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Fatal Adenovirus Pneumonia in an Immunocompetent Adult

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Abstract Adenovirus is a rare cause of severe respiratory disease in immunocompetent adults. Life-threatening infections are usually encountered in children and immunocompromised hosts, such as HIV/AIDS patients and transplant recipients. We present a case of adenovirus infection in a 64-year old woman who presented with unilateral rhinorrhea for two months and a one-week history of cough and malaise. She was intubated for urgent neurosurgical repair of a cerebrospinal fluid (CSF) leak. She rapidly developed severe pneumonia with acute respiratory distress syndrome. Broncheoalveolar lavage and stool were positive for adenovirus by polymerase chain reaction assay. No other clinically significant microbial pathogens were identified. Despite cardiopulmonary support with invasive mechanical ventilation, inhaled nitrous oxide and extracorporeal membrane oxygenation (ECMO), the patient did not survive. Our report highlights the need to consider adenoviral pneumonia as an etiology of acute respiratory distress syndrome with severe sepsis and multi-organ failure in immunocompetent adults. Current evidence for treatment of adenovirus pneumonia with antiviral agents and the role of ECMO is discussed.

Keywords: *adenovirus, pneumonia, respiratory failure, ribavirin, cidofovir, ECMO*

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1. Introduction

Adenovirus infection is usually associated with mild, self-limited upper respiratory illness. Severe or life-threatening infections are usually encountered in children and immunocompromised patients [1]. There are few reports of adenovirus causing severe disease or fatal acute respiratory distress syndrome (ARDS) in immunocompetent adults. We present a case of severe adenovirus infection in a woman who presented with mild respiratory symptoms and rapidly progressed to respiratory failure. Recent literature on the clinical presentation and management of adenovirus respiratory infection is reviewed.

2. Case Presentation

A 64 year-old African American woman presented to our emergency department with the complaint of clear rhinorrhea from the right nostril for two months. She also reported cough, generalized malaise and headache for one week. She had been treated for acute sinusitis with outpatient antibiotics two months prior to the onset of rhinorrhea without improvement. Her past medical history included diet-controlled diabetes mellitus, hypertension, chronic kidney disease and mild asthma. She denied tobacco use. On admission her temperature was 98.3^0F, heart rate 96 beats per minute, respiratory rate 15 breaths per minute, blood pressure 138/67 mmHg, and pulse oxygen saturation 99% on room air. Physical examination was normal except for clear watery discharge from the right nostril. Initial laboratory tests were remarkable for a white blood cell (WBC) count of 18.7 x 10^3 cells/mm^3, with 94% neutrophils and 4% lymphocytes; hemoglobin 10.3 g/dl, platelets 108 cells/mm^3, creatinine 2.9 g/dl and bicarbonate level 20 meq/l. C-reactive protein was elevated (105 mg/dl) and procalcitonin level was normal (0.38 ng/ml). Cardiac enzymes and lactic acid were normal. Urinalysis showed mild proteinuria, but was otherwise normal. HIV antigen-antibody test was negative. Chest radiograph showed minimal left basilar atelectasis (Figure 1).

Magnetic resonance imaging (MRI) brain without contrast showed no intracranial pathology. She was admitted to the neurosurgical intensive care unit for presumed cerebrospinal fluid (CSF) leak. On the first day of admission, she developed fever to 101^0F along with nausea, vomiting and worsening headache. She also developed worsening cough and hypoxemia (oxygen saturation of 87% on room air) that responded to nebulized albuterol and supplemental oxygen. She was empirically treated with high dose intravenous meropenem for possible central nervous system infection. Lumbar puncture was done and CSF studies were normal. Repeat chest radiograph taken 18 hours after her initial radiograph showed bilateral lung opacities, suggestive of pneumonia (Figure 2).

