Received: 4 February 2023 | Revised: 2 April 2023 | Accepted: 11 April 2023

DOI: 10.1002/ccr3.7254

CASE REPORT

Clinical Case Reports Open Access WILEY

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 present HAV-induced AAC in a young female, based on clinical, laboratory, and imaging findings, and conduct a literature review. The patient became irritable, which progressed to lethargy, as well as a significant decline in liver function, indicating acute liver failure (ALF). She was immediately managed in the intensive care unit with close airway and hemodynamic monitoring after being diagnosed with ALF (ICU). The patient's condition was improving, despite only close monitoring and supportive treatment with ursodeoxycholic acid (UDCA) and N-acetyl cysteine (NAC).

KEYWORDS

acalculous cholecystitis, HAV-induced AAC, Hepatitis A virus

1 | 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 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 worldwide; nevertheless, the incidence of HAV has declined considerably in countries that implementing 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 1 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] Extrahepatic manifestations of HAV include skin rash, acute renal failure, myocarditis, Guillain–Barre syndrome, ascites, pleural effusion, and acute acalculous cholecystitis (AAC).[12–15] AAC, a rare extrahepatic manifestation of HAV, is an acute inflammatory disease of the gallbladder without evidence of cholecystolithiasis that accounts for 5%–10% of all cases of acute cholecystitis.[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, cholestasis, and microbial infection.[16,20]

Although some patients, both children and adults, have been diagnosed with HAC-induced AAC around the world in recent years,[21–24] this is the first adult case of AAC as a HAV complication in Iran. We present a 35-year-old female with no prior medical history who developed HAV-induced AAC, liver encephalopathy, and acute liver failure (ALF), as well as a comprehensive literature review and discussion of the importance, challenges, and critical management of HAV-induced AAC.

2 | CASE PRESENTATION

A 35-year-old white woman 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. She was a housewife and had no history of contact with an individual with similar symptoms. Taking certain medication, recent travel in the last 6 months, and her family history was noncontributory. The patient was up-to-date on all the mandatory vaccinations 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 abdominal examination, there was severe tenderness in the right hypochondrium area (below the 9th-10th rib) during inspiration (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.

Complete blood count (CBC) results revealed a white blood cell count of 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 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 were detected using an enzyme-linked immunosorbent assay (ELISA) on a Roche Cobas C311 chemistry analyzer manufactured by HITACHI. Serum levels of antinuclear antibodies (ANA), anti-smooth muscle antibody (ASMA), and anti-liver kidney microsomal type 1 (anti-LKM-1) antibody were all normal in additional studies. IgM, IgG, and heterophile antibodies were all negative for EBV.

Abdominal ultrasound revealed normal parenchymal sizes in the liver and spleen, as well as homogeneous hepatic echotexture with no evidence of intra- and extrahepatic bile duct dilatation (the diameter of the common bile duct [CBD] was reported to be 4 millimeters). Notably, a distended gallbladder (red arrow in Figure 1) with a not mesh-like thickened wall (16 mm), positive sonographic Murphy's sign, as well as perivesical liquid collection without any calculous or sludge in gallbladder (Figure 1).

The suspected diagnosis was ACC as an extrahepatic complication of HAV, based on clinical, laboratory, and imaging findings. The patient was carefully monitored

TABLE 1 Laboratory investigations of the patient in the course of hospitalization and follow-up.

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)	INR
1th	3.2	13.3	162	3665	3036	116	4.47	2.31	1.2
3th	2.7	12.6	186	4607	3789	190	4.9	3.1	1.4
7th	6.8	12.1	280	4890	4130	163	3.9	2.1	1.8
14th (Discharge)	5.1	12.1	225	364	298	134	3.5	1.9	1.3
3 months later (Follow-up)	4.6	12.7	262	43	37	144	1.1	0.6	1.3

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

and conservatively treated with intravenous fluids while she became irritable, which gradually led to lethargy and disorientation. 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 acute liver failure; Table 1).

