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EBV-Associated Smooth Muscle Tumors In Immunocompromised Patients – A Case Series

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Abstract

BACKGROUND

Epstein-Barr Virus associated Smooth Muscle Tumor (EBV-SMT) is a rare oncological entity. However, there is an increasing incidence of EBV-SMTs, as the frequency of organ transplantation and immunosuppression grows. EBV-SMT diagnosis relies on histopathology and immunochemical staining to distinguish it from post-transplant lymphoproliferative disorder (PTLD). There is no clear consensus on the treatment of EBV-SMTs. However, surgical resection, chemotherapy, radiation therapy, and immunosuppression reduction have been explored with varying degrees of success.

CASE SUMMARY

Our case series includes six cases of EBV-SMTs across different age groups, with different treatment modalities, adding to the limited existing literature on this rare tumor. The median latency time between immunosuppression and disease diagnosis is four years. EBV-SMTs present with variable degrees of aggressiveness and seem to have worse clinical outcomes in patients with tumor multiplicity and worse immunocompetency.

CONCLUSION

It is imperative to continue building on this knowledge and keeping EBV-SMTs on the differential in immunocompromised individuals.

Key Words: Epstein Barr Virus; Smooth Muscle Tumors; Human Immunodeficiency Virus; EBV-Associated Smooth Muscle Tumors; Immunocompromised; Solid Organ Transplant; Orthotopic Heart Transplant; Orthotopic Liver Transplant; Living related Kidney transplant; Post-Transplant Lymphoproliferative Disorders

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Core Tip: Epstein-Barr Virus associated Smooth Muscle Tumor is a rare oncological entity. Only a handful of case series have shed light on the presence of EBV-SMT in individuals, most of whom are immunocompromised. EBV-SMT should not be confused with PTLD. Histopathology should help guide the diagnosis.

INTRODUCTION

Epstein-Barr virus associated smooth muscle tumor (EBV-SMT), first reported in 1970¹, is a rare oncological entity. Though EBV is present in 50-89% of children and >90% of adults worldwide, the virus often remains dormant until an individual becomes immunocompromised^{2,3}. EBV is better known for other malignancies including nasopharyngeal carcinomas and lymphomas but in a minority of cases, it can trigger the proliferation of smooth muscle cells, resulting in mesenchymal tumors termed EBV-SMT.

There are three different types of EBV-SMTs identified to date: 1) Post-transplant associated smooth muscle tumors (PT-SMT), 2) HIV associated smooth muscle tumors (HIV-SMT), and 3) Congenital immunodeficiency associated smooth muscle tumors (CI-SMT) such as in GATA2 and CARMIL2 deficiency⁴. EBV-SMTs can be encountered at any age, though it is more common in children^{5,6}. EBV-SMTs can arise in any organ system, however, they are most common in the liver, followed by the lungs, central nervous system (CNS), adrenal glands, and gastrointestinal tract^{7,8}. Unlike primary leiomyosarcomas where the histological grade is associated with disease severity, EBV-SMTs behave with variable severity, independent of their histological grade⁹. Clinical presentation is thus non-specific and depends on the location, size, and degree of organ involvement. EBV-SMTs can manifest either synchronously or metachronously in multiple organ systems and have a low propensity to metastasize^{7,8}.

PT-SMT can be confused with EBV associated post-transplant lymphoproliferative disorder (EBV-PTLD) as they are both caused by the same virus and occur in immunocompromised patients. Clinical presentation and radiographic findings cannot be used to tell the two entities apart. Instead, histopathology, immunohistochemistry, and EBV-encoded small RNA in situ hybridization (EBER ISH) are used to aid the diagnosis. Given its rarity, it is difficult to quantify the incidence of EBV-SMTs, however, it is estimated each subtype above may impact <1-5% of individuals. EBV-

PTLD, on the other hand, is more prevalent than EBV-SMT and has an incidence ranging from 1-20%¹⁰ with mortality rates around 50-90%^{11,12}.

Given how rare these tumors are, there is no standard treatment for EBV-SMTs which are instead treated on a case-by-case basis. Individuals with HIV-SMT are kept on appropriate antiretroviral treatment, and those with PT-SMT are treated with a reduction of immunosuppression. Surgical removal of tumors is considered when tumors impinge on the involved organ. Chemotherapy and radiation have also been utilized but without any obvious benefits on the disease course⁶. Allogeneic hematopoietic stem cell transplantation has also been used to treat CI-SMT with good outcomes^{13,14}.

