Leiomyomatoid angiomatous neuroendocrine tumor of the uterine myometrium with synchronous renal leiomyosarcoma: case report and review of the literature

Kathryn L. Jones · Prem B. Tripathi · Sucheta A. Srivastava ·
Anna L. Beavis · Koji Matsuo · Melissa N. Moffitt ·
Ana Maliglig · Yvonne G. Lin

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Abstract Uterine smooth muscle tumors of uncertain malignant potential, also called STUMP, lack uniformity in their clinical course and therefore prognosis. A recently described variant of STUMP, leiomyomatoid angiomatous neuroendocrine tumor (LANT), contains both neuroendocrine cells and smooth muscle leiomyomatous vascular components. We describe a case of a LANT originating in

the uterine myometrium, with a synchronous renal leiomyosarcoma, in a 53-year-old woman who presented with menometrorrhagia and unintentional weight loss. She underwent primary surgical treatment of both tumors and remains without evidence of disease 1 year later. Our discussion also includes a review of the literature guiding clinical management.

K. L. Jones · K. Matsuo · Y. G. Lin (✉)
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Norris Comprehensive Cancer Center, University of Southern California, 1441 Eastlake Ave, NOR 7419, MC 9180, Los Angeles, CA 90033, USA
e-mail: ylinliu@usc.edu

P. B. Tripathi
Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

S. A. Srivastava
Department of Pathology, University of Southern California, Los Angeles, CA 90033, USA

A. L. Beavis
Department of Obstetrics and Gynecology, Ronald Reagan University of California Los Angeles Medical Center, Los Angeles, CA 90095, USA

M. N. Moffitt
Division of Gynecology Oncology, Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR 97239, USA

A. Maliglig
Division of Radiology, University of Southern California, Los Angeles, CA 90033, USA

Y. G. Lin
Women's Cancer Program at Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA 90033, USA

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Introduction

The classification and clinical management of uterine smooth muscle tumors of uncertain malignant potential, also called STUMP, remain unclear. Uterine smooth muscle neoplasms have a wide range of histological features. Those with two of the three criteria:

1. cytologic/nuclear atypia;
2. tumor cell necrosis; and
3. ≥ 10 mitoses/high power field (HPF)

are classified as malignant, thereby enabling leiomyomas and its variants to be classified as benign, despite occasionally high mitotic rates [1]. Consequently, tumors fitting neither benign nor malignant classification are categorized as STUMP. Recent pathological data suggest gross similarities between the STUMP and the leiomyoma, with the added complexity of focal necrosis without lymphovascular space involvement and variable numbers of mitotic figures per HPF [2]. Pathologic variability, poor understanding of its prognosis, and disease rarity preclude definitive clinical management recommendations [3].

Fig. 1 Computed tomography of LANT and renal leiomyosarcoma. Axial (a) and coronal (b) contrast-enhanced computed tomography (CT) revealed a 4.1×4.8 cm cystic and solid mass within the endometrial cavity (black arrowhead). Axial (c) and coronal (d) contrast-enhanced CT of the abdomen revealed a 5.0×3.9 cm complex cystic mass posterior to the lower pole of the left kidney (black arrow)

A recently described tumor, the leiomyomatoid angiomatous neuroendocrine tumor (LANT) was first described in the pituitary gland and contained both cytoplasmic chromogranin A-positive neuroendocrine cells and a smooth muscle leiomyomatous vascular component [4]. Later characterization of a myometrial tumor in a 45-year-old hypermenorrheic woman revealed the same tumor by immunohistochemical analysis and raised the possibility that LANT may not be pituitary-specific [5]. Morphological analysis of LANT revealed prominent vasculature and a cellular stromal component, and electron microscopy revealed chromogranin A-positive neurosecretory granules within the cytoplasm. Ultrastructure analysis confirmed these findings, further characterizing the presence of electron-dense neuroendocrine granules in addition to smooth muscle actin [5].

We describe, as far as we are aware, the first case of myometrial LANT with a synchronous renal leiomyosarcoma.

