Adenovirus Hemorrhagic Cystitis in a Stem Cell Transplant Patient: The First Reported Case in Southeast Asia

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Adenovirus (AdV) infections are prevalent in bone marrow transplant patients, usually associated with significant morbidity and mortality. Hemorrhagic cystitis (HC) is a major complication mainly attributed to this virus. The authors report a case of AdV HC in a myelodysplastic patient undergoing peripheral blood stem cell transplantation. The diagnosis was confirmed by positive urine AdV antigen using indirect immunofluorescence assay. The patient gradually improved after adequate hydration, supportive treatment and reduced dose of cyclosporine, and was discharged on the ninth day of hospitalization. To the authors' knowledge, this is the first case of AdV HC in stem cell transplantation in Southeast Asia.

Keywords : *Hemorrhagic cystitis, Adenovirus, Stem cell transplantation and bone marrow transplantation*

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Adenovirus (AdV) infection is prevalent in bone marrow transplant (BMT) patients, usually associated with significant morbidity and mortality[1-4]. Hemorrhagic cystitis (HC) is a major complication mainly attributed to this virus[5]. Other viruses including BK virus (BKV)[6-8], JC virus (JCV)[9], cytomegalovirus (CMV)[10] and herpes simplex virus[11] as well as other noninfectious causes[12] including medications[13] (such as cyclophosphamide and busulphan) and graft-versus-host disease (GVHD) [14] have been suggested as possible causes of HC. The authors report a case of AdV HC in a myelodysplastic syndrome (MDS) patient undergoing peripheral blood stem cell transplantation. To the authors' knowledge, this is the first reported case of AdV HC in stem cell transplantation in Southeast Asia.

Case Report

A 30-year-old Thai man was admitted to Chulalongkorn Hospital, Bangkok, Thailand because of gross hematuria one day prior to admission. He had been diagnosed with MDS with subtype of refractory anemia and excess blasts 2 years ago when he presented with ecchymosis, epistaxis and pancytopenia. He was treated with a standard induction regimen for acute myeloid leukemia (7 day-course of cytarabine and 3 day-course of doxorubibin). He underwent allogeneic peripheral blood stem cell transplantation after conditioning with 3 days of fractionated total body irradiation (TBI) of 1,200 cGy, 2 days of intravenous cyclophosphamide (4,700 mg/day) and 2-mercaptoethane sulfonate (mesna). After transplantation, he received cyclosporine, mycophenolate mofetil, cotrimoxazole and acyclovir.

On day 52 posttransplantation, the patient developed generalized maculopapular rash over the face, pinnae, palms, soles and trunk. The skin biopsy showed lymphocytic infiltrates in the dermis, necrosis of epidermal cells and basal vacuolization, compatible with acute GVHD. He was partially improved after treatment with prednisolone.

On day 73 posttransplantation (three days prior to admission), he developed irritative voiding symptoms including frequency, dysuria and urgency. One day before admission, gross hematuria was noted. Physical examination revealed a temperature of 36.5°C, blood pressure of 130/80 mm Hg, heart rate of 80/min and respiratory rate of 18/min. There were generalized maculopapular rash over the trunk and extremities. The lungs, heart, and abdomen were normal.

A complete blood count showed a hematocrit of 33.4%; white blood cell count of 3,820/mm^3 with 32.5% polymorphonuclear cells, 46.3% lymphocytes

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and 10.7% monocytes; and a platelet count of 24,000/mm^3. Urinalysis showed many red blood cells and 5-10 white blood cells per high-power field. Liver function tests showed alkaline phosphatase of 75 mg/dl, aspartate transaminase of 38 units/dl, alanine transaminase of 78 units/dl. The prothrombin and partial-thromboplastin times were normal. Other blood chemistry tests were within normal limits. Serologic results for human immunodeficiency virus, hepatitis B virus and hepatitis C virus were negative. Anti-CMV IgG was positive, and anti-CMV IgM was negative.

Treatment included platelet and red blood cell transfusions, ciprofloxacin and intravenous hydration. The daily dose of cyclosporine was also reduced from 500 to 300 mg. Cystoscopy was deferred until the platelet counts normalized. A urine culture was subsequently negative for bacteria, hence ciprofloxacin was discontinued. CMV antigen and polymerase chain reaction (PCR) for CMV in blood, as well as PCR for BKV and JCV in urine were negative. Urine AdV antigen was positive twice using indirect immunofluorescence assay (Chemicon International Inc, Temecula, CA, USA). Isolation of AdV from urine and sputum in HEp-2 cell culture was negative. AdV HC was diagnosed. The patient gradually improved after adequate hydration and supportive treatment, and was discharged on the ninth day of hospitalization. He was followed at the outpatient department, and was seen for the last time after 12 months without urological impairment.

Discussion

HC is a major complication of BMT, with the incidence varying from 7% to as high as 70%[15,16]. There are two types of HC based on their temporal relationships with marrow engraftment. Pre-engraftment HC usually appears early in onset during or immediately after conditioning, with a mild and brief course of dysuria and microscopic hematuria[12,15,16]. It has been considered to be an effect of treatment with medications such as cyclophosphamide and busulphan, and is usually preventable with adequate hydration and the use of mesna. In contrast, post-engraftment HC is usually late in onset, with a severe and protracted course requiring persistent bladder irrigation and surgical interventions. It is usually associated with severe GVHD[15,16]. The present patient had late-onset HC.

