Mixed Endometrial Stromal and Smooth Muscle Tumor of the Uterus with Unusual Morphologic Features in a 35-Year-Old Nulliparous Woman: A Case Report

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Patient: Female, 35-year-old

Final Diagnosis: Mixed endometrial stromal and smooth muscle tumor

Symptoms: Menorrhagia

Medication: —

Clinical Procedure: Mass excision

Specialty: Obstetrics and Gynecology

Objective: Rare disease

Background: Mixed endometrial stromal and smooth muscle tumors (MESSMT) of the uterus are rare disease entities. The histogenesis is unclear, but its clinical manifestations are similar to those of other mesenchymal tumors. This unique uterine tumor was originally reported as having ultrastructural characteristics of both endometrial stromal and smooth muscle cells. Subsequently, MESSMT was defined as having at least 30% of each component present. Here we present an MESSMT with unusual features in a nulliparous woman and describe its morphological and immunohistochemical characteristics.

Case Report: A 35-year-old nulliparous woman presented with menorrhagia for 2 months. Transvaginal ultrasonography and magnetic resonance imaging revealed an enlarged uterus with a 6.0×5.5×4.5 cm mass and cystic degeneration. The patient underwent abdominal mass excision. Microscopically, the tumor consisted of 3 distinct components. The outermost area consisted of smooth muscle cells. Well-differentiated endometrial stromal cells that were centrally located showed irregular borders and were merged with smooth muscle cells. In addition, the endometrial stromal component showed focal sex-cord-like differentiation. Morphological and immunohistochemical evaluations were performed, and a MESSMT with focal sex-cord-like differentiation was diagnosed. The patient’s postoperative course was uneventful for 29 months.

Conclusions: The diagnosis of MESSMT is challenging due to its many overlapping features with other mesenchymal uterine tumors. Although this rare tumor was histologically and clinically consistent with low-grade endometrial stromal sarcoma, it can cause recurrence and metastasis. Therefore, regular follow-up with radiologic examination is essential for the timely detection of local recurrence and distant metastasis.

Keywords: Endometrial Stromal Tumors • Leiomyoma • Uterine Neoplasms

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**Background**

Mixed endometrial stromal and smooth muscle tumor (MESSMT) of the uterus has received little attention owing to its rarity and unknown histogenesis. Both endometrial stromal cells and smooth muscle cells have a common Müllerian-mesodermal origin and are closely related to each other [1]. Regarding the histogenesis of an MESSMT, some investigators have suggested the existence of pluripotent cells capable of differentiating into stromal cells and smooth muscle cells, among others [2]. Other investigators regarded the tumor as a variant of endometrial stromal tumor (EST), showing prominent smooth muscle differentiation, rather than a true composite tumor [3,4]. Practically, ESTs may show morphologic variants or unusual features, including sex cord-like differentiation [5], smooth muscle differentiation [2, 4], fibrous or myxoid changes [6,7], granular eosinophilic [8] or rhabdoid features [9,10], and skeletal muscle differentiation [11,12]. Therefore, Oliva et al suggested the MESSMT-defining criterion in which at least 30% of each component was present [2]. Its clinical presentations are not different from those of pure endometrial stromal or smooth muscle tumors. Abnormal uterine bleeding is the most common symptom, followed by abdominal distension due to an enlarged uterus or mass.

Here, we present the case of an MESSMT with unusual features in a nulliparous woman and describe its morphological and immunohistochemical characteristics.

**Case Report**

A 35-year-old woman (gravida 0, para 0) presented with menorrhagia for 2 months. Transvaginal ultrasonography revealed an enlarged uterus with a 6.0×5.5×4.5 cm mass and cystic degeneration in the posterior aspect of the uterus. Magnetic resonance imaging detected a well-defined intramural mass showing heterogeneous signal intensity on T2-weighted images and heterogeneous enhancement (Figure 1). Thus, a degenerative leiomyoma, rather than a uterine sarcoma, was suspected. The patient had no significant medical or gynecological history, with a regular menstrual cycle. She was not taking oral contraceptives at the time of admission and she was a non-smoker and drank socially. The serum levels of the tumor markers CA 125, CA 19-9, and squamous cell carcinoma antigen were within the normal ranges. The other laboratory findings, including hemoglobin level, were within normal ranges. The patient underwent abdominal mass excision. The resected specimen was relatively well dissected, and there were no other tears on the surface. The cut surface revealed a well-circumscribed soft mass measuring 6.5×6.0 cm. The mass was tan-to-yellowish in color and presented as an intracystic nodule in the center of the whole mass (Figure 2). Microscopically, the tumor consisted of 3 morphologically different components (Figure 3). First, the outermost area was composed of fascicular proliferation of monotonous spindle cells with eosinophilic cytoplasm and cigar-shaped nuclei, suggesting smooth muscle differentiation. These tumor cells had no apparent nuclear atypia or necrosis. A few mitoses were identified (3/10 high-power fields (HPFs)). The central area of the mass, which presented as an intracystic nodule on gross examination, consisted...
Figure 2. The patient underwent a myomectomy, and a (A) well-dissected specimen was submitted. (B) The cut surface of the specimen showed a tan-to-yellow soft mass, 6.5 cm in size, with cystic change.

