Epstein-Barr Virus–Associated Smooth Muscle Tumor

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• Immunodeficient individuals are prone to develop a number of opportunistic infections and unique neoplasms. Epstein-Barr virus–associated smooth muscle tumor is an uncommon neoplasm associated with immunodeficiency. It has been described in patients infected with human immunodeficiency virus, in the posttransplant setting, and in those with congenital immunodeficiency. Different anatomic sites can be involved by Epstein-Barr virus–associated smooth muscle tumor, and even multiple locations can contain these unique lesions within the same patient. The presence of variable numbers of intratumoral lymphocytes and primitive round cell areas are the unique defining features for this tumor. Histopathologic features may vary considerably in terms of cellular atypia, mitotic activity, and necrosis, with no correlation to the clinical behavior. Demonstration of Epstein-Barr virus infection by in situ hybridization within tumor cell remains critical for the diagnosis. The mechanism for Epstein-Barr virus infection of progenitor cells and neoplastic transformation has been an area of interest and conjecture. Different treatment strategies are proposed according to underlying disease status. This paper reviews the clinicopathologic features of this uncommon neoplasm with detailed discussion of the role of Epstein-Barr virus in the pathogenesis.

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Epstein-Barr virus (EBV)–associated smooth muscle tumor (SMT) is an uncommon neoplasm typically manifesting in immunodeficient individuals. The association between SMT and immunosuppression was first described in 1970 by Pritzker et al.[1] Subsequently, Chadwick et al[2] reported SMT in human immunodeficiency virus (HIV)–infected children and asserted the association between HIV and these rare neoplasms. It was only in 1995 that in 2 simultaneous publications[3,4] the clear association with EBV was linked. A detailed pathologic and molecular characterization of this tumor/entity was first described by Deyrup et al.[5]

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Epstein-Barr virus–associated SMT can occur in different locations and can manifest in multiple locations in the same patient. These lesions are considered to be independent primary lesions rather than metastatic disease when multiple tumors are encountered in the same patient. Also, the histopathologic features may vary considerably in different patients (see Table).

Epstein-Barr virus–associated SMT arises in different clinical settings related to immunosuppression, including (1) most commonly, HIV-associated SMT (HIV-SMT); (2) drug-related immunosuppression in posttransplant recipients (PT-SMT); and (3) congenital immunodeficiency disorder–associated SMT.

Authors have compared and analyzed the clinicopathologic features in different groups of patients, dividing them according to the underlying immune-deficient states.[6] A discussion and synopsis of the clinicopathologic features and treatment modalities is provided in this review.

CLINICAL FEATURES

Epstein-Barr virus–associated SMT is an uncommon soft tissue neoplasm affecting both adult and pediatric populations. The affected patients have one of the underlying diseases leading to immunodeficiency listed above. Though there is no significant sex bias, data analysis has revealed that there is a slight female preponderance.[6]

The clinical findings are related to the site of tumor manifestation. The main presentation in these patients is pain and organ dysfunction. The tumor tends to occur mainly in one location in most patients, but simultaneous occurrences in multiple sites have been reported.[7] There is a slight difference in the site predilection in the different subsets of patients.

Human immunodeficiency virus–SMT, which accounts for the majority of the reported cases so far, is most frequently encountered in the central nervous system, gastrointestinal tract and liver, skin, and larynx/lungs/pharynx.[6] A few cases occurring in the adrenal glands have been reported.[7] In contrast, PT-SMT occurs preferentially in the liver,[8] lungs/larynx/pharynx, gut, spleen, and kidneys, sometimes in the brain, and rarely in the adrenal gland and the iris of the eye.[9] Very few cases of congenital immunodeficiency disorder–associated SMT have been reported, and lungs/larynx are most frequently affected, followed by intracranial tumors, liver, adrenal, and spleen.[10–12]

HISTOPATHOLOGIC FEATURES

The tumor may vary in size (0.7–21 cm), with a median size of 3.7 cm. The tumor shows a fascicular arrangement of relatively well-differentiated smooth muscle cells with brightly eosinophilic cytoplasm, and elongated, blunt-ended

