Acalculous Cholecystitis, Acute Hepatitis and Hemolytic Anemia Associated With Epstein-Barr Virus: A Case Report

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Abstract- Epstein-Barr virus (EBV) is a member of the herpes virus family and is characterized by fever, lymphadenopathy, and sore throat. In this report, we present a 20-year-old woman with a four-day history of fever, chills, nausea, vomiting, jaundice and abdominal pain, and a diagnosis of acalculous cholecystitis, acute hepatitis with hemolytic anemia due to infectious mononucleosis. After the confirmation of acute acalculous cholecystitis along with hemolytic anemia, prednisolone was initiated for the patient. Supportive measures resolved the symptoms of acalculous cholecystitis.

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Introduction

Epstein-Barr Virus (EBV) is a member of the herpes virus family that is characterized by fever, lymphadenopathy, and sore throat. This viral disease is a self-limiting infection often occurring during adolescence and childhood. This infection is commonly associated with splenomegaly and a mild increase in the liver enzymes, but liver involvement in the form of acute hepatitis and jaundice is rare (1). Acalculous cholecystitis is an acute inflammation of the gallbladder without gallstones that can be a rare manifestation of EBV infection (2). This article presents a patient with acalculous cholecystitis, acute hepatitis, and hemolytic anemia in the context of EBV infection.

Case Report

The patient was a 20-year-old woman presenting to the emergency department with fever, shivers, nausea, and vomiting plus abdominal pain and jaundice in the last four days after eating Doner kebab. Her abdominal pain was in the epigastric region, spreading to the right upper quadrant (RUQ). The patient had a history of mild sore throat, no diarrhea or coughing, and no history of recent travel. The patient recalled darkening urine from the past two days. Upon admission, the patient was febrile (39° C). She had generalized jaundice. The examination did not show any positive findings, except for tenderness in the RUQ. Table 1 summarizes the tests performed on the patient after hospital admission.

Table 1. Laboratory data at admission

Day 1	
WBC (/mm^3)	19500
Lymphocyte (%)	52%
Hemoglobin (gr/dl)	10
PLT (/mm^3)	210000
ALT (U/L)	368
AST (U/L)	265
ALP (U/L)	325
Total Bilirubin (µmol/L)	15.7
Direct Bilirubin (µmol/L)	7.7
PT (s)	10.4
PTT(s)	28
INR	1.04

Given that she suffered from abdominal pain and jaundice alongside fever, both abdominal and pelvic ultrasounds were requested for the patient. Reports came out with 131-mm splenomegaly and thickened gallbladder (9 mm) with no stones, which suggested acalculous cholecystitis. Based on the tests, the diagnosis of acute hepatitis and icterus, anti-HBc IgM

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antibody, anti-HAV IgM antibody, anti-HCV antibody, HBs antigen, and an autoimmune hepatitis panel were also requested for the patient, but all of them reported negative. On the fourth day of admission, the patient's hemoglobin dropped to 5.4 gr/dl and given her high lactate dehydrogenase (=780) and high reticulocyte, the diagnosis of hemolytic anemia was proposed. Given that the acute hepatitis A, B, and C tests turned out negative, IgM VCA Ab (EBV) and IgM cytomegalovirus (CMV) antibody tests were requested. Until the EBV and CMV antibody test results came back, meropenem was initiated for the patient for high fever and abdominal pain in the RUQ. One day after the initiation of meropenem, the patient developed a generalized maculopapular rash, and the noted antibiotic was stopped in response to the appearance of cutaneous lesions. Since the IgM VCA EBV test reported positive, the diagnosis of EBV-induced acalculous cholecystitis, hemolytic anemia and acute hepatitis was confirmed. Also, atypical lymphocytes were observed in the patient's peripheral blood smear (Figure 1).

