Relapsing Infectious Mononucleosis-Like Symptoms Associated with Liver Insufficiency in a Chronic Hepatitis B Patient with Common Variable Immunodeficiency

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Patient: Female, 36-year-old
Final Diagnosis: Common variable immunodeficiency • EBV reactivation
Symptoms: Ascites • fever • lymphadenopathies
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology • Immunology • Infectious Diseases

Objective: Unusual clinical course
Background: Common variable immunodeficiency (CVID) is a rare disease. Infectious mononucleosis-like symptoms due to Epstein-Barr virus reactivation in adulthood are also rare. Here, we aimed to report a case of Epstein-Barr virus reactivation presenting with relapsing infectious mononucleosis-like symptoms with liver failure in common variable immunodeficiency with chronic hepatitis B virus infection.

Case Report: A 36-year-old Japanese woman with chronic hepatitis B virus infection developed relapsing fever, lymphadenopathy with marked splenomegaly, and ascites 6 months after treatment with propagermanium, a nonspecific immune modulator, and subsequent treatment with entecavir and pegylated interferon sequential therapy. Although the hepatitis B virus load was controlled, Epstein-Barr virus deoxyribonucleic acid was detected in her serum. Seven months later, her symptoms improved following corticosteroid treatment. Prior to sequential therapy, she developed pneumonia 4 times in 2 months and exhibited consistent hypoimmunoglobulinemia before corticosteroid treatment. Further examinations showed low amounts of switched memory B cells, and absence or barely detectable levels of isohemagglutinins. Subsequently, she was diagnosed with common variable immunodeficiency.

Conclusions: Epstein-Barr virus reactivation with relapsing infectious mononucleosis-like symptoms can occur following immune modulation therapy in patients with common variable immunodeficiency, and this can affect the patient’s primary disease. Therefore, immunoglobulin screening along with the consideration of CVID in all patients is required before immune modulation therapy is planned.

Keywords: Common Variable Immunodeficiency • Epstein-Barr Virus Infections • Hepatitis B • Proxigermanium

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/934003
**Background**

Epstein-Barr virus (EBV) infection is extremely common worldwide, and approximately 90% of adults are infected before 30 years of age [1]. Following primary infection, EBV persists for the remainder of an individual’s life. It can reactivate under physical and psychological stress and in individuals with a variety of autoimmune diseases and cancers [2]. Moreover, reactivation sometimes results in severe or fatal outcomes [3].

Common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterized by hypogammaglobulinemia, recurrent infections, and various complications, with a prevalence of 0.001-3.374 per 100,000 population, and the prevalence tends to be higher in countries with a high Human Development Index [4]. It is very rare for patients with CVID to present with relapsing infectious mononucleosis (IM)-like symptoms.

Propagermanium (PG) is an organic germanium that is used to treat chronic hepatitis B in Japan owing to its immune modulatory effects; it can reduce levels of hepatitis B e (HBe) antigen, hepatitis B virus (HBV) deoxyribose nucleic acid (DNA) polymerase, and alanine aminotransferase (ALT), as well as increase the HBe antibody titer [5]. In recent years, attempts have been made to use PG for the treatment of various diseases owing to its multiple effects, including anti-inflammatory, antitumor, and antiviral effects [6-8].

Here, we report a case of relapsing IM-like symptoms associated with liver insufficiency due to the reactivation of EBV after PG treatment in a patient with chronic HBV infection accompanied by CVID.

**Case Report**

A 36-year-old Japanese woman was diagnosed with chronic HBV infection through a medical examination and was followed up for 5 years. Her prior medical history revealed only a diagnosis of mild sinusitis when she was 24 years old. One year ago, her HBe antigens converted to HBe antibodies. However, her HBV DNA levels fluctuated between 4.0 and 8.1 log copies/mL, and her ALT levels fluctuated as well. Recent abdominal ultrasonography revealed chronic hepatitis with marked splenomegaly (Figure 1). Upper gastrointestinal endoscopy revealed no signs of portal hypertension. She was started on 30 mg of PG for the disease in February 2010. Laboratory data prior to PG administration are shown in Table 1. One month after the commencement of PG therapy, the patient developed pneumonia (positivity for Streptococcus pneumoniae urinary antigen), and she recovered following a course of oral antibiotics. However, pneumonia developed 3 more times within the following 2 months, and PG was discontinued 8 weeks after commencement. The level of ALT increased to 170 IU/L at week 8 of the PG treatment, but returned to the same lower abnormal level as before initiation and remained at a similar level. During this treatment, in May, she became aware of bilateral cervical lymphadenopathy, and she was followed up by an otolaryngologist. At this time, splenomegaly was also observed on breast computed tomography (CT), and a liver biopsy showed grade 2 activity and stage 3 fibrosis according to the Scheuer system [9]. We commenced sequential therapy with entecavir and pegylated interferon α (pegIFN α) in June. During the 6 months she received entecavir, the patient developed fever above 38°C several times, which subsided within a few days of taking loxoprofen. In October, weekly administration of pegIFN α was initiated. Subsequently, she developed fever again and took loxoprofen 1-3 times daily. The fever disappeared after 5

