Fatal Chronic Active Epstein-Barr Virus Infection in a Rheumatoid Arthritis Patient Treated with Abatacept

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Abstract:
Chronic active Epstein-Barr virus (CAEBV) T-cell type infection, systemic form, is characterized by persistent infectious mononucleosis-like symptoms, high Epstein-Barr virus (EBV) DNA levels in the peripheral blood, organ damage, and a poor prognosis. The association between CAEBV and rheumatoid arthritis (RA) is unclear. We report a case of fatal CAEBV T-cell type infection in an RA patient undergoing treatment with cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin fusion protein (abatacept, ABT). CAEBV can rapidly worsen in RA patients receiving ABT. Thus, we should try to establish an early diagnosis in patients with CAEBV infection.

Key words: chronic active Epstein-Barr virus infection, rheumatoid arthritis, abatacept

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Introduction
Chronic active Epstein-Barr virus (CAEBV) T-cell type infection, systemic form, is a lymphoproliferative disease of childhood that is associated with a poor prognosis. The clinical features include recurrent or persistent infectious mononucleosis (IM)-like symptoms, increased levels of EBV DNA in the peripheral blood, and the presence of EBV in affected tissues (1-3). CAEBV has been categorized as a disease of children and young adults without known associations such as immunodeficiency or autoimmune disorders (3, 4). However, adult-onset CAEBV has been reported in patients with autoimmune disorders such as rheumatoid arthritis (RA) or systemic lupus erythematosus (3, 5-8).

An association between RA and EBV has been reported. Patients with RA have an elevated EBV load in their peripheral blood, suggesting impaired control of EBV infection (9). Moreover, EBV has been detected in about 60% of RA patients with immunodeficiency-associated lymphoproliferative disorder (LPD) (10). However, the mechanism of the association between EBV infection and RA remains unclear. Moreover, little is known about the association between CAEBV and RA.

We report a case of fatal CAEBV T-cell type infection in an RA patient undergoing treatment with cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin fusion protein (CTLA-4 Ig) (abatacept, ABT).

Case Report
The patient was a 63-year-old Japanese woman who was admitted to our hospital for evaluation of liver injury and pancytopenia, who was diagnosed with RA at age 36 years of age. Her disease had been classified as Steinbrocker radiographic stage IV at 42 years of age. She had no history of IM or hypersensitivity to mosquito bites. Four years previously, she developed cervical and axillary lymphadenopathy during treatment with methotrexate (MTX) and infliximab (IFX), a tumor necrosis factor (TNF) inhibitor. Biopsy of a lymph node revealed LPD. The enlarged lymph nodes regressed spontaneously after the discontinuation of MTX and IFX.

Two years previously, during treatment with a TNF in-
At that time, a test of the patient’s peripheral blood revealed an EBV DNA level of 940 copies/10⁶ white blood cells (WBC); tests were positive for anti-EBV viral capsid antigen (VCA) immunoglobulin (Ig) G (1:320) and negative for anti-VCA IgM and anti-EBV nuclear antigen (EBNA) antibody. Anti-EBV early antigen (EA) IgG was not measured. Spleen enlargement and lymphadenopathy were also detected. These results suggested CAEBV. However, she had no episodes of recurrent or persistent IM-like symptoms, such as fever or hepatitis, and infected cells were not detected. Crescentic GN is not a common manifestation of systemic rheumatoid vasculitis (11); however, necrotizing crescentic GN has been reported to be the most frequent histopathological finding in patients with GN associated with TNF inhibitors-induced systemic vasculitis (12). Accordingly, the possibility of ETN-associated vasculitis was considered. High-dose corticosteroid treatment was initiated and ETN was discontinued and the patient’s clinical and laboratory findings subsequently improved.

Approximately 15 months earlier, monthly ABT (500 mg, intravenous) therapy was initiated due to an exacerbation of RA activity with a reduction in the dose of corticosteroid (prednisolone 4 mg/day) (Fig. 1). After the initiation of ABT treatment, the patient presented with mild hepatocellular injury. She had recurrent fever and liver injury for more than 5 months; the final dose of ABT was administered at approximately 4 months before the current presentation. She had persistent liver injury for more than 3 months after the final dose of ABT, and developed pancytopenia; she was then transferred to our hospital.

