Case Report

**Endometrial Stromal Nodule Showing Intense Positivity for \(\alpha\)-SMA**

Yoshiki Ohta\(^1\), Miki Kushima\(^2\), Masaru Isozaki\(^3\) and Toshiyuki Mitsuya\(^1\)

**Abstract**: A case of endometrial stromal nodule showing immunoreactivity for \(\alpha\)-SMA in a majority of the tumor cells, with smooth muscle as a minor component, is reported. This tumor was mainly composed of diffuse proliferation of uniform cells resembling those of endometrial stroma, and included blood vessels resembling arteria spiralis and prominent perivascular whorl arrangement of the tumor cells. In addition, the smooth muscle component was detected by light microscopy. Immunohistochemically, many tumor cells showed \(\alpha\)-SMA positivity. In previous studies of endometrial stromal tumor, we showed a variety of combinations and proportions of positivity for several myogenic antibodies, and suggested that endometrial stromal tumor is heterogeneous based on immunoreactivity for several myogenic antibodies. In the present case, a distinction between endometrial stromal nodule and cellular leiomyoma was necessary. We concluded that light microscopic findings, including staining with hematoxylin and eosin, are the most important means for differential diagnosis of this tumor.

**Key words**: endometrial stromal nodule, \(\alpha\)-smooth muscle actin (\(\alpha\)-SMA), smooth muscle, immunohistochemistry

**Introduction**

Endometrial stromal nodule is an uncommon benign uterine tumor which shows a well-circumscribed proliferation of endometrial stromal cells\(^1\).\(^2\). Occasionally this tumor is accompanied by smooth muscle differentiation, epithelial-like arrangement or sex cord-like appearance\(^3\). We encountered a case of endometrial stromal nodule with prominent immunoreactivity for \(\alpha\)-smooth muscle actin (\(\alpha\)-SMA) in the tumor cells. However, it was difficult to differentiate from cellular leiomyoma. We describe this case and discuss the pitfalls in the use of immunoreactivity against myogenic antibodies in diagnosis of endometrial stromal tumor.

**Materials and Methods**

Formalin-fixed and paraffin-embedded specimens were stained with hematoxylin and eosin (HE), periodic acid Schiff reaction (PAS), Masson's trichrome, phosphotungstic acid hematoxylin (PTAH) and reticulin silver impregnation. Immunohistochemistry was

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performed on the formalin-fixed tissue using the avidin-biotin peroxidase complex technique. The following antibodies were used: anti-
\( \alpha \)-SMA (1: 400 dilution, Sigma, St. Louis, MO, USA), anti-desmin (1: 100 dilution, DAKO, Kyoto, Japan) and anti-vimentin (prediluted, Nichirei, Tokyo, Japan).

**Case Report**

*Clinical findings*

A 50-year-old Japanese female (gravida 4, para 2) presented with a lower abdominal mass. An abdominal and pelvic ultrasound showed an isoechoic nodule measuring 9 × 9 cm at the right side of the uterine body and low echoic small lesions measuring 23.4, 8.3 and 9.4 mm in the maximum diameter at the fundus (Fig. 1). Other laboratory examination showed no abnormal data. A total abdominal hysterectomy was performed under the diagnosis of uterine myoma.

*Pathological findings*

**Gross findings**

Macroscopically, a grayish tan colored and elastic soft tumor, measuring 1.7 × 1.6 cm, was recognized in the middle portion at left side of the corpus uteri. It was considered that this lesion was incidental, because localization of this tumor differed from that of lesions pointed out by ultrasound examination. The boundary between this tumor and the surrounding myometrium was clear, and no scroll pattern was visible on the cut surface. This tumor was located at the intramural region and there was no visible continuity between the endometrium and this tumor (Fig. 2). Leiomyomatous lesions were also recognized at other sites on ultrasound examination.

**Microscopic findings**

The tumor in the middle portion of the corpus was composed of uniform small cells with round or oval nuclei with fine granular chromatin and inconspicuous or absent nucleoli. The cytoplasms were scant and eosinophilic (Fig. 3). The proliferation pattern of the

![Fig. 1. Ultrasound examination showing large mass and small lesions at the right side of the uterine body and fundus, respectively.](image_url)
Fig. 2. Gross finding of the tumor. Small leiomyomatous lesion was also seen.

