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Case Report

Clinical Course of a Rare Epstein-Barr Virus-Associated Smooth Muscle Tumor and Its Genomic Analysis

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Keywords
Epstein-Barr virus · Smooth muscle tumor · Immunosuppressant

Abstract
Epstein-Barr virus (EBV) can rarely induce smooth muscle tumors (SMTs). A 20-year-old female patient underwent kidney transplantation for renal failure. Since then, she has been treated with immunosuppressants, including a calcineurin inhibitor, tacrolimus, and prednisolone, owing to the immunological rejection. Three years later, she developed large liver tumors (diameter >5 cm) and multiple small lung tumors that were identified as EBV-SMTs based on the results of liver biopsy/histopathology. No intervention was performed except for the addition of a mammalian target of the rapamycin inhibitor, everolimus, which inhibits both immune reaction and SMT growth. Finally, after 8 years, the transplanted kidney became nonfunctional, and immunosuppressant administration became unnecessary as urinary dialysis was started. Under these circumstances, SMT growth was observed despite the absence of immunosuppressant administration. Three months after the cessation of the immunosuppressants, EBV-SMTs in the liver and lungs shrank slightly. To the best of our knowledge, this is the first report on the genomic profile of this rare tumor. The clinical course of our patient indicates that EBV can induce SMTs, and immunological suppression of EBV may inhibit the activity of these tumors.

Introduction

Soft tissue sarcomas (STSs) are rare, heterogeneous tumors that account for 1% of all malignancies [1]. In particular, smooth muscle tumors (SMTs) or leiomyosarcomas account for 12% of all STSs [1]. These tumors are moderately sensitive to chemotherapy, including

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doxorubicin and ifosfamide [1]. Moreover, compared with leiomyosarcomas occurring at other sites, those occurring in the uterus are more sensitive to chemotherapy [2, 3]. Notably, the clinical biomarkers identified in recent studies on STS were identical, and they were as follows: TP53, RB1, CDKN2A, MDM2, FRS, and CDK4 [4, 5]. However, currently, there are no established therapeutic agents targeting these molecules in cases of STS. Epstein-Barr virus (EBV) infection can increase the risk of cancers, such as gastric cancer, nasopharyngeal cancer, and Burkett lymphoma [6]. Additionally, in rare cases, it can cause SMTs [6–8]. We report a rare case of a young female patient with EBV-SMT who received a living-donor kidney transplant. In a previous study, the incidence of EBV-SMT was estimated to be 0.06% [9]. Moreover, it has been reported that EBV-SMT commonly develops in immunocompromised patients, such as posttransplantation patients [10, 11]. However, the selection of an appropriate therapeutic agent for EBV-SMT is difficult given that immunosuppressants are essential for kidney transplant patients to preserve their renal function. To the best of our knowledge, there are no established treatment options for EBV-SMT. Chemotherapy and radiotherapy have been used, but they provide no clinical benefits [12]. Recently, the mammalian target of the rapamycin (mTOR) inhibitor has attracted public attention as a potential therapeutic agent against EBV-SMT [11]. We expected that the administration of the mTOR inhibitor everolimus (EL) would inhibit both immune reaction and SMT growth [11–13]. In this report, we present the clinical course and genomic analysis results of a patient with EBV-SMT to identify potential molecular targets for treating EBV-SMT.

Case Report

A 20-year-old female patient who underwent kidney transplant surgery after she was diagnosed with focal segmental glomerulosclerosis in November 2015 experienced upper abdominal pain and was referred to our department in 2018 (Fig. 1). Her computed tomography (CT) scan revealed large liver tumors (>5 cm in diameter), multiple small lung tumors, and a left ovarian tumor (Fig. 1). The results of gallium scintigraphy performed in 2018 revealed the presence of gallium accumulation throughout the liver (Fig. 1). This could be attributed to the persistent inflammation caused by EBV-induced posttransplant hepatitis. Subsequently, histopathological examination of a liver biopsy specimen revealed spindle cell proliferation with overlapping fascicles; therefore, the tumor was considered to be one of the types of sarcoma (Fig. 1, 2a, b). Further, we performed immunohistochemistry of the liver specimen, and the results were positive for markers such as smooth muscle actin and desmin (Fig. 2c, d). Moreover, the result of in situ hybridization for EBV-encoded small RNA was positive (Fig. 2e). Thus, the tumor was identified as an EBV-SMT. The Ki-67 index was found to be low (2–5%) (Fig. 2f), and this tumor exhibited very low aggressive properties. In addition, as the patient was receiving immunosuppressants and had insufficient renal function for excreting cytotoxic drugs, the patient was determined to be unsuitable for treatment with cytotoxic drugs, such as doxorubicin, which is commonly administered as the first-line treatment for unresectable STS [14]. In contrast to the Ki-67 index, positron-emission CT scan revealed that the standardized uptake value (SUV) was relatively higher (SUVmax: 4.3–18.3) in some parts of the liver. Moreover, we found that this value did not completely correspond to the lesions indicated by CT scans. We considered that the lesions with higher SUV values corresponded to the sites with active EBV infection. Accordingly, we added EL (2 mg/day), considering that EL could have both immunosuppressive and antitumor effects, and decreased a simple immunosuppressant, tacrolimus, from 5 mg/day to 3 mg/day (Fig. 1). Further, the genome of her SMT was

