Immunosuppressant therapy-induced posterior reversible encephalopathy syndrome: an emerging cause, a rare case report

Vinay Kumar Rastogi[1], Paras Passi[1], Shashank Sadhwani[2*], Prashant Surolia[3]

European Journal of Medical Case Reports
Volume 9(6):130–134
DOI: 10.24911/ejmcr.9-2073

ABSTRACT

Background: Posterior reversible encephalopathy syndrome (PRES) is an acute or subacute cerebral syndrome, the main manifestations of which are headache, encephalopathy, seizures, or visual disturbances in various combinations; this case describes PRES related to drugs and toxic agents.

Case Presentation: We present a case of a 61-year-old female with a history of rheumatoid arthritis, hypothyroidism, dyslipidemia, and drug-induced neutropenia who developed PRES following the use of tab leflunomide. The patient presented with intense generalized itching, erythematous rash, and acute headache, progressing to confusion. Neuroimaging revealed leptomeningeal enhancement in the parieto-occipital regions, consistent with PRES. Prompt treatment with pulse steroid therapy, antihypertensive, and discontinuation of the tab leflunomide led to complete recovery.

Conclusion: This case highlights the importance of early recognition and management of triggering agent causing PRES in patients with autoimmune diseases on immunosuppressant therapy.

Keywords: Hypothyroidism, immunosuppressant therapy, posterior reversible encephalopathy syndrome (PRES), rheumatoid arthritis, case report.

Type of Article: CASE REPORT **Specialty:** Family Medicine, Neurology, Radiology

Correspondence to: Shashank Sadhwani
*DNB Family Medicine Trainee, Jaipur Golden Hospital, Delhi, India.
Email: sadhwanishashank@gmail.com
Full list of author information is available at the end of the article.

Received: 10 April 2025
Revised (1): 29 May 2025
Accepted: 12 June 2025

Background

Posterior reversible encephalopathy syndrome (PRES) is an acute neuroradiological disorder characterized by reversible vasogenic edema, typically in the posterior regions of the brain. The condition presents with a range of symptoms, including headache, seizures, loss of consciousness, confusion, visual disturbances, and other localized neurological impairments. It is often associated with labile hypertension, renal failure, eclampsia, exposure to immunosuppressive/cytotoxic drugs, or autoimmune diseases. Early diagnosis and treatment are crucial for favorable outcomes. History, clinical examination, and radiologic findings of symmetric bilateral hyper-intensities on T2-weighted magnetic resonance imaging (MRI) reflecting vasogenic edema are used to diagnose PRES [1]. Numerous mechanisms have been proposed to explain the pathophysiology of PRES, which remains uncertain. Many of these mechanisms can be present together, such as hyperperfusion due to loss of autoregulatory vascular tone, hypoperfusion due to systemic vasoconstriction, and malfunction or endothelial injury due to a blood–brain barrier lesion. The presence of white matter vasogenic edema involving the posterior cerebral lobes (parietal and occipital lobes) is seen in brain MRI [2]. Studies report PRES in up to 2.7%-25% of bone marrow transplant patients, 0.4% of solid organ transplant patients, 0.84% of patients with end-stage renal disease, and 0.69% of patients with systemic lupus erythematosus [3]. PRES was an underdiagnosed neurological disorder, but because of the increased availability and higher quality of imaging, awareness of the disease has markedly improved. We report a case of PRES in a patient with rheumatoid arthritis and hypothyroidism, emphasizing the role of immunosuppressive therapy in its pathogenesis.

The MRI T2-weighted sequences show signal changes that appear in the bilateral white matter regions and typically in the occipital lobes.

