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LETTER TO THE EDITOR - CASES WITH A MESSAGE

A case of PRES in an active lupus nephritis patient after treatment of corticosteroid and cyclophosphamide

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Abstract Posterior reversible encephalopathy syndrome (PRES) is primarily a radiological diagnosis. The syndrome is characterized by headache, altered mental status, seizures, and bilateral posterior white matter edema in a nonvascular distribution on neuroimaging with resolution of findings usually in 7–14 days (Casey et al. in AJNR Am J Neuroradiol 21:1199–1206, 2000). In most cases, computed tomography of the brain will show hypodense lesions in the parieto-occipital lobe. Although this syndrome is uncommon, prompt and accurate recognition allows early treatment, which has been shown to produce favorable outcomes. It is hypothesized that the dysfunction can be caused by a failure of autoregulation systemic hypertension or by the cytotoxic effects of vasculitides and immunosuppressive drugs. The present report is a possible second case of cyclophosphamide-induced PRES in a 16-year-old girl with systemic lupus erythematous and lupus nephritis. The initial suspected diagnosis was an ischemic stroke, but it was later changed, with resolution of symptoms after management of the underlying cause.

Keywords Reversible posterior encephalopathy syndrome (RPES) · Systemic lupus erythematosus (SLE) · Hypertension · Cyclophosphamide · Lupus nephritis

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Case report

A 16-year-old girl presented with a 5-month history of asthenia, joint pain, photosensitivity, a strongly positive ANA, and positive double-strain DNA antibodies, evoking systemic lupus erythematosus (SLE). Her family history was negative for arthritis and seizures. All immunizations were up to date, and she had no drug allergies.

On examination, the patient was alert and oriented. Her height was 160 cm, weight was 35 kg, and body mass index was 22 kg/m^2. Temperature was 37.7 °C, blood pressure was 137/73 mmHg, heart rate was 105 beats per minute, and oxygen saturation was 100 % while breathing ambient air. Neurological exam was normal. Meningeal signs were negative. The fundoscopic examination was normal. The remainder of the physical exam was normal.

The patient's serum creatinine level and creatinine clearance were 58 mg/l and 5 mL/min, respectively, and urinalysis revealed proteinuria (+3) and hematuria, as well as a total protein of 2.5 g/day. Investigations revealed anemia with hemoglobin of 8.4 g/dL, total leukocyte count of 5,200/mm^3, and platelet count of 180,000 cells/mm^3. Serum ANA was strongly positive (1:1,280) and homogenous; C-reactive protein was normal; Complements were low (C3: 27 mg/dL; C4: 8 mg/dL). Cerebrospinal fluid (CSF) was normal (Glucose: 55 mg/dL, protein (total): 20 mg/dL, gram stain: negative, culture: sterile). Electroencephalogram (EEG) did not show any underlying seizure disorder.

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was at 24.

Renal biopsy with light microscopy and immunofluorescence test showed severe and diffuse mesangial proliferative glomerulonephritis, focal endocapillary proliferativation, and cell crescent with basement membrane deposits

