CASE REPORT

VZV encephalitis following successful treatment of CMV infection in a patient with kidney transplant

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SUMMARY

A 73-year-old woman with a history of deceased donor kidney transplantation and a recent cytomegalovirus (CMV) infection, presented to the emergency department with an altered mental status. She was found to have varicella zoster virus VZV encephalitis based on cerebrospinal fluid analysis and was treated successfully with intravenous valaciclovir with an improvement in her mental status. A review of the literature shows very few case reports on patients with kidney transplantation developing VZV encephalitis. A few case reports and studies report an association between CMV and VZV infection. In these patients, CMV infection can cause a marked decline in immunity and this predisposes them to other infections. Such associations have also been reported between other types of virus infections from the Herpesviridae family. The risk of disseminated VZV infection increases in the presence of CMV infection.

BACKGROUND

Kidney transplantation is one of the most common types of solid organ transplants in the world. Like any other organ transplants, patients with kidney transplantation require high-dose immunosuppressants to prolong the life of the transplanted organ and recipient survival. The half-life of a living donor kidney is 12–20 years, and that of a deceased donor kidney is 8–12 years. Patients who get a kidney transplant before dialysis live an average of 10–15 years longer than if they stayed on dialysis. The reason for writing this case report is to assert the association between cytomegalovirus (CMV) and disseminated varicella zoster virus (VZV) infection. This association has been reported in a few case reports but the causality has not been established. This paper supports such an association. Another reason for writing up this case report is to promote awareness of such complications in patients with a history of solid organ transplantation.

CASE PRESENTATION

Our patient is a 73-year-old woman with a history of deceased donor kidney transplantation for end-stage renal disease secondary to hypertension and diabetes. The patient was CMV-seronegative (CMV IgG titre of 0.1 ELISA units) and VZV-seropositive (VZV IgG titre of 2.3 ELISA units) at the time of transplantation. Her donor was CMV-seropositive. Induction immunosuppression was with antithymocyte globulin. She had immediate graft function. She was enrolled in a study that randomised patients to receive a CMV vaccine versus placebo;

the investigators were blinded. She did not receive valganciclovir antiviral prophylaxis per transplant centre protocol. Her renal dysfunction settled to an estimated glomerular filtration rate of 55–60 mL/min at 2 weeks post-transplantation. Seven months post-transplantation, the patient was noted to have CMV viremia. Her CMV infection was classified as 'Primary' in the form of asymptomatic viremia.¹ She did not have tissue invasive disease. She received treatment with valganciclovir for a total of 3 weeks.

At this time, the patient presented to the emergency department with altered mental status, confusion and hallucinations. According to her family, the symptoms were acute in onset and had gotten worse in 24 h. Review of systems was negative for cough, chest pain, difficulty breathing, dysuria, frequent urination, diarrhoea, bloody stools, abdominal pain and fever. She did not have headaches but had emesis.

The patient's vital signs were normal at the time of presentation except for a low-grade fever of 37.7°C. Physical examination revealed an elderly woman in a confused state, alert but not oriented to time, place or person. The rest of the neurological examination was limited due to the patient's confusion, however, she was able to move her lower extremities without any evidence of focal neurological deficit. Her strength was normal in the upper and lower extremities and deep tendon reflexes were normal. The patient did not have any jugular venous distension or pitting oedema in the lower extremities. Her lungs were clear on auscultation and there was no organomegaly on abdominal examination. Bowel sounds were normal. Renal allograft in the right lower quadrant was non-tender. Examination of skin showed a vesicular rash involving the medial side of the right thigh along L2 dermatome distribution. It was painful to touch and was slightly warm with background erythema. Rest of the physical examination was unremarkable.

Given the patient's acute onset of change in mental status, a CT of the head without contrast was performed. It was negative for any acute abnormality. The patient also had an MRI of the brain done, which showed chronic ischaemic changes along with mild encephalomalacia involving the inferior surface of the frontal lobe (figures 1 and 2). Sagittal sections of MRI did not show any significant abnormalities (figure 3). Given her altered mental status and a normal CT scan, a lumbar puncture was performed. There was a high opening pressure; cerebrospinal fluid (CSF) was clear and

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Figure 1 MRI of the brain showing changes on the inferior surface of the left frontal lobe, consistent with mild encephalomalacia.

remarkable for an increase in white cell count (WCC) that was lymphocyte predominant, an increase in total protein and a normal glucose level. CSF was also positive for VZV DNA tested by PCR assay.

