Int J Clin Exp Pathol 2011;4(4):421-429
www.ijcep.com /IJCEP1104008

Case Report

Multicentric hepatic EBV-associated smooth muscle tumors in an AIDS patient: a case report, investigation of mTOR activation and review of the literature

Qi Shen[1], Wei Feng[2], Michael S. Long[1], Xiuzhen Duan[1], Siraya Jaijakul[3], Cesar A. Arias[3], Robert E. Brown[1], Bihong Zhao[1]

[1]Department of Pathology and Laboratory Medicine, the University of Texas Medical School at Houston, Houston TX, USA. [2]North Cypress Medical Center, Cypress TX, USA. [3]Division of Infectious Diseases, Department of Internal Medicine, the University of Texas Medical School at Houston, Houston TX, USA.

Received April 10, 2011; accepted April 19, 2011; Epub April 23, 2011; published April 30, 2011

Abstract: Epstein-Barr virus (EBV) - associated smooth muscle tumors (EBV-SMT) are a rare, recently recognized distinct group of mesenchymal tumors that develop exclusively in patients with immunosuppression. It is believed that tumorigenesis is, at least in part, through the activation of the Akt/mammalian target of rapamycin (mTOR) signal pathway. We describe the clinicopathologic and immunohistochemical features of a multifocal hepatic EBV-SMT in a 34-year-old acquired immunodeficiency syndrome (AIDS) patient and investigate the activation status of the mTOR signal pathway in this tumor. In addition, we provide a review of the literature on the clinicopathologic findings of hepatic EBV-SMT in adult AIDS patients, and discuss their biologies and possible therapeutic strategies.

Keywords: Smooth muscle tumor, HIV infection, acquired immunodeficiency syndrome, adult, Epstein-Barr virus, liver

Introduction

Epstein-Barr virus (EBV)-associated smooth muscle tumors (EBV-SMT) are a recently recognized distinctive group of mesenchymal tumors that develop exclusively in patients with clinical immunosuppression, predominantly in human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), and solid organ transplantation [1-2]. Since clonal EBV is consistently detected in these tumors but not in conventional smooth muscle tumors occurring outside the setting of immunosuppression, EBV virus is believed to play an essential role in the tumorigenesis of EBV-SMT [3]. The molecular mechanism by which EBV drives the smooth muscle transformation is unclear, however recent studies have suggested it is mediated, at least in part, through the activation of the Akt/mammalian target of rapamycin (mTOR) signaling pathway [4].

In organ transplant recipients, EBV-SMT most often involve the lung, gastrointestinal tract, and liver [5]. In AIDS patients, visceral EBV-SMT, particularly those involving the liver are rare, and occur mostly in the pediatric population, with only eight cases reported thus far in adults [1, 6-12]. The predisposition to visceral EBV-SMT in the pediatric HIV- infected population may be related to myocyte immaturity, whereas in HIV-infected adults, a mature visceral smooth muscle tissue may possess resistance to EBV infection or neoplastic transformation [13].

Here we describe a new case of multifocal hepatic EBV-SMT in a 34-year-old AIDS patient and investigate the activation status of the mTOR signaling in this tumor. In addition, we provide a review of the literature on the clinicopathologic findings of hepatic EBV-SMT in adult AIDS patients, and discuss their biologies and possible therapeutic strategies.

Case Report

The patient is a 34-year-old man who was first diagnosed with HIV/AIDS in 2000. He presented

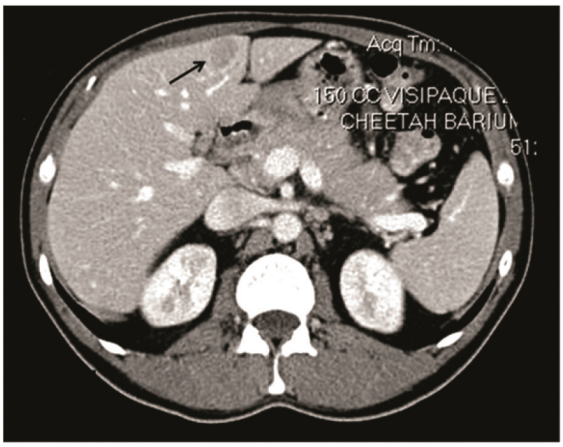

Figure 1. Contrast-enhanced computed tomography (CT) scan of the abdomen shows multiple hypodense lesions (arrow), 0.9 to 2.3 cm in maximal dimension, with minimal peripheral arterial enhancement throughout the liver.

