Epstein Barr Virus Associated Smooth Muscle Tumors in Pediatric Heart Transplantation Patients: A Case Series and Review

Jamie Pruitt[1], Gerard Boyle[1], Colleen Nasman[1], Josephine Kam Tai Dermawan[1], Rabi Hanna[2], Aron Flagg[3], Sarah Fracci[4], John Goldblum[2], and seth rotz[1]

[1]Cleveland Clinic Foundation
[2]Cleveland Clinic
[3]Yale-New Haven Hospital
[4]Loyola University Chicago

March 07, 2024

Abstract

Background: Epstein-Barr virus associated smooth muscle tumors (EBV-SMT) are rare neoplasms that occur in immunocompromised individuals. Although generally less aggressive in adults, data in pediatric solid organ transplant (SOT) recipients suggest these malignancies may be more difficult to manage. As pediatric SOT becomes more common, the occurrence of EBV-SMT is likely to increase. Understanding what incites and drives these tumors is paramount. Design/Methods: We retrospectively reviewed the electronic health record (EHR) of 152 pediatric cardiac transplant recipients at our single institution between 1985-2017. Three patients were identified as having EBV SMT. We reviewed their demographics, time to malignancy, histology, treatment, and subsequent course. Results: Of the 152 cardiac transplant recipients reviewed at our institution between 1985-2017, three were identified to have EBV SMT (confirmed by EBER CISH). In our series, the average time to diagnosis was approximately 32 months following transplant. Liver was the most common site of EBV SMT. Two patients were diagnosed with EBV SMT after a known PTLD diagnosis. All three patients had elevated EBV titers at (or around) time of diagnosis, and there was one patient with EBV donor/recipient mismatch. Treatment was individualized and varied case by case. Conclusion: EBV-SMTs are rare in pediatric SOT and are difficult to manage in the setting of required immunosuppression. While there is some literature to suggest the use of mTOR inhibition and CTL therapy is helpful in treatment of EBV SMT, data remains limited given the paucity of cases. At current, there remains no standard of care for treatment of pediatric EBV SMT.

Introduction

Epstein-Barr virus associated smooth muscle tumors (EBV SMT) are rare neoplasms that occur in immunocompromised individuals including recipients of solid organ transplant (SOT), patients with human immunodeficiency virus and other primary immunodeficiencies[1-3]. Unlike in EBV-driven lymphomas where CD21 permits B-cell entry, multiple reports have shown that SOT EBV-SMTs frequently lack this receptor. Thus, the tumorigenesis of EBV-SMT remains an ongoing area of importance, as further characterizing the mechanisms responsible for cell invasion will help direct novel treatments[1,4,5]. In the pediatric SOT setting, EBV-SMTs typically present shortly after transplant and can affect multiple sites, frequently including hepatobiliary and respiratory systems[1-3]. Multifocal lesions present in the majority of patients at diagnosis and likely represent primary tumors from multiple infectious events rather than metastasis from a single primary site[1,2,6]. The presence of multiple tumors in an immunocompromised host occurring in non-hollow visceral organs known to have limited smooth muscle i.e. liver, lung, dura, spleen, and bone should raise high suspicion for EBV SMT[2,6,7].

The overall incidence of EBV SMT in immunocompromised patients is estimated to be 1-5% with approximately 30 pediatric cases of EBV-SMT in post-solid organ transplant recipients having been reported[1,3,6,8,9]. An institutional review of greater than 5,000 SOT patients showed the incidence of EBV SMT disproportionality affects children[8]. With a paucity of knowledge about these rare tumors, we investigated the occurrence of EBV SMT in our pediatric heart transplantation population from 1985-2017. Of the 152 patients evaluated, three cases of EBV-SMTs were identified. We aim to highlight the similarities and differences found in our cohort and compare that to what has been previously reported in the literature. Further, we attempt to realize potential risk factors for the development of EBV-SMT in the pediatric population and discuss the role of current therapies.

