81461_Auto_Edited.docx

WORD COUNT 2321
TIME SUBMITTED 01-FEB-2023 03:55PM
PAPER ID 96137191

Hepatitis A virus-associated acute acalculous cholecystitis in an adult-onset Still's disease patient: A case report and review of the literature

Chu-Heng Chang, You-Yang Wang, Yang Jiao

Abstract

BACKGROUND

Acute acalculous cholecystitis (AAC) is inflammation of the gallbladder without evidence of calculi. Although rarely reported, its etiologies include hepatitis virus infection (*e.g.*, hepatitis A virus, HAV) and adult-onset Still's disease (AOSD). There are no reports of HAV-associated AAC in an AOSD patient.

CASE SUMMARY

Here we report a rare case of HAV infection-associated AAC in a 39-year-old woman who had a history of AOSD. The patient presented with an acute abdomen and hypotension. Elevated hepatobiliary enzymes and a thickened and distended gallbladder without gallstones on ultrasonography suggested AAC, but there were no signs of anemia nor thrombocytopenia. Serological screening revealed anti-HAV IgM antibodies. Steroid treatment did not alleviate her symptoms, and she was referred for laparoscopic cholecystectomy. The resected gallbladder was hydropic without perforation, and her clinical signs gradually improved after surgery.

CONCLUSION

AAC can be caused by HAV in AOSD patients. It is crucial to search for the underlying etiology for AAC, especially uncommon viral causes.

Key Words: Acalculous cholecystitis; Hepatitis A virus; Adult-onset Still's disease; Acute abdomen; Cholecystectomy; Case report

Chang CH, Wang YY, Jiao Y. Hepatitis A virus-associated acute acalculous cholecystitis in an adult-onset Still's disease patient: A case report and review of the literature. *World J Clin Cases* 2023; In press

Core Tip: Acute acalculous cholecystitis (AAC) can be caused by hepatitis A virus (HAV) infection or adult-onset Still's disease (AOSD). Cholestasis is more likely to occur in HAV-associated AAC, whereas hematological complications are more common in AOSD-associated AAC. When AAC cannot be explained by AOSD, it is necessary to find other causes of AAC. An acute abdomen caused by HAV-related AAC requires careful consideration of the surgical necessity, since most cases are self-limiting and gallbladder perforation is rare.

INTRODUCTION

Acute acalculous cholecystitis (AAC) accounts for 2%-15% of all acute cholecystitis cases[1]. In contrast to acute calculous cholecystitis (ACC), no gallstones can be identified in the gallbladder in AAC, and its pathogenesis is thought to be related to ischemia-reperfusion injury after surgery or trauma, cholestasis caused by long-term fasting or intestinal obstruction, bacterial infection, or abnormal biliary tract anatomy[2-4]. Although rarely reported, hepatitis A virus (HAV) infection or adult-onset Still's disease (AOSD) can also cause AAC. HAV-associated AAC has mostly been reported in children and teenagers in developing countries, and it is often accompanied by fever, vomiting, transient liver dysfunction, and cholestasis[5,6]. On the other hand, AOSD is a chronic, systematic inflammatory disease characterized by recurrent fever, arthralgia, rash, and anemia or thrombocytopenia[7]. Patients with AOSD also may have high ferritin levels and sometimes concurrent AAC[8].

However, there are no reports of co-morbid AAC, HAV infection, and AOSD, which would represent a diagnostic and management challenge. Here we describe the case of a 39-year-old woman with AAC complicated by AOSD who was found to be anti-HAV IgM positive. We also searched the PubMed database with the keywords "((hepatitis A virus) OR (adult-onset Still's disease)) AND acalculous cholecystitis" and found 14 HAV-associated AAC cases and three AOSD-associated AAC cases. Our case and review allow us to identify diagnostic clues that might help favor a particular diagnosis and discuss the necessity for surgical intervention to treat the AAC under these circumstances.

CASE PRESENTATION

Chief complaints

A 39-year-old woman presented to our hospital with a one-week history of fever (39-40 ℃) and headache, chest tightness, and a sharp right upper quadrant pain.