to our hospital in May 2010 with generalized fatigue, right upper quadrant abdominal pain and watery diarrhea for 3 months. The patient was initially placed on a regimen of highly active antiretroviral therapy (HAART) using tenofovir/emtricitabine combination and efavirenz, which were discontinued 5 years prior to admission due to the fact that he did not tolerate the medications. He had a history of *Pneumocystis jiroveci* pneumonia, oral and genital herpes infections, and perianal abscess. On admission, physical examination was unrevealing. His CD4+ T cell count was 15 cells/ml and the plasma HIV-1 RNA viral load was 79,600 copies/ml. Liver function test showed elevated liver enzymes. The diarrhea was attributed to his chronic HIV infection and ultrasound of the abdomen revealed two hypoechoic lesions in the right and left hepatic lobes, measuring 1.9 cm and 2.0 cm in diameter, respectively. Follow-up abdominal computed tomography (CT) scan **(Figure 1)** showed five hypodense lesions, ranging from 0.9 to 2.3 cm in greatest dimension, with minimal peripheral arterial enhancement throughout the liver. No extrahepatic masses were appreciated on the CT of chest, abdomen, and pelvis and in an magnetic resonance imaging (MRI) of the brain. CT-guided percutaneous fine needle aspiration biopsy of the lesions in the right hepatic lobe was performed. The patient was restarted on HAART with tenofovir, emtricitabine, and darunavir/norvir combination, and his diarrhea improved after starting the antiretroviral therapy with the addition of loperamide. He was discharged and referred to the University of Texas MD Anderson Cancer Center for further management of his liver lesions. The patient was clinically stable, exhibiting viral suppression in the latest follow-up at 7 months after this presentation.

Materials and methods

Bright field microscopy

Tissue was fixed in 10% formalin, embedded in paraffin, routinely processed, and stained with hematoxylin and eosin. Fite's acid fast stain and Warthin-Starry silver stain were also performed.

Immunohistochemical analysis

Formalin-fixed, paraffin-embedded sections of tissue were deparaffinized and rehydrated. Sections were stained with the primary antibodies against smooth muscle actin (SMA) (DAKO, Carpinteria, CA), desmin (DAKO), CD34 (Becton Dickinson, Franklin Lakes, NJ), CD31 (Novocastra, Newcastle upon Tyne, UK), human herpes virus 8 (HHV8) (Novocastra), S100 (DAKO), CD117 (DAKO), CD99 (DAKO), CD21 (DAKO), pan-cytokeratin cocktail (Novocastra), Ki-67 (DAKO), phosphorylated (p)-mTOR at serine 2448 (Cell Signaling, Beverly, MA), p-Akt at serine 473 (Cell Signaling), and EBV latent membrane protein 1 (EBV-LMP1) (DAKO). Those incubated with anti-phosphospecific probes were incubated at 4°C, per the vendor's recommended procedure; all other primary antibodies were incubated at room temperature. Sections were then stained with the biotinylated secondary antibodies as previously described [14], and the antibody complexes were detected with the direct avidin-biotin-peroxidase method (Dako), using 3, 3'-diaminobenzidine as the chromogen and hematoxylin as the counterstain. Positive and negative controls were run in parallel with the samples.

Chromogenic in situ hybridization for EBV-encoded small RNA 1 (EBER-1)

Formalin-fixed, paraffin-embedded sections of tissue were mounted on slides treated with 3-aminopropyltriethoxysilane, deparaffinized, digested with proteinase K, and dehydrated. The EBER-1 probe (Operon Technologies Inc, San

