Reminder of important clinical lesson

Posterior reversible encephalopathy syndrome postautologous peripheral stem cell transplantation for multiple myeloma

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Summary

This is a case of a 56-year-old lady with recent autologous peripheral stem cell transplantation for multiple myeloma. She was presented with a 48 h history of worsening headache, drowsiness, nausea/vomiting and some peripheral neurological symptoms. She developed status epilepticus, was intubated and transferred to intensive care unit. After full investigation with a CT head, CT cerebral angiogram, MRI brain and cerebral angiogram, she was diagnosed with posterior reversible encephalopathy syndrome (PRES) with the help of expert opinion, based on the clinical and radiological evidence. The MRI showed bilateral occipital signal changes suggestive of PRES. She was managed with nimodipine, phenytoin and clonazepam with good effect. Eventually extubated, she made good progress on the ward with no further seizure episodes. Functionally she did not appear to have any evidence of residual damage from the PRES. This case discusses PRES on a background of a haematological malignancy and its clinical features.

BACKGROUND

Posterior reversible encephalopathy syndrome (PRES) is relatively well documented in the literature, in various clinical circumstances. This case presented a diagnostic challenge with its presentation and background features. Several diagnoses were possible and after thorough clinical investigation and collaboration with haematology, intensive care and neuro-radiology the diagnosis was established. The case highlights the diagnostic challenge of PRES and considers its diagnosis in unusual neurological presentations.

CASE PRESENTATION

A 56-year-old lady with a background of multiple myeloma presented with a 48 h history of headache, worsening confusion/drowsiness and nausea/vomiting. She denied having any head injury in the previous weeks. She was found to be photophobic with left upper limb weakness and a fluctuating Glasgow Coma Score (GCS) between 13 and 14. Her condition deteriorated and developed status epilepticus.

She was diagnosed with multiple myeloma 6 months earlier after suffering from minimal trauma L1 crush fracture. She was started on chemotherapy (cyclophosphamide, thalidomide and dexamethasone). Two weeks prior to presentation she underwent autologous peripheral stem cell transplantation (PSCT). This was complicated with mucositis and febrile neutropaenia with blood culture positive *Streptococcus mitis* sepsis. Her other significant medical history includes recurrent pulmonary emboli for which she was on therapeutic enoxaparin; and pulmonary hypertension. She is a smoker of up to 10 cigarettes per day.

She lives with her supportive husband and is independent with her activities of daily living.

INVESTIGATIONS

Her presenting symptoms necessitated a CT of the head. The CT showed a subarachnoid haemorrhage (SAH) predominantly superficially in the right cerebral hemisphere

and along the right Sylvian fissure (figure 1). She was also found to have bilateral occipital pole wedge-shaped hypoattenuation, suggestive of an acute infarction. In view of the SAH, a CT angiogram of the head was done and no obvious aneurysms were found, although short-segment stenoses of multiple intracranial arteries were noted, suggestive of a possible vasculopathy.

Figure 1 Subarachnoid haemorrhage involving the right Sylvian fissure and the sulci of the right hemispheric frontal and parietal lobes.

The neurology team was contacted and MRI/magnetic resonance arteriography (MRA) of the head was arranged given the findings so far. The MRI/MRA was evident of several findings: bilateral occipital subcortical signal change suggestive of PRES, and irregularities particularly in the left middle cerebral artery suspicious of an underlying vasculopathy (figure 2). However, given her *S mitis* sepsis several weeks earlier, a mycotic-like aneurysm was unable to be excluded on the MRA as the possible cause of her SAH. The vasculitis screening blood tests were normal.

By this stage of her condition, she developed status epilepticus refractory to benzodiazepines and a loading of phenytoin. The seizures appeared to be mostly left-sided focal in nature but progressing to generalised seizures. Her GCS was 8–9 and at risk of airway compromise. She was intubated, ventilated and transferred to the intensive care unit (ICU) for further management.

After discussion with the neuro-radiologists, she had a cerebral angiogram to assess further for any mycotic aneurysms and vascular anomalies. No mycotic or saccular aneurysms were found. Of note, symmetrical and widespread anterior and posterior territory vasospasm was seen—a pattern not classical of cerebral vasculitis as advised by the neuro-radiologists. From thereon, she was treated as a PRES case.

DIFFERENTIAL DIAGNOSIS

Her presenting symptoms gave rise to several differential diagnoses. Based on history and examination, the most likely causes were either meningitis or a right-sided stroke.

Figure 2 Bilateral occipital subcortical signal change suggestive of posterior reversible encephalopathy syndrome. Subarachnoid haemorrhage along the right convexity can also be seen.

Less likely differentials were a peripheral sepsis, a new cerebral metastasis, intracerebral haemorrhage, vasculopathy, migraine with aura or severe transplant-related nausea/vomiting. The diagnosis of PRES was certainly not at the forefront prior to the MRI of the brain.

TREATMENT

The patient was intubated and ventilated for management of the status epilepticus with a decreasing GCS. She was loaded for with 1 g of phenytoin and started on 1 mg three times daily of clonazepam. She was also started on nimodipine (calcium channel antagonist) intravenously 30 mg 4 hourly for the cerebral vasospasm/blood pressure management.

