


# Adenovirus Hepatitis in Immunocompetent Adults

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## Abstract

A 35-year-old female with no medical history presented with fever. Laboratory work was normal except for elevated liver function test (LFT): alkaline phosphatase (AP) (296), aspartate transaminase (AST) (343), alanine transaminase (ALT) (378), and international normalized ratio (INR) (1.23). Ultrasound liver was normal. Infectious workup was negative for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes simplex virus (HSV), and COVID-19. Similarly, autoimmune hepatitis, Wilson, and alpha-1 antitrypsin workup were negative. She reported taking Yogi-Kanthika (ayurvedic-proprietary medicine) on/off for seasonal sore throat, yet RUCAM-score was 2 (unlikely a drug induced injury). Respiratory-viral-panel came positive for adenovirus. With supportive treatment, symptoms and LFT trended down, thus, liver biopsy decision was deferred. We believe this is the first reported case of adenovirus hepatitis in an immunocompetent adult. Hence, we suggest that clinicians should consider a refined differential diagnosis for elevated LFT (that includes adenovirus).

## Keywords

adenovirus infection, viral hepatitis, acute hepatitis, healthy adult

## Case Report

We present a 35-year-old female with no medical history who presented complaining of fever (102°F) and several episodes of nonbilious non-bloody vomiting for 5 days prior to admission with no other gastrointestinal symptoms, or any cardiopulmonary or genitourinary symptoms. On admission, the patient was found to be feverish (100.5°F). She had no leukocytosis, but blood film exhibited bandemia (7%). She had a normal kidney function and serum electrolytes. However, she was found to have elevated liver function test (LFT): alkaline phosphatase (AP) 296, aspartate transaminase (AST) 343, alanine transaminase (ALT) 378, and elevated INR (1.23) (Table 1). The patient reported no history of liver disease or prior history of elevated LFT. She reported that she was not taking any medications however she tried to self-medicate at home with 1 tablet of Ibuprofen as well as DayQuil (acetaminophen, dextromethorphan, and phenylephrine) and NyQuil (acetaminophen, dextromethorphan, and doxylamine succinate) for 4 days (3–4 doses daily), in addition to a herbal over the counter supplement that she had been using once every 1 to 2 weeks (Yogi Kanthika—Ayurvedic proprietary medicine) for throat relief for an on/off sore throat that was never worked up before but no currently complaining off. She reported no recent travel history,

she doesn't drink alcohol, and no family history of chronic liver disease.

Infectious work up included chest X-ray, urine analysis, and blood culture that were negative for any source of infection. Further workup for the patient's transaminitis included US abdomen and hepatic doppler that showed no cholelithiasis or common bile duct (CBD) dilation. Viral hepatitis panel was non-reactive for hepatitis A virus (HAV) IgM, hepatitis B virus (HBV) antibodies, hepatitis C virus (HCV) antibody, and PCR, hepatitis E virus (HEV) IgM. Further workup was negative for cytomegalovirus (CMV), COVID-19 virus, Herpes simplex virus (HSV) 1 and 2 IgM, Infectious mononucleosis (IMN), Epstein-Barr virus (EBV) IgM, and IgG as well as EBNA. Similarly, alpha 1 antitrypsin and ceruloplasmin within normal, and anti-smooth

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**Table 1.** Liver Function Test Trend.

	On admission	HD #2	HD #3	HD #4	HD #5	Five days post discharge
AP	296	238	263	342	301	250
AST	343	624	524	454	273	52
ALT	378	577	718	810	611	186
TB	0.8	0.6	0.7	0.9	0.7	0.5
Albumin	4	3.3	3.3	3.8	3.5	4.2
INR	1.23	NA	1.17	1	1.06	1

Abbreviations: HD, hospital day; AP, Alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; TB, total bilirubin; INR, international normalized ratio.

muscle antibody (ASMA) and antimitochondrial antibodies (AMA) negative. Nevertheless, respiratory viral panel came back positive for Adenovirus infection (using BioFire respiratory panel 2.1—EZ, nucleic acid amplification testing). The patient received supportive treatment for fever and vomiting control as well as intravenous N-acetylcysteine for the acute hepatitis, and over the next few days her liver enzymes down trended (Table 1). As the patient's LFT trended down, the decision of liver biopsy was deferred and follow up as an outpatient was opted.

