

CASE REPORT

## Epstein-Barr Virus로 인한 급성 간염 후 발생한 궤양성 대장염 1예

오승현, 유찬란, 김은옥, 배시현, 최종영, 윤승규, 최상욱

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### A Case of Ulcerative Colitis Following Acute Hepatitis Induced by Epstein-Barr Virus Infection

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Epstein-Barr virus (EBV) infection varies in its clinical manifestations and severity. EBV can be a causative agent of hepatitis and may have a role in the pathogenesis of chronic autoimmune diseases including inflammatory bowel disease. A 24-year-old woman was admitted to our hospital, presenting with fever and elevated liver enzymes. She was diagnosed with acute hepatitis and EBV infection according to serologic tests and liver biopsy. Within two months, she was re-admitted to our hospital, presenting with hematochezia and lower abdominal pain. She was diagnosed with ulcerative colitis. *In situ* hybridization for EBV was positive in initial liver biopsy and colon biopsy. Here we report an unusual case of acute EBV hepatitis followed at a short interval by ulcerative colitis. (*Korean J Gastroenterol* 2016;68:104-108)

**Key Words:** Hepatitis; Epstein-Barr virus; Epstein-Barr virus infections; Ulcerative colitis

### INTRODUCTION

Epstein-Barr virus (EBV), a member of the gamma subfamily of *Herpesviridae*, was discovered in the cultured lymphoblasts from African Burkitt's lymphoma specimens nearly 50 years ago.<sup>1</sup> The seropositivity rate for EBV is more than 90% in adults. In childhood, primary EBV infections are usually asymptomatic and subclinical. In adolescents and young adults, primary EBV infection presents as infectious mononucleosis, the clinical manifestations of which include fever, sore throat, and adenopathy. Mild self-resolving elevation of liver enzyme levels is seen in 80-90% of cases of infectious mononucleosis. Less commonly, jaundice and right upper quadrant discomfort because of hepatomegaly may occur.

Rarely, fatal infectious mononucleosis may manifest as fulminant hepatitis.

EBV infection is suspected to be a key factor in the development of certain autoimmune diseases. Sjögren syndrome and systemic lupus erythematosus were reported following EBV infection.<sup>2,3</sup> EBV had been found in gastrointestinal tissue from patients with inflammatory bowel disease (IBD) patients.<sup>4,5</sup> EBV seropositivity rates in adults range from 70% to 95% in the general population. A recent study suggested that EBV seropositivity in IBD patients was approaching 100%.<sup>6</sup> The prevalence of EBV seropositivity in patients with IBD may be comparable with that in general population. However, EBV positive cells in colonic lesions were detected in 60% of patients with IBD, but not at all in normal controls.<sup>5</sup>

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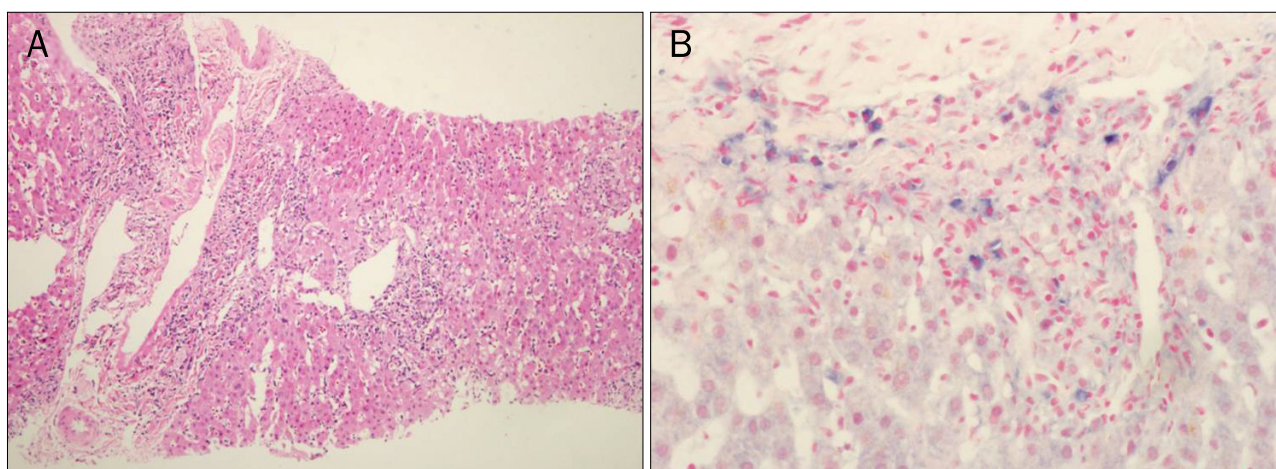
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We describe an unusual case of ulcerative colitis (UC) that occurred after acute EBV hepatitis.

