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NEUROCRITICAL CARE SOCIETY

LESSONS LEARNED

Hickam's Dictum: A Case of Intracerebral Hemorrhage with Multiple Contributing Risk Factors

Daniel S. Harrison*

The Patient

A 65-year-old previously healthy man presented to the emergency department, after waking up, with new right frontal headache, blurry vision, and perception of flashing lights. Preceding these symptoms, he had 3 weeks of watery diarrhea, sore throat, ankle swelling, and generalized fatigue. After arriving in the emergency department, he was noted to have a decreasing level of arousal, with intermittent periods of agitation, and was intubated.

Initial Course

On arrival to the emergency department, he was afebrile with a heart rate of 82 beats per minute, blood pressure of 203/100 mm Hg, and oxygen saturation of 94% on 4-L nasal cannula. The general examination was notable for diminished breath sounds at the bases, trace bilateral lower extremity edema, and bilateral lower extremity petechial rash. The neurologic examination was notable for inattention, left homonymous hemianopia, and extinction to double simultaneous stimulation in the left arm. Laboratory work up was notable for creatinine 1.7 mg/dL, blood urea nitrogen 97 mg/dL, hemoglobin 8.3 g/dL, mean corpuscular volume 83 fL, platelets 38,000 /uL, prothrombin time 11.6 s, partial thromboplastin time 23.9 s, fibrinogen 211 mg/dL, reticulocyte count 1.3%, haptoglobin < 10 g/L, lactate dehydrogenase 607 IU/L, and d-dimer 2703 ng/mL fibrinogen equivalent units. Chest X-ray revealed pulmonary edema and bilateral pleural effusions. Liver function tests, toxicology screen, and blood cultures were normal.

Computed tomography (CT) head revealed $5.4 \times 3.4 \times 4.5$ cm right occipitoparietal intracerebral hemorrhage with surrounding hypodensity and additional focus of hypodensity in the right cerebellar hemisphere (Fig. 1). CT angiogram with arterial and venous phase imaging of the head was normal. Given high suspicion for thrombotic thrombocytopenic purpura (TTP), the patient was started on steroids, a dialysis catheter was placed, and plasmapheresis was initiated while awaiting results of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity testing.

What Features of the Patient's Presentation are Suggestive of TTP?

TTP is a thrombotic microangiopathy (TMA) syndrome. Other TMA syndromes in adults include hemolytic uremic syndrome, complement-mediated TMA, and drug-induced TMA. In TTP, most patients present with nonspecific symptoms, such as generalized weakness, fatigue, nausea, and diarrhea. About one third of patients have no neurologic symptoms at presentation, one third have nonfocal neurologic symptoms, such as headache or confusion, and one third have a focal neurologic deficit. Severely deficient ADAMTS13 activity (less than 10–15%) confirms the diagnosis of TTP, however, the results for this assay typically take days to come back.

Patients with suspected TTP who may benefit from early initiation of plasma exchange while ADAMTS13 testing is pending can be identified with the platelet count, hemolysis, active cancer, history of solid-organ or stem-cell transplant, mean corpuscular volume < 90 fL, international normalized ratio < 1.5, and creatinine < 2.0 mg/dL (PLASMIC) score, which stratifies

*Correspondence: dsharri3@gmail.com
Department of Neurology, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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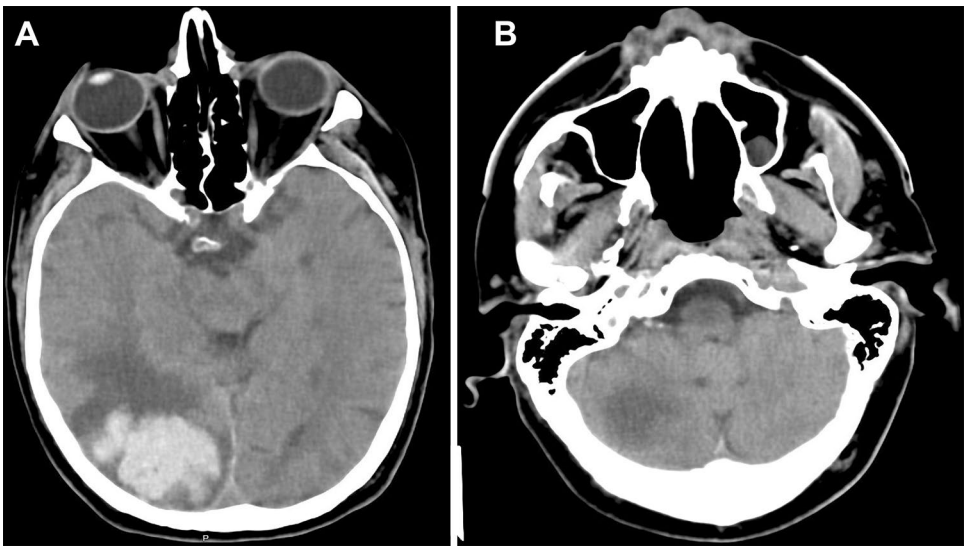

Fig. 1 Noncontrast head CT revealed right occipital intraparenchymal hemorrhage with surrounding hypodensity (**a**) and right cerebellar hypodensity (**b**). CT, computed tomography

patients into low-risk, medium-risk, and high-risk groups (0%, 6%, and 72% risk of severe ADAMTS13 deficiency, respectively) [1]. Our patient had a PLASMIC score of 6, corresponding to the high-risk group.