Fig. 3. The tumor cells are uniform, with oval-shaped nuclei and inconspicuous nucleoli. The cytoplasms of the tumor cells are scant and eosinophilic (HE × 40).

tumor cells was diffuse, and the tumor had an expansive margin which showed no myometrial or vessel infiltration at the periphery of the tumor. The mitotic rate was 0 per 10 high-power fields. Both capillaries and numerous blood vessels resembling arteria spiralis were seen and there was prominent perivascular whorl arrangement of the tumor cells (Fig. 4). These findings could be interpreted as an endometrial stromal nodule. There was no aggregation of foam cells or the sex cord-like component; these areas by the tumor cells showed a circular-like arrangement (Fig. 5). The cytoplasms of the tumor cells were negative for PAS and they did not stain with fuchsin for Masson's trichrome. Exceedingly fine and abundant reticular fibers were visible after reticulin silver impregnation. The individual tumor cells were surrounded by reticular fibers; many of these fibers were intertwined (Fig. 6). Collagen fibers were scarce.

Elongated tumor cells with cigar-shaped nuclei and a dull nucleus tip and eosinophilic cytoplasms were observed adjacent to hyaline substance. The proliferation pattern of these tumor cells was fasciculatus (Fig. 7). The cytoplasms of the elongated cells showed more
Fig. 4. A prominent perivascular whorl arrangement is observed (HE ×20).

Fig. 5. Circular-like arrangements of the tumor cells are noted (HE ×20).

Fig. 6. Numerous exceedingly fine reticular fibers surround the individual tumor cells (reticulin silver impregnation ×40).
Fig. 7. The tumor cells show fascicular proliferation (HE×20).

Fig. 8. Immunohistochemical staining for α-SMA (a: ×20) and for desmin (b: ×40). Almost all tumor cells are positive for α-SMA, while few show immunoreactivity for desmin.
fuchsin staining for Masson's trichrome than the surrounding cells resembling endometrial stromal cells, and a fascicular positive reaction along the long axis of the cytoplasm was seen on PTAH. In the immunohistochemical findings of the formalin-fixed specimen using α-SMA, the tumor cells were generally (over 90%) strongly positive regardless of the tumor cell shape (Fig. 8a). Only a few tumor cells were positive for desmin (Fig. 8b), and immunoreactivity for vimentin was recognized in the majority of tumor cells. The other leiomyomatous lesions were typical leiomyomas microscopically.

Discussion

Endometrial stromal tumors are rare. The tumor is composed of cells identical to or closely resembling those of proliferative endometrial stroma, and these uniform tumor cells show diffuse proliferation1,2). The present case was consistent with these definitions, except for the presence of an eosinophilic cytoplasm. Norris and Taylor have classified endometrial stromal tumor into endometrial stromal nodule as a benign tumor, low-grade endometrial stromal sarcoma (endolymphatic stromal myosis) and high-grade endometrial stromal sarcoma1). The present case was considered benign, since no invasion of the tumor cells into surrounding myometrium and vessels was seen. This case was partly associated with a smooth muscle component which was recognizable on light microscopy. Tavassoli and Norris described guidelines for combined muscle-stromal tumor2), but the present case could not be included in that category, because of the low level of smooth muscle.

Oliva et al. documented that frequent appearance of fascicular proliferation of the tumor cells, large blood vessels with thick muscular walls, a cleft-like space and small arterioles resembling arteria spiralis are useful in the differentiation between endometrial stromal nodule and highly cellular leiomyoma3). Other investigators have also indicated that perivascular whorl arrangement is important for diagnosis of endometrial stromal tumor4,5). Since the most powerful prognostic indicator is different between endometrial stromal tumor and smooth muscle tumor6), differential diagnosis between them is required. In the present case, the distinction between endometrial stromal nodule and cellular leiomyoma which metastasizes to the lung7,8) is critical. The findings of those peculiar blood vessels and the prominent perivascular whorl arrangement support the diagnosis of endometrial stromal nodule. Tavassoli and Norris observed a pseudorosette arrangement in their series2), and the circular-like arrangements of the tumor cells in the present case were similar to this pseudorosette arrangement. Cellular leiomyoma does not generally show such arrangements.

