Case Report

Epstein-Barr virus (EBV)-induced acute acalculous cholecystitis in children: a case report

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Background: The clinical manifestations of Epstein-Barr virus (EBV) infection are usually infectious mononucleosis, chronic active EBV infection, and related hemophagocytic lymphohistiocytosis. The incidence of non-calculous cholecystitis in children is not high, and non-calculous cholecystitis in children caused by EBV infection remains a rarity, which is often overlooked in clinical practice. The purpose of this study was to describe the clinical characteristics, laboratory tests, imaging findings, and treatment outcomes of a 9-year-old boy.

Case Description: This case details a 9-year-old boy who was diagnosed with infectious mononucleosis, acute non-calculous cholecystitis (ACC), and severe hepatic insufficiency. ACC is very rare in pediatric patients, especially because of its own liver function impairment, which is easily overlooked in clinical diagnosis. At the beginning of the disease, the patient presented with upper abdominal pain and vomiting, which was misdiagnosed as acute gastroenteritis, and later with fever, yellowing of the skin, dark yellow urine, repeated abdominal pain and vomiting, and serious liver damage, which was later found to be accompanied by ACC. After receiving regular treatment, the patient's condition improved, with no discomfort reported in the follow-up six months and one year thereafter. This case emphasizes that the clinical work should be carefully performed, in order not to miss any specific clinical manifestations. In this study, we highlight a new problem posed by EBV infection, as well as early awareness of rare cases of ACC in children caused by EBV infection.

Conclusions: This case report provides a new supplement for the diagnosis and treatment of rare non-calculous cholecystitis in children caused by EBV infection, and provides a clinical basis for young pediatricians to make a timely diagnosis, reduce misdiagnosis, and prevent missed diagnosis.

Keywords: Epstein-Barr virus (EBV); acute non-calculous cholecystitis (ACC); children; case report

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Introduction

Epstein-Barr virus (EBV) is a double-stranded deoxyribonucleic acid (dsDNA) herpes virus γ subculture capable of sustained latent infection in the memory B cells of the body (1). EBV infection can cause liver function damage in pediatric patients. Although EBV infection is the most common cause of liver function damage, severe liver damage or acute liver failure is exceedingly rare in clinical practice. Clinically, it is easy to overlook the extremely low incidence of acute cholecystitis in children. Moreover,

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the etiology of acute cholecystitis in children is diverse, including bile retention, bacterial infection, long-term intravenous nutrition in severe cases, and biliary ascariasis. Bacterial infections are often caused by the invasion of blood, lymph, intestines, or adjacent organs into the gallbladder. Non-calculous cholecystitis in children due to EBV infection is rare. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-2024-614/rc).

Case presentation

A 9-year-old boy was admitted to our hospital on account of vomiting and abdominal pain for three days and fever with scleral icterus for two days. The community hospital diagnosed him with acute gastroenteritis and prescribed cefixime orally for one day. However, the patient continued to vomit and experienced abdominal pain and fever with yellow sclera and urine. During this period, routine blood tests showed white blood cell (WBC) level of 13.69×10^9/L, neutrophil level of 7.8×10^9/L, lymphocyte level of 2.05×10^9/L, monocyte levels of 1.37×10^9/L, atypical lymphocytes level of 2.19×10^9/L, platelet (PLT) levels of 157×10^9/L, and a C-reactive protein (CRP) level of 3.74 mg/L. Blood biochemistry showed an alanine aminotransferase (ALT) level of 3,441 U/L, aspartate aminotransferase (AST) level of 3,295 U/L, total bile acid (TBA) level of 382 mmol/L, and a total bilirubin (TB) level of 144.2 μmol/L. The patient denied having recently consumed any contaminated food or water. There was no recent history of taking medication. His skin and sclera were yellow-stained, his abdomen was soft, and tenderness was observed around the navel and right side of the abdomen.

