

Case Records of the Massachusetts General Hospital

*Weekly Clinicopathological Exercises*

FOUNDED BY RICHARD C. CABOT

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Case 26-1998**PRESENTATION OF CASE**

A 15-year-old right-handed girl was admitted to the hospital because of hemiparesis, slurred speech, and urinary retention.

The patient had been in excellent health until two and a half weeks earlier, when she began to have urinary urgency but found it difficult to empty her bladder. A few days later she felt unsteady and fell several times. Her handwriting slowed, and she had

TABLE 1. HEMATOLOGIC LABORATORY VALUES.

VARIABLE	VALUE
Hematocrit (%)	42.4
Erythrocyte sedimentation rate (mm/hr)	21
White-cell count (per mm ³)	16,700
Differential count (%)	
Neutrophils	87
Lymphocytes	11
Monocytes	2
Platelet count (per mm ³)	411,000

TABLE 2. BLOOD CHEMICAL VALUES.

VARIABLE	VALUE
Glucose (mg/dl)*	129
Sodium (mmol/liter)	141
Potassium (mmol/liter)	3.5
Chloride (mmol/liter)	106
Carbon dioxide (mmol/liter)	21

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

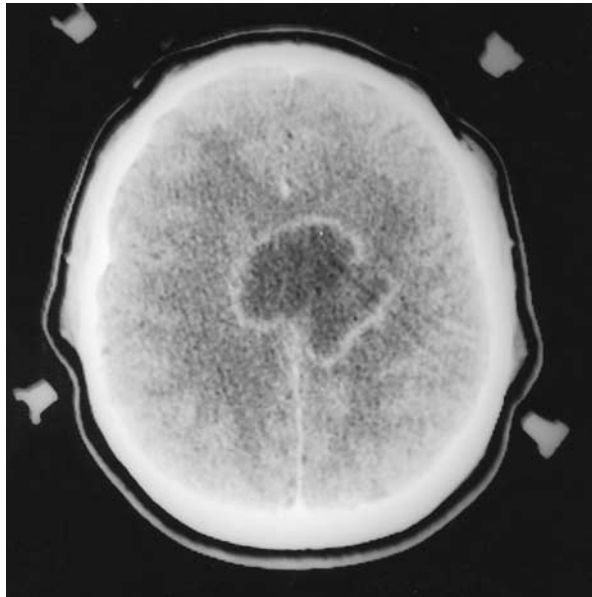


Figure 1. Contrast-Enhanced Axial CT Scan Showing a 5-cm Ring-Enhancing Lesion.

The lesion is centered in the body of the corpus callosum, with bilateral extension into the centrum semiovale. The rim is smooth, and there is little surrounding edema.

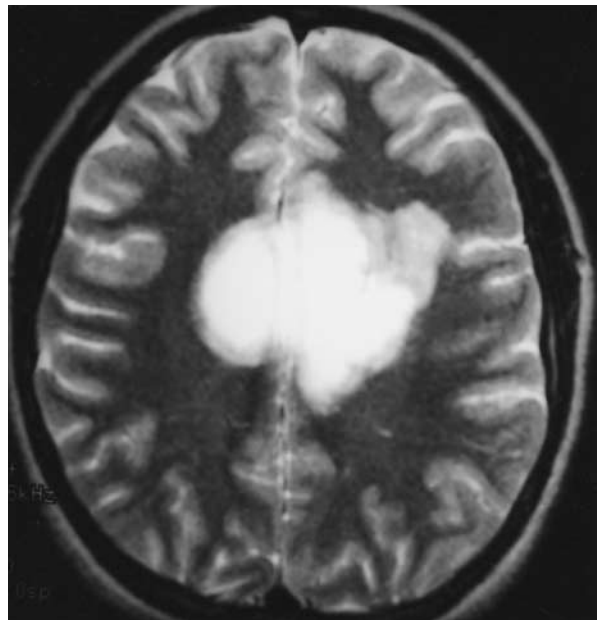


Figure 2. Axial T₂-Weighted MRI Scan Showing Marked Hyperintensity of the Lesion.

There is a small amount of edema with a hyperintense signal, which is best seen along the left anterior margin of the lesion.