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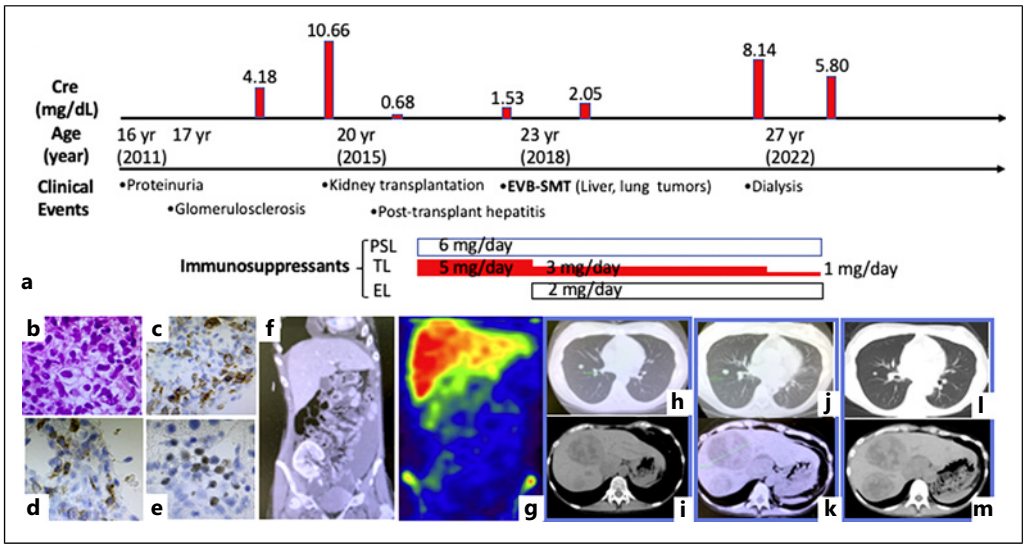

Fig. 1. a An overview of the clinical course. Immunosuppressants: tacrolimus (TL), prednisolone (PSL), and everolimus (EL). Hematoxylin-eosin staining (**b**), immunohistochemistry for CD8 (**c**) and CD4 (**d**), and in situ hybridization for Epstein-Barr virus-encoded small RNA (**e**) of the liver biopsy specimen after kidney transplantation conducted in 2015. CT (**f**) and Ga scintigraphy (**g**) images showing posttransplant hepatitis in 2015. CT images of the patient with EVB-SMT in 2018 (**h**, **i**), 2022 (**j**, **k**), and after dialysis (**l**, **m**).