Case Presentation

A 61-year-old female with a past medical history of rheumatoid arthritis, hypothyroidism, post-herpetic neuralgia, dyslipidemia, and drug-induced neutropenia presented with severe generalized itching for the last 4 weeks, which was progressive, aggravated in the last 3-4 days associated with erythematous rash over her bilateral lower limbs and abdomen. Oral medications she was taking -

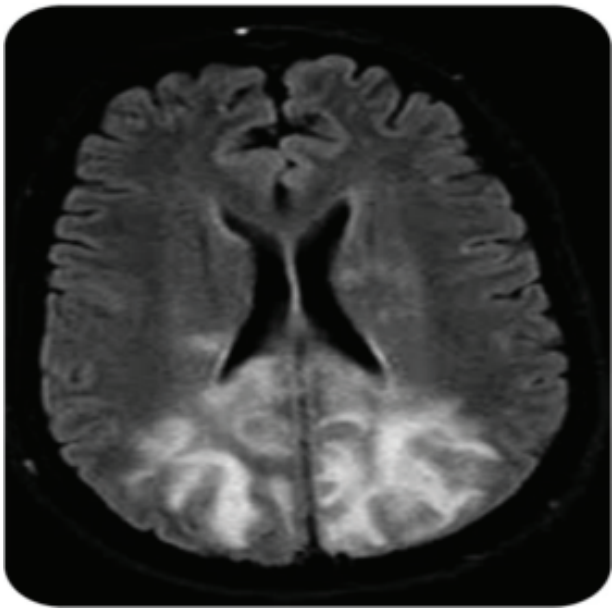

Figure 1. *Axial FLAIR MRI image demonstrating bilateral subcortical hyperintensities predominantly in the parieto-occipital lobes, consistent with vasogenic edema seen in posterior reversible encephalopathy syndrome (PRES).*

Hydroxychloroquine 200 mg twice daily, Leflunomide 20 mg once daily, Thyroxin 25 mcg once daily, and Rosuvastatin 10 mg once daily. On examination, she was hemodynamically stable and was having multiple erythematous pruritic plaques over her bilateral lower limbs and abdomen, which was diagnosed as acute urticaria, and she improved with the treatment. She developed a severe acute headache associated with raised blood pressure. She had no history of hypertension and was managed with analgesics and anti-hypertensive medications. The next day, the patient developed frequent bouts of severe acute headache and appeared confused, so fundoscopy and a computed tomography (CT) head were done. Fundoscopy was normal and CT head showed ill-defined white matter hypodensities in bilateral occipital lobes - edema. The following morning's MRI of the brain, with contrast, revealed leptomeningeal enhancement in the bilateral parieto-occipital regions, raising the possibility of PRES (Figure 1). Diagnosis of PRLI syndrome was done and neurologist advised for pulse therapy of steroids for 5 days. The patient was treated successfully with pulse steroid therapy of 5 days, anti-hypertensive, and discontinuation of leflunomide, leading to complete resolution of symptoms and normalization of imaging findings within a week. The patient was discharged and kept in a long follow-up.

Discussion

Hinchey et al. first described PRES in a series of 15 individuals in 1996 as the reversible posterior leukoencephalopathy syndrome [4]. PRES, a reversible neurological condition, involves white matter edema involving the occipital and parietal lobes. PRES appears in almost all age groups, from children to the elderly, but it is more common in young and middle-aged individuals, and women are disproportionately affected. While the incidence of PRES in the general population is unknown, it has been documented in a small group of patients. The incidence among hospitalized adults was 2.7%-25% following bone marrow transplantation, 0.4% after solid organ transplantation, 0.84% in those with end-stage renal disease, and 0.69% with systemic lupus erythematosus [1]. In the hospitalized pediatric population, the incidence of PRES is 0.04%, and 0.4% in pediatric intensive care units.

The actual pathophysiological process behind PRES is unknown. Three potential explanations exist as follows: (1) brain infarcts caused by cerebral vasoconstriction, (2) vasogenic edema due to cerebral auto-regulation failure, and (3) fluid and protein leakage into the brain from blood–brain barrier disruption due to endothelial damage [5,6] (Tables 1 and 2).

