Adenovirus Infections in Adult Recipients of Blood and Marrow Transplants

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Adenoviruses are increasingly recognized pathogens that affect blood and marrow transplant (BMT) recipients. Experiences with 2889 adult BMT recipients were reviewed to study the incidence, clinical spectrum, risk factors for dissemination, response to therapy, and outcome of adenovirus infections. Eight-five patients (3%) were diagnosed by means of culture (n = 85) or culture and histopathological examination (n = 6). Nine patients had asymptomatic viruria, and 76 had symptomatic infections, which included upper respiratory tract infection (n = 20), enteritis (n = 18), hemorrhagic cystitis (n = 10), pneumonia (n = 15), and disseminated disease (n = 13). The overall mortality rate was 26%. A higher mortality rate was observed among patients with pneumonia (73%) and disseminated disease (61%). Risk factors for dissemination included receipt of an allogeneic transplant, presence of graft-versus-host disease (GVHD), and receipt of concurrent immunosuppressive therapy. Intravenous ribavirin was not associated with an appreciable benefit among 12 patients who received this treatment. In conclusion, adenovirus infections are an important cause of morbidity and mortality in adult BMT recipients, particularly allogeneic transplant recipients with GVHD who are receiving immunosuppressive therapy. The need for an effective, nontoxic antiviral therapy is apparent.

Adenoviruses are nonenveloped, icosahedral virus particles with a linear double-stranded DNA genome. More than 50 serotypes have been described, and they have been classified into 6 subgroups (A–F). Adenoviruses cause a wide variety of clinical syndromes, including respiratory illness, enteritis, hepatitis, hemorrhagic cystitis, nephritis, conjunctivitis, and meningoencephalitis [1]. Infections most commonly occur during early childhood, but they continue to occur throughout life. Close contact with individuals in crowded institutions increases the risk for adenovirus infections. Outbreaks of such infection have been described in day care centers, hospitals, shipyards, and military quarters [1]. In most instances, these infections are limited by a type-specific immune response, but latent infection may be established in lymphoid tissue [1].

Immunocompromised individuals, such as blood and marrow transplant (BMT) recipients and solid-organ transplant recipients, may develop severe and frequently fatal localized or disseminated disease [2–19]. During the past decade, use of more potent chemotherapy and immunosuppressive agents, improvement of virological diagnostic methods, and better control of cytomegalovirus (CMV) infections have been associated with an increasing appreciation of the role that other viruses, such as adenovirus, play in the morbidity and mortality of BMT recipients [3–6, 9–15, 17–19]. To study the incidence, clinical spectrum of disease, risk factors for dissemination, response to therapy, and outcome of adenovirus infections, we reviewed experiences with 2889 adults who received a BMT at The University of Texas M. D. Anderson Cancer Center (MDACC), Houston.
PATIENTS AND METHODS

The virological examination records of all adults who received a BMT at MDACC from January 1990 through December 1998 were reviewed. The medical records of all patients who had an adenovirus infection diagnosed were studied. Adenovirus infections were diagnosed by means of isolation of adenovirus from cell line cultures that showed characteristic cytopathic effects, which then were confirmed by use of an indirect immunofluorescence antibody assay. When tissue samples were obtained, the pathological findings were reviewed for evidence of characteristic viral inclusions, and for confirmation done by means of in situ hybridization or immunohistochemistry.

During the study period, samples were obtained from symptomatic BMT recipients for complete viral culture performed at the discretion of the treating physician. Specimens were inoculated in 5 different cell lines, 3 of which (Hep-2, A549, and human foreskin fibroblasts) had the capacity to yield adenoviruses. In addition, from January 1990 through May 1997, active surveillance for CMV infections in allogeneic BMT recipients included weekly blood Buffy coat smears and CMV cultures of urine samples from day 0 to day 100 after transplantation. These surveillance urine samples were inoculated in human foreskin fibroblast cell lines, which also supported the growth of adenovirus. After May 1997, urine samples were no longer obtained for surveillance cultures.

