Pathologic Quiz Case
Male With Deterioration of Mental Status

Preetha Ramalingam, MD; Richard A. Prayson, MD

A 62-year-old white man presented with a 3-year history of progressive mental decline, including deterioration in memory and speech. He also experienced gait abnormalities and dysphagia. He had a family history significant for several relatives who had similar problems, some of whom died secondary to this condition. The patient had no significant past medical history and had been otherwise healthy. A neurologic examination was significant for decreased short-term memory, slurred speech, and a left peripheral VIIth nerve palsy.

Magnetic resonance imaging showed diffuse, multicentric cerebral white matter enhancement, most prominently noted in both temporal lobes (Figure 1). He underwent an excision of a portion of the anterior temporal lobe and inferior temporal gyrus. The patient tolerated the procedure well and was treated postoperatively with antibiotics, steroids, and anticonvulsant medication. His postoperative course was significant for a slight deterioration of mental status, which improved with discontinuation of steroid therapy.

Microscopically, the vessels in the meninges, cortex, and white matter were characterized by prominent hyalinized thickening of their walls. Many white matter vessels demonstrated perivascular atrophy (Figure 2). Electron microscopy revealed multiple large complex liposomes and occasional large lipid droplets in the cytoplasm of the perivascular cells. Focal deposits of granular, electron-dense material (arrow) were also seen in many of these perivascular cells (Figure 3). A faint basophilic granularity was present in the wall of several of the larger vessels; this granularity was highlighted by periodic acid–Schiff stain (Figure 4). Intimal fibroplasia, lipohyalinosis, and fibrinoid necrosis were absent. The vascular media was thickened; however, there was no evidence of amyloid deposition on Congo red staining.

What is your diagnosis?
Pathologic Diagnosis: Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a cerebral nonatherosclerotic, nonamyloid angiopathy primarily affecting the small arteries and arterioles penetrating the white matter.² CADASIL was initially thought to exclusively involve cerebral vessels, but similar pathology has been demonstrated in the small arteries of the skin, nerve, and muscle, and CADASIL is now regarded to be a systemic disease.³ The diagnosis of CADASIL is usually established by analyzing the family history, clinical picture, radiologic features, and histopathologic and ultrastructural findings.

Most patients have a family history of this disease, and it is clinically characterized by recurrent subcortical ischemic strokes, sometimes leading to pseudobulbar palsy and dementia.⁴ Migrainelike headaches with aura are often the earliest clinical manifestation. Other symptoms at presentation may include gait disturbances, pyramidal signs, sphincter incontinence, and mood disturbances.² The mean age at onset is 45 years with no evidence of gender proclivity.²

Magnetic resonance imaging of the brain often demonstrates signs of small infarcts and leukoencephalopathy. Well-delineated areas of abnormal signal (decreased on T1-weighted and increased on T2-weighted imaging) demonstrating lacunar infarcts are identified in the frontal, parietal, and occipital subcortical white matter and basal ganglia.⁵ Periventricular hyperintensities are seen even in asymptomatic patients, and CADASIL should be diagnosed with caution in its absence. Rarely, patients with incomplete penetrance of the defective gene may have a completely normal magnetic resonance imaging study.³ Cerebrospinal fluid examination is largely unremarkable; however, pleocytosis and oligoclonal bands have been reported.

Gross pathologic findings at autopsy are quite unimpressive and include slight uniform atrophy of the frontal, parietal, and occipital subcortical white matter and basal ganglia.⁵ Periventricular hyperintensities are seen even in asymptomatic patients, and CADASIL should be diagnosed with caution in its absence. Rarely, patients with incomplete penetrance of the defective gene may have a completely normal magnetic resonance imaging study.³ Cerebrospinal fluid examination is largely unremarkable; however, pleocytosis and oligoclonal bands have been reported.

Brain biopsy to assess the meningeal vessels is usually the test of choice, but a less invasive alternative would be skin, muscle, or nerve biopsy to establish the diagnosis.³ However, studies reported to date have shown variable presence of the characteristic basophilic granular osmophilic material (GOM) in peripheral locations, and a negative biopsy must be interpreted with caution.

