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CLINICAL CASE

Liver and colonic manifestation of active chronic infection by Epstein Barr virus

Manifestación hepática y colónica de la infección crónica activa por virus de Epstein Barr

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What do we know about the subject matter of this study?

Epstein Barr virus (EBV) is a microorganism that infects more than 90% of the world's population. Primary infection occurring during childhood is usually asymptomatic or may cause self-limiting symptoms. There is a small group of patients who may have a chronic persistent course of infection involving organs such as the liver and colon.

What does this study contribute to what is already known?

This work presents a relevant clinical case that will help in the early recognition of rare or atypical clinical manifestations of chronic Epstein Barr virus infection; it establishes differential diagnoses due to the particularities of its management and prognosis.

Abstract

Chronic active Epstein Barr virus infection (CAEBV) is a rare condition, where the body is unable to counteract Epstein Barr viral replication (EBV), leading the patient to a chronic state with variable symptoms. Early recognition of infrequent or atypical clinical manifestations is relevant due to the particularities of their management and prognosis. **Objective:** to describe a case of CAEBV manifested with colitis and hepatitis, summarizing the clinical-pathological and endoscopic characteristics and their evolution. **Clinical Case:** A 6-year-old girl, previously healthy, presented recurrent episodes of jaundice, hepatosplenomegaly, and fever. EBV hepatitis was diagnosed with a blood viral load of 328,000 copies / mL. Her liver biopsy revealed Epstein-Barr virus-encoded small RNAs (EBER). She evolved with mucosanguineous diarrhea and weight loss; the colonoscopy showed loss of the haustral pattern, multiple aphthous ulcers covered with fibrin, and 7 million copies of EBV / gram of tissue were found in the colon. T-cell lineage infection was identified, therefore Rituximab was started, with

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a decrease in viral load, complete resolution of diarrhea, and improvement in liver function tests. The definitive treatment was bone marrow transplantation. **Conclusions:** CAEBV is a serious disorder, little documented, and should be considered in the face of a prolonged or intermittent course of hepatitis, accompanied by general and gastrointestinal manifestations such as chronic diarrhea, hematochezia, and weight loss, since its outcome without treatment can be fatal.

Introduction

Epstein Barr virus (EBV) is a herpes virus that infects more than 90% of the world's population[1]. Primary infection occurring during childhood is usually asymptomatic; however, during adolescence or later, it can cause self-limited infectious mononucleosis[2]. In 20% of patients, after primary infection, EBV takes on a predominant latent state in B lymphocytes with limited gene expression ensuring evasion of recognition by T lymphocytes[3]. Some patients will have reactivation of the virus and develop a chronic course with persistent or intermittent symptoms, known as chronic active Epstein-Barr infection (CAEBV). Due to its multifaceted nature, it presents with diverse clinical manifestations and diagnostic criteria that include: a) mononucleosis-like symptoms such as fever, hepatosplenomegaly, and lymphadenopathy for more than three months duration, where hepatitis is common, elevated transaminases have been reported in 80% of patients and jaundice in 6.6%; b) EBV antibody titers and/or detection of a high virus load in peripheral blood or affected tissues; c) chronic disease that cannot be explained by other pathologic processes at the time of diagnosis[4].

In this regard, early recognition of rare or atypical clinical manifestations, such as chronic intermittent diarrhea with or without recurrent hepatitis in an immunocompetent patient, becomes relevant since it can often be diagnosed as inflammatory bowel disease, whose clinical, endoscopic, and histological features are similar, posing a challenge to discern whether or not the symptoms are attributable to the infection. The treatments for the two diseases are completely different; corticosteroids, immunotherapy, and cytotoxic drugs will be non-curative treatments in the case of CAEBV and patients may develop lymphoproliferative disorders with a poor prognosis and a high mortality rate[5], whereas allogeneic hematopoietic stem cell transplantation will change the natural history of this disease[6,7]. Detection of the presence of Epstein Barr virus encoded RNA (EBER) in tissue will be one of the diagnostic tools that will make a difference.

