**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 65884

**Manuscript Type:** CASE REPORT

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

Song *et al*. CAEBV treated with PEG-aspargase

De-Li Song, Jing-Shi Wang, Lei-Lei Chen, Zhao Wang

**De-Li Song, Jing-Shi Wang, Lei-Lei Chen, Zhao Wang,** Department of Hematology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

**Author contributions:** Song DL and Chen LL took care of the patient; Song DL wrote this article; Wang JS and Wang Z guided article writing; all authors have read and approved the final version for submission.

**Supported by** National Natural Science Foundation of China, No. 81871633; Beijing Natural Science Foundation, No. 7181003; and Beijing Municipal Administration of Hospitals’ Ascent Plan, No. DFL20180101.

**Corresponding author: Zhao Wang, MD, Professor,** Department of Hematology, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong An Road, Xicheng District, Beijing 100050, China. wangzhao@ccmu.edu.cn

**Received:** March 29, 2021

**Revised:** May 8, 2021

**Accepted:** August 13, 2021

**Published online:**

**Abstract**

BACKGROUND

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 hematopoietic stem cell transplantation is the only effective treatment. We here report a CAEBV patient treated with PEG-aspargase, who achieved negative 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-aspargase 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-aspargase in this patient was excellent.

CONCLUSION

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

**Key Words:** Chronic active Epstein-Barr virus infection; PEG-aspargase; Chemotherapy; L-asparaginase; Case report

Song DL, Wang JS, Chen LL, Wang Z. Chronic active Epstein-Barr virus infection treated with PEG-aspargase: A case report. *World J Clin Cases* 2021; In press

**Core Tip:** Chronic active Epstein-Barr virus (EBV) infection may lead to fatal diseases, including EBV-positive lymphoproliferative disorders, lymphomas, and lymphohistiocytosis. We present a chronic active EBV (CAEBV) patient who was treated with PEG-aspargase and achieved decreased load of EBV-DNA. PEG-aspargase requires further investigation as a chemotherapy drug for CAEBV to reduce the load of EBV-DNA.

**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-aspargase treatment. PEG-aspargase 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 × 105 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 previous 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 diatmeter.

***Laboratory examinations***

Complete blood count revealed bicytopenia with a white blood cell count of 1.39 × 109/L, hemoglobin 14.2 gm/dL, and platelet count of 89 × 109/L. ALT and AST were elevated to 95 U/L and 173.2 U/L, respectively. EBV-DNA (whole blood) was 5.1 × 104 copies/mL and EBV-DNA (plasma) was 5.60 × 104 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 retured 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 ≥ 102.5 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 ≥ 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-aspargase 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-aspargase 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-aspargase 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-aspargase may have an “eliminating” effect on EBV infection. In the present patient, EBV was eradicated after treatment with PEG-aspargase, and EBV-DNA remained negative for more than 6 mo.

The possible mechanisms underlying this may include the following aspects. First, PEG-aspargase 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-aspargase is not influenced by P-glycoprotein. Therefore, compared to other chemotherapeutic drugs, PEG-aspargase, which is not a substrate of P-glycoprotein, can more effectively reduce EBV-positive T/NK cells.

Whether CAEBV patients are suitable for PEG-aspargase 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-aspargase 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-aspargase still needs to be fully elucidated[14]. Therefore, further clinical study is required to confirm whether regimens containing PEG-aspargase are effective in treating CAEBV, who can respond to this treatment and how to achieve maximum therapeutic benefit.

**CONCLUSION**

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

**REFERENCES**

1 **Arai A**. Advances in the Study of Chronic Active Epstein-Barr Virus Infection: Clinical Features Under the 2016 WHO Classification and Mechanisms of Development. *Front Pediatr* 2019; **7**: 14 [PMID: 30805320 DOI: 10.3389/fped.2019.00014]

2 **Kimura H**, Ito Y, Kawabe S, Gotoh K, Takahashi Y, Kojima S, Naoe T, Esaki S, Kikuta A, Sawada A, Kawa K, Ohshima K, Nakamura S. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. *Blood* 2012; **119**: 673-686 [PMID: 22096243 DOI: 10.1182/blood-2011-10-381921]

3 **Cohen JI**, Jaffe ES, Dale JK, Pittaluga S, Heslop HE, Rooney CM, Gottschalk S, Bollard CM, Rao VK, Marques A, Burbelo PD, Turk SP, Fulton R, Wayne AS, Little RF, Cairo MS, El-Mallawany NK, Fowler D, Sportes C, Bishop MR, Wilson W, Straus SE. Characterization and treatment of chronic active Epstein-Barr virus disease: a 28-year experience in the United States. *Blood* 2011; **117**: 5835-5849 [PMID: 21454450 DOI: 10.1182/blood-2010-11-316745]