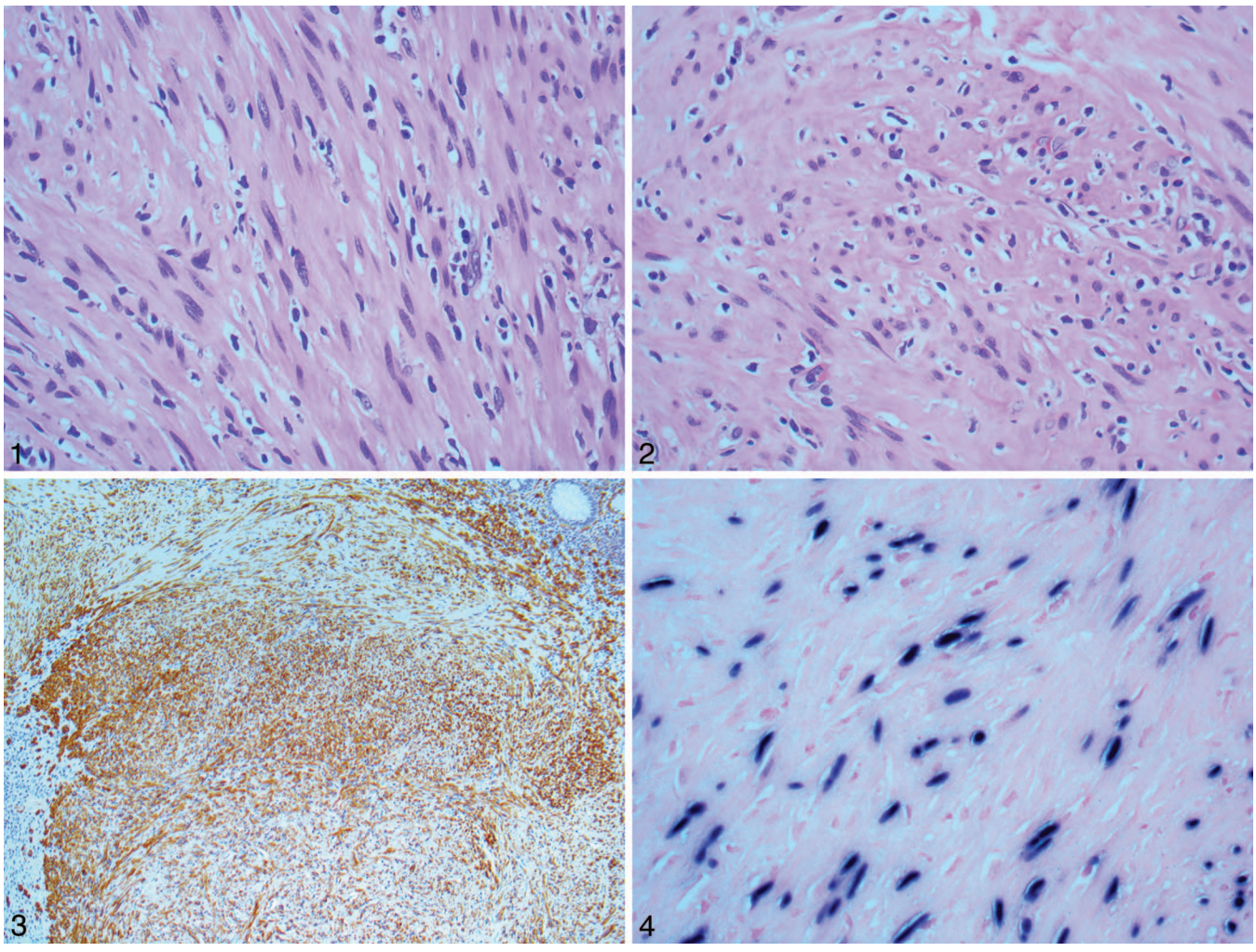

Figure 1. *Spindle cells with histologic features in keeping with a smooth muscle tumor: elongated slender blunt-ended nuclei and eosinophilic cytoplasm. Also noted are a scattering of intralesional lymphocytes (hematoxylin-eosin, ×400).*

Figure 2. *In areas the lesion is characterized by rounder, more primitive-appearing smooth muscle cells (hematoxylin-eosin, ×400).*