The objective of this article is to describe the case of a patient with colitis and EBV-related, summarizing the endoscopic, clinicopathologic features, and evolution.

Clinical Case

A 6-year-old girl, previously healthy, eutrophic, from a rural area, presented with high fever, myalgias, and arthralgias, associated with vomiting, diarrhea, poor appetite, and abdominal pain in the right hypochondrium. Two weeks later, jaundice, acholia, and choluria appeared; she was treated in her community as viral hepatitis, upon finding elevated inflammatory and hepatic excretion tests [aspartate aminotransferase (AST) 913IU/L, alanine aminotransferase (ALT) 1376IU/L, gamma-glutamyl transferase (GGT) 92.4IU/L, lactate dehydrogenase (LDH) 675IU/L, total bilirubin (TB) 2.64mg/dL, direct bilirubin (DB) 1.87mg/dL, normal synthesis tests, albumin (ALB) 4.1g/dL, and prothrombin time (PT) 12.3 seconds]. Serologies for Hepatitis A, B, and C were negative. Eight weeks later, the patient was completely asymptomatic, with liver enzyme levels at ALT 798IU/L and AST 655IU/L, however, an etiological diagnosis could not be defined.

Six months after this event, she was referred to a referral hospital due to a new episode of fever, jaundice, vomiting, intermittent watery diarrhea without blood, accompanied by abdominal pain in the right hypochondrium, cervical and axillary lymphadenopathy, abdominal distension, liver 4 cm, and spleen 2 cm below the rib cage. Abdominal ultrasound reported hepatosplenomegaly and gallbladder wall thickening of 3 to 4mm; liver inflammation tests were elevated (ALT 1945U/L, AST 956U/L), with cholestasis (GGT 980U/L, TB 6 mg/dL, DB 5 mg/dL, ALB 3.3g/dL). Serology was repeated in search of hepatotropic viruses, ruling out hepatitis A, B, and C; cytomegalovirus, parvovirus B19; Epstein-Barr virus viral capsid antigen IgM (EBV VCA IgM) negative, Epstein-Barr virus viral capsid antigen IgG (EBV VCA IgG) positive; Epstein-Barr virus early antigen (EBV EA) and Epstein-Barr virus nuclear antigen (EBV EBNA) positive. Viral load was measured with Elitech® reagent in whole blood by quantitative PCR with 328,000 copies/ml, lymphocyte subpopulations with CD3, CD4, and CD19/20 involvement. Autoimmunity and metabolopathy studies were negative (Table 1).

Due to the EBV viral load, a liver biopsy was performed which showed positive immunolabeling for

Epstein Barr virus (Figures 1 and 2), establishing the diagnosis of EBV-related hepatitis. Her general condition rapidly deteriorated, with high fever, jaundice, pain, abdominal distension, and inappetence; in addition, increased hepatomegaly of up to 6 cm below the costal ridge and spleen of 4 cm below the costal ridge were identified. Two weeks after admission, bloody mucus diarrhea appeared, associated with colicky abdominal pain and vomiting, with progressive weight loss of 5 kg during hospitalization, requiring the initiation of parenteral nutrition. Coprological studies, stool cultures, and gastrointestinal viral panel were negative.

Given the suspicion of a clonal expansion of EBV, treatment with anti CD20 monoclonal antibody was started, however, the viral load persisted at 328,000 copies/ml in blood. One week later, cyclosporine and methylprednisolone were added; however, there was no improvement and she continued with fever, diarrhea, jaundice, and hematochezia; therefore, the approach was oriented towards inflammatory bowel disease, presenting antinuclear antibodies (ANA), negative antibodies against neutrophil cytoplasm (p-ANCA). Clostridium difficile infection was ruled out.

