Clinical Reasoning:

A 52-year-old man with diplopia and ataxia

Michael J. Bradshaw, MD
Siddharama Pawate, MD
Karen C. Bloch, MD,
MPH
Paul Moorts, MD
Nishitha M. Reddy, MD

Correspondence to
Dr. Bradshaw:
michael.j.bradshaw@vanderbilt.edu

SECTION 1

A 52-year-old man presented with a month of progressive, painful, right-sided spasms, dysarthria, horizontal diplopia, left facial droop, and headaches. Over the last year, he had developed progressive gait ataxia that required use of a walker.

Six years before presentation, he had several episodes of syncope and transient decreased sensation in the right arm. Evaluation at that time included normal EEG, and contrasted brain MRI (not shown) demonstrated nonspecific T2-hyperintense lesions in the cerebellum and cortex. No further workup was pursued at that time. Medical history included hypertension, hyperlipidemia, gout, and recurrent candidiasis in the groin. He denied exposures, recent travel, or risk factors for tuberculosis. Review of systems was negative for constitutional symptoms such as fevers/chills, weight loss, oral/genital ulcers, or Raynaud or sicca symptoms.

On examination, vital signs were normal. There was right lateral rectus palsy, sustained jerk nystagmus to the right on rightward gaze with saccadic ataxia, flattening of the right nasolabial fold, and spasticity with hyperreflexia and clonus in all extremities with extensor plantar response on the right. There was dyssynergia in all extremities with an ataxic gait. Skin examination demonstrated macular rash in the groin without ulceration. The remaining neurologic and general examinations were unremarkable.

A contrasted brain MRI demonstrated diffuse contrast-enhancing lesions in the brainstem and subcortical white matter (figure).

Question for consideration:

1. What is the differential diagnosis and how would you approach the diagnostic evaluation of brainstem encephalitis?

Figure Brain MRI with and without gadolinium, and CT scan of the abdomen

(A) MRI fluid-attenuated inversion recovery sequences demonstrated enlargement and T2 hyperintensity extending from the midbrain (not shown) through the pons and cerebellar peduncles (shown) to the medulla oblongata (not shown) with (B) contrast enhancement in the pons. There were also scattered foci of lobar subcortical enhancement in the cerebral hemispheres (not shown). (C) Chest, abdomen, and pelvis CT scan revealed infiltrative soft tissue surrounding the kidneys (arrows), extending into the renal hila (arrowhead) and involving the adrenal glands. There were several ill-defined ground-glass pulmonary opacities predominantly in the upper lobes and a sclerotic lesion in the left ilium (not shown).

GO TO SECTION 2

From the Departments of Neurology (M.J.B., S.P., P.M.), Medicine (Infectious Disease) and Health Policy (K.C.B.), and Medicine (Hematology and Oncology) (N.M.R.), Vanderbilt University Medical Center, Nashville, TN.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

In combination with focal neurologic deficits, evidence of inflammation, such as contrast-enhancing lesions on MRI or CSF pleocytosis (≥ 5 nucleated cells/mL) characterize brainstem encephalitis. In considering the differential diagnosis, priority should be given to infectious etiologies, which can be rapidly fatal and often have specific treatments that may be curative. Infections associated with brainstem encephalitis include *Listeria monocytogenes*, *Brucellosis*, *Mycobacterium tuberculosis*, *Tropheryma whipplei*, *Blastomyces dermatitidis*, *Treponema pallidum*, herpes simplex viruses 1 and 2 and varicella zoster virus, JC virus (the cause of progressive multifocal leukoencephalopathy), HIV, enterovirus 71, and flaviviruses, among others (see reference 1). Our patient was treated empirically with broad-spectrum antimicrobials while confirmatory testing was performed.

Once infection has been excluded, immune-mediated and neoplastic etiologies should be addressed. Diagnoses to consider include demyelinating etiologies such as multiple sclerosis, neuromyelitis optica, and acute disseminated encephalomyelitis, neuro-Behçet, neurosarcoidosis (NS), chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), neuro-Sjögren syndrome, neuro-lupus, vasculitides such as Susac syndrome, and neuronal paraneoplastic (including anti-Hu,

anti-Ta, and anti-Ma) and nonparaneoplastic autoantibody syndromes (such as anti-GQ1b [Bickerstaff brainstem encephalitis]).

Intrinsic brainstem glioma is rare in adults but may mimic brainstem encephalitis. Primary CNS lymphoma, lymphomatosis cerebri, intravascular lymphoma, and even primary CNS germ cell neoplasms might rarely demonstrate this pattern. Infiltrative disorders such as Langerhans cell and non-Langerhans cell histiocytoses (such as Erdheim-Chester disease [ECD]) can mimic brainstem encephalitis and may require biopsy for diagnosis.² Noninflammatory causes, such neurodegenerative and metabolic etiologies, are beyond the scope of this article but are mimics that should be considered in the appropriate clinical context.

