Posterior Reversible Encephalopathy Syndrome and Subarachnoid Hemorrhage After Methylprednisolone Pulse Therapy for a Patient with Lupus Nephritis

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a chronic inflammatory systemic disease that can affect any organ including the central nervous system (CNS). Subarachnoid hemorrhage (SAH) is one of its rare CNS manifestations. Posterior reversible encephalopathy syndrome (PRES), with features of headache, seizures, altered mental status, visual loss, and typical imaging findings, has recently been associated with SLE and immunosuppression, including use of high dose steroids. The patient was seen in University of the Philippines-Philippine General Hospital (UP-PGH), a tertiary training hospital in Manila, Philippines

Case: A 33-year-old female with lupus had PRES and SAH after methylprednisolone pulse therapy (MPPT) for nephritis. She presented with headache, hypertension and seizure. Initial cranial imaging showed hypodense areas in both parietotemprooccipital regions and small acute infarcts. She was intubated and treated with anti-convulsants for seizure; hydrocortisone and mycophenolate mofetil for SLE. She regained awareness on the seventh hospital day and was extubated. On the eleventh hospital day, she had fever, cough and was noted to be drowsy. She had increasing serum creatinine and decrease in urine output. Repeat cranial CT scan showed subarachnoid hemorrhage at the right sylvian fissure and better delineation of the previously described hypodensities (consistent with PRES). She was treated for hospital acquired pneumonia and underwent hemodialysis. Pneumonia was resolved and patient became conscious with no recurrence of neurologic symptoms. Consecutive outpatient visits showed a conscious and less edematous patient. Hemodialysis was eventually discontinued until she had normal creatinine with adequate urine output. Anti-seizure medications were also discontinued. Cranial CT scan a year later revealed normal brain parenchyma indicating resolution of previously noted hypodensities and subarachnoid hemorrhage.

Conclusion: There is a need to recognize PRES and differentiate it from irreversible neurologic conditions. With early identification and prompt intervention, permanent neurologic deficits may be prevented.

Keywords: posterior reversible encephalopathy, systemic lupus erythematosus, lupus nephritis, subarachnoid hemorrhage, methylprednisolone pulse, philippines, case report

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiologic diagnosis referring to a combination of symptoms such as headache, visual loss, seizures, altered mental status and cerebral imaging abnormalities. These imaging abnormalities are often symmetric and predominate in the posterior white matter. PRES can develop in association with different conditions; eclampsia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, anti-rejection therapy for organ transplantation, chemotherapy for leukemia with cisplatin and interferon alpha, systemic infection, and autoimmune disorders such as systemic lupus erythematosus (SLE), systemic sclerosis and polyarteritis nodosa. Factors that have been identified to trigger PRES are hypertensive crisis (most common), immunosuppressive therapy and renal insufficiency.[2, 3]

Hemorrhage is also known to occur in PRES but its characteristics have not been analyzed in detail. Hefzy et al. (2008) described three distinct types of hemorrhage in PRES -minute hemorrhage, sulcal subarachnoid hemorrhage and hematoma.[1] This patient presents with subarachnoid hemorrhage as well.

Case Presentation

This is a case of a 33-year-old Filipina presented with bipedal edema, decrease in urine output, discoid rashes and hypertension. She had anemia, leukopenia, thrombocytopenia, positive antinuclear antibodies (ANA) test and significant proteinuria (24-hour urine total protein of 2.1grams). She was diagnosed with lupus nephritis probably

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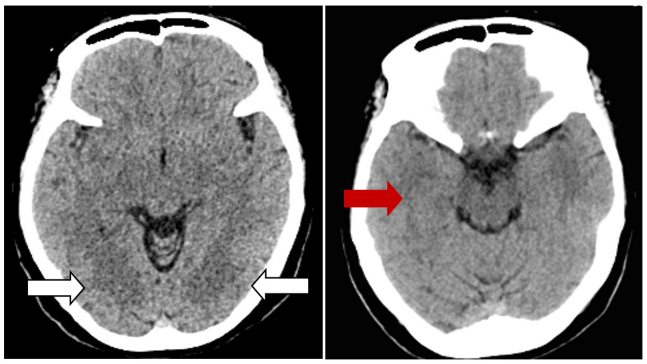

Figure 1. Cranial CT scan showed hypodense areas in both parietotemporooccipital regions (white arrows) and small acute infarcts in right centrum ovale (red arrow).

diffuse proliferative glomerulonephritis. Initial treatment consisted of prednisone (1 mg/kg/day), hydroxychloroquine, and calcium carbonate with vitamin D and subsequent methylprednisolone pulse therapy (MPPT) for three days.

