A 67-year-old kidney transplant patient with headache of uncertain origin

Maria E. Ostermann, Pranabh Gyawali, Susan A. Snowden, John B. Eastwood and Christopher P. Streather

St George's Hospital, Department of Renal Medicine, London, UK.

Introduction

Most patients with acute headache have benign disorders, and only occasionally do they prove to have a life-threatening illness. However, in immunosuppressed patients the diagnosis may be difficult because occult infection is always possible: yet symptoms, signs and routine tests can be misleading.

We present such a patient in whom several possibilities were entertained before the correct diagnosis was made.

Case report

A 67-year-old man presented with a 3-day history of severe left frontal headache of gradual onset associated with nausea and vomiting. He denied visual symptoms and was not aware of any precipitating factors. In 1985 he had been diagnosed as having Wegener's granulomatosis. Four years later he reached end-stage renal failure and was commenced on continuous peritoneal dialysis (CAPD). In 1995 he received a cadaveric renal transplant for which he had been taking azathioprine 100 mg and prednisolone 10 mg once a day in the recent past.

On admission he was in severe pain but alert and orientated. He was a pyrexial with no neck stiffness. There was obvious left-sided lacrimation with mild conjunctival oedema. Neurological examination was normal. Investigations showed: Hb 13.7 g/dl, WBC 12.4 x 10^9/l, platelets 241 x 10^9/l, Na^+ 138 mmol/l, K^+ 3.8 mmol/l, urea 8.8 mmol/l, creatinine 197 μmol/l, albumin 39 g/l, glucose 8.5 mmol/l, C-reactive protein 8 mg/l; anti-neutrophil cytoplasmic antibody (ANCA) titre was negative. Computer tomography (CT) head scan 6 h after admission demonstrated a small left frontal infarct (considered to be old); the scan was otherwise normal and in particular there was no evidence of blood in the subarachnoid space. A provisional diagnosis of severe migraine was made. The patient was admitted for observation and symptom control. Despite adequate doses of increasingly strong analgesics his severe headache persisted.

Twenty-four hours after admission he had developed a fever of 38.5°C and looked generally unwell. His left-sided peri-orbital oedema had increased and there was injection of the conjunctiva. Blood results are shown in Table 1. Lumbar puncture revealed colourless cerebrospinal fluid (CSF) at a pressure of 23 cm H_2O. Microscopy revealed RBC 83 μl, WBC (mainly lymphocytes) 7 μl but no organisms, and culture was negative; CSF glucose was 4.2 (serum glucose 8.5) mmol/l and protein 0.4 g/l.

Examination of the left eye revealed normal visual acuity, fundoscopy and intra-ocular pressure. In view of the marked conjunctival injection and an impression of protrusion of the left eye, a diagnosis of cavernous sinus thrombosis was considered despite the fact that the cranial nerves were intact. Review of the CT films showed the cavernous sinus to be normal. In addition, there was no radiological evidence of any pathology in the para-nasal sinuses. Unfortunately, it was not possible to obtain a magnetic resonance imaging scan of the head.

At a joint review with a neurologist, ophthalmologist and ear nose and throat surgeon the most likely diagnosis seemed to be periorbital cellulitis. The patient was therefore given high-dose intravenous...
benzylpenicillin, ceftazidime, metronidazole and fluconazole. Nevertheless, high resolution CT scan of the orbit (day 2) was normal with no evidence of intra-orbital pathology.

The following morning (day 3) the nursing staff noticed a vesicular eruption within the confines of the left eyebrow. By day 5 the rash had evolved into classic ophthalmic herpes zoster. Recovery was complicated by visual problems initially and an episode of acute confusion later. Regular ophthalmic review confirmed involvement of the retina and vitreous humour thereby explaining the deterioration in vision. In addition to intravenous aciclovir he was treated with intra-ocular injections of corticosteroid, topical aciclovir and corticosteroid eye drops. The episode of confusion was initially thought to be due to high dose intravenous aciclovir. However, much later, when he was no longer confused, polymerase chain reaction (PCR) analysis of his CSF was positive for Varicella zoster virus; such a finding is highly suggestive of viral involvement of the central nervous system. Fourteen days after the onset of his illness he was recovering well and the herpetic vesicles had become crusts. However, vision in the left eye remains markedly reduced.

Discussion

In immunosuppressed patients the differential diagnosis of headache is wide and includes atypical but life-threatening infections, cerebral malignancies and rare disorders such as reversible posterior leukoencephalopathy syndrome [1]. In addition, symptoms and clinical findings may be diminished because of the reduced inflammatory response.

Herpes zoster is due to reactivation of dormant varicella zoster virus and can develop in both healthy and immunosuppressed patients. This viral reactivation occurs especially when cell-mediated immunity is depressed, i.e. with increasing age, in patients with the acquired immunodeficiency syndrome or lymphoproliferative disorder, and in those on immunosuppressive drugs. In healthy adults the annual incidence of zoster is 1.3–1.6/1000, increasing to 14–20/1000 in patients over 70 years of age [2]. Though zoster may affect any sensory ganglion, there is a predilection for certain sites. In the Mayo Clinic series the distribution of neural involvement was: cranial 13%, cervical 13%, thoracic 56%, lumbar 13%, and sacral 4% [3]. Typically, herpes zoster is unilateral and presents as dysaesthesia or hyperaesthesia of the affected dermatome, severe pain and constitutional symptoms; the typical vesicular rash usually appears after 3–5 days. The pain is variable in character and severity, and can precede the rash by as much as 14 days. Furthermore, occasionally there are no cutaneous lesions at all [4,5]. In these cases, the diagnosis is easily overlooked and instead a number of alternative acute medical and surgical diagnoses are entertained (Table 2) [6–8].

The clinical course of herpes zoster in immunosuppressed patients is similar to that of healthy individuals but tends to be more severe and longer lasting. Although herpes zoster is essentially a clinical diagnosis, it is important to confirm the diagnosis by isolation of virus from vesicular fluid. During this vesicular stage, contacts who have never been exposed to varicella are at risk of acquiring the virus. In unexposed pregnant women there may be transmission to the fetus [9].
Ocular manifestations of herpes zoster include involvement of lids, cornea, conjunctivae, uvea and retina [10]. Our patient developed significant visual impairment, which is thought to be due to ischaemic retinal damage. Unilateral and even bilateral branch and central retinal vein and artery occlusions have been reported [11]. In these cases progression to complete retinal necrosis may occur leading to severe visual impairment [12,13]. In addition to treatment with intravenous aciclovir, corticosteroids have been reported to inhibit the inflammatory response.

Varicella zoster virus spreads from skin to the central nervous system both via blood and by retrograde axonal transport. The clinical picture in this setting can vary from asymptomatic pleocytosis of the CSF to encephalitis. In making a diagnosis of central nervous system involvement, PCR has been shown to be more sensitive than attempts at virus isolation or detection of Varicella zoster antibody [4,14]. Intravenous aciclovir is the treatment of choice.

Teaching point

Herpes zoster can mimic a variety of acute surgical and medical emergencies and needs to be included in the differential diagnosis of acute headache in renal transplant patients.

References