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**Title:** Fatal disseminated visceral Varicella Zoster Virus infection in a renal transplant recipient

**Running title:** Fatal disseminated varicella zoster virus

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### **Abstract**

We report a case of fatal disseminated varicella zoster virus (VZV) with delayed-onset rash in a 66-year-old female more than two years following uncomplicated deceased donor renal transplantation. Whilst on a stable regimen of maintenance immunosuppression, the patient presented with chest and abdominal pain with concomitant hepatitis and pancreatitis. After pursuing multiple other potential causes of her symptoms, the correct diagnosis of VZV was only suspected after the development of a widespread vesicular rash – 11 days after her initial symptoms. Despite antiviral therapy and inotropic support in the intensive care unit, the patient died. Simultaneous VZV hepatitis and pancreatitis in solid organ transplant recipients is uncommon. The new inactivated VZV vaccines have the potential to prevent post-transplant infections, with promising early clinical data on safety and efficacy in renal transplant recipients. VZV is an important preventable infection that should be considered in immunocompromised patients, even in the absence of rash.

**Keywords:** varicella zoster virus, kidney transplantation, immunocompromised.

### **Introduction**

Viral infections remain a major cause of morbidity and mortality in solid organ transplant (SOT) recipients, often presenting with atypical manifestations of disease.<sup>1</sup> Reactivation of latent varicella zoster virus (VZV) infection occurs more frequently in SOT recipients at approximately 22 per 1000 patient-years<sup>2</sup> compared to the general population at 1.5-3 per 1000 patient-years.<sup>3</sup> A classic and prominent feature of VZV infection is a vesicular rash that is usually apparent at presentation. Visceral involvement is less common but can include hepatitis, pneumonitis, or rarely pancreatitis.<sup>4</sup> We describe a case of fatal disseminated VZV in a renal transplant recipient, initially presenting as concomitant hepatitis and pancreatitis, with late-onset rash contributing to a delayed diagnosis.

### **Case Presentation**

A 66-year-old Caucasian woman presented with a four-day history of sharp, left-sided chest pain. She had received a deceased donor renal transplantation two years earlier for hypertensive nephropathy, with cytomegalovirus serostatus mismatch (donor negative/recipient positive). Her

allograft function was stable with a serum creatinine between 200-240  $\mu\text{mol/L}$  without significant proteinuria. She was on standard immunosuppression of everolimus (1.25 mg twice daily), mycophenolate mofetil (750 mg twice daily) and prednisolone (5 mg once daily), and was not on any antimicrobial prophylaxis. Recent trough everolimus levels were 4 mcg/L. Her other past medical history was significant for a pulmonary embolus (PE) 21 months earlier requiring 12 months of anticoagulation, hypertension, dyslipidaemia and osteoarthritis. She had no history of infection complications post-transplant.

On admission ('Day 1') she was afebrile, her blood pressure was 170/70mmHg, pulse rate 70/minute, respiratory rate 16/minute, and oxygen saturations 97% on room air. Chest examination demonstrated reduced air entry in the right base but no crepitations or wheeze, abdominal examination revealed no tenderness or guarding, and no rash was present on general inspection. Her creatinine on admission was similar to her baseline at 193  $\mu\text{mol/L}$  (reference range 45-90), sodium was 140mmol/L (135-145), total white cell count was  $7.72 \times 10^9/\text{L}$  (4.5-11.5), and her liver function tests were all within normal limits except ALP 174 units/L (30-110).

Given her past medical history, she was initially investigated for a PE. However, her D-dimer, a high-resolution computer topography scan of the chest and a ventilation/perfusion study all showed no evidence of PE. The patient experienced ongoing chest and worsening abdominal pain, and from Day 4 her liver function tests were increasingly abnormal (alanine aminotransferase [ALT] 150 units/L [reference range  $\leq 35$ ], gamma-glutamyl transferase [GGT] 259 units/L [ $\leq 38$ ]), associated with an elevated lipase of 653 units/L (10-70) (Figure 1). Investigations for hepatitis and pancreatitis included an unremarkable abdominal ultrasound, serum calcium levels that were within normal range and screening for viral hepatitis, which was negative. The patient drank minimal alcohol.

The patient's abdominal pain was so severe that input from the acute pain service was required, with commencement of oxycodone-based patient-controlled analgesia and an intravenous ketamine infusion two days later.

