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Diagnostic Biomarker Candidates Including NT5DC2 for Human Uterine Mesenchymal Tumors

Takuma Hayashi[1,2], Kenji Sano[3], Tomoyuki Ichimura[4], Susumu Tonegawa[5], Nobuo Yaegashi[6], Ikuo Konishi[1,7]

[1]National Hospital Organization Kyoto Medical Centre, Kyoto, Japan
[2]START Program, Japan Science and Technology Agency (JST), Tokyo, Japan
[3]Department of Laboratory Medicine, Iida City Hospital, Nagano, Japan
[4]Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, Osaka, Japan
[5]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, USA
[6]Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Miyagi, Japan
[7]Kyoto University Graduate School of Medicine, Kyoto, Japan

ABSTRACT

Unfortunately, uterine leiomyosarcoma still has a poor prognosis. The National Cancer Institute reported that the median overall survival (mOS) at stage I to stage IV of leiomyosarcoma was 31 months. Norwegian reports show that mOS of uterine leiomyosarcoma is as poor as eight years at stage I, four years at stage II, two years at stage III, and one year at stage IV. Preoperative diagnosis of uterine leiomyosarcoma is difficult in clinical practice. Treated as "uterine leiomyoma", however, tumors are often differentially diagnosed from uterine leiomyosarcoma by pathological diagnosis with hysterectomy or myomectomy. Histopathological diagnosis may result in a diagnosis of smooth muscle tumor of unmalignant potential (STUMP), and leiomyoma with bizarre nuclei that cannot be declared as malignant or benign. In about half of stage I patients, uterine leiomyosarcoma recurs. However, at present, no anticancer drug that has been shown to be effective in preventing postoperative recurrence has not been established. For this reason, we monitor patients without postoperative treatment, and start clinical treatment when recurrence is confirmed. Uterine leiomyomas, which occur in about 70% of women aged 40 and over in Japan and overseas, are benign tumors, but are extremely difficult to distinguish from uterine leiomyosarcoma. Although progress in diagnostic imaging such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography- Computed Tomography (PET-CT) is remarkable, uterine leiomyosarcoma is difficult to distinguish from other uterine mesenchymal tumors. No differential biomarker has been identified for uterine other uterine mesenchymal tumors and uterine leiomyosarcoma in surgical pathological diagnosis or clinical examination. This review describes the current diagnosis and treatment for uterine sarcoma, including new trends in the search for biomarker candidates for uterine leiomyosarcoma.

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Uterine sarcoma is a particularly unfavorable gynecological tumor, and standard treatment has not been established. A major reason for the lack of established treatment is that it is difficult to conduct clinical trials due to its low frequency of occurrence. The majority of uterine sarcomas originate in the uterine corpus, and clinical studies of 2,677 uterine sarcomas in patients aged 35 years and older have shown to account for 8% of all uterine corpus malignancies [1]. About half of the sarcomas are carcinosarcomas, and most of the rest are leiomyosarcomas, endometrial stromal sarcomas, and adenosarcomas. In Japan, 43-46% of uterine corpus sarcomas were carcinosarcoma, 36-38% were leiomyosarcoma, and 13-19% were endometrial stromal sarcoma [2,3]. The peak age of onset is around 50 years for leiomyosarcoma and endometrial stromal sarcoma, whereas the peak age of onset for carcinosarcoma is 60 years of age and relatively older [2-4]. The 50% survival for endometrial stromal sarcoma is 76 months, while the 50% survival for carcinosarcoma or leiomyosarcoma is 28 and 31 months, respectively. Histopathological diagnosis of uterine sarcoma is often difficult because of the low frequency of uterine sarcoma and the various morphologies of the same histological type. However, it is important to determine the diagnosis of uterine sarcoma by sharing information between gynecologists, radiologists, and pathologists, because the treatment strategy and prognosis for uterine sarcoma depend on histological diagnosis.

Carcinosarcoma is a tumor that consists of a carcinoma component and a sarcoma component. Therefore, carcinosarcoma was called malignant müllerian (mesodermal) mixed tumor. If the sarcoma component does

not show a differentiation tendency, it is called homologous, a sarcoma is called heterologous if it shows differentiation into mesenchymal tissue that does not naturally exist in the uterus, such as cartilage, striated muscle, and bone. In either case, a polyp-like ridge that protrudes into the intrauterine cavity is often formed macroscopically. Three theories have been proposed for the histogenesis of uterine sarcoma: combination tumor theory, collision tumor theory, and composition tumor theory. Chronality analysis showed that most of the carcinosarcomas were derived from single cells, and showed that during tumor development, they differentiated into epithelial-like and stromal-like morphologies [5]. Clinicopathologic findings indicate that carcinosarcoma is more like a carcinoma than a sarcoma, based on findings such as common risk factors and many lymphatic metastases. Therefore, surgery and postoperative treatment for carcinosarcoma are in accordance with high-grade endometrial cancer.