Among the causes and mimics of brainstem encephalitis, the most likely to present indolently without infectious signs or symptoms include CLIPPERS, NS, neuro-Behçet, infiltrative disorders, malignancy, and less likely tuberculosis, fungal infection, progressive multifocal leukoencephalopathy, and autoantibody syndromes.

Questions for consideration:

1. What neuroimaging characteristics help distinguish among the most likely etiologies?
2. What further studies should be obtained to secure the diagnosis?

GO TO SECTION 3

SECTION 3

CLIPPERS is distinguished by punctate curvilinear “peppering” of the pons and nearby structures on contrasted MRI with little, if any, T2 hyperintensity or edema and is a diagnosis of exclusion in this setting.³ Known as “the great mimicker,” NS is diagnostically challenging with highly variable MRI findings. Nodular dural enhancement and cranial nerve enhancement can be suggestive of NS.⁴ While NS may rarely be seen in the absence of pulmonary disease, abnormalities on chest CT may support the diagnosis and provide a more accessible site for biopsy. Behçet disease is clinically characterized by the triad of uveitis, oral aphthous, and genital ulcers, occurs most often in middle-aged men with ancestry traceable to countries along the ancient Silk Road (Turkey has the highest incidence), and may present with brainstem encephalitis. MRI lesions often extend outside the brainstem into the cerebellum or rostrally and classically spare the red nucleus. Atrophy of the brainstem and cerebellum may be identified.⁵ MRI may be normal in autoimmune brainstem syndromes²; for example, all 22 patients with anti-Hu brainstem encephalitis had normal MRI in one review of the literature.⁶

MRI findings are not specific enough to solidify a diagnosis; therefore, targeted laboratory investigations are important. Although these should not delay empirical antibiotics, pretreatment serum and CSF should be obtained and samples preserved for further testing. Serum studies were significant for an elevated C-reactive protein at 66.3, antinuclear antigen positivity at >1:160 with a smooth pattern, and rheumatoid factor elevated to 41. Normal studies included double-stranded DNA, anti-neutrophil cytoplasmic antibodies, CSF and serum angiotensin-converting enzyme levels, aquaporin-4 antibodies, autoimmune antibody panel, infectious serologies, and cultures. CSF studies revealed 11 nucleated cells/ μ L (31% neutrophils, 29% lymphocytes, 40% monocytes), glucose 100 mg/dL, elevated protein of 51 mg/dL, and elevated immunoglobulin G index of 0.68 with no oligoclonal bands. Flow cytometry and cytology were normal.

In the absence of a diagnosis, further imaging studies in search of systemic disease or malignancy is a reasonable next step. CT of the chest, abdomen, and pelvis revealed bilateral perinephric soft tissue infiltration extending into the renal hila and involving the adrenal glands. Sclerotic bony lesions and small ill-defined pulmonary nodules were also discovered. Biopsy of the right perinephric lesion was consistent with ECD, and B-Raf protooncogene serine/threonine kinase (*BRAF*) mutational testing was positive.

He was treated with 5 days of IV methylprednisolone and improved clinically. Once the *BRAF* mutation returned positive, he was treated with vemurafenib, a potent BRAF kinase inhibitor. Now more than 10 months from diagnosis, his neurologic function continues to improve and his brain MRI has improved dramatically with no contrast-enhancing lesions and only a few T2/fluid-attenuated inversion recovery lesions.

DISCUSSION ECD is a rare non-Langerhans CD68⁺ histiocytic infiltrative disease that can affect virtually every organ system⁷ and primarily affects men in their fifth to seventh decade of life. Signs and symptoms develop and progress insidiously, making the diagnosis challenging. Our patient’s initial presentation 6 years before diagnosis was likely related to early ECD, although the findings were nonspecific. Presenting symptoms are limited to the affected organ system and the most common manifestations include bilateral osteosclerotic lesions of the long bones, circumferential thickening of the aorta (“coated aorta”), retroperitoneal fibrosis (“hairy kidney”), and neurologic manifestations including diabetes insipidus. After the skeletal system (90%), the nervous system is next most commonly affected (50%). Cutaneous, cardiovascular, and pulmonary involvement have also been described. Diagnosis requires tissue acquisition from an affected site and histopathologic evaluation.

Skeletal plain films and CT or PET of the chest and abdomen are useful for detecting sclerotic hypermetabolic lesions in the long bones, perinephric fat infiltration, and soft tissue periaortic expansion.⁷ On MRI, the dentate nuclei of the cerebellum and the pons are the most frequently involved sites and are usually contrast-enhancing. Lumbar puncture is helpful for excluding alternative etiologies, but histiocytes are rarely detected in the CSF of patients with ECD.

