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CLINICAL AND EPIDEMIOLOGICAL STUDY

Fulminant hepatitis due to human adenovirus

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Abstract
Purpose To describe the demographics, clinical manifestations, treatment and outcomes of patients with human adenovirus (HAdV) hepatitis.
Methods A case of fulminant HAdV hepatitis in a patient with chronic lymphocytic leukemia receiving rituximab and fludarabine is described. We conducted a comprehensive review of the English-language literature through May, 2012 in search of definite cases of HAdV hepatitis.
Results Eighty-nine cases were reviewed. Forty-three (48 %) were liver transplant recipients, 19 (21 %) were bone marrow transplant recipients, 11 (12 %) had received chemotherapy, five (6 %) had severe combined immunodeficiency, four (4 %) were HIV infected, two had heart transplantation, and two were kidney transplant recipients. Ninety percent (46/51) of patients presented within 6 months following transplantation. Fever was the most common initial symptom. Abdominal CT scan revealed hypodense lesions in eight of nine patients. Diagnosis was made by liver biopsy in 43 (48 %), and on autopsy in 46 (52 %). The HAdV was isolated at other sites in 54 cases. Only 24 of 89 patients (27 %) survived: 16 whose immunosuppression was reduced, six with liver re-transplantation, and two who received cidofovir and intravenous immunoglobulin.
Conclusion HAdV hepatitis can manifest as a fulminant illness in immunocompromised hosts. Definitive diagnosis requires liver biopsy. Early consideration of a viral etiology, reduction in immunosuppression, and liver transplantation can be potentially life-saving.

Keywords Adenovirus · Hepatic failure · Hepatitis · Acute liver failure · Rituximab

Introduction

Human adenovirus (HAdV) is a commonly encountered pathogen. In immunocompetent patients, HAdV infection often leads to a self-limited upper respiratory, ocular, or gastrointestinal involvement [1]. Infections usually occur during childhood, leading to serotype-specific immunity. In immunosuppressed patients, adenovirus has been associated with severe infections involving various organ systems, and can lead to significant morbidity and mortality. Risk factors include stem cell or solid organ transplantation, graft-versus-host disease, and lymphopenia [2, 3]. This is especially true in immunosuppressed children, given higher rates of primary adenoviral infection. Both new infections and reactivation have been linked to severe adenoviral disease in immunocompromised hosts [2, 4].

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The spectrum of disease manifestations ranges from asymptomatic viremia to pneumonia, hemorrhagic cystitis, enterocolitis, hepatitis, meningoencephalitis, and disseminated disease [1, 2, 4].

Herein, we describe a patient with chronic lymphocytic leukemia (CLL) receiving rituximab and fludarabine, who subsequently succumbed to HAdV hepatitis, followed by an English-language literature review of all published cases of HAdV hepatitis.

Case presentation

A 70-year-old female with a past medical history of CLL was admitted to our hospital with fevers. She had been receiving fludarabine and rituximab up until 3 months prior to admission, when subsequent doses were held for urinary recurrent urinary tract infections and a bout of *Pneumocystis jirovecii* pneumonia. She had completed a steroid taper 2 days prior to developing fevers.

Physical exam was notable for a temperature of 38.3 °C, tachycardia, and lymphadenopathy related to her CLL. Laboratory testing revealed leukopenia, but no specific infectious etiology was identified for her fever. Empiric broad-spectrum antibiotics were initiated. Blood and urine cultures were negative. Bone marrow biopsy confirmed reduced leukemic involvement.