Case presentation

A 53-year-old Asian woman without notable past medical, surgical, or family history and a normal body mass index presented to the Gynecology Oncology Clinic with a 6-month history of menometrorrhagia and 20-pound unintended weight loss. An endometrial biopsy and endocervical curettage both showed a smooth muscle tumor with

neuroendocrine marker expression. Her pelvic examination was notable for a 12-week size uterus, and a computed tomography (CT) scan of the abdomen and pelvis showed bilateral renal lesions (Fig. 1). The right-sided cyst was simple and sub-centimeter without septa, calcification, or solid components and thus classified as Bosniak category I which are benign cysts and do not require intervention [6]. However, the left-sided mass was 5 cm, complex and cystic, and therefore classified as Bosniak category III, which is of concern with regard to malignancy and requires operative intervention [6] (Fig. 1). A CT-guided biopsy of this renal mass revealed an undifferentiated malignant neoplasm believed to be a low-grade leiomyosarcoma (LMS).

Given the preoperative findings, a modified radical hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy were performed. Uterine pathology was significant for a Stage IB smooth muscle tumor with neuroendocrine marker expression and intra-tumor hyalinized blood vessels consistent with a leiomyomatous angiomatous neuroendocrine tumor (LANT) invading 90 % through the myometrial wall in a background of weakly proliferative endometrium. The patient's post-operative course was uncomplicated, and she was discharged home on post-operative day #3. She subsequently underwent an interval left radical nephrectomy with final diagnosis of Stage II grade 3 renal capsular LMS with negative margins. Comparison of the uterine and renal specimens (submitted in their entirety) by soft tissue/

Fig. 2 Morphological and immunohistochemical features of leiomyomatoid angiomatous neuroendocrine tumor (LANT) of the myometrium. Biphasic tumor composed of solid nests of monomorphic cells (**a** *white arrow*) with intervening bundles of eosinophilic

stroma (**c** *white triangle*) containing spindled cells (**b** *black triangle*) (H&E). The nests of tumor cells are positive for synaptophysin (**d**), neuron-specific enolase (**e**), smooth muscle actin (**f**), vimentin (**g**), CD56 (**h**) and CD99 (**i**). **a, b, d-i** $\times 20$ and **c** $\times 40$. H&E

sarcoma and gynecologic pathologists led to the conclusion that the renal tumor was different from the uterine tumor. Given the two distinct histologic appearances, a metastatic process was deemed to be unlikely. No adjuvant treatment was recommended, and this patient remains without evidence of disease 1 year after her uterine LANT diagnosis and 9 months after her renal LMS diagnosis.

The uterus with its attached cervix weighed 202 g, and the corpus measured $4.5 \times 4.3 \times 4.4$ cm. A pedunculated $4.5 \times 2.6 \times 1.5$ cm lesion both projected into the endometrial cavity and infiltrated the uterine wall to within 0.4 cm of the uterine serosa. Microscopic examination of the uterus revealed a biphasic tumor composed of solid sheets and nests of tumor cells separated by thick bands of spindled cells (Fig. 2). The cells had large oval-round nuclei with irregular nuclear membranes, “salt and pepper” chromatin, and prominent nucleoli. The stroma was composed of fusiform cells and prominent blood vessels with

small lumina and hyalinized walls. Immunohistochemistry demonstrated that the tumor cells stained positive for synaptophysin, smooth muscle actin, vimentin, and CD99, and were only focally positive for CD56 and neuron-specific enolase (NSE). Immunohistochemistry of the tumor was negative for CD10, CKAE1/CKAE3, epithelial membrane antigen (EMA), CAM5.2, inhibin, calretinin, and chromogranin A. The tumor cells showed 80 % expression of estrogen receptor and progesterone receptor.

