Review

Epstein-Barr Virus (EBV) acute acalculous cholecystitis in an immunocompromised adult patient: a case report and a literature review of a neglected clinical presentation

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Keywords

EBV • Acute acalculous cholecystitis • Iimmunosuppressed patient • Cholecystitis • Hepatitis

Summary

Primary Epstein-Barr virus (EBV) infection may present with self-limiting abdominal involvement, characterized by hepatitis with mild elevation of aminotransferases, splenomegaly, and rarely with acute acalculous cholecystitis (AAC). Usually, treatment of EBV related AAC is symptomatic, without the need for surgery. Here, we describe a severe case of AAC occurring as the first manifestation of infectious mononucleosis in a young adult woman, receiving treatment with interleukin 6 receptor (IL-6r) inhibitor for rheumatoid arthritis (RA); moreover, we have performed a review of the literature on EBV-related AAC.

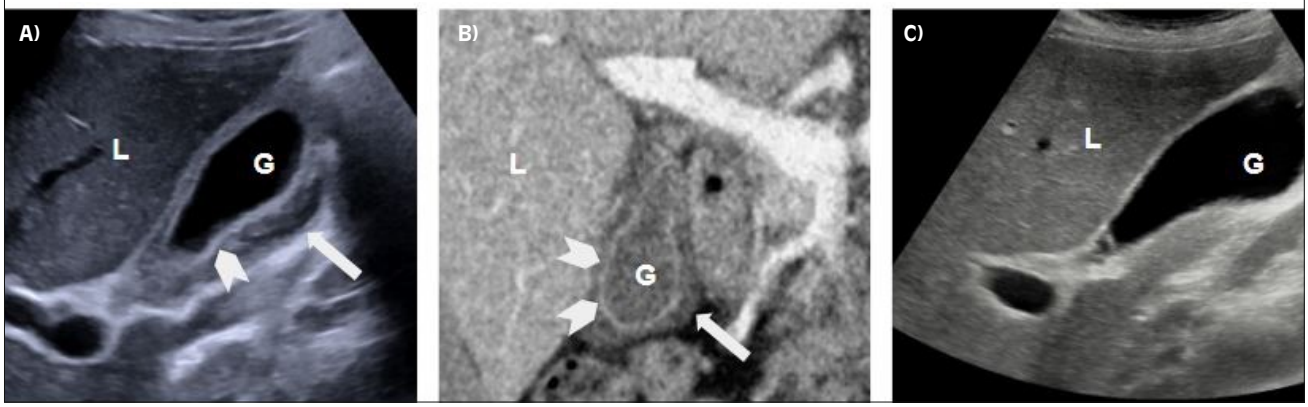
Introduction

Epstein-Barr virus (EBV), a double-stranded DNA virus with a genome of about 172 kilobases, belonging to the Herpesviridae family, is one of the most common life-long viral infection, with almost 95% of the human population being infected [1]. In particular, EBV is classified within the gamma-herpesviruses subfamily, and is the prototype of the Lymphocrypto-virus genus, with its formal designation of human herpesvirus 4 (HHV-4) [1]. EBV was the first isolated human tumour virus, identified in 1964 in a cell line derived from Burkitt lymphoma [1]. After infection, EBV resides persistently in memory B-cells and is usually transmitted through saliva to and between young children, often from asymptomatic individuals [1, 2]. EBV displays a broad range of clinical pictures, from asymptomatic infection (especially during childhood) to benign infectious mononucleosis, to EBV-related lymphoma, EBV-related epithelial cancers, and post-transplant lymphoproliferative disease (PTLD) due to virus-induced persistent cell activation [1-3]. Infectious mononucleosis, when symptomatic, is a self-limiting disease occurring after an incubation period of four to seven weeks [3, 4]. Clinical manifestations may include fever, pharyngitis, malaise or fatigue, and diffuse lymphadenopathy. The most common presenting symptoms are the triad of subacute pharyngitis, high-grade fever and lymphadenopathy [4]. Self-limiting abdominal involvement, characterized by hepatitis with mild elevation of aminotransferases and splenomegaly, is also frequently reported [4, 5]. Acute acalculous cholecystitis (AAC), defined as the inflammation of the gallbladder in the absence of gallstones, is usually described in critically ill patients due to major trauma and/or infections [5]. In a few cases reported in the literature, AAC has been associated with primary EBV infection in both children and adults [6]. Here, we describe a severe case of AAC occurring as the first manifestation of infectious mononucleosis in a young woman receiving treatment with interleukin 6 receptor (IL-6r) inhibitor for rheumatoid arthritis (RA); moreover, we performed a review of the literature on EBV-related AAC.