The patient was treated with intravenous valaciclovir, which resulted in gradual improvement in her mental status to her baseline mentation within 5 days. She was subsequently discharged in stable condition and continued to follow-up with the transplant nephrology clinic. Subsequent visits at the clinic showed that patient's clinical status continued to improve with eventual return to complete baseline mentation.

INVESTIGATIONS

Complete blood count with differential showed a WCC of 12 000/ μ L with 75% lymphocytes. Basic metabolic panel was normal. Urine analysis and urine cultures were unremarkable,

Figure 2 MRI of the brain showing similar changes in the left frontal lobe. Chronic ischaemic changes are also appreciated around the ventricles.

Figure 3 MRI of the brain, sagittal section, no abnormalities were appreciated on sagittal sections.

and primarily performed to rule out other causes of toxometabolic encephalopathy. Chest X-ray was negative for any acute cardiopulmonary process.

CT of the head without contrast was negative for any acute abnormalities. MRI of the brain showed chronic ischaemic changes. Mild encephalomalacia of the inferior surface of frontal lobe was noted. CSF analysis revealed normal glucose (67 mg/dL) and elevated protein (55 mg/dL). Red blood cell count was 32/ mm^3 with an elevated WCC of 247/ mm^3 (lymphocytes 84%, monocytes 13% and lining cells 3%). Infection screen was negative for herpes simplex virus, syphilis, enterovirus and *Cryptococcus* infection. CMV DNA PCR assays in CSF and blood were negative. VZV DNA by PCR (Quantitative) showed 52 000 copies/mL.

DIFFERENTIAL DIAGNOSIS

- ▶ *Acute bacterial meningitis* should be suspected in every individual presenting with fever and altered mental status. However, in this patient, lack of neck rigidity, presence of lymphocyte predominance in CSF and a complete response to valaciclovir supports the diagnosis of viral encephalitis.
- ▶ *Acute viral meningitis* is typically a mild, self-limiting infection. The majority of these patients present with a headache (which our patient did not have). The presence of altered mental status suggests involvement of brain parenchyma rather than meninges alone.
- ▶ *Toxometabolic encephalopathy* is one of the most common causes of encephalopathy in the elderly. Typical causes include infections such as a urinary tract infection, pneumonia and medications such as benzodiazepines and other narcotics. Our patient had a normal chest X-ray and urine analysis. There were no narcotics in her medication list. Her basic metabolic panel did not show any electrolyte abnormalities. There was no worsening of renal dysfunction. FK506 is known to cause neurological symptoms including a toxometabolic encephalopathy. It should be noted that this is a diagnosis of exclusion.

TREATMENT

The patient was treated with intravenous valaciclovir for a total of 14 days, which resulted in complete resolution of her

symptoms. Within 5 days of starting valaciclovir, her mental status had stabilised.

OUTCOME AND FOLLOW-UP

Subsequently, the patient was seen in the transplant nephrology clinic 5 days after being discharged and was found to have a normal physical examination and complete resolution of symptoms. The patient continues to follow-up with transplant nephrology as well as internal medicine clinics and continues to be in good health.

DISCUSSION

More than 50% of patients with kidney transplantation will have at least one infection in the first year following transplantation. Abbott *et al*² evaluated this and found that kidney transplant recipients have an adjusted incidence ratio of hospitalisations for septicaemia of 41.52 (95% CI 35.45 to 48.96) compared with that of the general population. The different types of infections in these patients change with time post-transplantation. In the first month, for example, intravenous line infections, respiratory tract infections and urinary tract infections are the most frequent. Pathogens are bacterial or candida. As time progresses, the cumulative effects of immunosuppressant medications begin to appear. From second to sixth month post-transplant, the risk of acquiring opportunistic viral infections such as CMV becomes high. As the duration of immunosuppression increases, the risk of other infections such as *Pneumocystis*, toxoplasmosis and *Cryptococcus* also increases.