On admission, the patient’s pulse, blood pressure, body temperature, respiratory rate (RR), and oxygen saturation on room air were 101 beats/min, 103/52 mmHg, 37°C, 22 breaths/min, and 99%, respectively. The patient was categorized as Eastern Cooperative Oncology Group Performance Status (PS) Grade 4. A physical examination showed tenderness in the right upper quadrant. A laboratory examination
revealed pancytopenia (white blood cell count, 2,200/μL; hemoglobin, 7.6 g/dL; platelet count, 61,000/μL), liver injury (aspartate aminotransferase, 411 U/L; alanine aminotransferase, 425 U/L; alkaline phosphatase, 7,883 U/L; γ-glutamyl transpeptidase, 1,223 U/L), hyperbilirubinemia (total bilirubin, 5.0 mg/dL), an inflammatory response (C-reactive protein, 8.97 mg/dL), high levels of ferritin (4,980 ng/mL) and soluble interleukin-2 receptor (sIL-2R) (4,220 U/mL), low levels of IgG (456 mg/dL) and albumin (2.4 g/dL), and a normal prothrombin time international normalized ratio (1.16). The patient was positive for cytomegalovirus (CMV) phosphoprotein 65 (pp65) antigen (3/50,000 WBC), Aspergillus (galactomannan) antigen, and anti-VCA IgG (1:160), and had an elevated EBV DNA level (1,200 copies/10⁶ WBC). The patient was negative for anti-VCA IgM, anti-EBNA antibody, antinuclear antibody, antimitochondrial M2 antibody, anti-hepatitis A virus IgM, anti-hepatitis E virus IgA, hepatitis B surface antigen, anti-hepatitis B surface antibody, anti-hepatitis B core antibody, and hepatitis C virus RNA tests and (1, 3)-β-D-glucan. The patient’s anti-EA IgG level was not measured. Ultrasound of the abdomen found no intra- or extrapleural bile duct dilatation. Contrast-enhanced computed tomography (CT) showed multifocal low-density lesions in the liver, splenomegaly, ascites, and mediastinal and para-aortic lymphadenopathy. Aspiration biopsy revealed hypocellular bone marrow and scattered cells with hemophagocytosis; in situ hybridization for Epstein-Barr virus-encoded small RNA (EBER) was negative. Percutaneous liver biopsy was not performed due to ascites. Bacteriologic cultures of blood specimens were negative.

A diagnosis of hemophagocytic lymphohistiocytosis (HLH) was made based on the diagnostic criteria for HLH (2009), including splenomegaly, pancytopenia, hepatitis, hemophagocytosis, and elevated ferritin and sIL-2R levels. The clinical findings, including the pulse, RR, and white blood cell count, fulfilled the diagnostic criteria for systemic inflammatory response syndrome (American College of Chest Physicians/Society of Critical Care Medicine consensus conference, 1992). There was a possibility of sepsis due to a hepatobiliary infection (e.g., pyogenic hepatic abscess), which was considered possible based on liver injury and the CT findings, and meropenem was administered. Tumors of the hematopoietic and lymphoid tissues associated with CAEBV were also considered as possible underlying causes of liver injury and HLH; however, these entities were not definitively diagnosed. The patient and her family were informed that intensive therapy was impossible due to her poor PS and the uncertain diagnosis; they requested supportive care, and she received supportive therapy (including Ig, blood transfusion, and liver support). The patient had a fever and scattered nodules in the lungs, and serum Aspergillus (galactomannan) antigen was positive; her CMV pp65 antigen level (19/50,000 white blood cells) was also increased during the course. Invasive pulmonary aspergillosis (IPA) and CMV antigenemia in an immunocompromised state were suspected based on the Infectious Diseases Society of America guidelines and the Japan Society for Hematopoietic Cell Transplantation’s guidelines for CMV infection; miconafungin and ganciclovir were administered. She died of hepatic failure on the 27th hospital day.