The "vasogenic theory," which proposes that rapidly increasing hypertension combined with a lack of cerebral autoregulation leads to a breach of the blood–brain barrier and secondary vasogenic edema, is the most popular. The auto-regulating response is insufficient when blood pressure rises rapidly and dramatically, resulting in hyperperfusion and extravasation of plasma and macromolecules. The posterior circulation of the brain is comparably less innervated with sympathetic nerves, which is most likely the cause of PRES's preferential involvement of the posterior portion of the brain [7].

PRES is characterized by a wide range of neurological symptoms that generally occur in the setting of elevated arterial blood pressure. Cases of PRES were first reported in patients with hypertension and later observed in normotensive and septic patients. Acute blood pressure elevation, renal insufficiency, pre-eclampsia/eclampsia, autoimmune disorders, infection, transplantation, and chemotherapeutic medications are all common risk factors for PRES [3]. PRES can be acute or subacute, with neurologic symptoms that may appear from a few hours to weeks [8]. Quantitative and qualitative illnesses of consciousness, including cognitive impairment, stupor, somnolence, or coma, may be manifested as signs of encephalopathy. Epileptic seizures, reported in roughly two-thirds of all PRES patients, can be focal and generalized [8-10]. Visual disturbances such as visual field abnormalities, including hemianopia and cortical blindness, worsening of visual acuity, or visual hallucinations, can be seen in approximately two-thirds of all PRES patients owing to the frequent involvement of the occipital lobes [4,8]. A few myelopathic symptoms and cases demonstrating spinal cord involvement have been reported. Other rare clinical manifestations include abulia, agitation, delusions, opisthotonus, optic ataxia, and ocular apraxia [3].

***Table1**. Conditions and procedures related to PRES.*

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) IS ASSOCIATED WITH VARIOUS CONDITIONS AND PROCEDURES*	
TYPES OF DISORDER OR CONDITION	**SPECIFIC ILLNESS OR PROCEDURE**
Systemic disorders	Acute and chronic renal failure, primary aldosteronism, sepsis and shock, and pheochromocytoma.
Pregnancy-related conditions	Preeclampsia, eclampsia, and the HELLP (hemolysis, elevated liver-enzyme levels, and low platelet count) syndrome.
Autoimmune or connective-tissue disorders	Systemic lupus erythematosus, scleroderma, Sjögren's syndrome, vasculitis, cryoglobulinemia, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Hashimoto's thyroiditis, primary sclerosing cholangitis, antiphospholipid antibody syndrome, granulomatosis polyangiitis (formerly known as Wegener's granulomatosis), systemic sclerosis, giant-cell arteritis, polyarteritis nodosa, and antineutrophil cytoplasmic antibody-associated vasculitis.
Post procedure conditions	Solid-organ transplantation, stem-cell transplantation, immune globulin transfusion, extracorporeal membrane oxygenation, bone marrow transplantation, blood transfusion, spine surgery, induced hypertension (aneurysmal subarachnoid hemorrhage), carotid surgery, and cardiac surgery.
Hematologic disorders	Sickle cell disease, hemolytic-uremic syndrome, thrombocytopenic purpura, acute myeloid leukemia, acute lymphocytic leukemia, and non-Hodgkin's lymphoma.
Neurologic disorders	Neuromyelitis optica spectrum disorder, carotid dissection, subacute sclerosing panencephalitis, moyamoya disease, and craniopharyngioma.
Metabolic disorders	Porphyria (acute intermittent porphyria) and primary hyperparathyroidism.

*The conditions may be commonly observed in conjunction with severe hypertension or moderate but acute hypertension outside the patient's normal range; however, this list is not exhaustive of all conditions related to PRES.

