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[Case Report] Characteristic of Endometrial stromal sarcoma by algorithm of potential biomarkers for uterine mesenchymal tumor

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Abstract

Background/Aim: The benign tumor uterine leiomyoma derives from the smooth muscle tissue that constitutes the uterus. In contrast, the malignant tumor uterine sarcoma can derive from either smooth muscle or stroma, and differs from both uterine leiomyoma and endometrial cancer. Uterine sarcoma is broadly classified into three types: uterine leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma. However, although uterine leiomyosarcoma and endometrial stromal sarcoma are both classified as uterine sarcoma, they differ significantly in their sites of occurrence, symptoms, and treatment methods, among other factors. Uterine leiomyosarcoma arises from the muscle tissue constituting the wall of the uterus and accounts for approximately 70% of all uterine sarcoma cases. Endometrial stromal sarcoma arises from the stromal tissue beneath the endometrium and accounts for approximately 25% of all uterine sarcoma cases. Endometrial stromal sarcoma is classified as either low-grade or high-grade.

Materials and Methods: A patient's symptoms suggested uterine sarcoma, transvaginal ultrasonography and endometrial biopsy or partial dilation and curettage were performed. However, in clinical practice, the sensitivity of those tests for detecting malignancy is limited, and endometrial stromal sarcoma and uterine leiomyosarcoma were diagnosed incidentally on histopathology examination of hysterectomy specimens or enucleated tumors.

Result: Histopathology examination of a surgical specimen from a patient who was thought to have submucosal uterine leiomyoma after contrast-enhanced magnetic resonance imaging (MRI) found that the patient actually had endometrial stromal sarcoma.

Conclusion: Despite the remarkable progress made in medical imaging technology, the accuracy of contrast-enhanced MRI for detecting uterine mesenchymal tumors is limited. Histopathologic diagnosis based on surgical specimens should therefore be performed when medical grounds for diagnosing a benign tumor on contrast-enhanced MRI are lacking.

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Key words: Endometrial stromal sarcoma, Mesenchymal tumor, Leiomyosarcoma, Leiomyoma.

1. Introduction

The benign tumor uterine leiomyoma (UL) derives from the smooth muscle tissue that constitutes the uterus[1][2]. UL is most frequently seen in relatively young to postmenopausal women [1] and is often found incidentally during medical examinations in the absence of any particular symptoms. Depending on the site of origin, UL is classified as either a subserosal, intramural, or submucosal leiomyoma [1][3] and can exhibit hemorrhage, necrosis, calcification, and edema. Symptoms of UL include hypermenorrhea, menstrual pain, palpable abdominal mass, and anemia, among others. When a UL enlarges, it puts pressure on the surrounding organs, and symptoms such as frequent urination, dysuria, constipation, and lumbago are observed. Infertility and miscarriage can also result [4]. A patient's chief complaint will depend on the site of onset and the size and number of ULs. For example, compared with other leiomyomas, a submucosal leiomyoma tends be associated with excessive menorrhagia, prolonged menstruation, and menstrual pain even when the tumor is small, and the patient tends to be prone to anemia [5]. Surgery is the typical treatment for patients with symptoms; however, when asymptomatic, patients with UL are often simply watchfully followed.

UL is diagnosed by pelvic exam, ultrasonography, and if necessary, contrast-enhanced magnetic resonance imaging (MRI) [6]. If the findings obtained from ultrasonography or contrast-enhanced MRI are not typical for UL or if the patient is experiencing rapid or postmenopausal mass enlargement, the rare malignant tumor uterine sarcoma, which also derives

from uterine smooth muscle, should be added to the differential [7]. Uterine sarcoma is broadly classified into three types—uterine leiomyosarcoma, endometrial stromal sarcoma (ESS), and carcinosarcoma [8]—which all have different treatment approaches.

The uterine tissues from which ESS and uterine leiomyosarcoma develop are different[9]. Uterine leiomyosarcoma arises in the smooth muscle tissue, and ESS arises in the endometrial or stromal tissue. Moreover, these two tumor types are associated with different ages of onset. Uterine leiomyosarcoma is typically found in women 50-55 years of age. ESS is typically found in premenopausal women in their 40s and can classified as either low-grade endometrial stromal sarcoma (LG-ESS) or high-grade endometrial stromal sarcoma (HG-ESS). Many cases of LG-ESS respond well to hormone therapy and have a favorable survival prognosis [10]. For the far rarer HG-ESS tumors, hormone therapy is not recommended [10]; patients therefore often receive chemotherapy, but the efficacy of that approach has not been confirmed. In uterine leiomyosarcoma, prognosis is typically poor, with the risk of recurrence and metastasis being significantly high. The first-line treatment for uterine leiomyosarcoma is surgical excision. Unfortunately, no low-toxicity and high-efficacy antitumor agents and radiation therapy for uterine leiomyosarcoma have so far been found [11].

