OBSERVATION

A New Association Between Castleman Disease and Immune-Mediated Cerebellitis

Report of a Case | A previously healthy man in his 30s awoke one morning with acute, extreme vertigo; unsteady gait; and dyscoordination. His symptoms progressed despite treatment with diazepam and meclizine, and he presented to our hospital 1 month after symptom onset unable to walk or feed himself. Neurologic examination was significant for oscillopsia, nystagmus in all directions of gaze, scanning speech, and profound truncal and appendicular ataxia. He could neither stand nor ambulate owing to imbalance.

Institutional review board approval was not obtained because it is not required for case reports at our institution; the patient provided oral consent.

Brain magnetic resonance imaging revealed leptomeningeal enhancement between the cerebellar folia (Figure 1A). Cerebrospinal fluid tests revealed white blood cell count of 16/μL (96% lymphocytes) (to convert white blood cell count to ×10⁹ per liter, multiply by 0.001), red blood cell count of less than 1 ×10⁶/μL (to convert to ×10¹² per liter, multiply by 1.0), and normal protein and glucose levels; viral, fungal, and bacterial culture results were negative (including varicella-zoster virus, herpes simplex virus types 1 and 2, enterovirus, Lyme, and cryptococcus); and oligoclonal bands, cytology, and flow cytometry were unremarkable. Cerebrospinal fluid test results were negative for autoantibodies to antineuronal nuclear antibody 1 (anti-Hu), antineuronal nuclear antibody 2 (anti-Ri), antineuronal nuclear antibody 3, antiglial nuclear antibody 1, Purkinje cell cytoplasmic antibody type 1 (anti-Yo), Purkinje cell cytoplasmic antibody type 2, amphiphysin, and collapsin response mediator protein 5 (anti-CV2). Serum paraneoplastic panel results were negative, which included the same cerebrospinal fluid antibodies plus anti-Ma1, anti-Zic4, anti-GAD65, Purkinje cell cytoplasmic antibody type Tr, P/Q- and N-type calcium channel antibodies, voltage-gated potassium channel, N-methyl-D-aspartate receptor, and acetylcholine receptor antibodies. Serum studies revealed only an isolated elevated interleukin 6 level at 26 pg/mL (normal, <5 pg/mL). Results from human immunodeficiency virus RNA polymerase chain reaction and human herpesvirus 8 IgG and DNA testing were negative. Computed tomographic scans of the chest, abdomen, and pelvis found multiple anterior mediastinal soft-tissue nodules that were metabolically active on positron emission tomography with fluorodeoxyglucose. Thymic and lymph node biopsies confirmed the diagnosis of hyaline vascular Castleman disease (Figure 2).

The patient underwent treatment with intravenous immunoglobulin for 5 days (0.4 g/kg/d), followed by 1 g intravenous solumedrol daily for 5 days along with intensive physical, occupational, and speech therapy but failed to improve clinically. The mediastinal mass was resected on hospital day 16, and repeated magnetic resonance imaging 3 weeks after presentation (6 days postresection) showed resolution of cerebellar enhancement and subtle cerebellar degeneration (Figure 1B). He was discharged to a rehabilitation facility and, at 6-month follow-up, remained wheelchair dependent with persistent ataxia and diplopia. He was lost to follow-up before more aggressive treatment could be instituted.

Figure 1. Brain Magnetic Resonance Imaging at Presentation and 3 Weeks Later

A At presentation
B At 3 wk

A, Magnetic resonance image at presentation shows axial T1 postcontrast sequence demonstrating abnormal enhancement in the bilateral cerebellar folia. B, Magnetic resonance image 3 weeks after presentation shows sagittal T2 image demonstrating subtle cerebellar atrophy. The previously seen enhancement is resolved.
Figure 2. Histopathological Slide With Castleman Follicle

Atretic germinal center surrounded by concentric rings of lymphocytes with “onion-skinning” appearance (hematoxylin-eosin; original magnification ×100).

Discussion | The cerebellum is a frequent immunologic target, perhaps because its Purkinje cells possess multiple optimal antigens. The most commonly described cerebellar syndromes are paraneoplastic, but many others have been described in the setting of non-neoplastic disease such as gluten ataxia, anti-GAD antibodies, or postinfectious cerebellitis.1 Immune-mediated ataxias tend to affect the cerebellar vermis first: imbalance, speech, and vision changes are common initial presentations. An early magnetic resonance image may show meningeal enhancement; atrophy is seen on later scans.7,3 Paraneoplastic cerebellar degeneration generally carries a poor prognosis but immune-mediated cerebellar syndromes can have variable outcomes.1,3 Our patient was lost to follow-up before maintenance immunotherapy could be instituted or more aggressive immunomodulatory therapies could be trialed, which may have improved his long-term outcome.

Castleman disease is a lymphoproliferative disorder subcategorized by morphology (unicentric vs multicentric) and histopathology (hyaline vascular, plasma cell, or human herpesvirus 8–associated variants). Although Castleman disease is by definition non-neoplastic, its more aggressive plasma cell and human herpesvirus 8–associated forms have been described with other paraneoplastic disorders such as POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome and Kaposi sarcoma, as well as with hematologic malignancies such as Hodgkin and non-Hodgkin lymphoma, which in turn have been associated with cerebellar syndromes.3-4 Our patient had the more common hyaline vascular form (representing approximately 90% of Castleman disease cases); this subtype has rare autoimmune or paraneoplastic associations. A specific autoantibody in this case was not identified. Neither anti-mGluR1 nor CASPR2 antibodies were tested; both have been found in cases of unexplained cerebellar ataxia.5,6 However, the rarity of both Castleman disease and immune-mediated cerebellitis strongly suggest a new association not previously described.

Sarah Lee, MD
Sheherazade Le, MD

Author Affiliations: Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, California.

Corresponding Author: Sarah Lee, MD, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, 300 Pasteur Dr, A343, Stanford, CA 94305 (slee10@stanford.edu).

Conflict of Interest Disclosures: None reported.


COMMENT & RESPONSE

Glucocerebrosidase Gene Mutation and Preclinical Markers of Parkinson Disease

In a study published in JAMA Neurology, Beavan et al1 reported a 2-year follow-up study of 30 patients with a diagnosis of type 1 Gaucher disease, 28 heterozygous glucocerebrosidase gene (GBA) mutation carriers, and 26 control individuals.1 It is well known that GBA mutations are a confirmed genetic risk for developing Parkinson disease (PD).2 Previously, Winder-Rhodes et al3 found that GBA mutations were present at a frequency of 3.5% in a UK PD population, confirming the important contribution of this gene in the clinical progression of PD. Indeed, the authors found that the hazard ratio for progression both to dementia and Hoehn and Yahr Scale stage 3 were significantly greater in GBA mutation carriers.3 In addition to confirming the well-established role of the GBA gene in PD, the study by Beavan et al4 emphasized the significant value of GBA mutations also in the prodromal motor and nonmotor features of PD. The authors went further by showing that those with Gaucher disease and heterozygous carriers exhibited worse scores of depression, rapid eye movement sleep behavior disorder, olfactory and cognitive assessment scores, and Unified Parkinson’s Disease Rating Scale part III scores. Notably, this study confirmed the results previously collected by the authors in the same cohort.5

In line with the current literature, the clinical markers investigated by Beavan et al4 are coherent with the prodrome of PD.4 Previous studies that investigated the risk factors and early features of PD highlighted the importance of detecting the neurodegenerations in as early a stage as possible for the efficacy of any neuroprotective or disease-modifying therapy.6 Addition-