OMCR

Oxford Medical Case Reports, 2019;8, 342–344

doi: 10.1093/omcr/omz072
Case Report

CASE REPORT

Rare but not beyond care: a young female with altered mental status and seizures

Samata Pathireddy[1], Subashish Bose[2], Krishna Baradhi[3] and Narothama Reddy Aeddula[1,*,†]

[1]Deaconess Health System, 600 Mary Street, Evansville, IN 47747, USA, [2]Lynchburg Nephrology, 2091 Langhorne Road, Lynchburg, VA 24501, USA, [3]University of Oklahoma, 4444 E. 41st Street Tulsa, OK 74135-2537, USA

*Correspondence address: Deaconess Health System, 600 Mary street, Evansville, IN 47747, USA. Tel: +001 812 492 5202; Fax: +001 812 426 6610; E-mail: dr.anreddy@gmail.com or nareddy@iu.edu

Abstract

A 40-year-old Caucasian lady with focal crescentic glomerulonephritis (p-ANCA) demonstrated by kidney biopsy, was treated with intravenous pulse steroids followed by weekly outpatient rituximab infusions (375 mg/m^2). Five days after the fourth and final rituximab infusion, she developed headaches, altered mental status and seizures. Upon transfer to our facility, magnetic resonance imaging of the brain revealed cortical white matter changes suggestive of possible progressive multifocal leukoencephalopathy (PML) or posterior reversible encephalopathy syndrome (PRES). She was aggressively treated with antihypertensives, anti-seizure medications, intravenous steroids, plasmapheresis and ventilatory support while awaiting cerebrospinal fluid analysis and polymerase chain reaction on John Cunningham virus DNA. She had a complete recovery and, at 1 year follow up, was found to be doing well. Awareness of potential complications of rituximab therapy, such as PRES or PML is critical in providing appropriate treatment.

INTRODUCTION

Rituximab treatment is associated with rare but significant adverse events of posterior reversible encephalopathy syndrome (PRES) or progressive multifocal leukoencephalopathy (PML) [1]. Our case highlights the need for clinical acumen, awareness, early recognition of neurological symptoms and diagnosis related to such rare complications. Both of these complications may have similar clinical presentations and may appear indistinguishable on magnetic resonance imaging (MRI) [1]. Rituximab, an anti-CD20 monoclonal antibody, carries a 'black box' warning for PML, raising a high degree of concern for PML when new neurological symptoms accompany white matter changes on the MRI [1]. We report PRES after rituximab use in a patient who had a clinical presentation and white matter changes on the MRI that are indistinguishable from PML.

CASE REPORT

A 40-year-old Caucasian lady with a prior medical history of chronic kidney disease stage 4 with a recently diagnosed biopsy-proven focal crescentic glomerulonephritis (p-ANCA), chronic obstructive pulmonary disease, obstructive sleep apnea (OSA), diabetes mellitus type 2, hypertension and morbid obesity was transferred from outside hospital (OSH) with altered mental status, headaches and generalized tonic-clonic seizures. Given rapid clinical deterioration and progressive cognitive decline, she was transferred to our facility. Upon arrival, the patient's Glasgow Coma Scale was 4, was hypoxic and required emergent endotracheal intubation.

After a recent diagnosis of focal crescentic glomerulonephritis, she had received three doses of 1 gm intravenous pulse methylprednisolone followed by oral prednisone(1 mg/kg/day)

†Narothama Reddy Aeddula, http://orcid.org/0000-0001-8530-668X
Received: December 18, 2018. **Revised:** June 2, 2019. **Accepted:** June 21, 2019