“Definite invasive disease” was defined by a compatible clinical presentation, by the isolation of adenovirus from viral cultures, and by documentation of adenovirus tissue invasion at the corresponding site, according to the presence of characteristic intranuclear viral inclusions, which was confirmed by means of in situ hybridization or immunohistochemistry. “Probable invasive disease” was defined by a compatible clinical presentation and by the isolation of adenovirus from viral cultures of samples that were obtained from the corresponding site. “Disseminated disease” was defined by the presence of invasive adenovirus disease in >=2 organ systems (respiratory, urinary, and gastrointestinal).

Among allogeneic and autologous transplant recipients, the proportion of patients with specific viral culture performed by use of the χ² test and Fisher’s exact test. Univariate analysis of the variables associated with dissemination was performed by use of the χ² test and Fisher’s exact test. The variables included in this analysis were as follows: the type of transplant, the presence of graft-versus-host disease (GVHD), the use of total body irradiation for conditioning, and the use of specific conditioning chemotherapy or immunosuppressive drugs (e.g., cyclophosphamide, fludarabine, busulfan, melphalan, carmustine, thiopeta, cis-platinum, Taxol, Ara-C, VP-16, cyclosporin A, tacrolimus, methotrexate, antithymocyte globulin, OKT3, and methylprednisolone). GVHD was included in the analysis when it was proven by means of analysis of biopsy specimens and was of grade II–IV. Immunosuppressive drugs, which were used for treatment of GVHD, were included in the analysis of risk factors associated with dissemination only when such treatment was initiated at least 1 week before the first sample that yielded adenovirus was obtained. Variables that reached statistical significance, according to univariate analysis, were subsequently studied via multivariate analysis, which was performed by use of a stepwise logistic regression model.

RESULTS

During the study period, 2889 adults received a BMT at MDACC; of these 2889, 85 (3%) had an adenovirus infection diagnosed. The number of cases that were diagnosed during each year of the study (1990–1998) were 0, 4, 10, 9, 17, 11, 18, 5, and 11, respectively. There was no apparent seasonal distribution of cases. The cumulative number of cases that were diagnosed during each month (January through December) were 4, 7, 10, 4, 8, 12, 7, 4, 5, 9, 8, and 7, respectively. The highest number of cases diagnosed during any single month in any year of the study was 4 (in both July 1992 and May 1996).

The demographic and clinical characteristics of these patients are described in table 1. The incidence of adenovirus infection was significantly higher among recipients of allogeneic BMTs than among recipients of autologous BMTs (69 [6%] of 1150 patients vs. 16 [0.92%] of 1739 patients, respectively; P < .001). Fifty-five infections (65%) were diagnosed during the first 100 days after the patient received the transplant (median time to diagnosis, 62 days; mean time to diagnosis, 155 days). Adenovirus was isolated from samples of urine (n = 32), nasopharyngeal washing (n = 28), stool (n = 28), bronchoalveolar lavage (n = 15), endotracheal aspirate (n = 5), conjunctival swab (n = 1), bone marrow (n = 3), and skin biopsy (n = 2).

Nine patients (10%) had asymptomatic viruria, which was detected during a period when CMV surveillance cultures of urine samples from allogeneic BMT recipients were being performed. Two of these patients had active GVHD at the time that the cultures were performed. Seven patients had a single episode, and 2 patients had 2 episodes.

Among 76 patients who had symptomatic infections, 6 (8%) had definite invasive disease and 70 (92%) had probable invasive disease. For all 3 patients who died and underwent autopsy, the diagnosis of invasive adenovirus infection was confirmed. Symptomatic infections had manifested as upper respiratory tract illness (n = 20), enteritis (n = 18), pneumonia (n = 15), cystitis (n = 10), disseminated disease without pneumonia (n = 8), and disseminated disease with pneumonia (n = 5).