With a diagnosis of ALF, she was immediately managed with close airway and hemodynamic monitoring in the intensive care unit (ICU). 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 computed tomography (CT) scanning (Table 2). The most likely cause of ALF, based on the results of the study, was HAV infection; no other findings were suggestive. A spiral abdominopelvic CT scan revealed a markedly thickened, distended (yellow arrow in Figure 2), and edematous gallbladder wall (blue arrow in Figure 2) with inflamed surrounding fat and mild free fluid in the right side of the abdominopelvic cavity, similar to the previous ultrasonography (Figure 2). In addition, consultations with intensive care gastroenterology specialists for metabolic parameter monitoring, infection surveillance, and liver biopsy were requested to further confirm the suggestive cause.

Nevertheless, the general condition of the patient was improving, and the patient became mentally alert, fully aware of the place and time, and able to communicate with others very well, and her asterixis was completely gone while being managed for 7 days with just close monitoring and supportive treatment with lactulose, N-acetyl cysteine (NAC), and ursodeoxycholic acid (UDCA), which has an anti-inflammatory effect, inhibits sludge formation, and reduces biliary pain.[25] 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 revisit 3 months later, the patient did not mention any

TABLE 2 Viral markers for viral hepatitis.

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

Abbreviations: HAV Ab, Hepatitis A virus antibody; HBc Ab, Hepatitis B core antibody (HBcAb); HBs Ag, Hepatitis B surface antigen; HCV Ab, Hepatitis C virus antibody; HEV Ab, hepatitis E virus antibody.

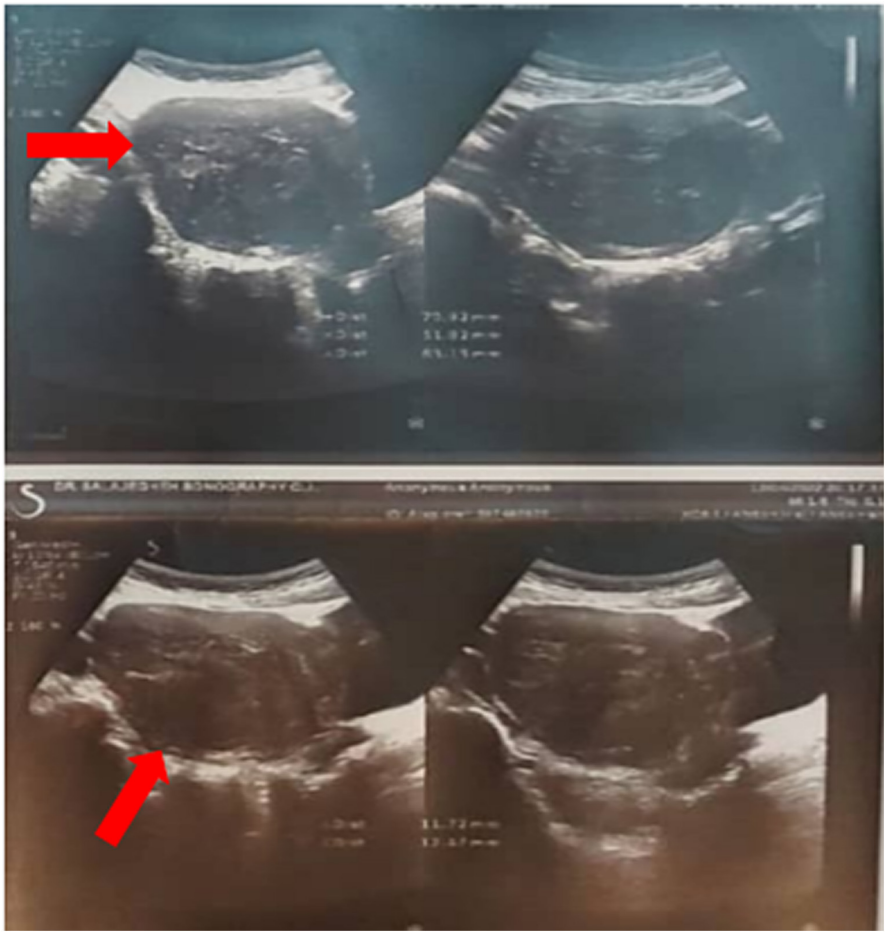

FIGURE 1 Abdominal ultrasonography showing distend gallbladder with the thickened wall with perivesical liquid collection without any calculous or sludge.

