Disseminated Adenoviral Infection Complicated by Fatal Hemorrhagic Enterocolitis in a Child with Acute Myeloid Leukemia

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Abstract

Adenovirus infection is very common in children < 5 years of age. Severe adenovirus infection is more common in children with compromised cellular immunity and rare in children with acute leukemia. Here we report a child with acute myeloid leukemia who developed disseminated adenoviral infection complicated by hemorrhagic enterocolitis and septic shock that resulted in a fatal outcome.

Keywords: Adenovirus; Hemorrhagic Enterocolitis; Children; AML.

Introduction

Although adenoviral infection is usually mild and self-limited in normal children, it can be severe, and the disseminated forms are almost always fatal, especially in children with impaired cellular immunity. However, only few cases with AML have been reported to have fatal disseminated adenoviral disease.

Case Report

Here we report a 15-months-old child with acute myeloid leukemia (AML M0-M1) managed at Sultan Qaboos University Hospital, Muscat, Oman according to AML Sheffield protocol. One-week post course II chemotherapy, she had worsening diarrhea and cough. Adenovirus was detected by Polymerase chain reaction (PCR) in stools and plasma at a level of 13200 (log 4.1) copies/ml. She was managed conservatively and continued on weekly monitoring of viral load. Two weeks later, she became sicker with bilious vomiting, tachycardia, progressive abdominal distension and tenderness. Intestinal perforation was suspected but ruled out on abdominal imaging (Figure 1). CT abdomen revealed diffusely distended, fluid-filled small and large bowel with increased enhancement. There was no focal mural thickening, hypoenhancement or pneumatosis intestinalis. (Figure 2) Her condition deteriorated, and she was admitted to pediatric intensive care unit (PICU) with gram-negative bacteremia complicated with septic shock that required inotropic support. She was started empirically on Meropenem and Vancomycin. Her blood culture grew E.Coli sensitive to Amoxicillin/Clavulanate, Cefuroxime and Gentamicin. Further blood cultures remained negative with no growth. While in PICU, she developed bloody diarrhea with significant blood loss. Laboratory evaluation revealed deranged coagulation, thrombocytopenia, and drop of Hb from 9 to 6 gm/dl, requiring multiple blood transfusions, fresh frozen plasma (FFP), platelet transfusions, and intravenous vitamin K. Her plasma adenoviral titer increased to 17200 copies/ml (log 4.2) and treatment with Cidofovir (5mg/kg/dose weekly) and probenecid started. Despite 2 doses of cidofovir, adenoviral load continued to increase to 1130000 copies/ml (log 6.1) and then to > 1000000 copies/ml (>log 7). Her stools and respiratory secretions were also positive for enteric adenovirus as well, denoting disseminated adenoviral infection.
Figure 1: Left lateral decubitus abdominal X-ray: Few gaseous distended bowel loops are noted with few scattered fluid levels denoting stagnation. No evidence of pneumatosis or pneumoperitoneum is noted.
Figure 2: CT abdomen and pelvis with IV and oral contrast showing hepatomegaly, diffuse bowel distension, fluid-filled small and large bowel loops with increased enhancement. No focal mural thickening, hypo-enhancement or pneumatosis intestinalis. No pneumoperitoneum.

During her PICU stay, she remained severely neutropenic despite treatment with filgrastim. She had significant upper and lower GIT bleeding, with sloughing of intestinal mucosa. Pathological examination of shed tissue revealed abundant blood clots mixed with occasional non-viable tissue with vague outlines resembling superficial mucosal surface. Bleeding diathesis presented also with ecchymosis, gum bleeding, conjunctival bleeding, and microscopic hematuria. Supportive measures using multiple FFP, platelet transfusions and activated Factor VII failed to improve her bleeding diathesis. Ultimately, she developed multisystem organ failure, with refractory hypotension, renal shutdown, coagulopathy, and transaminitis. Despite optimal supportive measures including ventilator support, renal replacement therapy as well as broad spectrum antimicrobials and cidofovir she continued to deteriorate and passed away with uncontrolled disseminated adenoviral infection complicated with multi-organ dysfunction.

Discussion

Adenovirus infection is very common in pediatric populations, with 80% of children 1-5 years of age having antibodies to one or more serotypes. Infections in immunocompetent hosts are usually benign and self-limited, and most commonly manifest as mild respiratory, gastrointestinal, and/or ocular disease. However, it is a potential cause of increased morbidity and mortality in immunocompromised patients especially transplant recipients.(1)

Adenovirus persists within the lymphoid tissue of infected hosts. Delayed clearance and prolonged shedding can result in reactivation of the virus in susceptible hosts, leading to a potentially fatal disseminated disease. Transmission of adenovirus can also occur by feco-oral route, droplet or contaminated fomites and medical utensils.(2)

The risk and severity of adenoviral disease increases with increasing immunosuppression. The most vulnerable population to viral reactivation or disseminated infection are patients with compromised cellular immunity like the transplant recipients and children with primary cellular immunodeficiency. The most common pathologic findings attributed to fatal adenovirus infection included pneumonia, hepatic necrosis, enterocolitis, epicardial hemorrhage, and ulcerations of the larynx, trachea, and ileum. (3)

