Am J Clin Exp Immunol 2018;7(1):1-7
www.ajcei.us /ISSN:2164-7712/AJCEI0068305

Case Report

Posterior reversible encephalopathy syndrome (PRES) attributed to mycophenolate mofetil during the management of SLE: a case report and review

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Received July 17, 2017; Accepted December 24, 2017; Epub February 5, 2018; Published February 15, 2018

Abstract: Posterior reversible encephalopathy syndrome (PRES) is a rare clinical entity associated with systemic lupus erythematosus which characterized by seizure, headache, and altered mental status. The pathophysiology involves subcortical vasogenic edema secondary to hypertension and endothelial damage. PRES is reversible with withdrawal of the offending agent, strict blood pressure control, and treating the underlying disease. We report present here a patient with lupus nephritis who developed PRES following mycophenolate administration.

Keywords: Posterior reversible encephalopathy syndrome, mycophenolate mofetil, systemic lupus erythematosus, adverse drug event

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity characterized by seizure, altered sensorium, visual disturbance and nausea, and vomiting, along with characteristic neuroimaging findings. Magnetic resonance imaging (MRI) often shows bilateral, symmetric areas of white matter edema predominantly in occipital and posterior parietal lobes. Autoimmune diseases are associated with 8-10% of PRES cases [1] PRES has been reported in patients with SLE. Otherwise, some immunosuppressive agents for the treatment of SLE and Lupus nephritis, including mycophenolate, are also considered as possible etiological agents. Herein, we report a case of PRES caused by mycophenolate.

Profiles and methods

Typical case

A 22-year-old female presented with a 6-year history of asthenia, joint pain, malar rash, photosensitivity, oral ulcers and polyarthritis, a strongly positive ANA (titre 1:1000) and positive double-strain DNA antibodies, positive anti-Smith antibody. Her family history was negative for arthritis and seizures. At another institution, she was diagnosed as SLE and treated with prednisone and hydroxychloroquine for a long period in a stable condition. The patient discontinued all medications for 1 month and soon developed fever and fatigue and admitted to our hospital.

On physical examination, her height was 165 cm, weight was 45 kg, and body mass index was 16.53 kg/m^2. Temperature was 41.0°C, blood pressure was 130/73 mmHg, heart rate was 105 beats per minute, respiratory rate 17/min and oxygen saturation was 98% while breathing ambient air. Neurological exam was normal. Meningeal signs were negative.

The patient's serum creatinine level and creatinine clearance were 130 μmol/l and 40 mL/min, respectively, and urinalysis revealed proteinuria (+3) and hematuria, as well as a total protein of 1.54 g/day. Investigations indicated anemia with hemoglobin of 6.2 g/dL, total leukocyte count of 8,200/mm^3, and platelet count of 66,000 cells/mm^3. The patient was positive for direct Coomb's test. Serum ANA was strongly positive with a diffuse homogenous pattern

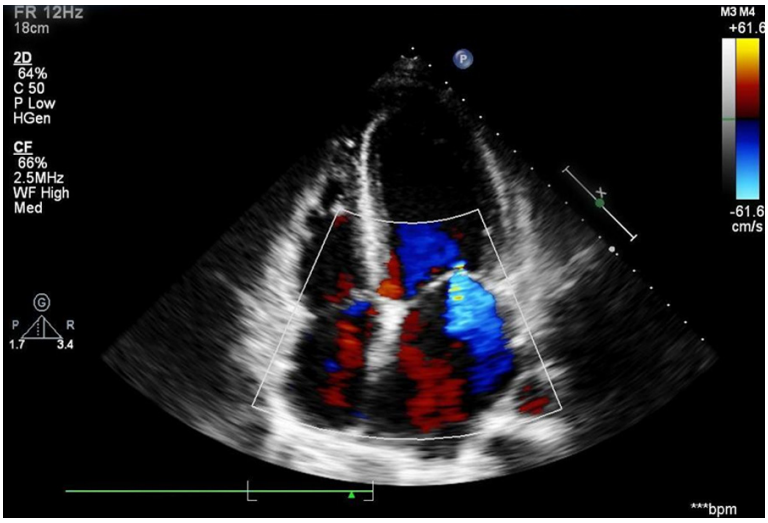

Figure 1. Echocardiography showed moderate mitral and three cusp regurgitation, mild aortic regurgitation, mild aortic valve regurgitation and left ventricular enlargement. Echocardiogram-systolic pulmonary artery pressure (SPAP): 53 mmHg.

