CASE REPORT

Disseminated adenovirus infection causing severe ARDS

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SUMMARY

A previously healthy young man with a rare genetic condition presented with severe acute respiratory distress syndrome secondary to pneumonia with septic shock. He did not improve with conventional therapy for his known causal organism thus prompting further workup. He was found to be profoundly immunosuppressed raising our suspicion for atypical organisms. A bronchoalveolar lavage sample was positive via PCR for adenovirus which we suspect exacerbated a pre-existing bacterial pneumonia and led to a severe and non-responsive respiratory failure. His serum adenovirus load was markedly elevated. Treatment was started once the diagnosis of disseminated adenovirus infection was made; however, at that time patient was suffering from refractory hypoxaemia, respiratory acidosis, right heart failure and septic shock. Despite maximal supportive measures our patient ultimately expired over the course of 6 days.

BACKGROUND

This case highlights the need to reassess the working diagnosis when there is a lack of clinical improvement with appropriate treatment or when the pattern of the suspected causal organism does not correlate with the severity of illness. In such instances of severe infection investigating for underlying immunosuppression and atypical pathogens, including viruses, can provide important diagnostic information thereby altering the course of illness.

CASE PRESENTATION

A 33-year-old man initially presented around the early summer time to an outlying hospital with shortness of breath. His history was notable for a chromosome 6p deletion syndrome and associated developmental delays. The patient's mother was the primary caregiver and revealed that for the past 7–10 days he had suffered from sinus drainage, cough productive of yellow sputum, fevers up to 103°F and shortness of breath. Early on his primary care provider had prescribed him a 7-day course of amoxicillin for presumed sinusitis which failed to resolve his symptoms. Prior to coming to our institution he was taken to an outside emergency department where the patient told his mother that he felt like he was 'drowning'. On arrival vitals were as follows: temperature was 103.2°F, blood pressure was 104/64 mm Hg, pulse was 133 bpm, respiratory rate was 22 breaths per minute and oxygen pulse oximetry was 63% on room air. Lung examination revealed bilateral wet

crackles. The patient was in severe respiratory distress and unable to provide any further history.

The haematocrit, haemoglobin level, platelet count, and results of coagulation and renal function tests were normal, as were blood levels of total protein, albumin, phosphorus, magnesium, calcium, troponin T, and B-type natriuretic peptide. His white cell count was normal at 8.8 with 89% granulocytes, 11% lymphocytes and 6.8% monocytes. His lactate was mildly elevated at 2. Hepatic function panel showed an elevation in serum transaminases aspartate transaminase/alanine transaminase 93/89, elevated alkaline phosphatase 336 and a total bilirubin of 1.6. An arterial blood gas was drawn on 100% non-rebreather mask that showed pH 7.48, pCO₂ 49 and pO₂ 69. A chest radiograph had bilateral patchy infiltrates and a left lower lobe consolidation (figure 1). Cultures of sputum, blood and urine were obtained while he was started on broad-spectrum antibiotics with vancomycin and piperacillin-tazobactam. The patient was intubated at the outside hospital's emergency department for ongoing respiratory distress and transferred to our intensive care unit for further management.

On arrival to our medical intensive care unit the patient was on 100% oxygen with a positive end expiratory pressure of 10 cm H₂O with oxygen saturations in the low 90s. He was sedated and unresponsive on a fentanyl infusion. We performed a bronchoscopy with bronchoalveolar lavage (BAL) to the left lower lobe. During the procedure copious purulent secretions were noted within each of the subsegments of the left lower lobe. The differential on the fluid was 99% neutrophils and 1% lymphocytes with a negative Gram stain. Owing to right ventricular dilation seen on echocardiography (figure 2), there was some concern for pulmonary embolism, though a subsequent dedicated CT study was negative. His CT did reveal extensive nodular opacifications, diffuse tree-in-bud markings and a densely consolidated left lower lobe (figure 3). With the abnormal liver function tests we obtained a right upper quadrant ultrasound scan that was unremarkable aside from cholelithiasis with a small collection of pericholecystic fluid. There was ductal dilation while an incidental liver haemangioma was also noted.

By the second day of hospitalisation blood and sputum cultures from the outside hospital were growing pan-susceptible *Haemophilus influenzae*. We thus transitioned his antibiotics to ceftriaxone plus azithromycin. We maintained a conservative fluid strategy and kept his central venous pressure around 8–12 mm Hg that ultimately required

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Figure 1 Presenting anterior–posterior chest radiograph showing diffuse airspace opacities.

