Antiretroviral therapy achieved metabolic complete remission of hepatic AIDS related Epstein-Barr virus-associated smooth muscle tumor

Takahide Ara1,2, Tomoyuki Endo1,2, Hideki Goto1,2, Kohei Kasahara1, Yuta Hasegawa1,2, Shota Yokoyama1,2, Souichi Shiratori1, Masao Nakagawa1, Ken Kuwahara3, Emi Takakuwa3, Satoshi Hashino2,4, Takanori Teshima1,2

1Department of Hematology, Hokkaido University Faculty of Medicine, Sapporo, Japan
2HIV infection Medical Support Center, Hokkaido University Hospital, Sapporo, Japan
3Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan
4Hokkaido University Health Care Center, Sapporo, Japan

Abstract
Epstein-Barr virus-associated smooth muscle tumor (EBV-SMT) is a rare mesenchymal tumor which occurs in immunocompromised patients. The immune status is an important factor in the treatment of EBV-SMTs, but the efficacy of antiretroviral therapy (ART) is not elucidated in acquired immune deficiency syndrome (AIDS) related EBV-SMTs. Here, we report the first successful case of a 29-year-old man with hepatic AIDS related EBV-SMT treated with ART solely. Positron emission tomography scan was useful for the evaluation of disease status. Recent advances in ART that enables to restore patient's immune status rapidly may change the treatment strategy in AIDS related EBV-SMT.

Keywords
antiretroviral therapy, Epstein-Barr virus, smooth muscle tumors, acquired immune deficiency syndrome

Introduction
Epstein-Barr virus (EBV) has been linked to the development of multiple malignancies including nasopharyngeal carcinoma and hematological malignancies. EBV-associated smooth muscle tumors (EBV-SMTs) are recently recognized a distinctive group of mesenchymal tumors that develop exclusively in immunocompromised patients such as organ transplant recipients and patients with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) [1]. Since EBV-SMTs are resistant to cytotoxic chemotherapy, surgical resection has been the main therapeutic approach [2]. However, recent several reports have demonstrated that the reduction of immunosuppressants is effective for EBV-associated post-transplant lymphoproliferative disorders [3], suggesting that restoration of immune function is important in the treatment of immunocompromised patients with EBV-associated tumors. In fact, there are some cases that combination with surgical resection and antiretroviral therapy (ART) achieved complete remission of
AIDS related EBV-SMTs [4,5]. However, the therapeutic effect of ART alone is still unclear. Here we report a successful case of a 29-year-old AIDS patient with unifocal hepatic EBV-SMT solely treated with ART. To our best knowledge, this is the first case that ART achieved complete remission of EBV-SMT without surgical resection.

