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Stromal Mystery with Cellular Secrets - Navigating Tumor Terrain: Insights Into Endometrial Tumors

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ABSTRACT

Uterine smooth muscle tumors and endometrial stromal tumors (ESTs) are the two major types of mesenchymal tumors of the uterus, the latter being fairly uncommon. Among these, endometrial stromal sarcoma (ESS) accounts for less than 1% of all uterine tumours. Endometrial stromal tumors (ESTs) are rare uterine mesenchymal neoplasms and on occasion pose a diagnostic dilemma for pathologists if it coexists with leiomyomata.[1] According to the current WHO classification, they have been categorized into endometrial stromal nodule, low-grade endometrial stromal sarcoma (LG-ESS), high-grade ESS, and undifferentiated uterine sarcoma. Cellular leiomyoma (CL) often simulates EST due to increased cellularity. We hereby report a series of 4 cases which posed a diagnostic challenge to us as all the cases had concurrent leiomyoma along with ESTs. We therefore discuss the histological features of ESTs which helped us resolve this dilemma as well as the utility of immunohistochemistry (IHC) as a diagnostic aid in arriving at a final diagnosis in such problematic cases.

Keywords: *Cellular leiomyoma, endometrial stromal sarcoma, endometrial stromal tumor.*

1. INTRODUCTION

Endometrial stromal tumors (ESTs) are among the least common neoplasms of the uterus. Among these, endometrial stromal sarcoma (ESS) accounts for less than 1% of all uterine tumours. ESTs closely recapitulate stroma seen in proliferative endometrium.There is an overlap in morphology between EST and cellular leiomyoma (CL). A patient's survival and prognosis may be impacted by overtreatment or undertreatment resulting from a misdiagnosis of EST and CL.

Currently, cluster of differentiation 10 (CD10) has been considered as the best immunomarker for endometrial stromal cells [2–6], but it is not expressed in all mesenchymal tumors [7–9]. Smooth muscle actin (SMA) is a common biomarker for smooth muscle, however, SMA is sometimes expressed in ESTs also [12–15], suggesting the need for novel immunomarkers and immunohistochemical panels for differentiating between EST and CL. In terms of diagnosis, low-grade ESS (LGESS) and cellular leiomyoma (CM) might significantly overlap, particularly in cases where there is noticeable smooth muscle or fibroblastic differentiation. This becomes extremely important in the light of limited experience with EST as these are rare tumors with limited case series in the literature. The role of immunohistochemistry (IHC) has also been evaluated by several authors in this regard, with few markers like CD-10 and H-caldesmon emerging as useful adjuncts in differentiating between ESTs and CMs.

We hereby report a case series which posed a diagnostic challenge to us as all the cases had coexisting leiomyomas with EST and morphological overlap with CM.. We therefore discuss the essential histological features which helped us resolve this dilemma as well as the utility of IHC as a diagnostic aid in arriving at a final diagnosis in our cases.

TABLE:1

	CASE 1	**CASE 2**	**CASE 3**
Age	**46yrs**	**48 yrs**	**50 yrs**
Chief complaints	heavy menstrual bleeding for 5 months	increased frequency of menstrual cycle and abdominal pain for one month	Abnormal uterine bleeding and abdominal discomfort
Radiologic findings	Magnetic resonance imaging of pelvis also revealed mutiloculated cystic lesion measuring 11.1 x 5.4 x 10.9 cm with thin septations in the left adnexa.	MRI Pelvis also reveals Bulky uterus with submucosal and Sub-serosal fibroids.	USG reveals multiple intramural fibroid.
Microscopic findings	Nodules of plump round to oval cells interspersed with prominent spiral arterioles and separated by smooth muscle bundles with invading tongues into myometrium	The other intramural soft nodule shows irregular and diffuse sheets of monotonous spindle cells with mild cytologic atypia. The tumour cells are seen concentrically around the arterioles extensively infiltrating into the surrounding myometrium	Histopathology reveled a low grade ESS along with a small leiomyoma.
Gross findings	Grey yellow to grey white nodule measuring 3.2 x 2 x 2 cm noted in the myometrium in the fundal aspect	Another large intramural soft, fleshy nodule measuring 10x7.5cm adjacent to the fibroid, the lesion is poorly circumscribed extending from the endometrium and invading into the myometrium and also shows focal yellowish areas	Two lesions were noted intramurally one measuring 1x1 cm located near the endometrium, another measuring 4x3 cm with yellowish areas
IHC	SMA -focal positivity CD 10 – strong positive	-	-

2. CASE REPORTS:

CASE 1:

A 46-year-old female presented with heavy menstrual bleeding for 5 months. On abdominal examination uterus appeared enlarged up to 14-16 weeks size and per vaginal examination revealed mass of 20 weeks size. Ultrasonography revealed a subserosal lesion measuring 8.1 x 4.3 cm, suggestive of a uterine fibroid. Magnetic resonance imaging of pelvis also revealed mutiloculated cystic lesion measuring 11.1 x 5.4 x 10.9 cm with thin septations in the left adnexa. However left ovary could not be visualized separately. In view of uncertain nature of large uterine mass and left adnexal cyst, a frozen section was requested keeping in mind the need for conservative approach. Grossly we received total abdominal hysterectomy with bilateral salpingo-oopherctomy specimen weighing 476 gms measuring 15 x 11x 5 cm. On cut surface multiple intramural fibroid largest measuring 8x4x3cm with grey white firm and gelatinous areas noted. Smallest intramural fibroid measuring 1x0.5x0.5cm noted. Another grey yellow to grey white nodule measuring 3.2 x 2 x 2 cm noted in the myometrium in the fundal aspect. Microscopically sections from fibroid showed a benign neoplasm composed of spindle cells arranged in interlacing fascicles and bundles with degenerative changes. Sections from the grey yellow nodule shows nodules of plump round to oval cells interspersed with prominent spiral arterioles and separated by smooth muscle bundles with invading tongues into myometrium. Left ovary showed a cyst wall lined by seromucinous epithelium. The diagnosis of seromucinous cystadenoma left ovary and leiomyomata (2) with degenerative changes in the largest fibroid. The grey yellow nodule was initially offered a differential diagnosis of endometrial stromal sarcoma low grade and cellular leiomyoma. Immunohistochemical markers with CD10 showed strong positivity in grey yellow tumour and the final diagnosis of low grade endometrial stromal sarcoma was given. [FIGURE 1]