VZV encephalitis is rare in patients with a history of kidney transplantation. The literature review shows a very small number of such cases. While primary or recurrent VZV infection is not uncommon in this patient population and usually presents as shingles, for VZV infection to present with encephalitis is fairly rare. VZV encephalitis has been most commonly reported in patients with a history of bone marrow transplantation.^{3–4} Disseminated VZV infection can be fatal in these patients and the global mortality can be as high as 80%.⁵ There is evidence to suggest that seropositivity against VZV infection does not have any significant impact on fatal outcomes. The median time interval between kidney transplantation and such an infection is usually 2–3 years (this duration can be as high as 19 years in some patients).⁶ Among the renal transplant recipients who develop VZV infection, most have a limited infection in one dermatome distribution. A very small percentage of these patients go on to develop a disseminated infection involving different organs. Postmortem studies have shown that disseminated VZV can also occur in patients without any skin involvement.⁷ There is some literature that points towards mycophenolate as a contributing agent;⁸ however, no specific studies in adults have been done to confirm this association. Currently, there is no evidence to suggest that one immunosuppressive agent might be associated with a higher risk of disseminated VZV as compared with other agents in adult patients. However, one study in paediatric patients with renal transplants did show an increase in VZV infection in patients on mycophenolate as compared with patients who did not receive mycophenolate.⁹

A decrease in immunosuppression along with acyclovir is the treatment of choice. Better outcomes have been observed when the disease has been recognised early and treated promptly.¹⁰ Even though valganciclovir has some activity against VZV, given its lower potency against VZV (as compared with CMV) the medication was likely insufficient in this case (when used for the primary CMV infection) to keep the VZV suppressed. Shortly after the valganciclovir was stopped and under effect of

continuous immunosuppression in our patient, VZV appeared to have reactivated and disseminated with encephalitis. There was a gap of 28 days between the last dose of valganciclovir and development of VZV encephalitis.

There was one study reported in 1987 that involved 610 adult patients with renal transplants. Five of these patients developed chickenpox.¹¹ The only survivor in this study was also the only patient to have received minimal doses of azathioprine and the full recommended dose of acyclovir for disseminated VZV infection. Those who had received suboptimal doses of acyclovir, or those whose immunosuppression was not significantly reduced, died in this study.

A review of the literature shows that the risk of disseminated VZV infection increases in the presence of pre-emptive therapy for CMV infection.¹² An article published in the *Journal of Medical Virology* supports such an association.¹³ Linear regression analyses using the log-transformed antibody titres identified a positive association between ageing and VZV antibody titres suggesting that ageing increasingly stimulates VZV reactivation. CMV infection further amplified the positive association between ageing and the reactivation rate. There is further evidence to suggest a similar association between other viruses belonging to the Herpesviridae family.¹⁴ A case report on brainstem encephalitis in a patient with CMV and VZV was also published.¹⁵ Other immunocompromised states such as HIV have also been shown to be associated with VZV encephalitis. A case report published in the *Journal of Neurovirology* showed encephalitis secondary to VZV and CMV in an immunocompromised (HIV-positive) patient. Imaging studies may not show any specific findings in the brain.¹⁶ Studies such as MRI can range from normal MRI to mild hyperintensities,¹⁷ as seen in our case. Animal studies have shown similar relationship between the two viruses, that is, infection with one virus was associated with systemic activation of the other.¹⁸

The proposed hypothesis for such an association is that CMV infection in immunocompromised patients is immunomodulatory and can lead to further decline in immunity, which predisposes them to have disseminated VZV, either from a primary infection or from reactivation. One report showed that in such patients with simultaneous dual viral infection, use of ganciclovir may be beneficial in improving outcomes by controlling early viremia.¹⁹ There is evidence to suggest that the use of prophylactic antiviral agents routinely in organ transplant recipients is associated with a decrease in incidence of viral infections.²⁰

Learning points

- ▶ Reviewing the differential diagnosis in an immunocompromised patient with altered mental status.
- ▶ Recognising the association between cytomegalovirus infection and subsequent disseminated varicella zoster virus (VZV) development in immunocompromised patients. The association has been reported in some case reports, including this one. It has also been shown in other human and animal studies. Similar association has also been reported between other members of the Herpesviridae family.
- ▶ Recognising that disseminated VZV with encephalitis is a rare but life-threatening condition, which, if recognised early can be easily treated with high-dose antiviral agents. If not treated in a timely manner, it can be fatal.

