HAV-induced Acalculous cholecystitis: A case report and literature review

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Abstract

Hepatitis A virus (HAV) has some life-threatening extrahepatic complications, such as acute acalculous cholecystitis (AAC). We herein reported a HAV-induced AAC case in a young female, who developed acute liver failure (ALF) during the course of her disease and preform a literature review.

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ABSTRACT

Hepatitis A virus (HAV) has some life-threatening extrahepatic complications, such as acute acalculous cholecystitis (AAC). We herein reported a HAV-induced AAC case in a young female, who developed acute liver failure (ALF) during the course of her disease and preform a literature review.

Keywords: Hepatitis A virus, Acalculous cholecystitis, HAV-induced AAC

INTRODUCTION

Hepatitis A virus (HAV), a positive-sense, single-stranded RNA virus in the Picornaviridae family, was discovered in 1976 by Feinstone and colleagues.[1–3] HAV is transmitted through person-to-person contact via the oral-fecal route from food and water contamination.[4] Infecting around 1.4 million cases per year globally, HAV is seen all over the world; nevertheless, the incidence of HAV has declined considerably in countries that implemented vaccination and immunization.[1,5,6] HAV mostly causes a self-limited infection that is usually clinically asymptomatic.[7] Prodromal symptoms, which are more common in children than adults, manifest as fever, malaise, nausea, vomiting, and anorexia about one month after exposure.[2] The main symptoms in adults include diarrhea and jaundice, while pediatric infections are often asymptomatic.[8]

Although mostly self-limiting, HAV has several unusual and life-threatening hepatic manifestations and complications, such as acute liver failure, relapsing hepatitis and HAV-associated prolonged cholestasis.[9–11] Additionally, HAV has important and less-distinguishing extrahepatic manifestations, including skin rash, acute renal failure, myocarditis, guillain barre syndrome, ascites, pleural effusion, and AAC.[12–15] As a rare extrahepatic manifestation of HAV, AAC is an acute inflammatory disease of the gallbladder without evidence of cholecystolithiasis which comprises 5-10% of all acute cholecystitis cases.[16]AAC usually manifests in critically-ill patients, especially those hospitalized in the intensive care unit (ICU), and is associated with several risk factors (e.g., fasting, total parenteral nutrition, mechanical ventilation, shock, and sepsis) and high mortality (around 30-50%).[17–19] The pathogenesis of AAC is multifactorial, anatomical and functional, such as gallbladder ischemia, bile excretion disorder, cholestasis, and microbial infection.[16,20]

Herein, we reported a case of AAC as a complication of HAV in a 35-year-old female without any past medical history, provided a comprehensive literature review, and discussed importance, challenges and critical management of HAV-induced AAC.

CASE PRESENTATION

A 35-year-old white woman was presented with anorexia, fever, nausea, nonbilious emesis and a five-day history of epigastric abdominal pain. There was no history of dark urine and stool discoloration. She denied any history of previous diseases such as sexual transmitted diseases or malignancy, in addition to using tobacco, alcohol, and illicit drug use. She was a housewife and had no history of contact with an individual with similar symptoms. taking certain medication or recent travel in the last 6 months and her family history was noncontributory. The vaccination history of the patient has been done in full according to the national protocol.

At the admission, physical examination showed body temperature of 37.3[?]C (axillary), heart rate of 75 beats/minute, blood pressure of 110/75 mmHg, and an icteric sclera. On the abdominal examination, there was severe tenderness during pressure in the right hypochondrium area (below the 9th-10th rib) during inhalation (positive Murphy's sign), without peritoneal signs or fluid wave. There was no evidence of splenomegaly and hepatomegaly on abdominal palpation. Skin examination revealed no evidence of characteristic skin lesions such as palmar erythema, spider angioma, and/or caput medusae.

Blood counts showed a white blood cell count at 3.2×10^9 /liter, hemoglobin level of 13.3 g/dl, and platelet count is 162×10^9 /liter. The serum level of aspartate aminotransferase (AST) was 3665 IU/L (Normal $<$ 40 IU/L), alanine aminotransferase (ALT) 3036 IU/L (Normal $<$ 40 IU/L), gamma glutamyl transferase (GGT) 26 IU/L, (Normal $<$ 40 IU/L) and alkaline phosphatase (ALP) 116 IU/L (Normal $<$ 206 IU/L). The

laboratory analysis revealed hyperbilirubinemia of 4.47 mg/dL (Normal < 1.1 mg/dL) with a conjugated bilirubin of 2.31 mg/dL. Further, the C-reactive protein (CRP) level was 71 mg/L. Laboratory investigations of the patient in the course of hospitalization are listed in Table 1.

