Rituximab-related posterior reversible encephalopathy syndrome in HUS patient post kidney transplant

Mohamad Habli, Nada Elyoussef, Mounir Khoury, Najat Joubran Fares

ABSTRACT

Abstract is not required for Clinical Images
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CASE REPORT

A 27-year-old female admitted for evaluation of anemia, thrombocytopenia, low grade fever and elevated creatinine two months after kidney transplantation.

Patient was receiving at home tacrolimus 2 mg bid, mycophenolate mofetil 1 g bid, prednisolone 20 mg daily, valgancyclovir 900 mg, and sulfamethoxazole/trimethoprim 900/160 mg three times/week. On admission patient was hemodynamically stable with blood pressure 110/70 mmHg, pulse rate 78/min, temperature 37.8°. No history of hypertension or hypertensive crisis. No elevated blood pressure recorded during hospitalization.

Upon admission, patient underwent kidney biopsy that showed features of thrombotic microangiopathy (TMA).

So patient was started on daily sessions of plasma exchange with fresh frozen plasma for five consecutive days without any improvement in platelet count or hemoglobin level and evidence of ongoing hemolysis (very low haptoglobin level, high LDH, low platelets and hemoglobin level).

Anti-CD20 rituximab was suggested as second line therapy for treatment of atypical HUS.

Eight hours following infusion of rituximab, patient started to complain of severe headache, blurred vision with scintillating scotomas, right hemianopsia that progressed to generalized constriction of the visual field with tunnel vision. Patient also developed simple focal seizures with rotation of eyes and head towards the right side. So, urgent MRI scan of brain was done (Figure 1) which showed extensive involvement of the posterior regions of both hemispheres, more prominent in the left posterior circulation, sparing the gray matter and unassociated with mass effect.

There are focal areas of increased signal on T2 FLAIR in the parietal and occipital lobes bilaterally and posteriorly. There are more prominent on the left. A similar subcortical patch of T2 increased signal is also noted in the left temporal lobe. These show faint or no restriction on diffusion. Signs in favor of posterior reversible encephalopathy syndrome (PRES).

Patient was started on antiepileptic drug (valproic acid IV) and pain killer for headache (paracetamol). During the same day patient complained from on and off visual symptoms and recurrent facial fasciculation, but headache subsided.

On the next day, patient developed more severe headache and facial fasciculation and blurred vision persist, so another MRI scan of brain was done (Figure 2).

The examination is compared to previous done on the previous day. There is increase in the extension of the previously described cortical and subcortical hyperintensities of the posterior aspects of the occipital and parietal lobes as well as of the left temporal lobe.

Decision was taken to do plasma exchange in order to remove rituximab as offending drug, because of severe neurological symptoms and worsening of radiological findings. So, on day-2 after rituximab therapy, patient underwent plasmapheresis with albumin. A Few hours following plasma exchange, patient started to have marked improvement in blurred vision and headache subsided. On day-3, patient was free of all neurological symptoms that developed after IV administration of anti-
CD 20. No blurred vision or hemianopsia, no headache, and no more simple focal seizures.

Follow-up brain MRI scan was done on day-3 to check if clinical improvement was associated with radiological improvement also.

There has been a significant decrease in the high signal intensity in the cortical and subcortical regions of the parietal and occipital lobes. In particulars the diffusion restriction has also decreased markedly.

**DISCUSSION**

Although posterior reversible encephalopathy syndrome (PRES) has been recognized after description by Hinchey et al. in the mid-nineties, both its clinical symptoms and underlying causes remain poorly defined.

The diagnosis of PRES includes the presence of neurological symptoms such as seizure, headache, encephalopathy, and visual disturbances, in addition to radiologic findings on brain MRI of focal vasogenic edema [1–7]. The syndrome was described in association with acute hypertension, preeclampsia or eclampsia, renal disease, sepsis, and exposure to immunosuppressive agents [8–14]. It has been less commonly described in the setting of autoimmune disease [15–19].

