**Received:** 2012.01.18
**Accepted:** 2012.05.10
**Published:** 2012.07.12

# Epstein-Barr virus – associated acute acalculous cholecystitis in an adult

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## Summary

**Background:** Gallbladder involvement during primary Epstein-Barr virus (EBV) infection in adults is rare.

**Case Report:** We report the case of a 29-year-old female with acute acalculous cholecystitis associated with EBV infection. The patient was successfully treated with conservative therapy.

**Conclusions:** Clinicians should be aware that acute acalculous cholecystitis may be present during viral infection, and surgical treatment is unnecessary in almost all cases.

**key words:** **acute acalculous cholecystitis • Epstein-Barr virus • infection • ultrasonography**

**Full-text PDF:** http://www.amjcaserep.com/fulltxt.php?ICID=883245

**Word count:** 1301
**Tables:** 1
**Figures:** 2
**References:** 23

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## Background

The Epstein-Barr virus (EBV) is a ubiquitous herpes virus that persists life-long in normal humans by colonizing memory B cells. Infection during childhood is usually asymptomatic, whereas it presents as typical infectious mononucleosis in about 50% of adolescents and young adults [1]. In the literature, uncommon complications of acute EBV infection have been described. Hepatitis with mild transient elevations in serum aminotransferases is often reported, and mild jaundice develops in approximately 5% of cases, possibly as a result of cholestasis or virus-induced hemolysis [2]. Isolated gallbladder wall thickening or hydrops have been reported in patients with EBV infectious mononucleosis [3,4]. However, acute acalculous cholecystitis (AAC) is an atypical clinical presentation of primary EBV infection, and it has been proposed as a sign of the severity of the illness [5]. We describe an adult patient with AAC associated with EBV infection successfully treated with conservative therapy. A review of the literature was also performed using PubMed and free text search engine up to December 2011. Search terms included: acute cholecystitis, viral diseases, and Epstein-Barr virus infection. The "related articles" function was used to broaden the search, and all abstracts were reviewed. Search limits were applied to include articles published in English, those with abstracts, human studies, and adult subjects.

## Case Report

A 29-year-old female was admitted to our hospital with a 7-day history of malaise, headache, fatigue, poor appetite, and the appearance, 2 days before hospitalization, of fever and right upper quadrant abdominal pain (RUQ). Physical examination showed a non-distended abdomen with normally active bowel sounds, tenderness localized over the right upper quadrant, and a positive Murphy's sign. Laboratory investigations on admission revealed a blood cell count (WBC) of 3960×10.9/L (51% lymphocytes), aspartate aminotransferase (AST) 121 U/L (normal reference, nr 10–35 U/L), alanine aminotransferase (ALT) 166 U/L (nr 10–35 U/L), alkaline phosphatase (ALP) 161 U/L (nr 53–151 U/L), gamma-glutamyltransferase (GGT) 145 U/L (nr 3–45 U/L), total serum bilirubin 23.2 umol/L (nr 1.7–17.0 umol/L), direct fraction 12.4 umol/L (nr 0–3.4 umol/L), lactate dehydrogenase (LDH) 709 U/L (nr 0–480 U/L), and C-reactive protein (CRP) 14.40 mg/L (nr 0–6 mg/L). Abdominal ultrasonography (US) showed a contracted gallbladder with wall thickening (15 mm) (Figure 1A) with pericholecystic fluid (Figure 1B), and absence of sludge, stones or dilatation of the biliary tract. A viral infection was suspected and was investigated by serological tests. Results of direct and indirect Coomb's test, laboratory research of hepatitis A, B and C virus, and cytomegalovirus were negative. The EBV panel result was indicative of acute primary infection: IgM antibodies against viral capsid antigen (VCA) were positive, whereas IgG antibodies for Epstein-Barr nuclear antigen (EBNA) were negative.

