Smooth muscle tumors of soft tissue and non-uterine viscera: biology and prognosis

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Smooth muscle tumors are here considered an essentially dichotomous group composed of benign leiomyomas and malignant leiomyosarcomas. Soft tissue smooth muscle tumors with both atypia and mitotic activity are generally diagnosed leiomyosarcomas acknowledging potential for metastasis. However, lesions exist that cannot be comfortably placed in either category, and in such cases the designation ‘smooth muscle tumor of uncertain biologic potential’ is appropriate. The use of this category is often necessary with limited sampling, such as needle core biopsies. Benign smooth muscle tumors include smooth muscle hamartoma and angioleiomyoma. A specific category of leiomyomas are estrogen-receptor positive ones in women. These are similar to uterine leiomyomas and can occur anywhere in the abdomen and abdominal wall. Leiomyosarcomas can occur at any site, although are more frequent in the retroperitoneum and proximal extremities. They are recognized by likeness to smooth muscle cells but can undergo pleomorphic evolution (‘dedifferentiation’). Presence of smooth muscle actin is nearly uniform and desmin-positivity usual. This and the lack of KIT expression separate leiomyosarcoma from GIST, an important problem in abdominal soft tissues. EBV-associated smooth muscle tumors are a specific subcategory occurring in AIDS or post-transplant patients. These tumors can have incomplete smooth muscle differentiation but show nuclear EBER as a diagnostic feature. In contrast to many other soft tissue tumors, genetics of smooth muscle tumors are poorly understood and such diagnostic testing is not yet generally applicable in this histogenetic group. Leiomyosarcomas are known to be genetically complex, often showing ‘chaotic’ karyotypes including aneuploidy or polyploidy, and no recurrent tumor-specific translocations have been detected.

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Smooth muscle hamartoma

There are (at least) two separate lesion types: one cutaneous and the other in the breast. Cutaneous smooth muscle hamartoma forms a small plaque-like, pigmented, sometimes hairy cutaneous lesion in young children, and the lesion is probably congenital in most cases. There is overlap with Becker’s nevus. Histologically there is a band-like infiltrate of mature pilar smooth muscle extending from dermis to the superficial subcutis (Figure 1).^{1–9} Smooth muscle hamartoma of the breast parenchyma entails bundles of non-atypical smooth muscle present within the breast parenchyma between the lobules, often along with fibrous stroma and scattered fat cells.¹⁰

Pilar (cutaneous) leiomyoma

This is a relatively rare skin tumor, which is often clinically painful. It occurs in adults of all ages with a wide site distribution. The most common sites of biopsies seem to be skin of upper extremities and trunk.

Pilar leiomyoma forms a poorly circumscribed, multinodular, or trabecular smooth muscle proliferation emanating from the arrector pili smooth muscle apparatus in the dermis (Figure 2). Multiple lesions are more common than solitary, except that solitary lesions seem to be more common in the genital and nipple area.^{11,12} Histologically pilar leiomyomas may contain nuclear atypia but mitotic activity is exceptional. Mitotically active tumors with atypia have been traditionally classified as leiomyosarcomas. However, there is some tendency to ‘down-grade’ them as atypical smooth muscle tumors when purely dermally located, as such lesions do not have metastatic potential.¹³

Most cases with multiple lesions are associated with hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome, which is caused by a fumarate

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hydratase (*FH*) gene loss-of-function germline mutation. This is coupled with a somatic loss of the other allele of *FH* in the tumor cells, and therefore *FH*

Figure 1 Cutaneous smooth muscle hamartoma contains a continuous streak of pilar smooth muscle involving mid to deep dermis and subcutis.

behaves as a classic tumor suppressor gene, with bi-allelic inactivation causing the disease.^{14–16}

Most HLRCC patients develop coalescent clusters and streaks of multiple pilar leiomyomas in the extremities or trunk at a relatively young age. Some tumors have atypical features by the presence of nuclear atypia and even some mitotic activity, but truly malignant behavior does not seem to be a clinical problem. However, these tumors can be troublesome as they are painful. Therefore, some patients are treated with experimental agents, such as botulinum toxin.¹⁷

Women with HLRCC syndrome typically develop multiple uterine leiomyomas of early onset, and this was already clinically observed much before the discovery of the HLRCC syndrome.¹⁸ HLRCC syndrome carries an estimated 15% lifetime risk for an aggressive renal cell carcinoma histologically corresponding to type 2 papillary carcinoma characterized by papillary or pseudorosette-forming architecture with variably eosinophilic cells with prominent nucleoli (Figure 3).^{19,20} These tumors are notable for common nodal, abdominal, and distant visceral metastases.