Figure 3. *The tumor cells show strong staining for actin (anti-actin, ×400).*

Figure 4. *Epstein-Barr–encoded RNA in situ hybridization highlights the presence of Epstein-Barr virus within the nuclei of the spindle cells (×400).*

nuclei exhibiting variable atypia (Figure 1). There are 2 important defining and unique features. The first is the presence of variable numbers of intratumoral lymphocytes (Figure 1). The lymphocytic infiltrate is composed primarily of T cells. The second distinctive feature is so-called primitive round cell areas arising gradually or abruptly from the well-differentiated smooth muscle cells (Figure 2).[5] These features may vary considerably in different cases. In our case, the lesion was predominated by spindle cells (~95%), and the primitive round cell component contributed to the remaining 5% of the tumor area. The HIV-SMT subtype shows the most histologic variation, ranging from standard leiomyoma-like to leiomyosarcoma-like and even angioleiomyoma or myopericytoma-like features. In such cases, the detection of EBV in the tumor cells remains the mainstay for distinguishing them from conventional leiomyosarcoma.

The histologic features may show foci with variable areas of cellular atypia, mitotic activity, and necrosis. However, unlike in somatic SMT, where the malignant behavior and clinical outcome are predicted by the histologic features, the behavior of EBV-SMTs does not correlate well with their histologic features and apparent grade of lesion.[6,8] Some of the well-differentiated tumors devoid of mitoses and atypia have proven to be lethal.[3] Thus, it has been proposed that these tumors be designated as SMT of uncertain potential.

Immunohistochemically, these tumors exhibit a smooth muscle immunophenotype with positive staining for α smooth muscle actin, muscle-specific actin, and desmin. The extent of immunoexpression of these muscle markers may vary.[13,14] In our case, immunohistochemistry revealed positivity for smooth muscle actin (Figure 3); however, desmin was not expressed in the tumor cells.

Demonstration of EBV–encoded small RNA by in situ hybridization (EBER DNP RNA probe in situ hybridization, Roche Diagnostics, Mississauga, Ontario, Canada) shows nuclear positivity in the spindle cells (Figure 4). The other methods of EBV detection, such as EBV seropositivity and EBV DNA detection by polymerase chain reaction, may provide unreliable results and are unreliable for the diagnosis of EBV-SMT.

Literature Review From 2012 to Present					
Source, y	Age, y/ Sex	Location	Size	Underlying Immunodeficient State	Associated Clinical Disease
Shaw et al,[11] 2012	12/F	Bilateral adrenal masses	21 × 12 × 11 cm and 6 × 5 × 4.5 cm	Natural killer cell deficiency	Nil
Kazmi et al,[14] 2014	8/F	Adrenal, small bowel, lung, brain	0.9–2.5 cm	Post–renal transplant	Nil
Conrad et al,[23] 2013	27/M	Liver	NS	Composite tissue allograft	EBV-positive high-grade B-cell lymphoma
Conrad et al,[23] 2013	1/F	Left colon	5-mm nodule	Liver transplant	Polymorphic EBV-driven SMT in tonsils and cervical nodes
Lohan et al,[24] 2013	37/M	Paraspinal	NS	HIV positive	Nil
Lohan et al,[24] 2013	55/F	Extra-axial with dural attachment	NS	Post–renal transplant	Nil
Takei et al,[25] 2013	27/M	Brain	2.6 × 4.0 × 3.3 cm	Nil, immunocompetent	Hodgkin lymphoma
Ibebuike et al,[26] 2012	37/M	Brain	4.8 × 4.6 × 5.2 cm	HIV positive	Nil
Dominelli et al,[27] 2014	38/F	Tonsil, lung, trachea	8 mm–1.5 cm	HIV positive	Nil

Abbreviations: CT, computerized tomography; EBER-ISH, Epstein-Barr–encoded RNA in situ hybridization; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HPF, high-power field; MRI, magnetic resonance imaging; NS, not specified; SMT, smooth muscle tumor.

