JINNY O. TAVEE, MD
Department of Neurology,
The Cleveland Clinic

CHARLES J. BAE, MD
Department of Neurology,
The Cleveland Clinic

RICHARD A. PRAYSON, MD
Department of Anatomic Pathology,
The Cleveland Clinic

ERIK P. PIORO, MD, PHD
Department of Neurology,
The Cleveland Clinic

A 25-year-old woman with hemiparesis and a solitary brain lesion

A 25-YEAR-OLD right-handed woman was in good health until 2 weeks ago, when she stubbed her right great toe and began limping on her right leg. A week later, she dropped a glass from her right hand while washing dishes and found that she could not hold any objects with that hand for an extended time.

The next day, she had an episode of dizziness and nausea while standing. Although she did not recall falling at the time, she woke up on the floor a minute later and had to use a chair to pull herself to her feet. Over the next several days, she became unable to bear weight on her right leg, dragging her foot when she walked, and continued to drop things from her right hand.

The patient presented to the Cleveland Clinic neurology outpatient clinic and was admitted for further evaluation.

History and physical examination

The patient has had left-sided migraine headaches since the age of 16. These occur about once a month and are controlled with aspirin.

The patient's vital signs and general medical examination are normal.

On neurologic examination, the patient is fully alert and oriented with normal speech. Language and cranial nerve functions are intact.

Motor examination demonstrates right spastic hemiparesis with moderate weakness (4 on the Medical Research Council [MRC] scale of 5) in the right arm proximally and distally, and severe weakness (MRC 3) in the right leg. Her strength is normal on the left side.

The sensory examination is normal for pinprick, light touch, vibration, and proprioception.

The deep tendon reflexes are brisk in all limbs, but increased on the right side. The Hoffmann sign (**FIGURE 1**) and the extensor plantar response (Babinski sign) are both present on the right.

The cerebellar examination is normal. The patient has difficulty walking and can only take a few steps with support.

DIAGNOSTIC STUDIES

1 What would be the most important initial diagnostic study to obtain?

- ❑ Computed tomography (CT) of the brain
- ❑ Magnetic resonance imaging (MRI) of the brain
- ❑ MRI of the cervical spine
- ❑ Proton magnetic resonance spectroscopy (^{1}H-MRS) of the brain
- ❑ Electroencephalography
- ❑ Lumbar puncture

Progressive right-sided hemiparesis points to a left hemispheric lesion

Progressive right-sided hemiparesis points to a left hemispheric lesion, which would best be visualized with MRI of the brain. Upper motor neuron signs on examination (spasticity, hyperreflexia, the Hoffmann sign, and the Babinski sign) indicate corticospinal tract involvement. Intracranial lesions such as tumor, abscess, and demyelinating disease should lead the differential diagnosis.

Facial-sparing hemiparesis may also suggest an ipsilateral cervical myelopathy. Therefore, MRI of the cervical spine would be appropriate to look for additional demyelinating lesions or other abnormalities, such as drop metastases (ie, metastases to the spinal cord from an intracranial malignancy spreading along the subarachnoid space). However, this patient's degree of weakness without any