This report presents a severe fatal disseminated adenoviral disease in a young child with AML, after receiving 2 courses of intensive chemotherapy which is uncommon in this population. A report from the Canadian infection in acute myeloid leukemia research group found that severe adenoviral infection in children with AML was rare.(4) Nevertheless, a similar fatal infection was reported in one patient wo had severe disseminated adenoviral infection and died from multiorgan failure.(4)

The possible explanation for this severe manifestation is the effect of intensive myelosuppressive chemotherapy. In addition, AML itself interacts with the immune system in two distinct ways: immune editing and immune evasion. Immune editing is mediated by the production of soluble molecules that directly suppress the lymphocytes, and lead to induction of T-reg. AML cells also have multiple strategies to evade being targeted and killed by T cells and natural killer (NK) cells (immune evasion). These interacting mechanisms result in T-cell exhaustion, anergy and apoptosis, and NK cell suppression.(5)

Early treatment might confer a better outcome. In addition, the European Conference on Infections in Leukaemia(6) recommend deferring chemotherapy/conditioning whenever possible to prevent dissemination. It is also recommended to check adenoviral load in plasma in these children to guide early treatment. Once the viral load is > 1000 copies/ml, initiating Cidofovir should be considered at a weekly dose of 5mg/kg/dose or 1mg/kg/dose thrice a week. Cidofovir/probenecid had been used successfully to treat adenovirus infection in immunocompromised patients after HSCT. Response to treatment and survival depends mainly on immune reconstitution/ withdrawal of immunosuppression and early treatment. Probenecid is prescribed along with cidofovir therapy to enhance plasma concentration of the antiviral drug and to prevent renal toxicity.(7) Although the first plasma adenovirus PCR titer in the current case was high (13200 (log 4.1) copies/mL), treatment with cidofovir only started upon getting a rising titer on the following week.
Disseminated disease is potentially fatal. An overall fatal outcome of 73% (83% among the immunodeficient, 60% in the immunocompetent) was reported. In immunocompromised patients, the ability of adenovirus to build up sufficient adenoviral particles in the bloodstream allows endothelial cell injury and progression to disseminated intravascular coagulopathy; another risk for the fatal outcome. (8)

There are no controlled trials confirming the efficacy of different antiviral agents in treating disseminated adenovirus infection in humans until now. Most of the available data on the successful treatment of adenovirus infection among immunocompromised patients is derived from case reports and small non-randomized studies among hematopoietic stem cell transplantation (HSCT) recipients. Before 1999 ribavirin was the only antiviral agent used to treat adenovirus infections with limited clinical response. (9) Gavin PJ et al reported successful use of intravenous ribavirin for severe adenoviral disease in two out of five immunocompromised children (solid organ and bone marrow transplant recipients, neonates, and children with immunodeficiency). (10) Oral Ribavirin was used successfully to treat adenovirus infection in an immunocompromised adult with myelodysplastic syndrome. (11) Cidofovir appears to be more active against adenoviral infections compared to ribavirin. Severe nephrotoxicity has been a major dose-limiting toxicity of Cidofovir. In their literature review, Neofytos D and his colleagues reported 19% mortality rate among 70 HSCT recipients with disseminated adenovirus infection who received at least 2 doses of Cidofovir compared to a mortality rate of 25-75%, reported previously in the literature. (12)

Focusing on the successful stories, Ramsey I et al reported successful treatment of disseminated adenoviral infection in 7 out of 10 adult recipients of HSCT of whom 4 had a reduction of their immunosuppression and 5 received antiviral therapy: cidofovir (3 patients), cidofovir followed by brincidofovir (1 patient), and brincidofovir alone (1 patient), while 2 survivors did not receive any antiviral medications. In addition, one patient received IVIg. (13) In a large cohort of pediatric recipients of HSCT, Bordigoni et al reported successful treatment of adenoviral infection in 8 out of 22 patients. Of those, ribavirin was successful in 3/13, cidofovir in 2/3, while combined ribavirin + cidofovir was successful in one patients, and combined ribavirin + donor lymphocyte infusion resulted in cure of two patients. (14)

Disseminated adenoviral infection is relatively rare in recipients of solid organ transplantation. Intravenous cidofovir along with the reduction of immunosuppression was used successfully to treat a child with disseminated adenoviral infection post liver transplantation. (15) Besides hemorrhagic cystitis, kidney transplant recipients might develop disseminated adenoviral infection that was treated successfully using a combined approach of reduction of immunosuppressants, IVIg, and antiviral therapy: cidofovir (16), or ribavirin for less nephrotoxicity. (17) Permpalung reported successful clinical and virological response among 5 solid organ transplant recipients with disseminated adenovirus infection with adjunctive use of IVIg + cidofovir in addition to reduction of immunosuppressants. (18) An orally bioavailable, lipid-ester derivative of cidofovir (Brincidofovir) with improved intracellular active drug delivery and less nephrotoxicity was used successfully to treat disseminated adenoviral infection in a combined liver-kidney transplant recipient, however, this drug is not available for compassionate use until now. (19) Using Adenovirus cytotoxic T-cells appear promising for the treatment of adenovirus infections in stem cell transplant recipients but it is not widely available. (20)

Conclusion

Disseminated adenoviral infection and hemorrhagic enterocolitis can be fatal in immunocompromised children with AML. Careful monitoring of clinical status and viral load, with early initiation of antiviral therapy in addition to appropriate supportive measures might be lifesaving.

References


