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Acute Renal Failure Induced by Adenovirus After Stem Cell Transplantation

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1. Introduction

Adenoviruses have been recognized as opportunistic and significant viral pathogens in immunocompromised patients such as recipients of hematopoietic stem cells or other solid organs treated with immunosuppressive agents, and among patients with acquired immunodeficiency syndrome. These patients are incapable of developing a normal immune response. Reactivation of adenoviruses in the impaired immunological response leads to acute or persistent infections with high morbidity or even mortality in these patients.

In the field of allogeneic stem cell transplantation in particular, adenovirus infection is one of the common complications. A representative consequence of adenovirus infection is hemorrhagic cystitis. The cumulative incidence of adenovirus-induced hemorrhagic cystitis was found to be 7%, which usually presents a favorable prognosis during the era of bone marrow and peripheral blood stem cell transplantation (El-Zimaity et al., 2004, Shields et al., 1985, Asano et al., 2003). Some cases, however, progress to a retrograde infection of the kidneys, and develop to acute renal failure and adenoviremia, resulting in a poor prognosis (Bruno et al., 2004). Lion et al. reported that mortality of adenoviremia after stem cell transplantation was 91% before the era of cidofovir (Lion et al., 2003).

In recent years, umbilical cord blood has been increasingly utilized as a source of hematopoietic stem cells for transplantation of patients without favorable donors despite its immature immune activity which often leads to a prolonged immunological deficiency and many kinds of early severe infectious complications such as bacteremia, cytomegalovirus disease, tuberculosis and fungal infection (Saavedra et al., 2002, Maeda et al., 2005). The

cumulative incidence of adenovirus-induced hemorrhagic cystitis after cord blood transplantation was, however, found to be relatively low (2.8%) among Japanese adults (Tomonari et al., 2006). It is important that cord blood transplantation is one of the risk factors of symptomatic adenoviremia (Robin et al., 2007), which develops to acute renal failure in the terminal stage (Abe T et al., 2009).

At present, there is no established consensus about the treatment for acute renal failure induced by adenovirus after stem cell transplantation. This chapter focuses on the recent advances in diagnosis, mostly due to the development of molecular methods, and therapeutic interventions. Furthermore, this chapter is intended to promote a consensus about the methods of early diagnosis and the treatment for this disease.

2. Serotypes of adenoviruses inducing cystitis and acute renal failure

The development of more sensitive diagnostic methods enabled us to increase awareness of this virus as a pathogen. At least seven human adenovirus species (A to F), including 52 serotypes, have been described.

Adenoviruses have mechanisms to escape from host immune responses, such as inhibition of interferon functions, inhibition of intrinsic cellular apoptosis in infected cells, and the prevention of major histocompatibility complex class I expression on the cell surface (Mahr et al., 1999) to reduce cytotoxic T-cell attack of the infected cells (Lichtenstein et al., 2004), especially in serotypes 1, 2, and 5 (species C). They persist focally in tonsils for years through low-grade replication. Surprisingly, T lymphocytes in tonsils and adenoids may harbor adenovirus-DNA (Garnett et al., 2007). This suggests that endogenous reactivation may occur during periods of immunosuppression after stem cell transplantation. Persistence of adenovirus species C is higher for younger age groups, in which primary infections predominantly with species C occur. The quantity of adenovirus-DNA decreases in an age-related manner, either from immune elimination or from depletion of latent stores. Persistent or latent infection of other species is still unknown.

Acute renal failure due to adenoviruses is caused by disseminated disease or retrograde infection from hemorrhagic cystitis. High persistence of serotype 2 at a young age is mentioned in lots of case reports regarding disseminated diseases of this serotype after stem cell transplantation. Other prevalent serotypes of disseminated diseases are 31 (species A), 11, 34, 35 (species B), 1 and 5. On the other hand, prevalent serotypes of hemorrhagic cystitis are 7, 11, 34 and 35 (species B) (Echavarría, 2008), especially serotype 11 (Asano et al., 2003). The organ tropisms of AdV serotypes remain unclear.

Multiple serotype infection was found to be more frequent in immunocompromised patients (30%) than in immunocompetent patients (5%) (Gray et al., 2007). Our group also experienced sequential adenovirus infection of serotype 14 hemorrhagic cystitis and serotype 35 disseminated infection after cord blood transplantation (Abe T et al., 2009). Serotype 14 is a group B adenovirus, which is associated with pharyngo-conjunctival fever (Tuck et al., 1957). This infection was infrequently reported as an acute respiratory disease in military recruits (Van der Veen & Kok, 1957, Hierholzer & Pumarola, 1976, Metzgar et al., 2007), and recently caused pediatric lower airway disease in Taiwan during 2001-2002 (Chen et al., 2002). A new variant of this serotype also caused life-threatening pneumonia in the United States (Louie et al., 2008). Serotype 35 has been detected in urine of patients with acquired immunodeficiency syndrome (AIDS) and other immunodeficiencies (de Jong et al., 1983, Shields et al., 1985, Stalder et al., 1977). Furthermore, an outbreak of serotype 35 pneumonia among residents and staff of a psychiatric facility was reported (Sanchez et al., 1997).

