Acute liver failure secondary to opportunistic viral infection in adult solid organ transplant recipients

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Introduction

Acute liver failure (ALF) is the product of a rapid, overwhelming insult to the liver that destroys parenchymal function, resulting in a multisystem illness characterized by coagulopathy and encephalopathy. Viral infections and drug induced liver injury are the most common causes of ALF.1

The most common viral precipitants are the hepatotropic viruses, hepatitis A, B and E (ALF due to hepatitis C is rare outwith the context of liver transplantation). Defective cell mediated immunity is associated with increased susceptibility to viral hepatitis; reactivation of hepatitis B may occur in those receiving chemotherapy or immunosuppression2 while hepatitis E follows a more severe course in pregnant women and is reported to cause chronic hepatitis in organ transplant recipients.3 Systemic viral infections such as herpes viruses (Epstein–Barr virus, cytomegalovirus, herpes simplex), parvovirus and adenovirus can also affect the liver. In immunocompetent hosts they usually cause a mild collateral hepatitis, but in immunosuppressed individuals, impaired immune surveillance may result in secondary visceral infection, which if severe, may precipitate ALF.4

We describe two fatal cases of ALF due to opportunistic non-hepatotropic viral infections in adult solid organ transplant recipients.

Case 1

A 46-year-old female cardiac transplant recipient was admitted with fever and dyspnoea. She had received a heart transplant 10 months earlier for complications of congenital heart disease and was receiving mycophenolate mofetil (MMF) and cyclosporine immunosuppression. While there was no obvious site of infection, she was commenced on broad spectrum antibiotics following a full sepsis screen (which included bacterial cultures and viral serology), and her immunosuppression was reduced. Liver enzymes were mildly deranged at the time of admission with an ALT of 57 IU/l.

Her condition deteriorated over the following 48 h with the development of severe hepatitis (ALT 1919 IU/l and INR 1.4) and renal impairment, which prompted her transfer to the Intensive Care Unit (ICU). Viral serology revealed acute adenoviral infection (DNA levels 1.4 \times 10^{8} \text{ copies/ml}) for which she was treated with the antiviral nucleotide analogue Cidofovir. However, on day 4 she became haemodynamically unstable and developed hypoglycaemia and encephalopathy consistent with ALF. An ultrasound confirmed a normal sized liver with no features of chronic liver disease. Despite anti-viral therapy and full ICU support, her liver function continued to deteriorate (ALT 10300 IU/l, INR >10) and she died 6 days after admission.
At post-mortem the liver was of normal size with a yellowish colour. Histologically there were large non-zonal areas of coagulative necrosis. Some hepatocytes had large smudged nuclei (Figure 1A) which stained positive for adenovirus by immunohistochemistry confirming that these were adenoviral nuclear inclusions (Figure 1B).

**Case 2**

A 35-year-old man with Senior Loken Syndrome (retinitis pigmentosa and nephronophthisis) was admitted 3 weeks after receiving a cadaveric renal transplant with fever, diarrhoea and right upper quadrant pain. The post-operative period had been complicated by an episode of acute cellular rejection which responded to high doses of oral prednisolone (200 mg daily for 3 days). His long-term immunosuppressive regimen was comprised of MMF and Tacrolimus.

On admission an acneiform rash was noted on his chest and this was attributed to the use of steroids.

Broad spectrum antibiotics were commenced following a full sepsis screen and his immunosuppression was reduced. Liver enzymes were normal at admission but an abdominal CT scan showed multiple hypodense hepatic lesions. By day 3 his ALT had risen to 1725 IU/l.

On day 4 the rash was noted to be more extensive and vesiculopustular in nature (Figure 2) resulting in a provisional clinical diagnosis of varicella zoster (VZV) infection, and the commencement of intravenous aciclovir. However, since records showed that he was VZV seropositive pre-transplantation, a diagnosis of disseminated herpes simplex virus (HSV) was also considered. PCR analysis of blood and vesicle fluid tested positive for HSV type 2. Analysis of stored serum samples revealed that he had been seronegative for HSV types 1 and 2 prior to his transplant, indicating that this was a primary infection with HSV type 2.