A 45-year-old woman suspected of having a submucosal leiomyoma of the uterus based on the results of imaging performed at a nearby hospital was referred to our clinical department. Contrast-enhanced MRI had revealed a 32 mm mass projecting from the posterior wall of the uterus into the uterine cavity. MRI T2-weighted imaging (T2WI) revealed a low signal within the mass, and so a submucosal UL was suspected. However, contrast-enhanced diffusion-weighted MRI performed by our medical staff revealed a high signal in the area of the mass, suggesting the possibility of malignancy. Subsequent histopathology of the surgically resected specimen resulted in a diagnosis of ESS. Although medical imaging technology has progressed remarkably, the accuracy of contrast-enhanced MRI for detecting uterine mesenchymal tumors is limited. Histopathologic diagnosis based on surgical specimens should therefore be performed when medical grounds for diagnosing a benign tumor in contrast-enhanced MRI are lacking.

2. Materials and Methods

2.1. Immunohistochemistry

Staining for caveolin-1, cyclin B, cyclin E1, LMP2/β1i, Ki-67, desmin, and myogenin was performed on serial tumor sections obtained from patients with uterine mesenchymal tumors (Supplementary material 1). The monoclonal antibody for cyclin E1 (CCNE1/2460) was purchased from Abcam (Cambridge Biomedical Campus, Cambridge, UK), and the monoclonal antibody for Ki-67 (clone MIB-1) was purchased from Dako Denmark A/S (DK-2600 Glostrup, Denmark). The monoclonal antibodies for desmin (clone RM234) and for myogenin (clone MGN185) were purchased from GeneTex, Inc. (Irvine, CA, USA). The monoclonal antibodies for caveolin-1, cyclin B1, and LMP2/β1i were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA, USA). All immunohistochemistry used the avidin–biotin complex method as previously described [12][13]. Briefly, one representative 5 mm tissue section was cut from the paraffin-embedded radical hysterectomy specimen obtained from each patient with a uterine mesenchymal tumor. The sections were incubated first

with a biotinylated secondary antibody (Dako, DK-2600 Glostrup, Denmark) and then with streptavidin complex (Dako). The completed reaction was developed using 3,39′-diaminobenzidine tetrahydrochloride hydrate (DAB), and the slide was counterstained with hematoxylin. Normal myometrium portions in the specimens were used as positive controls. Tissue sections incubated with normal rabbit immunoglobulin G instead of the primary antibody were used as negative controls. Brown DAB staining revealed the expression of cyclin E and Ki-67. Normal rabbit or mouse antiserum was the negative control for the primary antibody. The DAB-stained tissue was scanned in its entirety using a digital microscope (BZ-X800: Keyence Corporation, Osaka, Japan). Black dots indicate the expression of cyclin E and Ki-67. Normal rabbit or mouse antiserum was used as the negative control for the primary antibody.

2.2. Ethics approval and consent to participate

Shinshu University approved the experiments (approval no. M192). All experiments using human tissue were conducted at the National Hospital Organization, Kyoto Medical Center (approval no. NHO H31-02), in accordance with institutional guidelines issued August 17, 2019, by the Central Ethics Review Board of the National Hospital Organization Headquarters (Tokyo, Japan) and Shinshu University (Nagano, Japan). The authors attended educational lectures on medical ethics in 2020 and 2021, supervised by the Japanese government (completion numbers AP0000151756, AP0000151757, AP0000151769, and AP000351128). Consent to participate in this clinical research was required. After being briefed on the clinical study and agreeing with the clinical research objectives, participants signed consent forms. The authors attended a seminar on the ethics of experimental research using small animals on July 2, 2020, and July 20, 2021. The code number of the ethical approval for experiments with small animals was KMC R02-0702.

3. Case description

On March 14, 2021, a 45-year-old woman with suspected submucosal UL was referred to our general clinical facility. At that time, contrast-enhanced MRI had revealed a 1.9 cm submucosal mass suspected to be the UL. Blood tests revealed a serum hemoglobin concentration of 11.6 g/dL and carbohydrate antigen 19-9 **note1** and 72-4 values of 8 and 1.5 respectively. On the patient's return to our general clinical facility on October 10, 2021, for further testing, contrast-enhanced MRI revealed a 3.9 cm mass under the uterine mucosa, suggesting that the tumor had enlarged over the elapsed 6 months. Based on contrast-enhanced T1 weighted imaging, the possibility of malignancy could not be ruled out. Thus, based on the contrast-enhanced MRI results and blood tests, we believed that the mass might be a uterine mesenchymal tumor rather than a UL. In January 2022, the patient underwent a laparoscopic total hysterectomy and bilateral salpingo-oophorectomy.