![Figure 1](image_url)
months with completion of pegIFN α therapy. However, her fever returned, and she reported having cervical lymphadenopathy without pain 2 weeks later. She consulted with an otolaryngologist and was referred to a hematologist. A few bilateral lymphadenopathies were observed in the cervical lymph nodes (2-4 cm in diameter) and in the axillary and inguinal regions (1-2 cm in diameter). Histological findings of a cervical lymph node biopsy specimen were compatible with vascular transformation of the lymph node sinuses. The patient continued to take loxoprofen as needed. Although her fever and lymphadenopathies subsided temporarily, fever reoccurred starting in October 2011. In December, the patient visited our department reporting feeling a sense of abdominal fullness, marked swelling of the bilateral cervical lymph nodes, and frequent fever above 39°C. Abdominal CT revealed massive ascites and striking splenomegaly (Figure 2). Although her serum HBV DNA level had decreased to 2.1 log copies/mL following pegIFN α treatment, it increased to ≥9.0 log copies/mL after 4 months (September) and persisted at this level. However, the increase in her serum ALT level was modest. Her serum albumin level decreased to 3.4 g/dL, and an ascites examination through flow cytometry showed no abnormal cell populations. We again commenced the administration of entecavir, diuretics, and branched-chain amino acid granules. Gradually, her HBV DNA level decreased to 3.4 log copies/mL, and her serum albumin level recovered to 4.0 g/dL; further, her ascites was unremarkable by March 2012. However, splenomegaly and occasional fever with lymphadenopathy persisted. A second biopsy of the cervical lymph nodes showed no significant changes compared with the first biopsy. In May, the patient developed a fever of 38-40°C, which persisted for 2 weeks along with marked cervical and axillary lymphadenopathies. Ascites reappeared coincident with a decrease in the serum albumin level to 3.1 g/dL and in prothrombin activity to 58%. The HBV

Table 1. Laboratory data before treatment with propagermanium (Feb. 2010).

| Hematology       | Range     | Biochemistry   | Range       |
|------------------|-----------|----------------|-------------|
| WBC              | 68 ×10^3/µL | 36-96          | T-Bil       | 0.5 mg/dL | 0.2-1.2 |
| Neut             | 74 %       | 40-71          | AST         | 53 IU/L   | 11-32   |
| Ly               | 16 %       | 27-47          | ALT         | 51 IU/L   | 7-37    |
| Mono             | 8 %        | 2-8            | LDH         | 164 IU/L  | 115-230 |
| Eo               | 1.5 %      | 1-7            | ALP         | 367 IU/L  | 115-360 |
| Ba               | 0.5 %      | 0-1            | γ-GTP       | 31 IU/L   | 4-36    |
| Hb               | 9.4 g/dL   | 11.2-14.9      | TP          | 6.4 g/dL  | 6.7-8.3 |
| RBC              | 417 ×10^6/µL | 378-497       | ALB         | 4.5 g/dL  | 4.0-5.1 |
| Hct              | 28.5 %     | 33.6-44.6      |             |           |         |
| Plt              | 13.9 ×10^3/µL | 12.5-37.5    |             |           |         |

**Viral markers**

| HBsAg            | >2000 C.O.I. | <0.05         |           |           |
|------------------|-------------|---------------|-----------|-----------|
| HBeAg            | (-)         | (-)           |           |           |
| HBeAb            | (+)         | (-)           |           |           |
| HBV DNA          | 6.9 log IU/mL | <2.6          |           |           |
| HIVAb 1/2        | (-)         | (-)           |           |           |

| Albumin          | 71.1 %      | 62.0-72.0     |           |           |
| Hct              | 3.8 %       | 2.0-3.0       |           |           |
| Platelet         | 31 %        | 7.0-11.0      |           |           |

