CASE REPORT

Epstein-Barr Virus-associated Smooth Muscle Tumour: Two Case Reports

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ABSTRACT

Epstein-Barr virus-associated smooth muscle tumour (EBV-SMT) is an intermediate mesenchymal neoplasm recognised in immunocompromised patients, including HIV-infected patients. EBV-SMT is challenging to diagnose since it occurs in various age groups and anatomical sites and presents with nonspecific symptoms. The diagnosis is further complicated by the similarity of its histopathological features with other spindle cell tumours. A clinical history of immunosuppression, immunohistochemistry study and association with Epstein-Barr virus (EBV) infection can aid in the diagnosis. Here, we reported two cases of EBV-SMT in two patients with HIV infection, emphasising the histomorphology features and immunohistochemical profile that help in the diagnosis.
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INTRODUCTION

Epstein-Barr virus-associated smooth muscle tumour (EBV-SMT) is an uncommon mesenchymal neoplasm. In the recent WHO classification of smooth muscle tumours, EBV-SMTs are classified as intermediate tumours due to their ambiguous biological behaviour. (1) It is primarily observed in individuals with impaired immune systems, including patients with HIV/AIDS, post-organ transplant, and primary immunodeficiency. The involvement of the Epstein-Barr virus (EBV) in the pathogenesis of smooth muscle tumours was initially documented during the 1990s, with a primary focus on its presence in children infected with HIV. Since then, there has been an increasing number of cases of EBV-SMT in adult HIV-positive patients that were documented. In those cases, high EBV replication levels, positive Epstein-Barr encoding region in situ hybridisation (EBER-ISH) and viral gene expression in the tumour cells proved EBV infection. (2)

Due to their infrequency, understanding of EBV-SMTs largely stems from case reports or case series. In this report, we present two cases of EBV-SMT in two patients with HIV infection. We aim to report these cases to raise awareness about this entity and prompt its consideration in the differential diagnosis when encountering similar clinical presentations.

CASE REPORT

Case 1: A 41-year-old gentleman with a prolonged history of HIV infection presented with non-specific abdominal pain. The computed tomography (CT) of the abdomen showed multiple enhancing rounded hypodense lesions in the left 11th intercostal space, left temporal lobe, liver, and spleen. The lesions measured 1.5 to 4.5cm, with the largest lesion seen in the liver. Subsequently, he underwent a CT-guided liver biopsy.

Case 2: A 31-year-old gentleman with underlying HIV infection presented with right-sided lower limb pain. Magnetic Resonance Imaging (MRI) of the spine showed an oval, homogenously enhancing intrathecal extramedullary nodule at level L3/L4, causing nerve root compression. Subsequently, he underwent surgical tumour excision, and his symptoms improved post-operatively.

Histopathology

Haematoxylin and eosin-stained (H&E) tissue sections

of the tumours from both patients showed similar histomorphology (Figure 1A and Figure 2A). The tumours comprised bland spindle cells arranged in fascicles within the fibro-collagenous stroma. These spindle cells have elongated nuclei and abundant eosinophilic cytoplasm. Intratumoral lymphocytic infiltration was seen in some areas. The mitotic figure was rare. Mild nuclear atypia was observed. Tumour necrosis was not present.

Immunohistochemistry studies showed the tumour cells were positive for Smooth Muscle Actin (SMA) and H-Caldesmon (Figure 1B-C and Figure 2B-C). The tumour cells also showed nuclear positivity for EBER transcripts by in-situ hybridisation (EBER-ISH) (Figure 1D and Figure 2D).

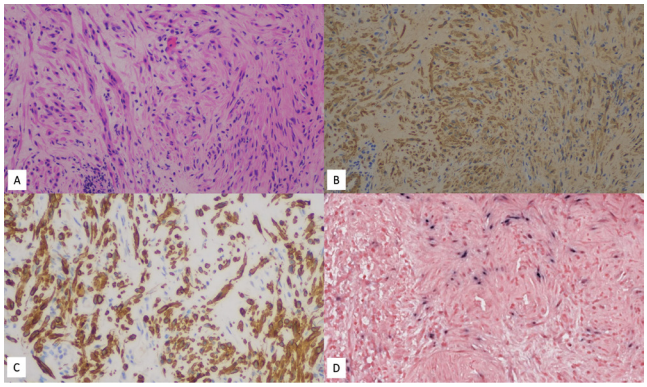

Figure 1: Histopathological findings of Case 1. (A) Haematoxylin and eosin (H&E) stain (200x): The tumour comprises spindle cells arranged in the fascicle. (B) Immunohistochemistry (200X): Smooth muscle actin (SMA) shows membranous positivity of the spindled neoplastic cell, (C) Immunohistochemistry (200X): H-Caldesmon shows membranous positivity of the spindled neoplastic cell, (D) Molecular EBER-ISH (200X) show nuclear positivity.