Furthermore, on the evaluation of acute liver disease, the initial routine liver testing was requested**,** in which positive serologies for viral hepatitis suggested acute hepatitis A infection (Table 2). Serologies was detected via Enzyme-linked immunosorbent assay (ELISA), using a Roche Cobas C311 chemistry analyzer, HITACHI. In additional investigations, serum levels of antinuclear antibodies (ANA), anti-smooth muscle antibody (ASMA), and anti-liver kidney microsomal type 1 (anti-LKM-1) antibody were measured, all of which were normal. EBV IgM, IgG, and heterophile antibody were negative.

On imaging. abdominal ultrasound revealed liver and spleen with normal parenchymal sizes and hepatic echotexture was homogenous without any evidence of intra- and extrahepatic bile ducts dilatation (the diameter of the common bile duct [CBD] were reported to 4 millimeters). Notably a distend gallbladder with the thickened wall (16 mm) and positive sonographic Murphy's sign, in addition to perivesical liquid collection without any calculous or sludge was observed on gallbladder ultrasound exam (Figure 1). There was no evidence of pancreatic ductal dilatation and peripancreatic lymphadenopathy.

Based on clinical, laboratory, and imaging findings, the presumptive diagnosis was acute ACC as an extrahepatic complication of HAV. The patient was being carefully monitored and treated with intravenous fluids conservatively, while she patient became irritable which gradually led to lethargy and disorientation to time. On physical examination, she had asterixis, dyspraxia, slurred speech (indicating a grade 2 hepatic encephalopathy), as well as a severe decline in liver function (indicating of acute live failure) (Table 1).

With a diagnosis of ALF, she was immediately managed with close airway and hemodynamic monitoring in the intensive care unit (ICU), while being candidate for liver transplantation. To investigate the possible etiologies of ALF in conjunction or addition to HAV, more thorough laboratory studies including autoimmune hepatitis markers, drug/acetaminophen screen, blood cultures, other viral studies, in addition to head and abdomen computer topography (CT) scanning (Table 3). Based on the study results, we could not find any other suggestive findings, and the most probable cause of ALF was HAV infection. Spiral abdominopelvic CT-scan also demonstrated a markedly thickened and edematous gallbladder wall and mild free fluid in right side of abdominopelvic cavity without any obvious signs of gallbladder stone, same as the previous ultrasonography (Figure 2). Moreover, consultations with intensive care, gastroenterology specialist for metabolic parameters monitoring, infection surveillance, and liver biopsy to further confirm the suggestive cause was requested.

Nevertheless, the general condition of the patient was improving and the patient became mentally alert, fully aware of the place and time, communicating with the people very well and the asterxia was completely gone, while being managed with just close monitoring and supportive treatment with ursodeoxycholic acid (UDCA), and N-acetyl cysteine (NAC). for another 7 days. Due to the relative recovery of the patient and the downward trend of the patient's liver enzymes titer, she was discharged from the hospital with the recommendation to follow up in another 3 months. At the patient's re-visit three months later, the patient did not mention any clinical complaints. The serum level of liver enzymes had reached the normal level (Table 1). Further abdominal ultrasonography 3 months after admission demonstrated that the liver had a normal size and parenchymal echo, intra and extrahepatic ducts had normal size (CBD=4 mm), and gallbladder had normal wall thickness (less than 3 mm) and without any calculous, sludge, and perivesical fluid collections (Figure 3).

DISCUSSION:

AAC was first reported in 1844 by Duncan J in a fatal case of AAC complicating an incarcerated hernia.[21] In fact, AAC is a type of acute cholecystitis which constitutes 5 - 10% of all acute cholecystitis without presence of gallstones,[19,22]which occurs in the setting of gallbladder dysfunction and often occurs in critically-ill patients in the ICU.[19] AAC is a life-threatening state in which the critical complications include necrosis and perforation of the gallbladder.[23]