3. Pathological findings and methods of diagnosis

3.1 Pathological findings of acute renal failure induced by adenovirus

Hemorrhagic, necrotizing tubulitis with intranuclear inclusion bodies is observed in autopsy of patients with acute renal failure induced by adenoviruses after stem cell transplantation or intensive chemotherapy for acute leukemia.

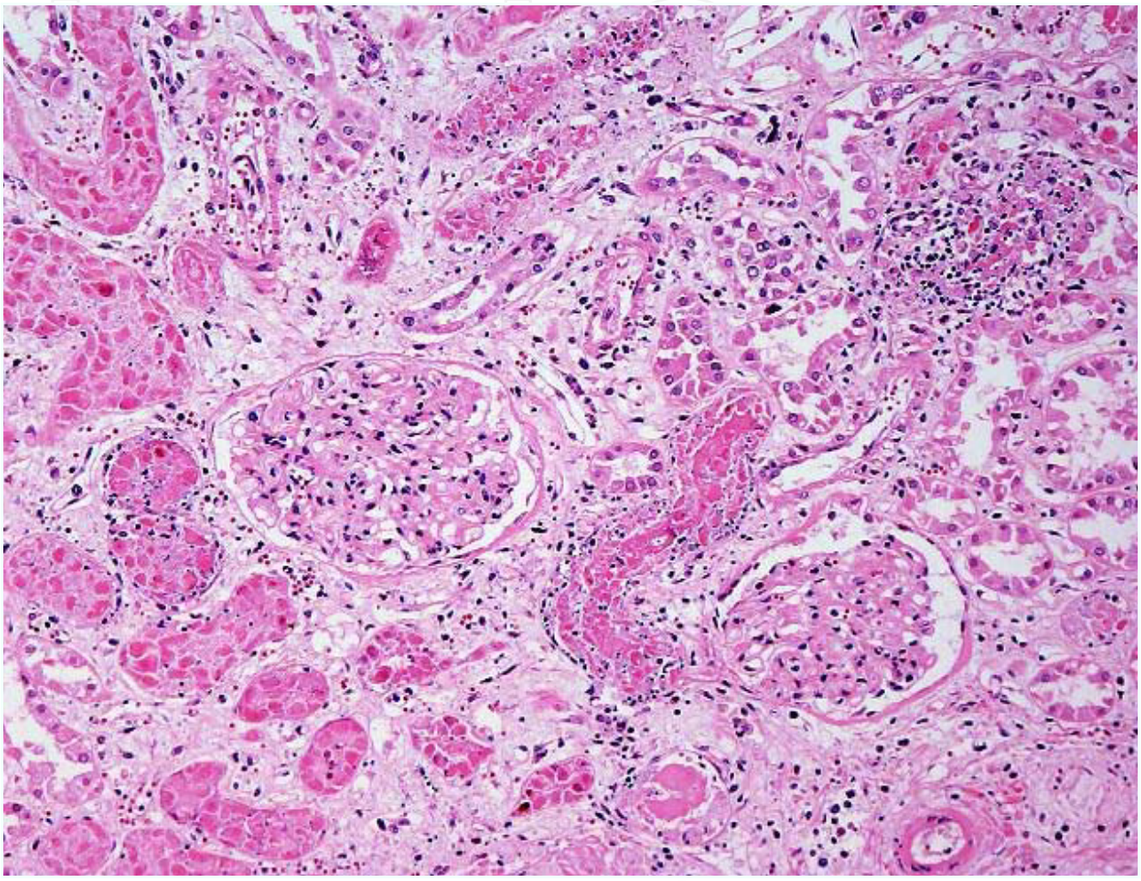


Fig. 1. Necrosis with interstitial hemorrhage of the kidneys of our autopsied patient. (hematoxylin–eosin stain, magnification x20)

Interstitial hemorrhage is specific to adenovirus (Figure 1) and is different from other viral nephritis after stem cell transplantation such as those with BK virus or cytomegalovirus (Colvin, & Nickeleit, 2007). Histopathologically, necrobiotic tubular cells are classified into inclusion-bearing cells of three types: 1) "smudge cells," 2) "Cowdry A" intranuclear inclusion cells including intranuclear eosinophilic amorphous or droplet-like bodies surrounded by a homogeneous clear halo, with marginations of chromatin on the nuclear membrane, and 3) "full-type" intranuclear-containing cells (Cowdry, 1934, Ito et al., 1991)(Figure 2).

Yuzawa et al. showed that these granular deposits contain adenovirus related antigens, immunoglobulins, and C3, which suggests that granular deposits may be formed "in situ" by viral antigens and circulating viral antibodies (Yuzawa et al., 1993).

It is definitive that immunofluorescent examination with anti-adenovirus antibody demonstrates specific fluorescence on the affected tubular cells (Figure 3).