Panendoscopy and colonoscopy were performed (Figure 2), which showed aphthous lesions in the colon mucosa, haustral pattern loss, increased vascular pattern, and extremely friable mucosa. Biopsies reported mild chronic inflammation in the gastric body, chronic colitis, and PCR of 7 million copies/gram of EBV in colonic tissue (Figure 2). In the lymphocyte subpopulations analysis, the T lymphocyte cell line was affected.

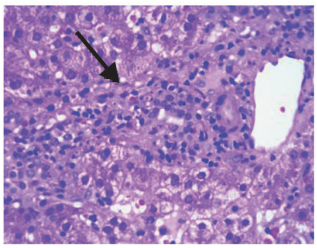
Seven months after the start of immunomodulatory treatment, hematopoietic stem cell transplantation was performed as the only curative treatment for this condition. Seven months after transplantation, the patient was asymptomatic, with liver function tests within normal ranges, without diarrhea, and adequate growth. (Table 1)

Table 1. Laboratory Test

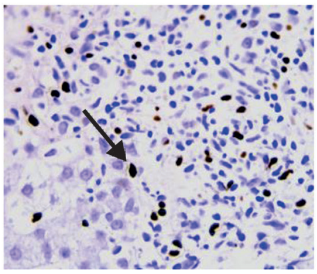
	Reference values	Hospital admission	Biochemical control 2 weeks after admission	Biochemical control with immunosuppressive therapy	Post-transplantation of hematopoietic cells
Alanine aminotransferase	9-25 U/L	1.945	856	58	32
Aspartate aminotransferase	21-44 U/L	956	287	40	22
Total bilirubin	0.05-0.40 mg/dl	4.3	4.0	0.85	0.76
Direct bilirubin	0.05-0.20 mg/dl	3.7	2.67	0.24	0.13
Gammaglutamyl transferase	6-16 U/L	----------	114	141	48
Alkaline phosphatase (IU/L)	93-309 IU/L	395	-/-	376	209
Albumin	3.8- 4.7 mg/dl	2.7	3.2	2.3	4.1
Prothrombin time(sec)/ INR	13.4 (11.7-15.1) 1.04 (0.87-1.20)	12.3 1.1	11.8 1.07	10.8 0.96	11.5 1.02
Hepatitis A IgM and IgG	Negative	Negative			
EBV VCA IgM	Negative	Negative			
EBV VCA IgG	Negative	Positive			
EBV EA	Negative	Positive			
EBV EBNA		Positive			
Hepatitis B and hepatitis C	Negative	Negative			
LKM-1	Menor a 10 (UR/mL)	2.71 (UR/mL)			
ASMA	Negative	Negative			
P ANCA	Negative	Negative			
Copper in urine	0.60 (mcg/24 h)	8.82			
Ceruloplasmin	0-60 (mg/dL)	41.95			
Copper in serum	80-180(mcg/dL)	210			
Alpha 1 Antitrypsin	102-157(mg/dL)	199			

IgM antibodies against the capsid of the Epstein-Barr virus (EBV VCA IgM) negative, IgG antibodies against the capsid of the Epstein-Barr virus (EBV VCA IgG) positive, early (EBV EA) and nuclear antigen positive (EBV EBNA), Immunoglobulin M and Immunoglobulin G against hepatitis A (Hep A IgM/IgG), liver and kidney microsomal type 1 antibodies (LKM-1), anti-smooth muscle antibodies (ASMA), antineutrophil cytoplasmic antibodies (p-ANCA).

Liver biopsies

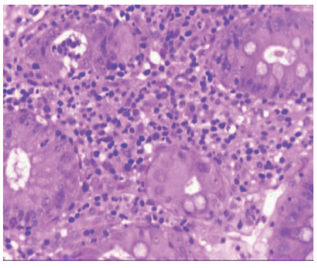


Portal space with distention at the expense of fibrosis, presence of lymphocytes, neutrophils and plasma cells.

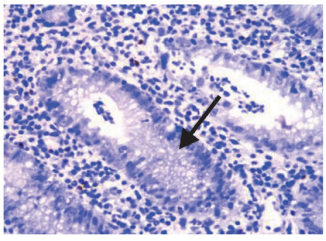


Immunoreaction with EBER (Epstein-Barr Virus) shows positivity in lymphocytes of the portal space and hepatic lobule.

