CASE 1

Occam's Razor through the Neuroaxis

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History

A 68-year-old lady with a long history of rheumatoid arthritis presented with urinary incontinence. Her arthritis had been quiescent for many years on treatment with methotrexate, leflunomide and low-dose prednisolone. She developed a 4-week history of progressive urinary incontinence and urgency and for 2 weeks had been unaware of the need to defecate and thus had some faecal incontinence. On directed questioning she described saddle anaesthesia and her husband had noticed that her gait was unusual.

There was no history of back pain, radiating pain or trauma. However, she had a history of osteoporosis for which she was receiving alendronic acid and calcium/vitamin D3 supplementation. There was no history of weight loss, night sweats, rash or fever; and no travel history.

Examination

On examination she had reduced power (Medical Research Council power grade 4/5) in all groups of the lower limbs bilaterally, knee jerks were present, but ankle jerks were absent bilaterally. Planters were flexor bilaterally. There was reduced sensation to pinprick in the S2–S4 dermatomes; otherwise sensation was normal. There was faecal loading in the rectum with impaired anal tone.

Upper limb and cranial nerve examinations were normal. She was apyrexial and there were no skin changes. Lower limb pulses were normal.

Initial Differential Diagnosis

- Conus medullaris syndrome
  - Prolapsed disc
  - Spinal stenosis
  - Vascular (malformation or ischaemia)
  - Neoplasia (primary or secondary)
  - Infection (pyogenic and non-pyogenic)
- Other

Results of Initial Investigations

She had a mild, stable, normocytic anaemia, normal white cell and platelet counts, normal renal and liver function and a normal serum calcium level. A magnetic resonance imaging (MRI) scan was performed (**Figure 1.1**).

Progress and Further Investigations

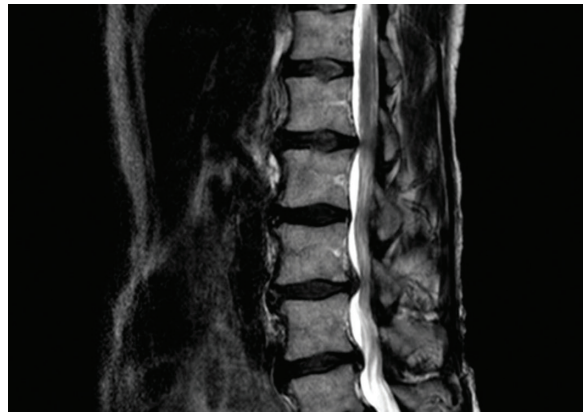
During the first 4 days of her admission, while her lower limb and sphincter disturbance remained stable, she began to develop blurring of vision in the left eye, predominantly in the central field. There were no episodes suggestive of amaurosis fugax and no transient visual obscuration with valsalva manoeuvres or eye movements. The left pupil was slightly more dilated than the right and poorly reactive to light. Visual acuity was normal in the right eye, but in the left it was reduced to 18/6 and slit-lamp examination demonstrated changes (**Figure 1.2**).

Refined Differential Diagnosis

Acute retinal necrosis and conus medullaris syndrome.

- Viral infection
  - Herpes simplex virus
  - Varicella zoster virus
  - Cytomegalovirus
- Treponemal infection
  - Syphilis
- Autoimmune vasculitis

Figure 1.1. T2-weighted sagittal MRI in a 68-year-old lady with rheumatoid arthritis, who presented with urinary incontinence.



This demonstrates multiple-level intervertebral disk disease. However, cerebrospinal fluid is visible either side of the spinal cord and there is no significant cord compression or oedema; therefore, this is not the cause of the patient's conus medullaris symptoms and signs.

