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Literature Review

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Superficial myofibroblastoma of the lower female genital tract: case report and literature review

Abstract

Introduction: Superficial myofibroblastoma of the lower female genital tract is a benign mesenchymal tumor preferentially located in the vagina, but may also arise in the cervix and vulva. This article provides a comprehensive review of the literature as well as describes a case report to help correlate presentation with management.

Methods: We conducted an extensive literature review without a defined time range and across three databases (Pubmed/Ovid, Embase, and Web of Science). Inclusion criteria specified all peer-reviewed publications of myofibroblastoma in the lower female genital tract in the English language.

Results: Six hundred and seventy-three articles were identified, with 15 articles being included in the review based on eligibility criteria. There were 12 case reports, 3 case series, with a total of 56 cases from 53 patients. Age ranges were 23-80years (mean=55). Most gross examinations were described as polypoid or nodular in appearance, measuring 2 mm to 120mm (mean=39). All cases were clinically managed with either local excision or incidentally identified after a hysterectomy. There are no published recommendations for an optimal follow-up interval.

Conclusion: The diagnosis of mesenchymal tumors in the female genital tract is challenging. Expression of Vimentin, Progesterone, Estrogen, Desmin, and CD34 is noted in the majority of SMGFT tumors while testing for CD99 and bcl-22 may assist in identification of challenging cases. Understanding the variety in presentation and immunohistochemical markers of superficial myofibroblastoma is significant as it may change surgical approach and follow-up to tumors of the lower female genital tract.

Keywords: myofibroblastoma, vagina, Lesion, immune-histochemistry, markers

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Introduction

Genital stromal tumors are a rare and unique subcategory of soft tissue tumors that are nearly exclusive to vulvovaginal sites. This subcategory includes fibroepithelial stromal polyp, superficial (cervicovaginal) myofibroblastoma (MFB), cellular angiofibroma, mammary type myofibroblastoma, angiomyofibroblastoma and aggressive angiomyxoma. Specifically, the superficial myofibroblastoma of the lower female genital tract (SMFGT) is a recently identified, benign, mesenchymal tumor that is preferentially located on the vagina. It was first described in 2001 by Laskin et al.[1] in a series of 14 seemingly unique mesenchymal tumors that occurs in the superficial lamina of the vagina and cervix of middle to older-aged women. Although this tumor characteristically arises from the subepithelial stroma of the vagina, it became evident that it may also arise in the cervix and vulva, leading to a proposed revision in 2005 from 'Superficial Cervicovaginal MFB' to 'Superficial MFB of the lower female genital tract'.[2] These terms are used interchangeably in literature.

In this paper, we describe a SMFGT case in a 47-year-old woman focusing on this uncommon tumor's histological, morphological, and immunohistochemical elements. We conducted a systematic review of the literature in order to meet the following aims:

1) To understand the various clinical presentations of this tumor
2) To identify potential associated risk factors
3) To provide diagnostic and clinical management recommendations based on accumulated evidence of current literature.

Case report

A 47-year-old woman presented with a vaginal mass that was noted in the shower two weeks prior to her clinic visit. She reported mild dyspareunia for a few months and her husband admitted to having felt the mass in the past. The patient is perimenopausal with increasing frequency of mood changes and increasingly irregular menstrual cycles. She has a history of abnormal pap smears approximately 30years ago with subsequent LEEP and Cold Knife Cone procedures. Per the patient, her recent several pap smears have been negative. She has no history of abnormal mammograms. No hormonal therapy was mentioned in her previous medical records.

On gynecologic examination, a 3cm pedunculated mass was found 1 cm from the vaginal introitus on the posterior vaginal wall with prominent vascularity. Local excision of the mass was performed. Gross examination of the specimen revealed a yellow/tan, irregular shaped, friable fragment of soft tissue measuring 2.8x1.5x0.5cm. The tissues appearance ranged from smooth and glistening with adherent hemorrhage, to dull and slightly friable.

