

SEVERE ACUTE HEPATITIS BY COINFECTION BY EPSTEIN-BARR VIRUSES AND CITOMEGALOVIRUS-CASE REPORTED AND REVIEW OF LITERATURE

HEPATITIS AGUDA GRAVE POR COINFECCIÓN POR VIRUS EPSTEIN-BARR Y
CITOMEGALOVIRUS - REPORTE DE CASO Y REVISIÓN DE LA LITERATURA

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ABSTRACT

We report the case of a 6-year-old patient with a history of atopic dermatitis. Some days before her hospitalization she presented rhinorrhea and cough. Subsequently she presented maculopapular lesions, increase of body temperature and yellowing of the skin. After being hospitalized, in addition to the symptoms described, she presented 2 episodes of spontaneous epistaxis, hematemesis and melena; while in the physical examination, mucocutaneous jaundice, fever, generalized maculopapular rash, lymphadenopathy, and hepatosplenomegaly were evident. In the images studies, signs that indirectly indicated acute hepatitis and pleural effusion, were found. On the other hand, among the serological results, it was found that the markers of acute infection by EBV and CMV, as well as the marker of chronic EBV infection, were positive.

As far as we know, this is the first report of CMV-EBV coinfection in our, due to an acute CMV infection. We report the case and we carry out a review of the literature.

Key words: Viral hepatitis; Cytomegalovirus; Epstein-Barr (source: MeSH NLM).

RESUMEN

Se reporta el caso de una paciente de 6 años con antecedente de dermatitis atópica. Días antes de hospitalizarse presentó rinorrea y tos. Posteriormente presentó lesiones maculopapulares, alza térmica y coloración amarillenta de la piel. Luego de ser hospitalizada, además de los síntomas descritos, presentó 2 episodios de epistaxis espontánea, hematemesis y melena; mientras que en el examen físico se evidenció ictericia mucocutánea, fiebre, rash maculopapular generalizado, adenopatías, y hepatoesplenomegalia. En el estudio de imágenes se encontraron signos que indicaron indirectamente hepatitis aguda y derrame pleural. Por otro lado, entre los resultados serológicos se encontró que los marcadores de infección aguda por VEB y CMV, al igual que el marcador de infección crónica por VEB, fueron positivos.

Hasta donde tenemos conocimiento, este es el primer reporte en nuestro medio de coinfección CMV-VEB, debido a una infección aguda por CMV. Reportamos el caso y realizamos una revisión de la literatura.

Palabras clave: Hepatitis viral; Citomegalovirus; Epstein-Barr (fuente: DeCS BIREME).

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Cite as: Ítalo Valero-Román, Grecia Claussen-Portocarrero, Alexander Paucar-Ancassi, Jaime Silva-Díaz. Severe acute hepatitis by coinfection by Epstein-barr viruses and citomegalovirus-case reported and review of literature. Rev. Fac. Med. Hum. Enero 2020; 20(1):158-161. DOI 10.25176/RFMH.v20i1.2253

Journal home page: <http://revistas.urp.edu.pe/index.php/RFMH>

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INTRODUCTION

Viral agents such as Cytomegalovirus (CMV), Epstein-Barr (EBV), Herpes simplex 1 and 2, varicella-zoster, human herpes 6, 7, and 8, parvovirus B19, and adenovirus can cause acute liver failure and even present as fulminant hepatitis¹. Of these, EBV is the one with the greatest hepatic involvement according to its intensity and duration, apart from being the viral etiological cause of hepatic cytotoxicity with the highest frequency after CMV².

Liver involvement, with or without hepatosplenomegaly, occurs in 30-60% of patients with increased AST and ALT, alkaline phosphatases (pathognomonic) and even jaundice due to increased bilirubin⁽¹⁻³⁾, having a less severe presentation in children than in adults over 30 years⁽²⁾. The majority of infectious mononucleosis cases have a mild and self-limited elevation of AST and ALT.

Epstein Barr virus is identified by markers such as heterophile antibodies (Paul-Bunnell test), determination of the viral genome nuclear antigen, presence of atypical lymphocytes in peripheral blood and IgM^(2,4) type antibodies.