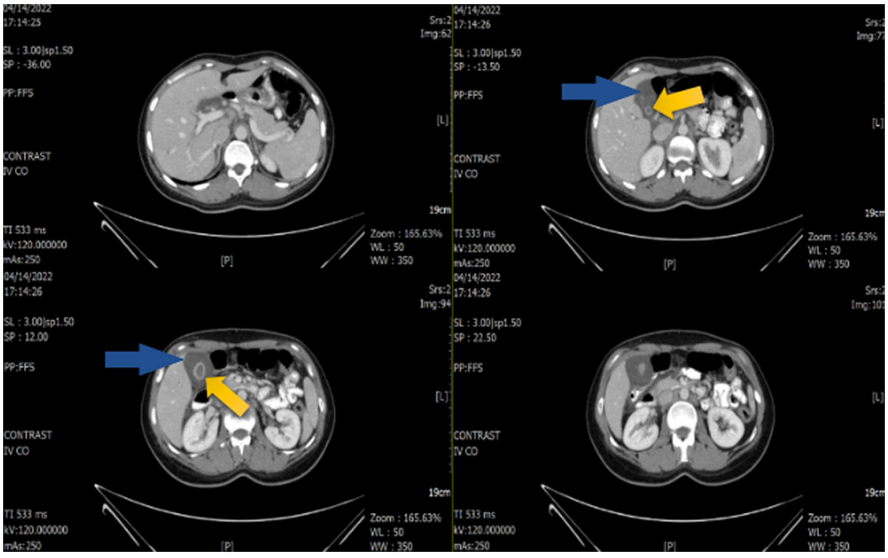

FIGURE 2 Abdominopelvic CT scan showing markedly thickened and edematous gallbladder wall without any obvious signs of gallbladder stone.

clinical complaints. The serum level of liver enzymes had reached the normal level (Table 1). Further abdominal ultrasonography 3 months after admission revealed that the liver was normal in size and parenchymal echo, that the intra- and extrahepatic ducts were normal in size (CBD = 4 mm), and that the gallbladder had normal wall thickness (less than 3 mm) and no calculous, sludge, or perivesical fluid collections (Figure 3).

3 | DISCUSSION

AAC was first reported in 1844 by Duncan J in a fatal case of AAC complicating an incarcerated hernia.[26] In fact, AAC is a type of acute cholecystitis that constitutes 5%–10% of all acute cholecystitis,[19,27] 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

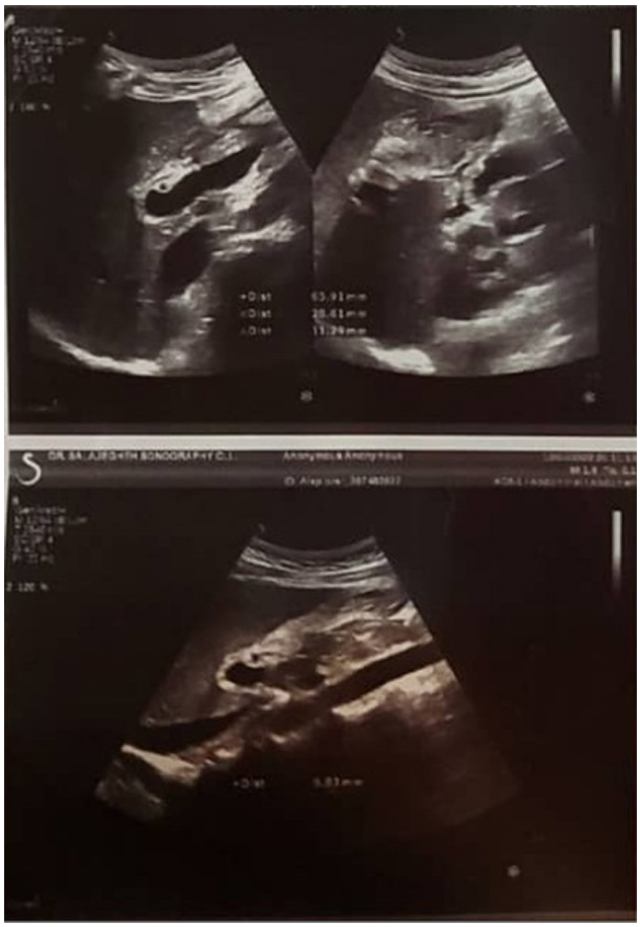

FIGURE 3 Abdominal ultrasonography 3 months after admission demonstrated a gallbladder with normal wall thickness (less than 3 mm) without acalculous, sludge, and perivesical fluid collection.