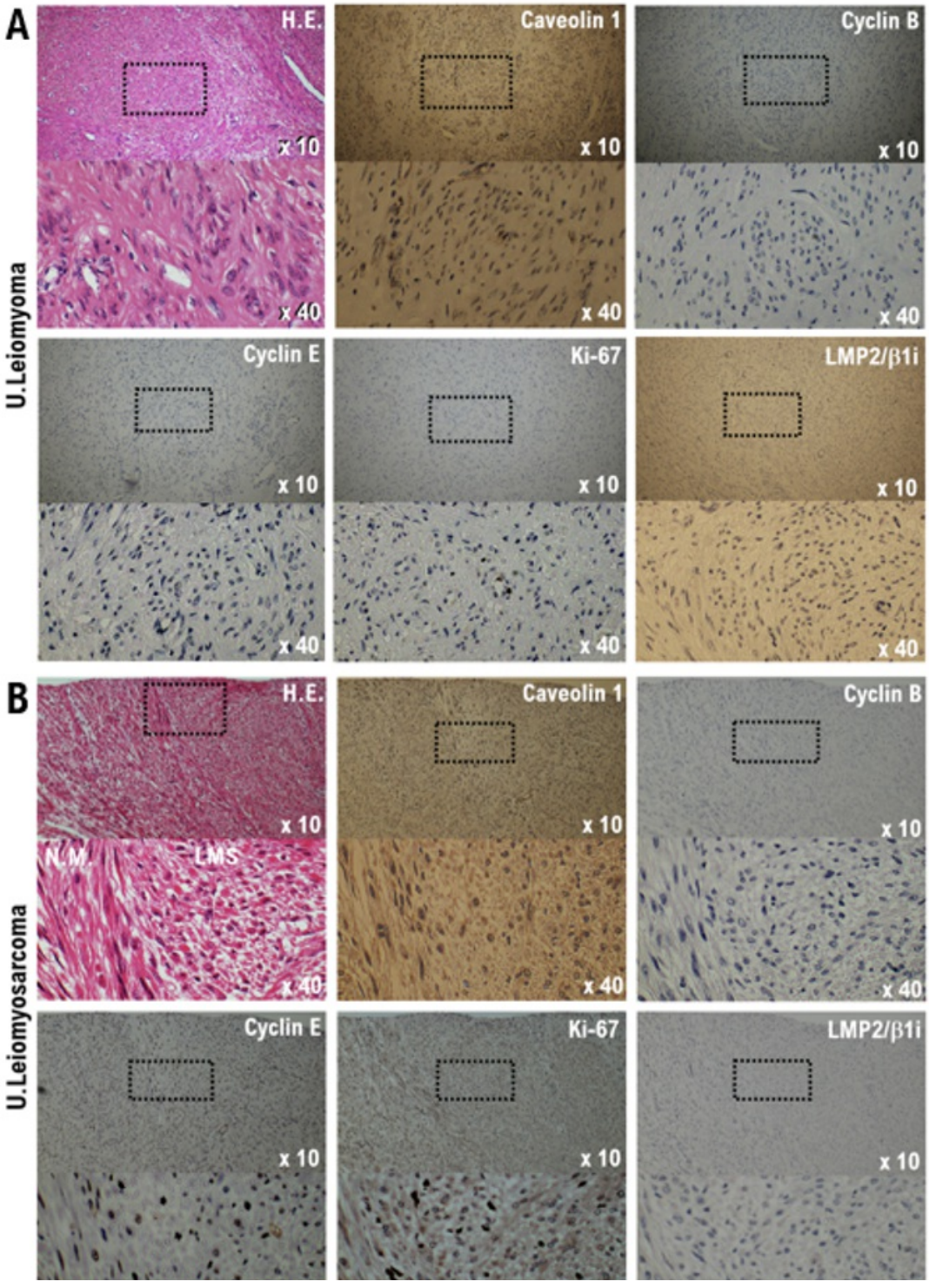
3.1. Details of the contrast-enhanced MRI

The contrast-enhanced MRI had revealed a mass of approximately 32 mm protruding from the posterior wall of the uterus into the lumen. On contrast-enhanced T2WI (sagittal high-pass; SAG H=F) the mass was observed to be of moderate- to

low-intensity, suggesting a submucosal UL (Supplementary Figure 1.A). In contrast, on diffusion-weighted imaging (echo-planar two-dimensional sequence; Ep2d), the mass was observed to have a high signal (Supplementary Figure 1.B).

The T2WI also revealed bilateral ovarian shading. On T2WI (transverse relaxation time), bilateral ovarian cystic lesions with a fat-suppressed high signal (30 mm in the right ovary, and 35 mm in the left ovary) were observed (Supplementary Figure 1.C). These masses were presumed to be endometriotic cysts.

No significant lymphadenopathy was detected; however, a small ascites accumulation was noted.