There are no specific criteria for the diagnosis of hepatitis by EBV, but there is general agreement to establish its suspicion, which is that the following data must be positive: elevation of aminotransferases, active EBV infection defined by serology, typical pathological changes according to liver biopsy and demonstration of the viral genome in hepatic tissue through molecular studies⁽¹⁾.

CASE REPORT

We present the case of a 6-year-old female patient from Huánuco, with a history of atopic dermatitis diagnosed at the age of 2. She began her illness 6 days before entering the hospital with rhinorrhea and cough, was self-medicated by her mother with azithromycin and paracetamol. Two days later, maculopapular erythematous lesions appeared on her face and spread all over her body. Fever, jaundice (skin pigmentation, sclera), and choloria were later added. Four days later she was hospitalized, where all symptoms persist, in addition to 2 episodes of spontaneous epistaxis, hematemesis, and melena. Physical examination found jaundice and paleness of mucosa, temperature of 38.2°C, maculopapular erythematous rash in the face, neck, both upper limbs, thorax, abdomen and pelvis; as well as adenopathy < 0.5 cm in the cervical, axillary and inguinal regions, decreased vesicular murmur in both pulmonary fields, shifting dullness, abdominal

distension, palpable liver 7.5 cm below the right costal ridge and palpable spleen tip. His laboratory results, since his admission and evolution, are as follows:

Upon admission to the hospital, the ultrasound reported hepatosplenomegaly and signs of reactive-type acalculous cholecystitis, which was interpreted as an indirect sign of acute liver disease. During his hospitalization, a CT scan was performed, which confirmed the presence of signs suggestive of a lymphoproliferative process, hepatosplenomegaly, free intraperitoneal fluid, as well as tomographic signs of cystitis and bilateral pleural effusion, which conditioned the development of atelectasis. The results of the viral panel were: anti-HVA IgG, anti-CMV IgM, and anti-VEB IgM and IgG positive.

The diagnosis was defined as hepatitis by EBV-CMV coinfection. The treatment was initiated with a globular package and fresh frozen plasma transfusion, in addition to the soft diet, ursodeoxycholic acid, conditional paracetamol for fever and daily weight control during the evolution.

The patient's evolution was favorable, coagulation disorder secondary to hepatitis was resolved, auxiliary examinations in the evolution showed that total and direct bilirubin decreased daily, as did transaminases and PCR.

Table 1. Results of auxiliary exams.

| Hemogram | Admission | Development |
|----------------------|----------------------|----------------------|
| Hemoglobin | 9.8 g/dl | 12.3 g/dl |
| Leukocytes | 6600/mm ³ | 3930/mm ³ |
| Platelet | 122 000 | 204 000 |
| Coagulation | Entry | Evolution |
| TP | 16.9 | 10.9 |
| TTP | 37.6 | 37.7 |
| Liver profile | Entry | Evolution |
| Bilirubin T | 10.6 mg/dl | 7.4 mg/dl |
| BD | 5.29 mg/dl | 6 mg/dl |
| BI | 5.4 mg/dl | 1.4 mg/dl |
| Alkaline phosphatase | 1698.1 UI/L | 871 UI/L |
| AST | 279 UI/L | 181 UI/L |
| ALT | 117 UI/L | 142 UI/L |
| | Entry | Evolution |
| PCR | 60 | 5.1 |
| LDH | 2653 UI/L | |

DISCUSSION

Cytomegalovirus belongs to the family of herpes viruses of class β . Primary infection with this virus is usually acquired during infancy, and subsequently establishes a period of persistence through myeloid or granulocytic cells^(5,6). Reactivation or reinfection by exogenous viruses is possible and causes a high mortality rate in immunocompromised patients, such as immunocompromised patients or transplanted patients^(5,7).

EBV is a herpes virus of the class γ . The primary infection usually manifests as infectious mononucleosis, characterized by fever, pharyngitis and cervical lymphadenopathy with or without hepatosplenomegaly. EBV develops persistence in B lymphocytes⁽⁵⁾.

Both viruses are common causes of mononucleoside syndrome, and their prevalence in adults is estimated to be greater than 90%⁽⁸⁾. Reactivation of these viruses is possible, especially in patients with some immunosuppression. Primary infection usually occurs shortly after the infant loses the maternal antibodies he or she possessed.

