Posterior Reversible Encephalopathy Syndrome Secondary to Cyclophosphamide

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ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological diagnosis defined as new onset seizures, headaches, impaired vision and consciousness. PRES is typically associated with hypertensive emergencies and pre-eclampsia but its association with autoimmune diseases is largely multifactorial with the combination of ongoing immunologic processes, sepsis and cytotoxic agents contributing to patient's presentation. Cyclophosphamide induced PRES is rare and has been reported in cases of patients with renal failure and active autoimmune processes.

INTRODUCTION

Cyclophosphamide is an alkylating agent commonly used in treating malignancies and autoimmune diseases. Though it is known for PRES to be associated with anticancer drugs[1], there are few cases where cyclophosphamide is solely implicated. The following highlights a case of the rare Anti-GBM disease in Trinidad and Tobago who developed a PRES on commencing Cyclophosphamide therapy.

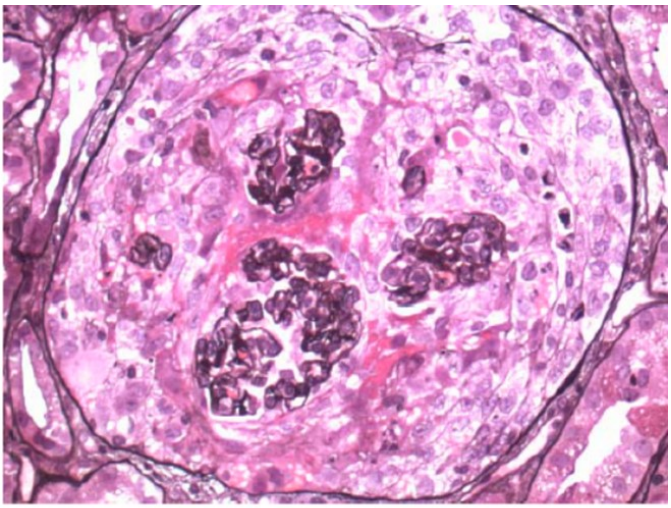
CASE

A 71-year-old Trinbagonian female of Caucasian descent who was previously well presented with a two-week history of generalized malaise, headache, arthralgia, nausea, dyspepsia and brown urine. The patient's past medical history is signification for hypertension (managed with enalapril and Bendroflumethiazide) and a prior history of smoking (ex-smoker of 4 years). Her admitting haematological investigations revealed a haemoglobin (Hb) of 80 g/dl (Conventional Units [CU] x 10 = SI units), white blood cell (WCC) of 11.1 x 10^9/L (CU k/ul x 1 = SI units), a platelet count (Plt) of 334 x 10^9/L (CU k/ul x 1 = SI units) and an erythrocyte sediment rate (ESR) of 147 mm/hr. Her biochemical investigations showed a blood urea nitrogen (BUN) of 68 mg/dl and creatinine (Cr) 8.3 mg/dl. with. Admitting urinalysis showed 3+ proteinuria with active urine sediment with red cells, red cell casts and leukocyturia.

This patient with acute kidney injury (AKI) secondary to a primary glomerulonephritis versus an autoimmune cause

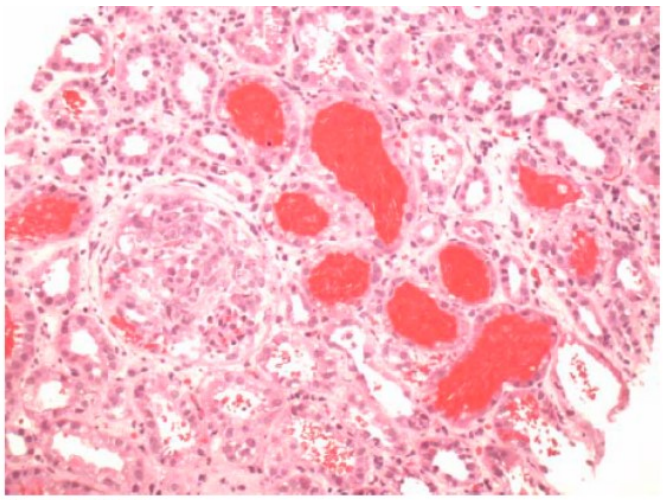
was started on haemodialysis (HD). Further blood investigations showed HIV negative, hepatitis B and C negative, p-ANCA and c-ANCA negative, anti-streptolysin O titres negative, negative serum protein