The left kidney with overlying perirenal fat weighed 278 g and measured $11.2 \times 7.4 \times 4.3$ cm. Abutting the renal capsule at the lower pole was a solid, white, smooth lesion measuring $4.6 \times 3.9 \times 1.0$ cm. This solid lesion was contained within a hemorrhagic cyst measuring up to 5 cm. Microscopic examination of the left kidney tumor also revealed sheets of spindled cells arranged with interlacing fascicles. The mitotic rate was 5 per 10 per HPF. The cells contained elongated, pleomorphic nuclei with

Fig. 3 Morphological and immunohistochemical features of leiomyosarcoma arising in the kidney. Tumor composed of sheets of spindle cells arranged in interlacing fascicles (a). Cells have elongated, pleomorphic nuclei with blunt ends and eosinophilic cytoplasm. Mitoses are prominent (b) (H&E). Tumor cells are

negative for RCC (c) and synaptophysin (d), positive for neuron-specific enolase (e), smooth muscle actin (f), CD56 (h) and CD99 (i). They are focally positive for vimentin (g). a, c–i $\times 20$ and b $\times 40$. H&E

blunt ends and eosinophilic cytoplasm (Fig. 3), and, in immunohistochemistry, stained positive for NSE, smooth muscle actin, CD56, and CD99. They were focally positive for vimentin. The spindle cells were negative for renal cell carcinoma antigen (RCC) and synaptophysin.

Discussion

To date, the largest published series of patients with STUMP diagnoses consists of 41 patients with a mean follow-up period of 45 months [7]. In their retrospective analysis, no clear risk factors could be identified, including tobacco use and ethnicity. Furthermore, surgical approach via a hysterectomy or myomectomy was also not found to significantly predict recurrence. Among the 3 (7.3 %) patients with documented relapse, recurrence occurred

13, 47, and 68 months after initial diagnosis. Of note, recurrence in 1 patient was a retroperitoneal and right ovarian LMS, suggesting STUMP could recur as a malignant neoplasm, and should be closely monitored.

In the case of the first pituitary LANT surgically resected in 2006, that patient developed local recurrence within a year, and was treated by partial surgical resection [4]. Three years later, substantial regrowth prompted repeat tumor resection. No adjuvant chemotherapy or radiation was delivered; however, the authors report the patient continues to do well with only subtle residual visual field defects (personal communication with Vajtai). The myometrial LANT was described as having low mitotic activity (<10 mitotic figures/HPF) [5]. Because of expression of chromogranin A in both stromal and vascular areas, the authors concluded that the myometrial LANT was neuroendocrine-derived, irrespective of location, and proposed

Table 1 Clinical characteristics of previously reported LANT

Report	Ethnicity	Pathologic findings	Organ of origin	Clinical course	Prognosis
Sakashita et al. [5]	Japanese	Prominent vasculature with small lumina and hyalinized walls. Also cellular stromal component with oval or spindle-shaped nuclei with fine chromatin and faint nucleoli, obscure cytoplasm, and very poor mitotic activity	Myometrium	Presented with increased menstrual bleeding and finding of uterine myometrial tumor. Myomectomy performed and diagnosis made post-operatively	Unknown
Guntupalli et al. [7]	Swiss	Moderately cellular biphasic tumor, characterized by alternate epithelial-like cuboidal cells and fascicles of spindly stroma	Pituitary	Presented with secondary amenorrhea and galactorrhea with finding of hyperprolactinemia. MRI revealed 3-cm sellar space-occupying lesion. Underwent surgical resection	Unknown
Jones et al. (this work)	Korean	Biphasic tumor composed of solid sheets and nests of tumor cells separated by thick bands of spindled cells	Myometrium	Presented with PMVB and finding of FIGO grade 3 endometrioid adenocarcinoma. Underwent surgical staging with TAH/BSO/BLPLND. Synchronous primary renal LMS diagnosed at second surgery. Now disease-free from both tumors over 1.5 years later	Unknown

Clinical characteristics are organized and described in Refs. [4, 5]

PMVB postmenopausal vaginal bleeding, *TAH/BSO/BLPLND* total abdominal hysterectomy/bilateral salpingo-oophorectomy/bilateral pelvic lymphadenectomy

that the neurosecretory component of LANT may arise as a result of TGF- β -induced differentiation into smooth muscle cells when residing in a pro-angiogenic tumor microenvironment [5]. This hypothesis stems from:

1. results indicating that neuroendocrine tumors with vascular proliferation may develop as a result of angiogenic environments created by the neoplasms and their associated cytokines and growth factors [8];
2. in-vitro and human genetic mutation models which support the importance of TGF- β in vascular smooth muscle differentiation and cell proliferation in angiogenic tumor microenvironments [9]; and
3. discovery of TGF- β -positive endothelium in the myometrium of LANTs [5].

