethasone were given daily for three days. Ceftriaxone was discontinued after five days. The patient twice pulled out an indwelling bladder catheter, causing gross hematuria. A magnetic resonance imaging (MRI) examination of the brain (Fig. 1) revealed small foci of increased signal intensity on T₂-weighted images in both cerebral hemispheres — findings consistent with the presence of small-vessel disease. The patient's mental status and gait improved, but on the 11th hospital day, he became agitated and confused and had ataxia. An electroencephalographic examination showed no evidence of seizure activity. He was transferred to this hospital.

The patient had been born in Italy, had migrated to Argentina in his teens, and had immigrated to the United States 28 years before admission. He worked predominantly outdoors as a landscape contractor and

had occasionally been stung by bees; there was no information about tick bites. He had a history of hypertension and type 2 diabetes mellitus. He did not have a history of diarrhea, arthralgia, use of alcohol or illicit drugs, or exposure to tuberculosis or meningitis, and he had not traveled recently.

The temperature was 36.2°C, the pulse was 72, and the respirations were 18. The blood pressure was 130/80 mm Hg.

A general physical examination showed no abnormalities. On neurologic examination, the patient was sleepy but was easily aroused and able to follow one-step and two-step commands. He was confused but not combative. His speech was good, with occasional paraphasic errors; for example, he mistook a ball for a watch. The cranial-nerve functions were intact. He had difficulty cooperating with the motor examination, but there were no obvious abnormalities. Sensitivity to a pinprick was intact in all the extremities. The finger-to-nose test was performed well. The gait was not tested. The biceps and knee jerks were ++ on the right and +++ on the left; the ankle jerks were + on both sides. There was a right Babinski reflex; the left plantar response was flexor. Bilateral palmar momentary reflexes were present; the right grasp reflex was stronger than the left. No snout, rooting, or sucking reflex was elicited.

The urine was positive (trace) for protein; the sediment contained more than 100 red cells, 3 to 5 white cells, and a few bacteria per high-power field. Laboratory tests were performed (Tables 2, 3, and 4). A radiograph of the chest showed no abnormalities. A second lumbar puncture was performed (Table 1). An MRI examination of the brain, performed without the administration of gadolinium and severely compromised by motion artifact, showed foci of nonspecific hyperintensity in the periventricular white matter on T₂-weighted images — findings consistent with the presence of small-vessel disease. The flow voids of the distal internal carotid arteries appeared normal on this suboptimal study.

An electroencephalographic examination showed no alpha activity. There was a cyclic pattern, with an interval of 30 seconds: 20 seconds of generalized, nonfocal theta activity at 10 to 15 μV, with superimposed symmetric beta activity of 20 to 25 Hz at 5 to 10 μV, and 10 seconds of increased amplitude (an approximate doubling of the beta and theta amplitudes and anterior predominant, symmetric delta activity at 25 to 30 μV), with increased muscle artifact. Many of the low-amplitude sections contained anterior predominant 15-Hz bursts lasting about one second, but no vertex waves were present; the elec-

TABLE 1. LABORATORY FINDINGS ON LUMBAR PUNCTURE.

VARIABLE	11 DAYS BEFORE ADMISSION	ON ADMISSION	ON FIFTH HOSPITAL DAY	ON EIGHTH HOSPITAL DAY
Appearance of fluid		Clear, slightly yellow	Yellow	Very yellow
Initial pressure (cm of water)			16	23
Cells (per mm ³)*				
Red	125	140	1915	693
White	14	25	83	53
Differential count (%)				
Neutrophils	32	2	4	5
Lymphocytes	68	97	93	88
Monocytes	0	1	3	7
Total protein (mg/dl)	123	211	223	705
Albumin (mg/dl)		128		
IgG (mg/dl)		22.9		
Glucose (mg/dl)†		70	73	52
Microscopical findings	No micro-organisms	No bacteria	No microorganisms or malignant cells	No microorganisms or malignant cells
Flow-cytometric findings				No monoclonal B cells or unusual T cells
Culture	Negative		Negative	
Agarose-gel electrophoresis		No banding‡		
Test for <i>Borrelia burgdorferi</i> infection	Negative			
Test for cryptococcal infection	Negative			
Test for western and eastern equine encephalitis	Negative			
Polymerase-chain-reaction test for herpes simplex virus	Negative			

*Values documented 11 days before admission are for the second tube; all other values are for the fourth tube.

†To convert the values for glucose to millimoles per liter, multiply by 0.05551.

‡The study was performed with a specimen concentrated by a factor of less than 31.

troencephalographic frequency increased in the posterior montages during photic stimulation.