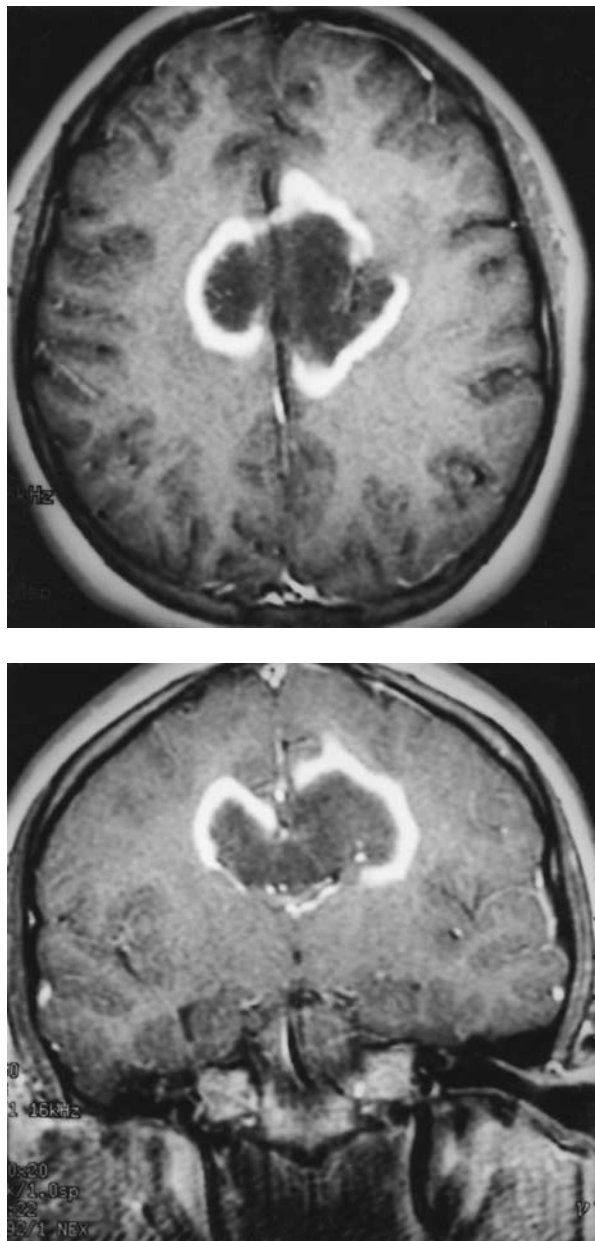


Figure 3. Gadolinium-Enhanced T₁-Weighted Axial (Upper Panel) and Coronal (Lower Panel) MRI Scans.

The mass is hypointense. There is relatively smooth enhancement of the rim, with almost no surrounding edema.

difficulty articulating her thoughts. Several days before admission, weakness and numbness developed in the right arm and leg, accompanied by right facial droop and slurred speech. On the evening before admission, she was found sleepwalking for the first time in her life. She continued to attend school until the day of admission, when her mother, observing that the girl needed to use her arms to rise from a chair, took her to a physician.

A computed tomographic (CT) scan of the brain

(Fig. 1), performed before and after the administration of contrast material, showed a ring-enhancing, mass-like lesion, 5 cm in diameter, in the corpus callosum, with extension into the centrum semiovale in each hemisphere and with little surrounding edema. The patient was referred to this hospital.

The family had a healthy cat. The patient had no history of antecedent viral infection or vaccination, foreign travel, neurologic symptoms, altered cognition or mental status, fever, headache, visual disturbance, seizures, weight loss, or tick bite, and she had no risk factors for sexually transmitted diseases. There was no family history of brain tumor, multiple sclerosis, or other neurologic disease.

The temperature was 37°C, the pulse was 84, and the respirations were 20. The blood pressure was 120/70 mm Hg.

The results of a physical examination were normal, except for obesity.

On neurologic examination, the patient was alert and fully oriented, with preserved memory and intact speech and comprehension. There was mild right-central facial paresis, with slight dysarthria. The medial aspects of the optic-disk margins were blurred. The right pupil was 4 mm in diameter and constricted to 2 mm on stimulation with light; the left pupil was 3.5 mm in diameter and constricted to 1.5 mm. The remaining cranial-nerve functions were preserved. Strength was graded 4/5 in the right biceps, triceps, and deltoid; 5/5 in the right grip; 4/5 in the right iliopsoas; and was 4-/5 in the right-knee flexors and extensors and the right plantar flexors and extensors. The strength in the left arm and left leg was 5/5. Sensitivity to a light touch, pinprick, and heat and cold was normal; stereognosis, graphesthesia, and coordination were intact. The deep-tendon reflexes were ++++ in the right arm and right knee, +++ in the right ankle with sustained clonus, and +++ in the left arm and left leg, with bilateral Babinski signs. The stance was stable, with a negative result on Romberg's test. Evaluation of the gait disclosed slight circumduction, with a minor limp in the right leg and diminished swing in the right arm. The patient had difficulty walking on her toes and performing tandem walking. While making a quick turn, she staggered.