OUTCOME AND FOLLOW-UP

She was weaned off the sedation and extubated on day 2 of her ICU admission. Given her occipital lesions, her postextubation vision was examined carefully. Fortunately, she only had some blurry vision and was able to recognise familiar faces. The clonazepam was weaned off and she remained seizure free. She was transferred to the haematology ward where she made a steady recovery.

DISCUSSION

PRES is characterised by neuroimaging findings of reversible vasogenic subcortical oedema without infarction on a background of various clinical scenarios.¹ PRES was first described formally by Hinchey *et al*¹ in 1996 as a clinical syndrome with predominantly posterior leukoencephalopathy that had findings of subcortical oedema without infarction on neuroimaging. However, the clinical description and its association can be traced back to 1897, when Vaquez and Nobecourt described a correlation with toxæmia of pregnancy and hypertension.² In the early 20th century, Oppenheimer and Fishberg³ coined the term hypertensive encephalopathy and attributed the cerebral disorder to transient arterial and arteriolar vasospasm.⁴ Initially, it was thought to be uncommon and occurring with other acute end organ damage as part of a malignant hypertension syndrome.⁵ With the advent of MRI in recent times, this syndrome is now recognised to be present in various clinical settings with sometimes minimal or no hypertension.

It has been postulated that two conditions underlie PRES pathophysiology: relative hypertension that leads to increased capillary filtration pressure and endothelial dysfunction that results in blood–brain barrier leakage. Severe hypertension can cause secondary endothelial dysfunction. PRES can also be caused by endothelial dysfunction in patients with relatively normal blood pressure. In this case, the maximum systolic pressure reached was 155 mm Hg, suggesting that the predominant causative factor at work was endothelial dysfunction.

The clinical features of PRES are distributed along a large spectrum. Headache, confusion (encephalopathy-like) and cortical visual symptoms such as blurred vision, hemianopia or even cortical blindness are the most common features. Seizures also present frequently, as was the case with this lady.⁶ Some also present with dysarthria, fluctuations in the level of consciousness, weakness and incoordination of the limbs. Intracranial haemorrhage

such as sulcal SAH is known to occur in PRES with the greatest frequency seen after allogeneic bone marrow transplantation (BMT) and in patients undergoing therapeutic anticoagulation.⁷ This lady had a Sylvian fissure SAH and just 2 weeks prior underwent autologous PSCT while on therapeutic enoxaparin. Unfortunately at this moment, data are scarce regarding PRES postautologous PSCT. The haematologist involved in this case had experienced PRES postallogeneic BMT but never postautologous PSCT. Currently, no single chemotherapeutic agent or regimen has been identified as posing a higher risk for PRES. Some agents such as cisplatin, cytarabine as well as combinations of adriamycin, cyclophosphamide, vincristine, corticosteroids, ifosfamide, etoposide and cytarabine have been implicated.⁸

With such a wide spectrum of symptoms, the diagnosis is difficult. The diagnosis should be considered in all patients who present with neurological signs and symptoms, in the setting of chemotherapy, transplantation, pre-eclampsia or other conditions that may impair endothelial dysfunction.⁴ Some pharmacological agents also predispose to PRES-like prohypertensives such as bronchodilators, sympathomimetic agents, tricyclic antidepressants. Drugs that cause endothelial dysfunction include chemotherapeutic agents as above and, others such as ciclosporin A and tacrolimus.⁴ PRES should be diagnosed early to prevent residual end organ damage such as cortical blindness.

The management of PRES is based on lowering the blood pressure appropriately and removal of the underlying cause when identified. In most cases, patients should be managed in the ICU with close blood pressure monitoring and the availability of vasopressors in the event of decompensation.⁴ The calcium channel blocker nimodipine is currently at the forefront in managing vasospasm post-SAH and thus the risk of secondary ischaemia.^{9–11} The latest guidelines from the *American Stroke Association* suggest the oral administration of nimodipine at a dose of 60 mg 4 hourly for 3 weeks from the start of the ICU admission.¹² A recent study has shown the nimodipine to be efficacious with intravenous management, although this is more often linked to hypotension.^{13 14} For this reason the use of nimodipine in this case was halved to 30 mg 4 hourly via the intravenous route. In the presence of seizures, intravenous antiepileptic agents should be used to ensure good seizure control. Once the underlying cause for the PRES has been identified, it is important to treat them promptly to prevent secondary irreversible damage. PRES appears to have a good short-term and long-term outcome with recurrence being infrequent.¹⁵

Since its formal clinical description in 1996, the major advances have been improvement in the neuroimaging diagnostics and the addition to the ever growing list of causes associated with PRES.¹⁶ With cases such as this, where literature is scarce in these clinical circumstances, further research is needed to ascertain rapid diagnosis and the prevention of irreversible damage.

Learning points

- ▶ Consider the diagnosis of posterior reversible encephalopathy syndrome (PRES) in a patient with headache, confusion and other neurological symptoms on a background of hypertension and seizures.
- ▶ Rapid diagnosis is essential to prevent irreversible damage.
- ▶ On a background of haematological malignancies, consult a haematologist early for advice.
- ▶ The cornerstone of management of PRES is good blood pressure control with identification of the underlying cause—nimodipine is the proven agent of choice.
- ▶ Further research is needed to examine the association between PRES and autologous stem cell transplantation.

Competing interests None.

Patient consent Obtained.

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