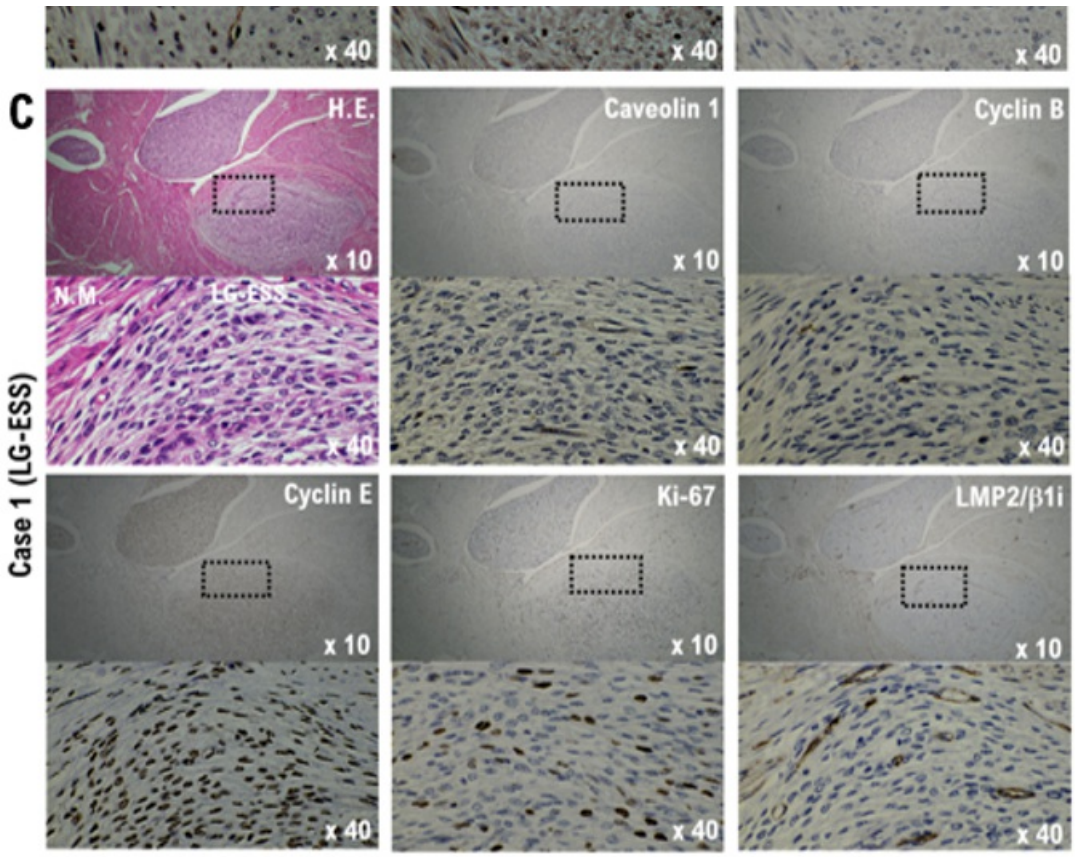


Figure 1. Differential expression of potential biomarkers cyclin B, cyclin E, caveolin-1, Ki-67, and LMP2/β1i in samples of normal myometrium, uterine (U.) leiomyoma, U. leiomyosarcoma, and our patient's uterine tumor (Case 1). Immunohistochemistry for all specimen sections was performed using appropriate monoclonal antibodies and standard procedures. **A.** The low-power (10×) view of leiomyoma shows a well-circumscribed tumor nodule in the myometrium; broad spindle cell fascicles are evident. In the high-power (40×) view, the spindle cells have bland cytologic features, with elongated nuclei and fine nuclear chromatin. **B.** The low-power (10×) view of uterine epithelioid leiomyosarcoma shows a mass having an irregular interface with the myometrium; the constituent cells are round to polygonal, with granular eosinophilic cytoplasm. Significant nuclear atypia and mitoses are easily found. In the high-power view (40×), the tumor cells are round to ovoid and have eosinophilic granular cytoplasm and irregularly shaped nuclei. **C.** In the low-power (10×) view, normal uterine smooth muscle differentiation is seen as a starburst morphology, with collagen bands radiating toward the periphery of the low-grade endometrial stromal sarcoma nodule, with its embedding round cells in a background of endometrial stromal neoplasia. The tumor is invading lymphatic vessels. In the high-power (40×) view, tumor cells can be observed to have a morphology quite different from that of normal uterine smooth muscle cells. Low-grade endometrial stromal sarcoma differentiation is evident. H.E., hematoxylin and eosin.

3.2. Details of the histopathologic examination

Supplementary Figure 2.A, B presents the macroscopic findings of the excised specimen. A solid white nodule measuring 4.0 cm can be observed within the wall of the uterine corpus.

On histopathology, the uterine mass was observed to be composed of short, spindle-shaped cells with a high nuclear/cytoplasmic ratio, surrounded everywhere by small spiral artery-like blood vessels. The cells constituting the mass demonstrated a mild degree of nuclear atypia. The number of mitotic figures was approximately one per high-power field,

and no cell necrosis was observed. At the margin of the mass, tumor cells demonstrated tongue-like extensions into the surrounding normal smooth muscle tissue and blood vessels. Based on those histopathologic findings, the tumor was diagnosed as an LG-ESS.

A molecular pathology analysis of multiple surgical specimens that used index markers for various soft tissue tumors, including candidate biomarkers for uterine leiomyosarcoma, clearly confirmed that caveolin, a candidate biomarker for uterine mesenchymal tumors, was expressed in both UL and uterine leiomyosarcoma (Figure 1A, B, Figure 2) [14]. Mild expression of caveolin was observed in our patient's tumor (Figure 1C, Figure 2). Mild expression of cyclin B, considered a potential biomarker for malignant tumors, and strong expression of cyclin E and Ki-67, candidate biomarkers for malignant mesenchymal tumors, were confirmed in multiple specimens of uterine leiomyosarcoma and uterine tumors (Figure 1B, C, Figure 2). In published research reports, spontaneous onset of uterine leiomyosarcoma has been observed in mice deficient in LMP2/β1i, a subunit of the immunoproteasome [15][16]. In human uterine leiomyosarcoma, LMP2/β1i expression is significantly reduced (Figure 1B, Figure 2) [17]; however, as in normal uterine smooth muscle and UL, strong expression of LMP2/β1i was observed in our patient's uterine tumor (Figure 1A, C, Figure 2).. The foregoing findings suggested that our patient's tumor was malignant, but that the possibility of a uterine leiomyosarcoma was low.