Despite appropriate treatment with aciclovir he went on to develop ALF (ALT 4798 IU/l and INR 6.2). HSV hepatitis was diagnosed on the basis of the temporal association between the acute HSV infection and onset of ALF, exclusion of other causes, and the hypodense liver lesions on CT which are a recognized radiological feature of HSV hepatitis. He was admitted to ICU for renal and ventilatory support and later transferred to the regional liver failure unit where his condition continued to deteriorate with worsening coagulopathy (INR >12) and increasing inotropic requirements. He was considered unsuitable for liver transplantation due to the high likelihood of recurrent HSV infection of the allograft and died 10 days after admission.

**Discussion**

Adenoviruses are non-enveloped, double stranded DNA viruses which target the respiratory and GI
tracts. There are more than 50 serotypes which typically cause infections in childhood. In immunocompetent hosts, infection is usually self-limiting, but in immunosuppressed individuals it can lead to severe complications including pneumonia, ALF and disseminated disease.

Adenoviral hepatitis has been reported in some paediatric transplant populations and adult bone marrow transplant recipients. Adenoviral infections in solid organ transplant recipients usually occur in the first 1–2 years post-transplantation and typically affect the transplanted organ. ALF secondary to adenovirus has been reported in adult liver transplant recipients and is associated with a high mortality. As far as we are aware there is only one other reported case of adenoviral hepatitis in an adult cardiac transplant recipient in whom the hepatitis was mild and resolved spontaneously.

While there is no definitive treatment algorithm for adenoviral infections in transplant recipients, supportive care, reduction of immunosuppressive agents and anti-viral agents are appropriate strategies. Ribavirin and cidofovir have both been shown to have in vitro activity and have been effective in uncontrolled case series.

HSV hepatitis is thought to represent <1% of all cases of ALF and <2% of all viral causes of ALF. It usually occurs in immunosuppressed patients or in the third trimester of pregnancy and can occur during both recurrent and primary HSV infection. It has a high mortality but is potentially treatable with aciclovir if recognized early. However, the diagnosis is often made post-mortem since the presentation is non-specific and not all patients have mucocutaneous lesions.

In a series of 137 cases of HSV hepatitis 74% progressed to death or liver transplantation. Those treated with aciclovir had an improved prognosis; 54% progressing to death or transplantation compared with 88% of untreated patients. Post-transplantation mortality was high; seven patients underwent liver transplantation and only three of these survived long term. Life-long antiviral therapy may be required if transplantation is performed since two patients had recurrent cutaneous vesicles within 2 weeks of discontinuing aciclovir.

Poor outcomes associated with liver transplantation for ALF secondary to non-hepatotropic viral infections are unsurprising given the ability of these viruses to replicate outside of the liver which may result in the transplanted liver being immediately exposed to high levels of virions after engraftment. The additional immunosuppression required also means that secondary graft infection is likely even in the presence of antiviral agents.

It is possible that the donor was the source of HSV infection in the second case as stored donor serum tested seropositive for HSV type 2. However, two other recipients of organs from the same donor remain well. The patient did not receive prophylactic valganciclovir post-transplantation because both he and the donor were cytomegalovirus seronegative; this is unfortunate because it may have conferred some protection against HSV. We can only speculate as to whether earlier treatment with aciclovir would have improved the outcome.

**Conclusions**

Rare viral aetiologies should be considered and screened for in all immunocompromised patients presenting with deranged liver function. The prognosis of those with ALF secondary to opportunistic non-hepatotropic viral infections is poor and these patients are not good candidates for liver transplantation. There is a case for commencing empirical treatment with aciclovir on presentation in those with significantly impaired liver function since this may improve the prognosis in HSV hepatitis. The donor is a possible source of infection in those who present with viral infection soon after solid organ transplantation. Donor serum should be traced and tested to allow monitoring of other organ recipients.

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**References**