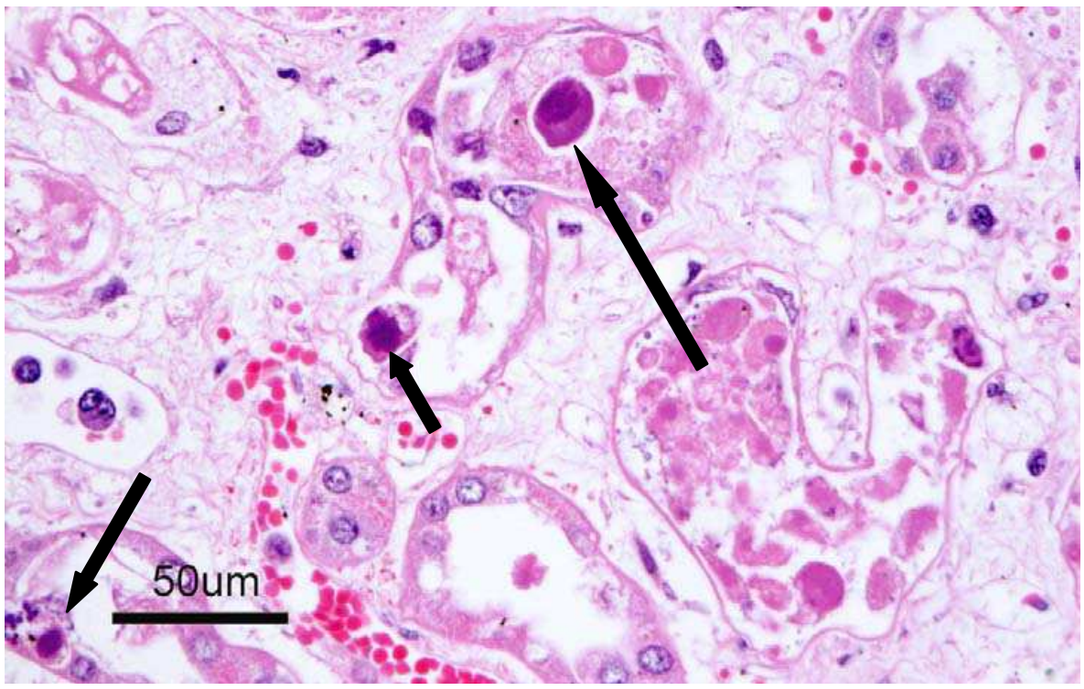


Fig. 2. The three types of inclusion bodies: Cowdry A(long arrow), full-type (intermediate-length arrow) and smudge-type (short arrow) are identified in the affected tubules (hematoxylin–eosin stain, magnification x40).

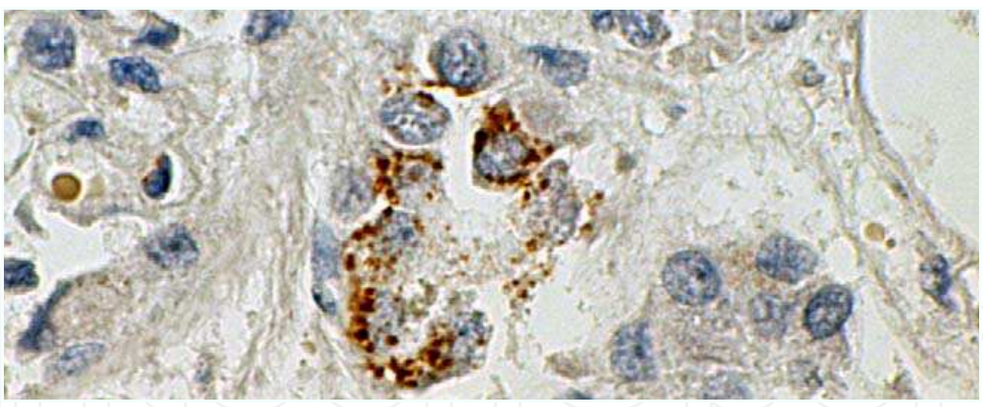


Fig. 3. Adenovirus antigens in affected tubular cells of our autopsied patient are revealed by immunofluorescent examination (magnification x100). Serotype-specific antigen can also be revealed by this method.

Electron microscopy can reveal intranuclear crystalline arrays of viral particles, 75 to 80 nm in diameter (Ito et al., 1991, Mori et al., 2003), but it is not routinely used in clinical laboratories.

3.2 Methods of diagnosis for acute renal failure induced by adenovirus

3.2.1 Clinical manifestations of acute renal failure induced by adenovirus

Adenovirus is usually detected in the recipients of stem cell transplantation within 100 posttransplant days. The mean time is 58 days, ranging from -44 to 333 days (Ljungman et

al., 2003). Adenovirus causes acute renal failure, which follows adenovirus-induced hemorrhagic cystitis or adenoviremia. At first, in hemorrhagic cystitis cases, the risk factors include acute graft versus host disease of more than grade II, male, old age, allogeneic stem cell transplantation and the use of busulfan in a conditioning regimen (Asano et al., 2003, Sencer et al., 1993, Seber et al., 1999, Leung et al., 2002). Common clinical symptoms are gross hematuria and lower abdominal pain. Some cases lead to hydronephrosis and acute post-renal failure due to obstruction of the terminal ureters by edematous change of the ureterovesical junction (Figure 4).