The autopsy findings included atrophy of the liver, with bridging fibrosis, zonal necrosis of hepatocytes, and the marked infiltration of medium-sized to large atypical lymphocytes of the portal areas was observed in a histological examination (Fig. 2a and b); these atypical lymphocytes (Fig. 2c) were mostly positive for CD3 (Fig. 2d), CD8 (Fig. 2e), and T-cell intracellular antigen 1 (TIA1) (Fig. 2f), but negative for CD20 (Fig. 2g), CD56, CD79a, and CD30; the expression of these markers was compatible with cytotoxic T-lymphocytes (CTLs). EBER was positive in some of the CTLs (Fig. 2h), but immunohistochemical staining for CMV was negative. Scattered histiocytes with hemophagocytosis were also observed. Infiltration by atypical lymphocytes and hemophagocytosis were also observed in the spleen, lymph nodes, and bone marrow. Branching septate hyphae of Aspergillus were found to have invaded the lung tissue, which is compatible with IPA. There was no evidence of malignancy or non-fungal infectious disease of the lungs.

The patient’s clinical and histopathological findings met the diagnostic criteria (3, 4) for CAEBV of T-cell type, systemic form, including recurrent or persistent IM-like symptoms (fever, hepatitis, splenomegaly, and lymphadenopathy) for >3 months, elevated EBV DNA levels in the peripheral blood, and the infiltration of EBV-infected CTLs in the liver.

**Discussion**

The current case highlighted an important clinical issue: CAEBV of the T-cell type can worsen and rapidly progress in RA patients receiving ABT. Thus, we should promote awareness about CAEBV and emphasize the importance of an early diagnosis of CAEBV for safe RA treatment.

In the current case, the clinical course and autopsy findings showed severe liver injury and HLH, suggesting that the major reason for the patient’s death was hepatic failure due to CAEBV of the T-cell type. Hepatic failure is considered to be one of the life-threatening complications of CAEBV (3). The immunophenotypes of EBV-infected cells include T-cell (59%) and natural killer (NK) cell (41%) types (3). Hepatic failure was considered to be the cause of death in approximately 30% of patients who died due to CAEBV of the T-cell type (2). The histopathological examination of the liver reveals sinusoidal and portal infiltration, which are suggestive of viral hepatitis (3). The clinical and histopathological findings of the current case were consistent with those of typical CAEBV of the T-cell type. The clinical and histopathological findings also showed HLH. HLH occurs in 24% of patients with CAEBV (3). However, EBV-positive HLH alone is not included in EBV-positive T-cell and NK cell lymphoproliferative diseases of childhood such as CAEBV because it is not considered neoplastic (3, 13).
Figure 2. The liver histopathology. The liver showed the marked infiltration of atypical lymphocytes in the portal area (a: Hematoxylin and Eosin (H&E) staining; scale bar, 300 μm; b: H&E staining, scale bar, 30 μm). The infiltrating lymphocytes (c: H&E staining, scale bar, 100 μm) were mostly positive for CD3 (d: immunohistochemistry, scale bar, 100 μm), CD8 (e: immunohistochemistry, scale bar, 100 μm), and T-cell intracellular antigen 1 (TIA 1) (f: immunohistochemistry, scale bar, 100 μm); negative for CD20 (g: immunohistochemistry, scale bar, 100 μm); and focially positive for Epstein-Barr virus-encoded small RNAs (EBER) (h: in situ hybridization, scale bar, 100 μm).
Although it was confirmed that CAEBV resulted in a fatal outcome in the present case, two clinical issues should be considered: whether CAEBV was present before treatment with ABT; and whether ABT resulted in the exacerbation of CAEBV.

