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CASE REPORT | LIVER

Hepatic Epstein-Barr Virus-Associated Smooth Muscle Tumor in a Heart and Liver Transplant Recipient

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ABSTRACT

Epstein-Barr virus (EBV)-associated smooth muscle tumors (SMT) have been described in immunosuppressed states, including in post-transplant patients. Here, we discuss a heart-liver transplant recipient who was found to have multifocal hepatic EBV-SMT. His immunosuppression was initially transitioned from tacrolimus to sirolimus because of the proposed benefits of the mechanistic target of rapamycin inhibitors on EBV-SMT. Unfortunately, he suffered acute rejection of his liver allograft while on sirolimus therapy, which ultimately led to consideration of retransplantation.

INTRODUCTION

Epstein-Barr virus (EBV) infection is associated with malignancies including nasopharyngeal carcinoma, nonmelanoma skin cancers, Kaposi sarcoma, and lymphomas. Rarely, EBV can be associated with smooth muscle tumors (SMT), typically in immunosuppressed states including solid organ transplantation.[1,2] Most reported cases of transplant-associated EBV-SMT have been in isolated liver or kidney transplant patients. We present a unique case of EBV-SMT in a heart and liver transplant recipient.

CASE REPORT

A 61-year-old man with familial transthyretin amyloidosis and a history of combined heart and liver transplant maintained on tacrolimus immunosuppression presented 3 years post-transplant with hematuria. A renal ultrasound incidentally revealed a new 2-cm hypoechoic lesion in the right inferior hepatic lobe.

On admission, his vital signs were within normal limits and physical examination was unremarkable. Initial laboratory evaluation was notable for normal liver biochemistries, acute kidney injury (creatinine 3.02 mg/dL, baseline 1.7–2.1 mg/dL in the setting of transthyretin amyloidosis), and lymphopenia (2.52 k/μL). Notably, on routine outpatient infectious disease post-transplant surveillance for chronic EBV viremia 1 month before presentation, his EBV deoxyribonucleic acid (DNA) had been found to be elevated (36,661 IU/mL, increased from 27,090 IU/mL 1 year earlier). Cytomegalovirus (CMV) DNA was undetectable. Before transplant, his serologies had been negative for both EBV and CMV, whereas the donor's serologies were positive for both EBV and CMV IgG.

A triple-phase computed tomography scan with intravenous (IV) contrast demonstrated multiple heterogeneously hypoenhancing liver masses, the largest measuring 4.4 × 3.8 cm, with peripheral enhancement on arterial phase and increasing enhancement with delayed phase (Figure 1). A percutaneous imaging-guided biopsy of a lesion demonstrated a proliferation of relatively uniform spindle cells arranged in intersecting fascicles (Figure 2). Immunohistochemical staining revealed a strong immunoreaction for smooth muscle actin. Chromogenic in situ hybridization studies for EBV showed strong reactivity in the tumor cell nuclei. The morphologic and immunohistochemical features in sum were diagnostic of EBV-SMT (Figure 3).

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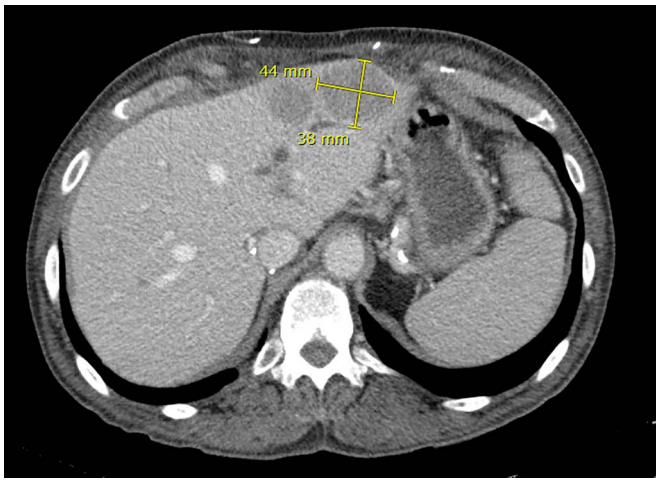

Figure 1. A computed tomography (CT) scan of the liver with intravenous (IV) contrast demonstrating multiple indeterminate liver masses, the largest measuring 4.4 × 3.8 cm. The masses were heterogeneously hypoenhancing relative to the background liver parenchyma with peripheral enhancement on arterial phase imaging and increasing enhancement on delayed phase imaging. Pictured is a representative slice during the arterial phase.