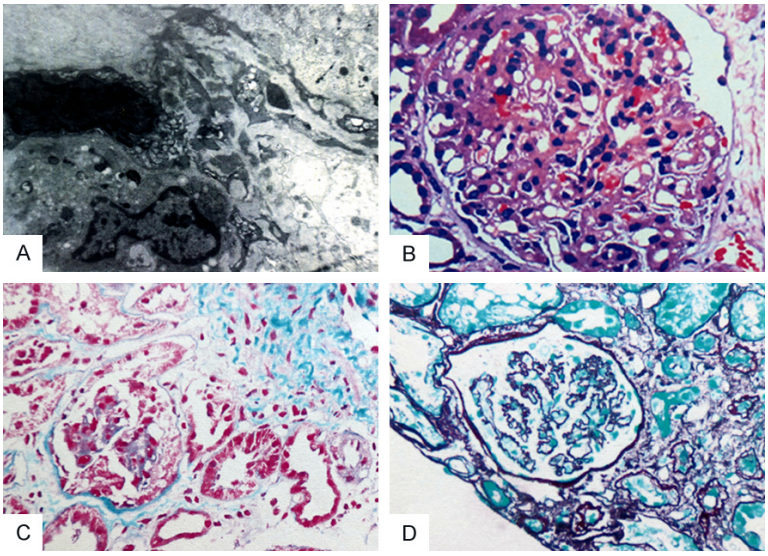

Figure 2. Renal biopsy: A: Diffuse proliferation of mesangial cells, mesangial matrix and endothelial cells, diffuse thickening of the basement membrane of the capillary wall, and electron dense deposits in the subepithelial, subendothelial, and mesangial regions (EM ×5000 magnification). B: Diffuse mesangial proliferative glomerulonephritis, diffuse mesenterium matrix hyperplasy, endotheliocyte hyperplasia. The diffuse thicked glomerular capillary walls, showing double track changes and narrowing of the lumen (H&E ×400 magnification). C: A large amount deposition of fuchsinophilic protein and the structure of "platinum ear" under the capillary endothelium (Masson ×200 magnification). D: Diffuse proliferative in the mesangial regions (Periodic acid-silver metheramine stain ×320 magnification).

by immunofluoroscence method at 1:1000 dilutions; C-reactive protein was normal; Complements were low (C3: 27 mg/dL; C4: 8 mg/dL). Antibodies to double-stranded DNA were positive by ELISA (390 IU/mL) in high titres. Anti-cardiolipin antibodies were absent. Lung CT showed increased bilateral pleural effusion, pericardial effusion and enlarged heart shadow. Echocardiography showed moderate mitral and three cusp regurgitation, mild aortic regurgitation, mild aortic valve regurgitation and left ventricular enlargement (**Figure 1**).

Diagnosis of SLE and lupus nephritis were made and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was at 24. Intravenous methylprednisolone was administered at 1000 mg/dose once daily, followed the use of prednisone 1 mg/kg/day and hydroxychloroquine (HCQ) at 400 mg/day. Clinical symptoms were markedly relieved and the platelet count then increased to 115,000 cells/mm^3. The serum creatinine level declined to 102 μmol/L and creatinine clearance was normal. On the tenth day of hospitalisation, pathological test of renal biopsies revealed severe and diffuse mesangial proliferative glomerulonephritis, diffuse mesenterium matrix hyperplasy, and deposits of IgG, IgA, IgM, Kappa, Lambda, C3, and C1q at capillary wall (**Figure 2**). ISN/RPS [2] class IV-G(A/C) lupus nephritis was diagnosed and mycophenolate at 500mg/dose twice daily were administered. After 5 days, the patient developed sudden onset of headache, nausea, vomiting, followed by a witnessed 3-minute seizure involving altered mental status. She was treated symptomatically with analgesics and anticonvulsants. Blood pressure was high during and after the seizure episode (190/110 mmHg). Strict blood pressure control below 140/90