Colon Biopsies



Colonic mucosa with moderate inflammatory infiltrate in the lamina propria that ascends to the glandular epithelium.



Immunoreaction with EBER (Epstein-Barr Virus) showing positivity in lymphocytes of the lamina propria.

Figure 1.

Discussion

EBV infection is acquired from a very early age; in most cases, it is asymptomatic or appears as a self-limited infectious process characterized by fever, coryza, and lymphadenopathy that generally lasts two weeks, so that, upon reaching adulthood, 90% of the population has antibodies against EBV[8]. However, in a small percentage of the population, the infection can be lethal since it may manifest as a hemophagocytic syndrome or hematolymphoid malignancies such as Burkitt's lymphoma, classical Hodgkin's lymphoma, and lymphoproliferative disorders associated with immunodeficiency[9]; in other patients, the course of the disease will evolve into a chronic active infection characterized by proliferation of B, T or Natural Killer cells of EBV whose diagnosis requires meeting specific criteria[4]. In our patient, hepatic and gastrointestinal involvement predominated.

Hepatitis caused by EBV is common, mild, and self-limited in most cases. The increase of transaminases observed in 90% of patients is transient, usually no more than 2 times the higher limit of normal levels and indicates parenchymal hepatic dysfunction; jaundice is secondary to cholestasis due to inhibition of bilirubin transport, as well as viral cytopathic damage to cholangiocytes[10,12]. Ultrasonographic findings in EBV-related hepatitis include nonspecific features such as hepatome-

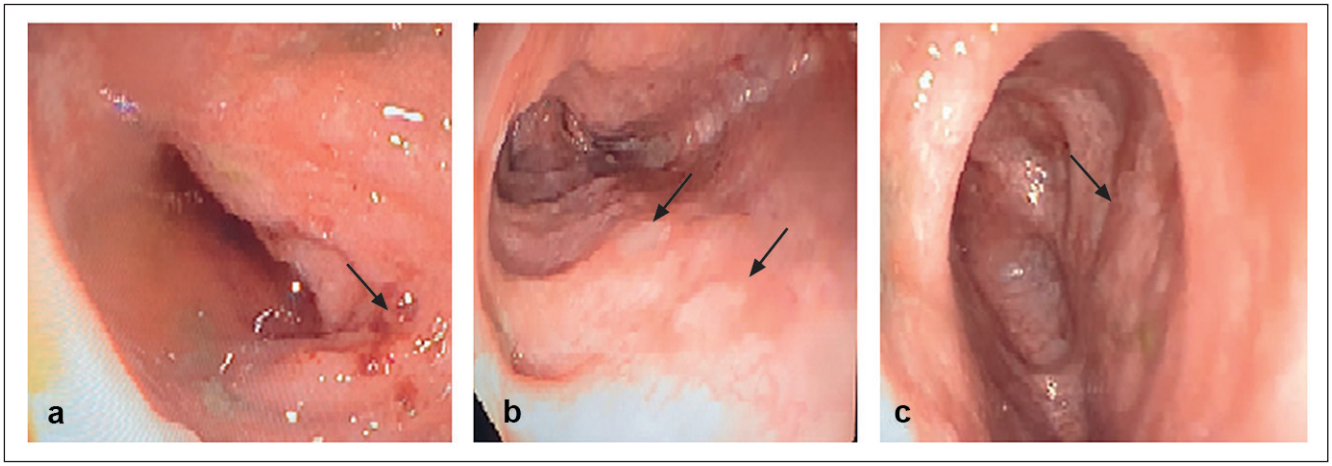


Figure 2. Ascending colon showing extremely friable mucosa, bleeding when passing the endoscope **(a)**, **(b)** transverse colon with loss of the haustral pattern, 5 mm ulcers covered with fibrin. **(c)** ascending colon with thinned mucosa, increased vascular pattern.

galy, splenomegaly, porta hepatis adenopathy, periportal edema, and gallbladder wall thickening. O'Donovan et al made an association between the thickening of the gallbladder wall and EBV-related hepatitis, postulating it as a sign of the severity of the disease[13]. In patients with acute primary EBV infection, fulminant hepatic failure is the main cause of death, although severe hepatic involvement is uncommon[10,11].

