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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Posterior Reversible Encephalopathy Syndrome After Azathioprine Administration in Severe Ulcerative Colitis

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ABSTRACT

Posterior reversible encephalopathy syndrome is a rare syndrome characterized by brain edema and neurological symptoms, often resulting from several drugs. Treatment is based on discontinuation, and diagnosis is thus essential. Only 13 cases of posterior reversible encephalopathy syndrome have been reported in inflammatory bowel diseases, and we present the first after azathioprine in adults. A 56-year-old patient with active ulcerative colitis was found unconscious 5 days after the institution of azathioprine. Right-sided hemiplegia was found after the patient regained consciousness. Magnetic resonance imaging showed altered signal associated with diffusion restriction in the occipital lobe and cerebral vasogenic edema. Complete regression of neurological signs occurred after azathioprine discontinuation.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a rare syndrome, first described by Hinchey et al.[1] The clinical and radiologic features are characterized by the following: (i) neurological symptoms, consisting of headache, seizure, altered consciousness, focal neurological deficits, and visual abnormality; (ii) subcortical vasogenic edema in the white matter of the occipital and/or the parietal lobes as shown by magnetic resonance imaging; and (iii) resolution of symptoms and imaging findings in most cases.[1] Etiology is poorly understood, possibly resulting from endothelial dysfunction and increased vascular permeability caused by inflammatory cytokines or from acute changes in blood pressure (BP).[2] The syndrome often represents the side effect of drugs, in many instances immunomodulators. Treatment is mainly supportive and symptomatic, but control of hypertension is essential, as is elimination of possible factors, drugs included.[3] PRES is a rare condition, and inflammatory bowel diseases (IBDs) represent 4.4% of patients in large series from the Mayo Clinic.[4] In IBD, PRES has been reported in association with cyclosporin and infliximab, but so far never in the English literature after azathioprine, in adults (Table 1). Only one case was reported by Ogawa in Japanese in a pediatric patient.[5]

CASE REPORT

A 56-year-old man from Albania presented with worsening of abdominal symptoms, consisting of bloody diarrhea (6–8 daily bowel movements and with night awakening) and colicky pain in the lower abdomen improving after defecation. His body temperature was 37.5°C. The physical examination showed mild abdominal tenderness, and bowel sounds were normal. No rebound tenderness was present. BP was within the normal range. The body mass index was 21.7 kg/m^2 after a weight loss of about 9 kg in the past month. Left-side moderate ulcerative colitis (UC) had been diagnosed 1 year before after a complete ileocolonoscopy scored with Mayo Endoscopic subscore of 2, and successfully treated with mesalamine and oral steroids. He had experienced no disease relapse and currently was under oral mesalamine (2.4 g/d). The patient's history was negative for other diseases or surgery and was not consuming other drugs.

On admission, the blood tests showed: high C-reactive protein, 83.9 mg/L; low albumin, 24 g/L; hyposideremic anemia (red blood cell 3.47×10^{12}/L; hemoglobin 10.6 g/L; mean corpuscular volume 82 fL); and WBC within the normal range. No metabolic, liver, and

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Table 1. Cases of posterior reversible encephalopathy syndrome reported in IBD

Reference	Disease	Disease classification[a]	Sex	Age	Drug
Brandeo et al[14]	UC	—	F	28	Adalimumab
Kikuchi et al[15]	UC	E3	F	25	Prednisolone, metronidazole, and blood transfusion
Mishra et al[16]	CD	A1L3B3	F	18	Ustekinumab
Mishra et al[16]	CD	A2L3B3	F	54	Ustekinumab
Chow et al[17]	CD	A2L2B3	F	24	Infliximab
Cherian et al[18]	CD	A2L2B1	F	32	Mesalamine and multiple antibiotics
Gümüs et al[19]	UC	—	M	14	Granulocyte colony stimulating factor for neutropenia
Haddock et al[20]	CD	A1L2B1	F	8	Infliximab
Zamvar et al[21]	CD	A1L2B2	M	14	Infliximab
Zamvar et al[22]	UC	—	F	15	Infliximab
Drummond et al[23]	CD	—	F	33	Infliximab
Sood et al[24]	UC	—	F	44	Cyclosporine
Ogawa et al[5]	UC	—	F	15	Azathioprine
Fugate et al[4]	3CD; 2UC	—	—	—	Undefined

CD, Crohn's disease; IBD, inflammatory bowel diseases; UC, ulcerative colitis.
[a] Disease characteristics and extent of lesions according to Montreal classification.[25]

kidney abnormalities were noted. Bacterial infections and parasitological infestation were excluded. Serology was negative for viruses (Epstein-Barr Virus, Varicella-Zoster Virus, B and C Hepatitis, and human immunodeficiency virus) except previous exposure to Cytomegalovirus. Fecal calprotectin was >5,900 μ/g. Relapsing UC was thus diagnosed. A plain abdominal radiograph did not show colonic or small bowel gas distention. A proctosigmoidoscopy without insufflation was performed for 30 cm to evaluate disease activity, and showed deep ulcerations surrounded by hyperemic and edematous mucosa and pseudopolyps (Mayo Endoscopic subscore 3) (Figure 1). The patient was treated with methylprednisolone 60 mg/d iv, oral mesalamine 3.6 g/d, and enoxaparin 4000 UI/bid for antithrombotic prophylaxis. Improvement of symptoms was observed over 5 days (2–4 bowel movements, reduction of fecal blood, and abdominal pain), as well as reduction of C-reactive protein.