Desmin, myoglobin, myogenin, MyoD1, α-SMA, and HHF-35, among others, are used as markers for myogenic tissue[18]. CD10 is expressed in cells that constitute the endometrial stromal tissue, which are difficult to identify as epithelial cells [19]. Desmin and α-SMA are expressed in the myogenic cells of uterine smooth muscle. Immunohistochemical staining of our patient's surgical specimen revealed strong expression of CD10 in the patient's tumor. However, CD10 expression was not detected in normal uterine smooth muscle tissue (Figure 3, Supplementary Figure 2.C). Desmin was not observed to be strongly expressed in the patient's uterine tumor (Figure 3, Supplementary Figure 2.C). However, strong expression of desmin was observed in normal uterine smooth muscle tissue and in uterine leiomyosarcoma tissue (Figure 3, Supplementary Figure 2.C]. Similarly, α-SMA was not observed to be strongly expressed in the patient's uterine tumor (Figure 3, Supplementary Figure 2.C)., but strong expression of α-SMA was observed in normal uterine smooth muscle tissue and uterine leiomyosarcoma tissue (Figure 3, Supplementary Figure 2.C). Based on those observations, the patient's tumor was considered to originate from endometrial stromal cells rather than from uterine smooth muscle cells.

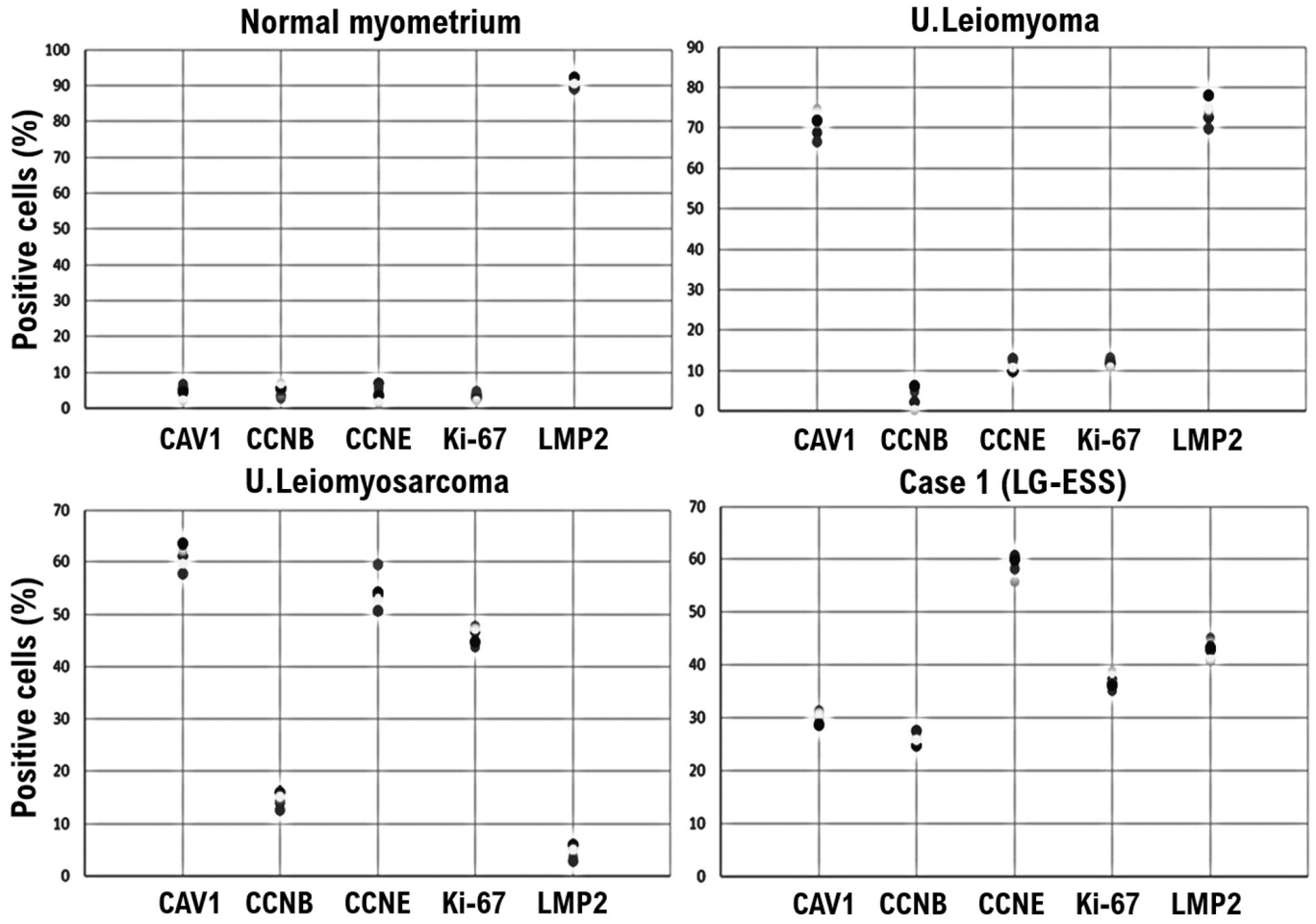


Figure 2. LMP2/β1i-positive endometrial stromal tumor cells in our patient's uterine tumor (Case 1), contrasted with normal myometrium and uterine (U.) leiomyoma. Immunohistochemistry for all five randomly selected specimen sections was performed using appropriate monoclonal antibodies and standard procedures. In a 40× view, the positivity rates of the five factors were calculated for the four specimens and are presented in a scatterplot. CAV1, caveolin-1; CCNB, cyclin B; CCNE, cyclin E; LMP2, LMP2/β1i; LG-ESS, low-grade endometrial stromal sarcoma.

