Fulminant Adenovirus Hepatitis Following Bone Marrow Transplantation

A Case Report and Brief Review of the Literature

Wei Hua Wang, MD; Hanlin L. Wang, MD, PhD

Adenovirus infections are frequently encountered in immunocompromised patients and transplant recipients. However, fulminant hepatic failure due to adenovirus infection as a fatal complication in bone marrow transplant recipients is extremely rare. We report a case of fulminant adenovirus hepatitis in a 21-year-old allogeneic bone marrow transplant recipient who subsequently died of the disease. The diagnosis was established by histologic and immunohistochemical examination of a liver biopsy and was confirmed by liver tissue and blood cultures.

REPORT OF A CASE

A 21-year-old man obtained an allogeneic BMT for acute T-cell leukemia. One month after transplantation, gastrointestinal graft-versus-host disease (GVHD), grade 3/4, was diagnosed based on colonoscopic biopsy. Four months later, the patient developed fulminant hepatic failure with jaundice. Laboratory studies showed a total bilirubin level of 9.8 mg/dL (normal range, 0.3–1.1 mg/dL); aspartate transaminase, 7352 U/L (7–53 U/L); alanine transaminase, 2501 U/L (7–53 U/L); alkaline phosphatase, 1074 U/L (38–126 U/L); lactate dehydrogenase, 11322 U/L (100–250 U/L); plasma ammonia, 53.0 μmol/L (9.0–33.0 μmol/L); prothrombin time, 26.5 seconds (10.5–14.5 seconds); partial thromboplastin time, 67.1 seconds (23.0–35.0 seconds); total plasma protein, 4.8 g/dL (6.5–8.5 g/dL); and albumin, 2.2 g/dL (3.6–5.0 g/dL). Serologic tests were negative for antibodies against hepatitis A virus, hepatitis B virus core antigen, and hepatitis C virus and for hepatitis B virus surface antigen and anti–Epstein-Barr virus immunoglobulin (Ig) M antibody (IgG antibody was positive). Polymerase chain reaction assays performed on blood cells were negative for cytomegalovirus, herpes simplex virus types 1 and 2, human herpesvirus 6, and parvovirus B19. A clinical diagnosis of hepatic GVHD was suspected, and a transjugular liver biopsy was performed. Liver tissue and blood cultures were also sent. The patient died the day after the liver biopsy despite supportive measures. An autopsy was not performed.

PATHOLOGIC FINDINGS

Histologic sections of the liver biopsy contained large, random foci of coagulative hepatocyte necrosis with mild canalicular and cytoplasmic cholestasis and some steatosis (Figure 1). No significant inflammatory response was present. The portal tracts had only minimal amounts of mononuclear cell infiltrate composed of lymphocytes admixed with rare eosinophils and neutrophils. No bile duct damage or loss and no endotheliitis were evident to suggest a diagnosis of acute or chronic GVHD. Higher power examination of sections revealed a slight variation in the size of hepatocyte nuclei. Some of the hepatocytes, particularly those surrounding the necrotic foci, contained smudgy nuclei with chromatin margination (Figure 2). These histologic findings are highly suggestive of a diagnosis of adenovirus hepatitis. Immunohistochemical processing for adenovirus produced strong and predominantly nuclear staining (with some cytoplasmic positivity) in approximately 30% of the hepatocytes, with more concentrated staining around the necrotic foci (Figure 3). The histopathologic diagnosis of adenovirus hepatitis was subsequently confirmed by liver tissue and blood cultures, which were positive for adenovirus and negative for cytomegalovirus, herpes simplex viruses, and bacterial and fungal growth.

COMMENT

Adenoviruses are a group of nonenveloped double-stranded DNA viruses that have been recovered from virtually every organ system in humans. In immunocompetent individuals, the viruses may cause mild self-limited illnesses, including respiratory infection, keratoconjunctivitis, hemorrhagic cystitis, and gastroenteritis. Adenovirus infections occur more often in immunocompromised patients and may result in more severe diseases, such as pneumonia, nephritis, hepatitis, encephalitis, pancreatitis, or disseminated disease. In BMT recipients, adenovirus used to be the third most common viral infection after herpes simplex and cytomegalovirus.24 With the introduc-
Adenovirus Hepatitis After Bone Marrow Transplant—Wang & Wang e247

Figure 1. Low-power view of liver biopsy showing foci of coagulative necrosis with minimal inflammatory cell response and focal mild steatosis (hematoxylin-eosin, original magnification ×100).

