Clinical Pathologic Conference

A Case of Early-Onset Rapidly Progressive Dementia

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A 62-year-old man presented with rapidly progressive cognitive decline associated with ataxia, spasticity, and eventually seizures. Multiple bihemispheric foci of calcification in the brain were seen on computed tomography scan, with magnetic resonance imaging (MRI) showing relatively symmetrical areas of enhancement in the brain corresponding mostly to the areas of calcification. Cerebrospinal fluid analysis and 2 brain biopsy specimens showed no evidence of an infectious, inflammatory, or malignant process. Despite being treated empirically with high-dose corticosteroids, the patient continued to deteriorate, with the family deciding for hospice care. The final autopsy diagnosis and the approach to the clinical data are discussed.

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Report of a Case

A 62-year-old man originally from Ghana presented with a 2-month history of rapidly progressive cognitive decline. The patient was unable to continue managing the family finances, quit his job as a respiratory therapist, and was neglecting his personal hygiene. He was noted to have occasional word-finding difficulties and his handwriting became less legible. He was having increasing problems with gait instability, leading to many near falls. Further questioning revealed that subtle cognitive changes had started about 1 year prior to presentation, with the patient’s wife noticing that her husband was avoiding driving on highways due to the fear of getting lost, forgetting directions, and becoming more argumentative. He was previously in good health except for a history of coronary artery bypass surgery and hypertension. There was no history of exposure to toxic chemicals or chemotherapy for any malignant tumors. His last visit to Ghana was 6 years prior to presentation. On physical examination, spasticity in the lower extremities was noted with a spastic-ataxic gait. Reflexes at the knees were brisker than in the arms (3+), with nonsustained clonus at both ankles. A positive Hoffman sign was present bilaterally. Plantar responses were flexor bilaterally. A startle reflex was absent. Mental status examination revealed disorientation to date and significantly impaired short-term recall and visuospatial memory with limited attention span. Speech was tangential and fluent, with frequent paraphasic errors and difficulty naming objects. Dilated eye examination results were normal.

Laboratory and Radiologic Data

Laboratory tests included an extensive workup for infectious, inflammatory, vasculitic, and metabolic processes. However, results of both serum studies (Box) and cerebrospinal fluid analyses were unremarkable. Cerebrospinal fluid analysis was performed on 3 separate occasions throughout the patient’s clinical course, each time showing no evidence of an ongoing inflammatory, infectious, or malignant process, including absent 14-3-3 protein and normal angiotensin-converting enzyme levels.

Computed tomography scan of the head showed multiple bihemispheric, brainstem, and cerebellar foci of calcification (Figure 1A). Computed tomographic angiography showed no signs of vasculitis.

Magnetic resonance imaging of the brain showed relatively symmetrical patchy areas of bilateral enhancement in the corona radiate, frontal white matter, periventricular white matter, thalamus, globus pallidus, brainstem, and cerebellar white matter mostly corresponding to the areas of calcification (Figure 1B and C) with an associated increased choline to N-acetyl-aspartate ratio on magnetic resonance spectroscopy. T2-signal hyperintensity was seen in the areas of enhancement (Figure 1D). Multiple areas of restricted diffusion were also present. Magnetic resonance imaging of the cervical spinal cord showed small areas of enhancement at the lateral aspect of the cord at C3 and C5 levels. The thoracic spinal cord showed similar enhancement present at T2-T3 levels. Findings on imaging of the chest and abdomen were normal. A whole-body positron emission tomography scan did not show increased uptake to suggest the presence of fluorodeoxyglucose F18-avid lymphoma.

The patient underwent 2 brain biopsies from 2 separate institutions. These were obtained from a right frontal lesion that showed enhancement on MRI. The first biopsy showed nonspecific gliosis and adventitial thickening of some microvessels. The second biopsy showed multiple fragments of white matter with gliosis, focal white matter rarefactions, and calcifications, with focal accumulations of macrophages and intraparenchymal blood vessels with thickened walls. In both cases no necrotizing or demyelinating lesions, or inflammatory, infectious, or neoplastic processes were observed or identified.

Neuropsychological evaluation 6 months after presentation demonstrated significant functional deficits in all areas tested, including profound impairment in attention, receptive and expressive language, visuospatial/verbal memory, and executive functions, which was suggestive of global decline in cognitive function.
Despite the extensive workup, no conclusive diagnosis was made. The patient was started empirically on prednisone, 60 mg/d, that was gradually tapered down after about 2 months since clinically there was no substantial improvement in the patient’s symptoms. Immunosuppressants were considered but the patient’s wife declined further aggressive treatment. The patient continued to decline cognitively and neurologically. He became totally dependent for activities of daily living. On examination there was worsening of his spasticity, emergence of cerebellar signs, frontal release signs, and paraparesis. Later in the course of the disease (2 years, 6 months after initial presentation) he started having generalized tonic-clonic seizures; at this point, the family decided for hospice care. The patient died 3 years after initial presentation.