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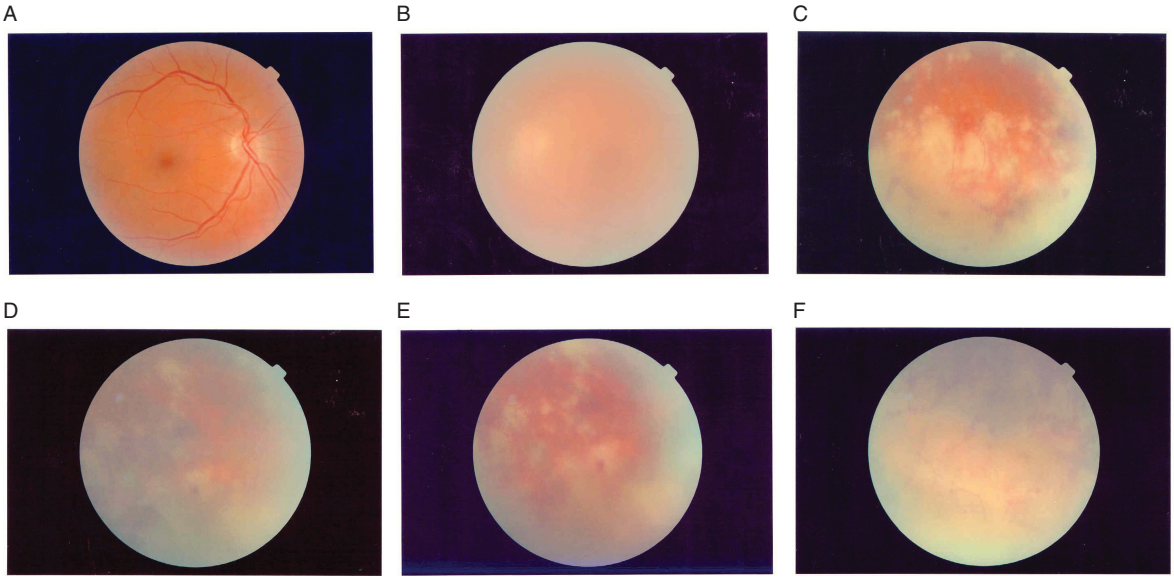
Figure 1.2. Funduscopy findings of the asymptomatic right eye (A) compared with the affected eye (B–F).



This shows disk oedema and acute retinal necrosis in the left eye.

Definitive Investigation Results

She had a lumbar puncture (LP), which demonstrated an opening pressure of 16 cm H_2O of cerebrospinal fluid (CSF), white cell count (WCC) 16 per mm^3 (lymphocyte predominance), red cell count (RCC) 2 per mm^3, protein 0.61 g/l and glucose ratio 69%.* Microscopy, Gram stain and culture were negative. Polymerase chain reaction (PCR) of the CSF for herpes simplex virus and cytomegalovirus were negative, but PCR for varicella zoster virus (VZV) was positive.

She also underwent a tap of the vitreous fluid of the left eye and PCR analysis of this was also positive for VZV.

Diagnosis

Varicella zoster virus retinitis and conus medullaris infection.

Management and Outcome

Aciclovir was commenced under the advice of the regional virology unit. Her HIV antibody and antigen tests were both negative.

Despite treatment, her vision continued to deteriorate. Therefore, she was changed to intravenous ganciclovir and intraocular foscarnet. In addition, her rheumatological drugs were withheld because of the concern that immunosuppression had caused the VZV reactivation. The retinal necrosis gradually improved over a couple of weeks and her gait returned to normal. However, her vision remained impaired, she continued to have abnormal perianal sensation, and she remained under the care of the community continence team, requiring intermittent self-catheterisation. At follow up, her rheumatoid arthritis remained under control, requiring only intermittent pain relief with diclofenac.

Prevention

Patients on long-term immunosuppressive therapies are at increased risk of reactivation of latent viruses, particularly neurotropic viruses such as herpes viruses. In the USA, vaccination is given against VZV during childhood. However, because it is a live attenuated vaccine its use in people with immunocompromise is not straightforward. It is used in those with no evidence of pre-existing immunity against VZV under some circumstances.

Discussion

VZV (**Figure 1.3**) is an alpha herpes virus that can infect any part of the neuraxis. Primary infection with VZV causes chicken pox (varicella) in children. The virus then becomes latent in the nervous system,

* Reference ranges are given in Appendix B (pp. 297–300).

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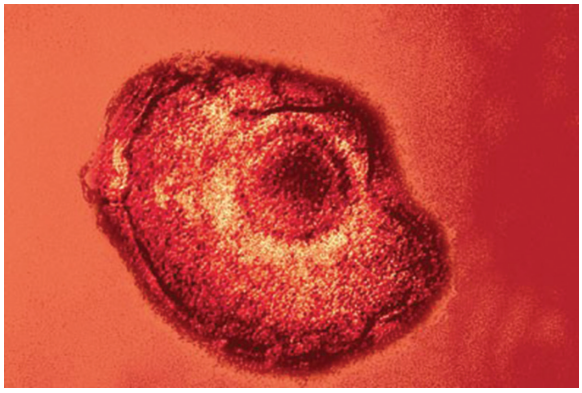

Figure 1.3. Electron micrograph of varicella zoster virus. (Photo courtesy of Cavallini James/BSIP)

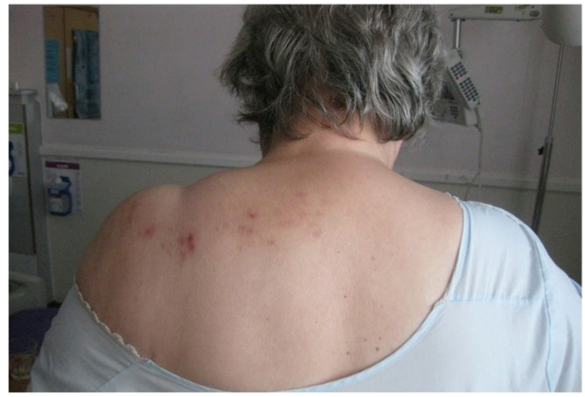

Figure 1.4. A different patient with a dermatomal vesicular eruption of varicella zoster virus.