Figure 3. (A) The resected mass showed 3 morphologically distinct components (white star: center of the mass; yellow star: middle area; black star: outermost area) (×1.25). (B) In the center of the mass, a tubular or cord-like arrangement of ovoid cells was noted. (C) The middle area consisted of well-differentiated endometrial stromal cells. (D) The outermost area was composed of spindle cells suggesting smooth muscle differentiation (×400). Circles indicate mitotic figures for each component.
of cells showing round-to-ovoid nuclei, inconspicuous nucleoli, and scant cytoplasm with indistinct cell borders within small tubules, and a cord-like arrangement. There was marked hyalinized stroma containing numerous small blood vessels. Morphologically, this component resembled an ovarian sex-cord tumor. There was no necrosis, but occasional mitotic figures were observed (7/10 HPFs). The middle areas between the 2 components described above consisted of well-differentiated endometrial stromal cells exhibiting only minimal nuclear atypia. In addition, no necrosis or mitosis was observed. The interface with the outermost area showing smooth muscle differentiation presented a distinct but focally irregular and infiltrative boundary (Figure 4). These findings were pathologically consistent with low-grade endometrial stromal sarcoma. Lymphovascular tumor invasion was not observed in any mass component. The results of immunohistochemical staining were clearly distinguished for each of the 3 components (Figure 5). Smooth muscle cells in the outermost area were positive for SMA.
(smooth muscle actin) and desmin but negative for CD10. The central area was positive for SMA, desmin, and CD10. Well-differentiated endometrial stromal cells were positive for CD10 only.

Finally, the uterine tumor was pathologically confirmed to be a MESSMT with focal sex-cord differentiation. The patient was discharged 3 days after the surgery. She did not receive any adjuvant therapy and was alive and well at 29 months after surgery with no symptoms or recurrence on transvaginal ultrasonography.

**Discussion**

Endometrial stromal neoplasms account for less than 10% of all uterine sarcomas. They are classified into 3 categories based on their invasion into the myometrium and lack of differentiation: endometrial stromal nodule (ESN), endometrial stromal sarcoma (ESS), and undifferentiated endometrial sarcoma (UES) [13]. ESN is a well-circumscribed tumor resembling proliferative-phase endometrial stroma with no lymphovascular invasion. In comparison, ESS is a malignant stromal tumor that shows permeative growth into the myometrium with or without lymphovascular invasion. UES exhibits severe nuclear pleomorphism and a lack of specific differentiation [14,15]. Leiomyomas, including variants, are the most common uterine tumors and are usually found in women in their fifth decade of life [16]. Although many subtypes are well known, including cellular, mitotically active, epithelioid, myxoid, and leiomyoma with bizarre nuclei, approximately 90% of leiomyomas are of the conventional type [17]. However, the broad morphologic spectrum can be a diagnostic challenge for the differential diagnosis of leiomyosarcoma and ESTs.

Uterine mesenchymal tumors exhibiting both endometrial stromal and smooth muscle differentiation are relatively rare. Tang et al [18] originally proposed the term “stromomyoma” to describe a unique uterine tumor with ultrastructural characteristics of both endometrial stromal and smooth muscle cells. Tavassoli and Norris initially suggested restricting the diagnosis of combined muscle-stromal neoplasm to tumors in which each component accounts for at least one-third of the tumor [19]. Subsequently, Oliva et al followed these criteria in their study by defining the MESSMT as having at least 30% of each component present [2].

Concerning the histogenesis of a mixed endometrial stromal and smooth muscle tumor, some investigators have suggested the presence of multipotent cells capable of differentiating into stromal cells, smooth muscle cells, and other cell types [3,4]. Oliva et al demonstrated the presence of the JAFZ1/JJAZ1 fusion gene in both the conventional endometrial stromal and smooth muscle components of ESTs analyzed by fluorescence in situ hybridization (3/6 cases, 50%). This result supports the contention that both components bear the same cytogenetic abnormality and that they have the same origin, either from a common precursor cell with pluripotent differentiation or from endometrial stromal cells undergoing smooth muscle metaplasia [20].

The clinical presentation of MESSMT does not differ from that of uterine tumors of pure endometrial stromal or smooth muscle origin. On radiologic examination, the softer areas of the endometrial stroma may be misinterpreted as either leiomyoma with cystic degeneration or leiomyosarcoma [21]. Histologically, the smooth muscle component typically presents as irregular islands merge with the endometrial stromal component and in most cases includes prominent central and thin bundles of collagen radiation toward the periphery (the so-called “starburst” pattern) [2].

