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A CASE REPORT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME FOLLOWING RITUXIMAB THERAPY

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Abstract:-

Posterior reversible encephalopathy syndrome (PRES) is a rare clinical disorder that is manifested by headache, confusion or altered consciousness, visual changes, and seizures, along with characteristic neuroimaging findings involving posterior cerebral white matter. Early recognition and prompt treatment are cardinal to prevent permanent damage of the cerebrum in this otherwise reversible condition.

In this case, we report a 23-year-old female diagnosed with Stage 4 lupus nephritis who was started on rituximab, following which the patient developed visual disturbances, headaches, and seizures. MRI brain revealed posterior reversible encephalopathy. Eventually, the patient made a full recovery after 2 months of hospital stay and was discharged.
Keywords: - Encephalopathy , lupus nephritis, rituximab.

Introduction:-

Posterior reversible encephalopathy syndrome (PRES) belongs to a group of syndromes namely reversible posterior leukoencephalopathy syndrome (RPLS) which is characterized by episodes of headache, seizures, visual disturbances and involvement of posterior cerebral white matter, evidenced on neuro-imaging. Contrary to the names, these conditions are neither always reversible nor are always confined to the posterior cerebral white matter.

Aisen et al were the first to report Posterior reversible encephalopathy syndrome (PRES) in 1985.[1] In 1996, Hinchey et al, [2] observed that 15 patients had presented with acute onset of headaches, visual disturbances, altered level of consciousness, and seizures. All 15 patients had similar neuro-radiological findings of involvement of posterior cerebrum and all of them had complete resolution of symptoms over 2 weeks.

PRES can be attributed to several conditions like hypertension, pre-eclampsia/eclampsia, post-carotid endarterectomy, autoimmune disorders, and immunosuppressive drugs. The primary underlying mechanism is hyper-perfusion leading to cerebral vasogenic edema.

In previously reported cases of SLE with PRES, the majority had severe hypertension (BP = >170/100 mmHg) and renal failure. The occurrence of PRES in patients with SLE was unclear, but it could be due to lupus disease activity or as a result of immune-modulatory therapy.

Rituximab is a murine/human-chimeric monoclonal antibody that decreases CD20+ B cells through both cell-mediated and complement-mediated cytotoxic effects. It has been increasingly used for the treatment of autoimmune diseases like lupus nephritis, malignancies, and glomerular disorders unresponsive to conventional treatment. [4, 5]

Case report:-

A 23-year-old female diagnosed with SLE 8 years ago, had developed Stage 4 Lupus nephritis (in February 2022) which was confirmed with renal biopsy. The patient was initially started on mycophenolate mofetil and eventually tacrolimus was added. After few months of therapy with MMF and tacrolimus, a second renal biopsy was taken which confirmed the progression of lupus nephritis indicating poor response to the above drugs, and hence she was started on rituximab. The patient had developed pedal edema after the first dose of rituximab. One month later, the second dose of rituximab was given after which the patient started to experience retro-orbital pain, visual disturbances, and headache. She presented to the ER with status epilepticus, with history of multiple episodes of vomiting. On arrival, the patient had altered level of consciousness, tachycardia (pulse = 137 bpm), her BP was 180/120, and temperature-99.1^{o} F. There were no signs of meningeal irritation. Her cardiovascular system and respiratory system examination did not show any abnormality. At the time of admission, her hemoglobin was 7.1 g%, total WBC count was 14,100 /mm3, and platelet count was adequate. Her creatinine was elevated (2mg/dL), blood urea was 87 mg/dL. Her liver function tests, electrolytes were within normal range. MRI brain revealed asymmetrical focal areas of hyper intensities on T2 and FLAIR in bilateral cerebral hemispheres, cerebellum, dorsal and ventral surface of hemipons, and bilateral middle cerebellar peduncles, suggesting posterior reversible encephalopathy syndrome (PRES).

Propofol infusion was started to control further seizure episodes. The patient was intubated after 4 days of admission due to poor respiratory effort and tracheostomy done after 1 week on mechanical

ventilator. The patient was started on anti-epileptic drugs, diuretics, anti-hypertensive drugs, and other supportive treatments. CSF analysis was done, which was not significant. In view of elevated renal parameters, hemodialysis was initiated. A few days later, the patient developed ventilator-associated pneumonia, and Klebsiella was isolated from culture. She was given appropriate antibiotic coverage. Her condition improved and the patient was weaned off from mechanical ventilation after 41 days. The tracheostomy stoma was closed eventually and after 2 months, the patient was discharged with full recovery.

Discussion:

Posterior reversible encephalopathy syndrome typically presents with reversible white matter vasogenic edema involving predominantly the posterior cerebral circulation.[6] Vessel imaging demonstrates vessel narrowing of posterior cerebral vasculature. Patients in all age groups appear susceptible as reported cases exist in patients as young as 2 years and as old as 90 years. [7-9] It usually has favorable outcomes; however, mortality also has been reported in a few cases.[4]

The pathogenesis of PRES is not fully understood, but it appears to be owing to deranged cerebral auto regulation and endothelial dysfunction. The tendency to affect posterior cerebral hemispheres may be owing to a lower threshold for cerebral auto-regulation defect or due to any vasculopathy affecting the posterior circulation. Disorders like hypertensive encephalopathy, post-carotid endarterectomy, and pre-eclampsia are postulated to derange cerebral autoregulatory mechanisms. While immunomodulators, and conditions like hemolytic uremic syndrome cause endothelial dysfunction and disruption of the blood-brain barrier which leads to cerebral edema. [10-12]

In patients with SLE, renal failure, nephritis, and intense immunosuppression with immunomodulators have been linked to PRES.[4]

Rituximab, an anti-CD20 monoclonal antibody is used in the treatment of malignancy, organ transplant, and in auto-immune diseases. It can cross the intact blood-brain barrier in only negligible amounts. However, in patients with a breach in blood brain barrier due to elevated blood pressure, renal failure, or immunosuppressants, rituximab can reach significant levels in CSF and subsequently may lead to complements activation. [13, 14] Mustafa et al,[4] reported occurrence of PRES 11 days after 1st dose of Rituximab in patient with lupus nephritis. Few other patients with SLE nephritis who developed PRES post Rituximab therapy were reported out of which 2 patients had developed PRES after 3rd dose.[15-17] The onset of PRES post Rituximab therapy may be immediately after infusion or may occur as a late complication. Siddiqui et al[6], reported PRES in a 66yr old female diagnosed with non-Hodgkin's lymphoma, who had received R- CHOP chemotherapy regimen 10 days prior to onset of seizures and headache. Stübgen et al[18] who reported inflammatory demyelinating lesions of the cervical spinal cord and cerebellum after rituximab infusion, postulated that an imbalance between B-cell and T-cell populations in the CNS might have triggered a predominantly cell-mediated immune attack against unidentified

nervous system antigens.

Conclusion:-

We report a 23 yr old female with lupus nephritis, who had developed PRES after therapy with rituximab and had recovered after 2 months. To conclude, one should always be on alert when using rituximab. Early identification and resolution of the underlying cause remain the cornerstones of the management of PRES.

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