Adenovirus Infection in Adult Orthotopic Liver Transplant Recipients: Incidence and Clinical Significance

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Adenovirus infection occurs in 10% of pediatric orthotopic liver transplant recipients; however, no cases have been described in adult liver transplant recipients. A retrospective review of 191 adults who underwent liver transplantation from January 1988 through October 1995 was done to describe the incidence and clinical significance of adenovirus infection in this population. There were 11 (5.8%) patients with 16 cultures positive for adenovirus. Sites of isolation were urine (9), blood (2), liver biopsy (2), colonic biopsy (1), lung biopsy (1), and stool (1). Adenovirus infection was classified as either disease or asymptomatic infection. There were 7 cases of adenovirus disease (2 definite, 1 probable, and 4 possible). Disease was disseminated in 3 patients: All had pneumonia and 2 died. Of the 3 patients with pneumonia, 2 had evidence of multiorgan involvement. Adenovirus disease occurs in adult orthotopic liver transplant recipients and may be associated with significant morbidity and occasional mortality.

There is accumulating evidence implicating adenovirus as a cause of serious disease in immunocompromised hosts [1, 2], including patients with AIDS [3] and renal [4], bone marrow [5], and lung transplant recipients [6]. About 10% of pediatric orthotopic liver transplant recipients develop adenovirus infection [7]. However, adenovirus infection in adult liver transplant recipients has not yet been described. We therefore reviewed our experience with adenovirus infections in the adult liver transplant population in order to describe the incidence and clinical significance of adenovirus infection in this population.

Methods

Patient population. All orthotopic liver transplant recipients (at least 18 years of age) treated at New England Medical Center formed the study group. Those with adenovirus isolated from one or more sites were retrospectively identified from clinical microbiology laboratory records for the period 1 January 1988 through 31 October 1995. Clinical information, including microbiologic studies, biopsy results, concurrent infections, immunosuppressive regimen, and outcome was obtained from medical records using a structured data collection instrument.

Virus studies. Specimens (buffy coat, urine, stool, respiratory secretions, tissue biopsies, and bronchoalveolar lavage fluid) were collected for microbiologic and virologic studies when clinically indicated. Many patients had viral cultures of serial blood specimens as part of several controlled clinical trials during the period of this study [8]. Specimens were inoculated into single tubes of MRC-5 cells (Viromed Laboratories, Minneapolis) from January 1988 through December 1989; thereafter, AS49 cells (Viromed Laboratories) were used. Cultures were maintained for 4 weeks. Adenovirus was identified by its cytopathic effect and confirmed by indirect fluorescent antibody testing using murine monoclonal antibody (Cambridge Biosciences, Cambridge, MA) or viral respiratory screening and identification kits (Bartels; Baxter Diagnostics, Deerfield, IL).

Definitions of clinical illness. Adenovirus infection was classified as asymptomatic or disease. Patients who had adenovirus cultured from a tissue or body fluid in the absence of any clinical event or evidence of organ dysfunction were classified as having asymptomatic infection. Adenovirus disease was defined by increased temperature (>37.5°C) or organ dysfunction (or both) that was not attributable to any other cause.

We divided disease into definite, probable, or possible. Definite adenovirus disease required isolation of adenovirus from tissue in which pathologic changes typical of adenovirus infection were found. Probable adenovirus disease required isolation of adenovirus from a tissue or body fluid along with organ dysfunction for which no other cause could be found. Possible adenovirus disease was used for patients who had virus isolated from urine in association with organ dysfunction for which no other cause was found.

Pneumonia was diagnosed by new or worsening lower respiratory symptoms or hypoxemia and radiographic pulmonary changes. Urinary tract infection was diagnosed by urine microscopy findings of >10 leukocytes/high-power field. A diarrheal illness was defined as new onset of diarrhea (≥3 unformed stools a day) for at least 2 consecutive days. Hepatitis was diagnosed by an elevation of transaminases ≥2.5 times the upper limit of normal. Concurrent bacterial, viral, or fungal infections were diagnosed when organisms were isolated within 1 week of the adenovirus isolation; definitions for such infections have been reported previously [8, 9].

