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Authors

Abraham, Peter
Longardner, Katie
Chen, Patrick
et al.

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Case 279: Central-Variant Posterior Reversible Encephalopathy Syndrome

Peter Abraham, MD, MAS • Katie Longardner, MD • Patrick Chen, MD • Branko Huisa, MD • Jason Handwerker, MD

From the School of Medicine (P.A.) and Departments of Neurosciences (K.L., P.C., B.H.) and Radiology (J.H.), University of California San Diego Medical Center, 200 West Arbor Dr, San Diego, CA 92103. Received June 30, 2018; revision requested August 9; revision received October 31; accepted November 5. **Address correspondence to** J.H. (e-mail: *jhandwerker@health.ucsd.edu*).

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Conflicts of interest are listed at the end of this article.

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History A 25-year-old woman with recently diagnosed systemic lupus erythematosus and class IV lupus nephritis confirmed with biopsy and treated with mycophenolate mofetil presented with a 2-day history of progressively worsening edema of her face and lower extremities. She had no antecedent infection or vaccination. She was admitted to the hospital and treated with methylprednisolone, furosemide, and C1 esterase inhibitor. On hospital day 2, she experienced a witnessed generalized tonic-clonic seizure. At that time, she became hypoxic and was intubated for airway protection. Her laboratory study results preceding the seizure were remarkable for hyponatremia, with a blood sodium level of 122 mEq/L (122 mmol/L) (normal range, 135–145 mEq/L [134–145 mmol/L]), which was corrected to 137 mEq/L (137 mmol/L) over 48 hours. Same-day cerebrospinal fluid analysis was unremarkable, and unenhanced head CT findings (not shown) were normal, with no evidence of intracranial hemorrhage or edema.

Her subsequent hospital course was complicated by renal failure requiring continuous renal replacement therapy, hypertension (systolic blood pressure ranging from 140 to 190 mm Hg), anemia requiring blood transfusions, thrombocytopenia, and pneumonia. She remained intubated with a limited neurologic examination due to sedative medications until hospital day 10. After extubation, she was noted to have a right gaze preference. She was able to speak in short phrases and follow simple commands. Neurologic examination was notable for drowsiness, right gaze deviation, direction-changing torsional nystagmus, horizontal ophthalmoplegia, and generalized symmetric weakness without upper motor neuron signs. The following day (hospital day 11), unenhanced MRI of the brain was performed along with MR angiography of the brain. Biopsy of the temporal artery was normal, without evidence of inflammation.

Part one of this case appeared 4 months previously and may contain larger images.

Imaging Findings

Axial diffusion-weighted images (Fig 1a, 1d) showed symmetric areas of bilateral paramedian thalamic and pontine hyperintensity that had corresponding hypointensity on the apparent diffusion coefficient map (not shown); this was compatible with diffusion restriction and was thought to represent cytotoxic edema. Axial T2 fluid-attenuated inversion recovery images (Fig 1b, 1e) showed more extensive confluent T2 hyperintensity with swelling involving the bilateral thalami, brainstem, and middle cerebellar peduncles, compatible with vasogenic edema. Within the areas of diffusion restriction, the susceptibility-weighted images (Fig 1c, 1f) showed punctate hypointensity within the areas of restricted diffusion in the bilateral thalami and pons, compatible with microhemorrhages. Meanwhile, MR angiography of the circle of Willis (Fig 2) showed no stenosis of the basilar artery. There were subtle short segment stenoses involving bilateral external carotid arteries, the right V4 segment, and the right P2 segment. This was confirmed with diagnostic catheter angiography (not shown). However, biopsy of an affected narrowed temporal artery revealed no evidence of vasculitis. At 1-month follow-up in the setting of improved symptoms and treatment of hypertension, axial diffusion-weighted images (Fig 3a, 3d) showed resolution of the prior diffusion restriction involving the paramedian thalami and pons. In addition, axial T2 fluid-attenuated inversion recovery imaging (Fig 3b, 3e) showed resolution of the prior extensive confluent T2 hyperintensity and associated swelling involving the bilateral thalami, pons, and middle cerebellar peduncles. Meanwhile, axial susceptibility-weighted imaging (Fig 3c, 3f) showed persistent punctate microhemorrhages in the bilateral thalami and pons.

