CASE REPORT

Fulminant hepatic failure secondary to acyclovir-resistant herpes simplex virus

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SUMMARY

Liver failure is a frequent and serious complication that causes morbidity and mortality in haematopoietic stem cell transplantation (HCT) recipients. Liver dysfunction in these patients can be related to infectious causes, most common viral hepatitis. We report a case of disseminated acyclovir-resistant herpes simplex virus (HSV) infection following HCT that led to acute liver failure and death. Although rare, HSV hepatitis leads to high morbidity and mortality and should be considered in the differential diagnosis of HCT recipients with marked elevation of hepatic transaminase. Acyclovir is a first-line therapy for HSV infection; however, acyclovir-resistant viral strains should be considered and alternative HSV therapies given in HCT recipients whose HSV infection does not improve on acyclovir therapy.

BACKGROUND

Liver dysfunction is a frequent and serious complication that causes morbidity and mortality in haematopoietic stem cell transplantation (HCT) recipients. Some degree of hepatic dysfunction is expected to occur in up to 80% of HCT recipients, and liver failure is responsible for up to 15% of deaths following HCT.¹

Viral infections following HCT are an important aetiology for liver dysfunction, and although rare herpes simplex virus (HSV) dissemination and hepatitis represents <2% of all viral causes of acute liver failure.² Although challenging to diagnose and rare to occur, HSV hepatitis is associated with significant mortality and morbidity.³ Early antiviral therapy with acyclovir has been associated with a significantly decreased mortality,³ and hence the diagnosis of HSV hepatitis should be considered early in the course. Furthermore, the presence of acyclovir-resistant HSV strains can make the treatment challenging and hence clinicians should be aware of factors that predispose patients to have infection with a drug-resistant virus. We report a case of disseminated acyclovir-resistant HSV infection following HCT that led to acute liver failure and death. To the best of our knowledge, this is the first of such reported case and highlights some of the problems mentioned above, in diagnosing and treating this condition.

CASE PRESENTATION

A 51-year-old man with myelodysplastic syndrome underwent HCT from a matched unrelated donor and received a conditioning regimen of fludarabine, busulfan, clofarabine and antithymocyte globulin. The patient received oral valacyclovir, posaconazole,

cefepodoxime and trimethoprim-sulfamethoxazole prophylaxis after HCT. The patient's post-HCT course was complicated by grade II (Glucksberg grade) graft-versus-host disease (GvHD) that affected the skin and gastrointestinal tract and was treated with oral methylprednisolone (2 mg/kg per day), intravenous pentostatin and extracorporeal photopheresis.

One week before the current presentation, on day +54 after the HCT the patient reported a new onset of perianal ulcers, confirmed by a PCR test to be caused by HSV type 2. The prophylactic valacyclovir dose was increased from 500 mg two times per day to 1 g two times per day for 1 week, leading to only minimal improvement in the perianal ulcers.

The patient presented to the hospital on day +61 post-HCT with acute onset of fever and abdominal pain. On initial evaluation, the patient was febrile (38.8°C); however, the rest of his vital signs were within normal limits (pulse=86 bpm, respiratory rate=18 bpm, blood pressure=129/99 mm Hg). On examination, the patient had abdominal tenderness predominantly in his right upper quadrant; however, no hepatomegaly was noted. The perianal area had multiple painful ulcerations with an erythematous base and surrounding erythema.

INVESTIGATIONS

Laboratory tests revealed normal white cell count and absolute neutrophil counts and a decreased absolute lymphocyte count (70 cells/mm³). Serum transaminase levels were mildly elevated at presentation (aspartate aminotransferase level=263 IU/L, alanine aminotransferase level=242 IU/L), with normal levels of serum alkaline phosphatase and serum bilirubin.

To further investigate the aetiology of the right upper quadrant abdominal pain and elevated liver enzymes, the patient underwent CT of the abdomen, which demonstrated numerous hypodense liver lesions 0.5–2 cm diameter in size (figure 1).

