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A woman with acute headache and sacral dermatomal numbness

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Case description

A 54-year-old woman was admitted to hospital with a 5-day history of increasing headache, neck pain and photophobia. The working clinical diagnosis was bacterial meningitis.

Over the previous 2-week period the patient stated that she had developed malaise with occasional episodes of vomiting. On admission, the neurological examination was normal. Routine blood count, C-reactive protein and a head CT scan were normal. The CSF contained 513 white blood cells (WBCs)/mm³, predominantly polymorphonuclear leukocytes (PMN); the CSF protein was 2.68 g/L (normal < 0.45 g/L) and glucose was normal (Table 1). A gram stain and acid-fast stain and culture of the CSF for bacteria and mycobacteria were negative. Real-time PCR of the CSF amplified varicella zoster virus (VZV) DNA (Ct value 28), but herpes simplex virus (HSV) 1 and 2 and enterovirus were negative.

The patient was treated with intravenous acyclovir, 10 mg/kg every 8 h for 7 days, 8 days later, she was well enough to be discharged on oral acyclovir, 800 five times daily for an additional 7 days. Despite clinical improvement, neck pain and mild headache persisted. Two days after discharge (10 days since her initial admittance), she was re-admitted complaining of increasing headache and neck pain. Left leg numbness and urinary and faecal incontinence had developed. The neurological examination revealed left-sided S2-3 hypalgesia. MRI scanning of the head, lumbar and sacral spine was normal. The CSF contained 43 WBCs/mm³, predominantly mononuclear; CSF protein was 0.56 g/L and glucose was normal; PCR did not amplify VZV DNA, and no other pathogens were detected.

What is the working diagnosis?

Would you do any other tests?

What treatment would you recommend?

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The presence of headache, neck pain and a CSF pleocytosis indicates that the patient had meningitis. Despite treatment, symptoms persisted and urinary and fecal incontinence developed and there was sacral numbness and sensory loss. These symptoms suggest a

myeloradiculitis. Thus, the working clinical diagnosis was meningitis that had progressed to meningomyeloradiculitis (infection extending from the meninges to involve the spinal cord and/or cauda equina), prompting consideration of viral disorders, Lyme disease, sarcoidosis and lymphomatous meningitis.

The presence of VZV DNA in the CSF during the first week of illness indicated that VZV was the causative organism. Further virological confirmation was provided by the detection of anti-VZV IgG antibody in CSF Using the Diamedix assay (Miami, US), the first CSF ELISA value for anti-VZV IgG antibody was 1.9, and the titer increased to 8.3 in the second CSF. On the second CSF sample and serum obtained three days later, the serum/CSF ratio for anti-VZV IgG was 0.9 compared to a ratio for albumin of 128 and IgG of 233. Using the Reiber-Peter method,¹ the antibody index for VZV IgG was >1.5, indicative of intrathecal antibody synthesis. We recognize that a few days separated CSF and serum collection, but given the values obtained, even if serum and CSF had been obtained the same day, the antibody index for VZV IgG would likely still have been far in excess of 1.5.

We were concerned however that her progression might have been related to underlying immunosuppression. However, an HIV test was negative. The patient was restarted on IV acyclovir, 10 mg/kg every 8 h, and a repeat MRI 1 week later was still normal with no evidence of infarction/inflammation. Her symptoms improved after 2 weeks of IV acyclovir, and she was discharged on oral valaciclovir, one gram three times daily for an additional 7 days.

Review of the literature

The spectrum of neurological and ocular disorders caused by VZV in the absence of rash is not fully appreciated. In particular, VZV is an under recognized cause of aseptic meningitis. Herein, we present a case of aseptic meningitis which progressed to include features of radiculopathy and myelopathy. Diagnostic investigations revealed VZV as the causative agent, as verified by (1) the detection of VZV DNA in CSF, (2) rising titers of anti-VZV IgG in CSF, and (3) intrathecal synthesis of anti-VZV IgG. Even after five days, the initial CSF pleocytosis consisted mostly of PMNs; importantly, PMNs often predominate in CSF of patients with VZV encephalomyelitis and VZV vasculopathy.² Thus, along with bacterial and granulomatous disease, the differential diagnosis of subacute to chronic nervous system infection with increased PMNs in CSF should include both cytomegalovirus (CMV) and VZV.

