Clinical Reasoning: A young man with acute encephalopathy, loss of vision, and upper motor neuron signs

SECTION 1
A 22-year-old man with no significant medical history presented at the hospital emergency department with a 1-day history of confusion and gradual loss of vision. Seven days before the presentation, he started complaining of holocranial headache, which was initially mild but eventually progressed to become severe in intensity, associated with nausea and vomiting, and was not responsive to paracetamol. There were no associated seizures.

His blood pressure upon arrival was 210/110 mm Hg with normal oxygen saturation and pulse rate and no fever. Neurologic examination revealed a drowsy and confused patient, disoriented to place and time. He answered simple questions and opened his eyes to verbal stimuli. Funduscopy revealed retinal exudates with no papilledema. His visual acuity was limited to light perception in both eyes. Pupillary reflexes were preserved. He moved his 4 limbs spontaneously. Deep tendon reflexes in the upper limbs were normal but exaggerated in the lower limbs with bilateral upgoing plantar responses. The remainder of the neurologic examination was normal.

Questions for consideration:
1. Based on the clinical presentation, what is your preliminary differential diagnosis?
2. What is the next step in the management of this patient?
SECTION 2
In view of the patient's clinical presentation (acute confusional state, gradual loss of vision, headache associated with nausea and vomiting), an acute encephalopathic process should be considered. The acute-onset visual loss with preserved pupillary reflexes provided a clue that neuroradiologically the lesion was located in the occipital lobe (bilateral occipital or parieto-occipital lesions). Several neurologic conditions should be considered in the etiologic differential diagnosis of acute encephalopathy with headache and visual loss including intracranial hemorrhage, acute ischemic stroke (e.g., brainstem stroke, in particular top of the basilar syndrome, thalamic stroke), cerebral venous thrombosis, multiple cerebral emboli, central nervous system tumors, encephalitis (e.g., tuberculous and herpes encephalitis), or systemic conditions (e.g., renal failure, liver failure, malignant hypertension). In a patient with confusion, headache, and loss of vision associated with a very high blood pressure, the diagnosis of posterior reversible leukoencephalopathy syndrome (PRES) should be considered.

Laboratory testing revealed significant renal impairment (creatinine was 888 μmol/L [62–124 μmol/L] and urea 23.6 mmol/L [1.7–8.3 mmol/L]) with severe anemia (hemoglobin 6.5 g/dL [13–17 g/dL]). A peripheral blood smear showed hypochromic microcytic red cells with few schistocytes and normal platelets. ECG showed evidence of left ventricular hypertrophy suggestive of long-standing hypertension. Brain CT scan revealed mild diffuse cerebral edema and bilateral subtle hypodensities in the parieto-occipital cortical/subcortical region. As initial management, the blood pressure was controlled with IV labetolol and he was admitted to the intensive care unit for further observation. In view of the broad differential, the inconclusive brain CT findings, and the suspicion of PRES, MRI of the brain (figure, A) was done on day 4 after admission and confirmed the subtle lesions in both parieto-occipital areas with resolution of the brain edema.

In the presence of acute hypertension, PRES is considered a neurologic syndrome caused by failure of cerebral autoregulation.1 Hence, aggressive blood pressure reduction gradually improved the patient's condition, and on the second day of admission, he became fully oriented and his vision improved significantly to finger counting at 1 m. Renal replacement therapy via regular hemodialysis was commenced.

Questions for consideration:
1. How do you explain the presence of bilateral upper motor neuron signs in this patient?
2. What would be your next diagnostic investigations?

Figure
Brain and spinal cord MRI

Axial fluid-attenuated inversion recovery sequence of the brain (A) done after 4 days showing bilateral subtle parieto-occipital subcortical white matter hyperintensities (arrows). Note that the sulci are seen, suggestive of interval improvement of the brain edema. Sagittal T2-weighted image of the cervical spine (B) and thoracic spine (C) showing longitudinally extensive central cord hyperintensity extending from the medulla superiorly up to the distal cord just above the conus inferiorly (arrows). Axial T2 weighted MRI of the cervical spine (D) at C3 level demonstrates that the intramedullary spinal cord involvement is confined to central gray matter (arrow).
SECTION 3
The presence of symmetric hyperreflexia and bilateral upgoing plantar responses refers to corticospinal tract dysfunction at the level of the brain and/or spinal cord.2 Because of the presence of signal changes in cervicomedullary junction on the brain MRI, spinal cord MRI (figure, B–D) was performed, which revealed a longitudinally extensive central intramedullary T2 hyperintense signal starting from the medullary region all the way down to the lumbar spinal cord (no contrast was given because of renal failure). Subsequently, serologic and CSF analyses were done to rule out infectious and noninfectious inflammatory myelitis. A lumbar puncture revealed normal opening pressure and unremarkable routine CSF analysis. Immunoglobulin G index was within normal limits and oligoclonal bands were absent. CSF cytology was negative for the presence of malignant cells. CSF cultures for common bacterial pathogens, Mycobacterium tuberculosis, and fungi were negative. TB PCR and VDRL were negative. In addition, routine laboratory investigation including full blood count, C-reactive protein, erythrocyte sedimentation rate, hepatic biochemical markers, serum protein electrophoresis, vitamin B12, complement, and thyroid function tests were all normal. Autoimmune screening (antinuclear antibodies, antineutrophil cytoplasmic antibodies, antibodies against double-stranded DNA, anti-Sm antibody, Ro antigen, La antigen, and rheumatoid factor) was negative. Serologic examination for HIV and hepatitis B and C viruses was also negative.

