Progressive Aphasia and Vision Loss in a Teen-Aged Girl

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Dr. Yoon:

A 16-year-old female honor student presented for evaluation of vertigo, headache, mild aphasia, and blurred vision. Her symptoms started approximately 2 months earlier when she experienced 3–4 days of intense vertigo and ear pain that waxed and waned and then gradually subsided. Her bifrontal headache initially was intermittent, but over the next several months, increased in severity and duration and by the time of presentation had become persistent. Her family indicated that she understood language normally but was having increasing difficulty with word finding. Visual symptoms were vaguely characterized as blurriness with intermittent diplopia. She occasionally stumbled while walking, which she attributed to difficulty seeing. She had no significant medical history.

The patient was assessed at another hospital where brain MRI was abnormal. Lumbar puncture revealed a protein of 53 mg/dL (normal, 14–45 mg/dL), glucose of 36 mmol/L (normal, 50–80 mmol/L), 1 leukocyte, and 1 erythrocyte. The opening pressure was not recorded, and cytological examination was not performed. IgG index was normal, and

oligoclonal bands were absent. Other unremarkable CSF studies included polymerase chain reaction (PCR) for herpes simplex viruses 1 and 2, cytomegalovirus, and JC virus, assay for myelin basic protein, and staining for acid-fast bacillus. Serologic and blood studies were negative or normal, including white blood cell count, hemoglobin, hematocrit, platelet count, ferritin level, angiotensin-converting enzyme, anti-nuclear antibody, single-stranded DNA, double-stranded DNA antibody, PCR for human immunodeficiency virus, rapid plasma reagin, rheumatoid factor, very long-chain fatty acids, Lyme disease, and aquaporin-4 channel antibodies.

When evaluated at our institution, the patient's visual acuity was 20/20 in each eye with no relative afferent pupillary defect. Extraocular motility showed slight limitation of abduction of the left eye. External examination, anterior segment examination, and intraocular pressure were normal in both eyes. Dilated fundus examination revealed moderate bilateral optic disc swelling (Fig. 1). There was no evidence of vitritis or other posterior segment abnormalities. Automated perimetry revealed a right homonymous hemianopia and a left inferior homonymous quadrantanopia (Fig. 2).

The patient had normal vital signs and was afebrile. No abnormalities were found on general physical examination. Neurologic examination revealed normal sensation and strength in the face and extremities. Cerebellar function, deep-tendon reflexes, and gait were normal. The patient's speech was moderately fluid with poor naming of low-frequency objects. Comprehension was moderate with slowing during 3-step commands. Reading was poor, and she was able to write only simple sentences. Brain MRI was obtained.

Dr. Sharma:

There are 2 lesions identified, both with similar imaging characteristics (Fig. 3). The larger lesion involves the left occipital lobe, extending into the posterior temporal lobe,

FIG. 1. Right and left optic discs with moderate disc edema.
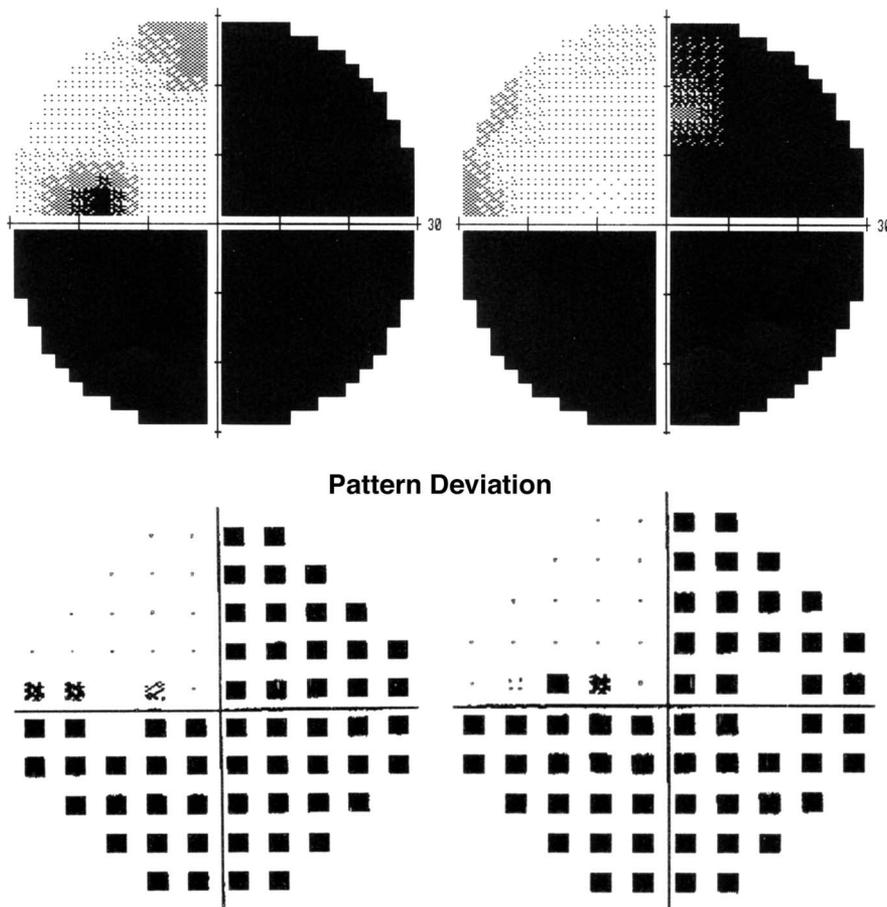