A day after the MPPT, she complained of severe bitemporal headache. She had vomiting, generalized tonic-clonic seizures and elevated blood pressure. At the emergency room, she was drowsy but easily arousable and oriented. Seizure was initially responsive to diazepam but became refractory (status epilepticus). She became unresponsive and was intubated. Cranial computed tomography (CT) scan showed hypodense areas in both parietotemporooccipital regions (suggestive of PRES) and small acute infarcts at the right centrum semiovale and lentiform nucleus, left caudate nucleus, right thalamacapsuloganglionic region, left cerebellar hemisphere and pons. (Figure 1)

Lumbar tap opening pressure was elevated at 36mm H2O. Cerebrospinal fluid (CSF) sample was light yellow and turbid, with red blood cell (RBC) 2,600x10^6/L, white blood cell (WBC) 8x10^6/L, polymorphonuclear leukocyte (PMN) 100%, glucose 3.63 mmol/L (2.2-3.9) and total protein 1.16 g/L (0.2-0.6). There was no bacterial growth in the CSF culture. Electroencephalogram (EEG) showed a background activity of low voltage monotonous theta activity admixed with intermittent low voltage delta activity; consistent with a moderate degree of diffuse or bilateral cerebral injury or dysfunction.

She was treated with anti-hypertensives and the following anti-convulsants-midazolam drip, leviteracetam and phenobarbital. Hydrocortisone 300mg/day, mycophenolate mofetil 2g/day and hydroxychloroquine 200mg/day were continued. She regained consciousness on the seventh hospital day and was successfully extubated.

On the eleventh hospital day, she developed cough, fever and sensorial deterioration to stupor. She also had anasarca, progressive decrease in urine output and azotemia. A new cranial CT showed a small hypodensity

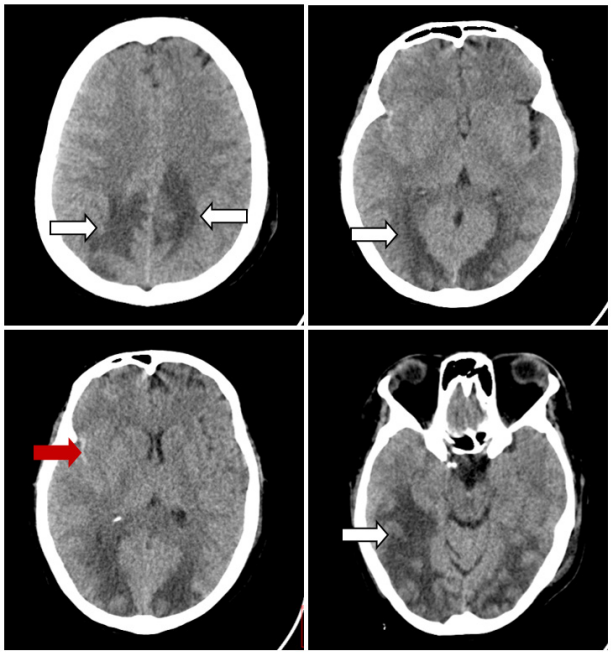

Figure 2. CT scan of the head showing hypodense areas in bilateral parietotemporooccipital as well as frontal regions. (White arrows) A small hyperdensity in the right Sylvian fissure which may be minimal subarachnoid hemorrhage. (Red arrow)

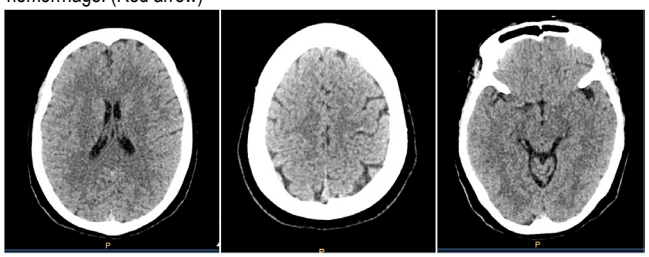

Figure 3. Follow up study done one year after the seizure shows complete resolution of the above mentioned hypodense foci.

(HU 56) at the right Sylvian fissure (a subarachnoid hemorrhage) and better delineation of the previously described hypodensities (consistent with PRES). (Figure 2) She underwent hemodialysis and treatment for hospital-acquired pneumonia.