## CASE REPORT

A 24-year-old woman was admitted to our hospital with a two-week history of fever, chills and myalgia. She had no history of liver disease, alcohol consumption, use of drugs or herbal medicines or blood transfusions. She had no familial history of IBD or autoimmune disease. On admission, she had a temperature of 37.4°C. Physical examination findings revealed mildly icteric sclera, bilateral tonsil enlargement and hepatosplenomegaly. Abdominal CT scan revealed hepatosplenomegaly and diffuse thickening of the gallbladder wall. Laboratory tests showed a white blood count of 12,590/mm<sup>3</sup> with 44% segment neutrophils, 42% lymphocytes and 4% atypical lymphocytes, a hemoglobin level of 13 g/dL and a platelet count of 261,000/mm<sup>3</sup>. Both ESR and CRP were elevated at 32 mm/hour (normal range, 0-20 mm/hour) and 1.64 mg/dL (normal range, 0.01-0.47 mg/dL), respectively. She had a serum AST of 275 IU/L, ALT of 352 IU/L, ALP of 553 IU/L, GGT of 301.6 IU/L, total bilirubin of 3.85 mg/dL, serum protein of 6.5 g/dL, serum albumin of 3.24 g/dL and an INR of 1.12. Serologic tests for hepatitis A virus, hepatitis B virus and hepatitis C virus were negative. Immediately, we examined serologic tests for autoimmune hepatitis and atypical virus including EBV and cytomegalovirus (CMV). We could rule out autoimmune hepatitis because