Her fevers persisted and she developed leukopenia with lymphopenia (absolute lymphocyte count 280 cells/μL). On hospital day-6, computed tomography (CT) scans of the chest, abdomen and pelvis were obtained. A 1.6 cm hypodense non-enhancing lesion was noted in the liver (Fig. 1), with concern for neoplasm versus focal fatty infiltration. An initial attempt at liver biopsy was aborted as the lesion could not be localized by ultrasound. Liver enzymes (which were normal on hospital admission) were elevated with an aspartate aminotransferase (AST) of 965 U/L, alanine aminotransferase (ALT) of 626 U/L, and alkaline phosphatase of 282 U/L; serum bilirubin was normal. Abdominal magnetic resonance imaging (MRI) and indium-labeled white blood cell scan showed no evidence of liver abscess, but rather a focal area of uptake in the right lobe of the liver consistent with either inflammation or infection. The patient was initiated on empiric antimicrobial therapy directed towards a hepatic abscess (meropenem, vancomycin, and voriconazole). The following studies (blood or serum) were all Negative: Hepatitis A, B, and C serologies, hepatitis B virus DNA, hepatitis C virus RNA, Epstein-Barr virus (EBV) DNA PCR, cytomegalovirus (CMV) DNA PCR, aspergillus antigen, malaria smear, *Ehrlichia* serology, *Bartonella* serology and PCR, Q fever serology, human herpesvirus-6 PCR, fungal serology panel (coccidioidomycosis, histoplasmosis, blastomycosis), cryptococcal antigen, herpes simplex (HSV) type-1 and -2 antibodies, varicella zoster virus (VZV) serology, and multiple sets of peripheral blood cultures. There was evidence of prior exposure to EBV and CMV. On hospital day-10, an ultrasound-guided liver biopsy was performed, as her liver enzymes had doubled over the past 24 h. High-dose intravenous acyclovir was added to her empiric antimicrobial regimen. Her liver enzymes increased exponentially over the next 3 days, peaking at an AST of 5,590 U/L and ALT of 1,699 U/L. Her serum alkaline phosphatase remained modestly elevated at 173 U/L, and total bilirubin peaked at 5.4 mg/dL. Serum lactate dehydrogenase (LDH) was 307 U/L (normal: 122–222 U/L) on admission, and peaked at 2,046 U/L.

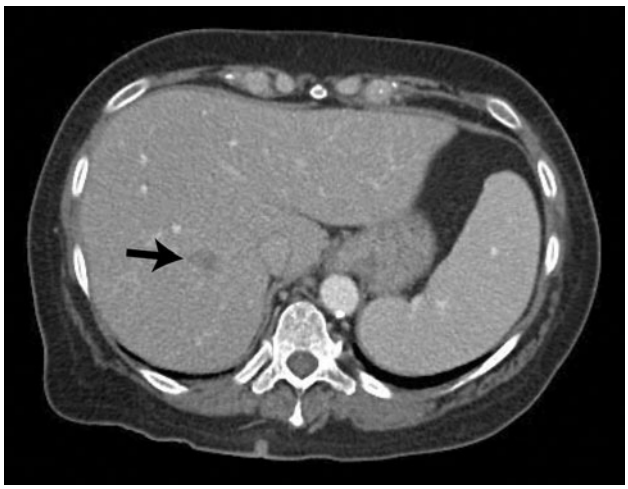

Fig. 1 CT scan of the abdomen with contrast demonstrates a hypodense lesion (*arrow*) in segment VII of the liver

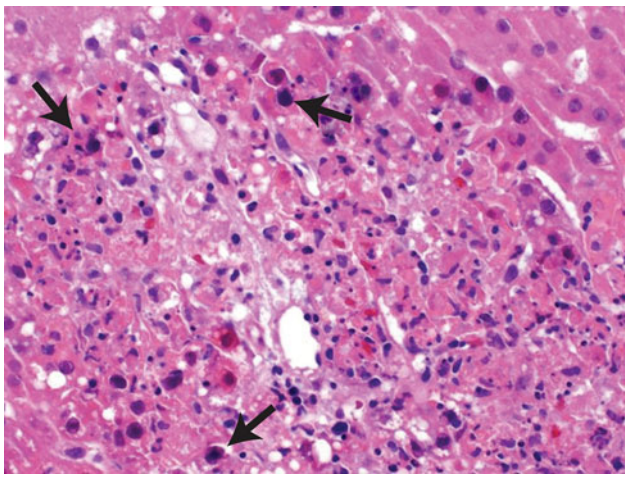

Fig. 2 Liver biopsy specimen showing hepatocytes with enlarged nuclei and intranuclear inclusions resulting in a 'smudged' appearance (*arrows*) (H & E; original magnification, ×200)