The incidence of cyclophosphamide-induced HC ranges from 2-40%, and may be up to 70% of patients without urinary prophylaxis[13,17-19]. It is considered to be dose-related, with varying reported minimum cumulative dose from 2.8-400g. There are two types of cyclophosphamide-induced HC: early- and late-onset HC. Early-onset HC, a more common type, tends to occur immediately or shortly after cyclophosphamide administration, and is usually less than seven days of hematuria. Late-onset HC is usually late in onset (may be up to six months after drug administration)[17] and long duration of more than seven days. Due to advanced knowledge in molecular microbiology, some reports have recently suggested an association between this late-onset HC and a viral etiology including CMV, BKV, JCV and AdV[5,6]. The presented patient developed HC on day 73 posttransplantation, hence it was less likely to be caused by cyclophosphamide.

Radiation cystitis occurs most frequently as a complication of therapy for cancer of the genitourinary system or the rectum. TBI is rarely complicated with HC[20-22].

AdV can cause a wide spectrum of clinical presentations including respiratory infections, gastrointestinal infections, hepatitis, HC, nephritis, conjunctivitis and meningoencephalitis[2,3,5,23-26]. Most immunocompetent children are asymptomatic, mild or self-limited. However, in immunocompromised patients AdV infection may be severe localized or disseminated disease with high mortality rates. AdV is a well known cause of HC in patients undergoing BMT. The timing of AdV infection is variable. Most of the pediatric patients developed infection within 30 days after BMT, whereas AdV was commonly detected after 90 days in adult patients[2,3,5]. The incidence of AdV infections in BMT patients varied from 4.9-21%[2,3]. No cases of AdV infection have been reported in Thailand or Southeast Asia. This is probably an underestimation because diagnostic tests are not available or applied systematically to all BMT recipients. AdV infection is defined as the demonstration of a virus in body fluids or tissue with or without associated symptoms[2]. AdV disease is defined as the identification of a virus at a body site with a compatible clinical syndrome in the absence of other identifiable cause[2]. The presented patient was documented as definite AdV infection and probable AdV disease (HC) because the virus was demonstrated in body fluid (urine) without proven histopathology, and accompanied with compatible clinical syndrome of HC. Other known viruses causing HC including CMV, BKV and JCV were excluded by the absence of their demonstration. Traditionally, the standard method to identify AdV in clinical specimens has been performed by viral isolation. Recently, electron microscopy, antigen-based and PCR-based assays have been accepted for routine use in clinical practice for

the detection of AdV in a variety of tissues and body fluids with reasonable sensitivity and specificity[2,3,23,27,28].

The risk factors to develop AdV infection in the presented patient were allogeneic BMT, acute GVHD and a TBI-containing conditioning regimen. This is consistent with previous reports[2,3,5]. Severe or disseminated AdV disease was less likely to develop in our patient because the virus was identified from only one site. Carrigan demonstrated that the likelihood of developing of severe AdV disease was only 10%, if the virus was identified from one site[3].

To date, no antiviral agents have proven efficacy for the treatment of AdV infection[2,3,5]. The high mortality rates were observed among patients with pneumonia, meningoencephalitis and disseminated disease. Clinical improvement was observed in patients with mild infection or localized disease in the absence of specific antiviral treatment, like the presented patient who responded to adequate hydration, supportive treatment and reduced dose of cyclosporine. Successful treatment of severe or disseminated disease with intravenous ribavirin[29], cidofovir[30-32], ganciclovir[33] or immunotherapy[34] was limited to case reports or small case series.

In summary, AdV infections should be included in the differential list of a wide spectrum of clinical syndromes especially late-onset HC in adult BMT recipients. To the authors' knowledge, this is the first case of AdV HC in stem cell transplantation in Southeast Asia.

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กระเพาะปัสสาวะอักเสบเลือดออกจากอะดีโนไวรัสในผู้ป่วยปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด: รายงานผู้ป่วยรายแรกในเอเชียตะวันออกเฉียงใต้

ประสิทธิ์ เผ่าทองคำ, สนทนา ศิริตันติกร, ชุษณา สวนกระต่าย

การติดเชื้ออะดีโนไวรัสพบได้บ่อยในผู้ป่วยปลูกถ่ายไขกระดูกและเป็นสาเหตุที่สำคัญของอัตราป่วยและตาย กระเพาะปัสสาวะอักเสบเลือดออกเป็นภาวะแทรกซ้อนที่พบบ่อยในการติดเชื้อไวรัสนี้ ผู้เขียนได้รายงานผู้ป่วยที่มีปัญหากระเพาะปัสสาวะอักเสบเลือดออกจากอะดีโนไวรัสในผู้ป่วย myelodysplastic syndrome ที่ได้รับการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด โดยวินิจฉัยจากการตรวจพบแอนติเจนของอะดีโนไวรัสในปัสสาวะด้วยวิธี indirect immunofluorescence ผู้ป่วยรายนี้มีลักษณะทางคลินิกที่ค่อยๆ ดีขึ้นหลังการรักษาด้วยการให้น้ำให้เพียงพอ การประคับประคอง และการลดขนาด cyclosporine จากความรู้ในขณะนี้ผู้ป่วยรายนี้เป็นผู้ป่วยรายแรกที่มีกระเพาะอักเสบเลือดออกจาก อะดีโนไวรัสในการปลูกถ่ายเซลล์ต้นกำเนิดในเอเชียตะวันออกเฉียงใต้