Case report

A 29-year-old man, having sex with men, visited our hospital with a history of persisting fever for 4 months. He was diagnosed with HIV by Western blotting, and had high HIV viral load (939,000 copies/mL) and low CD4 positive T cell count (43 cells/μL). Serum EBV viral capsid antigen (VCA) IgG and EBV nuclear antigen (EBNA) was positive, whereas VCA IgM was negative, indicating that he had already infected with EBV. One month after his first visit, he complained with abdominal pain. On physical examination, he had a low grade fever and lower right abdominal pain with rebound tenderness. Contrast enhanced computer tomography scan demonstrated two hypodense lesions in hepatic segment III and VIII, in addition to the enlarged appendix. At this time, laboratory data demonstrated that his liver function was normal. Concurrently, his previous exposure to Hepatitis B virus (HBV) infection was confirmed by the negativity of HB surface antigen and HBV-DNA and the positivity of HB surface antibody and HB core antibody. On the other hand, Hepatitis C virus antibody was negative. He was diagnosed with appendicitis and treated with ceftriaxone 2 g/day for a week. In addition, upper gastrointestinal endoscopy showed mild esophageal candidiasis and he was diagnosed with AIDS. His esophageal candidiasis was treated with fluconazole 200 mg/day for 2 weeks. Abdominal ultrasound scan showed the well-defined hypoechoic area in the liver segment III and the well-defined hyperechoic area in segment VIII. We then performed the ultrasound-guided fine needle aspiration biopsy of these lesions. Both of these specimens were parenchymal cells, not abscesses. Histopathological examination of the hepatic lesion in segment III showed interlacing fascicles composed of short spindle cells with slightly plump nucleus. Ki-67 proliferation index was 10% and there were neither mitosis nor necrosis. Immunohistochemically, the neoplastic cells exhibited positivity for alfa-smooth muscle actin (alfa-SMA), desmin, and EBNA2, whereas the stainings for cytokeratin7, CD34, kit, S-100 and latent membrane protein 1(LMP1) were negative. Moreover, in situ hybridization was positive for EBV encoded small RNA (EBER) (Figure 1). Based on these findings, he was diagnosed with AIDS related EBV-SMT. On the other hand, the lesion in segment VIII was diagnosed as perisinusoidal fibrosis. We discussed with him the possibility of surgical resection, but he refused the surgery. Since he had already initiated ART including Dolutegravir, Abacavir, and Lamivudine without any side effects and had only a single lesion without any symptoms, we decided to continue ART without surgical resection of the tumor. One year after starting ART, HIV RNA level had been suppressed below 20 copies/mL and CD4 positive T cell count had recovered to 347 cells/μL without any new symptoms. Hepatic EBV-SMT was regularly evaluated by abdominal magnetic resonance imaging (MRI) every 3 months and annual positron emission tomography (PET). MRI demonstrated that the tumor size at 19 months after

**Figure 1.** Histological findings of hepatic lesions in segment III. Hematoxylin and eosin stained section showed interlacing fascicles composed of spindle cells with slight plump nucleus (A). Immunohistochemically, the neoplastic cells exhibited positivity for alfa-SMA (B), desmin (C), EBNA2 (D), whereas the staining for LMP1 was negative (E). Moreover, in situ hybridization was positive for EBER (F). Bar, 50μm.
starting ART was decreased compared to that at 3 months after starting ART (22 mm–10 mm in diameter) (Figure 2A and 2B). On the other hand, PET scan demonstrated that the tumor had high 18F-fluorodeoxyglucose (FDG) uptake (standardized uptake value max=4.657) at 3 months after starting ART. Interestingly, PET scan at 19 months after starting ART showed the disappearance of FDG uptake of the tumor, indicating that he achieved metabolic complete remission of AIDS-related EBV-SMT by ART without any other treatment (Figure 2C and 2D).

Discussion

The development of SMT in immunocompromised patient was initially described 50 years ago [6]. In 1995, McClain et al. reported that SMT in AIDS patients was associated with EBV infection [7]. Over the last 25 years, the incidence of AIDS related EBV-SMTs increased significantly because this association became well known. However, causative role of EBV infection on EBV-SMTs remains to be investigated.

Previous reports indicate that EBV-SMTs tend to be multifocal with propensity to arise in virtually any anatomical location. Interestingly, studies of clonality analysis in patients with multifocal EBV-SMTs demonstrated the presence of different clones in tumors from different locations, suggesting the simultaneous development of multiple clones rather than metastases [1,7]. The central nerve system was a common site in AIDS related EBV-SMTs, whereas liver was less frequent than the patients with post-transplant EBV-SMTs [2]. The patients with EBV-SMTs may present with various symptoms based on tumor location, while they may be asymptomatic and detected incidentally by imaging studies like our case. Furthermore, the real time quantitative polymerase chain reaction for EBV DNA is not highly sensitive and not a useful diagnostic tool for AIDS related EBV-SMTs [4,5]. We used PET scan for systemic evaluation and treatment response evaluation of AIDS related EBV-SMTs and he achieved metabolic complete remission. Although the effectiveness of PET scan for identifying of uterine

