Clinical Pathologic Conference

Progressive Neuropsychiatric Symptoms and Motor Impairment

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A 42-year-old white man presented with cognitive impairment and behavioral changes followed by rapidly progressive motor and gait impairment. Magnetic resonance imaging revealed striking multifocal white matter signal change, areas of restricted diffusion, diffuse callosal signal change, and atrophy and hyperintensity of the corticospinal tracts. A broad range of etiologies warrant consideration in this case, including degenerative, vascular, inflammatory, metabolic, and neoplastic diseases.


Report of a Case

A 42-year-old white man presented with a 14-month history of progressive cognitive difficulties, behavioral changes, and mood disturbance culminating in severe depression and several suicide attempts. He experienced mild imbalance but no other focal neurological symptoms. He had a history of mild anxiety and depression, dyslipidemia, and chronic sinusitis. A neurological examination revealed no focal abnormalities.

Two years after symptom onset, he had developed lower-limb weakness (left greater than right), gait disturbance, and ataxia (imbalance and incoordination) and had numerous falls despite the use of walking aids. He reported dysphagia and speech disturbance. His disease rapidly progressed over months, and he became unable to mobilize independently, doubly incontinent, and required assistance for self-care.

His mother had celiac disease and had a stroke in her mid-50s. The patient did not know his biological father. There was no known family history of dementia or multiple sclerosis.

On examination, his Mini-Mental State Examination score was 23/30: he was oriented only to month and year, recalled 2 of 3 items, and was unable to write a sentence. He was able to attend, perform calculations, and follow 3-stage commands. The results of a cranial nerve examination, which included funduscopia, were unremarkable. Tone was increased in all his limbs, with sustained clonus at both ankles. His reflexes were generally brisk, although his plantar responses were flexor. There was mild proximal pyramidal-pattern weakness of all limbs, more severe on the left. He had significant motor apraxia and bilateral cerebellar signs, including upper limb dysdiadochokinesis and dysmetria. Cortical sensory signs were present on the left. He appeared to have a severe frontal gait disorder: he was unsteady and walked with small, cautious steps with difficulty initiating gait. The gait disorder was not fully explained by the demonstrable upper motor neurone or cerebellar signs.

Laboratory and Neuroradiological Data

Magnetic resonance imaging (MRI) of his brain revealed patchy and confluent areas of altered signal in the periventricular and subcortical white matter (Figure 1A and D). Diffuse signal change and atrophy were present in the body of the corpus callosum (Figure 1D and E). Several white matter lesions, especially within the centrum semiovale bilaterally, showed restricted diffusion in the absence of gadolinium enhancement (Figure 1B and C). The corticospinal tracts were hyperintense (Figure 1F). Fluorine 18-labeled fluorodeoxyglucose positron emission tomography of his brain revealed a mild generalized reduction in glucose metabolism in the cerebral and cerebellar hemispheres. Magnetic resonance angiography and formal 4-vessel cerebral angiography revealed no evidence of vasculitis.

A full blood examination revealed mild leukopenia (white blood cell count, 3.5 × 10^3/μL), neutropenia (neutrophil count, 1.8 × 10^3/μL), and thrombocytopenia (platelet count, 127 × 10^3/μL). His erythrocyte sedimentation rate was mildly elevated at 15 mm/h; his C-reactive protein level was normal. He tested positive for antinuclear antibodies at a titer of 1:640, and an assay for extractable nuclear antibodies disclosed anti-Ro52 antibodies. The results of assays for double-stranded DNA, anticardiolipin, β2 glycoprotein I, glutamic acid decarboxylase, anti-gliadin, antithyroid, antineuronal, and antineutrophil cytoplasmic antibodies were negative. IgG, IgM, and complement levels were normal. The results of serum immunoelectrophoresis were normal, and he tested negative for rheumatoid factor. The results of a biochemical profile and a nutritional screen were normal, and his lactate level, angiotensin-converting enzyme level, and levels of very-long-chain fatty acids and lysosomal enzymes were normal. Results of serology for human immunodeficiency virus, syphilis, human T-lymphotropic virus I and II, and Borrelia burgdorferi were negative.

The cerebrospinal fluid (CSF) was acellular, with an elevated protein level of 0.072 g/dL (to convert to grams per liter, multiply by 10.0). He tested negative for oligoclonal bands and the 14-3-3
protein. The results of electron microscopy of a skin biopsy were negative for granular osmiophilic material.

Clinical Discussion (Dr Sutton)

The presentation is that of a subacute dementing illness with prominent neuropsychiatric manifestations in a young adult. Sporadic Alzheimer disease is rare before 50 years of age, and, although spastic paraparesis and cerebellar dysfunction can be observed in individuals with presenilin mutations, the MRI findings are not typical of Alzheimer disease, frontotemporal lobar degeneration, dementia with Lewy bodies, or prion disease. Instead, the clinical and imaging abnormalities point toward a vascular, inflammatory, or metabolic etiology.

