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CASE REPORT

The hidden face of mononucleosis: report of two atypical cases involving this clinical syndrome

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Abstract

The Epstein Barr virus (EBV) is a common infectious agent in the pediatric population, and one responsible for infections that are not symptomatic and are self-limiting. However, in some situations, the virus presents with atypical manifestations and severe outcomes. Therefore, we report one case of hepatitis and another case of hemophagocytic lymphohistiocytosis, both related to EBV infection, accompanied at the Pediatric Unit of the Santa Casa Hospital of the Santa Casa Group of Belo Horizonte, followed by a literature review on the topics, in order to alert pediatricians about the importance of early recognition of these clinical conditions.

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INTRODUCTION

The Epstein Barr virus (EBV) is an infectious agent of worldwide distribution, found in approximately 90% of the population under 20 years of age[1-3]. It is a DNA virus belonging to the herpes family, whose transmission occurs through saliva[1,4]. Initially, the virus penetrates the nasopharynx and oropharynx cells, causing viremia and infecting the B-lymphocytes present in the lymphoreticular node system, where it will replicate, generating cervical lymphadenopathy in 80-100% of cases, splenomegaly in up to 75% of cases, and hepatomegaly in less of 25% of the patients.

During childhood, especially in children younger than 5 years, the EBV infection is oligosymptomatic, with trivial respiratory and gastrointestinal symptoms. However, in adolescence, 30-50% of the patients develop the infectious mononucleosis (IM) clinical syndrome, characterized by: fever, lymphadenopathy and pharyngitis[2,5,6]. On the other hand, the systemic involvement and the severity of the infection are related to the virus-induced immune response[8].

Diagnosis is based on clinical examination and laboratory findings that include CBC with leukocytosis and lymphocytosis, thrombocytopenia and increased transaminases. The appearance of antibodies against the IgG viral capsid coincides with the onset of symptoms and remains positive throughout life, whereas IgM is not always positive in primary infections. When positive, they can disappear in a few weeks[6,9]. Finally, the detection of virus DNA by the polymerase chain reaction (PCR) in the serum is a good indicator of active infection.

IM infection management is supportive, since it is a self-limited condition. However, IM has been associated with atypical manifestations and severe outcomes.

As a result, we report two cases followed at the Pediatric Unit of the São Lucas Hospital of the Santa Casa Group of Belo Horizonte between 2016 and 2017, followed by a literature review in a PUBMED database, in order to tend to the hidden manifestations associated with the EBV infection, alerting the pediatrician that the early recognition of these conditions interferes with the patients' morbimortality.

CLINICAL CASES

Case 1: Female patient, 4 years old, admitted with a history of abdominal pain of 5 days of evolution associated with vomiting and an isolated febrile peak. Upon the examination, she presented with cervical lymph node enlargement and tonsillar hypertrophy without exudate, distended abdomen with hepatomegaly (6 cm from MCM). The lab workup revealed leukocytosis with shifting and lymphocytosis (LG 20,800, 3% Bat, 57% Lymphocytes), increased transaminases (TGO 521, TGP 459) and cholestasis (Alkaline Phosphatase 763, GGT 120), without hyperbilirubinemia (BT 0, 79, BD 0.42). Adequate pancreatic enzymes, coagulation tests, albumin, fibrinogen and renal function. The abdominal ultrasound showed mild hepatomegaly and gallbladder with parietal edema. The patient remained without fever and clinically stable. However, she progressed with worsening of hepatic enzymes, with a 12-day course, reaching values of TGP 684, TGO 918, FA 1393, and GGT 788. Serologies for Hepatitis A, B and C, HIV and Cytomegalovirus, all negative. Serology and PCR were positive for EBV, with the latter presenting 116,728 copies, evidencing EBV hepatitis. The patient progressed with reduction of hepatic enzymes and hepatomegaly, maintaining outpatient follow-up.

Case 2: A 7-year-old male patient, admitted with a history of prolonged fever of 13 days, without improvement after treatment with Azithromycin and Amoxicillin + Clavulanic acid for tonsillitis. At that time, he also had periorbital edema, vomiting and intense abdominal pain. He was referred to the ICU, where he developed hemodynamic instability, requiring albumin, amines and blood components. He presented a suggestive diagnosis of colitis associated with ascites and hepatosplenomegaly. He underwent laparoscopy, which revealed only edema of the loops and free fluid in the cavity. He used wide-spectrum antibiotic therapy without improvement. Serology for EBV with IgM negative and IgG positive, but PCR positive for the same virus with 169,174 copies. The laboratory workup showed anemia and thrombocytopenia, hypofibrinogenemia (195), increased ferritin (432,45), and was diagnosed with hematopoietic lymphohistiocytosis, secondary to EBV. The case was discussed with the Pediatric Immunology and Hematology teams and the HLH-94 protocol was performed with Dexamethasone, Etoposide and Rituximab. Due to the return of fever and abdominal distention, we suspected of treatment failure and started him on human immunoglobulin. He had symptoms improvement. He was followed up at the Hematology and Immunology clinics, having his immunodeficiency diagnosis still inconclusive. He is being administered human immunoglobulin, maintaining positive PCR with high viral load.

