

# EBV-associated hepatic smooth muscle tumor of uncertain biologic behavior after heart transplantation in a pediatric patient: case report

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**Abstract:** Epstein-Barr virus-associated smooth muscle tumor (EBV-SMT) is a rare neoplasm recognized in immunocompromised patients. There are less than 30 cases of EBV-SMT reported in pediatric population following solid organ transplantation. Herein, we report a case of an 8-year-old female who was incidentally noted to have multiple lesions in the liver 8 years after heart transplantation. The tumor was composed of a cellular proliferation of spindle-shaped cells with low mitotic activity. The diagnosis of EBV-SMT was confirmed by *in situ* hybridization for EBV-encoded small RNA (EBER) transcripts. Multiple additional lesions were detected by whole body positron emission tomography-computed tomography (PET-CT) scan 4 months after the initial finding of the hepatic lesions. Immunosuppression was switched to a mechanistic target of rapamycin (mTOR) inhibitor. We conclude that EBV-SMT should be included in the differential diagnoses in post-transplantation patients and further investigations should be performed to evaluate additional lesions.

**Keywords:** Epstein-Barr virus (EBV); smooth muscle tumor (SMT); pediatric; post transplantation; heart transplantation

Submitted Sep 13, 2016. Accepted for publication Oct 28, 2016.

doi: 10.21037/jgo.2016.12.05

View this article at: <http://dx.doi.org/10.21037/jgo.2016.12.05>

## Introduction

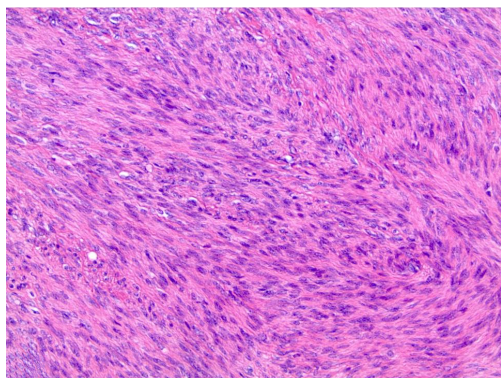
Epstein-Barr virus (EBV) has been involved in the pathogenesis of different types of malignancies. The most frequently reported EBV-associated malignancies are Burkitt lymphoma, Hodgkin lymphoma, post-transplant lymphoproliferative disorder (PTLD), and nasopharyngeal carcinoma (1-4). Recently, the strong relation of EBV to the development of smooth muscle tumors (SMTs) in immunocompromised patients has been increasingly recognized, mainly in post-transplantation and AIDS patients (5,6). EBV-SMTs are rare neoplasms, with less than 30 cases reported in post solid organ transplantation pediatric patients. They are usually multicentric and

exhibit a predilection to occur in sites that are unusual for conventional SMTs, most commonly the liver and lung (5,6).

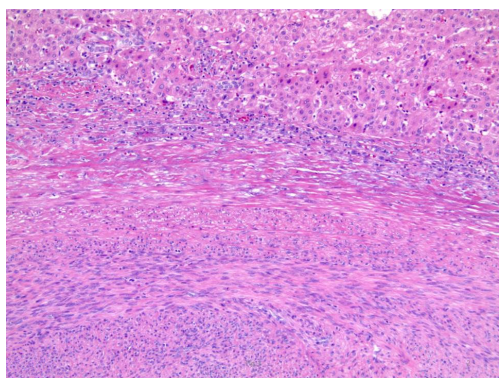
Herein we present a pediatric case of multiple EBV-SMTs identified first in the liver, and subsequently in the abdominal wall and mesentery, 8 years after heart transplantation.

## Case presentation

The patient is an 8-year-old female who received a heart transplant at 6 weeks of age for truncus arteriosus. Initial immunosuppression was achieved with mycophenolate mofetil and cyclosporine, and later changed to tacrolimus. EBV serology was not determined at the time of

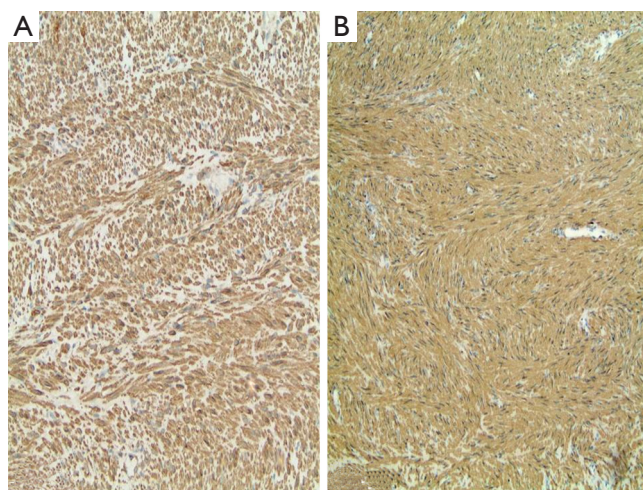


**Figure 1** Hepatic lesion showing interlacing fascicles of spindle cells with eosinophilic cytoplasm and elongated, blunt-ended nuclei with stippled chromatin. There are rare interspersed blood vessels within the fascicles, and mitotic figures are inconspicuous (H&E, 200 $\times$ ).