Eliciting the Hoffmann sign

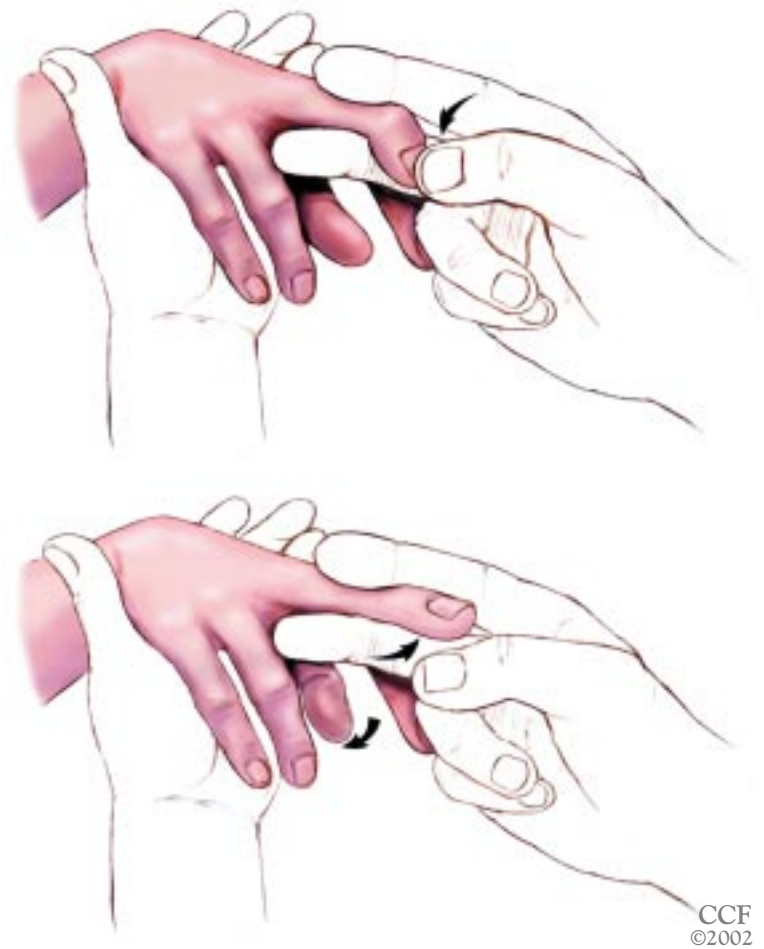

FIGURE 1. Checking for the Hoffmann sign is deceptively difficult to do correctly. **Top,** while supporting the patient's hand and flexing the distal phalangeal joint of the middle finger, the examiner quickly releases the bent phalanx and looks for a flexion movement of the patient's thumb (**bottom**). Its occurrence, a positive Hoffmann sign, usually indicates upper motor neuron disease, particularly when present asymmetrically. Many neurologists consider the Hoffmann sign in the hand to be equivalent to the extensor plantar response (Babinski sign) in the foot.

sensory findings, lower motor neuron signs, or bowel or bladder dysfunction makes a cord lesion less likely.

The patient underwent an MRI scan of the brain, which showed an intra-axial lesion in the left posterior frontal lobe that measured 5.0 × 3.5 × 3.5 cm, causing a mass effect. The mass had a heterogeneous increased signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. It also had a decreased signal intensity on T1-weighted images (FIGURE 2). There was patchy enhancement of the lesion on post-gadolinium infusion. No other lesions were seen.

A subsequent MRI scan of the cervical spine showed no abnormalities.

WHAT IS THE DIAGNOSIS?

2 What is the most likely diagnosis, based on the history, physical examination, and MRI findings?

- ❑ Multiple sclerosis (MS)
- ❑ Neoplasm
- ❑ Abscess
- ❑ Progressive multifocal leukoencephalopathy
- ❑ Acute disseminated encephalomyelitis

A solitary space-occupying lesion with edema and a small degree of mass effect in a young, otherwise-healthy woman could certainly represent a primary brain tumor or, less characteristically, a single MS plaque.

An abscess is less likely: on MRI these usually have a ring-enhancing appearance, representing an area of necrotic tissue surrounded by a thick, irregular rim.

Progressive multifocal leukoencephalopathy is also unlikely: it is a diffuse, multifocal process typically found in immunocompromised persons.

Acute disseminated encephalomyelitis also appears as multifocal lesions on MRI in most cases and is commonly preceded by a viral infection or vaccination.