Discussion

This case presented a diagnostic challenge. Given the patient's array of clinical symptoms, aberrancies in serum chemistries, and complicated medical history, a thorough diagnostic work-up was performed, including repeat cerebrospinal fluid analyses and serum diagnostic studies. As these tests were largely unrevealing, brain MRI was instrumental in first indicating the diagnosis of central-variant posterior reversible encephalopathy syndrome (PRES). The key features on MRI scans that led to this diagnosis were the extensive bilateral symmetric T2 hyperintensities with punctate areas of hemorrhage. With conservative medical management, this patient's neurologic symptoms nearly resolved within 2 weeks. We subsequently confirmed the diagnosis of PRES when the vasogenic edema rapidly improved, and edema completely resolved by 1 month (Fig 3).

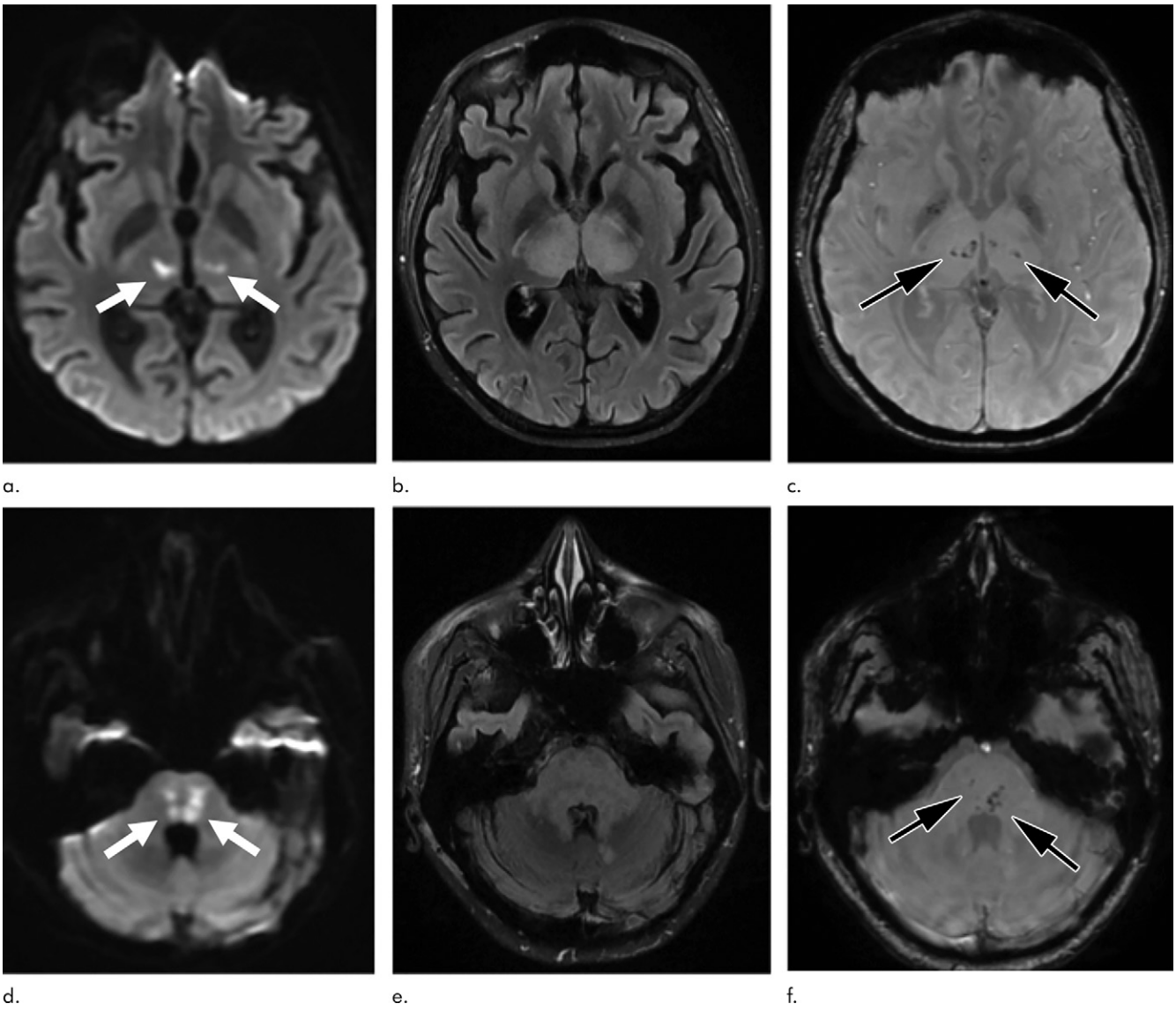

Figure 1: Images obtained at the level of the **(a, b, c)** thalami and **(d, e, f)** pons. **(a, d)** Axial diffusion-weighted MRI scans (repetition time msec/echo time msec, 6887/76; *b* value = 1000 sec/mm^2) show symmetric areas of bilateral paramedian thalamic and pontine hyperintensity (arrows) that had corresponding restriction on the apparent diffusion coefficient map (not shown). **(b, e)** Axial T2-weighted fluid-attenuated inversion recovery MRI scans (repetition time msec/echo time msec/inversion time msec, 11 000/99/2650) show confluent T2 hyperintensity throughout the bilateral thalami, pons, and middle cerebellar peduncles. **(c, f)** Axial susceptibility-weighted MRI scans (51/24) show punctate hypointensity (arrows) within the areas of restricted diffusion in the bilateral thalami and pons.

PRES was first described in 1996, with the very first patient in that original case series also presenting with systemic lupus erythematosus (SLE) and hypertensive encephalopathy (1). Since its first description, PRES has been increasingly recognized in patients with SLE. Case series have shown that among patients with SLE, PRES