Tumor board discussion yielded a recommendation to decrease his tacrolimus dose gradually, simultaneous with bilobar liver wedge resections and microwave ablations of the tumors. Postoperatively, he was fully transitioned to sirolimus immunosuppression. Liver biochemistries remained within normal ranges throughout this transition.

One month later, the patient was admitted with acute elevations of aspartate aminotransferase (600 U/L), alanine aminotransferase (678 U/L), alkaline phosphatase (815 U/L), total bilirubin (3.8 mg/dL), and conjugated bilirubin (3.1 mg/dL). Imaging-guided liver biopsy was performed; histopathology demonstrated diffuse portal and periportal inflammation, bile duct injury, portal and central endotheliitis, and perivenular hepatocellular injury consistent with severe acute cellular rejection (ACR) of the allograft. He received IV corticosteroids, and tacrolimus was restarted in addition to sirolimus. He was discharged home on prednisone after improvement in liver parameters.

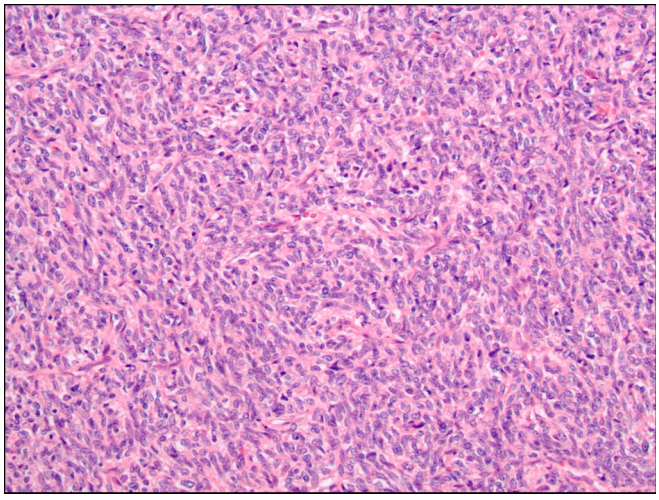

Figure 2. Hematoxylin and eosin (H&E) stain of liver graft biopsy demonstrating relatively uniform monomorphic spindle cells arranged in intersecting fascicles with pale eosinophilic cytoplasm and elongated, blunt-ended nuclei with dark vesicular chromatin. Cellular atypia, pleomorphisms, mitotic figures, or necrosis was not readily identified. Magnification ×20.

