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Case reports

Cyclic recovery of adenovirus in a stem cell transplant recipient: an inverse association with graft-versus-host disease

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Summary:

Adenovirus (AdV) infections have been increasingly recognized as significant pathogens that may cause severe morbidity and mortality among stem cell transplant (SCT) recipients. AdV can cause localized infections such as hemorrhagic cystitis (HC), pneumonia, hepatitis and also disseminated disease that can lead to death. We report a case of severe hemorrhagic cystitis in a SCT recipient who died 83 days after transplant. In this patient, AdV recovery was not constantly detected. In fact, fluctuations of the AdV detection in leukocytes and urine were observed by culture and PCR. When analyzing this viral cyclic recovery with different signs or symptoms in the patient, we observed an inverse association with the presence of acute graft-versus-host disease (GVHD). Whether these fluctuations represent donor-derived reactivity, indirectly manifested by the presence of GVHD, requires further study. This is the first case describing a dynamic pattern of AdV replication in leukocytes and urine samples from a patient with severe HC and the temporal correlation with GVHD.

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Adenovirus (AdV) infection is increasingly recognized as a major cause of morbidity and mortality after allogeneic stem cell transplantation (SCT).[1] Although the reason for this increase is not completely understood, it may be related to higher awareness, manipulation of the graft and more sensitive methods of detection. Hemorrhagic cystitis (HC) can be one of the first clinical manifestations of dissemination with a fatal outcome in these patients.[2] The viral mechanisms for dissemination and pathogenesis of AdV are not completely understood. AdV diagnosis can be made by cell culture, direct detection, or molecular methods that have proven more sensitive in some cases.[2] We report the case of a stem cell transplant recipient who developed severe HC from which AdV was intermittently recovered in leukocytes and urine samples tested by culture and PCR.

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Case report

A 42-year-old female with chronic myelogenous leukemia of 24 months duration who had been treated with α interferon and hydroxyurea developed a myeloid blast crisis. She received an allogeneic peripheral blood stem cell transplant from an identical HLA-sibling donor. Conditioning was with cyclophosphamide, busulfan, and etoposide. Prophylaxis for graft-versus-host disease (GVHD) included tacrolimus and methotrexate; antimicrobial prophylaxis included fluconazole and acyclovir.

Sequential blood and urine samples were obtained before and after transplantation. The presence of AdV was retrospectively sought in leukocytes, plasma and urine samples using a culture method developed in our laboratory and a new direct PCR.[2] AdV detection and clinical manifestations are shown in Figure 1. Pretransplant leukocytes and urine samples obtained on day −7 were positive for AdV by culture and PCR. On day 3 post-transplant she developed neutropenia, fever, severe mucositis and abdominal pain that resolved with antimicrobial therapy. Engraftment was achieved on day 15. On day 18, she developed severe diarrhea and palmar erythema. Parasitologic examinations and bacterial stool cultures were negative. Colonic biopsy was consistent with GVHD. AdV-PCR was negative in that biopsy. Prednisone (2 mg/kg/day) was added to the regimen until day 31, with progressive clinical recovery when she was discharged. Leukocytes and urine samples collected on days 18 and 22 were negative for AdV. On day 40, she completely resolved her GVHD. On day 47, AdV was positive in leukocytes by PCR and on day 55, she developed severe HC. Bacterial cultures from urine were negative. Leukocyte and urine samples obtained on day 61 were positive for AdV by culture and PCR. Neutralization tests done from blood and