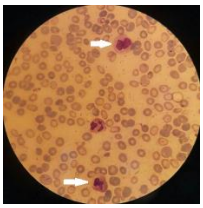

Figure 1. Atypical lymphocyte in the patient's peripheral blood smear

After the confirmation of acute acalculous cholecystitis along with induced hemolytic anemia, prednisolone was initiated for the patient at a dose of 50 mg. Two days after the initiation of prednisolone, the patient's general condition improved, her hemoglobin levels began to rise, and by the end of the prednisolone treatment course and after reducing its dosage and stopping its administration over two weeks, her liver enzymes and hemoglobin levels returned to normal. Besides, abdominal pain and nausea resolved entirely throughout her hospital stay. No evidence of recurrence was found on follow up at three months.

Discussion

This article presents a patient with EBV-induced acalculous cholecystitis, acute hepatitis, and hemolytic anemia. EBV is one of the rare causes of acute hepatitis (3). Acalculous cholecystitis often occurs as a result of surgery, trauma, and prolonged fasting in patients with poor health, and its incidence in EBV infection is rare (4). Table 2 presents similar cases reported in adults over the age of 18 years with acalculous cholecystitis associated with EBV infection (5 to 19).

In the case reported by Hagel (9), hemolytic anemia was reported to have coincided with acute cholecystitis without stones, which is similar to the case reported in this article. However, their patient had a history of using azathioprine, while the patient in the present article had no underlying diseases. In the case reported by Sheybani in 2016 (18), the patient had EBV infection and acalculous cholecystitis plus skin rash and mucosal involvement and responded well to corticosteroid. In the reported cases, all except one of the patients were female, as in the present case. In nearly all the reported cases, the patients had leukocytosis with a lymphocytic predominance (as in the present case), except in the case reported by Yesilbag, in which the patient had leukocytosis with PMN predominance (66.4%). The pathogenesis of acalculous cholecystitis in the context of EBV infection has not been identified, but the virus' direct invasion of the gallbladder wall mucosa followed by biliary stasis and gallbladder inflammation might facilitate the incidence of acute cholecystitis (20). The diagnosis of acute acalculous cholecystitis is based on clinical symptoms and laboratory tests, and this diagnosis is confirmed by ultrasound and the observation of a thickening gallbladder without stones and the collection of liquid around the gallbladder along with sonographic Murphy sign. Treatment is mainly by cholecystectomy or cholecystostomy. When bacteria are the cause, using antibiotics becomes necessary (21). In the present case, surgery was not performed on the patient because of the viral cause of her acute cholecystitis and also the improvement in her clinical symptoms, which were resolved by supportive measures. Since the patient had indication for corticosteroids (hemolytic anemia), corticosteroid was administered. Another significant point in the present case was the incidence of generalized maculopapular cutaneous lesions after using meropenem for one day.

The other cited studies did not report any rash after the use of antibiotics. The incidence of these cutaneous lesions can be attributed to the following two mechanisms: Antibiotic allergy and maculopapular rash after the use of antibiotics in EBV infection, with the second mechanism having nothing to do with antibiotic allergy and being caused by a change in antibiotic metabolism or immune-mediated processes.

Given that the patient had no history of penicillin allergy, Naranjo score of five (22) and the confirmation

of the potential association between meropenem and rash, the incidence of rash in the patient can be probably attributed to the EBV infection. Although with the second mechanism, the rash often occurs in EBV infection after using aminopenicillins, a number of case reports have reported the incidence of rash with the use of other antibiotics too. Meanwhile, the present case is remarkable in that no rash was reported with EBV infection after using meropenem.