A series of examinations was performed upon the patient's admission, including testing for anti-nuclear antibodies; hepatitis A, B, C, D, and E tests; a toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH) test; exams testing for cytomegalovirus antibodies, cytomegalovirus DNA, human immunodeficiency virus (HIV)-p24 antigens and antibodies, treponema pallidum antibodies, respiratory adenovirus, respiratory syncytial virus, influenza virus, mycoplasma, and chlamydia; a sputum culture; a blood culture; and tests concerning alpha-fetoprotein, ceruloplasmin, cytokines, blood ammonia, blood amylase, and urine amylase. The results of all these tests were in the normal range. The findings of chest X-ray, electrocardiogram, and echocardiography were also normal. A whole-abdomen computed tomography (CT) scan indicated decreased liver parenchyma density, increased gallbladder edema, and possible cholecystitis (*Figure 1*). An abdominal ultrasound revealed that the gallbladder wall was rough, edematous, and thickened, with a thickness of approximately 1.0 cm. Poor translucency of bile was observed in the cavity, and no obvious abnormalities were evident within the lumen. All of these findings indicated cholecystitis (*Figure 2A*). After admission, the symptoms persisted, including nausea and vomiting, particularly after the consumption of greasy foods; pain in the upper right part of the abdomen; yellowing of facial skin and sclera; dizziness; weakness in limbs; and yellowish urine color. Details of the blood biochemistry and coagulation function are shown in *Table 1*. Following admission, the patient was administered a regimen of low-fat soft food, bed rest, albumin, vitamin K_1, fluid replacement, liver-protecting, enzyme-lowering, choleretic, and antiviral medicines. One week later, the patient's coagulation function returned to normal, and the EBV-DNA result was 5.4×10^5 copy/mL. After 10 days, liver, gallbladder, spleen, and pancreatic ultrasounds showed no gallbladder wall thickening (*Figure 2B*), and bilateral neck lymph node enlargement had significantly subsided. Liver function significantly improved after 12 days of follow-up examination, and the

Highlight box

Key findings

- This case report highlights the successful and definitive diagnosis and treatment of non-calculous cholecystitis in a 9-year-old boy, and emphasizes the importance of early and accurate diagnosis and treatment of non-calculous cholecystitis caused by Epstein-Barr virus (EBV) infection in children.

What is known and what is new?

- The most common clinical manifestations of EBV infection include fever, angina, cervical lymph node enlargement, and liver function damage, but in children, non-calculous cholecystitis is rare, and the symptoms are not typical, making it easy to miss a diagnosis.
- This case indicates that for the clinical manifestations caused by EBV infection, it is necessary to remain vigilant for non-calculous cholecystitis in children, and timely diagnosis and treatment can be achieved through the awareness of clinical manifestations, careful physical examination, and improvement of abdominal ultrasound.

What is the implication, and what should change now?

- This case highlights the importance of early diagnosis of acute non-calculous cholecystitis (ACC) in children and emphasizes the need for accurate diagnostic criteria and enhanced awareness among pediatric clinicians.

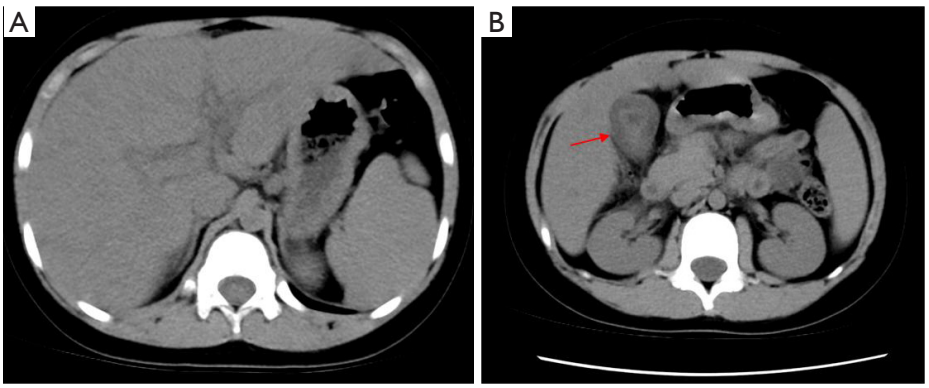

Figure 1 Abdominal CT. (A) Decreased hepatic parenchymal density. (B) Thickened gallbladder edema, indicating cholecystitis. CT, computed tomography.