Pathologic studies. Evidence of adenovirus disease was considered diagnostic when tissue sections stained with hematoxylin-
Table 1. Adult orthotopic liver transplant (OLT) recipients from whom adenovirus was isolated during 1988–1995.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Indication for OLT</th>
<th>Time of isolation of adenovirus after OLT (days)</th>
<th>Sites of isolation</th>
<th>Adenoviral infection/disease</th>
<th>Concurrent infection</th>
<th>Immunosuppressive regimen at time of isolation</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>Sclerosing cholangitis</td>
<td>84</td>
<td>Urine</td>
<td>Asymptomatic</td>
<td>None</td>
<td>FK, Pred, Az</td>
<td>None</td>
<td>Recovered fully</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>Cryptogenic cirrhosis</td>
<td>59</td>
<td>Urine</td>
<td>Asymptomatic</td>
<td>None</td>
<td>FK, Pred, Az</td>
<td>None</td>
<td>Recovered fully</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>Autoimmune CAH</td>
<td>180, 210, 240, 365</td>
<td>Urine</td>
<td>Asymptomatic</td>
<td>None</td>
<td>CsA, Pred, Az</td>
<td>None</td>
<td>Recovered fully</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>Cryptogenic cirrhosis</td>
<td>27</td>
<td>Urine</td>
<td>Asymptomatic</td>
<td>Axillary cellulitis</td>
<td>CsA, Pred, Az</td>
<td>None</td>
<td>Recovered fully</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Cryptogenic cirrhosis</td>
<td>41</td>
<td>Urine</td>
<td>Urinary tract (PS)</td>
<td>None</td>
<td>CsA, Pred, Az</td>
<td>None</td>
<td>Recovered fully</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>Alcoholic cirrhosis</td>
<td>3</td>
<td>Urine</td>
<td>Urinary tract (PS)</td>
<td>Pneumonia (P), gastroenteritis (P)</td>
<td>CsA, Solu, Az</td>
<td>Antibiotics</td>
<td>Died: progressive multiorgan failure</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>Acetaminophen overdose</td>
<td>50</td>
<td>Urine</td>
<td>Urinary tract (PS)</td>
<td>Pneumonia (PS)</td>
<td>CsA, Pred, Az</td>
<td>Antibiotics</td>
<td>Died: progressive multiorgan failure</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>CAH due to hepatitis C</td>
<td>10</td>
<td>Blood</td>
<td>Pneumonia (P), gastroenteritis (P)</td>
<td>None</td>
<td>CsA, Pred, Az</td>
<td>Antibiotics</td>
<td>Recovered fully</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>Sclerosing cholangitis</td>
<td>7</td>
<td>Urine</td>
<td>Pneumonia (PS)</td>
<td>None</td>
<td>CsA, Pred, Az</td>
<td>Antibiotics</td>
<td>Recovered fully</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
<td>Sclerosing cholangitis</td>
<td>180</td>
<td>Blood, lung, colon, liver, stool, urine</td>
<td>Pneumonia (D), colitis, hepatitis, urinary tract hepatitis (D)</td>
<td>None</td>
<td>CsA, Pred, Az</td>
<td>Antibiotics</td>
<td>Died: progressive multiorgan failure</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
<td>Alcoholic cirrhosis</td>
<td>90</td>
<td>Liver</td>
<td>Hepatitis (D)</td>
<td>CsN line infection</td>
<td>CsA, Pred, Az</td>
<td>Antibiotics</td>
<td>Died: progressive multiorgan failure</td>
</tr>
</tbody>
</table>

NOTE. CAH, chronic active hepatitis; CsN, coagulase-negative staphylococci; UTI, urinary tract infection; amB, amphotericin B (Apothecon, Princeton, NJ); PS, possible disease; P, probable disease; D, definite disease (see text for definitions); CsA, cyclosporin A (Sandoz, East Hanover, NJ); FK, FK506 (Fujisawa USA, Deerfield, IL); Pred, prednisone; Solu, Solumed (Upjohn, Kalamazoo, MI); Az, azathioprine (Glaxo Wellcome, Research Triangle Park, NC); ?, possible.