Microbial infections can be one of the main causes of AAC.[16] The most common microbial causes of AAC are: 1. Gram-negative bacteria, such as *K.bacillus, Samonella spp, Brucellosis, Vibrio cholera* , *Coxiella burnetii* , and*leptospirosis* , 2. gram positive bacteria, such as*E.faecalis, S.fusarium spp, Lactococcus spp, Proteus,* and*Psuedomonas,* 3. viral infections, such as *Cytomegalovirus (CMV), Epstein–Barr virus (EBV), Dengue virus, Human Immunodeficiency Virus (HIV)* and *viral hepatitis (A, B, C, E).* [16,24–39]

The main clinical features of AAC are fever, nausea and vomiting, icterus, abdominal pain (mostly in the right upper quadrant), and positive Murphy's sign.[22] Laboratory investigations may show increased ALT, AST, ALK, total and direct bilirubin; however, normal levels do not rule out the disease.[40] The initial AAC diagnosis is done clinically, which is confirmed with the help of abdominal ultrasound.[22] The five main ultrasonographic diagnostic criteria of AAC are: 1. Gallbladder distention; 2. Gallbladder wall thickening greater than 3.5 mm; 3. Absence of stone (no acoustic shadow) or sludge in the gallbladder; 4. Perivesical liquid collection; 5. Absence of intra- and extrahepatic bile duct dilatation with a sensitivity, specificity, and accuracy 88.9%, 97.8%, and 96.1%, respectively.[40,41]

On the other side, in term of a rare etiology for AAC, HAV presents with various clinical manifestations which are distinguishing in pediatrics and adults. In pediatrics, most patients are asymptomatic; although infection usually is symptomatic in adults.[10] After an incubation of period of 15-50 days, typical symptoms include fever, malaise, nausea, vomiting, abdominal pain, dark urine, and jaundice appear.[42,43] HAV is usually self-limiting and improves with supportive treatments such as hydration, antiemetics for severe vomiting, and antipyretics for high fever.[44] However, the potential complications of HAV are ascites, pleural effusion, sinus bradycardia, renal failure, hepatic necrosis and fulminating hepatitis, and AAC.[12,14,41]

HAV-induced AAC is rare with only 29 reports from 1992 to 2022 consisted of a total 71 patients in the literature; of these patients, 44 (61.9%) were under 18 years old and 27 (31.8%) were over 18 years old (Table 3).The incidence of HAV-induced AAC in the adult population is less than pediatrics, and it is mostly seen in the developing and endemic areas of HAV;[22,45] We found that the youngest patient was 2.5-year-old and the most elderly was 81-year-old.[46,47] HAV-induced AAC can lead to gallbladder perforation, cholangitis, pleural effusion, ascites, acute pancreatitis, and co-infection with various microorganisms.

The case presented here is a 35-year-old female patient without any past medical history with the clinical sign and symptoms relevant to HAV-induced AAC which was confirmed by elevated liver function tests (LFT), positive serology (HAV IgM +) and abdominal ultrasonography, Despite being monitored and treated conservatively, our patient developed hepatic encephalopathy and acute liver failure (ALF) suggested by worsening LFT. Thus, she went under critical care as well as consultation and investigation for further etiologies of ALF, while candidate for liver transplantation. However, with just close monitoring and supportive treatment (without performing any surgery or liver transplant), the patient responded and her general condition improved.

The most important educational point of this study is that although HAV infection is typically an asymptomatic and self-limited disease, it can be associated with serious complications that may deteriorate patient's condition, prognosis and outcome. With prompt diagnosis of AAC, consideration of rare microbial causes such as viral hepatitis such as HAV, and implantation of close monitoring and conservative therapy, serious complications (e.g., gallbladder gangrene and perforation), and surgeries (i.e., cholecystectomy) can be prevented; even in young adult patients without any past medical history in which this usually self-limiting disease may progress rapidly towards hepatic encephalopathy and ALF.

CONCLUSION

AAC is one of the rare extra-hepatic manifestations caused by HAV, in which a person experiences worsening abdominal pain, progressive decline in liver function, hepatic encephalopathy and ALF. Considering the possibility of HAV-induced AAC can be vital to manage such a rarely described condition and to prevent the critical and life-threatening complication associated with this condition, such as necrosis and perforation of the gallbladder

ABBREVIATIONS

HAV: Hepatitis A virus

AAC: Acute acalculous cholecystitis

AST: Aspartate transaminase

ALT: Alanine transaminase

GGT: gamma-glutamyl transferase

ALP: alkaline phosphatase

LFT: liver function test

ALF: acute liver failure

CRP: C-reactive protein

ELISA: Enzyme-linked immunosorbent assay

ANA: antinuclear antibodies

ASMA: anti-smooth muscle antibody

Anti-LKM-1: Anti-Liver kidney microsomal type 1

EBV: Epstein-Barr virus

CBD: common bile duct

CMV: Cytomegalovirus

HIV: Human Immunodeficiency Virus

UDCA: ursodeoxycholic acid

NAC: N-acetyl cysteine

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CONFLICT OF INTREST

The authors declare that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

The datasets supporting the conclusions of this article are included within the article. The datasets used during the current study are available from the corresponding author on reasonable request.

