CASE REPORT

Varicella zoster virus encephalomyelitis as a late complication following haematopoietic stem cell transplantation

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SUMMARY

Varicella zoster virus (VZV) causes the primary infection manifesting as varicella or chickenpox, with possibility of reactivation later in life. A 71-year-old man presented with headache and lower extremity weakness. There was no evidence of skin lesions to suggest a recent zoster infection. The patient had a history of multiple myeloma diagnosed 2 years earlier, treated with chemotherapy and autologous stem cell transplant. Antimicrobial prophylaxis was discontinued 12 months after the transplant. MRI of the brain demonstrated areas of T2/fluid-attenuated inversion recovery hyperintensity in bilateral cerebral white matter and MRI of the spine demonstrated enhancement along the cauda equine. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis and VZV DNA was detected by PCR in the CSF. The patient was treated with 8 weeks of antiviral therapy with complete resolution of symptoms. VZV should be considered in patients with haematopoietic stem cell transplantation presenting with similar neurological manifestations even in the absence of dermatological signs.

including aseptic meningitis, acute radiculitis, multiple cranial neuropathies, myelitis and encephalitis has been reported in the literature.⁴ The diagnosis is usually suggested by the close temporal relationship between the onset of neurological symptoms and the appearance of skin lesions. However, skin lesions could be absent at times, making the diagnosis clinically difficult.⁵ The author reports a case of a patient presenting with VZV encephalomyelitis 18 months following haematopoietic stem cell transplantation with no preceding skin lesions making the diagnosis clinically challenging.

CASE PRESENTATION

A 71-year-old man presented to the hospital with weakness and left frontal headache for the past 3 days. The headache was new, severe and persistent even after taking over the counter pain medications. The symptoms were associated with low-grade fever and perceived psychomotor slowing. The patient also suffered new lower lumbar back pain associated with symptoms suggestive of bilateral lumbar radiculopathy. He denied any recent skin lesions to suggest zoster infection.

The patient had a history of multiple myeloma diagnosed 2 years prior to this presentation, which was currently in remission. He was treated at that time with a combination chemotherapy regimen of lenalidomide, bortezomib and dexamethasone for eight cycles, followed by an autologous stem cell transplant 18 months prior to this presentation. He had not experienced any infectious complications in the post-transplant period and antimicrobials (oral sulfamethoxazole/trimethoprim 800 mg/160 mg daily, oral acyclovir 800 mg twice daily, oral voriconazole 200 mg twice daily) were discontinued 12 months after the transplant (6 months prior to this presentation). Of note, the patient remembered having chicken pox infection as a child and had a positive VZV serology prior to the transplant. He had not received the zoster vaccine prior to the transplant.

On examination, the patient was afebrile and haemodynamically stable. Significant findings included bilateral mild symmetrical weakness in the lower extremities; however, reflexes in the bilateral lower extremity were preserved. There was no evidence of any skin lesions to suggest recent zoster infection.

INVESTIGATIONS

Initial laboratory examination revealed complete blood count and complete metabolic profile within

BACKGROUND

Varicella zoster virus (VZV) is a neurotropic α herpes virus known to cause the primary infection manifesting as varicella or chickenpox. After the primary infection, the virus becomes latent in the ganglionic neurons and can reactivate later in life. A nationally representative cross-sectional health examination survey conducted in the USA prior to introduction of a vaccine showed seroprevalence of IgG antibody to wild-type VZV to be greater than 99% in adults over 40 years of age.¹ The varicella vaccine (Varivax, Merck) is a live attenuated viral vaccine that was first licensed in the USA in 1995. Owing to the relatively recent introduction of the varicella vaccine, a majority of older adults living in the USA still have presence of IgG antibody wild-type VZV, secondary to varicella infection in their childhood in the pre vaccine (prior to 1995) era.

Reactivation of the latent VZV is influenced by immunocompromising situations where there is a decline in cellular immunity. Reactivation occurs in 0.1–0.3% of immunocompetent individuals, but can occur in up to 35% of immunocompromised patients.² VZV reactivation usually occurs in the first 6–9 months (80% during first year) following haematopoietic stem cell transplantation and serious neurological complications occur in <2% of these cases.³ A wide variety of neurological complications,

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Figure 1 MRI of the brain with contrast demonstrating multiple foci and confluent areas of T2/fluid-attenuated inversion recovery hyperintensity asymmetrically distributed in bilateral cerebral white matter.

normal limits. A CT of the brain without contrast, initially done to rule out an intracranial haemorrhage, failed to reveal any intracranial pathology. A subsequent MRI of the brain with contrast demonstrated multiple foci and confluent areas of T2/fluid-attenuated inversion recovery hyperintensity asymmetrically distributed in bilateral cerebral white matter (figure 1). A lumbar puncture was then performed and the cerebrospinal fluid (CSF) analysis showed a lymphocytic pleocytosis (177 cell/ μ L, 92% lymphocytes) with elevated protein (72 mg/dL) and normal glucose levels. The initial Gram stain of the CSF fluid was negative.

DIFFERENTIAL DIAGNOSIS

The differentials at this time included a viral cause for the patient's encephalitis. Viral aetiologies such as herpes simplex virus, cytomegalovirus, VZV, human herpes virus 6 (HHV-6), Epstein-Barr virus and John Cunningham virus were considered. The patient was started on intravenous acyclovir and the results of the appropriate diagnostic tests were awaited. The patient at this time had reported worsening back pain with disabling symptoms of lumbar radiculopathy. Recurrence of multiple myeloma causing back pain was considered. MRI of the lumbar spine with contrast did not show any lytic lesions; however, it did demonstrate mild enhancement along the cauda equina (figure 2), indicating an infectious aetiology. The patient's viral work up showed presence of 70 300 copies/mL of VZV DNA in the CSF, detected by real-time PCR assay. The concomitant presence of encephalitis and myelitis in the presence of VZV DNA in the CSF made the diagnosis of VZV encephalomyelitis.