Figure 2 Pilar leiomyoma (here seen in the context of HLRCC syndrome) consist of dermal smooth muscle proliferation originating from pilar smooth muscle and forming coalescent nodules, often without much atypia.

Figure 3 Kidney cancer in hereditary leiomyomatosis shows an eosinophilic cells in a papillary pattern with large nuclei and prominent nucleoli (so-called renal papillary carcinoma type 2).

Angioleiomyoma

This is the most common peripheral soft tissue leiomyoma typically occurring in the subcutis of extremities (especially lower leg), trunk wall, and less commonly head and neck. Some authors indicate that angioleiomyomas in the lower leg have a predilection to women.²¹ Angioleiomyoma is also clinically notable for often being painful.

Angioleiomyoma forms usually a small 1–2 cm homogeneous and well-circumscribed rubbery nodule. Histologically it is composed of eosinophilic smooth muscle cells intimately associated with the vein wall. The recognized variants are solid (very small lumens), venous (medium-size lumens), and cavernous (large lumens and thin smooth muscle elements in-between).²⁰ The latter two variants may overlap with myopericytoma showing less complete smooth muscle differentiation.^{22,23} Unusual morphologic patterns include fat infiltration (sometimes incorrectly designated angiomylipoma), and focal calcification (Figure 4).²⁴

Typical angioleiomyoma is positive for smooth muscle actin and desmin and negative for S100 protein.²⁵ Some examples are positive for CD34, and this is especially true for those that are classified as myopericytomas.²³

Differential diagnosis includes nerve sheath tumors and fibromas, with which angioleiomyomas are sometimes confused. Another pitfall is metastatic leiomyosarcoma, which can form well-demarcated subcutaneous nodules superficially resembling angioleiomyoma. Clues in identification of a metastatic tumor include multiplicity and presence of atypia and mitotic activity. A peculiar angioleiomyoma-like lesion can occur in the lymph node hilum, and this has been designated as angiomatous hamartoma of lymph node. These lesions

have usually occurred in the inguinal area and occasionally in the neck.^{26,27}

Estrogen receptor-positive (Mullerian) leiomyomas in women

This is a special subcategory of histologically non-atypical smooth muscle tumors supposedly of Mullerian derivation that specifically occurs in women and is closely related to uterine leiomyoma, including the morphologic patterns. These tumors occur relatively commonly in the pelvis and parametria and were long ago likened to uterine leiomyomas and sometimes referred to as ‘parasitic leiomyomas’ under the assumption that they once were located in the uterus and subsequently became separated and reattached to adjacent structures. However, this is probably not the case, but rather their occurrence is a manifestation of peritoneal origination of smooth muscle tumors.

Reports of uterine type-leiomyomas elsewhere in the retroperitoneum date back >10 years.^{28,29} Although specifically reported in the retroperitoneum, these tumors can also occur elsewhere in the abdomen in locations such as omentum, peritoneal surfaces, mesenteries, and in peritoneal region, such leiomyomas may arise from the round ligament.³⁰ Occurrence in the abdominal wall is also possible. Retroperitoneal leiomyomas can reach a very large size (several kilograms), whereas some present as small nodules. Similar tumors are also known in the external female genitalia.^{31,32} The significance of the specific identification of this group includes the assumption that prognostic criteria for uterine smooth muscle tumors can be applied to this group.^{28,29,33} Retroperitoneal leiomyomas typically have mitoses <5/50 HPFs. Although higher counts are allowed in uterine smooth muscle tumors, there is no specific data on such tumors so that they should be approached with caution.

The histologic patterns of estrogen receptor-positive leiomyomas include those encountered in the uterus: solid, macro- and microtrabecular, and hyalinized. Lipoleiomyoma histology with focal mature adipose tissue component may also be encountered. Nuclear atypia is absent, and mitotic activity is very low, usually <5/50 HPFs, with general difficulty to find mitoses (Figure 5).

Immunohistochemical studies are positive for SMA, desmin, heavy caldesmon, and estrogen and usually also progesterone receptor (Figure 6), and contain nuclear WT1-immunoreactivity.

