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Epstein-Barr Virus-Associated Smooth Muscle Tumor of the Liver and Suspected Multifocal Disease Involving the Tonsil, Central Nervous System, Spine, Adrenal Glands, and Small Intestine in an HIV-Positive Man

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Data Interpretation D
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Conflict of interest: None declared

Patient: Male, 47-year-old
Final Diagnosis: Epstein–Barr virus-associated smooth muscle tumor
Symptoms: Progressive abdominal pain that eventually becomes excessive
Clinical Procedure: —
Specialty: Pathology
Objective: Rare disease

Background: Epstein-Barr virus (EBV)-associated smooth muscle tumor (EBV-SMT) is a recently characterized histopathologic diagnosis. EBV-SMTs are rare mesenchymal tumors comprising EBV-infected smooth muscle cells that usually follow an indolent course, may be multifocal, occur in immunocompromised individuals, and can present with nonspecific symptoms. Diagnosis requires histopathologic examination, immunohistochemistry for smooth muscle cell markers, and in situ hybridization for Epstein-Barr virus-encoded RNA (EBER-ISH). This report describes a human immunodeficiency virus (HIV)-positive individual with hepatic EBV-SMT and suspected multifocal disease.

Case Report: Beginning at age 47, a Thai man with HIV infection developed multiple leiomyomatous lesions over 2 decades, including tumors involving the tonsil, central nervous system, and spine. In 2023, computed tomography demonstrated masses in the liver, adrenal glands, and small intestine. Because of progressive abdominal pain and mass effect, left hepatectomy was performed. Histopathologic examination of the hepatic lesion revealed a well-circumscribed spindle cell tumor arranged in interlacing fascicles without significant atypia or mitotic activity. Immunohistochemically, tumor cells showed smooth muscle actin positivity and desmin/CD117 (KIT) negativity. EBER-ISH demonstrated positive nuclear staining in hepatic tumor cells, confirming the diagnosis of EBV-SMT. Additional extrahepatic lesions were clinically suspected to represent EBV-SMT but were not pathologically confirmed as EBV-associated in this report.

Conclusions: This case documents a prolonged course of apparently multifocal smooth muscle tumors in an HIV-infected patient, culminating in an EBER-ISH-confirmed hepatic EBV-SMT; additional lesions remain clinically suspected without pathologic confirmation of EBV association. This case suggests that EBV-SMT should be considered and confirmed by EBER-ISH when smooth muscle tumors arise at unusual anatomic sites in immunocompromised patients.

Keywords: HIV • Leiomyomatosis • Liver Diseases • Tumor Virus Infections • Virus Diseases
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Introduction

Epstein-Barr virus (EBV)-associated smooth muscle tumor (EBV-SMT) is a recently characterized histopathologic diagnosis [1,2]. EBV-SMTs are rare mesenchymal tumors composed of EBV-infected smooth muscle cells; they were historically reported as leiomyomas or leiomyosarcomas because of their close histologic resemblance to conventional smooth muscle tumors [1]. Unlike conventional smooth muscle tumors, EBV-SMTs predominantly occur in immunocompromised individuals, including patients with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), solid organ or hematopoietic stem cell transplant recipients, and individuals with primary (congenital) immunodeficiency disorders [1,2]. Multifocal lesions are common and are thought to represent independent clones arising from separate infection events, rather than metastases [1,3]. Because histologic features do not reliably predict clinical behavior, diagnosis relies on the combination of spindle cell morphology, immunohistochemical evidence of smooth muscle differentiation, and demonstration of EBV within tumor cells by in situ hybridization for Epstein-Barr virus-encoded RNA (EBER-ISH) [1,2].

EBV contributes to tumorigenesis through interactions with the host immune system, promoting cellular transformation through immune evasion and oncogenic signaling pathways [4]. The association between EBV-SMT and other immunodeficiency-related disorders, including post-transplant lymphoproliferative disorder, suggests overlapping pathogenetic mechanisms related to impaired immune surveillance [5].