Treatment with haloperidol and acyclovir was continued, and lisinopril, acetaminophen, cimetidine, and thiamine were administered. The temperature was slightly elevated at times but never exceeded 38.3°C. The hypertension was easily controlled. The patient's mental status fluctuated, but he remained confused and agitated most of the time. He was intermittently able to obey simple commands, especially when they were given in Italian or Spanish. The glucose level ranged from 98 to 158 mg per deciliter (5.4 to 8.8 mmol per liter) in the absence of treatment with hypoglycemic agents. On the fifth hospital day, another lumbar puncture was performed (Table 1).

On the eighth day, a tuberculin skin test (purified protein derivative, 5 TU) and a test for candida, performed as a control, were positive. An MRI study of the brain, performed before and after the administration of gadolinium, showed scattered foci of bright

signal intensity in the periventricular deep white matter, corona radiata, and centrum semiovale, suggesting microangiopathic changes. There was minimal, diffuse meningeal enhancement. The major vascular flow voids and visible paranasal sinuses appeared normal. A fourth lumbar puncture was performed (Table 1).

On the 10th day, questioning of the patient's wife revealed that, for a period of about three months before admission, he had had difficulty concentrating, performing numerical calculations, and paying bills; he had had slurred speech and visual hallucinations. Repeated neurologic examination revealed either neglect or mild weakness of the left arm and leg. On the next day, the patient thought he was in the first hospital. On the 12th day, CT scans of the thorax, abdomen, and pelvis, obtained without the administration of contrast material, revealed no important changes.

On the 13th day, acyclovir was discontinued. A cerebral angiographic study showed no abnormalities. Laboratory tests were repeated (Table 2). All bacte-

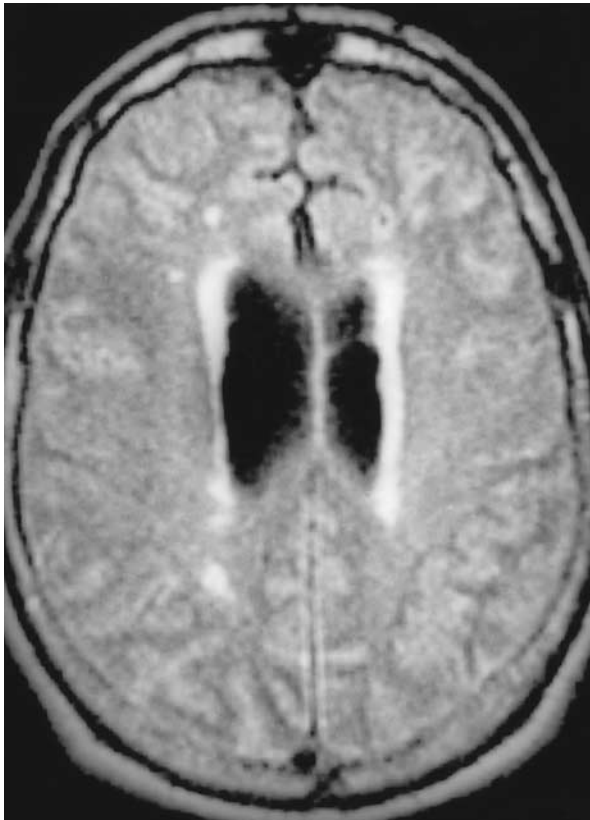


Figure 1. An MRI Scan of the Brain Obtained with Fluid-Attenuated Inversion Recovery, Showing Areas of Hyperintensity Primarily in the Periventricular White Matter.

TABLE 2. HEMATOLOGIC LABORATORY VALUES.

VARIABLE	ON ADMISSION	ON 13TH HOSPITAL DAY
Hematocrit (%)	40.5	31.3
Mean corpuscular volume (per mm ³)	88	89
Erythrocyte sedimentation rate (mm/hr)	15	70
White-cell count (per mm ³)	16,900	9,700
Differential count (%)		
Neutrophils	81	
Myelocytes	2	
Metamyelocytes	1	
Lymphocytes	10	
Monocytes	6	
Platelet count (per mm ³)	339,000	274,000
Prothrombin time	Normal	Normal
Partial-thromboplastin time	Normal	Normal

TABLE 3. BLOOD CHEMICAL VALUES.