The urine was normal. The levels of urea nitrogen, creatinine, conjugated and total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase were normal, as was the osmolality. The prothrombin and partial-thromboplastin times were normal. The results of other laboratory tests are shown in Tables 1 and 2. An electrocardiogram revealed sinus tachycardia at a rate of 113 beats per minute.

Radiographs of the chest were normal. A gadolinium-enhanced magnetic resonance imaging (MRI) study of the brain (Fig. 2 and 3) disclosed a mass-

like lesion, 5 cm in diameter, centered in the corpus callosum, with extension into the centrum semiovale in each hemisphere. The lesion was hyperintense on T₂-weighted images (Fig. 2) and hypointense on T₁-weighted images (Fig. 3), and it had a smooth enhancing rim. Little edema surrounded the lesion.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWIN L. ZALNERAITIS*: May we review the radiologic studies?

DR. PAMELA W. SCHAEFER: A contrast-enhanced CT scan of the head (Fig. 1) shows a ring-enhancing lesion in the center of the corpus callosum, with bilateral extension into the centrum semiovale. A gadolinium-enhanced MRI study of the brain shows that the lesion is hyperintense on T₂-weighted images (Fig. 2) and hypointense on T₁-weighted images (Fig. 3), with smooth enhancement of its rim and little surrounding edema.

DR. ZALNERAITIS: Problem solving in medicine is heavily dependent on the recognition of patterns. To establish the pattern and reach a diagnosis, one must consider the location, radiologic characteristics, and pace of the disease process, as well as associated findings.

Can the single lesion found on the imaging studies in this patient account for her presentation and all the findings? A lesion in this location could have disrupted a number of the functions controlled by the frontal and prefrontal regions of the brain, accounting for several features of the patient's presentation, including the urinary urgency and sensation of bladder fullness. Although the supratentorial sites of urinary urgency and a sensation of bladder fullness have not been fully established, these symptoms have been produced by electrical stimulation of the sensory cortex and by the presence of tumors of the frontal lobe or lesions of the corpus callosum and adjacent anterior cingulate gyrus.^{1,2} The patient's unsteady gait, slow handwriting, and difficulty with articulation of thoughts could be due solely to a disruption of pyramidal function, as suggested by her accentuated reflexes and bilateral Babinski signs. The extent of her disability, however, suggests in addition a dyspraxic state due to a prefrontal disconnection. Prefrontal lesions have also been associated with proximal weakness and could thus account for the patient's need to use her arms when rising from a chair.^{3,4}

Ruled out by the patient's history are predisposing factors for her illness. Particularly notable on examination was the absence of fever, alteration in vital

signs, and meningismus. The preservation of cognitive functions, including most aspects of speech, supports the presence of isolated pyramidal and premotor dysfunction, reflecting a localized process caused by the single lesion that was identified by imaging. The patient's right-sided weakness and slurred speech are consistent with the presence of pyramidal dysfunction. No elements of the examination as reported in the case record addressed the specific features of the dyspraxia. Despite the right-sided numbness, both primary and cortical sensory perception was unimpaired, a finding consistent with the preservation of postcentral-gyrus sensory ability. Other parietal functions are not delineated. Since there was no visual disturbance or other ophthalmologic abnormality that would explain the blurred disk margins, they presumably resulted from papilledema due to increased intracranial pressure caused by the mass effect of the lesion, even though the patient had no headache. Unequal but otherwise intact pupillary function may be a normal finding or may reflect asymmetric pupillary constriction caused by pressure on the anterior cingulate region. The patient's other motor and reflex changes are consistent with the presence of bilateral but primarily right-sided pyramidal dysfunction.³

Most of the laboratory test results were normal, and stress probably accounts for the abnormal results, including the slightly increased white-cell count, mild neutrophilia, high platelet count, and slightly increased glucose level.

The progression of this patient's disease can be judged by the development of its manifestations over a period of two and a half weeks. Although the lesion undoubtedly preceded the symptoms, its appearance on the unenhanced CT scan — with a rim of radiodensity greater than that of the surrounding normal cerebral tissue — reflects a loss of the characteristics of normal brain tissue, a loss common in rapidly advancing lesions. A recent and symptomatically critical change or the progression of a chronic condition is much less likely.

What pathologic processes can result in the imaging findings in this case? The contrast enhancement seen on both the CT and MRI scans represents a breach in the blood-brain barrier. This breach may be caused by a destructive process or by the growth of tissue that lacks the normal barrier of the central nervous system, thus allowing contrast material to pass from the vascular space to adjacent tissue.^{5,6} The processes to be considered in this case are those that can evolve without headache, fever, malaise, or other abnormalities aside from the local effects of the mass-like lesion. Accordingly, we need not consider known causes of ring-enhancing lesions, such as a thrombosed aneurysm or an infarct or intracerebral hematoma.⁷

The information in the case record cannot support a precise diagnosis but can be used to generate

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a differential diagnosis and then select the most probable diagnosis.