EBV-SMT may arise at a wide range of anatomic sites and frequently presents as multifocal disease involving the central nervous system (CNS), liver, lungs, adrenal glands, and gastrointestinal tract [2]. EBV-SMTs have also been identified in patients with HIV infection. In a series of 9 HIV-infected Thai patients, Suankratay et al described EBV-SMTs arising at multiple and unusual sites, most frequently the epidural space, with additional lesions involving the adrenal glands, liver, lung, orbit, and vocal cords; all patients had CD4 counts below 200 cells/μL [6]. Subsequent case reports have described EBV-SMTs involving the brain [7], adrenal glands and spinal extradural space [8], and multiple visceral sites [9] in HIV-infected adults. More recently, Hafez et al observed hepatic EBV-SMT in a 25-year-old woman with congenital HIV infection who was nonadherent to antiretroviral therapy and had a CD4 count of 22 cells/μL [10]. Among these sites, hepatic involvement may pose diagnostic challenges because of overlapping imaging and morphologic features with metastatic disease and other spindle cell neoplasms [10].

This report describes a 47-year-old HIV-positive Thai man with an EBV-SMT of the liver, confirmed by EBER-ISH, and suspected multifocal disease involving the tonsil, CNS, spine, adrenal glands, and small intestine that developed over approximately 2 decades. The extrahepatic lesions either were histologically diagnosed as leiomyomas without EBV testing or were detected only radiologically and thus remain clinically suspected, rather than pathologically confirmed EBV-SMTs. The present report aims to document this prolonged, multifocal-appearing disease course and to emphasize that EBV-SMT should be considered—and confirmed by EBER-ISH—when smooth muscle tumors arise at unusual anatomic sites in immunocompromised patients.

Case Report

A Thai man with a history of HIV infection initially exhibited a right tonsillar leiomyoma and underwent tonsillectomy in 2004, at age 47. He had been diagnosed with HIV infection in 2003 and was receiving a fixed-dose combination antiretroviral regimen of stavudine, lamivudine, and nevirapine (GPO-VIR S30); he had no history of opportunistic infections. CD4 counts documented between 2009 and 2023 ranged from 348 to 782 cells/μL; the most recent count and lowest documented value, obtained in November 2023, was 348 cells/μL (29%). HIV viral load was persistently suppressed in all documented measurements between 2009 and 2013, ranging from less than 20 to less than 50 copies/mL; the most recent value was less than 20 copies/mL in June 2013. No more recent viral load measurements were documented in the available records. In 2008, he developed right cranial nerve VI palsy, and imaging revealed multiple intracranial masses involving the bilateral cavernous sinuses. A right temporal craniotomy with biopsy confirmed leiomyoma.

Follow-up magnetic resonance imaging (MRI) demonstrated progressive tumor growth. Clinically, the patient developed left-eye diplopia and persistent limitation of right lateral gaze. In 2011, the right-sided tumors were resected via frontal craniotomy; however, residual neurologic deficits persisted. Additional frontotemporal craniotomies were performed in 2015 and 2016 to remove the remaining lesions, with histopathologic confirmation of leiomyoma in all specimens. In the 2015 specimen, the mitotic count was less than 1 mitosis per 10 high-power fields, although Ki-67 immunostaining showed focally increased proliferative activity, prompting a recommendation for close clinical follow-up.

In 2023, disease progression was noted. MRI revealed a 1-cm intradural mass at the C2 level and a T7-T8 intradural mass causing spinal cord compression. The patient subsequently developed progressive numbness in both lower extremities, extending to the waist and resulting in impaired ambulation. Whole-spine MRI in September 2023 demonstrated multiple

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Figure 1. Contrast-enhanced computed tomography showing multifocal lesions (May 2023). (**A**) Multiple well-circumscribed, heterogeneously enhancing masses in both hepatic lobes, with the largest lesion in the left lobe measuring 12.7 × 8.2 cm; this lesion was later resected and confirmed as an Epstein-Barr virus (EBV)-associated smooth muscle tumor (EBV-SMT). (**B**) Bilateral adrenal masses, with the largest lesion in the right adrenal gland measuring 9.2 × 8.6 cm. (**C**) Hypervascular, heterogeneous mass in the wall of the small intestine (arrow). (**D**) A 0.9-cm pulmonary nodule in the left lower lobe. The adrenal, small intestinal, and pulmonary lesions were not biopsied and remain clinically suspected EBV-SMTs.

intradural and epidural masses at C2, T4, and T7-T8, consistent with leiomyomatous lesions and associated compressive myelopathy. Decompressive laminectomy at T6-T8 was performed in October 2023, followed by C2 laminectomy in March 2024.