VARIABLE	VALUE
Glucose (mg/dl)*	120
Sodium (mmol/liter)	135
Potassium (mmol/liter)	4.2
Chloride (mmol/liter)	98
Carbon dioxide (mmol/liter)	26.8
Vitamin B ₁₂	Normal
Lactate dehydrogenase (U/liter)	234
Angiotensin-converting enzyme (U/liter)	8

*To convert the value for glucose to millimoles per liter, multiply by 0.05551.

TABLE 4. IMMUNOLOGIC TESTS WITH NORMAL OR NEGATIVE RESULTS.

IgG
IgA
IgM
Kappa
Lambda
Kappa:lambda
Serum protein electrophoresis
Cryoprotein
Rheumatoid factor
Antinuclear antibodies
Anti-double-stranded DNA antibodies
Antineutrophil cytoplasmic antibodies
Antibodies against human immunodeficiency virus
Fluorescent treponemal antibodies
Bence Jones protein in urine*

*The test was performed with a specimen concentrated by a factor of 50.

rial, fungal, and viral cultures were negative; the results of mycobacterial cultures were pending.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. LOUIS R. CAPLAN*: The best way to learn from single case presentations is to place yourself in the position of the physicians caring for the patient and analyze the information as it evolved for them. On admission to this hospital, the patient under discussion was thought to have an acute (13-day) change in brain functions accompanied by headache, slight fever, and leukocytosis.

*Senior neurologist and director, Stroke Service, Beth Israel Deaconess Medical Center; professor of neurology, Harvard Medical School — both in Boston.

The syndrome he had at that time is usually referred to as acute encephalopathy, which encompasses many diffuse and multifocal disorders that affect both cerebral hemispheres. The encephalopathy syndrome is recognized on the basis of clinical rather than laboratory findings.¹ Table 5 lists the clinical features of encephalopathy, and Table 6 lists its most common causes. Evaluation of patients with encephalopathy usually begins with tests of organ function, measurements of electrolytes, tests of endocrine function, and screening for toxins. In patients with headache, fever, and leukocytosis, infectious disorders are considered; cultures, serologic tests, and cerebrospinal fluid analysis are performed without delay. Neuroimaging

TABLE 5. CLINICAL FEATURES OF THE ENCEPHALOPATHY SYNDROME.

Decreased alertness: drowsiness, agitation with hyperactivity, stupor, and coma
Globally decreased intellectual functions: impaired memory, speech, visual-spatial function, and ability to perform numerical calculations
Absence of a localized cognitive abnormality such as severe aphasia
Performance that fluctuates from moment to moment or hour to hour
Absence of prominent focal abnormalities of motor, sensory, and visual functions
Asterixis (when the patient is alert enough to be tested)

TABLE 6. MOST COMMON CAUSES OF THE ENCEPHALOPATHY SYNDROME.

Systemic causes
Endogenous
Liver failure
Hypoxia or carbon dioxide narcosis
Kidney failure
Heart failure
Severe anemia
An excess or deficiency of thyroid hormone, parathyroid hormone (and calcium from other sources), or adrenal or pituitary hormones
Electrolyte, acid-base, and metabolic disturbances (abnormalities of electrolytes, glucose, ketones, or vitamins)
Exogenous (toxins)
Alcohol and drugs
Heavy metals and hydrocarbons
Primary nervous system causes
Meningitis (viral, bacterial, or fungal)
Encephalitis (usually viral)
Multifocal cerebral lesions
Hemorrhages and infarcts
Tumors
Inflammatory or demyelinating lesions
Infectious lesions such as abscesses
Traumatic lesions

and electroencephalography are sometimes helpful when preliminary testing does not show a toxic or metabolic problem or an obvious infectious cause.

In this patient, the absence of clinical and laboratory evidence of an important electrolyte, acid-base, or organ-function abnormality, coupled with the abnormal cerebrospinal fluid findings, clearly ruled out a toxic or metabolic cause of the brain dysfunction. Appropriately, infectious causes of meningitis and encephalitis were considered, and the patient was treated with an antiviral agent (acyclovir), an antibacterial drug (ceftriaxone), and pulsed doses of dexamethasone. Corticosteroids are sometimes given to patients with acute brain and meningeal infections. All tests for viral, bacterial, and fungal pathogens were negative, and treatment was ineffective except for a transient improvement that may have been related to the administration of corticosteroids. A CT scan and three MRI scans showed multifocal white-matter abnormalities in the cerebral hemispheres and slight, diffuse meningeal enhancement, but these neuroimaging studies did not identify a cause of the encephalopathy.