Microscopic examination revealed a hypercellular, spindle cell neoplasm with a storiform growth pattern. There were also areas of dense, plaque-like collagen. Cytologically, the spindled cells have elongated, oval, hyperchromatic nuclei, with rounded ends. The nucleoli were not well visualized and there was minimal eosinophilic cytoplasm. No significant mitotic activity or necrosis was identified.

Immunohistochemical studies were also performed using the following panel of antibodies: CD10, CD34, Smooth muscle actin (SMA), desmin, CD117, Estrogen receptor (ER), pancytokeratin,

S-100, SF-1, inhibin, and STAT6. Immunohistochemically, the cells were positive for CD34, desmin, and ER, and negative for all other antibodies. All immunoperoxidase stains were interpreted in conjunction with their appropriate controls. Following this pathological analysis of the mass, the diagnosis of myofibroblastoma was made.

Literature review

Methods

We sought to identify all peer-reviewed publications pertaining to myofibroblastomas occurring in the lower female genital tract in order to achieve the following aims:

1) To understand the various clinical presentations of this tumor
2) To identify potential associated risk factors
3) To provide diagnostic and clinical management recommendations based on accumulated evidence of current literature.

We discussed important keywords and database vocabulary in order to determine a search strategy (Appendix A). Databases searched included Pubmed, Ovid, Embase, and Web of Science.

Our inclusion criteria specified all peer-reviewed studies of myofibroblastoma in the lower female genital tract published in the English language. There was no predetermined range in publication dates. All potential articles were reviewed by two reviewers for inclusion in this study, with arbitration performed by discussion. There was no restriction on the type of study allowed in this review. The bibliographies of all publications were manually reviewed and were searched for any references that could have been missed in the initial search through the databases.

Results

Of the 673 articles reviewed from the three databases, 15 articles were eligible for inclusion. There were 12 case reports and three case series. In total, there were 56 cases from 53 patients that were included in this review. In three of the studies, two cases were from one patient.[2–4] Table 1 represents a succinct summary of the outcome of this review. Patient ages ranged from 23 to 80years with a mean of 55years. Most gross examinations were described as polypoid or nodular in appearance, measuring 2mm to 120mm (mean, 39mm). All cases were clinically managed with either local excision, or incidentally identified after a hysterectomy (2/51) was performed. There was only one published recurrence. In this patient, the tumor appeared to be a local recurrence of a lesion incompletely excised 9years prior.[3] There was also one published case of SMFGT in a pregnant patient who presented with a vaginal mass protrusion associated with intermittent vaginal spotting.[5] There are no published recommendations for an optimal follow-up interval. There were no post-operative complications reported.

Table 1 Clinical features and course of patients with superficial myofibroblastoma of the lower female genital tract

Reference	Cases (# Patients)	Mean patient age in years (age range)	Location	Mean size in mm, greatest dimension (size range)	# Patients with History of Exogenous Hormone Exposure	History of Breast Cancer (# of patients)	Imaging	Median F/U per patient (months)	Clinical course	Number of recurrences
Laskin WB, et al.[1]	14	57	Vagina (12)	27	7 (5 HRT, 1 BCP, 2 Tam)	14-Feb	NR	48	12 CE, 2 IE	0
		(40-74)	Cervix (2)	(10-65)						
Ganesan R, et al.[2]	12* (11)	52	Vagina (10)*	19	3 (3 Tam)	NR (3/11)	NR	12	10 CE, 1 IE	0
		(23-80)	Vulva (2)	(2-45)						
Stewart CJ, et al.[3]	5* (4)	55	Vagina (4)*	24	1 Tam	4-Jan	NR	36	CE	1
		(40-71)	Cervix (1)	(16-45)						
Olinci CD, et al.[14]	1	63	Vagina	40	0	NR	NR	N/A	CE	0
Adams B, et al.[5]	1	27	Vagina	45	NR		NR	6	CE	0
Cinel L, et al.[12]	1	45	Cervix	65	0	NR	NR	96	TAH/BSO	0
Wang Q, et al.[4]	5* (4)	55	Vagina (5)	25	1 (Tam)	4-Feb	US	5	4 CE	0
		(47-63)		(15-37)						
Liu JL, et al.[6]	1	59	Vagina	18	0	1-Jan	US	12	CE	0
Magro G, et al.[13]	10	66	Vagina (8)	17	1 HRT, 1BCP	NR	NR	19.5	5 CE, 5 IE	0
		(44-77)	Vulva (2)	(4-30)						
Wallenfels I, et al.[19]	1	70	Vagina	12	0	1-Jan	NR	N/A	CE	0