**Clinical Discussion (Dr Pomorska)**

Early-onset dementias, which are defined by onset of first symptoms before age 65, are distinguished from dementias in elderly patients since they differ in etiology and presentation. Magnetic resonance imaging is sometimes helpful in identifying underlying causes of dementia (eg, degenerative, vascular, infectious, inflammatory, metabolic, toxic), but in this case it does not point to any specific common etiology. Although more than 95% of cases of dementias are due to Alzheimer disease or vascular dementia, Lewy body, or frontotemporal dementia, these dementias would not be at the top of the differential diagnosis in this case, given this patient’s unique clinical presentation, which included gait disorder and pyramidal and extrapyramidal findings, as well as imaging and pathologic findings. A broad differential of dementias that should be considered in this case and the reason why they should be excluded is presented in the eTable in the Supplement. What makes this case unusual is the combination of the following 6 factors:

1. early onset;
2. rapid progression;
3. calcifications and enhancement on brain MRI;
4. pathology findings with thickening of microvessels without signs of infection, inflammation, or vasculitis;
5. negative laboratory workup; and
6. lack of systemic symptoms.

The differential diagnosis of dementias with early onset and calcifications on brain MRI is limited to rare disorders, some of which have only been described as case reports in the literature. Brain calcinosi syndrome (BCS) is a disorder of unknown pathogenesis characterized by bilateral calcium accumulation in the brain parenchyma, primarily in the basal ganglia. Most patients with BCS have no clinical symptoms, and probably the most common cause is due to aging. Most cases of BCS are sporadic, but some cases are familial. Familial BCS with calcium, phosphorus, and parathyroid hormone (PTH) metabolism abnormalities (familial isolated hypoparathyroidism, autoimmune polyglandular syndrome type I, pseudohypoparathyroidism) can be excluded in this patient given the lack of calcium, phosphorus, and PTH abnormalities. Familial BCS without calcium, phosphorus, and PTH metabolism abnormalities (eg, Aicardi-Coutières syndrome, dihydropteridine reductase deficiency, Cockayne syndrome) were also excluded since age at onset, ethnicity, and clinical presentation in this case did not suggest these conditions. Fahr disease should be considered owing to the presence of intraparenchymal calcifications; however, this patient was found to have lesions in the spinal cord and enhancement of the lesions in the central nervous system. These are not characteristic features of Fahr disease.²

Diffuse neurofibrillary tangles with calcification is a rare, slowly progressive dementia characterized by circumscribed atrophy centered in the temporal or frontotemporal lobes with prominent basal ganglia and cerebellar calcifications. Microscopically diffuse neurofibrillary tangles are present with no senile plaques.³ In this case, 2 biopsy specimens did not show any neurofibrillary tangles, making this entity less likely.
Coats plus syndrome and leukoencephalopathy with calcifications and cysts (LCC) are 2 rare disorders originally described in the pediatric population that present with extensive cerebral calcifications and leukoencephalopathy. The term cerebroretinal microangiopathy with calcifications and cysts (CRMCC) has recently been proposed to suggest the possible common pathogenesis of LCC and Coats plus syndrome. Adult-onset cases have been described rarely. Clinically, the combination of progressive ataxia, seizures, and cognitive dysfunction as seen in this case has been described in adult-onset cases of CRMCC, while the vessel wall thickening seen microscopically could indicate an underlying microangiopathy. As more cases are described it seems that patients with CRMCC can present with a spectrum of clinical features ranging from asymptomatic to a rapidly progressive disease. Unfortunately the diagnosis is usually obtained at autopsy, where a diffuse cerebral microangiopathy resulting in microcystic/macrocystic parenchymal degeneration is seen. The fact that on imaging no cysts were seen with relatively limited white matter involvement together with the lack of cysts on biopsy specimens would argue in favor of looking for other etiologies, which the authors in this case did. Despite an extensive workup, no other entity would explain the constellation of radiographic and clinical findings in this case, hence the reason why CRMCC is the one disorder that most closely fits the description given above.

Neuropathologic Discussion (Dr Smith)

The autopsy was restricted to examination of the brain. A prior biopsy site was identified on the anterior–superior surface of the right frontal lobe. Coronal sections revealed tan-yellow calcifications, 0.1 to 0.7 cm in greatest dimension, scattered throughout the white matter of the cerebral hemispheres bilaterally, which were most conspicuous in the periventricular regions of the parietal–occipital lobes. Calcifications were not present in the basal ganglia or thalamus. The cerebral white matter and corpus callosum were moderately reduced in volume and there was moderate ventricular enlargement. A few smaller calcifications were present in the basis pontis and cerebellar white matter. None of the calcifications were accompanied by visible cavitation.