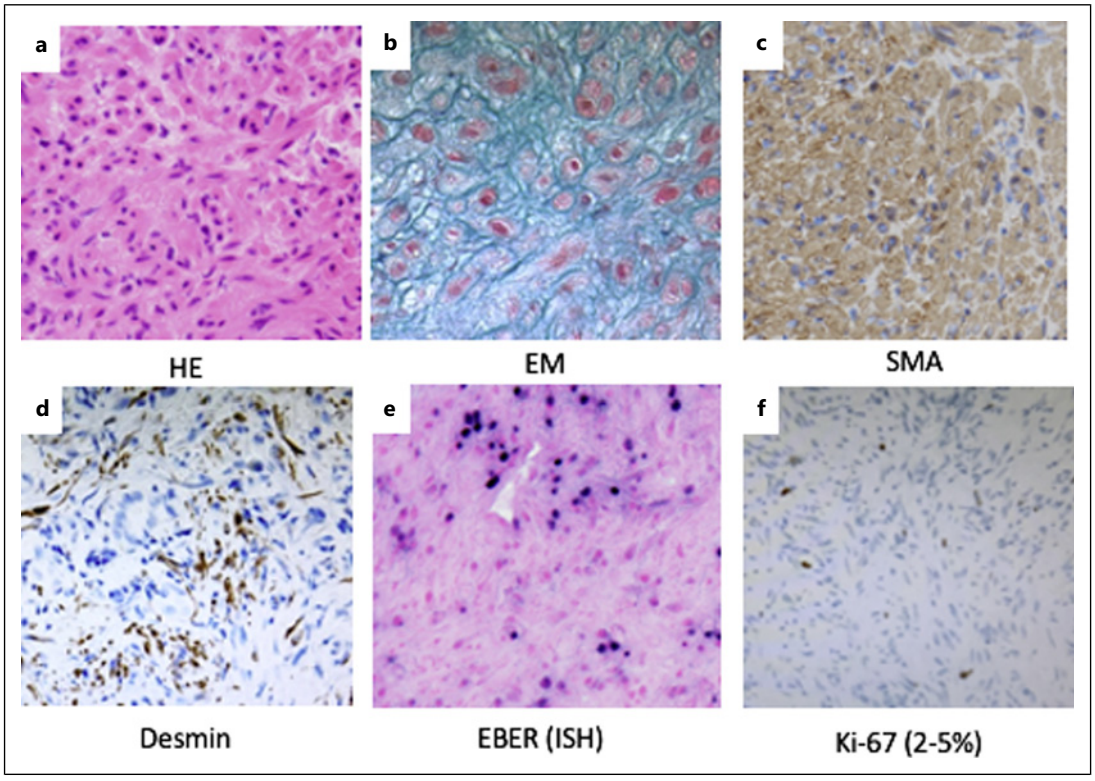

Fig. 2. Pathological analyses of the liver tumor. **a** Hematoxylin-eosin staining (HE). **b** Elastica-Masson staining (EM). **c** Immunohistochemistry (IHC) with an anti-SMA antibody. **d** IHC with an anti-desmin antibody. **e** In situ hybridization (ISH) of Epstein-Barr virus-encoded small RNA (EBER). **f** IHC with an anti-Ki-67 antibody.

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Table 1. Results of cancer genome profiling of EBV-SMT in this case

Microsatellites stable
TMB low: 1.26 Muts/Mb
HHV-4 (human herpesvirus 4) = EBV
BRD4: p.T210S (0.475)
EZH2: p.K634T (0.461)
KEAP1: p.T543M (0.505)
LTK: p.W707* (0.541)
LTK: p.S183F (0.516)
MED12: p.R1989H (0.492)
NOTCH3: p.R1175W (0.493)
RICTOR: p.I518T (0.510)
TEK: p.P304L (0.489)
WT1: p.P804A (0.507): exon 10