is most common in young women who have concurrent hypertension and renal disease, as well as those treated with steroid-sparing cytotoxic immunosuppressive medications (2,3). Typical clinical symptoms of PRES include headache, encephalopathy, vomiting, visual disturbances, and seizure. The pathophysiology of PRES is thought to be related to rapid fluctuations in blood pressure leading to cerebrovascular autoregulatory failure and endothelial dysfunction. One proposed mechanism of PRES in patients with SLE is activation of T cells resulting in production of inflammatory cytokines, which may contribute to cerebral endothelial dysfunction. Inflammatory cytokines may also trigger intracranial vessels to produce nitrous oxide, a vasodilator that can lead to breakdown of the blood-brain barrier, further predisposing patients to cerebral vasogenic edema (2,4). Anticardiolipin antibodies may also play a role in endothelial activation (5). Cytotoxic medications, such as tacrolimus, vascular endothelial growth factor inhibitors, and cyclosporine, which are often used to treat SLE and other inflammatory diseases, as well as malignancy, may also induce PRES (3). The exact pathophysiology is uncertain, but in cases associated with tacrolimus and vascular endothelial growth factor inhibitors, it is likely related to induction of systemic hypertension (6,7). Cyclosporine has a direct cytotoxic effect on vascular endothelium and generates release of vasoconstrictive substances, which may lead to cerebral hypertension (1). PRES is frequently

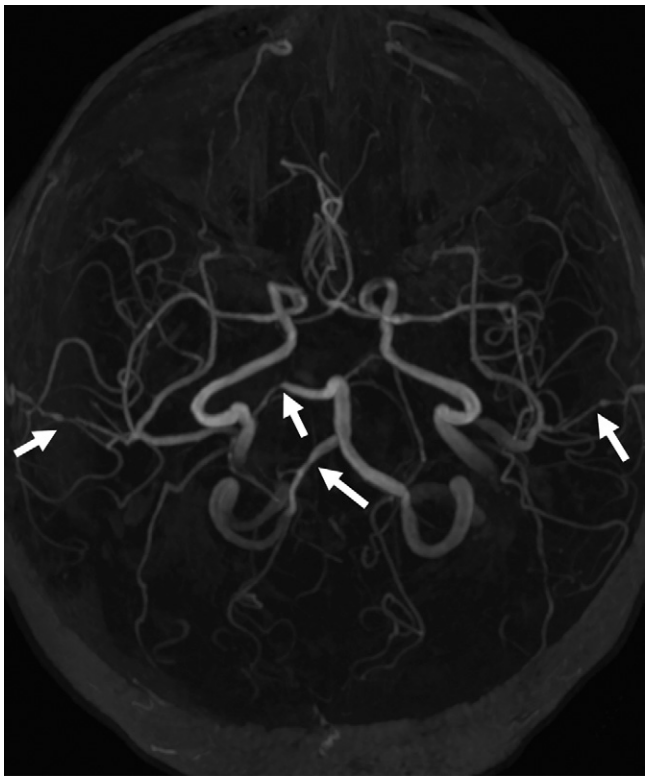

Figure 2: Three-dimensional time-of-flight maximum intensity projection MR angiogram of the circle of Willis shows no stenosis of basilar artery. There is subtle short-segment stenosis involving the bilateral external carotid arteries, right V4 segment, and right P2 segment (arrows).

reversible with supportive care and withdrawal of the offending agent (if implicated), although cytotoxic edema and hemorrhage can complicate recovery of symptoms (8).