Multiple sclerosis can mimic a brain tumor

MRI is superior to CT for identifying and delineating lesions of the central nervous system, including tumors and demyelinating disease such as MS. However, differentiating these two types of lesions may be difficult, even with MRI.[1]

The classic radiographic features of MS include high signal intensities on T2-weighted and FLAIR sequences in subcortical regions, including the periventricular white matter, corpus callosum, and brainstem structures. Although the diagnosis of MS, by definition, requires clinical evidence of multifocal

lesions, up to 10% of patients with MS do not have multiple lesions visible on MRI.

Like tumors, MS lesions can enhance on post-gadolinium images, indicating an active breakdown of the blood-brain barrier. Very importantly, the lack of mass effect seen with MS plaques helps differentiate them from tumors. However, large demyelinating plaques can cause a mass effect because of acute edema (FIGURE 2).

In the last decade, an increasing number of reports in the neurologic and neurosurgical literature have described demyelinating lesions that presented as distinct, solitary, space-occupying lesions. Of note, some cases of demyelinating disease, predominantly involving the corpus callosum, had the appearance of a "butterfly glioma" on CT and MRI.[2–5] A 14-year-old girl who presented with seizures and a ring-enhancing lesion in the right frontal lobe was thought to have a cystic astrocytoma until a brain biopsy showed changes of demyelination.[1]

Other less-common radiographic appearances of demyelinating disease include multifocal multicystic lesions and "ping-pong ball"-type lesions, both mistaken for gliomas.[5]

Thus, in addition to tumor and abscess, the differential diagnosis of solitary brain lesions should also include less-common presentations of MS—especially, in young adults, progressive multifocal leukoencephalopathy and acute disseminated encephalomyelitis.[1,6] In children, it is also important to consider adrenoleukodystrophy, an inherited metabolic disease of the cerebral white matter.[7] Although it is unusual for these diseases to present with the typical clinical and radiographic appearance of a brain tumor, they have all been reported to present as mass lesions.

FURTHER DIAGNOSTIC TESTS

3 What further tests would aid in establishing the diagnosis?

- ❑ Lumbar puncture
- ❑ Evoked potentials (visual and auditory)
- ❑ Brain ^{1}H-MRS
- ❑ Brain biopsy
- ❑ All of the above