Case report

A 24-years-old woman presented to the Emergency Department of IRCCS Sacro Cuore Don Calabria Hospital, Verona, Italy, in August 2020 complaining of low-grade fever, abdominal pain, nausea, and jaundice. She suffered from juvenile rheumatoid arthritis (diagnosed at the age of 8 months) in treatment since 2013 with tocilizumab 162 mg subcutaneously once a week (last administration one week before

Fig. 1. Ultrasound and CT scan images of EBV-related AAC. **A)** US b-mode, day 1: gallbladder distention and thickened wall > 3 mm (arrowhead), pericholecystic fluid (arrow); **B)** Contrast Enhanched CT, venous phase, day 2, mucosal hyperenhancement (arrowheads), pericholecystic fluid and inflammatory fat stranding (arrow); **C)** A) US b-mode, day 7, after terapy: gallbladder with regular wall, no more pericholecystic fluid visible (G: gallbladder lumen; L: liver).



admission), without any hepatic side-effects reported, and methotrexate, since 2010, 10 mg once a week (discontinued 6 weeks before admission). In July 2020 she underwent right hip arthroplasty due to arthritis.

On admission to our hospital, an abdominal ultrasonography showed diffuse, severe thickening of the gallbladder's walls with multi-layered appearance, associated with pericholecystic fluid, suggesting AAC (Fig. 1A). Splenomegaly (bipolar diameter 15 cm; normal value < 13 cm) was also reported.

Blood examination showed lymphocytosis (70% of the total white blood cell count) with activated lymphocytes, hypertransaminasemia (AST 919 U/L and ALT 914 U/L; normal values < 50 U/L), and hyperbilirubinemia (total bilirubin 4.4 mg/dL, normal values 0.3-1 mg/dl; direct bilirubin 3 mg/dL, normal values 0-0.3 mg/dl). C-reactive protein was slightly increased (42 mg/dL; normal value < 5 mg/dL), while procalcitonin was negative. Major hepatitis virus tests (HAV, HBV, HCV) as well as serum B-D-glucan, to exclude opportunistic fungal infection, were negative. Stool culture, to investigate for salmonellosis, was also negative.

To cover empirically for bacterial cholecystitis, antibiotic therapy with piperacillin/tazobactam 4/0.5 g every 8 hours was started.

In the following three days, symptoms persisted despite fasting, antibiotic therapy and intravenous hydration. A computed tomography (CT) scan of the abdomen confirmed the ultrasound picture: a distended gallbladder with wall thickening, increased enhancement following administration of iodinated contrast medium, and no visible gallstones (Fig. 1B). The need for urgent cholecystectomy was discarded after surgical consultation, which suggested elective surgery depending on the clinical development.

Testing for minor hepatitis viruses revealed a negative serology for cytomegalovirus but positive serology for EBV, with an immunological profile characterized by positive anti-VCA IgM and anti-VCA IgG, negative anti-EBNA IgG, indicating acute infection.

Upon diagnosis of EBV infection, antibiotic therapy was discontinued. After 72 hours from admission, the patient improved spontaneously, with resolution of abdominal pain, normalization of liver function tests, and progressively resumed feeding.

Abdominal ultrasound before discharge showed resolution of the gallbladder walls' thickening (Fig. 1C). The patient was discharged after 7 days from admission in good clinical condition and with no symptoms left.

Literature review

On 30 September 2020 we performed a MEDLINE/PubMed search using the following query ((EBV) OR(Epstein-Barr)OR(infective mononucleosis)) AND ((Cholecystitis)OR(gallbladder))". No restrictions were applied regarding publication date or language; only original papers describing cases of human AAC caused by serology-confirmed EBV were included. Data regarding the number of patients, age (children or adults aged older than 18), immune status (immunocompetent or immunocompromised), and treatment were recorded.