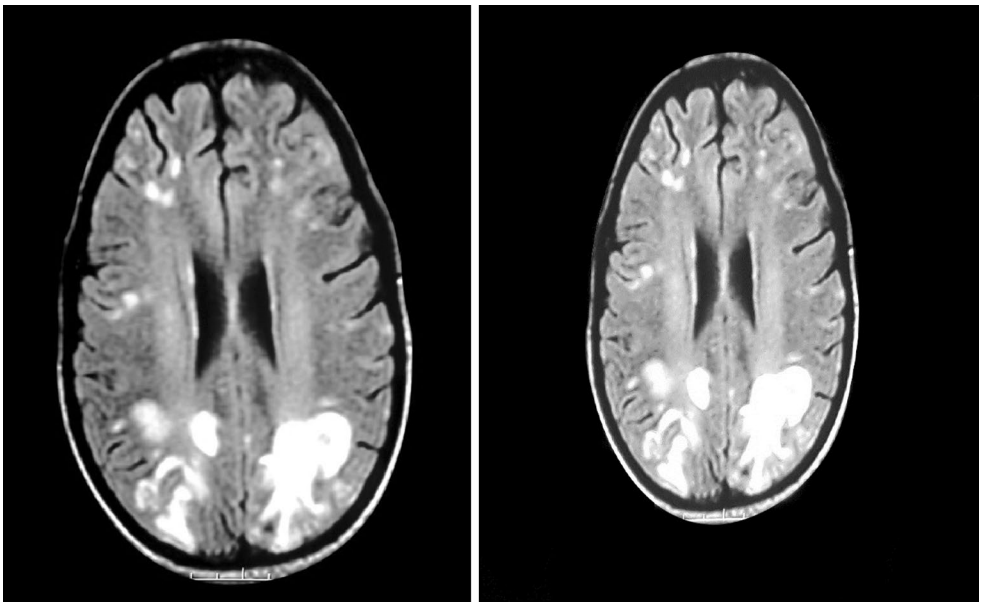

Fig. 1 FLAIR MRI image of the patient on April 23, 2014 showing bilateral posterior parietal and occipital abnormal signal intensity involving parietal and occipital regions in T1, T2 weighted, and FLAIR, with small areas of ischemia in hypersignal at the two semioval center

of IgG, IgM, C3, and C1q. Class VI lupus nephritis was diagnosed.

Intravenous cyclophosphamide pulse therapy at 300 mg/m^2 of body surface was administered after three daily pulses of intravenous methylprednisolone (10 mg/kg/day). Renal function improved and returned to baseline over the next 3 days. Simultaneously, the patient developed sudden onset of headache, blurring of vision, followed by three episodes of generalized seizures. There was no evidence of meningitis and her blood pressure was normal (120/70 mmHg) during and after the seizure.

Magnetic resonance imaging (MRI) of the brain was done 18 h after the onset of headache and showed abnormal signal intensity involving parietal and occipital regions in T1, T2 weighted, and FLAIR, consistent with the diagnosis of posterior reversible encephalopathy syndrome (PRES) (Fig. 1). The patient became asymptomatic 24 h after onset.

An MRI 15 days after demonstated resolution of the initial cerebral lesions (Fig. 2).

Discussion

In 1996, Hinchey et al. [2] first described the link between immunosuppressive medication, renal disease, hypertension, and PRES, but until now the pathogenesis of PRES is not yet fully understood. In 2000, Casey et al. [3] proposed the term PRES for this entity.

Although several cases of PRES have been observed and documented, the exact cause of PRES has not been determined. It is possible that multiple pathophysiological processes can generate the clinical and radiological findings consistent with PRES.

In a series of 120 cases of PRES, autoimmune disorders were identified in 45 % of the patients [4]. Systemic lupus erythematosus is one of the predisposing conditions related to PRES, particularly when accompanied by lupus nephritis. [5, 6] and the first description of PRES in SLE patients is as recent as 2006. PRES has been claimed as a particular form of neurological manifestation of SLE with characteristic MRI findings and a usual good outcome [7, 8].

Risk factors for PRES in SLE include vascular disease with endothelial damage, disrupted blood–brain barrier, hypertension, systemic inflammation, and cytotoxic treatment regimens.

In patients who develop PRES in the absence of hypertension, endothelial dysfunction is believed to be the major causative factor. Gasparovic et al. [9] observed in lupus patients the relationship between cerebral blood pressure and mean arterial blood pressure, suggesting pathologic dysregulation of cerebral blood flow at normotensive or prehypertensive levels.

There have been reports of PRES during high dose of steroids even in the absence of arterial hypertension which is a well-known adverse effect of this therapy [10].

The particularity of our patient is that no hypertension was recorded and low doses of cyclophosphamide have been used.