The current first-line treatment is interferon alpha, although no clinical trials have been performed. Several chemotherapeutic agents and cyclophosphamide have also been used with some success. Other treatments include infliximab, tocilizumab, and vemurafenib.⁷ The recent discovery of activating mutations in the protooncogene *BRAF* in approximately 50% of patients with ECD has supported the use of novel targeted agents with therapeutic benefit.⁸ Early studies in patients with *BRAF* mutation demonstrated positive results and a clinical trial is currently under way (clinicaltrials.gov identifier NCT02089724).^{9,10} Given these promising, albeit early results, treatment with vemurafenib should be considered in severe or refractory cases of

ECD. In cases with neurologic involvement, expert recommendations suggest MRI every 3 months until the disease has stabilized, at which point imaging can be extended to 6 months or as clinically indicated.⁷ Given the high mortality rate, any evidence of radiologic progression should trigger consideration of alternate or more aggressive therapy.

Patients with brainstem encephalitis should be evaluated emergently and aggressively. The differential diagnosis and approach to brainstem encephalitis is challenging and requires familiarity with clinical, laboratory, and radiologic features of a myriad of infectious, immune-mediated, and malignant etiologies. Empiric antimicrobial therapy should be directed against the most likely infectious etiologies, including listeria (ceftriaxone, vancomycin, and ampicillin) and herpes simplex encephalitis (acyclovir), with de-escalation once diagnostic testing returns negative. Decisions regarding empiric antifungal or antimycobacterial therapy should be individualized, and taking into account epidemiologic risk factors, clinical findings, and supporting laboratory studies. Contrasted brain MRI is important in the evaluation, as are serum and CSF investigations. Body PET or CT imaging may identify extraneuronal sites of involvement for biopsy, which may be necessary to establish the diagnosis.

AUTHOR CONTRIBUTIONS

Michael J. Bradshaw, MD: study design, clinical review, imaging review, manuscript preparation, editing. Siddharama Pawate, MD: manuscript editing and critical review. Karen C. Bloch, MD, MPH: manuscript editing and critical review. Paul Moorts, MD: manuscript editing and critical review. Nishitha M. Reddy, MD: manuscript editing and critical review.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Jubelt B, Mihai C, Li TM, Veerapaneni P. Rhombencephalitis/brainstem encephalitis. *Curr Neurol Neurosci Rep* 2011; 11:543–552.
2. Moragas M, Martinez-Yelamos S, Majos C, Fernandez-Viladrich P, Rubio F, Arbizu T. Rhombencephalitis: a series of 97 patients. *Medicine* 2011;90:256–261.
3. Pittock SJ, Debruyne J, Krecke KN, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain* 2010;133: 2626–2634.
4. Carlson ML, White JR Jr, Espahbodi M, et al. Cranial base manifestations of neurosarcoidosis: a review of 305 patients. *Otol Neurotol* 2015;36:156–166.
5. Guzman-De-Villoria JA, Ferreira-Arguelles C, Fernandez-Garcia P. Differential diagnosis of T2 hyperintense brainstem lesions: part 2: diffuse lesions. *Semin Ultrasound CT MR* 2010;31:260–274.
6. Saiz A, Bruna J, Stourac P, et al. Anti-Hu-associated brainstem encephalitis. *J Neurol Neurosurg Psychiatry* 2009; 80:404–407.
7. Campochiaro C, Tomelleri A, Cavalli G, Berti A, Dagna L. Erdheim-Chester disease. *Eur J Intern Med* 2015;26:223–229.
8. Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. *Blood* 2012;120:2700–2703.
9. Haroche J, Cohen-Aubart F, Emile JF, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. *Blood* 2013;121:1495–1500.
10. Haroche J, Cohen-Aubart F, Emile JF, et al. Reproducible and sustained efficacy of targeted therapy with vemurafenib in patients with BRAF(V600E)-mutated Erdheim-Chester disease. *J Clin Oncol* 2015;33:411–418.

Neurology®

Clinical Reasoning: A 52-year-old man with diplopia and ataxia

Michael J. Bradshaw, Siddharama Pawate, Karen C. Bloch, et al.

Neurology 2016;87:e140-e143

DOI 10.1212/WNL.0000000000003150

This information is current as of September 26, 2016

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/87/13/e140.full
References	This article cites 10 articles, 4 of which you can access for free at: http://n.neurology.org/content/87/13/e140.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology All Immunology http://n.neurology.org/cgi/collection/all_immunology Encephalitis http://n.neurology.org/cgi/collection/encephalitis MRI http://n.neurology.org/cgi/collection/mri
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.