On the 10th hospital day, the patient's physicians took a wise but unfortunately rare step in a technologically dominated medical environment. They obtained a more detailed history, reexamined the patient, and found that the disorder was not acute but progressive, beginning with cognitive dysfunction and dysarthria and progressing over a period of approximately three months. Neurologic examination showed previously unrecognized weakness or neglect of the left arm and leg. These findings pointed to a multifocal, progressive brain disorder. An important feature of the disease was the consistent presence of red and white cells and an elevated protein level in the cerebrospinal fluid. Diseases that affect the meninges often cause an increase in the cerebrospinal fluid protein level. When the blood vessels of the brain are involved, their fragility and the occurrence of perivascular hemorrhages and infarcts allow spillage of red and white cells and protein into the Virchow-Robin spaces, which communicate with the cerebrospinal fluid.

The differential diagnosis at this point includes chronic, progressive conditions that cause multifocal involvement of both cerebral hemispheres (Table 6). May we review the MRI scans and angiographic studies with this broad differential diagnosis in mind?

DR. R. GILBERTO GONZALEZ: An image obtained with fluid-attenuated inversion recovery, which provides contrast on T₂-weighted images but suppresses the cerebrospinal fluid, was available from the MRI study performed before admission (Fig. 1). It shows nonspecific and probably chronic areas of hyperintensity located predominantly in the periventricular white matter. This abnormality is commonly caused by small-vessel disease and is often seen in older patients. Two additional MRI scans, obtained after admission to this hospital, reveal no important change

from the previous findings. Diffusion-weighted scanning, a very sensitive method for the detection of acute and subacute infarcts, does not show infarcts in this case. Imaging studies with contrast enhancement show a minimal abnormality of the meninges, but not the prominent change that is commonly seen with meningitis. A cerebral angiographic study shows normal vessels.

DR. CAPLAN: The neuroimaging abnormalities are not striking and do not suggest either metastatic carcinoma, which usually causes well-circumscribed, round, enhanced nodules surrounded by edema, or primary lymphoma, which is most often manifested as multiple, well-defined lesions that abut meningeal and ependymal surfaces. Carcinomatous and lymphomatous meningitis can cause a syndrome characterized by abnormalities of the cranial nerve and spinal nerve root, headache, increased cerebrospinal fluid pressure, prominent meningeal enhancement, low cerebrospinal fluid glucose levels, and cytologic abnormalities in the cerebrospinal fluid — all of which are absent in this patient.

Infectious diseases are more difficult to rule out in this case. Viral meningitis and encephalitis usually cause neurologic symptoms and signs that are most pronounced during the first days of infection, although, in rare cases, they evolve over a period of several months. In this case, a polymerase-chain-reaction (PCR) test was negative for herpes simplex virus infection. A serologic test was negative for both eastern and western equine encephalitis, which are arthropod-borne diseases that occur predominantly in clusters during the summer months. The symptoms, neurologic signs, course, and cerebrospinal fluid findings in this case are not characteristic of any particular viral disease of the nervous system.

Human immunodeficiency virus (HIV) infection can cause an acute, rapidly fatal meningoencephalitis² and is also associated with a chronic encephalopathy, with symptoms developing years after seroconversion. An illness similar to this patient's, however, has not been reported in association with HIV infection, and he did not have antibodies against HIV. Although syphilis and Lyme disease can cause clinical and cerebrospinal fluid abnormalities similar to those in this patient, the negative serologic tests make these disorders very unlikely. Chronic tuberculous and fungal meningitis involve the basal meninges and cause cranial-nerve abnormalities and low glucose levels in the cerebrospinal fluid, findings that were not present in this case.³ A test for the most common causative fungus, *Cryptococcus*, was negative. Brain infarcts are caused by *Mucor* and *Aspergillus* species, but the patient had no risk factors for these infections, and the clinical and neuroimaging findings are not consistent with their presence.⁴

Demyelinating diseases such as acute multiple sclerosis, acute disseminated encephalomyelitis, and pro-

gressive multifocal leukoencephalopathy merit only superficial consideration. Elementary neurologic signs, including visual loss, nystagmus, motor and sensory loss, and abnormalities of the brain stem and spinal cord, predominate clinically, and the neuroimaging abnormalities differ greatly from those in this patient. In the demyelinating disorders, the white-matter lesions are more prominent and distinctive than the minor parenchymal abnormalities on this patient's MRI scans.

