Rare complication of primary infection with Epstein-Barr virus: a case report and short review of literature

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Abstract

Acute acalculous cholecystitis (AAC) is a rare complication of primary infection with Epstein-Barr virus (EBV). A 17-year old male was admitted to the hospital due to abdominal pain, severe vomiting, tonsillitis and splenomegaly. Infectious mononucleosis was suspected and confirmed using agglutination test to detect heterophile antibodies IgM against EBV. Ultrasonography showed thickened and stratified gallbladder wall with no gallstones. Full recovery following conservative therapy with a broad-spectrum antibiotic, analgesic and rehydration therapy was noted. To our knowledge, this is the first case of EBV related AAC in the Slovenian medical literature. AAC is a possible severe complication of infection with EBV and should be taken into consideration in cases of EBV infection presenting with severe abdominal pain.

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1 Introduction

Acute acalculous cholecystitis (AAC) is an acute disease of the gallbladder in the absence of gallstones (1). Unlike in adults, where it accounts for only 5–10 % of cases, AAC is the most common form of acute cholecystitis in children (50–70 % of cases) (1,2). Although it is mostly described in literature as a complication of severe trauma or burns, severe systemic disease (Mb. Kawasaki, systemic lupus eritematosus, nephrotic syndrome), complete parenteral nutrition or severe dehydration, it is most often the effect, in immunocompetent paediatric population, of infection with diffetent organisms (1,3,4). AAC development both in adults and children has been noted following infection with bacteria (*Brucella* spp., *Campylobacter jejuni, Coxiella burnetii, Leptospira* spp, *Mycobacterium* spp., *Salmonella* spp and *Vibrio cholerae*), fungi (*Candida* spp), viruses (hepatitis A and B viruses – HAV, HBV, Epstein-Barr virus – EBV, cytomegalovirus – CMV and flavivirus) and parasites (*Plasmodium* spp, *Ascaris lumbricoides* and *Echinococcus*); of which infections with EBV and HAV are described the most often (1,5). The article

presents a case of AAC following primary EBV infection.

2 Case presentation

A seventeen year old male was admitted following 14 days of nausea, fatigue and decreased appetite. On the day of admission, the patient began to complain about epigastric pain, which responded poorly to treatment with pantoprazole and metamizole. The patient had previously been healthy and had not been receiving any medication. Upon admission, the patient looked tired and pale, had no temperature, had mild pharyngitis and no signs of tonsillitis. The abdomen was at chest level and very sensitive to touch in the area of xiphoid process and upper right quadrant, while the liver and spleen were not enlarged to touch. Upon auscultation, peristaltic action was observed in all four quadrants. Otherwise, physical status was normal. Laboratory reports showed mild leucocytosis (13.70×10^9/L in differential blood count, with 78 % lymphocytes, 4 % monocytes, 3 % banded neutrophils, 15 % segmented neutrophils) and mildly elevated values of C-reactive protein 5.1 mg/L (reference range (RR) 0–3.5 mg/L). Electrolyte and blood urea nitrogen values were within normal range. The patient was first treated for acute inflammation of the stomach lining. Parenteral therapy with H2 receptor antagonist and analgesics was introduced, and the patient was put on gastric diet. The second day of hospitalisation the pain began to escalate, and the patient began to vomit. Clinically, enlarged and hyperemic tonsils with spots, and an enlarged spleen was noted. Follow-up laboratory reports showed elevated values of total bilirubin 63 µmol/L (RV:3–17 µmol/L), and direct bilirubin 42 µmol/L (RR: 0–3 µmol/L), aspartate aminotransferase 9.23 µkat/L (RR: 0.01–0.58 µkat/L), alanine aminotransferase 16.48 µkat/L (RR: 0.01–0.74), gamma glutamyl transferase 5.00 µkat/L (RR 0.03–0.70 µkat/L), amylase 3.53 µkat/L (RR: 0.01–1.92 µkat/L) and lipase 21.73 µkat/L (RR: 1.21–6.55 µkat/L).

Extensive microbiological testing was performed to look for pathological values of liver enzymes. Rapid agglutination test based on Paul Brunnel was used to detect the presence of IgM heterophile antibodies to EBV (PB-HA), which mostly indicate acute infection with EBV. CMV antibody titres were also elevated, which was established using *(angl.* Chemiluminescence Assay (CLIA), with IgM: 33.2 U/ml, IgG: 129.00 U/ml. Rapid step test from a pharynx swab was negative. Possible infection with HAV and HCV was excluded. When testing for hepatitis b viral infection (HBV), HBV surface antigen (HBs Ag) was negative, while IgG antibodies to HBV surface antigen (anti HBs) were positive, which is consistent with an immune response following vaccination. Haemocultures were sterile. A stool sample was taken to detect the presence of Helicobacter pylori antigen using *angl.* Enzyme-Linked Immunosorbent Assay, ELISA.

Ultrasound (US) of the abdomen was performed, which showed contracted gallbladder with striated thickened wall (1–1.5 cm), and a small amount of free fluid by the liver. Although the sonography of the gallbladder was not clear, there were no signs of hardened deposits and the ducts were not dilated. The spleen was enlarged and palpable, with a diameter of up to 16 cm, with lymph nodes in the upper part of the abdomen enlarged too. The original therapy was continued and an antiemetic agent added (setronone). The US was repeated the fourth day of hospitalisation, when the diagnosis of AAC was confirmed.