ETHICAL APPROVAL

The Institutional Review Board and Ethics Committee of Kerman University of Medical Sciences waived the requirement for ethical approval. Also, written informed consent was obtained from the patient to publish this case report and any accompanying images.

AUTHOR CONTRIBUTIONS

FS, SS and SJ was responsible for the patient's care. ZN were involved in patient documents and data collection. MN, PP, RS, AG and MR. reviewed the literature and drafted the manuscript. MR reviewed and edited the final version. All authors read and approved the final manuscript.

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Figure legends:

Table 1: Laboratory investigations of the patient in the course of hospitalization and follow-up

(WBC: white blood cell; Hb: hemoglobin; AST: aspartate transaminase; ALT: alanine

transaminase; ALP: alkaline phosphatase; INR: international normalized ration)

Table 2: Viral markers for viral hepatitis(HAV Ab: Hepatitis A virus Antibody; HBs Ag: Hepatitis B surface antigen; HBc Ab: Hepatitis B core antibody (HBcAb); HCV Ab: Hepatitis C virus Antibody; HEV Ab: hepatitis E virus antibody)

Table3: Review of the age, country, main clinical presentation, associated complications, and treatment modalities of patients with acalculous cholecystitis due to viral hepatitis A published in the literature. (HAV: Hepatitis A virus; ACC: Acute Acalculous Cholecystitis; HEV: Hepatitis E virus; CMV: Cytomegalovirus; NA: not available)

Figure 1 :Abdominal ultrasonography showing distend gallbladder with the thickened wall with perivesical liquid collection without any calculous or sludge

Figure 2 : Abdominopelvic CT-scan showing markedly thickened and edematous gallbladder wall without any obvious signs of gallbladder stone

Figure 3 : Abdominal ultrasonography 3 months after admission demonstrated a gallbladder with normal wall thickness (less than 3 mm) without acalculous, sludge, and perivesical fluid collection.

Parameters Days	WBC (4-10 $*10^9$ /L)	Hb (12-16 gr/dl)	Platelet (150-400$*10^9$ /L)	AST (5-40 IU/L)	ALT (up to 40 IU/L)	ALP (0-206 IU/L)	Total Bilirubin (0.2-1.1 mg/dl)	Direct Bilirubin (0-0.3 mg/dl)	IN
1^{th}	3.2	13.3	162	3665	3036	116	4.47	2.31	1.2
3^{th}	2.7	12.6	186	4607	3789	190	4.9	3.1	1.4
7^{th}	6.8	12.1	280	4890	4130	163	3.9	2.1	1.8
14^{th} (Discharge)	5.1	12.1	225	364	298	134	3.5	1.9	1.3
3 month later (Follow-up)	4.6	12.7	262	43	37	144	1.1	0.6	1.3

Table 2: Laboratory investigations of the patient in the course of hospitalization and follow-up

(WBC: white blood cell; Hb: hemoglobin; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; INR: international normalized ration)

Viral Marker	Result
HAV Ab (IgM)	Positive
HAV Ab (IgG)	Negative
HBs Ag	Negative
HBc Ab (IgM)	Negative
HCV Ab	Negative
HEV Ab(IgM)	Negative

