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Short Communication

Laboratory aspects and therapy response of patients with complication of the EBV infection

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Primary Epstein-Barr virus infection in children is usually asymptomatic, but some children or young adults manifest infectious mononucleosis with typical symptoms of fever, pharyngitis, lymphadenopathy, hepatosplenomegaly and a typical lymphocytosis. The infection caused by Epstein-Barr Virus (EBV) can be followed by immunological complications. One of these is autoimmune hemolytic anemia (AIHA) that it is rare but well known ~1:1000 patients with infectious mononucleosis. Two male patients, aged 2 and 2.5 years old with autoimmune hemolytic anemia caused by Epstein-Barr virus admitted to our hospital with pallor, palpitation, fever and scleral icterus. Viral capsid antigen -IgM was positive in both cases, indicating the presence of primary Epstein-Barr virus infection. AIHA risk of EBV infection in the first two weeks might be considered closely because of life threatining complications such as autoimmune hemolytic anemia.

Key words: Epstein-Barr Virus, coombs positive, autoimmune hemolytic anemia.

INTRODUCTĐON

Epstein-Barr virus (EBV) is one of the human herpesvirus. In developing countries, primary Epstein-Barr virus (EBV) infection in infants and children is usually asymptomatic and occurs through close contacts between parents and children within the first 3 years of life. The majority of the world population acquire primary infection within their first 10 years of life (Andersson, 2000; Rea et al., 2001).

In more industrialized countries, primary infection occurs in up to 50% of the population and presents later than the first decade of life (Crawford, 2001). Here the virus transmission is mostly through intimate contacts between adolescents, hence, a synonym for infectious mononucleosis (IM) is the kissing disease. After an incubation time of 2 to 4 weeks, primary infection may be accompanied by symptoms such as tonsillitis, fever, malaise, lymphadenopathy in up to 50% of cases.

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However, IM may very rarely also cause severe complications, like a fulminant hepatitis, splenic rupture, chronic active EBV infection. It can be fatal in carriers of Duncan's disease, a rare X-chromosomal linked lymphoproliferative syndrome (Yuge et al., 2004; Domachowske et al., 1996).

We describe two patients with AIHA as a rare complication of the EBV infection and discuss the main clinical, laboratory aspects and therapy response.

PATIENTS

Two male patients, aged 2 (case 1) and 2.5 (case 2) years old with autoimmune hemolytic anemia caused by EBV admitted to our hospital for pallor, palpitation, fever and scleral icterus. The patients were previously healthy and had no prior serious infections, Neither had contributory family histories until 2 week earlier, when both of them presented high-grade fever (39^0 c), **(**thirty-nine degrees celsius) and malaise.

The patients had been getting antibiotic (amoxicillin-

azitromycin) therapy for 6 to 7 days. One day before admission, the hemoglobin of case 1 and 2 were 11.6 and 12.1 g/dl, respectively, during admission acute onset, both of cases were presented with pallor, jaundice, tachypnea, tachycardia and hematuria but case 2 also had oligouria. On examination, the patients looked pale, scleral icterus, and were febrile. A moderate hepatosplenomegaly was noted on palpation and heart and lung auscultation did not reveal any significant pathology.

Laboratory tests of case1 and 2 showed platelet (757 to 275×10^9 /L), hemoglobine (6.6 to 3.9 g/dl), and leukocyte (8450 to 25000 /mm^3) with a predominantly lymphocytic type, C-reactive proteins <0.5 to 10.3 mg/L (<0.5 normal level) respectively. The percentage of a typical lymphocytes not exceeded 10% in patients.prothrombine times were normal. Fragmented red blood cells were not presented in the peripheral smear but there were too much spherocytes**.** For both cases, there were hemolysis values for serum lactate dehydrogenase (LDH): 2507 to 5800 IU/L, the reticulocyte count; 3.6 to 5.4% ındirect bilirubin; 2.4 to 3.5 mg/dl, urine sediment; hemoglobinuria: ++/+++ (apart from transient hematuria), eritrocyte: Negative and biochemistry values for AST: 27 to 269 IU/dl, ALT: 22 to 60 IU/dl; BUN: 17 to 80.3 mg/dl; Ure: 29 to 172 mg/dl; creatinin: 0.4 to 2.68 mg/dl, respectively. In both cases, direct antiglobulin test (DAT) were negative for IgG and were strongly positive(+3) for C3d (Complement 3d). There was no evidence of a cold agglutinin. In case 2, acute renal failure due to acute hemolytic anemia was thought on diagnosis. of kidney function began to improve in response to peritoneal dialysis on hospital day
12. Neither patient was transfused with red blood cells.There was no serologic evidence of infection by cytomegalovirus, parvovirus B19, human immunodeficiency virus, hepatitis B virus, or hepatitis C virus. Antinuclear antibodies were not detected. C3 and C4 levels were normal.