**Figure 2** A thin pseudocapsule separates the tumor and the adjacent liver with a lymphocytic reaction seen at the interface (H&E, 100 $\times$ ).

transplantation. Serial testing for EBV DNA by quantitative polymerase chain reaction (PCR) was performed on peripheral blood starting 3 years after the heart transplant (she presented with cough and fever), which showed amplification with up to 131,600 copies/mL. Her EBV viral load has been consistent since then. She developed acute abdominal pain and an appendiceal perforation was diagnosed 8 years post-transplant. Two liver masses were incidentally identified in the left and right hepatic lobes by abdominal computed tomography (CT) scan. Both appeared hypoechoic and individually measured up to 2.5 cm. Whole body positron emission tomography (PET)-CT scan was performed thereafter with no evidence of lymphadenopathy or other lesions. The mass in the right lobe was excised and

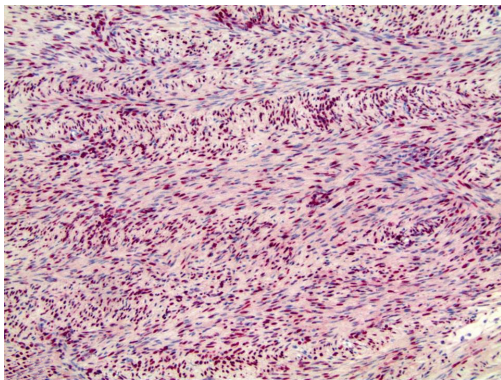


**Figure 3** The immunostains from the liver lesion with antibodies against smooth muscle actin (A) and HHF 35 (B). Tumor cells were diffusely positive for smooth muscle actin and HHF 35 (100 $\times$ ).

found to be well circumscribed, white, and firm on gross examination. The mass in the left lobe was not removed due to its deep location.

Histologically, the hepatic lesion was well demarcated from the adjacent liver parenchyma, and exhibited interlacing fascicles of spindle cells with eosinophilic cytoplasm and elongated, blunt-ended nuclei with stippled chromatin (Figure 1). Rare (less than 5%) primitive round cell component was identified. There was no evidence of necrosis or hemorrhage. Few small blood vessels were interspersed within the fascicles of spindle cells. Mitotic activity was less than 1 per 10 high power fields (HPF). Occasional lymphoid cells were seen at the junction between the tumor and adjacent liver parenchyma (Figure 2). Immunohistochemical (IHC) stains were performed to categorize the lesion. Smooth muscle actin (Figure 3A) and HHF 35 (Figure 3B) were positive, and desmin showed focal and weak equivocal staining consistent with smooth muscle origin. Ki67 showed only 1–2% of proliferative activity. EBV *in situ* hybridization was positive with a diffuse staining pattern (Figure 4), diagnostic of EBV infection. All these features were consistent with a diagnosis of EBV-SMT.

Whole body PET-CT scan performed 4 days after surgery showed a new intramuscular lesion in left anterior abdominal wall and a new left upper quadrant mesenteric metastatic mass (corresponding with an ill-defined 1.1 cm soft tissue density). Her EBV viral load 3 days



**Figure 4** The lesion showing a diffuse nuclear staining pattern with EBV *in situ* hybridization (200 $\times$ ). EBV, Epstein-Barr virus.

after surgery was 60,400 copies/mL by PCR. Immediately prior to surgery, the EBV viral load had been 16,000 copies/mL. Subsequent to the pathologic diagnosis, immunosuppression was switched from tacrolimus to the mechanistic target of rapamycin (mTOR) inhibitor, everolimus. Her EBV viral load after 2 months of therapy dropped to 39,900 copies/mL.

## Discussion

Post-transplant SMTs are a rare entity first described by Pritzker *et al.* in 1970 (7). Twenty-five years later, their association with EBV was described by Lee *et al.* (8). Although EBV-SMTs can be seen in different clinical settings in immunosuppressed patient, the majority of patients affected by EBV-SMT are (60%) posttransplant (9) and in HIV patients (10). Few cases associated with congenital immunodeficiency are also reported.