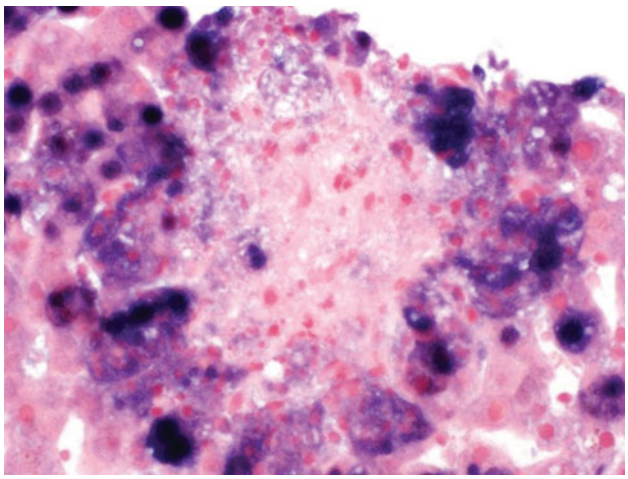

Fig. 3 Liver biopsy specimen with positive in situ hybridization for HAdV

Liver biopsy specimens revealed severe necrotizing hepatitis with multiple round necrotic foci surrounded by cells with enlarged nuclei, consistent with a viral etiology (Fig. 2). The patient required transfer to the intensive care unit for presumed sepsis. She remained persistently febrile, developed multisystem organ failure, and died on hospital day-13. Autopsy was refused by her family.

Immunohistochemical stains of the antemortem liver biopsy specimens were negative for VZV and HSV. Tissue cultures for HSV, VZV and CMV were negative. In-situ hybridization was negative for EBV, VZV, BK virus and human herpes virus-8, but positive for adenovirus (Fig. 3). Adenovirus DNA was also detected post-mortem in the liver biopsy specimen and peripheral blood by PCR. Serotype testing was not performed.

Materials and methods

A comprehensive search of the English language literature for definite cases of HAdV hepatitis was performed using OVID Medline, EMBASE and PubMed (National Library of Medicine) databases between 1960 and May 2012.

A definite (proven) case of HAdV hepatitis was defined as a patient with clinical and laboratory evidence of hepatitis in whom: (a) liver tissue (obtained either by biopsy or during autopsy) revealed histopathologic evidence of hepatic involvement, and (b) the presence of HAdV in the liver was confirmed by one of the following: immunohistochemistry, in situ hybridization, polymerase chain reaction, culture, or electron microscopy [3]. Probable and possible adenovirus hepatitis cases wherein only serology or histology was positive were excluded from our study.

The following Medical Subject Headings (MeSH) terms were used: "adenovirus hepatitis," "hepatitis, viral, human," "adenoviridae infections," "liver failure, acute," "fulminant hepatitis," "hepatic failure," "liver necrosis," and "fulminant hepatic failure."

This search yielded 217 articles. Further review of these articles yielded 69 articles that mentioned cases of HAdV hepatitis. Eighteen case reports were excluded due to insufficient documentation of HAdV hepatitis. The remaining 51 articles yielded a total of 88 cases of definite HAdV hepatitis [5–54]. With our case, the total cohort consisted of 89 cases of definite HAdV hepatitis.