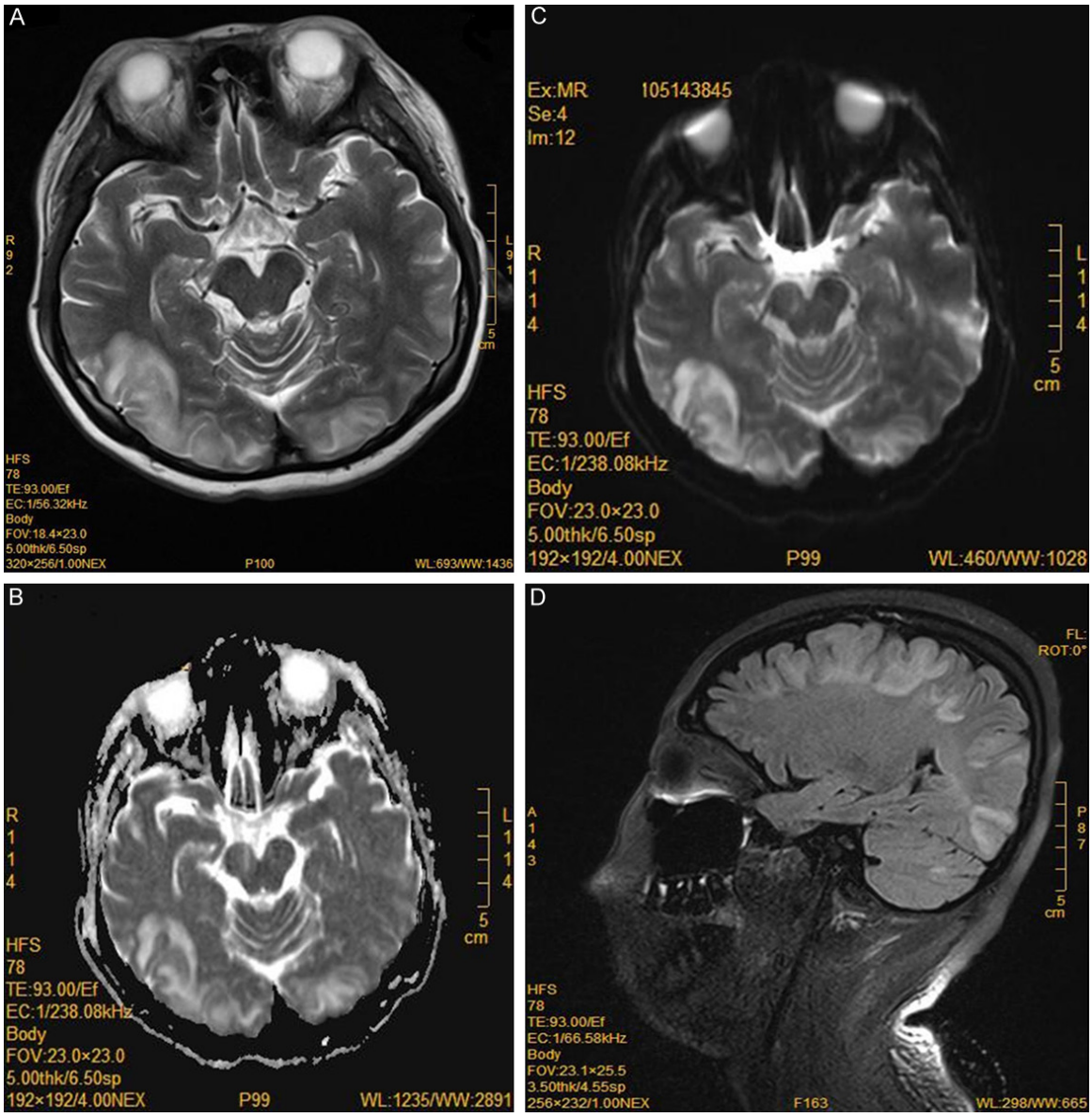

Figure 3. (A) T2 weighted: T2-weighted sequences involving the cortical and subcortical regions of parietooccipital lobes. (B) ADC map showed an increase of the apparent diffusion coefficient (ADC) value, suggestive of vasogenic edema in the same regions. (C) Diffuse weighted image (DWI). (D) Fluid-attenuated inversion recovery magnetic resonance imaging (FLAIR) MRI image. Brain MRI image of the patient showed high intensity involving the cortical and subcortical regions of the parietooccipital lobes in T2 weighted, DWI, and FLAIR (A, C, D).

mmHg was maintained initially with intravenous nicardipine drip and then transitioned to oral felodipine and hydrochlorothiazide, and losartan with close monitoring of blood pressure. Cerebrospinal fluid (CSF) was normal (Glucose: 55 mg/dL, protein (total): 20 mg/dL, gram stain: negative, culture: sterile). Mycophenolate mofetil was discontinued in consideration of that it could be cause of PRES. The patient remained seizure-free and became asymptomatic 24 h after onset. MRI of the brain was done 7 h after the onset of headache and showed abnormal signal intensity involving parietal and occipital regions in T2 weighted, DWI, ADC and FLAIR, consistent with the diagnosis of PRES (**Figure 3**). A brain MRI 12 days after demonstrated resolution of the initial cerebral lesions (**Figure 4**). A week later, she was discharged from hospital at the dose of leflunomide 30 mg/d. The patient has been on follow-up for 6 months without any major lupus flare.