Figure 2. Computed tomography scan of the abdomen showing massive ascites and striking splenomegaly. The volume was 1152 cm³, which was calculated based on methods proposed by Kuczybala et al [11].
DNA load decreased to 2.8 log/mL, ALT levels remained normal for 5 months, and the increase in C-reactive protein levels was modest (3.48 mg/dL). However, the soluble interleukin 2-receptor (sIL-2R) levels were extremely high (29 800 IU/mL), and a serum EBV DNA load of 1300 copies/mL was detected. Anti-EBV capsid antigen immunoglobulin (Ig)M or anti-EBV nuclear antigen antibodies were not detected (Table 2). We commenced daily treatment with 30 mg of prednisolone (PSL). Five days after PSL administration, her fever disappeared, and her lymphadenopathy subsided. Ascites was not observed physically, and normalization of serum albumin levels occurred after 3 weeks. Therefore, the dose of PSL was reduced to 25 mg. Two weeks later, it was further reduced to 20 mg. Thereafter, the dose of PSL was reduced by 2.5 mg every 3-8 weeks to ensure that there was no tendency for symptoms and sIL2-R to relapse. Although the decrease in splenomegaly was very modest, her other symptoms improved remarkably, and her lymphadenopathy subsided. Ascites was not observed physically, and normalization of serum albumin levels occurred after 3 weeks. Therefore, the dose of PSL was reduced to 25 mg. Two weeks later, it was further reduced to 20 mg. Thereafter, the dose of PSL was reduced by 2.5 mg every 3-8 weeks to ensure that there was no tendency for symptoms and sIL2-R to relapse. Although the decrease in splenomegaly was very modest, her other symptoms improved remarkably, and her sIL2-R level decreased to 1700 IU/mL at 14 weeks after the start of the PSL treatment. Five months after PSL administration, EBV DNA load decreased to < 100 copies/mL. The dose of PSL was reduced to 7.5 mg daily. However, her fever started occurring repeatedly 2 months later. The dose of PSL was increased to 30 mg daily in March 2013. Although her fever resolved and the dose of PSL was reduced as before, it appeared again 8 weeks after reducing the dose of PSL to 12.5 mg daily. The dose was then increased to 20 mg daily and was reduced very slowly (1 mg every 3-4 months). At this time, it was found that the patient’s Ig levels remained consistently low, which started prior to PSL administration. The IgG level was 421 mg/dL, the IgA level was 17 mg/dL, and a low IgM level of 17 mg/dL was observed after PSL administration (Table 3). We tried 5.0 g of intravenous immunoglobulin (IVIG) once when the dose of PSL was reduced to 13 mg, and 2 months later, the sIL2-R, which had been mildly abnormal and had stopped decreasing, normalized. Subsequently, the dose of PSL was further reduced to 10 mg daily and was maintained for more than 3 years. In 2015, her Ig levels were still low (Table 3), and we found that isohemagglutinins were absent or barely detectable (Table 4), and she had few switched memory B cells (Table 5). Because she did not have antibodies to human immunodeficiency virus, she was diagnosed with CVID.

### Table 2. Viral markers before prednisolone administration (June 2012).

| Epstein-Barr virus | Range | Cytomegalovirus |
|-------------------|-------|----------------|
| VCA antibody-IgG  | ×10   | Antigen*       |
| VCA antibody-IgA  | <10   | Antibody-IgG   |
| VCA antibody-IgM  | <10   | Antibody-IgM   |
| Nuclear antigen antibody | <10 | (Herpes simplex virus) |
| DNA               | 1300 copies/mL | <100 |

* pp65: antigenemia method.

### Table 3. Immunoglobulin levels before and after prednisolone administration.

| Date       | June 2012 | Nov. 2014 | July 2017 |
|------------|-----------|-----------|-----------|
| PSL dosage (/day) | –         | 14 mg     | 10 mg     |

| Immunoglobulin level (mg/dL) | Range |
|-----------------------------|-------|
| IgG                         | 421   |
| IgA                         | 17    |
| IgM                         | 118   |

Table 4. The titers of isohemagglutinins.

| Anti-A IgM | 2 | 2-64 (32) |
|------------|---|-----------|
| IgG        | Absent | 2-128 (16) |
| Anti-B IgM | 2 | 2-64 (4) |
| IgG        | 8 | 8-1024 (32) |

(Blood type O+).
Discussion

Our patient presented with 2 unique clinical manifestations. The first was relapsing IM-like symptoms due to EBV reactivation. The second was CVID that became apparent after the commencement of PG treatment.