Figure 1 Renal Biopsy (Courtesy Histopathology Laboratory Columbia University)



cellular crescent

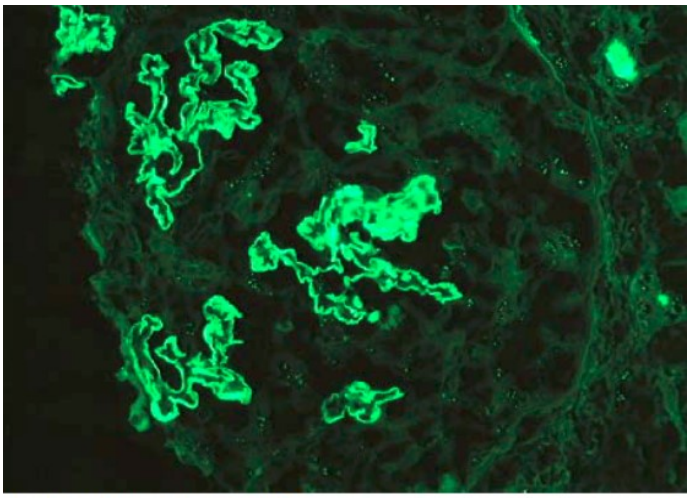
Figure 2 Renal Biopsy (Courtesy Histopathology Laboratory Columbia University)



ATN + RBCs

Immunofluorescence showed 3+ linear staining for IgG along the basement membrane with 2+ lambda and kappa and 1+C3. These findings supported a diagnosis of anti-glomerulo -basement antibody (anti-GBM) nephritis and anti-GBM titers were strongly positive (Figure 3).

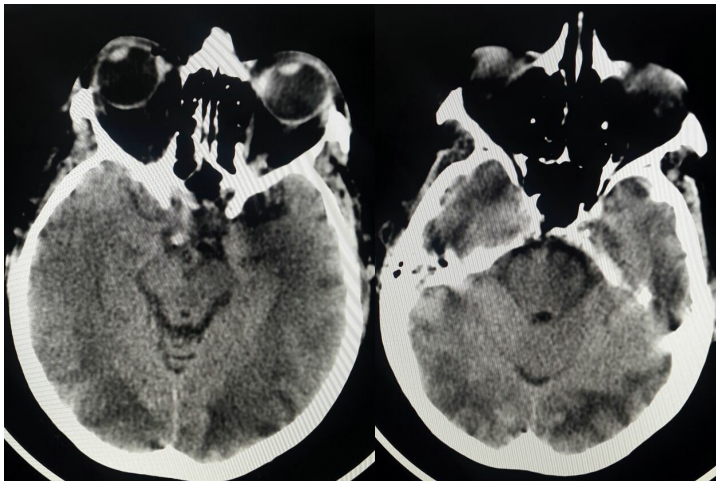
Figure 3 Immunofluorescence (Courtesy Histopathology Laboratory Columbia University)



IF glom: strong linear IgG

Cyclophosphamide at 1mg/kg/day was then instituted approximately four days after review of the renal biopsy report. This delay, as well as a suboptimal dosage was attributed to a thrombocytopenia, which had resolved prior commencement. However, after one week, she presented with new onset generalized tonic-clonic seizures, headaches, delirium and blurry vision. She was normotensive on admission with a BP of 122/56 mmHg and her CT- brain showed areas of decreased attenuation noted in both occipital lobes consistent with posterior reversible encephalopathy syndrome (Figure 4).

Figure 4: CT Brain of PRES (Courtesy of Port-of-Spain General Hospital)

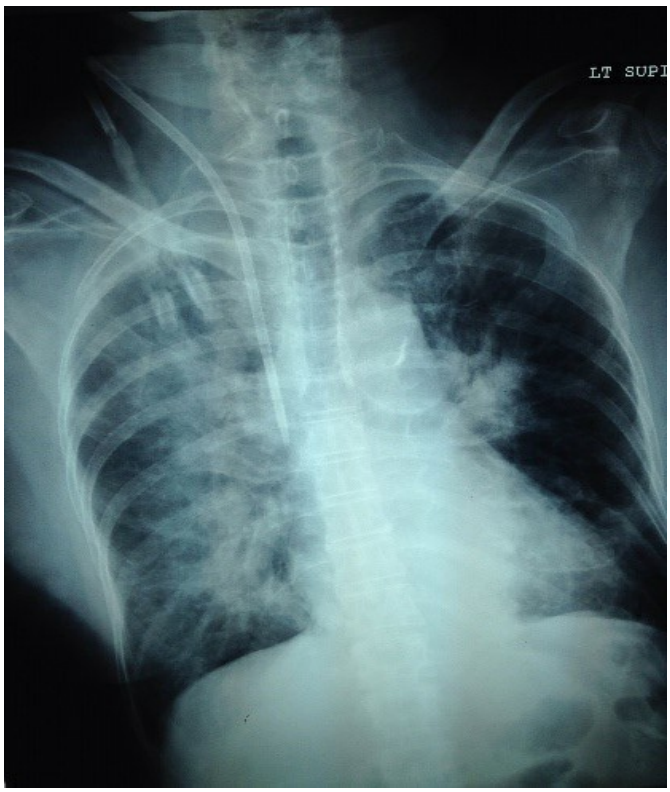


electrophoresis with immunofixation. Renal ultrasound scan showed increased echogenicity of the kidneys with no hydronephrosis.