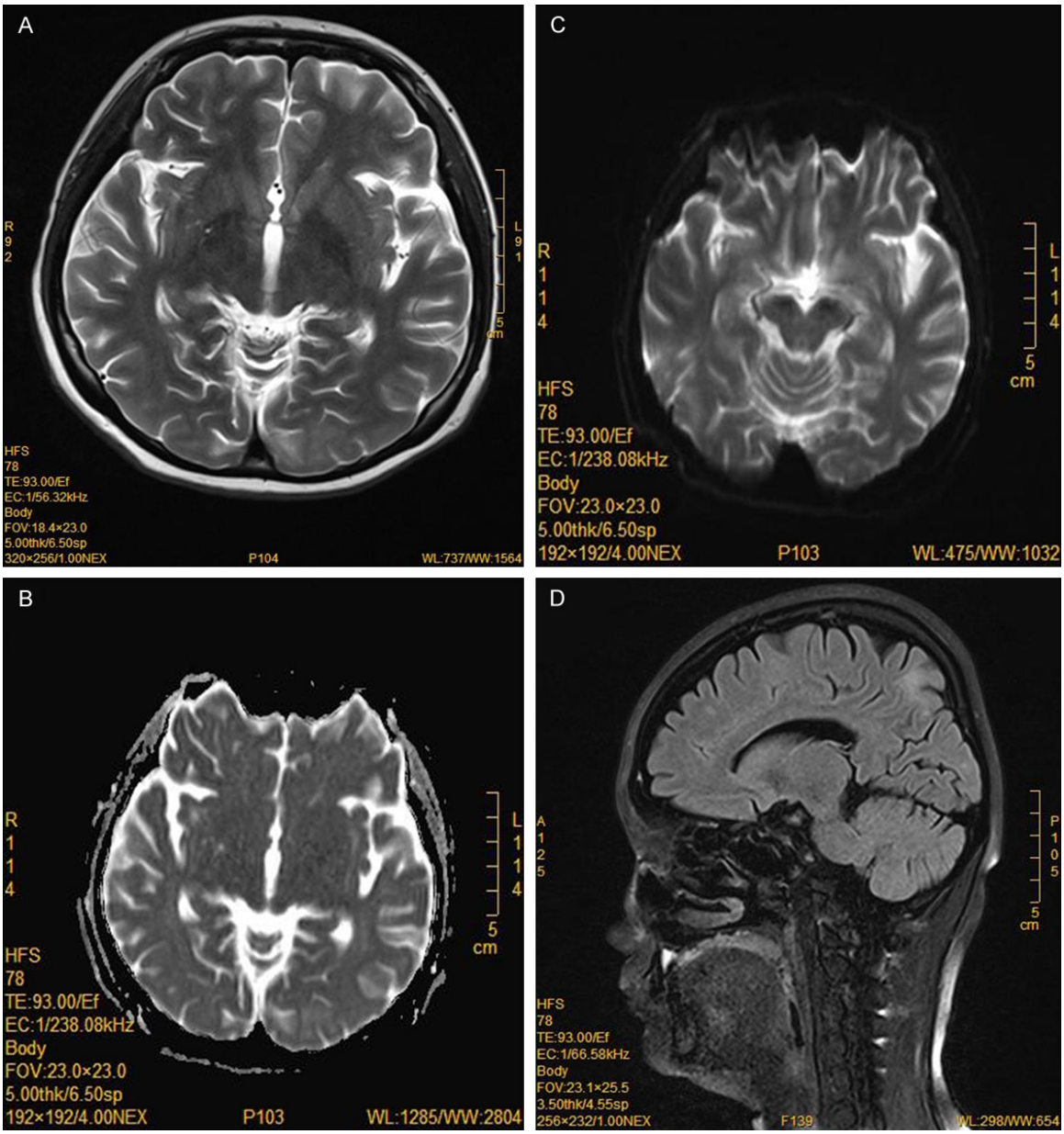

Figure 4. Brain magnetic resonance image 12 days after discontinuing Mycophenolate. Complete resolution of high signal intensities is shown compared with **Figure 3**.

Discussion

Hinchey et al. [3] first described the link between immunosuppressive medication, renal disease, hypertension, and PRES, but until now the pathogenesis of PRES is not yet fully understood. Most researchers agree with the hyperperfusion theory in the pathophysiology of PRES [4, 5]. The arteriolar constriction and dilation maintain constant flow and cerebral perfusion. Severe elevations of blood pressure and toxins, in addition to harmful conditions to the endothelium, could lead to a deregulation of arteriolar constriction, causing a relative vasodilation of the cerebral arteriole and hyperperfusion. This large perfusion is able to damage the hematoencephalic barrier, allowing extravasation of liquid, macromolecules, and even red blood cells into the brain parenchyma. The predilection for involvement of posterior circulation is generally accepted to result from the relatively poor sympathetic innervation of the vertebrobasilar system [6, 7]. Hypertension is believed to be the cause of PRES in lupus