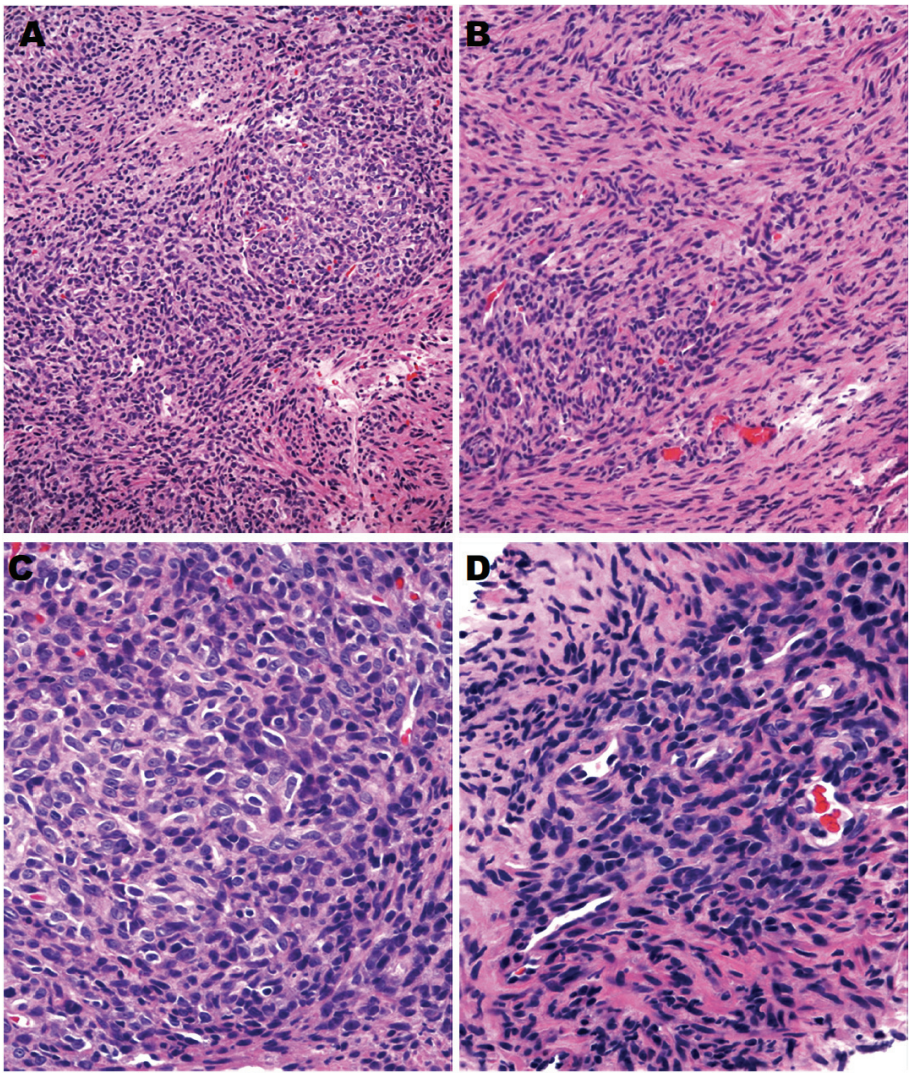

Figure 2. Histologic features of EBV-SMT. **A**. The tumors contain two cell populations composed of spindle cells arranged in short fascicles and oval to round cells forming distinct nodules. **B**. The spindle cells have elongated blunt-ended nuclei and abundant eosinophilic cytoplasm. **C**. The oval-round cells show mild to moderate nuclear atypia. **D**. Hemangiopericytoma-like vascular pattern is focally present.

Pablo, Ca), an oligonucleotide probe that detects a non-poly(A) RNA EBV transcript expressed in latently infected cells, was applied. The slides were incubated at 37°C for 1 hour before being washed with probe wash, developed with an in situ hybridization detection system (Biomeda, Foster City, CA), and counterstained with hematoxylin.

Literature review

A literature search was performed from 1990 to February 2011 on PubMed using the search terms of "liver", "Epstein-Barr virus", "HIV infection", "acquired immunodeficiency syndrome", "smooth muscle tumor", "leiomyoma", "leiomyosarcoma", and "muscle neoplasms". All reported cases with diagnoses of EBV associated SMT in the liver were reviewed. Only cases of adult HIV-infected patients (≥ 18 years old) were included, excluding the pediatric cases. A total of 9 cases of intrahepatic EBV-SMT in adult AIDS patients, including our current case, fulfilled these criteria and were included in the review.

Results

Microscopic and Immunohistochemical findings

On light microscopy (**Figure 2**), these hypercellular hepatic lesions are comprised of two cell populations: relatively monomorphic spindle cells arranged in short intersecting fascicles, and more primitive-looking oval to round cells