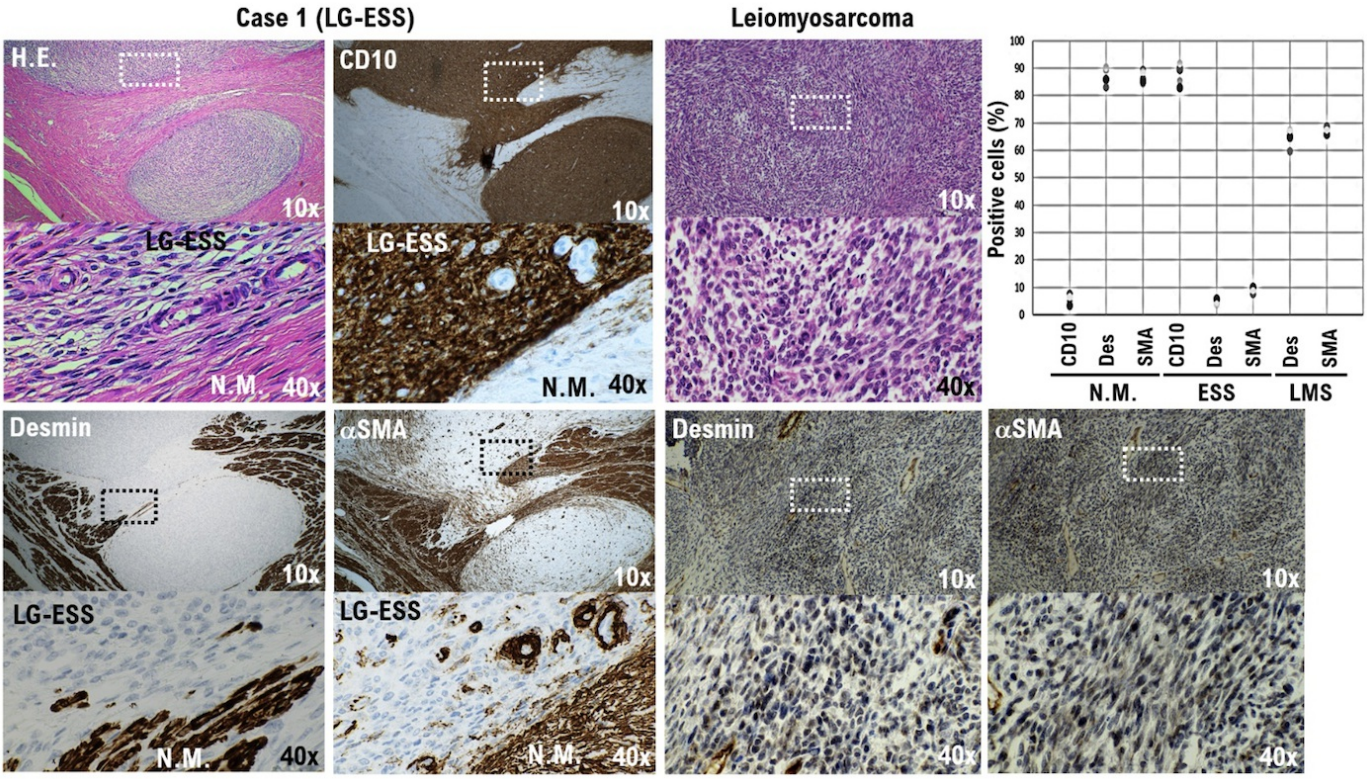


Figure 3. CD10-positive low-grade endometrial stromal sarcoma (LG-ESS) cells in our patient's tumor (Case 1). The differential expression of the potential biomarkers desmin and α-SMA in the sarcoma cells, normal myometrium, and uterine leiomyosarcoma is presented. Immunohistochemistry for all specimen sections was performed using appropriate monoclonal antibodies and standard procedures (right lower panel). The low-power (10×) view at the farthest right in the first row shows the irregular interface of a uterine epithelioid leiomyosarcoma with normal myometrium. The tumor is observed to consist of round to polygonal cells having granular eosinophilic cytoplasm, with significant nuclear atypia and mitoses being easily found. In the accompanying high-power (40×) view, the tumor cells are round to ovoid, with eosinophilic granular cytoplasm and irregularly shaped nuclei. The low-power views on the left in the first row show the low-grade endometrial stromal sarcoma cells of our patient's tumor. The cells are an admixture of round, polygonal, bizarre, and spindle types, with marked atypia and the occasional presence of giant cells. A tongue-like pattern of infiltration consisting of irregular islands of purple cells lacking an associated stromal response is evident. In the accompanying high-power views, the tumor cells can be seen to have a morphology quite different from that of normal uterine smooth muscle cells. In a 40× view, the positivity rates of desmin and α-SMA were calculated for the three specimens and are presented in a scatterplot.