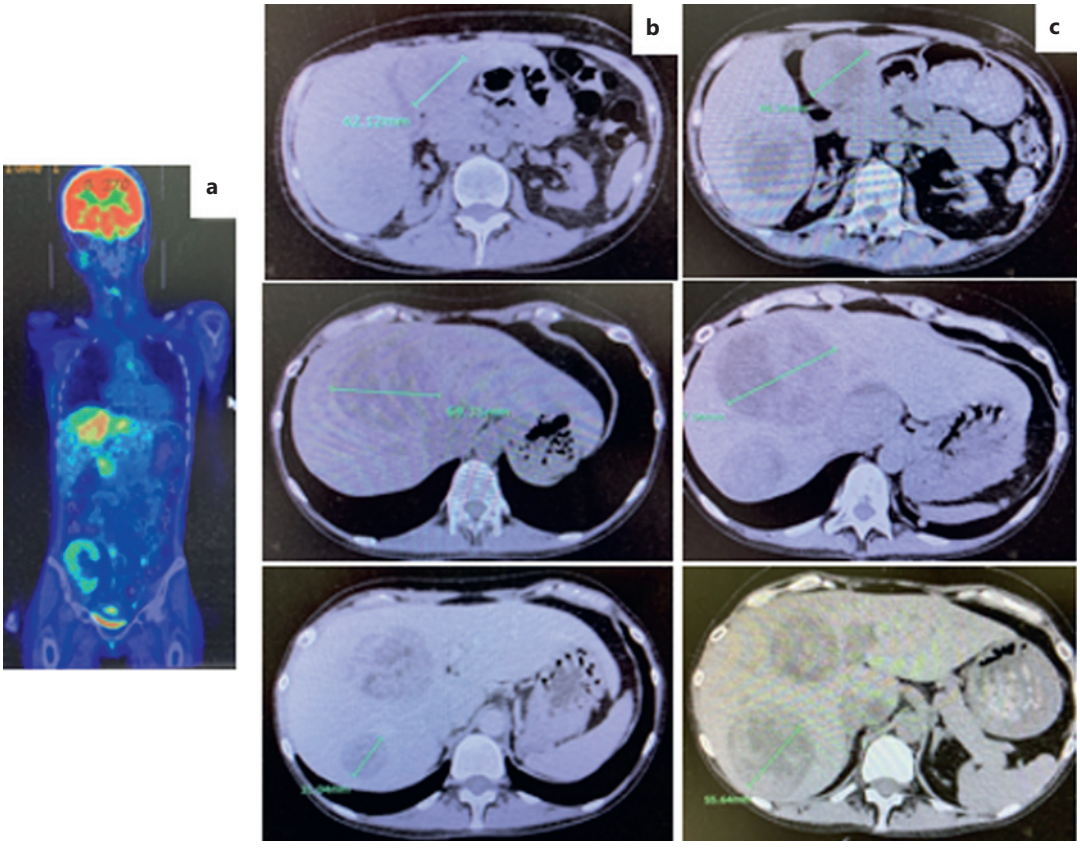

Fig. 3. Changes in CT images of the EBV-SMTs in the lung and liver. **a** PET-CT image in July 2018. **b** CT images in July 2018. **c** CT images in January 2022.

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analyzed using the FoundationOne® CDx Cancer Genomic Profile (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan). The data obtained from the analysis indicated that the tumor was microsatellite-stable, had a low tumor mutation burden (1.26 mutations/megabase), and exhibited 10 gene alterations, including those for enhancer of zeste homolog 2 (EZH2), a histone methyltransferase (p.K634T) [15], Wilms tumor 1 (WT1), and a tumor suppressor gene (p.P804A) [16] (Table 1). However, the pathogenesis of these gene alterations remained unknown. These data indicate that immune checkpoint inhibitors and agents for molecular targeting have been unidentified to date. Moreover, the data revealed the genomic DNA of EBV (also known as human herpesvirus 4). Based on the findings of CT performed during the follow-up in 2022, we noted a slight enlargement of the liver and lung tumors (the average percentage of the size of three targets compared with the baseline: 125.5%) compared to the previous 4 years. Finally, her creatinine level increased to 8.14 mL/min, and the transplanted kidney deteriorated. Since then, the patient has been undergoing maintenance dialyses. The systemic condition of the patient was found to be stable under these circumstances. Therefore, an immunosuppressant administration became unnecessary, and we continued monitoring SMT growth without administering immunosuppressants. Three months later, the liver and lung tumors had slightly diminished in size (Fig. 3).

Discussion

In the present case, the most important issues were the choice of treatment and determining what would happen if immunosuppressive drugs were discontinued. Although the standard treatment for EBV-SMT remains unestablished, it is considered that its treatment involves a combination of decreasing immunosuppressant doses, chemotherapy, surgical resection, mTOR inhibitor administration, and prophylactic or postonset administration of antiviral agents (including ganciclovir, valganciclovir, acyclovir, and famciclovir) [9, 17, 18]. In a previous study of patients with EBV-SMT who received solid organ transplants from December 1970 to January 2018 [9], immunosuppressant dose reduction was performed in 63% of the adult patients (32/51; age ≥17 years), chemotherapy in 8% patients (4/51), surgery in 59% patients (30/51), administration of the mTOR inhibitor sirolimus – an original form of EL – in 29% patients (15/51), prophylactic administration of antiviral agents in 10% patients (5/51), and postonset administration of antiviral agents in 16% patients (8/51). Subsequently, 29% (15/51) of the patients experienced a recurrence of EBV-SMT, whereas 25% (13/51) patients did not; further, 14% (7/51) of the patients died due to EBV-SMT, 24% (12/51) died of other causes, and 8% (4/51) deaths were unreported. EBV-SMT is considered a slow-growing tumor associated with a 1-year overall survival rate of 50–76% [12]. The first-line therapy for this tumor is the reduction in the dose of immunosuppressants; however, in the present case, the patient was a renal transplant recipient; therefore, we opted for the administration of an mTOR inhibitor (EL). Notably, this agent is not only administered as an immunosuppressant but also as an antitumor agent for sarcoma.