Although ring enhancement is a common finding in scans of brain abscesses, and although ring abscesses may develop in as short a period as two and a half weeks, the ring enhancement in this case is thicker than usual and more characteristic of a neoplasm than of an abscess. Moreover, an abscess of this size would be associated with marked edema,^{7,8} fever, and malaise. Also, predisposing conditions such as cyanotic congenital heart disease have been reported in as many as 73 percent of patients with brain abscesses,⁹ but none of these conditions were present in this case.

Chronic or opportunistic infections, such as tuberculosis or toxoplasmosis, can have this radiographic appearance. When tuberculosis presents as a mass lesion, however, it is usually more uniformly radiodense, with noticeable edema.¹⁰ In addition, this patient's normal chest film and the absence of fever, cough, night sweats, or exposure to mycobacteria make tuberculosis an unlikely diagnosis. Exposure to a cat can result in toxoplasmosis, even if the cat is healthy. Lesions due to toxoplasma infection can be radiographically indistinguishable from the lesion in this case; surrounding edema is often prominent but can be minimal, as in this case. Usually there are multiple lesions. This patient was not immunocompromised and had no additional manifestations of toxoplasmosis, although such manifestations are not always present in cases of cerebral infection.¹¹

Demyelinating processes, other than the infectious demyelination found in progressive multifocal leukoencephalopathy, can present with radiologic findings similar to those seen in this case. Autoimmune inflammatory demyelination may follow infection with agents such as varicella-zoster virus or may occur after vaccination. This disorder can result in a solitary lesion with a mass effect and ring enhancement. With this radiologic appearance, however, the disorder usually has a fulminant course,¹² with fever, lethargy, stiffness of the neck, photophobia, malaise, or other manifestations. Therefore, autoimmune inflammatory demyelination is an improbable cause of this patient's illness.

Demyelination due to leukodystrophy usually appears as a diffuse rather than localized hyperintense signal on T₂-weighted MRI scans. Enhancement is typically not as prominent as it is in this case, but in its acute phase leukodystrophy can have a similar radiologic picture.⁶ Of all the possible explanations for this patient's lesion, demyelination due to leukodystrophy is the most likely to be associated with little surrounding edema, but it probably would not have as extensive a mass effect as that seen in this case. Among the leukodystrophies, the most likely to occur in a teenage patient would be a late-juvenile form of metachromatic leukodystrophy. Other forms of leukodystrophy occur in an X-linked pattern, such as

adrenoleukodystrophy, or in other age groups, such as Krabbe's disease. The patient under discussion had an isolated lesion, no prior evidence of white-matter disease such as spasticity or visual impairment, and no family history of leukodystrophy. Therefore, although metachromatic leukodystrophy is a possible diagnosis on the basis of the radiologic findings, it is not a likely cause of the clinical findings.¹³

In a 15-year-old girl who is otherwise well, a solitary, contrast-enhancing mass lesion in the central nervous system is most likely a neoplasm. Among the less common tumors, a lipoma, which is often located in the corpus callosum, is not a consideration because a lipoma has a lower density on CT scans and a uniformly high density on T₁-weighted MRI scans. The corpus callosum would be an unusual site for a meningioma, which typically does not produce an intense signal on either T₁-weighted or T₂-weighted MRI scans; its enhancement is typically dense and diffuse. Angiomas most often present with focal neurologic findings, and complications of bleeding are the usual cause of acute neurologic changes. In this case, no changes consistent with the presence of hemorrhage were noted on the unenhanced CT scan, and the enhancement of an angioma would have been prominent but diffuse. Neither the clinical course nor the radiologic findings support the diagnosis of angioma.^{5,6}

A primary lymphoma of the central nervous system typically results in diffuse enhancement, and the signal on T₂-weighted MRI scans is usually not as intense as it is in this case; often there is little surrounding edema. A lymphoma can present with necrosis, a mass effect, and ring enhancement. This presentation is particularly common with immunoblastic lymphomas, which are not usually located near the corpus callosum but can occur there.^{5,11,14} This patient had no immunodeficiency conferring a predisposition to the development of a lymphoma, but such a predisposition need not be present. No clinical features distinguish a lymphoma of the central nervous system from a glioma.