The patient's MRI

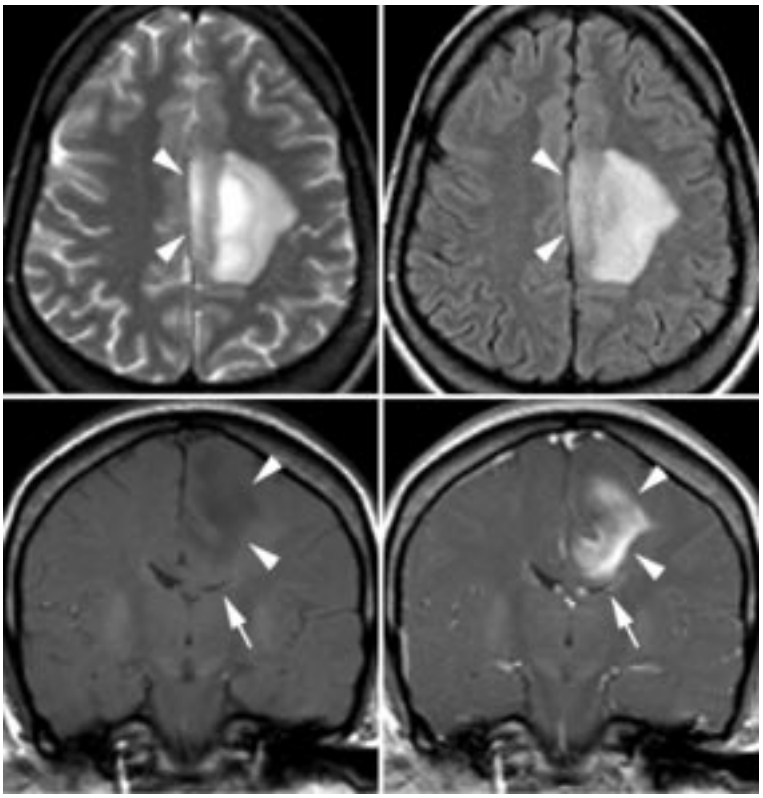

FIGURE 2. Axial T2-weighted (**upper left**) and FLAIR-weighted (**upper right**) brain MRI scans reveal a large hyperintense area in the left posterior frontal lobe, which also involves the ipsilateral corpus callosum (arrowheads in upper panels). Coronal T1-weighted images through the lesion (arrowheads) demonstrate a primarily subcortical hypointensity without gadolinium (**lower left**), which enhances peripherally after gadolinium administration (**lower right**). The lesion causes a mass effect with effacement of the underlying left lateral ventricle (arrows in lower panels) and rightward displacement of the falx cerebri (arrowheads in upper panels).

All of the above tests may be helpful in reaching a definitive diagnosis.

Lumbar puncture would support the diagnosis of a disseminated demyelinating process if special cerebrospinal fluid studies demonstrated evidence of intrathecal antibody production and myelin breakdown. Malignant cells in the cerebrospinal fluid would suggest a neoplastic process; acute inflammatory cells would suggest an infection.

Evoked potentials are the electroencephalographic responses to visual and auditory stimuli. Delayed or absent responses on this test would support the diagnosis of a more dis-

