LETTER TO THE EDITOR

To The Editor

Posterior Reversible Encephalopathy Syndrome Due to Chronic Obstructive Pulmonary Disease

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Posterior reversible encephalopathy syndrome (PRES) refers to a clinicoradiological entity characterized by headache, altered level of consciousness, visual disturbances, and seizures.[1] Magnetic resonance imaging (MRI) shows hyperintensity signal changes on T_2/fluid-attenuated inversion recovery (FLAIR) sequences that are focal and symmetric and predominantly affect the posterior cerebral hemispheres. Although classically associated with acute hypertension, renal failure, pre-eclampsia/eclampsia, and immunosuppressive therapy, recently, a relationship between chronic obstructive pulmonary disease (COPD) and PRES has come to light.[2] Here, we describe a case with clinical and neuroimaging evidence of PRES in a patient presenting to hospital with an acute exacerbation of COPD (AECOPD). We also review other cases in the literature, discuss the pathophysiology, and current clinical experiences with the diagnosis and management of PRES.

A 62-year-old female smoker with a history of COPD on 3 L of home oxygen presented with decreased level of consciousness and severe shortness of breath following an upper respiratory tract infection. Following a diagnosis of AECOPD, she was intubated, started on inhalers, prednisone, and an intravenous (IV) course of antibiotics and transferred to the intensive care unit for further care. Other than COPD, she had hypertension, dyslipidemia, a history of upper gastrointestinal bleed, coronary artery disease, anemia, depression, and a metatarsal fracture. Her home medications consisted of fluticasone/salmeterol, montelukast, fludrocortisone 0.1 mg daily, aspirin 81 mg daily, oxycodone 5 mg four times per day as needed, ferrous gluconate, atorvastatin 80 mg daily, ezetimibe 10 mg daily, bisoprolol 5 mg daily, ramipril 2.5 mg daily, pantoprazole 40 mg daily, and escitalopram 20 mg daily.

On examination, the patient was intubated and had been off sedation (propofol) for 30 min. Vitals were as follows: temperature of 37.5 °C, blood pressure of 139/61 mmHg, heart rate of 83, and respiratory rate of 16. There was no abnormal respiratory pattern. She was drowsy, only rousable with moderate physical stimulation (not responsive to voice) and was unable to follow simple commands. Glasgow Coma Scale (GCS) was 7T ($E_2V_TM_5$). Cranial nerve exam revealed pupils that were 5 mm bilaterally and reactive to light. Fundoscopy examination was normal. There were conjugate eye movements. Corneal reflex was intact bilaterally, and a gag reflex was present. Tone assessment was normal. The patient was able to move all four limbs spontaneously against gravity and equally, but was not following commands, as noted above. Deep tendon reflexes were 2+ bilaterally but brisker throughout right side without spread. Plantar responses were equivocal bilaterally. Sensory examination revealed withdrawal in all four limbs to pain. There were no signs of meningismus. There were no signs of subclinical seizures; in particular, the patient's level of consciousness was not fluctuating, and there was no repetitive eye blinking, spontaneous pupillary dilatation, twitches, or oral automatisms noted.

Her laboratory tests on admission were as follows: hemoglobin of 108 g/L, elevated white blood cell count of 14.5×10^9/L, urea 3 mmol/L, and creatinine 63 mmol/L. Chest radiography revealed patchy subsegmental consolidation in left lower lobe in keeping with pneumonia. Computed tomography of the head did not reveal any acute intracranial abnormality. Arterial blood gas at presentation showed acidosis with a pH of 7.08, partial pressure of oxygen (pO_2) of 43 mmHg, severe hypercarbia with a partial pressure of carbon dioxide (pCO_2) of >150 mmHg (exact value exceeded quantifiable upper limit by the laboratory), and a bicarbonate that could not be calculated by the laboratory. Total CO_2 was 48 on blood chemistries. Before this presentation, her baseline pCO_2 was between 60 and 70 mmHg. Other relevant investigations included a normal lactate of 1.4 and a normal creatine kinase of 33.