1 Received OKT3 for rejection within 1 month.
2 Received pulse steroids for rejection within 1 month.

Eosin revealed typical “smudge cells” with nuclei containing basophilic material surrounded by a thin rim of cytoplasm or eosinophilic or amphophilic intranuclear inclusions surrounded by a clear halo of cytoplasm [10].

Statistical analysis. A limited analysis of risk factors for adenovirus infection was performed among adult recipients of orthotopic liver transplants. The Wilcoxon rank sum test was used for analysis of continuous variables, and Fisher’s exact test for discrete variables.

Results

Eleven (5.8%) of 191 adult patients who underwent orthotopic liver transplantation from 1 January 1988 through 31 October 1995 had adenovirus isolated from one or more sites (table 1). Four patients were female, 7 were male. The mean time to initial isolation of adenovirus for the patients with adenovirus infection was 66 days after transplantation (range, 3–180); the mean time to disease was 55 days (range, 3–180). Urine was the most common site of isolation (9 patients; table 1). Urinalyses of 4 patients showed normal findings, indicating asymptomatic infection, and 5 patients had abnormal findings, suggesting possible urinary tract disease. One patient had prolonged asymptomatic shedding of virus into the urine at 6, 7, 8, and 12 months after transplantation. Two patients had adenovirus viremia, and 2 had positive liver biopsy cultures. One patient had positive cultures from colonic and lung biopsy specimens and from stool, liver, blood, and urine (case 10).

Clinical features. Of the 11 patients from whom adenovirus was isolated, 4 were classified as asymptomatic infection, and 7 were considered to have disease (table 1). Of those with disease, 2 were definite, 1 was probable, and 4 were possible. Three patients were diagnosed as having only urinary tract infection (cases 5–7; table 1). Of the 3 patients with disseminated disease (cases 8–10), all had pneumonia. One patient had fulminant hepatitis (case 11). Three of the 7 patients with adenovirus disease died; death was attributable to adenovirus in 2 patients (cases 10 and 11).

Details for 2 patients with adenovirus disease are provided for illustrative purposes. Patient 10 (table 1) received two liver transplants for sclerosing cholangitis; one occurred 1 week after the first transplant because of acute rejection. His subsequent postoperative course was complicated by cytomegalovirus (CMV) hepatitis treated with CMV immune globulin (Massachusetts Biological Public Health Laboratory, Jamaica Plain,
MA) and ganciclovir (Roche Laboratories, Nutley, NJ). He was admitted 4 months after his orthotopic liver transplantation because of an episode of mild rejection (diagnosed on liver biopsy) and was treated with steroids and then a 14-day course of OKT3 (Ortho Biotech, Raritan, NJ). His hospital course was complicated by persistent fever, leukopenia, thrombocytopenia, and elevated liver function enzymes. Despite extensive investigation, no cause for fever was identified. His initial liver biopsy specimen did not reveal any viral inclusions or evidence of CMV by in situ hybridization, and cultures did not yield any bacteria, fungi, or viruses. A follow-up biopsy after OKT3 therapy revealed characteristics of mild rejection. He was discharged after 5 weeks of hospitalization but was readmitted 24 h later with fever, chills, myalgias, and diarrhea. He had a fulminant course with pneumonia, colitis, and hepatitis and died 7 days later. The patient had adenovirus isolated from stool, colonic biopsy, colonic brushings, urine, and 2 blood specimens, all taken within a 3-day period prior to death. No other bacteria, fungi, or viruses were isolated. Postmortem examination of the liver revealed massive hepatocyte necrosis with cell dropout, predominantly in the centrilobular zone, with a polymorphonuclear infiltrate. A lymphocytic infiltrate was noted within the portal tracts. In addition, several hepatocytes with numerous basophilic intranuclear inclusions (smudge cells) were noted (figure 1). Liver tissue was also culture-positive for adenovirus. Culture and in situ hybridization studies were negative for CMV. Intranuclear inclusions were noted within the lungs, and adenovirus was isolated from lung tissue culture. A colonic biopsy taken 2 days before the patient died showed karyorrhectic nuclei, suggestive of viral infection.