4. Discussion and conclusions

Most uterine sarcomas (40%–50%) are diagnosed as leiomyosarcoma, followed by LG-ESS, HG-ESS, undifferentiated uterine sarcoma, and adenosarcoma of the uterus [20]. Using contrast-enhanced MRI or other clinical examinations to determine the degree of malignancy or diagnose a mass found in uterine smooth muscle tissue is not easy [21]. Contrast-enhanced MRI in our patient revealed a 32 mm mass projecting from the posterior wall of the uterus into the uterine cavity. Based on the low signal observed within the mass on sagittal high-pass T2WI, a submucosal UL was suspected (Supplementary Figure 2.A). However, diffusion-weighted imaging revealed a high signal within the mass, suggesting malignancy (Supplementary Figure 2.B). After a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, histopathologic examination of the resected specimen demonstrated strong expression of CD10, a molecular marker for endometrial stromal cells. Moreover, desmin and α-SMA, known molecular markers of uterine smooth muscle cells, were

not observed to be strongly expressed. Based on the MRI results and the histopathology, the tumor was diagnosed as deriving from endometrial stromal cells.

If symptoms suggesting uterine leiomyosarcoma or ESS are observed, transvaginal ultrasonography and partial cervical dilatation and curettage or histopathology of an endometrial biopsy specimen is usually performed. However, limitations in the detection sensitivity of those clinical examinations make an accurate diagnosis difficult [22]. In the clinic, ESS or uterine leiomyosarcoma might therefore more often be incidentally detected by histopathologic examination of specimens obtained from hysterectomy or enucleation.

ESS has a cytologic appearance similar to that of normal endometrial stromal cells. As part of our differential, histopathology revealed that the tumor cells had a high nuclear/cytoplasmic ratio, irregular nuclei with notches and constrictions, increased amounts of chromatin, and many mitotic figures [23][24]. The characteristic histopathology of ESS includes naked nucleate and stoma cells with small nucleoli [23][24]. However, it has been established that the lower the degree of malignancy, the weaker the cell atypia, and the fewer the number of cells with mitotic figures. Making a diagnosis based solely on findings from individual cells is therefore difficult. In general practice, when cell necrosis is not observed during the cytologic examination of the uterine body, and poorly atypical cells and clumps are observed, either atypical endometrial hyperplasia or benign endometrial hyperplasia is suspected. However, in HG-ESS, routine somatic cytology might reveal tumor cells, and thus cytology should be carefully performed. Although ESS is currently a rare tumor, the suspicion is that cases might increase in future as the Japanese population ages. Careful assessment of non-epithelial cells is therefore necessary in endometrial cytology. Based on the contrast-enhanced MRI in our patient, the mass observed under the uterine mucosa was thought to possibly be a submucosal UL. However, histopathology of the surgical specimen revealed an ESS. The characteristic shadows of ESS are difficult to observe on contrast-enhanced MRI.

MRI, especially contrast-enhanced MRI, is indispensable for distinguishing between benign and malignant tumors in the uterine corpus and for determining the tumor's tissue type. Compared with ultrasonography, MRI can more clearly visualize the characteristics of malignancy. T2WI, including a dynamic contrast-enhanced approach, is suitable for detecting small tumors. On T2WI, endometrial tumors are often less intense than normal endometrium and slightly more intense than myometrium. However, unlike UL, ESS does not appear as a localized mass with clear margins, and the gadolinium enhancement effect is weaker in the tumor than in normal uterine endometrium and normal uterine smooth muscle. The usefulness of T2WI in all gynecologic tumors is therefore uncertain. When contrast-enhanced MRI fails to provide medical evidence of a benign tumor, appropriate surgical treatment must be the next step. A definitive diagnosis can only be made by histopathology examination of the surgical specimen.

Table 1. Differential expressions of SMA, Caveolin1, Cyclin B, Cyclin E, LMP2, NT5DC2, CD133, and Ki-67 in human uterine mesenchymal tumors and uterine LANT-like tumor.

