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Severe community acquired adenovirus pneumonia in an immunocompetent host successfully treated with IV Cidofovir

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ABSTRACT

Adenovirus is a common cause of acute febrile respiratory infection in children and are generally self-limiting although pneumonia can occur in neonates and adults with compromised immunity. However, severe adenovirus pneumonia in healthy adults has been rarely described. Here, we report a case of severe community-acquired adenovirus pneumonia in a previously healthy patient successfully treated with intravenous Cidofovir.

1. Case presentation

A previously healthy 36-year-old Filipino male presented with fever, diarrhea and cough 7 days after a trip to the Philippines. He was treated with intramuscular Ceftriaxone and Clarithromycin by his family physician for 4 days without improvement. On day 7, he developed shortness of breath and was admitted to the hospital. He was febrile at 40.9 °C, normotensive but tachycardic at 100bpm, tachypneic at 25 breaths/min and saturating at 96% on facemask (FM) 5L/min. He was dehydrated with decreased air entry over the left lung. Infective markers C-Reactive Protein (CRP) and procalcitonin were markedly elevated at 245mg/dL and 5.3 μg/L respectively. There was leukopenia $2.1x10^9$/L with 9% atypical mononucleosis, hyponatremia 128 mmol/L and hypoalbuminemia 34 g/L. Platelet and glucose were normal whilst SGPT and SGOT were both elevated at 114 U/L and 353 U/L, [Fig. 1]. Mycoplasma IgM, influenza A & B IF, dengue NS1 Ag, dengue serology and urine Streptococcus Ag and Legionella Ag were all negative. Melioidosis serology, Legionella antibody, Leptospira IgM and HIV were also negative. Stool was watery brown and had no leukocytes, ova, cysts or parasites. His arterial blood gas (ABG) on FM 5L/min was pH 7.59, $PaCO_2$ 23.9 mmHg, PaO_2 108.5 mmHg, bicarbonate 23 mmol/L, BE 1.3 mmol/L and oxygen saturation 99.1%. Chest x-ray (CXR) showed consolidation of the left upper lobe and the superior segment of the left lower lobe [Image 1A].

He was started on IV Moxifloxacin 400mg daily and IV Meropenem 1g 8 hourly. White cell count fell to 1.7x10^9/L the following day and Oseltamivir 75mg 12 hourly was added. He became more hypoxic requiring 100% oxygen in a non-rebreather mask and then non-invasive positive pressure ventilation the next day. He was eventually intubated on day 4 of hospitalisation. His CXR had progressed to consolidation of the right upper lobe and the whole of the left lung [Image 1B]. Respiratory virus multiplex PCR from the throat detected Adenovirus serotype 7 and IV Cidofovir 5mg/kg was given with 1L normal saline hydration before Cidofovir infusion and 1L hydration immediately thereafter to prevent renal toxicity. Probenecid 2 g was given 3 hours before, 1g at 2 and 8 hours after the Cidofovir infusion. IV hydrocortisone 100mg 6 hourly was added. Prone ventilation was employed during the first two days of mechanical ventilation. His respiratory support came down on the fourth day of mechanical ventilation. Fever stopped swinging and CXR showed less infiltrates over the left lower zone [Image 1C]. He was given a second dose of Cidofovir 8 days after the first dose and was successfully extubated the same day.

Of note, Adenovirus PCR was positive in his blood (day 11) and stool (day 12). It remained detectable in the sputum on day 19 but finally cleared on day 24. As his fever persisted around 38 °C despite negative cultures from the blood, sputum, stool and CVP tip, he was empirically covered with IV Levofloxacin 750 mg daily and IV Tedizolid 200 mg daily [Fig. 1]. He was weaned off intranasal oxygen and fever lysed on day 23 and 27 of illness respectively. CXR showed residual patchy shadowing only in the lower zones [Image 1D] and he was discharged on