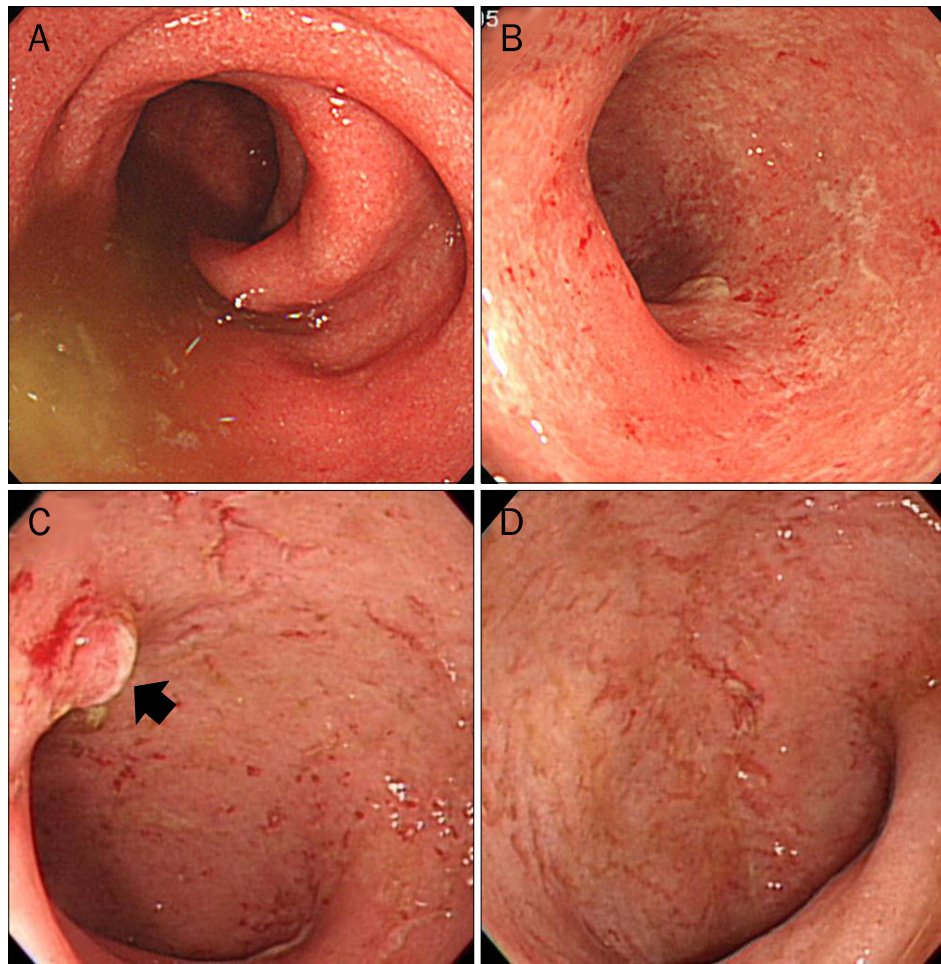
serum IgG concentration was within the normal range, and anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody and anti-mitochondrial antibody were all negative. There was no evidence of hepatitis E virus, CMV or human immunodeficiency virus. The patient was treated with general management for acute hepatitis and with empirical antibiotics for seven days because mild fever persisted. However, her symptoms and the abnormal liver function test results did not resolve and body temperature was elevated consistently between 37.3°C and 37.9°C. On the eighth hospital day, acute EBV infection was detected. The titers of antibodies to EBV were as follows: viral capsid antigen (VCA)-IgM 3+, VCA-IgG 2+, early antigen-IgG weakly positive and EBV nuclear antigen (EBNA)-IgG negative. On the 12th hospital day, serum AST level was 262 IU/L, ALT level: 343 IU/L and total bilirubin level: 3.78 mg/dL. The liver enzyme elevation did not improve for two weeks despite conservative treatment. An ultrasound-guided liver biopsy was performed on her 14th hospital day. The liver specimen showed active hepatitis with moderate piecemeal necrosis and infiltration of inflammatory cells in the portal area (Fig. 1). *In situ* hybridization for EBV was positive in lymphocytes. We started prednisolone 1 mg/kg (about 50 mg) on the 18th hospital day because of sustained fever and liver enzyme abnormalities. Mild fever subsided rapidly after prednisolone treatment. After this treatment, liver enzyme levels decreased and her general condition improved. She was discharged on prednisolone 35 mg.



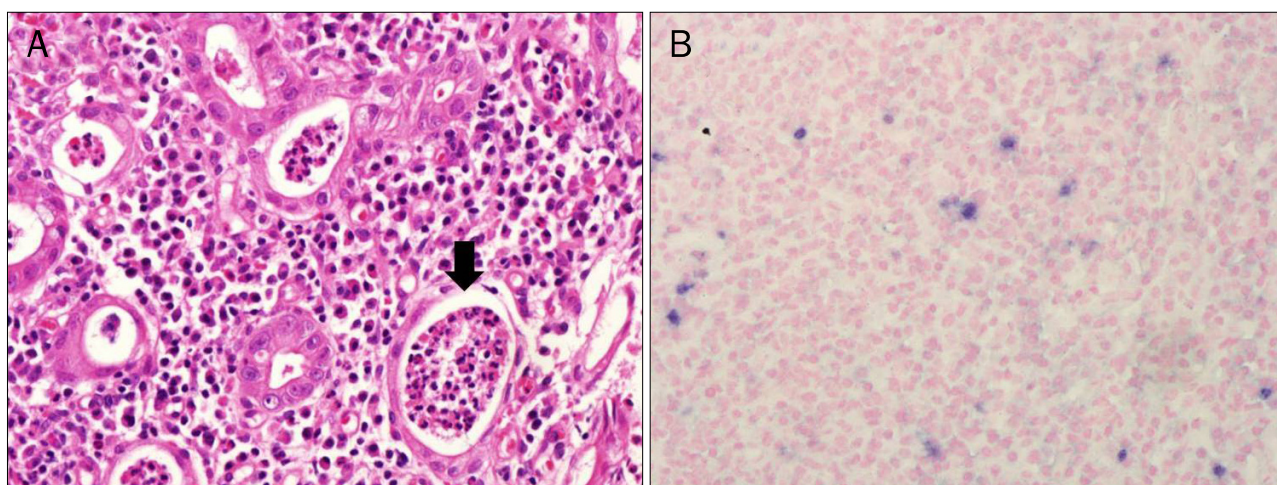
**Fig. 1.** Initial liver biopsy findings. (A) H&E (×100). Intralobular focal necrosis and infiltration of inflammatory cells in portal area are shown. A linear sinusoidal lymphocytic infiltration is also seen. (B) Epstein-Barr virus *in situ* hybridization (×400). Positive staining cells (blue color) were detected within lymphocytes infiltrating in periportal area.