Table 3: viral markers for viral hepatitis(HAV Ab: Hepatitis A virus Antibody; HBs Ag: Hepatitis B surface antigen; HBc Ab: Hepatitis B core antibody (HBcAb); HCV Ab: Hepatitis C virus Antibody; HEV Ab: hepatitis E virus antibody)

author	Year	Age	Gender	Main clinical presentation	Associated complications	Treatment	country
Black and Mann.[14]	1992	6-year-old	Male	NA	NA	Surgery	UK
Mourani et al.[48]	1994	68-year-old	Male	Fever, N/V	Cholangitis	Surgery	USA
Ciftci et al.[49]	2001	7-year-old	Male	Abdominal pain Icterus, Dyspnea	Pleural effusion	Surgery	Turkey

author	Year	Age	Gender	Main clinical presentation	Associated complications	Treatment	country
Ozaras et al.[13]	2003	28-year-old	Male	Abdominal pain dark urine	NO	Conservative therapy	Turkey
Ozaras et al.[13]	2003	20-year-old	Female	Jaundice, N/V Malaise, Pruritus	NO	Conservative therapy	Turkey
Dalgic et al.[50]	2005	11-year-old	Female	Abdominal pain Fever, N/V	NO	Conservative therapy	Turkey
Basar et al.[51]	2005	19-year-old	Female (pregnant)	N/V, Fatigue	NO	Conservative therapy	Turkey
Bouyahia et al.[52]	2008	14-year-old	Male	Abdominal pain Fever	NO	Conservative therapy	Tunisia
Melero Ferrer et al.[53]	2008	39-year-old	Female	Abdominal pain Fever, Jaundice	NO	Surgery	Spain
de Souza et al.[41]	2009	16-year-old	Male	Abdominal pain Fever, N/V	NO	Conservative therapy	Brazil
Arroud et al.[54]	2009	11-year-old	Male	Abdominal pain Fever, N/V	NO	Conservative therapy	Morocco
Suresh et al.[47]	2009	2.5-year-old	Female	Abdominal pain Fever, Dark urine	NO	Conservative therapy	India
Erdem et al.[55]	2010	12-year-old	Male	Fever, Icter, N/V	Pleural effusion ascites	Conservative therapy	Turkey
Arcana et al.[29]	2011	14-year-old	Male	Abdominal pain Fever, Icter, N/V	Acute pancreatitis	Conservative therapy	Peru
Hasosah et al.[56]	2011	13-year-old	Female	Fever, Icter, N/V	NO	Conservative therapy	Saudi arabia
Herek et al.[57]	2011	9-year-old	Male	Abdominal pain Fever, N/V	NO	Conservative therapy	Turkey
Prashanth et al.[58]	2012	12-year-old	Female	Abdominal pain N/V	NO	Conservative therapy	India
Kaya et al.[40]	2013	31-year-old	Female	Abdominal pain N/V	NO	Conservative therapy	Turkey
Cuk et al.[46]	2014	81-year-old	Female	Fever, Icter	Perforated ACC	Surgery	Denmark

author	Year	Age	Gender	Main clinical presentation	Associated complications	Treatment	country
Aldaghi et al.[59]	2015	5-year-old	Male	Abdominal pain Icter	NO	Conservative therapy	Iran
Bura et al.[60]	2015	Case series of 18 patients	Male & Female	Abdominal pain	NO	Conservative therapy	Poland
Ghosh et al.[61]	2017	4-year-old	Female	Fever, Icter	Pleural effusion Salmonella paratyphi A co-infection	Conservative therapy	India
Dalai et al.[62]	2018	3-year-old	Female	Abdominal pain Fever	Pleural effusion ascites	Conservative therapy	India
Ormarsdottir et al.[63]	2018	Case series of 4 patients	Male & Female	Abdominal pain N/V	NO	later elective surgery	Iceland
Velev et al.[64]	2019	Case series of 6 patients	Male & Female	Abdominal pain	NO	Conservative therapy	Bulgaria
Palacios et al.[65]	2020	32-year-old	Female	Abdominal pain Fever, Dyspnea	Pleural effusion Ascites HEV co-infection	Conservative therapy	Peru
Hamid et al.[66]	2021	37-year-old	Male	Abdominal pain Vomiting, Dark urine	CMV co-infection	Conservative therapy	India
Cortellazo et al.[67]	2022	14-year-old	Female	Abdominal pain Fever, Icter	NO	Conservative therapy	Italy
shahi et al.[68]	2022	16-year-old	Male	Abdominal pain, Dyspnea, Fever, N/V	Pleural effusion ascite	Conservative therapy	Nepal

Table 4:Review of the age, country, main clinical presentation, associated complications, and treatment modalities of patients with acalculous cholecystitis due to viral hepatitis A published in the literature.

(HAV: Hepatitis A virus; ACC: Acute Acalculous Cholecystitis; HEV: Hepatitis E virus; CMV: Cytomegalovirus; NA: not available)