The MRI finding of multifocal areas of restricted diffusion is consistent with acute infarction and suggests a vascular etiology. Although the constellation of neuropsychiatric findings and symptoms, antinuclear antibodies at a titer of 1:640 with positive Ro52 antibodies, neutropenia, and thrombocytopenia suggest a connective tissue disorder, there is no accompanying hemolytic anemia, and the patient tested negative for Smith and double-stranded DNA antibodies. Therefore, the patient’s presentation does not fulfill the 1997 American College of Rheumatology diagnostic criteria for systemic lupus erythematosus, and antibodies binding to the Ro52 antigen, recently identified as the TRIM21 protein, are associated with a number of autoimmune diseases. Furthermore, although a variety of MRI abnormalities can be observed in neuropsychiatric systemic lupus erythematosus, a neurological presentation without other clinical manifestations of systemic lupus erythematosus is exceptional. Primary central nervous system vasculitis is a rare disorder seen most commonly in individuals 40 to 60 years of age, and “angiogram-negative” cases, diagnosed by cerebral biopsy, are more likely to present with cognitive dysfunction and a CSF protein level of greater than 0.070 g/dL.

Cognitive impairment is common in primary progressive multiple sclerosis but rarely the dominant presenting feature, and the absence of CSF-specific oligoclonal bands militates strongly against this diagnosis. In contrast, neuromyelitis optica spectrum disorder frequently is associated with the absence of CSF-specific antibodies and high CSF protein levels.

Figure 1. Magnetic Resonance Imaging Findings

An axial fluid-attenuated inversion recovery (FLAIR; [A]) image, a diffusion-weighted imaging (DWI; [B]) scan, and an apparent diffusion coefficient (ADC) map (C) at the level of the centrum semiovale are shown. A, The FLAIR image demonstrates extensive subcortical white matter hyperintensities (circle). B, Many of these areas show a high signal on the DWI scan (circle). C, The ADC map shows corresponding areas that are predominantly of high signal representing facilitated diffusion, but it also reveals islands of hypointensity signifying true restricted diffusion (circle). D, An axial FLAIR image through the lateral ventricles reveals confluent involvement of the genu and splenium of the corpus callosum and generalized cerebral atrophy. E, A sagittal FLAIR image reveals hyperintensity of the corpus callosum and marked callosal atrophy. F, An axial FLAIR image at the level of the midbrain reveals hyperintensity of the corticospinal tracts bilaterally (arrowheads).
oligoclonal bands and encompasses a wide range of MRI features, including large, confluent hemispheric white matter lesions and longitudinally extensive lesions involving the corticospinal tracts. However, neuromyelitis optica spectrum disorder remains unlikely in the absence of aquaporin-4 antibodies, optic neuritis, or transverse myelitis. Only 5% of cases of central nervous system sarcoidosis occur in the absence of systemic disease, and typically they demonstrate leptomeningeal involvement and, in 29% to 43% of cases, parenchymal lesion enhancement. Hashimoto encephalopathy can present with progressive dementia, gait and motor abnormalities, and, infrequently, diffuse white matter signal change on MRI scans. However, it is defined by the presence of thyroid autoantibodies. Limbic encephalitis typically produces mesial temporal lobe abnormalities detected on MRI scans, although paraneoplastic syndromes may affect the central nervous system more diffusely. The atypical MRI features, including the presence of multifocal areas of restricted diffusion and the absence of serum antineuronal antibodies, render paraneoplastic disease unlikely in this case.

Gliomatosis cerebri may present with cognitive impairment and results in diffuse and contiguous infiltration of white matter that is isointense on T1-weighted and hyperintense on T2-weighted MRI sequences. Although bitemporal extension through commissural pathways, potentially suggested by the MRI scans in this case, is characteristic of gliomatosis cerebri, the lack of mass effect and the presence of multifocal areas of restricted diffusion suggest more viable alternative diagnoses.

In young-onset dementia-plus syndromes (disorders in which cognitive impairment is accompanied by additional neurological or systemic features), inborn errors of metabolism usually present in patients before they reach 30 years of age, but 3 adult-onset leukoencephalopathies bear consideration. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is excluded because of the absence of granular osmiophilic material (determined by electron microscopy of a skin biopsy). Examination for granular osmiophilic material by electron microscopy is a highly sensitive test for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, showing 100% congruence with NOTCH3 gene analysis in a recent study. Cerebrotendinous xanthomatosis and adult-onset leukodystrophy with neuroaxonal spheroids and pigmented gliosis (ALS) have a wide range of presentations, and both can show a predilection for involvement of the corticospinal tracts. However, cerebrotendinous xanthomatosis, which is caused by a deficiency of the enzyme 27-sterol hydroxylase, is typically associated with premature cataract formation and tendon xanthomas.

