Intravesical Instillation of Cidofovir in the Treatment of Hemorrhagic Cystitis Caused by Adenovirus Type 11 in a Bone Marrow Transplant Recipient

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Hemorrhagic cystitis that occurs late after bone marrow transplantation (BMT) in BMT recipients is often associated with adenovirus or polyomavirus BK infections. Intravesical instillation of cidofovir in a BMT recipient with intractable hemorrhagic cystitis resulted in clinical improvement. Local cidofovir therapy for viral hemorrhagic cystitis could be an alternative to intravenous administration of cidofovir.

The incidence of hemorrhagic cystitis in bone marrow transplant (BMT) recipients ranges from 10% to 70%, with the incidence of grade II to IV hemorrhagic cystitis being ~25%. Late hemorrhagic cystitis has a protracted course and severe symptoms and is associated with adenovirus and polyomavirus BK (BKV) shedding. Dysuria, hematuria, lumbar pain, and an increase in the creatinine level are the typical manifestations of hemorrhagic cystitis. Adenovirus-associated hemorrhagic cystitis as the origin of disseminated disease has been reported in a previous case report [1] and in a review [2].

Case report. A 34-year-old man was admitted to the hospital because of hematuria and renal insufficiency on day 105 after receiving a BMT. Four years earlier, Philadelphia-positive chronic myeloid leukemia was diagnosed. Five months before hospital admission, the patient successfully underwent familial haplo-identical BMT. The conditioning regimen included fludarabine, melphalan, antithymocyte globulin, and total body irradiation. Cyclosporin A was given as prophylaxis for graft-versus-host disease (GVHD). Acute GVHD occurred on day 27 after BMT, necessitating therapy with a combination of cyclosporin A, mycophenolic mofetil (500 mg q.i.d.), and methylprednisolone (initially at 1 mg/kg, but later at 2 mg/kg). Complete morphological and molecular remission and 100% donor chimerism were confirmed by examination of a bone marrow aspirate obtained on day 30. On day 50 after BMT, microscopic hematuria was demonstrated, associated with positive PCRs for BKV in the urine. The patient was discharged on day 90 after BMT while receiving methylprednisolone (0.3 mg/kg), mycophenolic mofetil (1.5 g q.d.), and cyclosporin A. A urine sample was obtained just before discharge from the hospital; in addition to BKV viruria (revealed by PCR), an antigen detection test was positive for adenovirus, and a viral culture was positive for an adenovirus cytopathogenic effect.

The patient was admitted to the hospital on day 105 after BMT because of severe hemorrhagic cystitis (grade IV) [3], acute renal failure, and encephalopathy. Cyclosporin A therapy was discontinued because of toxicity, and a regimen with methylprednisolone (12 mg), mycophenolic mofetil (1–1.5 mg), and tacrolimus (0.3 mg/kg) was started. The results for 3 of 7 samples tested by antigen detection and 7 of 7 viral cultures were positive for adenovirus, but the results of PCR for BKV were repeatedly negative. No PCRs of blood samples for adenovirus were performed, but the results of viral cultures of blood and tracheal aspirate specimens were negative; a stool culture yielded positive results. The adenovirus was typed as species B, serotype 11. Adenovirus serotype 11 has been frequently and preferentially (over other adenovirus serotypes) associated with hemorrhagic cystitis [4, 5].

For adenovirus PCR and nucleotide sequencing, total DNA was isolated from urine samples with the use of the QIAamp DNA Blood Mini Kit (Qiagen). A set of degenerated consensus primers (forward primer, 5’-GCCSCARTGGKWCATGCA-CATC-3’; and reverse primer, 5’-CAGCACCCCGGTATGTCGC-AAA-3’) allowed the amplification of a 301-bp fragment of the adenoviral hexon gene. Negative and positive controls were run in parallel with the clinical sample. The PCR was conducted in a Geneamp PCR System 9700 thermal cycler (Applied Biosystems). The amplified fragments were visualized using polyacrylamide gel electrophoresis and ethidium bromide staining. The PCR products were purified with the QIAquick PCR Purification Kit (Qiagen). Sequencing with the same primers was performed on an ABI Prism 3100 Genetic Analyzer (Perkin-Elmer Applied Biosystems).