The location of the lesion in the white matter of the corpus callosum and the centrum semiovale suggests a glioma, the most common supratentorial neoplasm seen in this patient's age group. Oligodendrogliomas can develop rapidly, as did the lesion in this case, but on T₂-weighted MRI scans they produce only a mild signal and slight enhancement with a fine chicken-wire pattern. A rapidly progressing glioma with the radiologic characteristics described in this case would have to be a high-grade astrocytoma or a glioblastoma multiforme. The intense signal on T₂-weighted images, low signal on T₁-weighted images, and ring enhancement best fit the radiologic appearance of a glioblastoma multiforme, although the absence of edema around the mass remains puzzling.^{5,6} The clinical presentation is entirely consistent

with the presence of an isolated malignant glioma. Although other possibilities, such as a demyelinating process, cerebral toxoplasmosis, or a primary central nervous system lymphoma, cannot be eliminated without more information, the combined clinical and epidemiologic features of this case indicate that the lesion is probably a malignant glioma.

DR. DAVID N. LOUIS: Dr. Ebb, you cared for this patient. What was your diagnosis?

DR. DAVID H. EBB: Like Dr. Zalnereitis, I favored the diagnosis of a tumor, most likely a high-grade glioma such as glioblastoma multiforme or a primary lymphoma.

CLINICAL DIAGNOSIS

Brain tumor: ? high-grade glioma, ? lymphoma.

DR. EDWIN L. ZALNERAITIS'S DIAGNOSIS

Brain tumor, probably malignant glioma.

PATHOLOGICAL DISCUSSION

DR. JEAN-PAUL VONSATTEL: The diagnostic procedure was a biopsy of the left frontal white matter. Examination of the specimen revealed perivenular cuffs of lymphocytes and plasma cells (Fig. 4) and sheets of foamy macrophages containing intracytoplasmic neutral lipids or, in a few instances, myelin debris (Fig. 5). Also present were reactive mononucleated and multinucleated astrocytes (Fig. 5 and 6) and a few large protoplasmic glial cells with fragmented chromatin, known as Creutzfeldt cells (Fig. 7 and 8). Myelin was absent, but the axons were relatively preserved (Fig. 9). These histologic features are consistent with the presence of a reactive demyelinating process, such as multiple sclerosis.

Creutzfeldt cells may be glial cells undergoing abnormal mitosis.¹⁵ They are often found in acute plaques of multiple sclerosis or in astrocytomas.^{15,16} Creutzfeldt cells are short-lived. Initially their chromatin fragments are located near the center of the cell (Fig. 7). Later, the fragments move toward the cell membrane, cytoplasmic vacuoles appear, and the cell degenerates (Fig. 8).¹⁷

In typical cases of multiple sclerosis, numerous well-outlined gray or tan areas, or plaques, range in diameter from a few to many centimeters and have a predilection for the subependymal or periventricular white matter and the subpial white matter of the brain stem and spinal cord.¹⁸ In addition, they tend to involve the junction of the cortex and subcortex and may damage the white-matter tracts that traverse the gray matter, as in the globus pallidus. Usually the lesions are of different ages; recent or active lesions are hypercellular, whereas old lesions are hypocellular.¹⁷ Frequently a vein occupies the center of a plaque. Perivenular cuffs of lymphocytes and plasma cells may be prominent in recent or active lesions but are minimal or absent in old lesions.

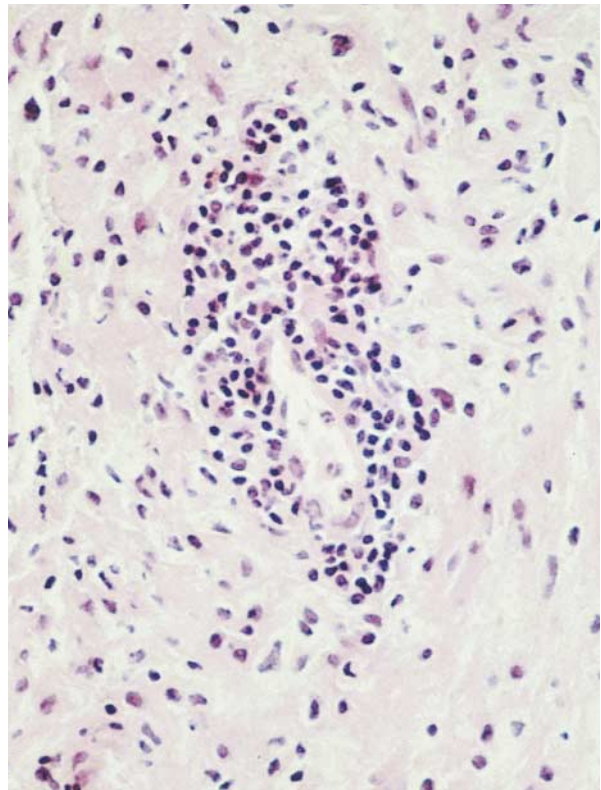


Figure 4. A Vein with a Cuff of Lymphocytes and Plasma Cells (Hematoxylin and Eosin, $\times 300$).