Histologic sections of the cerebrum, cerebellum, and pons revealed multifocal necrotizing lesions of varying sizes. Many...
were associated with prominent calcifications. The necrotic lesions primarily involved white matter but were also focally present in some gray matter structures, including the hippocampus, amygdala, and cerebellar cortex. The lesions varied in character, ranging from very small zones of pallor and hypocellularity to larger, more confluent necrotic foci with axonal degeneration, myelin destruction, macrophage infiltration, gliosis, and macro- and microcalcification (Figure 2A and B). Macrocysts were not apparent, but some of the larger necrotic lesions showed marked tissue rarefaction with partial microcystic degeneration. Rosenthal fibers were not observed. Special stains for myelin (Luxol fast blue) and axons (neurofilament protein) showed myelin loss commensurate with axonal damage, consistent with a necrotizing rather than demyelinating process.

Microangiopathic changes were a conspicuous feature of all necrotic lesions, and showed considerable variation in histologic character and severity. Most lesions, regardless of size and location, showed an overall reduction in the number of microvessels. The remaining vessels demonstrated histologic changes that ranged from complete luminal obliteration with loss of all vascular components including smooth muscle, endothelium, and basement membranes to less severe injury with preserved endothelium but narrowed lumens and perivascular collagen deposition (Figure 2C and D). No amyloid deposition (Congo red, β-amyloid) or periodic acid-Schiff-positive granular deposits (as seen in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) were observed in either affected or normal-appearing vessels, and no inflammatory or vasculitic changes were present. Larger-sized vessels, both arteries and veins, within the brain parenchyma and subarachnoid space had a normal histologic appearance.

Selected sections stained immunohistochemically for τ, β-amyloid, and α-synuclein showed no histologic changes characteristic of Alzheimer disease, Parkinson/Lewy body disease, or tauopathy.

Conclusions
The triad of microangiopathic necrotizing leukoencephalopathy, microcystic degenerative changes, and calcifications is a rare combination of histologic findings that led to the diagnosis of CRMCC as the most likely in our patient. Clinically, symptoms vary depending on the location and distribution of the microangiopathy and cystic changes, ranging from cerebral to cerebellar or spinal cord manifes-
tations. However, patients usually present with progressive extrapyramidal, pyramidal, and cerebellar signs with cognitive impairment, and/or seizures. Progression of the disease is variable, ranging from typical MRI findings found incidentally in asymptomatic patients to a more rapid course leading to death in a few years after diagnosis. As described in the original report on LCC by Labrune et al,4 the essential feature of this disorder seems to be “diffuse cerebral microangiopathy resulting in microcystic, then macrocystic, parenchymal degeneration.” The proposed pathogenetic mechanism is the result of a diffuse obliterator microangiopathy that leads to microcystic parenchymal degeneration, evolving into white matter changes, gliosis, calcium deposits, and eventually to macroscopic cyst formation.5 The histologic changes noted in our patient were quite similar to those described in CRMCC, with the exception that only microcysts were present on microscopic examination, and the white matter involvement on MRI was less extensive than in the adult cases described in the literature. However, it is quite possible that macrocystic changes would have developed if our patient had survived longer.

Due to the rarity of this condition, especially in adults, the underlying etiology and true incidence are currently unknown, with no clear ethnic predisposition. Due to some reports of affected sibling pairs and consanguinity in some families, an autosomal recessive pattern of inheritance is possible, although more cases are needed to confirm this.6 Whether this is also true for adult-onset cases is currently unknown.

Recently, mutations in the conserved telomere maintenance component 1 (CTC1) gene (OMIM 613129) have been linked to CRMCC5; interestingly, this mutation was present in only 1 of 3 patients with late-onset CRMCC, with all 3 patients not showing any retinal abnormalities, as was the case in our patient. The fact that CTC1 mutations have only been found in patients with extra-neurologic features besides intracranial calcification, leukoencephalopathy, and cysts has led some authors to question the validity of the umbrella term CRMCC incorporating LCC and Coats plus syndrome as disorders with a common pathologic origin.6 In fact, some authors propose the concept that while LCC is a purely neurologic disorder, Coats plus syndrome is more of a multisystem disorder genetically defined by CTC1 mutations. However, there is still lack of consensus on this issue, highlighting the fact that more cases need to be studied to get a clearer picture of the etiology, clinical course, and prognosis of this rare disorder.

REFERENCES

ARTICLE INFORMATION
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