

# Acute Acalculous Cholecystitis as a Rare Initial Presentation of Epstein-Barr Virus Infection in an Immunocompetent Adult Female

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## ABSTRACT

Epstein-Barr virus (EBV) infection is a self-limited disease usually characterized by a sore throat, fever, and lymphadenopathy. Mild to moderate hepatitis may also occur during the course of the infection. The disease is very rarely complicated with acalculous cholecystitis. Herein, we report a 22-year-old immunocompetent female patient who initially presented with fever and moderate abdominal pain that was revealed to be due to acute acalculous cholecystitis. The EBV infection was diagnosed both clinically and serologically. Typical findings of sore throat and cervical lymphadenopathy appeared later the fifth day of admission. In this case report, the patient was treated conservatively, without surgery. Atypical presentation, inverse timing of clinical manifestations, and the conservative management of acalculous cholecystitis in contrast to critically ill patients' acalculous cholecystitis management are noteworthy for both surgeons and internists to be aware of.

Keywords: Epstein-Barr Virus Infection, acalculous cholecystitis, viral hepatitis

Epstein-Barr virus (EBV) is a double-stranded DNA virus that infects B lymphocyte cells. Almost 95% of adults have been infected with EBV worldwide.<sup>1</sup> It is primarily transmitted through saliva that contains virus-infected epithelial cells.<sup>2</sup> Infectious mononucleosis's major clinical manifestations are fever, sore throat, lymphadenopathy, and hepatosplenomegaly. The disease can be diagnosed with a detailed history, physical examination, and serological tests, heterophil antibodies and anti-EBV viral capsid antigens (VCA). Treatment is generally supportive care.<sup>3</sup> Complications can be classified as early or late. Hepatitis, splenic rupture, and airway compromise are the early complications. Hepatic involvement is usually transient but quite frequent.<sup>4</sup> On the other hand, splenic rupture is a very rare and most

feared complication of EBV.<sup>5, 6</sup> Lymphoproliferative cancers, multiple sclerosis, and chronic active EBV infection, which are relatively rare clinical scenarios, may appear as late-onset complications of EBV.

We reported a patient who presented with acute acalculous cholecystitis (AAC), rarely reported in EBV-associated infectious mononucleosis. There are less than 70 cases of EBV-related acalculous cholecystitis in the current literature.<sup>7</sup> There are considerable similarities and differences between our case and the previous reports concerning clinical presentation, laboratory, and disease courses. Considering the benign clinical course of this rare complication, which rarely requires surgery, it is crucial to diagnose patients to avoid unnecessary interventional or surgical steps that may expose patients to harm.

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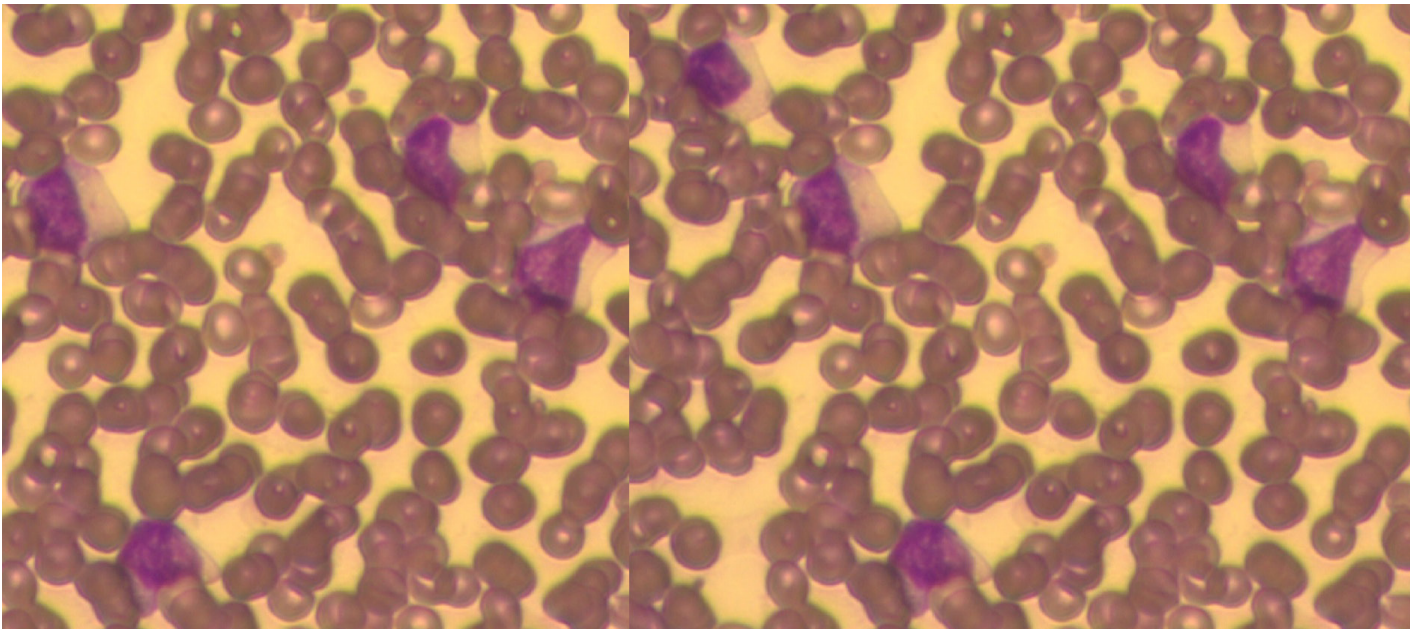
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## CASE REPORT