History of present illness

The woman had a five-month history of AOSD, for which she had been taking oral methylprednisolone (26 mg/d) as maintenance therapy. She had suddenly developed a cough and sore throat two weeks previously, for which she was prescribed amoxicillin and clavulanate potassium (3.75 g/d), which was ineffective. In the week preceding admission, she had a fever of 39°Caccompanied by malaise, cutaneous icterus, and loss of appetite. Her methylprednisolone dose was increased to 48 mg/d and moxifloxacin hydrochloride (0.4 g iv, once) was administered, but this failed to control the symptoms.

History of past illness

The patient had ovarian endometriosis ten years previously and underwent laparoscopic ovarian cystectomy. She also had a history of a skin rash after taking a cephalosporin antibiotic.

Personal and family history

There was no personal nor family history of cholecystitis, nor was there a family history of AOSD or other auto-immune diseases.

Physical examination

On admission, she had cutaneous icterus and her temperature was 40 °C Her blood pressure dropped to 83/45 mmHg and her heart rate increased to 100-110 bpm. Her liver was palpable under the costal margin, and she had abdominal distension and tenderness in the right upper quadrant and a positive Murphy's sign.

Laboratory examinations

Laboratory tests (Table 1) showed elevated lactate (1.9 mmol/L), white blood cell (WBC) count (17.34 × 10^9/L), and inflammatory markers [high-sensitivity C-reactive protein (hsCRP) 15.35 mg/L]. Moreover, total/direct bilirubin (TBil/DBil) (12.2/10.5 mg/dL) and hepatobiliary enzymes [aspartate aminotransferase (AST) 724 U/L, alanine aminotransferase (ALT) 223 U/L, gamma-glutamyl transferase (GGT) 735 U/L, alkaline phosphatase (ALP) 336 U/L] were elevated, and the prothrombin time (PT) was prolonged at 15.1 s. Her hemoglobin 14.7 g/dL and platelets 292 × 10^9/L were within normal limits. Further serological screening demonstrated anti-HAV IgM antibodies.

Imaging examinations

Ultrasonography revealed a dilated gallbladder (9.1 cm × 4.1 cm) with an evenly thickened wall (approximately 1.8 cm) and hepatosplenomegaly, but the intrahepatic bile duct was not dilated. Computed tomography (CT) suggested pericholecystic and hepatic fluid collection, a thickened gallbladder wall, a right pleural effusion, and ascites (Figure 1). No calculi were present.

FINAL DIAGNOSIS

The evidence suggested that the patient had HAV-associated AAC. The AAC could not be explained by the active state of AOSD, since steroid treatment did not alleviate the symptoms.

TREATMENT

Hypovolemia and septic shock were considered, and she was given supportive intravenous fluid treatment and norepinephrine as a vasoactive agent (0.2 μg/kg/min). However, the acute abdominal pain, chest tightness, and acute abdomen signs such as positive Murphy's sign and epigastric guarding continued. Gallbladder perforation was suspected, and she was referred for emergent laparoscopic cholecystectomy. During the surgery, the gallbladder was found to be hydropic without perforation with no evidence of calculi. Prednisone was maintained at the same dose (48 mg/d) after cholecystectomy.

OUTCOME AND FOLLOW-UP

Her clinical signs gradually improved after surgery. Microscopic examination of the gallbladder revealed normal epithelial architecture with mild lymphocyte infiltration. There was no perforation nor necrosis. During follow-up, her liver function returned to normal and the cutaneous icterus resolved.

DISCUSSION

Literature review

Here we present a case of AAC complicated by HAV infection and AOSD. We searched the PubMed database for published articles on the topic using the search terms "acalculous cholecystitis", "hepatitis A virus", and "adult-onset Still's disease". Fourteen patients have been reported in the literature with AAC due to acute HAV infection and three due to AOSD, and we compared these with our case.

