Posterior Reversible Encephalopathy Syndrome (PRES) Associated with Thrombotic Thrombocytopenic Purpura in a Systemic Lupus Erythematosus Patient

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Posterior reversible encephalopathy syndrome (PRES) is a rare and potentially devastating neuroradiological condition characterized by non-specific clinical features and a diagnostically specific magnetic resonance imaging (MRI) pattern. It is characterized by altered mental status, headaches, vomiting, seizures, severe hypertension, eclampsia, and loss of vision.

Neuro-imaging is essential for the diagnosis of PRES. The most common MRI finding in PRES is brain edema, mainly in the white matter of the parieto-occipital region. MRI shows hyperintensity in the subcortical white matter on fluid-attenuated inversion recovery (FLAIR) sequences resulting in vasogenic edema predominantly affecting the posterior occipital and parietal lobes of the brain.

Both endothelial dysfunction and disturbed cerebral autoregulation may play a role in the pathophysiology of the disease. Early diagnosis and treatment is essential for prognosis since irreversible neurological impairment or death occurs in a minority of cases. Severe manifestations of PRES, such as status epilepticus, cerebral hemorrhage, or herniation, may require admission to the intensive care unit (ICU). Treatment recommendations are limited because few examples and case reports are available. Blood pressure lowering and antiepileptic drugs, as well as reduction or removal of cytotoxic agents are common methods of treatment [2].

PRES is a rare neurological manifestation in patients with systemic lupus erythematosus (SLE). With either the acute onset of neurological deficits or accelerated hypertension, the diagnosis of PRES syndrome should be considered, particularly in those with high disease activity and previous renal involvement. Increased serum levels of proinflammatory cytokines, such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor-aleph (TNF-α) may stimulate endothelial cells to produce reactive oxygen species causing blood–brain barrier leakage, focal cerebral edema, ischemic changes, and parenchymal hematoma.

The use of immunosuppressant drugs, including high dose corticosteroids, cyclosporine A, cyclophosphamide, mycophenolate mofetil, and rituximab, may also predispose lupus patients to PRES due to fluid overload and abnormal endothelial activation. The treatment of PRES in SLE patients is more complicated due to a possible association between disease induction and immunosuppressants; however, many clinicians have treated it with pulse corticosteroid and cyclophosphamide assuming PRES is a consequence of active disease. A benign prognosis with a complete neurological recovery has been described in 65–80% of the cases of SLE-related PRES [3].

Reviewing the literature published in English before 2014 and included in the PubMed database, we found more than 90 published cases of PRES in SLE patients; however, its unique association with thrombotic thrombocytopenic purpura (TTP) are rarely reported [4,5].

In this case report, we describe a young Hungarian female patient with SLE and TTP who developed PRES syndrome resulting in a fatal outcome.

PATIENT DESCRIPTION

A 20 year old female patient with a 4 year history of seronegative non-erosive polyarthritis had a longstanding history of noncompliance to regular checkups and immunosuppressant treatment. She had been diagnosed with SLE. In April 2013, she presented with fatigue, malaise, weight loss, fever, and dyspnea at rest. Rapid progression in the neurological symptoms, respiratory failure, and associated TTP required prompt treatment in the ICU. An MRI showed extended edema in the temporal and occipital subcortical white matter regions and petechial hemorrhages. Besides supportive treatment, high-dose corticosteroid, pulse cyclophophamide and rituximab therapy, plasmapheresis, and intravenous immunoglobulin (IVIg) substitution were needed due to critical thrombocytopenia. A chest X-ray and echocardiogram showed pleuritis and pericarditis with marked effusion on both sites. The laboratory findings revealed anemia, leukopenia, thrombocytopenia, high erythrocyte sedimentation rate, elevated transaminases and lactate dehydrogenase, and hypoglycemia. Urinary total protein was 0.2 g/24 hours and her renal function was normal. Blood and urine culture showed no growth. A Coombs test