DISCUSSION

Hepatic impairment in patients with EBV infection is common, with 80-90% of cases evidencing elevation of transaminases by about 2-3 fold. The increase in liver enzymes begins in the first week of the disease, peaks at the second week and returns to normal levels within 6 weeks[3,5].

However, severe liver or gallbladder dysfunction is rare in immunocompetent patients[1,3]. Increased transaminases, GGT, AF and hyperbilirubinemia should be considered for the occurrence of cholestatic hepatitis. In these cases, jaundice occurs in less than 5% of the patients, contributing little to the clinical diagnosis. The patient of case 1 presented parameters indicative of cholestasis; however, without an increase in bilirubin. The biliary stasis in question may still produce acute, acalculous cholecystitis resulting from vesicle wall ischemia. Ultrasonographic finding of thickening of the gallbladder wall serves as an alert for the severity of cholestatic hepatitis[1,2,5].

The explanation for biliary stagnation results from the release of cytokines by the immune response or the viral invasion itself into the epithelium of sinusoidal capillaries or biliary canaliculi[2]. Another theory advocates the production

of autoantibodies against anti-oxidant enzymes, favoring the occurrence of autoimmune hemolysis[11].

The prognosis of EBV-induced hepatitis is generally favorable, since most cases resolve spontaneously. Less than 1% of cases progress to acute liver failure. Treatment is supportive but in cases of fulminant hepatitis, liver transplantation is a therapeutic option[5].

In the second case, we present an even less common condition that is hemophagocytic lymphohistiocytosis (HLH), a potentially fatal hematological disorder characterized by an uncontrolled immune response[9,11,14].

HLH is divided into two types: primary or familial, resulting from a genetic defect, or secondary, when associated with autoimmune diseases, malignancies and infections. Among the infectious causes, the viruses are the main responsible for triggering this clinical condition, with EBV being the most prevalent[11,14]. A study with Japanese children found that the annual incidence of HLH in the pediatric population is 51.7 cases per year, with half of these patients having EBV infection[15,16].

It is possible that, by infecting B cells, the EBV would induce the proliferation of CD8 T cells or NK cells, via CD21, a protein present in the membrane of these cells, resulting in increased production of cytokines, generating hemophagocytosis[1,13,15].

Clinical manifestations result from histiocytic infiltration in the reticuloendothelial system and include fever, splenomegaly and/or hepatomegaly, lymphadenopathy, jaundice, ascites, edema, skin rash and neurological symptoms such as irritability, hypotonia and seizures[17].

The HLH diagnosis is not easy, since the symptoms may simulate a systemic inflammatory response syndrome or even a sepsis[12]. According to the Histiocyte Society, HLH can be established by molecular diagnosis or by clinical and laboratory criteria (five of the eight criteria must be present), which are: persistent fever, splenomegaly; cytokines (at least 2 of 3 lines - hemoglobin <9g/dL or 10g/dL in newborns, neutrophils <1,000/mL) or platelets <100,000/mL), hypertriglyceridemia (> 265mg/dL) or hypofibrinogenemia (<150g/dL), hemophagocytosis in the bone marrow, spleen or lymph node, with no evidence of malignancy, increased ferritin (> 500mcg/L), decreased or absent NK cell activity and CD25s (> 2400U/mL) dosage[18].

Cytokine dosing has been used as a biological marker for HLH and combines the search for tumor necrosis factor (TNF-alpha), interleukin-6 (IL-6), or increased interleukin-2 receptor (IL-2), CD25, suggesting activation of T lymphocytes and low NK cell activity[15,18].

Hashemi-Sadraei[14] and colleagues contend that EBV viral load above 1000 copies/mL, hyperbilirubinemia (> 1.8mg/dL) and higher levels of 20,300 µg/L ferritin are associated with poor prognosis. If untreated, the estimated survival is less than 2 months.

For treatment, the HLH 94 protocol of the Histiocyte Society recommends an 8-week induction phase with Dexamethasone and Etoposide, with intrathecal methotrexate, when neurological symptoms are present. In 2004, the protocol was reviewed and cyclosporin A was included in the induction phase. However, induction with triple therapy is associated with neurotoxicity, and we decided to use the HLH94 protocol for the patient of case 2[18,19]. In cases of EBV infection, Rituximab, an anti-CD20 monoclonal antibody, is recommended to promote viral load reduction[15,16]. The indication for bone marrow transplantation is reserved for progressive disease or central nervous system involvement, and the therapeutic option is curative[16].

CONCLUSION

According to the above, due to the high prevalence of EBV infection in the pediatric age group, the knowledge and appreciation, especially by pediatricians, of the symptoms discordant with the usual for this clinical condition is of paramount importance, since we can be faced with atypical manifestations of MI.

In fact, its recognition and diagnostic confirmation may not be easy, which requires an individualized analysis for each patient, excluding probable differential diagnoses, in order to avoid unnecessary treatments, capable of increasing patient morbidity.

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