Classic imaging findings of PRES include T2 hyperintense vasogenic edema that is most pronounced in the occipital and parietal lobes, as well as the watershed zones of the frontal lobes, temporal lobes, and cerebellum (9). The cortical and subcortical regions are also often affected. There can be associated areas of cytotoxic edema on diffusion-weighted images and hemorrhage on susceptibility-weighted images, as in this case. There can also be associated contrast enhancement, although this patient did not receive a gadolinium-based contrast agent because of her renal insufficiency. MRI findings are usually reversible, but areas of cytotoxic edema and hemorrhages may result in persistent abnormalities at follow-up imaging. Vascular abnormalities in patients with PRES can be seen on MR angiograms and catheter angiograms, typically with reversible focal or diffuse vessel irregularity or pruning of distal intracranial arteries (10).

Atypical regions of signal abnormality due to PRES have been described, including brainstem variants that were initially termed *hypertensive brainstem encephalopathy* (11,12). Cases involving the brainstem or basal ganglia but lacking cortical or subcortical cerebral edema, as seen in this patient, were described by McKinney et al, who advocated for the more inclusive term *central-variant PRES* (13). Central-variant PRES was first reported in the setting of SLE in 2010 (14). There are no known risk factors that predispose patients to this atypical variant of PRES.

The differential diagnosis for this case also included lupus-associated central nervous system vasculitis, osmotic myelinolysis syndrome, inflammatory demyelination, reversible cerebral vasoconstriction syndrome, rhomboencephalitis, and infiltrative glioma.

Manifestations of lupus-associated central nervous system vasculitis include strokes due to thrombotic events, cognitive dysfunction, and psychosis (15). While SLE is commonly associated with cutaneous or visceral vasculitis, cerebral vasculitis is rare. However, cerebral vasculopathy without true vasculitis has been described at autopsy in up to 65% of patients with lupus; the pathogenic mechanism is thought to be related to antiphospholipid antibodies (15,16). Central nervous system vasculitis was ruled out in this patient based on normal cerebrospinal fluid, normal temporal artery biopsy without inflammation, and rapid clinical improvement of the neurologic symptoms. We suspect the intra- and extracranial vessel vasoconstriction in this patient was likely related to an underlying vasculopathy associated with lupus and superimposed PRES, although she did not undergo repeat vascular imaging.

Osmotic myelinolysis was also considered as a possible cause given this patient's hyponatremia, which required sodium correction. The rate of this patient's sodium correction was far below the 12 mmol/L/day rate at which this syndrome typically occurs (17). Classic MRI findings in osmotic myelinolysis include symmetric trident-shaped hyperintensity on T2-weighted sequences in the central pons, typically sparing the lateral pons and corticospinal tracts. Extrapontine involvement may also affect portions of the basal ganglia and central thalami. The patient's clinical presentation was relatively mild compared with the severe deficits that would be expected with diffuse white matter lesions seen on MRI. Additionally, follow-up imaging in patients with osmotic myelinolysis would be expected to demonstrate malacia in the central pons rather than complete resolution of the T2 signal abnormality (18).

Inflammatory demyelination is rarely associated with SLE and may be related to SLE as well as concurrent autoimmune processes affecting the central nervous system, such as multiple sclerosis or neuromyelitis optica spectrum disorder (19). While demyelination may also show T2 hyperintensity and diffusion-restricting lesions, spinal fluid in demyelinating disorders would be expected to show mild pleocytosis with an elevated protein level. The normal spinal fluid in this case argued against this diagnosis. Furthermore, this patient's symptoms and MRI changes developed while she was being treated with immunosuppressive medications and steroids, which would suppress inflammation. Diffuse demyelination of the brainstem and both basal ganglia would have also caused more profound neurologic symptoms, such as cranial neuropathies, paraplegia, or coma, which were absent in this case.

Acute disseminated encephalomyelitis is another inflammatory demyelinating condition that can manifest as multifocal areas of edema involving the brainstem and thalamus, but it would likely demonstrate more diffuse or peripheral restricted diffusion involving the affected areas (19). In addition, this patient did not have any antecedent viral illness or vaccination, which usually precede acute disseminated encephalomyelitis.