DIFFERENTIAL DIAGNOSIS

Initial workup, including bacterial, mycobacterial and fungal blood cultures and tests for serum Cryptococci antigen and urine histoplasma antigen, yielded negative results. Testing for viral hepatitis (antihepatitis A immunoglobulin M, hepatitis B surface antigen, antihepatitis B core antibody, hepatitis B DNA PCR and antihepatitis C virus antibody) and serologic testing and plasma PCR for *Toxoplasma gondii* all yielded negative results as well. HSV1 and HSV2 plasma PCR, varicella zoster

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Figure 1 CT of the abdomen, which demonstrated numerous hypodense liver lesions 0.5–2 cm diameter in size.

virus (VZV) plasma PCR, cytomegalovirus (CMV) plasma PCR, human herpes virus 6 PCR and adenovirus PCR in plasma were all sent out, and results were awaited.

TREATMENT

The patient was initiated on broad-spectrum antimicrobials, including intravenous vancomycin and meropenem for bacterial liver abscess coverage, intravenous liposomal amphotericin for empirical mould coverage and intravenous acyclovir (10 mg/kg every 8 hours) for continued treatment of the HSV perianal ulcers. Within 48 hours of admission, the patient's clinical status rapidly deteriorated secondary to acute liver failure. Serum transaminase levels rapidly rose (aspartate aminotransferase level=3240 IU/L, alanine aminotransferase level=4860 IU/L), and total bilirubin levels rose as well (9.8 mg/dL). Owing to abrupt elevation of liver enzymes, empirical treatment for opportunistic viral hepatitis (*Herpesviridae* family, including drug-resistant HSV or VZV and adenovirus) was initiated with intravenous cidofovir at 5 mg/kg/dose on day 3 of hospitalisation; while we awaited further workup. Subsequently, the patient developed severe coagulopathy with a platelet count of 3000/mm³, prolonged prothrombin time (32 s) and elevated international normalised ratio of 3.1. A liver biopsy was clinically indicated but could not be performed owing to the bleeding risk associated with the severe coagulopathy.

OUTCOME AND FOLLOW-UP

The patient was transferred to the intensive care unit owing to his altered mental status, secondary to liver failure and gastrointestinal bleeding. The workup for viral aetiologies revealed negative serum PCR results for VZV, CMV and adenovirus; however, plasma PCR for HSV type 2 revealed 10⁸ DNA copies/mL. Owing to suspicion of acyclovir-resistant HSV, on day 5 of hospitalisation, the patient was transitioned from intravenous acyclovir to intravenous foscarnet therapy (40 mg/kg/dose every 8 hours). Over the next few days, the patient was progressively more icteric and developed multiorgan system failure with hypotension, deranged renal function and progressive encephalopathy. The liver transplant team at an outside institution was notified of his case; however, the patient was too clinically unstable to be transferred for a liver transplant. Despite aggressive supportive care, the patient clinically deteriorated and required vasoconstrictor support, mechanical

Figure 2 Haematoxylin and eosin stain of liver tissue demonstrating multifocal areas of necrosis and haemorrhage with minimal inflammation.

ventilation and haemodialysis. The patient's family was made aware of his poor prognosis, and they decided to withdraw life-sustaining measures, leading to the patient's death.

Postmortem microscopic examination of the liver tissue revealed multifocal necrosis and haemorrhage with minimal inflammation (figure 2) and classic changes suggestive of HSV infection, including multinucleation and margination of chromatin (figure 3). Immunohistochemical nuclear staining analysis revealed HSV in many of the necrotic hepatocytes (figure 4). The HSV was isolated in viral cultures performed on liver tissue, and antiviral susceptibility analysis demonstrated acyclovir resistance.