which the critical complications include necrosis and perforation of the gallbladder.[28]

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*, *Salmonella spp*, *Brucellosis*, *Vibrio cholera*, *Coxiella burnetii*, and *leptospirosis*, 2. gram-positive bacteria, such as *E. faecalis*, *S. fusarium spp*, *Lactococcus spp*, *Proteus*, and *Pseudomonas*, 3. viral infections, such as *Cytomegalovirus* (*CMV*), *Epstein–Barr virus* (*EBV*), *Dengue virus*, *Human Immunodeficiency Virus* (*HIV*), and *viral hepatitis* (*A*, *B*, *C*, *E*).[16,29–44]

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.[27] Laboratory investigations may show increased ALT, AST, ALP, total and direct bilirubin; however, normal levels do not rule out the disease.[45] The initial AAC diagnosis is made clinically, which is confirmed with the help of abdominal ultrasound.[27] 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; and 5. absence of intra- and extrahepatic bile duct dilatation with a sensitivity, specificity, and accuracy of 88.9%, 97.8%, and 96.1%, respectively.[45,46] Most AAC patients are candidates for percutaneous cholecystostomy, a definitive treatment option with a low mortality rate and following cholecystectomy (except in patients with gallbladder perforation or gangrene). Although cholecystectomy may be advantageous for patients with low surgical risk, both treatment options may be successful.[47–49]

HAV is a rare etiology for AAC that manifests differently in pediatrics and adults. In pediatrics, most patients are asymptomatic, although infection usually is symptomatic in adults.[50] After an incubation period of 15–50 days, typical symptoms include fever, malaise, nausea, vomiting, abdominal pain, dark urine, and jaundice appear.[51,52] HAV is usually self-limiting and improves with supportive treatments such as hydration, antiemetics for severe vomiting, and antipyretics for high fever.[53] However, the potential complications of HAV are ascites, pleural effusion, sinus bradycardia, renal failure, hepatic necrosis and fulminating hepatitis, and AAC.[12,14,46]

HAV-induced AAC is rare with only 28 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[27,71] we found that the youngest patient was 2.5-year-old and the most elderly was 81-year-old.[60,65] 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 with no prior medical history who developed clinical signs and symptoms consistent with 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), as indicated by worsening LFT. Thus, she went under critical care as well as consultation and investigation for further etiologies of ALF. 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

TABLE 3 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.

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.[12]	1994	68-year-old	Male	Fever, N/V	Cholangitis	Surgery	USA
Ciftci et al.[54]	2001	7-year-old	Male	Abdominal pain, icterus, dyspnea	Pleural effusion	Surgery	Turkey
Ozaras et al.[13]	2003	28-year-old And 20-year-old	Male	Abdominal pain dark urine	NO	Conservative therapy	Turkey
Dalgic et al.[55]	2005	11-year-old	Female	Abdominal pain, fever, N/V	NO	Conservative therapy	Turkey
Basar et al.[56]	2005	19-year-old	Female (pregnant)	N/V, fatigue	NO	Conservative therapy	Turkey
Bouyahia et al.[57]	2008	14-year-old	Male	Abdominal pain fever	NO	Conservative therapy	Tunisia
Melero Ferrer et al.[58]	2008	39-year-old	Female	Abdominal pain, fever, jaundice	NO	Surgery	Spain
de Souza et al.[46]	2009	16-year-old	Male	Abdominal pain Fever, N/V	NO	Conservative therapy	Brazil
Arroud et al.[59]	2009	11-year-old	Male	Abdominal pain fever, N/V	NO	Conservative therapy	Morocco
Suresh et al.[60]	2009	2.5-year-old	Female	Abdominal pain, fever, dark urine	NO	Conservative therapy	India
Erdem et al.[61]	2010	12-year-old	Male	Fever, icter, N/V	Pleural effusion ascites	Conservative therapy	Turkey
Arcana et al.[34]	2011	14-year-old	Male	Abdominal pain, fever, icter, N/V	Acute pancreatitis	Conservative therapy	Peru
Hasosah et al.[62]	2011	13-year-old	Female	Fever, icter, N/V	NO	Conservative therapy	Saudi Arabia
Herek et al.[63]	2011	9-year-old	Male	Abdominal pain fever, N/V	NO	Conservative therapy	Turkey
Prashanth et al.[64]	2012	12-year-old	Female	Abdominal pain N/V	NO	Conservative therapy	India
Kaya et al.[45]	2013	31-year-old	Female	Abdominal pain N/V	NO	Conservative therapy	Turkey
Cuk et al.[65]	2014	81-year-old	Female	Fever, icter	Perforated ACC	Surgery	Denmark
Aldaghi et al.[66]	2015	5-year-old	Male	Abdominal pain Icter	NO	Conservative therapy	Iran
Bura et al.[67]	2015	Case series of 18 patients	Male & Female	Abdominal pain	NO	Conservative therapy	Poland
Ghosh et al.[68]	2017	4-year-old	Female	Fever, icter	Pleural effusion Salmonella paratyphi A co-infection	Conservative therapy	India
Dalai et al.[21]	2018	3-year-old	Female	Abdominal pain Fever	Pleural effusion ascites	Conservative therapy	India
Ormarsdottir et al.[22]	2018	Case series of 4 patients	Male & Female	Abdominal pain N/V	NO	later elective surgery	Iceland