Pattern Deviation

FIG. 2. Automated visual fields showing a right homonymous hemianopia and a left inferior quadrantanopia, with a few abnormal test areas in the remaining left superior homonymous quadrants.
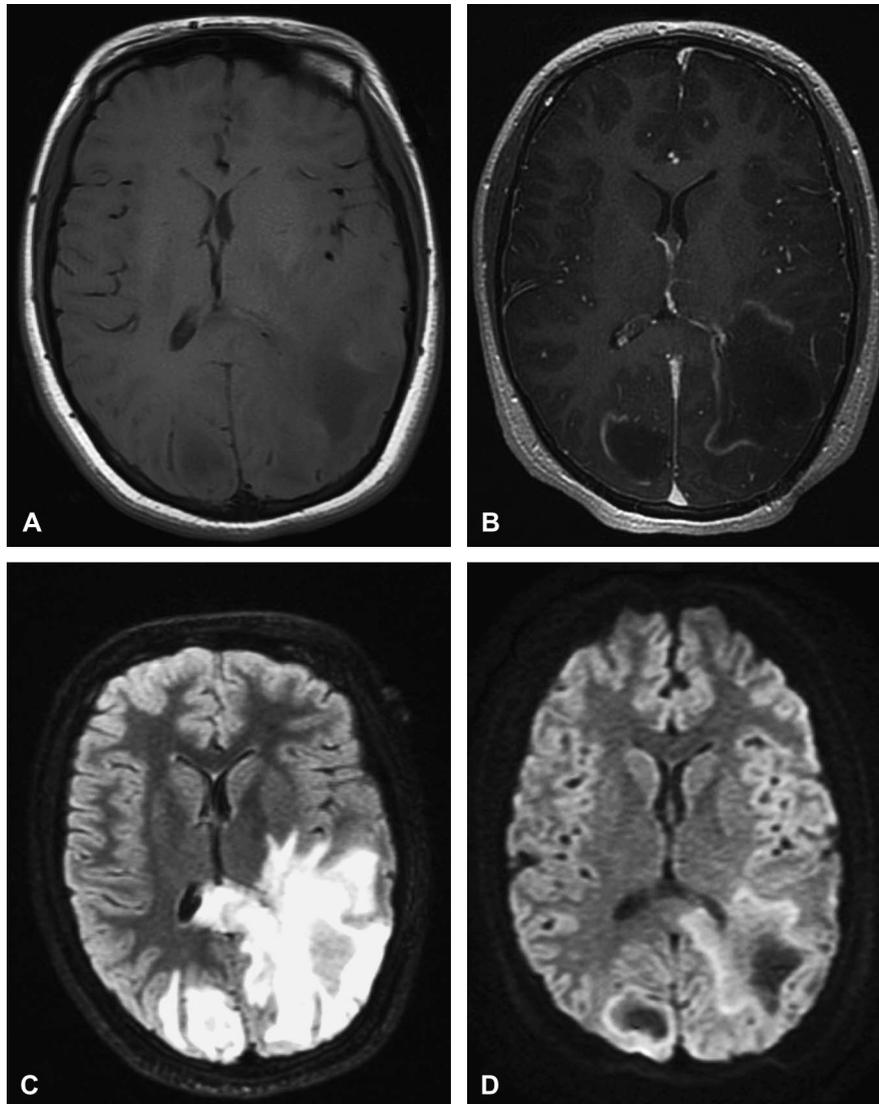
FIG. 3. T1 axial (**A**), FLAIR (**B**), contrast-enhanced T1 (**C**), and diffusion-weighted (**D**) MRIs demonstrating right occipital and the left temporo-occipital white matter lesions. Both lesions demonstrate central nonenhancing regions of T1 hypointensity (**A**) and T2 hyperintensity (**B**), and incomplete rim of enhancement (**C**), with minimal perilesional edema. Despite the large size of the lesions, there is a relative lack of mass effect. The central nonenhancing portion does not demonstrate diffusion restriction (**D**). Decreased apparent diffusion coefficient (ADC) values were noted on the ADC map (not shown), corresponding to the areas of increased signal along the rim of the lesions on diffusion-weighted images.

and the splenium of the corpus callosum. The smaller lesion involves the right occipital lobe. The lesions predominantly involve the white matter. Both lesions demonstrate central nonenhancing regions of T1 hypointensity and T2 hyperintensity, with a surrounding incomplete rim of enhancement (Figs. 3A–C). Diffusion restriction is noted along this rim but not centrally (Fig. 3D). A thin zone of vasogenic edema is also seen in the white matter around the enhancing rim (Fig. 3B). The anterior visual pathways and the spinal cord appear normal on imaging (not shown).