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Table Continued...

Reference	Cases (# Patients)	Mean patient age in years (age range)	Location	Mean size in mm, greatest dimension (size range)	# Patients with History of Exogenous Hormone Exposure	History of Breast Cancer (# of patients)	Imaging	Median F/U per patient (months)	Clinical course	Number of recurrences
Atinga A, et al.[7]	1	50	Vagina	28	0	NR	US	96	TLH/BSO	0
							MRI			
Peng WX, et al.[8]	1	37	Vulva	73	NR	NR	MRI	12	CE	0
Patrizi L et al.[9]	1	77	Labia	120	0	NR	US	NR	CE	0
Smith SA et al.[10]	1	73	Vagina	47	1 Tam	NR (1/1)	MRI	NR	TAH/BSO	0
							CT			
Abdelaziz et al.[11]	1	45	Cervix	38	0	NR	TVUS	NR	TAH	0

US, ultrasound; TVUS, transvaginal ultrasound; MRI, magnetic resonance imaging; CE, complete excision; IE, incomplete excision; TAH, total abdominal hysterectomy; TLH, total laproscopic hysterectomy; BSO, bilateral salpingo-oopherectomy; NR, not reported

*Two cases from the same patient

There were seven studies that included imaging.[4,6–11] Four cases included ultrasounds and three cases had MRI study findings. While Liu et al. found their ultrasound imaging to be unremarkable (2012), Wang et al. described two well-defined solid neoplasms with mild heterogeneity in the vagina (2010). In the case of labial involvement, ultrasound showed that the swelling consisted of mixed content (liquid and possibly mucous), did not have evidence of intestinal loops within, and did not appear vascularized (2010). In cases of cervical involvement, Abdelaziz et al.[11] found that the transvaginal ultrasound suggested the presence of multiple fibroids (2017). The ultrasound findings from Atinga et al. reported findings of normal uterus and adnexa with detection of a solitary, vascular, soft tissue nodule in the vagina (2018). MRI findings from this case confirmed a well-defined, predominantly cystic structure of mildly hyperintense signal, on T2 weighted images and intermediate to high signal on T1 weighted. The internal solid component was of intermediate signal with a hyperintense rim on T2W images and low signal on T1W images. Smith et al. found that on the T1 weighted images, the signal intensity of the abnormality was intermediate, similar to that of skeletal muscles (2017). On T2 imaging, the anteroinferior aspect was of high signal with no enhancement, whereas the posterosuperior aspect was of low T2 signal with strong enhancement. Due to initial concern of metastasis, a staging portal venous phase CT scan was done; the vaginal lesion showed fluids and soft tissue attenuation areas with regions of enhancement (2017).

Microscopically, the tumor consistently presented as an unencapsulated, well-circumscribed, solitary nodule or polyp. The tumor cells were situated in the sub-epithelial stroma, have no evidence of deep infiltration, and generally accompanied by small to medium-sized thin-walled blood vessels.[4]

There was low to moderate cellularity of spindle or stellate-shaped cells present in a background of edematous and myxoid stroma with interspersed collagenous matrix.[1–3] Additionally, there was generally low to no mitotic activity present and no evidence of inflammatory cells or necrotic activity.[6] The spindle-shaped cells contained lightly eosinophilic cytoplasm, with oval-shaped nuclei, containing finely dispersed chromatin and small nucleoli. The spindled cells generally grew in a lace-like or sieve-like pattern parallel to the collagenous matrix.[1] The 'grenz zone', which refers to a rim of collagenized stroma, is commonly present in these tumors with an unremarkable overlying epithelium.

