Chronic active Epstein-Barr virus infection treated with PEG-asparagase: A case report

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BACKGROUND
Chronic active Epstein-Barr virus (EBV) infection may lead to fatal diseases, including EBV-positive lymphoproliferative disorders, lymphomas, and hemophagocytic lymphohistiocytosis. We present a chronic active EBV (CAEBV) patient who was treated with PEG-asparagase and achieved decreased load of EBV-DNA.

CASE SUMMARY
A 33-year-old female Chinese patient who had fever for approximately 3 mo was admitted to our hospital in December 2017. EBV-DNA was positive with a high copy number. She was diagnosed with chronic active EB virus infection. PEG-asparagase was administered at a dose of 1500 U/m² at a 14-d interval, resulting in eradication of EBV for more than 6 mo. The effect of PEG-asparagase in this patient was excellent.

CONCLUSION
A chemotherapy regimen containing PEG-asparagase for CAEBV may be further considered.

Key Words: Chronic active Epstein-Barr virus infection; PEG-asparagase; Chemotherapy; L-asparaginase; Case report
Aspargase requires further investigation as a chemotherapy drug for CAEBV to reduce the load of EBV-DNA.

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**INTRODUCTION**

Chronic active Epstein-Barr virus infection (EBV) is a systemic EBV-positive lymphoproliferative disease, which may lead to fatal illness. There is currently no standard treatment regimen for chronic active EBV (CAEBV), and the only effective treatment is hematopoietic stem cell transplantation (HSCT) [1]. We here report a patient with CAEBV who achieved eradication of EBV for more than 6 mo following the completion of PEG-asparagase treatment. PEG-asparagase may provide a new treatment regimen to reduce EBV load for CAEBV.

**CASE PRESENTATION**

**Chief complaints**

A 33-year-old female Chinese patient was admitted to our hospital with intermittent fever and weakness for 3 mo.

**History of present illness**

About 2 mo previously, this patient was admitted to a local hospital due to fever and decreased appetite. The laboratory examination showed leukopenia and liver function damage. EBV-DNA was 6.09 × 10^5 IU/mL in September 2017. Fever was not effectively improved with cephalosporin and ganciclovir. Interferon was given; EBV-DNA decreased slightly, but fever persisted. The fever had lasted 3 mo when she was admitted to our hospital in December 2017.

**History of past illness**

The patient had no other previous medical history.

**Personal and family history**

The patient had no personal or family history of similar illnesses.

**Physical examination**

Physical examination revealed enlargement of multiple superficial lymph nodes and splenomegaly. Abdominal ultrasonography showed that the spleen was 15.7 cm in diameter.

**Laboratory examinations**

Complete blood count revealed bicytopenia with a white blood cell count of 1.39 × 10^9/L, hemoglobin 14.2 gm/dL, and platelet count of 89 × 10^9/L. ALT and AST were elevated to 95 U/L and 173.2 U/L, respectively. EBV-DNA (whole blood) was 5.1 × 10^4 copies/mL and EBV-DNA (plasma) was 5.60 × 10^4 copies/mL in December 2017. Natural killer cell was mainly involved in lymphocyte subsets of EBV infection, despite the accumulation of all lymphocyte subsets. Flow cytometry of the bone marrow revealed about 2.26% abnormal phenotype natural killer (NK) cells, expressing CD56bri, CD2, CD7, CD94bri, CD161, and CD159a. Biopsy was taken from the swollen left inguinal lymph node and bone marrow. However, no tumor was detected, and EBV-encoded small RNA (EBER) was not found by in situ hybridization of two biopsies. The tests of hepatitis virus, human immunodeficiency virus, antinuclear antibody, and rheumatoid antibody were all negative.
FINAL DIAGNOSIS

According to the diagnostic criteria for CAEBV, she was finally diagnosed with CAEBV.

TREATMENT

The patient started on PEG-aspargase (1500 U/m²) treatment every 14 d from December 2017. The informed consent was obtained from the patient and this therapy was approved by the institutional ethics committee.

OUTCOME AND FOLLOW-UP

The patient’s body temperature gradually dropped, and fever improved on the 7th day during the first treatment course with PEG-aspargase. On the 14th day, the patient’s liver enzymes had returned to normal and the spleen shrank to normal size. EBV-DNA (whole blood) was 760 copies/mL and EBV-DNA (plasma) was < 500 copies/mL in January 2018. EBV-DNA had maintained negative for more than 6 mo (Figure 1) since February 2018. Re-examination of the bone marrow showed that abnormal NK cells disappeared. Hypofibrinogenemia was recorded during PEG-aspargase treatment, but bleeding or thromboembolism did not occur. No other side effects of PEG-aspargase, such as allergy, pancreatitis, and hepatotoxicity, were noted. The patient rejected allogeneic HSCT for personal reasons. Unfortunately, the patient eventually died due to relapse of CAEBV and occurrence of hemophagocytic lymphohistiocytosis (HLH) after more than 6 mo of PEG-aspargase treatment. Due to severe liver dysfunction at the time of relapse, the patient could no longer receive PEG-aspargase therapy.

DISCUSSION

CAEBV is a chronic disease with persistent infectious mononucleosis-like symptoms, such as fever, lymphadenopathy, and hepatosplenomegaly. CAEBV may develop into fatal diseases, including multi-organ failure, EBV-associated T/NK cell lymphoproliferative disorder, T or NK cell lymphomas, and HLH[1].