Table 2. Similar cases reported in adults over the age of 18 years

Authors, Year	Age (Year)/ Gender	Sore Throat	AST/ALT	GGT/ALP	WBC Lymph %	Total/Direct Bilirubin	Ultrasound Findings	Antibiotic
Koch *et al.*, (2007)	53/F	-	422/339	17.72 kat/L/ 1081	-	120/-	Cholecystitis with a gallbladder wall thickness of 10 mm, no stones, no dilatation of the biliary ducts, and an enlarged liver with steatosis	-
Iaria *et al.*, (2008)	18/F	Yes	220/328	142/312	70%	7/ 4.26	Contracted gallbladder with the thickened wall (9 mm), presence of sludge and absence of stones, no dilatation of the biliary tract, positive sonographic Murphy's sign	Amoxicillin-clavulanic acid
Cholongitas *et al.*, (2009)	19/F	Yes	426/584	156/710	55%	6.5/ 5.17	Thickened gallbladder wall (8 mm) without pericholecystic fluid, gallstones or sludge	-
Chalupa *et al.*, (2009)	22/F	-	6.87/12.79	3.06/2.2	56%	143/ 80	Collapse and hyperdensity of the gallbladder, thickened gallbladder wall, and contrast-enhanced fluid	Pefloxacin
Yang *et al.*, (2010)	20/F	Yes	171/299	202/727	70%	0.7/ -	Abdominal CT scan showed a severe degree of hepatosplenomegaly and diffuse edematous changes of the gallbladder wall with mucosal enhancement and without stones or dilatation of the biliary tract	amoxicillin/clavulanic acid
Hagel *et al.*, (2009)	22/F	-	-	-		254micro mol/ L/ -	Contracted gallbladder with wall thickening (7 mm) with mural striations	Gentamicin+ ceftazidime+ metronidazole
Beltrame *et al.*, (2012)	29/F	-	121/166	145/161	51%	23.2/12.4	Contracted gallbladder with wall thickening (15 mm) with pericholecystic fluid and absence of sludge, stones or dilatation of the biliary tract	Cephalosporin
Nagdev and Ward (2011)	18/F	No	118/ -	-/ 146	-	1.2/0.6	No gallstones but a thickened gallbladder wall (greater than 1 cm) with mild pericholecystic fluid	piperacillin-tazobactam
Carrascosa *et al.*, (2012)	22/F	-	329/464	-/ 239	61%	42/ 41	A contracted gallbladder with wall thickness of 14 mm and pericholecystic fluid	-
Gagneux-Brunon *et al.*, (2014)	18/F	-	321/ 214	64/ 165	30.5%	20/ -	Striated thickened gallbladder (12 mm) with microabscesses	Ceftriaxone+ metronidazole
Gagneux-Brunon *et al.*, (2014)	20/F	-	453/ 494	286/ 133	41.6%	38.2/ -	Gallbladder wall thickening (16 mm) without calculus	Amoxicillin/clavulanic acid
Celik *et al.*, (2014)	48/F	-	221/165	224/516	45.5%	14.4/12.9	Pronounced thickening of the gallbladder wall, positive Murphy's sign	Antibiotic
Agergaard and Larsen (2015)	34/F	No	-/ 61	-/ 429	-	42/ -	Thickened and edematous gallbladder wall (11.3 mm) and small amount of ascites	Ceftriaxone
Koufakis and Gabranis (2016)	21/M	No	172/ 232	350/ 179	57%	6.31/ 4.96	Thickening of the gallbladder wall (4.5 mm, Figure 1) and positive sonographic Murphy sign	-
Sheybani *et al.*, 2016	23/F	Yes	169/ 641	-/ 909	62%	2.3/ 1.1	Distended gallbladder with thickened wall, without any stones, suggesting acalculous cholecystitis	-
Yesilbag *et al.*, (2017)	30/F	No	233/220	471/376	27.1%	15.4/14.5	Thickened and edematous gallbladder wall (7.4 mm) with pericholecystic and perihepatic fluid and absence of cholelithiasis	-
Our Case (2019)	20/F	Yes	265/368	-/325	52%	15.7/7.7	Thickening of the gallbladder (9 mm) with no stones	Meropenem

Infectious mononucleosis should be considered in patients with acute acalculous cholecystitis and acute hepatitis so as to prevent invasive surgical procedures and unnecessary antibiotic administration. In patients with jaundice and a diagnosis of EBV, the possibility of hemolytic anemia should also be considered.