Radiographic findings in PRES are rarely isolated to the posterior white matter, despite the syndrome’s name, and instead often involve the cortex, frontal, occipital lobes, brainstem and basal ganglia [20, 21]. No strong evidence supports a clear relationship between severity of clinical symptoms and specific imaging findings, although some studies correlated greater vasogenic edema in normotensive patients [11] and basal ganglia involvement in patients with preeclampsia or eclampsia [22].

The pathophysiology of PRES remains unclear, but the most widely accepted theory appears to be related to disordered cerebral autoregulation, particularly in the posterior head region. When the upper limit of cerebral

| Date | WBC(10^3/mm^3) | Hb (g/dl) | platelets(10^3/mm^3) | LDH (U/L) | Haptoglobin (g/l) | Creatinine(g/dl) |
|------|----------------|-----------|----------------------|----------|-------------------|-----------------|
| Day a2 | 3.2           | 7.3       | 41                   | 781      | 0.07              | 2.4             |
| Day b3 | 5.8           | 8.84      | 43                   | 1014     | 0.11              | 3.6             |
| Day c5 | 4             | 9.1       | 33                   | 656      | 0.16              | 3.8             |
autoregulation is exceeded, arterioles dilate and cerebral blood flow increases resulting brain hyperperfusion causes extravasation of fluid and blood products into the brain parenchyma [7, 16, 23].

An alternative theory proposes that endothelial dysfunction has also been implicated in the pathogenesis of PRES, especially in cases associated with preeclampsia or cytotoxic drugs [24, 25].

In some clinical settings, renal failure, sepsis, hypomagnesemia, and other metabolic disturbances may be responsible for the associated symptoms and radiologic findings [26–28].

Rituximab (anti-CD 20 monoclonal antibody) has increasingly been used for the treatment of hematological malignancies and autoimmune diseases [29]. Rituximab is used in the treatment of patients with non-Hodgkin’s lymphoma in addition to its use in conditions such as lupus nephritis, glomerular disease refractory to conventional treatment, and sarcoidosis. There have been a lot of reports detailing cases of patients developing PRES after receiving rituximab [30, 31]. Similar to our case, patients in these reports developed symptoms early, even within a few hours of receiving rituximab, and symptoms lasted for a day or two before disappearing without leaving any neurological deficit.

The PRES was also reported in patients with thrombotic thrombocytopenic purpura (TTP) as a predominant radiological finding [32–34]. In these reports, authors evaluated neuroimaging studies performed over a 10-year period. Of the patients who had acute abnormalities on brain magnetic resonance imaging, PRES was found in about half of the cases. PRES findings on brain MRI scan were not related to drug administration or initiation of therapy.

In our case, the typical onset of classical neurological symptoms after administration of rituximab and their resolution in less than 48 hours favors the theory of rituximab-associated PRES rather than association with thrombotic microangiopathy (TMA).

CONCLUSION

Posterior reversible encephalopathy syndrome (PRES) is a clinical radiographic syndrome of heterogeneous etiologies that are grouped together because of similar findings on neuroimaging studies. The syndrome is not always reversible, and it is often not confined to either the white matter or the posterior regions of the brain.

The posterior reversible encephalopathy syndrome is most commonly encountered in association with acute hypertension, preeclampsia or eclampsia and sepsis. Anti-CD20 related PRES is a rare entity, reported in patients with lymphoma and neuromyelitis optica. Rituximab is increasingly used in the treatment of some glomerular diseases refractory to conventional treatment. So nephrologists should be aware of this major side effect when using this drug.

Keywords: Encephalopathy syndrome, Kidney transplant, Plasma exchange, Posterior reversible encephalopathy syndrome (PRES), Rituximab

How to cite this article

Habli M, Elyoussef N, Khoury M, Fares NJ. Habli. Rituximab-related Posterior reversible encephalopathy syndrome in HUS patient post kidney transplant. Int J Case Rep Images 2016;7(2):135–139.

doi:10.5348/ijcri-201603-CL-10096

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Author Contributions

Mohamad Habli – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Nada Elyoussef – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Mounir Khoury – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Najat Joubran Fares – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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