A Rare Case of Cyclophosphamide-Induced Posterior Reversible Encephalopathy Syndrome in a Patient with Anti-GBM Vasculitis, and Review of Current Literature

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Posterior reversible encephalopathy syndrome (PRES) is a clinical syndrome of headache, altered mental status, and seizures with reversible mainly posterior leukoencephalopathy on neuroimaging. Precipitating factors for PRES are multifactorial and include autoregulatory failure due to changes in blood pressure, metabolic derangements, and cytotoxic medications. We report the second case of cyclophosphamide-induced PRES in a patient with anti-glomerular basement membrane (Anti-GBM) positive vasculitis.

In the acute setting, PRES can be challenging to distinguish from cerebral venous sinus thrombosis or cerebral vasculitis based on clinical presentation. Neuroimaging with magnetic resonance imaging (MRI) of the brain along with a vessel imaging, can help reach the diagnosis.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinical syndrome of headache, altered mental status, and seizures with reversible mainly posterior leukoencephalopathy on neuroimaging [1]. Precipitating factors for PRES are multifactorial and include autoregulatory failure due to changes in blood pressure, metabolic derangements, and cytotoxic medications [2]. As the name implies, PRES is generally reversible and resolves by treating the underlying cause [1–3]. The use of immunosuppressants is a known risk factor for the development of PRES [4]. Among cytotoxic medications, cyclosporine is the best reported to cause PRES, but many other medications have also been reported to have PRES as a complication [2, 5]. We report a rare case of a patient who was given cyclophosphamide for the treatment of Anti-glomerular basement membrane (Anti-GBM) positive vasculitis, and developed PRES.

2. Case Report

29-year-old African American woman presented to the emergency department for three weeks of nausea, vomiting, and diarrhea; and five days of anuria. She was found to be uremic with renal failure (Creatinine: 5.5 mg/dl, blood urea nitrogen: 34 mg/dl, creatinine clearance: 6 ml/min). Renal biopsy showed necrotizing glomerulonephritis (Immunoglobulin G, perinuclear anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane positive). She was treated with intravenous methylprednisolone started on day 5 of hospitalization (1 g intravenous daily for three days followed by 24 mg twice a day), plasmapheresis on day 8 of hospitalization, and cyclophosphamide (induced at a dose of 510 mg because of renal failure and plasmapheresis) on day 9 of hospitalization. Two days after cyclophosphamide induction, the patient became encephalopathic and developed clinical seizures consisting of left gaze deviation, left neck tonic deviation, left eye blinking, left arm flexion with rhythmic jerking in conjunction with the head. Fosphenytoin (loaded with 20 mg/kg followed by phenytoin maintenance at 100 mg three times a day) was initiated for seizures, and the patient was intubated and sedated on propofol drip. Blood pressure remained normotensive throughout hospitalization (Mean: 122.5/77, Median: 122/78 over a range of ten days of the event). The initial working diagnosis was cerebral vasculitis versus cerebral venous thrombosis. Magnetic
resonance angiography (MRA) showed clear patent vessels, with no signs of venous thrombosis. Magnetic resonance imaging (MRI) revealed areas of cortical and subcortical white matter T2 Fluid-attenuated inversion recovery (FLAIR) hyperintensities in bilateral occipital-parietal and the right frontal region, as shown in Figure 1. Continuous electroencephalogram monitoring showed diffuse interictal slowing. Seizures and encephalopathy in the setting of chemotherapy treatment with the radiographic findings were most consistent with PRES. Patient self-extubated three days later and was oriented to person, place, and time with no clear neurologic deficits on examination. Repeat MRI done six days after the initial scan showed resolution of previously seen areas of T2 FLAIR, white matter hyperintensities as shown in Figure 2. She was discharged home on carbamazepine 400 mg BID and taper of phenytoin (100 mg every third day followed by stopping), and a steroid taper (methylprednisolone 16 mg BID for two weeks with a plan to taper by 4 mg BID every two weeks if tolerated).

3. Discussion

First described in 1996, PRES is a clinical syndrome with seizures, headache, altered mental status, and visual disturbances [1]. Data from case series suggest generalized tonic-clonic seizure is the most common presentation, followed by encephalopathy and headache [6, 7]. The exact incidence of PRES is unknown, though it is being increasingly reported [2]. PRES has a female preponderance and usually afflicts middle-aged patients though the range of patient’s age can range from 4 years to 90 years [1–4]. Neuroimaging shows symmetrically posterior leukoencephalopathy that improves with time [1, 3]. The classic description is the parietooccipital pattern of vasogenic edema.
in predominantly subcortical areas, though cortical involvement is also common [1, 8]. Involvement of parieto-occipital lobe (≥98%) is more common than frontal lobe (around 70%), though temporal lobe (around 65%), cerebellar (30–53%), basal ganglia (630%), and midbrain involvement (630%) have also been reported [5, 16–24]. Immunosuppressive therapies are thought to have a direct toxic effect on endothelium causing arteriolar and capillary damage with disruption of the blood–brain barrier and subsequent vasogenic edema, causing PRES [1, 22].

