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Intravenous Ribavirin Therapy for Adenovirus Pneumonia

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Summary. We report on the effectiveness of intravenous ribavirin for severe adenoviral pneumonia in a 10-month-old male following orthotopic liver transplantation. On day 20 post-transplantation, he developed high fever, marked respiratory compromise, and hypoxemia. The chest radiograph showed bilateral pulmonary infiltrates. Samples of bronchoalveolar lavage fluid grew adenovirus, serotype 1. Marked clinical and radiological improvement was noted after intravenous ribavirin therapy. A prospective clinical trial is needed to determine the efficacy of ribavirin therapy for severe adenovirus disease. **Pediatr Pulmonol. 2000; 29:69–73.**

Key words: adenovirus; pneumonia; ribavirin; liver transplantations; infant.

INTRODUCTION

Adenovirus infections are ubiquitous and are responsible for a wide spectrum of illnesses in children, including respiratory tract infection and gastroenteritis.[1] Infections are often subclinical and result in mild disease. It is believed that 10% of pneumonias that require hospitalization in children are caused by adenoviruses.[2] Fulminant pneumonia in children[3] and epidemic disease with significant mortality (15%) in military recruits have been reported.[4] Fatalities from adenoviral infection are rare in the normal host. In contrast, this rather innocuous pathogen can be life-threatening in immunocompromised patients, and often has a poor outcome.[5]

No well-defined therapy for severe invasive adenovirus infections is currently available. Ribavirin is a relatively broad-spectrum antiviral agent with activity against adenoviruses in vitro and is thus potentially effective for the treatment of infections caused by this pathogen.[6] Intravenous (IV) ribavirin has been used in a small number of compromised patients with severe invasive adenovirus infection, and anecdotal evidence of clinical efficacy has been described.[7–15] We report a case of severe adenovirus pneumonia in an infant following orthotopic liver transplantation (OLT) successfully treated with IV ribavirin.

CASE REPORT

A 10-month-old male underwent an OLT for end-stage liver disease caused by extrahepatic biliary atresia. Immune suppression was achieved with prednisone (4 mg once daily) and tacrolimus (0.5 mg bid). Both donor and recipient were cytomegalovirus (CMV) seropositive. The post-transplant course was complicated by resistant *Serratia marcescens* sepsis requiring treatment with meropenem (60 mg/kg/day). Following transplantation, the patient was maintained on mechanical ventilation at low settings with an inspired oxygen fraction (Fio_2) of 25%.

On day 16 post-transplant, he developed leukopenia and thrombocytopenia. The low counts persisted and progressively declined. The white blood cell (WBC) count was in the range of $2.2–4.3 \times 10^9$/L; absolute neutrophil count was consistently above 1,000/mm^3. The platelet count was in the range of 20,000–64,0000/mm^3. Polymerase chain reaction (PCR) performed on a blood specimen was positive for CMV, and preemptive treatment with ganciclovir (5 mg/kg every 12 h) plus CMV-specific intravenous immune globulin was begun.

On day 20 post-transplant, while on meropenem and immunosuppressive therapy, he developed a high fever up to 39.9°C. Blood and urine cultures were obtained and vancomycin was empirically added.

On day 23 post-transplant, fever persisted and the infant developed acute respiratory distress with severe hypoxemia requiring increased ventilator support. Physical examination revealed a critically ill infant with a tem-

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TABLE 1—Hematologic Laboratory Values

Parameter	Value	Normal range
Hemoglobin (gm/dL)	11.1	10.0–13.5
Hematocrit (%)	33	30–41
Mean corpuscular volume (μm^3)	87	75–98
WBC count (per mm^3)	3,700	5,000–16,000
Differential count (%)		
Neutrophils	28	15–35
Band forms	39	6–13
Lymphocytes	19	41–73
Monocytes	11	0–10
Platelet count (per mm^3)	34,000	150,000–450,000
Prothrombin time (sec)	11.8	9.3–10.9
Partial-thromboplastin time (sec)	35.5	24.8–34.7
D-dimer (ng/mL)	500–1,000	<250
Fibrinogen (mg/dL)	169	158–398

TABLE 2—Liver function test values

Parameter	Value	Normal range
Protein (g/dL)	3.9	5.9–7.0
Albumin (g/dL)	2.0	3.4–4.2
Bilirubin (mg/dL)		
Total	1.2	0.6–1.4
Conjugated	0.1	0–0.3
Lactate dehydrogenase (U/L)	628	500–950
Alkaline phosphatase (U/L)	145	145–320
Aspartate transaminase (U/L)	26	18–53
Alanine transaminase (U/L)	18	5–45
γ-glutamayl transpeptidase (U/L)	44	8–78

perature of 40°C, heart rate of 160 beats/min, and blood pressure of 105/60 mm Hg. He was ventilated with an Fio_2 of 60% and a ventilator rate of 30/min, and he required high peak inflating pressures of 35 cm H_20 and peak end-expiratory pressure of 6 cm H_20. Flaring of nostrils, with subcostal and intercostal retractions were noted. Respiratory examination was remarkable for diffuse, coarse breath sounds with soft wheezes and inspiratory crackles throughout both lung fields. The abdomen was soft with evidence of hepatosplenomegaly.