PRES in SLE is uncommon and few pediatric cases have been reported. In general, SLE-PRES is associated

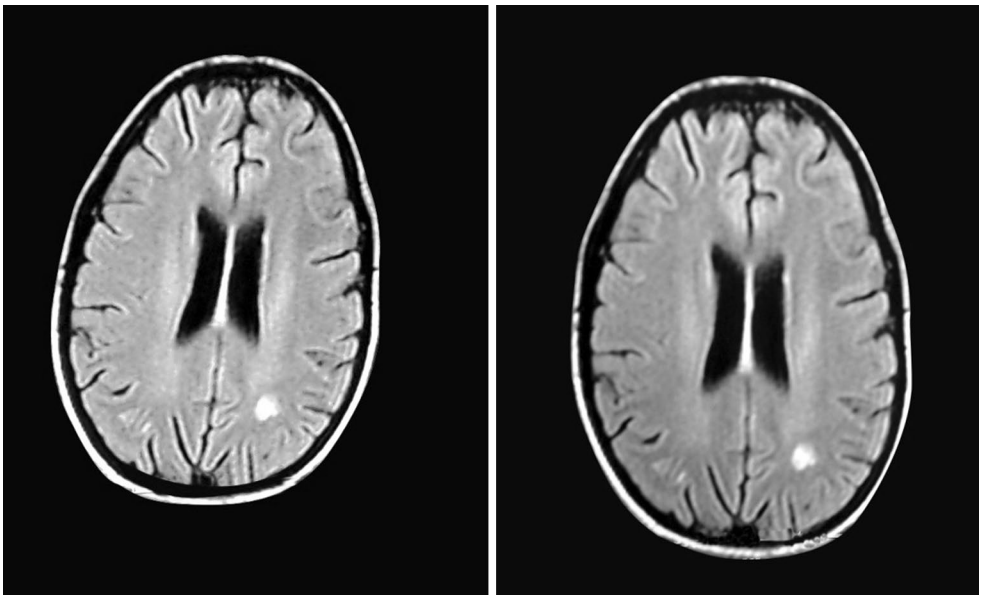

Fig. 2 FLAIR MRI of the patient obtained on May 7, 2014, showing almost complete resolution of the bilateral occipital lesions with persistence of small areas of ischemia at the left semioval center

with hypertension (95 %), renal involvement (91 %), SLE flare (87 %), and recent treatment with immunosuppressive drugs. The most commonly associated drugs are high doses of i.v. steroids (43 %), cyclophosphamide (26 %), and cyclosporine (9 %) [11].

The differential diagnosis for a patient with lupus who develops headache, hypertension, and seizures includes cerebrovascular disease, neuropsychiatric lupus, and PRES.

All of these diagnosis may occur early in the course of disease and in the presence or absence of immunosuppressive medications. Neuroimaging is then more helpful to distinguish among these conditions [12].

However, may be more in distinguishing typical findings are white matter edema in the posterior regions of the cerebral hemispheres, often with a strikingly symmetrical involvement of the parietal and occipital lobes, but variations do occur [13].

The treatment for PRES depends on the underlying cause; however, antiepileptic drugs should be used to control acute seizures [14]. Patients presenting with PRES who are also on immunosuppressive therapy should have their medications temporarily withheld or the dosages decreased until the neurological symptoms of PRES improve [15]. The first reported case in the literature of cyclophosphamide-induced RPLS in a 27-year-old man with high blood pressure (HBP) and glomerulonephritis caused by Goodpasture syndrome but when cyclophosphamide was replaced by rituximab and hypertension was controlled, the patient did not have neurological symptoms [13].

Many immunosuppressive drugs are implicated with this syndrome, associated with arterial hypertension in almost all cases. The symptoms of this syndrome are very common and can simulate other pathologies which makes it a difficult diagnosis [13].

In practical terms, patients with SLE presenting headache, altered sensorium, seizures, and visual loss should be suspected of PRES.

Conflict of interest None.

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