Results

Of the 89 definite cases of HAdV hepatitis, 43 (48 %) were liver transplant recipients, 19 (21 %) were bone marrow transplant recipients, and 11 (12 %) had recently received chemotherapy for underlying malignancy (Table 1). In transplant patients (bone marrow or solid organ), 47 % of HAdV hepatitis occurred in the first month after transplant, and 90 % within 6 months post-transplant. Seventy-four percent of patients were on corticosteroids prior to the onset of symptoms. Calcineurin inhibitors were commonly utilized, particularly in solid organ transplant recipients. Of the 89 cases, 57 (64 %) were younger than 18 years of age, while 32 (36 %) were adults. The median age of pediatric cases was 1 year.

Fever was the initial symptom in 92 % of patients (Table 2). Other common symptoms at the time of presentation included lethargy or malaise (20 %), diarrhea (12 %) and jaundice (10 %). Transaminases were elevated anywhere from two to 110 times the upper limit of normal

Table 1 Characteristics of 89 patients with HAdV hepatitis

Characteristic	Number of patients (%)
Age	
Pediatric (0–17)	57 (64)
Adult (18 and older)	32 (36)
Gender	
Male	32 (53)
Female	28 (47)
Underlying condition	
Liver transplant	43 (48)
Bone marrow transplant	19 (21)
Chemotherapy	11 (12)
SCID	5 (6)
HIV infection	4 (4)
Renal transplant	2 (2)
Heart transplant	2 (2)
Neonates (no known comorbidity)	2 (2)
CLL	1 (1)

Table 2 Clinical manifestations, imaging findings, histopathology and outcomes of patients with HAdV hepatitis

	Number of patients (%)
Presenting symptoms ($N = 74$)	
Fever	68 (92)
Lethargy/malaise	15 (20)
Diarrhea	9 (12)
Jaundice	7 (10)
CT imaging findings ($N = 9$)	
Multiple hypodense lesions	7 (78)
Single hypodense lesion	1 (11)
Normal	1 (11)
Liver histopathology ($N = 64$)	
Necrosis	60 (94)
Intranuclear inclusions	46 (72)
Smudge cells	13 (21)
Method of adenovirus detection in the liver ($N = 89$)	
Culture	58 (65)
Immunohistochemistry	53 (60)
Electron microscopy	48 (54)
Polymerase chain reaction	5 (6)
In-situ hybridization	4 (5)
Outcome ($N = 89$)	
Survival	24 (27)
Death	65 (73)

on presentation. Abdominal CT scan showed hypodense lesions in eight of nine cases (Table 2), while abdominal ultrasound was normal in six of nine cases in whom these studies were performed.

Diagnosis of AH was made by antemortem liver biopsy in 43 (49 %), and on autopsy in 45 (51 %) of patients. The method used to identify adenovirus in the liver tissue is detailed in Table 2. Adenovirus viremia was detected by PCR in 11 of 12 cases (92 %) in whom the test was performed. In several cases, including our own, the liver biopsy and serum PCR results became available after the death of the patient, highlighting the rapid progression of this disease.

Hepatic necrosis was the most common histopathologic finding (94 %), followed by viral inclusions (72 %) and smudge cells (21 %) (Table 2). Serotypes 5 and 2 were the most frequently isolated (50 and 22 %, respectively). Liver transplant patients were more likely to have infection with serotype 5 than any other serotype (25 of 37), while bone marrow transplant recipients frequently had serotype 2 (five of 11). Serotype 5 was the most commonly identified serotype in children with AH, found in 33 of 54 cases (61 %). In adults serotypes 2 and 5 were found with equal frequency (5/14 cases or 36 %). HAdV was isolated at other sites in 54 cases (50 % from lung or bronchoalveolar lavage samples, 43 % from the urinary tract, 33 % from the gastrointestinal tract and 22 % from throat culture).