Given their rarity, much of what we know about EBV-SMTs is through case reports and case series. However, as the frequency of organ transplantation grows with reliance on immunosuppression to prevent graft loss, it is pertinent to continue gathering information on EBV-SMTs. Many questions remain regarding incidence, prevalence, latency period, survival rates, and appropriate treatment strategies, amongst other crucial facts. Here, we describe six cases of EBV-SMT at a quaternary academic referral center.

CASE PRESENTATION

Chief complaints

See case details

History of present illness

See case details

History of past illness

See case details

Personal and family history

See case details

Physical examination

See case details

Laboratory examinations

See case details

Imaging examinations

Figure 1. **Epstein-Barr virus associated smooth muscle tumor (EBV-SMT)** in **the** sigmoid colon in case 1. 1A: Proliferation of smooth muscle cells undermining and distorting the colonic mucosa (H&E stain, 70X). 1B: EBER in situ hybridization is positive within the smooth muscle cell population (70X, inset box 200X).

Figure 2. EBV-SMT in the rectum in case 1. 2A: Proliferation of smooth muscle cells undermining the rectal mucosa (H&E stain, 40X). 2B: EBER in situ hybridization is positive within the smooth muscle cell population (40X, inset box 200X).

Figure 3: EBV SMT liver biopsies for cases 2-4. Hematoxylin and eosin-stained tissue sections showed fascicles of well-differentiated **spindle cells with pale eosinophilic cytoplasm and blunt-ended, ovoid nuclei with** smooth nuclear contours. No significant cytologic atypia or nuclear pleomorphism is appreciated (3A, 3D, 3G). All three cases show strong, diffuse reactivity for smooth muscle actin, confirming smooth muscle differentiation (3B, 3E, 3H), confirming smooth muscle tumor lineage. Chromogenic in situ hybridization studies for the Epstein-Barr virus (EBER) confirm the presence of viral genetic material in all three cases (3C, 3F, and 3I).

Figure 4. Positron emission tomography scan showing a hypermetabolic mass arising from the medial segment of the left liver lobe, measuring about 5.1 × 4.7 cm in the axial and anteroposterior dimension and 6.9 cm in the craniocaudal dimension in case 2.

Figure 5. T2 weighted turbo spin echo magnetic resonance images of the brain showing ring-enhancing lesion in the left temporal region in case 3. Figure 5B. T1 Fl3d magnetic

resonance images of the brain showing resolution of ring-enhancing lesion six years post-treatment in case 3.

Figure 6. Positron emission tomography scan showing a hypermetabolic right hepatic mass in case 3.

Figure 7A. Computed tomography scans of the liver with intravenous contrast in arterial phase showing multiple hepatic lesions in case 4. Figure 7B. Computed tomography scans of the liver in venous phase showing multiple hepatic lesions in case 4.

Figure 8A. Axial HASTE sequence abdominal magnetic resonance imaging demonstrating numerous cystic appearing hepatic EBV-SMTs, including the largest lesion in segment VII in case 5. Figure 8B. Axial HASTE sequence abdominal magnetic resonance imaging demonstrating stable/deceased hepatic lesions with no new lesions in case 5.

Figure 9. Axial and sagittal cuts of a T2 weighted MRI of the thoracic spine demonstrating an EBV-SMT centered in the left T9/T10 neuroforamina with a rightward displacement of the spinal cord in Case 6.

Table 1. Demographic characteristics and clinical summary of six EBV-SMT at a major quaternary academic referral center.

Case Series Details

Case 1

2
A five-year-old female with a history of idiopathic dilated cardiomyopathy status post orthotopic heart transplant (OHT) at eight months old, on tacrolimus, and previous EBV viremia at age 22 mo presented with her third infection-related hospitalization in the previous six months. Presenting symptoms included fever, thrush, diarrhea, and neutropenia with an absolute neutrophil count of 260 cells per μL . She was placed on broad-spectrum antibiotics and antifungals but continued to have diarrhea, failure to thrive, as well as new oral ulcers. Due to concern for PTLT, she underwent total body computed tomography (CT) which was unrevealing. She also underwent

esophagogastroduodenoscopy and colonoscopy. In addition to the presence of colonic candidiasis, colonoscopy revealed 6-10 mm polypoid lesions with central ulceration in the sigmoid colon and rectum with biopsies consistent with an EBV-driven smooth muscle tumor (figures 1A, 1B, 2A, 2B). The patient was EBV negative before transplant with repeat EBV titers high on admission (table 1). She was treated for colonic candidiasis as well as a *pseudallescheria boydii* complex infection of her lungs with symptomatic improvement. She did not undergo any EBV-SMT-directed treatment or surveillance and remains well at age 16 years.