The collection of immunohistochemical studies from all studies investigating MFB of the lower tract are summarized in Table 2. Immunohistochemical investigations included the following antibodies: CD34, Vimentin, Desmin, a-SMA, Muscle Specific Actin, Calponin, CD99, bcl-2, Estrogen receptors (ER), Progesterone receptors (PrR), and S-100. Appropriate positive controls were run simultaneously in all studies. Of the immunohistochemical studies that were performed for at least 50% of the cases present in the literature, expression of Vimentin (36/47, 77%), Progesterone receptor (31/32, 97%), Estrogen receptor (41/44, 93%), Desmin (46/50, 92%), and CD34 (37/47, 77%) were all consistently positive for expression on tumor cells of MFBs. One study demonstrated positive expression for Calponin in all 5 patients, but no other studies investigated positivity for this specific antibody.[3] This study also first to investigate expression for CD99. Three other studies that followed exhibited positivity for this tumor marker in nine out ten cases.[7,12,13] These same studies also indicated nine out of ten cases positive for bcl-2 following a prior study that indicated positivity in five out of five patients.[3] Positive expression for CD10 were found in eight out of nine cases (Adams, Margo). Percent expression for a-SMA (12/49), Muscle Specific Actin (2/10) and S-100 (0/10) were 24%, 20%, and 0% respectively.

There were multiple studies that addressed past medical history including previous HRT use, tamoxifen therapy, prior pregnancies, history of cervical neoplasia, and history of breast cancer. These findings are summarized in Table 3. Prior HRT use was identified in 6 out 42 (14%) patients and prior or concurrent tamoxifen use was documented in 6 out of 43 (14%) patients. Positive prior pregnancy status was confirmed in 15 out of 18 (83%) patients. One study reported a patient that had documented superficial MFB of the lower female genital tract during pregnancy.[5] The clinical course in this case was uneventful, and the patient successfully delivered vaginally followed by subsequent resection.

Table 2 Results of Immunohistochemical Investigations, per case

Reference	CD34	Vimentin	Desmin	a-SMA	MSA	Calponin	CD99	CD10	bcl-2	ER	PrR	S-100
Laskin WB, et al.[1]	11/13	5/5	13/13	5/11	2/8	NP	NP	NP	NP	10/10	10/10	NP
Ganesan R, et al.[2]	6/12	11/11	9/12	0/12	NP	NP	NP	NP	NP	9/11	NP	NP
Stewart CJ, et al.[3]	5/5	5/5	5/5	2/5	NP	5/5	5/5	NP	5/5	5/5	5/5	NP
Olinci CD, et al.[14]	1/1	1/1	NP	0/1	NP	NP	NP	NP	NP	0/1	0/1	0/1
Adams B, et al.[5]	NP	1/1	0/1	0/1	NP	NP	NP	1/1	NP	1/1	1/1	0/1
Cinel L, et al.[12]	NP	1/1	1/1	1/1	NP	NP	0/1	NP	0/1	1/1	1/1	0/1
Wang Q, et al.[4]	1/1	1/1	1/1	0/1	0/1	NP	NP	NP	NP	1/1	1/1	0/1
Liu JL, et al.[6]	1/1	NP	1/1	1/1	NP	NP	NP	NP	NP	1/1	1/1	0/1
Magro G, et al.[13]	7/8	NP	10/10	0/10	NP	NP	8/8	7/8	8/8	8/8	8/8	NP
Wallenfels I, et al.[19]	0/1	NP	1/1	1/1	NP	NP	NP	NP	NP	1/1	1/1	0/1
Atinga A, et al.[7]	1/1	NP	1/1	0/1	NP	NP	1/1	NP	1/1	1/1	1/1	0/1
Peng WX, et al.[8]	1/1	1/1	1/1	1/1	NP	NP	NP	NP	NP	1/1	1/1	0/1
Patrizi L et al.[9]	1/1	NP	1/1	0/1	NP	NP	NP	NP	NP	1/1	NP	0/1
Smith SA et al.[10]	1/1	1/1	1/1	0/1	0/1	NP	NP	NP	NP	1/1	1/1	0/1
Abdelaziz et al.[11]	1/1	NP	1/1	1/1	NP	NP	-/1	NP	NP	NP	NP	NP