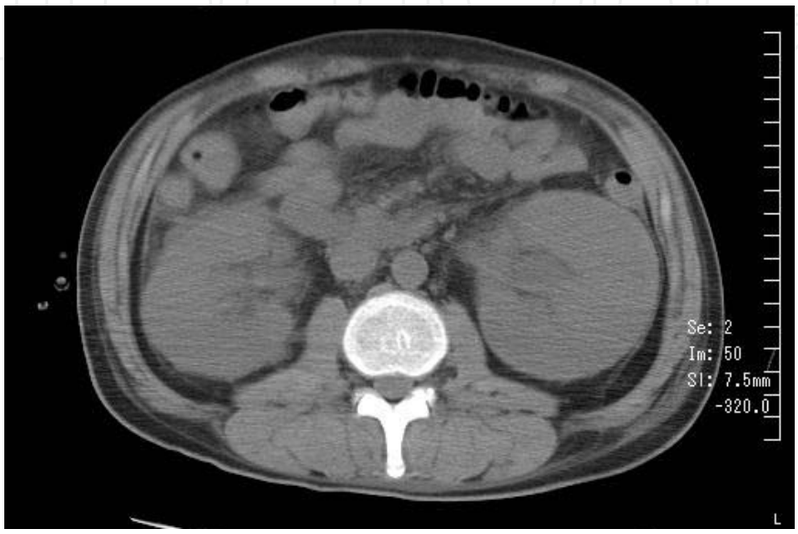


Fig. 4. Hydronephrosis and acute post-renal failure in our patient due to obstruction of the terminal ureters by edematous change of the ureterovesical junction after the onset of adenovirus-induced hemorrhagic cystitis.

Back or flank pain is a critical symptom that indicates a retrograde infection to kidneys, risk factor for which is graft versus host disease. Furthermore, adenovirus-induced nephritis is a high risk factor for disseminated adenovirus infection including symptomatic adenoviremia (Bruno et al., 2004). Clinical presentation of adenoviremia is low to high grade fever refractory to antibiotic or antifungal agents followed by multiple organ failure including acute renal failure which presents oliguria, elevation of serum creatinine and enlarged kidneys with hypo-density in CT scan. Risk factors of disseminated adenovirus infection including symptomatic adenoviremia are graft versus host disease, and, T-cell-depleted graft and cord blood transplantation (Robin et al., 2007, Kampemann et al., 2005). On the other hand, asymptomatic infections with detection of adenovirus from blood or urine have been observed (Lion et al., 2003).

3.2.2 Methods of molecular diagnosis for acute renal failure induced by adenovirus

Adenovirus-DNA has been detected in almost all clinical samples. In adenovirus-induced hemorrhagic cystitis cases before acute renal failure, the most rapid and handy qualitative diagnosis kit is immunochromatography, for example, adenocheck (Santen, Osaka, Japan, or SA Scientific, Texas, U.S.) (Nagafuji et al., 2004). This kit enables us to detect more than $1x10^4$ viral particles /ml in urine at the bedside, although it was developed for the diagnosis of adenovirus conjunctivitis.

Polymerase chain reaction (PCR) has been used as a rapid and very useful method, and is the most prevalent assay for the diagnosis of adenovirus infection. The clinical specificity of the PCR for urine was found to be 96% (Echavarría et al., 1998). To diagnose symptomatic adenovirus infection such as hemorrhagic cystitis, adenoviremia or acute renal failure, at first, DNA is extracted from the patient's urine, blood or renal biopsy sample. When acute renal failure and adenoviremia occur simultaneously, the patient may be diagnosed with adenovirus-induced acute renal failure without renal biopsy. Then nested PCR is performed to amplify the RNA gene, hexon gene or fiber gene of adenovirus with more than one pair of primers in a thermal cycler as shown in Figure 5. (Saito-Inagawa et al., 1996, Shimada et al., 2004, Lu & Erdomann, 2006, Leruez-Ville et al., 2004, Lion et al., 2003).