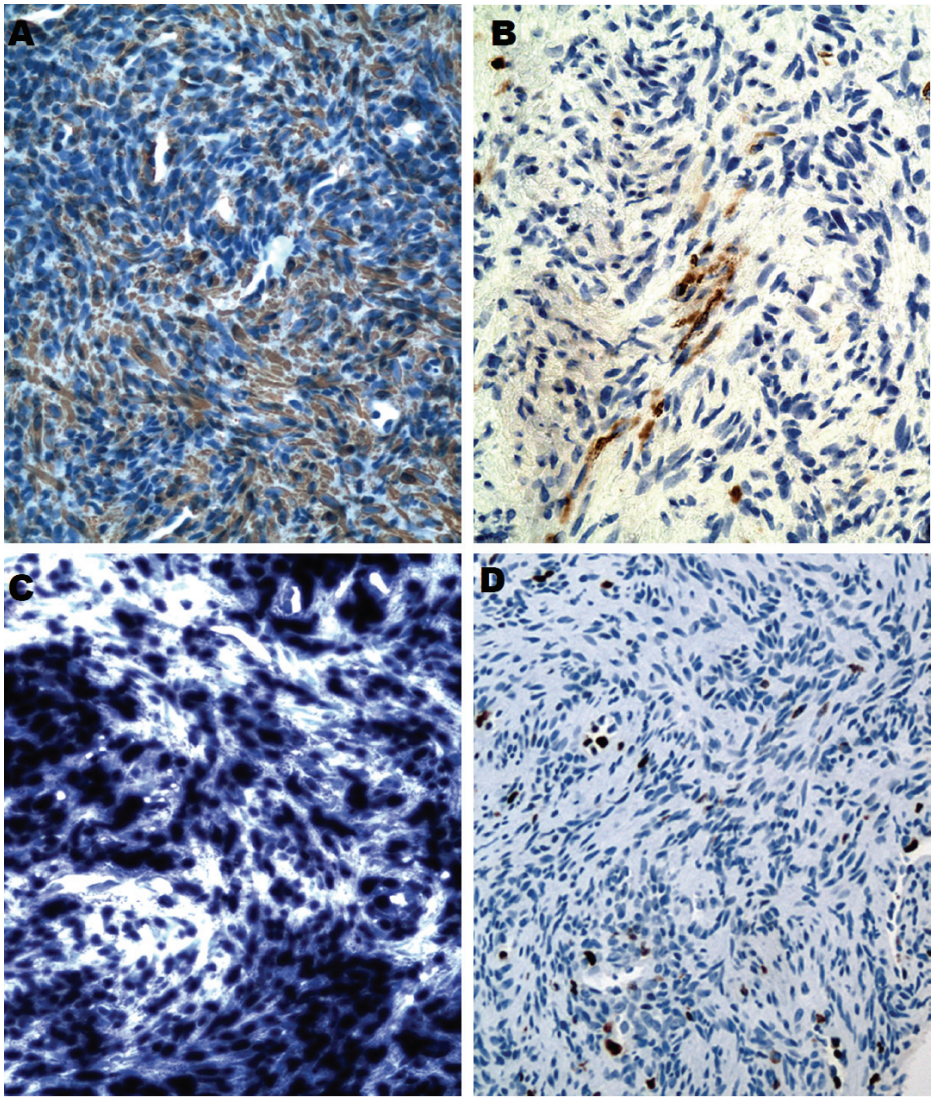

Figure 3. A. Immunohistochemical stain for smooth muscle actin produces strong diffuse cytoplasmic staining in the tumor cells. **B.** The tumor cells show focal immunoreactivity for desmin. **C.** EBER in situ hybridization produces strong distinct nuclear staining in the tumor cells. **D.** Ki-67 immunostain highlights a few proliferating tumor cells.

that form separate nodules. The nuclei of the tumor cells are slightly hyperchromatic with delicate chromatin and inconspicuous nucleoli. The cytoplasm was deeply eosinophilic. There were mild to moderate nuclear atypia with a minimal mitotic activity of 1 mitotic figure per 10 high power fields. Focal single cell necrosis was seen. Additionally, some tumor cells were intimately related to the walls of small blood vessels, suggesting smooth muscle cells in the preexisting vessels as the potential origin of the lesions. The residual non-neoplastic hepatic parenchyma showed intact architecture with no evidence of cirrhosis.

Immunohistochemical stains demonstrated that the tumor cells were diffusely positive for SMA, focally positive for desmin (**Figure 3**), and negative for CD34, CD31, HHV8, S100, CD117, CD99, and pan-cytokeratin. The proliferation marker Ki-67 highlighted only a few proliferating tumor cells (**Figure 3**). Fite's acid fast stain and Warthin-Starry stain failed to demonstrate the presence of mycobacteria or *Bartonella henselae* microorganisms, as are seen in the mycobacterial spindle cell pseudotumor and bacillary angiomatosis, respectively.

EBV analysis

EBV was studied by chromogenic in situ hybridization using EBER1 oligonucleotides. The nuclei of the tumor cells showed strong positivity for EBER-1 in greater than 95% of the cells, indicat-

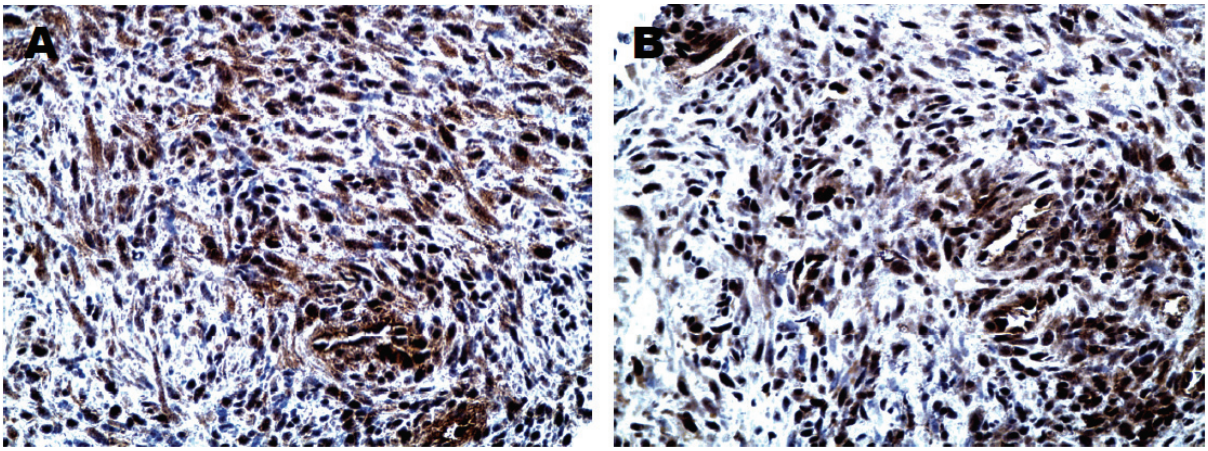

Figure 4. Expression of p-Akt at serine 473 (**A**) and p-mTOR at serine 2448 (**B**) in the current case of hepatic EBV-SMT.

ing latent EBV viral infection (**Figure 3**). There was no in situ hybridization signal in the nuclei of the adjacent hepatocytes. Immunohistochemical stain of EBV-LMP1 was negative in tumor cells. CD21, the EBV receptor on B lymphocytes, could not be detected in the tumor cells by immunostaining. *Polymerase chain reaction* (PCR) analysis of the patient's plasma failed to detect the presence of EBV DNA. A diagnosis of EBV-associated smooth muscle tumor with uncertain malignant potential was made.