At the intestinal level, the endoscopic pattern of superficial ulcers has been confused with inflammatory bowel disease (IBD), however, its prognosis is poor and, without treatment, its mortality rate is high[14]. Misdiagnosis of CAEBV can have fatal outcomes, so an extensive anamnesis is recommended to look for consistent and persistent symptoms of infectious mononucleosis.

In a retrospective study, Xu et al.[15] compared twelve patients with CAEBV and enteritis with twenty-four patients with diagnosed IBD, analyzed clinicopathological and endoscopic features, and found that the main clinical presentations of patients with CAEBV were intermittent fever (100%), hepatosplenomegaly (58%), lymphadenopathy (50%), diarrhea (50%), and hematochezia (50%). Compared with IBD patients, the incidence of intermittent fever and increased ferritin level was significantly higher among CAEBV patients.

The main endoscopic findings of CAEBV included multifocal or isolated, irregular, multiform ulcers, and diffuse inflammation, without the typical cobblestone appearance. The median survival in this series was 21 months. Liu et al[16] found that the frequency of intermittent fever, hepatomegaly, splenomegaly, lymphadenopathy, C-reactive protein value, and serum Epstein-Barr virus DNA was significantly higher in patients with active Epstein-Barr virus chronic infectious enteritis compared with IBD ($p < 0.01$).

The gold standard for detecting Epstein-Barr virus in biopsies is in situ hybridization for Epstein-Barr virus-encoded RNA[17]. Histologic findings showed transmural inflammation with widespread lymphoid infiltration, fissuring ulcers, and intraepithelial lymphocytosis. However, chronic active infectious enteritis due to Epstein-Barr virus lacked granulomas and connective tissue changes, such as neural hypertrophy and thickening of the *muscularis mucosae*.

The difference between these two entities is fundamental for treatment since multiple therapies with steroids and immunosuppressants have been tried[18] concluding that these can decrease the viral load and prevent clonal expansion; however, allogeneic transplantation of hematopoietic stem cells is the only definitive curative treatment, since it allows substitution with virus-free blood cells[19]. Current treatment protocols are based on chemotherapy followed by transplantation, similar to the therapeutic strategies developed for hemophagocytic lymphohistiocytosis[20,21]. It is important to highlight the importance of knowing the lymphocyte lineage affected to establish the appropriate immunomodulatory therapy.

In our patient, multiple immunomodulatory drugs were used to reduce viral DNA, obtaining lower viral load and resolution of symptoms, with monthly applications of rituximab, as has been described in the literature with success in EBV-associated lymphoproliferative disorders[22]. She subsequently received successful bone marrow transplantation, with resolution of both gastrointestinal and hepatic symptoms.

Conclusions

Chronic active Epstein-Barr virus infection is a serious condition, which should be considered in the

presence of multiple joint or isolated hepatic and gastrointestinal manifestations. Our patient exemplifies the need to maintain a high suspicion of CAEBV if intermittent fever, hepatosplenomegaly, lymphadenopathy, atypical ultrasonographic and endoscopic findings, unexplained by other disorders, are present. Blood tests for EBV-DNA and biopsy for EBER by in situ hybridization should be performed to confirm the diagnosis and not delay immunomodulatory treatment, avoiding viral clonal expansion. In those patients whose onset presents with digestive symptoms, such as chronic diarrhea, it is necessary to establish a diagnostic pathway that includes infectious etiologies in the first place and, when positive for EBV, to identify the presence of the affected cell lineage to guide immunomodulatory treatment.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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