The results of the hematological and liver function tests are shown in Tables 1 and 2, respectively. Serum electrolytes, blood urea nitrogen, creatinine, and glucose were normal. Tacrolimus serum levels ranged from 5–10 ng/mL. An arterial blood gas measurement at an FiO_2 of 60% revealed a pH of 7.26, Pco_2 of 70 mm Hg, Po_2 of 49 mm Hg, and bicarbonate of 28 mmol/L. Blood and urine cultures obtained on multiple occasions were sterile. The initial chest radiograph showed bilateral consolidation with air bronchograms and no evidence of pleural effusion or pneumothorax (Fig. 1). Computed tomography of the chest revealed bilateral alveolar densities with air space consolidation.

On day 24 post-transplant fever rose to 40°C and respiratory failure worsened, despite increased ventilator support and an FiO_2 of 70%. A flexible bronchoscopy with bronchoalvolar lavage (BAL) was performed. A direct viral examination of the BAL fluid sample and a nasopharyngeal (NP) aspirate were positive for adenovirus. Viral cultures later grew adenovirus, subsequently identified as adenovirus serotype 1. Additionally, BAL specimen cultures were positive for CMV (PCR, shell vial, and viral culture) but negative for bacteria, mycobacteria, fungi, *Legionella* spp., and *Norcardia* spp. Silver stains were negative for *P. carinii*. Persistent fever and a transient rise in γ-GGT to 90 U/L on day 26 post-transplant raised concerns of early rejection. A liver biopsy was performed which showed no evidence of rejection or infection; viral culture and PCR were negative for CMV, and no viral inclusions or cytopathic changes were noted for CMV or adenovirus. Repeat liver enzymes and serum bilirubin values were normal. Epstein-Barr virus PCR from a blood sample and serology were negative.

A probable diagnosis of adenovirus pneumonia was made, and IV ribavirin was considered because the patient continued to be critically ill with worsening respiratory failure despite ganciclovir therapy. On day 27 post-transplant, following approval from the Food and Drug Administration and the institutional review board

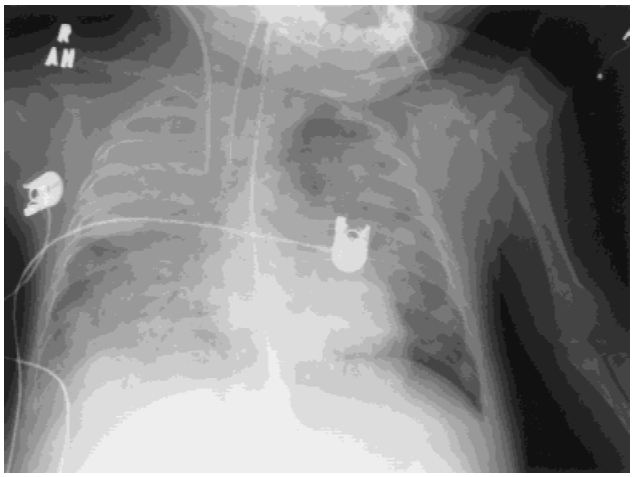

Fig. 1. Chest radiograph, showing bilateral consolidation with air bronchograms consistent with severe pneumonia.

Abbreviations

AIDS	Acquired immune deficiency syndrome
BAL	Bronchoalveolar lavage
CMV	Cytomegalovirus
FiO_2	Fraction of inspired oxygen
GGT	Glutamayl transpeptidase
IG	Immunoglobulin
IV	Intravenous
NP	Nasopharyngeal
OLT	Orthotopic liver transplantation
Pco_2	Partial pressure of carbon dioxide
PCR	Polymerase chain reaction
Po_2	Partial pressure of oxygen
WBC	White blood cell

