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Pathobiological Study of Leiomyomatoid Angiomatous Neuroendocrine Tumor (LANT)-Like Tumor in the Myometrium

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Abstract

Leiomyomatoid angiomatous neuroendocrine tumor (LANT) is a possible new disease entity that was reported as a dimorphic neurosecretory tumor with a leiomyomatous vascular component; it was found in the pituitary. We describe here uterine LANT-like malignant tumor in a 45-year-old woman with myometrial tumor, diagnosed clinically as uterine leiomyoma (LMA). She underwent laparoscopic myomectomy. The tumor consisted of hyalinized vasculature, containing factor VIII-positive endothelium and α smooth muscle actin (α SMA)-positive vascular smooth muscle cells (SMCs), and stromal cells, expressing neuroadhesion molecules. Both vascular and stromal components diffusely expressed chromogranin A. Molecular pathological studies of uterine LANT-like malignant tumor revealed the common characteristic abnormalities of myometrial malignant tumors, i.e. leiomyosarcomas. By our research, defective expression of CALPONIN h1 and proteasome beta 9 (PSMB9)/ β 1i is observed in uterine LANT-like malignant tumor such like molecular pathological findings of uterine leiomyosarcoma (Ut-LMS). These findings meet the definition of uterine LANT-like malignant tumor, and our clinical case suggests that LANT is a special type of neuroendocrine neoplasm and is not organ specific.

Keyword: LANT; PSMB9/ β 1i, CALPONIN h1; Leiomyosarcoma; Myometrial tumor

Introduction

Leiomyomatoid angiomatous neuroendocrine tumor (LANT) was firstly reported as a new neoplastic category [1]. Molecular pathologic concept of LANT is that of a dimorphic neoplasm consisting of an admixture of neurosecretory cells and leiomyomatous stroma surrounding intratumor vessels [1]. The original clinical case was reported as a pituitary neoplasm. Histopathological studies with LANT revealed 2 major tumor components [1]. The first cell population comprised cytokeratin-negative neuroendocrine cells positive for neuroadhesion molecules and chromogranin A as a serum marker of neuroendocrine tumors [1]. The second constituent was α SMA-positive leiomyomatous vascular

component associated with a cell-cell adhesion molecule, CD34-positive endothelia [1]. Based on this histopathologic pattern and immunophenotype, we proposed the descriptive diagnosis of LANT and suggested that possible variant of a dimorphic pituitary neoplasm, probably related to null cell adenoma. Because no further reports of this entity have since been published, whether LANT is a pituitary-specific tumor or a type of soft tissue tumor is unclearly understood. We report here uterine LANT-like malignant tumor, but this one occurring in the uterus, and histopathological studies of LANT revealed the common characteristic abnormalities of myometrial malignant tumors, i.e. Ut-LMS. This dimorphic tumor contained both vascular and stromal components. We suggest that uterine LANT-like malignant tumor may be derived from neuroendocrine cells that probably have differentiated into uterine SMCs under the influence of transforming growth factor- β (TGF- β).

During an annual health studies, a healthy 45-year-old woman was found to be anemic, and a gynecologist found a uterine tumor causing hypermenorrhea. Magnetic resonance imaging (MRI) testing disclosed a myometrial mass with heterogeneous intratumor signals. The radiologic diagnosis was uterine LMA with partial degeneration. At the patient's request, laparoscopic myomectomy was performed. The soft, white tumor had a cauliflower-like surface, which was incompatible with the radiologic diagnosis. Histologically, the tumor possessed 2 major components: first, a prominent vasculature with small lumina and hyalinized walls, and, second, a cellular stromal component. Specifically, we noted oval- or spindle shaped nuclei with fine chromatin and faint nucleoli, obscure cytoplasm, and very poor mitotic activity. All randomly obtained histopathologic samples showed the same histopathologic pattern.