First, the diagnosis of CAEBV before treatment with ABT is a limitation of this case report. The EBV DNA level was not measured immediately before the initiation of ABT treatment; however, the presence of high EBV DNA levels in the peripheral blood, splenomegaly, and lymphadenopathy 2 years previously suggested the possibility of CAEBV. However, there were no characteristic IM-like symptoms, such as fever and hepatitis. Furthermore, no infected cells (T cells or NK cells) were identified and EBV was not detected in the affected tissues; both findings are important for the diagnosis (3, 4).

Second, ABT can trigger the exacerbation of CAEBV. In the current case, the patient developed mild hepatocellular injury immediately after the initiation of ABT treatment. The patient subsequently presented with recurrent fever and a worsening of hepatocellular injury. Moreover, the EBV DNA loads in the peripheral blood were increased after ABT treatment (940 to 1,200 copies/10^6 WBC). The duration from the onset of IM-like symptoms to death was approximately 7 months. The clinical course of CAEBV is usually protracted without disease progression (3). Although adult-onset disease might be rapidly progressive, the mean duration from the onset to death is reported to be 27 months (3, 5). The time-course of the current case was shorter and suggested that ABT treatment may result in rapid disease progression. On the other hand, the possibility that corticosteroid therapy triggered an exacerbation of CAEBV is considered unlikely because low-dose corticosteroid therapy was administered without any change in the dose before or after the initiation of ABT treatment. Furthermore, there are no previous reports of CAEBV with autoimmune disorders (7, 8). Moreover, EBV infection is not a typical infection in patients receiving corticosteroid therapy (14), and corticosteroids have not been described as an immunosuppressive agent associated with LD in patients with iatrogenic immunodeficiency (15).

With regard to the association between CTLA-4 Ig and EBV, there have been reports of EBV-associated HLH (16) and reactivation of EBV (17). In the case of EBV-associated HLH (Table), the RA patient, who was treated with MTX and ABT, presented with fever, anemia, and splenomegaly. Liver and bone marrow biopsies revealed histiocytes with hemophagocytosis. The patient was positive for EBV IgM and the DNA level was 127,000 IU/mL (16). EBV-associated HLH is different from CAEBV; however, the case report shows that ABT might lead to uncontrolled EBV infection. It has also been reported that belatacept, an anti-rejection drug, increased the rate of EBV infection in renal transplant recipients (17). However, to our knowledge, there have been no prior reports of an RA patient receiving ABT who had an aggressive exacerbation of CAEBV and a fatal clinical course.

With regard to the use of biologics other than ABT in the treatment of RA, a previous case report described the worsening of CAEBV in an RA patient receiving a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody (tocilizumab, TCZ) (7) (Table). The patient had a history of lymphadenopathy during MTX treatment and high EBV DNA loads in the peripheral blood before treatment with TCZ. The patient presented with IM-like symptoms and elevated EBV DNA levels after the initiation of TCZ. An autopsy showed the presence of CAEBV of T-cell type and Hodgkin’s disease. This report concluded that blockade using TCZ might have resulted in the breakdown of immune surveillance for EBV because IL-6 regulates the growth, differentiation, and activation of CTLs.

Similarly, the current case indicated that ABT may also lead to worsening of CAEBV. The patient had a history of lymphadenopathy during treatment with MTX and IFX and had high EBV DNA loads in her peripheral blood before treatment with ABT. After the initiation of ABT, she presented with IM-like symptoms, the further elevation of her EBV DNA levels, and a rapidly progressive clinical course with HLH and hepatic failure. The final diagnosis of CAEBV of T-cell type was made based on the autopsy findings. The clinical course was similar to that of a patient receiving TCZ.

With regard to the association between RA and EBV, impaired CTL activity due to RA was also taken into account as a possible factor in the exacerbation of CAEBV. Although the etiology of CAEBV is unknown, patients have impaired EBV-specific CTL activity (3). It has been reported that the EBV load in RA patients is similar to that in asymptomatic organ transplant recipients, suggesting the impaired control of EBV infection in RA patients (9). However, it has been reported that the EBV load was not increased in RA patients receiving biologics such as TNF inhibitors, ABT, and TCZ (18, 19). These results might indicate that some predisposing factor, such as a history of iatrogenic immunodeficiency-associated lymphoproliferative disorder, which was present in the current and previous cases, also played an important role in the exacerbation of CAEBV.