Computed tomography (CT) performed in May 2023 (**Figure 1**) revealed multiple heterogeneous enhancing masses in both hepatic lobes and both adrenal glands, as well as hypervascular lesions in the small intestine. A 0.9-cm pulmonary nodule was also identified in the left lower lobe. Given the patient's history, these findings raised suspicion for EBV-associated smooth muscle tumors. Also in May 2023, image-guided core needle biopsy of the liver demonstrated a leiomyoma with a smooth muscle immunophenotype (smooth muscle actin-positive, desmin-negative, and CD117 [KIT]-negative) and a Ki-67 proliferation index below 1%; EBER-ISH was not performed on the biopsy specimen. The patient developed progressive abdominal pain, distension, and early satiety, prompting surgical intervention.

Left hepatectomy was performed in December 2023. Intraoperatively, multiple masses were identified in both hepatic lobes; large tumors in the left lobe compressed adjacent structures (**Figure 2**). The procedure was completed without complications; estimated blood loss was 200 mL and operative time was 260 minutes. The patient had an uneventful recovery and was discharged on postoperative day 8.

Gross examination of the left hepatectomy specimen (**Figure 2**) revealed a lobulated, firm, well-circumscribed white mass with a fasciculated cut surface, occupying approximately 70% of the resected hepatic parenchyma. Focal degenerative changes were identified.

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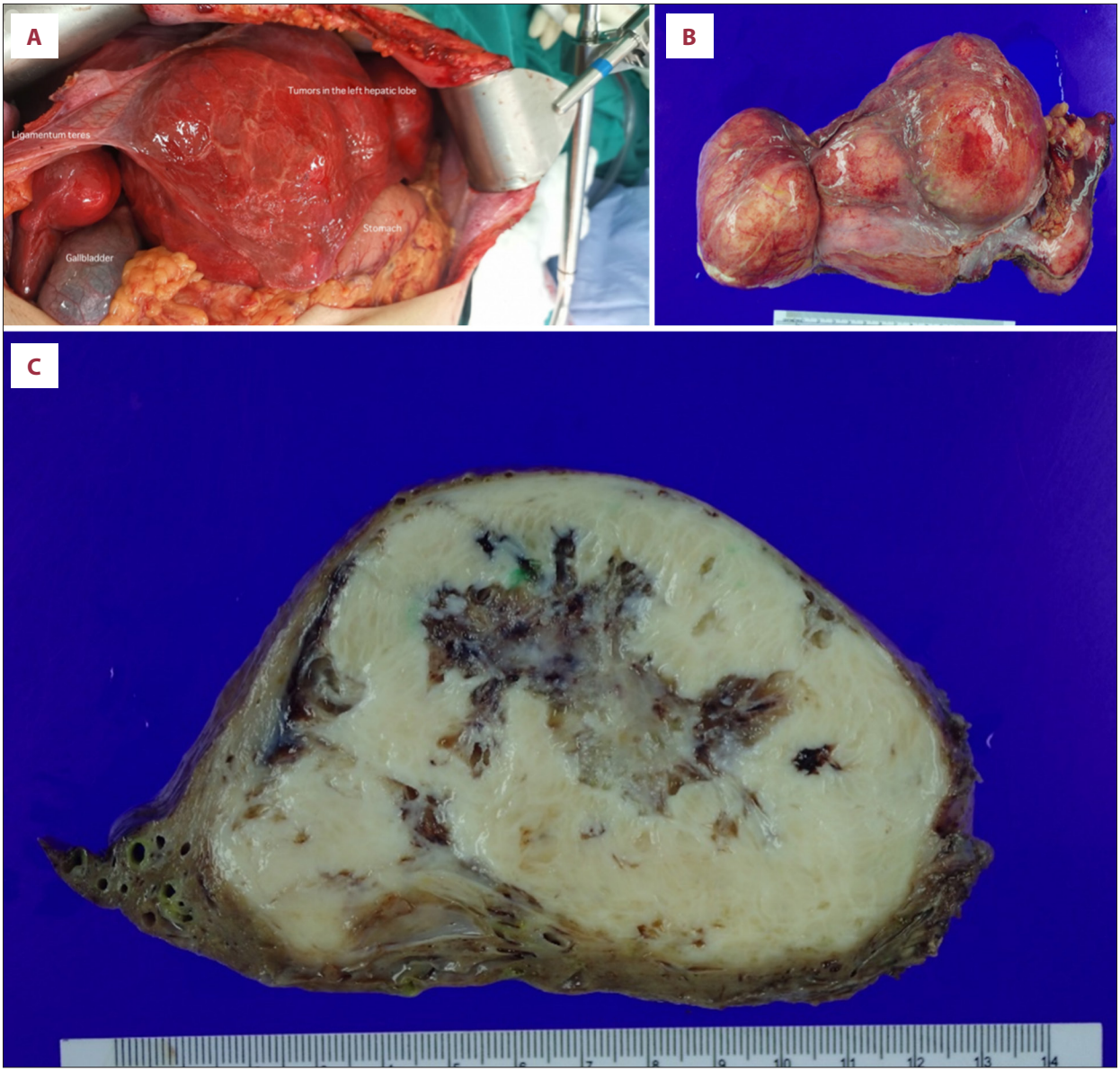