In this case, the findings of H.E specimens were confused by the immunohistochemical results, since almost all tumor cells showed intense α-SMA positivity. Immunohistochemical results of endometrial stromal tumors are diverse3,4,9-12) (Table 1). It is unclear whether the diversity of these results is the result of variation in tissue fixation, antibody and staining method or whether it is due to differences in features of the tumor itself. Abrams et al. reported that the proportion of desmin-positive cells in endometrial stromal sarcoma varies with the type of fixation13). However, Mikami et al. showed that it is possible to subdivide endometrial stromal sarcoma with smooth muscle differentiation into three groups14). In their second classification, which is light microscopically typical endometrial stromal sarcoma with immunohistochemical or electron microscopic evidence of smooth muscle differentiation, the endometrial stromal sarcoma may show diverse expression of myogenic antibodies in many or few of the components showing smooth muscle features. When many
Table 1. Literature review of immunohistochemistry for myogenic antibodies in endometrial stromal tumor

<table>
<thead>
<tr>
<th>Study</th>
<th>Vimentin</th>
<th>α-SMA</th>
<th>Desmin</th>
<th>MSA</th>
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<tr>
<td>Present case</td>
<td>positive</td>
<td>positive</td>
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NSC: normal endometrial stromal cell; ESN: endometrial stromal nodule; ESS: endometrial stromal sarcoma; α-SMA: α-smooth muscle actin; MSA: muscle specific actin (HHF-35); N.D.: not done.

The specific MSA antibody used by Oliva et al. was not described in their paper. Only rare cells showed immunoreactivity.

Tumor cells express myogenic markers, the distinction between endometrial stromal tumor and smooth muscle tumor may be difficult on immunohistochemistry.

Immunohistochemical data by the same investigators using the same staining method have shown varied results in the proportion of positive cells against myogenic antibodies. In the formalin-fixed specimens of Farhood and Abrams, the proportion of cells positive for α-SMA was from negative to diffuse (30–70%), and that of desmin-positive cells was from negative to generalized (more than 70%). In three cases of extrauterine endometrial stromal sarcoma described by Fukunaga et al., α-SMA or desmin-positive cells ranged from focal to diffuse. Franquemont et al. reported that α-SMA was expressed from focally to diffusely, and desmin positivity was diffuse in four cases, although three cases only showed scattered positive cells. These results suggest that the diversity of immunoreactivity for myogenic antibodies in endometrial stromal tumor is probably not merely due to methodology.

The fact that α-SMA and desmin are coexpressed in various combinations in endometrial stromal sarcoma and the diversity of immunoreactivity in endometrial stromal tumor even when the same methodology is applied, taken together suggest that endometrial stromal tumor also includes a group which expresses various combinations of myogenic antigens, namely, endometrial stromal tumor may have a heterogeneous immunohistochemical phenotype. The endometrium of the uterus repeats shedding and reconstruction throughout the menstrual cycle, which is thought to be mediated by myofibroblasts. Because myofibroblasts, which are considered to participate in wound healing, have been divided...
into four subtypes based on variations of immunoreactivity using vimentin, α-SMA and desmin\(^{18}\), it is not surprising that endometrial stromal cells show immunoreactivity for myogenic markers. And if endometrial stromal tumors are derived from totipotential primitive cells, immunohistochemical heterogeneity is compatible with this hypothesis.

In conclusion, it was considered that the majority of endometrial stromal tumor cells in our case possessed smooth muscle features. In Mikami's second classification like our case, when results of immunohistochemistry are stressed, differentiation between endometrial stromal tumor and smooth muscle tumor may be misdiagnosed. We conclude that several myogenic antibodies should be used, if so, endometrial stromal tumor and smooth muscle tumor may be distinguished by immunohistochemistry using our desmin profile. Immunohistochemical results should also be compared to hematoxylin-eosin specimens without precedence of immunohistochemistry.

References


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