We must bear in mind that RA patients may have CAEBV. A strong racial predisposition to this condition has been noted, with most cases being reported from East Asia (3, 5). In Japan, The Japan College of Rheumatology has declared that CAEBV is a contraindication for TCZ based on adverse events that occurred in a patient with RA (20).

Thus, we should promote awareness about CAEBV and emphasize the importance of an early diagnosis. In the current case, the main reason why the diagnosis was delayed was that ABT was not discontinued at an early stage due to suspected drug-induced liver injury. When abnormalities are detected in RA patients, we should consider the possibility
There should be considered to confirm the diagnosis with and discontinue treatment at an early stage. Moreover, a bi-

Table. Review of Published Cases.

| Reference, Country | Age | Sex | Past history | RA Disease duration | Treatment history | Treatment | CAEBV EBV DNA | Characteristic findings | Treatment | Outcome, Cause of death | Autopsy findings |
|--------------------|-----|-----|--------------|---------------------|-------------------|-----------|-------------|-----------------------|-----------|------------------------|------------------|
| (7) Japan | 60 | Female | Two episodes of lymphadenopathy during MTX therapy; - regression after MTX cessation; - the second episode: necrotizing lymphadenitis in biopsy, VCA IgG 1:1,280, EA IgG 1:640, and EBV DNA 3,100 copies/mL | 10 months before therapy; 3,100 copies/mL ↓ 2 months after therapy; 520 → 2,600 copies/10⁶ WBC | Fever, Liver enzymes ↑ Hepatosplenomegaly, HLH | High-dose CS, CyA, IL-2 activated T-cells | Death, DIC and MOF | LN: EBER-1+Hodgkin’s lymphoma cells | Liver: infiltration of EBER-1 and CD45RO+ T-cells | Stomach ulcers: infiltration of Hodgkin’s lymphoma cells and EBER-1+lymphocytes | BM: hemophagocytosis |
| Current case, Japan | 63 | Female | LpD during MTX and IFX therapy; spontaneous regression after MTX and IFX cessation; Leukocytoclastic vasculitis and crescentic GN due to DIv | 10 months before therapy; 940 copies/10⁶ WBC ↓ 14 months after therapy; 1,200 copies/10⁶ WBC | Fever, Liver injury, Splenomegaly, Lymphadenopathy, HLH | Supportive therapy | Death, Hepatic failure | Liver: infiltration of CTLs and EBER+CTLs, and hemophagocytosis | Splenic, LN, and BM: infiltration of atypical lymphocytes and hemophagocytosis |
| (16) USA | 48 | Male | NR | EBV IgM+, EBV DNA 127,000 IU/mL | Fever, Anemia, Splenomegaly, Ferritin ↓ sIL-2R ↑ | DMS, Biopside Rituxan | Death, Sepsis and respiratory failure | Liver: histiocytes packed in the sinuses, many with erythrophagocytosis | BM: phagocytosis of non-nucleated erythroid autopsies | |

RA: rheumatoid arthritis, EBV: Epstein-Barr virus, CAEBV: chronic active Epstein-Barr virus, MTX: methotrexate, VCA: viral capsid antigen, EA: early antigen, IFX: infliximab, ETN: etanercept, DIV: drug-induced vasculitis, GN: glomerulonephritis, NR: not reported, BUC: bucillamine, SASP: salazosulfapyridine, TAC: tacrolimus, TCZ: tocilizumab, ABT: abatacept, WBC: white blood cells, HLH: hemophagocytic lymphohistiocytosis, CS: corticosteroid, CyA: cyclosporine A, DMS: disseminated intravascular coagulation, MOF: multiple organ failure, LN: lymph node, BM: bone marrow, CTLs: cytotoxic T-lymphocytes, EBER: Epstein-Barr virus-encoded small RNAs, USA: United States of America, sIL-2R: soluble interleukin-2 receptors, DMS: dexamethasone.
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