Neonatal Adenovirus Infection Complicated by Hemophagocytic Lymphohistiocytosis Syndrome

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Two infants with disseminated adenoviral infections are described. Both these infants had a similar clinical course and were also diagnosed with secondary hemophagocytic lymphohistiocytosis (HLH). Previous reports of immunocompromised adults with adenovirus-associated HLH are in the literature; however, this is the first report that we are aware of with this pathology occurring in infants. These cases are used to demonstrate the importance of thinking about HLH in patients who are diagnosed with adenovirus and exhibit prolonged fevers that are unresponsive to antimicrobial agents with hepatosplenomegaly and cytopenias.

Although adenovirus infections can occur at all ages, >80% of infections occur among children <4 years old.[1] A wide spectrum of clinical manifestations exist, ranging from self-limited respiratory or gastrointestinal disease to disseminated disease requiring extracorporeal membrane oxygenation (ECMO) therapy.[2,3] Adenovirus in the neonatal period carries great significance because mortality rates exceed 50% for adenoviral pneumonia[3] and 85% for disseminated disease.[3–6] In a cohort of 37 neonates with adenovirus infection over a 17-year period, 22% required ECMO support; all 8 infants had disseminated disease, with 6 infants eventually succumbing to their illness (75%).[1] We present the clinical course of 2 neonates who were diagnosed with disseminated adenovirus with rapid clinical deterioration because of virus-associated hemophagocytic lymphohistiocytosis (HLH). Both developed pediatric acute respiratory distress syndrome and cardiovascular failure, ultimately succumbing to their illness despite prolonged ECMO support. These cases represent the potential consequences of an uncontrolled and ineffective immune response during a neonatal adenoviral infection. This case report was referred to our institutional review board, which deemed that case reports are not research. Health Insurance Portability and Accountability Act documents were received and signed by each family, and families were contacted by telephone by the principal investigator to confirm their knowledge of the plan to report the cases devoid of protected health information.

CASE 1

A 10-day-old girl presented to the emergency department (ED) with a fever of 103°F and irritability. She was born by spontaneous vaginal delivery at 39 weeks' gestation to a group B streptococcus–positive mother. The mother received appropriate antibiotics, and the infant was discharged on the third day of life. An ED examination was unremarkable, and significant laboratories included a total white blood cell count of 22.5 ×

abstract

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10^9/L. She was admitted and started on broad-spectrum antimicrobial agents after blood, urine, and cerebrospinal fluid cultures were obtained. Culture results remained negative; however, on hospital day 2, the patient developed progressive respiratory failure requiring endotracheal intubation. Repeat chest radiographs demonstrated perihilar bronchial streaking, and viral nasopharyngeal swab results were positive for adenovirus. Because of progressive respiratory failure with concomitant cardiovascular collapse, she was transferred to our institution for venoarterial extracorporeal membrane oxygenation (VA-ECMO) on hospital day 6 and required full cardiopulmonary support (flows of 150 mL/kg per minute). Further investigation into the etiology of the patient's progressive multiorgan dysfunction syndrome demonstrated a systemic adenovirus infection with a serum adenovirus polymerase chain reaction (PCR) of 2.8 × 10e8 DNA copies/mL. Additionally, on the day of transfer to our institution, the patient had an increased ferritin level of 24 132 ng/mL (normal value: 6–155 ng/mL) and was also found to have declining cell counts, including the following: thrombocytopenia (platelets: 106 K/μL), anemia (9.4 g/dL), and hypofibrinogenemia (fibrinogen: <25 mg/dL) concerning for HLH. Cidofovir was initiated for the treatment of adenoviremia. Additional laboratory investigations for HLH were performed, showing an elevated soluble interleukin-2 (IL-2) receptor level at 5156 U/mL, absent natural killer (NK) cell activity, and a low fibrinogen level. Therefore, she met criteria for HLH, fulfilling 5 of the 8 HLH criteria: fever, a ferritin level of ≥500 ng/mL, hypofibrinogenemia (≤150 mg/dL), soluble IL-2 receptor >2400 U/mL, and low or absent NK cell activity (Table 1). The treatment of HLH was not initiated because of a concern for immunosuppression in the setting of a disseminated adenoviral infection while being anticoagulated on VA-ECMO.