Figure 2. High-power view of liver biopsy showing hepatocytes with smudgy nuclei and chromatin margination (arrowheads) (hematoxylin-eosin, original magnification ×400).

Figure 3. Immunohistochemical staining of liver biopsy for adenovirus. The mouse anti-adenovirus monoclonal antibody (blend of clones 20/11 and 2/6, Chemicon International, Temecula, Calif) is reactive with all 41 serotypes of adenovirus. The staining was performed with proteinase K pretreatment and 1:2000 dilution of the primary antibody (original magnification ×400).

The reported incidence of adenovirus infections in BMT recipients varies from 3% to 21%. The high mortality is largely attributed to pneumonia, renal failure, fulminant hepatitis, and the lack of effective therapy, although successful treatment with ribavirin, cidofovir, or serum immunoglobulin containing high titers of neutralizing antibody to adenovirus has been reported.

The most common adenovirus isolates from BMT patients are serotypes 5, 11, 34, and 35. Other serotypes, such as 2, 4, 6, 7, 12, 29, and 31, have also been reported. Several authors have postulated that adenovirus infections in pediatric cases, which usually occur within the first 30 days after transplantation, are most likely to result from recent exposure, whereas in adults many of the infections probably represent reactivation as indicated by the time of onset, which is usually 90 days or more after transplantation. In a few studies, moderate to severeGVHD, isolation of the virus from 2 or more anatomic sites, and receipt of concurrent immunosuppressive therapy have been identified as risk factors for adenovirus infections and for severe disease in BMT patients. However, these findings have not been confirmed by other investigators.

Orthotopic liver transplant recipients appear to be vulnerable to development of hepatitis as a major manifestation of adenovirus infection, which usually leads to either patient death or allograft loss. However, fulminant hepatic failure, as seen in the patient in the present case, is not a common sequel of adenovirus infections in BMT patients. Most published reports concern single cases. In the study of Shields et al, who evaluated 51 cases of adenovirus infection, only 2 patients had adenovirus hepatitis; 1 patient died of pneumonia and the other died of GVHD and sepsis. In other surveys of 42 adenovirus infections, fulminant hepatitis was reported as the initial presentation in only one patient, although mild hepatitis as a later component of disseminated disease was observed in 3 patients. A more recent study by Baldwin et al included 100 BMT patients with adenovirus infections, and in only one patient were characteristic nuclear inclusions found in hepatocytes. In other surveys including fewer cases, liver involvement by the virus was either not documented or occurred in only rare cases. Fulminant adenovirus hepatitis in BMT recipients, as in other immunocompromised patients, is usually fatal. Serotypes 5, 1, and 2 are most frequently associated with liver infection.

Histologically, adenovirus hepatitis is characterized by small or large areas of coagulative necrosis with no particular zonal distribution. Inflammatory response is usually sparse or absent. Intranuclear viral inclusions with characteristic smudgy appearance and chromatin margination are unique and should be readily recognizable. However, because the incidence of coinfection with other viruses is high in BMT recipients, particularly infection with herpes simplex virus or cytomegalovirus or both viruses, immunohistochemical studies may be necessary for a definitive diagnosis.

Other important differential diagnoses for adenovirus hepatitis in BMT recipients include acute and chronic GVHD and drug toxicity. In acute GVHD (<90 days after transplantation), portal inflammation, dystrophic changes in bile duct epithelium with lymphocytic infiltrate, endothelitis, and apoptosis in hepatocytes may be prominent. These histologic features somewhat resemble those seen in cases of acute cellular rejection in transplanted livers or in cases of hepatitis C virus infection. In chronic GVHD (after 90 days), ductopenia and portal fibrosis may
be characteristic, reminiscent of chronic liver allograft rejection. Extensive hepatocyte necrosis with little or no bile duct damage is usually not typically associated with GVHD. However, the presence of necrosis, particularly when associated with cholestasis and steatosis, should raise the possibility of drug toxicity. Again, the presence of characteristic smudgy cells should point to adenovirus hepatitis, and ancillary studies (immunohistochemistry, culture, and polymerase chain reaction analysis) should aid the diagnosis. Pathologists should be alert to the possibility of adenovirus infection when examining liver biopsies from immunocompromised patients.

References