Table 1. Clinical Data for the patients treating with ART alone for AIDS related EBV-SMTs.

| Reference | Age(yr)/Sex | Tumor Site(s) | HIV viral load copies/mL | CD4 cell count, cells/μL | ART regimen | CD4 cell count recovery, cells/μL | The reasons for ART alone | Outcome |
|-----------|-------------|---------------|--------------------------|--------------------------|-------------|-----------------------------------|--------------------------|---------|
| (12)      | 7/F         | Colon (single) and lungs(multiple)* | >750,000 | 1 | d4T/3TC/IDV | Yes, 132 | Poor PS | No remission but alive for 3 years |
| (13)      | 27/M        | Liver (multiple) | NA | 39 | TFV/3TC/EFV | No, 16 | Poor PS | Patient died with no remission |
| (14)      | 34/M        | Arm (single)   | 74,129 | 1 | TFV/3TC/NVP | NA | NA | Multiple liver metastasis were found 5 months later |
| Current Study | 29/M    | Liver (single) | 939,000 | 43 | DTG/ABC/3TC | Yes, 347 | Single Lesion | Metabolic complete remission for 19 months |

ABC, abacavir; ART, antiretroviral therapy; d4T, stavudine; DTG, dolutegravir; EFV, efavirenz; IDV, indinavir; NA, not available; NVP, nevirapine; PS, performance status; TFV, tenofovir; 3TC, lamivudine.

*no pathologic confirmation.
smooth muscle tumor grade has reported [8], there were few reports of its use in EBV-SMTs [9,10] and none in AIDS related EBV-SMTs. Since EBV-SMTs are often systemic but asymptomatic, PET scan may be useful for screening of HIV related tumors including EBV-SMTs.

Surgical resection is the main therapeutic approach to relieve symptoms associated with the tumors [1,11], but complete resection is often limited by the anatomical location and multifocal nature of the tumors. Given that post-transplant lymphoproliferative disorder can be led to remission by reducing immunosuppressants, immune restoration by ART may be effective in AIDS related EBV-SMTs. While some cases reported that combination with surgical resection and ART achieved complete remission in AIDS related EBV-SMTs [4,5], case reports of ART alone were extremely rare. Previous case reports of ART alone for AIDS related EBV-SMTs are summarized in Table 1 [12-14]. Unfortunately, it is difficult to evaluate the effectiveness of ART alone for AIDS related EBV-SMTs from these cases. Moreover, another interesting issue is whether ART has a direct effect on EBV. In fact, some of antiretroviral drugs had been reported to have anti-EBV activity [15], but there were no reports of the anti-EBV activity of the drugs contained in the ART regimen used in this case. Moreover, Gianella et al. demonstrated that EBV-DNA in blood remained positive in almost all the patients receiving ART [16]. Based on these studies, we believe that ART had little direct effect on EBV in this case. Recent advances in antiretroviral drugs have made it possible to achieve rapid immune restoration [17,18], and the cause of death in AIDS related EBV-SMTs patients was more often to be attributed to immunosuppression-related but not with tumor-related [19]. Therefore, even in the patients with AIDS related EBV-SMTs who are difficult to surgical resection due to poor general condition, rapid immune restoration with ART may improve the tumor and survival.

**Conclusion**

Although EBV-SMTs are relatively rare neoplasm, this entity should be included one of the differential diagnoses in HIV-infected patients with single or multiple tumor lesions. Surgical resection is the main therapeutic approach, but this case suggests that immune restoration by ART can improve AIDS related EBV-SMTs. Moreover, PET scan may be useful for the evaluation of systemic screening and therapeutic response in AIDS related EBV-SMT patients. ART is an important treatment option in patients with AIDS related EBV-SMTs who are not eligible for or decline surgical resection because of anatomical location or poor clinical condition.