On Day 8, 11 days after the initial onset of chest pain, the patient deteriorated with hypotension (80/55mmHg) and tachycardia (140/minute) in the absence of fevers. She was admitted to the intensive care unit (ICU) for inotropic support. A new widespread vesicular rash was noted over her neck, chest, abdomen and back, with similar but far fewer lesions on her soft palate, arms and legs (Figure 2). This rash had not been present earlier that day. The patient was referred for an Infectious

Diseases consult and immediately commenced on intravenous acyclovir 10mg/kg twice daily, corrected for renal function. The diagnosis of disseminated VZV was confirmed the following day with detection of VZV via qualitative polymerase chain reaction (PCR) in both vesicular fluid as well as peripheral blood. On Day 10 the patient's serum VZV IgG was positive, and VZV IgM was equivocal. No pre-transplant VZV serology results were available.

Despite high-dose antiviral therapy and supportive care in ICU, the patient developed increasing confusion, agitation and drowsiness. Her lipase peaked on Day 9 at 3262 units/L and her ALT and AST peaked on Day 11 at 1974 units/L and 4252 units/L respectively. A lumbar puncture and magnetic resonance imaging of her brain were planned, however due to new thrombocytopenia  $40 \times 10^9/L$  (150-396) and agitation, these investigations were postponed. Following a family meeting and consideration of the patient's previously expressed wishes, active management was withdrawn on Day 13 and the patient died on Day 14. An autopsy was not performed.

### **Discussion**

We have presented a case of fatal, disseminated VZV in a renal transplant recipient who was otherwise well two years post-transplant, without prior episodes of rejection and on stable, relatively modest levels of maintenance immunosuppression. The correct diagnosis was delayed despite being hospitalised to investigate and manage her severe pain, contributed by the initial absence of a rash and the atypical combination of syndromes (hepatitis and pancreatitis). SOT recipients have a much greater risk of disseminated VZV, occurring in up to 40% of patients<sup>5,6</sup> and it is associated with high mortality rates of between 12.5-34% despite treatment.<sup>7-9</sup> Visceral VZV infection is associated with a triad of hyponatremia, right upper-quadrant pain and transaminitis.<sup>10</sup>

Typically, post-transplant VZV infection occurs within the first year after transplantation, with a median onset post-transplant of 9 months.<sup>5,6,11</sup> However, disseminated VZV is often delayed, with median onset of 1.8 to 4.0 years following transplantation.<sup>8,9</sup> Although VZV infection can occur at any stage post-transplantation, augmented immunosuppression for either increased risk or treatment of organ rejection is a recognised risk factor,<sup>12</sup> which was not present in this case. Some papers have suggested mycophenolic acid exposure as an additional risk factor for VZV reactivation,<sup>13,14</sup> however other observational studies have suggested a possible protective association with this agent over azathioprine.<sup>9</sup> Mammalian target of rapamycin (mTOR) inhibitors such as everolimus have been shown to possess some antiviral properties, and there is some data to support their use in the management of other herpes viruses including cytomegalovirus and human

herpesvirus-8 related Kaposi sarcoma. However, there have been no studies assessing their role in VZV.<sup>15</sup>

While VZV is a well-described cause of hepatitis,<sup>3</sup> and less commonly of pancreatitis; there are few published cases of these manifestations occurring simultaneously in transplant recipients. In a study of disseminated VZV among 56 adult renal transplant recipients, hepatitis was a complication in 31% and pancreatitis in only 4%.<sup>9</sup> One recent case from India involved a renal transplant recipient presenting with a week of abdominal pain and four days of a vesicular rash.<sup>16</sup> Another case from the Netherlands described an autologous stem cell transplant recipient presenting with abdominal pain, who developed a vesicular rash in hospital and was found endoscopically to have oesophageal and gastric ulceration.<sup>17</sup> Both patients had elevated liver transaminases and pancreatic enzymes, and in both cases their symptoms and biochemical abnormalities resolved quickly with intravenous acyclovir.<sup>16,17</sup>

The very late onset of the VZV rash, occurring 11 days after the onset of abdominal symptoms, may have contributed to the fatal outcome in our patient. The absence or late onset of an indicative rash can lead clinicians to consider alternative diagnoses for hepatitis, such as acalculous cholecystitis or drug toxicity.<sup>18</sup> The uncommon nature of our case's presentation is highlighted by a cohort of 56 renal transplant recipients with disseminated VZV in which rash was an almost universal initial symptom of illness, occurring in 96%.<sup>9</sup> Along with the absence of a fever, the delayed onset of rash contributed to an infective aetiology not being considered as a cause for our patient's symptoms until very late, despite the patient's immunocompromised state. This represents yet another example of atypical manifestations of infection in immunocompromised patients, a persistent challenge for physicians caring for transplant recipients.<sup>1</sup> When available, transplant infectious diseases experts should be consulted for unusual or enigmatic post-transplant presentations.