Clinical and pathologic characteristics of our myometrial LANT are compared with previously described LANT in Table 1. Pathology is similar, although different surgical treatments were performed.

Histologic and immunohistochemistry characteristics of uterine mesenchymal tumors including STUMP are summarized in Table 2. The rarity of LANT and STUMP coupled with their variable pathological findings complicate clinical management. Previously described studies indicate relatively benign disease courses [3] for these two entities, and significantly longer disease-free survival than for classical uterine LMS [10], yet the data are complicated by sporadic cases of STUMP-related death despite low-grade histopathology. Although, recommendations for treatment include clinical observation and conservative

treatment without immediate surgical cytoreduction and adjuvant chemotherapy, consensus for treatment has not been reached.

Distinction between LANT and endometrial stromal sarcoma (ESS) is also important. Morphologically the two tumors are remarkably similar. The distinction is made on the basis of immunohistochemistry. In contrast with ESS, LANT is composed of tumor cells that are synaptophysin, smooth muscle actin, vimentin, and CD99 positive. These cells are also focally positive for CD56 and NSE, and negative for CD10, CKAE1/CKAE3, EMA, CAM5.2, inhibin, calretinin, and chromogranin. They show 80 % expression of ER and PR.

As this is the only other case of myometrial LANT, and the malignant potential of this tumor remains unknown, we cannot exclude the possibility that the renal LMS may represent a metastatic focus or malignant transformation of a LANT into an LMS. Recognition of classic familial cancer syndrome, including the Li–Fraumeni syndrome of soft-tissue sarcomas [11], coupled with maturing data from Genome Wide Association Studies (GWAS) emphasize the need for a heightened level of awareness for potential predisposition for other cancers [12].

The presence of concurrent or synchronous abdominal malignancies further complicates treatment strategies, but requires special attention, especially when considering the rarity of both LANT and renal LMS. Although a consensus advocating concurrent versus separate cytoreductive efforts is unavailable, a report by Wong et al. on 3 patients with

Table 2 Classification of uterine mesenchymal tumors

Type	Atypia	Mitoses	Necrosis	Vimentin	Smooth muscle actin	Muscle-specific actin	Cytokeratin	CD10 [21] (cluster of differentiation 10)	Estrogen receptor/progesterone receptor	Desmin	H-caldesmon	Epithelial membrane antigen	Comments
Endometrial stromal nodule	Minimal	Infrequent	—/inconspicuous	+	+	+	+	+/-	+++	—	—	— ^a	Absence of myometrial infiltration
Endometrial stromal sarcoma, low grade	—	Infrequent	—/inconspicuous	+	+/-	+	+/-	+	+++	—	—	—	Myometrial infiltration present, inhibin/calretinin/CD99/WT-1/melan A: area of sex-cord differentiation
Undifferentiated endometrial sarcoma	Marked	Frequent (often atypical MF)	+	+	—	— ^a	+/-	+	—	+/-	— ^a	— ^a	Lacks specific differentiation
Leiomyoma, NOS	—	<5 MF/10 HPF	—	— ^a	+	+	+/-	+/-	+++	+	+	—	Well-circumscribed, pseudocapsule
Mitotically active leiomyoma	—	>5 MF/10 HPF	—	— ^a	+	+	— ^a	+/-	+++	+	+	—	
Cellular leiomyoma	—	Infrequent	—	— ^a	+	+	— ^a	+/-	+++	+	+	—	Increased cellularity
Hemorrhagic cellular leiomyoma	—	Infrequent	—	— ^a	+	+	— ^a	+/-	+++	+	+	—	Hormone-induced changes
Epithelioid leiomyoma	—	<5 MF/10 HPF	—	— ^a	+	+	— ^a	+/-	+++	+	+	—	Epithelial-like cells
Myxoid leiomyoma	—	<5 MF/10 HPF	—	— ^a	— ^a	— ^a	— ^a	— ^a	— ^a	— ^a	— ^a	— ^a	Myxoid material separates tumor cells
Atypical leiomyoma	Moderate/ marked	<10 MF/ 10 HPF	—	— ^a	+	+	—	+/-	+++	+	+	—	
Lipoleiomyoma	—	Infrequent	—	— ^a	+	+	— ^a	+/-	+++	+	+	—	Scattered adipocytes
STUMP	—	Infrequent	—	— ^a	+	+	— ^a	+/-	— ^a	+	+	—	
	+/-	>10 MF/ 10 HPF	+/-	— ^a	+	+	— ^a	+/-	— ^a	+	+	—	
	Marked	Borderline	—	— ^a	+	+	— ^a	+/-	— ^a	+	+	—	
	—	Infrequent	+/-	— ^a	+	+	— ^a	+/-	— ^a	+	+	—	