The surrounding parenchyma is hypercellular.

Biopsy specimens of diffusely enhancing or ring-enhancing lesions are characterized by hypercellularity, the presence of macrophages, and extensive loss of myelin, occasionally with edema, with or without cyst formation¹⁹; edema is not observed at postmortem examination, however.¹⁸ Nonenhancing demyelinating lesions tend to be characterized by fibrillary astrocytosis, with few macrophages and few or no inflammatory cells of other types.

The size and distribution of white-matter lesions can point to the correct diagnosis. In postinfectious or postvaccination encephalomyelitis, the lesions may appear large on neuroimaging²⁰ but small and perivenular on microscopical examination.¹⁸

Large white-matter lesions in young children can be due to Schilder's disease, a very rare, aggressive form of multiple sclerosis. In boys, adrenoleukodystrophy, an X-linked recessive disorder of lipids, can cause extensive damage to the white matter. Broad demyelination of the centrum semiovale can be the result of subacute sclerosing panencephalitis or the acute hemorrhagic leukoencephalitis of Weston Hurst, which is distinguished by hemorrhagic foci surrounding necrotic venules.²¹

Multiple sclerosis can be difficult to diagnose by

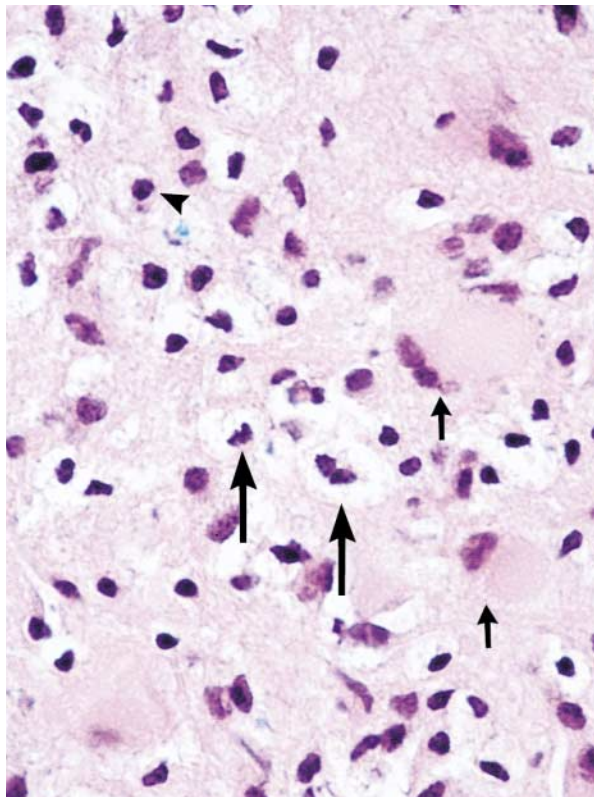


Figure 5. Mononucleated and Multinucleated Reactive Astrocytes (Small Arrows) and Macrophages with Foamy Cytoplasm (Large Arrows) (Luxol Fast Blue–Hematoxylin and Eosin, $\times 450$). One macrophage (arrowhead) contains intracytoplasmic myelin debris (stained blue). Otherwise, myelin is virtually absent.

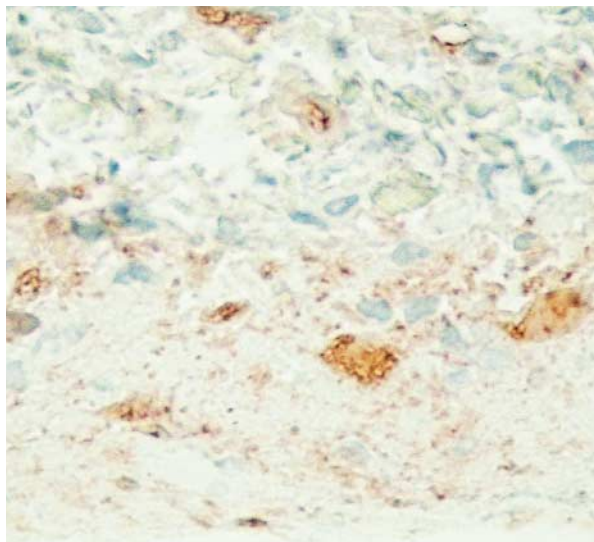


Figure 6. Astrocytes Reactive for Glial Fibrillary Acidic Protein (Immunoperoxidase Method, $\times 345$).