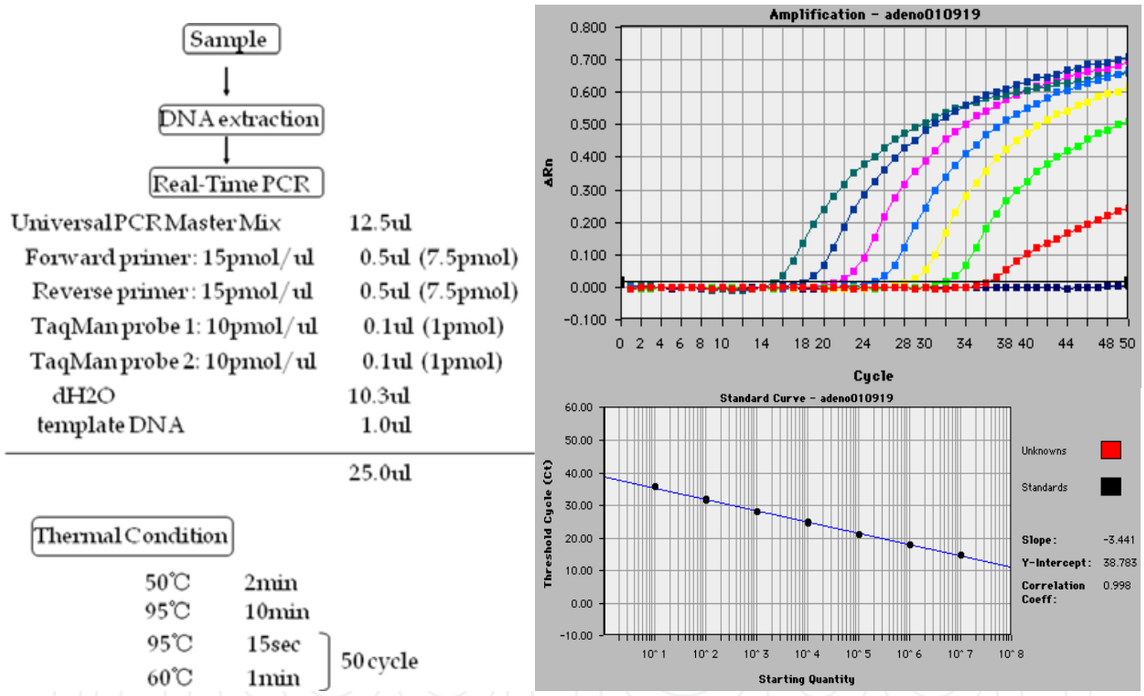


Fig. 5. Quantitative PCR using DNA extracts from the patient's samples is performed with a pair of primers, for example, as shown in the paper of Lion et al., and with a pair of TaqMan probes for quantification, for example, 5'-(FAM)-CCCATGGATGAGCCCACCCT-(TAMRA)-3' and 5'-(FAM)-CCCATGGACGAGCCCACCCT-(TAMRA)-3', in a thermal cycler. The thermal conditions were 50°C for 2 min, 95°C for 10 min, then 50 cycles at 95°C for 15 sec and 60°C for 1 min. Amplification standard was made for each number of control DNA copies from 10^1 to 10^7, which enabled us to quantify the number of viral DNA copies from the patient's samples.

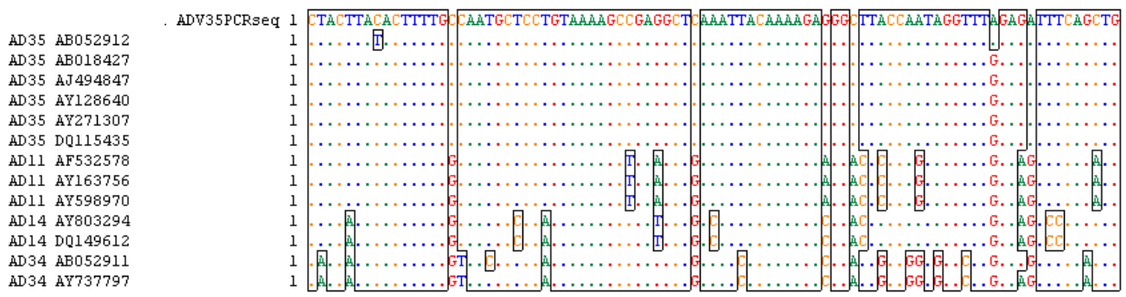


Fig. 6. The nucleotide sequences of amplified fragments were determined with a DNA auto sequencer with fluorescent dideoxy chain terminators. For example, the sequences of the amplified adenovirus-DNA from our autopsied patients (at the first line) were analyzed and compared with the 51 prototype strains in the GenBank database (below the next line), and finally the serotype was identified as 35.

This method is real-time PCR, which can be a qualitative or quantitative assay since amplification and detection of amplified products occur simultaneously. Then, typing is performed. Typing is primarily used for epidemiologic investigations, for studies on pathogenesis such as multiple serotype infections, for unusual or especially severe infections, or for treatment approaches such as high titer γ-globulin. The nucleotide sequences from these fragments were determined by a DNA auto sequencer with fluorescent dideoxy chain terminators. The sequences of the amplified adenovirus-DNA were analyzed and compared with the 51 prototype strains in the GenBank database, and finally the serotypes were identified (Figure 6)(Abe T et al., 2009). This method with sequencing is increasingly performed because it is rapid and now available in many laboratories with molecular equipment, and does not require expensive or difficult-to-obtain antisera. However, there is no clear viral load cut-off value that predicts disease outcome. Thus, it may be preferable to analyze the viral kinetics for each patient, considering the adenoviral load over time rather than the absolute value among symptomatic patients (Leruez-Ville et al., 2004).

