Treatment of Disseminated Adenovirus with Cidofovir in a Patient with HIV and ESRD

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INTRODUCTION

We present a case of disseminated adenovirus in a well-controlled person living with HIV (PLWHIV). We treated the patient successfully with dose-reduced cidofovir in the setting of end-stage renal disease (ESRD) on hemodialysis (HD). We conducted a literature review to investigate the management options for severe or disseminated adenovirus disease as well as use of cidofovir in patients with ESRD.

BACKGROUND

- Adenovirus infections are common causes of upper respiratory infections and gastroenteritis.
- Severe adenovirus infections and disseminated disease are known to occur in immunocompromised hosts.[1-4]
- Persons living with HIV (PLWHIV) who have obtained virologic control and immune recovery are unlikely to develop the severe manifestations or disseminated disease that can be associated adenovirus.[5-9]
- Cidofovir has been associated with clinical improvement in patients with severe or disseminated adenovirus disease in which immunosuppression cannot be readily reversed or those unresponsive to supportive care.[10-12]
- Cidofovir's efficacy is supported by in-vitro data and clinical experience however its use is limited by a narrow therapeutic index with resulting nephrotoxicity, myelosuppression, notably neutropenia, as well as ocular toxicities.
- Cidofovir is not currently FDA-approved for use in patients with chronic kidney disease or end-stage renal disease (ESRD) given concerns of associated toxicity in patients with depressed renal function.[13]

CASE PRESENTATION

- Our patient was a 59 year-old woman who presented with a two day history of fever, mild non-productive cough, and diarrhea.
- She had a past medical history HIV/AIDS with virologic control and CD4 count of 470 (CD4 nadir of 139) treated with dolutegravir and dose adjusted tenofovir and lamivudine in the setting of ESRD on intermittent hemodialysis. She also has a history of chronic hepatitis B, group I pulmonary hypertension, mitral stenosis, and history of *Clostridioides difficile* colitis.
- On admission, she was febrile, tachycardic, and hypertensive. Her chest x-ray showed increased vascular congestion without consultation. Her stool was positive for *C. difficile* by PCR. Oral vancomycin and systemic empiric broad spectrum antibiotic therapy were started.
- On HD 3, despite oral vancomycin and discontinuation of broad spectrum antibiotics, the patient's diarrhea persisted and she developed progressive hypoxic respiratory failure.
- A computerized tomography (CT) of her chest showed multifocal ground glass and consolidate opacities suggestive of multifocal pneumonia. Near total occlusion of the left lower lobar bronchus without pulmonary embolus were also noted (Image 1).
- A transthoracic echocardiogram (TTE) was obtained which showed evidence of mild right ventricular dysfunction in the setting of significantly elevated pulmonary arterial pressures however stable from her previous assessment.
- A multidisciplinary discussion was held with the patient to weigh the risks and benefits of intubation and bronchoscopy for both therapeutic and diagnostic evaluation. However, the patient declined intubation if necessary due to a concern for prolonged ventilation or hemodynamic compromise in the setting of her severe pulmonary hypertension.
- Empiric antibiotic therapy was resumed for possible bacterial pneumonia and additional non-invasive testing was obtained given lack of clinical improvement.
- Ultimately, stool, nasopharyngeal, and serum adenovirus PCR tests were positive.

DIAGNOSTIC EVALUATION

Admission	Course of Hospitalization
Blood cultures (x2) - Negative	Blood cultures (x2) - Negative
Sputum Culture - Normal oral flora	Sputum Culture - 1+ *C. albicans*
C. difficile Stool PCR - Positive	Cryptococcal Serum Ag - Negative
HIV Viral Load - Undetectable	Coccidioides IgM/IgG - Negative
CD4 - 178 (previously 470)	CMV serum PCR - Negative
Bacterial Enteric Pathogen PCR, stool - Negative	Norovirus stool PCR - Negative
Parasite Enteric Pathogen PCR, stool - Negative	Rotovirus stool PCR - Negative
Sputum MTB PCR (x3) - Negative	Adenovirus stool PCR - Positive
Sputum AFB Smear and Culture (x3) - Negative	Respiratory Pathogen Panel PCR, Nasopharyngeal - (+) Adenovirus
Fungal sputum culture - Negative	Adenovirus serum PCR - 3.2 million copies