Out of the 100 papers retrieved, 45 were excluded by title/abstract screening. The full-text of the remaining 55 papers was retrieved, the content examined for eligibility, and the references lists examined to individuate further potentially eligible papers. Eventually, data were extracted from the finally eligible 57 papers.

Details of the eligible papers are shown in Table I (review containing multiple case reports were reported excluding papers with the single case). Since 1987, the first reported case in an adult immunocompetent female patient by Hammond [7], 70 cases were retrieved, of whom 52 (74,2%) in females and 18 (25,8%) in males. Forty-four (62.8%) patients were children (3-18 years old), while 26 (37.2%) patients were adults. Immune status was available in 55 cases (78.5%), of which

Tab. I. Review of the published EBV case report.

Author (year)	Number of patient	Immunecompromised/ immunecompetent	Adult/ child	Sex	Surgical treatment
Langenohl et al. (2020) [8]	1	Immunecompetent	Child	M	No
Guri et al. (2020) [9]	1	Immunecompetent	Child	F	No
Ntelis et al. (2020) [10]	1	Immunecompetent	Child	F	No
Lamprianidis et al. (2020) [11]	1	Immunecompetent	Adult	F	No
Young et al. (2019) [12]	1	Immunecompetent	Child	F	No
Mazur-Melewska et al. (2019) [13]	15	Not available	Child	9 M/ 6 F	No
Rezkallah et al. (2018) [14]	1	Immunecompetent	Adult	F	Laparoscopic cholecystectomy
Höhn et al. (2018) [15]	1	Previous major surgery	Adult	M	No
Cameron et al. (2018) [16]	1	Immunecompetent	Adult	F	No
Yesilbag et al. (2017) [17]	1	Immunecompetent	Adult	F	No
Rodà et al. (2017) [18]	1	Immunecompetent	Child	M	No
Khoury et al. (2017) [19]	1	Immunecompetent	Adult	M	No
Sheybani et al. (2016) [20]	1	Seronegative spondyloarthropathy	Adult	F	No
Ono et al. (2016) [21]	1	Immunecompetent	Adult	F	No
Majdalani et al. (2016) [22]	1	Immunecompetent	Child	F	No
Koufakis et al. (2016) [23]	1	Immunecompetent	Adult	M	No
Branco et al. (2015) [24]	1	Immunecompetent	Child	F	No
Hernández-Rodríguez J et al. (2014) [25]	1	Immunecompetent	Child	F	No
Pawłowska-Kamieniak et al. (2015) [26]	1	Immunecompetent	Child	F	No
Alkhoury et al. (2015) [27]	1	Immunecompetent	Child	F	No
Agergaard et al. (2015) [28]	1	Immunecompetent	Adult	F	No
Suga et al. (2014) [29]	1	Immunecompetent	Child	F	No
Gagneux-Brunon et al. (2014) [30]	2	Immunecompetent	Adult	2F	No
Celik et al. (2014) [31]	1	Immunecompetent	Adult	F	No
Fretzayas et al. (2014) [32]	2	Immunecompetent	Child	2F	No
Strehle et al. (2014) [33]	1	Immunecompetent	Child	F	No
Kim et al. (2014) [34]	1	Immunecompetent	Child	F	No
Hamdy et al. (2014) [35]	1	Immunecompetent	Child	F	No
Poddighe et al. (2014) [36]	1	Immunecompetent	Child	F	No
Teke et al. (2013) [37]	1	Immunecompetent	Child	F	No
Beltrame et al. (2012) [38]	1	Immunecompetent	Adult	F	No
Dylewski et al. (2012) [39]	1	Immunecompetent	Adult	F	No
Carrascosa et al. (2012) [40]	1	Immunecompetent	Adult	F	No
Nagdev and Ward (2011) [41]	1	Immunecompetent	Adult	F	No
Arya et al. (2010) [42]	1	Immunecompetent	Child	F	No
Yang et al. (2010) [43]	1	Immunecompetent	Adult	F	No
Attilakos et al. (2009) [44]	2	Immunecompetent	Child	1 F / 1 M	No
Hagel et al. (2009) [45]	1	Immunecompromised (ulcerative colitis)	Adult	F	Laparoscopic cholecystectomy
Cholongitas et al. (2009) [46]	1	Immunecompetent	Adult	F	No
Chalupa et al. (2009) [47]	1	Immunecompetent	Adult	F	No
Iaria et al. (2008) [48]	1	Immunecompetent	Adult	F	No
Pelliccia et al. (2008) [49]	1	Immunecompetent	Child	F	No
Koch et al. (2007) [50]	1	Immunecompetent	Adult	F	No
Prassouli et al. (2007) [51]	1	Immunecompetent	Child	F	No
Lagona et al. (2007) [52]	1	Immunecompetent	Child	F	No
Yoshie et al. (2004) [53]	1	Immunecompetent	Child	F	No
O'Donovan et al. (1996) [54]	2	Immunecompetent	Adult	1 F/ 1 M	No
Maruyama et al. (1994) [55]	2	Immunecompetent	Child	1 F / 1 M	No
Sainsbury et al. (1994) [56]	1	Immunocompromised (end-stage renal disease)	Child	M	No
Sung et al. (1989) [57]	1	Immunecompetent	Child	F	No
Hammond et al. (1987) [7]	1	Immunecompetent	Adult	F	No

