Severe adenovirus infections in young adults

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ABSTRACT

Background: Despite traditionally affecting individuals with compromised immune systems, severe human adenoviruses (HAdV) infections have been observed in young adults without immunodeficiency over recent decades.

Case Presentation: This case study documents two young patients infected with HAdV who experienced multi-organ failure, manifesting as respiratory distress, vasoplegia, myocardial injury, and kidney impairment. The resolution of organ failure correlated with the clearance of viral load, suggesting a potential prognostic indicator for infection outcomes. While the first case demonstrated a positive outcome with the resolution of viremia, regrettably, the second case succumbed to myocardial infarction followed by cardiac arrest. The use of cardiac monitoring may aid in the identification of significant myocardial complications associated with HAdV. Although various treatments, including the antiviral CIDOFOVIR, have been reported for immunocompromised individuals, it was not administered to our patients due to the favorable trajectory of the first case. Tragically, the second case passed away before any potential antiviral intervention could be initiated.

Conclusion: HAdV infections can cause severe acute respiratory distress syndrome with multi-organ failure including severe cardiac complications in young non-immunocompromised adults.

Keywords: Case report, adenovirus, acute respiratory distress syndrome, intensive care unit, extracorporeal membrane oxygenation, pneumonia, viral pneumonia.

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Background

Human adenoviruses (HAdV) are DNA viruses that usually induce mild infections occurring in the upper and/or lower respiratory or gastrointestinal tract or in the conjunctiva. HAdV infections are more common in children, due to lack of humoral immunity. Increased severity and dissemination in adult patients are more common in immunocompromised individuals [1]. Mortality of severe HAdV infections (severe pneumonias or generalized infections) may exceed 50% in those patients [1,2]. Few isolated cases of these severe infections were reported in immunocompetent young adults [3-6] and implicate the B and C HAdV species. These cases have been described especially in military recruits owing to stress and crowding during training [6-8]. This phenomenon led to the US military's decision to vaccinate all new recruits against HAdV-B4 and B7 [9]. Emerging HAdV type 55 (HAdV-55, a combination of both B11 and B14 types) was responsible for severe and sometimes fatal pneumonia in immunocompetent patients especially in Asia [4], whereas few cases were described in Europe [5]. Pathogenicity and management of severe HAdV infections remain unobvious and is based on immunocompromised patient experience.

Cases Presentation

During winter 2022-2023, 2 cases of severe HAdV pneumonias were diagnosed in the University Hospital of Lille in France.

Case 1

In December 2022, a Woman in her twenties was admitted to our hospital, at the Emergency Department (ED), with a 15-day history of an influenza-like syndrome (i.e., odynophagia, myalgia, and productive cough) and worsening dyspnea.

Preliminary clinical examinations showed a body temperature of 38.8ºC, a systemic arterial blood pressure of 125/68 mmHg, a heart rate of 90 /minute, and a SpO2 of 86% on room air.

Investigations

Blood tests at admission revealed a normal renal function, a lymphopenia (0,9 × 10.9/l), liver cytolysis (alanine

transaminase (ALT) 139U/l, aspartate transaminase (AST) 317 U/l), and hyponatremia (132 mmol/l).

Chest computed tomography (CT)-scan (Figure 1) found bilateral ground-glass opacities (GGOs) and bilateral lower lobe consolidation.

On intensive care unit (ICU) admission, the echocardiogram showed an increase in pulmonary vascular resistance with acute pulmonary hypertension associated with right ventricle dysfunction. During hospitalization, ECG revealed an intermittent first-degree atrioventricular block associated with elevated cardiac biomarkers on blood tests suggesting myocarditis (Table 1). This hypothesis was confirmed on delayed cardiac magnetic resonance imaging (MRI) (Figure 2).

Virological molecular analysis with real-time reverse transcription-polymerase chain reaction (RT-PCR) on nasopharyngeal swab, broncho-alveolar lavage (BAL), and bloodstream were positive for HAdV with viral loads on BAL and bloodstream of 7,75 log copies/ml and > 9 log copies/ml, respectively.

Differential diagnosis

Bacteriological and mycological tests on blood, urine, and BAL samples were repeatedly negative.