Furthermore, a case study was performed at the Singapore General Hospital [19]. The study identified 16 patients who suffered from EBV-SMT after the kidney transplant surgery, and it compared patients who were switched to sirolimus-based therapy with those who continued cyclosporine-based immunosuppressants. The group that switched to sirolimus therapy had better outcomes than the group that continued receiving cyclosporine therapy. Based on these results, it is important to examine whether switching to an mTOR inhibitor has the potential for treating EBV-SMT after kidney transplantation.

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At present, our patient is being treated with kidney dialysis, and we are monitoring her SMT growth under these circumstances without immunosuppressants. We anticipated a spontaneous disappearance of EBV-SMT based on the recovery of her immune function.

Clinical trials on the benefits of EL in STS, including EBV-SMT, have been conducted only up to phase 2, and the disease control rate of patients with SMTs who were administered EL was 44.4% (4/9) [20]. This indicates that EL is effective in treating leiomyosarcoma. However, further studies are warranted to clarify whether an mTOR inhibitor is effective against EBV-SMT.

Cancer genome analyses indicated mutations in EZH2 (p.K634T) and WT1 (p.P804A) genes in our case of EBV-SMT. Moreover, it has been reported that activation mutations in EZH2 genes contribute to follicular lymphomas, and tazemetostat (an oral EZH2 inhibitor) is effective for treating patients with activation mutations in EZH2 [21]. However, the pathogenesis of the alterations in EZH2 (p.K634T) remains unknown. Furthermore, tazemetostat is not approved for treating SMT in Japan. A previous study reported that some alterations in WT1 are associated with steroid-resistant nephrotic syndrome (SRNS) [22]. Notably, SRNS is histologically characterized by focal segmental glomerulosclerosis, and the renal histology findings of our patient were similar to these histological characteristics. Moreover, WT1 gene alterations are detected in 10% of the patients with sporadic SRNS; however, these gene alterations are localized in exons 8 and 9 and intron 9. In contrast, the WT1 variant p.P804A is located in exon 10, and the relationship between this variant and SRNS remains unknown. Thus, cancer genome analyses of the rare EBV-SMT have never been conducted; to the best of our knowledge, this is the first report to analyze the same. The two major types of malignancies associated with EBV-induced tumors are Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) [23]. The upregulation of c-Myc in BL and the degradation of TP53 in NPC are both characteristic genetic signatures [6]. However, no genetic alterations in the c-Myc and TP53 pathways were detected in EBV-SMT in our patient. Thus, the carcinogenesis pathway of EBV-SMT may be different from those of BL and NPC. EBV-SMT has a relatively good prognosis, as indicated in our case; however, some of these tumors have poor prognoses. Thus, it is important to identify some target molecules of EBV-SMT in order to control this tumor effectively. In particular, patients receiving living kidney transplants are at a high risk of EBV infection because they need immunosuppressants. Thus, newer agents should be used safely in immunocompromised patients. EBV-SMTs can occur in patients receiving immunosuppressants. Some of these tumors have less aggressive properties and do not need to be treated with cytotoxic agents. As there are currently no molecularly targeted drugs for EBV-SMT identified using cancer genome analysis, careful monitoring may be most beneficial in some patients. If immunosuppressant discontinuation is possible, tumor shrinkage could be achieved, as reported previously [12]. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530383).

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Statement of Ethics

The Ethical Review Board of Akita University Hospital approved the Cancer genome analysis project (#2007). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Miyahara J., Shimazu K., Saito A., Saito M., Fukuda K., Yoshida T., Taguchi D., Shinozaki H., and Takahashi N. treated the patients. Nanjyo H. performed the histopathological analysis. Miyahara J. mainly described this manuscript. Shibata H. overviewed this study.

Data Availability Statement

All data of this study are included in this article. Further inquiries can be directed to the corresponding author.

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