Infants are a high-risk population for infection with CMV and EBV, and these viruses can cause depression of the immune system in children, leading to recurrent infections of various types^(8,9).

Because CMV and EBV have so much in common, coinfection is common in pediatric patients^(8,9). To explain coinfection by these two viruses of the herpes family, several mechanisms are proposed⁽¹⁰⁾. It could be coinfection or reactivation of EBV that was latent in lymphocytes as a consequence of cytomegalovirus infection. Coinfection has been described, but it is infrequent and almost restricted to pediatric age^(8,10). These viruses can infect immunocompetent patients simultaneously with other agents such as respiratory syncytial virus, Chlamydia pneumonia, measles virus, among others^(8,9).

Hepatitis caused by EBV can rarely occur without a previous picture of infectious mononucleosis, which makes etiological diagnosis more difficult⁽¹¹⁾. It is postulated that the virus infects T lymphocytes, in which they perpetuate by causing greater T cell activity. This causes inflammation of the hepatic parenchyma with increased enzymes⁽¹²⁾.

CMV infection is generally asymptomatic; and when it is not, its manifestations vary due to age and the state of the patient's immune system. For example, infected

newborns have intrauterine growth retardation, jaundice, hepatosplenomegaly, microcephaly, brain damage, intracerebral calcifications, and chorioretinitis. If the infection is acquired during school and preschool ages, it usually manifests as pneumonia (bronchial or interstitial), petechial skin rash, diarrhea, or hepatitis with discrete hepatomegaly⁽¹³⁾.

The patient presented elevation of AST and ALT with values three times above the normal value, with AST predominating over ALT. In addition, there was an increase in direct bilirubin and GGTP, which implies an intrahepatic cholestatic syndrome, which is related to viral infections^(14,15).

For the diagnosis of primary EBV infection, serological markers are needed, among these the presence of antibodies against the capsid antigen (VCA) gives the positive diagnosis, may be IgM or IgG, because it is produced early between days 4 to 7^(15,16). For CMV is needed to have IgM against CMV for acute cases, and the presence of IgG expresses previous infection^{8,16}. The patient presented positivity to IgM for both CMV and EBV, and IgG for EBV. This established the diagnosis of viral coinfection, where EBV infection was probably exacerbated due to acute CMV infection.

The evolution of the patient was favorable, she did not develop hepatic insufficiency. Management was only with support measures (paracetamol) and ursodeoxycholic acid.

The exanthema presented by the patient was related to an allergy reaction to the drug azithromycin. The type of rash most associated with antibiotics is maculopapular.⁽¹⁷⁾

Authorship Contributions: The authors participated in the conception, collection of information, writing and approval of the final version of the article.

Financing: Self-financed

Interest conflict: The authors declare no conflicts of interest in the publication of this article.