Autoimmune disease and immunodeficiency were ruled out. Initial lymphopenia and hypogammaglobulinemia were normalized on discharge.

Treatment

The initial antibiotic therapy consisted of an association of CEFOTAXIM and SPIRAMYCIN rapidly switched to PIPERACILLIN/TAZOBACTAM and LINEZOLID because of worsening respiratory symptoms and multi-organ failure (MOF) including hemodynamic instability and kidney failure. She was intubated and transferred to the ICU. She required vasopressor support up to 0.5 µg/Kg/minute of NOREPINEPHRINE and renal replacement therapy at day 7. After prone positioning failure, veno-venous extra corporal membrane oxygenation (ECMO) support was initiated in the case of refractory acute respiratory failure on day 8.

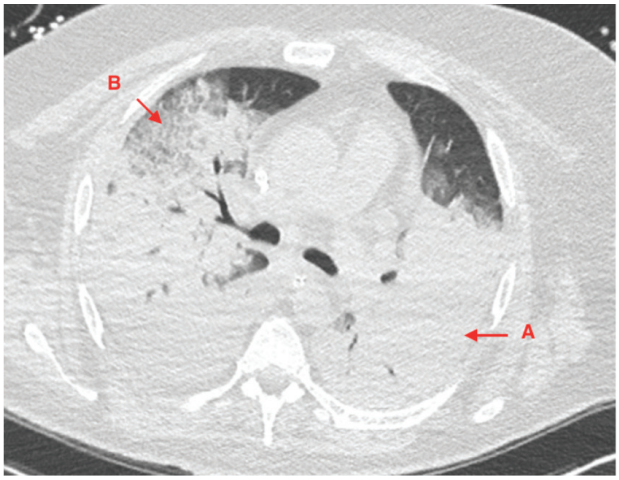


Figure 1. *Initial CT-scan revealing bilateral posterior consolidation (A) and anterior GGO (B). GGO: ground-glass opacities.*

Outcome and follow-up

ECMO was weaned three days later and she was extubated 2 weeks after admission.

Clinical symptoms and bloodstream viremia underwent a parallel evolution. No viremia was detectable when she was discharged. A follow-up chest CT scan on day 26 showed some remaining consolidation and pleural effusion with a significant viral load on BAL and pleural puncture (Table 1).

She was off oxygen 7 days after extubation and then transferred to a respiratory ward for pulmonary rehabilitation.

After a week in the respiratory ward, she was discharged from the hospital.

A few months later, a follow-up cardiac MRI showed complete recovery of the heart, and a chest X-ray showed her lung tissue had returned to normal.

Case 2

A 45-year-old man with a medical history of chronic hypertension, 20 pack-year smoking, and chronic alcohol consumption, presented an influenza-like syndrome revealed by fever, cough, asthenia, myalgia, and diarrhea. Seven days later, he was admitted to the ED for worsening symptoms and dyspnea.

On arrival, vital signs were as follows: body temperature 38ºC, systemic arterial blood pressure 90/50 mmHg, heart rate 120 /minute, and SpO2 90% on room air.

Investigations

Laboratory investigations on admission revealed severe inflammation, acute kidney injury (serum creatinine 4.7 mg/dl, blood urea nitrogen 1.5 g/l), lymphopenia (<0,1 × 10.9/l), liver cytolysis (AST 372 U/l, SGPT 52 U/l), rhabdomyolysis (CPK 2730 U/l), myocardial injury with increased high-sensitive cardiac troponin T level in the plasma (140 ng/l), and hyponatremia (132 mmol/l).

Chest X-ray (Figure 3) showed severe pulmonary infiltrates and CT scan (Figure 4) found severe bilateral consolidations and GGO.

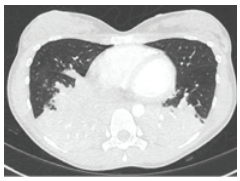
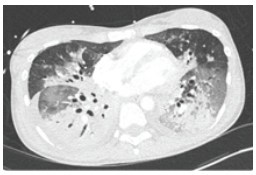
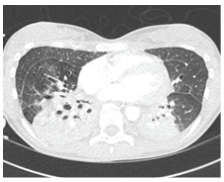
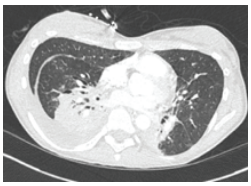
The microbiological assessment did not reveal any bacterial or fungal infection. The only microbiologic result was a positive HAdV RT-PCR in the BAL and bloodstream (>8.00 Log copies/ml).