During her first night in hospital, she developed a focal seizure involving tonic posturing followed by rhythmic convulsive movements of the left upper extremity. The seizure terminated after treatment with IV lorazepam and diazepam, and she was simultaneously loaded with IV phenytoin. Electroencephalography (EEG) performed the next day showed independent bi-temporal sharp wave discharges, more prominent over right than left temporal regions. MRI showed multifocal, predominantly white matter T_2/FLAIR hyperintensities involving bilateral frontoparietal and right occipital lobes, bilateral thalami, and less prominent patchy involvement of the cerebellar hemispheres (Figure 1). No areas of diffusion restriction were present. These MRI changes were felt to be more in keeping with PRES rather than a post-ictal state as post-ictal MR usually consists of T2 hyperintensities and diffusion restriction involving the cortical grey matter, subcortical white matter, and hippocampi.[3] Our diagnosis, given the clinical and radiological context, was hypercarbia-induced PRES. The presence of a pneumonia and that the patient was taking an opiate were also likely contributing factors to the hypercarbia and hypoxia at presentation. She was continued on phenytoin and remained seizure-free during her hospital stay. She was reexamined after extubation where there was no focality noted. She was alert, oriented, fluent, and able to follow complex commands. Visual fields were full and normal. Extraocular movements were full and intact. Facial strength and sensation were normal. Strength was full (MRC grade 5/5) bilaterally, and sensation was normal. Coordination and gait were normal. At the time of 3-month follow-up, she was asymptomatic with a normal neurological exam. A follow-up MRI was ordered, but not performed as the patient was from an outside town and did not feel she could come back to the city to get the MRI done.

Others have also reported on cases of PRES associated with AECOPD, and in most cases, hypercarbia. All cases (including ours described above) are summarized in Table 1. Notably, in all four cases, patients were normotensive. In two of the cases, the patients had severe hypercarbia.

One of the first theories about the pathophysiology of PRES was that it was likely related to failure of cerebral vascular autoregulation to compensate for acute arterial hypertension,

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Table 1: Cases of COPD and hypercarbia manifesting as PRES

Case	Age	Sex	ICU	Intubation	BP	pCO_2 (mm Hg)	Altered LOC	Seizure	Brain MRI	References
1	55	F	Not specified	Yes	Normal	139	Yes	Yes	Bilateral hyperintensities occipital lobes and border zones. MRA: Multiple segmental stenosis	4
2	55	F	Yes	No	130/ 80 mmHg	46.2	Yes	Yes	Hyperintensities in parieto-occipital regions	5
3	65	M	No	No	Normal	Unknown	No	Yes	Hyperintensities in left temporal and occipital lobes, right frontal and parietal lobes	6
4	62	F	Yes	Yes	135/ 80 mmHg	>150	Yes	Yes	Predominantly white matter hyperintensities in frontoparietal and right occipital lobes, thalami bilaterally, patchy cerebellar involvement.	This study