Studies on Akt/mTOR signal pathway

The chromogenic signals for p-Akt (serine 473) and p-mTOR (serine 2448) were both primarily localized in the nuclei of the tumor cells. Moderate to strong nuclear staining of p-Akt and p-mTOR was observed in > 90% of tumor cells, indicating constitutive activation of the mTOR signaling in this EBV-related tumor (**Figure 4**).

Discussion

The clinicopathologic findings of the current and 8 previously reported cases of hepatic EBV-SMT occurring in HIV-infected adults are summarized in **Tables 1** and **2**. The male to female ratio was 8: 1, and 8 of 9 patients were in their third decade of life. Hepatic EBV-SMT were detected from 48 to 120 months (mean 96 months) after the diagnosis of HIV infection. CD4 cell count at the initial presentation ranged from 2 to 150 cells/ul (mean 39 cells/ul; median 18 cells/ul). Plasma HIV RNA levels were extremely variable ranging from < 400 to 796,000 copies/ml. The hepatic tumors can be single or multiple, with a maximal diameter varying greatly between 0.9 cm and 14.0 cm. Follow-up information was available in eight patients. Five patients were alive: one patient (case 9) underwent resection of the liver tumors and had no recurrence 8 months post surgery, whereas the remaining four receiving no treatment were alive with persistent liver tumors at least 7, 7, 11, and 12 months after presentation. Three patients died. Of note, only one patient (case 8) died of EBV-SMT nine months following diagnosis, whereas the other two died of opportunistic infections. This patient (case 8) had a very high tumor burden with SMT involving multiple organs including the liver, lungs, gallbladder, and spinal cord. Regarding microscopic features, mitotic activity was documented in 7 of 9 cases, with virtually all 7 cases having less than 3 mitoses per 10 high power fields. Focal necrosis was present in 2 cases.

Together, the observations in these 9 cases suggest that hepatic EBV-SMT usually present as relatively well-differentiated tumors in adult HIV patients. The natural evolution of these tumors appears to be slow, and even in the face of multiple lesions, death in these patients is only occasionally due to the direct effects of EBV-SMT. Accordingly, it is very important to distinguish hepatic EBV-SMT from the non-EBV-related primary or metastatic leiomyosarcomas that occur in the liver, which typically pursue a far more aggressive clinical course and may potentially necessitate different clinical man-

Table 1. Hepatic EBV-SMT in Adult HIV Infection Patients: Clinical Data

Case #	Ref.	Age/ Sex	Interval between HIV and EBV-SMT (months)	CD4 count (cells/ul)	Plasma HIV RNA level (copies/ml)	EBV-SMT locations	Single/ Multiple tumor(s)	Liver SMT(s) size (cm)	Tx	Outcome/ Follow-up time
1	(1)	24/M	NA	20	1,437	Liver	NA	NA	NA	NA
2	(6)	33/M	60	9	NA	Liver	S	2.0	NA	Death due to disseminated atypical mycobacteriosis/1
3	(7)	32/M	96	43	NA	Liver	S	1.8	None	No remission/7
4	(8)	35/M	NA	8	360,000	Liver	M	1.0 & 3.5	None	Enlargement of liver masses/12
5	(9)	37/F	120	2	< 400	Liver	S	5.0	None	Size of liver mass unchanged/11
6	current case	34/M	114	15	796,000	Liver	M	0.9 – 2.3	None	No remission/7
7	(10)	38/M	120	150	470,870	Liver, lung	M	14.0	None	Death, opportunistic infection?/6
8	(11)	38/M	114	NA	NA	Liver, lung, gallbladder, spinal cord	M	NA	NA	Death of disease/9
9	(12)	34/M	48	66	NA	Liver, brain, spinal cord	M	NA	Removal surgery	No recurrence/8

Abbreviations: NA = not available; Ref. = reference number; M = male; F = female; S = single nodule; M = multiple nodules; Tx = treatment

agement [15-16].

EBV-SMT has many unique biological and histologic features that are rarely seen in the non-EBV-related SMT. These include occurrence exclusively in immunosuppressed patients, frequent multifocal involvement at very uncommon sites, presence of dual cell populations composed of not only the typical spindle-shaped cells but also primitive-appearing oval to round cells, hemangiopericytoma-like vascular pattern, variable intratumoral T lymphocytes, only mild to moderate nuclear atypia, and consistently sparse mitotic activity [11], [17]. The presence of multifocal masses, as seen in our patient, certainly raises the concern for malignancy and metastases. However, previous molecular analysis of different tumors in a given patient have shown that each tumor is derived from a different clone and therefore, represents multiple independent primaries rather than metastases from a single tumor [11], [2], [1]. Clonal analysis was not performed in the current case. Immunohistochemical stain for SMA and EBER in situ hybridization are diffusely positive in all EBV-SMT examined thus far, and are currently used as the most sensitive and reliable markers for the diagnosis of EBV-SMT. Expression of desmin is variable in EBV-SMT.