For histopathological diagnosis of uterine leiomyosarcoma, the diagnostic criteria proposed by the group of Hendrickson and Kempson are widely used [6]. In other words, in the diagnosis of uterine leiomyosarcoma, (1) cell atypia, (2) fission (index), and (3) coagulation necrosis are comprehensively evaluated. As the initial treatment for uterine leiomyosarcoma, simple abdominal total hysterectomy and bilateral adnexal excision may be the basic treatments in cases that can be removed. There is no clear evidence that extended surgery or additional lymph node dissection improves prognosis. Phase III clinical trials have provided no clear evidence of the efficacy of radiation or chemotherapy as a postoperative treatment.

Endometrial stromal sarcomas were classified as low-grade and high-grade. However, according to the current WHO classification (2003), high-grade endometrial stromal sarcoma does not necessarily have similarity to endometrial stromal. Therefore, high-grade endometrial stromal sarcoma is called undifferentiated endometrial sarcoma [7]. Like leiomyosarcoma, treatment of endometrial stromal sarcoma is based on simple abdominal total hysterectomy and bilateral appendectomy. However, 9 to 33% of low-grade endometrial stromal sarcomas and 15 to 18% of undifferentiated endometrial sarcomas have metastases to the pelvic or para-aortic lymph nodes, lymph node dissection is required [8,9]. The efficacy of irradiation and chemotherapy, regardless of grade, is unclear, so phase II clinical trials will show the results of their therapeutic effects. Since hormone receptors are positive in low-grade endometrial stromal sarcoma, the efficacy of endocrine therapy is also an important issue to be studied [10].

In collaboration with Professor Susumu Tonegawa (Massachusetts Institute of Technology), Hayashi's group reported that uterine leiomyosarcoma spontaneously develops after 6 months of age in proteasome component, low molecular mass polypeptide 2/β1i (LMP2/β1i)-deficient female mice [11-13]. Hayashi *et al*. also demonstrated that the incidence of uterine leiomyosarcoma up to 12 months of age is approximately 37% of in all LMP2/β1i-deficient female mice [11-13]. Therefore, in a joint study with a collaborating medical institution, Hayashi *et al*. examined the efficacy and reliability of LMP2/β1i as a biomarker for uterine leiomyosarcoma. Hayashi *et al*. examined the expression status of LMP2/β1i in 40 cases of normal myometrium tissue, uterine leiomyoma tissue, and uterine leiomyosarcoma tissue obtained from the pathological file by immunohistochemical staining using an anti-LMP2/β1i antibody [14,15]. As a result, LMP2/β1i expression was significantly reduced specifically in uterine leiomyosarcoma tissue. Even in cases where differential diagnosis was difficult with the current pathological diagnosis, it was easy to distinguish between uterine leiomyosarcoma and uterine leiomyoma based on the expression status of LMP2/β1i [14]. Currently, Hayashi *et al*. are collaborating with a comprehensive reagent and diagnostics manufacturer to examine a differential diagnosis method for uterine leiomyosarcoma by immunohistochemical staining using a combination of LMP2/β1i with other candidate cellular factors; CAVEOLIN, CYCLIN B, CYCLIN E, Ki-67 (Table 1). As a health and welfare activity of national and international governments, uterine cancer screening (including uterine leiomyoma with high incidence regardless of race) is recommended for women aged 20 and over. Although serum miRNAs with high diagnostic performance for preoperative uterine mesenchymal tumor screening have been investigated, there are still issues to be solved for the results of this research to be practically applied in the clinical practice.