There is a paucity of case reports identifying cyclophosphamide as a trigger for PRES in the rheumatologic population. Many of these cases developed PRES in the setting of acute renal failure when treated with cyclophosphamide for a rheumatologic condition, similar to our case [25–30]. These cases are summarized in Table 1. Chang-Hoon Lee reported a case of a 42-year-old woman with systemic lupus erythematosus (SLE) who presented with renal failure secondary to glomerulonephritis and developed PRES after two cycles of cyclophosphamide [30]. Jabrane et al. reported a case of a 16-year-old girl with SLE and lupus nephritis who presented with renal failure and developed sudden onset of a headache, blurring of vision, followed by three episodes of generalized seizures after being treated with IV cyclophosphamide pulse therapy at 300 mg/m² of the body surface [28]. Zekić et al. reported a case of an 18-year-old girl who presented with renal failure due to lupus nephritis and developed PRES after administration of the second dose of cyclophosphamide [25]. Jayaweera et al. reported a case of a 33-year-old woman who presented with renal failure due to lupus nephritis who developed PRES after the second dose of cyclophosphamide [27].

Table 1: Case reports of posterior reversible encephalopathy syndrome (PRES) in patients given cyclophosphamide.

| Case reports       | Demographics | Rheumatological condition | Laboratory investigations | Treatments given                                      | MRI findings                                         |
|--------------------|--------------|---------------------------|----------------------------|-------------------------------------------------------|-----------------------------------------------------|
| Chang-Hoon Lee et al. [30] | 42-year-old female | SLE                        | Cr: 2.68 mg/dl, BUN: 41.7 mg/dl | Cyclophosphamide, steroids, anticonvulsives and antihypertensive medications | T2 hyperintensities involving the bilateral parieto-occipital lobes, frontal lobes, and basal ganglia |
| Jabrane et al. [28]  | 16-year-old female | SLE                        | BUN: 58 mg/dl, CrCl: 5 ml/min, Proteinuria 2.5 g/day | Cyclophosphamide, steroids                               | T2 hyperintensities on bilateral occipital lobes     |
| Zekić et al. [25]   | 18-year-old female | SLE                        | Proteinuria 2.7 g/day            | Cyclophosphamide, steroids                               | T2 hyperintensities involving the bilateral parieto-occipital lobes and right frontal lobe |
| Jayaweera et al. [27] | 33-year-old female | SLE                        | Cr: 5.79 mg/dl                  | Cyclophosphamide, steroids, midazolam, phenytoin, valproate, topiramate | T2 hyperintensities on bilateral occipital lobes     |
| Abenza-Abilua et al. [29] | 27-year-old male | Anti-GBM disease          | Cr: 8.50 mg/dl, BUN: 149 mg/dl, CrCl: 6 ml/min | Cyclophosphamide, steroids                               | T2 hyperintensities involving the bilateral parieto-occipital lobes |
| Di Pan et al. [26]   | 22-year old female | Sjogren's syndrome        | Cr: 1.47 mg/dl, BUN: 41.7 mg/dl | Cyclophosphamide, steroids                               | T2 hyperintensities involving the bilateral parieto-occipital lobes and cerebellum |

MRI, Magnetic Resonance Imaging; SLE, Systemic Lupus Erythematosus; Anti-GBM, Anti-Glomerular Basement Membrane; Cr, Creatinine; BUN, Blood Urea Nitrogen; CrCl, Creatinine Clearance.
Abenza-Abildua reported another case of PRES in a 27-year-old man with high blood pressure (HBP) and glomerulonephritis caused by anti-GBM disease treated with cyclophosphamide [29]. Di Pan reported PRES in a 22-year-old woman with a history of Sjogren's syndrome who had an acute respiratory failure from diffuse alveolar hemorrhage concurrent with renal failure from glomerulonephritis, who was treated with cyclophosphamide on day 2, and developed seizures on day 5, with findings concerning for PRES on neuroimaging [26]. All of these case reports are young individuals with an underlying rheumatological condition causing renal failure who developed PRES while receiving cyclophosphamide for their underlying rheumatologic condition. Majority of these cases had SLE with nephritis, however along with Abenza-Abildua et al., our case reports PRES caused by cyclophosphamide use to treat Anti-GBM vasculitis [26]. Our case report provides further insight into the pathophysiology of immunosuppressants causing PRES; specifically in patients with renal failures and Anti-GBM vasculitis undergoing treatment with cyclophosphamide.

4. Conclusion
To our knowledge, this is only the second reported case in the literature associated with the development of PRES due to cyclophosphamide given for (Anti-GBM) vasculitis. There are several other case reports of young individuals with underlying rheumatological conditions developing renal failure and subsequent PRES after receiving cyclophosphamide. In the acute setting, PRES can be difficult to distinguish from cerebral venous sinus thrombosis, cerebral vasculitis based on clinical findings. Neuroimaging with magnetic resonance imaging (MRI) of the brain along with vascular imaging can help reach the diagnosis.

Disclosure
This case was presented as a poster at the American Academy of Neurology Conference, 2018.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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