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Research Article

Severe Acute Hepatitis Associated with Hemolytic Anemia: Rare Manifestations of EBV infection: Case Report

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Abstract

Introduction: Epstein Barr virus (EBV) infection is widespread with more than 90% of sero-positive adults worldwide. The majority of primary EBV infections are subclinical. Acute complications are very rare but can be fatal.

Case Report: A 28-year-old young woman was admitted for acute hepatitis with jaundice secondary to hemolytic anemia. The biological results were compatible with severe acute viral hepatitis associated with autoimmune hemolytic anemia. The diagnosis of acute EBV infection was confirmed by serological markers, and indirect histological signs of viral infection on liver biopsy.

Conclusion: Although common, liver damage is generally mild with transient increase of serum transaminases, cases of severe hepatitis as well as autoimmune hemolytic anemia are rare. We report this case to draw attention to the unexpected severity of liver damage from this virus.

Keywords: Epstein Barr Virus; Hepatitis; Mononucleosis Infection; Autoimmune Hemolytic Anemia

Introduction

Epstein-Barr virus (EBV), a member of the herpes virus family, infects oropharyngeal epithelial cells and B cells, resulting in an expansion of cytotoxic CD8 T cells and consequent atypical lymphocytosis. Approximately 90% of the world's population is sero-positive.

Symptomatic EBV infection typically presents in adolescents with tonsillitis, cervical lymphadenopathy and fever characteristic of infectious mononucleosis.

In more than 90% of EBV-related mononucleosis cases, liver involvement is present, but it is often sub-clinical and manageable with symptomatic treatment only.

In general, it is manifested by transient and mild (2-3 times the upper limit of normal) transaminase elevations; severe or fulminant acute hepatitis and hemolytic anemia are rare manifestations of the disease [1].

We report a case of severe EBV-related acute hepatitis associated with autoimmune hemolytic anemia in an immunocompetent patient treated with Acyclovir and steroids.

Patient and observation

Patient information: a 28-year-old woman, followed for Hashimoto's thyroiditis and polycystic ovary syndrome. The patient is admitted for asthenia, vomiting and mild diffuse abdominal pain evolving for one month, with appearance of a mucocutaneous ic-

terus for one week. She had received the estrogen-progestin pill and protected amoxicillin the previous 3 days, in addition to Levothyroxine 50 micrograms per day. There was no history of surgery, blood transfusion, risky contact, taking of toxic substances, food supplements, phytotherapy or alcohol. There was no family history of liver disease or metabolic disease.

Clinical results: on physical examination, the patient was conscious, apyretic, mucocutaneous icterus, no asterixis noted, there were no cervical adenopathy or pharyngitis, the hemodynamic state was stable, on abdominal examination there was hepatomegaly with a liver arrow at about 14 cm, without signs of portal hypertension.

Diagnostic approach: The biological work-up showed hepatic cytolysis with ALT, alanine transaminase at 462 IU/l or 13x NL Normal Limit, and AST, aspartate transaminase at 683 IU/l or 19xNL, and an elevated total bilirubin at 63.24 umol/l. Cholestasis with gamma-GT at 140 U/l or 3.6xNL, alkaline phosphatase at 135 U/l or 1.12xNL. The prothrombin level was 58%. Albumin levels and renal function were without abnormalities. Viral serologies A, B, C and E were negative. Thyroid stimulating hormone (TSH) level was normal. Abdominal ultrasound revealed a liver with a heterogeneous echostructure and regular contours, a gallbladder with a laminated wall, and hepatosplenomegaly.

The patient was then managed by symptomatic treatment with cessation of all hepatotoxic treatment and close clinico-biological surveillance.

Ten days later, the patient was admitted to Sheikh Zayd Hospital in Rabat for severe acute hepatitis, without neurological disorders: there was an increase in cytolysis with AST at 35xNL and ALT at 23xNL, without cholestasis (GGT and PAL correct), and total bilirubin at 244.8 umol/l at the expense of free which was 175.1 umol/l. The prothrombin level had also dropped to 27%. The blood count showed an anemia of 9.8 g/dl normocytic normochromic hemoglobin, without hyperleukocytosis or thrombocytopenia, but a monocytosis of 1026 e/ul was noted. The hemolysis work-up was positive (Haptoglobin: 0.18 g/l, direct Coombs test positive, reticulocytes: 199430/mm3).

The second-line workup was performed, showing hyper-gammaglobulinemia at 30.9 g/L on EPP, total IGG at 52.84 g/, 3.5xNL. ANA antinuclear antibody, anti-smooth muscle antibodies and anti-LKM1 antibodies were all negative. Ceruloplasmin and cupruria were within the norms. CMV and HVS serologies were negative for IgM and positive for IgG.