The clinical, imaging, and cerebrospinal fluid findings in this case are most consistent with a disease involving blood vessels of the brain and meninges. The patient had hypertension and diabetes, both of which are risk factors for disease of the penetrating arteries, such as lipohyalinosis and microatheromatous disease,^{5,6} but the absence of lacunar infarcts and prominent white-matter abnormalities, such as those found in Binswanger's disease,^{7,8} and the cerebrospinal fluid findings rule out a degenerative disease of the penetrating arteries as the cause of the illness. Thrombotic thrombocytopenic purpura and disseminated intravascular coagulation can cause neurologic abnormalities similar to those in this patient, but he did not have the hematologic abnormalities that are characteristic of these syndromes. Similarly, there was no evidence of hyperviscosity, which can cause microinfarcts and hemorrhages. Carcinomas, particularly the mucinous type, can be associated with hypercoagulability⁹ and can cause nonbacterial thrombotic endocarditis and multiple brain infarcts and hemorrhages. Coagulation tests were consistently normal in this patient, however, and the cerebrospinal fluid findings are inconsistent with the presence of bland infarcts related to hypercoagulability or noninfective emboli.

Infective endocarditis merits more serious consideration because of the patient's fever, leukocytosis, and hematuria, although the hematuria was probably due to urethral trauma. Multiple emboli associated with infective endocarditis can cause clinical and cerebrospinal fluid abnormalities similar to those in this case. I am surprised that the case record does not include the results of a detailed cardiac examination and an echocardiographic study. Although the available information is insufficient to rule out infective endocarditis, I doubt that it was the cause of the neurologic disease.

Sarcoidosis and lymphomatoid granulomatosis can involve the brain parenchyma, meninges, and blood vessels. Sarcoidosis is sometimes associated with a lymphocytic pleocytosis and an elevated cerebrospinal fluid protein level, and it often involves veins, producing a perivenous exudate in the retina and brain, sometimes accompanied by multiple small infarcts in the brain.¹⁰ In this case, however, the absence of involvement of the eyes, lungs, lymph nodes, and other organs and the absence of pronounced meningeal enhancement weigh strongly against the diagnosis of sarcoidosis.

Lymphomatoid granulomatosis is an angiocentric lymphoreticular proliferative disease¹¹ that infiltrates and destroys blood vessels, which become surrounded by pleomorphic infiltrates and granulomas. The vascular damage can cause multiple small brain infarcts. Central nervous system abnormalities are present in about 20 percent of cases and can be both the initial and the predominant manifestations of the illness. MRI findings have been described in only a few patients with lymphomatoid granulomatosis. One patient had linear enhancement of the meninges and the adjacent cerebral cortex.¹² Mass lesions have also been noted in the brain and surrounding cisterns.¹² Although a lymphocytic pleocytosis can occur in cases of lymphomatoid granulomatosis, in most cases it is minimal, and the cerebrospinal fluid protein content is usually only slightly elevated (less than 100 mg per deciliter).¹¹ In most patients, the white-cell count is normal or low, whereas in this patient it was elevated. The lungs are invariably involved, and the skin and kidneys are affected in nearly half the patients.¹¹ In this patient, however, there were no important lesions on films or CT scans of the chest or on the CT scan of the abdomen and pelvis. There are too many atypical features of this case to support the diagnosis of lymphomatoid granulomatosis.

I believe this patient probably had either angitis limited to the nervous system or an intravascular lymphoma. Central nervous system vasculitis is rare but often considered in the differential diagnosis. The diagnosis in the last case record that I discussed was giant-cell arteritis.¹³ Subsequent PCR testing of tissue obtained at autopsy showed that the vasculitis was related to herpes-zoster virus infection.¹⁴ The absence of asthma and eosinophilia in the patient under discussion rules out the small-vessel angitis found in patients with the Churg-Strauss syndrome,¹⁵ and the clinical, serologic, angiographic, and cerebrospinal fluid findings are not compatible with the diagnosis of either polyarteritis nodosa or vasculitis associated with systemic lupus erythematosus or Wegener's granulomatosis.

The only form of vasculitis that merits serious consideration in this case is isolated angitis (granulomatous or giant-cell granulomatous angitis) of the central nervous system,¹⁶⁻¹⁹ a necrotizing process involving segments of leptomeningeal and brain vessels. Arteries or veins of any size, although usually those 200 to 500 μm in diameter, and precapillary arterioles are involved.¹⁷ The vessel walls, predominantly the intima and adventitia, are infiltrated by lymphocytes, plasma cells, macrophages, epithelioid cells, and multinucleated giant cells. Granulomas may affect brain parenchyma adjacent to vessels that have a disruption of the elastic lamina. Multiple infarcts and sometimes hemorrhages are scattered throughout the brain. Some cases of isolated granulomatous angitis are caused by the varicella-zoster virus. A PCR test of the

cerebrospinal fluid for this virus would have been helpful in establishing the diagnosis.