Case 2

A 20-year-old male with a history of Idiopathic dilated cardiomyopathy status post OHT at age 17 on tacrolimus and mycophenolate mofetil (MMF), Crohn's disease, alopecia, juvenile idiopathic arthritis, and common variable immune deficiency (CVID) presented to the hospital with weight loss, headaches, and myalgias. The patient had abruptly stopped his immunosuppression agents a month before admission. He was treated with antibiotics for Group A streptococcus infection. The patient was previously EBV seronegative before transplant but had elevated titers on admission (table 1). A whole-body positron emission tomography (PET) scan showed multiple fluorodeoxyglucose (FDG) avid foci suspicious for widespread PTLD in the thymus, lung, liver, mesenteric lymph nodes, retroperitoneal lymph nodes, ascending colon, and proximal left femoral bone marrow (figure 4). A neck magnetic resonance image (MRI) revealed a mass in the right Meckel's cave. The patient's tacrolimus was decreased due to suspicion for PTLD. Biopsies taken during colonoscopy and bone marrow biopsies were negative for PTLD. A liver biopsy was performed and showed a proliferation of bland spindle cells with pale eosinophilic cytoplasm and ovoid nuclei with smooth contours and pale chromatin (figure 3A). Immunohistochemical stain for smooth muscle actin showed strong, diffuse reactivity in the neoplastic cells (figure 3B). EBER highlighted the presence of viral genetic material, confirming the diagnosis of PT-SMT (figure 3C). During this admission, he became febrile prompting a chest X-ray which

revealed left upper lobe haziness, concerning for pneumonia. He rapidly deteriorated, developing acute renal failure requiring dialysis and respiratory distress with encephalopathy requiring intubation. He then sustained a fatal cardiac arrest. An autopsy revealed severe acute cellular rejection, negative for antibody-mediated rejection, and confirmed multisite PT-SMT.

Case 3

² A 16-year-old female with a history of dilated cardiomyopathy status post OHT at 12-years-old, on MMF and tacrolimus presented to the hospital with severe headaches and altered mental status. MRI brain showed a left temporal ring-enhancing lesion (figure 5). The patient was previously EBV seronegative before transplant but had elevated titers on admission (table 1). She underwent a brain biopsy which showed EBV-PTLD, with morphology consistent with diffuse large B-cell lymphoma. Her immunosuppression therapy was reduced. She underwent a CT abdomen which showed a 2 cm low-attenuating hypervascular lesion in the right hepatic dome and another 0.6 cm lesion in the right anterior inferior hepatic lobe, redemonstrated on a PET Scan (figure 6). Liver biopsy showed a proliferation of spindle cells with eosinophilic cytoplasm, mild to moderate nuclear pleomorphism, and focal tumor necrosis (figure 3D). No severe nuclear pleomorphism or mitotic activity was identified. The neoplastic cells were strongly immunoreactive for smooth muscle actin, and showed diffuse nuclear reactivity for EBER, confirming the diagnosis of PT-SMT (figures 3E, F). A subsequent CT scan of the abdomen and pelvis showed two nonspecific small low density lesions in the left kidney, three months after the initial diagnosis of PTLD. For her CNS-PTLD, the patient had a ventriculoperitoneal shunt placed and underwent six cycles of intrathecal rituximab with methotrexate, systemic chemotherapy, whole-brain radiation, and T-cell therapy with subsequent decrease and ultimate resolution in the CNS lesion on subsequent imaging (figure 5). Her cerebrospinal fluid studies were negative for infection. She started having generalized tonic-clonic seizures in the post-treatment setting and was treated with anti-epileptics.

She remains well at the age of 22 years, with yearly liver MRI showing stable hepatic lesions (figure 6).