The Paul-Bunnell test was performed on serum samples from two patients, but was negative. In the EBV-specific serology, viral capsid antigen (VCA)-IgG antibody was positive and EB nuclear antigen (EBNA) antibody was negative in both case.

VCA-IgM was positive in both case, indicating the presence of primary EBV infection.

Each patient received different treatments. Patient 1 was administered of methylprednisolone pulse therapy. Case 2 was administered intravenously with antibiotic (Cephtriaxon) combined with methylprednisolone pulse therapy.

In case 1, there was clinical improvement with cessation of fever was on the 6th day of treatment. In case 2, there was clinical improvement with cessation of fever and renal function was on the 12th day of treatment. The patients showed gradual improvement in the hemoglobin level with a corresponding decrease in the reticulocyte count. The DAT (Coombs') became negative for C3d over the subsequent 18 days (Table 1).

High dose methyl prednisolone for first 3 days (30 mg/kg) and for the following 4 days (20 mg/kg) and after rapidly been tapered for 2 months. Cases 1 was hospitalized for about 16 days, while cases 2 was hospitalized for about 45 days. They were discharged without sequelae. Follow-up of the patients for 6 months did not reveal any relapses.

DISCUSSION

Primary EBV infection in children is usually asymptomatic, but some children or young adults manifest infectious mononucleosis with typical symptoms of fever, pharyngitis, lymphadenopathy, hepatosplenomegaly and atypical lymphocytosis. Although infectious mononucleosis is usually benign, self-limiting and heals completely within about four weeks, during the acute phase of infectious mononucleosis has been showed rare complication such as neurological manifestations, autoimmune hemolytic anemia, as well as hepatic and renal involvement (Grillo et al., 2008; Khanna and Kumar, 2003).

Since the discovery of elevated antibody levels against EBV antigens in autoimmune diseases, EBV has been suspected as a candidate trigger of autoimmune diseases (Evans et al., 1971; Pender, 2003). One of these is autoimmune hemolytic anemia that up to today has been observed during infective mononucleosis only a few times (Whitelaw et al., 1995; Gelati et al., 1987).

The proof for a causal role in the generation of autoimmune diseases is still lacking. All autoimmune diseases are complex in origin and multifactorial, as genetic and environmental risk factors are always involved. However, cross-reactivity between viral antigens and self-antigens, and the immortalization of preexisting autoreactive B cells through infection with EBV with the consequent production of monoclonal autoantibodies seem to be plausible viral mechanisms for triggering autoimmunity (Wong and Tsao, 2006). AIHA in the course of EBV infectious mononucleosis had been usually seen in adults and immuncompromise people In children. Our studies showed that AIHA and hepatitis can be presented together. The mechanism of EBV-induced hepatitis remains unclear but different tissue express identical antigens or that different autoantibodies would be generated against different antigens expressed on those tissues were showed as reasons (Kimura et al., 2001; Palanduz et al., 2002; Hara et al., 2006). Only case 2 was presented with mild hepatitis and acute renal failure and both of our cases were presented with AIHA. There are three possible major patterns of direct antiglobulin reaction (direct coombs) in AHA: (1) RBCs coated with IgG alone; (2) RBCs coated with IgG plus complement components, and (3) RBCs coated with