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Case report

Herpes simplex virus 2 hepatitis in a lung transplant recipient: a diagnostic challenge

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Abstract: Herpes simplex virus (HSV) hepatitis is a rare and serious complication in immunocompromised patients. We report the case of an HSV hepatitis occurring 4 years after lung transplantation in a cystic fibrosis patient. The presentation was nonspecific, mimicking acute cholecystitis; orogenital signs were absent. The diagnosis was made based on viral cultures performed during cholecystectomy and confirmed by blood quantitative polymerase chain reaction. Although the diagnosis and treatment were delayed, the patient fully recovered with acyclovir, reduced immunosuppression, and intravenous immunoglobulins. The diagnostic difficulties, prognostic factors, and treatments of this infection are discussed.

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Herpes simplex virus (HSV) hepatitis is an uncommon disorder occurring almost exclusively in immunocompromised patients, such as solid organ transplant recipients. In most cases, it leads to acute liver failure requiring emergency liver transplantation or to death (1–3), although it is a treatable disease, provided an early diagnosis is made. Lack of awareness and its nonspecific clinical presentation might explain why the diagnosis is often retrospective at post-mortem examination (2, 4). New techniques such as real-time quantitative polymerase chain reaction (qPCR) are of great help in establishing a quick diagnosis, once HSV is suspected (5, 6).

We report the first case, to our knowledge, of an HSV2 hepatitis mimicking acute cholecystitis, in a lung transplant patient. The pitfalls, early signs toward the diagnosis, and the favorable outcome under specific therapy are discussed.

Case report

A 34-year-old woman with bilateral lung transplantation (LT) 4 years earlier for cystic fibrosis was admitted to our department for a 1-week history of diarrhea, nausea, and vomiting. Her past medical history was noteworthy

for type 1 diabetes preexisting to the transplantation and her significant post-transplant complication was only a recurrent asymptomatic cytomegalovirus infection treated by valganciclovir, with a temporary switch from mycophenolate mofetil (MMF) to everolimus, owing to an acquired ganciclovir resistance.

Clinical examination showed right abdominal pain with no tenderness. Body temperature was 39°C. White cell count and liver function tests were normal, while the C-reactive protein level was elevated to 102 mg/L. Her immunosuppressive therapy included tacrolimus (serum level of 6.8 μg/L), MMF 500 mg twice a day, and prednisolone 7.5 mg daily. She was not taking any antiviral therapy at time of presentation. Blood PCR for cytomegalovirus was negative.

Initial medical evaluation was suggestive of a viral gastroenteritis, and supportive care was initiated. Over the next 4 days, her clinical status deteriorated with persistent fever and vomiting, as well as new right upper quadrant abdominal tenderness and a slight increase in liver enzymes. Aspartate aminotransferase (AST) level was 148 U/L (normal 13–40 U/L), alanine aminotransferase (ALT) was 107 U/L (normal 7–40), alkaline phosphatase and bilirubin remained normal, and C-reactive protein increased to 240 mg/L (Fig. 1). Screening for drug-induced hepatitis was negative.

Because of the abdominal tenderness and the inflammatory syndrome, an enhanced abdominal computed tomography was ordered. It showed a calculous gallbladder with edematous thickening of its walls (Fig. 2), consistent with the clinical hypothesis of uncomplicated acute cholecystitis. Intra- and extra-hepatic biliary ducts were not dilated. Multiple ill-defined hypodense micronodules ranging from 3 to 5 mm were described and remained unexplained at that time.

Intravenous antibiotic therapy (piperacillin/tazobactam and levofloxacin) was started, MMF was discontinued, and a laparoscopic cholecystectomy was performed 5 days after the admission. Macroscopically, the liver had a microvesicular aspect, which led the surgeon to request a viral study of the peritoneal fluid. The gallbladder pathology examination was consistent with a chronic calculous cholecystitis.

Despite the surgery, the abdominal symptoms worsened and liver enzymes continued to rise (AST 466 U/L, ALT 231 U/L; Fig. 1). White blood cell count was 9.3×10^9/L, hemoglobin 10.6 mg/dL, and platelet count 218,000/μL. Prothrombin time remained normal at 82%. There were no signs of encephalopathy.