PCR is highly sensitive and especially applicable for asymptomatic adenovirus infection surveillance of blood samples, perhaps weekly, and at present, it is commonly applied in stem cell recipients. The virus can be detected in blood 2 to 3 weeks before development of clinical symptoms, which offers the opportunity for intervention (Lion et al., 2003) to avoid acute renal failure and hemodialysis.

4. Treatment to avoid hemodialysis before and during hemorrhagic cystitis

Conventional treatments of hemorrhagic cystitis are hyper-hydration, diuresis and bladder irrigation to wash out viral particles and clots, and to prevent retrograde infection to kidneys and post-renal failure due to urethral obstruction caused by clots. High titer γ-globulin to specific adenovirus serotype is also administrated. In particular, serotype 35 specific antibody was present only at a very low titer in pooled gamma globulin (Flomenberg et al., 1987). Our group experienced sequential different serotype adenovirus infection of serotype 14 hemorrhagic cystitis and serotype 35 disseminated infection after cord blood transplantation, which is too confusing to treat because of the contrast between the improvement of adenovirus-induced hemorrhagic cystitis by serotype 14 high titer γ-globulin and the progression of acute renal failure (Abe T et al., 2009).

At present, Ribavirin and Cidofovir are antiviral agents used in the treatment of adenovirus. More evidence has been obtained for the efficacy of Cidofovir. Recent reports showed that 69-98% of patients with adenovirus disease were successfully treated with Cidofovir (Yusuf et al., 2006, Ljungman, 2003). Nagafuji et al. reported that 71% of patients with adenovirus-induced hemorrhagic cystitis were successfully treated with Cidofovir (Nagafuji et al., 2004). Therefore, Cidofovir is recommended as the first line treatment for adenovirus-induced hemorrhagic cystitis. Cidofovir is a monophosphate nucleotide analog of cytosine that can inhibit viral DNA polymerase and viral replication.

For a preemptive therapy before the onset of adenovirus-induced hemorrhagic cystitis, Ljungman et al. showed tthat, for 13 (81%) of 16 patients, asymptomatic infection was resolved when Cidofovir was given as a preemptive therapy (Ljungman et al., 2003). Lindemans et al. presented a practical guidelines for the treatment of adenovirus infections in recipients of stem cell transplantation by using Cidofovir including a preemptive therapy (Lindemans et al., 2010). The guidelines take three risk factors into consideration: cord blood transplantation, T-cell-depleted graft, and immune-suppression, and divide the patients into low-, intermediate-, and high-risk groups, each with a different treatment approach depending on the viral load measured by weekly or twice weekly peripheral blood quantitative PCR. The presence of these risk factors determines individual susceptibility to the development of adenovirus disease in the case of reactivation. At first, the low-risk group includes cases other than cord blood transplantation or T-cell-depleted graft, or at more than 4 months after stem cell transplantation for any donor source with immune-suppression by a lymphocyte proliferation inhibitor such as calcineurin inhibitor and/or less than0.5 mg/kg predonisolone. Furthermore, low risk group is divided into two groups by CD3 positive T cell count in peripheral blood. When adenovirus is detected in peripheral blood more than 100 copies/ml, absence of T cells (CD3+< 25/μL) or the immunoresponse failure to adenovirus shortly after adenovirus detection (CD3+ T cells < 300/μL within 2 weeks of adenovirus detection) leads to the same treatment of intermediate risk group because it has been associated with a poor outcome. The number of CD3-positive T cells has been shown to be critical in the development of infectious disease in the case of viral reactivation, and in the ultimate clearance of the virus (Chakrabarti et al., 2002, Heemskerk et al., 2005). The intermediate-risk group includes cases of cord blood transplantation or T-cell-depleted graft 1 to 4 months after stem cell transplantation with immune-suppression by more than two lymphocyte proliferation inhibitors (e.g., cyclosporine-A and mycophenolate mofetil) or a lymphocyte proliferation inhibitor and 0.5-1 mg/kg prednisolone. The high-risk group includes cases of cord blood transplantation or T-cell-depleted graft within a month after stem cell transplantation, and immune-suppression by more than one lymphocyte proliferation inhibitor and more than 1 mg/kg prednisolone. Critical viral load in peripheral blood for pre-emptive treatment is more than 10,000 copies in low-, more than 1,000 copies in intermediate-, and more than 100 copies in high-risk groups, respectively. Symptomatic adenovirus diseases are also critical for treatment. The treatment regimen for Cidofovir is 1 mg/kg per day three times weekly until viral load decreases to less than 400 copies/ml for more than two weeks and CD3+ T cells increase to more than 300/μl (Kampmann et al., 2005, Chakrabarti et al., 2002). If possible, immunosuppressive drugs should be tapered (Kampmann et al., 2005, Chakrabarti et al., 2002). Because of the marked nephrotoxicity of Cidofovir, hyperhydration together with oral Probenecid (2 g) given 3 h before Cidofovir administration is essential for nephroprotection (Nagafuji et al., 2004, Anderson et al., 2008, Hoffman et al., 2001). Viral load increases of more than 1 log /week or

patient presentation of adenovirus disease symptoms is indicative of therapy failure and immunotherapy (described later) should be considered.