Table 1. Previous case reports of immunosuppressive drugs induced-PRES in patients with lupus

Author/year	Patient	Diagnosis	Clinical features	Vasogenic oedema sites	Immunosuppressive drug	Therapy change	Outcomes
Mavragani CP etc./2004 [21]	F/38y	SLE/LN/APS	S/H/V	(bilateral) P/T	RTX (after the third)	Drd	CR
Shin Ki Chul etc./2005 [22]	F/24y	SLE/TP	S/H/perspiration	(bilateral) P/F	CsA	Drd	CR
Abenza-Abildua MJ/2009 [23]	M/27y	SLE/LN/GPS	Hyp/S/H/AMS	(bilateral) P	IVCYP	Rep (by RTX)	CR
Chennareddy Srinivasa etc./2013 [24]	F/17y	SLE	S/H/V	(left) O	IVMP	Drd	CR
	F/16y	SLE/	H/V	(bilateral) O	IVMP	Drd	CR
Jayaweera Jayamalee L et al./2014 [25]	F/33y	SLE/LN	S/AMS	(bilateral) O	IVCYP	Drd	CR
Jabrane M et al./2014 [26]	F/16y	SLE/LN	S/H/V	(bilateral) P/O	IVMP/IVCYP	Drd	CR
Harirchian Mohammad Hossein etc./2015 [27]	F/28y	SLE	Hyp/S/V	(bilateral) P/O	CsA	Rep (by tacrolimus)	CR
Mondal S/2016 [28]	F/17y	SLE/LN	S/V	(bilateral) O	RTX (after the third)	Drd	CR
Khajuria Bhavik etc./2016 [12]	F/22y	SLE/LN	S	(bilateral) P	MMF	Rep (by CYC)	CR