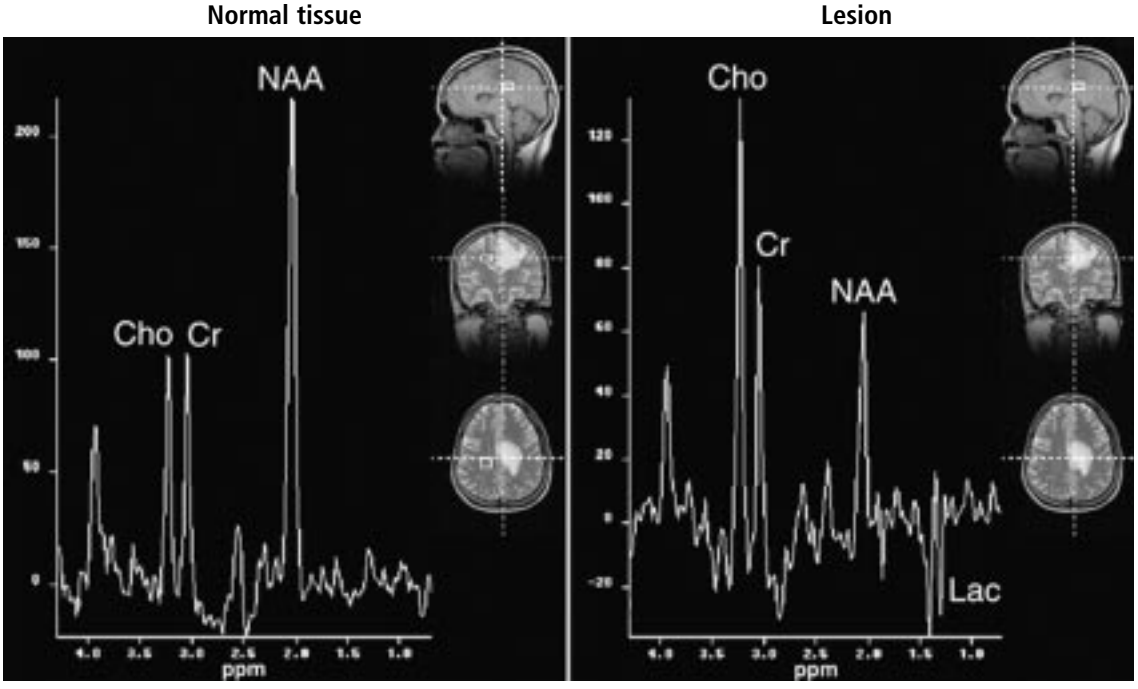

FIGURE 3. Multivoxel ^{1}H-MRS (TE 135 msec) of subcortical white matter in the unaffected hemisphere (left panel) and at the lesion edge (right panel). Anatomic localization of the 1-cm^{3} voxel from which spectroscopic information was collected can be seen in the three MRI planes on the right side of each panel. Normal levels of *N*-acetylaspartate (NAA) and choline (Cho), relative to creatine (Cr), are detected in the uninvolved right hemisphere (left panel). In contrast, the lesion reveals decreased NAA and increased Cho signals relative to Cr (right panel), which are consistent with acute demyelination. However, the presence of lactic acid (Lac), seen as an inverted peak at 1.32 parts- per- million (ppm, right panel), raises the possibility of a malignant tumor.

A solitary brain lesion could be a tumor—or, less likely, MS

seminated demyelinating process.

Brain ^{1}H-MRS can sometimes help in differentiating various disorders, including neoplasm and demyelination.[8] This noninvasive technique, related to MRI, reveals the signal intensities of certain metabolites (containing non-water protons) as a pattern of peaks (spectra) specific to normal or diseased brain tissue. Unfortunately, large demyelinating plaques can show metabolic changes that are also found in malignant tumors—eg, elevated lactate—limiting the usefulness of ^{1}H-MRS in these cases.

Brain biopsy, the most invasive procedure of the group, would provide tissue for a pathologic, conclusive diagnosis.

Case continued

Our patient sequentially underwent all of these tests.

Her cerebrospinal fluid was normal on routine analysis and culture, with no oligoclonal bands (a marker of intrathecal antibody production). Her myelin basic protein (MBP) concentration was significantly elevated at 203 ng/mL (normal range 0–1.6), indicating substantial myelin breakdown, although this finding is relatively nonspecific.

Auditory and visual evoked potential studies were normal.

^{1}H-MRS data were consistent with demyelination, but an elevated lactate signal at the center of the plaque raised the possibility of a malignant tumor (**FIGURE 3**).

The neurosurgical service was consulted, and the patient underwent a CT-guided stereotactic brain biopsy. The final pathologic diagnosis showed focal areas of demyelination marked by increased numbers of macrophages,

reactive astrocytes, and perivascular chronic inflammatory cells, consistent with a demyelinating lesion (FIGURE 4).

TUMOR-LIKE DEMYELINATING LESIONS

Hunter et al[3] reported four cases of demyelinating disease in a series of 1,200 biopsies done because of clinically suspected brain tumors. All four were misinterpreted as primary gliomas on frozen section analysis (intraoperative consultation), and two were treated with radiation because of the mistaken diagnosis of astrocytoma on final pathologic analysis.

The largest series of such cases, reported by Kepes[5] in 1993, described 24 patients who had solitary mass lesions that were subsequently proven by biopsy to be demyelinating disease. The typical clinical course of MS ensued in only 2 of the 24 patients, while the remaining 22 patients did not develop any additional lesions. Most of the patients had an excellent response to steroids, with disappearance of large lesions on follow-up MRI.

Kepes[5] suggested that focal tumor-like demyelinating lesions may be a distinct entity, intermediate between MS and acute disseminated encephalomyelitis. In contrast to MS, the tumor-like demyelinating plaque typically occurs as a single event in time. And unlike acute disseminated encephalomyelitis, it is a much larger, more confluent lesion that does not seem to follow a viral illness (although it is possible that a preceding infection was subclinical). Tumor-like demyelinating lesions generally appear to have a relatively benign clinical course and favorable prognosis compared with more aggressive variants of MS, namely Schilder disease and Marburg disease.

Key histopathologic features of tumor-like demyelinating lesions overlap those of MS and acute disseminated encephalomyelitis, with perivascular lymphocytic cuffing, reactive astrocytes, loss of myelin with relative preservation of axons, and foamy macrophages. Confluence of an intense area of demyelination with associated edema and contrast enhancement lends the radiographic appearance of a mass lesion, mimicking a primary brain tumor.