Case 4

A 61-year-old male with a pre-transplant negative cytomegalovirus (CMV) and EBV serology underwent orthotopic heart and liver transplant from a CMV and EBV positive donor (CMV Donor+/Recipient-, EBV Donor+/Recipient-) at the age of 58 years for cirrhosis secondary to Hereditary Familial Amyloidosis (Thr60A1a mutation). He was on tacrolimus for immunosuppression and post-transplant developed asymptomatic EBV and CMV viremia as well as stage 3 chronic kidney disease secondary to calcineurin inhibitory nephrotoxicity. He was admitted for new-onset hematuria and acute kidney injury. A kidney ultrasound noted a 2 cm hypoechoic lesion in the right inferior liver lobe. A CT scan of the liver revealed multiple indeterminate liver masses (figures 7A, 7B). Biopsy of one lesion showed a monotonous proliferation of relatively uniform spindle cells arranged in intersecting fascicles with pale eosinophilic cytoplasm and elongated, blunt-ended nuclei with darkly staining vesicular chromatin (figure 3G). There was again, no significant cytologic atypia, nuclear pleomorphism, or tumor necrosis. The tumor cells were strongly immunoreactive for smooth muscle actin and showed diffuse nuclear reactivity for EBER (figures 3H,3I). These morphologic and immunohistochemical findings were consistent with a diagnosis of PT-SMT. He subsequently underwent a left lateral liver segmentectomy with additional superficial hepatic wedge resections in segments 4A, 4B, and 8. Pathology showed positive margins. Immunosuppression was initially lowered and eventually discontinued. He was later found to have elevated liver enzymes on follow-up testing and a liver biopsy confirmed severe acute cellular rejection (ACR). He was treated with steroids and restarted on sirolimus and tacrolimus with resolution of ACR as proven on subsequent biopsy and improvement of liver enzymes on laboratory testing. He also completed a course of valganciclovir for CMV viremia. However, he developed worsening neutropenia with bone marrow

suppression, low-grade fevers, altered mental status requiring intubation, and anuria requiring dialysis. He was empirically started on broad-spectrum antibiotics. Infectious workup demonstrated streptococcus Gordonii bacteremia. Despite optimal treatment and supportive measures, his condition deteriorated rapidly and ended up having multi-organ failure, followed by a fatal cardiac arrest.

Case 5

A 63-year-old male with a history of a living-related donor kidney transplant at age 55 for end-stage renal disease of unknown etiology, was maintained on prednisone, MMF, and sirolimus. The patient was hospitalized for community-acquired pneumonia complicated by a parapneumonic effusion necessitating antibiotics and decortication. On CT and subsequent MRI imaging of the ³abdomen, he was incidentally found to have over 20 cystic hepatic masses, with the largest measuring 12.5 x 9.2 cm (figure 8A). Fine needle aspiration confirmed PT-SMT. EBV DNA quantification was at 4,765 copies per milliliter with no prior pre-transplant levels. He had no evidence of distant or intracranial disease on imaging. MMF was stopped and sirolimus was decreased from 1.5 mg to 1 mg daily initially, and down to 0.5 mg one year later. He was also treated with a course of valganciclovir at the time of diagnosis. Annual hepatic MRIs demonstrated initial size reduction followed by stable disease without any new lesions, with the most recent imaging performed at age 72 (figure 8B). He continues to do well with intact kidney function, despite decreasing his immunosuppression.

Case 6

A 45-year-old female with a long-standing history of HIV (CD 4 count unknown) on anti-retroviral therapy with dolutegravir, abacavir, and lamivudine presented to the primary care clinic with neck, back, and shoulder pain with associated proximal and distal left upper extremity numbness and paresthesias. With worsening symptoms after conservative therapy, she underwent cervical and thoracic spine MRI which showed a 1.9x1.2x2.4 cm intradural heterogeneous mass centered within the left T9-T10

neuroforamina, with abutment of the left lateral spinal cord resulting in rightward cord displacement as well as moderate canal stenosis (figure 9). She underwent T8-T10 Laminectomy with mass excision, with pathology consistent with EBV-SMT. Subsequent PET revealed no FDG avid lesions. Serum EBV viral levels were not obtained and prior seronegative status was also unknown. She did not undergo any further treatment or surveillance and has not had any complications of her disease, now at age 55.

¹ **FINAL DIAGNOSIS**

Epstein-Barr virus associated smooth muscle tumor (EBV-SMT)

TREATMENT

See case details

OUTCOME AND FOLLOW-UP

See case details

DISCUSSION

Here we report six cases of EBV-SMT, two of which were in pediatric patients with ages ranging from 6-61. There was an equal number of males and females in the cohort. Five out of six cases were PT-SMT while the sixth patient had HIV-SMT. One patient had CVID in addition to being a transplant recipient. Two patients died at the time of diagnosis, though neither death was attributed directly to the SMTs. Three patients in the group had single organ involvement while the rest had multiple organs involved. Two patients with CNS involvement (one with EBV-PTLD and another with HIV-SMT) underwent surgical removal of the tumor without recurrence. Interestingly, one patient in this cohort had both biopsy-proven PTLD and EBV-SMT.