Note: SLE: Systemic lupus erythematosus; LN: lupus nephritis; GPS: Goodpasture syndrome; TP: thrombocytopenia; APS: antiphospholipid; S: seizures; Hyp: hypertension; V: visual disturbance; H: headaches; AMS: altered mental state; O: occipital; P: parietal; F: frontal; T: temporal; AMHA: autoimmune hemolytic anemia; IVMP: intravenous methylprednisolone; MMF: mycophenolate mofetil; CsA: Cyclosporine; RTX: rituximab; CYC: cyclophosphamide; IVCYP: intravenous cyclophosphamide; CR: complete resolution; Drd: discontinue related drug; Rep: replaced.

nephritis [8]. High-dose corticosteroid therapy and cyclosporine may induce the occurrence of PRES by this way. However, the grade of hypertension is not correlated with the severity of PRES [9]. PRES lesions have been reported to occur in the anterior circulation territory as well as in normotensive patients [10]. Our study finds that 80% of patients had no history of hypertension before and during development of syndrome. In patients who develop PRES in the absence of hypertension, endothelial dysfunction is believed to be the major causative factor. Other factors include disrupted blood-brain barrier, systemic inflammation and immunosuppressive regimens [11]. Mycophenolate is an immunosuppressive medication commonly used for the treatment of lupus nephritis, which has been reported in a case of PRES [12]. The WHO causality assessment scale [13] and The Naranjo Adverse Drug Reaction Probability Scale [14] rate our association of mycophenolate to PRES as "probable". Immunomodulatory drugs may have a direct toxic effect on cerebral vasculature [15]. Cyclosporine, rituximab can cause vasculopathy and has direct or indirect toxic effects on vascular endothelial cells [16]. The exact pathogenesis of PRES following mycophenolate is not definitely known. MPA inhibited the expression of VCAM-1 and ICAM-1 and inhibited the remodeling of the vessel wall by the means of leading to the impairment of smooth muscle cell proliferation and to the reduction of connective tissue component secretionthus [17]. Through the mechanisms aboved, whether or not mycophenolate would affect the homing of endothelial progenitor cells and the repair of impaired vascular endothelium in some patients? Further research is necessary to fully understand.

In a study of 120 cases of PRES, autoimmune disorders were identified in 45% of the patients [18]. PRES is found more commonly among Asian patients. Approximate prevalence of PRES among patients with systemic lupus erythematosus (SLE) is 0.69% [19]. PRES has been described as an uncommon neurological manifestation in SLE, mainly associated with hypertension, renal insufficiency and use of immunosuppressive drugs [11]. An review of the English-language literature was performed, using the PubMed database with the following keywords: 'posterior reversible encephalopathy syndrome', 'reversible posterior leukoencephalopathy syndrome', 'systemic lupus erythematosus', 'lupus', 'drug side effect', 'drug toxicity' and 'immunosuppressant'. We included in our review all patients presenting with clinical and MRI findings of PRES and diagnosed as having SLE, fulfilling the 1997 ACR of Rheumatology criteria [20]. Characteristics and MRI findings of 10 patients with PRES were showed in **Table 1**. Of all the patients, women were in the majority (90%). The median age was 23 years (16-38 years). The commonest manifestations were seizures (90%), headaches (60%), and visual symptoms (60%), followed by altered mental state (20%) and hypertension (20%). The most common sites of involvement on neuroimaging were the occipital (60%), parietal (60%), fol-

lowed by frontal lobe (10%) and temporal lobe (10%). 90% was involved in bilateral cortical and subcortical areas, which is consistent with the previous findings [29].

In conclusion, a variety of many immunosuppressive drugs including mycophenolate are implicated with PRES. A caution is required in the clinical practice of the treatment of SLE and related diseases. Prompt discontinuation of the offending drug and correction of the potentiating factors will probably result in a complete resolution of the encephalopathy.

Disclosure of conflict of interest

None.

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