Histopathologic study of the brain lesion

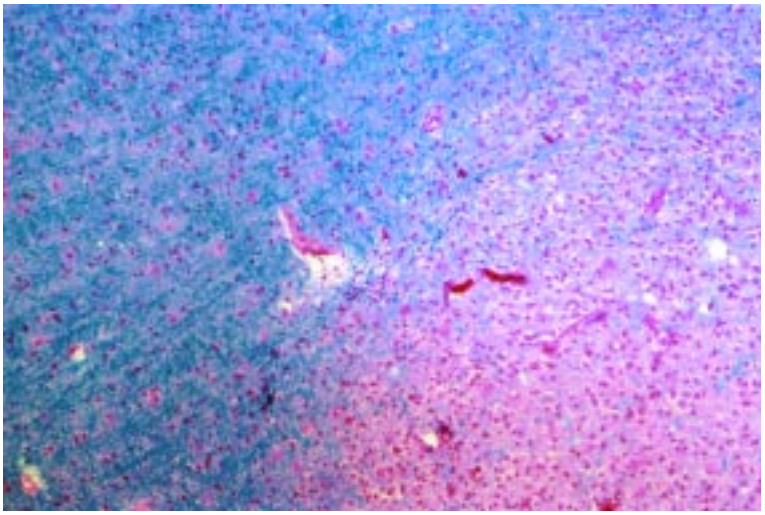

FIGURE 4. A section of biopsied white matter from the edge of the lesion shows demyelination, as indicated by diminished blue staining, especially nearer its center (right of figure). Although not visible at this magnification, most of the cells in the lesion are macrophages and reactive astrocytes. No malignant cells are seen. (Luxol fast blue stain, × 200).

TREATMENT

4 What would be the most appropriate treatment for this patient?

- ❑ Intravenous corticosteroids
- ❑ Oral corticosteroids
- ❑ Surgical excision
- ❑ Observation

Even biopsy can mistake a solitary MS lesion for a tumor

The treatment for tumor-like demyelinating plaques is similar to that for other acute demyelinating processes, and consists primarily of intravenous (IV) steroids. Antiepileptic drugs may be indicated for patients with seizures due to cortical irritation from the plaque and accompanying edema.

Follow-up serial MRI scans are also important to document gradual resolution of the lesion.

Patients tend to respond well to a course of IV steroids, with only a small percent not responding or experiencing recurrence and progressing to MS.[5] In cases in which IV steroids may be ineffective or are not advised, such as in patients with poorly controlled diabetes mellitus, intravenous immunoglobulin

(IVIG) may be beneficial, as has been reported in some cases of acute disseminated encephalomyelitis.[9]

Overall, most patients with tumor-like demyelinating lesions have a good prognosis, with a clinical course consisting of an isolated event in time, as reported by Kepes in his series of 31 patients.[5]

Case continued

Our patient received methylprednisolone 1 g/day IV for 5 days, followed by an oral prednisone taper. Although her symptoms initially worsened, her strength gradually improved with physical therapy and she did well at a rehabilitation facility. She required no further treatment with steroids, and at 1-year follow-up she is at near baseline strength bilaterally with occasional severe spasms of the right foot.

Although the prognosis for recovery is very good in a young patient after a single episode of demyelination, the dramatically elevated MBP concentration in our patient's cerebrospinal fluid indicates substantial tissue destruction. Consequently, residual deficits are more likely. The risk of further demyelinating episodes and the eventual development of MS is higher with the presence of other lesions (on MRI and evoked potentials) or intrathecal antibody production (oligoclonal bands), both of which were absent in our patient. Repeat MRI has demonstrated almost complete resolution of the left frontal lesion and no new abnormalities on neurologic examination at 1-year follow-up.

The patient has done well after a course of steroids

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ADDRESS: *Erik P. Pioro, MD, PhD, Department of Neurology, S90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail pioroe@ccf.org.*