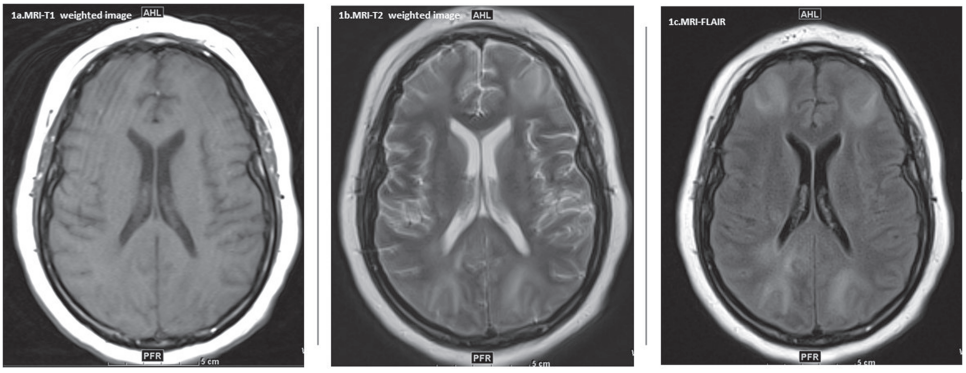

Figure 1: a-c: Multi-planar, multi-sequence, non-contrast MRI brain (T1-, T2-weighted images and FLAIR). Extensive white matter changes predominantly in subcortical and to a lesser extent in periventricular white matter, seen symmetrically throughout the cerebral hemispheres in the bilateral frontal lobes, parietal, temporal lobes and occipital lobes.

along with weekly outpatient rituximab intravenous infusions (375 mg/m^2). The last and fourth dose of rituximab was 5 days before her presentation.

She was an active smoker with 15 pack years history, and family history was not relevant to her current presentation. Her physical examination was notable for obesity, intubated status, with reduced air entry in the posterior lung fields and trace pedal oedema. Blood pressure on presentation was 162/79 mm Hg. Her husband endorsed good compliance with medications and continuous positive airway pressure for her OSA. Laboratory studies showed serum creatinine of 2.2 mg/dL and blood urea nitrogen of 29 mg/dL. White cell count was 10.8 (1000/uL), haemoglobin was 12 gm/dL and platelets was 230 (1000/uL). Urine analysis showed 3+ protein, 40 RBCs and 4 WBCs. She underwent extensive serological work up 5 weeks prior and were relevant with her pauci-immune ANCA vasculitis. HIV, hepatitis B and C serologies were unremarkable. A lumbar puncture with cerebrospinal fluid (CSF) examination showed normal opening pressure, clear fluid, 0 WBCs, protein of 47 mg/dL and glucose of 131 mg/dL. An MRI showed cortical white matter changes suggestive of possible PML or PRES (Fig. 1a–c). CSF polymerase chain reaction (PCR) for herpes simplex virus (HSV) and John Cunningham virus (JCV) were negative. Flow cytometry and cytology were negative. Serum JCV PCR was negative. Brain biopsy deferred given clinical improvement.

TREATMENT

The patient received intravenous levetiracetam (Keppra), antihypertensives, empiric broad spectrum antibiotics and had two sessions of plasmapheresis (with albumin replacement) to remove rituximab to avoid further ill effect on the central nervous system from it and to promote immune reconstitution while awaiting final CSF analysis. She opened eyes, responded to verbal commands on Day 5 and was extubated on Day 7 of her hospitalization.

DISCUSSION

PRES is a clinico-radiographic syndrome of various etiologies, first described by Hinchey *et al.* [2] in a case series in 1996. This complex clinical syndrome presents with varied clinical features such as headache, confusion, altered mental status, visual disturbances and seizures. Seizures are often presenting manifestation and are usually tonic-clonic. The clinical syndrome is associated with characteristic neuroimaging findings of bilateral posterior cerebral white matter oedema. The pathogenesis is unclear, but it appears to be related to disordered cerebral autoregulation and endothelial dysfunction [2]. A wide variety of medical conditions and medications are implicated as causes of PRES [3]. PRES is usually benign. However, cases with progressive cerebral oedema, intracerebral haemorrhage leading to death have been reported [4].

PML is a severe demyelinating disease of the central nervous system, caused by reactivation of the JCV, which can induce a lytic infection involving the central nervous System myelin-producing cells, the oligodendrocytes [5]. Usually, PML occurs almost exclusively in immunosuppressed individuals. However, there are isolated case reports of PML in patients without apparent immunosuppression [6]. In a retrospective population-based analysis of a health insurance database, the incidence rates of PML in patients with autoimmune vasculitis was 10.8 per 100 000 person years [7]. Clinically, PML presents with subacute neurological symptoms such as altered mental status, hemiparesis, ataxia and visual symptoms such as hemianopia and diplopia. On MRI scan, PML lesions are seen as areas of a decreased signal on T1-weighted images and increased signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [8]. Seizures can occur in up to 44% of patients who survive PML. In patients with PML, the course is usually progressive and fatal, and those who survive are left with severe neurologic sequelae.

