

CLINICAL VIGNETTE

Epstein Barr Virus Associated Acalculous Cholecystitis

Geoffrey L. Graham, M.D., MBA, and Hamed Nayeb-Hashemi, M.D.

Case Presentation

An 18-year-old female college student presented to Student Health complaining of a sore throat, fevers, chills, and diaphoresis. She was diagnosed with a 'viral syndrome' and was told to increase fluid intake and use acetaminophen for discomfort. Three days later, she presented to urgent care where a rapid strep test (RST) was positive. She was treated with intravenous vancomycin and started on oral levofloxacin. She initially felt somewhat better but developed severe right upper quadrant abdominal pain with associated nausea, fevers, and vomiting, which resulted in her presentation to the emergency department and admission.

Her initial exam in the hospital was notable for a temperature of 38.8°C and tenderness to light palpation of the right upper quadrant without rebound or guarding. There was no significant lymphadenopathy, tonsillar enlargement, or exudate. Her labs demonstrated a total white blood cell count of 6000 with 29% neutrophils and 64% lymphocytes. Her initial liver chemistries were also significantly elevated with AST of 297 U/L, ALT of 280 U/L, Alkaline Phosphatase of 238 U/L, and Total bilirubin of 0.7 mg/dL. Abdominal ultrasound showed a markedly thickened gallbladder wall (10mm) without stones or sludge and with a positive sonographic Murphy's sign (Figure 1). The spleen was also enlarged at 14.2 cm. She was placed on IV antibiotics, and a surgical and gastroenterology consult were placed. She underwent a HIDA scan the following day, which demonstrated non-visualization of the gallbladder. At this time, initial labs returned with a positive Epstein Barr Virus (EBV) early Ag at 92.3 U/mL, this was followed by a positive EBV IgM at >160 U/mL. There was discussion between her managing consultants about possible surgery, but ultimately, she was followed expectantly with close observation. The patient slowly improved so that at discharge she was tolerating an adequate diet and fever had resolved. Serial abdominal ultrasounds showed a progressive decrease in the size of the gallbladder wall from an initial 10 mm 4 days later to normal size one day before discharge, which was 8 days after admission. Her liver chemistries remained abnormal at discharge but returned to normal at follow-up.

Discussion

Epstein-Barr Virus is a herpes virus, which is spread through contact with bodily fluids between susceptible individuals and symptomatic or asymptomatic carriers. It is commonly recognized as the infectious agent of infectious mononucleosis. Mononucleosis is characterized by the classical presentation of fatigue, lymphadenopathy, and fevers. Patients with

mononucleosis often have a peripheral blood lymphocytosis composed of atypical lymphocytes. The diagnosis of mononucleosis is made in the setting of supportive clinical symptoms along with positive heterophile antibody testing. This test relies on the presence of antibodies produced in response to EBV infection reacting with cells from phylogenetically disparate species (e.g., goat, horse, sheep). Though testing is highly specific there is limited sensitivity in the early phase of illness with false negatives being as high as 25% in the first week of illness.¹ Testing for specific antibodies to EBV, viral antigens, or Viral DNA through PCR testing can be performed when clinical suspicion is high, and heterophile antibody testing is negative as in our case.

EBV can affect any organ system and hepatic involvement with EBV is a well-known complication of primary infection. Hepatic involvement with EBV is often detected incidentally in patients with symptoms of Infectious mononucleosis. EBV hepatitis can be associated with abdominal pain and manifests as a self-limited elevation in liver chemistries. Clinically significant liver injury is infrequent and acute liver failure is rare. Amongst 1887 patients enrolled in the acute liver failure study group, 4 patients (0.21%) had EBV related liver failure.²

Acalculous cholecystitis is an acute inflammatory disease of the gallbladder. It is most often associated with critical illness though it can also be seen in the outpatient setting. Given the association with critical illness, these patients are often unable to provide a history and a high index of suspicion is required for diagnosis. The pathogenesis of acalculous cholecystitis involves an underlying condition leading to gallbladder stasis and ischemia, which leads to an inflammatory response. Secondary infection with enteric organisms is common, but primary viral infection including HIV, Cytomegalovirus, or as in this case, EBV can predispose to development of acalculous cholecystitis. Symptoms may include right upper quadrant pain and fevers. In other cases, the diagnosis may simply be suggested by an otherwise unexplained leukocytosis and elevated liver chemistries. Ultrasound imaging of the gallbladder has good sensitivity and specificity for the diagnosis with a gallbladder wall ≥ 3.5 mm having a sensitivity of 80 percent and a specificity of 99 percent for detecting acalculous cholecystitis.³ Cholescintigraphy can be used when the diagnosis is unclear after ultrasound. Attention should be paid to conditions that can result in a false positive test including prolonged fasting, TPN administration, and severe underlying liver disease. Management includes use of antibiotics targeting enteric pathogens and either