Because of the non-European Union Citizenship and the lack of health insurance, azathioprine was prescribed, being less expensive than biologics. The starting dose was 100 mg/d, with strict laboratory tests and clinical monitoring. The drug was initially well tolerated, except for mild headache.

Five days after the institution of azathioprine, the patient was found unconscious. When he regained consciousness, right-sided hemiplegia, deviation of the gaze with reagent mydriatic pupils, and normal BP were observed. No sphincteric release occurred. A computed tomography and angiocomputed tomography excluded cerebrovascular abnormalities. Magnetic resonance imaging was thus performed, showing bilateral alteration of the signal associated with diffusion restriction in the occipital lobe (Figure 2). Findings suggested vasogenic/cytotoxic edema of the cerebral white matter, and PRES was diagnosed. An electroencephalography excluded seizure activity. Azathioprine was discontinued, and methylprednisolone maintained at full doses. Slow, complete regression of neurological signs was observed over the following 4 weeks, further supporting the role of the immunosuppressor as the cause.

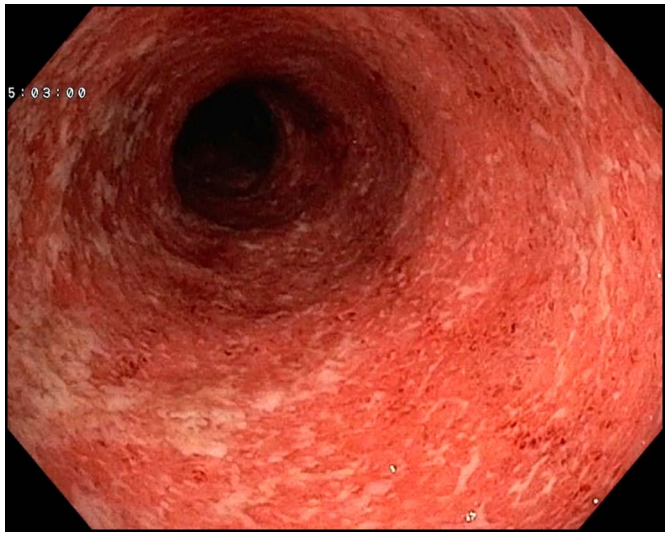

Figure 1. Proctosigmoidoscopy showing mucosal ulcerations surrounded by hyperemic and edematous mucosa.