was negative. She was hypocomplementemic and had a positive anti-nuclear antibodies (ANA) at a titer of > 1:160 and her anti-double stranded DNA test (anti-dsDNA) was positive [Table 1]. She was diagnosed with SLE on the basis of a positive serology result, cytopenias, low complement levels, pleuropericarditis, fingertip vasculitis, and previous arthritis. At the same time she had no renal or central nervous system involvement. She was admitted to the ICU and given pulse corticosteroids at a daily dose of 250 mg for 3 days, parenteral nutrition via a subclavian vein, and a blood transfusion. Despite treatment, an echocardiograph detected rapidly accumulating pericardial fluid with right ventricular collapse necessitating pericardial fenestration in the cardiac surgery department. Improving blood cell counts, lowering levels of liver enzymes, and decreasing pericardial and pleural effusion allowed us to taper the corticosteroid dose. However, her blood culture was positive for *Staphylococcus epidermidis* and oral candidiasis; therefore, moxifloxacin and fluconazole were initiated. Thirteen days after her initial hospitalization, confusion, unconsciousness, and a new onset of seizure activity was observed, accompanied by a sudden fall in platelet count. Computed tomography (CT) of the brain showed diffuse low density in bilateral temporal-occipital lobes. T2-weighted and FLAIR MRI sequences confirmed high signal intensity lesions involving the subcortical white matter in the previously mentioned regions, but also small petechial hemorrhages were found [Figure 1]. Extended brain edema suggested PRES syndrome, but at the same time, some irreversible ischemic lesions and hemorrhaging were also suspected. TTP and deteriorating neurological status of the patient was an absolute indication for plasma exchange and high doses of corticosteroids were reinitiated in addition to supportive and antihypertensive treatment. Further decreasing platelet count and occurrence of spontaneous bleeding, diffuse hemorrhages, and suffusions made it necessary to proceed with immunosuppression treatment. The patient was prescribed an additional 1000 mg dose of cyclophosphamide; 400 mg/kg body weight high-dose human intravenous immunoglobulin (hIVIG) was administered for 3 days and recombinant human coagulation factor VIIa was also needed. She was intubated for airway protection due to progressive bleeding. Subsequently, 1000 mg rituximab was administered with continuous plasmapheresis due to treatment refractory TTP. Nine days after the diagnosis of PRES had been established, further progression was observed. Anisocoria was observed and an MRI revealed progression of the edema with supratentorial compression of the ventricles as well as hemorrhage in the left frontal lobe. To avoiding life threatening compression of the medulla, bifrontal craniectomy was indicated to reduce cranial pressure. After surgical intervention, continuous intensive supportive and vasopressor therapy failed to achieve further improvement, and brain death was declared. The patient died 28 days after her initial hospital admission.

COMMENT

In our case, PRES syndrome occurred very early in the course of the disease–only 1 month after the diagnosis of SLE. Generally, the onset of PRES occurs after a mean SLE duration of 12.2 ± 13.2 months. Since SLE is known to be very aggressive in the early periods of the disease, the vast majority of SLE patients presented with PRES have high disease activity with renal involvement and hypertension [3]. This patient also exerted a severe disease activity with a Systemic Lupus Erythematosus Disease Activity Index score of 17.

Clinically, our case was similar to previously reported cases in the context of the neurological symptoms, but to the best of our knowledge, this is the first publication from Hungary in which PRES syndrome is associated with severe TTP in a patient with SLE. We were only able to find two reports of patients with the same presentation [4,5]. The diagnosis was based on the clinical and the neuroradiological findings.

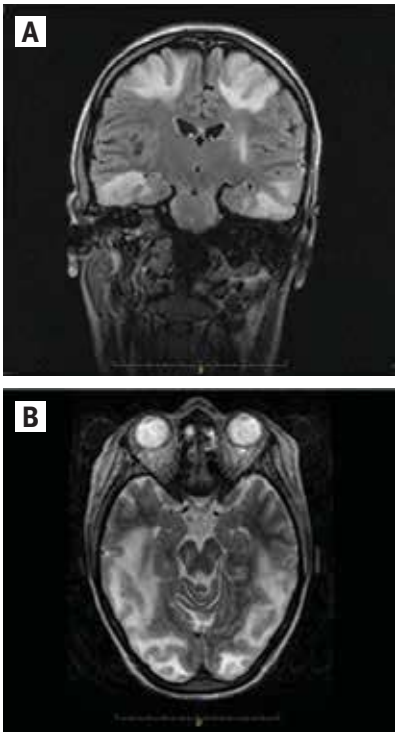
Changes related to edema are usually reversible, especially if early diagnosis and adequate early treatment can be initiated. Ischemic changes and microhemorrhages

Table 1. Laboratory findings of the patient

Lab test	Results
Leukocytes	5660 (NR 4500–10 800/mm^3)
Hemoglobin	7.7 (NR 11.5 at 15 g/dl)
Hematocrit	24 (NR 35 at 47%)
Platelets	94,000 (150,000–400,000/mm^3)
CRP	0.31 (NR < 0.45 mg/dl)
Aspartate aminotransferase	534 (NR < 40 U/L)
Alanine aminotransferase	115 (NR < 40 U/L)
Gamma-glutamyl transpeptidase	826 (NR 7–50 U/L)
Complement C3	0.25 (0.9–1.8 g/L)
Complement C4	0.08 (0.1–0.4 g/L)
Anti-double-stranded DNA antibody	> 200 U/L
ESR	78 (NR 6–20 mm/h)
Urea	2.2 (3.6–7.2 mmol/L)
Creatinine	27 (44–97 umol/L)
24 hour protein	0.2 g/24 hours (NR < 300 mg)

