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# Acute acalculous cholecystitis during the course of primary Epstein–Barr virus infection: a new case and a review of the literature

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## KEYWORDS

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## Summary

**Objective:** The aim of this study was to describe a case of acute acalculous cholecystitis occurring in the course of primary Epstein–Barr virus (EBV) infection.

**Methods:** The clinical features of the case were analyzed and compared to those of three other similar cases reported in the international literature.

**Results:** All cases occurred in European females with cholestatic hepatitis, presented with gallbladder wall thickening, and recovered uneventfully without the need for surgical intervention.

**Conclusions:** Acute acalculous cholecystitis may occur during the course of acute EBV infection, especially in patients with cholestatic hepatitis. Clinicians should be aware of the possible involvement of the gallbladder during EBV infection to avoid unnecessary invasive procedures or the overuse of antibiotics.

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## Introduction

Infection with Epstein–Barr virus (EBV) during childhood is mainly asymptomatic, whereas infectious mononucleosis, with clinical signs such as fever, pharyngitis, lymphadenopathy, hepatosplenomegaly, and hepatocellular dysfunction,

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occurs in at least 50% of adolescents and adults with primary infection.<sup>1</sup>

Acute acalculous cholecystitis (AAC) is a severe illness that is a complication of various other medical or surgical conditions. The condition causes approximately 5–10% of all cases of acute cholecystitis and is usually associated with more serious morbidity and higher mortality rates than calculous cholecystitis. It is most commonly observed in the setting of very ill patients (e.g., those on mechanical ventilation, those with sepsis or severe burn injuries, and after severe trauma). In addition, acalculous cholecystitis is associated with a higher incidence of gangrene and perforation compared to calculous disease.<sup>2</sup>

We report herein a case of AAC that occurred in the course of a primary EBV infection.

## Case report

A previously healthy, 18-year-old girl was admitted to our hospital in June 2007 with a 4-day history of decreased appetite, malaise, fever (peak 39.0 °C), and sore throat, for which she was being treated with amoxicillin–clavulanic acid. For the last 36 hours she had also been complaining of vomiting, colicky right upper quadrant abdominal pain radiating to the back, and hyperchromic urine.

Physical examination showed a seriously ill patient; her temperature was 39.0 °C, pulse rate 120 bpm, and respiratory rate 25 breaths/min. The sclerae were icteric, while hyperemic tonsillopharyngitis and bilateral cervical adenopathy were noticed, with the largest nodes measuring 1.5 cm in diameter. Abdominal examination revealed a non-distended abdomen with normally active bowel sounds, tenderness localized over the right upper quadrant, and a positive Murphy's sign. The liver was palpable 1 cm under the costal margin, while the spleen edge was palpable 2 cm below the left costal margin. The remaining physical findings were normal.

Laboratory investigations on admission revealed a white blood cell count (WBC) of  $21.9 \times 10^9/l$  (70% lymphocytes), CD4 10% (reference range (RR) 20–58%), CD8 63% (RR 13–38%), CD4/CD8 0.15 (RR 0.9–1.9), aspartate aminotransferase (AST) 220 IU/l (RR 5–45 IU/l), alanine aminotransferase (ALT) 328 IU/l (RR 5–45 IU/l), alkaline phosphatase (ALP) 312 IU/l (RR 38–148 IU/l), gamma-glutamyltransferase (GGT) 142 IU/l (RR 7–32 IU/l), total serum bilirubin 7.0 mg/dl (RR 0.1–1.9 mg/dl), direct fraction 4.26 mg/dl (RR 0–0.4), lactate dehydrogenase (LDH) 1023 IU/l (RR 50–350 IU/l), erythrocyte sedimentation rate (ESR) 26 mm/h (RR <15 mm/h), and C-reactive protein (CRP) 6.5 mg/l (RR 0–5 mg/l).

Chest X-ray and electrocardiogram did not show any changes. Abdominal ultrasonography showed a contracted gallbladder with wall thickening (9 mm) with presence of sludge and absence of stones or dilatation of the biliary tract, and a positive sonographic Murphy's sign. In addition, a mild hepatosplenomegaly, a reactive enlarged celiac lymph node (16 mm), and a minimal amount of free fluid in the pouch of Douglas were found.

IgM and IgG antibodies against Epstein–Barr viral capsid antigen (VCA) were positive, whereas IgG antibodies for Epstein–Barr nuclear antigen (EBNA) were negative. Extensive laboratory evaluation ruled out hepatitis A, B, and C viruses and other possible infectious agents.