The clinical, serologic, MRI, and cerebrospinal fluid findings in this patient are all compatible with the diagnosis of isolated angitis of the central nervous system. The sedimentation rate is elevated in two thirds of patients with this disorder, and the leukocyte count is increased in half of such patients, but other serologic and antibody tests are usually normal, as in this case.¹⁷ Most patients have segmental narrowing and dilatation on angiographic examination, but in some patients with biopsy-confirmed isolated angitis of the central nervous system, the vessels appear normal.¹⁶⁻²²

Lymphoma can be manifested as a purely intravascular neoplasm. Formerly called neoplastic angioendotheliosis,^{23,24} intravascular lymphoma is characterized by the proliferation of large pleomorphic mononuclear cells with B-cell or T-cell markers, or both, within the lumens of capillaries, venules, arterioles, and small arteries.^{11,25,26} Patients with this disease usually present with nervous system and skin abnormalities. Headache, multifocal neurologic signs, and a progressive course are typical. The brain lesions seen on MRI are either small foci of hyperintensity or large areas of signal change in the white matter of the cerebral cortex. Meningeal enhancement has been attributed to microinfarcts in the meninges or a slow flow through meningeal vessels.²⁶ Angiographic findings are usually normal, because the involved blood vessels are too small to be seen. In patients with tumor cells of B-cell origin, the cerebrospinal fluid IgG level may be elevated, as it was in this patient.²⁵

Both isolated angitis and intravascular lymphoma cause destruction of small blood vessels, and the two disorders cause similar clinical, MRI, and cerebrospinal fluid abnormalities. I find it difficult to distinguish between them in this case. The high level of IgG in the cerebrospinal fluid and the normal angiographic findings lead me to favor intravascular lymphoma. I would have carefully examined the skin for lesions, and if any had been present, I would have performed a skin biopsy, which is much less invasive than a biopsy of the brain or meninges. In the absence of skin lesions, the probable diagnostic procedure was a biopsy of the meninges and underlying brain.

CLINICAL DIAGNOSIS

Primary vasculitis of the central nervous system.

DR. LOUIS R. CAPLAN'S DIAGNOSES

- ? Intravascular lymphoma.
- ? Granulomatous angitis of the central nervous system.

PATHOLOGICAL DISCUSSION

DR. DAVID N. LOUIS: Biopsies of a temporal artery, the dura mater, and the leptomeninges and brain were performed. The specimens of the temporal ar-

tery and dura mater appeared normal. Examination of the biopsy specimen of the leptomeninges and brain showed a focus of prominent leptomeningeal inflammation within a small sulcus. It was characterized mostly by lymphocytes and scattered macrophages clustered around a small leptomeningeal artery without involving its wall. There were also rare giant, multinucleated histiocytes, adjacent to the vessel (Fig. 2), which were positive for CD68 on immunohistochemical staining. Other, smaller vessels in the leptomeninges and adjacent cerebral cortex had round profiles with thickened eosinophilic walls — findings that are strongly suggestive of amyloid angiopathy (Fig. 3). Congo red staining of these vessels was positive, with apple-green birefringence, and immunohistochemical staining for the β 4-amyloid protein showed substantial deposits in the vessels (Fig. 4), as well as focally within the larger leptomeningeal vessel that was surrounded by the inflammatory infiltrate. The multinucleated giant cells contained innumerable granules that were also positive for β 4-amyloid protein (Fig. 5).

Intracortical neuritic plaques, some of which had dense amyloid cores, were also noted on staining for β 4-amyloid protein, as well as on Bielschowsky's silver staining. The number of intracortical plaques, however, was not sufficient to establish the diagnosis of Alzheimer's disease, in view of the patient's age and his prior mental status. Special stains for infectious organisms were negative. A few small infarcts were present in the cortex and underlying white matter, characterized by tissue rarefaction and shrinkage of neurons with cytoplasmic eosinophilia and pyknotic nuclei (red-neuron change). There were no inflammatory infiltrates, however. These infarcts, which appeared to be less than 48 hours old, may have been related to the angiographic procedure. There was no evidence of prior hemorrhage.