Previous studies reporting HAV-associated AAC are summarized in Table 2. These patients commonly presented with fever (11/14), fatigue (7/14), nausea (5/14),

vomiting (9/14), and abdominal pain (12/14). On physical examination, icterus (12/14), right upper abdominal tenderness (12/14), and an enlarged liver or spleen (6/12) were common. Ultrasonography and CT revealed thickened gallbladders accompanied by pericholecystic fluid and hepatosplenomegaly. Laboratory tests showed that all patients had elevated TBil/DBil, ALT, and AST. Anemia (2/8) and thrombocytopenia (3/10) occurred in several cases. However, despite advanced imaging and laboratory techniques, the diagnosis of complicated HAV-associated AAC as a cause of an acute abdomen seems to be challenging. Ciftci *et al*[10] presented a case of HAV-associated AAC in a child whose initial diagnosis was an acute abdomen due to blunt abdominal trauma. After physical examination, laboratory testing, and CT scanning, the patient was suspected to have gangrenous cholecystitis, but the exploratory laparotomy revealed no gallbladder necrosis nor perforation.

With respect to treatment and prognosis, most patients received conservative treatment (12/14) and only two patients underwent surgery. All patients had good outcomes. Most HAV-associated AAC cases were self-limiting, and the thickened, hydropic gallbladder decompressed within two weeks following conservative treatment. These findings were consistent with those of Kaya and colleagues[18].

Cases of AAC in patients with AOSD (three cases) are summarized in Table 3. AOSD-associated AAC patients, all female, had recurrent fever, rash, and arthritis. On physical examination, two presented with a palpable liver and spleen, which was further confirmed by CT. All cases showed gallbladder enlargement or wall thickening but no calculi by ultrasonography or CT. Laboratory findings showed liver dysfunction (elevated TBil and hepatobiliary enzymes), anemia, and thrombocytopenia. Moreover, hyperferritinemia was presented in these patients, which might reflect the inflammatory state in autoimmune disease.

Arai *et al*[8] found several shared characteristics in AOSD patients. Two cases were complicated by macrophage activation syndrome (MAS) based on the findings of splenomegaly, cytopenia, and pathological changes in myeloid cells revealed by bone marrow biopsy. In addition, two cases were complicated by disseminated intravascular

coagulation (DIC). The hypercytokinemia caused by MAS and widespread hypercoagulable state might aggravate multi-organ failure and severe illness. Furthermore, they showed that by inhibiting cytokine production and immune activation with glucocorticoids and cyclosporin A, both AAC and AOSD-related MAS or DIC could be resolved, suggesting that MAS and DIC might be secondary to their primary AOSD and that prompt and correct management of the primary disease can also slow or halt the progression of MAS and DIC.

It is worth considering whether surgery is needed in patients with AOSD-associated AAC. From the three previously reported cases, two patients received conservative treatment and one had cholecystectomy. The patient who underwent surgery[21] experienced hypovolemic shock, including no peripheral pulse and a systolic blood pressure of 50 mmHg. However, the surgery did not fully ameliorate the disease, since the patient experienced a rise in temperature after surgery and was later successfully treated with prednisone and naproxen. This leads us to consider whether surgical intervention is necessary in these cases. However, Arai and colleagues[8] claimed that surgery should remain a treatment option for AOSD-associated AAC due to the possibility of gallbladder perforation as a complication. All three patients survived and had good outcomes. Overall, given the rarity of the condition, further reporting of individual cases would be helpful for guiding evidence-based treatment of AOSD-associated AAC.

Discussion

AOSD-associated AAC and HAV-associated AAC share several common characteristics. They both present with acute abdomen symptoms, elevated bilirubin and hepatobiliary enzymes, and imaging findings of hepatosplenomegaly and a thickened gallbladder without gallbladder calculi. However, cholestasis is often more severe in HAV-associated AAC, resulting in higher bilirubin levels and cutaneous icterus[22]. Meanwhile, hematological abnormalities are more obvious in AOSD-associated AAC: Anemia and thrombocytopenia were more frequent in AOSD-

associated AAC, as was MAS or DIC[20]. In this patient, a differential diagnosis of MAS was considered. However, anemia, thrombocytopenia, and DIC were not present. Steroid treatment did not alleviate the patient's symptom, disfavoring AOSD as the cause of AAC in this case. Thus, based on serology and other laboratory findings, our final diagnosis for the patient was HAV-associated AAC.

