Clinical Reasoning:

A 73-year-old man with diplopia and ataxia

Harsh V. Gupta, MD
Rohan Samant, MD
Murat Gokden, MD
Ricky W. Lee, MD
Kinshuk Sahaya, MD
Tuhin Virmani, MD,
PhD

Correspondence to
Dr. Gupta:
dr.harshgupta@gmail.com

SECTION 1

A 73-year-old right-handed man with a history of hypertension and hyperlipidemia presented with an 18-month history of diplopia and unsteady gait. He also noted oscillating vision when turning his head to the left. The diplopia was horizontal and was worse looking at objects on his right or at a distance. Over a year, his balance worsened to the point where he required a walker due to recurrent falls. Six months prior to presentation, he developed dysphagia (liquids more than the solids). He was also noted to have short-term memory problems in the last 3 months. On examination, he had moderate cognitive impairment with a Montreal Cognitive Assessment (MoCA) score of 20/30 with predominant deficits in visuospatial functions and language. Glabellar, bilateral palmomental, and snout reflexes were present. The left pupil was surgical and

nonreactive to light, and there was mechanical ptosis on the left. He had left exotropia with full eye movements, bilateral horizontal gaze-evoked nystagmus, and upbeat nystagmus on upgaze. Motor strength and tone were normal. He was diffusely hyperreflexic with bilateral extensor plantar responses. Detailed sensory examination was normal. Dysmetria was present bilaterally, more prominent on the left compared to right, with finger to nose testing and finger chase. His gait was ataxic with wide base and a tendency to fall toward the left side. He was unable to tandem walk (video on the *Neurology*® Web site at Neurology.org). Systemic examination was unremarkable.

Questions for consideration:

1. Where would you localize his lesions?
2. What is your initial differential diagnosis?

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From the Departments of Neurology (H.V.G., R.W.L., K.S., T.V.), Radiology (R.S.), and Pathology (M.G.), University of Arkansas for Medical Sciences, Little Rock.

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SECTION 2

There are clues in the history and examination that can help us localize his symptoms. Hyperreflexia and bilateral extensor plantar responses indicate upper motor neuron involvement. Palmomental, snout, and glabellar reflexes indicate disruption of the cortical inhibitory pathways. Visuospatial deficits on cognitive testing indicate nondominant parietal lobe involvement, while language impairments indicate dominant temporal lobe deficits. Impaired suppression of the vestibulo-ocular reflex by cerebellar or brainstem lesions results in symmetric gaze-evoked nystagmus and oscillopsia. Upbeat nystagmus could be due to lesions in the dorsal central medulla or central mid pons. Dysmetria with gait ataxia (in the absence of sensory findings) also localizes to the cerebellum. Horizontal diplopia with distance vision that worsens on lateral gaze localizes to an ipsilateral lateral rectus palsy.

These findings suggest a progressive disorder involving the posterior fossa along with a multifocal process in the cerebral cortex.

Based on the history and examination, the differential diagnosis includes the following:

1. Neurodegenerative conditions (multisystem atrophy or spinocerebellar ataxia)
2. Inflammatory/autoimmune disorders (sarcoidosis, anti-GAD, Sjögren syndrome, demyelinating disease, or steroid-responsive encephalopathy associated with autoimmune thyroiditis)
3. Vascular causes (arteriovenous malformation, vasculitis, or superficial siderosis)
4. Paraneoplastic disorders (anti-Yo, anti-Ri, anti-Hu, or anti-CV2)
5. Neoplastic disorders (leptomeningeal carcinoma, metastatic cancer, or lymphoma)
6. Infectious disorders (Creutzfeldt-Jakob disease, Whipple disease, syphilis, tuberculosis, HIV, or fungal meningitis)
7. Nutritional deficiencies (vitamin E, vitamin B₁₂, or celiac disease)

MRI of the brain (figure 1) demonstrated numerous punctate randomly scattered foci of intraparenchymal enhancement in the brainstem, basal ganglia, and cerebral and cerebellar hemispheres (figure 1, C and D). They correspond to subtle fluid-attenuated inversion recovery (FLAIR) hyperintensities (figure 1, A and B) and the pattern suggested perivascular distribution of lesions.