Within two months, her prednisolone was tapered to 10 mg and her liver function test results were within the normal range. However, she presented at the emergency center com-

plaining of hematochezia and lower abdominal pain. Her vital signs were stable, without fever. Laboratory results were within the normal ranges except for a mild leukocytosis.



**Fig. 2.** (A, B) Colonoscopic images of sigmoid colon at second admission. Loss of vascular pattern and some friability of the mucosa is seen. (C, D) Follow-up colonoscopic images of sigmoid colon and rectum after one year. This image shows multiple mucosal erosions, loss of vascular appearance and an inflammatory polyp (arrow).



**Fig. 3.** Microscopic findings of colon biopsy. (A) H&E (×400). The infiltration of mixed inflammatory cells and acute cryptitis (arrow) are shown. (B) Epstein-Barr virus *in situ* hybridization (×400). Positive staining cells (blue color) were detected within lymphocytes infiltrating in area of active inflammation.

Serum AST and ALT remained normal. An abdominal CT scan showed diffuse wall thickening of the descending colon, sigmoid colon and rectum in contrast with the non-specific findings of gastrointestinal tract at her first admission. Colonoscopy was performed for evaluation of hematochezia, which showed diffuse inflammation with exudates and loss of the vascular pattern in the mucosa of the left colon and the rectum (Fig. 2A, B). The microscopic findings suggested UC. There were marked infiltrations of inflammatory cells in the intestinal mucosa, inflammations of crypts and crypt abscess. *In situ* hybridization for EBV was positive in a few lymphocytes (Fig. 3). Serological tests for EBV infection showed that, even though EBNA-IgG was still negative, the titer of VCA-IgM had decreased to 1+ and VCA-IgG increased to 3+. The diagnosis of UC was based on the compatible endoscopic and pathologic findings. The patient's symptoms improved gradually after administration of methylprednisolone 0.5 mg/kg/day intravenously. Over a follow up period of three years, no evidence of hepatitis was detected and the clinical course of UC was stable, although periodic aggravation of UC occurred. Follow-up colonoscopy was performed after one year, because she again developed hematochezia and diarrhea (Fig. 2C, D). Typical endoscopic findings of UC were identified in rectum and left side colon. She continues treatment with mesalazine and/or low dose azathioprine. Occasionally, budesonide enema was used depending on the UC symptoms. However, systemic steroids have not been administered for three years.