The main differential diagnosis is cellular leiomyoma because the densely cellular areas resemble the endometrial stromal component of MESSMT. Cellular leiomyomas, however, show several different histologic findings within large blood vessels throughout the tumor and no starburst pattern. In addition, ESS with smooth muscle differentiation may be included in the differential diagnosis. For the pathologic diagnosis of MESSMT, it is essential that the component of smooth muscle differentiation is more than 30% of the total tumor volume. Therefore, sufficient sampling of the tumor with careful gross examination should be performed to measure the volume of each component. A more important aspect is that smooth muscle differentiation within the tumor should not be interpreted as myometrial invasion at the edge.

Despite the morphologic differences described above, differentiation between these 2 distinct components of MESSMT – endometrial stromal cells and smooth muscle cells – is often challenging under a light microscope. Therefore, additional immunohistochemical staining is helpful for the diagnosis of MESSMT. In this tumor, smooth muscle cells are extensively positive for desmin, whereas endometrial stromal cells are negative for desmin and positive for CD10 [22].

The present case was notable for its uncommon morphologic features, consisting of 3 distinct components. In most cases of MESSMT, the smooth muscle component is present as irregular islands within the endometrial stromal component. However, the present case was grossly similar to conventional leiomyoma, and the endometrial stromal components, including sex-cord-like differentiation, were located in the center of the tumor. Furthermore, the characteristic “starburst” pattern of an MESSMT identified in previous studies [2,23,24] was not identified here. The boundary of the tumor was

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well-circumscribed, and there was no obvious cellular atypia or necrosis of the smooth muscle component. However, endometrial stromal components irregularly invaded the smooth muscle component, suggesting ESS. Moreover, mitotic figures were slightly more abundant in the endometrial stromal components with sex-cord-like differentiation (up to 7/10 HPFs). In addition to the morphological features, the differentiation of each component was well validated through immunohistochemical staining. The smooth muscle component was diffuse and strongly positive for desmin and SMA but negative for CD10. However, the endometrial stromal component was positive for CD10 and negative for desmin and SMA. The area of sex-cord-like differentiation was positive for desmin, SMA, and CD10. Finally, this case was diagnosed as an MESSMT with focal sex-cord differentiation.

In terms of prognosis, it has been proposed that MESSMT presentation depends on whether the underlying EST is an ESN (benign) or ESS (malignant). Chang et al studied 117 cases of endometrial stromal neoplasms, 11% of which showed smooth muscle differentiation. The presence of a smooth muscle component did not influence patient prognosis [3]. Oliva et al demonstrated that 1 tumor with infiltrating margins recurred in the pelvis at 48 months after surgery as a pure ESS [2]. Yilmaz et al published a case series describing the histologic features of metastatic endometrial sarcomas with variant histology. In many cases, the histologic features of the metastasis were not similar to those of the primary uterine tumor, indicating a great deal of morphological plasticity. Although there was 100% survival, the mean time to first recurrence was 6.8 years. Surprisingly, a case presenting the first metastasis 20 years after the initial diagnosis has been reported [4]. Given the rarity of MESSMT, data from large, prospective randomized trials are absent. There is no consensus about optimal treatment strategies for these patients. However, adjuvant therapy has been determined by experience gained through retrospective case series and case reports. Given that ESS, with the exception of UES, is an indolent, hormone-sensitive tumor [25], adjuvant hormone therapy can be a treatment option. However, since prognosis may be primarily dependent on stage of disease at the time of initial diagnosis, patients with stage I or II ESS treated surgically and with negative surgical margins can be followed without further treatment [26]. Especially for women younger than 35 years of age with small tumors, hysterectomy without bilateral salpingo-oophorectomy can be appropriate [27]. In this context, the young nulliparous woman in the present case report did not need adjuvant therapy, but careful follow-up is mandatory due to a tendency for late recurrence. Interestingly, Devaney and Tavassoli described an ESS with only a minor component of smooth muscle differentiation, which metastasized to the lungs as a solely smooth muscle neoplasm [28]. Accordingly, when MESSMT is initially diagnosed, the details of each component, including morphologic features and percentage of each component within the tumor, should be described, even if only a small amount appears. In addition, clinicians and pathologists should be aware of a prior diagnosis of uterine tumors to avoid misinterpreting metastatic lesions.

Conclusions

MESSMT is a rare mesenchymal tumor of the uterus. For accurate diagnosis and differentiation of uterine mesenchymal tumors, including MESSMT, pathologists should be aware of heterogeneous and unusual morphological features. Sufficient sampling and careful microscopic examination should be performed, and in some cases immunohistochemical analysis can be supportive. The course of MESSMT is not fully predictable due to its rarity, and a few cases with distant metastasis after a long time have been reported. Therefore, regular follow-up with radiologic examination is essential for the timely detection of local recurrence and distant metastasis.

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Declaration of Figures’ Authenticity

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