Case 11 was admitted with fever, diarrhea, a rash, and abnormal liver function 90 days after orthotopic liver transplant for alcoholic cirrhosis. A liver biopsy performed 6 days after admission showed acidophilic bodies, a finding consistent with viral hepatitis. The patient was treated with intravenous acyclovir (Glaxo Wellcome, Research Triangle Park, NC) and pulse steroids for presumed herpes simplex infection and mild rejection, respectively. Seven days later, his liver function tests showed increasing abnormalities, and he received OKT3. OKT3 was discontinued because of high fever and alteration of mental status 4 days later. The patient developed multiorgan failure, leukopenia, and an intracerebral hemorrhage. He died 4 weeks after admission. His liver biopsy yielded adenovirus. No other bacteria, fungi, or viruses were identified from liver tissue or any other site. An autopsy was not performed.

Risk factors. A risk factor analysis comparing adult liver transplant recipients with and without adenovirus infection revealed that UNOS (United Network for Organ Sharing) status (on life support at the time of transplantation) and intraoperative veno-venous bypass were associated with adenovirus infection \( (P = .029 \text{ and } 0.01, \text{ respectively}) \). Patients with adenovirus infection tended to be younger than those without infection (median age, 40 vs. 48.2 years; interquartile range, 24.6–53.4 vs. 40.0–56.0; \( P = .072 \)). The duration of transplant surgery, cold ischemia time, warm ischemia time, units of packed red blood cells, cryoglobulin, fresh frozen plasma, or platelets received during transplantation were not associated with adenovirus infection. There was no association with OKT3 or CMV immune globulin use and adenovirus infection or disease.
Discussion

Adenovirus disease in adult liver transplant recipients has not been described previously. The incidence of adenovirus infection among adult liver transplant recipients at our institution was 5.8%. This is less than the 10.1% seen in the pediatric liver transplant population [7]. Given that routine viral surveillance cultures were not done for all transplant recipients, we may have underestimated the incidence of asymptomatic adenovirus infection.

Clinically significant adenovirus disease in adult liver transplant recipients presented as disseminated disease with pneumonia in 3 patients and hepatitis in 1 patient (case 11). In the latter case, we suspect that the patient had disseminated adenovirus disease, but no autopsy was performed. Of the 3 patients who died, 2 had biopsy-proven adenovirus disease in the liver as one manifestation of disseminated disease. The assessment of urinary tract disease was more problematic because pathologic evidence was lacking, and adenovirus excretion from urine can occur without disease, especially in immunocompromised patients.

The clinical manifestations of adenovirus disease in adult liver transplant recipients contrast somewhat with those in pediatric patients, in whom hepatitis was the predominant manifestation of adenovirus disease [7]. However, the rate of adenovirus disease and the timing of isolation of adenovirus in adult liver transplant recipients appear to be similar to those in the pediatric population [7].

Risk factors associated with adenovirus infection in this study were advanced UNOS status and use of intraoperative veno-venous bypass. However, no clear pathogenic mechanism to support an etiologic relationship between these variables and adenovirus infection could be determined. These variables may only be surrogate markers for severity of illness at the time of transplantation.

The source of adenovirus infection in our patients and other immunocompromised patients is unclear [2]. Latency is a known characteristic of adenovirus [10]. Among bone marrow and solid organ transplant recipients, it has been suggested that reactivation of the virus during immunosuppression is the source of posttransplant adenovirus disease [5, 11]. Acute adenovirus infection in a donor has also been implicated as the source of infection in a liver transplant recipient [12]. Community acquisition is also possible. We have no information on the source of the adenovirus in patients in this series.

There is no well-defined treatment for adenovirus infection. Possible approaches to the management of invasive disease might be to lessen immunosuppression, use antiviral agents (e.g., ribavirin, cidofovir), or use immunoglobulin or combina-
tions of the above, for which limited clinical information on effectiveness is available [13–15].

In conclusion, adenovirus infection and clinically significant adenovirus disease occur more commonly than previously appreciated in adult orthotopic liver transplant recipients and should be considered in the differential diagnosis of patients who present with fever and a viral syndrome.

Acknowledgments

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References