## DISCUSSION

The present study describes a case of UC following acute EBV hepatitis in a young adult. EBV infection is the primary cause of infectious mononucleosis and is associated with the development of lymphoma and nasopharyngeal carcinoma. Reactivation of latent EBV does not produce noticeable symptoms in most people, but it has been related to lymphoproliferative disease in transplant recipients. Hepatic involvement in infectious mononucleosis is common, found in 80-90% of patients as self-limited and transitory elevation of liver enzyme.<sup>7,8</sup> Serum ALT and AST are two or three times the upper limit of normal. Serum alkaline phosphatase and bilirubin are mildly elevated in about half the patients, but clinical jaundice is rare (less than 5% of patients). In immune-com-

petent individuals, severe hepatitis associated with EBV infection is uncommon. Fulminant hepatitis can occur in immune-deficient states such as HIV infection, during cancer chemotherapy and post transplantation.<sup>9</sup>

The presence of atypical lymphocytes in peripheral blood can be a diagnostic clue for hepatitis by non-hepatotropic viruses such as EBV and CMV. These atypical large peripheral blood lymphocytes are activated CD8 T cells, most of which are probably responding to EBV-infected B lymphocytes.<sup>10</sup> The present case had 4% atypical lymphocytes in peripheral blood smear. Acute EBV infection can be diagnosed by using a heterophile antibody test and EBV-specific antibody tests. The heterophile antibody test, based on the characterization of the agglutination of various mammalian erythrocytes by heterophile antibodies in patient's serum, is a sensitive diagnostic tool for EBV infectious mononucleosis. However, the specificity of this test is not high because it can be falsely negative for young children<sup>11</sup> and falsely positive in other infectious diseases, neoplasms, and autoimmune diseases.<sup>12</sup> Specific antibody tests for EBV include VCA-IgM, VCA-IgG, EBNA-IgG and EA-D IgG antibody. Indirect immunofluorescence assays or enzyme immunoassays can be used for detection of EBV specific antibodies. Acute EBV infection is identified sufficiently by the detection of EBV VCA-IgM. VCA-IgM antibodies decline and disappear within two to six months, whereas VCA-IgG and EBNA-IgG antibodies persist for life. EBNA-IgG antibody develops between three to six months after EBV infection, while VCA-IgG antibody is detected within two weeks of illness.<sup>13</sup>

Most EBV-induced hepatitis spontaneously resolves. The liver enzyme abnormalities peak during the second week after the onset of the illness and return to normal within the third week. In patients such as ours, who have sustained symptoms and elevated liver enzymes, corticosteroid treatment seems effective.<sup>14</sup> Corticosteroids have been used for control of the symptoms of infectious mononucleosis, but there is insufficient evidence to recommend them.<sup>15</sup> Antiviral medications (e.g., acyclovir, ganciclovir) have been utilized to treat cases of severe EBV hepatitis,<sup>11,12</sup> but randomized studies have not been performed. Our patient did not recover from clinical symptoms including fever, myalgia and anorexia and biochemical abnormalities over three weeks. She recuperated rapidly after the initiation of systemic steroid treatment.

EBV infection may be involved in the pathogenesis of UC

and Crohn's disease.<sup>4</sup> EBV is detected frequently in intestinal mucosa from patients with IBD.<sup>5,16</sup> Ryan et al.<sup>17</sup> reported that the detection of EBV DNA was more frequent in colonic mucosa from patients with UC than in normal controls and patients with Crohn's disease. Chronic EBV infection is a possible triggering factor for not only IBD but for other autoimmune diseases including autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis.<sup>2,3,18</sup> The pathogenesis of autoimmune disease related to EBV infection is not clear. Autoimmunity may develop because of molecular mimicry, which is defined as immunological cross-reactivity between EBV and self-antigens.<sup>19,20</sup> Another hypothesis is that EBV-infected autoreactive B cells make pathogenic autoantibodies and provide co-stimulatory survival signals to autoreactive T cells, which induce chronic inflammation in the target organ.<sup>21</sup> EBV infection could be suspected of involvement in the occurrence or aggravation of UC in this case, because we found no evidence of UC at the patient's first admission and she had no history of IBD.

In conclusion, we describe a case of acute EBV hepatitis followed by UC. However, we should keep in mind that, as in this case, a range of clinical manifestations of EBV infection can develop within a short interval after infection. Further investigation into the pathophysiology of EBV infection is necessary to identify how to prevent its progression to a chronic condition.