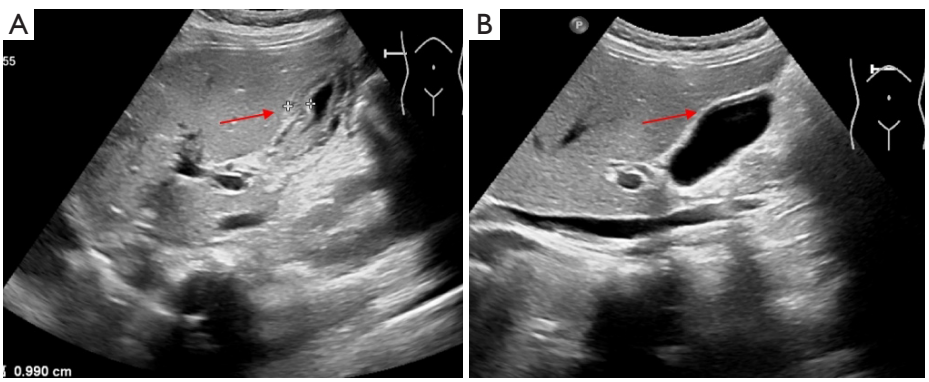

Figure 2 Gallbladder ultrasound results: comparison chart before and after treatment. (A) Abdominal ultrasound: the gallbladder wall was rough and thickened, the thicker part was about 10 mm (arrow), the bile in the cavity was transparent, and no abnormal echo was found in the sac. The thickening and edema of the gallbladder wall indicated the presence of inflammation. (B) After treatment, the capsule wall was smooth without thickening (arrow), the bile in the cavity was clear, and no abnormal echo was found in the capsule.

patient was discharged with medication, including oral liver-protective medicine. Liver function was reassessed one week after discharge, showing 62 U/L ALT, 53 U/L AST, 28.8 μmol/L TB, 21.4 μmol/L of direct bilirubin, and normal TBA levels. At the follow-up of six months and one year after discharge, the patient had normal liver function and had not experienced any further acute non-calculous cholecystitis (ACC) attacks.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Human beings are the sole hosts of EBV, and approximately 95% of adults globally exhibit serological characteristics of prior infections, primarily transmitted through saliva (including kissing, coughing, or sharing food), genital secretions, blood transfusions, transplants, and other routes of infection. The incubation period is approximately 30–50 days, and children and adolescents are the most affected (2,3). A relatively high proportion of children in China are infected with EBV (4). Primary EBV infection in children under 6 years of age predominantly manifests as asymptomatic or mild respiratory infections. School-aged children and adolescents can exhibit infectious mononucleosis, chronic active EBV infection, or hemophagocytic lymphohistiocytosis, which causes liver

Table 1 Details on the blood biochemistry and coagulation function[†]

Tests (normal ranges)	Pre-treatment results	Post-treatment results
White cell count (4.0×10^9/L–11×10^9/L)	14.1	5.59
Abnormal lymphocytes (0–0%)	16	0
Total bilirubin (0.0–26 μmol/L)	130.7	28
Direct bilirubin (0.0–8.0 μmol/L)	123.9	21.4
Total bile acid (0.0–10.0 μmol/L)	324.6	4.2
Alanine aminotransferase (<40 IU/L)	2,904	62
Aspartate aminotransferase (<40 IU/L)	2,405	52
Serum alkaline phosphatase (80–280 IU/L)	462	265
γ-glutamyl transferase (<50 IU/L)	383	117
Triacylglycerol (0.4–1.7 mmol/L)	4.96	1.94
International normalized ratio (0.85–1.15)	1.75	0.91
Activated partial thromboplastin time (25.1–38.4 s)	42.1	28.8
Prothrombin time (9.4–12.5 s)	19.9	10.5

[†] Laboratory comparison before and after treatment.