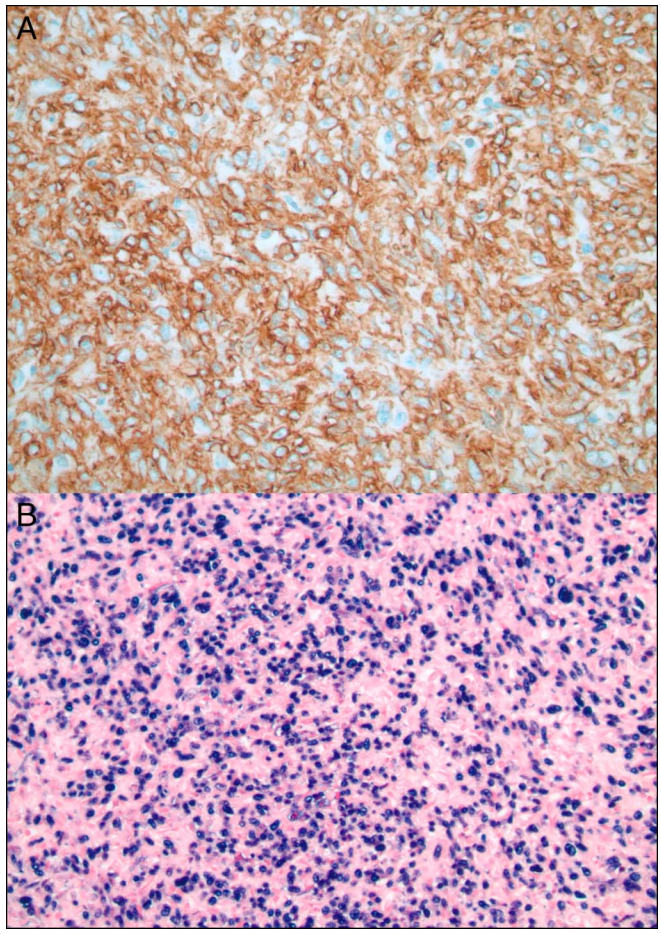

Figure 3. Immunohistochemical staining of liver graft biopsy. Not shown are negative stains for CD117, DOG-1, desmin, S100, SOX10, CD34, and STAT6. Positive and negative controls stained appropriately but are not included. (A) Tumor cells are strongly immunoreactive to smooth muscle actin (SMA). Magnification ×20. (B) Tumor cells demonstrate strong immunoreactivity in tumor cell nuclei to EBV-encoded small RNA (EBER) by chromogenic in situ hybridization studies. These findings support a diagnosis of EBV-associated smooth muscle tumor. Magnification ×10. EBV, Epstein-Barr virus.

The patient was readmitted 1 week later with jaundice. His laboratory work was significant for total bilirubin 12.9 mg/dL, alkaline phosphatase 434 U/L, aspartate aminotransferase 226 U/L, and alanine aminotransferase 492 U/L. His liver parameters did not respond to enhanced therapy for ACR. His case was discussed at the liver transplant selection committee; the decision was made to proceed with high-risk retransplantation. Unfortunately, the patient died to sepsis secondary to *Streptococcus*

gordonii bacteremia in the setting of increased immune suppression shortly thereafter.

DISCUSSION

In part because of its rarity, the incidence of post-transplant EBV-SMT is unclear. A single Canadian center database including 4,532 adult and 474 pediatric transplant recipients older than 31 years identified 3 cases of EBV-SMT exclusively in pediatric heart transplant recipients (incidence 0.7% per 1,000 cases).[3] By comparison, a single-center case series in Singapore described 16 cases of post-transplant EBV-SMT among 975 adult kidney transplant recipients from 1985 to 2000 (incidence 1.67%).[4] The differences in these 2 studies suggest possible geographic or genetic risk factors associated with the disease.

The chief risk factor for the development of EBV-SMT is believed to be high EBV viral load.[3,5,6] Although the mechanism of EBV-SMT is not known, one theory proposed that EBV entry into mesenchymal cells or their precursors may be mediated by high local levels of viremia without access to the B cell receptor CD21.[7,8] Once infected, EBV alters molecular signaling pathways, particularly the mechanistic target of rapamycin/Akt (also known as protein kinase B) pathway. Molecular analysis of post-transplant EBV-SMTs has indicated increased expression of transcription factors that lead to unchecked cellular proliferation by altering controls on the cell cycle, such as apoptosis.[9]

Treatment of EBV-SMTs focuses on reversing the mechanism of immunosuppression if possible. For post-transplant patients, this can be achieved through a reduction in immunosuppression to restore T-cell function. Sirolimus has been proposed as a therapy because of its impact on cell cycle arrest in cells with high Akt activity, including EBV-SMT cells.[10] Some have suggested transitioning the immunosuppressive regimen from traditional calcineurin inhibitors to the mechanistic target of rapamycin inhibitor sirolimus in these cases.[11] In a single-center case series, adult kidney transplant patients with EBV-SMT on a cyclosporine-based immunosuppressive regimen (n = 7) were compared with those on a sirolimus-based regimen (n = 7). There was no significant difference in the survival rate (sirolimus 100% vs cyclosporine 42.9%, $P = .08$), graft survival (71.4% vs 28.7%, $P = .53$), or disease-free status (42.9% vs 14.3%, $P = .73$).[4] Surgical resection is a viable option for patients who are surgical candidates with accessible lesions, especially if the SMT induces organ dysfunction.