At present, how EBV infects and transforms the myocytes is largely unknown. Immunostaining for CD21, the EBV receptor on B lymphocytes and epithelial cells [18], was negative in the current case, similar to the findings of other investigators [7-8]. In contrast, McClain et al reported strong staining of CD21 in all 6 cases of EBV-SMT in HIV-infected children [1] , [19]. These discrepancies may reflect different antibodies utilized in immunohistochemistry or lower expression of CD21 in some cases that is below the threshold of technique sensitivity. Alternatively, EBV may enter the myocytes via other routes, such as fusion with EBV-infected lymphocytes [20-21]. Recently, a novel EBV receptor was identified in EBV-associated gastric carcinoma cells [22], raising the possibility that EBV-SMT tumor cells may similarly express a receptor protein that is distinct from CD21. EBV-LMP1 has clearly established transforming

Table 2. Hepatic EBV-SMT in Adult HIV Infection Patients: Histologic Features

Case #	Ref.	Histology	# of mitosis/ 10 HPFs	Tumor necrosis	HPC-like pattern	IHC	EBER ISH	Blood EBV DNA level (copies/mL)
1	(1)	Leiomyosarcoma	NA	NA	NA	SMA+, desmin+, CD21 weakly +	Positive	16,470 (whole blood)
2	(6)	Leiomyoma	0	0	NA	SMA+, vimentin-, C34-, factor XIII-	Positive	NA
3	(7)	Leiomyomatous tumor	< 1	0	NA	SMA+, CD68-, CD21-	Positive	NA
4	(8)	SMT of LMP	0	0	NA	SMA+, desmin focally +, S100-, CD117-, CD68-, CD21-, EBV-LMP1 faintly focally +	Positive	NA
5	(9)	SMT	NA	NA	NA	NA	Positive	Positive
6	current case	SMT of UMP	1	Focally present	Present	SMA+, CD31-, CD34-, S100-, HHV8-, CD117-, CD99-, CD21-, EBV-LMP1-	Positive	Negative
7	(10)	SMT	2	NA	Present	SMA+, desmin focally +, S100-, EMA-, CD34-, CD99-	Positive	45,108 (plasma)
8	(11)	SMT	1-3	Present	NA	SMA+, desmin+, EBV-LMP1+	Positive	NA
9	(12)	Myopericytoma	0	NA	Present	SMA+, caldesmon+, desmin-, CD99-, CD34-, factor XIII-, S100-, HHV8-	Positive	NA

Abbreviations: HPFs = high power fields; NA = not available; Ref. = reference number; IHC = immunohistochemistry; ISH = in situ hybridization; HPC = hemangiopericytoma; LMP = low malignant potential; UMP = unknown malignant potential

properties [23-24]. However, reports on LMP1 expression in EBV-SMT are equivocal, with negative immunostaining observed in the vast majority of cases, including the present case, focal faint reactivity in three cases, and detection by reverse transcriptase-polymerase chain reaction (RT-PCR) but not by immunohistochemistry in two cases [25], [11], [26]. Thus, the role of LMP1 in EBV-SMT remains to be determined.

Due to the relative rarity, the malignant potential of EBV-SMT is uncertain, revealing neither the benign behavior of leiomyomas nor the apparently aggressive behavior of leiomyosarcomas. Accordingly, optimal treatment for EBV-SMT aside from surgery is yet to be determined. Currently, complete surgical resection remains the mainstay therapy and has been shown satisfactory results, as in case 9 of our review [27]. Chemotherapy and radiotherapy appear to be ineffective in these tumors. Improvement of immune status, which is effective in the treatment of EBV-related posttransplant lymphoproliferative disease, might also improve the outcome of EBV-SMT in AIDS patients [10].

The mammalian target of rapamycin (mTOR) has a central role in the regulation of cell growth [28]. Various growth factors and nutrients activate mTOR via multiple signaling pathways, which in turn stimulate protein synthesis by phosphorylating key translation regulators such as ribosomal S6 kinase and eukaryote initiation factor 4E binding protein 1 [29]. High levels of dysregulated mTOR activity are associated with many human diseases, including tumorigenesis. Studies by Sodhi [30] and Stallone [31] et al revealed that activation of the Akt/mTOR signal pathway played an essential role in AIDS-related Kaposi sarcoma's tumorigenesis, and sirolimus, an mTOR inhibitor, blocked the progression of Kaposi sarcoma. Very recently, overactivation of the Akt/mTOR signaling was also detected in EBV-SMT [4]. In one transplant patient, sirolimus induced complete remission of EBV-SMT in the liver [32]. Interestingly, Wittek et al published data demonstrating a close relationship between cultured Kaposi sarcoma cells from AIDS patients and leiomyoblasts [33]. In our case, the Akt-mTOR signal pathway is constitutively activated and more importantly the ex-

pression is mainly nuclear. The nuclear subcompartmentalization of p-mTOR (Ser 2448) and its putative downstream effector, p-Akt (Ser 473) more likely reflects mTOR complex 2 (mTORC2) activation, which is less responsive to inhibition by rapamycin (sirolimus) [34]. The mechanism of rapamycin antitumorigenic effect in such cases needs further study. Specifically, further studies are needed to investigate the possible etiologic relationship between EBV-SMT and Kaposi sarcoma, to examine additional therapeutic molecular strategies aimed at inhibiting this Akt/mTOR pathway, and to search for other alternative explanations for the efficacy of sirolimus in EBV-SMT cases.