The principal vascular findings are diagnostic of cerebral amyloid angiopathy,^{27,28} a condition primarily affecting elderly persons, in which amyloid is deposited in cerebral vessels, predisposing patients to lobar cerebral hemorrhages and in rare cases to other neurologic events.²⁹ In most cases of sporadic cerebral amyloid angiopathy, the amyloid is β 4-peptide, as in this case. The multinucleated giant cells in the biopsy specimen from the patient under discussion raised the additional possibility of a giant-cell or granulomatous vasculitis, but inflammation was not present in the vessel walls themselves, and the giant cells appeared to be reacting to the abundant β 4-amyloid in the vessel walls. Similar giant cells have frequently been reported in cases of cerebral amyloid angiopathy, and their presence has been attributed to either the coexistence of vasculitis and cerebral amyloid angiopathy or a giant-cell reaction to the amyloid deposits.³⁰⁻³² The histopathological changes in the case under discussion favor the latter interpretation. Al-

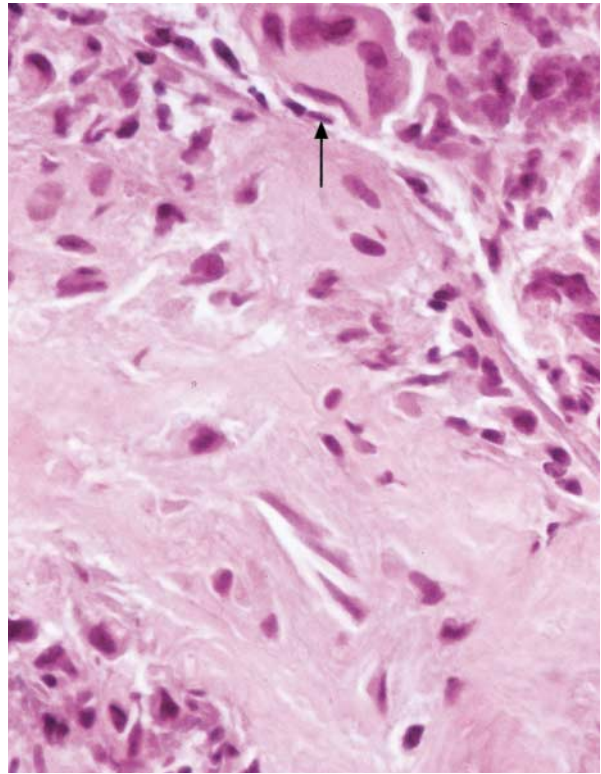


Figure 2. Biopsy Specimen of the Brain, Showing a Thickened Leptomeningeal Blood Vessel Surrounding an Area of Inflammation, with a Multinucleated Giant Cell (Arrow) (Hematoxylin and Eosin, $\times 275$).

though a histologic diagnosis of vasculitis cannot be made with certainty, the therapeutic implications of this histologic picture center on its vasculitis-like characteristics.³¹ Dr. Greenberg will comment further on this point.

DR. STEVEN M. GREENBERG: One question is whether the vascular amyloid deposits in this patient were coincidental and unrelated to his symptoms. This interpretation is unlikely, in view of the extent of amyloid angiopathy in one small specimen of tissue, which suggests that there was severe enough disease throughout the brain to cause the patient's symptoms.³³ Another question is whether vasculitis related to cerebral amyloid angiopathy differs substantially from other forms of vasculitis in the central nervous system, with respect to either its clinical features or its response to therapy. The literature suggests that this disorder is not markedly different from other forms of vasculitis³¹ and that it is reasonable for the neurologist to treat the disorder as if it were an idiopathic central nervous system vasculitis.

Vasculitis related to cerebral amyloid angiopathy may provide biologic insight into the more common, nonvasculitic form of cerebral amyloid angiopathy,