Table 3 Management-based outcomes of patients with HAdV hepatitis. ($N = 47$)

Treatment	Number of cases	Survival
Reduced immunosuppression	25	14 (59 %)
Reduced immunosuppression + antiviral	1 cidofovir	1
	1 ribavirin	1
Liver re-transplantation	12	6 (50 %)
Cidofovir + IVIG	2	2
IVIG alone	4	0
Cidofovir alone	2	0

In the 25 patients in whom the only treatment modification was a reduction in immunosuppression, 14 (59 %) survived (Table 3). Two additional patients treated with a reduction in their immunosuppression and an antiviral agent (cidofovir or ribavirin) also survived. Retransplantation in liver transplant recipients was successful in six of 12 patients. Of those who did not survive retransplantation, five died in the perioperative period, and one had recurrence of HAdV hepatitis in the second transplanted liver. Intravenous immunoglobulin therapy alone was unsuccessful in all four patients in whom it was administered. Three of five patients who received cidofovir survived. One of these three patients also had a reduction in immunosuppressive therapy, and the other two also received IVIG in addition to cidofovir. The diagnosis of HAdV hepatitis was delayed in the two patients in whom cidofovir was unsuccessful, and therapy was initiated after multisystem organ failure was present. In three patients who received ribavirin, the only survivor also had a reduction in immunosuppression. Unfortunately, overall outcomes in patients with HAdV hepatitis was poor, with only 24 of 89 (27 %) published cases surviving regardless of treatment. Recipients of liver transplants were more likely to survive (21/43 cases, 49 %) than those with bone marrow transplants (2/19 cases, 10 %).

Discussion

Fulminant hepatic failure is characterized by the acute onset of severe liver dysfunction with resultant coagulopathy and hepatic encephalopathy. Coma, multisystem organ failure, and death are potential consequences. In a prospective study of fulminant liver failure in the United States (1998–2001), acetaminophen toxicity was the leading cause, accounting for 39 % of cases, followed by liver failure of indeterminate cause (17 %), idiosyncratic drug

reactions (13 %) and Hepatitis A and B viruses (12 %). Less common etiologies were autoimmune hepatitis, shock liver, Budd–Chiari syndrome, Wilson's disease and pregnancy. Outcomes and transplant-free survival varied with the etiology of liver failure [55].

Although the majority of HAdV infections in immunocompetent hosts are self-limited, immunosuppressed patients are at risk for severe and fatal HAdV disease. Risk factors for severe HAdV infection include allogeneic hematopoietic stem cell transplantation with an unrelated donor graft or cord blood graft, solid organ transplantation, T cell depletion, severe (grade III–IV) graft-versus-host disease, severe lymphopenia (<200 cells/μL), alemtuzumab-containing conditioning regimens, corticosteroid therapy, and HIV infection [1–4, 20, 56, 57]. In solid organ transplant recipients, adenovirus tends to infect the transplanted organ [1]. Indeed, our review found that most reported HAdV hepatitis cases occurred in liver transplant recipients.

The HAdV hepatitis is an uncommon manifestation of adenoviral infection. In one review, the incidence of HAdV hepatitis in pediatric liver transplant recipients was noted to be 2–4 % [57]. Pediatric patients seem to be at highest risk, as has been acknowledged in previous reviews [1, 2, 4]. This is thought to be related to the higher likelihood of primary infection in younger patients, as the majority will have serologic evidence of prior infection by age 10. However, viral reactivation has also been implicated in patients with HAdV hepatitis [1, 2, 4, 57]. The proportion of patients with primary infection versus HAdV reactivation in immunosuppressed patients is unknown [4].

This literature review highlights the potential for rapidly fatal fulminant hepatic failure in patients with HAdV hepatitis, which resembles fulminant hepatitis caused by herpes simplex virus [58]. Fever is the single most common presenting symptom; others include malaise and diarrhea. These symptoms are non-specific and would not lend any clues towards the diagnosis of HAdV hepatitis at this stage of the illness. Jaundice or hepatomegaly is less frequently noted on presentation. The utility of various imaging techniques for HAdV hepatitis has not previously been studied. In our literature review, an abdominal CT scan showed hypodense lesions in eight of nine cases (Table 2), while abdominal ultrasound was normal in six of nine cases.