In conclusion, we have described a case of multicentric hepatic EBV-SMT affecting an adult patient with AIDS and examined the activation of the mTOR signal pathway in this tumor. A review of the literature suggests that the behavior of such tumors appears far less aggressive than the non-EBV- related primary or metastatic leiomyosarcomas involving the liver. Given the increased incidence and prolonged survival of AIDS patients, hepatic EBV-SMT are expected to be encountered more frequently in the future. This case demonstrates that EBV-SMT need to be included in the differential diagnoses of liver mass(es) in HIV-infected patients and that SMA immunohistochemistry and EBER in situ hybridization are the most useful ancillary studies.

Acknowledgements

We thank Richard A. Breckenridge, Pamela K. Johnston, and the histology technologists at the Lyndon B Johnson General Hospital for their technical assistance, and Bheravi Patel for her secretarial and graphic support.

Address correspondence to: Bihong Zhao, MD, PhD, Department of Pathology & Laboratory Medicine, The University of Texas Medical School at Houston, 6431 Fannin Street, MSB-2.274, Houston TX, 77030, USA. Tel: (713) 500-5349; Fax: (713) 500-0733; E-mail: Bihong.Zhao@uth.tmc.edu

References

[1] McClain KL, Leach CT, Jenson HB, Joshi VV, Pollock BH, Parmley RT, DiCarlo FJ, Chadwick EG and Murphy SB. Association of Epstein-Barr virus with leiomyosarcomas in children with AIDS. N Engl J Med 1995; 332: 12-18.

[2] Lee ES, Locker J, Nalesnik M, Reyes J, Jaffe R, Alashari M, Nour B, Tzakis A and Dickman PS. The association of Epstein-Barr virus with smooth-muscle tumors occurring after organ transplantation. N Engl J Med 1995; 332: 19-25.

[3] Boman F, Gultekin H and Dickman PS. Latent Epstein-Barr virus infection demonstrated in low-grade leiomyosarcomas of adults with acquired immunodeficiency syndrome, but not in adjacent Kaposi's lesion or smooth muscle tumors in immunocompetent patients. Arch Pathol Lab Med 1997; 121: 834-838.

[4] Ong KW, Teo M, Lee V, Ong D, Lee A, Tan CS, Vathsala A and Toh HC. Expression of EBV latent antigens, mammalian target of rapamycin, and tumor suppression genes in EBV-positive smooth muscle tumors: clinical and therapeutic implications. Clin Cancer Res 2009; 15: 5350-5358.

[5] To KF, Lai FM, Wang AY, Leung CB, Choi PC, Szeto CC, Lui SF, Yu AW and Li PK. Posttransplant Epstein-Barr virus-associated myogenic tumors involving bone. Cancer 2000; 89: 467-472.

[6] Prevot S, Neris J and de Saint Maur PP. Detection of Epstein Barr virus in an hepatic leiomyomatous neoplasm in an adult human immunodeficiency virus 1-infected patient. Virchows Arch 1994; 425: 321-325.

[7] Wang MH, Wu CT, Hung CC, Liang JD and Chen PJ. Hepatic leiomyomatous neoplasm associated with Epstein Barr virus infection in an adult with acquired immunodeficiency syndrome. J Formos Med Assoc 2000; 99: 873-875.

[8] Cheuk W, Li PC and Chan JK. Epstein-Barr virus-associated smooth muscle tumour: a distinctive mesenchymal tumour of immunocompromised individuals. Pathology 2002; 34: 245-249.

[9] Wong KH, Chan KC, Lee SS, Lai ST, Lee N, Cockram C, Poon WS, Tsang TY, Tso YK and To KF. Epstein-Barr virus-associated smooth muscle tumor in patients with acquired immunodeficiency syndrome. J Microbiol Immunol Infect 2007; 40: 173-177.

[10] Suankratay C, Shuangshoti S, Mutirangura A, Prasanthai V, Lerdlum S, Shuangshoti S, Pintong J and Wilde H. Epstein-Barr virus infection-associated smooth-muscle tumors in patients with AIDS. Clin Infect Dis 2005; 40: 1521-1528.

[11] Deyrup AT, Lee VK, Hill CE, Cheuk W, Toh HC, Kesavan S, Chan EW and Weiss SW. Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol 2006; 30: 75-82.