Methylprednisolone 500mg was then commenced for three days followed by oral prednisolone 40mg daily along with proton-pump inhibitor coverage. During this time she underwent sessions of acute haemodialysis. Her antihypertensive medication was changed to telmisartan which maintained normotension over the following month on HD whilst on prednisolone. A kidney biopsy was arranged and the report obtained after approximately eight days showed severe acute diffuse crescentic glomerulonephritis with acute tubular injury, tubular atrophy, and interstitial fibrosis (Figures 1 and 2).

Cyclophosphamide was discontinued and the patient started to improve neurologically. Negative blood and urine cultures made a septic component an unlikely contributing factor and normal liver enzymes meant a metabolic encephalopathy was unlikely as well. The patient rapidly developed hypoxic episodes followed by a respiratory arrest due to fulminant pulmonary hemorrhage before plasmapheresis could be commenced (Figure 5).

Figure 5: CXR (Courtesy Port-of-Spain General Hospital)



DISCUSSION

Goodpasture's syndrome (GS) or anti-glomerular basement membrane disease (Anti-GBM) is a rapidly progressive glomerulonephritis (RPGN) with or without pulmonary haemorrhage. It is characterized by a type 2 hypersensitivity reaction against type 4 collagen in the basement membrane, more specifically the NC1 epitope of the alpha-3 chain of type 4 collagen. This variant is restricted to the basement membranes on the alveolar and glomerular capillaries mainly but is also present on the retina, choroid plexus and cochlea where it is not typically associated with the disease process.

PRES has been postulated to be the result of the loss of cerebral autoregulation, especially the autonomic innervation of the vertebrobasilar system with resultant endothelial dysfunction and vasogenic edema affecting the very susceptible loosely packed myelinated fibers of the cerebral white matter[2]. PRES, though typically seen in hypertensive emergencies, has also been documented in normotensive patients with severe sepsis, fluid overload and cerebral vasculitis thus postulating autoimmune causes as well as uremia being culprits.

Immunosuppressive therapies have also been postulated to cause endothelial dysfunction and the development of PRES. Though cyclophosphamide has decreased plasma clearance in kidney failure with its increased toxicity, its neurotoxic effect is quite rare with few documented case reports. In this case, a diagnosis of PRES was likely as the discontinuation of the offending agent, cyclophosphamide, resulted in improvement of her neurological symptoms. This is also supported by other cases of PRES that were reported over time which saw development of symptoms after day 3 of cyclophosphamide therapy[3]. This timeframe coincides with this patient's case and thus heavily implicates cyclophosphamide as the causative agent. As the patient was already established on haemodialysis, the development of PRES secondary to uremia due to her renal failure was unlikely.

One important differential diagnosis in this case would have been cerebral vasculitis as it is known that the glomerular basement membrane antigen implicated in the disease process is also found in the choroid plexus. What would have refuted this differential would have been the fact that this patient had a clear inciting event, the use of cyclophosphamide, that lead to her presentation.

However, one can speculate that the development of PRES in this case was indeed multifactorial in nature.

The timely recognition of PRES is critical to the adequate management of patients who develop this syndrome. Delays in its identification can lead to a series of disastrous events which may involve ischemia, infarction or even death. A case series [4] has postulated that severe vasogenic edema in PRES can progress to cytotoxic edema and that the extent of involvement in PRES has prognostic implications.

PRES may present with a myriad of neurological manifestations. These include: fluctuations of consciousness, seizures, headaches and even visual disturbances which manifest as visual field defects, cortical blindness, and hallucinations. Other signs and symptoms include nausea, vomiting and variation in blood pressures. The diagnosis of PRES is usually considered once the criteria suggested by Fugate et al[5] is met and includes acute onset of neurological symptoms, vasogenic edema on imaging (ideally MRI for posterior circulation imaging), and reversibility of clinical and/or radiological findings.

Neuroimaging findings in PRES include vasogenic edema classically in the occipital and parietal lobes but cerebellar and brainstem involvement is also common. The calcarine and paramedian areas of occipital lobe are usually spared in PRES which is useful in excluding posterior cerebral infarction as a differential. Treatment for PRES is usually supportive, with management of the underlying disease and/or the elimination of any triggering agents being key interventions.

CONCLUSION

PRES is a distinct clinical entity that is usually associated with an inciting factor and clear pathognomonic clinical and radiological signs. In this case, the use of cyclophosphamide was thought to be the inciting event. As evidenced by literature, the onset of symptoms coincided with three days after initiation of this drug. Clinicians must keep this in their differential diagnoses for any patient presenting with neurological symptoms whilst on cyclophosphamide or autoimmune conditions.

Ethical approval statement: not applicable

Informed consent statement: this case is of a deceased patient since 2016. Attempts to contact a next of kin has been unsuccessful as contact numbers are outdated and the information in this case report cannot be linked to the patient.

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Conflict of Interest statement: None declared

Authors' contribution: Amit Ramrattan- preparation of Manuscript; Dr Emile Mohammed- Discussion; Dr Dominic Santoriello- histopathologist of this case

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