The walls of small and medium-sized leptomeningeal and penetrating arteries are markedly thickened and show loss of vascular smooth muscle cell nuclei. Accumulation of characteristic GOM in the thickened tunica media is the hallmark of the disease. The granular material is periodic acid-Schiff–positive and appears red with Masson trichrome stain. Congo red for amyloid, von Kossa for calcium, and Perl stain for iron are consistently negative. Immunohistochemistry is noncontributory, and the granular material may nonspecifically stain positively with a host of antibodies, including immunoglobulin (Ig) A, IgG, IgM, κ light chain, λ light chain, and complement. The vessel wall is marked by an increase in types I, III, IV, and V collagen, as well as laminin deposition. Other nonspecific features include intimal proliferation, duplication and/or fragmentation of the internal elastic lamina, a sparse perivascular inflammatory infiltrate, and fibrinoid necrosis of the intima. Apart from the granular material, all other vascular changes observed in CADASIL can be seen inBinswanger subcortical arteriopathy.² Partial or complete occlusion of the vessel is rare, but can occur secondary to intimal proliferation.

Electron microscopy confirms the destruction of vessel wall myocytes. The GOM consists of electron-dense extracellular granular deposits located either free between degenerating smooth muscle cells or in the indentations of these cells, often in association with thickened basal lamina.² The GOM deposits vary in size from 0.2 to 0.8 μm and are composed of 10- to 15-nm granules. Separation of astrocyte feet from the vascular smooth muscle cells secondary to edema is an early finding in the vessels of the gray matter and cerebellum.²

The CADASIL gene is located on chromosome 19p13.1-13.2, and the defective gene was found to be the human homologue of Notch3, which encodes a transmembrane receptor protein.³ The extracellular N-terminal domain of the Notch3 molecule contains 34 epidermal growth factor–type repeats, and it has been demonstrated that more than 90% of CADASIL cases are a result of missense point mutations of these epidermal growth factor repeats.² Genetic linkage analysis using several chromosome 19 markers and screening for Notch3 mutations using single-strand conformation polymorphism are currently used to confirm CADASIL in suspected or high-risk patients.³ A recent report has documented the presence of a de novo mutation of the Notch3 gene in a patient with no family history and absence of mutation in both biological parents.² These findings indicate that the diagnosis of CADASIL should not be rejected in the absence of a family history. Genetic testing is still not available on a widespread basis to the majority of suspected patients.

The diagnosis of CADASIL can be difficult, owing to overlapping features with other cerebrovascular disorders. The differential diagnosis includes a host of sporadic and familial conditions associated with strokes, such as coagulopathy (ie, thrombotic thrombocytopenic purpura), MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), abetalipoproteinemias, cerebral amyloid angiopathy, Fabry disease, and homocystinuria. These diseases can be differentiated from CADASIL based on distinct clinical settings or by appropriate laboratory investigations. The most common histologic differential is that of atherosclerotic vascular disease; however, it characteristically lacks the vascular basophilic granularity and the GOM ultrastructurally. Additionally, patients with CADASIL are usually normotensive. Cerebral amyloid angiopathy can be differentiated from CADASIL because it presents in older individuals, and staining with Congo red is negative in the latter condition. AlthoughBinswanger disease and CADASIL have overlapping features, the former usually occurs in a nonfamilial setting and in older patients, most of whom are hypertensive. In challenging cases, genetic and ultrastructural studies may be employed.

In summary, CADASIL is a rare, hereditary, nonarteriosclerotic vasculopathy associated with early-onset multi-
infarct dementia that is both debilitating and fatal. It is important to distinguish CADASIL both from other common vascular diseases, such as atherosclerosis andBinswanger disease, and rare familial disorders, such as ME-LAS syndrome and homocystinuria. Patients with CADASIL have characteristic clinical and radiological features. Additionally, histologic and ultrastructural evaluation of the brain, skin, nerve, or muscle can be useful in establishing a diagnosis with reasonable certainty. Direct genetic testing to demonstrate mutations in the Notch3 gene can be used to confirm the disease.

References