DISCUSSION

Herein, we report a case of disseminated acyclovir-resistant HSV infection in an HCT recipient, leading to acute liver failure and death. The patient's recent transplantation requiring the T-cell-depleting agent antithymocyte globulin and diagnosis of acute GvHD requiring treatment with steroids and pentostatin constituted his main risk factors for disseminated HSV infection. Furthermore, the patient's long-term exposure to oral valacyclovir, associated with his compromised T-cell immunity, likely played a role in the development of acyclovir-resistant HSV strains.

Figure 3 High power view of haematoxylin and eosin stain of liver tissue demonstrating multinucleation and margination of chromatin.

Figure 4 Immunohistochemical nuclear staining of liver tissue demonstrating acyclovir-resistant herpes simplex virus infection in many of the necrotic hepatocytes.

Viral infections following HCT are an important aetiology of early-phase and late-phase liver dysfunction. Several viruses have been associated with acute liver failure, including hepatitis A, B, C, D and E. Reactivation of hepatitis B infection is common and is frequently seen in the early posttransplant period. In addition, acute liver failure can occur on reactivation of viral infections such as CMV, HSV, VZV, human herpesvirus 6 and adenovirus in the early posttransplant period and in patients with GvHD; however, few such cases have been reported.¹

Primary infection with HSV occurs most commonly in the oral and genital mucocutaneous areas. After primary infection, HSV remains dormant in the nerve root ganglia with the potential for reactivation. Dissemination with viral encephalitis is the most common complication of latent HSV; however, visceral dissemination to the oesophagus, lungs and liver has been reported.⁴

HSV dissemination with hepatitis is rare and represents <2% of all viral causes of acute liver failure.² First described in adults in 1969,⁵ HSV hepatitis most commonly affects immunosuppressed individuals and women in the third trimester of pregnancy. Early administration of antiviral therapy against HSV will prevent progression to an irreversible level of hepatic injury.³ In a retrospective study, of the 34 cases with HSV hepatitis, significantly longer time from symptom onset to treatment initiation (mean 4.7 ± 0.48 vs 3.5 ± 0.27 days; $p=0.03$) was noted in patients who died or required liver transplant compared to those who survived. Given the high mortality rate associated with HSV hepatitis (74%) and the reduction in mortality risk associated with antiviral therapy,³ early detection and diagnosis of this condition is essential to improve survival.

HSV hepatitis should be considered and tested in patients with acute hepatitis associated with features such as leucopenia, right upper quadrant pain and fever. Less than half of the patients with HSV hepatitis have the characteristic cutaneous herpetic lesions; hence, the absence of a vesicular rash should not lower the physician's index of suspicion for HSV hepatitis.³ Certain other viruses such as CMV, human herpesvirus 6, adenovirus and VZV can present with hepatitis on presentation and therefore need to be excluded. Clinical course for disseminated HSV and VZV is similar and hepatic involvement is more often associated with fulminant hepatic failure.^{1 2} Hepatitis is a well-described complication of adenovirus infections in immunocompromised hosts, especially with subgroup C type 5.

Adenovirus hepatitis is a particular problem in paediatric liver transplant recipients and may be fatal in these patients.⁶ In contrast, hepatitis with CMV and human herpesvirus 6 is usually mild to moderate in severity and rarely associated with hepatic failure.^{1 2} CT findings can be non-specific; however, diffuse liver microabscesses have been described with HSV in pregnant patients and patients who had liver transplant in a few case reports.⁷⁻⁹ The classic histological findings in HSV hepatitis are areas of coagulate necrosis predominantly centrilobular in distribution, with scattered internuclear eosinophilic bodies in the peripheral irregular zones of haemorrhagic necrosis.^{8 10} Microabscesses have also been described in patients who had liver transplant with CMV infection and are associated with ballooning of hepatocytes and Kupffer cell reaction on the histological section,^{11 12} and related to adenovirus in paediatric patients who had liver transplant.¹³