Three days after the surgery, the viral study (rapid culture on MRC5 cells) of the peritoneal fluid came back positive for HSV. The blood qPCR (HSV2 R-gene® real-time quantitative PCR kit; bioMérieux, Marcy-l'Etoile, France) was highly positive for HSV type 2 (HSV2) (>70,000,000 copies/mL).

In light of these findings, a thorough skin examination revealed 2 isolated necrotic vesicles on the arm and back, that came back positive for HSV2 (by qPCR). No gynecologic or oral sign of infection were found, and subsequent systematic vaginal viral cultures were negative 3 months later. HSV 1 and 2 serology, which was negative before LT, became highly positive for immunoglobulin (Ig)M and weakly positive for IgG, suggesting a primary infection.

The patient was treated with intravenous acyclovir 500 mg every 8 h and intravenous immunoglobulins (IVIG) 20 g per day for 3 days. MMF was temporarily stopped. After 17 days of treatment, clinical evolution was excellent, with normalization of liver enzymes and blood qPCR for HSV (Fig. 1). Intravenous acyclovir was switched to oral valacyclovir, 1 g twice daily for 4 months. Because of the history of viral infections in this patient, MMF was replaced by everolimus.

We retrospectively looked for the donor HSV serology, but it was not available. At 1-year follow-up, the patient's condition was excellent, without any clinical or laboratory evidence of relapse.

Discussion

HSV hepatitis is a serious and very rare complication in neonates, the immunocompromised, and during pregnancy. In solid organ transplantation, it has been reported in <50 cases of liver or kidney transplantation, and in only 2 cases of heart transplantation (3, 7). HSV hepatitis is often caused by type 2, rather than type 1, HSV (2). To the best of our knowledge, this is the first reported case of HSV hepatitis in a lung transplant patient.

This case illustrates the difficulties of diagnosing this condition, owing to its rarity, but also because of its nonspecific signs on clinical examination, imaging, and on laboratory tests. The common features of clinical presentation are flu-like symptoms and abdominal pain. Norvell et al.'s literature review (2) showed that a clinical suspicion of HSV hepatitis was raised in only 22.6% of 137 cases. Laboratory investigations often demonstrate leukopenia, thrombocytopenia, coagulopathy, a relatively low bilirubin level, and a significant increase in liver enzymes (100- to 1000-fold), with AST greater than ALT (4, 8). In our case, the diagnosis was mistaken for an acute cholecystitis, because of the confirmed calculous gallbladder and major gallbladder wall edema, which are common findings in cystic fibrosis patients. The diagnosis was finally made during