Among patients who had no concomitant infections, the mean duration of symptoms was 8 days for patients who had upper respiratory tract infection (URI; range, 3–21 days), 21
days for those who had pneumonia (range, 12–46 days), 23 days for those who had enteritis (range, 7–44 days), 26 days for those who had hemorrhagic cystitis (range, 10–49 days), 40 days for those who had disseminated disease without pneumonia (range, 13–68 days), and 60 days for those who had disseminated disease with pneumonia (range, 27–104 days). It is of note that only 2 of the 20 patients with pneumonia initially presented with signs and symptoms of a URI.

The frequency of the different clinical syndromes (excluding asymptomatic viruria) in 60 allogeneic BMT recipients, in comparison with that in 16 autologous BMT recipients, was as follows: URI, 28% versus 19%; enteritis, 22% versus 31%; pneumonia, 18% versus 25%; hemorrhagic cystitis, 10% versus 25%; and disseminated disease, 22% versus 0%, respectively. No statistically significant difference was observed, except for disseminated disease ($P = .03$).

The 13 patients with disseminated disease had a combination of $\geq 2$ of the following diagnoses: enteritis ($n = 10$), hemorrhagic cystitis ($n = 9$), URI ($n = 6$), pneumonia ($n = 5$), hepatitis ($n = 1$), and conjunctivitis ($n = 1$). In 3 patients, the virus was isolated from bone marrow samples, and in 2 patients, it was isolated from skin lesions (histological examination revealed nonspecific inflammation). Six patients with disseminated disease had biochemical evidence of hepatitis; only 1 patient underwent a liver biopsy; analysis of the biopsy specimens confirmed the diagnosis of invasive adenovirus infection.

All 13 patients with disseminated disease were allogeneic BMT recipients, and 11 (85%) had GVHD. All 13 patients were receiving therapy with at least 2 immunosuppressive agents, including cyclosporin A ($n = 9$), methylprednisolone ($n = 12$), and tacrolimus ($n = 7$). Among the 56 allogeneic BMT recipients with localized disease, 27 (48%) had GVHD and 28 (50%) were receiving therapy with at least 2 immunosuppressive agents, including cyclosporin A ($n = 20$), methylprednisolone ($n = 39$), and tacrolimus ($n = 16$). The duration of viral shedding was longer among patients with disseminated infection than among patients with localized disease (mean duration, 33 vs. 9 days, respectively). However, follow-up cultures were not obtained uniformly.

Univariate analysis revealed that allogeneic transplants ($P = .049$), GVHD ($P = .0023$), and the use of methylprednisolone ($P = .022$), cyclosporin A ($P = .005$), and tacrolimus ($P = .02$) were associated with dissemination. Because these variables were interrelated, a multivariate analysis was performed for the allogeneic graft recipients. GVHD (OR, 6.23; 95% CI, 1.2–34.2; $P = .01$) and treatment with $\geq 2$ immunosuppressive agents (OR, 74.0; 95% CI, 44.9–122; $P < .001$) were associated with dissemination on a stepwise logistic regression model (Hosmer-Lemeshow fitness of data, 0.96).

The mortality rates associated with the different clinical syndromes are summarized in Table 2. The overall mortality rate for patients with symptomatic disease was 26% (20 of 76 patients). Disseminated disease without pneumonia, isolated pneumonia, and disseminated disease with pneumonia were associated with the highest mortality rates: 50% (4 of 8 patients), 73% (11 of 15), and 80% (4 of 5), respectively. One
Table 2. Mortality associated with different clinical presentations of adenovirus infections in adult recipients of blood and marrow transplants.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Type of transplant</th>
<th>No. of patients</th>
<th>Deaths, n (%)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adenovirus only, n (%)</td>
<td>Adenovirus and comorbidities</td>
</tr>
<tr>
<td>Enteritis</td>
<td>Autologous</td>
<td>5</td>
<td>2 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Allogeneic</td>
<td>13</td>
<td>4 (31)</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pneumonia (n = 2)</td>
</tr>
<tr>
<td>Isolated pneumonia</td>
<td>Autologous</td>
<td>4</td>
<td>3 (75)</td>
<td>1 (25)</td>
</tr>
<tr>
<td></td>
<td>Allogeneic</td>
<td>11</td>
<td>8 (73)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without pneumonia</td>
<td>Allogeneic</td>
<td>8</td>
<td>4 (50)</td>
<td>4 (50)</td>
</tr>
<tr>
<td></td>
<td>With pneumonia</td>
<td>Allogeneic</td>
<td>5</td>
<td>4 (80)</td>
</tr>
</tbody>
</table>