There is weak evidence for the efficacy of Ribavirin against adenovirus, and its in vitro anti-adenovirus activity differs widely against different serotypes (most active against group C, subtype 1, 2, or 5) (Morfin et al., 2005). There are several case reports suggesting therapeutic benefit for some patients (Homma et al., 2008, Abe S et al., 2003, Lankester et al., 2004). Recently, a strategy combining prophylactic Ribavirin and preemptive Cidofovir treatment was described (Greil et al., 2006). Comparing the outcome with Historical controls in which no prophylaxis and Cidofovir alone was given as a preemptive treatment, the combined strategy with Ribavirin prophylaxis resulted in a significantly lower incidences of adenovirus infection (29% vs 66%) and adenovirus-associated mortality (0% vs 14%).

Although prophylaxis or preemptive therapy shows favorable effects on adenovirus infection, even Cidofovir has only limited efficacy when started as therapeutic treatment for disseminated adenovirus diseases in intermediate- and high-risk groups (Robin et al., 2007, Symeonidis et al., 2007). It is important that early detection of Adenoviremia enables us to initiate therapy before a significant increase in mortality (La Rosa et al., 2001).

Although less efficient than Cidofovir or Ribavirin, Ganciclovir can interfere with the function of adenovirus DNA polymerase, thus inhibiting viral replication in vitro (Lenaerts et al., 2008). In retrospective studies, lower incidences of adenovirus infections appeared to be reported in patients treated with Ganciclovir as cytomegalovirus prophylaxis (Bruno et al., 2003). Reports of a positive outcome in patients with adenovirus infection treated with Ganciclovir are uncommon (Chen et al., 1997). In some countries like Japan, Cidofovir is not available. Ganciclovir may be useful in these countries until Cidofovir becomes available.

Vidarabine is also active in vitro against adenovirus (Kurosaki et al., 2004). There have been a few case reports of successful vidarabine therapy of adenovirus hemorrhagic cystitis. Bordigoni et al. reported results obtained in seven recipients of stem cell transplantation treated with vidarabine, but none survived (Bordigoni et al., 2001).

5. Treatment for acute renal failure induced by adenovirus

Adenovirus causes acute renal failure through hemorrhagic cystitis or as a symptom of disseminated disease. In this phase, treatment options are severely limited. If possible, tapering or termination of immunosuppressive agents is indicated to prompt immune reaction against adenovirus, although the risk of graft versus host disease progression may increase. Of course, oliguria is an indication of hemodialysis. When post-renal failure with hydronephrosis is caused by clots or swelling of the ureterovesical junction in patients with adenovirus-induced hemorrhagic cystitis, percutaneous nephrostomy may be indicated (Mori et al., 2003). Regarding the administration of antiviral agents in severe renal dysfunction, serum elimination half-time of Cidofovir increases so significantly that its nephrotoxicity may force the patients into hemodialysis. Therefore, drug clearance should be carefully considered. Brody et al. showed that mean +/- SD of Cidofovir clearance in patients with renal dysfunction was 0.94 x cleatinine clearance (mL/min/kg) + 0.064 mL/min/kg while its clearance in normal control was 1.7 +/- 0.1 mL/min/kg (Brody et al., 1999). Ribavirin is contraindicated for patients with renal failure whose creatinine clearance is less than 50 ml/min. During the period of hemodialysis, high-flux hemodialysis resulted in the removal of 52% +/- 11% of Cidofovir administered (Brody et al., 1999). Ribavirin, however cannot be removed by hemodialysis (Kramer et al., 1990). In a case report,

reduction of immunosuppression and one dose of Cidofovir (2 mg/kg) were effective for adenovirus-induced acute renal failure on hemodialysis, and showed resolution of viremia and viruria and return of renal function to near baseline without coadministration of Probenecid to ensure adequate drug delivery to the proximal tubular cells (Sujeet et al., 2010). Nevertheless, treatment failure with Cidofovir indicates immunotherapy such as donor lymphocytes or adenovirus-specific cytotoxic T cells in the initial therapy of adenovirus-induced hemorrhagic cystitis or acute renal failure, and in the preemptive therapy according to the guidelines descrived above.