## Discussion

Adenovirus infection is typically self-limited among immunocompetent host, however fatal infection with multiple organs involvement can occur among immunosuppressed patients. Microbiologically, Adenoviruses are a double-stranded DNA that are classified into 7 subgroups (A-G) based on hemagglutination properties, DNA homology, and oncogenic potential. These subgroups can be further divided into 67 immunologically distinct serotypes based on genomic sequencing.<sup>1</sup> Serotypes 7, 40, and 41 cause mainly gastroenteritis and hepatitis.<sup>2,3</sup>

The available literature has shown that around 65% of adenovirus hepatitis cases develop in pediatric patients, and that the most encountered predisposing factor in the pediatric setting is history of liver transplantation, other risk factors include stem cell transplantation, chemotherapy for lymphoblastic leukemia and solid malignancies. Furthermore, few case reports among immunocompetent children have been reported.<sup>4-6</sup> In comparison, Adenovirus infection is significantly less common among adult population, and has been almost entirely reported among immunocompromised adult patients, mostly following liver transplantation or hematopoietic stem cell transplantation or solid organ transplantation.<sup>2,7</sup> Furthermore, fulminant hepatic failure is an infrequently seen sequela among immunocompromised adults, with the most published cases are single reports. Retrospective literature review showed that among 51 immunocompromised patients who developed adenovirus infection, only 2 had adenovirus hepatitis.<sup>8</sup> Similarly, a recently published study that included 100 bone marrow transplantation patients with adenovirus infections concluded that only

one patient had histological diagnosis of Adenovirus hepatitis.<sup>9</sup>

Definite adenovirus infection was defined, according to the Wisconsin criteria, by either the presence of adenovirus nuclear inclusions, by a positive result of tissue culture or PCR assay from a sterile site (respiratory tract in our patient).<sup>10</sup> Furthermore, in all reported cases of adenovirus hepatitis, diagnosis was made after exclusion of all other common causes of hepatitis. To the best of our knowledge, we here present the first case of Adenovirus hepatitis among an immunocompetent adult. Histologically, coagulative necrosis seems to be the highlight of Adenovirus hepatitis. The extent of necrosis can vary dramatically from extremely focal, spotty necrosis to extensive, massive necrosis. Interestingly, inflammatory response is mostly sparse to absent. Even more, the presence of the characteristic intranuclear viral inclusions with smudgy appearance and chromatin margination is relatively unique to Adenovirus hepatitis.<sup>2</sup>

In most cases, the treatment of adenovirus infection is supportive, mainly with hydration, NSAIDs, and bed rest. Antiviral drugs may be used in immunosuppressed people. Since invasive adenovirus disease is associated with a very high risk of mortality, therefore, it is imperative to treat adenovirus infection in a manner similar to that used for CMV infection, before it develops into a fulminant disease. Nevertheless, there are no antiviral agents approved by FDA for the treatment of adenovirus infections to date., with the use of cidofovir and ribavirin is based on case reports and case series.<sup>1</sup>

One potential argument is the likelihood of the over-the-counter Yogi Kanthika to induce drug induced liver injury (DILI). However, the onset, duration, and frequency of using the medication makes it less likely. Furthermore, using the Roussel Uclaf Causality Assessment Method (RUCAM) scale, our case scored "2," which indicates that it is unlikely to be a herbal medication adverse drug reaction.<sup>11</sup>

Literature has shown that liver tests may not be accurately predictive (or reflecting) of underlying specific diagnosis.<sup>12</sup> Hence liver biopsy has been considered the cornerstone in determining the underlying liver disease.<sup>13</sup> Nevertheless, as the patient's LFT started to trend down during the hospital admission, the decision to biopsy the radiologically normal

looking liver, was deferred and close monitoring was elected. Out-patient follow up showed further down trending of the previously elevated LFT.

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### Ethics Approval

Our institution does not require ethical approval for reporting individual case.

### Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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