Intravenous rehydration therapy with glucose and electrolyte solution was started, and because the cause of AAC was not obvious, the antibiotic treatment with amoxicillin–clavulanic acid was (erroneously) continued until the results of EBV serology were obtained (48 h later).

After 2 days, an exudative pseudomembranous tonsillitis was noticed, while a continuous remittent fever lasted for a further 5 days; both were attributed to acute EBV primary infection. Notwithstanding the amoxicillin–clavulanic acid therapy, no rash occurred. The symptoms and clinical course progressively ameliorated. Sonography performed on the sixth hospital day showed a distended gallbladder with a slight thickening of the wall (4 mm) and with a small amount of sludge and no signs of deterioration. The sonographic Murphy's sign disappeared and the previous reported free fluid in the pouch of Douglas was no longer found.

Our patient recovered uneventfully without needing surgical intervention and was discharged on the seventh day following admission in good clinical condition and with considerable improvement in biochemical results (WBC  $9.7 \times 10^9/l$  (60% lymphocytes), total serum bilirubin 3.5 mg/dl (direct fraction 1.9 mg/dl), AST 130 IU/l, ALT 188 IU/l, ALP 369 IU/l, GGT 158 IU/l). The patient was encouraged to keep in close contact with the medical staff and to come back to the hospital in the event that any symptom should appear. During a follow-up of 3 months, she remained in good condition without any complaint. Hepatosplenomegaly and all liver chemistry abnormalities had resolved, whereas EBV nuclear antigen IgG antibodies became positive, confirming the diagnosis of the EBV primary infection.

## Discussion

Hepatitis is a common characteristic of infection by EBV, although severe hepatocellular liver injury is rare and its pathogenesis uncertain.<sup>3,4</sup> Hepatitis with mild transient elevations in serum aminotransferases is often reported in EBV infectious mononucleosis, while mild jaundice develops in approximately 5% of cases and may result from cholestasis or virus-induced hemolysis.<sup>5</sup>

In the literature there are only three cases, all published in the last 2 years, in which an association between AAC and EBV infection is reported. All these cases occurred in Europe, in females, and relate to one child, one adolescent and one adult (see Table 1).<sup>6–8</sup> AAC has a slight male predominance, unlike calculous cholecystitis, which is more frequent in females;<sup>9</sup> it is curious that all the cases of EBV-associated AAC occurred in females. AAC can affect persons of any age, and the highest frequency is reported in persons in their fourth and eighth decades of life;<sup>9,10</sup> in children it represents 50–70% of all cases of acute cholecystitis.<sup>10</sup> Three of the four patients with EBV-associated AAC were younger than 20 years. This can be easily explained by the fact that primary EBV infection occurs mostly under the age of 25 years. The fact that all the cases occurred in Europe cannot be easily explained. Of the four patients with EBV-associated AAC, only in the case reported by Prassouli et al. did cholecystitis represent the initial presentation of EBV infection.<sup>6</sup>

The main cause of AAC is thought to be due to bile stasis and increased lithogenicity of bile. Critically ill patients are

**Table 1** Cases of Epstein–Barr virus associated acute acalculous cholecystitis

Author, year [Ref.]	Nation	Age/sex	Vital signs (temperature, pulse rate, respiratory rate)	Symptoms	GWT	Sludge	Total bilirubin (mg/dl)	Direct bilirubin (mg/dl)	AST (IU/l)	ALT (IU/l)	ALP (IU/l)	GGT (IU/l)	LDH (IU/l)	WBC × 10 <sup>9</sup> /l	Lymphocytes%
Prassouli, 2006 [6]	Greece	13/F	39.6 °C, 96 bpm, 20/min	Fever and chills, vomiting, and abdominal pain; painful fullness in the right hypochondrium	Yes (13.6 mm)	Yes	4	3.5	394	674	721	352	616	13.8	53
Lagona, 2006 [7]	Greece	4/F	NR	Decreased appetite, vomiting and mild abdominal pain	Yes (9 mm)	No	4.6	3.6	188	304	236	241	NR	22.1	NR, 10 % atypical
Koch, 2007 [8]	The Netherlands	53/F	38 °C, NR, NR	Jaundice and colicky right upper quadrant abdominal pain radiating to the back, nausea without vomiting, night sweats	Yes (10 mm)	Yes (on day 7)	NR	7	339	422	1081	NR	NR	NR	NR
Present case	Italy	18/F	39.0 °C, 120 bpm, 25/min	Colicky right upper quadrant abdominal pain radiating to the back, nausea and vomiting	Yes (9 mm)	Yes	7	4.26	220	328	312	142	1023	21.9	70