[12] Calderaro J, Polivka M, Gallien S, Bertheau P, Thiebault JB, Molina JM and Gray F. Multifocal Epstein Barr virus (EBV)-associated myopericytoma in a patient with AIDS. Neuropathol Appl

Neurobiol 2008; 34: 115-117.
[13] Zevallos-Giampietri EA, Yanes HH, Orrego Puelles J and Barrionuevo C. Primary meningeal Epstein-Barr virus-related leiomyosarcoma in a man infected with human immunodeficiency virus: review of literature, emphasizing the differential diagnosis and pathogenesis. Appl Immunohistochem Mol Morphol 2004; 12: 387-391.
[14] Shen Q, Stanton ML, Feng W, Rodriguez ME, Ramondetta L, Chen L, Brown RE and Duan X. Morphoproteomic analysis reveals an overexpressed and constitutively activated phospholipase D1-mTORC2 pathway in endometrial carcinoma. Int J Clin Exp Pathol 4: 13-21.
[15] Lang H, Nussbaum KT, Kaudel P, Fruhauf N, Flemming P and Raab R. Hepatic metastases from leiomyosarcoma: A single-center experience with 34 liver resections during a 15-year period. Ann Surg 2000; 231: 500-505.
[16] Gates LK, Jr., Cameron AJ, Nagorney DM, Goellner JR and Farley DR. Primary leiomyosarcoma of the liver mimicking liver abscess. Am J Gastroenterol 1995; 90: 649-652.
[17] Gallien S, Zuber B, Polivka M, Lagrange-Xelot M, Thiebault JB, Bertheau P, Gray F and Molina JM. Multifocal Epstein-Barr virus-associated smooth muscle tumor in adults with AIDS: case report and review of the literature. Oncology 2008; 74: 167-176.
[18] Okano M, Thiele GM, Davis JR, Grierson HL and Purtilo DT. Epstein-Barr virus and human diseases: recent advances in diagnosis. Clin Microbiol Rev 1988; 1: 300-312.
[19] Deyrup AT. Epstein-Barr virus-associated epithelial and mesenchymal neoplasms. Hum Pathol 2008; 39: 473-483.
[20] Timens W, Boes A, Vos H and Poppema S. Tissue distribution of the C3d/EBV-receptor: CD21 monoclonal antibodies reactive with a variety of epithelial cells, medullary thymocytes, and peripheral T-cells. Histochemistry 1991; 95: 605-611.
[21] Bayliss GJ and Wolf H. Epstein--Barr virus-induced cell fusion. Nature 1980; 287: 164-165.
[22] Kim YS, Paik SR, Kim HK, Yeom BW, Kim I and Lee D. Epstein-Barr virus and CD21 expression in gastrointestinal tumors. Pathol Res Pract 1998; 194: 705-711.
[23] Wang D, Liebowitz D and Kieff E. An EBV membrane protein expressed in immortalized lymphocytes transforms established rodent cells. Cell 1985; 43: 831-840.
[24] Henderson S, Rowe M, Gregory C, Croom-Carter D, Wang F, Longnecker R, Kieff E and Rickinson A. Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. Cell 1991; 65: 1107-1115.
[25] Rougemont AL, Alfieri C, Fabre M, Gorska-Flipot I, Papp E, Champagne J, Phan V, Fournet JC and Sartelet H. Atypical Epstein-Barr virus (EBV) latent protein expression in EBV-associated smooth muscle tumours occurring in paediatric transplant recipients. Histopathology 2008; 53: 363-367.
[26] Rogatsch H, Bonatti H, Menet A, Larcher C, Feichtinger H and Dirnhofer S. Epstein-Barr virus-associated multicentric leiomyosarcoma in an adult patient after heart transplantation: case report and review of the literature. Am J Surg Pathol 2000; 24: 614-621.
[27] Boudjemaa S, Boman F, Guigonis V and Boccon -Gibod L. Brain involvement in multicentric Epstein-Barr virus-associated smooth muscle tumours in a child after kidney transplantation. Virchows Arch 2004; 444: 387-391.
[28] Bhaskar PT and Hay N. The two TORCs and Akt. Dev Cell 2007; 12: 487-502.
[29] Holz MK, Ballif BA, Gygi SP and Blenis J. mTOR and S6K1 mediate assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. Cell 2005; 123: 569-580.
[30] Sodhi A, Montaner S, Patel V, Gomez-Roman JJ, Li Y, Sausville EA, Sawai ET and Gutkind JS. Akt plays a central role in sarcomagenesis induced by Kaposi's sarcoma herpesvirus-encoded G protein-coupled receptor. Proc Natl Acad Sci U S A 2004; 101: 4821-4826.
[31] Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, Ranieri E, Gesualdo L, Schena FP and Grandaliano G. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005; 352: 1317-1323.
[32] Toh HC, Teo M, Ong KW, Lee V, Chan E, Lee AS and Vathsala A. Use of sirolimus for Epstein-Barr virus-positive smooth-muscle tumour. Lancet Oncol 2006; 7: 955-957.
[33] Wittek AE, Mitchell CD, Armstrong GR, Albini A, Martin GR, Seemann R, Levenbook IS, Wierenga DE, Ridge J, Dunlap RC and et al. Propagation and properties of Kaposi's sarcoma-derived cell lines obtained from patients with AIDS: similarity of cultured cells to smooth muscle cells. Aids 1991; 5: 1485-1493.
[34] Dhingra S, Rodriguez ME, Shen Q, Duan X, Stanton ML, Chen L, Zhang R and Brown RE. Constitutive activation with overexpression of the mTORC2-phospholipase D1 pathway in uterine leiomyosarcoma and STUMP: morphoproteomic analysis with therapeutic implications. Int J Clin Exp Pathol 4: 134-146.