What is the Differential Diagnosis for Lobar Hemorrhage in this Patient?

Cerebral amyloid angiopathy should always be considered in patients aged 50 and older with spontaneous lobar intracerebral hemorrhage. Magnetic resonance imaging (MRI) would be helpful to evaluate for absence of deep hemorrhagic lesions and cerebral microbleeds, superficial siderosis, severe perivascular spaces in the centrum semiovale, or white matter hyperintensities in a multispot pattern [2]. Hemorrhagic conversion of ischemic stroke is another possibility, perhaps more likely in this patient with suspected diagnosis of TTP (which would increase his risk of stroke) and concomitant cerebellar hypodensity (which could represent an additional infarct). The patient's hemorrhage and cerebellar hypodensity could alternatively be explained by multifocal brain metastases with hemorrhage and surrounding edema (occult malignancy could also cause microangiopathic hemolytic anemia and thrombocytopenia mimicking TTP). Hemorrhagic posterior reversible encephalopathy syndrome (PRES) should also be considered given hypertension, renal failure, and suspected TMA syndrome. Vascular malformations, such as arteriovenous malformations, mycotic aneurysm rupture, cerebral venous sinus thrombosis, primary angiitis of the central nervous system, and reversible cerebral vasoconstriction syndrome are less likely but not fully excluded in this patient with normal CT angiogram of the head.

Case Continued

ADAMTS13 activity was normal (85%), and plasmapheresis was discontinued. Additional records obtained from the patient's primary care physician revealed longstanding history of dry eyes and dry mouth, which the patient had been treating with over-the-counter eye drops. Additional laboratory work up was notable for antinuclear antibody titer 1:320 (diffuse pattern), anti-Ro antibody > 1374 chemiluminescent units, C3 50 mg/dL, and C4 undetectable. In addition to pleural effusions and pulmonary edema, CT chest revealed multiple thin-walled pulmonary cysts. There was no evidence of superficial siderosis or microbleeds on MRI brain. However, there were multiple areas of T2 hyperintensity in subcortical white matter not appreciated on CT head, and the previously noted right cerebellar lesion demonstrated T2 hyperintense stripes in the subcortical white matter (Fig. 2). Taken together, the clinical and imaging findings were thought to be most consistent with hemorrhagic PRES.

Other than Hypertension, What Risk Factors did this Patient have for PRES?

Hypertension is present in most patients with PRES. Therapy with tacrolimus, cyclosporine, and other immunosuppressant agents is another frequently invoked association [3]. Other risk factors for PRES