PATHOGENESIS

The pathogenesis of these rare tumors and the role of EBV in the tumorigenesis is poorly understood. Two EBV strains primarily infect humans: types 1 and 2 (formerly types A and B). These 2 strains differ in their biologic properties, epidemiology, and geographic distribution. Type 1 has greater transforming ability and has been identified in immunocompetent patients with EBV-positive Hodgkin lymphoma and Burkitt lymphoma, whereas type 2 is pathogenic primarily in immunodeficient patients. The virus is transmitted by close contact, frequently through saliva, and EBV uses the CD21 receptor on the surface of B cells to gain entry into cells. Though limited data are available for strain typing in EBV-SMT, EBV type 2 has been detected.[5]

The progenitor cell for EBV-SMT is thought to be derived from an aberrant myogenous vascular smooth muscle cell.[15] Normal smooth muscle cells have been shown to express the CD21 receptor[15] or a protein with a related, cross-reactive epitope.[16] In support of this theory, tumor cells in EBV-related SMT express CD21.[4,16] These observations have led to the proposal of a model suggesting that EBV infects the smooth muscle cells directly by attaching to CD21 and thereby facilitating and promoting replication within these cells.[17] However, in cases of PT-SMT, examination for CD21 has yielded negative results, suggesting an alternative, as yet unidentified route of EBV integration.[3,18,19] In such cases, fusion of smooth muscle cells with an infected B cell prior to tumor proliferation has been postulated.[13]

Overexpression of *myc*, a proto-oncogene, has been demonstrated in some in EBV-SMT.[16] Upregulation of *myc* proto-oncogene leads to increased cell proliferation. However, no further rearrangement or translocation of *myc* has been shown, suggesting that EBV itself may elicit increased *myc* expression. In addition, the Akt/mTOR pathway is considered to play a significant role in the proliferation of smooth muscle cells. Activation of mTOR has been shown to be triggered by LMP2A,[19,20] which is a latency membrane protein expressed by EBV. Activation of this pathway has been demonstrated in PT-SMT[21] and HIV-SMT.[22] These associations suggest that EBV plays a pivotal and critical role in tumor formation and growth.[8]

Extended			
Radiologic Findings	Histologic Findings	Mitosis	Patient Survival
NS; mass identified on CT scan	Elongated spindle cells with eosinophilic cytoplasm were present along with inflammatory cells, including lymphocytes and histiocytes; hemangiopericytoma-like pattern seen	NS	>26-mo follow-up
MRI brain-enhancing, complex, hemorrhagic extra-axial masses in the right frontal-temporal and right frontal areas measuring 2.5 cm and 0.9 cm in greatest dimension	Spindle to round cells forming irregular short fascicles and small sheetlike areas	Variable, 1–15/10 HPF	>36-mo follow-up
CT, multiple hypodense lesion with annular contrast enhancement	NS	Low mitotic activity, NS	>15 mo
NS	NS	Moderate mitotic activity	>48 mo
MRI, intradural extramedullary mass in the thecal sac posteriorly at the T6 vertebra, isointense to mildly hyperintense on T2-weighted images, isointense on T1-weighted images, and depicted intense uniform enhancement on postcontrast sequences	Compact proliferation of spindle cells with elongated, blunt-ended nuclei and ample eosinophilic cytoplasm, arranged in short intersecting fascicles, EBV-positive by EBER-ISH	NS	NS
MRI, extra-axial with a dural attachment to the lesser wing of the sphenoid, isointense to mildly hyperintense to the grey matter on T2-weighted images and isointense on T1-weighted images; intense homogenous postcontrast enhancement	Interlacing fascicles of mild to moderately pleomorphic atypical spindle cells with ample eosinophilic cytoplasm, mild to moderate increase in cellularity, and few to no areas of necrosis	Low mitosis (<1/10 HPF)	NS
MRI, 2.6 × 4.0 × 3.3-cm homogeneously enhancing intra-axial tumor with marked surrounding edema, extending into the corpus callosum and deep white matter, in the anteromedial aspect of the right frontal lobe	Variable hypercellularity; areas of tumor cells with increased nuclear to cytoplasmic ratio and multiple foci of tumor necrosis	Brisk mitosis (23/10 HPF)	NS
MRI, right frontal lobe mass (measuring 4.8 × 4.6 × 5.2 cm) with irregular rim enhancement and an enhancing solid component invading the superior sagittal sinus	Variably cellular spindle cell neoplasm with degenerative changes	0/10 HPF	>3 mo postoperation
CT scan, polypoid tracheal mass from 8 mm to 1.5 cm in diameter, an increase in the right tonsil mass to 1.1 cm and a left upper lobe nodule measuring 11 mm	Well-circumscribed mass composed of tightly packed fascicles of mildly atypical short spindle cells with scattered intratumoral lymphocytes, no necrosis	Up to 20/10 HPF	>6-mo follow-up