A special clinicopathologic variant of estrogen receptor-positive leiomyoma is peritoneal leiomyomatosis, in which innumerable small nodules of a few millimeters are present in the omentum or elsewhere on the peritoneal surfaces. This is a

Figure 4 Angioleiomyoma. (a) A solid pattern. (b) Example originating from vein wall. (c) Focal atypia. (d) Examples with lipomatous components should not be confused with angiomyolipoma.

clinically indolent condition, which is sometimes associated with peritoneal endometriosis, sometimes coexisting in the same lesions. These tumors are often histologically composed of solid smooth muscle nodules without atypia, and mitotic figures are rare (Figure 7). Immunohistochemical features are similar to those of ER-positive leiomyomas (see below).^{34,35}

The differential diagnosis of ER-positive smooth muscle tumors includes PEComa and aggressive angiomyxoma. The former is at least focally HMB45-positive and the latter forms a dominant pelvic mass typically composed of oval cells that are positive for desmin and ER but often only focally if at all SMA-positive. Also, abdominal metastases of uterine leiomyosarcomas have to be considered. These usually display nuclear atypia and greater mitotic activity, and not infrequently, presence of multiple tumors as opposed to one. ER-positive primary retroperitoneal leiomyosarcoma is a rare possibility, and this is also recognized by atypia and mitotic activity.

Leiomyosarcoma of peripheral soft tissue

Smooth muscle tumors that contain both nuclear atypia and mitotic activity are generally designated leiomyosarcomas to denote their malignant (metastatic) potential. An exception to this rule is purely cutaneous (dermal) leiomyosarcoma that does not have significant metastatic potential.^{13,36–38} Some authors more recently have designated such tumors ‘atypical smooth muscle tumors’ noting that they had a 30% local recurrence rate but developed no metastases.¹³ However, subcutaneous extension should not be accepted for these cutaneous tumors, as this is already known to introduce metastatic potential. At any rate, complete excision with negative margins is necessary also for the dermal tumors, as they may otherwise progress into metastasizing tumors. There has been sometimes a quest for more accurate prediction (eg, plotting mitotic rate with recurrences/metastases), but very small sample size in most series of soft tissue leiomyosarcomas has hampered

Figure 5 Mullerian leiomyoma of soft tissues shows patterns similar to uterine leiomyoma. (a) Macrotrabecular. (b) Microtrabecular. (c) Example with mildly myxoid stroma. (d) Lipoleiomyoma with a mature fatty component.

Figure 6 Mullerian leiomyomas are characterized by nuclear estrogen receptor-positivity, as seen in uterine leiomyomas. These tumors show similar WT1-positivity.

Figure 7 Peritoneal leiomyomatosis can form numerous smooth muscle nodules on the peritoneal surfaces.

that effort. A great majority of soft tissue leiomyosarcomas are high or intermediate grade, and low-grade tumors are rare.

Series of peripheral soft tissue leiomyosarcomas have noted that subcutaneous leiomyosarcomas have a metastatic rate varying from 0 to 39%.^{39–42}

Figure 8 Examples of leiomyosarcoma. (a) Example composed of uniform cells with blunt-ended nuclei with mild general atypia and high mitotic activity. (b) Focal nuclear pleomorphism is a common feature even in low-grade tumors. (c) Example with transition into a pleomorphic sarcoma ('dedifferentiated leiomyosarcoma'). (d) Extensively pleomorphic leiomyosarcoma, which would be difficult to recognize unless for differentiated areas elsewhere in the tumor.

The largest recent series from the Scandinavian Sarcoma Group showed a metastatic rate of 20% for subcutaneous and 60% for deep intramuscular leiomyosarcomas.⁴² Tumors with lower mitotic rates may show longer recurrence-free survivals. Disruption of tumor (previous partial surgery) was found an adverse factor in one series.⁴¹ It is likely that many peripheral (non-cutaneous, non-retroperitoneal) leiomyosarcomas arise from vascular smooth muscle, although it is difficult to observe vascular origin in practice. Gross origin of tumor from a vein wall has been noted two small series.^{43,44} One series detected venous origin microscopically in 90% of cases.⁴¹