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Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002;34:1094–7.
- 2 Abbott KC, Oliver JD III, Hypolite I, et al. Hospitalizations for bacterial septicemia after renal transplantation in the United States. *Am J Nephrol* 2001;21:120–7.
- 3 Blennow O, Fjaertoft G, Winiarski J, et al. Varicella zoster reactivation after allogeneic stem cell transplantation without routine prophylaxis—the incidence remains high. *Biol Blood Marrow Transplant* 2014;20:1646–9.
- 4 Umezawa Y, Kakiyama K, Oshikawa G, et al. Clinical features and risk factors for developing varicella zoster virus dissemination following hematopoietic stem cell transplantation. *Transpl Infect Dis* 2014;16:195–202.
- 5 Parnham AP, Flexman JP, Saker BM, et al. Primary varicella in adult renal transplant recipients: a report of three cases plus a review of the literature. *Clin Transplant* 1995;9:115–18.
- 6 Mustapic Z, Basic-Jukic N, Kes P, et al. Varicella zoster infection in renal transplant recipients: prevalence, complications and outcome. *Kidney Blood Press Res* 2011;34:382–6.
- 7 Grant RM, Weitzman SS, Sherman CG, et al. Fulminant disseminated varicella zoster virus infection without skin involvement. *J Clin Virol* 2002;24:7–12.
- 8 Lauzurica R, Bayes B, Frias C, et al. Disseminated varicella infection in adult renal allograft recipients: role of mycophenolate mofetil. *Transplant Proc* 2003;35:1758–9.
- 9 Rothwell WS, Gloor JM, Morgenstern BZ, et al. Disseminated varicella infection in pediatric renal transplant recipients treated with mycophenolate mofetil. *Transplantation* 1999;68:158–61.
- 10 Fehr T, Bossart W, Wahl C, et al. Disseminated varicella infection in adult renal allograft recipients: four cases and a review of the literature. *Transplantation* 2002;73:608–11.
- 11 Bradley JR, Wreghitt TG, Evans DB. Chickenpox in adult renal transplant recipients. *Nephrol Dial Transplant* 1987;1:242–5.
- 12 Ko GB, Kim T, Kim SH, et al. Increased incidence of herpes zoster in the setting of cytomegalovirus preemptive therapy after kidney transplantation. *Transpl Infect Dis* 2013;15:416–23.
- 13 Ogunjimi B, Theeten H, Hens N, et al. Serology indicates cytomegalovirus infection is associated with varicella-zoster virus reactivation. *J Med Virol* 2014;86:812–19.
- 14 Razonable RR, Brown RA, Humar A, et al. Herpesvirus infections in solid organ transplant patients at high risk of primary cytomegalovirus disease. *J Infect Dis* 2005;192:1331–9.
- 15 Saji N, Taniguchi K, Tadano M, et al. [A case of brainstem encephalitis following multiple cranial neuropathy in a hepatocellular carcinoma patient—association with cytomegalovirus and varicella-zoster virus infection]. *Brain Nerve* 2007;59:1273–9.
- 16 Nebuloni M, Vago L, Boldorini R, et al. VZV fulminant necrotizing encephalitis with concomitant EBV-related lymphoma and CMV ventriculitis: report of an AIDS case. *J Neurovirol* 1998;4:457–60.
- 17 Halling G, Giannini C, Britton JW, et al. Focal encephalitis following varicella-zoster virus reactivation without rash in a healthy immunized young adult. *J Infect Dis* 2014;210:713–16.
- 18 Ohtaki S, Kodama H, Hondo R, et al. Activation of cytomegalovirus infection in immunosuppressed cynomolgus monkeys inoculated with varicella-zoster virus. *Acta Pathol Jpn* 1986;36:1537–52.
- 19 Aitken C, Hawrami K, Miller C, et al. Simultaneous treatment of cytomegalovirus and varicella zoster infections in a renal transplant recipient with ganciclovir: use of viral load to monitor response to treatment. *J Med Virol* 1999;59:412–14.
- 20 Rahal EA, Chakhtoura M, Dargham RA, et al. The impact of prophylactic antiviral agents and statin administration on graft longevity in kidney allograft recipients. *Immunopharmacol Immunotoxicol* 2012;34:763–7.

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