Conventional and quantitative real-time PCR are available for the detection of HSV DNA in clinical samples, including liver biopsies. Although the gold standard for the diagnosis of HSV hepatitis is a liver biopsy, coagulopathy may be a contraindication for the procedure, as in our case; and serum PCR for HSV may be a helpful alternative diagnostic tool.¹⁴

Acyclovir therapy has improved the morbidity and mortality associated with HSV infections.³ Early empirical initiation of therapy can be helpful in cases of fulminant liver failure when a viral aetiology is considered in immunocompromised patients. Furthermore, it is important to keep in mind the possibility of acyclovir-resistant viral strains in immunocompromised patients, such as those with HIV infection and recipients of HCT, who may have been chronically exposed to acyclovir and have decreased immune clearance of the virus. The prevalence of HSV infections caused by acyclovir-resistant isolates in these populations varies from 3.5% to 11.0%, and these infections are associated with significant morbidity, including that due to persistent and/or acyclovir-resistant HSV.¹⁵ The emergence of resistance to acyclovir through mutations in viral thymidine kinase, encoded by the UL23 gene in HSV, has been described.¹⁵ The severity of immunosuppression and the dose and duration of acyclovir prophylaxis/treatment are important risk factors in the development of drug resistance.^{16 17} However, drug-resistant HSV mutants have been isolated in some patients in the absence of a known history of acyclovir exposure.^{18 19} Acyclovir-resistant HSV strains should be considered especially when a patient who has been previously exposed to prolonged acyclovir therapy does not show signs of lesion improvement while on acyclovir or new lesions appear while being on acyclovir prophylaxis.¹⁵

Foscarnet and cidofovir are alternative agents to be used in cases of acyclovir-resistant HSV, as these agents inhibit the catalytic subunit of viral DNA polymerase without requiring activation by thymidine kinase. Foscarnet inhibits the DNA polymerase by reversibly binding to its pyrophosphate-binding site.²⁰ Cidofovir is a monophosphate analogue that is further phosphorylated by cellular kinases and incorporated into the genome of the virus. Cidofovir has broad-spectrum activity against double-stranded DNA viruses, including human herpesviruses and adenoviruses,²¹ and hence was prescribed empirically to the reported patient. It is important for clinicians to consider the diagnosis of drug-resistant HSV early and order appropriate testing to determine resistance through genotypic or phenotypic testing, for example, dye uptake assay. As genotypic or phenotypic testing results are not promptly available, determining the risks and benefits of changing therapy to either foscarnet or cidofovir and consulting with infectious disease specialists is recommended.

Despite the rarity of HSV-related hepatitis, in light of the mortality and morbidity associated with this condition, we recommend considering the diagnosis of HSV-related hepatitis in immunocompromised patients presenting with marked elevation of hepatic transaminase after common causes of fulminant hepatitis have been excluded. Early therapy with acyclovir should be initiated, but if acyclovir-resistant HSV is suspected, thymidine kinase resistance should be tested for and alternative therapy with foscarnet or cidofovir promptly instituted.

Learning points

- ▶ Viral infections following haematopoietic stem cell transplantation are an important aetiology for liver dysfunction, and acyclovir-resistant herpes simplex virus (HSV) dissemination and hepatitis represents <2% of all viral causes of acute liver failure.
- ▶ Early antiviral therapy with acyclovir has been associated with a significantly decreased mortality, and hence the diagnosis of HSV hepatitis should be considered early in the course.
- ▶ Acyclovir-resistant HSV strains should be considered especially when a patient who has been previously exposed to prolonged acyclovir therapy does not show signs of lesion improvement while on acyclovir or new lesions appear while being on acyclovir prophylaxis.
- ▶ Early therapy with acyclovir should be initiated, but if acyclovir-resistant HSV is suspected, thymidine kinase resistance should be tested for and alternative therapy with foscarnet or cidofovir promptly instituted.

Competing interests None declared.

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