furosemide infusion. Initial bronchoscopy cultures obtained shortly after transfer were negative for bacterial pathogens. Despite empiric community-acquired pneumonia therapy, which was directed at his isolated *H. influenzae*, he continued to decompensate clinically. He became more difficult to oxygenate and ventilate in addition to worsening septic shock requiring vasopressors. As he met the criteria for severe acute respiratory distress syndrome as per the Berlin definition (eg, arterial oxygen tension/fractional inspired oxygen <100), he was prone and paralysed to improve oxygenation as well as mortality.^{1 2} He was also started on inhaled epoprostenol, three separate vasoactive medications (norepinephrine, vasopressin and dopamine), stress dose steroids and continuous renal replacement therapy for refractory respiratory acidosis and volume overload. Throughout his course he had persistent fever up to 103°F, copious purulent endotracheal secretions and diffuse bronchospasm with significant intrinsic positive end expiratory pressure further complicating his ventilator management. All of our initial culture data were negative aside from *H. influenzae* that grew at the transferring institution. Based on his clinical deterioration, particularly in the face of seemingly appropriately directed therapy of the only isolated pathogen we undertook a further workup for occult pathogens and possible underlying immunocompromise. We broadened our antimicrobial strategy to include vancomycin, piperacillin-tazobactam and liposomal amphotericin while sending additional tests for fungal and viral organisms off the serum and bronchial lavage fluid. For

Figure 2 Echocardiogram, parasternal short axis view showing flattened interventricular septum and a dilated right ventricle.

detecting viral pathogens in the immunosuppressed population our institution uses a multiplex PCR assay that detects over 10 different viral strains. In addition, HIV, cytomegalovirus and Epstein-Barr virus PCR studies were negative. All fungal studies including complement fixation and immunodiffusion assays were negative. Our workup included screening for T-cell subsets and immunoglobulin deficiency.

Results of immunological studies were notable for a decreased absolute CD4 lymphocyte count, but with a relatively preserved CD4:CD8 ratio and CD4 lymphocyte percentage. Additionally, there were undetectable levels of IgG, IgA and IgE, with low levels of IgM. Antibody titres to tetanus, diphtheria and pneumococcus were non-existent thus suggesting the diagnosis of common variable immunodeficiency (CVID). Intravenous immunoglobulin therapy was given to help bolster his immune response. Results of the aforementioned additional microbiological evaluation revealed a positive adenovirus C PCR from the BAL fluid. Notably, the respiratory viral panel taken as a nasal swab on admission despite using the same multiplex PCR assay as the BAL fluid was negative for adenovirus. Given concern for disseminated adenoviral infection in the setting of his immunocompromised state, cidofovir therapy was started and his serum was sent to an outside laboratory for adenovirus testing. Unfortunately, our patient further declined and ultimately expired late into the evening of his sixth hospital day after he had gotten his first dose of cidofovir. Postmortem his serum adenovirus PCR resulted at over 2 million copies/mL (reference range 500–2 000 000 copies/mL).

DISCUSSION

This case highlights some of the difficulties associated with recognising an undiagnosed immunosuppressive condition in the settings of acute (or critical) illness, particularly in adulthood. The patient's mother reported that despite being born 2 months premature and spending a week in the neonatal intensive care unit he was otherwise a healthy baby. Throughout childhood he received age-appropriate immunisations without any complication(s). He had no issues with chronic infections aside from occasional sinusitis requiring antibiotics about 1–2 times per year. He had no prior episodes of pneumonia or any other severe infection such as meningitis. He had no prior hospitalisations and was a healthy and active young man prior to presentation. He enjoyed being outdoors and camping; he also attended an adult day care several times per week and was an active participant. There was no family history of immune deficiency or autoimmune disease. The patient had a sister who was healthy. The patient had developmental delay and dysmorphic facial features (eg, low set ears) related to his chromosome 6p deletion syndrome. He walked around age 3 and started to talk in the first to second grade. He was seen by a genetics counselor in early childhood and was told that he had a deletion on chromosome 6 but that he needed no further follow-up.

Chromosome 6p deletion syndromes are rare entities only described in isolated cases. The main features being developmental delay, craniofacial malformations, hypotonia, and congenital defects of the heart and kidney.^{3–5} Experts suggest individuals with this deletion should have an ophthalmological examination, cardiac evaluation, head imaging, renal ultrasound scan and formal hearing evaluation.⁶ To the best of our knowledge, there is no association between this syndrome and immunodeficiencies or chronic lung conditions.

Adenovirus infections are usually self-limited in the immunocompetent host with mild upper respiratory, gastrointestinal and conjunctival disease.⁷ The pathogen is more common in

Figure 3 CT with intravenous contrast bolus, representative axial slices showing diffuse nodular opacities and dense left lower lobe consolidation.

children where around 10% of all mild upper respiratory illnesses are likely attributable to adenovirus.⁸ Disseminated adenovirus is recognised as a cause of significant morbidity and mortality in immunocompromised patients such as recipients of haematopoietic stem cell transplants and solid organ transplants.⁹ The entity carries a high mortality as was demonstrated in a case series at a paediatric hospital where the overall case fatality rate was over 70%.¹⁰ There are reported cases of adenovirus causing severe pneumonia in the immunocompetent population suggesting that it may be an oft overlooked pathogen.^{11 12}