TABLE 1 Diagnostic Criteria for HLH, Diagnosis Requires 5 of the Following 8 Findings

Diagnostic Criteria
Fever of ≥38.5°C
Splenomegaly
Peripheral blood cytopenia with at least 2 of the following: hemoglobin of <9 g/dL (for infants <4 wk old, hemoglobin of <10 g/dL), platelets of <100 000/μL, and an absolute neutrophil count of <1000/μL
Hypertriglyceridemia (fasting triglycerides: >265 mg/dL) and/or hypofibrinogenemia (fibrinogen: <150 mg/dL)
Hemophagocytosis in bone marrow, spleen, lymph node, or liver
Low or absent NK cell activity
Ferritin >500 ng/mL (ferritin >3000 ng/mL is more indicative of HLH)
Elevated soluble IL-2 receptor α of 2 SDs above age-adjusted, laboratory-specific norms

Adapted from Henter J-I, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr. Blood Cancer. 2007;48(2):124–131.

Her course was complicated by rapidly worsening pulmonary function and fluid overload, requiring continuous renal replacement therapy. Despite both adenovirus and ferritin levels declining (Fig 1), her pulmonary function continued to deteriorate, and a chest computed tomography (CT) scan showed progressive cystic changes (Fig 2). She developed evidence of pulmonary hypertension on ECMO day 15, with an echocardiogram demonstrating suprasystemic right-ventricular pressure that was unresponsive to inhaled nitric oxide. She eventually developed a nearly occlusive thrombus in the inferior vena cava and progressive and refractory left-ventricular dysfunction. ECMO support was electively discontinued on ECMO day 38.

CASE 2

A 9-day-old girl presented to an ED because of a fever of 102°F and poor feeding. She was born by spontaneous vaginal delivery at 40 weeks' gestation to a group B streptococcus–positive mother, who received appropriate antibiotic treatment. She was discharged on the third day of life. On ED presentation, she was tachypneic, febrile, and hypoxic, requiring 1 L of nasal cannula. She was admitted and started on broad-spectrum antimicrobial agents after blood, urine, and cerebrospinal fluid cultures were obtained. All culture results remained negative; however, she developed progressive respiratory failure, requiring endotracheal intubation on hospital day 2. A chest radiograph revealed left-lower lobe consolidation with diffuse peribronchial thickening. She exhibited progressive cardiorespiratory failure and was subsequently transferred to our institution for VA-ECMO on hospital day 3 and required full cardiopulmonary support (flows of 150 mL/kg per minute). A respiratory viral panel result was positive for adenovirus with a serum adenoviral PCR of 1.3 × 10e8 million DNA copies/mL, and she was initiated on cidofovir for treatment of disseminated adenovirus. Her ferritin level was elevated at 19 700 ng/mL (normal value: 6–155 ng/mL), with hepatosplenomegaly being present on examination. An additional laboratory investigation confirmed HLH with IL-2 >3000 U/mL, depressed-to-absent NK cell function, and hypofibringemia (fibrinogen: 50 mg/dL). She was treated with high-dose dexamethasone, but additional immunosuppression was not initiated because of concern for significant bone marrow suppression in an infant with disseminated adenovirus and in the setting of anticoagulation on ECMO. A follow-up echocardiogram on hospital day 19 revealed a severely dilated left-anterior descending coronary, and she was given intravenous immunoglobin because of the similarity of her findings to Kawasaki disease (KD). Throughout