A 22-year-old female patient with no prior medical history was admitted to our institution's general internal medicine outpatient clinic with severe abdominal pain. She reported fever, nausea, and a loss of appetite, persisting for four days. She denied the use of any medication, herbal product, smoke, alcohol, or illicit drug. She denies risky sexual behavior. Vital signs were typical besides the fever (38,5 °C). Physical examination revealed tenderness in the abdomen's epigastric, right, and left upper quadrants with a positive Murphy's sign. Tender lymphadenopathy in the left submandibular region was also noted. Laboratory tests revealed prominent lymphocytosis, markedly elevated liver transaminases, cholestatic

enzymes, and bilirubin tests. Peripheral blood smear assessment identified abundant Downey cells (Figure 1). The heterophile antibody test (monospot test) was positive, and the EBV-VCA IgM antibody confirmed infectious mononucleosis. Abdominal computed tomography (CT) demonstrated pericholecystic fluid, periportal and pericaval lymph nodes, hepatomegaly, and splenomegaly (Figure 2). Table 1. illustrates the laboratory and imaging findings upon admission in detail. She was admitted to the internal medicine ward with a diagnosis of EBV-associated acute acalculous cholecystitis. She was conservatively managed with discontinuation of oral intake and intravenous hydration. Although our patient's cholecystitis was due to viral infection and not due to obstruction, it was not possible to exclude the bacterial components of



**Figure 1.** The peripheral blood smear revealed multiple reactive lymphocytes, namely Downey cells, in all smear areas. Note their characteristic erythrocyte “hugging” appearance.

acute cholecystitis. Hence, we initiated piperacillin-tazobactam antibiotics as well. Also, she was followed up with abdominal point of care ultrasonography (POCUS) every other day, which revealed a decrease in pericholecystic fluid and gallbladder wall edema. On the 5<sup>th</sup> day of the admission, abdominal tenderness and pain had significantly subsided, and oral intake was initiated gradually. General surgery consultation was obtained during the admission, but daily follow-up was recommended, and no cholecystectomy was needed during cholecystitis. A daily laboratory evaluation showed an apparent decrease in lymphocytosis and liver function tests. Table 2 demonstrates the improvement in liver function

tests and lymphocytosis in detail. The patient was discharged on the 7<sup>th</sup> day of the follow-up with the recommendation to limit her physical activities. She was free of symptoms on day 15 except for the very mild abdominal pain after eating a large meal, and her laboratory results had almost returned to their baseline values. On day 30, she was free of symptoms, and her laboratory results had turned to their baseline values. Table 2 demonstrates the laboratory results on days 15 and 30 in detail.