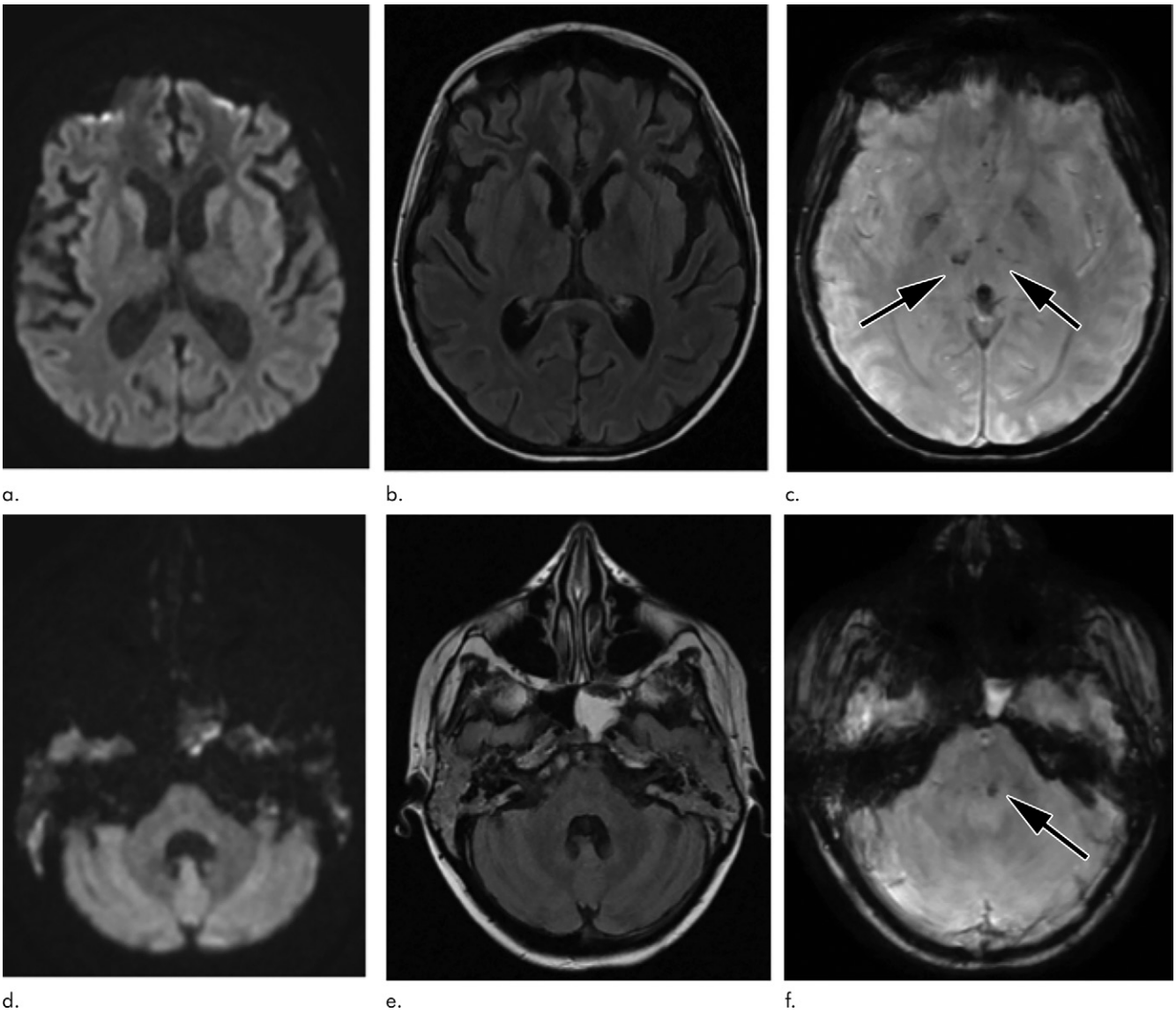

Figure 3: Images obtained 1 month after presentation at the level of the **(a, b, c)** thalami and **(d, e, f)** pons. **(a, d)** Axial diffusion-weighted MRI scans (repetition time msec/echo time msec, 9000/97; ***b*** value = 1000 sec/mm^2) show resolution of the prior diffusion restriction involving the thalami and pons. **(b, e)** Axial T2 fluid-attenuated inversion recovery MRI scans (repetition time msec/echo time msec/inversion time msec, 9605/127/2500) show resolution of the prior confluent T2 hyperintensity throughout the bilateral thalami, pons, and middle cerebellar peduncles. **(c, f)** Axial susceptibility-weighted MRI scans (74/46) show persistent punctate hypointensity (arrows) in the bilateral thalami and pons.