In conclusion our investigation reviewed the current clinical evidence comparing different adjuvant strategies for the postoperative management of uterine-confined uterine leiomyosarcoma patients. On the light of these data, it seems that the administration of adjuvant chemotherapy does not improve progression free survival of early stage uterine leiomyosarcoma. Large prospective, randomized, multi-institutional studies are needed to better assess the value of different adjuvant strategies. Innovative target therapies need to be tested in order to improve patients' outcome that remains unsatisfactory. Defective expression of LMP2/β1i is likely to be one of the risk factors for the development of human uterine leiomyosarcoma, as it is in the LMP2/β1i deficient mouse. Thus, combination of LMP2/β1i with other functional candidates is useful for a novel diagnostic biomarker for distinguishing human uterine leiomyosarcoma from other mesenchymal tumors. Additionally, gene therapy with LMP2/β1i expression vectors may be a new treatment for human uterine leiomyosarcoma that exhibit a defect in LMP2/β1i expression. Because there is no effective therapy for unresectable human uterine leiomyosarcoma, our results may bring us to specific molecular therapies to treat this malignant tumor.

5'-Nucleotidase Domain Containing 2 (NT5DC2) is a novel oncoprotein, the regulatory effects of which have not been well characterized. Our clinical facility has been investigating the expression profile and functional regulation of NT5DC2 and its potential interplay in uterine leiomyosarcoma and other uterine mesenchymal tumors. Our preliminary data to date shows that NT5DC2 is aberrantly upregulated in human uterine leiomyosarcoma. Overexpression of NT5DC2 was associated with unfavorable survival. The artificial deficiency of NT5DC2 significantly reduced the expression of cyclin B1, cyclin A2, cyclin E1, and CDK1 and increased G1 phase arrest in human uterine leiomyosarcoma cell lines and suppressed their proliferation both *in vitro* and *in vivo*. Further studies are required to investigate whether NT5DC2 can be a biomarker for differentiating uterine leiomyosarcoma from other mesenchymal tumors.

Conclusion

Uterine leiomyosarcoma is a malignant tumor with a poor prognosis that repeats recurrence and distant metastasis. Preoperative diagnosis of uterine leiomyosarcoma is difficult in clinical practice. Therefore, in order to distinguish uterine leiomyosarcoma from other uterine mesenchymal tumors, it is important to establish a simple diagnostic method using biomarkers. Currently, clinical studies are being conducted to verify the specificity and superiority of candidate cell factors specific to uterine leiomyosarcoma as differential biomarkers. We hope that a simple diagnostic method would be established based on the results of future clinical studies.

Disclosure of potential conflicts of interest

The authors declare no potential conflicts of interest.

Ethical approval and consent to participate

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo Japan). The authors attended a 2020 educational lecture on medical ethics supervised by the Japanese government. The completion numbers of the authors are AP0000151756 AP0000151757 AP0000151769 AP000351128. This research is not clinical study, therefore consent to participate is not required.

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Data availability and Consent to publish

This manuscript is an editorial and does not contain research data. Therefore, there is no research data or information to be published or opened.

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Table 1 Classification of human uterine mesenchymal tumours

Tumor type	*Atypia*	Mitotic activity	*Necrosis*	A. Protein expression*													*Cliical comments*
				Cyt	Des	CAV	SMA	Vim	ER/PR	End	EGF	CyB	CyE	LMP2	Cal	Ki67	
Endometrial stromal tumors.																	
Endometrial strimal nodule	minimal	infrequent	-/inconspicuous	+	-	++	+	+	+++	+	*	+	-	++	++	-	Absence of myometrial infiltration
Endometrial strimal 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# Leiomyoma with bizarre nuclei	-	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 (ref.16), SMA; smooth muscle actin, Vim.; vimentin, ER/PR; estrogen receptor/progesterone receptor, End.; Endoglin; CD105/TGFb receptor (stem cell marker), EGF, EGFR; epidermal growth factor receptor, CyB; cyclin B1, CyE (ref.17); cyclin E, LMP2; low molecular mass polypeptide 2, Cal.; calponin h1, CD56; neural cell adhesion molecule (N-CAM), WT-1; wilms tumor 1, NOS; not otherwise specified, MF; magnification factor, HPF; high power field, Foc.; focal, STUMP; smooth muscle tumours 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, PSMB9, cyclin E, calponin h1, Ki-67 (ref.18). STUMP#. Cyclin E, PSMB9, calponin h1 are potential biomarker for human uterine mesenchymal tumours. LANT#, leiomyomatoid angiomatous neuroendocrin tumour (LANT) is described as a dimorphic neurosecretory tumour with a leiomyomatous vascular component (ref.19). NOTE1, Low-grade neuroendocrine tumour possibly related to null cell adenoma.

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