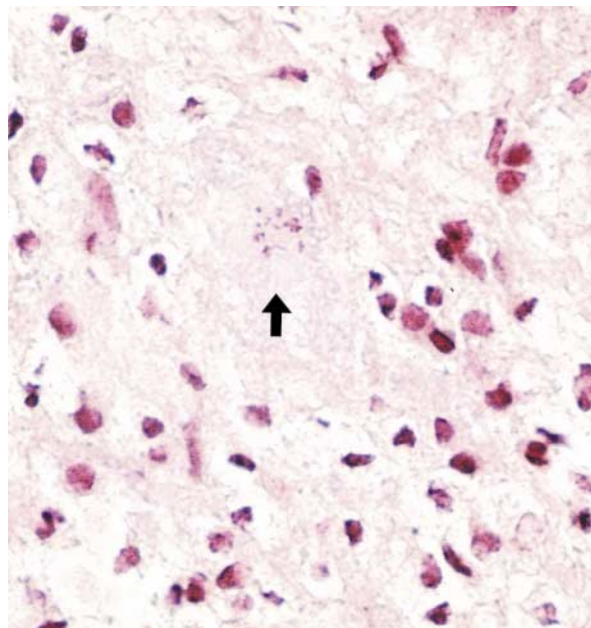


Figure 7. Hypercellular Parenchyma with a Creutzfeldt Cell (Arrow) (Trichrome, $\times 310$).

Fragments of chromatin are visible in the center of the cell. Myelin is absent.

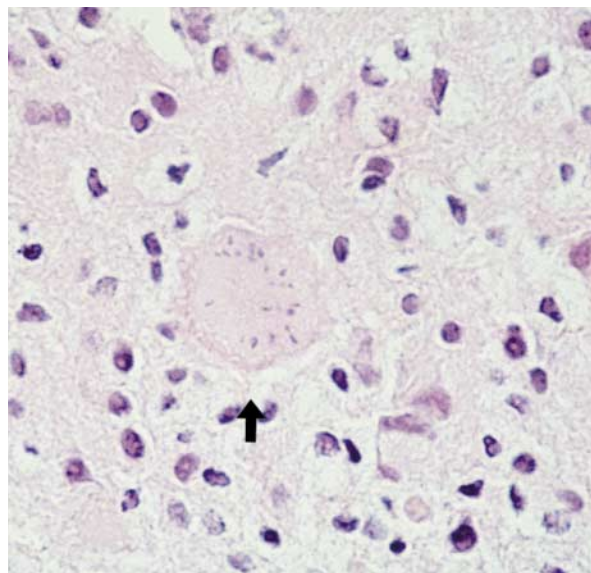


Figure 8. Macrophages and a Central Creutzfeldt Cell (Arrow) with Fragments of Chromatin along the Cell Membrane (Hematoxylin and Eosin, $\times 310$).

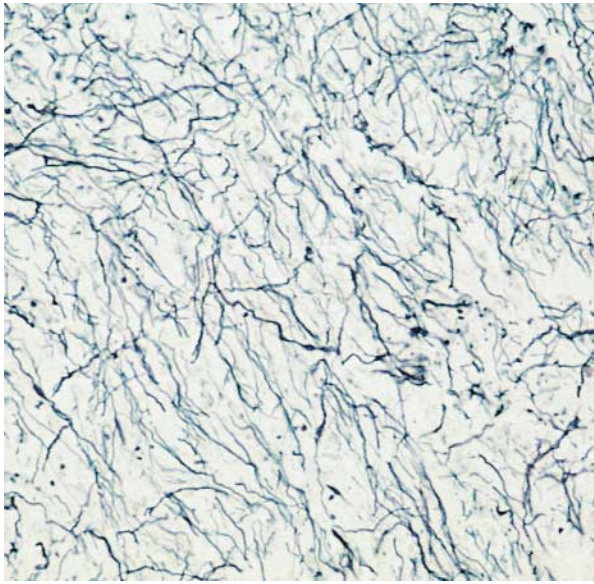


Figure 9. Preserved Axons (Bodian Silver Stain, $\times 310$).

biopsy. An active demyelinating process may mimic the histologic appearance of a malignant glioma, which likewise contains pleomorphic astrocytes, including large Creutzfeldt cells. In 1993, Zagzag et al.¹⁹ listed the pathological patterns found in active demyelinating processes that make them difficult to differentiate from gliomas, including hypercellularity, pleomorphic astrocytes, mitotic figures, necrosis, and cystic changes. Histologic features favoring diagnosis of a reactive process include the presence of foamy macrophages, reactive astrocytes, and inflammatory infiltrates; loss of myelin; and absence of vascular proliferation. Pleomorphic astrocytes, including multinucleated forms, may be conspicuous in active plaques, especially at the periphery.¹⁷ These astrocytes may suggest a neoplasm, but in contrast to neoplastic astrocytes, the reactive cells are not characterized by hyperchromatic nuclei.