***Table2**. Drugs and toxic agents associated with posterior reversible encephalopathy syndrome include several categories of substances.*

DRUGS AND TOXIC AGENTS RELATED TO POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME	
DRUG CLASS OR EXPOSURE	**SPECIFIC DRUGS OR TOXIC AGENTS**
Chemotherapeutic drugs	Bevacizumab, tyrosine kinase inhibitors, bortezomib, cytarabine, gemcitabine, L-asparaginase, methotrexate, vincristine, and cisplatin (platinum-based agents)
Immune-modifying drugs	Tacrolimus, sirolimus, cyclosporine A, rituximab, interleukin, tumor necrosis factor antagonists, and interferon alfa
Pharmacologic agents	Erythropoietin, granulocyte colony-stimulating factor, voriconazole, butalbital-acetaminophen-caffeine therapy, pseudoephedrine, and antiretroviral therapy for human immunodeficiency virus infection
Intoxications and exposures	Alcohol intoxication, drug overdose (e.g., lithium, dextroamphetamine, acetaminophen, ephedrine, phenylpropanolamine, digitoxin, bismuth), chemical substances (e.g., organophosphates), illicit drugs (e.g., cocaine, amphetamine, mephedrone, kratom, amide of lysergic acid), and natural toxins (e.g., from snake bites, scorpion bites, wasp stings, mushrooms, licorice)

It is important to note that this list provides examples and does not represent a full listing of all drugs and toxic agents associated with PRES.

The following diagnostic criteria for PRES were proposed by Fugate and Schmutzhard: acute onset of neurological symptoms, radiologic evidence of (typically posterior) vasogenic edema, and the reversibility of both clinical and imaging findings in appropriate clinical context [8]. Comorbidities or triggering factors in the clinical context and the presence of acute onset neurological symptoms, concurrent labile blood pressure, and vasogenic edema reflected on neuroimaging findings suggest PRES. The cornerstone of confirming a diagnosis of PRES is brain imaging. Although non-contrast CT can detect vasogenic edema in some cases, brain MRI, particularly the T2-weighted and fluid-attenuated inversion recovery sequences, is far more sensitive [11]. The traditional imaging patterns usually demonstrate bilateral, subcortical, and symmetrical vasogenic edema involving the parieto-occipital region. Other than the parietal occipital pattern, the holohemispheric watershed and superior frontal sulcus pattern are different patterns described in the literature [3]. Differential diagnoses of PRES include cerebrovascular accidents, meningoencephalitis, demyelinating disorders of the brain, and cerebral venous thrombosis. Early imaging is the key to making the diagnosis [12].

Because there is no specific management strategy currently available for PRES, it is treated symptomatically. The treatment of the underlying condition that leads to the

development of PRES is critical. Eliminating the triggering factor or treating the underlying pathology should be initiated as soon as possible in the course of the disease [8]. Supportive care should be provided, including hydration, correction of electrolyte imbalance, airway monitoring, and ventilation support, especially for patients with altered mental status. Prompt dialysis is recommended for patients with renal failure. For patients in hypertensive crisis, no more than 20%-25% of the blood pressure should be decreased in the first few hours to reduce the risk of cerebral, coronary, and renal ischemia [3]. Since the neurological symptoms of PRES are largely reversible in most patients, the prognosis is mainly dictated by underlying conditions. Although reversible, secondary complications, including massive ischemic infarction, intracranial hemorrhage, and status epilepticus, may lead to permanent neurologic deficits and death. Although inciting factors commonly recur, the recurrence of PRES has been recorded to be infrequent (<10%) [12]. PRES is a rare but serious condition that can occur in patients with autoimmune diseases on immunosuppressive therapy. The pathophysiology involves cerebrovascular dysregulation and endothelial dysfunction, leading to vasogenic edema. In this case, the patient's history of rheumatoid arthritis and use of leflunomide likely contributed to the development of PRES. Early recognition and management, including control of hypertension and discontinuation or dose reduction of the offending drug, are essential for recovery. This case underscores the importance of monitoring patients on immunosuppressive therapy for neurological symptoms.

Conclusion

PRES is a reversible illness that is defined by acute neurologic symptoms and radiographic evidence of vasogenic edema, typically involving parieto-occipital areas. Acute to subacute neurologic symptoms, including confusion, visual symptoms, headache, and posterior transitory alterations on neuroimaging, are used to identify PRES. Treatment is primarily determined by the underlying disease, and success is dependent on early detection and treatment of the underlying condition. Early detection and treatment of this uncommon condition are critical for decreasing the risk of persistent neurologic impairments and death.