After a series of hemodialysis sessions and completion of antibiotics, she regained full wakefulness and alertness. On discharge from the hospital, hemodialysis was continued and she was maintained on prednisone 0.75 mg/kg/day, hydroxychloroquine 200mg/day, mycophenolate mofetil 2g/day and calcium supplement.

She was seen at the outpatient clinic two weeks later and was found to be alert, ambulatory, with no new skin lesions and less edema. Anti-seizure medications were discontinued. Hemodialysis was discontinued inasmuch as she had adequate urine output and a normal creatinine.

Repeat cranial CT scan a year after the seizure showed resolution of hypodensities with no focal brain parenchymal lesions. (Figure 3)

Discussion

In SLE, 14%-75% of patients present with central nervous system (CNS) symptoms. These manifestations include headache, seizure, transverse myelitis, psychosis, stroke, neuropathy, myopathy, intracerebral aneurysm, intracerebral hemorrhage, and subarachnoid hemorrhage (SAH).[4,5,6]

There are few reports of SAH in SLE. Chang et. al (2013) in a nationwide population-based study showed that SAH is a rare complication of SLE. It was associated with higher mean daily dose of steroids and a history of platelet or red blood cell transfusion. Mimori et. al (2000) identified SAH in 10 out of 258 (3.9%) SLE patients; five had no apparent cause other than SLE while others had saccular aneurysm.[7,8]

Recently, there is recognition of PRES as one of the CNS syndromes in lupus.[9] There may be an active nephritis, hypertension and MPPT use associated with PRES. It is recognized because of multiple symptoms such as headache, loss of vision, changes of mental status and seizures and specific radiographic findings. Pathogenesis is not clearly understood but different mechanisms were postulated. One of which is the auto-regulatory failure (in hypertensive encephalopathy) resulting to vasodilatation. Other mechanisms include endothelial dysfunction probably due to the cytotoxic effects of immunosuppressive agents or systemic inflammation in patients with SLE.[2,4] The resulting vasogenic edema which may result from hypertension and endothelial damage may be evident in the parieto-occipital lobes of the brain on computed tomography and magnetic resonance (MR) imaging. Other findings include bilateral symmetrical hypodensities localised to the subcortical white matter areas on CT and hypointense and hyperintense areas on T1- and T2-weighted MR images, with the grey matter usually spared.[10] These imaging findings resolve completely when the condition is recognized and treated early.

Management of PRES consists of anti-convulsants for seizures, addressing the triggers such as aggressive control of hypertension, airway protection by early intubation if indicated especially in status epilepticus patients and removal of the offending drug.[11] Glucocorticoids have been implicated in PRES. In this case, treatment with hydrocortisone improved her symptoms.

Similar to the patient's case, Streck et. al in 2012 reported a case of a 30-year old Caucasian female with SLE who developed PRES after infusion with MPPT for nephritis. She had severe headache and right hemianopsia but normal mental status noted on the fourth day of MPPT. Cranial MRI with T2 and fluid-attenuated inversion recovery sequences (MRI-T2/FLAIR) showed a subcortical T2 hyperintensity without enhancement on both occipital lobes. MPPT was discontinued and she was given analgesics for headache. Her vision normalized and headache subsided in five days. Repeat cranial MRI done after three weeks was normal.[2]

A study by Chan and colleagues reported 10 SLE patients who had PRES in a Chinese cohort of 725. Eight were newly diagnosed lupus nephritis. Two out of eight patients had elevated lumbar tap opening pressure and negative CSF cultures.[10] These findings are comparable to our patient who also had nephritis, elevated opening pressure on lumbar tap and negative CSF cultures.

Although it is known that clinical and radiologic manifestations of PRES may be reversed, it is not yet determined when this resolution will happen. It may range from days to weeks. However, when left untreated, PRES may lead to ischemia, infarction, and death.[4] It is essential that this condition is not erroneously diagnosed for other conditions such as an ischemic stroke because thrombolysis could result in detrimental outcomes in PRES patients.[10,12]

It is important to recognize PRES as a manifestation of lupus nephritis or of MPPT and to act quickly to ensure its resolution.

Conclusion

There are varied CNS presentations in SLE. When there is sensorial deterioration, it is prudent to rule out CNS infection, cerebrovascular ischemia or hemorrhage, and PRES. Occasionally, conditions may occur in combination; like PRES and SAH in the patient as discussed. Accurate and timely recognition of PRES and other CNS manifestations is emphasized to reduce sequelae of permanent damage to the nervous system.

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