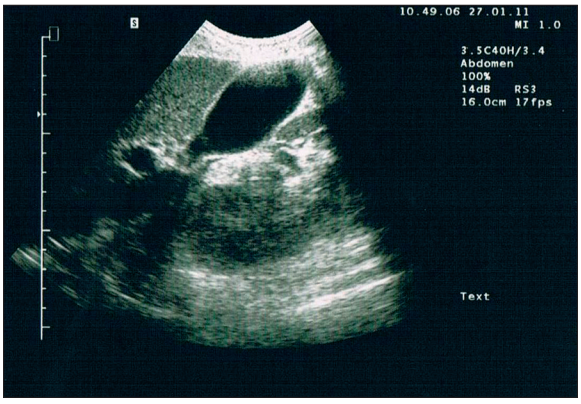


**Figure 2.** Abdominal ultrasonography performed after discharge, showing a normal gallbladder wall.

Intravenous rehydration therapy with glucose and electrolyte solution was started, and because the cause of ACC was not immediately discovered, the antibiotic treatment with cephalosporin was continued until the results of EBV serology were obtained. ACC regressed gradually. During the hospital stay, the symptoms and clinical course progressively ameliorated – abdominal pain, gall bladder abnormalities and fever resolved, and she was discharged 6 days after hospital admission.

Only 2 days after hospital discharge, she had significant posterior cervical lymphadenopathy and more prominent tonsillar enlargement with exudates. She continued to have some fever for a few days, but her appetite gradually improved.

Seven days after hospital discharge, she underwent an abdominal ultrasonography that showed a normal gallbladder with disappearance of wall thickening (Figure 2). Laboratory evaluation done the same day showed a marked improvement of AST, ALT, ALP, CRP. During a follow-up of 10 months, she remained in good condition without any complaints.

## Discussion

EBV is known to be one of the causes of viral hepatitis, even if severe hepatocellular liver injury is rare and its pathogenesis

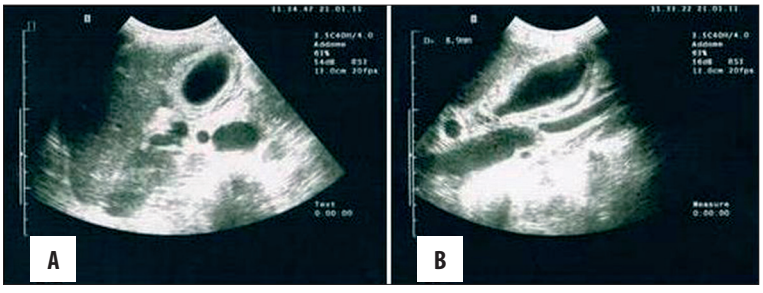


**Figure 1.** Abdominal ultrasonography showing a thickening of the gallbladder wall (15 mm) without evidence of cholelithiasis (**A**) and with pericholecystic fluid (**B**).

**Table 1.** Summary of reported cases of EBV-associated acute acalculous cholecystitis in adults.

| Authors | Age/gender | Symptoms | Ultrasound Wall Thickening | Treatment |
|---|---|---|---|---|
| Kock et al., 2007 [19] | 53/F | Fever,,nausea, jaundice, pain, | 10 mm | Medical |
| Iaria et al., 2008 [20] | 18/F | Fever, nausea, vomiting, pain | 9 mm | Medical |
| Hagel et al., 2009 [21] | 21/F | Fever, pain, jaundice | 7 mm | Surgery |
| Cholangitas et al.,2009 [22] | 19/F | Fever, nausea, vomiting | 8 mm | Medical |
| Chalupa et al., 2009 [23] | 22/F | Fever, malaise, pain | 6 mm | Medical |
| Yang et al., 2010 [17] | 20/F | Fever, pain, vomiting | NR | Medical |
| Present case | 29/F | Fever, malaise, pain | 15 mm | Medical |

NR – not reported.

uncertain [6,7]. Mild transient elevations in serum aminotransferases is reported, and mild jaundice is described in approximately 5% of cases, possibly caused by cholestasis or virus-induced hemolysis [2].