Several recent publications have identified lesions exhibiting restricted diffusion in cases of ALS, thereby serving to potentially differentiate the condition from other disorders that result in multifocal or diffuse white matter abnormalities with preferential tractal involvement detected on MRI scans. While mutations in the colony stimulating factor 1 receptor (CSF1R) gene have recently been identified as the cause of ALS, this test is not available as a diagnostic investigation, and brain biopsy is indicated to differentiate ALS from “angiogram-negative” primary central nervous system vasculitis.

Neuropathological Discussion (Dr Buckland)

A biopsy of the right frontal lobe was performed. The cortex and attached leptomeninges were unremarkable. The deeper white matter showed patchy pale areas of rarefaction accompanied by
reactive astrogliosis and infiltration by macrophages, some of which contained cytoplasmic yellow-brown pigment (Figure 2A). Luxol fast blue staining revealed a marked loss of myelin in the deep white matter (Figure 2B) with sparing of subcortical U fibers. Prominent axonal spheroids and axonal loss were shown by Garvey silver stain, as well as by neurofilament (Figure 2C) and amyloid precursor protein immunostains. CD68 and HLA-DR immunostains highlighted the macrophage infiltrate (Figure 2D), which was almost exclusively seen in white matter. Further staining of these pigmented cells was consistent with the presence of iron and ceroid. Many of these pigmented cells tested positive on Perls iron stain (Figure 2D), diastase-resistant periodic acid Schiff positive stain, and prolonged Ziehl-Neelsen stain (Figure 2D). There was no metachromasia on Toluidine blue staining. These features are characteristic of ALSP.

Adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia is a new term encompassing hereditary diffuse leukoencephalopathy with axonal spheroids and pigmented orthochromatic leukodystrophy, which were recently recognized as sharing similar pathological features.17,18 Mutations in the CSF1R gene have been demonstrated in hereditary ALS/L 16,19,20 Sequencing of the coding region of exons 12 to 22 of the CSF1R gene was performed in this case. A novel missense mutation, located in a phylogenetically conserved amino acid residue just outside the receptor tyrosine kinase domain of CSF1R, was identified (c.1736G>A, p.Arg579Gln).

Conclusions

Adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia is a rare, degenerative white matter disease that is universally fatal. The term encompasses hereditary diffuse leukoencephalopathy with axonal spheroids and pigmented orthochromatic leukodystrophy, which are now understood to have the same underlying neuropathology and genetics.17,20 At least 11 sporadic cases and 20 kindreds demonstrating autosomal dominant or autosomal recessive inheritance have been described.17,21 There is significant clinical heterogeneity in ALS/L that overlaps with other white matter diseases. Disease onset is usually in the fourth to fifth decades of life. Neuropsychiatric features such as depression, anxiety, behavioral changes, and cognitive dysfunction typically predominate early and may precede other symptoms by several years.17,22 There is progressive motor and gait disturbance, which can include pyramidal dysfunction, parkinsonism, and ataxia. Epilepsy has been reported in almost 50% of published cases.12-16,21-23 The results of laboratory investigations, including CSF studies, are normal. The disease course is one of relentless progression, and death occurs within 10 years of onset.12,17

Magnetic resonance imaging findings include periventricular, callosal, and deep white matter nonenhancing T2-weighted hyperintensities that are initially patchy but later become confluent.22 There is often a relative sparing of the occipital lobes. Islands of restricted diffusion among larger areas of facilitated diffusion, similar to that seen in our case, have been reported14,15 and may persist for months,17 perhaps longer. Frontal-predominant atrophy is common in established disease. A high T2-weighted signal in descending corticospinal tracts, as seen here, has previously been described.12,13

The definitive diagnosis of ALS/L requires neuropathological examination of affected white matter. Widespread demyelination with sparing of subcortical U fibers, axonal damage with neuroaxonal spheroids, and nonmetachromatic, sudanophilic lipopigment within macrophages and glia are characteristic.12,17,22 Rademakers et al16 described mutations in the CSF1R gene in hereditary ALS/L, and our case demonstrates a novel mutation in this gene. CSF1R modulates microglial proliferation, differentiation, and survival in the brain. Mutations in the CSF1R gene may cause a partial loss of function of the receptor, and ALS/L is therefore considered a primary microglial disorder.16

Adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia may be mistaken for inflammatory, vascular, metabolic, infectious, and other dementias. This is highlighted in this case, in which the patient’s condition was initially misdiagnosed as primary progressive multiple sclerosis. No treatment was tried, and his referral for a further opinion led to the diagnostic brain biopsy. The patient’s condition has continued to deteriorate, and he is now fully dependent on nursing home care.

An accurate diagnosis in early dementia is important in order to exclude treatable causes, avoid unnecessary toxic therapies, and allow for prognostication and genetic counselling. Adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia should be considered as a differential diagnosis in young-onset dementia, particularly when prominent neurobehavioral features, motor or gait impairment, a family history of early dementia, or supportive MRI features are seen. A definitive diagnosis currently requires a brain biopsy, although the future availability of clinical genetic testing may obviate the need for a tissue diagnosis.
Additional Information: Written informed consent to publish this case was given by the patient’s next of kin.

REFERENCES