Figure 2. Intraoperative and gross findings for Epstein-Barr virus (EBV)-associated smooth muscle tumor (EBV-SMT) of the liver (left hepatectomy, December 2023). (**A**) Intraoperative view showing the large tumor in the left hepatic lobe. (**B**) Left hepatectomy specimen demonstrating a lobulated mass. (**C**) Cut surface revealing a firm, white, well-circumscribed mass with a fasciculated appearance, occupying approximately 70% of the resected hepatic parenchyma.

Microscopically (**Figure 3**), the tumor was composed of spindle-shaped cells arranged in interlacing fascicles. The tumor cells exhibited elongated nuclei and moderate-to-abundant eosinophilic cytoplasm. No significant cytologic atypia or mitotic figures were identified. Areas of degeneration containing eosinophilic proteinaceous material were present.

Immunohistochemically (**Figure 3**), the tumor cells showed smooth muscle actin positivity and desmin/CD117 negativity. EBER-ISH demonstrated positive nuclear staining in the tumor cells, confirming EBV-associated smooth muscle tumor. EBER-ISH was not performed on previously resected or biopsied specimens because of suboptimal tissue quality. Ki-67, DOG1 (discovered on gastrointestinal stromal tumor [GIST]-1), and CD34 immunostaining and molecular testing were not performed on the hepatectomy specimen; however, Ki-67 immunostaining performed on the 2023 core needle biopsy and the lesion resected from T6-T8 laminectomy showed a proliferation index below 1% in both specimens. The chronological disease course, including all procedures, pathologic findings, and EBV-related testing, is summarized in **Table 1**.