but can reactivate years later to cause the dermatomal rash that characterises zoster (shingles; **Figure 1.4**). Following primary infection, VZV can cause a primarily immune-mediated, usually self-limiting demyelinating cerebellitis [1], or an encephalitis. There is a wide range of neurological syndromes associated with VZV reactivation (**Table 1.1**). They appear to be primarily caused by immune-mediated reactions to the virus, rather than viral replication itself.

In the case described here, VZV caused disease in the optic nerve and the conus medullaris. The virus accounts for around one-third of all viral central nervous system (CNS) infections. It is the second most commonly identified sporadic cause of encephalitis after herpes simplex virus type 1 [1–3]. VZV can also cause a vasculopathy, which may involve small or large vessels, or both, and can occur in a segmental or diffuse fashion [1]. This usually presents as an ischaemic stroke. Other vasculopathic complications of VZV include aneurysm development and sub-arachnoid haemorrhage.

Neurological complications of VZV reactivation can occur before, during or after the development of a rash. They may also occur in the absence of the any rash at all, so-called '*Zoster Sine Herpete*', as in the case described here [3]. This underscores the importance of investigating for VZV in patients in whom a viral CNS infection is suspected, even if there is no rash, and especially if they are immunocompromised.

In acute infection, CSF PCR will often be positive, as in the case described here. However, if the presentation is a post-infectious phenomenon, such as cerebellitis, or if testing is delayed due to a sub-acute presentation or the treatment is commenced prior to testing, the PCR may be negative. In such cases the detection of CSF antibodies is useful. However, this titre should be interpreted in the context of the serum antibody level and the CSF:serum albumin ratio [5]. Imaging changes at the grey/white matter interface, which are typically ischaemic although occasionally haemorrhagic, are suggestive of VZV. However, cortical and deep structure changes are also often seen [3]. As in this case, the spinal cord changes on neuroimaging may be subtle or absent (**Figure 1.3**).

Post-infectious VZV cerebellitis, which typically occurs in children, does not require any specific

Table 1.1 Neurological complications of varicella zoster virus. Reproduced with permission from reference [4].

Complications of acute infection (varicella)
Cerebellitis
Acute encephalitis
Complications of viral reactivation (zoster)
Cranial neuropathies
Ramsay Hunt syndrome
Herpes zoster ophthalmicus
Trigeminal neuronitis
Optic and oculomotor neuropathies/retinitis
Mononeuritis of other cranial nerves
Polyneuritis cranialis
Stroke syndromes
Herpes zoster ophthalmicus with delayed contralateral hemiparesis
Cervical zoster with posterior circulation infarcts
Granulomatous angiitis of the basilar artery
Encephalitis syndromes
Encephalitis
Diffuse small/medium vessel arteritis
Myelitis

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treatment, as the course is usually self-limiting [5]. However, neurological complications of VZV re-activation, as confirmed by PCR detection of the virus, should be treated with intravenous aciclovir. Acute VZV CNS infection is less responsive to aciclovir than herpes simplex virus and therefore some advocate higher doses, such as the 15 mg/kg used in the case [5]. Prolonged courses may be required in patients with immune compromise, as in the case described [2]. The dose should be adjusted in patients with renal impairment and renal function should be monitored in all. If there is evidence of a vasculitic component, adjunctive steroids may be useful [5].

Key Points

- Varicella zoster virus (VZV) can affect both the central and peripheral nervous system.
- Consider VZV infection in patients with a lymphocytic pleocytosis even when a rash is absent.
- VZV antibodies in the CSF should be analysed in the context of serum antibody levels and adjusted for the CSF:serum albumin ratio, to establish intrathecal production.

Looking Back

Although one of the most ancient neurotropic viruses, the discovery that VZV could cause a vasculopathy is a fairly recent discovery; 50 years ago, Cravioto and Faigin described a neurological granulomatous angiitis and 10 years later Rosenblum and Hadfield found this to be due to VZV in patients with lymphosarcoma [6,7]. VZV causing retinal vascular disease was only identified in the 1980s [8].

Did You Know?

Varicella and zoster were initially described as two distinct skin conditions. In the early twentieth century physicians began to realise that children often developed chickenpox soon after their parents had suffered shingles, and eventually they were shown to be caused by the same virus, hence the name varicella zoster virus.

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