In conclusion, an active demyelinating process such as multiple sclerosis is the most likely pathologic event when a biopsy specimen from a diffuse or ring-enhancing white-matter lesion shows perivascular infiltrates of lymphocytes and plasma cells, reactive astrocytes, Creutzfeldt cells, foamy macrophages, extensive loss of myelin, and relative preservation of axons.

Dr. Stein saw the patient after the diagnosis was made.

DR. MARION C. STEIN: The patient initially received corticosteroid therapy, and after three weeks of treatment, she had recovered enough to return to school for one day. However, as we tapered the dose, her condition rapidly deteriorated. Five weeks after

the diagnostic biopsy, she was readmitted to the hospital with severe spontaneous extensor spasms and progressive spastic diplegia that was greater on the right side than on the left. She had marked emotional disinhibition, and the dysarthria recurred. Repeated imaging showed ring-enhancing lesions similar to those seen previously, except that the enhancement was somewhat diminished, perhaps because of the corticosteroid treatment. The right side of the centrum semiovale was somewhat enlarged, as it had been previously, but the edema in the area of involvement on the left side was slightly diminished.

The patient's condition improved clinically only with intravenous administration of very high doses of corticosteroid medication (1000 mg of methylprednisolone) and worsened again when the dose was tapered. An induction regimen of cyclophosphamide was immediately added. After the patient had received 6 g of cyclophosphamide over a 10-day period, administered according to the published regimen for its use in patients with multiple sclerosis,²² her clinical condition stabilized. She tolerated tapering of the oral corticosteroid, and her neurologic condition continued to improve. Two months after treatment, she was able to return to school but had emotional instability, fatigue, and mild visuospatial defects. Her academic performance was variable, but she was able to maintain her grade level. A year and a half after the diagnosis, on a very hot day, she had tingling of the right hand and foot, which resolved completely by the next day. No further imaging studies were done. The patient has had no additional episodes, has remained well, and is college-bound.

DR. LOUIS: The literature suggests that acute episodes such as those in this patient tend not to lead to more typical manifestations of multiple sclerosis. Has that been your experience?

DR. STEIN: Yes. I expect that the clinical course of this patient's disease will be monophasic. In the past 10 years, we have seen three other cases of aggressive bilateral, confluent demyelination around the corpus callosum. There was biopsy confirmation in all the cases. None of the lesions have recurred. All the patients had only transient responses to corticosteroid therapy, but their conditions stabilized after they received cyclophosphamide therapy. Only the younger patients had considerable clinical improvement.

DR. ZALNERAITIS: All the children I have seen who had monophasic acute episodes of demyelination were lethargic and had other symptoms, unlike this patient. In your experience, Dr. Stein, do most of these patients have other symptoms?

DR. STEIN: Lethargy, and even obtundation, fever, and seizures, may occur in cases of monophasic disseminated myelitis, particularly those that develop after infection or vaccination. Neither the patient under discussion nor the other, similar patients I have

treated had any identifiable preceding illness, and the lesion on the cerebral MRI scan was deep and confluent, not multifocal and disseminated as in postinfectious and postvaccination cases. Although some of our patients had mutism, aphasia, and diminished interaction, the clinical and radiologic development of disease in these patients was still distinct from that of the patients with postinfectious or postvaccination demyelinating disorders.

DR. SCHAEFER: Demyelinating lesions centered in the corpus callosum frequently have an imaging pattern different from that of malignant tumors in the same location. The latter tend to be high-grade tumors with more surrounding edema and a thicker, more nodular enhancing rim. Therefore, a smooth rim with little surrounding edema suggests a demyelinating rather than a neoplastic process.

ANATOMICAL DIAGNOSIS

Demyelinating process consistent with the presence of multiple sclerosis.

ADDENDUM

DR. ZALNERAITIS: Since this clinicopathological exercise, I have found two additional reports that address the MRI findings in multiple sclerosis. Brück et al.²³ described a case in an adult with clinical findings that were similar and radiologic findings that were identical to those in the case under discussion. Takahashi et al.²⁴ reported a case in a child that was similar to this case clinically but not radiologically; that patient had recurrences during methylprednisolone therapy but was free of relapses for 18 months after plasmapheresis.

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