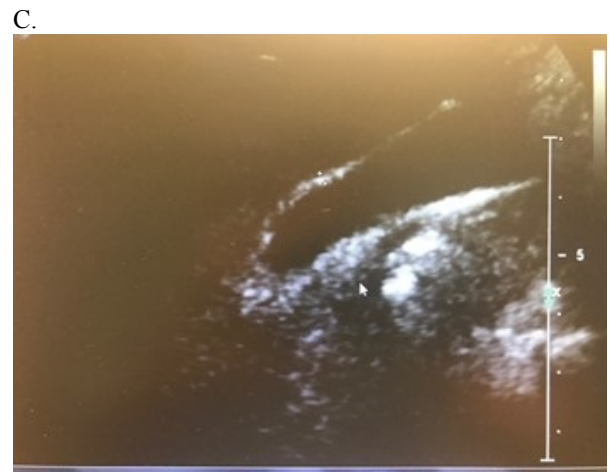
cholecystectomy or in patients who have contraindication to surgery placement of a cholecystostomy tube. Tube placement is successful in the vast majority of cases with rates measuring from 90-100% in various case series.⁴ In patients who respond to cholecystostomy tube placement eventual cholecystectomy may not be required if the underlying cause of cholecystitis is resolved.

EBV as a cause of acalculous cholecystitis is rare, with only several case reports in the literature. In contrast to most patients with acalculous cholecystitis from other causes, these patients can be managed without surgery or cholecystostomy tube placement. Outcomes are also similar regardless of use of antibiotics. Once the diagnosis of acalculous cholecystitis secondary to EBV is confirmed, antibiotics can be discontinued. In our case, as with all but one other published case, the patient was female. This is also unique in that acalculous cholecystitis has a male gender predominance. The pathogenesis of acalculous cholecystitis secondary to EBV is unclear. Putative mechanisms include direct invasion of the gallbladder wall by the virus or infection leading to cholestasis and subsequent inflammation.⁵

This case highlights a rare manifestation of EBV virus infection. The association with acalculous cholecystitis with EBV infection is important as these patients will in the majority of cases do well without surgery. Recognition is important to avoid a potentially unnecessary surgery. This is also one of the first reported cases of EBV associated acalculous cholecystitis reported in North America and demonstrates that conservative management in a North American patient population may also be appropriate.

Figures

Figure 1. Ultrasound images showing decrease in gallbladder wall thickness for 10mm on day 1 (A) to 5mm on day 3 (B) to normal on day 7 (C).



REFERENCES

1. **Ebell MH.** Epstein-Barr virus infectious mononucleosis. *Am Fam Physician.* 2004 Oct 1;70(7):1279-87. Review. PubMed PMID: 15508538.
2. **Mellinger JL, Rossaro L, Naugler WE, Nadig SN, Appelman H, Lee WM, Fontana RJ.** Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. *Dig Dis Sci.* 2014 Jul;59(7):1630-7. doi:10.1007/s10620-014-3029-2. Epub 2014 Jan 25. Review. PubMed PMID: 24464209; PubMed Central PMCID: PMC4250929.
3. **Barie PS, Eachempati SR.** Acute acalculous cholecystitis. *Gastroenterol Clin North Am.* 2010 Jun;39(2):343-57, x. doi: 10.1016/j.gtc.2010.02.012. Review. PubMed PMID: 20478490.
4. **Chung YH, Choi ER, Kim KM, Kim MJ, Lee JK, Lee KT, Lee KH, Choo SW, Do YS, Choo IW.** Can percutaneous cholecystostomy be a definitive management for acute acalculous cholecystitis? *J Clin Gastroenterol.* 2012 Mar;46(3):216-9. doi: 10.1097/MCG.0b013e3182274375. PubMed PMID: 21814147.
5. **Yesilbag Z, Karadeniz A, Kaya FO.** Acute Acalculous Cholecystitis: A Rare Presentation of Primary Epstein-Barr Virus Infection in Adults-Case Report and Review

of the Literature. *Case Rep Infect Dis.*
2017;2017:5790102. doi:10.1155/2017/5790102. Epub
2017 Jan 17. PubMed PMID: 28194287; PubMed Central
PMCID: PMC5282411.

Submitted September 12, 2017