After consulting surgeons, conservative treatment was continued and antibiotic therapy with amoxicillin combined with clavulanic acid introduced. The patient's general condition improved, the pain and tonsillitis went away, and laboratory testing noted a drop in the values of liver enzymes. The tenth day of hospitalisation the patient was released into home care and prescribed oral antibiotic. US before release revealed a normal gallbladder without visible pathological changes. Three months after the end of hospitalisation the patient had appropriate physical ability, and biochemical values of liver function were within the normal range.

Due to positive HP antigen in the stool, triple therapy with clindamycin, amoxicillin and proton pump inhibitor was introduced following the end of treatment with amoxicillin and clavulanic acid. The follow-up stool sample, tested for HP antigen 8 weeks after eradication treatment was negative.

3 Discussion

AAC is a rare complication of primary EBV infection. Since 2000, 23 cases have been described among pediatric population (6-26), most of them in Europe, of which seven were described in Greece (7,8,11-13,20). This article is the first presentation of AAC linked to EBV based on a clinical case in Slovene medical literature.

AAC has diverse and non-specific clinical presentation. Most common clinical symptoms in children are fever and abdominal pain (1). Like in most other described cases, the reason that prompted a visit to the physician was abdominal pain. Upon admission, while the patient had mild pharyngitis, he lacked typical clinical presentation of infectious mononucleosis (IM) with generalised lymphadenopathy and fever (12). Only splenomegaly and tonsillitis with spots that manifested on the second day of hospitalisation led us to suspect infection with EBV infection. The patient also reported early signs of IM, including nausea, fatigue and decreased appetite, which had appeared 14 days earlier together with abdominal pain.

Although US criteria for diagnosing AAC remain unspecific, the following descriptions are most often reported in literature: absence of gallstones, striated thickened wall (> 3.5–4 mm), expanded gallbladder, pericholecistic fluid, localised sensitivity (sonographic Murphy sign) and the presence of sludge (*angl.* sludge) in the gallbladder. In addition to characteristic clinical presentation, at least two signs should be observed; the patient had at least four (1,27,28).

Although the pathogenesis of AAC following EBV infection is not fully known, two mechanisms are mentioned in literature: systemic inflammation activity and/or cholestasis (25,27,29,30). The crucial role of systemic inflammation is inferred in the analysis of clinical cases of AAC published by 2016 by Kottanattu et al. (31), where laboratory testing had a cholestatic pattern was reported in the laboratory test of only one out of 37 patients (25). Systemic inflammation mechanism can also explain other complications of IM, such as acute pancreatitis (31).

However, substances in the bile, such as β-glucuronidase and lysophosphatidylcholine, can directly cause damage of gallbladder mucosa, release of proinflammatory cytokines and development of cholecystitis (5,27,32-34). Additionally, lymphadenitis with extrinsic obstruction of the cystic duct, direct damage of hepatocytes caused by EBV-infected cytotoxic lymphocytes and genetic polymorphism of the enzymes assisting in the synthesis

and transport of bile acids are thought to contribute to the development within liver cholestasis (1,5,34-36). This would explain a more difficult course of infection in patients with Gilbert syndrome with homozygous or heterozygous mutation UGTA1*28, which was described by Attilakos et al (11). We did not pursue genetic testing of our patient. Oestrogen is also considered to play a significant role in the development of AAC by promoting the production of proinflammatory mediators, which would explain the fact that most reported cases are women (12,34,37).

With a single exception, AAC was treated conservatively with parenteral rehydration, analgesic therapy and nutrition support (7,10,26). In most cases, after diagnosing AAC, treatment with a broad-spectrum antibiotic or a combination of antibiotics, such as amoxicillin with clavulanic acid or a combination of ceftazidime, gentamicine and metronidazole (7,10,26). However, after reviewing both paediatric and adult cases, Agergaard et al (38) established that disease did not progress more unfavourably even when no antibiotic was introduced. Therefore, with AAC diagnosis following EBV the individual decision on whether to introduce antibiotic is left to the physician.

Our patient had elevated anti-CMV IgM titres and more expressed anti-CMV IgG antibodies determined with CLIA method, which could point to concurrent subacute infection with CMV virus. According to available literature, clinical presentation of IM in case of concurrent infection with EBV and CMV is atypical, more intensive and complex, particularly in adolescents (39). However, lowered immunity as the result of lower relationship between CD4/CD with infection with EBV could lead to reactivation of a latent CMV infection (39-41). Moreover, Nishikawa et al. established that acute infection with EBV can lead to cross-reactivity with the synthesis of anti-M protein antibodies *angl.* of other herpes viruses, one of which is CMV (42). As we did not choose to further diagnose potential CMV infection of the patient, we cannot reliably interpret serology results.

Microbiologic testing of the patient's stool sample indicated HP-positive antigen. While HP is mentioned in literature as an etiological factor for the development of acute and chronic cholecystitis. We failed to establish a link between AAC and HP in available literature (43,44,45,46).

4 Conclusion

AAC is the most common form of cholecystitis in paediatric population. In immunocompetent children, the disease of most often of viral etiology, generally caused by EBV (1). In case of suspected IM presented with severe pain, an abdominal ultrasound and testing for liver function biomarkers should be performed. Usually, the disease is treated symptomatically and has a favourable outcome. While opinion on the need to introduce antibiotic therapy remains divided, a broad-spectrum antibiotic was introduced in most cases presented in literature.

5 Consent

We have obtained the consent of the patient, who had already turned 18 years old before the article was submitted.

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