Donor lymphocyte infusion in allogeneic stem cell transplantation is an adoptive T cell transfer protocol based on the hypothesis that donor peripheral blood containing T cells can mediate antiviral activity. Hromas et al. reported a case of a 19-year-old man who underwent a T-cell-depleted allogeneic stem cell transplantation for T-cell lymphoblastic lymphoma. After treatment failure with antiviral drugs for adenovirus-induced hemorrhagic cystitis, he was given donor leukocytes (1 x 10^6 CD3 cells/kg) and subsequently cleared the virus (Hromas et al., 1994). A number of other case studies followed with similar positive outcomes (Chakrabarti et al., 2002, Howard et al., 1999, Bordigoni et al., 2001, Chakrabarti et al., 2000). Patients were infused with cell doses ranging from 1 x 10^5 to 3 x 10^7 CD3 cells/kg. Donor lymphocyte infusion is, however, impossible in patients after cord blood transplantation and often regarded as the last choice of the treatment option because the efficacy of this approach is limited by the low frequency of T cells specific to adenovirus and the relatively high frequency of graft versus host disease caused by alloreactive T cells. Graft versus host disease itself is a risk factor of disseminated adenovirus diseases because the therapy for graft versus host disease requires steroids, which suppress adenovirus-specific T cells. To reduce the risk of donor lymphocyte infusion, inactivation or selective removal ex vivo of alloreactive T cells, or suicide gene transfer has been investigated (Davies et al., 2008, Comoli et al., 2008, Andre-Schmutz et al., 2002, Solomon et al., 2002, Amrolia et al., 2003, Montagna et al., 1999, Ciceri et al., 2009, Tey et al., 2007).

To improve the safety and efficacy of the adoptive transfer approach to donor lymphocyte infusion, adenovirus-specific T cell selection from donor peripheral blood and expansion in vitro have been investigated. Feuchtinger et al. directly identified and isolated donor peripheral blood T cells that secreted IFN-γ in response to stimulation with adenovirus antigen, and expanded the cells with the stimulation of adenovirus lysate in vitro. Then the isolated T cells were transferred into 9 pediatric recipients of allogeneic stem cell transplantation with systemic adenovirus infection despite conventional therapy. The frequency of adenovirus-specific T cells in donor peripheral blood increased from 1.1% +/- 1% to 45.7% +/- 24% after selection. None of the infusions (range, 1,200-50,000 CD3+ cells/kg) was associated with toxicity in vivo, and 5 of 6 evaluable patients showed a significant decrease of adenoviral DNA in peripheral blood and stool with a corresponding increase in the frequency of adenovirus-specific T cells in vivo (Feuchtinger et al., 2006). Leen et al. has achieved similar success in adoptive immunotherapy by using in vitro–expanded adenovirus, EB virus, and cytomegalovirus-specific cytolytic T-cell (CTL) lines (Leen et al., 2006). For the production of the trivirus CTL lines, EB virus-transformed lymphoblastoid cell lines were used as antigen-presenting cells, which also presented EB virus antigens, and adenovirus vectors into which a cytomegalovirus antigen was introduced were transduced with these antigen-presenting cells. Cells were infused as a prophylaxis from day 30 after transplantation in recipients of HLA- haploidentical stem cell

transplantation as well as HLA-matched related, and matched unrelated cases within grade II acute graft versus host disease. The infused doses ranged from 1.7×10^5 to 4.5×10^6 cells / kg, and could control ongoing drug-resistant virus infections. No toxicity or acute graft versus host disease was observed. Adenovirus-specific T cells increased only in patients with recent or concurrent adenovirus infection, although the reactive T cells against the latent EB virus and cytomegalovirus routinely increased independently of detectable viral reactivation. None of the treated patients developed a de novo adenovirus infection for at least 8 weeks. All patients with detectable adenovirus in blood, stool, or tracheal aspirate (7 of 24) had a marked reduction in adenoviral load coincident with the rise in their adenovirus-specific T cells irrespective of infection serotype, including one patient who recovered from progressive adenoviral pneumonia requiring ventilatory support. Although adenovirus-specific CTL may be a safe and effective therapy, there are some serious problems such as high cost, preparation of large blood volume, and a prolonged period for the manufacturing process with special technical skill for 10-12 weeks. Therefore, the indication of this therapy should be limited in cases resistant to antiviral agents, but the preparation of this therapy should be started as early as possible.

6. Future perspectives (conclusion)

In the future, preemptive therapy for adenovirus will be established, and CTL therapies will be more standardized, rapid, cost-effective and available in all institutes. Other methods such as boosting immune recovery, dendritic therapy and new antiviral drugs are now also being developed. These new methods will enable resolution of the severe limitations in the treatment of adenovirus-induced acute renal failure.

7. Acknowledgment

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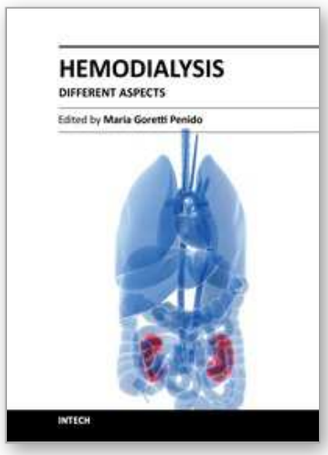
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