In this case, the patient's immune suppression was transitioned from tacrolimus to sirolimus simultaneously with surgical resection to address the heavy hepatic tumor burden. Unfortunately, he suffered from severe ACR of his liver allograft, which was refractory to augmentation of immunosuppression and reinstitution of tacrolimus. This unique case highlights the delicate interplay of altered T-cell and B-cell function affected by immunosuppression in solid organ transplant recipients. Chronic EBV viremia, through its alteration of cell cycle transcription factors, may tip the scales and threaten the equilibrium of allograft function and neoplasia.

DISCLOSURES

Author contributions: BM Johnson, J-P Iskandar, and N. Farha reviewed the literature and wrote the article. BM Johnson approved the article. L. Yerian provided pathologic images. J. Modaresi Esfeh and C. Lindenmeyer revised the article for intellectual content and are the article guarantors.

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Informed consent could not be obtained for this case report. All identifying information has been removed.

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REFERENCES

1. Sprangers B, Smets S, Sagaert X, et al. Posttransplant Epstein-Barr virus-associated myogenic tumors: Case report and review of the literature. *Am J Transpl.* 2007;8(1):253–8.
2. Sadahira Y, Moriya T, Shirabe T, Matsuno T, Manabe T. Epstein-Barr virus-associated post-transplant primary smooth muscle tumor of the liver: Report of an autopsy case. *Pathol Int.* 1996;46(8):601–4.
3. Stubbins RJ, Alami Laroussi N, Peters AC, et al. Epstein-Barr virus associated smooth muscle tumors in solid organ transplant recipients: Incidence over 31 years at a single institution and review of the literature. *Transpl Infect Dis.* 2019;21(1):e13010.
4. Tan CS, Loh HL, Foo MW, Choong LH, Wong KS, Kee TY. Epstein-Barr virus-associated smooth muscle tumors after kidney transplantation: Treatment and outcomes in a single center. *Clin Transpl.* 2013;27(4):E462–8.
5. Piriou E, Asito AS, Sumba PO, et al. Early age at time of primary epstein-barr virus infection results in poorly controlled viral infection in infants from western Kenya: Clues to the etiology of endemic Burkitt lymphoma. *J Infect Dis.* 2012;205(6):906–13.
6. Das B, Morrow R, Huang R, Fixler D. Persistent Epstein-Barr viral load in Epstein-Barr viral naïve pediatric heart transplant recipients: Risk of late-onset post-transplant lymphoproliferative disease. *World J Transpl.* 2016;6(4):729.
7. Rickinson AB. Co-infections, inflammation and oncogenesis: Future directions for EBV research. *Semin Cancer Biol.* 2014;26:99–115.
8. Shannon-Lowe C, Rickinson A. The global landscape of EBV-associated tumors. *Front Oncol.* 2019;9(August):1–23.
9. Jonigk D, Laenger F, Maegel L, et al. Molecular and clinicopathological analysis of Epstein-Barr virus-associated posttransplant smooth muscle tumors. *Am J Transpl.* 2012;12(7):1908–17.
10. Penney SW, Bishop BN, Howell DL. Treatment response with sirolimus for a pediatric patient with an EBV-associated smooth-muscle tumor after bone marrow transplantation. *Pediatr Blood Cancer.* 2019;66(5):e27585.
11. Toh HC, Teo M, Ong KW, et al. Use of sirolimus for Epstein-Barr virus-positive smooth-muscle tumour. *Lancet Oncol.* 2006;7(11):955–7.