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Case Report

ANOTHER FACE OF EPSTEIN-BARR VIRUS INFECTION: ACUTE ACALCULOUS CHOLECYSTITIS WITH CHOLESTASIS IN A PREVIOUSLY HEALTHY FIVE-YEAR-OLD GIRL WITH PRIMARY INFECTION

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SUMMARY – Acute acalculous cholecystitis (AAC) is a rare disease, particularly in children. The clinical and laboratory presentation of AAC is variable. The diagnosis is based on radiological criteria. AAC is an atypical and rare complication of Epstein-Barr virus (EBV) infection, therefore we present a girl with AAC and cholestasis due to EBV primary infection. Conservative treatment and careful monitoring was followed by clinical, radiological and laboratory improvement, and finally complete recovery. Our aim was to highlight the importance of recognizing AAC as a differential diagnosis in children with abdominal pain and/or acute cholestasis.

Key words: *Acute acalculous cholecystitis; Children; Epstein-Barr virus*

Introduction

Acute acalculous cholecystitis (AAC) is a rare disease, particularly in children. The clinical and laboratory presentation is variable[1,2]. Diagnosis is based on radiological ultrasound criteria[3,4]. AAC is an atypical and rare complication of Epstein-Barr virus (EBV) infection, therefore we present a girl with AAC and cholestasis due to the EBV primary infection.

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Case Report

A 5-year-old previously healthy girl was admitted to the Pediatric Department due to jaundice, severe liver injury, and cholestasis. One week before admission, the girl manifested pruritus, pale and yellowish discoloration of the skin, and occasionally complained of poor appetite and abdominal pain. No fever, nausea or vomiting was reported. She had one hypocholic stool. Revision of her past medical history revealed a brief course of inhalation therapy (corticosteroids, salbutamol) five months and supplement usage (iron, vitamin C) two days before admission. Her family history was negative for Gilbert's syndrome and chronic diseases; however, her father's

aunt had been treated for juvenile idiopathic arthritis in childhood.

On admission, icteric skin and sclera, enlarged liver (3 cm in the medioclavicular line) and negative Murphy's sign were noticed. Vital signs (no fever, heart rate 132/min, blood pressure 80/50 mmHg) and anthropometric data (body height 116.3 cm (88th centile), body mass index 18 kg/m^2 (93rd centile)) were normal. No lymphadenopathy or pharyngitis were detected. Laboratory tests revealed severe liver injury with conjugated hyperbilirubinemia (Table 1). Synthetic and metabolic liver function was normal. No elevation of inflammatory

Table 1. Relevant laboratory findings during hospital stay and follow-up

Laboratory finding	Day 1	Day 3	Day 7	Discharge (day 9)	Day 15	Day 22	3-month follow-up
Bilirubin total (μmol/L; r.v. <20)	83.6	85.9	36.1	29.1	24.6	16.1	5.1
Bilirubin conjugated (μmol/L; r.v. <0.8-3.4)	68.5	69.8	27.3	21.7	16.7	10.4	2.4
ALT (U/L; r.v. 9-20)	3222	2531	1856	1629	900	260	17
AST (U/L; r.v. 24-49)	1908	1645	1152	899	370	85	27
GGT (U/L; r.v. 4-22)	51	56	48	47	49	35	11
ALP (U/L; r.v.100-400)	385	382	375	342	-	-	-
LDH (U/L; r.v. 150-360)	626	573	463	402	311	-	-
Total bile acids (μmol/L, r.v. <10)	-	-	61.2	-	6.6	5.2	3.8
PT (%, 70-999)	52	62	79	71	-	84	-
Albumin (g/L, r.v. 28-48)	41.8	40.3	43	-	-	46.4	-
Ammonia (μmol/L, r.v.18-72)	56	45	-	-	-	28	-

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; PT = prothrombin time; r.v. = reference value

Table 2. Additional tests performed during hospital stay in our pediatric patient with severe liver injury and cholestasis