Reversible cerebral vasoconstriction syndrome is a clinical and radiologic syndrome characterized by a severe acute-onset "thunderclap" headache in patients with clinical risk factors, such as eclampsia, use of sympathomimetic medications, and trauma, all of which were absent in this patient. Vascular imaging typically shows widespread segmental narrowing of cerebral arteries. MRI of the brain most commonly shows convexity subarachnoid hemorrhage with associated infarct, followed by vasogenic edema and parenchymal hemorrhage; these findings were absent in this case. MR angiograms may also show multiple reversible bilateral areas of intracranial distal arterial narrowing but rarely affect extracranial vessels. Patients with reversible cerebral vasoconstriction syndrome may also demonstrate transient brain edema on MRI; however, patients with reversible cerebral vasoconstriction syndrome do not usually present with seizures or severe cerebral or brainstem edema, as were seen in this patient. Endothelial dysregulation and reversible arterial constriction may play a role in both reversible cerebral vasoconstriction syndrome and PRES (20).

Rhombencephalitis due to infection or postinfectious inflammation (eg, Bickerstaff brainstem encephalitis) was also considered. Clinically, patients present with cranial neuropathies, ataxia, or an altered level of consciousness. Cerebrospinal fluid commonly shows a pleocytosis and elevated protein level. In the case of Bickerstaff brainstem encephalitis, it may show albuminocytologic dissociation. While MRI in patients with rhomboencephalitis may also show extensive edema in the brainstem and thalami, this diagnosis was excluded given the lack of severe brainstem dysfunction on neurologic examination and normal cerebrospinal fluid studies (21,22).

Infiltrative brainstem glioma may also manifest with expansile edematous signal abnormality at MRI. However, the subacute

clinical presentation combined with the reversible symmetric edema and preserved architecture at imaging in the setting of conservative management enabled us to exclude the diagnosis of glioma.

In conclusion, this patient's clinical and radiologic findings, combined with her rapid normalization, were consistent with central-variant posterior reversible encephalopathy syndrome (PRES). Among her array of clinical comorbidities, hypertension, renal disease, and lupus represented risk factors for the development of PRES, albeit with an atypical imaging distribution. Correlation of the clinical and imaging findings was essential for establishing the diagnosis and avoiding additional invasive testing and potentially harmful therapy. While the posterior cerebral distribution of PRES has been well recognized since its first description, radiologists should be aware of the central variant of this syndrome.

Disclosures of Conflicts of Interest: P.A. disclosed no relevant relationships. **K.L.** disclosed no relevant relationships. **P.C.** disclosed no relevant relationships. **B.H.** disclosed no relevant relationships. **J.H.** disclosed no relevant relationships.