References

1. Macsween KF, Crawford DH. Epstein-Barr virus-recent advances. Lancet Infect Dis 2003;3:131-40.
2. E. Lagona, F. Sharifi, A. Voutsioti, A. Mavri, M. Markouri, and A. Attilakos, Epstein-barr virus infectious mononucleosis associated with acute acalculous cholecystitis. Infection 2007;35:118-9.
3. Jimenez-Saenz M, Perez-Pozo JM, Leal-Luna A, Herrerías-Gutiérrez J M. Lethal liver failure in an elderly patient with hepatitis B superinfected with Epstein-Barr virus. Eur J Gastroenterol Hepatol 2002;14:1283-84.
4. Barie PS, Eachempati SR. Acute acalculous cholecystitis. Gastroenterol Clin North Am 2010;39:343-57.
5. Koch D, H. C. M. Van Den Bosch, Bravenboer B, Epstein-Barr virus-associated cholecystitis. Ann Intern Med 2007;146:826-7.
6. Iaria Ch, Arena L, Di Maio G, Grazia Fracassi M, Silvana Leonardi M, Famulari C, et al. Acute acalculous cholecystitis during primary Epstein-Barr virus infection: a new case and a review of the literature, Int J Infec Dis 2008;12:391-5.
7. Cholongitas K, Katsogridakis, and Dasenaki. Acalculous cholecystitis during the course of acute Epstein-Barr virus infection. Int J Infec Dis 2009:13:e129-30.
8. Chalupa P, Kaspar M, Holub M. Acute acalculous cholecystitis with pericholecystitis in a patient with Epstein-Barr Virus infectious mononucleosis. Med Sci Monit 2009;15:CS30-3.
9. Hagel S, Bruns T, Kantowski M, Fix P, Seidel T, Stallmach A. Cholestatic hepatitis, acute acalculous cholecystitis, and hemolytic anemia: primary Epstein–Barr virus infection under azathioprine. Inflamm bowel dis 2009;15:1613-6.
10. Beltrame A. Andres F. Tona F and Sperti C. Epstein-barr virus—associated acute acalculous cholecystitis in an adult. Am J Case Rep 2012;13:153-6.
11. Nagdev A and Ward J. Bedside ultrasound diagnosis of acalculous cholecystitis from Epstein-Barr virus. West J Emerg Med 2011;12:481-3.
12. Dylewski J. Acute acalculous cholecystitis caused by Epstein-Barr virus infection. Clin Microbiol Newsl 2012;34,7-8.
13. Carrascosa F, Caviedes J.-R. S, Soler-Dorda G, Saiz-P´erez C. Epstein-Barr virus acute cholecystitis BMJ Case Rep 2012; 2012.
14. Gagneux-Brunon A, Suy F, Pouvaret A, Pillet S, Tarantino E, Bouchet D, et al. Acute acalculous cholecystitis, a rare complication of Epstein-Barr virus primary infection: report of two cases and review J Clin Virol 2014;61:173-5.
15. Celik F, Tekin F, Yamazhan T, and Gunsar F. Epsteinbarr virus associated acute acalculous cholecystitis. J Gastroenterol Hepatol Res 2014;3:1179- 80.
16. Agergaard J and Larsen C. S. Acute acalculous cholecystitis in a patient with primary Epstein-Barr virus infection: a case report and literature review. Int J Infect Dis 2015;35:67-72.
17. Koufakis T and Gabranis I. Another report of acalculous cholecystitis in a greek patient with infectious mononucleosis: a matter of luck or genetic predisposition? Case Reports Hepatol 2016;2016:6080832.
18. Sheybani F, Naderi H, Erfani SS, Gharib M. A complicated course of acute viral induced pharyngitis, icteric hepatitis, acalculous cholecystitis, and skin rash. Case rep med 2016;2016:6796094.
19. 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.
20. Prassouli A, Panagiotou J, Vakaki M, Giannatou I, Atilakos A, Garoufi A, et al. Acute acalculous cholecystitis as the initial presentation of primary Epstein-Barr virus infection. J Pediatr Surg 2007;42:E11-3.
21. Barie PS, Eachempati SR. Acute acalculous cholecystitis. Gastroenterol Clin North Am 2010;39:343-57.
22. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 198;30:239-45.