Histologically, leiomyosarcoma shows a smooth muscle-like appearance, being composed of irregularly intersecting fascicles of spindled cells with variably eosinophilic cytoplasm and variable mitotic activity (Figure 8a). Focal pleomorphism is common even in low-grade tumors with low mitotic activity (Figure 8b). In some cases, this eosinophilic cytoplasm is clumped to form so-called contraction

bands.⁴⁵ Nuclei are typically blunt-ended, 'cigar-shaped'. These histologic features are sufficient for the recognition of most leiomyosarcomas. In rare cases, leiomyosarcoma can undergo pleomorphic evolution ('dedifferentiation') so that specific diagnosis can be difficult unless differentiated component is also recognized (Figure 8c and d). This evolution is more common in retroperitoneal tumors that typically reach a larger size than the peripheral examples.^{40,46}

Immunohistochemically, leiomyosarcomas are almost invariably and strongly positive for α -smooth muscle actin, but SMA-positivity alone is not sufficient as myofibroblastic tumors (nodular fasciitis, myofibroblastic sarcomas) are also positive. A good majority (70–80%) are also positive for desmin. Most cases are positive for heavy-caldesmon and smooth muscle myosin. The latter two markers can be useful in the differential diagnosis of leiomyosarcoma and myofibroblastic sarcomas, because the latter are negative for heavy caldesmon and smooth muscle myosin.^{47,48} Occurrence of keratin- and

EMA-positive cells should not lead into the diagnosis of carcinoma; two studies have found these in 40–60% of leiomyosarcomas.^{49,50}

Genetically, leiomyosarcomas are complex with no recurrent translocations and have large numbers of copy number alterations in comparative genomic hybridization studies.⁵¹ A common finding is loss of retinoblastoma protein.⁵² There is also an association between retinoblastoma syndrome and leiomyosarcoma, which seems to be the most common sarcoma in retinoblastoma survivors.⁵³ Similarly, leiomyosarcomas often show loss of functional p53 and are associated with *TP53/p53* germline mutations (Li-Fraumeni syndrome).

Retroperitoneal leiomyosarcoma

Being pathologically essentially similar to peripheral leiomyosarcoma, retroperitoneal tumors are clinically distinctive but have been frequently intermixed with GISTs in the older series so that only few pure series exist.⁵⁴ Our AFIP experience showed that there are more GISTs in the retroperitoneum than true leiomyosarcomas. In general, immunohistochemical presence of KIT and Ano-1/DOG1 and absence of desmin help to identify GIST, but SMA and h-caldesmon can be present in both smooth muscle tumors and GIST.

Retroperitoneal leiomyosarcoma often arises from larger veins, most commonly inferior vena cava and sometimes from the renal or iliac veins. Tumors with intraluminal involvement of middle segment of inferior vena cava are often complicated by vascular compromise of liver (Budd-Chiari syndrome) and have a worse prognosis. In addition, large tumor size is also an adverse prognostic factor. In general, the prognosis of leiomyosarcomas of inferior vena cava^{55–59} and other retroperitoneum is poor.⁵⁴ Tumors with lower mitotic rates (1–2/10 HPFs) may have longer survivals (10+ years in some cases) but in our experience often develop late metastases, nevertheless.

Smooth muscle tumors of soft tissue of uncertain biologic potential

This is a practical designation and not a biologic entity reflecting situations where definitive determination of biologic potential cannot be made. Usually, this is due to limited sampling with insufficient opportunity to detect diagnostic criteria such as atypia or mitotic activity, and therefore malignancy cannot be excluded in the context. In some cases, soft tissue smooth muscle tumors can have conflicting diagnostic features that lead to similar conclusion (eg, tumors with no or low atypia with significant mitotic activity). As there are far fewer such soft tissue tumors than uterine ones, the diagnostic criteria predictive for malignancy are not

Figure 9 Esophageal leiomyoma is composed of bland smooth muscle cells, some of which contain eosinophilic inclusions that are typically desmin-positive.

equally developed. Similar rationale applies to other visceral smooth muscle tumors.

Gastrointestinal smooth muscle tumors

Although most mesenchymal tumors in the GI tract are now classified as GISTs rather than smooth muscle tumors, true leiomyoma occurs in all segments of the GI tract in two forms: mural and muscularis mucosae.

Mural leiomyoma involves gut wall and is most common in the esophagus, where it is five times or more common than GIST. These tumors vary from small nodules to large masses >10–15 cm. Mural leiomyomas are rare in the stomach and small intestine (1 for every 50 GISTs). GI leiomyomas occur in all ages but often in younger patients than GISTs.^{60–62} Most of them are sporadic but they occur in connection with two rare familial syndromes.