Continuous bladder irrigation with saline was initiated without improvement. Catherization of the bladder mucous mem-
brane was impossible because of diffuse bleeding. Because of renal failure (creatinine level, 2.3 mg/dL), we decided to administer cidofovir locally. A dose of 5 mg/kg diluted in 100 mL of saline was slowly instilled in the bladder via a Foley catheter, which was clamped for 1 h (twice per day). Hemorrhagic cystitis was markedly improved during the following days. Blood clotting stopped, and urine cleared progressively. The results of adenovirus culture and antigen detection tests of 2 consecutive samples became negative 4 days after the first dose of cidofovir was administered. The creatinine level improved (1.7 mg/dL) concurrently with the discontinuation of cyclosporine therapy and the improvement of hemorrhagic cystitis. Twelve days later (day 145 after the BMT), the patient developed sepsis due to Klebsiella oxytoca and severe alveolar hemorrhage with respiratory distress, and he died of multiple organ failure (figure 1). No autopsy was performed.

Discussion. Adenoviruses are double-stranded DNA viruses responsible for respiratory tract infections in children, such as pharyngitis, conjunctivitis, and pneumonia. In immunocompromised patients, the spectrum of manifestations varies widely, from asymptomatic excretion of virus to fatal disseminated disease, including interstitial pneumonia, fulminating hepatitis, and hemorrhagic diathesis [6]. The incidence of adenovirus-associated hemorrhagic cystitis varied from 1% to 8.4%. The risk factors identified thus far are GVHD and its immunosuppressive therapy, receipt of an allogeneic BMT from a nonfamilial donor, receipt of a T cell–depleted BMT, and receipt of a conditioning regimen with fludarabine. BKV is a DNA human polyomavirus associated with viruria and hemorrhagic cystitis in BMT recipients [7]. In our patient, however, the temporal link between the occurrence of hemorrhagic cystitis and the detection of adenovirus clearly suggests its pathogenic role. Asymptomatic BKV viruria had been present in our patient for several weeks, but at the time of the last admission to the hospital, the results of a BKV PCR were negative.

Different strategies have been advocated for the management of severe intractable hemorrhagic cystitis. Continuous bladder irrigation with saline is accepted as a general measure. Instillation of formalin into the bladder to stop severe hematuria and bladder irrigation with alum have yielded disappointing results. Intravesical instillation of E-aminocaproic acid proved to be successful in 1 case [8]. Prostaglandins have been ad-

**Figure 1.** Major events and important biological markers during the posttransplantation period. Elevated creatinine level was defined as >2 mg/dL. Allo BMT, allogenic bone marrow transplantation; Gran., granulocytopenia (polymorphonuclear cell count, <500 cells/μL); GVHD, graft-versus-host disease; HC, hemorrhagic cystitis; Lymp., lymphocytopenia (T lymphocyte count, <200 cells/μL).
ministered intravesically with variable results [9]. There is no established antiviral therapy for adenovirus- or BKV-associated hemorrhagic cystitis. Intravenous ribavirin has been used successfully in several isolated cases of adenovirus infection in immunocompromised patients, including in patients with cystitis, nephritis, gastroenteritis, and pneumonitis [10, 11]. However, a recent study failed to reveal any benefit of intravenous ribavirin among blood transfusion and BMT recipients with either localized or disseminated adenoviral infection, compared with nontreated patients [2]. Cidofovir has in vitro activity against BKV and adenovirus [12, 13]. However, systemic use of cidofovir among BMT recipients has been hampered by the nephrotoxicity of this drug [14, 15]. Nevertheless, a case of hemorrhagic cystitis attributed to BKV and adenovirus type 11 treated successfully with low-dose intravenous cidofovir was reported recently [4].

To our knowledge, this is the first case of instillation of cidofovir into the bladder for treatment of hemorrhagic cystitis due to adenovirus type 11. This method could be an alternative to intravenous administration of cidofovir, providing that the drug is not absorbed through the inflamed bladder mucosa. Although a potential complication of intravenous use of cidofovir is nephrotoxicity, in our patient, local treatment was followed by improvement of the serum level of creatinine. No blood concentrations of cidofovir were determined in this patient. There was a clinical improvement, with relief of all symptoms associated with hemorrhagic cystitis, and adenovirus was cleared from the urine.

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References