Case 1

A previously healthy 12-year-old female underwent orthotopic heart transplant (OHT) for dilated cardiomyopathy. Pre-transplant serologies were EBV donor positive/recipient negative. She received postoperative immunosuppression with anti-thymocyte globulin (ATG) and corticosteroids and was maintained on tacrolimus and mycophenolate mofetil (MMF). She presented approximately 38 months post OHT with altered mental status, weight loss, nausea and diarrhea. Central nervous system (CNS) imaging revealed a left temporal ring enhancing lesion which was found to be EBV Post-Transplant Lymphoproliferative disorder (PTLD). Serum EBV levels peaked at 11,848 copies/mL around time of diagnosis. Further imaging revealed a two cm lesion in the right hepatic dome and another one cm lesion in the right inferior hepatic lobe, presumed to be additional PTLD lesions (Fig 4). Immunosuppression was subsequently reduced, and she was started on PTLD directed chemotherapy with rituximab, methotrexate, cyclophosphamide, and triple intrathecal therapy[10].

Repeat imaging one month following therapy showed interval improvement of her CNS PTLD, but demonstrated interval growth of the liver lesions, with increased FDG avidity on PET and newly visualized left kidney lesions (Fig 4). Due to the presumed discrepant response, an ultrasound-guided liver biopsy was performed which revealed hepatic EBV-SMT (Fig 1). At diagnosis, EBV PCR was negative in the peripheral blood with less than 200 copies/mL found in the cerebrospinal fluid; likely due from PTLD directed treatment effects. Her tacrolimus was changed to sirolimus and her mycophenolate was discontinued in an effort to reduce overall immunosuppression and provide potential antitumor effect through mammalian target of rapomycin (mTOR) inhibition[7]. She went on to receive 4,500 cGy whole brain radiation and EBV targeted cytotoxic T-lymphocyte (CTL) therapy[11]. CNS remission of her PTLD was achieved approximately 1.5 years after diagnosis and EBV liver lesions remain stable at approximately six years post EBV SMT diagnosis. She was restarted on tacrolimus due to mild acute cellular rejection and remains currently on a combination of sirolimus and tacrolimus for immunosuppression.

Case 2

A 17-year-old male with a past medical history of b cell deficiency and inflammatory colitis was admitted to our facility after failed treatment for presumed pneumonia and found to have severe dilated cardiomyopathy (idiopathic vs autoimmune) eventually necessitating heart transplant. Pre-transplant serologies were EBV donor positive/recipient positive. Peri-operatively, he received two doses of ATG and corticosteroids. Initial immunosuppression consisted of tacrolimus, MMF, prednisone, and sulfasalazine (for colitis), which were eventually weaned. Approximately three years following transplant, he was admitted to the hospital for evaluation of weight loss, headache, anemia and diarrhea. On admission, EBV DNA was elevated at 10,058 copies/mL; previously negative the year prior. EBV levels continued to increase during admission to a peak of 161, 476 copies/mL. PET showed FDG avid lesions in multiple areas including the liver (six cm lesion in the caudate lobe), colon, femur, thymus, and lungs. MRI brain and PET demonstrated a mass in the right meckel's cave suspicious for PTLD. He underwent colonoscopy which revealed lesions in the gastric antrum (not visualized on PET) and ascending colon concerning for PTLD. Biopsies of the gastric antrum and colon were negative for immunophenotypic evidence of lymphoproliferative disorder. However, subsequent liver biopsy confirmed EBV SMT (Fig 2). He was started on Imatanib which was discontinued shortly thereafter due to concerns of severe drug rash. Surgical resection of the liver mass was felt to have limited efficacy given

the multiple foci of disease and was not pursued. Following Imatinib, in an effort to promote anti-tumor immune response due to advanced disease, all immunosuppression was discontinued approximately three weeks following diagnosis. At approximately 2 months following EBV SMT diagnosis, he developed acute respiratory distress and multi-organ failure that led to death secondary to progressive malignancy.

Case 3

A previously healthy 7-year-old female underwent OHT after developing viral induced cardiomyopathy leading to heart failure. Pre-transplant serologies were: EBV donor positive/recipient unknown. She was started tacrolimus, Azathioprine and steroids to prevent transplant rejection. The rest of the immediate post-transplant history is limited given incomplete chart.