GWT, gallbladder wall thickening; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; WBC, white blood cell count; NR, not reported.

more predisposed because of increased bile viscosity due to fever and dehydration and because of prolonged absence of oral feeding resulting in a decrease or absence of cholecystokinin-induced gallbladder contraction. Gallbladder wall ischemia that occurs because of a low-flow state due to fever, dehydration, or heart failure may also play a part in the pathogenesis of acalculous cholecystitis. The effects of eicosanoid proinflammatory mediators seem to play a pivotal role.<sup>2</sup> AAC may also develop from secondary infection of the gallbladder during systemic infection with various pathogens.<sup>2</sup>

All the cases had cholestatic hepatitis with jaundice and markedly elevated activities of gamma-glutamyltransferase and alkaline phosphatase, whereas imaging studies excluded biliary obstruction.<sup>6–8</sup> Recently, EBV-induced hepatitis has been recognized as an important cause of cholestasis even in the absence of clinical signs of infectious mononucleosis.<sup>11,12</sup> Thus, it could be postulated that, in these patients, EBV-related cholestasis induced gallbladder inflammation and the development of AAC. One other possible pathogenetic mechanism is the direct invasion of the gallbladder. This mechanism has been documented in a case of AAC due to viral hepatitis A, where the viral antigen was detected in most epithelial cells of the gallbladder of the patient.<sup>13</sup> This mechanism was not proved in a previous report of two children with hydrops of the gallbladder and EBV infection.<sup>14</sup>

The present case occurred in a hot summer (temperatures up to 37 °C) and, considering that she had a 4-day history of decreased appetite, it could be hypothesized that she suffered from a certain degree of dehydration. Dehydration is considered a common precipitant of AAC.<sup>15</sup> The enlarged celiac lymph node of our patient could have caused extrinsic cystic duct obstruction and then precipitated AAC.<sup>15,16</sup>

Ultrasound of the gallbladder is the most accurate imaging modality for diagnosis of AAC in the critically ill patient.<sup>2</sup> Deitch and Engel<sup>17,18</sup> reported a specificity of 90% using a 3.0-mm wall thickness and 98.5% with a 3.5-mm wall thickness, whereas sensitivity was 100% at 3.0 mm but only 80% at 3.5 mm. Accordingly, a gallbladder wall thickness of 3.5 mm or more is generally accepted to be diagnostic of AAC. Other helpful ultrasonographic findings include pericholecystic fluid, the presence of intramural gas, or a sonolucent intramural layer or 'halo' that represents intramural edema.<sup>19</sup> Distention of the gallbladder of more than 5 mm in transverse diameter has also been reported.<sup>2,19</sup>

In our case and in all the others a gallbladder wall thickening (GWT) was noted. Sludge was reported in three cases. An association between gallbladder changes and EBV infection has been described in children.<sup>14</sup> O'Donovan and Fitzgerald have described the phenomenon of GWT on ultrasonography during acute EBV hepatitis.<sup>20</sup> Isolated GWT has been described during the course of mononucleosis syndromes and has been proposed as a sign of the severity of the illness.<sup>21</sup> In that series the GWT was reported more frequently in females even if, due to the small sample size, the differences were not statistically significant.

A contracted gallbladder was reported only in our case; this sign can advocate hepatic dysfunction.<sup>22</sup> It can be suggested that, during an episode of acute hepatitis, the

hepatocyte injury may cause sufficient transient decrease in the outflow of bile to decrease filling of the gallbladder lumen.

It is worthy of notice that a colicky right upper quadrant abdominal pain radiating to the back was reported in our 18-year-old girl and in the 53-year-old woman.<sup>8</sup> Only a painful fullness in the right hypochondrium was complained of by the 13-year-old girl and only mild abdominal pain by the 4-year-old girl.<sup>6,7</sup> All the cases recovered uneventfully without needing surgical intervention.<sup>6–8</sup>

AAC may occur during the course of acute EBV infection, especially in patients with cholestatic hepatitis. Clinicians should be aware of the possible involvement of the gallbladder during EBV infection to avoid unnecessary invasive procedures or overuse of antibiotics.

*Conflict of interest:* No conflict of interest to declare.

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