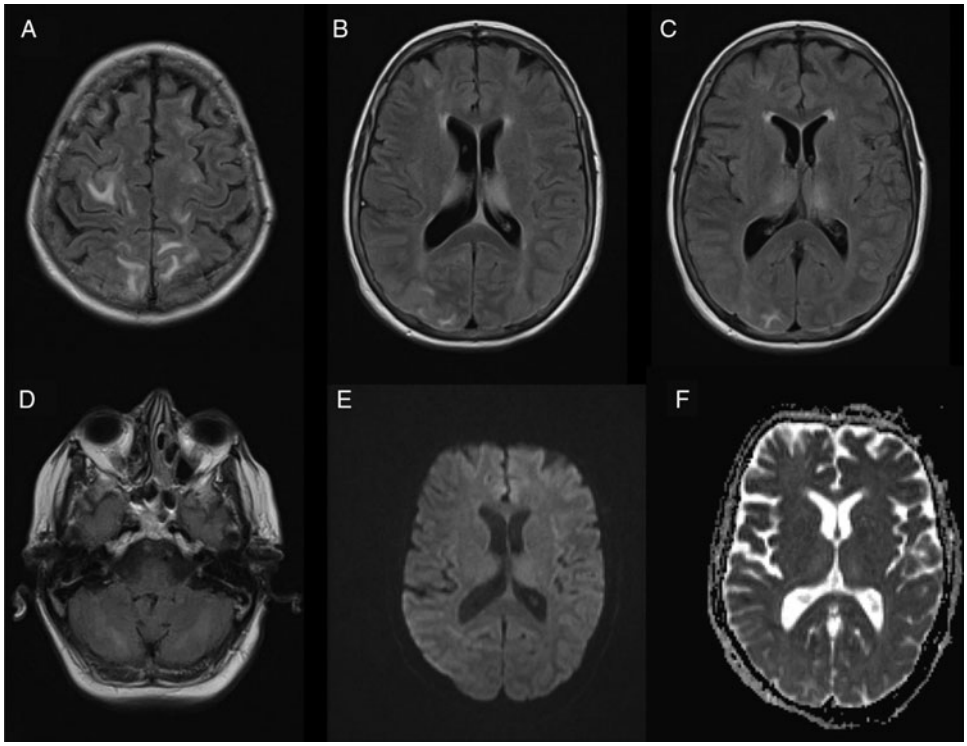

Figure 1: *Constellation of findings most supportive of posterior reversible encephalopathy syndrome (PRES). Magnetic resonance imaging (MRI) of the brain revealed multifocal, predominantly subcortical increased T2 signal primarily involving the frontal and parietal lobes (A), superior aspect of the thalami bilaterally and right occipital lobe (B and C), and cerebellar hemispheres (D) with no diffusion restriction (E and F).*

thereby leading to cerebral hyperperfusion resulting in blood–brain barrier (BBB) breakdown and subsequent vasogenic edema.[1] In an experimental model where acute hypertension was induced, abnormal brain signals were reversed and disappeared soon after controlling the blood pressure, suggesting that the cerebral autoregulation and edema were the principle causes rather than ischemic injury.[7] Another proposed pathogenesis supported by histopathology suggests PRES to be the result of T-cell activation and endothelial dysfunction, which leads to vasoconstriction, hypoperfusion, and ischemia.[8] This may cause BBB breakdown and leaking of fluid. COPD is a predisposing factor for endothelial dysfunction which is mediated by peripheral T-cells and cytokine activation (i.e. interleukin-1 and tumor necrosis factor-alpha). This cascade upregulates the vasoconstrictor endothelin-1, which

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subsequently causes cerebral vasoconstriction, platelet activation, disruption of the BBB, and brain injury.[2] The type of brain injury determines the reversibility, as it can be reversible in vasogenic edema or permanent in tissue infarction.

The clinical context and judgment are crucial in guiding assessment of these cases. Brain MRI remains the most important diagnostic tool in the evaluation of PRES and ruling out other underlying etiologies. MRI signal changes and reduced level of consciousness may be seen with subclinical status epilepticus and EEG can assess ongoing seizures in such patients. In our case, the MRI changes seen were felt to be more in keeping with PRES than seizures, but not having a repeat MRI and EEG precluded making this diagnosis definitive. Cerebrospinal fluid studies are warranted when meningitis or encephalitis is suspected. As seen in these cases, it is imperative that the diagnosis of PRES be considered in the clinical context of hypercarbia in AECOPD, especially when there is a disturbance in level of consciousness, headache, seizures, or visual disturbances or any focal neurological deficits, and arterial blood gases may be prudent. It is possible that other conditions that cause hypercarbia, possibly acutely, may lead to development of PRES, and this association needs to be explored further.

With regard to management, the treatment for PRES currently remains symptomatic and focuses on treating the underlying disease. Our reported cases suggest that treatment of hypercarbia may lead to improvement of PRES. Antiepileptics are warranted if patients develop clinical seizures, though their prophylactic use is not advised.

Disclosures

The authors have no conflicts of interest to declare.

Statement of authorship

HG, AA, and ZAS drafted the manuscript. HG, AA, NN, TN, and ZAS critically reviewed and edited the manuscript. HG, AA, TN, and ZAS were involved in the medical management of the patient. All authors approved the final version of the manuscript.

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