Approximately seven months post-transplant she developed enlarged lymph nodes of the neck, axilla and groin and was diagnosed with polymorphous PTLD via biopsy. Her immunosuppression was decreased briefly, but due to graft rejection she required re-escalation of her immunosuppressive medications. One year following initial PTLD diagnosis, she again developed diffuse palpable adenopathy of the groin and axilla that was found to be recurrence of PTLD confirmed on biopsy. She concomitantly had chronic EBV DNAemia with peak documented levels of 7,365 copies/mL (presumed to be higher but records are incomplete). She underwent total lymphoid irradiation to the periaortic, splenic and pelvic lymph nodes delivering a total of 4.8 Gy in six fractions before therapy was truncated and not resumed due to ongoing medical issues surrounding chronic EBV infection. Despite radiation therapy, she developed two new liver lesions with the largest lesion measuring appx 2 cm on CT. No evidence of additional disease outside the liver was seen. Liver biopsy was consistent with EBV SMT (Fig 3). At the same time, she underwent scheduled cardiac catheterization which revealed severe coronary artery disease of her graft. She was admitted to the hospital in heart failure and re-listed for transplant. During this hospitalization, she went into cardiac arrest and required brief placement on ECMO before being re-transplanted 2 days later. After a prolonged four-month hospitalization, she was discharged home on cyclosporine, MMF, and prednisone.

Once recovered, she underwent planned resection of the known solitary hepatic SMT which was successful. Surveillance CT following resection showed recurrence of the hepatic SMT, in addition to the development of a second hepatic tumor that was deemed unresectable at the time. With increasing growth of the tumors now measuring 8.5 cm and 4.5 cm along with chronic GI complaints of diarrhea and abdominal pain, chemoembolization was briefly considered but dismissed after CT angiography demonstrated the tumors were poorly vascularized. She underwent palliative radiation to the liver and received a total tumor dose of 3500 cGy. Given the positive response to radiotherapy, she was evaluated for second resection at an outlying facility and underwent full resection of now three liver tumors with subsequent remission.

Due to progressive coronary artery disease and continued heart failure symptoms, she was re-listed for a third cardiac transplant in addition to a kidney transplant due to ESRD. Shortly thereafter, she was admitted to the hospital with new onset hematemesis secondary to new fungating mass in the gastric antrum. Upper GI series showed diffuse thickening of the esophagus thought to be secondary to recurrence of SMT although not confirmed with biopsy given her tenuous clinical state. In the setting of heart failure and ESRD, the mass was deemed inoperable. She was no longer eligible for transplant and was placed on comfort care and passed away in the hospital due to progressive disease.

Results/Discussion

Of the 152 cardiac transplant recipients reviewed at our institution between 1985-2017, three were identified to have EBV SMT. All tumors were confirmed by EBER CISH; a chromogenic in situ hybridization stain against viral RNA. Liver was the most common site of EBV SMT consistent with current pediatric reports[1,3,12]. In our series, the average time to diagnosis was appx 32 months (range 25-38 months) following transplant. Lui et al describes the interval between transplantation and tumor to be a mean of 42 months in pediatric patients compared with the adult population mean of 73–114 months[6].

Outcomes in pediatric populations differ from current adult literature which describe EBV SMT as having

excellent prognosis[2,3,8]. Pediatric data has shown EBV SMTs occurring in children are linked to higher mortality rates[7,9]. One explanation may be that children are at increased risk of primary infection with associated higher EBV viral loads post-transplant[3,8]. Our cohort demonstrated one case with EBV donor/recipient mismatch although she had a favorable course and remains alive today. All three patients in our series had EBV DNAemia/viremia at time of diagnosis with levels that ranged from 7,365 to 161,475 copies/mL. Stubbins demonstrated EBV SMT occurring exclusively in the pediatric cardiac transplant population despite similar numbers of EBV seronegative patients in their study who underwent liver transplant. This suggests there are risk factors other than EBV seronegatively that contribute to the development of EBV SMT. Stubbins postulated that the aggressive immunosuppression used in cardiac transplant recipients may increase the risk of developing EBV SMT. Another unique aspect of pediatric heart transplant is the surgical removal of the thymus which may result in skewed profiles of peripheral T cells leading to premature immunosenescence[8].

