A Case of Concurrent Cholestatic Jaundice and Hemolytic Anemia Due to Epstein-Barr Virus Infection

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The patients infected with Epstein-Barr virus (EBV) experienced asymptomatic or mild flu-like illness. Most of symptoms with EBV infection were disappeared within several weeks, although there were various clinical manifestations. Jaundice with elevated liver enzymes was shown about 5∼25%, but hemolytic anemia was rare during EBV infection. Some cases due to EBV infection had been persistent or aggravated course of hemolytic anemia. A twelve-year-old boy was admitted due to fever, and jaundice. Total bilirubin with direct bilirubin was elevated with moderately increased aminotransferase levels. He developed mild hemolytic anemia with positive Coomb’s test and high titer of cold agglutinin during hospitalization. The symptoms were spontaneously improved with conservative care. We report a case of concurrent cholestatic jaundice with hemolytic anemia during acute EBV infection. (Clin Pediatr Hematol Oncol 2010;17:59∼63)

Key Words: Epstein-Barr virus, Cholestatic jaundice, Hemolytic anemia

Infections due to Epstein-Barr virus (EBV) were common in worldwide, and most of children or young adolescents with EBV infection were asymptomatic or mild1,2). Infectious mononucleosis due to EBV was resolved without serious complications within several weeks. Cholestatic jaundice with elevated liver enzymes was experienced in 5∼25% of infectious mononucleosis, and clinical manifestations were mild and spontaneously recovered without sequelae1,3). Hemolytic anemia was reported about 0.1∼3% with EBV infection1,4), and occurred due to cold agglutination with i antigen on surface of red blood cells within early 2 weeks of infection5-7). There was persistent or aggravated course of jaundice due to hemolytic anemia in some cases. There was died in very rare cases due to progression of hemolytic anemia, although most of cases were resolved8,9).
Now, we reported a case of concurrent cholestatic jaundice with hemolytic anemia due to EBV infection.

**Case Report**

A 12-year-old boy was admitted due to fever and generalized icteric skin color. He was suffered from intermittent high fever with sore throat for 2 days, and previously in good health. On examinations, right sided cervical lymph nodes were palpable with 2×1 cm without heatness and tenderness. Icteric sclera and hepatomealy with tenderness were observed. On initial laboratory findings, hematocrit was 33.9% with normocytic, normochromic state, white blood cell counts 11,700/μL with 4% of atypical lymphocytes, and platelets 205,000/μL. In biochemical analysis, there was shown alanine aminotransferase (ALT) 106 IU/L, aspartate aminotransferase (AST) 123 IU/L, total bilirubin (TB) 9.9 mg/dL with 5.2 mg/dL of direct bilirubin (DB), lactate dehydrogenase (LDH) 1,015 IU/L, C-reactive protein 59 mg/dL, prothrombin time 86% versus internal control, and activated partial thromboplastin

![Fig. 1](image_url)

**Fig. 1.** Changes of laboratory data according clinical course. (A) There was shown in total bilirubin (diamond), indirect bilirubin (square), and lactate dehydrogenase (triangle) in hospitalization. (B) The changes of hematocrit (diamond) and reticulocyte counts (square) during admission and follow up. Direct Coombs’ test was positive on 6th hospital day (HD) and 8th HD, but converted to negative state on 36th HD.
Concurrent Jaundice and Hemolytic Anemia Due to EBV Infection

Bilirubin and urobilinogen were positive in urinalysis. Sonography was shown mild hepatosplenomegaly and increased liver echogenicity with edema of gall bladder. There was no serologic evidence of infection with hepatitis A, B, and C. For EBV test, there was positive anti-VCA IgM, and positive PCR of peripheral mononuclear cells. Other serologic markers of EBV including anti-VCA IgG, anti-EA or anti-EBNA IgG and IgM was negative.

On 3rd hospital day (HD), fever was persistent, and he developed general weakness and pale appearance. Laboratory data were 26.2% of hematocrit with 2.52% reticulocyte counts, and ALT 108 IU/L, AST 112 IU/L, LDH 1,026 IU/L, TB 9.8 mg/dL, DB 6.9 mg/dL. There were negative results for recent viral infection including rubella, cytomegalovirus, herpes simplex, toxoplasma, and parvo virus. We had positive in direct Coombs’ test with high cold agglutinin (1:128), but negative in indirect Coombs’ test. On 4th HD, symptoms including fever were resolved with conservative care. On 6th HD, icteric skin was improved and liver not palpable. Hematocrit was 27.2% with 6.12% of reticulocyte, ALT 62 IU/L, AST 95 IU/L, TB 1.8 mg/dL, and DB 1.2 mg/dL. There was no evidence of mycoplasma infection. He was discharged without any complications on 10th HD. On 36th HD, we re-examined his conditions and laboratory findings. Anemia and hyperbilirubinemia were improved with negative Coomb’s test and cold agglutinin (Fig. 1).