SMCs in a benign myometrial tumor, uterine LMA markedly expresses α SMA and neuroadhesion molecule/CD56; however, no cell was positive for neuron-specific enolase, chromogranin A. Most cells of uterine LANT-like malignant tumor diffusely express CD56 and chromogranin A [2]. In addition, the cytologic features of each major component were quite similar. We demonstrate differential expression of several proteins in human myometrial tumors and normal myometrium (Table 1). IHC studies with myometrial tumors demonstrated that although CALPONIN h1 and proteasome beta subunit (PSMB9)/ β 1i markedly expressed in three types of myometrial tumors and normal myometrium, loss of expression of CALPONIN h1 and PSMB9/ β 1i is observed in human myometrial tumor, i.e. Ut-LMS (Table 1). It is likely that CALPONIN h1 and PSMB9/ β 1i are potential biomarkers, which can distinguish Ut-LMS from other myometrial tumors. We therefore examined expression pattern of both proteins, CALPONIN h1 and PSMB9/ β 1i in uterine LANT-like malignant tumor. IHC studies demonstrated that although CALPONIN h1 and PSMB9/ β 1i markedly expressed in normal myometrium, loss of expression of CALPONIN h1 and PSMB9/ β 1i is observed in uterine LANT-like malignant tumor such like immunopathological findings of Ut-LMS (Table 1). In section of uterine LANT-like malignant tumor, the vascular structure was reportedly composed of factor VIII-, CD31-, and CD34-positive endothelial cells,

and α SMA and sarcomeric muscle actin-positive vascular SMCs [2,3]. Results for O-linked sialoglycoprotein/D2-40, a lymphatic endothelial marker, were reportedly negative, suggesting that the vascular structure was not a lymphatic tumor such as lymphangiomyoma [4].

Here, we present histologic and immune-pathologic characteristics of a complex, dimorphic neurosecretory tumor possessing a SMC-rich vascular component and a population of stromal cells expressing neuronal differentiation molecules. Based on its histologic aspects and immune-pathologic observations, we first ruled out the possibility of a uterine LMA with a heterologous paraganglioma element [5]. We also ruled out the possibility that the tumor was a glomangioma, perivascular epithelioid cell tumor, paraganglioma, solitary fibrous tumor, extra gastrointestinal stromal tumor with/without neuroectodermal differentiation [6-11]. Therefore, histological studies of the uterine LANT-like malignant tumor revealed the common characteristic abnormalities of LANT, which was reported as a pituitary neoplasm [1]. Although the characteristics of the uterine tumor were indeed those of a LANT, we found 2 significant differences between the original LANT reported by Schürch C et al. and our clinical case [1]. First, the original LANT was identified as a pituitary neoplasm, but our clinical case was a myometrial tumor. Soft tissue tumors are known to appear in various organs, including the pituitary and uterus. Instead, LANT is probably a soft tissue tumor with a neurosecretory phenotype. Therefore, we accepted the possibility that the tumor described here was a second clinical case of LANT. Second, in the original LANT report, chromogranin A and synaptophysin were predominantly detected in a "neurosecretory" component of the tumor. However, most tumor cells in uterine LANT-like malignant tumor expressed chromogranin A, but not synaptophysin. Thus, tumor cells in the present clinical case were neuroendocrine regardless of their location, whether vascular or stromal. In the initial report, a few stromal "leiomyomatoid" cells appeared to express chromogranin A [1]. Synaptophysin and chromogranin A, both of which are neuroendocrine marker molecules, are localized in distinctive neurosecretory vesicles, the former predominantly in small transparent looking vesicles and the latter in large dense-cored granules [12]. The part of the leiomyomatous stromal component of the pituitary LANT may have contained small, immature neuroendocrine vesicles. Recent experiment with electron microscopy demonstrated that the tumor cells in uterine LANT-like malignant tumor contained predominantly chromogranin A-positive, dense-cored neurosecretory granules [2]. This result suggests that the diffuse distribution of tumor cells with a neurosecretory phenotype in uterine LANT-like malignant tumor is consistent with the features of the first reported LANT. Other research facility reported that a significantly elevated serum chromogranin A was detected in 2 of 12 patients with uterine LMA without any histologic observations [13,14].

The histogenesis of this newly reported type of neoplasia is unclearly understood. Recent studies shown that a group of neuroendocrine neoplasms represented florid vascular proliferation resulting from angiogenic factors produced by the tumor cells themselves [15,16].