Treatment

The initial antimicrobial therapy consisted of an association of CEFOTAXIM and LEVOFLOXACIN.

The outcome was initially similar to case 1 with MOF and refractory acute respiratory failure requiring veno-venous ECMO support on day 1 after ICU admission.

Table 1. *Evolution of different organ dysfunctions according to human adenovirus (HAdV) loads in patient 1. ECMO: Extra-Corporal Membrane oxygenation, APRV: Airway Pressure Release Ventilation, VC: Volume controlled ventilation, FiO2: Fraction of inspired Oxygen, FmO2: Membrane fraction of oxyge,n P-high: highest level of pressure applied, P-low: lowest level of pressure applied, PEEP: Positive End-Expiratory Pressure, cmH2O: centimetre of water, NO: Nitric Oxyde, ppm: parts per million, CVVH: Continuous Veino-Veinous Hemofiltration, RV: Right Ventricle, AVB: Atrio-Ventricular Block, PAP: Pulmonary Artery Pressure, TAPSE: Tricuspid Annular Plane Systolic Excursion, S-DTI: tricuspid annular S' wave on Doppler Tissue Imaging, BAL: Broncho-Alveolar Lavage, N: normal, CC: Creatinine clearance. CC was calculated by the following formula: (U*V)/(p*1440), where U is the number of milligrams of creatinine in each deciliter of urine within 24 hours; V is the volume of urine output per minute in milliliters; P is the serum creatinine in milligrams per deciliter.*

DAYS SINCE ICU ADMISSION	DAY 1	DAY 7	DAY 20	DAY 26
Respiratory support	- ECMO FmO2: 100% - Mechanical ventilation APRV FiO2: 90% P-high: 20 cmH2O P-low: 8 cmH2O - Added NO 10 ppm	- OFF ECMO - Mechanical ventilation VC FiO2: 40% PEEP: 10 cmH2O - OFF NO	- OFF Mechanical ventilation - 4 l/minute oxygen nasal cannula	- On room air
Lung				
Liver	Cytolysis ALT : 186 UI/L AST : 627 UI/L N : 10-35 UI/l	Cytolysis ALT : 153 UI/l AST : 199 UI/l N : 10-35 UI/l	Cytolysis ALT : 111 UI/l AST : 124 UI/l N : 10-35 UI/l	Cytolysis ALT : 68 UI/l AST : 114 UI/L N : 10-35 UI/l
Kidney	CVVH	Urine output recovery CC = 37 ml/minute	Full recovery CC = 63 ml/minute	Full recovery CC = 81 ml/minute
Hemodynamic	Norepinephrine up to 0.5 µg/Kg/minute	OFF Norepinephrine	OFF Norepinephrine	OFF Norepinephrine
Heart	RV dysfunction (TAPSE 15 mm, S-DTI 9 cm/s) Elevated PAP (PAPS 55 mmHg) Normal ECG Troponin T us 300 ng/l (N : < 14 ng/l)	RV dysfunction (TAPSE 16 mm, S-DTI 10 cm/s) Elevated PAP (PAPS 35 mmHg) 1st degree AV block Troponin T us 45 ng/l (N : <1 4 ng/l)	Normalised RV (TAPSE 21 mm, S-DTI 12 cm/s) Normalised PAP (PAPS 27 mmHg) Normal ECG	Normalised RV (TAPSE 25 mm, S-DTI 15 cm/s) Normalised PAP (PAPS 27 mmHg) Normal ECG
HAdV RT-PCR Viral Load *(Log copies/ml)*	No data	Bloodstream : > 9 log copies/ml BAL : 7.75 log copies/ml	No data	Bloodstream : - day 26 : 1.32 log copies/ml - day 29 : undetectable BAL : 5.43 log copies/ml Pleural : 3.57 log copies/ml

Outcome

Eventually, the patient developed a type three atrioventricular block with extreme bradycardia revealing an acute coronary syndrome. The coronary angiogram displayed an occlusion of the left coronary artery. Although a coronary angioplasty was performed on the causal artery, the patient presented a refractory cardiac arrest. Despite receiving cardiopulmonary resuscitation and being upgraded to veno-veno-arterial ECMO support, the patient died on day 3.