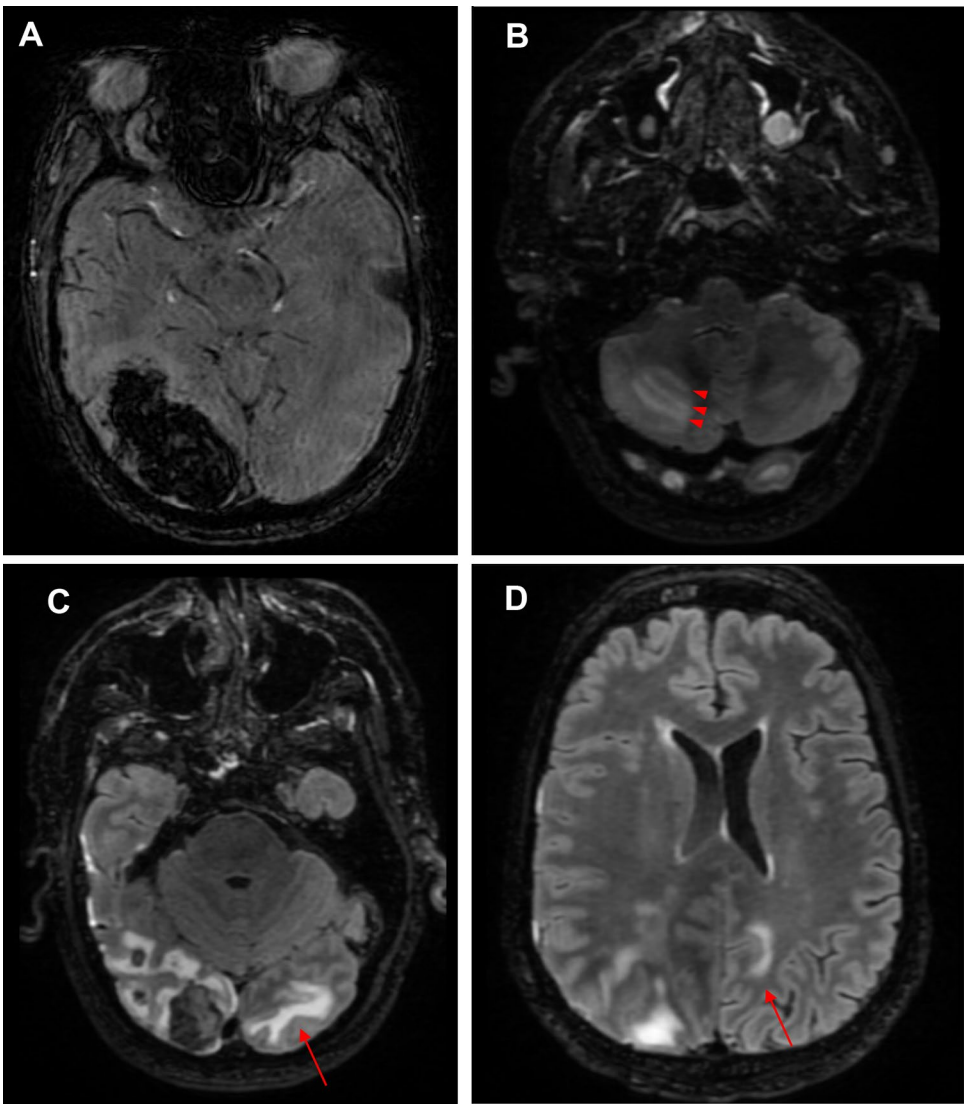

Fig. 2 MRI brain redemonstrated intraparenchymal hemorrhage (susceptibility weighted imaging **a**) without other stigmata of cerebral amyloid angiopathy. **b** The right cerebellar lesion consisted of T2 hyperintense bands (arrowheads) in the subcortical white matter alternating with relatively hypointense cerebellar cortex in a "white stripes" pattern. **c**, **d**, T2 hyperintensities were appreciated adjacent to the hemorrhage and in multiple areas of subcortical white matter (arrows). MRI, magnetic resonance imaging

include TMA syndromes (including TTP and hemolytic uremic syndrome), solid-organ or stem-cell transplant, sepsis, hyperammonemia, sickle cell disease, renal failure, and systemic lupus erythematosus. PRES has also been reported to affect patients with other connective tissue disorders, including Sjogren's syndrome [4, 5]. In addition to hypertension, TMA, and renal failure, this patient had many features of Sjogren's syndrome, including sicca symptoms, positive antinuclear antibody and anti-Ro antibodies, hypocomplementemia, and cystic lung disease [6].

What Accounts for the "White Stripes" Pattern of T2 Abnormality in the Cerebellum?

Posterior reversible encephalopathy syndrome may affect both white and gray matter structures but has a predilection for subcortical white matter. Cerebellar involvement in PRES is common [7]. On this patient's MRI, bands of abnormal, T2 hyperintense subcortical white matter alternate with unaffected, relatively hypointense gray matter, giving an appearance of white stripes. This imaging finding is likely not sensitive enough to rule out PRES when absent but may be specific for diseases preferentially affecting the cerebellar subcortical white matter.

The "zebra sign," which may be present on CT head of patients with remote cerebellar hemorrhage, visually mimics this white stripes pattern but is pathologically distinct [8].

Follow-Up

Renal biopsy was pursued and revealed immune complex-mediated focal crescentic and membranoproliferative glomerulonephritis with rare glomerular capillaries containing "pseudothrombi," strongly suggestive of a cryoglobulinemia-associated glomerulonephritis as can be seen in Sjogren's syndrome. Notably, cryoglobulinemia is yet another risk factor for PRES. The patient had a prolonged intensive care unit and hospital course, complicated by seizures, delirium, and ileus. He was, however, successfully extubated, started on rituximab (for membranoproliferative glomerulonephritis), and later discharged to acute rehabilitation on levetiracetam, prednisone, and amlodipine. Six months after presentation, he had a left homonymous inferior quadrantanopia with impaired tandem gait. Neurologic examination was otherwise normal, he was able to look after his own affairs, and he resumed driving.

Lessons Learned

1. The PLASMIC score can be used to stratify risk of severe ADAMTS13 deficiency and acutely identify patients who may benefit from plasma exchange while awaiting confirmatory testing.
2. The differential diagnosis of lobar hemorrhage in older patients includes cerebral amyloid angiopathy, hemorrhagic conversion of ischemic stroke, PRES, arteriovenous malformations, mycotic aneurysm rupture, cerebral venous sinus thrombosis, reversible cerebral vasoconstriction syndrome, primary angiitis of the central nervous system, and intratumoral hemorrhage.
3. Hypertension, immunosuppression, TMA syndromes, transplant history, sepsis, hyperammonemia, sickle cell disease, renal failure, and connective tissue disorders are independent risk factors for PRES. Identification of one of these features in a patient presenting with PRES should not preclude evaluation for concomitant contributing pathologies.
4. The "white stripes" sign (T2 hyperintense bands in the subcortical white matter alternating with relatively hypointense cerebellar cortex) may be present in diseases preferentially affecting the cerebellar subcortical white matter, including PRES.

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