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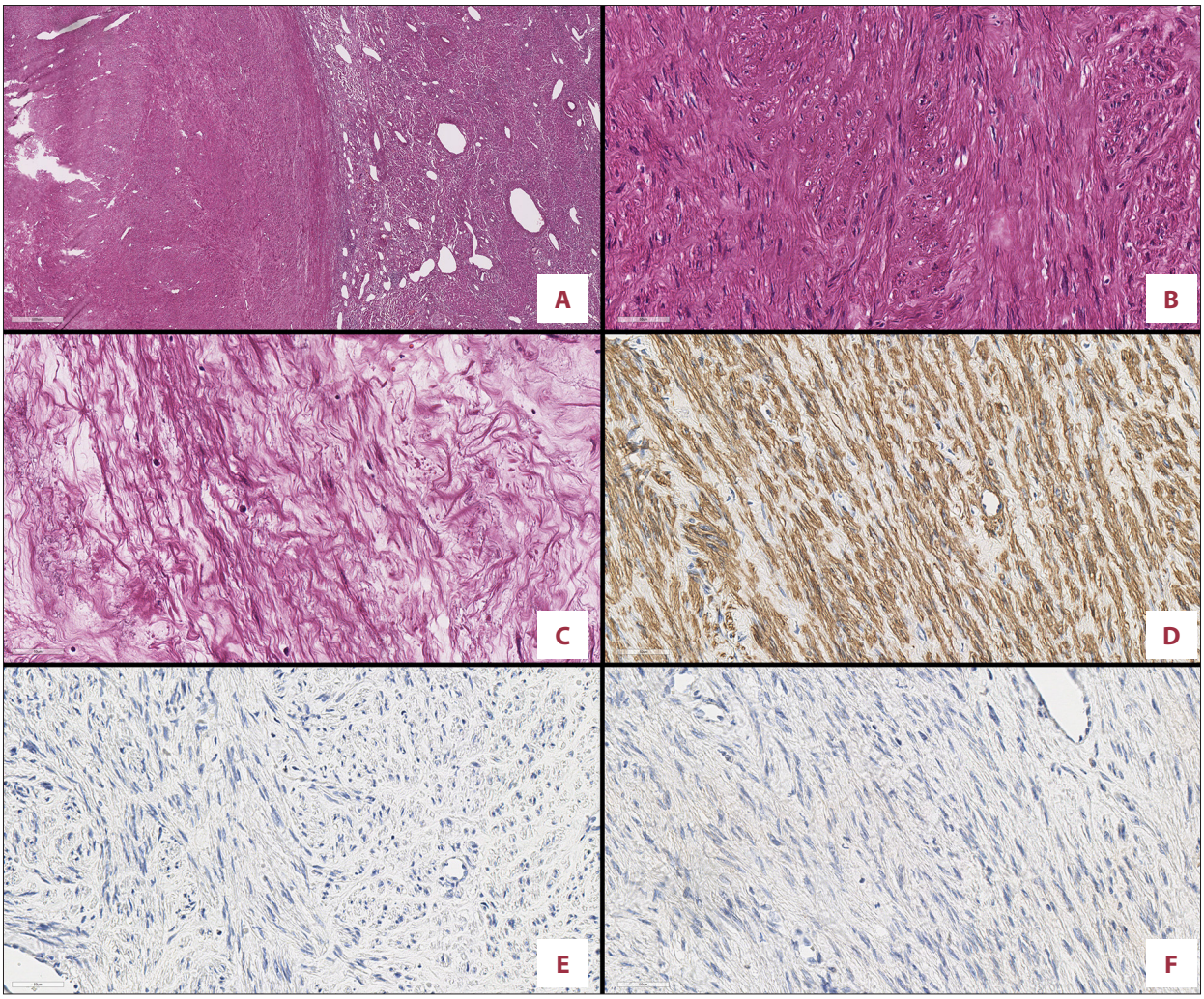
Discussion

EBV-SMTs are rare neoplasms that predominantly occur in immunocompromised individuals, including patients with HIV/AIDS, post-transplant recipients, and those with congenital immunodeficiency [1,2]. The association between EBV and smooth muscle tumors was first described by McClain et al in 1995 [11]. Although initially recognized mainly in children and young adults, EBV-SMTs have increasingly been reported in older adults [2,6].

EBV-SMT frequently presents as multifocal disease involving multiple organ systems and often arises at unusual anatomic sites compared with conventional smooth muscle tumors. Commonly involved sites include the CNS, liver, lungs, adrenal glands, and gastrointestinal tract; less frequent sites include the gallbladder, bone, bladder, spleen, thyroid, and heart [3,6]. Molecular studies suggest that multifocal lesions may represent separate primary tumors arising from independent EBV infection events rather than metastatic spread, although the precise mechanisms of tumorigenesis are not fully understood [1,3,12].

In the present case, this distinction has direct implications for interpretation. Lesions resected or biopsied between 2004 and 2024, apart from the hepatic tumor, were histologically diagnosed as leiomyomas without EBV testing; only the hepatic tumor was examined by EBER-ISH and confirmed as EBV-associated. Accordingly, the multifocal pattern in our patient may represent multiple independent EBV-related tumor foci, clinically suspected disseminated disease, or a combination of EBV-associated and unrelated smooth muscle lesions [3,12]; the available data do not allow these possibilities to be distinguished. Such uncertainty emphasizes that the extent of pathologically confirmed EBV-associated disease in the present report is limited to the hepatic tumor.