EBV infection is one of the most common infections in humans, and approximately 90% of humans acquire EBV infection by young adulthood [1]. Following infection, EBV remains latent in infected B cells in healthy individuals; however, it occasionally reactivates and sometimes causes severe illness. Even when EBV reactivation is asymptomatic, it influences the severity of a patient’s primary disease [12]. Our patient presented with relapsing IM-like symptoms with positivity for serum EBV DNA, which was suspected to be a result of chronic active EBV infection [13].

However, 2 examinations of lymph node biopsy specimens only revealed the vascular transformation of the lymph node sinuses, posing a clinical diagnostic challenge. The consistently low Ig levels seen prior to PSL administration led to the suspicion of CVID, and subsequent findings of decreased switched memory B cells and lack of isohemagglutinins were consistent with this diagnosis [14]; further, this condition was thought to be an important cause of the atypical IM-like symptoms in this case.

CVID is a primary immunodeficiency characterized by reduced serum levels of IgG, IgA, and sometimes IgM, with reduced or absent specific antibody production [14]. The prevalence of CVID in Japan is estimated to be 0.25 per 100 000 population [15]. The clinical features of CVID vary and can include acute and chronic infections, inflammatory diseases, autoimmune diseases, and increased incidence of cancer and lymphoma. There are several known atypical forms of EBV infection in patients with primary immune deficiencies [16]; however, to the best of our knowledge, reactivation of EBV in patients with CVID has not yet been reported.

The hallmark of CVID is the loss of B-cell function, but CVID is a heterogeneous disease, and some patients may have additional hidden abnormalities in T cells or natural killer (NK) cells [17], which play an important role in EBV latency [18].

PG was formerly used in Japan for the treatment of chronic hepatitis B and had ameliorating effects on biochemical and virological markers. The mechanism underlying these effects is thought to be immunomodulation, including activation of cytotoxic T cells and NK cells [5]. Furthermore, PGs have also been reported to stimulate and proliferate B-cell lines [19].

In this case, we thought it was highly likely that CVID, which had been asymptomatic until then, stimulated the immune system including NK cells, T cells, and B cells via PG, which destabilized the latent state of EBV and reactivated EBV, leading to the onset and recurrence of IM-like symptoms.

With regard to chronic HBV, although the HBV DNA level was increased, exacerbation of hepatitis did not occur after discontinuation of PG. However, liver insufficiency occurred in association with relapsing IM-like symptoms, suggesting the influence of EBV reactivation. Recently, Goh et al reported that EBV reactivation in sepsis caused by pneumonia is associated with increased morbidity [12]. Additionally, Hu et al reported

Table 5. Lymphocyte subpopulations in peripheral blood by flowcytometry.

(July 2015, Taking prednisolone 10 mg/day)

|            | Percentage | Absolute count (cells/μL) |
|------------|------------|----------------------------|
|            | Range      | Range (mean)               |
| WBC        |            | 9000                       |
| Lymphocyte | 6.4        | 18.0-49.0                  |
|            | 576        | 3300-9000                  |
| CD4        | 35         | 29-55                      |
|            |            | 201                        |
|            |            | 344-1289                   |
| CD8        | 23         | 19-41                      |
|            |            | 132                        |
|            |            | 110-1066                   |
| CD4/CD8    | 1.5        | 0.6-2.4                    |
| CD3        | 63         | 56-86                      |
|            |            | 362                        |
|            |            | 547-2155                   |
| CD19       | 7          | 6-23                       |
|            |            | 40                         |
|            |            | 77-470                     |
| CD20       | 8          | 7-30                       |
|            |            | 46                         |
|            |            | 70-663                     |
| CD27*IgD- |            | 66                         |
| CD19*CD27*IgD- | 0.296  | 27                           |
|            |            | 23-321 (91) *              |

* Blanco et al [10].
that EBV infection is associated with a high Child-Pugh score in patients with liver cirrhosis and that it has an influence on the liver function of patients with HBV-related acute-on-chronic liver failure [20,21]. These studies also suggest the influence of EBV reactivation on liver insufficiency.

Since PG has various immunomodulatory effects, the use of PG in patients with CVID with a latent EBV infection may lead to immune imbalance and reactivation of EBV. As PG can be used for the treatment of various diseases in the future, we recommend screening for CVID by testing immunoglobulin levels prior to PG administration.

Conclusions

We present a case of relapsing IM-like symptoms due to EBV reactivation associated with liver insufficiency after PG treatment in a patient with chronic hepatitis B, and CVID was diagnosed during the subsequent clinical course. EBV reactivation can occur in patients with CVID after immune modulation therapy, and it can affect the patient's primary disease; therefore, immunoglobulin levels should be checked along with the consideration of CVID before administering this therapy.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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