## DISCUSSION

Acalculous cholecystitis is a rare complication in

**Table 1.** Laboratory and imaging findings upon admission

Parameter	Result	Parameter	Result
ALT (U/L)	515	Hemoglobin (g/dL)	13.2
AST (U/L)	350	Leukocyte ( $\times 10^3/\mu\text{L}$ )	12.7
ALP (U/L)	404	Neutrophil ( $\times 10^3/\mu\text{L}$ )	3.09
GGT (U/L)	257	Lymphocyte ( $\times 10^3/\mu\text{L}$ )	7.66
Total bilirubin (mg/dL)	3.20	Monocyte ( $\times 10^3/\mu\text{L}$ )	1.9
Direct bilirubin (mg/dL)	1.9	Platelets ( $\times 10^3/\mu\text{L}$ )	197
Albumin (g/dL)	4	Ferritin ( $\mu\text{g/L}$ )	53
BUN (mg/dL)	7	ESR (mm/saat)	9
Creatinine (mg/dL)	0.79	CRP (mg/L)	5.6
EBV-VCA IgM	Positive	Heterophile antibody	Positive
Viral hepatitis serology	No hepatitis A, B, C present		
Peripheral blood smear	Prominent reactive lymphocytes (Downey cells), normal erythrocyte morphology, occasional large platelets		
Abdominal US	Hepatosplenomegaly, Periportal edema, portocaval and perisplenic lymph nodes, Pericholecystic fluid, No stones in bile ducts or in the gallbladder		
Abdominal CT	Hepatosplenomegaly (15cm.), gallbladder wall thickening, and edema, paraaortic, periceliac, and portal lymph nodes		

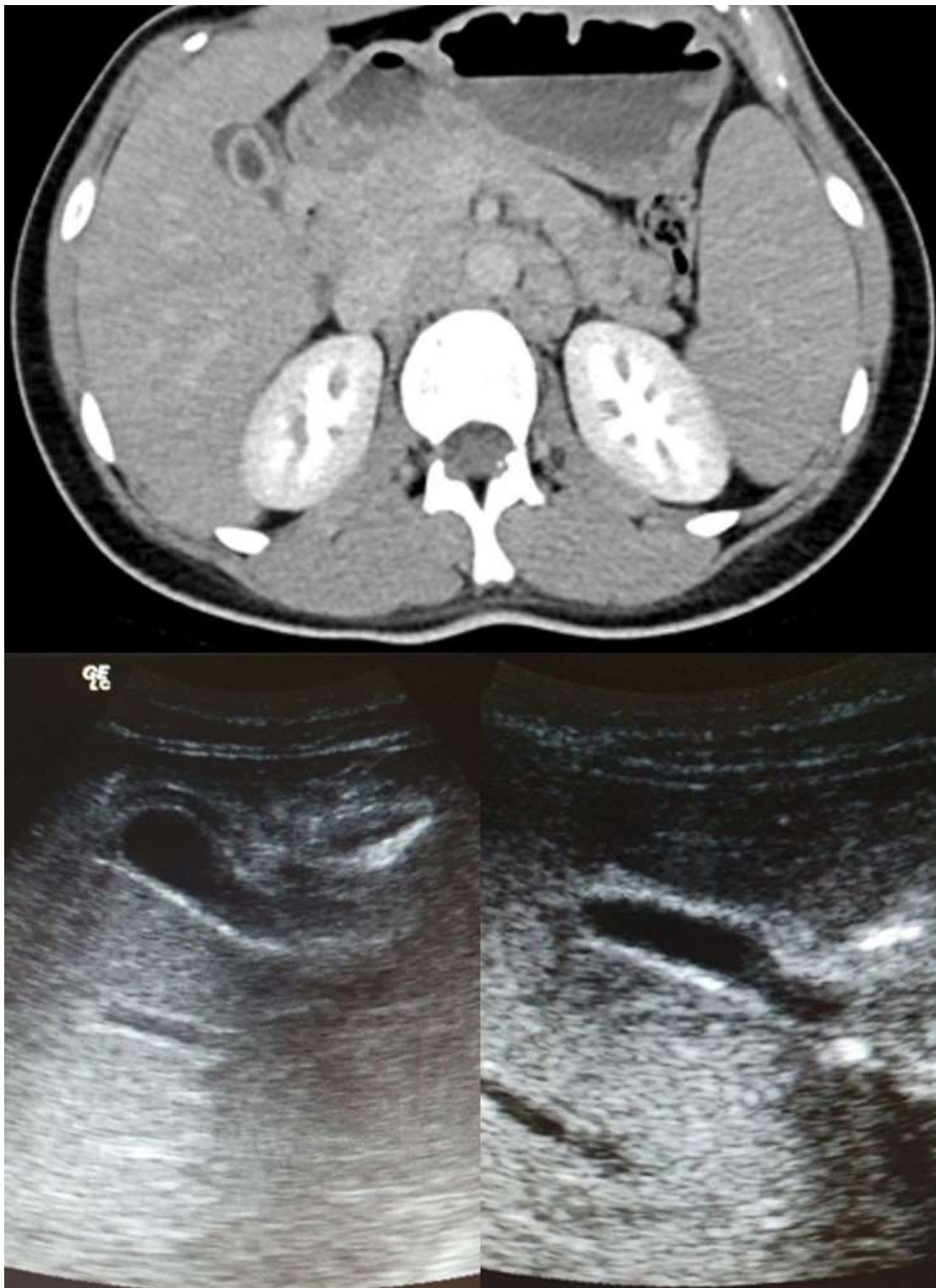
ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, EBV-VCA: Epstein-Barr Virus-Viral capsid antigen, ESR: erythrocyte sedimentation rate, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase,