Mesenchymal tumor types	Age years	n	Protein expression*							
			SMA	CAV1	CCNB	CCNE	LMP2	NT5DC2	CD133	Ki-67
Normal	30s-80s	76	+++	-	-	-	+++	-	-	-
Leiomyoma (LMA)	30s-80s	40	+++	++	-/+	-/(+)	+++	-/+	-	+/-
(Ordinally leiomyoma)		(30)	+++	++	-/+	-	+++	-/+		+/-
(Cellular leiomyoma)		(10)	++	++	-/+	-/(+)	++	-/+		+/-
STUMP	40s-60s	12	++	++	+	-/+	-/+	-/+	NA	+/+++
Bizarre Leiomyoma	40s-50s	4	++	++	-/+	+	Focal+	+	NA	+
Intravenous LMA	50s	3	++	++	+	+	-	NA	++	+
Benign metastasizing	50s	1	++	++	+	++	-	NA	NA	++
LG-ESS#	40s 50s	2	+++	++	++	+++	+++	NA	NA	++
Leiomyosarcoma	30s-80s	54	-/+	+	++	+++	-/+	++	++	++/+++
Rhabdomyosarcoma	10s,50s	2	NA	++	-/+	+++	+++	NA	NA	NA
U.LANT#-like tumour	40s	1	++	+	NA	++	-	NA	NA	-

Staining score of expression of SMA, CAV1 (Caveorin 1), CCNB (Cyclin B), CCNE (Cyclin E), LMP2 (low molecular protein 2), NT5DC2 (5'-Nucleotidase Domain Containing 2) and Ki-67 from results of IHC experiments. Protein expression; estimated-protein expressions by immunoblot analysis, immunohistochemistry (IHC) and/or RT-PCR (quantitative-PCR),-/+; partially positive (5% to 10% of cells stained), Focal+; Focal-positive (focal or sporadic staining with less than 5% of cells stained),++; staining with 5% or more, less than 90% of cells stained, +++; diffuse-positive (homogenecus distribution with more than 90% of cells stained), -; negative (no stained cells). U.LANT-like tumour; uterine leiomyomatoid angiomatous neuroendocrine tumour-like tumour, LMP2, cyclin E, caveolin1, NT5DC2, CD133, Ki-67. STUMP (Smooth muscle tumor of uncertain malignant potential). Cyclin E, LMP2, Caveolin1 are potential biomarker for human uterine mesenchymal tumors. LG-ESS#, low-grade endometrial stromal sarcoma, LANT#, leiomyomatoid angiomatous neuroendocrin tumour (LANT) is described as a dimorphic neurosecretory tumor with a leiomyomatous vascular component. NA; no answer.

Table 1. Differential expression of various potential biomarkers in specimens of several human uterine mesenchymal tumor types.

Note 1

Carbohydrate antigen 19-9 (CA19-9) is associated with cancers of the colon, stomach, and bile duct. Elevated serum CA19-9 can indicate advanced cancer of the pancreas or an ovarian sclerosing stromal tumor, but is also associated with noncancerous conditions including gallstones, pancreatitis, cirrhosis of the liver, and cholecystitis.[25][26]

Supplementary Materials

Available here.

Acknowledgements

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Competing Interest statement

The authors state No competing interest.

Clinical Research

A multi-center retrospective observational clinical study of subjects who underwent cancer genomic medicine at a cancer medical facility in Kyoto, Japan.

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 18, 2020, and Kyoto University School of Medicine (Kyoto, Japan) on August 24, 2022, with approval codes NHO R4-04 and M237.

All participants agreed to take part in the present study. We have obtained Informed Consent Statements from people participating in clinical studies.

Ethical Compliance with Human/Animal Study

This manuscript contains personal and/or medical information about an identifiable individual. This manuscript also contains a case report/case history about identifiable individual. All authors confirmed my manuscript is sufficiently anonymized in line with our anonymization policy. Authors obtained directly Consent from patient. This study involves human participants and was approved by an Ethics Committee(s) and Institutional Board(s). This study does not involve the research studies with animals.

The authors attended research ethics education through the Education for Research Ethics and Integrity (APRIN e-learning program (eAPRIN)). The completion numbers for the authors are AP0000151756, AP0000151757, AP0000151769, and AP000351128. Consent to participate was required as this research was considered clinical research.

Institutional Review Board Approval

Institutional Review Board Statement and Consent to Participate. These experiments with human tumor tissues derived from patients with high grade-serous ovarian cancer were conducted at Shinshu University and National Hospital Organization Kyoto Medical Center in accordance with institutional guidelines (i.e., IRB approval no. M192, H31-cancer-2). Subjects signed an informed consent form when they were briefed on the clinical study and agreed with content of the research.

Ethic Committee Name: Institutional Review Board (IRB) of Shinshu University Approval Code: M192 Approval Date: April 05, 2014, and June 16, 2016.

Ethic Committee Name: Institutional Review Board (IRB) of National Hospital Organization Headquarter Approval Code: H31-cancer-2 Approval Date: November 09, 2019, and June 17, 2022.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Conceptualization, T.H., K.S., K.A. and I.K.; Writing-Original Draft, T.H. and I.K.; Writing-Review & Editing, I.K.; Visualization, T.H., N.Y. and I.K.; Supervision, T.H., N.Y. and I.K.; Funding Acquisition, T.H. and I.K.

Abbreviations

α-SMA; alpha-smooth muscle actin, CA125; ovarian carcinoma antigen-125, CA19-9; carbohydrate antigen 19-9, CD; clusters of differentiation, CT; computed tomography, H.E., hematoxylin and eosin, Ep2d; echo-planar two-dimensional sequence, IHC; immunohistochemistry, LMP2/β1i; large multifunctional peptidase 2/β1i, MRI; Magnetic Resonance Imaging, LMS; leiomyosarcoma, SAG H-F; sagittal high-pass, WHO; World Health Organization

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