NP, not performed; SMA, smooth muscle actin; ER, estrogen receptor; PrR, progesterone receptor; MSA, muscle specific antigen

-/1: testing was conducted but was non-contributory (i.e. weakly positive in some cells; most of the section washed off even on repeat stain)

Table 3 Relevant past medical history of patients with superficial myofibroblastoma of the lower female genital tract reported

Reference	HRT	Tamoxifen	Pregnancy	CIN (HPV)	Breast cancer
Laskin WB, et al.[1]	5/14	2/14	9/12	NR	2/14
Ganesan R, et al.[2]	0/6	3/6	NR	NR	3/6
Stewart CJ, et al.[3]	0/4	1/4	1/1	2/4	1/4
Olinci CD, et al.[14]	0/1	0/1	NR	NR	NR
Adams B, et al.[5]	0/1	0/1	*1/1	0/1	0/1
Cinel L, et al.[12]	0/1	0/1	1/1	0/1	NR
Wang Q, et al.[4]	NR	1/1	NR	NR	1/1
Liu JL, et al.[6]	0/1	0/1	NR	1/1	1/1
Magro G, et al.[13]	1/10	NR	NR	NR	NR
Wallenfels I, et al.[19]	0/1	0/1	1/1	1/1	1/1
Atinga A, et al.[7]	0/1	0/1	1/1	0/1	0/1
Peng WX, et al.[8]	NR	NR	1/1	NR	NR
Patrizi L et al.[9]	0/1	NR	1/1	NR	NR
Smith SA et al.[10]	NR	1/1	NR	NR	0/1
Abdelaziz et al.[11]	0/1	0/1	1/1	0/1	NR

NR, not reported

*Patient was pregnant when diagnosed with superficial MFB

A history of abnormal cervical pathology, cervical intraepithelial neoplasia (CIN), was identified in 3 out of 10 (30%) patients. These patients were managed using loop-excision, cold-knife conization, or hysterectomy. Additionally, there were two patients with a documented history of breast cancer without tamoxifen therapy who had SMFGT.

Discussion

Our systematic review demonstrates that the vast majority of superficial myofibroblastomas of the lower female tract are primarily located on the vaginal walls (45/56, 79%), but they may also involve

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from the vulva or cervix. The majority of diagnostic imaging studies utilized included ultrasound and MR; however, these appear useful specifically in identifying co-pathologies. Diagnostic guidance appears more likely through immunohistochemical investigations where SMFGTs show a native positivity for Vimentin, Desmin, Estrogen receptors, Progesterone receptors, and while not as strong, CD34.

The macroscopic findings in our case are similar to that of previous descriptions in literature, which is typically illustrated a polypoid or nodular mass.[1,2] The microscopic features of SMFGT are illustrated quite extensively in the literature. The microscopic examination of our case demonstrates most of the histological features mentioned consistently in the literature. In addition, the literature review of SMFGT, had limited utilization of Calponin, CD99, and bcl-2 immunohistochemical investigations.[14] While no future studies performed Calponin reactivity studies, 14/16 demonstrated reactivity to CD99 and 14/15 demonstrated reactivity to bcl-2. Therefore, both CD99 and bcl-22 are likely reliable antibodies that can be utilized when diagnosing difficult cases of superficial MFBs.