A systemic review by Chen *et al* on EBV-SMT with CNS invasion found that HIV-SMTs have a predilection for the central nervous system¹⁵. This was seen in our patient with HIV-SMT whose EBV-SMT was found in the thoracic spine. In contrast, patients with PT-SMT have a propensity for extra-CNS involvement, primarily lung and liver as confirmed in a study by Jonigk *et al*⁷. The pathophysiology is unclear but it has been proposed these organ systems are hypervascular and may attract the proliferation of smooth muscle tumors. This is also seen in other lymphoproliferative disorders such as PTLT and non-Hodgkin lymphomas in patients with Acquired Immunodeficiency Syndrome (AIDS). Interestingly, Chen *et al* notice a concomitant lung and liver involvement in patients with PT-SMT¹⁵. This was true for two of our patients who had both lung and liver SMTs; one patient with solitary lung involvement. This raises the question of whether a liver lesion increases the chance of getting a lung lesion and not vice versa. Regardless, concomitant lung and liver lesions should be kept in mind during workup.

The latency period between either HIV infection or immunosuppression initiation and the occurrence of EBV-SMT is variable. In PT-SMT patients, previous studies have found an average latency period of three years in children compared to four years in adults^{7,15}. The latency period in our patients ranged from three to eight years. For HIV-SMT patients, it was more difficult to determine the timeline between HIV infection and diagnosis of AIDS. However, latency time could be as high as 8.5 years^{16,17}. For our patient with HIV, we were unable to determine this latency period. In contrast, PTLT can develop at any point after transplant, up to 10 years later, whereby a majority of cases occur within the first year post transplantation^{13,14}.

Additionally, multiple cases of synchronous or metachronous EBV-SMTs were seen in our patients, consistent with prior publications^{15,18,19}. Jonigk *et al* showed that patients with multiple organs involvement had worse overall survival than those with single organ involvement, while individuals with intracranial disease had the worst outcomes⁷. However, in the study by Chen *et al*, presence of CNS SMTs, tumor multiplicity, or pre-existing medical conditions did not impact the survival rate¹⁵. In our

case series, one-third of our patients died and had tumor multiplicity in addition to a multitude of chronic medical conditions. These patients did not die directly due to EBV-SMTs but died of the disease while battling other complications. Age differences did not impact survival, raising the question whether age has any role in prognosis. However, it does supplement the theory that the degree of immunocompetency may determine the degree of disease aggressiveness and subsequent survival rates.

EBV-SMTs have been generally thought of as slow-growing tumors with a 1-year overall survival rate of 50-76% for patients with HIV-SMT and PT-SMT patients and 0% for CI-SMT^{8,15}. 5-year survival rate is estimated at 60% for patients with CNS involvement¹⁵. Patients with HIV-SMTs have been known to have higher survival but with a shorter follow-up period. A separate analysis by Jonigk *et al* suggested that PT-SMT and CI-SMT have better outcomes than HIV-SMT⁸. Four out of six patients in our group continue to live with stable disease or no evidence of disease. It will be prudent to continue follow-up for all EBV-SMTs to help us study the disease course and prognosis over time.

Previous studies have found that pre-transplant EBV seronegativity is a risk factor for EBV-PTLD²⁰. However, the role of this factor is not known for EBV-SMT, though it is postulated that pre-transplant seronegativity and post-transplant primary EBV infection could be considered a risk factor for PT-SMT²¹. In our study, EBV status was not known for HIV patient, however, the other transplant patients were seronegative ³ at the time of transplant and became highly seropositive at the time of diagnosis (table 1). It would be interesting to see if any absolute levels of EBV titers have any bearing on the severity of disease course and outcomes.

There is no standardized treatment for EBV-SMT, given its rarity. In the study by Jonigk *et. al*, patients who underwent surgical resection had similar outcomes to those who underwent reduced immunosuppression alone without any surgery, suggesting that either may be an appropriate strategy⁷. Most patients with CNS involvement undergo surgical resection to alleviate parenchymal tumor compression¹⁵. No statistically significant difference was seen in outcomes between PT-SMT and HIV-SMT in these

patients. Surgical resection to alleviate parenchymal tumor compression in individuals with CNS involvement is a reasonable strategy.

CONCLUSION

EBV-SMTs are a rare oncological entity found in immunocompromised patients with either primary immunodeficiency as in Congenital Immunodeficiency or secondary immunodeficiency as seen in patients with HIV or post-transplant patients on long term immunosuppression. As the number of patients who undergo organ transplantation increases with time, the incidence of EBV-SMT may also increase. It is imperative to keep EBV-SMT on the differential in immunosuppressed individuals who develop tumors. Questions regarding the best treatment modality remain as patients are treated on a case-by-case basis.

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