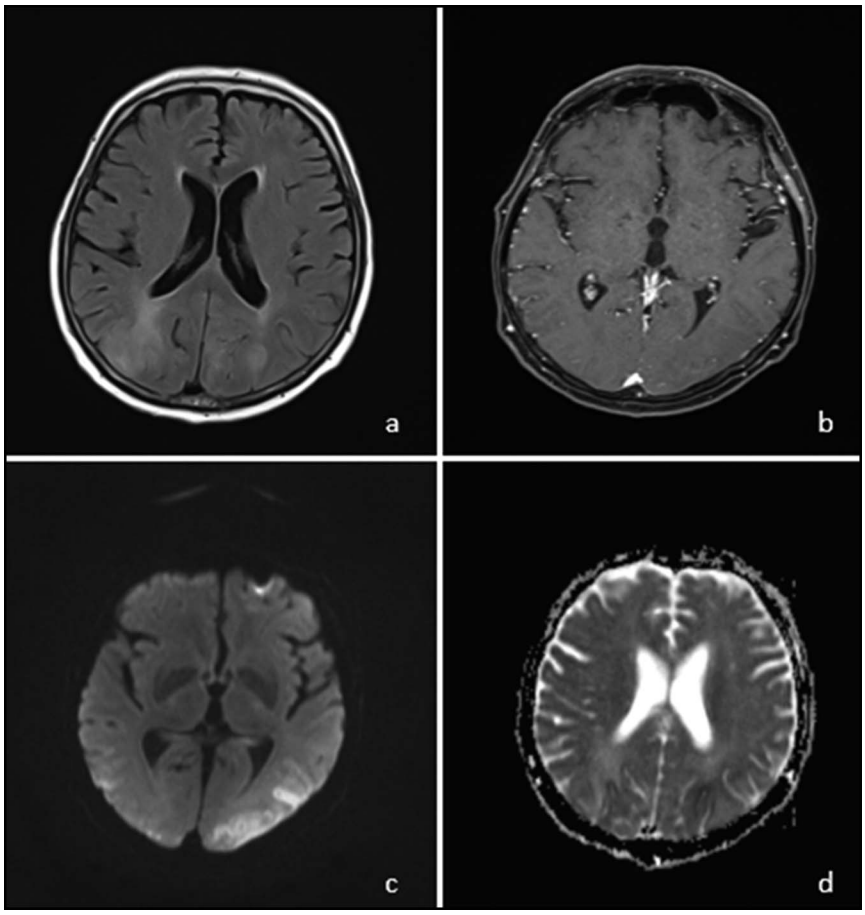

Figure 2. Magnetic resonance imaging alteration of the signal associated with diffusion restriction in the occipital lobe, suggestive of cerebral edema in (A) fluid-attenuated inversion recovery sequence, (B) after contrast injection, (C) diffusion weighted imaging sequence, (D) apparent diffusion coefficient sequence.

DISCUSSION

PRES is a rare and reversible neurological disorder, usually presenting with headache, seizure, altered consciousness, focal neurological deficits, and visual abnormalities (Table 2). In a minority of severe cases, when stroke or acute brain hemorrhage are present, it is potentially lethal.[6]

Four patterns of imaging have been reported in PRES—(i) parietal-occipital pattern (22% of cases), (ii) holohemispheric pattern (23%), (iii) superior-frontal pattern (27%), and (iv) mixed expression of the aforementioned patterns (28%).[7]

The frequent development of lesions in the posterior parieto-occipital lobes is consistent with the sympathetic innervation, less effectively regulating the blood flow in the vertebrobasilar system when compared with the carotids.[8] Two etiopathogenetic theories have been proposed.[2] The first one involves acute hypertension, leading to a failure in the autoregulatory mechanisms controlling cerebral perfusion and to a disruption in the blood-brain barrier, both causing edema. This hypothesis is supported by the association of PRES with elevated BP but has been questioned because acute increases in BP rarely overcome the autoregulatory limits of the blood-brain barrier.

The second theory suggests that endothelial disfunction and capillary leakage may result from direct toxic effect (cytotoxic, autoimmune, or drug related), triggering fluid extravasation.

Table 2. Symptoms associated to posterior reversible encephalopathy syndrome

Seizures
Nonconvulsive status epilepticus
Headache
Visual field deficits
Impaired visual acuity
Focal neurological deficits
Peripheral facial paralysis
Altered sensorium
Paraplegia
Cerebellar syndrome
Acute arterial hypertension/blood pressure fluctuations
Nausea
Vomiting

Table 3. Medications associated to posterior reversible encephalopathy syndrome

Immunosuppressants (cyclosporin A, interferon α, tacrolimus/FK-506, and methotrexate)
Biologics (anti-TNFα, bevacizumab, and rituximab)
Tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib, regorafenib, lenvatinib, and cediranib)
Cytostatics (doxorubicin, vincristine, cyclophosphamide, cytarabine, cisplatin, and tiazofurin)
Erythropoietin
Granulocytic stimulating factor
Antibiotics (linezolid)
Antimycotics (amphotericin B)
Antiretrovirals
Sympaticomimetics and abuse drugs (phenylpropanolamine, ephedrine, pseudoephedrine, and cocaine)
Intravenous contrast agents
Hypercalcemia
Clonidine (after withdrawal)

TNF, tumor necrosis factor.

Non–drug-related causes include hypertension, (pre-)eclampsia, sepsis, autoimmune disorders, chronic renal failure, blood transfusion, electrolyte imbalance, acute liver failure, and human immunodeficiency virus infection.[9] The role of endothelial dysfunction/capillary leakage in the presence of circulating proinflammatory cytokines is likely.[2]

The same mechanisms have also been advocated when PRES is reported in association with several drugs or sepsis[1,10] (Table 3). Differing classes of drugs are supposedly implicated in the genesis of PRES. Indeed, chemotherapy agents (such as 5-fluorouracil and cisplatin), monoclonal antibodies, small molecules, antibiotics (metronidazole), nonsteroidal anti-inflammatory drugs, and immunomodulators (cyclosporin and tacrolimus) are most often involved.[9] Treatment is aimed at resolving potential underlying causative factors such as BP control or the use of anticonvulsant agents, when seizures are present. Steroids improve vasogenic edema and help recovery.[11] The high-dose steroid therapy used for controlling the UC flare in our patient before the occurrence of PRES may have contributed to complete regression of neurological signs.

A systematic electronic search of the literature up to January 2020 using Medline, Embase, and the Cochrane Library identified only 3 reports involving azathioprine. One of them was affected by systemic lupus erythematous[12] and the second by mixed connective tissue disease.[13] The third case, involving a pediatric UC patient, was reported in a Japanese study.[5]

To our knowledge, only 13 cases of PRES have been reported in IBD patients, and the present is the first reporting azathioprine-induced encephalopathy in adults. The absence of hypertension, the occurrence of symptoms shortly after the institution of azathioprine therapy, and the complete recovery after suspension of the drug strongly support the role of the immunosuppressor.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. F. Vernia is the article guarantor.

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