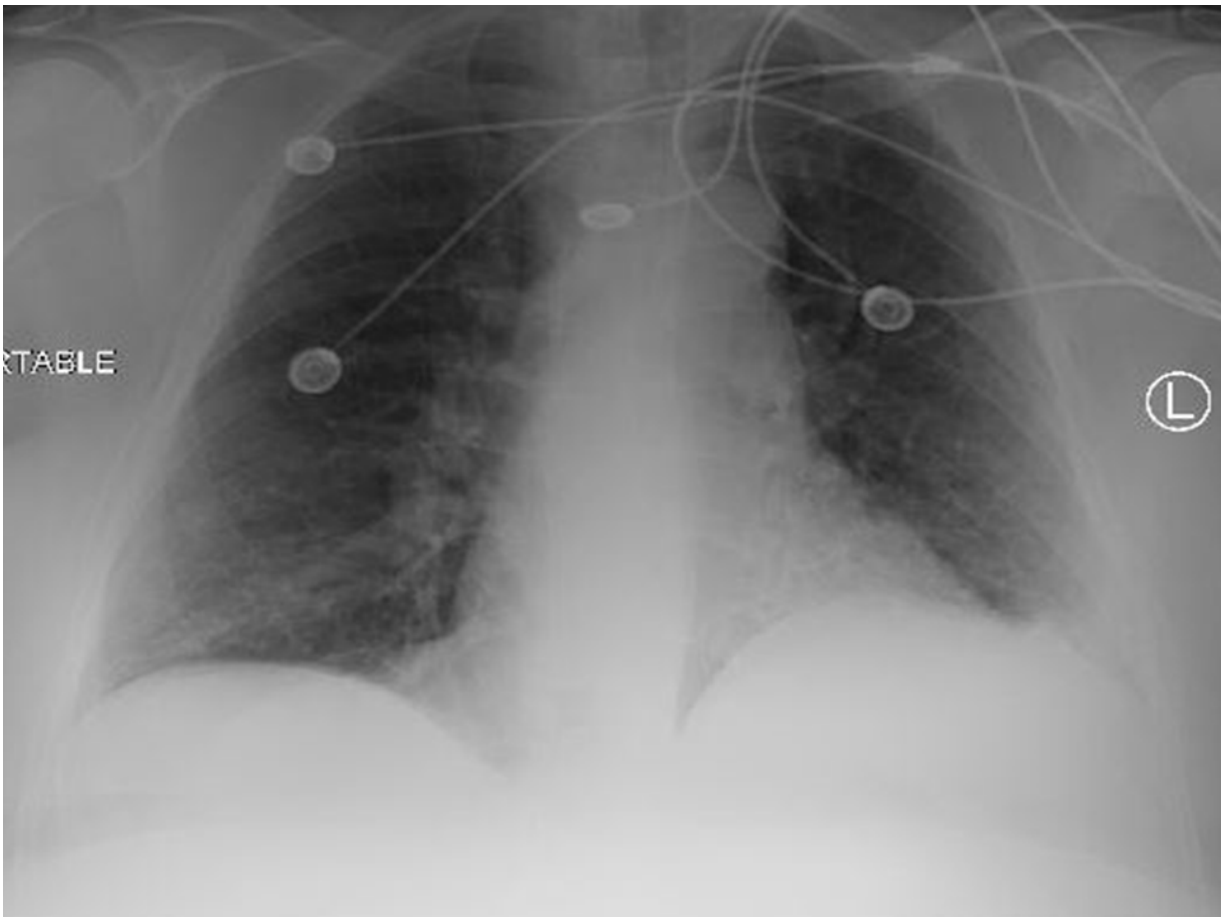

Figure 1. Chest radiograph of the patient on the first day of hospital admission, showing left basilar atelectasis with no infiltrates or consolidation