The clinical course after diagnosis of SMFGT was unremarkable. All patients underwent excision, either through local excision or hysterectomy, with varying levels of follow-up length. Hysterectomies were often performed if the lesion was of cervical pathology or if the patient had comorbid conditions such as fibroids. As previously mentioned, only one case of recurrence was documented in the literature out of 53 patients. The author attributes this outcome to incomplete initial excision of the mass.[3] The general consensus among authors is that follow-up is recommended, but no recommendations are made as to the appropriate length of follow-up. It appears that despite incomplete excision, all other cases did not demonstrate signs of recurrence. Thus, it might be judicious to proceed with regular post-operative follow-up, and then evaluate at routine pelvic exams unless otherwise symptomatic.

Diagnosis of SMGFT may be a challenge for many pathologists due to its low incidence rate. In addition, there is considerable overlap in in the morphological and immmunohistochemical features with other mesenchymal tumors found in the lower female genital tract. This group of mesenchymal tumors includes superficial angiomyxoma, aggressive angiomyxoma, angiofibroblastoma, fibroepithelial stromal polyp and cellular angiomyofibroma. One study published a summary of this group of mesenchymal tumors with a description of histological features and immunohistochemical expression profiles.[14] While there is considerable overlap between the different tumors, they can be generally distinguished based on one or two key features. It is particularly important to distinguish SMGFT from aggressive angiomyxoma as they have very different clinical prognoses. SMGFT can be differentiated by its superficial location, sharp borderline from adjacent tissue, adjacent tissue, expansive growth pattern, and specific vascular pattern.[8]

Currently, the etiology of SMGFT is unclear. The majority of superficial MFB tumors typically arise during the peri- and post-menopausal period. However, because most of these tumors are estrogen and progesterone receptor positive, the change in hormonal status during this transition has been postulated as a potential etiology for the growth of SMGFT. There have also been suggestions of a possible role of tamoxifen or HRT use in driving the growth of the tumor due to the high prevalence of estrogen receptors present on immunohistochemical examination.[1] However, the same author also postulated that patients on tamoxifen likely have higher detection rates for this tumor due to the increased surveillance of pathological endometrial changes. An association with HPV is seemingly unlikely. One study specifically investigated the viral association of this tumor and found no correlation.[6] Additionally, there is no documented evidence of a family history association for this tumor.

Due to the great overlap in features for SMGFT and other mesenchymal tumors, it has been speculated that this tumor can be grouped with the mesenchymal tumors previously mentioned. These tumors also originate in the lower female tract and are all likely histologically related, possibly originating from a pluripotential primitive cell.[15–18]

Major limitations

Due to the paucity of literature on SMGFT, it is difficult to accurately summarize the findings. Moreover, not every study included details of past medical history and select immunohistochemical markers. Additionally, all of the articles included in this review were either case reports or case series, which fall under the lowest level of evidence category.[19]

Conclusion

The diagnosis of mesenchymal tumors in the female genital tract is challenging due to low incidence rate, shared similarities in clinical presentation, and resemblances in pathology. Moreover, while SMGFT often presents as a vaginal lesion, it may also present as a vulvar or cervical lesion further complicating diagnosis. Based on the literature review, expression of Vimentin, Progesterone, Estrogen, Desmin, and CD34 were all consistently positive for expression on the majority of SMGFT tumors. CD99 and bcl-22 seemingly have the potential to diagnose difficult cases of SMGRT tumors, but further research is necessary. Based on the literature, SMGFT is a tumor with very low recurrence. Thus, regular post-operative follow-up and evaluation at routine pelvic exams unless otherwise symptomatic is recommended based on the comprehensive literature. Lastly, SMGFT must particularly be included in the differential diagnosis for patients with lower genital tract lesions who have a history of tamoxifen, hormonal replacement therapy, or breast cancer (even without use of tamoxifen therapy). There appears a hormonal association to SMGFT, but further research to investigate this is necessary. Understanding the variety in presentation and immunohistochemical markers of superficial myofibroblastoma is significant as it may change surgical approach and follow-up to tumors of the lower female genital tract.

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Conflicts of interest

Authors had no conflict of interest.

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