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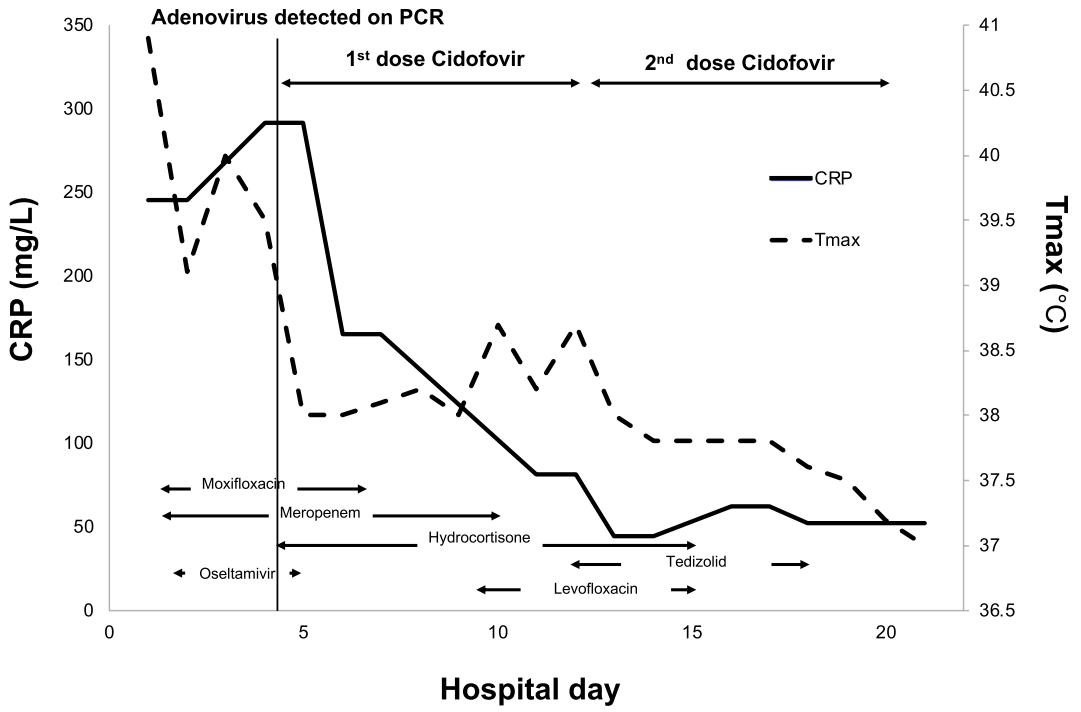

Fig. 1. CRP & Temperature Charting.
CRP, C-Reactive Protein; Tmax, Temperature Maximum.

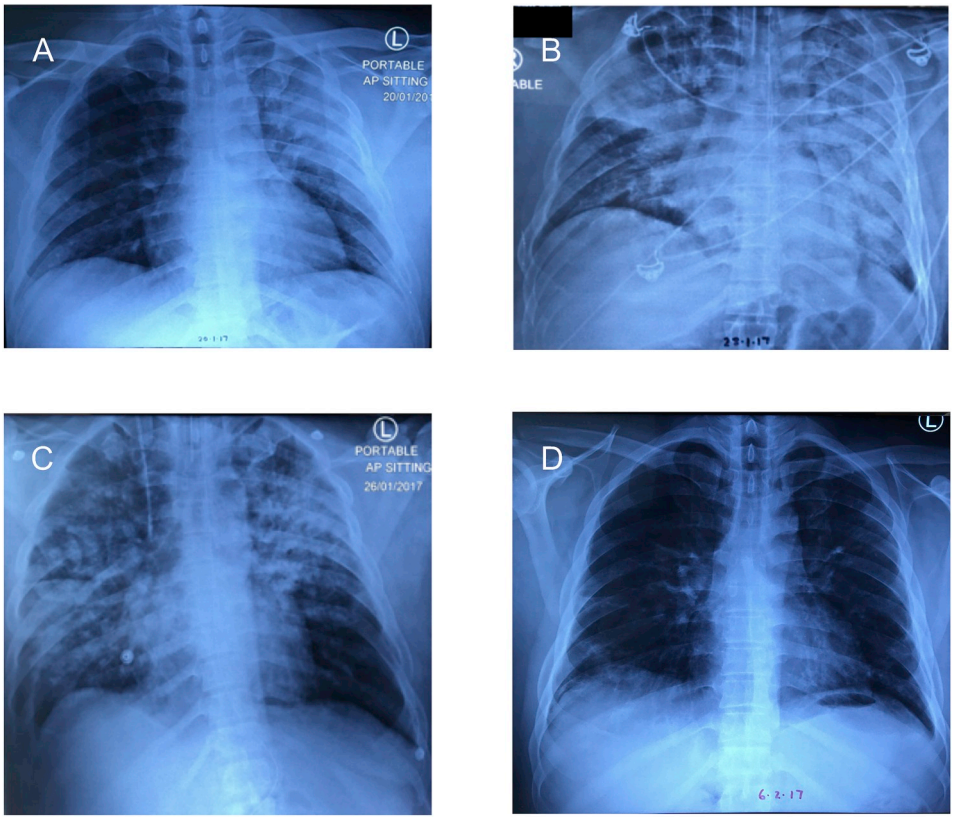

Image 1. Chest X-Ray.
1A, Hospital day 1; 1B, Hospital day 4; 1C, Hospital day 7; 1D, Hospital day 18.

day 27 of illness, after 21 days in hospital.