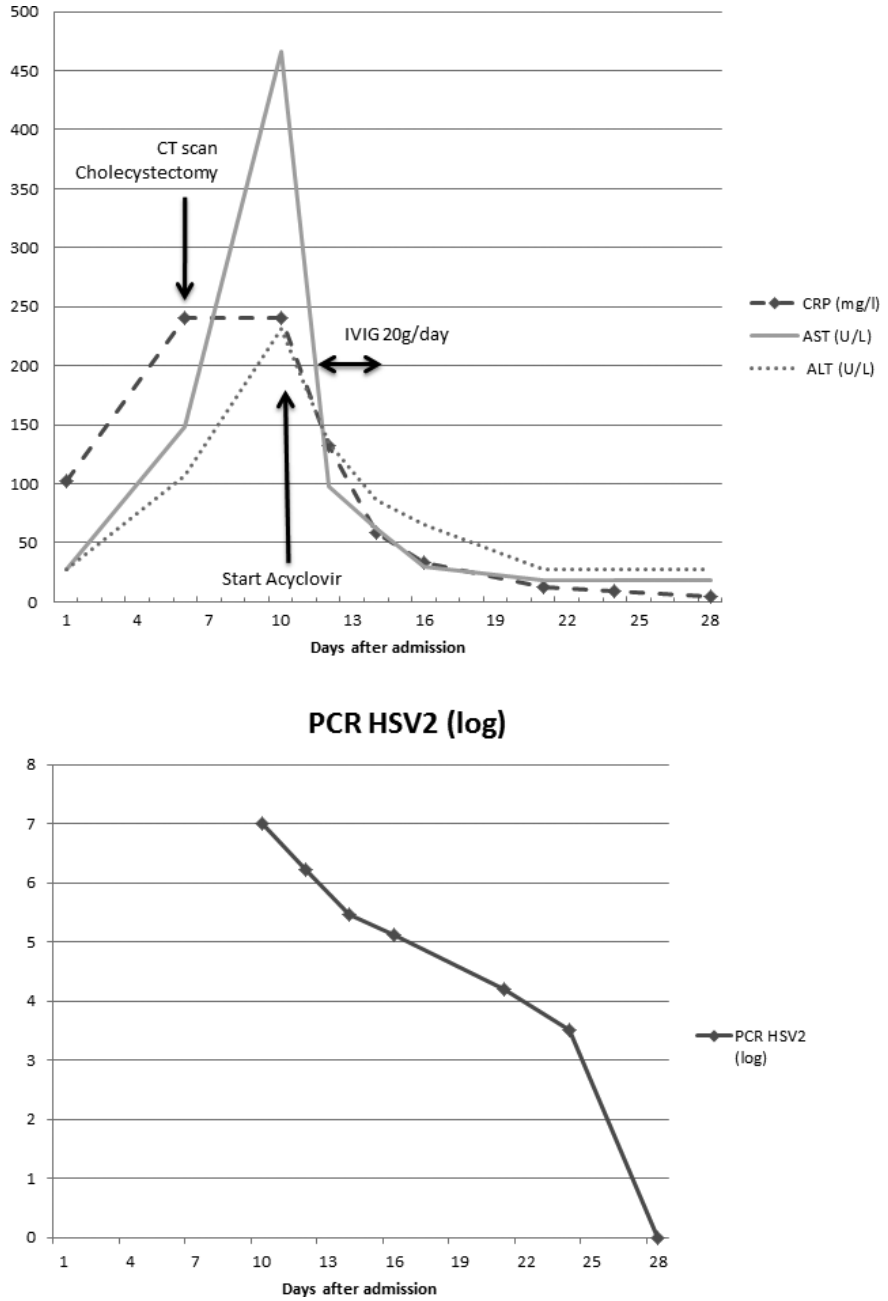

Fig. 1. Graph showing (above) the C-reactive protein (CRP), liver enzymes (AST, ALT), and (below) blood polymerase chain reaction (PCR) for herpes simplex virus 2 (HSV2) outcome, before and after the treatment was initiated. CT, computed tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IVIG, intravenous immunoglobulin.

surgery, when the microvesicular aspect of the liver troubled the surgeon and peritoneal fluid virology was obtained.

In retrospect, the unexplained micronodular aspect on the liver computed tomography scan should have drawn our attention. This nonspecific aspect has already been described and represents foci of hepatic necrosis secondary to the viral infection (3, 9, 10). The gold standard for diagnosis is liver biopsy (11), but it is an invasive procedure with possible contraindications in