The principal contribution of the present case is documentation of a prolonged, multifocal-appearing smooth muscle tumor course in an HIV-infected adult that culminated in



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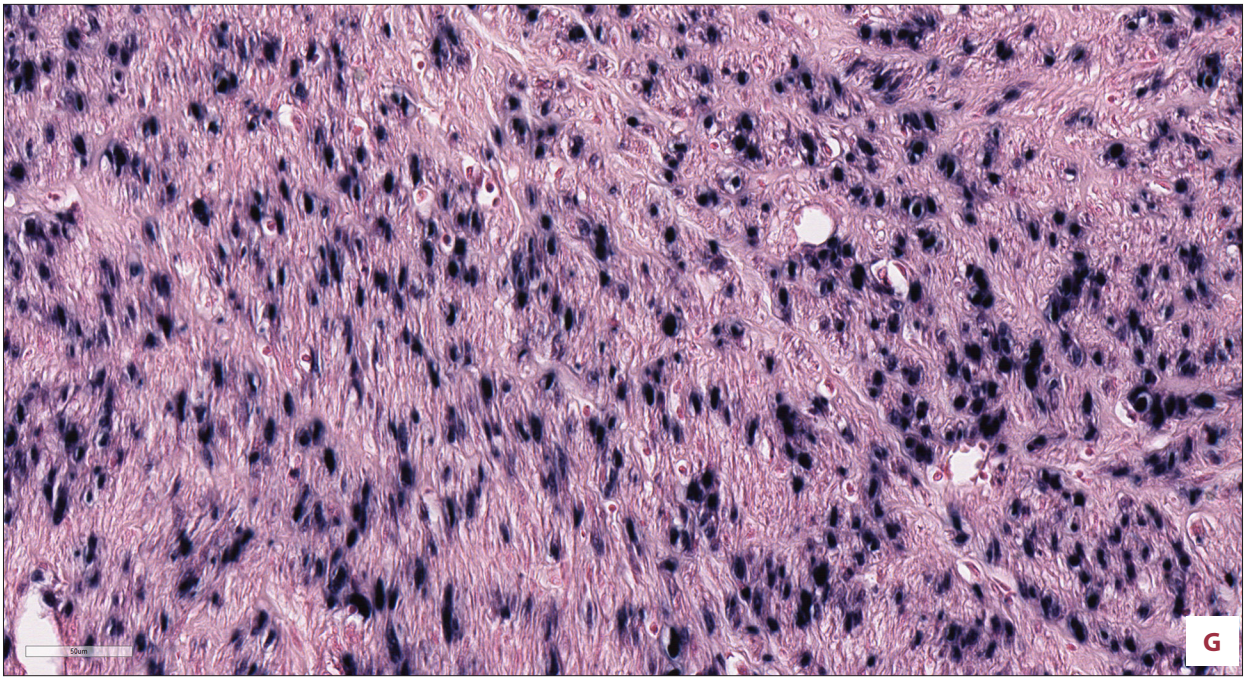


Figure 3. Histopathologic, immunohistochemical, and in situ hybridization findings for Epstein-Barr virus (EBV)-associated smooth muscle tumor (EBV-SMT) of the liver (left hepatectomy specimen). (**A**) Hematoxylin and eosin (H&E) staining at low power (objective × 4; original magnification × 40) showing a spindle cell tumor (**left**) adjacent to compressed non-neoplastic liver tissue (**right**). (**B**) H&E staining at high power (objective × 40; original magnification × 400) showing interlacing fascicles of spindle cells with elongated, blunt-ended nuclei and moderate-to-abundant eosinophilic cytoplasm, without significant nuclear atypia or mitotic figures. (**C**) H&E staining at high power (objective × 40; original magnification × 400) showing an area of degeneration containing eosinophilic proteinaceous material. (**D**) Immunohistochemistry for smooth muscle actin (objective × 40; original magnification × 400) showing diffuse, strong cytoplasmic staining in tumor cells. (**E**) Immunohistochemistry for desmin (objective × 40; original magnification × 400) showing negative staining in tumor cells. (**F**) Immunohistochemistry for CD117 (KIT) (objective × 40; original magnification × 400) showing negative staining in tumor cells. (**G**) In situ hybridization for Epstein-Barr virus-encoded RNA (EBER-ISH) (objective × 40; original magnification × 400) showing dark blue-black nuclear signals in most tumor cells, confirming EBV presence within neoplastic smooth muscle cells.