A chimeric anti-CD20 monoclonal antibody, rituximab is increasingly used in the treatment of haematological malignancies such as non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, systemic lupus erythematosus, neuromyelitis optica and ANCA-associated vasculitis. First approved in 1997, it is routinely used with more than two million prescriptions between 1997 and 2017 in the USA (http://www.rituxan.com, accessed on 4 May 2019). Adverse effects range from the familiar (infusion reactions, pancytopenia, bacterial and viral infections and cardiac events) to the rare (PML, cytokine release syndrome and respiratory failure). Given the expression of CD20 in activated endothelial cells, rituximab may cause direct cell damage, endothelin-mediated vasospasm and dysfunction, which may lead to PRES.

The clinical overlap between PRES and PML can make differentiating these two neurologic disorders challenging. PML can resemble PRES on MRI, making the clinical presentation a critical distinguishing factor between these two conditions [1]. One cannot rely on radiographic imaging to establish the diagnosis of

PML; confirmatory evidence should include the demonstration of the JCV in the CSF or the brain [9]. In our patient, rather an acute onset of symptoms was more in line with PRES than PML. Laboratory findings were also relatively supportive of the later.

On the literature review, we found a few other cases of PRES associated with the use of rituximab. Patients had rituximab therapy for a variety of diseases: B-cell lymphoma, systemic lupus erythematosus, solid organ transplantation, hepatitis C, lupus nephritis, cryoglobulinemia and neuromyelitis optica. To the best of our knowledge, this is the first reported case of rituximab use associated with PRES in a patient with ANCA vasculitis. Perhaps, our case contributes to the debate, whether ANCA vasculitis is an established risk factor for the development of PRES as reported previously [10]. Rituximab is indicated in the management of the pauci-immune ANCA vasculitis. It should be notable that our case has other risk factors for the development of PRES, such as hypertension and ANCA vasculitis. Rituximab association with PRES is rather weak as both the underlying conditions, e.g. systemic lupus erythematosus, and the treatments utilized for these disorders may contribute to PRES.

Rituximab is rarely associated with severe adverse reactions, and usually that happens in patients with pre-existing risk factors for such adverse effects as in our case. Treatment of PRES consists mainly of blood pressure control, infection treatment, seizure control, renal replacement therapy and withdrawal of the inciting factor. To differentiate between PML and PRES, careful history, physical and laboratory examinations are extremely important.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

None needed.

CONSENT

Consent obtained from the patient and available on request.

GUARANTOR

Narothama Reddy Aeddula, Subhasish Bose.

REFERENCES

1. Berger JR, Neltner J, Smith C, Cambi F. Posterior reversible encephalopathy syndrome masquerading as progressive multifocal leukoencephalopathy in rituximab treated neuromyelitis optica. *Mult Scler Relat Disord* 2014;**3**:728–31. http://dx.doi.org/10.1016/j.msard.2014.08.004. Accessed May 1st 2019.
2. 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.
3. Lamy C, Oppenheim C, Mas JL. Posterior reversible encephalopathy syndrome. *Handb Clin Neurol* 2014;**121**:1687–701. doi: 10.1016/B978-0-7020-4088-7.00109-7.
4. Stott VL, Hurrell MA, Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. *Intern Med J* 2005;**35**:83–90.
5. Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. *Lancet Neurol* 2010;**9**:425–37. doi: 10.1016/S1474-4422(10)70040-5. Review.
6. Grewal J, Dalal P, Bowman M, Kaya B, Otero JJ, Imitola J. Progressive multifocal leukoencephalopathy in a patient without apparent immunosuppression. *J Neurovirol* 2016;**22**:683–687.
7. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology* 2010;**75**:1326–32. doi: 10.1212/WNL.0b013e3181f73600.
8. Sahraian MA, Radue EW, Eshaghi A, Besliu S, Minagar A. Progressive multifocal leukoencephalopathy: a review of the neuroimaging features and differential diagnosis. *Eur J Neurol* 2012;**19**:1060–9. doi: 10.1111/j.1468-1331.2011.03597.x.
9. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, *et al.* PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. *Neurology* 2013;**80**:1430–8. doi: 10.1212/WNL.0b013e31828c2fa1.
10. Patel UV, Patel NJ. Posterior reversible leukoencephalopathy syndrome as a presenting manifestation of p-ANCA-associated vasculitis. *BMJ Case Rep* 2014; pii: bcr2013202022. doi: 10.1136/bcr-2013-202022..