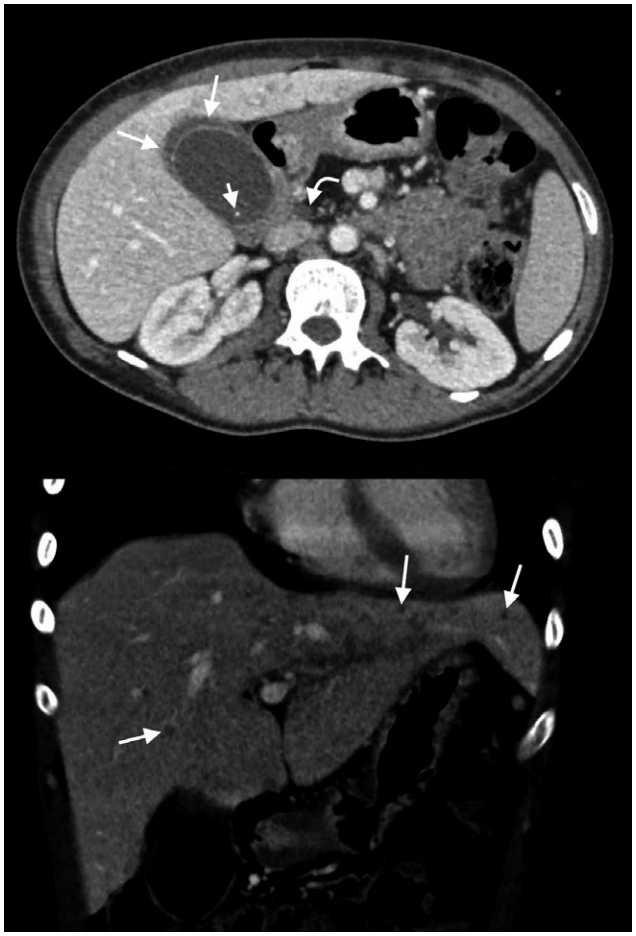

Fig. 2. Initial contrast-enhanced computed tomography of the liver. (Above) Axial slice: Calculous gallbladder (stone – short arrow) with severe wall edema (long arrows), consistent with acute cholecystitis. Common bile duct is not enlarged (curved arrow). (Below) Coronal slice: Multiple ill-defined hypodense micronodules are scattered within the liver parenchyma (arrows).

case of hepatitis-induced coagulopathy. In contrast, HSV qPCR is the most sensitive non-invasive diagnostic method for HSV infection in solid organ transplant recipients (11). HSV qPCR can be performed on blood samples as well as other clinically relevant specimens. This technique is currently becoming more widely implemented and results can be available within a few hours (12). HSV qPCR has thus been shown to be an essential tool for the rapid diagnosis of HSV hepatitis (13). Indeed, HSV viral loads in blood correlate with liver enzyme levels, and a threshold of 100,000 copies/mL has been suggested as highly indicative for HSV hepatitis (5, 6). Monitoring of HSV loads by qPCR can also be useful in ascertaining the efficacy of antiviral therapy (5, 13).

In an extensive review of the literature, Pietrucha-Dilanchian et al. (3) underline that the majority of HSV hepatitis occurs during the first weeks or months after the transplantation, usually liver or kidney transplant. In our case, the long interval between LT and the HSV hepatitis is noteworthy.

No new immunosuppressive event had occurred, but interestingly the everolimus had been switched 4 months before with MMF, in anticipation of an ovarian cyst celioscopic ablation. In the majority of the reported cases, the infection is attributed either to a primary infection, or to reactivation under intensive immunosuppressive treatment. Exceptional cases of graft transmission have been reported (3). In our case, the 4-year duration since LT argues against graft transmission. Moreover, the patient was seronegative for HSV before LT and became highly positive with IgM at the time of HSV hepatitis, which suggests a primary and asymptomatic infection, with no oral or genital signs.

Although most cases of HSV hepatitis have a poor prognosis, our case had a favorable outcome. Maintenance-dose immunosuppressive therapy and early treatment initiation may have protected our patient from fulminant disease. Moreover, the absence of poor prognosis factors (2), including encephalopathy, coagulopathy, severely elevated ALT (>5000), male gender, and age over 40 years, all favored the positive outcome.

The reference treatment consists of high-dose antiviral therapy with acyclovir (3, 14, 15). Norvell et al.'s literature review (2) reports a reduced death rate from 88% down to 51% when acyclovir is initiated, with a mean time from overt symptoms to treatment of 4.2 days.

Because of the poor prognosis of HSV in solid organ transplantation, some authors added IVIG, in addition to acyclovir, with recovery noted in all cases (16–20). In accordance with these data, we also initiated complementary treatment with IVIG. The therapeutic role of such a treatment remains yet to be elucidated.

In conclusion, HSV hepatitis can complicate the course of LT, but this rare condition is challenging to diagnose, with very few diagnostic clues. The increased availability of rapid diagnostic methods, such as blood qPCR, may contribute to earlier diagnosis as well as to optimal clinical management by monitoring response to antiviral treatment. Prognosis might be improved by early treatment.

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