EBER-ISH-confirmed hepatic EBV-SMT, which underscores the diagnostic value of EBER-ISH for smooth muscle tumors arising at unusual anatomic sites in immunocompromised patients. Over approximately 2 decades, the patient developed multiple leiomyomatous lesions involving the tonsil, CNS, and spine, followed by radiologically detected lesions in the liver, adrenal glands, small intestine, and lung; however, EBV infection was confirmed only in the hepatic tumor. Additional lesions either were not histologically evaluated or were diagnosed as leiomyomas without EBV testing and thus remain clinically suspected, rather than pathologically confirmed EBV-SMTs. This distinction is essential when interpreting the extent of disease.

Comparison with previously reported HIV-associated cases highlights several features of the present case. First, most HIV-associated EBV-SMTs have been described in the setting of advanced immunosuppression: all patients in the Thai series by Suankratay et al had CD4 counts below 200 cells/μL [6], and the patients reported by Chong et al and Hafez et al had CD4 counts of 6 and 22 cells/μL, respectively, at presentation [8,10]. In contrast, our patient had documented CD4 counts of 348 to 782 cells/μL with suppressed viral loads during the available follow-up, suggesting that EBV-SMT can continue to develop or progress even when HIV infection appears to be controlled. However, CD4 counts before 2009, when the tonsillar and initial intracranial tumors were diagnosed, were unavailable; a period of more severe immunosuppression earlier in the disease course cannot be excluded. Second, the distribution of lesions in our patient, including intracranial, spinal intradural and epidural, adrenal, and hepatic lesions, closely resembles the sites reported in previous HIV-associated cases, such as epidural and adrenal involvement [6,8], intracranial disease [7], and multiple hepatic masses [10]. This similarity supports, but does not prove, the clinical suspicion that extrahepatic lesions in our patient were also EBV-SMTs. Third, the disease course in our patient spanned approximately 2 decades and required repeated surgical interventions, illustrating the chronic, slowly progressive course that multifocal EBV-SMT can follow. Tonsillar involvement, the first manifestation in our patient, appears to be rare; because EBV testing

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Table 1. Chronological summary of the clinical course, procedures, pathology results, and Epstein-Barr virus-related testing.

Year	Site(s)	Key clinical and imaging findings	Procedure	Pathology	EBER-ISH
2004	Right tonsil	Tonsillar mass	Tonsillectomy	Leiomyoma	Not performed
2008	Intracranial (right cavernous sinus)	Right cranial nerve VI palsy; multiple intracranial masses on MRI	Right temporal craniotomy with biopsy	Leiomyoma	Not performed
2011	Right orbit	Diplopia; limited right lateral gaze; tumor progression on MRI	Frontal craniotomy with resection	Leiomyoma	Not performed
2015-2016	Intracranial (residual lesions in bilateral cavernous sinus)	Residual tumors on follow-up imaging	Frontotemporal craniotomies	Leiomyoma with focal areas of increased proliferative activity	Not performed
May-June 2023	Liver, bilateral adrenal glands, small intestine, lung	Multiple heterogeneously enhancing masses; 0.9-cm pulmonary nodule on CT	Core needle biopsy of liver	Leiomyoma (SMA+, desmin–, CD117–, Ki-67 < 1%)	Not performed
Oct 2023	Spine (T6-T8)	Progressive lower-extremity numbness; multiple intradural and epidural masses at C2, T4, and T7-T8 with compressive myelopathy on MRI	T6-T8 decompressive laminectomy	Leiomyoma (Ki-67 < 1%)	Not performed
Dec 2023	Liver (left lobe)	Progressive abdominal pain, distension, and early satiety	Left hepatectomy	EBV-SMT (SMA+, desmin–, CD117–)	Positive
Mar 2024	Spine (C2)	C2 intradural mass	C2 laminectomy	Leiomyoma	Not performed

EBER-ISH was not performed on previously resected or biopsied specimens because of suboptimal tissue quality.
Abbreviations: C2, second cervical vertebra; CD117 (KIT), KIT proto-oncogene receptor tyrosine kinase; CT, computed tomography; EBER-ISH, Epstein-Barr virus-encoded RNA in situ hybridization; EBV-SMT, Epstein-Barr virus-associated smooth muscle tumor; Ki-67, cell proliferation marker; MRI, magnetic resonance imaging; SMA, smooth muscle actin; T4, fourth thoracic vertebra; T6-T8, sixth to eighth thoracic vertebrae; T7-T8, seventh to eighth thoracic vertebrae; +, positive; –, negative.

was not performed on the tonsillar specimen, its relationship to EBV remains uncertain.