The clinical landscape around prevention of VZV in SOT recipients is changing. The development of inactivated VZV vaccines such the adjuvanted recombinant subunit vaccine Shingrix (GSK) and a vaccine inactivated by gamma radiation (Merck) have the potential to alter the risk of post-transplant VZV infection. Previously, use of the live zoster vaccine was contraindicated post-transplant, and within four weeks prior to transplantation.<sup>19,20</sup> Furthermore, vaccine response rates in recipients of SOT and patients with chronic kidney disease can be poor.<sup>21,22</sup> However, recently published phase III data on renal transplant recipients receiving the adjuvanted recombinant subunit vaccine demonstrated high immunogenicity persisting for 12 months, without evidence of worse

safety outcomes.<sup>23</sup> It is anticipated that non-live zoster vaccines will provide safe and effective options for prevention of VZV infection in both the pre- and post-transplant settings in the near future.

In conclusion, we have presented a fatal case of disseminated VZV infection in a renal transplant recipient whose diagnosis was delayed due to an atypical presentation of hepatitis and pancreatitis in combination with the initial absence of a rash. VZV is an important infection that should be considered in immunocompromised patients, even in the absence of rash. In the coming years it is hoped that it will be possible to safely use an inactivated VZV vaccine in SOT recipients to reduce the rates of serious post-transplant VZV infections.

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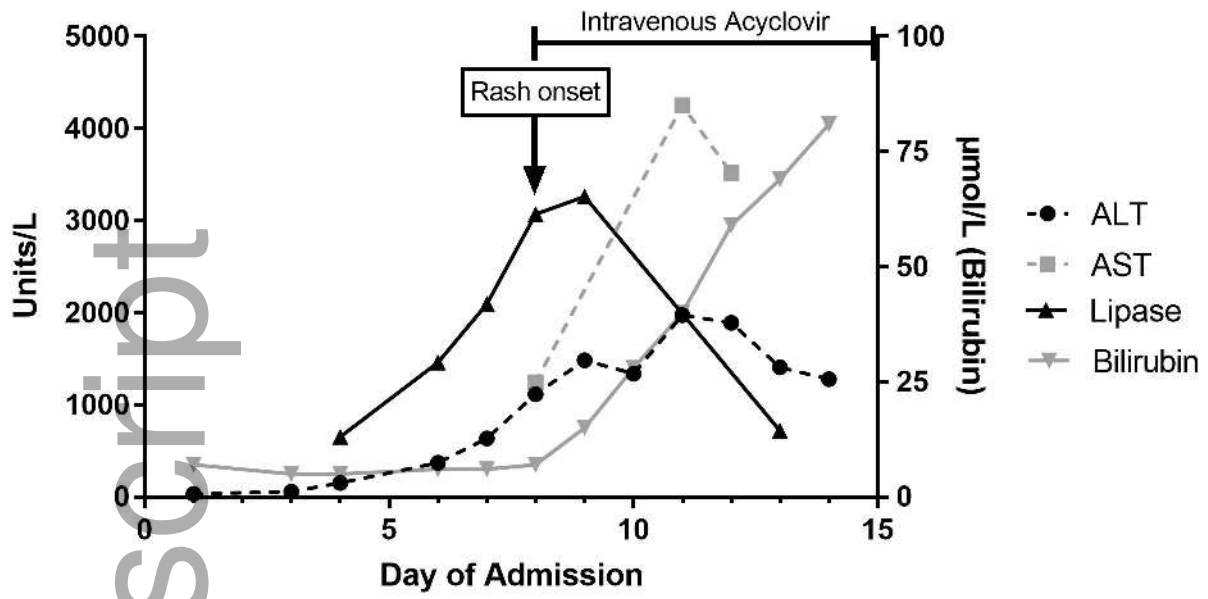
### **Author Contributions**

Michael Loftus collected the patient's clinical data and wrote the first draft of the manuscript. All authors analysed the clinical data and contributed to drafting and revision of the manuscript.

### **Figure Legends**

**Figure 1** – Summary of key blood results, rash onset and treatment course during admission. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Figure 2** – Photograph of vesicular rash over back, with patient in right lateral position (with permission).



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