Table 1: Differential expression of PSMB9/β1i and CALPONIN h1 in human normal myometrium, several myometrial tumor types and uterine LANT-like malignant tumor.

Tumor type	Atypia	Mitotic activity	Necrosis	Protein expression*														Clinical comments
				Cyt	Des	CAV	SMA	Vim	ER/PR	End	EGF	CyB	CyE	PSMB9	Cal	Ki67		
Endometrial stromal tumors.																		
Endometrial stromal nodule	minimal	infrequent	-/inconspicuous	+	-	++	+	+	+++	+	*	+	-	++	++	-		Absence of myometrial infiltration
Endometrial stromal sarcoma	-	infrequent	-/inconspicuous	-/+	-	++	+	+	+++	+	+	+	-	-/+	++	-/+		
Undifferentiated endometrial sarcoma	marked	Frequent (atypical MF)	+	-/+	foc	*	*	-	-	+	+	+	+	-/+	+	+		Lack specific differentiation
Smooth muscle tumors																		
Leiomyoma, NOS	-	<5 MF/10HPF	-	foc	+	++	+	*	+++	-/+	-/+	+	-	++	++	-/+		Well-circumscribed
Mitotically active leiomyoma	-	>5 MF/10HPF	-	*	+	++	+	*	+++	-/+	-/+	+	-	++	++	-/+		Pseudocapsul
Cellular leiomyoma	-	infrequent	-	*	+	++	+	*	+++	-/+	-/+	+	-	++	++	-/+		Increased cellularity
Hemorrhagic cellular leiomyoma	-	infrequent	-	*	+	++	+	*	+++	-/+	-/+	+	-	++	++	-/+		Hormone induced changes
Epithelioid leiomyoma	-	<5 MF/10HPF	-	*	+	++	+	*	+++	-/+	-/+	*	-	++	++	-/+		Epithelial-like cells
Myxoid leiomyoma	-	<5 MF/10HPF	-	*	*	*	*	*	*	-/+	-/+	*	+	-/+	+	+		Myxoid material
Atypical leiomyoma	moderate	<10 MF/10HPF	-	-	+	++	+	*	+++	+	-/+	+	+	-/+	-/+	+		Separates tumor cells
Lipoleiomyoma STUMP#	-	infrequent	-	*	+	++	+	*	+++	*	-/+	*	+	-/+	*	-/+		Scattered adipocytes
	-	infrequent	-	*	+	++	+	*	*	*	-/+	*	-/+	-/+	*	-/+		
	-/+	>10 MF/10HPF	+/uncertain	*	+	++	+	*	*	*	-/+	*	-/+	-/+	*	-/+		
	Marked	borderline	-	*	+	++	+	*	*	*	-/+	*	-/+	-/+	*	-/+		
	-	infrequent	+ /difficult classify	*	+	++	+	*	*	*	-/+	*	-/+	-/+	*	-/+		
Leiomyosarcoma	moderate	>10 MF/10HPF	+	+	+	++	-/+	-	-	+	-/+	++	+++	-	-	++		Infiltrative
Leiomyosarcoma epithelioid variant	moderate	>5 MF/10HPF	+	+	+	++	-/+	-	-	+	-/+	++	+++	-	-	++		Infiltrative, >50% epithelioid cells
Leiomyosarcoma myxoid variant	moderate	Any MF	+	+	+	++	-/+	-	-	+	-/+	++	++	-	-	++		Infiltrative, myxoid extracellular matrix
Leiomyomatoid tumor																		
LANT#	absent	frequent	+	-	-	+	+	+	*	*	+	*	++	-	-	-/+		NOTE1

*insufficient data or not applicable.