4 **Kawamoto K**, Miyoshi H, Suzuki T, Kozai Y, Kato K, Miyahara M, Yujiri T, Choi I, Fujimaki K, Muta T, Kume M, Moriguchi S, Tamura S, Kato T, Tagawa H, Makiyama J, Kanisawa Y, Sasaki Y, Kurita D, Yamada K, Shimono J, Sone H, Takizawa J, Seto M, Kimura H, Ohshima K. A distinct subtype of Epstein-Barr virus-positive T/NK-cell lymphoproliferative disorder: adult patients with chronic active Epstein-Barr virus infection-like features. *Haematologica* 2018; **103**: 1018-1028 [PMID: 29242302 DOI: 10.3324/haematol.2017.174177]

5 **Sawada A**, Inoue M, Kawa K. How we treat chronic active Epstein-Barr virus infection. *Int J Hematol* 2017; **105**: 406-418 [PMID: 28210942 DOI: 10.1007/s12185-017-2192-6]

6 **van der Sluis IM**, Vrooman LM, Pieters R, Baruchel A, Escherich G, Goulden N, Mondelaers V, Sanchez de Toledo J, Rizzari C, Silverman LB, Whitlock JA. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica* 2016; **101**: 279-285 [PMID: 26928249 DOI: 10.3324/haematol.2015.137380]

7 **Wang JH**, Wang L, Liu CC, Xia ZJ, Huang HQ, Lin TY, Jiang WQ, Lu Y. Efficacy of combined gemcitabine, oxaliplatin and pegaspargase (P-gemox regimen) in patients with newly diagnosed advanced-stage or relapsed/refractory extranodal NK/T-cell lymphoma. *Oncotarget* 2016; **7**: 29092-29101 [PMID: 27093153 DOI: 10.18632/oncotarget.8647]

8 **Liu T**, Zhu F, Xiao Y, Li Q, Liu X, Yang K, Wu G, Zhang L. Pegaspargase, gemcitabine, dexamethasone, and cisplatin (P-GDP) combined chemotherapy is effective for newly diagnosed extranodal NK/T-cell lymphoma: a retrospective study. *Cancer Manag Res* 2018; **10**: 5061-5069 [PMID: 30464606 DOI: 10.2147/CMAR.S179567]

9 **Wang J**, Wang Y, Wu L, Zhang J, Lai W, Wang Z. PEG-aspargase and DEP regimen combination therapy for refractory Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *J Hematol Oncol* 2016; **9**: 84 [PMID: 27613189 DOI: 10.1186/s13045-016-0317-7]

10 **Ando M**, Sugimoto K, Kitoh T, Sasaki M, Mukai K, Ando J, Egashira M, Schuster SM, Oshimi K. Selective apoptosis of natural killer-cell tumours by l-asparaginase. *Br J Haematol* 2005; **130**: 860-868 [PMID: 16156856 DOI: 10.1111/j.1365-2141.2005.05694.x]

11 **Jinta M**, Imadome K, Komatsu H, Yoshimori M, Kurata M, Fujiwara S, Miura O, Arai A. L-Asparaginase monotherapy for EBV-positive T/NK lymphoproliferative diseases: A pilot Study. *J Med Dent Sci* 2015; **62**: 1-9 [PMID: 26111530 DOI: 10.11480/620101]

12 **Yamaguchi M**, Kita K, Miwa H, Nishii K, Oka K, Ohno T, Shirakawa S, Fukumoto M. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer* 1995; **76**: 2351-2356 [PMID: 8635042 DOI: 10.1002/1097-0142(19951201)76:11<2351::aid-cncr2820761125>3.0.co;2-1]

13 **Yoshimori M**, Takada H, Imadome K, Kurata M, Yamamoto K, Koyama T, Shimizu N, Fujiwara S, Miura O, Arai A. P-glycoprotein is expressed and causes resistance to chemotherapy in EBV-positive T-cell lymphoproliferative diseases. *Cancer Med* 2015; **4**: 1494-1504 [PMID: 26153782 DOI: 10.1002/cam4.494]

14 **Heo YA**, Syed YY, Keam SJ. Pegaspargase: A Review in Acute Lymphoblastic Leukaemia. *Drugs* 2019; **79**: 767-777 [PMID: 31030380 DOI: 10.1007/s40265-019-01120-1]

**Footnotes**

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** March 29, 2021

**First decision:** April 28, 2021

**Article in press:**

**Specialty type:** Hematology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Renzo ND **S-Editor:** Liu M **L-Editor: P-Editor:**

**Figure Legends**



**Figure 1 Graph of the Epstein-Barr virus-DNA change trend of the patient after PEG-aspargase treatment.** There is a significant decrease after the first PEG-aspargase treatment. After the third course of treatment, the patient's Epstein-Barr virus-DNA (EBV-DNA) turned negative (according to our hospital test standard, EBV-DNA < 500 copies/mL is negative). The arrow indicates the time of for PEG-aspargase treatment. EBV: Epstein-Barr virus.