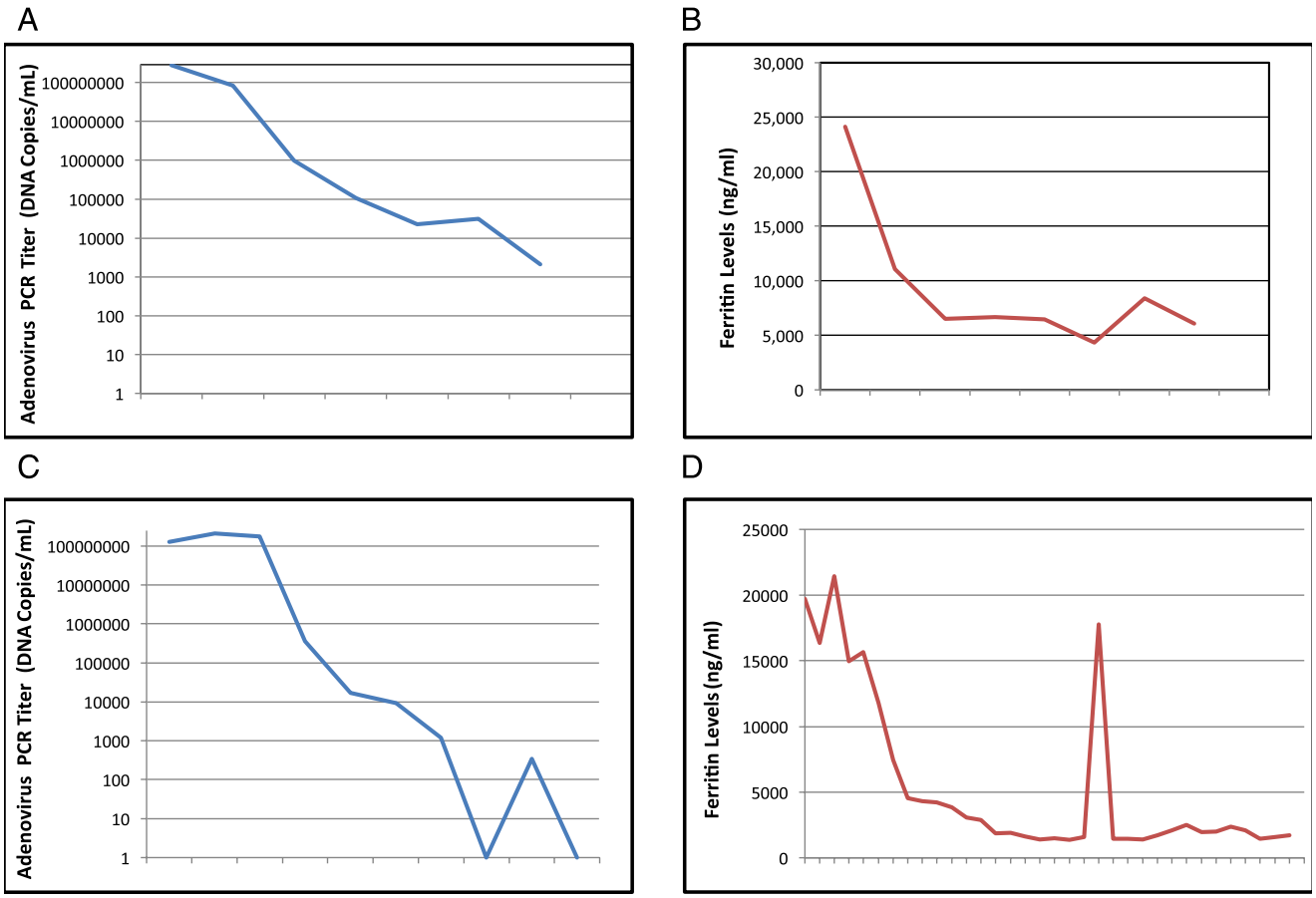

FIGURE 1

A, A time-sequential representation of the adenoviral titers of case patient 1. B, A time-sequential representation of the ferritin values of case patient 1. C, A time-sequential representation of the adenoviral titers of case patient 2. D, A time-sequential representation of the ferritin values of case patient 2.

her admission, her adenovirus titers and markers of inflammation continued to trend down (Fig 1); however, she continued to decline from a cardiopulmonary standpoint. She developed severe, recalcitrant pulmonary hypertension and chest CT scan revealed severe interstitial disease with multiple cystic changes and a diffuse, ground-glass appearance of the lungs (Fig 2). She suffered from frequent infections and ultimately an acute pulmonary hemorrhage. Given her progressive decline, she was electively removed from ECMO support on hospital day 52. Her family consented to a limited autopsy (Fig 3) that confirmed a dilated left atrium with dilated coronary arteries, cystic changes to the entire lung with parenchyma diffusely exhibiting fibrosis, hemorrhage, and granulation tissue.