Discussion

Epstein-Barr virus (EBV) was first isolated from Burkitt lymphoma, and a major cause of infectious mononucleosis in adolescents or young adults2,10). Primary EBV infection usually occurs during infancy and early childhood and is generally asymptomatic or mildly symptomatic1,2). Clinical manifestations of infectious mononucleosis are characterized by systemic complaints with prominent fever, fatigue, malaise, and lymphadenopathy9). The majority of children with infectious mononucleosis recover uneventfully without complications. However, EBV infection with unusual symptoms or complications is important to evaluate both the biologic plausibility and the virologic basis.

In this case, we had initially confused diagnosis between hepatitis A and hepatic manifestations of infectious mononucleosis, because of cholestatic jaundice and fever in adolescent age11). Also, we were impressed as suspicious viral hepatitis A because of cholestatic jaundice due to total bilirubin with high level of direct bilirubin. Hepatic involvement due to EBV is exceedingly common and varies in severity and frequency with age, which is estimated to be 10% in young adults and 30% in the elderly12). Jaundice during EBV infection was developed about 5% of infectious mononucleosis1). The mechanism is assumed to be related with a mildly swollen bile duct13,14). Hepatitis of EBV infection can be spontaneously resolved, although rare cases were progressed in fulminant course5). In our case, cholestasis with elevated liver transaminase was resolved within 10th hospital day.

The patients developed mild hemolytic anemia with positive direct Coombs’ test and high titer cold agglutinin. Laboratory findings revealed high reticulocyte counts with increased LDH, but no evidence of mycoplasma infection. Hemolytic anemia with infectious mononucleosis reported by Dameshek in 194315), and is very rare in EBV infection (0.1 ~ 3.0%)16). The mechanisms of hemolytic anemia in EBV infection suggest formation of autoantibody, splenomegaly, toxicity of metabolism, and aggravation of defective red blood cell, but is not clear16). However, high titer of IgM cold agglutinin
was shown in 70~80% of EBV infection. IgM antibody have specificity to anti-I or anti-i antigen on surface of red blood cells. Cold agglutinin from healthy persons or some other diseases react specifically with anti-I antigen. Anti-i antibody was associated with EBV infection or lymphoproliferative disease. In this case, there was high titer of cold agglutinin with positive direct Coombs' test during acute phase, which was disappeared. The clinical manifestations in our patient suggested an abnormal immune response to EBV infection. The generation of autoantibodies may be due to T and B cells responding to EBV infection. Autoantibody responding to EBV might be formed by the alteration of B cell glycolipid which was recognized by the human monoclonal antibody to i-blood group antigen. The post-EBV antibody is usually anti-i with lambda light chains. The hemolysis tends to develop 1~2 weeks after the onset of infectious mononucleosis, and moderately severe. The hemolytic events due to EBV normally undergoes spontaneous recovery but corticosteroids have been recommended in severe cases. In our case, hemolysis developed within 1 week of onset, and recovered with conservative care without steroid.

We conclude that acute EBV infection may develop concurrent hepatitis with cholestatic jaundice and hemolytic anemia. These complications due to EBV may be expected gradual recovery, although it may be severe cases controlled by corticosteroids.

요 약

Epstein-Barr 바이러스(EBV)에 감염된 환자들은 대부분 무증상이거나 가벼운 인플루엔자 증상 증상을 앓는다. 다양한 임상 양상을 나타내지만, EBV에 의한 대부분의 증상은 수 주 내에 소실된다. EBV 감염 동안 간호소의 증가를 동반한 황달은 약 5~25%에서 나타나지만, 용혈빈혈은 드물다. 일부 증례에서는 용혈빈혈이 지속되거나 악화되기도 한다. 12세 된 남아가 발열과 황달을 주소로 내원하였으며 환아는 중등도의 aminotransferase 증가와 함께 총혈액요소 및 직접 빌리루빈이 증가하였다. 환아는 입원 기간 동안 Coombs 검사에서 양성을 보이면서 높은 저온응집소(cold agglutinin) 수치를 나타내는 경미한 용혈빈혈이 있었다. 환아의 증상은 보존적인 치료로 증상이 소실되었다. 이에 저자들은 급성 EBV 감염으로 동시에 발생한 담즙저항가황달과 용혈빈혈을 경험하였기에 보고하는 바이다.

참 고 문 헌

Concurrent Jaundice and Hemolytic Anemia Due to EBV Infection


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