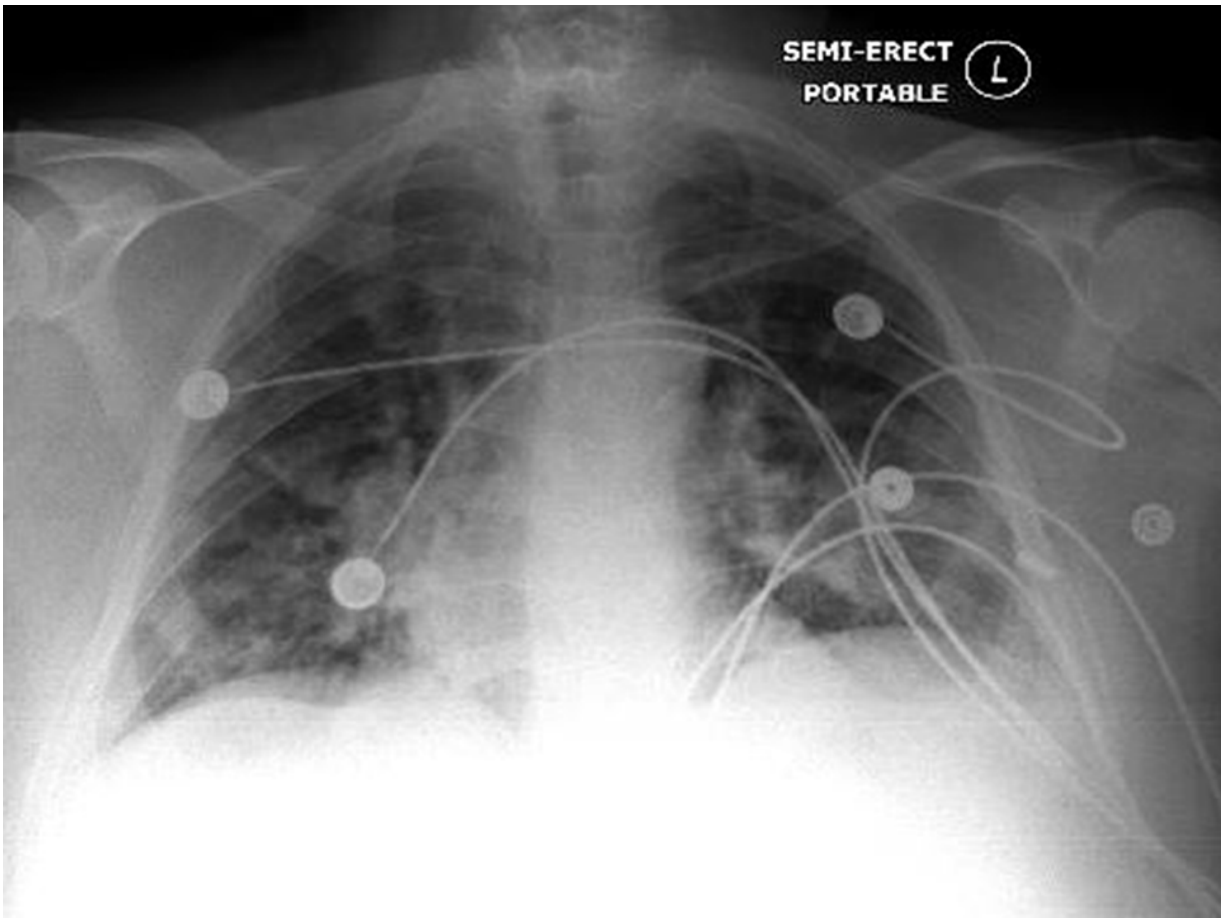

Figure 2. Repeat chest radiograph the next day, showing bilateral lung opacities, predominantly in the lower lung zones

She was intubated and underwent urgent operative endoscopic endonasal surgery for exploration and repair of a CSF leak. Resection of ethmoid and sphenoid encephaloceles, and repair of associated skull base defects was performed with placement of a lumbar drain. She was unable to be extubated post-operatively due to hypoxemic respiratory failure and had recurrence of fever to 103°F. Intravenous azithromycin and vancomycin were added for empiric treatment of pneumonia. Broncheoalveolar lavage was performed with sampling for bacterial and fungal cultures, and respiratory pathogen virus panel polymerase chain reaction (PCR) assay. Subsequent chest radiographs demonstrated worsening bilateral lung opacities. Repeat procalcitonin on the third hospital day was elevated at 13.4 ng/ml. Aspartate aminotransferase (AST) was mildly elevated at 106 U/l. She became increasingly hypoxemic requiring 100% supplemental oxygen, consistent with severe acute respiratory distress syndrome. Inhaled nitrous oxide therapy was administered with no clinical improvement. Bacterial, fungal and mycobacterial sputum cultures and blood cultures were negative, as were Legionella and pneumococcal urine antigen tests. The respiratory pathogen virus panel and stool PCR assays for adenovirus were reported as positive. The patient developed oliguric renal failure requiring continuous veno-venous hemodialysis. Due to respiratory failure refractory to medical management and cardiogenic shock, veno-venous extracorporeal membrane oxygenation (ECMO) was initiated. Within ten minutes of starting ECMO the patient developed bradycardia, followed by cardiac arrest. Cardiopulmonary resuscitation was unsuccessful and the patient expired.

3. Discussion

Adenovirus is a non-enveloped double-stranded DNA virus that was first isolated from adenoid tissue in the 1950's [2]. It is transmitted through droplets and direct contact and causes diseases of the upper and lower respiratory tract, gastrointestinal tract, and eye [3,4]. The incubation period is between 4-8 days [5]. It is one of the most common causes of upper respiratory infections in adults and children [4]. Most infections are self-limited acute febrile illnesses. Severe lower respiratory infections with pneumonia and ARDS have been reported in immunocompromised populations including transplant recipients and HIV patients, and in children. Outbreaks of specific serotypes of adenovirus infection are described in immunocompetent adults in military recruits [6] and mental health centers [7], with sporadic cases reported in immunocompetent adults with life-threatening or fatal respiratory illness [8].

The patient we describe did not have any known risk factors for severe adenoviral infection. However, she had multiple comorbid conditions including diabetes mellitus, hypertension, asthma, and chronic kidney disease and it is possible that the combination of comorbid conditions increased her risk for severe illness from what is usually a mild infection in adults. She underwent endo-tracheal intubation for urgent repair of her CSF leak around the time she manifested symptoms of worsening lower respiratory tract infection with onset of hypoxia, new lung infiltrate, and fever. Endotracheal intubation and mechanical ventilation have been postulated to predispose to bacterial pneumonia through mucosal injury that impairs mucociliary function, stimulation of mucus secretion that stagnates and harbors organisms, and reducing cough effectiveness [9]. In this case, it is possible that intubation and mechanical ventilation may have contributed to the severity of adenovirus pneumonia.