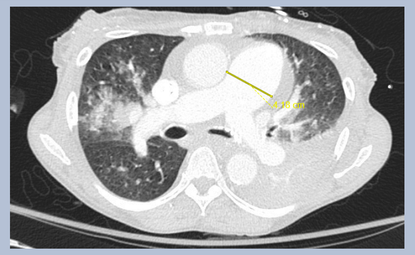
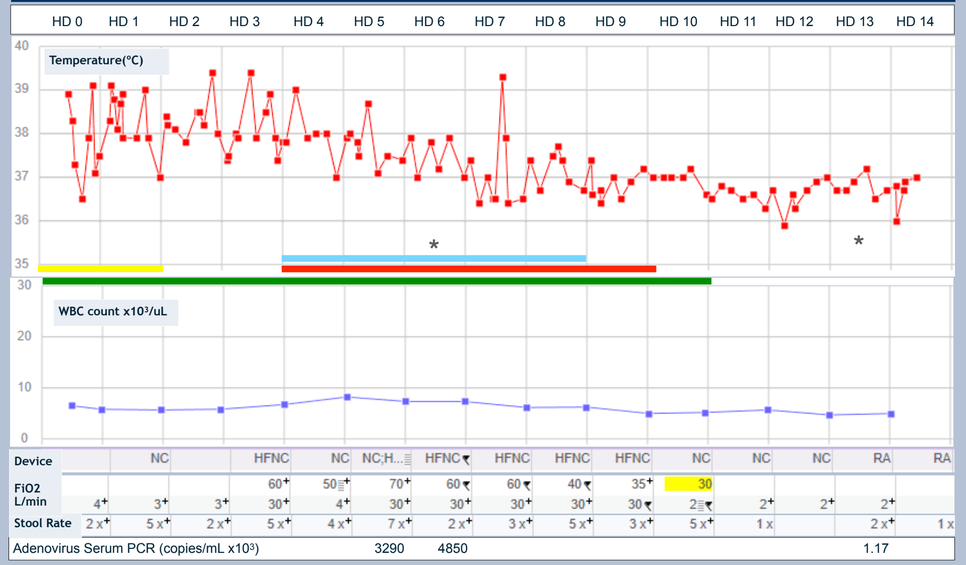


Image 1: Near total occlusion of the left lower lobar bronchus with resultant near-total left lower lobe volume loss and consolidation. Multifocal groundglass and consolidative opacities are also seen in the right greater than left upper lobes

CLINICAL COURSE



- On HD 6, she was started on dose-reduced cidofovir of 0.5 mg/kg weekly given several hours prior to hemodialysis to reduce the risk of toxicities while on therapy.
- Our patient received dose-reduced cidofovir twice over a treatment and follow up period of 3 weeks. She had clinical improvement in symptoms and no medication-related side effects were identified. Her complete blood counts and metabolic panel were monitored and showed no significant abnormalities.
- One month following admission repeat adenovirus serum PCR was undetectable and the patient reported complete resolution of her symptoms.

Antibiotics/Therapeutics Key

Vancomycin IV/Piperacillin-tazobactam

Oral Vancomycin

Cefepime/Vancomycin

Azithromycin

Cidofovir ***** (0.5mg/kg)

DISCUSSION

- We present a case of disseminated adenovirus leading to gastroenteritis, multifocal pneumonia, and hypoxemic respiratory failure in a patient living with well-controlled HIV/AIDS. The patient was treated successfully with dose-reduced cidofovir in the setting of end-stage renal disease on intermittent hemodialysis.
- A literature review was conducted to investigate the treatment options of severe adenovirus disease as well as use of cidofovir in patients with ESRD.
- Fourteen primary and review articles were reviewed discussing adenovirus pathology and management.
- Management of adenovirus infections is challenging given a wide spectrum of disease, variation in natural history of the infection, and treatment data limited to in-vitro studies, case reports, and retrospective analyses with treatment relying on reductions of immunosuppression and in some cases antiviral agents.
- Brody et al.[14] proposed a single dose 0.5 mg/kg/week of cidofovir administered two to three hours before dialysis provided comparable drug levels to patients with standard dosing without underlying renal dysfunction.
- Our patient received dose-reduced cidofovir twice over a treatment period of three weeks with clinical and symptomatic improvement without development of medication-related side effects.
- Further research is needed regarding therapeutics for severe and disseminated adenovirus infections in immunocompromised patients. Brincidofovir and developing antiviral immunotherapy with adenovirus-specific T-cells may be future therapeutic options.

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DISCLOSURES

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