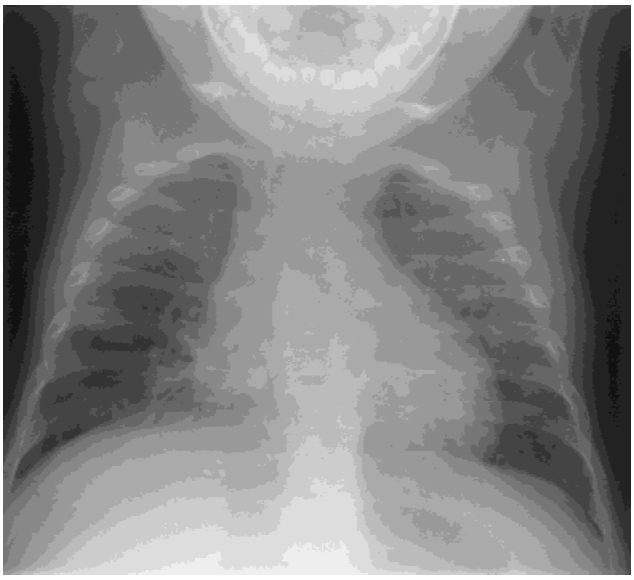

Fig. 2. Chest radiograph, showing dramatic resolution of pneumonia following ribavirin therapy.

and informed consent from the parents, a 7-day course of IV ribavirin was given according to an experimental-use protocol: a loading dose of 33 mg/kg, then 16 mg/kg q 6 h for 4 days, and 8 mg/kg q 8 h for 3 additional days. IV ribavirin was obtained as an investigational agent on compassionate plea basis from ICN Pharmaceutical (Costa Mesa, CA). The dosage schedule was based on the prospective, double-blind, placebo-controlled clinical trial of IV ribavirin in the therapy of hemorrhagic fever with renal syndrome.[16] All immunosuppressive therapy consisting of prednisone and tacrolimus was stopped on day 28 post-transplant. Immunosuppressive therapy was resumed after intravenous ribavirin was discontinued.

A dramatic response in the infant's clinical condition was noted; fever resolved by day 2 of ribavirin treatment. Respiratory failure improved rapidly and by day 7 of therapy, the infant required only 30% Fio_2. The infant was extubated 2 days after completion of treatment. A tracheal aspirate on day 4 of ribavirin therapy and an NP aspirate obtained a week later were negative for adenovirus. Repeat chest X-rays showed significant improvement on day 8 of therapy and dramatic resolution on day 41 post-transplant (Fig. 2). No adverse effects of IV ribavirin therapy were noted.

The infant was treated with meropenem, ganciclovir, and CMV-IGIV infusions for 3 weeks. Repeat CMV PCR from a blood sample was negative. The WBC and platelet counts returned to normal by day 32 post-transplant. On day 48 post-transplant, he was discharged. One month after discharge, he was asymptomatic.

DISCUSSION

There is increasing evidence implicating adenovirus infection as a cause of serious disease in the immunocompromised host, particularly in bone marrow and solid organ recipients, primary immunodeficiency disorders, and patients with acquired immune deficiency syndrome (AIDS).[5] Although the lungs are frequently affected in all cases, the primary site of disease in compromised hosts varies according to the underlying conditions. A wide spectrum of serious clinical syndromes caused by adenovirus has been reported, including fatal pneumonia, hepatitis, hemorrhagic cystitis, and nephritis in bone marrow transplant recipients,[17,18] gastrointestinal tract disease, including hepatitis, pancreatitis, and gastrointestinal hemorrhage in liver transplant recipients,[19–21] and disseminated disease associated with hepatic necrosis in patients with severe combined immunodeficiency and AIDS.[22] A fulminant sepsis-like picture with high fever and multiorgan involvement has been reported.[23] In most series, children are more likely to develop adenovirus disease than adults.[21]

About 10% of pediatric liver transplant recipients develop adenovirus infection.[19] Serotypes 1,2, and 5 are most commonly implicated; hepatitis in the transplanted organ is the predominant clinical manifestation.[19–21] If the infection becomes disseminated, mortality is high, with reported case fatality rates of 50–83%.[5,21] The median time from transplantation until isolation of adenovirus in one series of pediatric liver transplant recipients was 25.5 days, ranging from 4–69 days.[19] The use of immunosuppressive drugs or broad-spectrum antibiotics, prolonged hospitalization, multiple invasive diagnostic and therapeutic procedures, and surgical interventions are possible risk factors for invasive adenovirus disease.[19,21]