NOTE. No deaths were observed among patients with upper respiratory infections, hemorrhagic cystitis, or asymptomatic viruria. CMV, cytomegalovirus; DAH, diffuse pulmonary alveolar hemorrhage; GVHD, graft versus host disease; M. tuberculosis, Mycobacterium tuberculosis; P. aeruginosa, Pseudomonas aeruginosa; PCP, Pneumocystis carinii; S. maltophilia, Stenotrophomonas maltophilia.

Patient with biopsy-confirmed adenovirus enteritis died of severe intestinal bleeding with no other apparent etiology. Whether adenovirus contributed to the deaths of 5 additional patients with enteritis could not be determined. No deaths were observed among patients with isolated URI or hemorrhagic cystitis. Coinfections with potentially lethal organisms were identified in 6 patients who had pneumonia and in 1 patient with disseminated disease who also had pneumonia.

Mortality among autologous BMT recipients was only related to isolated pneumonia, because there were no cases of disseminated disease. Three of the 4 patients who had adenovirus pneumonia died. These 3 patients included 2 patients with breast cancer, one of whom had concurrent CMV pneumonia, and 1 patient with a relapse of acute myelogenous leukemia who had been treated with fludarabine and who had concurrent CMV and Pneumocystis carinii pneumonia.

Treatment of the 13 patients included the use of iv ribavirin (n = 12) and/or aerosolized ribavirin (n = 4). Clinical improvement was observed in only 2 patients who received iv ribavirin (table 3). One patient with acute promyelocytic leukemia, who had received an allogeneic BMT and who developed GVHD that required treatment with cyclosporin A and methyprednisolone, had adenovirus enteritis, pneumonia, and hepatitis diagnosed. He received 2 courses of treatment with iv ribavirin (duration, 2 and 3 weeks, respectively) and he had clinical improvement after 6 and 15 days of therapy, respectively. The decision to administer the second course of treatment was prompted by a relapse of his symptoms after the first course was discontinued. These 2 patients were treated sooner after the onset of symptoms (mean time to treatment, 5 days vs. 35 days) and for a longer duration (mean duration of therapy, 28 days vs. 9 days) than were the treated patients who did not have improvement. However, 3 of the 5 patients with disseminated disease who did not receive ribavirin therapy also had improvement.

DISCUSSION

The role of adenoviruses in the morbidity and mortality of BMT recipients is being increasingly recognized. In the present study, the overall incidence of adenovirus infections in adult BMT recipients was 3%. This is probably an underestimation of the true incidence rate, because diagnostic tests were not applied systematically to all BMT recipients. Adenovirus infections were detected in a significantly higher proportion of adult recipients of allogeneic BMTs than adult recipients of autologous BMT (6% vs. 0.92%; P < .001). To some extent, this may
Table 3. Clinical outcomes among patients treated with and without iv ribavirin.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>No. of patients</th>
<th>Patients treated with iv ribavirin</th>
<th>Patients not treated with iv ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory illness</td>
<td>20</td>
<td>0/0</td>
<td>20/20</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>0/2</td>
<td>4/13</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>10</td>
<td>0/1</td>
<td>5/9</td>
</tr>
<tr>
<td>Enteritis</td>
<td>18</td>
<td>0/1</td>
<td>6/17</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>13</td>
<td>2/8</td>
<td>3/5</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of patients with clinical improvement/no. of patients treated either with or without ribavirin.

reflect a more intense monitoring of viral infections among allogeneic BMT recipients.