Outpatient review showed complete resolution of CXR infiltrates and the blood tests normalised. Lung function however showed impaired diffusion but recovered to 81% predicted 4 months after the illness [Table 1].

Table 1
Lung function test results.

	Reference	Day 46		Day 130	
		Reading	% Predicted	Reading	% Predicted
FVC	3.6	3.75	104	3.9	108
FEV1	3.15	3.2	101	3.29	104
FEV1/FVC	87	85		84	
TLC	5.18	4.74	91	5.44	105
RV	1.03	0.98	95	1.28	124
VC	3.6	3.76	104	4.16	116
DL/VA Adjusted	2.07	1.31	63	1.68	81

FVC, Full Vital Capacity; FEV1, Full Expiratory Volume in 1 Second; TLC, Total Lung Capacity; RV, Residual Volume; VC, Vital Capacity; DL/VA Adjusted, Diffusing capacity/Alveolar Volume Adjusted.

2. Discussion

Adenovirus is a double stranded DNA virus from the Family Adenoviridae, with more than 50 serotypes. It was first isolated in 1950 from adenoid tissue derived cell culture. This virus can survive long outside the host and is also resistant to disinfectants, gastric and biliary secretions [1]. It is transmitted through droplets, direct contact (i.e. conjunctiva, water, surface) and oral faecal route. The incubation period ranges 4–8 days. The clinical presentations include acute respiratory disease, gastroenteritis (both present in our case), pharyngo-conjuntival fever, epidemic keratoconjunctivitis and acute hemorrhagic cystitis. Most infections are self-limited. However, adenovirus pneumonia in immunocompromised hosts usually leads to rapid deterioration with a high fatality rate. While rare, life threatening and even fatal outcomes in adenovirus pneumonia have been reported in immunocompetent hosts [2–4].

In an acute respiratory disease presentation, it is predominantly serotype 1, 2, 4, 5 and 6. It is highly contagious [1]. It accounts for 80% of the adenoviral infections in children below 4 years old [1] and 1–7% of adult respiratory tract infections. Treatment often requires just supportive care.

A review conducted by Clark et al. (n = 21) [5] demonstrated that adenovirus pneumonia usually presents with fever (90%), cough (80%), dyspnoea (70%) and respiratory failure within hours to days, requiring mechanical ventilation in 67% of the cases. This was associated with a mortality rate of 24%.

Common laboratory findings include lymphopenia, leukopenia, thrombocytopenia, elevated transaminases and occasionally leukocytosis with neutrophilia [5]. The radiological findings are usually widespread interstitial shadows but there may be ground glass, pleural effusion as well as consolidation. Lobar consolidation, a pattern more suggestive of bacterial infection was observed in one quarter of the cases [6,7]. Likewise, our case presented with consolidations. Histology can illustrate a necrotizing bronchitis or bronchiolitis picture which will start to resolve two weeks after the onset of the illness. Fibrosis is not common.

In the past, diagnosis was made by culture and specific immunofluorescent staining which were costly and time consuming. Since the advent of multiplex PCR assays, early detection has led to the option of early initiation of antiviral therapy. Kim et al. reported favourable outcomes to Cidofovir in 7 non-immunocompromised adults with severe adenovirus pneumonia when the drug was administered early in the course of respiratory failure [8]. Cunha et al. also reported successful response to Cidofovir in a 22-year old male [9]. Two other reports [14,15] also showed successful outcome with Cidofovir. Although the efficacy of antiviral therapy for severe adenovirus pneumonia has not been established [4], ECIL-4 guideline recommends the use of Cidofovir at 5mg/kg with probenecid in leukemic patients with adenovirus pneumonia which we used in our patient [12].

Unfortunately, outcomes were often poor when Cidofovir was given late in the course of illness [2,10,11]. It is also expensive, not always available and associated with renal and hematologic toxicity. However, Cidofovir may have a role in the early treatment of severe pneumonia due to adenovirus. Possible antiviral alternatives include Ribavirin which was given to a 39-year old Korean male on day 4 of hospitalisation with a favourable outcome [13].

3. Conclusion

Firstly, severe viral pneumonia caused by adenovirus can occur in immunocompetent hosts and present with radiological findings of consolidation more typical of a bacterial etiology. Secondly, respiratory virus PCR assays which allow for the rapid and accurate diagnosis of viral etiology should be used whenever available as it can guide the implementation of infection control measures, avoid the unnecessary use of antibacterial antibiotics and allow the option of early antiviral therapy. Lastly, the early use of IV Cidofovir should be considered in severe adenovirus pneumonia. More work needs to be done to understand the relationship between who and when to use IV Cidofovir in this cohort of patients.

4. Consent to publish

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of competing interest

The authors declare that they have no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101037.

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