The role of HAdV serology is limited in the immunosuppressed host due to the lack of sensitivity and the presence of serum antibodies in the majority of the pediatric and adult population from prior exposure [1]. Positive serum adenovirus PCR in conjunction with clinical and laboratory findings of hepatitis favors a probable diagnosis of HAdV hepatitis. In our review, although serum HAdV PCR testing was infrequently done (in only 12 of 89 cases), it was positive in most (11 of 12 cases). Serum (or plasma) HAdV PCR testing should be considered in immunosuppressed patients with persistent fever, or in those with progressive elevation of liver enzymes. However, definitive diagnosis requires liver biopsy. On histopathology, necrosis with hepatocytes containing enlarged nuclei and intranuclear inclusions with a smudged appearance are seen (Table 2; Fig. 2). The HAdV hepatitis can be confirmed by a positive PCR, in situ hybridization, specific immunostains, or culture of the liver tissue [1].

There is no proven effective treatment for HAdV hepatitis [1]. Ribavirin and cidofovir have been utilized in anecdotal cases [1, 2, 38, 59]. In our review of the literature, timely diagnosis and reduction in the intensity of immunosuppression was associated with favorable outcomes. Indeed, liver transplant recipients had more favorable outcomes compared to bone marrow transplant recipients, possibly due to the ability to reduce immune suppression in that population. The utility of antiviral agents (cidofovir or ribavirin) in patients with HAdV hepatitis is currently unclear, and requires further study. In our review, patients who were given antivirals alone (without concurrent IVIG or reduction in immunosuppression) did not survive.

Rituximab is a monoclonal antibody that binds to the CD20 antigen on B cells. It is frequently used in hematologic malignancies such as non-Hodgkin lymphoma and CLL. Rituximab induces B-cell depletion and can lead to prolonged hypogammaglobulinemia [60, 61]. Reactivation of viral infections such as CMV, hepatitis B, EBV, and varicella-zoster virus, as well as several opportunistic infections (toxoplasmosis, *P. jirovecii* pneumonia, and progressive multifocal leucoencephalopathy) has been reported following rituximab therapy [27, 60–63]. Ours is the second reported case of HAdV hepatitis after treatment with rituximab [27].

Our study has several limitations. Being a retrospective review that spanned six decades, it is subject to reporting bias and varied management practices over the years. We used strict criteria for defining a case of HAdV hepatitis in order to capture confirmed cases; we may have, therefore, excluded some cases of probable or less severe HAdV hepatitis, and those that did not undergo liver biopsy. There were several case reports that lacked detailed information about the diagnostic workup and management, limiting the strength of our conclusions. For example, only 18 of the 89 cases reported abdominal imaging findings. In addition, we were unable to determine the role of antivirals in HAdV hepatitis given the lack of timely diagnosis and institution of antiviral therapy in a majority of patients.

Conclusions

The HAdV hepatitis is an uncommon, progressive, and rapidly fatal illness mostly limited to immunosuppressed

patients. Its clinical course mimics progressive and fulminant hepatitis due to herpes simplex virus. Clinical manifestations are nonspecific. Physicians must consider adenovirus in the list of potential etiologic agents causing fever and elevated liver enzymes in the immunocompromised host. Liver biopsy demonstrating characteristic viral inclusions, along with a positive PCR, immunostain, or culture can confirm the diagnosis of HAdV hepatitis. Timely consideration of a viral etiology, serum PCR testing, reduction in the intensity of immunosuppression, and initiation of antiviral therapy directed towards herpes simplex virus and adenovirus while awaiting diagnostic confirmation can be potentially life-saving. Liver transplantation is a viable option in the setting of progressive hepatic failure, especially in liver transplant recipients who develop HAdV hepatitis.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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