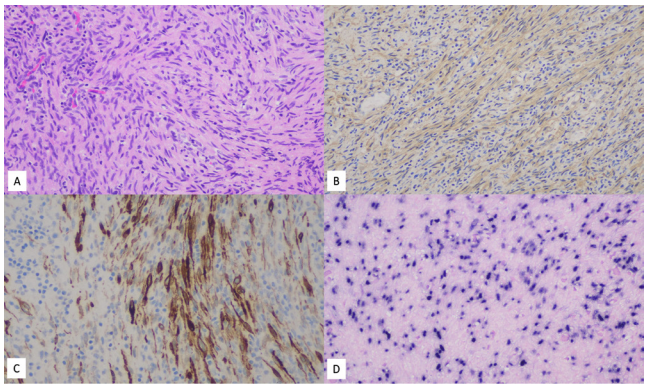

Figure 2: Histopathological findings of Case 2. (A) Haematoxylin and eosin (H&E) stain (200X): The tumour comprises spindle cells arranged in the fascicle. (B) Immunohistochemistry (200X): Smooth muscle actin (SMA) shows membranous positivity of the spindled neoplastic cell, (C) Immunohistochemistry (200X): H-Caldesmon shows membranous positivity of the spindled neoplastic cell, (D) Molecular EBER-ISH (200X) show nuclear positivity.

DISCUSSION

Epstein-Barr Virus-associated smooth muscle tumours primarily affect immunocompromised individuals, such as those with HIV/AIDS, post-transplant recipients or patients with primary immunodeficiency. In HIV-infected patients, EBV-SMT appears to affect adult patients predominantly (72%), although cases have been documented across a wide age range (1-66 years). (1) Table I summarises the clinical presentations of 10 recently reported cases of EBV-SMT cited by a comprehensive article by Lee et al. (2023). (3) It is a rare tumour without epidemiological data in this region. To date, two cases have been reported in Malaysia. Both involved HIV-infected patients; one case occurred in the T10 vertebral body, and the other involved the malar region.(4) Here, we reported two cases of EBV-SMT in patients infected with HIV, in which both patients are adults aged 31 and 41 years old.

Table I: Clinical presentations of recently reported cases of Epstein-Barr virus-associated smooth muscle tumour

Authors	Age, Sex	Immunosuppression	Sites	Treatment
1. Anbardar et al. (2022)	28-year-old, Male	Liver transplant	Liver, spleen, lungs, and colon	Immunosuppressive therapy reduction
2. Chong et al. (2022)	38-year-old, Male.	HIV infection	Adrenal glands and spine.	Surgical resection and radiotherapy
3. Barrett et al. (2022)	42-year-old, Male.	AIDS	Brain	Antiretroviral, antifungal treatment and surgical resection.
4. Fournier et al. (2022)	18-year-old, Female	Heterozygous 22q11.2 deletion/DiGeorge syndrome and homozygous mutation in TNFSF9*	Lungs, liver, spleen, bowel, bone and limbs	Surgical resection, chemotherapy and Rapamycin
5. Johnson et al. (2022)	61-year-old, Male.	Heart and liver transplants.	Liver	Immunosuppressive therapy reduction, liver wedge resections and microwave ablations
6. Yuan et al. (2022)	2.5-year-old, Male	Heart transplant	Multiple in liver	Antiviral and oral sirolimus as a mammalian target of rapamycin (mTOR) inhibitor
7. Galeano-Piedrahita et al. (2021)	40-year-old, Male	HIV infection	Skin and spine	Not mentioned

CONTINUE

Table I: Clinical presentations of recently reported cases of Epstein-Barr virus-associated smooth muscle tumour. (CONT.)

Authors	Age, Sex	Immunosuppression	Sites	Treatment
8. Hansen et al. (2021)	20-year-old, Male.	Heart transplant	Liver, lungs and bowel	Adoptive cell transfer (ACT) of allogeneic EBV-specific T cells
9. Kang et al. (2021)	6-year-old, Female.	Juvenile idiopathic arthritis.	Skull, lung, vertebral body	Surgical resection
10. Zhou et al. (2020)	27-year-old, Male	HIV infection	Liver	Conservative management, including antiretroviral therapy

*Tumor Necrosis Factor Ligand Superfamily member 9

EBV-SMTs represent a unique pathological entity within the spectrum of EBV-related malignancies. Several mechanisms have been proposed to explain how EBV enters the precursor cells of these tumours. Some authors propose that EBV binds to smooth muscle cells through the CD21 receptor. In contrast, others say that EBV-infected lymphocytes and smooth muscle cells may fuse. However, a thorough immunohistochemical analysis conducted by Soares et al. demonstrated that the lymphoid cells within the tumour were positive for CD3 and CD8, but none exhibited positivity for EBER-ISH. This finding cast doubt on the fusion theory. Once inside the host cells, EBV-LMP2A, a latent membrane protein expressed in latency III, initiate the reactivation of the Akt/mammalian target of the rapamycin (mTOR) signaling pathway, leading to MYC overexpression, which promotes cell proliferation and tumour formation. (3)

The diagnosis of EBV-SMTs is challenging due to its diverse clinical presentations and histological features. The tumours can arise anywhere across the body, including areas unusual for sporadic leiomyomas and leiomyosarcomas. Notably, in individuals with HIV infection, the tumour exhibits a distinct predilection for the central nervous system (CNS), with approximately 41% of cases occurring in intra-axial or extra-axial CNS locations. (1) This was observed in both of our patients, where the tumour was in the lumbar spine and left temporal lobe. The predilection of CNS involvement underscores the importance of considering EBV-associated smooth muscle tumours in the differential diagnosis of CNS masses, particularly in HIV-positive individuals.