Microbiological assessment

Samples of the HAdV were sent to Saint-Louis Hospital in Paris for strain genotyping. Both strains were identified as HAdV-B7d.

There was no evidence that the 2 patients had been in contact with each other or shared any common friends or family members. They lived in different cities in northern France. There was no indication of a common cluster of HAdV infections.

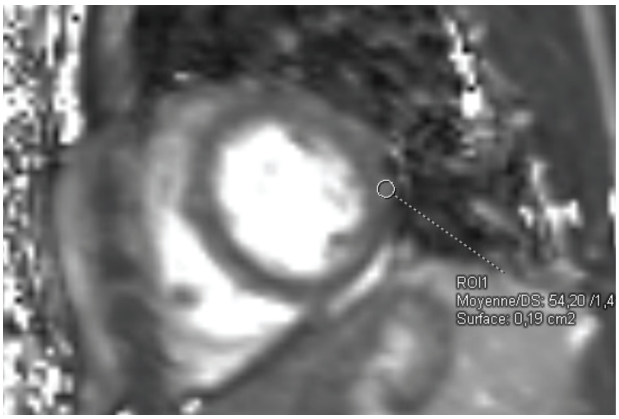


Figure 2. *CMR showed areas of edema in inferolateral, mid-cavitary, and basal positions in T2 parametric imaging in favor of edema.*

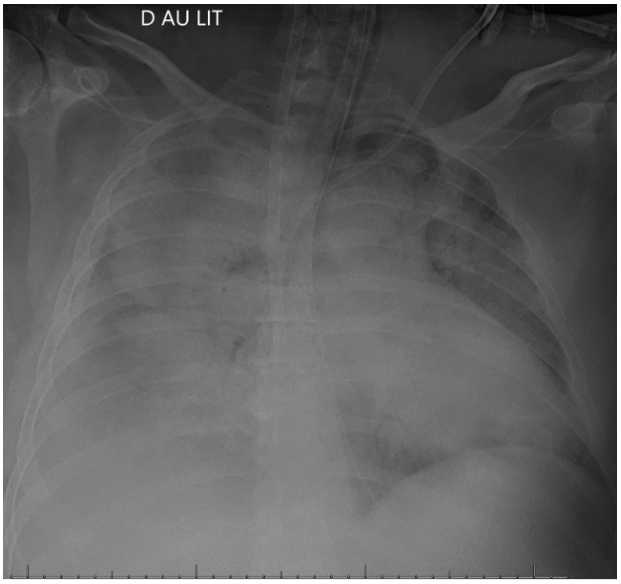


Figure 3. *Initial Chest X-ray with bilateral pulmonary infiltrates.*

Discussion

Several serious HAdV outbreaks have been reported in the last years all over the world [3-6]. To date, only a few severe HAdV cases have been isolated in France [5], none with the B7d genotype. This HAdV B7d genotype has been identified in patients with severe acute respiratory failure in the USA [3,10,11] and China [12] since 2013. Our case report highlights the emergence of HAdV-B7d genotype-related acute respiratory distress syndrome (ARDS) in young adults on the French territory.

Given the uncommon nature of these infections, they could be underdiagnosed if viral screening is not available or if positive tests are not considered clinically relevant. These two case reports showed the importance of screening for viral pneumonias especially when no obvious infectious agent is identified or could explain the clinical picture. If blood or respiratory samples are positive for Adenovirus, then we should consider an HAdV infection