Although multiple cases of VZV meningitis and meningoradiculitis have been described, the most common viral cause of acute meningoradiculitis in immunocompetent individuals is HSV. Herein, HSV was ruled out by the absence of amplifiable HSV DNA in CSF. Cytomegalovirus also produces meningoradiculitis, but neurological disease is usually subacute or chronic, and almost always in HIV+ individuals. Epstein-Barr virus (EBV) causes myeloradiculitis and encephalomyeloradiculitis in immunocompetent individuals.³ Acute meningoradiculitis also occurs in patients with sarcoidosis, Lyme disease and lymphoma.

The advent of PCR has revealed VZV reactivation in an increasing number of neurological and ocular disorders, which, like the case outlined above, often occurs in the absence of distinctive zoster rash. This is only the second published account in which detection of both VZV DNA and intrathecally produced VZV IgG in CSF was used to confirm the diagnosis of VZV meningitis. The first case was in an immunocompetent woman without rash who developed acute VZV meningitis with hypoglycorrhachia.⁴ Other instances of aseptic meningitis or meningoencephalitis caused by VZV in the absence of rash include two patients with aseptic meningitis,⁵ four additional patients with aseptic meningitis,⁶ and one

patient with acute meningoencephalitis,⁷ all verified exclusively by intrathecal synthesis of antibodies to VZV. Powell et al.⁸ reported a patient with meningoencephalitis without rash whose CSF contained VZV DNA, and Mancardi et al.⁹ described a patient with encephalomyelitis without rash, in whom intrathecal VZV IgG was detected in the CSF.

There are reports of myelitis, including recurrent myelopathy,^{10,11} along with coexisting meningoencephalitis and multifocal vasculopathy^{12–14} and acute cerebellitis,¹⁵ all produced by VZV in the absence of rash. In fact, 37% of cases of VZV vasculopathy develop without rash.¹⁶ Isolated cranial nerve palsies,¹⁷ including facial paralysis (known as the Ramsay Hunt syndrome zoster sine herpette)¹⁸ and polyneuritis cranialis¹⁹ produced by VZV all occur without rash. Various ocular disorders produced by VZV without rash include progressive outer retinal necrosis,²⁰ retinal periphlebitis,²¹ uveitis,²² iridocyclitis²³ and disciform keratitis.²⁴ Overall, VZV should be considered as an etiological agent in virtually all inflammatory diseases of the eye, central or peripheral nervous system, as detailed in a recent review of the protean neurological and ocular disorders produced by VZV reactivation without rash.²⁵

The value of virological verification in the absence of rash cannot be overemphasized. Detection of either VZV DNA or intrathecal IgG to VZV or both in CSF provides valuable confirmatory evidence that VZV is the etiological agent. Whilst we did not require demonstration of intrathecal synthesis of anti-VZV IgG antibody results to confirm the diagnosis of VZV-associated neurological disease in our patient, we believe it is important that clinicians are aware of this test and its potential to help diagnose neurological disease of the central or peripheral nervous system produced by VZV in the absence of rash. Importantly, detection of intrathecally synthesized anti-VZV IgG antibody is a more sensitive indicator of VZV vasculopathy than detection of VZV DNA.²⁶ The value of detection of intrathecally synthesized anti-VZV IgG relative to that of VZV DNA in other neurological disorders produced by VZV has not been studied, although Haug et al.² described three episodes of CNS disease produced by VZV (recurrent myelitis and inflammatory brain stem disease) in which there was intrathecal synthesis of anti-VZV IgG during each episode, while VZV DNA was never present in CSF. In addition, the presence of anti-VZV IgM in serum or CSF is also useful diagnostically. In contrast, the detection of anti-VZV IgG in serum is of no practical value, since nearly all adults have serum anti-VZV IgG antibody due to natural varicella infection or chickenpox vaccination in childhood.

Unfortunately there is little in the literature to guide the duration of treatment in these cases. A 14–21 day course of acyclovir is recommended for treating HSV encephalitis and it may be the case that similar durations are required for serious neurological complications caused by VZV.

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Table 1

Laboratory results for patient.

Sample	Date	Day of illness	Cell count	Micro	Glucose	Protein	Virology	
							PCR	IgG
CSF1	8/9 admittance	Day 5	WBC 513 per cu.mm (predominantly neutrophils)	Neg	3.2	2.68	Pos (Ct 28)	+(1.9)
CSF2	18/9 re-admittance	Day 15	WBC 42 per cu.mm (90% lymphocytes)	Neg	3.6	0.56	Neg	+(8.3)
Serum	21/9	Day 18						+(7.83)