Cyt.; cytokeratin, Des.; Desmin, CAV; caveolin 1, SMA; smooth muscle actin, Vim.; vimentin, ER/PR; estrogen receptor/progesterone receptor, End.; Endoglin; CD105/TGFβ receptor (stem cell marker), EGF, EGFR; epidermal growth factor receptor, CyB; cyclin B1, CyE; cyclin E, PSMB9; proteasome beta subunit 9, Cal.; calponin h1, CD56; neural cell adhesion molecule (N-CAM), WT-1; wilm's tumor 1, NOS; not otherwise specified, MF; magnification factor, HPF; high power field, Foc.; focal, STUMP; smooth muscle tumors of uncertain malignant potential. Protein expression*, estimated-protein expressions by immunoblot analysis, immunohistochemistry (IHC) and/or RT-PCR (quantitative-PCR), +/-; partial expression, +; expression, ++; medium expression, +++; high expression, -; no evidence of expression, ER/PR(ref.24), PSMB9 (ref.22,23), cyclin E(ref.24,32), calponin h1(ref.29,30,31), Ki-67(ref.24,33). STUMP#(ref.33,34). Cyclin E, PSMB9, calponin h1 are potential biomarker for human uterine mesenchymal tumors. LANT#, leiomyomatoid angiomatous neuroendocrin tumour (LANT) is described as a dimorphic neurosecretory tumor with a leiomyomatous vascular component (ref.35,36). NOTE1, Low-grade neuroendocrine tumor possibly related to null cell adenoma.

Different from this type of florid vascular proliferation, the vascular component of uterine LANT-like malignant tumor consisted of endothelial cells and vasculature-related SMCs with neurosecretory features. Based on this specific feature, we propose that uterine LANT-like malignant tumor probably be derived from neurosecretory cells that differentiated into SMCs in an angiogenic microenvironment. At present, the nature of a putative neurosecretory cell with the potential to differentiate into SMCs is unclearly understood. However, our research finding of TGF-β-positive endothelial cells in uterine LANT-like malignant tumor tissue offers support for this differentiation hypothesis because this molecule is crucial for vascular SMCs differentiation as well as cell proliferation during tumor angiogenesis [2,3]. Physiological significances of PSMB9/β1i and CALPONIN h1 in sarcomagenesis of myometrial tumor, Ut-LMS is reportedly demonstrated by our research findings. Both factors, PSMB9/β1i

and CALPONIN h1 are useful as biomarkers to distinguish human Ut-LMS from other myometrial tumors [17-19]. Our research findings show effectiveness of PSMB9/β1i and CALPONIN h1 as potential diagnostic biomarker, which possibly distinguish uterine LANT-like malignant tumor from other myometrial tumors. These factors probably play key role in tumorigenesis of uterine LANT-like malignant tumor.

In summary, we report a uterine LANT-like malignant tumor arising in myometrium. Findings for this clinical case suggest possibility that LANT is not organ specific and may be instead a type of soft tissue tumor composed of neuroendocrine cells with the potential to differentiate into a leiomyomatous phenotype in a TGF-β-dependent manner. Further studies including histological analyses should be performed to confirm this hypothesis.

Methods and Materials

Tissue Collection

A total of 51 patients aged between 32 and 83 years who were diagnosed with myometrial tumors in the uterus were selected from pathological files. Serial sections were cut from at least 2 tissue blocks from each patient for hematoxylin and eosin staining and immunostaining. All tissues were used with the approval of the Ethical Committee of Shinshu University after obtaining written consent from each patient. The pathological diagnosis of human myometrial tumors was performed using established criteria with some modifications [20,21]. Briefly, usual leiomyoma (usual LMA) was defined as a tumor showing typical histological features with a mitotic index (MI) [obtained by counting the total number of mitotic figures (MFs) in 10 high-power fields (HPFs)] of <5 MFs per 10 HPFs. Cellular leiomyoma (cellular LMA) was defined as a tumor with significantly increased cellularity (>2000 myoma cells/HPF) and a MI<5, but without cytologic atypia. Bizarre leiomyoma (BL) was defined as a tumor either with diffuse nuclear atypia and a MI<2 or with focal nuclear atypia and a MI<5 without coagulative tumor cell necrosis. A myometrial tumor of uncertain malignant potential (STUMP) was defined as a tumor with no mild atypia and a MI<10, but with coagulative tumor cell necrosis. Ut-LMS was diagnosed in the presence of a MI>10 with either diffuse cytologic atypia, coagulative tumor cell necrosis, or both. Of the 113 myometrium tumors, 52 cases were diagnosed as uterine LMA, 3 cases were Bizarre LMA, 58 cases were Ut-LMS, and 1 case was uterine LANT-like malignant tumor, which was obtained from Tokushima University School of Medicine. Protein expression studies with cervical epithelium and carcinoma tissues were performed using tissue arrays (Uterus cancer tissues, AccuMax Array, Seoul, Korea). Details regarding tissue sections are indicated in the manufacturer's literature (AccuMax Array).