CSF studies showed 7 leukocytes, 0 erythrocytes, protein 69 mg/dL (15–45 mg/dL), and glucose 61 mg/dL (40–70 mg/dL). Culture for bacterial, fungal, and acid-fast organisms did not demonstrate any growth. CSF immunoglobulin G (IgG) index, IgG synthesis, oligoclonal bands, and CSF myelin basic protein were within normal limits. CSF cytology was negative for malignant cells in 3 samples sent over a period of 2 weeks. Paraneoplastic panel results were normal. Testing for autoimmune etiologies in the serum (antinuclear antibodies, SSA, SSb, anti-GAD, gliadin antibodies, antiphospholipid antibodies, rheumatoid factor, antineutrophil cytoplasmic antibody, and angiotensin-converting enzyme) had normal results. Vitamin E and vitamin B₁₂ levels were within normal range. CT scan of the chest, abdomen, and pelvis and a whole-body PET scan did not reveal evidence of malignancy.

Questions for consideration:

1. Based on these results, how would you narrow your differential diagnosis?
2. What further investigations would you consider?

GO TO SECTION 3

Figure 1 MRI brain

Axial fluid-attenuated inversion recovery images at the level of the pons (A) and basal ganglia (B) show very small hyperintense foci. Postcontrast axial T1-weighted images at the level of the pons (C) and basal ganglia (D) show punctate areas with morphology suggestive of perivascular enhancement.

SECTION 3

The differential diagnosis with the inclusion of imaging findings included neuro-Behçet disease, isolated CNS vasculitis, lymphomatoid granulomatosis, Erdheim-Chester disease, and chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Further testing for lactic dehydrogenase, $\beta 2$ microglobulin, antineutrophil cytoplasmic antibody, and HIV was negative. The level of serum immunoglobulin E (IgE) was found to be elevated at 346 kU/L (normal <214 kU/L); absolute CD4 and CD8 counts were low at 270/ μ L (normal range 720–1,348/ μ L) and 100/ μ L (normal range 318–710/ μ L), respectively, with a CD4:CD8 ratio of 2.7 (high).

Due to worsening balance and more frequent falls, the patient became very limited in his ability to walk and was readmitted to the inpatient neurology service. A repeat MRI of the brain with a double dose of gadolinium contrast was performed to evaluate for additional regions that could be more amenable to biopsy. The repeat MRI brain demonstrated new lesions over the bilateral frontoparietal and right

occipital pole regions (figure 2). A biopsy from the right frontal gyrus was taken. The patient tolerated the procedure well without complications. Histopathology was remarkable for a vasculocentric population of small round lymphocytes and histiocytes. The lymphocytic infiltrate was composed primarily of T cells (CD3 positive) with a smaller subpopulation of B cells without any evidence of vessel wall damage or thrombosis in the lumen to suggest vasculitis (figure 3). No giant cells or well-defined granulomata were present. The lymphocytic population was composed of small and round mature lymphocytes, which were predominantly CD3-positive T cells with a small subpopulation of CD20-positive B cells, consistent with a reactive, rather than a neoplastic, lymphoid population. Special staining for viral (herpes simplex virus and cytomegalovirus), fungal (Gomori methenamine silver), and acid-fast microorganisms (Ziehl-Neelsen) was negative. Luxol fast blue stain demonstrated no myelin loss to suggest a demyelinating process.

Based on the clinical, radiologic, and pathologic findings, the diagnosis of CLIPPERS was made. The patient received 1 g IV methylprednisolone for 5 days. He was discharged home on 60 mg of oral prednisone and has not yet been started on any steroid-sparing immunosuppressive agent. At a 1-month follow-up visit, the patient had improved gait ataxia and was able to walk slowly with wide base without the use of a walker and stand with feet together for 10 seconds with mild sway, but still had difficulty with tandem more than 2–3 steps. He reported no improvement in his diplopia, but mild subjective improvement in dysphagia. A very slow wean in his steroid dose over months with repeat MRI was planned.