Although endoscopic endonasal surgery is associated with increased risk of post-surgical meningitis [10], there is no reported association in the literature regarding CSF rhinorrhea and increased susceptibility to pneumonia or other systemic infections. Therefore, in our case, it is uncertain whether the presence of a CSF leak contributed to the patient's risk for pneumonia.

The most common presenting symptoms of severe adenovirus pneumonia in immunocompetent patients hospitalized with adenovirus pneumonia are fever (90%), cough (81%) and dyspnea (70%) [11]. Patients may have upper respiratory symptoms that progress to respiratory failure over hours to days [12]. In our patient, these symptoms developed rapidly over several hours. Patients may have leukopenia and thrombocytopenia, suggesting a viral etiology [3,11], or alternatively present with neutrophilia and leukocytosis [13], mimicking a bacterial infection. Elevated transaminases and CPK can also be observed [11]. Leukocytosis, rather than leukopenia, was observed on admission in our patient and she had only mild AST elevation. Renal failure is uncommon among immunocompetent patients with severe adenovirus pneumonia with ARDS; we found only 2 cases in the literature of patients requiring renal replacement therapy [7,14]. Our patient had stage IV CKD and developed worsening renal failure with oliguria and electrolyte abnormalities necessitating renal replacement therapy.

An abnormal chest radiograph on presentation is observed in 90% of patients with adenovirus pneumonia [11]. Findings can mimic bacterial pneumonia with bilateral infiltrates, multilobar consolidations and pleural effusions [11,13]. Our patient presented with a normal chest radiograph but developed bilateral infiltrates and consolidation over three days, consistent with other reports in the literature.

The efficacy of antiviral therapy for severe adenovirus pneumonia has not been established. There are multiple reports of patients in the intensive care unit improving with supportive care without the use of antiviral therapy [7,8,11]. Intravenous ribavirin and more recently, intravenous cidofovir, has been used with varying degrees of success. Kim et al. reported a series of seven immunocompetent adult patients with severe adenovirus pneumonia treated with cidofovir 5mg/kg weekly within 7 days (median) of symptom onset; three required mechanical ventilation. There was clinical, radiological and laboratory improvement in all patients with resolution of all symptoms within a median of 12 days [3]. Renal impairment was not reported or accounted for in these patients. Cidofovir therapy was considered for our patient but was not given due to the patient's oligouric renal failure and lack of data regarding its efficacy.

When hypoxic respiratory failure occurs in severe adenovirus pneumonia, invasive mechanical ventilation can provide respiratory support to allow time for recovery [8,11]. In respiratory failure not improving with mechanical ventilation, veno-venous ECMO can provide life-sustaining

oxygenation and CO_2 removal, allow pulmonary parenchymal rest and time for the lung to heal, therefore increasing chances of survival. ECMO was used for severely hypoxemic patients during the H1N1 influenza pandemic of 2009, and was reported to improve survival rates [15]. It has since been used in treatment of refractory respiratory failure from other viral infections in adults and children. Low and colleagues reported a series of 3 patients with severe adenovirus pneumonia who were treated with anti-viral therapy, continuous mechanical ventilation, followed by ECMO after 2, 5 and 13 days. Only one patient survived in that study. In another report, an immunocompetent adult with severe adenovirus pneumonia who developed heart failure with decreased ejection fraction, was started on veno-arterial ECMO after one day of mechanical ventilation and subsequently given ribavirin and oseltamivir. The patient's respiratory function improved after ECMO lasting 12 days, with eventual complete recovery [14]. The major risk of ECMO is bleeding and vascular injury [16]. Our patient was intubated for urgent surgery and subsequently could not be extubated due to rapid-onset respiratory failure. ECMO was initiated on the sixth day of mechanical ventilation. However, cardiac arrest and death occurred within minutes.

4. Conclusion

Our care report illustrates that while rare in immunocompetent adults, adenovirus can cause severe pneumonia, acute respiratory distress syndrome and severe sepsis and multi-organ failure, and should be considered in the differential diagnosis. The mortality in cases such as ours is high, and the clinical benefit of various treatment strategies, including anti-viral agents, is controversial. ECMO may be beneficial in severely hypoxemic patients on mechanical ventilation. Further research is needed to establish effective treatment options for patients with severe adenovirus pneumonia.

Statement of Competing Interests

There are no competing interests to report.

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