function damage in 82% of children. EBV infection is also the most prevalent cause of liver function damage. However, it rarely causes severe liver injury or even acute liver failure, and the pathogenetic mechanism by which EBV infection induces liver function damage is currently not completely understood. It may occur through the direct viral infection of cells or immune response-mediated liver cell damage. Current studies indicate that EBV does not infect hepatocytes or bile duct epithelial cells. The liver damage caused by EBV is mostly immune damage induced by lymphocyte infiltration. Consequently, the mechanism of liver function damage caused by EBV infection is related to the immune response of the body, and older children are more prone to liver function damage. It is speculated that older children may have relatively complete immune function development and stronger immune responses, causing more severe liver damage (5,6). In our case, the child exhibited severe liver function impairment (ALT up to 3,441 U/L). We wonder whether this could be related to the high copy number of EBV-DNA (2.19×10^6 copy/mL of EBV-DNA) in this particular case. Research has suggested that children with a high copy number also have a high probability of experiencing liver function impairment (7). Our patient experienced vomiting and abdominal pain throughout the course of the disease, with obvious upper right abdominal pain and brief jaundice. Abdominal CT and ultrasound examinations revealed edema and thickening of the gallbladder wall, indicating cholecystitis. These findings, in combination with the nausea, vomiting, and pain in the upper right abdomen, led us to identify the underlying condition as ACC.

Abdominal ultrasonography of ACC often reveals cholestasis, thickening of the gallbladder wall, edema, gallbladder dilation (effusion), and peri-gallbladder effusion. The incidence of acute cholecystitis in children is very low in clinical settings, resulting in it being easily disregarded. Furthermore, the etiology of acute cholecystitis in children is diverse, encompassing bile retention, bacterial infection, severe disease with long-term intravenous nutrition, biliary ascariasis, and others. Bacterial infections are often caused by blood, lymph, intestinal, or adjacent organs that invade the gallbladder. Acute cholecystitis caused by viral infection is rare, and individual cases of primary cytomegalovirus infection, EBV infection, and human herpes virus type 6 infection have been reported in the literature (8,9). Currently, there are no reports regarding non-calculous cholecystitis in children in China caused by EBV infection.

Clinical manifestations of EBV infection in children are complex and variable. However, acute cholecystitis is not recognized as a primary infection caused by EBV (10). The predominant form of acute cholecystitis in children is ACC. The literature contains few reports regarding ACC in

children caused by EBV and hepatitis A virus infections (11). Mazur-Melewska *et al.* (12) reported that ACC is an atypical clinical manifestation of EBV infection, which often occurs in severe cases. They retrospectively evaluated 181 children infected with EBV presenting with abdominal pain and positive for Murphy's sign, and abdominal ultrasonography revealed significant gallbladder wall thickening. They found that the incidence of ACC in children was about 8.3%. This may indicate that ACC is a prevalent occurrence in children with primary EBV infection, but the manifestation is relatively mild, without laboratory abnormalities, and easily overlooked in the clinical setting.

The clinical manifestations of the patient, including fever, nausea, vomiting, abdominal pain, and jaundice, were similar to those documented in the literature. Moreover, the prognosis was favorable and surgical intervention was not required, mirroring the positive outcomes of most pediatric cases examined in prior research (13,14). Additionally, it has been reported that EBV infection leads to ACC and cholestasis, and complete recovery is achieved through symptomatic treatment and monitoring of laboratory indicators (15). The prognosis of the patient was validated via liver function, bilirubin, bile acid, and biliary ultrasonography during monitoring at two weeks and one month after discharge. Hence, this observation provides a significant contribution to determining the necessity of cholecystectomy for children infected with EBV (10,16). At present, most cases of children with ACC caused by EBV infection documented in the literature have a favorable prognosis; the vast majority of these cases were not recommended to receive antibiotic or surgical intervention.

Conclusions

In clinical practice, physicians should routinely investigate the presence of ACC in EBV infections. When ACC occurs in children and adolescents without a history of cholecystitis, EBV serological testing is also required to prevent missed diagnosis, misdiagnosis, and even overtreatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-2024-614/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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