Clonal analysis of multifocal EBV-SMT has indicated that individual tumors in a given patient contain distinct EBV-insertion events.[4,5] As EBV infection is an early event in SMT associated with immunosuppression, this observation suggest that multifocal SMT represents independent primary lesions rather than metastases.

DIFFERENTIAL DIAGNOSIS

The major differential diagnosis considered for a spindle cell lesion in an immunosuppressed individual includes Kaposi sarcoma (KS) and mycobacterial spindle cell pseudotumor. Kaposi sarcoma is a low-grade vascular tumor associated with human herpesvirus 8. It predominantly involves mucocutaneous sites but other anatomic locations can be involved as well. Well-developed KS (tumors) consists of fascicles of spindle-shaped tumor cells often admixed with a variable chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and dendritic cells. Various histologic subtypes have described, including anaplastic, hyperkeratotic, lymphangioma-like, bullous, telangiectatic, ecchymotic, keloidal, pyogenic granuloma–like, micronodular, intravascular, glomeruloid, and pigmented KS, as well as KS with sarcoidlike granulomas and, importantly, KS with myoid nodules.[22] Kaposi sarcoma shows immunoreactivity for vascular markers CD31 and CD34 and is negative for smooth muscle–related antigens. Epstein-Barr virus–associated SMT can resemble KS histologically in view of the presence of intratumoral lymphocytes and spindle-shaped cells; however, the negative staining for endothelial markers (CD31 and CD34) and positivity for desmin along with demonstration of EBV in tumor cells by in situ hybridization helps in clinching the diagnosis. Mycobacterial spindle cell pseudotumor shows numerous acid-fast bacilli within the spindle cells and thus can be differentiated from EBV-SMT on this basis.

Other differential diagnosis that needs to be excluded in pertinent cases is myopericytoma, as the EBV-SMT may exhibit some myopericytoma-like features. Myopericytoma is a benign perivascular myoid tumor composed of oval to short fusiform cells with a striking multilayered concentric growth around the vessels. The immunophenotype shows myoid features with positive staining for α smooth muscle actin, caldesmon, and desmin. The index of suspicion should be high in immunocompromised patients and a positive staining for EBV–encoded small RNA in situ hybridization, helps in distinguishing the EBV-SMT from this tumor.

MANAGEMENT AND PROGNOSIS

Different treatment modalities have been described for EBV-SMT, including chemotherapy, surgical resection, antiviral therapy, and reduced immunosuppression. However, given the rarity and uncertain behavior of these tumors, no fixed approach has been described to treat these tumors.

In PT-SMT, surgery and/or reduced immunosuppression remain the main therapeutic approaches and provide comparable results.[16] Sirolimus, which is an mTOR/Akt signal inhibitor, shows therapeutic benefits; however, it's not clear if it alone is responsible for disease stability. As suppression of tumor neoangiogenesis is used as a potential target for therapy in several neoplasms including sarcomas, antiangiogenic molecules are being tried in these patients, although somewhat unsuccessfully.[13]

A review of the literature has revealed that HIV-SMT has the poorest prognosis among the 3 subtypes.[6] Also, patients succumb to infectious complications in most cases rather than local tumor progression, especially in HIV and posttransplant patients. It is interesting to note that although HIV-SMTs most commonly occur in the brain, posttransplant patients who develop intracranial EBV-SMTs are associated with poor prognosis.[6]

CONCLUSION

Epstein-Barr virus–associated SMTs are rare soft tissue spindle cell neoplasms that occur in immunosuppressed individuals. There is a slight female preponderance for all subtypes and they can be seen in pediatric as well as adult patients. Histologic features and behavior are variable in HIV-SMT and immunosuppression-associated complications are more relevant and important for predicting outcome than tumor morphologic characteristics. Therapeutic strategies target the tumor location as well as the etiology of immunosuppression.

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