Received: October 20, 2019

Approved: November 7, 2019

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BIBLIOGRAPHIC REFERENCES

- Gallegos-Orozco JF, Rakela-Brödnér J. Hepatitis viruses: Not always what it seems to be. *Rev Med Chil.* 2010;138(10):1302–11. Disponible en: <https://www.ncbi.nlm.nih.gov/pubmed/21279280>
- Pina DI, Cantón OS. Hepatopatía aguda. *Protoc diagnóstico-terapéuticos Gastroenterol Hepatol y Nutr Pedriátrica SEGHNP-AEP* [Internet]. 2014. Disponible en: https://www.aeped.es/sites/default/files/documentos/hep_aguda.pdf
- Moreira E, Machado Â, Machado L, Xavier C, Monteiro C, Cunha J, et al. Infecção pelo vírus Epstein Barr e hepatite. *Nascer e Crescer.* 2011; 20(2): 73–5. Available from: <http://www.scielo.mec.pt/pdf/nas/v20n2/v20n2a03.pdf>
- Barreales M, Pérez-Carreras M, Meizoso T, Garrido M, Masedo A, Colina F, et al. Infección por el virus de Epstein-Barr y hepatitis aguda colestásica. *An Med Interna.* 2006;23(10):483–6. Disponible en: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0212-71992006001000006
- Hu J, Zhao H, Lou D, Gao H, Yang M, Zhang X, et al. Human cytomegalovirus and Epstein-Barr virus infections, risk factors, and their influence on the liver function of patients with acute-on-chronic liver failure. *BMC Infect Dis.* 2018; 18(1): 577. Disponible en: <https://www.ncbi.nlm.nih.gov/pubmed/30445927>
- Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. *Infect Dis Clin North Am* [Internet]. 2010 Jun 1 [cited 2019 Jun 13];24(2):319–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20466273>
- Vietzen H, Görzer I, Honsig C, Jaksch P, Puchhammer-Stöckl E. Association between antibody functions and human cytomegalovirus (HCMV) replication after lung transplantation in HCMV-seropositive patients. *J Hear Lung Transplant* [Internet]. 2018 Feb 18 [cited 2019 Jun 13]; 37(2): 299–302. Disponible en: <http://www.ncbi.nlm.nih.gov/pubmed/28750933>
- Wang X, Yang K, Wei C, Huang Y, Zhao D. Coinfection with EBV/CMV and other respiratory agents in children with suspected infectious mononucleosis. *Virol J.* 2010;7:247. Disponible en: <https://doi.org/10.1186/1743-422X-7-247>
- Owayed AF, Campbell DM, Wang EEL. Underlying Causes of Recurrent Pneumonia in Children. *Arch Pediatr Adolesc Med* [Internet]. 2000 Feb 1 [cited 2019 Jun 13];154(2):190. Disponible en: <http://archpedi.jamanetwork.com/article.aspx?doi=10.1001/archpedi.154.2.190>
- Peña Irún Á, González Santamaría A. Inmunoglobulina M positiva para citomegalovirus y virus de Epstein-Barr en un paciente con mononucleosis infecciosa. ¿Cómo lo interpretamos? *Semergen* [Internet]. 2012 Oct 1 [cited 2019 Jun 13];38(7):479. Disponible en: <https://linkinghub.elsevier.com/retrieve/pii/S1138359312001530>
- PAULA VIVIANI G. CSA. Falla hepática fulminante por virus Epstein Barr. Rol de los corticoides. Caso clínico. *Rev. Chil. Pediatr.* 2013; 84(3): 313 – 17. Disponible en: https://scielo.conicyt.cl/scielo.php?script=sci_arttext&pid=S0370-41062013000300010
- Hernández-Estrada S, Aguilar Domínguez C, Lizardi Cervera J. Hepatitis por virus Epstein-Barr: Reporte de un caso. *Médica Sur.* 2005; 12(3): 177–9. Disponible en: <https://www.medigraphic.com/pdfs/medsur/ms-2005/ms053e.pdf>
- Tori C, Leon Barua R, Roe C. Hepatitis por citomegalovirus: Presentación de dos casos. *Rev Med Hered.* 1995; 6(2):102–4 Disponible en: http://www.scielo.org.pe/scielo.php?pid=S1018-130X1995000200008&script=sci_arttext
- Del Valle Díaz S, Piñera Martínez M, Medina Gonzales N, Sanchez Vega J. Colestasis un enfoque actualizado. *MEDISA.* 2017;21(7):876. Disponible en: <http://scielo.sld.cu/pdf/san/v21n7/san14217.pdf>
- Khoo A. Acute cholestatic hepatitis induced by Epstein-Barr virus infection in an adult: A case report. *J Med Case Rep.* 2016 Mar 27;10(1). Disponible en: <https://www.ncbi.nlm.nih.gov/pubmed/27037083>
- Cameron B, Flamand L, Juwana H, Middeldorp J, Naing Z, Rawlinson W, et al. Serological and virological investigation of the role of the herpesviruses EBV, CMV and HHV-6 in post-infective fatigue syndrome. *J Med Virol.* 2010 Oct;82(10):1684–8. Disponible en: <https://www.ncbi.nlm.nih.gov/pubmed/20827765>
- Cordero Castro C, Martínez Moreno C, Rojo Conejo P. Guía ABE Infecciones en Pediatría. Guía rápida para la selección del tratamiento antimicrobiano empírico. 2010. Disponible en: <https://guia-abe.es/anexos-reacciones-cutaneas-por-antibioticos>

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