Immunohistochemistry (IHC)

We evaluated the characteristics of uterine LANT-like malignant tumor and myometrial tumors by means of immunohistochemistry (IHC) staining. We used formalin-fixed, paraffin-embedded tumor to prepare 3- μ m-thin sections that we deparaffinized and subjected to IHC staining. Samples underwent pretreatment to recover immunoreactivity and were incubated with methanol containing 1% hydrogen peroxidase for 30 minutes unbound secondary antibodies, via incubation with diaminobenzidine-hydrogen peroxidase solution. IHC staining samples were counterstained with hematoxylin and mounted with SUPER Mount (Matsunami Glass Industry Co, Osaka, Japan). IHC staining for CALPONIN h1, CAVEOLIN1, CYCLIN B1, CYCLIN E1, CYTOKERATIN, DESMIN, ENDOGLIN, EGFR, Estrogen Receptor (ER), Ki-67/MIB1, proteasome beta 9 (PSMB9)/ β 1i, Progesterone Receptor (PR), α SMA, TP53, and VIMENTIN, CD31, CD34, CD56, D2-40, factor VIII, TGF- β , were performed on the serial human Ut-LMS sections, human myometrial tumors, and uterine LANT-like malignant tumor. Antibodies for CALPONIN h1, CD31 (bs-0195R), CD34 (bs-2038R), CD56 (bs-0805R), were purchased from Bioss Inc. (Woburn, MA). Antibody for D2-40(ACR266A) was

purchased from BIOCARE Medical LCC (Pacheco, CA). Antibodies for factor VIII (F8/86) and TGF- β (ARG53688) was purchased from Arigo biolaboratories Corp (Hsinchu City Taiwan). Antibodies for CAVEOLIN1, ER (ER1D5), Ki-67(MIB-1), PR (PR10A), and TP53 (DO-1) were purchased from Immunotech (Marseille, France). Anti- α SMA antibody was purchased from Dako (Agilent Technologies Glostrup Denmark). Antibodies for ENDOGLIN, and EGFR were purchased from Santa Cruz Biotechnology, Inc. Inc. (Dallas, TX). Antibodies for CYCLIN B1, CYCLIN E1, and VIMENTIN, were purchased from Cell Signaling Technology, Inc. (Danvers, MA). Antibodies for CYTOKERATIN, and DESMIN was purchased from VLVbio (Hästholsmvägen Nacka, Sweden). Anti-human PSMB9/ β 1i antibody was produced by SIGMA-Aldrich collaboration Laboratory (SIGMA-Aldrich, Japan Science and Technology Agency (JST) and Shinshu University). IHC was performed using the avidin-biotin complex method previously described. Briefly, one representative 5- μ m tissue section was cut from a paraffin-embedded sample of the radical hysterectomy specimen from patients with human Ut-LMS. Sections were deparaffinized and rehydrated in graded alcohols. After the samples were washed with phosphate buffered saline (PBS)-pH7.4, the samples were incubated with normal mouse serum for 20 min. Sections were incubated at room temperature for 1 hour with primary antibody. After extensive washing, the samples were reacted for 60 minutes with adequate peroxidase-labeled secondary antibody (Histofine Simple Stain MAX-PO, Nichirei Bioscience, Tokyo, Japan). The immunoreaction was visualized, after removal of unbound secondary antibodies, via incubation with diaminobenzidine (DAB)-hydrogen peroxidase solution. Immunostained samples were counterstained with hematoxylin and mounted with SUPER Mount (Matsunami Glass Industry Co, Osaka, Japan). Normal myometrial portions in the specimens were used as positive controls. Negative controls consisted of tissue sections also incubated with normal rabbit IgG instead of the primary antibody. These studies are registered, at Shinshu University in accordance with local guidelines (approval no. M192).

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