Dr. Yoon:

Because of the concern that the patient had a malignant tumor, a stereotactic biopsy of the right occipital lesion was performed.

Dr. Corbo:

Sections of the biopsy specimen demonstrated sheets of foamy macrophages associated with interspersed reactive hypertrophic astrocytes and blood vessels (Fig. 4A). A sparse population of reactive lymphocytes is also evident. A luxol fast blue/PAS stain shows extensive loss of myelin, including
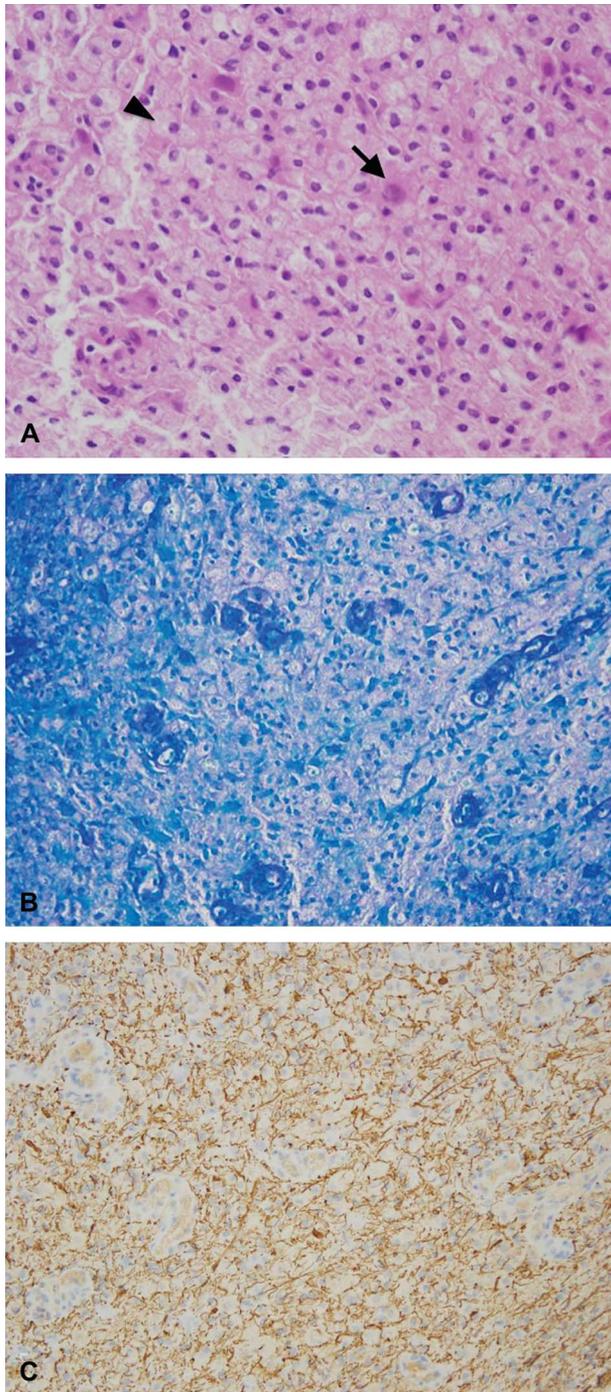
FIG. 4. Right occipital biopsy. **A**. There are sheets of foamy macrophages (arrowhead) in a background of reactive astrocytes (arrow) (hematoxylin and eosin, ×400). **B**. Luxol fast blue/PAS stain showing extensive loss of myelin (×200). **C**. Neurofilament immunostain revealing relative preservation of axons in the areas of demyelination (×200).

some macrophages with fragments of partially metabolized myelin in their cytoplasm (Fig. 4B). An immunohistochemical stain for neurofilament shows relative preservation of axons (Fig. 4C). An occasional axonal spheroid is also

apparent. There is no evidence of either a glioma or a lymphoma.

Final Diagnosis:

Tumefactive demyelinating lesion.

Dr. Yoon:

Following biopsy, the patient began treatment with intravenous methylprednisolone 1 g daily. Over the next several days, she showed modest improvement with a stable ophthalmologic examination. The treatment was continued for 5 days, following which the patient was placed on oral prednisone for several weeks. At the last follow-up 4 months later, the patient's visual acuity was still 20/20 bilaterally, with minimal improvement in her visual fields but complete resolution of her optic disc swelling.