References

1. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334(8):494–500.
2. Barber CE, Leclerc R, Gladman DD, Urowitz MB, Fortin PR. Posterior reversible encephalopathy syndrome: an emerging disease manifestation in systemic lupus erythematosus. Semin Arthritis Rheum 2011;41(3):353–363.
3. Zhang L, Xu J. Posterior reversible encephalopathy syndrome (PRES) attributed to mycophenolate mofetil during the management of SLE: a case report and review. Am J Clin Exp Immunol 2018;7(1):1–7.
4. Baizabal-Carvallo JF, Barragán-Campos HM, Padilla-Aranda HJ, et al. Posterior reversible encephalopathy syndrome as a complication of acute lupus activity. Clin Neurol Neurosurg 2009;111(4):359–363.
5. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol 2015;14(9):914–925.
6. Seet RC, Rabinstein AA. Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. QJM 2012;105(1):69–75.
7. Hammerstrom AE, Howell J, Gulbis A, Rondon G, Champlin RE, Popat U. Tacrolimus-associated posterior reversible encephalopathy syndrome in hematopoietic allogeneic stem cell transplantation. Am J Hematol 2013;88(4):301–305.
8. Chen HA, Lin YJ, Chen PC, Chen TY, Lin KC, Cheng HH. Systemic lupus erythematosus complicated with posterior reversible encephalopathy syndrome and intracranial vasculopathy. Int J Rheum Dis 2010;13(4):e79–e82.
9. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. AJNR Am J Neuroradiol 2008;29(6):1036–1042.
10. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol 2008;29(3):447–455.
11. McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol 2007;189(4):904–912.
12. Chang GY, Keane JR. Hypertensive brainstem encephalopathy: three cases presenting with severe brainstem edema. Neurology 1999;53(3):652–654.
13. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical cerebral edema. AJR Am J Roentgenol 2013;201(3):631–638.
14. Bag AK, Curé JK, Sullivan JC, Roberson GH. Central variant of posterior reversible encephalopathy syndrome in systemic lupus erythematosus: new associations? Lupus 2010;19(2):225–226.
15. Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. Nat Rev Rheumatol 2010;6(6):358–367.
16. Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955--1977. Semin Arthritis Rheum 1979;8(3):212–221.
17. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 1986;314(24):1535–1542.
18. Balasubramanya KS, Kovoor JM, Jayakumar PN, et al. Diffusion-weighted imaging and proton MR spectroscopy in the characterization of acute disseminated encephalomyelitis. Neuroradiology 2007;49(2):177–183.
19. Magro Checa C, Cohen D, Bollen EL, van Buchem MA, Huizinga TW, Steup-Beekman GM. Demyelinating disease in SLE: is it multiple sclerosis or lupus? Best Pract Res Clin Rheumatol 2013;27(3):405–424.
20. Miller TR, Shivashankar R, Mossa-Basha M, Gandhi D. Reversible Cerebral Vasoconstriction Syndrome, Part 1: Epidemiology, Pathogenesis, and Clinical Course. AJNR Am J Neuroradiol 2015;36(8):1392–1399.
21. Odaka M, Yuki N, Yamada M, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. Brain 2003;126(Pt 10):2279–2290.
22. Jubelt B, Mihai C, Li TM, Veerapaneni P. Rhombencephalitis / brainstem encephalitis. Curr Neurol Neurosci Rep 2011;11(6):543–552.

Congratulations to the 29 individuals and three resident groups that submitted the most likely diagnosis (central-variant posterior reversible encephalopathy syndrome) for Diagnosis Please, Case 279. The names and locations of the individuals and resident groups, as submitted, are as follows:

Individual responses

Eric L. Bressler, MD, *Minnetonka, MN*
Marc G. De Baets, MD, *Collina D'Oro, Switzerland*
Daniel Ginat, MD, *Chicago, IL*
Taku Gomi, *Tokyo, Japan*
Osamu Hasegawa, MD, *Koriyama, Japan*
D. C. Heasley, Jr, MD, *Dallas, TX*
Christoph Hefel, *Feldkirch, Austria*
Takashi Ikeuchi, MD, *Moriyama, Japan*
Akitoshi Inoue, MD, PhD, *Rochester, MN*
Koki Kato, MD, *Utsunomiya, Japan*
Richard A. Levy, MD, *Saugerties, NY*
Takaki Murata, MD, *Sendai, Japan*
Tammam N. Nehme, MD, *Hinsdale, IL*
Ananya Panda, MD, MBBS, *Rochester, MN*
Ioannis E. Papachristos, MD, *Agrinio, Greece*
Diogo L. Pinheiro, MD, *Curitiba, Brazil*
John Raseman, MD, *Wauwatosa, WI*
Yusuke Sakurai, *Nagoya, Japan*
Parviz Samadov, MD, *Baku, Azerbaijan*
Taro Shimono, MD, PhD, *Osaka, Japan*
Taku Tajima, MD, PhD, *Minato-ku, Japan*
Taro Takeda, MD, *Hashima-gun, Japan*
Stamos J. Trakadas, MD, *Athens, Greece*
Umit Tuzun, MD, *Istanbul, Turkey*
Meric Tuzun, MD, *Ankara, Turkey*
Harsha Vardhan, MD, *Chennai, India*
Christopher P. Vittore, MD, *Belvidere, IL*
Takayuki Yamamoto, MD, *Bordeaux, France*
Ahmed Zidan, MD, *Barcelona, Spain*

Resident group responses

Hospital De Santa Maria Radiology Residents, *Lisbon, Portugal*
Mater Dei Hospital Radiology Residents, *Msida, Malta*
Mie University Hospital Radiology Residents, *Tsu, Japan*