Acknowledgments

The authors thank the patient for consenting to this case report and the multi-specialty teams for their support in the early detection and management of the case.

What's New?

Discontinuation of tab leflunomide, which was supposed to be an offending agent, leads to complete recovery clinically as well as radiologically, soon it was re-initiated at a modified low dose and the patient was kept in long-term follow-up.

List of Abbreviations

CT	Computed tomography
MRI	Magnetic resonance imaging
PRES	Posterior reversible encephalopathy syndrome

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Due permission was obtained from the patient to publish the case.

Author details

Vinay Kumar Rastogi[1], Paras Passi[1], Shashank Sadhwani[2], Prashant Surolia[3]

1. Consultant, General Medicine, Jaipur Golden Hospital, Delhi, India
2. DNB Family Medicine Trainee, Jaipur Golden Hospital, Delhi, India
3. General Medicine Trainee, Jaipur Golden Hospital, Delhi, India

References

1. Cherniawsky H, Merchant N, Sawyer M, Ho M. A case report of posterior reversible encephalopathy syndrome in a patient receiving gemcitabine and cisplatin. Medicine (Baltimore). 2017;96:e5850. https://doi.org/10.1097/MD.0000000000005850
2. Fonseca J, Oliveira K, Cordeiro M, Real MV. Posterior reversible encephalopathy syndrome: a case report. Neurologia (Engl Ed). 2019;34(2):135–7. https://doi.org/10.1016/j.nrl.2016.07.011
3. Hinduja A. Posterior reversible encephalopathy syndrome: clinical features and outcome. Front Neurol. 2020;11:71. https://doi.org/10.3389/fneur.2020.00071
4. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996;334:494–500. https://doi.org/10.1056/NEJM199602223340803
5. Sodalagunta MB, Sudulagunta SR, Kumbhat M, Sepehrar M, Settikere Nataraju A, Bangalore Raja SK. Posterior reversible encephalopathy syndrome: a case report. J Neurol Res. 2016;6(5–6):106–10. https://doi.org/10.14740/jnr402w
6. Romergryko G, Geocadin MD. Posterior reversible encephalopathy syndrome. N Engl J Med. 2023;388:2171–8. https://doi.org/10.1056/NEJMra2114482
7. 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(5):427–32. https://doi.org/10.4065/mcp.2009.0590
8. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol. 2017;264(8):1608–16. https://doi.org/10.1007/s00415-016-8377-8
9. Kozak OS, Wijdicks EF, Manno EM, Miley JT, Rabinstein AA. Status epilepticus as initial manifestation of posterior reversible encephalopathy syndrome. Neurology 2007;69(9):894–7. https://doi.org/10.1212/01.wnl.0000269780.45472.16

10. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol. 2008;65:205–10. https://doi.org/10.1001/archneurol.2007.46
11. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol. 2007;28(7):1320–7. https://doi.org/10.3174/ajnr.A0549
12. Rijal JP, Giri S, Dawadi S, Dahal KV. Posterior reversible encephalopathy syndrome (PRES) in a patient with late postpartum eclampsia. BMJ Case Rep. 2014;2014:bcr2013203162. https://doi.org/10.1136/bcr-2013-203162

Summary of the case

1	**Patient (gender, age)**	A 61-year-old female
2	**Final diagnosis**	Immunosuppressant therapy-induced posterior reversible encephalopathy syndrome
3	**Symptoms**	Severe generalized itching for the last 4 weeks, which was progressive, aggravated in the last 3-4 days associated with erythematous rash over her bilateral lower limbs and abdomen
4	**Medications**	Discontinuation of tab leflunomide, which was supposed to be an offending agent lead to complete recovery clinically as well as radiologically, soon it was re-initiated at a modified low dose and patient kept in long-term follow-up.
5	**Clinical procedure**	-
6	**Specialty**	Family Medicine, Neurology, Radiology