DISCUSSION CLIPPERS was first described by Pittock et al.¹ in 2010 as a distinct form of encephalitis responsive to immunosuppression with glucocorticoid therapy. Patients with CLIPPERS present with brainstem and cerebellum predominant symptoms, including ataxia, diplopia, dysarthria, vertigo, and long tract signs.^{1,2} MRI findings described in this condition include multiple punctate and curvilinear patterned gadolinium contrast-enhancing lesions with faint visualization on T2- and FLAIR-weighted images suggesting scarce edema. The contrast enhancement is typically concentrated around the pons, giving a salt and pepper appearance with spread rostrally (midbrain and supratentorial structures) and caudally (medulla oblongata and spinal cord).^{1–3} The pathology in most cases demonstrated perivascular lymphohistiocytic infiltrate in the absence of characteristic features of vasculitis, granulomatous inflammation, lymphoma, or sarcoidosis. The lymphocytes present in the perivascular

Figure 2 Double-dose contrast

Axial T1-weighted images at the level of the frontal lobes following standard dose of gadolinium contrast (A, B) and following double dose of the gadolinium (C, D). Notice the additional punctate areas of enhancement in the frontal and parietal region following the double dose of gadolinium contrast.

(A) Perivascular infiltrates are composed predominantly of small lymphocytes. No infiltration of blood vessel walls, vasculitis, or evidence of other vasculopathy is seen (hematoxylin & eosin [H&E]; 400 $\times$). (B) Some perivascular infiltrates contain histiocytes and have a loose granuloma appearance (H&E; 400 $\times$). (C) Perivascular infiltrates are composed predominantly of T cells (CD3; 100 $\times$). (D) Perivascular histiocyte population and parenchymal microglial proliferation is seen (CD163; 100 $\times$).

location were mainly composed of CD4 T cells but this finding is not specific for CLIPPERS.¹⁻³

Pittock et al.¹ suggested that clinical and radiologic features may be sufficient to diagnose CLIPPERS if other disorders have been rigorously excluded. However, brain biopsy needs to be considered in patients when alternative diagnoses remain likely. Given the primary location of pathology within the brainstem, the decision to pursue brain biopsy cannot be taken lightly. The cerebral cortex tends to be a safer site for tissue diagnosis, but classically the lesions of CLIPPERS on neuroimaging have been described to be smaller and less numerous as the distance from the pons increases.¹ Double-dose gadolinium-enhanced images have been reported to have an advantage over single-dose gadolinium in detecting early and small brain metastases.⁴ In our patient, we demonstrated that double-dose gadolinium contrast can help in guiding the brain biopsy to a less eloquent site by improving visualization of the cortical lesions.

Pittock et al.¹ proposed that CLIPPERS was a distinct form of brainstem encephalitis. Recently, a few cases of CLIPPERS have also been reported to progress to CNS lymphoma, which may suggest that it is a prelymphoma stage.^{5,6} Moderate pancytopenia, elevation of serum IgE, and

elevation of serum autoimmune antibodies have also been seen in some cases of CLIPPERS, and while the significance of these findings remains unknown,^{7,8} they could be the first manifestation of a systemic disease such as Sjögren syndrome.⁹ Further studies are needed to elucidate the pathophysiology of CLIPPERS.

High-dose glucocorticoids lead to variable improvement in symptoms and MRI findings but there is a risk of relapse during the reduction or discontinuation of glucocorticoid treatment. This can necessitate the use of chronic steroid therapy or use of other immunosuppressive agents such as cyclophosphamide, methotrexate, or azathioprine.^{1,3,8} Follow-up MRI in patients with CLIPPERS has demonstrated atrophy of the cerebellum, cortex, brainstem, and spinal cord despite clinical improvement.^{1,3}

AUTHOR CONTRIBUTIONS

Dr. Gupta and Dr. Sahaya: study concept and design, acquisition of data, and drafting of the manuscript. Dr. Gupta and Dr. Virmani: examination of the patient and summarizing the examination findings. Dr. Lee and Dr. Virmani: critical review of the manuscript for important intellectual content. Dr. Gupta and Dr. Samant: review of the imaging findings. Dr. Gokden: review of pathology findings.

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