Table 2 continued

Type	Atypia	Mitoses	Necrosis	Vimentin	Smooth muscle actin	Muscle-specific actin	Cytokeratin (cluster of differentiation 10)	CD10 [21]	Estrogen receptor/progesterone receptor	Desmin	H-caldesmon	Epithelial membrane antigen	Comments
Leiomyosarcoma	Moderate/ marked	>10 MF/ 10 HPF	+	- ^a	+	- ^a	+	+/-	+	+	+	+	Infiltrative
Leiomyosarcoma, epithelioid variant	Moderate/ marked	>5 MF/10 HPF	+	- ^a	+	- ^a	+	+	+	+	+	+	Infiltrative, >50 % epithelioid cells
Leiomyosarcoma, myxoid variant	Moderate/ marked	Any MF	+/-	- ^a	+	- ^a	+	+	+	+	+	+	Infiltrative, myxoid extracellular matrix

Comments: LANT is composed of tumor cells that are synaptophysin, smooth muscle actin, vimentin, and CD99 positive. These cells are also focally positive for CD56 and neuron-specific enolase (NSE), and negative for CD10, CKAE1/CKAE3, epithelial membrane antigen (EMA), CAM5.2, inhibin, calretinin and chromogranin. They show 80 % expression of ER and PR
 MF mitotic figures, HPF high power field, ER estrogen receptor, PR progesterone receptor, SMA smooth muscle actin, EMA epithelial membrane antigen, MSA muscle specific actin, NOS not otherwise specified, STUMP smooth muscle tumor of uncertain malignant potential. Data are cited and modified from Refs. [15–20]

^a Insufficient data or not applicable

synchronous RCC and gynecologic malignancies suggested that concurrent surgical cytoreduction with radical nephrectomy did not add significant post-operative morbidity [13]. Although simultaneous cytoreductive therapy for synchronous genitourinary and intra-abdominal extra-urinary lesions may be associated with greater intraoperative blood loss and longer hospital stays compared with patients with only solitary genitourinary lesions undergoing surgical management, this association has not been shown to be statistically significant, and no complications were reported among the subset of patients receiving concurrent genitourinary cytoreduction with total hysterectomy, salpingo-oophorectomy, or resection of synchronous gynecologic malignancies [14]. Concurrent management, however, should include a thorough risk–benefit analysis to minimize chemoradiation-associated tissue toxicity if adjuvant therapy is indicated, evaluation for hereditary syndromes with referral for genetic counseling, and optimization of multi-disciplinary clinical management strategies [15].

Uterine LANT is a rare tumor with unknown prognosis and, therefore, unpredictable clinical course. Even rarer is the simultaneous and incidental finding of synchronous primary renal capsular LMS. In this patient both primary tumors were localized to their tissues of origin and surgical margins were negative. She continues to have no evidence of disease 1 year after her initial surgical treatment.

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Conflict of interest The authors declare they have no conflict of interest.

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