Blood test		Microbiological analysis	Other
α-fetoprotein 3.9 kIU/L Ferritin 131…36 ug/L α1 antitrypsin 2.98…1.02 g/L Ceruloplasmin 0.38 g/L	ANA negative Immunodiffusion normal Anti-LKM negative Anti-SMA negative	Coproculture: adenovirus, rotavirus negative; salmonella, shigella negative; parasite test negative Perianal fold analysis negative	Electrocardiogram normal
Lipid profile normal Anti-tTG IgA negative	ASO 336 IU/mL anti-DNase B 738…14.2 E/mL	Urine culture negative	
	Serologic testing: - CMV, HAV, HCV, Parvovirus B19 negative - HBV (vaccination status)	Nasopharyngeal smear negative Pharyngeal swab - BHSA	

Anti-tTG IgA = anti-transglutaminase IgA; ANA = antinuclear antibody; anti-LKM = anti-liver-kidney microsomal antibody; anti-SMA = smooth muscle antibodies; ASO = anti-streptolysin O; CMV = cytomegalovirus; BHSA = Group A β-hemolytic *Streptococcus*; HAV = hepatitis A virus; HCV = hepatitis C virus; HBV = hepatitis B virus

markers was recorded. White blood cell differential analysis found no abnormalities. Only 2-3 atypical (reactive) lymphocytes were recorded on repeated blood tests. Urinalysis showed excessive urobilinogen and bilirubin.

Ultrasonography revealed mild hepatosplenomegaly, hyperechogenic liver parenchyma, normal bile ducts, slightly dilated gallbladder with thickened and layered wall, significant pericholecystic edema, and absence of gallstones (Fig. 1A, B, C).

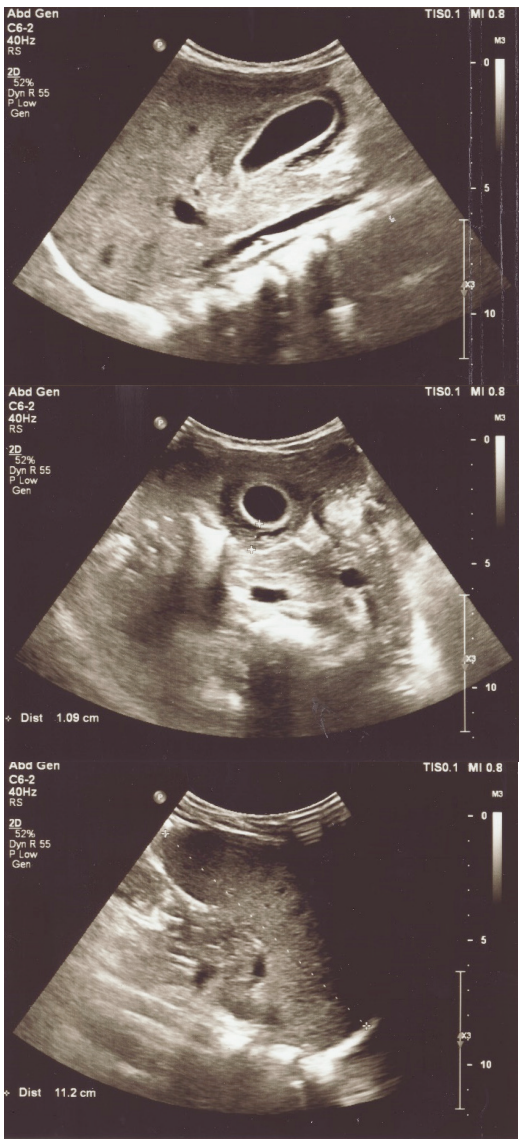

Fig. 1. Abdominal ultrasonography at presentation (day 1 of hospital stay): (A and B) dilated gallbladder with thickened and layered wall, significant pericholecystic edema and absence of gallstones; (C) mild splenomegaly.

The child's throat culture was positive for Group A β-hemolytic *Streptococcus* with slightly elevated antistreptolysin O titer (336 IU/mL) and elevated anti-DNase B (738 E/mL), which indicated recent streptococcal infection although its pathophysiological role in our patient remained unclear. No elements of malignancy, autoimmune etiology, chronic liver diseases, dyslipidemia, bacterial or parasitic infection were found (Table 2).

Epstein-Barr virus primary infection was confirmed by serologic analysis (IgM VCA positive 44.5 U/mL, IgG VCA positive 145.0 U/mL, EBV EA IgG positive 94.8 U/mL, EBNA IgG borderline 15.1 U/mL) and significant viremia (28 000 copies/mL on polymerase chain reaction (PCR) test). Seroconversion was detected two weeks later.