DISCUSSION

Neonatal adenovirus is associated with poor morbidity and high mortality, particularly with disseminated disease. The cases presented highlight the treatment complexities for disseminated adenovirus and the consequences of virally mediated inflammation and vascular dysregulation in neonatal adenoviral infections.

Currently, the antiviral treatment of disseminated adenovirus remains controversial, with no Food and Drug Administration–approved therapies.[1] In patients who are immunocompromised, the use of broadly acting antiviral agents (such as ganciclovir, ribavirin, and cidofovir) have shown variable results.[7] In both of our cases, adenovirus-associated HLH was diagnosed concurrently with active adenoviral disease. This posed a clinical dilemma because the treatment of HLH with steroids and/or chemotherapy agents also poses inherent risks during a systemic viral infection. Fortunately, case patient 2 exhibited a remarkable decline in the viral load despite the immunosuppression she received.

HLH is a life-threatening condition that occurs as a genetic disease or secondary to an acute process, such as an infection, rheumatologic disease, or malignancy.[8] It is described as a hyperinflammatory state with a pathologic accumulation and stimulation of monocytes and/

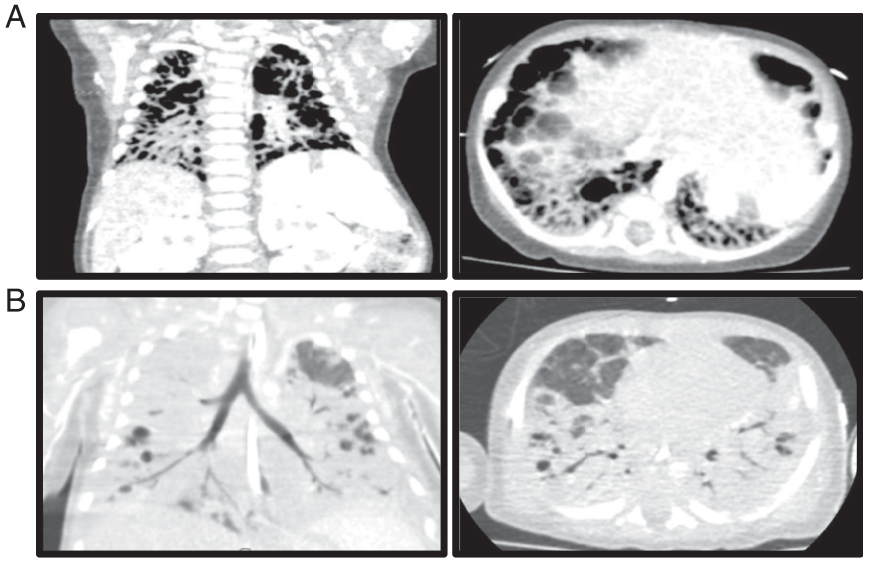

FIGURE 2
A, CT scan images of case patient 1 demonstrating extensive patchy airspace consolidation superimposed on multifocal areas of cystic formation and ground-glass attenuation. Additionally, there are various areas of bronchiectasis throughout the lungs. B, Chest CT scan images of case patient 2 demonstrating extensive bilateral pulmonary consolidation with numerous small, cystic areas that are compatible with pneumatoceles and necrotizing pneumonia.