## REFERENCES

1. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1964;1:702-703.
2. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB. An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. *J Clin Invest* 1997;100:3019-3026.
3. Whittingham S, McNeilage LJ, Mackay IR. Epstein-Barr virus as an etiological agent in primary Sjögren's syndrome. *Med Hypotheses* 1987;22:373-386.
4. Gehlert T, Devergne O, Niedobitek G. Epstein-Barr virus (EBV) infection and expression of the interleukin-12 family member EBV-induced gene 3 (EBI3) in chronic inflammatory bowel disease. *J Med Virol* 2004;73:432-438.
5. Yanai H, Shimizu N, Nagasaki S, Mitani N, Okita K. Epstein-Barr virus infection of the colon with inflammatory bowel disease. *Am J Gastroenterol* 1999;94:1582-1586.
6. Linton MS, Kroeker K, Fedorak D, Dieleman L, Fedorak RN. Prevalence of Epstein-Barr virus in a population of patients with inflammatory bowel disease: a prospective cohort study. *Aliment Pharmacol Ther* 2013;38:1248-1254.
7. Crum NF. Epstein Barr virus hepatitis: case series and review. *South Med J* 2006;99:544-547.
8. Gupta E, Bhatia V, Choudhary A, Rastogi A, Gupta NL. Epstein-Barr virus associated acute hepatitis with cross-reacting antibodies to other herpes viruses in immunocompetent patients: report of two cases. *J Med Virol* 2013;8:519-523.
9. Donhuijsen-Ant R, Abken H, Westerhausen M, et al. Aggressive hepatitis in a patient with acute myeloid leukaemia during complete remission and detection of Epstein-Barr virus DNA in a liver biopsy. *Br J Haematol* 1990;76:557-558.
10. Odumade OA, Hogquist KA, Balfour HH Jr. Progress and problems in understanding and managing primary Epstein-Barr virus infections. *Clin Microbiol Rev* 2011;24:193-209.
11. Horwitz CA, Henle W, Henle G, et al. Clinical and laboratory evaluation of infants and children with Epstein-Barr virus-induced infectious mononucleosis: report of 32 patients (aged 10-48 months). *Blood* 1981;57:933-938.
12. Horwitz CA, Henle W, Henle G, Penn G, Hoffman N, Ward PC. Persistent falsely positive rapid tests for infectious mononucleosis. Report of five cases with four-six-year follow-up data. *Am J Clin Pathol* 1979;72:807-811.
13. Hess RD. Routine Epstein-Barr virus diagnostics from the laboratory perspective: still challenging after 35 years. *J Clin Microbiol* 2004;42:3381-3387.
14. Thompson SK, Doerr TD, Hengerer AS. Infectious mononucleosis and corticosteroids: management practices and outcomes. *Arch Otolaryngol Head Neck Surg* 2005;131:900-904.
15. Candy B, Hotopf M. Steroids for symptom control in infectious mononucleosis. *Cochrane Database Syst Rev* 2006;(3):CD004402.
16. Wakefield AJ, Fox JD, Sawyerr AM, et al. Detection of herpesvirus DNA in the large intestine of patients with ulcerative colitis and Crohn's disease using the nested polymerase chain reaction. *J Med Virol* 1992;38:183-190.
17. Ryan JL, Shen YJ, Morgan DR, et al. Epstein-Barr virus infection is common in inflamed gastrointestinal mucosa. *Dig Dis Sci* 2012;57:1887-1898.
18. Rigopoulou EI, Smyk DS, Matthews CE, et al. Epstein-barr virus as a trigger of autoimmune liver diseases. *Adv Virol* 2012; 2012:987471.
19. Pender MP. CD8+ T-Cell deficiency, Epstein-Barr virus infection, vitamin D deficiency, and steps to autoimmunity: a unifying hypothesis. *Autoimmune Dis* 2012;2012:189096.
20. Nickerson C, Luthra H, David C. Antigenic mimicry and autoimmune diseases. *Int Rev Immunol* 1991;7:205-224.
21. Pender MP. Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases. *Trends Immunol* 2003; 24:584-588.