The association between EBV infections and ACC has been previously reported, but it was described as an uncommon event [4].

Acute acalculous cholecystitis is an inflammatory process of the gallbladder in the absence of gallstones. The pathogenesis of ACC is related mainly with bile stasis due to increased bile viscosity that is accompanied, in ill patients, by fever, dehydration or prolonged absence of oral feeding, and consequent decrease of cholecystokinin-induced gallbladder contraction. AAC can occur independently, but often develops as a complication of different medical or surgical conditions [8,9], and has been associated with long-term total parenteral nutrition, trauma [8–11] or with systemic diseases such as Kawasaki disease or polyarteritis nodosa [11,12]. ACC may also develop during systemic infection with various pathogens [13]. More recently, the relationship between ACC and EBV has been documented [2,3]. EBV-related hepatitis has been recognized as an important cause of cholestasis, even in the absence of clinical signs of infectious mononucleosis [14,15]. In this patient, gallbladder inflammation was due to EBV-related cholestasis with consequent development of ACC [16]. A second possible pathogenetic mechanism is the direct invasion of the gallbladder caused by viral hepatitis A, since the viral antigen was detected in most epithelial cells of the gallbladder [17].

The diagnosis of acute cholecystitis is based on clinical and radiological findings, whereas acute EBV infection is confirmed only serologically; thus, it is detect the involvement of gallbladder and confirm EBV as the cause of acute cholecystitis for the first time in a clinician's experience. US criteria for ACC are still under discussion. Gallbladder wall thickening over 3 mm, globular distention of the gallbladder, localized tenderness (sonographic Murphy's sign), sludge, pericholecystic fluid and striated gallbladder wall were the useful features at the time. The combination of 2 or more of the above-mentioned criteria in the appropriate clinical setting are considered to be diagnostic of AAC [18].

In our case, initial US showed a contracted gallbladder with wall thickness of 15 mm, associated with pericholecystic fluid, absence of biliary duct dilation or cholelithiasis, which are typical radiologic features of AAC (Figure 1). From the biochemical point of view, in contrast to the report by Yang et al [23] of EBV cholecystitis in a 20-year-old woman with normal bilirubin levels and no evidence of cholestasis, our patient had an increase of ALP, GGT and bilirubin level. Growth of cholestasis indices seems to indicate this as the main cause of development of cholecystitis. However, the hypothesis of direct invasion of the gallbladder could not be documented or excluded because our patient did not undergo cholecystectomy.

In a review of the English language literature, only 7 cases (including the present) of EBV-associated AAC in adults were collected [17,19–23] (Table 1). All cases were described in the last 4 years, probably due to increased awareness of this condition in recent years. Patients showed common clinical features, including malaise, decreased appetite, nausea, fever, jaundice with RUQ pain and tenderness, and sometimes tonsillar pharyngitis and cervical lymphadenopathy. Hyperbilirubinemia and moderately elevated liver enzymes with transaminase levels less than 1000 U/L were the most common associated laboratory findings. Markers of severe involvement, such as hyperammonemia or prolonged prothrombin time, were neither seen in our patient nor documented in other case reports. Common US findings include gallbladder wall thickening, without biliary dilatation, and sometimes pericholecystic fluid (Table 1). Only 1 patient underwent cholecystectomy for severe septic cholecystitis.

## Conclusions

AAC may occur during the course of EBV infection. All cases reported in literature, including our patient, were female and all but 1 (a 53-year-old woman) were young adults. First-time diagnosis can be difficult; clinical and hematological findings of viral infection are helpful in forming diagnostic suspicion. Ultrasound of the gallbladder is the most accurate imaging modality for diagnosis of AAC, whereas acute EBV infection is confirmed serologically only late in the course of infection. EBV infection should be considered in the differential diagnosis of US evidence of AAC.

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