Viral infections other than HAV may also lead to AAC. Hepatitis B virus[23,24] and hepatitis C virus[25,26] have both been reported as causes of AAC. Other viruses such as Epstein-Barr virus (EBV)[27,28], dengue virus[29,30], and human immunodeficiency virus[31,32] have also been implicated in AAC and have presented with an acute abdomen. More recently, coronavirus (COVID-19) has been reported in AAC cases[33], even leading to gangrenous cholecystitis[34]. Therefore, viral serology is an important diagnostic modality to search for a possible underlying etiology when a patient presents with AAC of unknown cause.

Due to the complexity of the case, our patient received intravenous fluid support, a vasoactive agent, steroid treatment, antibiotic management, and surgical intervention. Surprisingly, no perforation nor necrosis was found in the gallbladder after cholecystectomy. Due to the limitations of current imaging modalities and laboratory testing, it can be difficult to accurately determine the actual condition of the gallbladder prior to operation. However, as summarized previously, most HAV-associated AAC cases are self-limiting, and conservative management of AAC may be adequate[18]. Thus, cholecystectomy may be an option when faced with AAC but requires careful consideration and evaluation of the surgical necessity, not least given the positive outcomes of most patients with HAV-associated AAC with conservative therapy alone.

This study has several limitations. First, we only showed the association between hepatitis virus infection and AAC, and the cause-effect relationship between them is still debatable. Further validation of the cause of HAV-associated AAC requires evidence from animal experiments or cohort studies. Second, we did not examine whether the patient had hyperferritinemia, which is often present in active AOSD. However, our patient did not have anemia, thrombocytopenia, and did not develop

DIC, and steroid treatment did not control the clinical course. These findings strongly disfavor active AOSD causing the AAC. This study is also limited by the availability of only three cases of AOSD-associated AAC, so we cannot be certain that these cases are representative. More cases of AOSD-associated AAC need to be described to verify our conclusions.

CONCLUSION

In conclusion, although AAC caused by HAV or AOSD is rare, it is possible that these conditions can overlap and complicate the diagnosis and management of AAC. When AAC cannot be explained by AOSD, it is important to search for other primary causes of AAC, and viral serology should form part of the diagnostic work-up. HAV-associated AAC is mostly self-limiting, and conservative therapy is usually adequate management for these patients unless gallbladder perforation is likely. Overall, however, the prognosis of AAC caused by HAV is very good, with conservative management the cornerstone of treatment.

Figure 1 Computed tomography scan of the gallbladder and its surroundings. Axial computed tomography image confirmed distended gallbladder (9.1 cm × 4.1 cm) with an evenly thickened, hydropic gallbladder wall (approximately 1.8 cm). Pericholecystic and hepatic fluid was also seen. No calculi were present.

81461_Auto_Edited.docx

ORIGINALITY REPORT

6%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.docme.ru Internet	47 words — 2%
2	f6publishing.blob.core.windows.net Internet	19 words — 1%
3	academic.oup.com Internet	14 words — 1%
4	bsdwebstorage.blob.core.windows.net Internet	13 words — 1%
5	www.jove.com Internet	12 words — < 1%
6	balkanmedicaljournal.org Internet	10 words — < 1%
7	www.pnas.org Internet	9 words — < 1%
8	www.science.gov Internet	8 words — < 1%
9	www.unboundmedicine.com Internet	8 words — < 1%

10 Marco Tana, Claudio Tana, Giulio Cocco, Giovanni Iannetti, Marcello Romano, Cosima Schiavone. "Acute acalculous cholecystitis and cardiovascular disease: a land of confusion", Journal of Ultrasound, 2015
Crossref

6 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF