

# Acute Hepatitis: An Unusual Presentation of Adenovirus Infection

Tanushree Joshi<sup>1</sup>, Tanmay Anand<sup>2</sup>

<sup>1</sup>Head, Department of Paediatrics, Northern Railway Central Hospital, New Delhi, India, <sup>2</sup>3<sup>rd</sup> Year Post Graduate Student, Department of Paediatrics, Northern Railway Central Hospital, New Delhi, India

## Abstract

Adenovirus is a long known human infection presenting mostly in the form of upper and lower airway disease, pharyngitis, gastroenteritis, conjunctivitis, and hemorrhagic cystitis. However, adenovirus infection presenting in the form of hepatitis is an infrequent presentation, particularly in immunocompetent host. We hereby report a case of unexplained hepatitis with lower respiratory infection in a 6-year-old boy later confirmed on RTPCR to be adenovirus infection.

**Key words:** Adenovirus hepatitis, Quantitative RTPCR, Symptomatic management

## INTRODUCTION

Adenovirus is well known infection in humans with presentation ranging from asymptomatic virus shedding to conjunctivitis to severe respiratory infections requiring mechanical ventilation. Hepatitis has been mentioned as an uncommon presentation. Nine cases of adenovirus hepatitis have been reported by CDC USA in April 2022 and issued an alert regarding the same.<sup>[1]</sup> Almost 300 similar cases of adenovirus hepatitis were reported in "The Lancet."<sup>[2]</sup> We hereby report a case of adenovirus infection presenting as unexplained hepatitis. The recent rise in number of cases of adenovirus hepatitis reported from around the globe makes our case worth reporting.

## CLINICAL DESCRIPTION

A 6-year-old boy presented in pediatric OPD with complaints of cough (non-productive non-paroxysmal) for 5 days, fever (high grade, continuous, without chills) for 2 days. On evaluation, patient's weight was 20 kg (weight for age at 24<sup>th</sup> centile), height was 124.8 cm (height for

age 84<sup>th</sup> centile), and BMI 12.8 (1<sup>st</sup> centile) without any signs of nutritional deficiency. On examination, the child was awake conscious oriented with HR 102bpm, RR 32bpm, SpO<sub>2</sub> 98% under room air in the right upper limb, and BP – 100/70 mmHg (between 50 and 90<sup>th</sup> centile). On auscultation, chest was full of wheeze and occasional crepitations with mild respiratory distress. Abdomen was soft with mild tenderness in the right hypochondriac region. Rest of the systemic examination was non-contributory. Patient was admitted with provisional diagnosis of LRTI and started on nebulisation with levo-salbutamol, iv. PCM, oral chlorpheniramine plus phenylephrine, I/V fluids. Investigations revealed marginally raised TLC (12090) with DLC (P86.5% L9.7% M3.7% E0 B0.6%), positive CRP (2.1), normal LFT (SGOT 48 SGPT 50), normal KFT (Urea 30.7 S Creatinine 0.7), negative COVID RAT and RTPCR, and a negative typhi dot and widal. X-ray chest suggestive of increased bronchovascular markings in the right middle and lower zones. USG abdomen was done which was normal study except for minimal effusion in B/L lower lung fields. Diagnosis of bronchopneumonia was made and started on inj. Amoxicillin-clavulanic acid with amikacin. However, the patient did not respond in view of persistent fever and wheeze. Hence, oral oseltamivir was added on day 3 of admission and investigations were repeated which showed a normal TLC (4580) and DLC with mild thrombocytopenia (138000) along with a remarkably high SGOT (1227) SGPT (663) with normal values of bilirubin. PT/INR was normal. Proton pump inhibitors were added and the child was kept on IV fluids

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**Corresponding Author:** Dr. Tanmay Anand, Department of Paediatrics, Northern Railway Central Hospital, New Delhi, India.

as oral intake was poor. Hepatitis viral panel (HbsAG HAV HCV HEV EBV HSV CMV Enterovirus) was sent which came to be entirely negative. Repeat CBC next day revealed leukopenia (TLC 2620) with further falling platelet count (119000). Patient developed conjunctival irritation with epiphora (without any congestion/discharge) on day 4 of admission. Ophthalmology reference was done and CMC and tobramycin eye drops were advised and improved next day. Fever was still persisting with B/L wheeze in chest for which antibiotics were upgraded to i/v Piperacillin Tazobactam with oral Azithromycin. IgM for Leptospira and rickettsia serology was negative. Dengue NS1 antigen and serology were negative. TB work up (Monteux/CBNAAT for gastric aspirate) was negative. Blood culture was sterile. Respiratory viral panel was sent which showed negative H1N1 infection while confirmed Adenovirus infection instead. Repeat CBC showed TLC (2870) and platelet count (143,000) showed a modest increase while SGOT (654) SGPT (640) values were decreasing. Fever spikes were also improving with reduced chest wheeze. Patient was asymptomatic by 9<sup>th</sup> day of admission. Repeat investigations along with X-ray chest were entirely normal except for slightly raised SGPT and thrombocytosis (584000). Oral oseltamivir 5-day course was completed before the respiratory viral panel report was available. Rest all the antibiotics were discontinued as soon as the blood culture came sterile. Patient discharged after 12 days of hospital stay.

## DISCUSSION

Adenoviruses are non-enveloped, icosahedral viruses of medium size (90–100 nm) that contain double-stranded DNA. Human infections can be caused by more than 100 immunologically different adenovirus types. Common disinfectants are unable to kill adenoviruses, although they can be found on surfaces such as doorknobs, items, and even the water of swimming pools.<sup>[3]</sup> Human adenovirus causes a variety of human clinical syndromes in both immunocompromised and immunocompetent hosts usually presenting in the form of severe conjunctivitis, upper and lower respiratory disease, pharyngitis, gastroenteritis, and hemorrhagic cystitis. While hepatitis, myocarditis, and meningoencephalitis are noted as less frequent presentations.<sup>[4]</sup> Polymerase chain reaction is described as a rapid, sensitive, and specific technique in establishing the diagnosis of adenovirus infection.<sup>[4]</sup> Although we did only qualitative RTPCR, quantitative PCR is considered superior as it can establish diagnosis and aids in assessing the response to treatment as well.

A notable finding in CBC was gradual increase in lymphocytes as the disease progressed starting from

9.7% to 54.2%, which was gradually reduced as the acute phase was over. Due to the increasing lymphocytes and no clinical improvement, atypical pneumonia was suspected and first oral oseltamivir and, later oral azithromycin was added. Transaminitis was associated with modest rise of serum bilirubin but remained subclinical throughout. PT/INR and serum albumin levels were normal. Since the diagnosis was not established and clinically the patient was not improving, we were convinced to upgrade antibiotics to inj. Piperacillin with tazobactam; however, as soon as adenovirus was confirmed and culture came to be sterile inj. piperacillin with tazobactam was stopped. Oral oseltamivir was already given for 5 days. More than 100 serotypes have been identified so far with nearly 49 infecting human belonging to species A–G with replication defective HAdV-5-based vectors playing important role in gene transfer therapy.<sup>[5,6]</sup> Various serotypes have affinity for different tissues which correlates with the clinical presentation. We could not get the serotyping done but the previously reported cases state the serotype 41 to be most frequently associated.<sup>[3]</sup> The predominant serotypes circulating at a given time differ among countries or regions and change over time.

Transmission of novel strains between countries or across continents and replacement of dominant viruses by new strains may occur.

Although supportive care is the mainstay of management, cidofovir have been mentioned to be effective in vitro against adenovirus, with nephrotoxicity being an adverse effect to be watched for. There are mentions of other agents such as IVIG and adoptive immunotherapy involving infusion of HAdV specific T cells but experience is very limited and is yet not considered as standard therapy. Oral live vaccines are under routine use in US military and are effective against severe respiratory infections but not available for civilians.<sup>[7]</sup> In our case, the mainstay of management, that is, supportive care, was only provided and patient showed the signs of clinical improvement gradually and discharged.

## CONCLUSION

Adenovirus should be considered as an important differential in cases of hepatitis without a known cause, particularly when associated with atypical symptoms such as kerato-conjunctivitis, pharyngitis, or pneumonia. Quantitative PCR should be done to establish the diagnosis and to assess the response to treatment. No antiviral agent is yet recommended hence making the supportive care as the mainstay of management.

Investigations	Admission day	Day 3	Day 5	Day 7	Day 9
Hb	10.8	10.7	10.3	9.3	11.6
TLC	12.09	4.58	2.62	2.87	8.29
DLC	P86.5 L9.7 M3.7E0B0.6	P76.7 L21.4 M1.7E0B0.2	P40 L54.2 M5E0.4B0.4	P40.8 L50.5 M8.4E0.3B0.0	P65.5 L21 M11E2.3B0.2
Platelet	243	138	119	143	584
CRP	2.1	2.5	2.3	2.2	0.2
SGOT	50	1227	640	509	47
SGPT	48	663	654	357	182
S. bilirubin	0.39	1.36	1.00	0.76	0.65
Hepatitis viral panel (HBsAG, HCV, HAV, HEV, EBV, HSV, CMV, enterovirus)	Negative				
TB wokup	Negative				
Rickketsial serology	Negative				
Serology for leptospira	Negative				
Dengue NS1 and serology	Negative				
Typhidot and widal	Negative				
COVID-19 RAT and RTPCR	Negative				
Blood culture	Sterile				
Throat swab for H1N1	Negative				
RTPCR for EBV	Negative				
RTPCR for RSV	Negative				
RTPCR for CMV	Negative				
RTPCR for adenovirus	Positive				

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We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

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