The patient was monitored closely with serial ultrasonographic examinations by expert radiologist and reviewed by expert pediatric GI-hepatologist. Ultrasound reports were performed with the Affiniti 50 Diagnostic Ultrasound Systems (Philips Ultrasound Inc., Bothell, WA, USA) using a curvilinear transducer (2-6 MHz).

Conservative treatment was followed by spontaneous clinical, laboratory (Table 1) and radiological regression (Fig. 2A, 2B, 2C), and hence there was no indication for invasive diagnostic evaluation or therapy. The girl manifested complete recovery. After three-month follow-up, normal laboratory findings were recorded (Table 1), PCR EBV was negative. Challenging management of this young patient took place during SARS-CoV 2 pandemic, therefore previous contact with SARS-CoV 2 was excluded during investigation and follow-up (SARS-CoV2 IgG was 0.1 S/C index, i.e., negative).

Discussion

Although a rare disease, AAC accounts for about half (30%-70%) of pediatric cholecystitis cases[1,2,5,6]. The main cause is gallbladder stasis and stagnation of bile[7]. AAC is usually observed in critically ill, post-surgical, septic, immunocompromised or traumatized (severe burns, rhabdomyolysis) patients, in malignances, long-term total parenteral nutrition, opiate usage, ileus due to dehydration, gallbladder wall ischemia, increased bile viscosity, decreased oral intake, and gallbladder dysmotility or proinflammatory mediators[1,3,6,7]. Man-

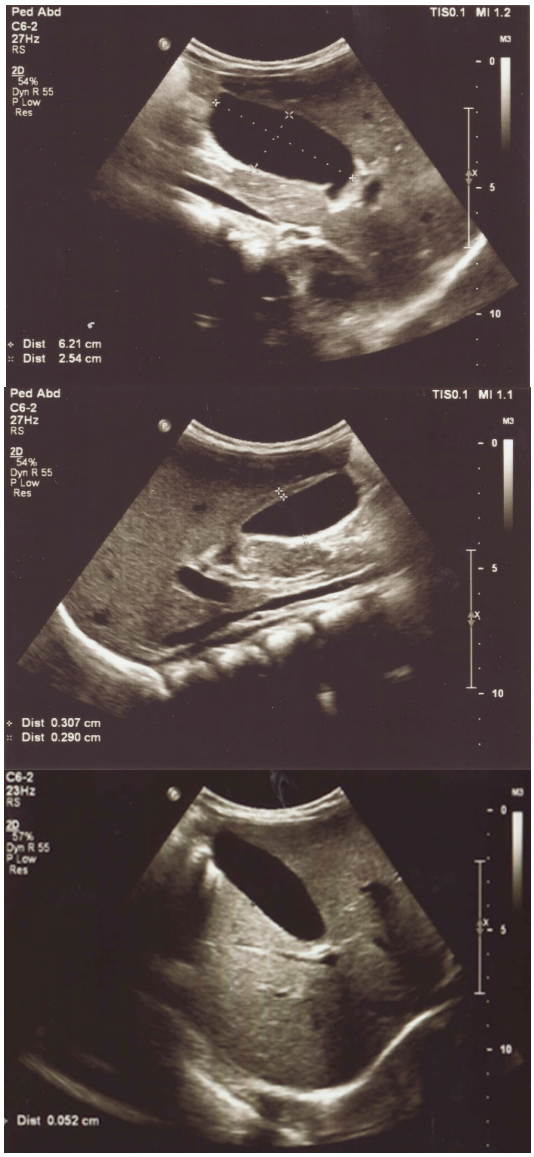

Fig. 2. Ultrasonography on day 3 of hospital stay (A and B) showing improvement: (A) slightly dilated gallbladder without pericholecystic fluid/edema; (B) gallbladder wall still thickened, without effusion; (C) normal gallbladder on follow-up day 22.

agement is conservative or surgical. Antimicrobial therapy is often prescribed in order to prevent complications. The potentially life-threatening complications include gangrene, empyema and perforation[1,5,8]. Although considered as a mild disease in children, AAC can lead to poor outcomes. The reported signs and risk factors of AAC mortality in children include elevated C-reactive protein, hepatomegaly, anorexia, anemia, thrombocytopenia, bile sludge formation, hepatitis, and sepsis plus hepatitis[9].