A broad spectrum of clinical presentation was observed, ranging from asymptomatic infections (in 10% of patients) to localized disease (in 75%) and disseminated disease (in 15%). Localized disease (excluding asymptomatic viruria) manifested primarily as respiratory infections (in 56% of patients), gastrointestinal infections (in 28%), and urinary tract infections (in 16%). Disseminated disease manifested as a combination of these syndromes plus either hepatitis or conjunctivitis. The overall mortality rate of 26% among patients with symptomatic disease was primarily attributable to pneumonia and disseminated disease. The relatively low frequency (8%) of confirmed invasive disease was probably an underestimation, because invasive diagnostic procedures were frequently contraindicated. In 5 other studies, which included both pediatric and adult recipients of BMT, the frequency of confirmed invasive disease had a range of 8%–26% [3–6, 18].

The type of transplantation (allogeneic vs. autologous), the presence of GVHD (grades II–IV), and the intensity of immunosuppressive treatment were the variables that affected clinical presentation and outcome. Autologous BMT recipients developed the same types of localized disease as did allogeneic BMT recipients, but they did not develop disseminated disease. In contrast, 13 (22%) of 60 symptomatic allogeneic transplant recipients developed dissemination. Among the 13 patients with disseminated disease, 11 (85%) had GVHD, and all were receiving aggressive immunosuppressive therapy. Previous studies have also identified GVHD as a risk factor for dissemination [3, 4]; however, this is the first study to show that the intensity of immunosuppressive therapy, expressed as the number of drugs being used, had an independent contribution to the risk of dissemination.

The broad spectrum of clinical presentation in adenovirus infections stresses the importance of obtaining samples for viral analysis from BMT recipients with compatible clinical syndromes. Although conventional viral cultures remain the standard means of diagnosis, they may require several days for isolation of the virus. Newer methods, including PCR analysis, shell vial culture, and immunochromatographic techniques, have been reported to provide a more rapid diagnosis with reasonable sensitivity and specificity [20, 21].

There is no established antiviral therapy for adenovirus infections. Successful treatment of isolated hemorrhagic cystitis, nephritis, enteritis, and pneumonitis with iv ribavirin have been reported [22–27]. However, treatment failures have also been reported [28–30]. In the present study, the use of ribavirin therapy was not associated with an appreciable benefit. Clinical improvement was observed in 2 (17%) of 12 patients who were treated with iv ribavirin, compared with 18 (41%) of 44 patients who had similar clinical presentations but who were not treated with ribavirin. Among patients with disseminated disease, in whom severity of illness was more homogeneous, clinical improvement was observed in 2 of 8 patients who were treated with ribavirin and in 3 of 5 patients who were not treated with ribavirin. Two patients developed hemolysis while receiving iv ribavirin; treatment with ribavirin was discontinued for 1 patient.

Cidofovir, a broad-spectrum antiviral agent approved by the US Food and Drug Administration for the treatment of CMV retinitis in patients with AIDS, has been reported to be effective against adenoviruses in vitro and has been associated with a favorable outcome in 2 recent case reports of serious adenovirus disease in immunocompromised patients [31, 32]. Unfortunately, the toxicities of this drug are considerable.

In summary, adenoviruses can cause a broad spectrum of manifestations in adult BMT recipients; these manifestations range from asymptomatic shedding to locally invasive and disseminated disease, which is frequently fatal. These infections should be included in the differential diagnosis of a wide variety of clinical syndromes, including URI, pneumonia, enteritis, hepatitis, hemorrhagic cystitis, conjunctivitis, and disseminated disease. The highest mortality rates were observed among patients with pneumonia and disseminated disease. Fatal adenovirus pneumonia occurred in autologous, as well as allogeneic, BMT recipients.
neic, BMT recipients; however, disseminated disease occurred only in allogeneic BMT recipients, particularly those with GVHD who were receiving immunosuppressive therapy. The need for an effective, nontoxic therapy is apparent.

References