Alport syndrome is a basement membrane defect (mutated collagen type 4), also associated with hearing loss and renal disease. Alport syndrome-associated esophageal leiomyomas may already manifest in childhood and occur in siblings.^{63–65} Interestingly, similar somatic changes involving collagen 4 gene have also been detected in sporadic esophageal leiomyomas indicating that disruption of basement membrane collagen may be related their pathogenesis.⁶⁶

Even rarer syndrome associated with GI mural leiomyoma is multiple endocrine neoplasia type 1 (also known as Werner syndrome, with pituitary, parathyroid, and pancreatic/duodenal neuroendocrine tumors, with mutated *MEN1* tumor-suppressor gene). In addition, these *MEN-1* patients can have multiple cutaneous fibromas (somewhat reminiscent but distinctive from usual dermatofibromas).⁶⁷

Histologically, GI leiomyomas are composed randomly oriented or fascicularly organized eosinophilic smooth muscle cells. These often contain

Figure 10 KIT-positive Cajal may colonize gastrointestinal leiomyomas, and this should not lead into confusion with a GIST.

cytoplasmic globoid inclusions that are positive for desmin (Figure 9). Focal atypia may occur, but mitoses are exceptional if they occur. If both nuclear atypia and mitoses occur, it is appropriate to designate these tumors either smooth muscle tumors of uncertain biologic potential or low-grade leiomyosarcomas.

Immunohistochemically, typical is the presence of full complement of smooth muscle cell antigens (SMA, desmin, and h-caldesmon). The tumor cells are negative for KIT, but caveat in differential diagnosis from GISTs is that some GI leiomyomas are colonized by KIT-positive Cajal cells that can be moderately numerous, although always as a minority population among the smooth muscle component (Figure 10).

Muscularis mucosae leiomyomas usually occur in the colon and rectum, where these tumors are far more common than GISTs. They exceptionally occur in the small intestine but almost never in the stomach. These leiomyomas form small, usually <1 cm, polypoid mucosal lesions that can rarely approach 2 cm in diameter. Histologically they are composed of mature smooth muscle and have continuity with muscular mucosae layer (Figure 11). The immunohistochemical profile is similar to that of soft tissue leiomyomas.⁶⁸

GI leiomyosarcoma is far less common than GIST. These tumors occur in all segments of the GI tract, although they are extremely rare in the esophagus and stomach. In the small intestine, their frequency seems to be 1 for every 30 GISTs, although in the colon and rectum their relative frequency to GIST is higher 1:10. Most GI leiomyomas form polypoid intraluminal masses of a few cm in diameter. Some form extensive transmural masses.^{69–71}

Most GI leiomyosarcomas are high-grade tumors with mitotic rate frequently ranging 50–100/50 HPFs. Nevertheless, smaller tumors have a relatively good prognosis, better than GISTs with similar mitotic rates. Tumors with low mitotic rates are rare

so that there are limited data on their behavior. However, such tumors have at least potential to recur, although distant metastases have not been reported.⁷¹

GIST is the first differential diagnosis. Eosinophilic cytoplasm, immunohistochemical presence of smooth muscle markers, and absence of KIT and Ano1-/DOG1 are a good diagnostic help in problem cases to support a smooth muscle tumor. When multiple leiomyosarcomas are present, then the possibility of metastasis from another source has to be considered. EBV-associated tumor has to be kept in mind in AIDS and post-transplant patients (these are EBER-positive).

Other visceral smooth muscle tumors

Leiomyomas can occur in a wide variety of internal locations, although they are rare. One of them is bronchial leiomyoma, which is usually a small, clinically indolent well-demarcated smooth muscle nodule originating from the smooth muscle components of the bronchial wall.⁷²

Benign metastasizing leiomyoma is a term for often multiple, clinically indolent pulmonary tumors that occur in women with previous uterine or extrauterine ER/PR-dependent smooth muscle tumors. They are histologically generally similar to cellular uterine leiomyomas and are immunohistochemically positive for desmin, SMA, and estrogen receptor. Their genetic profile seems to be similar to uterine leiomyomas in that they often contain rearrangements of the *HMGA1* locus (at 6p21) and have losses in chromosome 7q.^{73,74}

In the urinary bladder, both benign smooth muscle tumors (leiomyomas) and leiomyosarcomas occur, and these are distinguished by the presence of atypia and any mitotic activity in the latter. Leiomyosarcomas seem to be almost twice more common than leiomyomas. Lower mitotic activity (and lower grade) of leiomyosarcomas correlate with a less aggressive behavior.⁷⁵

Leiomyosarcomas have been reported in almost all visceral sites although in small numbers. They may arise from vessel (vein) walls of practically any organ-based location. For example, renal parenchymal leiomyosarcomas may be of renal vein origin and clinicopathologically these tumors are probably closely related to retroperitoneal leiomyosarcomas. Criteria for identifying malignant potential are similar to those applied for smooth muscle tumors of soft tissues.