Most authors define tumefactive demyelinating lesions (TDLs) as focal areas of demyelination of greater than 2 cm in size (1). Causative diseases include multiple sclerosis (MS), acute disseminated encephalomyelitis (2), neuromyelitis optica (3), and myelinoclastic diffuse sclerosis (Schilder disease) (4). TDLs are rare in the pediatric population with approximately 30 cases reported in the literature (1,2,4–22). On neuroradiological studies, these lesions may mimic both intracranial abscess and tumor, making diagnosis difficult to establish by imaging alone.

There are no pathognomonic imaging characteristics that distinguish TDLs from other lesions; however, there are several neuroimaging features that may help suggest the correct diagnosis. On MRI, TDLs have variable degrees of mass effect and edema, but typically, there is relatively little compared with a similarly sized neoplasm, infiltrate, or infarct (10,21,23). A classic finding associated with TDLs is the "open-ring" enhancement of the lesion. This appearance is believed to result from contrast leaking from an incomplete ring of active inflammation with the loss of the normal blood-brain barrier surrounding the lesion. The incomplete portion typically abuts the gray matter or basal ganglia (24,25); however, this is not a uniform finding, as Kiriyama et al (21) found this in only 4 of 14 patients in their series. A T2 hypointense rim is found in the majority of patients with a TDL. A central dilated vascular structure may be seen within the lesion on T2 echnoplanar imaging, believed to be a dilated vein draining toward subependymal veins (26). Zivadinov et al (27) noted venular dilation and enhancement within 57% of TDLs, consistent with focal vascular structural abnormalities without vascular destruction.

Despite the above findings on MRI, the diagnosis of a TDL can be difficult. For example, Riva et al (18) reported a 10-year-old girl with rapidly progressive headache, projectile vomiting, and mild right hemiparesis over days. The MRI findings were thought to be most consistent with a high-grade malignancy, but an excisional biopsy revealed

a TDL. Other cases with similarly misleading or nonspecific imaging findings have been published (5,7,28,29).

Other imaging modalities may improve diagnostic specificity. The combination of typical features on conventional MRI as well as hypoattenuation of the lesion rim in unenhanced CT is characteristic for TDL and usually not seen in glioma or lymphoproliferative disease (23). A report dealing with MRI perfusion suggested that a lower relative cerebral blood volume (rCBV $<0.88\times$ the contralateral normal white matter) was more suggestive of a TDL than a neoplasm (26). In this study, intracranial neoplasms had elevated rCBVs greater than 6 times those on the contralateral normal side. Tsui et al (30) published a single case report in which there also was no elevation in perfusion in the TDL (30). However, it has also been shown that there may be no significant difference in normalized rCBV values in TDLs compared with gliomas (31).

Magnetic resonance spectroscopy has been assessed for its ability to distinguish tumefactive lesions from neoplasms. Elevations in glutamate, glutamine, choline, lactate, and lipid peaks, with a decrease in the N-acetyl-aspartate peak, have been described (17,31,32). Yet other studies, however, have demonstrated similarities in spectroscopy findings in both gliomas and TDLs (28).

Stereotactic biopsy often is employed in cases of lesions in which the differential diagnosis includes TDL, intracranial abscess, and neoplasm. Although this may be the only way to obtain a definitive diagnosis, potential complications of the procedure include hematoma, herniation, infection, neurologic deficits related to the site of the biopsy, and death (0.3%–0.7%). The overall risk of a biopsy-related complication is approximately 3.5% (33,34). Despite these risks, brain biopsy is diagnostic in the majority of cases. Analysis of intraoperative frozen sections can, in many cases, obviate inappropriate surgical excision in patients with a presumed diagnosis of glioma who turn out to have a TDL.

Although intracranial pressure (ICP) was not measured in our patient, elevated ICP was likely the cause of her optic disk swelling. We are unaware of any previously published cases of TDL associated with elevated ICP. Newman et al (35) described 3 patients with MS without TDLs but with elevated ICP with papilledema (35). Although the exact mechanism remains speculative, they attributed the elevation in ICP to the demyelinative disease.

The diagnostic challenge in this case centered on whether a confirmatory biopsy was necessary. The patient presented with a first episode of neurologic deficit consisting of aphasia and visual loss, without a previous demyelinating event. Although the MRI findings were consistent with a TDL, neither oligoclonal bands nor myelin basic protein were present in the CSF, and the IgG index in the CSF was normal. Also, the patient had papilledema, an infrequent finding in patients with demyelinating disease. Given the potential risk of a delay in diagnosis, the decision was made

to proceed with a biopsy that established the correct diagnosis.

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