The diagnosis of EBV-SMT can be challenging because of its heterogeneous clinical presentation and histopathologic overlap with other spindle cell neoplasms [13]. Demonstration of EBV within tumor cells by EBER-ISH remains the most reliable diagnostic method when combined with immunohistochemical evidence of smooth muscle differentiation. EBV detection by polymerase chain reaction or serologic testing is less sensitive and thus not recommended for diagnostic confirmation [2,6]. In the present case, the diagnosis of hepatic EBV-SMT was established based on characteristic spindle cell morphology, a smooth muscle immunophenotype, and positive EBER-ISH findings in an immunocompromised host.

Histologically, EBV-SMT typically resembles conventional leiomyoma, with interlacing fascicles of spindle cells, eosinophilic cytoplasm, and elongated nuclei, as observed in the present case. However, unlike leiomyosarcoma, significant cytologic atypia and high mitotic activity are often absent. In some cases, mitotic activity may reach more than 10 mitoses per 10 high-power fields [2,3,6]. Importantly, histologic features do not reliably predict clinical behavior, and even morphologically bland tumors may exhibit progressive or multifocal disease [2,3,6,13]. Prognosis appears to be more closely correlated with the patient's immune status than with conventional histologic parameters [1,8].

In this case, immunohistochemistry demonstrated smooth muscle actin positivity and desmin/CD117 negativity, findings

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consistent with previous reports in which smooth muscle actin expression is common, whereas desmin expression is variable [3,6]. The absence of CD117 expression, along with the positive EBER-ISH result, argued against GIST, an important differential diagnosis with distinct therapeutic implications [14]. Additional GIST-related studies, including DOG1 and CD34 immunostaining and molecular testing, were not performed; therefore, exclusion of GIST in the present case relies on the combination of morphology, smooth muscle immunophenotype, and EBV positivity rather than a comprehensive GIST-directed workup. This case further emphasizes the importance of EBV testing, particularly EBER-ISH, when smooth muscle tumors arise at unusual anatomic sites in immunocompromised patients.

Currently, there is no standardized treatment for EBV-SMT; management is individualized according to disease extent, symptoms, and immune status. Surgical resection remains the primary treatment modality for symptomatic or localized lesions and may provide substantial clinical benefit. In the present case, left hepatectomy was performed to relieve compressive symptoms caused by the large hepatic mass. In patients with HIV infection, immune status optimization through antiretroviral therapy is also considered an important component of management; EBV-SMT regression after immune reconstitution with antiretroviral therapy alone has been documented [8], and reinitiation of antiretroviral therapy was the principal intervention in the hepatic case reported by Hafez et al [10]. Other treatment modalities, including chemotherapy and radiotherapy, have shown limited efficacy, particularly in unresectable disease [1,6,8,9,12]. Given the unpredictable clinical course and potential for multifocal disease, long-term follow-up is recommended.

Conclusions

This report documents an EBV-SMT of the liver, confirmed by EBER-ISH, which arose after a 2-decade course of multiple leiomyomatous lesions in an HIV-infected patient; additional lesions remain clinically suspected without pathologic confirmation of EBV association. This case suggests that EBV-SMT should be considered and confirmed by EBER-ISH when smooth muscle tumors arise at unusual anatomic sites in immunocompromised patients. Individualized management and careful long-term follow-up remain essential given the potential for multifocal disease.

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AI Disclosure

During the preparation of this manuscript, the authors used ChatGPT (GPT-4o; OpenAI, San Francisco, CA, USA) and Claude (Anthropic, San Francisco, CA, USA) to improve the English language, grammar, clarity, and organization of the text, and to assist in revising the manuscript in response to reviewer comments. These tools were used because all authors are non-native English speakers. AI tools were not used to collect, analyze, or interpret the clinical, radiologic, or pathologic data, or to create or modify any figures. All AI-assisted text was reviewed, verified, and edited by the authors, who take full responsibility for the content of this publication.

Institution Where Work Was Done

Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand.

Patient Consent

This case report was approved by the Human Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (approval number NONE-2567-0279). This research was conducted in accordance with Good Clinical Practice (ICH GCP). The patient was de-identified, and the requirement for written informed consent was waived after review by the ethics committee.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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