Whereas approximately 29% of EBV-SMT cases in HIV patients are multicentric, either they occur concurrently or sequentially without demonstrating actual metastatic behaviour as displayed by several reported cases in Table 1. (1) This was observed in our second case, where multiple lesions were observed in different organs. In 2006, Deyrup et al. conducted a study on EBV-SMTs in 19 individuals with several organs affected. The study found that the tumours were genetically different in each case. The results indicate that the multiorgan involvement found in EBV-SMT results from the formation of many primary tumours rather than the dissemination of tumour cells to other parts of the body. (2)

Histologically, the tumours demonstrated interlacing fascicles of spindle cells exhibiting elongated nuclei and eosinophilic cytoplasm. The cytological atypia typically ranges from mild to moderate, although it can be particularly pronounced in individuals with HIV. (1) Roughly half of the cases show a secondary group of small, round tumour cells, which was not observed in our cases. Additionally, EBV-SMTs often demonstrate an infiltrate of intratumoral lymphocytes, which are usually sparse, as seen in the reported cases.(1, 5)

The histological similarities between EBV-SMTs and other spindle cell tumours, including leiomyoma and leiomyosarcoma, pose challenges in accurate diagnosis and underscore the importance of ancillary tests, such as immunohistochemistry and molecular analysis, to distinguish between the entities and confirm the presence of EBV infection. In EBV-SMTs, the spindle cells are positive for smooth muscle markers, including H-Caldesmon and smooth muscle actin (SMA). Desmin occasionally shows focal positivity. The presence of EBV infection in the tumour cells is confirmed by nuclear positive in EBER-ISH, highlighting the virus's involvement in the pathogenesis of these neoplasms and distinguishing them from other spindle cell tumours. (3, 5) Epstein–Barr encoding region in situ hybridisation (EBER-ISH) is the methodology for detecting latent EBV infection in tissue samples. Epstein–Barr virus-encoded small RNAs (EBERs), which include EBER1 and EBER2, are expressed in latently infected cells, primarily localised in the nucleus. Positive EBER-ISH studies show staining in the nuclei of the EBV-infected cells, accentuating the chromatin and often excluding the nucleolus. Currently, there are no established criteria for defining EBV-positivity based on the percentage of EBER-positive cells, particularly in the context of EBV-SMT. The lack of standardised thresholds for EBER positivity means that interpretations can vary, and the definition of EBV-positivity in such cases remains somewhat subjective. It may depend on the specific diagnostic context and clinical guidelines used. (3)

Currently, there are no widely agreed-upon standard treatment methods for EBV-SMTs. However, various techniques have been proposed, as evidenced by recent cases reported in Table 1. The primary approach has typically involved complete surgical resection of the tumour. At the same time, some data suggest that prioritising immune system restoration is a crucial therapy approach due to the multifocal character of EBV-SMT and its correlation with immunodeficiency.

Patients diagnosed with HIV are advised to undergo antiretroviral medication to restore their immunological function. The other potential treatment option is mTOR inhibitors, such as Sirolimus, as the mTOR pathway significantly involves the tumours' development. Several data suggest that administering Sirolimus leads to disease control and regression. Besides that, radiotherapy and chemotherapy are often employed, yet they are generally deemed unsuccessful in the treatment of these tumours. (3) The first patient was successfully treated with surgical tumour excision in the present case. Meanwhile, the second patient did not continue with his follow-up appointments, preventing us from assessing his further management and current condition.

The prognosis is mainly dependent on the patient's immune system. (1) Nevertheless, the involvement of multiple organs and intracranial areas is associated with reduced overall survival in patients with EBV-SMTs. (3) In 2011, Purgina B. et al. conducted a comprehensive analysis of 64 reported cases of EBV-SMTs. This assessment's findings indicated no significant disparities in clinical outcomes between cases classified as smooth muscle tumours (SMT) and those categorised as leiomyosarcomas (LMSs). This concludes that the histological grading of EBV-SMTs does not consistently predict the prognosis. (5)

CONCLUSION

The two presented cases emphasise the importance of including EBV-SMTs in the differential diagnosis of HIV-infected patients presented with atypical clinical manifestations and unusual anatomical locations of spindle cell neoplasms. A clinical history of immunosuppression, immunohistochemistry study and association with EBV infection can aid in diagnosing EBV-SMT. With the growing number of HIV infections and organ transplant recipients, the occurrence of EBV-SMTs may rise accordingly. Therefore, it is crucial to consider EBV-SMTs when evaluating tumours in immunocompromised patients. Further studies are needed to understand better this rare tumour biology and optimal management.

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