Treatment options are limited for severe adenoviral disease, with no recognized generally effective therapy. Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), a structural analog of guanosine, is a broad-spectrum antiviral agent. It has in vitro activity against a wide range of DNA and RNA viruses, including adenoviruses.[6] Review of the English language literature revealed 7 cases (including the present case) of successful treatment of adenovirus infection with IV ribavirin in children (Table 3).[7,8,11,14,15,21] One patient was immunocompetent.[21] The clinical syndromes included hemorrhagic cystitis,[7,8] gastroenteritis,[11] pneumonia,[14] and disseminated disease.[15,21] Five cases were receiving supplemental immunosuppressive therapy at the onset of adenovirus infection. Disseminated adenovirus disease may be accompanied by polymicrobial infections.[21] In the present case, severe adenovirus pneumonia occurred at a time of further suppressed immunity, as suggested by the presence of concurrent CMV infection. However, the role of concomitant viral or bacterial infections in precipitating more severe adenovirus disease is unclear. Clinical response to ribavirin therapy was dramatic, and clearance of adenovirus infection was documented in all

TABLE 3—Intravenous Ribavirin Therapy for Adenovirus Disease in Children[1]

Case no.	Age/ gender	Underlying condition	Clinical syndrome	Site of isolation (adenovirus type)	Coinfection (pathogens)	Risk factors	Therapy (duration)	Reference no.
1	14 mo/M	ALL	Disseminated disease	Urine, NP, blood (1)	None	Chemo	21 d	15
2	3 yr/M	Wiskott-Aldrich syndrome, BMT	Gastroenteritis	Colon stool (NA)	Gastroenteritis (rotavirus)	Prednisone, GVHD	10 d	11
3	8 mo/M	SCID, BMT	Pneumonia	BAL, NP, stool (31)	None	CSA	14 d	14
4	9 yr/M	AML, BMT	Hemorrhagic cystitis	Urine (NA)	None	Prednisone, CSA, GVHD	9 d	7
5	8 yr/M	ANLL, BMT	Hemorrhagic cystitis	Urine (NA)	None	Prednisone, Chemo, GVHD	8 d	8
6	21 mo/M	None	Disseminated disease	Blood, respiratory tract, stool, pleural fluid conjunctiva (7)	None	None	8 d	21
7	10 mo/M	Biliary atresia, OLT	Pneumonia	BAL, NP (1)	Sepsis (*S. marcescens*), CMV viremia	Prednisone, FK506	7 d	Present case

[1]ALL, acute lymphoblastic leukemia; BAL, bronchoalveolar lavage; BMT, bone marrow transplantation; Chemo, chemotherapy; CSA, cyclosporine; GVHD, graft vs. host disease; MTX, methotrexate; NP, nasopharyngeal; NA, not available; OLT, orthotopic liver transplantation; mo, months; yr, years; d, days; M, male.

listed patients. In the majority of cases, IV ribavirin was administered early in the course of illness. Additionally, nebulized ribavirin was used in one case.[21] Immunosuppressive therapy was discontinued in all cases.[20] Because ribavirin accumulates in erythrocytes, hemolytic anemia is the only significant side effect; it is directly dose-related and does not occur until the second week of treatment. [24] In our patient, no adverse effects were noted with ribavirin therapy. The source of adenovirus infection remains unclear. Latency is a known characteristic of adenovirus infection.[25] Infection from reactivated latent adenovirus has been shown in bone marrow and liver transplant recipients.[16,26] Donor organ-associated transmission and nosocomial infection have also been implicated in liver transplant recipients.[27,28]

At present, there are limited therapeutic options for invasive adenovirus disease, and early diagnosis in conjunction with prompt discontinuation of immunosuppression remains the best strategy. Virus isolation from affected organs provides the most conclusive evidence of infection in the context of disseminated adenoviral disease.[21] Adenovirus is readily isolated in specimens from multiple sites, particularly respiratory secretions, stool, and affected organs. Although PCR has shown promise for the rapid detection of adenovirus infections, it lacks sensitivity of culture at present.[1] Furthermore, viremia and viral excretion in respiratory or gastrointestinal secretions are significantly more common and prolonged in immunocompromised patients; therefore, adherence to standard infection control practices is crucial to prevent nosocomial outbreaks.[21]

In view of the patient's poor prognosis, we decided to treat with IV ribavirin. Following the initiation of therapy there was prompt resolution of fever and rapid improvement in oxygenation. It is possible his recovery was due to spontaneous resolution of adenoviral pneumonia assisted by discontinuation of immunosuppressive therapy. However, the speed and timing of his recovery were related to the initiation of ribavirin therapy, and suggest that it did play a part. The therapeutic success in our patient is anecdotal as in other reported cases. Failures have been reported,[29,30] and the outcome has been poor despite antiviral therapy in neonates with disseminated disease.[21,31] Prospective studies addressing the role of IV ribavirin therapy in severe adenovirus disease are warranted because mortality without treatment is very high, especially in immunocompromised patients.

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