The diagnostic criteria for CAEBV are as follows: (1) Sustained or recurrent infectious mononucleosis-like symptoms persistent for > 3 mo; (2) Increased amounts of EBV detected by Southern blot hybridization, EBER-positive cells in affected tissues or the peripheral blood, or $ \geq 10^{5.5} $ copies/µg of EBV-DNA in peripheral blood mononuclear cells (PBMCs); and (3) No evidence of previous immunological abnormalities or other recent infection that might explain the existing condition[2]. Our patient met the above three criteria, and was diagnosed with CAEBV. Cohen et al[3] have suggested that the diagnosis of CAEBV must be combined with lymphocytic infiltration and EBV in the tissues to ensure that the organ damage was attributed to EBV-infected lymphocytes. However, EBER was not detected by in situ hybridization of the biopsy samples taken from the left inguinal lymph node and bone marrow of the patient that we reported. In a study by Kawamoto et al[4], the median count of EBER-positive cells in the affected lesion of patients with CAEBV was 53 per high-power field, and 86.3% (44/51) of the cases showed $ \geq 10 $ EBER-positive cells per high-power field. Hence, in some patients, EBER may be negative in tissues, but high EBV-DNA load is detected in PBMCs.

There is currently no standard treatment for CAEBV. Sawada et al[5] suggested a sequential treatment strategy consisting of prednisolone, cyclosporine A, and etoposide, a so-called cooling therapy as the first step, and combination chemotherapies, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen. However, the conventional chemotherapy regimen for CAEBV is unsatisfactory, and the resolution rates of CAEBV disease activity by chemotherapy are very low, approximately 10%[1]. The only effective treatment for this disease is HSCT. The high load of EBV-DNA before HSCT may lead to a high risk of recurrence after HSCT. Therefore, more effective chemotherapy could improve outcome and reduce EBV-DNA load of CAEBV patients[1].

PEG-aspargase, a pegylated form of L-asparaginase, has a prolonged circulation time and diminished immunogenicity compared with native L-asparaginase[6].
Therefore, PEG-asparagase requires less frequent administration and has better treatment efficacy compared to L-asparaginase. Multiple studies on NK/T-cell lymphoma have found that chemotherapy regimens containing PEG-asparagase significantly reduce the load of EBV-DNA while treating lymphoma, and the reduced load of EBV-DNA after treatment suggests longer survival[7,8]. Our study on refractory relapsed EBV-HLH found that the L-DEP regimen (PEG-asparagase and DEP combination therapy) can reduce EBV-DNA load while effectively controlling HLH-induced fever and organ dysfunction[9]. Therefore, it can be speculated that PEG-asparagase may have an “eliminating” effect on EBV infection. In the present patient, EBV was eradicated after treatment with PEG-asparagase, and EBV-DNA remained negative for more than 6 mo.

The possible mechanisms underlying this may include the following aspects. First, PEG-asparagase accelerates apoptosis in EBV-positive T and NK cells, which has been confirmed in in vitro experiments. Ando et al[10] have reported specific antitumor activity of L-asparaginase against NK-cell tumors in vitro. Jinta et al[11] confirmed that L-asparaginase decreased the number of living cells in all examined EBV-positive cell lines in a dose-dependent manner, an effect not seen in the PBMCs. The “apoptosis” induced by L-asparaginase of EBV-infected T/NK cells may decompose asparagine, an essential amino acid for protein synthesis, such as the effect of treating NK/T cell lymphomas. Second, the expression of P-glycoprotein may be a cause of chemoresistance of EBV-positivity-related malignant disease. Yamaguchi et al[12] found that tumor cells from nine of 10 patients with Extranodal natural killer/T-cell lymphoma, an EBV-positive NK-LPD, were positive for P-glycoprotein. They also examined P-glycoprotein expression in ENKL by immunohistochemistry. Yoshimori et al[13] reported that EBV-infected T cells in EBV-T-LPDs expressed functional P-glycoprotein. The effect of PEG-asparagase is not influenced by P-glycoprotein. Therefore, compared to other chemotherapeutic drugs, PEG-asparagase, which is not a substrate of P-glycoprotein, can more effectively reduce EBV-positive T/NK cells.

Whether CAEBV patients are suitable for PEG-asparagase therapy remains unclear. Ando et al[10] found that the level of asparagine synthetase expression in NK-cell tumors was related to sensitivity and clinical response to L-asparaginase in ENKL. However, Jinta et al[11] suggested that the level of asparagine synthetase did not sufficiently determine the response to L-asparaginase on EBV-T/NK-LPDs. Therefore, which indicators reflect the response of patients to PEG-asparagase should be further explored. In addition, the mechanism of asparaginase therapy is asparagine depletion. However, the optimum target of asparaginase activity to achieve optimal asparagine depletion of PEG-asparagase still needs to be fully elucidated[14]. Therefore, further clinical study is required to confirm whether regimens containing PEG-asparagase are effective in treating CAEBV, who can respond to this treatment and how to achieve maximum therapeutic benefit.
CONCLUSION

PEG-asparagase may be effective in reducing the load of EBV-DNA in CAEBV patients. A chemotherapy regimen containing PEG-asparagase for treatment of CAEBV may warrant further study.

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