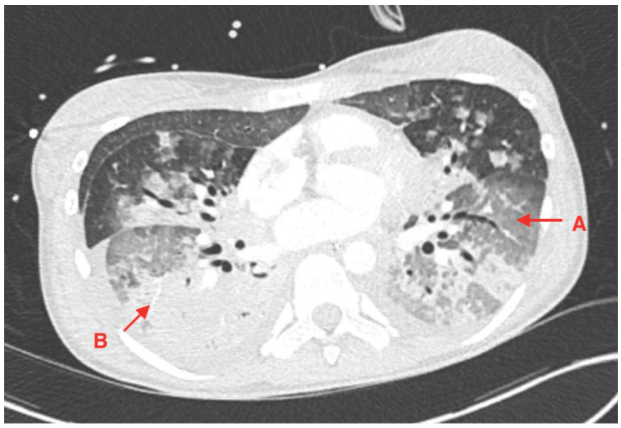


Figure 4. *Initial CT scan revealing bilateral anterior GGO (A) and posterior consolidations (B). GGO: ground-glass opacities.*

as a potential cause of severe ARDS, even in a young immunocompetent adult patient [10].

In our two patients, the initial severity may be associated with very high viral loads in bloodstream and BAL. Moreover, a decrease in viral load was associated with a good clinical evolution in patient one. We suggest that in severe forms of HAdV-related infections, initial assessment and kinetics of viral load in blood samples or BAL could help clinicians predict patients' outcomes and guide therapeutic decisions.

Our clinical experience further highlights the necessity of cardiac monitoring for severe cardiac complications related to HAdV-B7d infections. Myocardial injury related to HAdV was not described in most case reports, but like many other viral infections, HAdV could be associated with myocarditis with a large spectrum of clinical symptoms (arrhythmias, AV blocks, acute coronary syndrome-like, ventricular dysfunction, and so on) [13]. HAdV was described in rare cases to be associated with pericarditis with pericardial effusion [14].

There are no validated treatments for HAdV, several molecules have been tested in immunocompromised patients, including IV immunoglobulin, RIBAVIRIN, GANCICLOVIR, and CIDOFOVIR [1]. CIDOFOVIR is a broad-spectrum antiviral drug. CIDOFOVIR is a nucleoside phosphonate analogue with proven action against all serotypes of HAdV [15]. CIDOFOVIR had a broader antiviral spectrum on HAdV *in vitro* than other antivirals such as RIBAVIRIN [15]. CIDOFOVIR is proposed as the first-line treatment of severe HAdV infections. We have not used this treatment in patient 1 because of her positive evolution. Patient 2 died rapidly before initiating the treatment.

Eventually, the HAdV-B7 vaccine is available and used in the US military because of several severe cases in this particular population [9]. Vaccination is an alternative strategy in case of a HAdV endemic spread. Nevertheless, most epidemics were described in children or military

troops [6-8], and none in adult civilians, which makes it a less plausible option.

Conclusion

Viral pneumonias are often underdiagnosed, which complicates treatment. HAdV infections can cause severe ARDS and multi-organ failure in young, non-immunocompromised adults, highlighting the importance of cardiac monitoring due to potential myocardial complications. Assessing viral load in initial blood or BAL samples and tracking changes over time can help predict outcomes and guide treatment decisions, improving patient care.

What is new?

Viral pneumonias are frequently under-diagnosed. Human adenovirus infections can cause severe acute respiratory distress syndrome with multi-organ failure in young non-immunocompromised adults including severe myocardial complications. Assessment of viral load in initial blood or BAL samples, and monitoring changes over time, may help clinicians predict patient outcomes and guide treatment decisions.

List of Abbreviations

AST	Aspartate Transaminase
BAL	Broncho-Alveolar Lavage
CT	Computed tomography
ED	Emergency department
GGO	Ground-glass opacities
HAdV	Human adenovirus
ICU	Intensive care unit
MRI	Magnetic resonance imaging
RT-PCR	Reverse transcription-polymerase chain reaction

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this case report.

Funding

None.

Consent for publication

Written informed consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	Patient (gender, age)	27 years, female (case 1) and 45 years, male (case 2)
2	Final diagnosis	Severe Adenovirus (AdV) infection
3	Symptoms	Respiratory failure, circulatory failure, renal failure
4	Medications	Symptomatic organ support, antiviral treatment : CIDOFOVIR
5	Clinical procedure	Mechanical ventilation, VV-ECMO, vasopressors, dialysis
6	Specialty	Critical care, infectious disease, virology