As clinical presentation is nonspecific, diagnosis is challenging, especially when AAC is superimposed on acute hepatitis[1]. Thus, clinicians rely on ultrasonography which typically shows distended gallbladder with thickened striated wall (>3 (3.5) mm) as the most reliable sign, absence of gallstones and dilatation/obstruction of intra- and extrahepatic bile ducts (no acoustic shadow or biliary sludge), and pericholecystic fluid accumulation/edema (halo)[1,2,4,6,10]. A combination of these major and minor signs, in the appropriate clinical setting, is considered to be diagnostic (a triad including wall thickness, sludge and hydrops)[4,10].

The occurrence of AAC has been described in some chronic disorders and systemic autoimmune diseases including hematologic malignances, renal diseases, genetic diseases, as well as Kawasaki's disease, polyarteritis nodosa and systemic lupus erythematosus due to possible visceral vasculitis[1,3,5,11]. During three-month follow-up, no signs or markers were suggestive of autoimmune disease, chronic or systemic diseases, and additional evaluation was not required in our patient. In otherwise healthy children, AAC can occur during the course of sepsis, gastroenteritis or pneumonia. Several bacterial, fungal, viral and parasitic agents have been associated with AAC[1,4,5,12].

Acute acalculous cholecystitis is an atypical and rare complication of EBV infection[2,3]. Although EBV may cause cholestasis and mild abnormal liver function tests, AAC, jaundice and acute symptomatic hepatitis are rare in infectious mononucleosis syndrome (IM), and are especially rare in primary EBV infection without IM, as it was found in our case[2,7,13]. According to recent data, AAC was found in 8% of hospitalized pediatric patients due to IM and in 2% of all pediatric patients treated for hepatobiliary manifestations of EBV infection[6,14]. The pathophysiology of AAC in EBV infection is insufficiently described. Direct viral invasion of gallbladder, biliary dyskinesia or associated cholestasis causing the gallbladder wall irritation has been proposed as a pathophysiological mechanism, yet not proven[3,7]. Abdominal pain remains the most common symptom (in the right upper quadrant, sometimes diffuse). Sore throat, pharyngitis, lymphadenopathy, abdom-

inal tenderness, Murphy's sign and female gender are commonly observed[1,3,14]. Prognosis is favorable, conservative (supportive) treatment is sufficient including intravenous rehydration, analgesia (nonsteroidal anti-inflammatory drugs), usually temporary suspension of oral feeding until the amelioration and tolerance[1,2,15]. Therefore, unnecessary surgery and antimicrobial therapy (antibiotics) should be avoided, except for some immunosuppressed patients[1,3,4,7]. Hospital admission should be considered to monitor improvement and prevent complications[2]. Differential diagnosis includes drug-induced liver injury[16], which was excluded in the presented patient.

Conclusion

We presented a rare hepatobiliary pathology in children, which is also a rare manifestation of EBV infection. We aimed to highlight the importance of recognizing AAC as a differential diagnostic entity in children with abdominal pain and/or cholestasis. Radiological evaluation and monitoring, as well as collaboration of gastroenterologists and radiologists are essential in the management of these patients.

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Sažetak

JOŠ JEDNO LICE INFEKCIJE EPSTEIN-BARROVIM VIRUSOM: AKUTNI AKALKULOZNI KOLECISTITIS S KOLESTAZOM U PRETHODNO ZDRAVE PETOGODIŠNJE DJEVOJČICE S PRIMARNOM INFEKCIJOM

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Akutni akalkulozni kolecistitis (AAK) je rijetka bolest, osobito u djece. Klinička i laboratorijska slika AAK-a je raznolika, a dijagnoza se temelji na radiološkim kriterijima. AAK je atipična i rijetka komplikacija infekcije Epstein-Barrovim virusom (EBV). Prikazujemo djevojčicu s AAK i kolestazom posljedično primarnoj infekciji EBV-om. Konzervativno liječenje praćeno je kliničkim, radiološkim i laboratorijskim poboljšanjem te na koncu potpunim oporavkom djevojčice. Cilj ovoga prikaza je naglasiti važnost prepoznavanja AAK-a kao diferencijalne dijagnoze u djece s bolovima u trbuhu i/ili akutnom kolestazom.

Ključne riječi: *Akutni akalkulozni kolecistitis; Djeca; Epstein-Barrov virus*