Recently there have been small, localised outbreaks of pulmonary adenovirus infections described in Oregon and Illinois further highlighting the need to consider the pathogen in clinical practice.^{13 14}

The high mortality of disseminated adenovirus infections has prompted evaluating antiviral therapy. None of the available agents has been evaluated for efficacy in a prospective, randomised, placebo-controlled study. Regardless while no drug is approved for treating adenovirus infections, cidofovir is currently the agent of choice among bone marrow transplant recipients and solid organ transplant recipients. Cidofovir is a broad-spectrum antiviral agent to which all adenovirus subtypes are susceptible in vitro. Note that cidofovir has significant side effects including nephrotoxicity, myelosuppression and uveitis.¹⁵

Clinical outcome data from prior studies within the transplant community are encouraging as to the efficacy of cidofovir and its relative safety.^{16–19} In fact, within the immunosuppressed population some experts advocate for aggressive screening and pre-emptive treatment of adenovirus prior to the development of symptoms.^{16 20} Nevertheless cidofovir remains controversial as the clinical data are variable and there is a need for randomised controlled trials to better assess the therapeutic options.²¹ Brincidofovir, a new broad-spectrum antiviral derived from cidofovir, is a promising agent with good preliminary data in clinical trials. Investigators are also looking into harvesting antiadenovirus-specific T cells from healthy donors and infusing them back into infected patients. Future therapy may involve a combination of an antiviral and infusions of adoptive T cells for improved outcomes.²²

In our patient we suspected that the initial insult was a bacterial pneumonia secondary to *H. influenzae* that then left him susceptible to a viral process. In vitro studies have demonstrated the ability of *H. influenzae* to alter the respiratory epithelium and cause an exaggerated inflammatory response to a subsequent viral pathogen.²³ There have also been data to suggest a synergistic effect between adenovirus and *H. influenzae* in respiratory infections.^{24 25} A similar phenomenon, albeit in reverse order, occurs following influenza infections where patients develop secondary pulmonary infections with

encapsulated bacteria including *Streptococcus pneumoniae* and *Staphylococcus aureus*. At the molecular level recent data point to a dysregulated immune response induced by the influenza virus as opposed to alterations within the respiratory epithelium.²⁶ Another example can be seen with respiratory syncytial virus leading to a more severe *S. pneumoniae* infection via alteration of virulence genes.²⁷ Clearly there is a complex interplay between viral and bacterial pathogens within the lung milieu which is incompletely understood and remains an area of active investigation. Our patient become co-infected with two synergistic organisms, he also had an underlying immunodeficiency. Patients with CVID are more susceptible to respiratory infections due to the development of immunoglobulin deficiencies that leave them vulnerable to a wide range of organisms. Within the CVID population the prevalence of *H. influenzae* and adenovirus is unexpectedly high.²⁸ In addition, a recent study demonstrated that individuals with an abnormal humoral immunity are predisposed to invasive infections with *S. pneumoniae* or *H. influenzae*.²⁹

Our study highlights the importance of maintaining a broad differential in cases of severe pneumonia that do not respond to conventional antibiotic therapies. In patients with an invasive *H. influenzae* or *S. pneumoniae* infection that does not rapidly begin to recover following 24 hours of appropriate antibiotic coverage, screening for immunoglobulin abnormalities, given the known association, may be a reasonable proposition. With our patient there was a period of several days of clinical decline until we decided to look for an immunodeficiency. In addition, if there is a strong suspicion for adenovirus infection in an immunocompromised patient prompt antiviral therapy is warranted which at this point would be cidofovir. The most recent surviving sepsis campaign guidelines recommend early antiviral therapy in patients with septic shock of viral origin.³⁰ Ultimately, this case serves as a reminder for providers to maintain an appropriate clinical suspicion for immunodeficiency and co-infection, even in the context of common clinical syndromes and pathogens.

Learning points

- Maintain a broad differential in cases of severe pneumonia that do not respond to conventional antibiotic therapies. Adenovirus should be included in this differential.
- In patients with an invasive *Haemophilus influenzae* or *Streptococcus pneumoniae* infection that does not rapidly begin to recover following 24 hours of appropriate antibiotic coverage, screening for immunoglobulin abnormalities, given the known association, may be a reasonable proposition.
- If there is a strong suspicion for adenovirus infection in an immunocompromised patient prompt antiviral therapy is warranted.
- Maintain an appropriate clinical suspicion for immunodeficiency and co-infection, even in the context of common clinical syndromes and pathogens.

Contributors All authors were intricately involved in the case and contributed to the development of the manuscript. SJC was the intensive care unit fellow on the team directly taking care of the patient. He took the lead in drafting the case report and recruiting the assistance of other faculty. JAK was the attending physician who was directly taking care of the patient. She suggested the case be submitted to a journal and provided feedback regarding its presentation. JAD was the consulting

infectious disease specialist who helped to take care of the patient. He assisted SJC in revising the manuscript for submission and suggested certain thematic topics.

Competing interests None declared.

Patient consent Obtained.

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