TREATMENT

The patient was continued on intravenous acyclovir 10 mg/kg every 8 h for 21 days and MRI of the brain and spine were performed at this time. Improvement was noted both in the symptoms and radiological images, hence the patient was transitioned to oral valacyclovir 1 g twice a day and continued for a further 5 weeks. After 8 weeks of antiviral therapy, the patient had complete symptomatic recovery and complete resolution of pathology on MRI of the brain and spine.

DISCUSSION

The author reports a patient presenting with VZV encephalomyelitis 18 months following haematopoietic stem cell transplantation

Figure 2 MRI of the lumbar spine with contrast demonstrating mild enhancement along the cauda equine.

with no preceding skin lesions. The learning point that needs to be highlighted is the risk of VZV reactivation with severe neurological complications even after a year of successful transplant with no ongoing immunosuppressive therapy. The current American Society for Blood and Marrow Transplantation guidelines for preventing infectious complications among haematopoietic cell transplantation recipients recommends acyclovir prophylaxis to prevent VZV infection in the first year after transplant.⁶ Acyclovir prophylaxis may be continued beyond 1 year in allogeneic stem cell transplant recipients who have evidence of graft-versus-host disease or require systemic immunosuppression.

VZV prophylaxis following stem cell transplant has been shown to be effective in at least two randomised trials.^{7 8} In a double-blind controlled trial, 77 haematopoietic cell transplant recipients at risk for VZV reactivation were randomised to acyclovir 800 mg twice daily, or placebo, given from 1 to 2 months until 1 year after transplantation.⁷ Acyclovir significantly reduced VZV infections at 1 year after transplantation (HR 0.16; 95% CI 0.035 to 0.74; $p=0.006$). The second trial randomly allocated 82 patients to receive acyclovir or matching placebo after allogeneic bone marrow transplantation, and demonstrated VZV infections were significantly reduced during the period of administration of acyclovir.⁸ Retrospective analyses have further demonstrated that acyclovir prophylaxis prevents early VZV reactivation, although the long-term incidence is not affected as infection occurs once prophylaxis is discontinued.⁹ These issues were further addressed in a retrospective population-based study of three sequential cohorts of VZV-seropositive patients who were undergoing allogeneic or autologous HCT.¹⁰ The first cohort received acyclovir from the day of transplantation until engraftment ($n=932$), the second cohort received acyclovir or valacyclovir for 1 year ($n=1117$)

and the third cohort received acyclovir or valacyclovir for 1 year or for 6 months after immunosuppressive drugs were discontinued, whichever was longer (n=586). In multivariable statistical models, prophylaxis for 1 year or more significantly reduced VZV disease compared with prophylaxis only through engraftment (8.8% vs 25% in allogeneic stem cell transplant recipients and 8.2% vs 22% in autologous stem cell transplant recipients). Continuation of prophylaxis beyond 1 year in allogeneic recipients who remained on immunosuppressive drugs led to a further reduction in VZV disease (4.5%) but VZV disease developed in 6.1% during the second year while receiving this strategy. The authors concluded that acyclovir/valacyclovir prophylaxis given for 1 year led to a persistent benefit after drug discontinuation and no evidence of a rebound effect.

The literature search revealed just two previous reported cases where patients presented with a severe neurological complication secondary to VZV reactivation as late complication following allogeneic haematopoietic stem cell transplant in the absence of dermatological signs.^{11 12} In a single institution experience of 80 cases of VZV reactivation,¹³ disseminated neurological disease occurred in just 5 cases (6.2%). Further among the 26 cases of disseminated infection, 10 cases (38.5%) were not preceded by any localised dermatological symptoms. VZV dissemination can occur without any signs of cutaneous disease because cell-associated viremia can arise without replication of the virus in skin, presumably by the entry of VZV into T cells through the sensory ganglia.^{13 14} No general consensus exists for the duration of treatment for severe disseminated disease in this population, however, durations of 2–8 weeks have been reported in the literature.¹⁵

Learning points

- ▶ Reactivation of the latent varicella zoster virus (VZV) is influenced by immunocompromising situations where there is a decline in the cellular immunity, where the prevalence of reactivation ranges from 0.1% to 0.3% in immunocompetent individuals, to 35% in immunocompromised patients.
- ▶ VZV reactivation usually occurs in the first 6–9 months (80% during first year) following haematopoietic stem cell transplantation and serious neurological complications occur in <2% of these cases.
- ▶ Acyclovir prophylaxis in the first 12 months after haematopoietic cell transplant reduces the incidence of reactivation.
- ▶ VZV should be considered in patients with haematopoietic stem cell transplantation presenting with neurological manifestation even in the absence of dermatological signs.

In conclusion, the author reports a case of VZV encephalomyelitis 18 months following haematopoietic stem cell transplantation with no preceding skin lesions. The two factors, absence of dermatological signs and late reactivation (greater than 12 months after haematopoietic stem cell transplant), make this reported case a challenging diagnosis as the current patient did not have any known risk factor. VZV should be considered in patients with haematopoietic stem cell transplantation presenting with similar neurological manifestations even in the absence of dermatological signs.

Competing interests None.

Patient consent Obtained.

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