EBV serology: VCA (viral capsid antigen) was positive for IgM and IgG, IgG EA (Early Antigen) was also positive, the serological profile was consistent with an active EBV infection. The liver biopsy (PBH) performed after normalization of the blood count showed a 9 mm core with 5 portal spaces, containing an inflammatory infiltrate of mature lymphocytes and plasma cells, neutrophils and eosinophils with extensive patchy necrosis. The hepatic lobules are made of hepatocytic trabeculae, composed of clarified and ballooned hepatocytic cells. Minimal foci of intra-lobular necrosis.

Thus, the diagnosis of severe acute EBV hepatitis was retained and the patient was put on Acyclovir 10mg/kg/8h for 10 days in addition to corticosteroid therapy at a dose of 1mg/kg/d in the theory of an autoimmune component induced by EBV infection, given the hyper-gamma-globulinemia, the associated autoimmune hemolytic anemia, and the dysimmune background of the patient.

The evolution was marked by a regression of the mucocutaneous icterus and a decrease in cytolysis: ASAT to 127 U/L (3.5xNL) ALAT to 184 U/L (5.2xNL), a normalization of the TP and factor V on the 10th day of treatment figure 1.

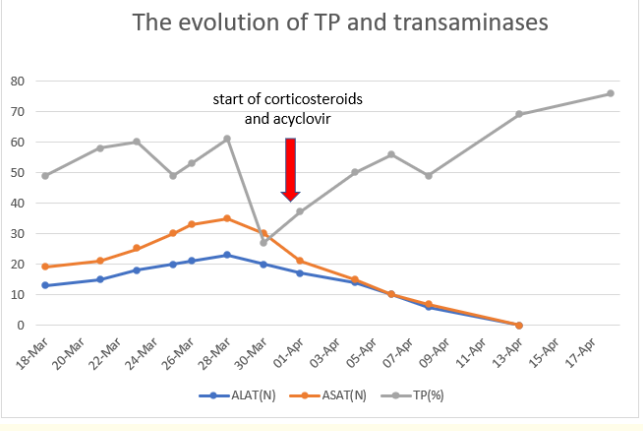

Figure 1

A reduction in corticosteroid therapy had been started, without recurrence of the symptomatology.

Discussion

EBV hepatitis most often presents as moderate cytolysis, ranging from 3 to 5 times normal, spontaneously resolving, in rare cases, it can present as severe acute or fulminant hepatitis [2]. Our patient had acute liver damage with cytolysis exceeding 10 times normal and a PT of less than 50%, defining her as severe acute cytolytic hepatitis, which represents less than 1% of cases of mononucleosis infection [3]. The exact pathogenesis of mononucleosis hepatitis is not fully understood, but the most widely accepted model is activation of the immune system against direct viral invasion of hepatocytes. It has been shown that CD8+ T cells are activated and sequester in the liver via the intracellular adhesion molecule 1 [3] This leads to the activation of numerous cytokine cascades involving interferon, tumor necrosis factor TNFα, and Fas ligand, among others [4].

In a study of 47 patients with EBV hepatitis, 93% of patients had elevated ALT levels, 83% had elevated GGT levels, 20% had hyperbilirubinemia (mostly conjugated), and only 6% had clinical jaundice [5].

Icterus in EBV infection is not only due to cholestatic hepatitis, but also to hemolytic anemia associated with mononucleosis infection as in our patient with predominantly free hyperbilirubinemia, collapsed haptoglobin and a positive direct Combs test [6].

The patient had no exposure to heparin and the platelet count was normal. Based on these data, we concluded that the patient had associated autoimmune hemolytic anemia, and a decision was made to start corticosteroid therapy.

Primary EBV infection associated with AAI is a rare association 0.1 to 3% of cases [7].

As in our patient's history, the post-infectious CA titer increase may be very pronounced, accompanied by hemolysis and relatively mild anemia [8].

The mechanism by which AAI develops during EBV infection has not been elucidated. The possibility that antibodies to EBV cross-react with antigens expressed on erythrocyte membranes and activate the complement cascade has been suggested [9].

Treatment of EBV infectious mononucleosis with corticosteroids is recommended for complications such as upper airway obstruction, acute hemolytic anemia, myocarditis or neurological complications [10].

Specific treatment of acute EBV infection by acyclovir was studied in a meta-analysis of seven randomized controlled trials, including three trials of intravenous treatment in patients with severe disease, The efficacy of antiviral agents in acute IM is uncertain, Although two trials had results that favored treatment over control [11].

Although EBV hepatitis is generally a self-limiting disease, the rapid clinical response and improvement in liver enzymes immediately after the start of acyclovir in our patient strongly suggests a therapeutic benefit. There was no recurrence of disease after discontinuation of corticosteroids, suggesting that viral suppression results in improved symptomatology.

Conclusion

EBV is a common infection that is usually self-limiting.

Hemolytic anemia and severe hepatitis due to EBV are rare manifestations, but cases like this one highlight the variable presentations that can be seen with this virus.

Recognition of EBV infection in the context of a non-specific viral syndrome, hemolytic anemia, cholestasis, or liver enzyme abnormalities will result in prompt management to prevent the sometimes-severe complications of this infection.

Conflict of Interest

None.

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