**Table 2.** Improvement of liver function tests and lymphocytosis on days 1 to 5 and on days 15 and 30

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 15	Day 30
ALT (U/L)	451	319	284	193	166	47	17
AST (U/L)	329	204		105	84	50	10
ALP (U/L)	345	353		327	353	141	48
GGT (U/L)	219	232		230	237	102	19
Total bilirubin (mg/dL)	2.4	1.5		0.9	0.9	0.8	1.4
Direct bilirubin (mg/dL)	1.53	0.83		0.48	0.43	0.41	0.37
Lymphocyte ( $\times 10^3/\mu\text{L}$ )	7.9	7.1	6.3	5.2	4.7	3.2	2.2
Monocyte ( $\times 10^3/\mu\text{L}$ )	1.59	1.28	1.06	0.62	0.89	0.7	0.4

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase





**Figure 2.** Upper image: Abdominal computed tomography on the day of admission demonstrates splenomegaly (15cm.), gallbladder wall thickening, and edema. Lower left image: The point of care ultrasound on day 2 demonstrates ongoing thickening of the gallbladder anterior wall and edema. lower right image: Point of care ultrasound on day 5 demonstrates subsided gallbladder anterior wall thickening and edema. The patient was put on oral liquids from then on.

the course of an EBV infection.<sup>8</sup> There are 69 cases reported in the medical literature to date. Of whom, the majority were female and immunocompetent. EBV-associated AAC can occur from the pediatric age group

into adulthood. Only 2 female patients were treated with laparoscopic cholecystectomy, of whom one was immune-compromised and the other was immune-competent. Others were treated with conservative

management, similar to our patient. Splenic rupture is the most urgent and not-to-be-missed complication in patients with fever and abdominal pain diagnosed with infectious mononucleosis; however, the risk of cholecystitis should also be evaluated along with the spleen rupture.<sup>9</sup> AAC linked to EBV has been linked to pro-inflammatory substances like higher bile viscosity, ischemia of the gallbladder wall, and echosonoid. In the course of EBV mononucleosis, thickening of the gallbladder wall and bile sludge may be observed. Although patients with EBV-associated AAC may be febrile and jaundiced with right upper quadrant pain and tenderness, they do not typically appear sickly or toxic, as seen in cholecystitis with or without acalculous from other causes.<sup>10</sup> Abdominal CT helps exclude gallbladder perforation and spleen rupture.<sup>11, 12</sup> However, daily gallbladder POCUS served as a helpful tool to evaluate gallbladder wall edema and thickness and helped us decide when to initiate oral intake.

Another intriguing finding about this patient is that neither c-reactive protein (CRP) nor erythrocyte sedimentation rate (ESR) showed a prominent increase. Clinicians should know that a lack of CRP and ESR elevation does not necessarily mean a lack of inflammation.

In conclusion, EBV-associated AAC is mostly a self-limiting condition and can usually be managed with conservative treatment. Surgical treatment is generally not needed. Clinicians should keep in mind this rare complication in infectious mononucleosis patients who present with abdominal pain. Besides, patients who present with acalculous cholecystitis and are not critically ill should be considered for EBV infection.

#### *Consent*

Written informed consent has been obtained from the patient before manuscript preparation

#### *Conflict of Interest*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### *Authors' Contribution*

Study Conception: ATG, BÇ, GG; Study Design: ATG, BÇ, GG; Supervision: ATG, BÇ, GG; Funding: ATG; Materials: ATG, BÇ, GG Data Collection and/or Processing: ATG, BÇ, GG; Analysis and/or Data Interpretation: ATG; Literature Review: ATG, BÇ, GG; Critical Review: ATG, BÇ, GG; Manuscript

preparing: ATG.

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