In our series, two patients were diagnosed with EBV SMT after a known PTLD diagnosis, while the other patient presented with a primary EBV SMT. A meta-analysis by Jonigk et al shows 12/68 patients were diagnosed with PTLD prior to the development of EBV SMT. Of the 12 patients, 11 were pediatric (92%)[3]. Comparably, Stubbins et al showed EBV SMT occurring after primary diagnosis of PTLD in 14 of 36 cases (39%). This was observed less frequently in adults 2/51 cases (4%)[8]. The high association between EBV SMT and PTLD that was also seen in our cohort strongly suggests that immunosuppression plays a key role. It is well understood that EBV PTLD lymphomas are driven by latent EBV infected B-cells via latent membrane proteins (LMP), and generally occur in the initial one to two years following transplant[13]. Known risk factors include type of organ transplant, age, and EBV seronegativity[14]. Given the similar timeline of pediatric EBV SMT and PTLD occurring post-transplant in association with high immunosuppressive states, we may be able to apply those same risk factors when trying to stratify patients at highest risk for developing EBV SMT.

Current therapies for the treatment of EBV SMT include resection when possible, although this can be limited due to the multi-focal nature of disease at diagnosis. Other therapies include reduction of immunosuppression alone or in conjunction with surgery, chemotherapy, immunotherapy, and the use of MTOR inhibitors such as sirolimus. In our cohort, one patient received CAR-T therapy. While not curative, it resulted in stabilization of her disease, and she remains alive today. The remaining cases, for which reduction in immunosuppression, surgery and imatinib were used, resulted in death from progressive disease. Treatment for EBV SMT is still poorly understood because the mechanism for EBV cell entry and tumorigenesis has yet to be identified. Although the study by Tan et al did not reach statistical significance, their work demonstrated improved mortality in patients who were switched from cyclosporine-based immunosuppression to mTOR inhibition after SMT diagnosis[7]. Similarly, in our cohort, case one demonstrated a positive response to Sirolimus, although to what degree is difficult to conclude given she had multiple therapeutic interventions.

Conclusion

With the increase in pediatric transplants and more evidence revealing EBV SMT are not as benign in the pediatric population as previously thought, further investigations to understand the immune system with focus on the pediatric transplant population is warranted[15]. At present, the treatment for EBV SMT in the pediatric population remains individualized with varying reported successes[1,3]. With the limited number of current cases, a multi-center approach assessing current therapeutic approaches and their efficacies is needed to create a more standardized approach to the treatment of EBV SMT.

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Figure Legends

FIGURE 1. A, B: Histologic sections from the liver biopsy demonstrate a cellular proliferation of monomorphic spindle cells arranging in intersecting fascicles and admixed with a lymphocytic infiltrate (A: 20X, inset: 8X; B: 40X; hematoxylin & eosin). The spindle cells show elongated nuclei with inconspicuous nucleoli and abundant eosinophilic cytoplasm. They show diffuse and strong immunoreactivity for smooth muscle actin, patchy but strong reactivity for desmin (D), and strong, diffuse reactivity for h-caldesm (E). An EBER chromogenic in situ hybridization (CISH) is strongly positive in the lesional cells.

FIGURE 2. A, B: Sections from the liver biopsy demonstrate a cellular spindle cell proliferation forming short intersecting fascicles and admixed with an inflammatory infiltrate (A: 20X; B: 40X; hematoxylin & eosin). The spindle cells show elongated, slender nuclei and abundant eosinophilic cytoplasm. They are diffusely

and strongly positive for smooth muscle actin (C) and desmin and show focal positivity to h-caldesmon. An EBER chromogenic in situ hybridization (CISH) is strongly positive in the lesional cells (D).

FIGURE 3. Sections from liver biopsy including H&E image (A: 20X; B: 40X; hematoxylin & eosin) and EBER CISH (C, D). There are multiple fragments with cellular spindle cell neoplasm which stain strongly for smooth muscle actin and focally for desmin. *(EBER CISH was not widely available in 2000, instead EBV immunohistochemistry (IHC) was routinely performed which was negative on this specimen. For the purposes of this study, we were able to perform EBER CISH on the original biopsy which was strongly and diffusely positive for EBER)*

FIGURE 4. Case 1: CT demonstrating a two cm lesion in the right hepatic dome and one cm lesion in the right inferior hepatic lobe (top and bottom left). The same hepatic lesions demonstrating increased FDG avidity on PET (top and bottom right).

Acknowledgements

None

Financial Support

None

Conflicts of Interest

None

Hosted file

`EBV SMT - Table 1 Case Demographics.docx` available at https://authorea.com/users/726931/articles/709098-epstein-barr-virus-associated-smooth-muscle-tumors-in-pediatric-heart-transplantation-patients-a-case-series-and-review