**Acknowledgements**

The authors would like to thank to the staff of HIV Infection Medical Support Center, Hokkaido University Hospital for their support.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**

Takahide Ara  <https://orcid.org/0000-0001-9609-3202>

**References**

1. Deyrup AT, Lee VK, Hill CE, et al. Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. *Am J Surg Pathol* 2006; 30(1):75–82.
2. Hussein K, Rath B, Ludewig B, et al. Clinicopathological characteristics of different types of immunodeficiency-associated smooth muscle tumours. *Eur J Cancer* 2014; 50(14):2417–2424.
3. Dierickx D, Habermann TM. Post-Transplantation Lymphoproliferative Disorders in Adults. *N Engl J Med* 2018; 378(6):549–562.
4. Suankratay C, Shuangshoti S, Mutirangura A, et al. Epstein-Barr virus infection-associated smooth-muscle tumors in AIDS patients: a largest case (series). *Intern Med* 2014; 53(20):2391–2396.
5. Issarachaikul R, Shuangshoti S, Suankratay C. Epstein-Barr virus-associated smooth muscle tumors in AIDS patients: a clinical and pathologic and molecular analysis of 29 tumors. *Clin Infect Dis* 2005; 40(10):1521–1528.
6. Pritzker KP, Huang SN, Marshall KG. Malignant tumours following immunosuppressive therapy. *Can Med Assoc J* 1970; 103(13):1362–1365.
7. McClain KL, Leach CT, Jenson HB, et al. Association of Epstein-Barr virus with leiomyosarcomas in young people with AIDS. *N Engl J Med* 1995; 332(1):12–18.
8. Yoshida Y, Kurokawa T, Sawamura Y, et al. Comparison of 18F-FDG PET and MRI in assessment of uterine smooth muscle tumors. *J Nucl Med* 2008; 49(5):708–712.
9. Garg I, Baladron Zanetti MJ, Yasir S, et al. PET/CT in an 8-year-old girl with Epstein-Barr virus-associated smooth muscle tumor. *Clin Nucl Med* 2017; 42(10):770–772.
10. Liu Y, Chintalapati S, Dietz R, et al. EBV-associated smooth muscle tumor of uncertain biologic behavior after heart transplantation in a pediatric patient: case report. *J Gastrointest Oncol* 2017; 8(1):E21–E25.
11. Yin X, Wu T, Yan Y, et al. Treatment for leiomyosarcoma and leiomyoma in children with HIV infection. *Cochrane Database Syst Rev* 2010; 5:CD007665.
12. Molle ZL, Bornemann P, Desai N, et al. Endoscopic features of intestinal smooth muscle tumor in a child with AIDS. *Dig Dis Sci* 1999; 44(5):910–915.

13. Zhou Q, Wu F, Guo Y, et al. Epstein-Barr virus associated hepatic smooth muscle tumor in a patient with acquired immunodeficiency syndrome: a case report. *Medicine (Baltimore)* 2020; 99(18):e19930.

14. Reddy MP, Mosenthal WP, Lee CS, et al. Rare Epstein-Barr virus-associated smooth muscle tumor in a patient with AIDS: a case report. *JBJS Case Connect* 2020; 10(1):e0210.

15. Kerr JR. Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors. *J Clin Pathol* 2019; 72(10):651–658.

16. Gianella S, Moser C, Vitmiov A, et al. Presence of asymptomatic cytomegalovirus and Epstein–Barr virus DNA in blood of persons with HIV starting antiretroviral therapy is associated with non-AIDS clinical events. *AIDS* 2020; 34(6):849–857.

17. Powderly WG, Landay A, Lederman MM. Recovery of the immune system with antiretroviral therapy: the end of opportunism? *JAMA* 1998; 280(1):72–77.

18. Deeks SG, Overbaugh J, Phillips A, et al. HIV infection. *Nat Rev Dis Primers* 2015; 1:15035.

19. Purgina B, Rao UN, Miettinen M, et al. AIDS-related EBV-associated smooth muscle tumors: a review of 64 published cases. *Patholog Res Int* 2011; 2011:561548.