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Posterior reversible encephalopathy syndrome associated with deoxycoformycin and alemtuzumab

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ABSTRACT Posterior reversible encephalopathy syndrome (PRES) is a combined clinical and radiological syndrome characterised by headaches, encephalopathy, seizures and visual loss. We present the case of a 55-year-old male who developed this condition following treatment with deoxycoformycin and alemtuzumab. We review the literature considering diagnosis, pathophysiology and optimal strategies for treatment of this condition.

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CASE REPORT

A 55-year-old man presented with acute onset of a constant, generalised, severe headache. He described a two-day history of intermittent fevers but had no other infective symptoms. He had no visual symptoms. The patient had a history of T-cell prolymphocytic leukaemia for which he was undergoing chemotherapy with deoxycoformycin (7.2 mg–4 mg/m^2) and alemtuzumab (30 mg three times a week). He was not known to be hypertensive and had not had any previous seizures. He had no other significant medical history.

His condition deteriorated over the next few hours. He became more agitated and confused and developed grand mal seizures. The patient was treated with intravenous (IV) benzodiazepines but developed status epilepticus and required intubation and ventilation. He was commenced on IV phenytoin.

Figure 1 shows the patient's blood pressure and pulse rate, via intra-arterial monitoring, during his time in critical care. He had episodes of low-grade fever (37.4°C). His initial blood results showed a pancytopenia (white cell count [WCC] 1.0 x 10^9/l, haemoglobin 9.5 g/dl, platelet count 78 x 10^9/l with normal urea and electrolytes [creatinine 67 µmol/l]) and an international normalised ratio of 1.4. His initial arterial blood gas on 60% oxygen, post-seizure, showed a respiratory acidosis with a pH of 7.24, partial pressure of oxygen of 18.9 kPa, partial pressure of carbon dioxide of 9.4 kPa, bicarbonate ion of 28.4 mmol/l and base excess of –0.4 mEq/l. His electrocardiogram showed a sinus tachycardia with no other abnormalities.

Initial computerised tomography (CT) of the patient's brain showed white matter oedema in both occipital lobes with no evidence of raised intra-cranial pressure.

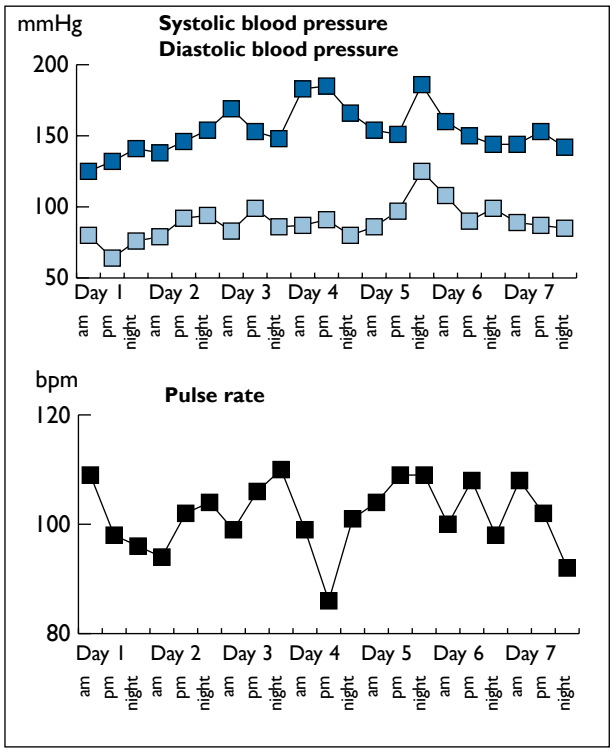

FIGURE 1 The patient's blood pressure and pulse rate, via intra-arterial monitoring, during his time in critical care.

Cerebrospinal fluid (CSF) was clear and colourless in appearance with normal results (WCC <3 x 10^6/l, red cell count 10 x 10^6/l, glucose 3.6 mmol/l and protein 0.36 g/l). Gram stain was negative and subsequent CSF testing for cytomegalovirus, Epstein-Barr virus, enterovirus, JC virus, BK virus, meningococcus and toxoplasma were all negative. The patient did not receive an electroencephalograph as there is not an inpatient neurophysiology service at our hospital (a specialist tertiary oncology centre).