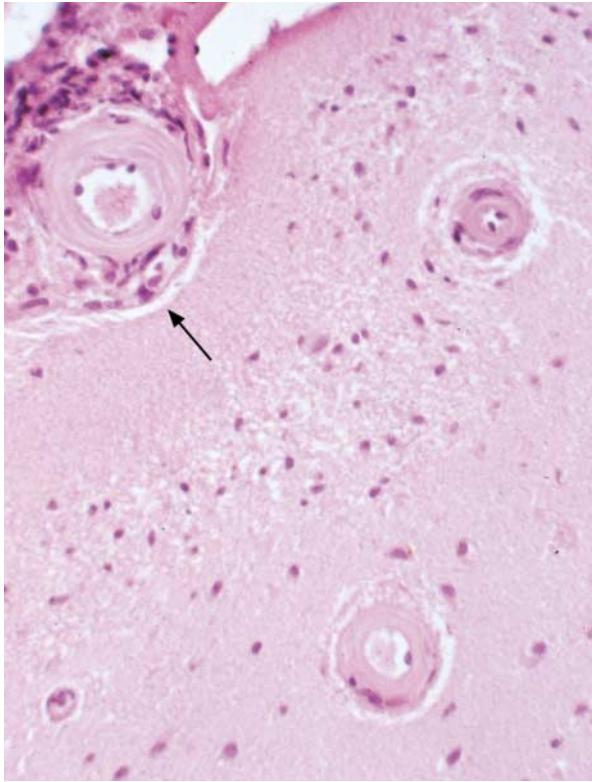


Figure 3. Two Rounded Superficial Blood Vessels with Thickened Walls in the Cerebral Cortex (Hematoxylin and Eosin, $\times 80$). A similar vessel in the leptomeninges (arrow) is surrounded by inflammatory cells. The vascular abnormalities are characteristic of cerebral amyloid angiopathy.

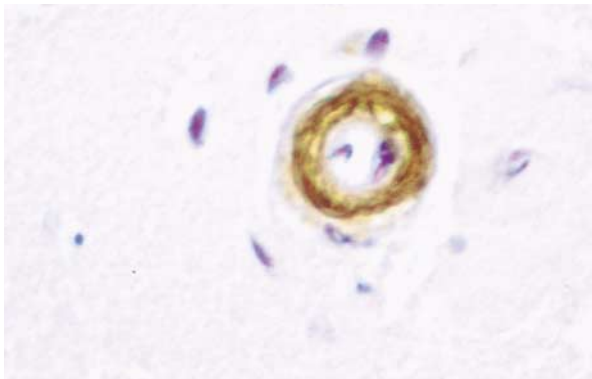


Figure 4. Superficial Blood Vessel in the Cerebral Cortex, Stained Dark Brown for $\beta 4$ -Amyloid Protein (Immunohistochemical Stain, $\times 160$).

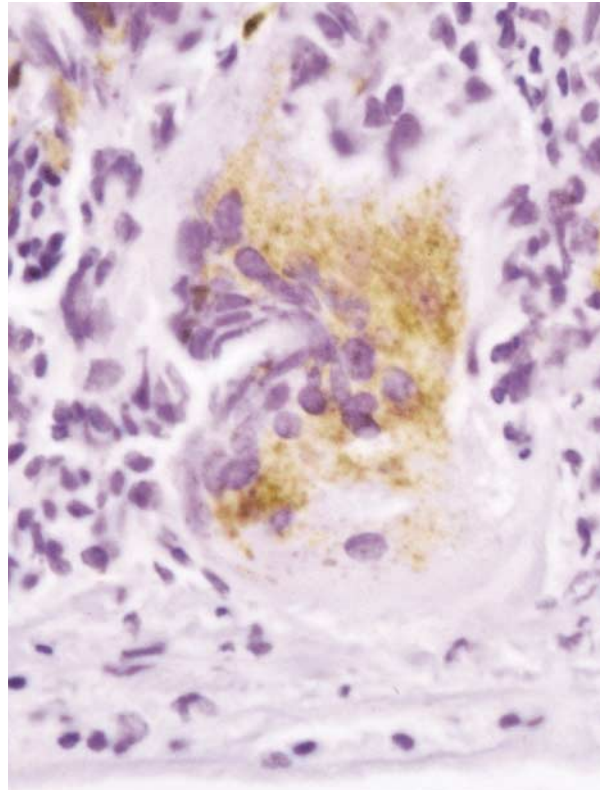


Figure 5. Multinucleated Giant Cell Stained Brown for Intracytoplasmic $\beta 4$ -Amyloid Protein (Immunohistochemical Stain, $\times 275$).

which is an important cause of hemorrhagic stroke in the elderly.²⁹ Although frank vasculitis is not a feature of these cases, several authors have noted perivascular inflammatory cells in the brains of patients with severe cerebral amyloid angiopathy,^{27,30,34} suggesting that an inflammatory response to amyloid may contribute to the rupture of the vessel wall in patients with cerebral hemorrhage related to cerebral amyloid angiopathy.

The patient was treated with high-dose cyclophosphamide. His condition has slowly deteriorated during the 13 months since his discharge from this hospital. He is still able to recognize some people but requires considerable care.

DR. CAPLAN: Biopsy of the meninges in this patient showed both amyloid angiopathy and a granulomatous angitis. In amyloid angiopathy, small arteries and arterioles often crack. Perhaps the release of amyloid into the meninges incited the granulomatous reaction in meningeal blood vessels.

ANATOMICAL DIAGNOSIS

Cerebral amyloid angiopathy with giant-cell inflammatory reaction to $\beta 4$ -amyloid and vasculitis.

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