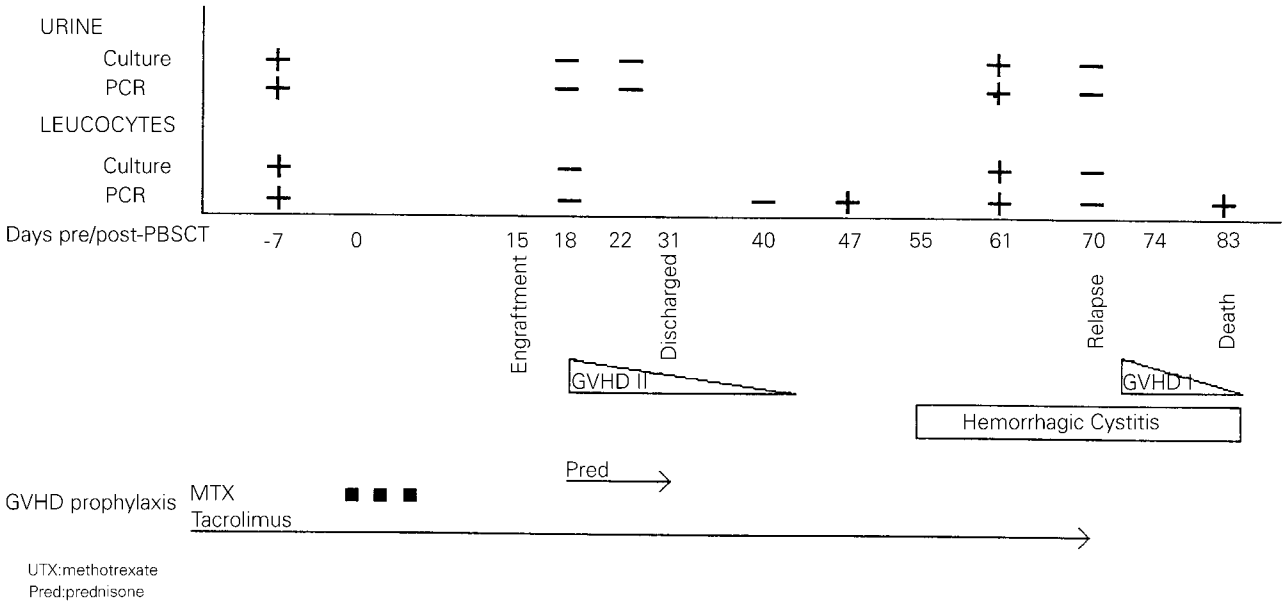

Figure 1 Adenovirus recovery in urine and blood by culture and PCR in a SCT recipient: association with GVHD, clinical manifestations and immunosuppressive/chemotherapy treatment.

urine indicated that AdV was serotype 2. On day 70, she developed blast crisis and immunosuppressive drugs were withdrawn to induce a 'graft-versus-tumor effect'. She was re-admitted (day 74) due to relapse of leukemia; her HC became more severe requiring morphine. The following day, she developed erythema and fever; antibiotics were started. A skin biopsy was consistent with GVHD; blood and urine samples obtained 5 days before this second episode of GVHD (day 70) were negative for AdV. On day 82, the patient's condition worsened with generalized edema, hypotension, gross hematuria and 70% blasts in peripheral blood. AdV was positive by PCR from a leukocyte sample obtained on day 83. Antigenemia pp65 for CMV was repeatedly negative, as were blood and urine cultures for bacteria and fungi. Plasma samples from days -7, $+18$, $+61$ and $+70$ were negative for AdV by PCR. Cytosine arabinoside plus idarubicine were started for resistant leukemia. On day 83, she developed respiratory distress syndrome and died. Permission for a post-mortem examination was refused.

Discussion

An increasing incidence of AdV infections has been reported in the past years, particularly among SCT recipients.[1] Some of the risk factors in this population are young age, conditioning regimen, manipulation of the graft with T-cell depletion and total body irradiation. Although GVHD (its treatment) has also been postulated as a risk factor for AdV infection,[3] other authors have not seen that association.[1]

We report a 42-year-old female who received SCT from an identical HLA donor transplant, and developed severe HC. She did not receive total body irradiation, nor was T-cell depletion performed. AdV serotype 2 was intermittently recovered from leukocytes and urine samples and she died 83 days post-transplant.

As part of an ongoing prospective study, several samples were obtained from this patient to study the presence of AdV. The patient was positive for AdV before transplantation but became negative after engraftment. She developed severe HC with AdV recovery in leukocytes and urine samples on day 61 but she was negative for AdV on day 70 despite her clinical manifestations. These unexpected fluctuations of AdV recovery correlated with her immunosuppressive therapy, episodes of GVHD and clinical manifestations (Figure 1). Viral replication was apparently controlled during her first episode of GVHD (grade II) and immediately before her second episode of GVHD (grade I), although she still had HC and no specific antiviral therapy was administered. These fluctuations may represent immunological control of the virus. It has been postulated that depending on the dose of donor lymphocytes, these may produce a 'graft-versus-tumor effect' or 'graft-versus-host disease'. Since donor lymphocytes may have an antiviral effect which is the basis of donor lymphocyte infusions,[4] these fluctuations in AdV recovery may represent donor-derived control, indirectly manifested by the presence of GVHD.

All plasma samples tested by PCR were negative for AdV although AdV was positive in the corresponding leukocyte samples. These results may reflect a low viral load in blood that was not detected in cell free samples such as plasma. The precise pathogenesis where by a localized infection becomes disseminated is not known. It has been recently reported that AdV in plasma could be used as a marker for dissemination in SCT with AdV infection.[5] Although this patient was negative for AdV in plasma samples, final AdV dissemination has not been completely excluded, especially since no samples were available at the time of death and no autopsy was performed.

Neutralization tests performed on blood and urine samples identified the presence of AdV serotype 2, which is not the subtype most frequently associated with HC. AdV serotype 2 belongs to Group C which can remain latent and may reactivate during immunosuppression. Characterization of this serotype and the presence of AdV before transplantation suggest that reactivation of endogenous virus was the cause of this infection.

The intermittent detection of AdV in leukocytes may reflect a dynamic interaction between viral replication and immunological control. Whether donor lymphocytes, indirectly represented by the presence of GVHD, are involved in this control, requires evaluation.

Sequential screening for AdV infection in SCT recipients will be necessary to determine if this situation occurs in other patients. Studies including T-cell receptor rearrangements will be useful to identify T-cell populations that control AdV replication. Furthermore, characterization of clones to identify target antigens of immune responses will be necessary to improve understanding to support immunotherapeutic interventions such as donor lymphocyte infusions.[4,6,7]

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