4 (7.2%) were immunocompromised: 1 patient with previous major surgery (left adrenal gland resection, distal pancreatectomy, and splenectomy due to a large pheochromocytoma), 1 with seronegative spondyloartropathy in treatment with disease-modifying antirheumatic drugs (DMARDs), 1 with ulcerative colitis in treatment with azathioprine, and 1 patient with end-stage renal disease. Surgical management with colecistectomy was reported in 2 (2.8%) cases, of whom 1 was immunocompromised.

Discussion

Acute acalculous cholecystitis contributes to 5-10% of all cholecystitis in adults and it is usually observed in patients with viral hepatitis, salmonellosis, major trauma, extensive burns, long term parenteral nutrition, critically ill patients and systemic diseases such as diabetes, malignancies, abdominal vasculitis, congestive heart failure, cholesterol embolization, and shock [6, 58]. EBV is a relatively rare cause of AAC; to the best of our knowledge, 4 patients with immunocompromised conditions and EBV-related AAC have been reported in the literature (Tab. I). It should be noted that the AAC could be potentially related to the acute hepatitis induced by EBV or to immunesuppressive agents. Our patient did not need any supplementary treatment or treatment adjustment (e.g. reduction of the immunosuppressive treatment) or surgical intervention, being only supporting treatment apparently of benefit, as highlighted in previous reports [59]. Moreover, in our case report, a mild case of EBV hepatitis with transient elevation of serum aminotransferases and jaundice has been noted, while it is occasionally reported in the literature (in 5% of cases), possibly caused by cholestasis or virus-induced haemolysis [60].

EBV-related AAC should be suspected when no other cause of AAC can could be identified, especially in young patients, who seem to be more prone to its development, and its diagnosis is suspectable in order to avoid unnecessary antibiotic treatment or more invasive and costly procedures [60] (Tab. I).

Likewise, if an EBV first-infection displays clinical symptoms compatible with cholecystitis, ultrasonographic examination should be performed in order to confirm or rule out the diagnosis of ACC [13, 38].

Conclusions

EBV primary infection can lead to acute acalculous cholecystitis, especially in adult immunocompromised patients: clinical suspicion, coupled with ultrasound of the gallbladder are needed for a correct and timely diagnosis. Conversely, when ultrasound of the gallbladder shows evidence of AAC, with coherent clinical presentation, EBV infection should be considered and serological test for EBV should be performed.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

SR, SS, NR, MS took care of the patient, draft and approved the final version of the manuscript.
EO acquired radiological images, gave radiological consultation and approved the final version of the manuscript. FT, PB, MM and AF draft, reviewed and approved the final version of the manuscript.

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