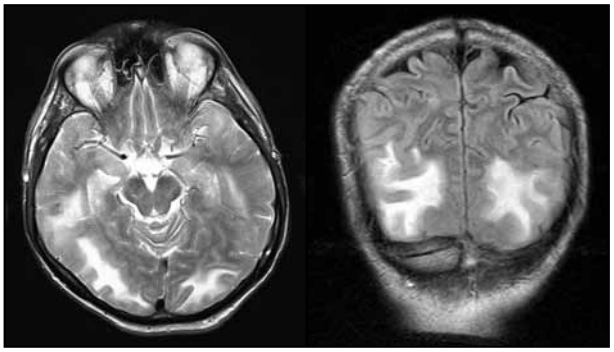

FIGURE 2 T2-weighted magnetic resonance scans of the brain of a 55-year-old man showing bilateral symmetrical white matter oedema in the parieto-occipital lobes typical of posterior reversible encephalopathy syndrome associated with deoxycoformycin and alemtuzumab.

He underwent a magnetic resonance image scan (MRI) of his brain (T1- and T2-weighted images with contrast), which showed bilateral symmetrical white matter oedema in the parieto-occipital lobes on T2-weighted images (Figure 2). There was sparing of the medial occipital cortex and calcarine. There was no enhancement on T1-weighted images. Thus, a diagnosis of posterior reversible encephalopathy syndrome (PRES) was made.

The patient was transferred to intensive care where he remained intubated and ventilated for 24 hours. He was empirically treated with IV antimicrobial agents (meropenem, linezolid, voriconazole and ganciclovir). He received supportive treatment with IV metoprolol to maintain tight blood pressure control and IV phenytoin infusion.

He had periods of agitation post extubation requiring intermittent doses of sedative agents. He had no further seizures and made steady progress to discharge from hospital, with his symptoms resolving within two weeks. Anti-convulsants were discontinued after the resolution of his symptoms. A repeat MRI of the patient's brain, four weeks after his initial scan, showed significant improvement in the high signal abnormalities within the parieto-occipital lobes.

DISCUSSION

PRES is a combined clinical and radiological syndrome characterised by headaches, encephalopathy, seizures and visual loss.[1,2] Seizures are usually tonic-clonic in nature and often precede the other symptoms. Cortical blindness is the most common visual disturbance.[3]

Neuroimaging typically shows vasogenic oedema of the bilateral parietal-occipital lobes.[2] The abnormalities are often symmetrical. The changes are best visualised via MRI which is able to detect even small lesions. Recent analyses of MRI images in patients with PRES found that a significant proportion of patients had atypical findings, with around 50% having involvement of the frontal lobe and around one third having temporal lobe abnormalities.[4,5]

The pathogenesis of PRES remains poorly understood but is associated with a wide range of conditions, particularly acute hypertension, sepsis and renal failure.[1,3,5] A significant percentage of patients with PRES also have autoimmune disorders.[6] The condition is also associated with the use of immunosuppressive agents and has been reported in patients being treated with gemcitabine, rituximab, cisplatin and bevacizumab.[7–10] This is the first reported case of PRES with deoxycoformycin and alemtuzumab.

The mechanism by which immunosuppressive agents cause PRES is unclear, but it is suggested that a rapid increase in blood pressure overcomes the brain's autoregulation of cerebral blood flow. This results in dilatation of cerebral arterioles with an opening up of endothelial tight junctions and leakage of plasma and red cells into the extracellular space producing cerebral oedema.[11] The posterior portion of the cerebrum is felt to be more vulnerable due to decreased sympathetic innervation.[12] There may be an autoimmune-mediated disruption of the endothelial aquaporin-4 water channels, which may result in a predisposition to PRES.[6]

Although, as the name implies, PRES is typically reversible, some lesions may produce irreversible damage.[5] The features are typically reversed within two weeks of the onset of symptoms.[1] Haemorrhage is a potential complication, particularly in patients with a coagulopathy (especially those with a platelet count less than 80 x 10^9/l) and those treated with immunosuppressive agents.[13]

The key goal of management is controlling blood pressure and stopping any trigger agents. Given the wide range of conditions associated with PRES and the variation in signs and symptoms described in the syndrome, an awareness of the condition among all physicians is important. Early treatment of blood pressure has been associated with improvemed outcomes in PRES.[1,3,11] Anticonvulsant therapy is required for the acute management of PRES, but long-term treatment is not necessary.[1,14]

CONCLUSION

Posterior reversible encephalopathy syndrome is a rare but probably under-recognised syndrome. Consideration of the diagnosis, particularly in those receiving chemotherapeutic agents, is important as early treatment has been associated with improved outcomes.

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