ESR = erythrosedimentation rate, CRP = C-reactive protein, NR = normal range

Figure 1. [A] MRI on FLAIR sequence **[B]** MRI on T2 weighted sequence showing subcortical edema in the temporal and occipital region and in the basal ganglia



MRI = magnetic resonance imaging, FLAIR = fluid-attenuated inversion recover

take longer to disappear and radiologic improvement lags behind clinical recovery. MRI findings can be helpful in identifying patients with worse prognosis. Diffusion weighted imaging (DWI) has been shown to be reliable in distinguishing between vasogenic edema in PRES and cytotoxic edema in the setting of cerebral ischemia. Hyperintensive signals on DWI suggest cytotoxic edema, which seems to be predictive of irreversible infarction and worse outcome. Death may result from progressive edema or intracerebral hemorrhage [2].

MRI findings showed that our patient had a high risk for potential grave consequences of PRES syndrome. In addition, suspected cytotoxic edema and hemorrhages potentially associated with TTP were noted. Antihypertensive therapy was used according to the recommended treatment, although we could not withdraw or even lower the dose of immunosuppressive therapy since PRES syndrome was complicated with severe TTP. High dose corticosteroids may predispose patients to hypertension and fluid overload. Other cytotoxic agents, such as cyclophosphamide, are considered to cause endothelial and mitochondrial dysfunction [5]. In our case, we cannot conclude that cyclophosphamide had any potential relationship with inducing PRES syndrome since the diagnosis had been established before administration of the treatment. Hence, we agreed to treat life-threatening complications of TTP aggressively with immunosuppressants.

CONCLUSIONS

It is unknown whether this treatment worsened the symptoms of PRES syndrome. Further investigations are needed to conclude whether cytotoxic agents should be discontinued or maintained, even though a high lupus activity is associated with PRES.

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References

1. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc* 2010; 85: 427-32.
2. Lai CC, Chen WS, Chang YS, et al. Clinical features and outcomes of posterior reversible encephalopathy syndrome in patients with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2013; 65 (11): 1766-74.
3. Mehta Y, Ramachandran K, Gundre P, Kupfer Y, Tessler S. Posterior reversible encephalopathy syndrome in a patient with newly diagnosed systemic lupus erythematosus and thrombotic thrombocytopenic purpura. *Chest* 2009; 136 (4): 8S.
4. Cassano G, Góngora V, Zunino A, Roverano S, Paira S. Reversible posterior leukoencephalopathy in systemic lupus erythematosus with thrombotic thrombocytopenic purpura. *J Clin Rheumatol* 2007; 5. Wijdicks, E.F. Neurotoxicity of immunosuppressive drugs. *Liver Transpl* 2001; 7: 937-42.
5. Wijdicks, E.F. Neurotoxicity of immunosuppressive drugs. *Liver Transpl* 2001; 7: 937-42.

Capsule

Cold-induced conversion of cholesterol to bile acids in mice shapes the gut microbiome and promotes adaptive thermogenesis

Adaptive thermogenesis is an energy-demanding process that is mediated by cold-activated beige and brown adipocytes, and it entails increased uptake of carbohydrates, as well as lipoprotein-derived triglycerides and cholesterol, into these thermogenic cells. Worthmann and co-authors reported that cold exposure in mice triggers a metabolic program that orchestrates lipoprotein processing in brown adipose tissue (BAT) and hepatic conversion of cholesterol to bile acids via the alternative synthesis pathway. This process is dependent on hepatic induction of cytochrome P450, family 7, subfamily b, polypeptide 1 (CYP7B1) and results in increased plasma levels, as well as fecal excretion, of bile acids that are accompanied by distinct changes in gut microbiota and increased heat production. Genetic and pharmacological interventions that targeted the synthesis and biliary excretion of bile acids prevented the rise in fecal bile acid excretion, changed the bacterial composition of the gut and modulated thermogenic responses. These results identified bile acids as important metabolic effectors under conditions of sustained BAT activation and highlight the relevance of cholesterol metabolism by the host for diet-induced changes of the gut microbiota and energy metabolism.

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Capsule

The good side of ceramides

Tumor growth is enhanced by some members of the ceramide family of lipids and the enzymes that produce them. However, Gencer and colleagues found that C18-20 ceramides synthesized by the enzyme CerS4 acted as tumor suppressors. The ceramides prevented a transforming growth factor-β (TGF-β) receptor complex from activating the Shh pathway. CerS4 inhibited metastases from mammary tumors and the development of the hairloss disorder alopecia in mice. The TGF-β and Shh pathways are challenging to target pharmacologically. These findings suggest that some ceramides may have therapeutic potential against these pathways in various disorders.

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