Visceral (especially liver, lung also and also osseous) occurrence of a smooth muscle tumor should prompt consideration of metastasis from another source. In women, history of uterine tumor may be a diagnostic clue, and some metastases retain ER expression supporting uterine origin. The possibility of EBV-associated smooth muscle tumor has to be considered especially in post-transplant and AIDS patients.

Figure 11 Muscularis mucosae leiomyoma forms a polypoid colonic lesion immediately adjacent to the mucosa. (a) Low magnification. (b) High magnification.

Figure 12 EBV-associated smooth muscle tumor. (a) This tumor forms an eccentric intramural appendiceal mass. (b) These smooth muscle tumors are often composed of oval cells that appear less mature than typical smooth muscle cells. The tumor cells are positive for SMA but only variably positive for desmin. Nuclear positivity for Epstein–Barr virus RNA is a typical finding.

EBV-associated smooth muscle tumors

This is a special, rare subset of smooth muscle tumors that occur in immunosuppressed individuals.

Traditionally, the condition has been more common in AIDS patients, and a minority of patients has been solid organ transplant recipients (liver, kidney, heart). Many of the AIDS patients are

young, including children, whereas the organ transplant recipients are usually middle-aged adults. The smooth muscle tumors can occur in peripheral soft tissue, intracranial space, or visceral sites, and tumor multiplicity is common.^{76–85} Molecular genetic analysis has shown that multiple tumors represent independent clones rather than dissemination of a single neoplastic clone.⁸⁵ In multiple tumor cases, tumors arising in the transplant are of donor cell origin, whereas those at the other sites arise from recipient cells, which also points to polyclonal origin of multiple tumors.⁸²

Although these tumors were originally divided into EBV-associated leiomyomas and leiomyosarcomas, current classification holds them all collectively as smooth muscle tumors as they are usually indolent although somewhat unpredictable in behavior. True metastatic behavior is rare, and was observed only in 4 of 51 AIDS-associated (8%)⁷⁷ and 1 of 19 cases (5%) in a mixed AIDS and transplantation-associated series.⁸⁵ Based on a large survey of AIDS-associated cases, mitotic rate does not seem to distinguish cases with malignant outcome.⁷⁷

Histologically, the EBV-associated smooth muscle tumors have a spectrum from a well-differentiated conventional-appearing spindle cell smooth muscle tumors to those composed of ovoid cells with incomplete smooth muscle differentiation (Figure 12). Intratumoral T lymphocytes may be present and even be prominent, but this is not a uniform feature. These tumors are smooth muscle actin positive but often desmin negative. Some have also been classified as myopericytomas reflecting differentiation intermediate to smooth muscle cell and pericyte.⁸⁶ A diagnostic test is demonstration of EBV RNA by *in situ* hybridization, which highlights the tumor cell nuclei (Figure 12).

Conclusion

Smooth muscle tumors of soft tissues and non-uterine visceral organs can be largely separated into leiomyomas and leiomyosarcomas. The latter group refers to tumors with both nuclear atypia and mitotic activity denoting potential for metastasis (purely cutaneous tumors may be exceptions in lacking metastatic potential). The designation 'smooth muscle tumor of uncertain biologic potential' is appropriate in small specimens and when facing conflicting criteria. Estrogen receptor-positive (Mullerian-type) non-atypical smooth muscle tumors can occur in women anywhere in the abdomen and abdominal wall and generally behave in a benign manner even if the tumor is large. Epstein-Barr virus-associated smooth muscle tumors are a special group of neoplasms associated with immunosuppression (AIDS, post-transplant immunosuppression). These tumors generally have a low biologic potential and involve both peripheral

soft tissues and viscera, sometimes forming multiple independent tumors and often showing incomplete smooth muscle differentiation. Demonstration of EBV-RNA (EBER) is their typical diagnostic feature.

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Disclosure/conflict of interest

The author declares no conflict of interest.

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