The cells of origin for EBV-SMT are thought to be derived from aberrant myogenous venous wall cells (6). As smooth muscle cells are not an usual target for EBV infection, immunosuppression may allow an abnormal entry of EBV into smooth muscle cells which could lead to a latent infection and subsequent neoplastic transformation altered by cytogenetic events (11). The underlying pathogenesis of EBV-related lymphomas has been well established, and found to be due to latent infection of B-lymphocytes through CD21 receptors with subsequent neoplastic proliferation. A similar mechanism was proposed for EBV-SMT, except CD21 receptors are not detected on smooth muscle cells. Fusion of smooth muscle cells with an infected B-lymphocyte prior to tumor proliferation

has therefore been postulated (12). EBV has two strains (types 1 and 2) with different biological behavior, which are distinguished by polymorphisms in *EBNA* genes. Type 1 was identified in immunocompetent patients, and type 2 was detected in EBV-SMT (6). The EBV genome has more than 100 genes, but only a few are relevant in transmission and replication, including the latent membrane proteins (LMP1, LMP2A, and LMP2b), EBV nuclear antigens (EBNA1, EBNA2, EBNA3A, EBNA3B and EBNA3C), and EBV early RNAs (EBER1, and EBER2).

Overexpression of *myc* was observed in some of the EBV-SMT, which results in cellular hyperplasia (13). The latent membrane proteins (LMP2A) of EBV have been shown to activate mTOR (14). Activation of AKT/mTOR pathway was demonstrated in post transplantation related SMTs (15).

EBV-SMTs in pediatric patients appear earlier (interval between transplantation and tumor: mean, 42 months; range, 1.5–84 months) compared with adult patients (mean, 73–114 months) (14,16,17), and have a higher mortality rate. It has been hypothesized that the greater risk of EBV infection in children is related to the shorter interval from transplantation to the diagnosis of EBV-SMT. The lack of prior EBV immunity may additionally contribute to the higher mortality rate in children (18). A review by Jossen *et al.* found a female predominance of EBV-SMTs following solid organ transplantation (21 female patients and only 8 male patients) (19). Most EBV-SMTs are multifocal at the time of diagnosis, with some occurring in sites with little smooth muscle, such as the dura, spleen, tonsils, and glottis (6,20). Their multifocal nature is thought to be the result of multiple independent infections, rather than metastasis (6). Despite the multifocal nature of the disease, EBV-SMTs mostly appear to be indolent and discovered by means of surveillance imaging studies, especially in the absence of intracranial involvement (8,21). However, fever, abdominal pain, anorexia, weight loss, graft dysfunction, neurologic symptoms and pulmonary symptoms has been reported (8,22–24). Our patient's liver lesions were discovered subsequent to work up for an appendiceal perforation.

Histologically, EBV-SMTs are typically well-differentiated SMTs that show mild nuclear pleomorphism with no or inconspicuous mitotic activity, and frequent round cells and prominent intratumoral T lymphocytes (6). Three histologic classifications are used to describe the EBV-SMTs: leiomyoma, tumor of uncertain malignant potential, and leiomyosarcoma (9). However, morphologic features have not been shown to predict the clinical and biological behaviors of EBV-SMTs, as some

well-differentiated tumors are lethal (8), while others classified as leiomyosarcomas follow a more benign clinical course (9,21,25,26). The location and immune status of the patient appear to play a more significant role in the clinical outcome. Therefore, it was proposed that all EBV-SMTs be designated as having uncertain malignant potential. EBV involvement using *in situ* hybridization for EBV-encoded small RNA (EBER) confirmed the diagnosis of EBV-SMT in all reports. Association with PTLD is common, ranging from 38–82% (18,19). Although PTLD was the working diagnosis at the time of appendiceal surgery, to date no PTLD has been identified in our patient.

The treatments for EBV-SMT in post-transplantation patients reported in the literature include surgical resection, reduction in immunosuppression, anti-viral therapies, and chemotherapy (27–29). Given the multifocal nature of the majority of these tumors, surgical resection can be challenging. However, multiple case reports suggested this approach as a first line treatment if surgical resection was possible (8,21). Reduction in immunosuppression to induce an immune response to the viral antigens is a commonly used approach. Sirolimus, a mTOR inhibitor, has shown efficacy in tumors with mTOR pathway activations (30). In addition, sirolimus also appears to prevent oncogenesis (31). In EBV-SMT, it is suggested that the AKT/mTOR pathway is activated and that inhibition of this pathway may have therapeutic benefits (14,32). Reports have described spontaneous tumor regression after conversion to sirolimus compared to those who remained on cyclosporine (17). In our patient, the right liver lobe lesion was redemonstrated and there was no significant reduction in size 3 months after starting treatment.

In conclusion, EBV-SMTs are rare tumors in pediatric patients, but should remain in the differential diagnosis in post-transplantation patients. The multifocal nature of these tumors and concurrence with PTLD should prompt evaluation for additional lesions after the diagnosis of EBV-SMT, as discovery of additional tumors may alter the treatment approach. Sirolimus, or a comparable mTOR inhibitor, in combination with surgical resection appears to be effective in the treatment of post-transplantation patients.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Informed Consent:* Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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**Cite this article as:** Liu Y, Chintalapati S, Dietz R, Raza AS, Wang J, Raza AS. EBV-associated hepatic smooth muscle tumor of uncertain biologic behavior after heart transplantation in a pediatric patient: case report. *J Gastrointest Oncol* 2017;8(1):E21-E25. doi: 10.21037/jgo.2016.12.05