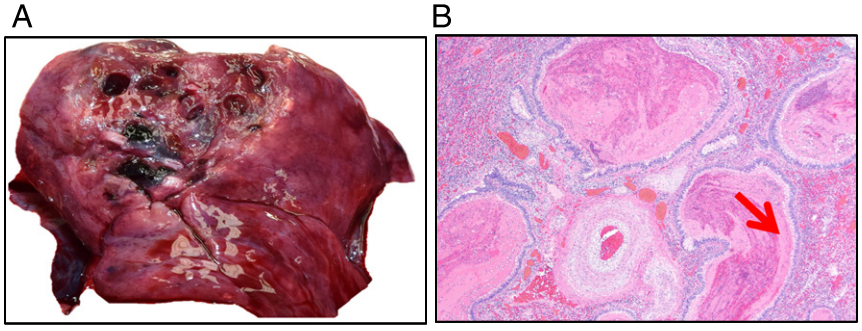

FIGURE 3
Autopsy images from case patient 2. A, A cut section of the lung with cysts representing dilated bronchi and some hemorrhage. B, Dilated bronchi with luminal hemorrhage and surrounding parenchyma with granulation tissue formation. The arrow points to a thick pulmonary artery with intimal fibrosis and luminal narrowing.

or macrophages, resulting in the phagocytosis of blood cells in the bone marrow, liver, and spleen.[9] Numerous viruses have been associated with secondary HLH; however, adenovirus-associated HLH is unusual.[10] There have been few reports in which researchers describe adenovirus pneumonia complicated with HLH,[9,11–14] but in patients who are well beyond the neonatal period, 5 infants (age range: 6–11 months) have been reported.[15,16] Other reports in children include a 2 year old, a 15 month old, and a 12 year old.[9,13,17] In adults, adenovirus-associated HLH has been diagnosed in patients who received stem cell transplants and those who are immunocompromised.[7,18]

We conclude that adenovirus-related HLH is rare; however, it should be considered in patients who are diagnosed with adenovirus and exhibit prolonged fevers that are unresponsive to antimicrobial agents, hepatosplenomegaly, and/or cytopenias.[5,19] This is of particular importance because secondary HLH may respond to immunomodulatory therapeutic agents. No certain protocols have been established; however, researchers in several studies have shown the beneficial effect of intravenous immunoglobin.[20] Other therapies, such as dexamethasone, cyclosporin A, etoposide, and methotrexate, could also be considered depending on the clinical scenario.[10,11,15,21]

The discovery of a severely dilated coronary in the second case is perhaps further evidence of immunologic and vascular dysregulation in neonatal adenoviral infections. The diagnosis of KD is based on meeting clinical criteria, including fever for at least 5 days and 4 of the following: erythema and cracking of lips, bilateral bulbar conjunctival injection without exudate, rash, erythema and edema of the hands and feet, and cervical lymphadenopathy. KD is associated with panarteritis of medium-sized arteries, especially the coronaries.[4,22,23] Incomplete KD is suspected with prolonged fevers, elevated inflammatory markers, and specific laboratory abnormalities or with positive echocardiogram findings. Although case patient 2 did not meet clinical criteria for KD, one must consider that ECMO may alter clinical characteristics, such as the development of fevers and platelet, fibrinogen, and hemoglobin values. Additionally, it is difficult to diagnose in this age group because infants <6 months of age are most likely to develop prolonged fever without other clinical criteria for KD but are at risk for developing coronary artery abnormalities.[23] Coincidentally, HLH and KD share some similar pathophysiology on the basis of the abnormality of immune and inflammatory responses.[24] In a disseminated viral infection, cytokines or inflammatory mediators may cause vascular endothelial damage, which further cause

coronary artery complications that are similar to those that occur with KD.[22,25,26]

The patient in case 1 was treated for disseminated adenovirus with cidofovir but not with concomitant treatment for HLH; the patient in case 2 received cidofovir but additionally received treatment for HLH with Decadron and subsequent treatment for KD with methylprednisolone. Despite the medical management of adenovirus, both patients succumbed to severe pulmonary and vascular injury that ultimately led to severe pulmonary hypertension, biventricular failure, and death. In expressing the features of HLH and KD, these cases are used to demonstrate the importance of recognizing a dysregulated immune response in neonatal adenoviral infections.

ABBREVIATIONS

CT: computed tomography
ECMO: extracorporeal membrane oxygenation
ED: emergency department
HLH: hemophagocytic lymphohistiocytosis
IL-2: interleukin-2
KD: Kawasaki disease
NK: natural killer
PCR: polymerase chain reaction
VA-ECMO: venoarterial extracorporeal membrane oxygenation

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