TABLE 3 (Continued)

Author	Year	Age	Gender	Main clinical presentation	Associated complications	Treatment	Country
Velev et al.[69]	2019	Case series of 6 patients	Male & Female	Abdominal pain	NO	Conservative therapy	Bulgaria
Palacios et al.[70]	2020	32-year-old	Female	Abdominal pain fever, dyspnea	Pleural effusion Ascites HEV co-infection	Conservative therapy	Peru
Hamid et al.[27]	2021	37-year-old	Male	Abdominal pain, vomiting, dark urine	CMV co-infection	Conservative therapy	India
Cortellazzo et al.[23]	2022	14-year-old	Female	Abdominal pain fever, icter	NO	Conservative therapy	Italy
Shahi et al.[24]	2022	16-year-old	Male	Abdominal pain, dyspnea, fever, N/V	Pleural effusion ascite	Conservative therapy	Nepal

Abbreviations: ACC, Acute acalculous cholecystitis; CMV, Cytomegalovirus; HAV, Hepatitis A virus; HEV, Hepatitis E virus; NA, not available.

asymptomatic and self-limited disease, it can be associated with serious complications. With prompt diagnosis of AAC, consideration of rare microbial causes such as viral hepatitis such as HAV, and implementation of close monitoring and conservative therapy, serious complications can be prevented; even in young adult patients with no prior medical history who presented to the hospital with HAV-induced AAC, which is usually self-limiting but can quickly progress to hepatic encephalopathy and ALF.

4 | CONCLUSION

AAC is one of the rare extrahepatic manifestations caused by HAV, in which a person experiences worsening abdominal pain, progressive decline in liver function, hepatic encephalopathy, and ALF. The combination of clinical, laboratory, and imaging information enables the detection of HAV-induced AAC. 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 complications associated with this condition, such as necrosis and perforation of the gallbladder. Future research should focus more on the relationship between HAV-induced AAC and other co-infections, such as EBV and CMV.

AUTHOR CONTRIBUTIONS

Faranak Salajegheh: Methodology. **Sara Shafieipour:** Supervision. **Zoher Najminejad:** Data curation. **Pouria Pourzand:** Writing – review and editing. **Mohsen Nakhaie:** Writing – original draft. **Samaneh Jahangiri:** Investigation. **Roham Sarmadian:** Writing – review and editing. **Abolfazl Gilani:** Writing – review and editing. **Mohammad Rezaei Zadeh Rukerd:** Supervision; validation; writing – original draft; writing – review and editing.

ACKNOWLEDGEMENTS

All the authors thank the patient for allowing publication of this case study.

FUNDING INFORMATION

No fundings were used to support this study.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Supporting data for this study can be obtained from the corresponding author upon reasonable request.

ETHICS STATEMENT

Kerman University of Medical Sciences' Institutional Review Board and Ethics Committee waived the need for ethics approval. In addition, the patient provided written informed consent for the publication of this case report.

INFORMED CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Salajegheh F, Shafieipour S, Najminejad Z, et al. HAV-induced acalculous cholecystitis: A case report and literature review. *Clin Case Rep*. 2023;11:e7254. doi:10.1002/ccr3.7254