The patient showed remarkable neurologic recovery over the next few days, but the exaggerated deep tendon reflexes in the lower limbs with bilaterally Babinski sign persisted on discharge (day 9). Unfortunately, the patient traveled back to his home country for further medical care and no further follow-up was possible.

DISCUSSION PRES—also referred to as reversible posterior cerebral edema syndrome, posterior leukoencephalopathy syndrome, hyperperfusion encephalopathy, or brain capillary leak syndrome—is a potentially reversible clinicoradiographical entity of heterogeneous etiologies, lumped together because of their similarity in neuroimaging properties. PRES is seen with a vast array of systemic processes or conditions, including hypertensive encephalopathy, the use of cytotoxic and immunosuppressant drugs in bone marrow or solid organ transplantation, systemic inflammatory response syndrome, uremic syndrome, autoimmune disorders, and eclampsia.1,3

Classically, PRES presents with fast evolving symptoms such as headache, seizures (including nonconvulsive status epilepticus), altered consciousness, and visual disturbance.1 Although not consistently a feature of PRES, acute hypertension has been reported in more than two-thirds of patients with PRES but may be absent in the presence of infection, systemic inflammatory response syndrome, or immunomodulation.3,5 If promptly recognized and treated, the clinical syndrome usually resolves within a week,3,6 with MRI changes resolving over days to weeks.3,7

Recently, 8 patients with PRES with spinal cord involvement (PRES-SCI) have been reported in the literature.2 The condition typically affected young patients presenting with severe acute hypertension, renal failure, and hypertensive retinopathy.2 Except for the absence of papilledema, our patient matched the profile of patients with PRES-SCI. Last but not least, and unlike the majority of patients with classic PRES, our patient did not report any seizure. In accordance with the observation of de Havenon et al.,2 seizures are not a consistent feature and were reported in less than 15% in PRES-SCI.

In hypertensive patients, impaired cerebral autoregulation leading to cerebral hyperperfusion and blood-brain barrier dysfunction resulting in vasogenic edema is the presumed mechanism in PRES.1,3,8 The subcortical vasogenic edema, as best visualized on MRI, has typically been described in the parieto-occipital areas and, less commonly, the temporal and frontal regions, basal ganglia, cerebellum, and brainstem. On brain MRI, our patient had a few subtle subcortical lesions in the parieto-occipital area. It is likely that some of these subtle MRI lesions had already subsided at the time the imaging was done (day 4). Of note, however, his spinal MRI revealed a longitudinally extensive T2 hyperintensity lesion starting from medulla oblongata down to the inferior part of the spinal cord. Such longitudinally extensive involvement of the spinal cord can be seen in a variety of conditions such as demyelinating disease (e.g., neuromyelitis optica), spectrum disorders, multiple sclerosis, acute disseminated encephalomyelitis, ischemic lesions (spinal vascular malformations), myelopathy secondary to connective tissue diseases (e.g., systemic lupus erythematosus, Sjögren syndrome), neuro-Behçet disease, neurosarcoïdosis, infections (e.g., herpes simplex virus 2, varicella zoster virus, cytomegavirus, syphilis, HIV), and primary or metastatic spinal cord tumors or idiopathic transverse myelitis.2 The acute onset of symptoms in a previously asymptomatic patient makes conditions such as vascular malformations, multiple sclerosis, or neuromyelitis optica remote possibilities. Furthermore, the lack of diffusion restriction (cytotoxic edema) on diffusion-weighted MRI excludes an ischemic event. Finally, the disproportionality between the impressive neuroimaging findings in the spinal cord and
relative minimal clinical findings as well as the benign course without specific treatment strongly favors PRES-SCI. In the presence of severe anemia and renal failure, thrombotic thrombocytopenic purpura, which is also associated with PRES, needs to be ruled out. However, the peripheral blood smear and rapid improvement of the patient’s condition with supportive therapy (blood pressure reduction, hemodialysis) were not consistent with this diagnosis.

Prompt recognition and management of PRES and PRES-SCI is important in preventing permanent damage and complications that may occur in this otherwise typically reversible syndrome. The management of PRES/PRES-SCI is based on the rapid withdrawal of the trigger factor(s) to accelerate recovery and to avoid complications (e.g., aggressive blood pressure management, discontinuation of the offending drug, or delivery in eclampsia).6 Antiepileptic drugs are used when seizures are suspected (particularly in classic PRES), in addition to supportive care in comatose patients. Evidence supporting routine use of steroids in PRES is lacking.1

AUTHOR CONTRIBUTIONS

Dr. Elkhider: attending physician, drafting manuscript, and review of the literature. Dr. Mesraoua: supervision of clinical care, patient follow-up, interpretation of imaging results, review of the manuscript for intellectual content, and contribution in the study concept/design. Dr. Vattoth and Dr. Abbas: interpretation of imaging results and review of the manuscript for intellectual content. Dr. Ibrahim: attending physician and review of the manuscript for intellectual content. Dr. Deleu: drafting manuscript, study concept/design, and review of the manuscript for intellectual content.

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