FIGURE 1:

Fig A: Gross specimen of uterus showing leiomyoma with grey white gelatinous areas.

Fig B: On further sectioning, another tumour mass noted, with cut surface showing grey white areas.

Fig C: High power view showing (40X),showing endometrial stromal tumour cells with prominent spiral arterioles and separated by smooth muscle bundles.

Fig D: IHC with CD 10 showing diffuse positivity in stromal nodule.

Fig E: IHC with CD 10 showing strong positivity favouring endometrial stromal sarcoma.

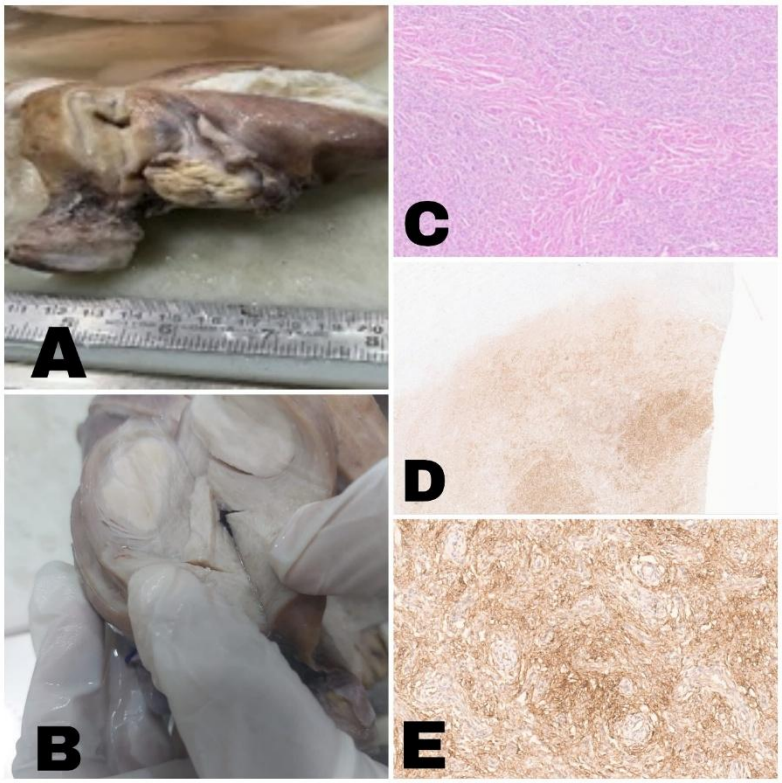

FIGURE 1

CASE 2:

A 48-year-old female came with complaints of increased frequency of menstrual cycle and abdominal pain for one month. On per vaginal examination, uterus anteverted and bulky. Ultrasound abdomen reveals Bulky uterus with multiple uterine fibroids. MRI Pelvis also reveals Bulky uterus with submucosal and Sub-serosal fibroids. Following total abdominal hysterectomy with bilateral salpingo-oophorectomy, the specimen was sent for histological analysis. Grossly Uterus is enlarged and congested with multiple subserosal fibroids. Cut surface reveals large intramural lesion measuring 18x 15 cm, after giving serial sections specimen was kept for fixation in formalin overnight. The next day grossing reveals two separate lesions with different morphology, the large intramural fibroid in the right side measuring 8.5x6cm protruding and seems to obliterate the endometrial cavity. Cut surface of fibroid is grey white, whorled with focal myxoid degeneration. Serial sections reveals another large intramural soft, fleshy nodule measuring 10x7.5cm adjacent to the fibroid, the lesion is poorly circumscribed extending from the endometrium and invading into the myometrium and also shows focal yellowish areas. Both the ovaries showed corpus luteal cysts and both the tubes appears unremarkable. Microscopy also revealed two separate nodules of different histomorphology. One was large intramural fibroid with myxoid degeneration. Sections from the other intramural soft nodule shows irregular and diffuse sheets of monotonous spindle cells with mild cytologic atypia. The tumour cells are seen concentrically around the arterioles extensively infiltrating into the surrounding myometrium. Areas of foamy histiocytes, cholesterol cleft formation is also noted and finally diagnosed as Endometrial stromal sarcoma of low grade.[FIGURE 2]

FIGURE 2:

Fig A: Gross specimen of the uterus showing leiomyoma on one side

Fig B: On further parallel sectioning, it showed another tumour on the other side of the uterus with yellowish cut surface

Fig C: Low power view(10x) showing EST with infiltrating tongue like growth in the myometrium

Fig D: High power view (40x) showing small dark tumour cells concentrically arranged around the arterioles

Fig E: scanner view (4x) showing the oring of the sromal tumour from endometrial stroma

Fig F: vascular invasion of LG ESS.

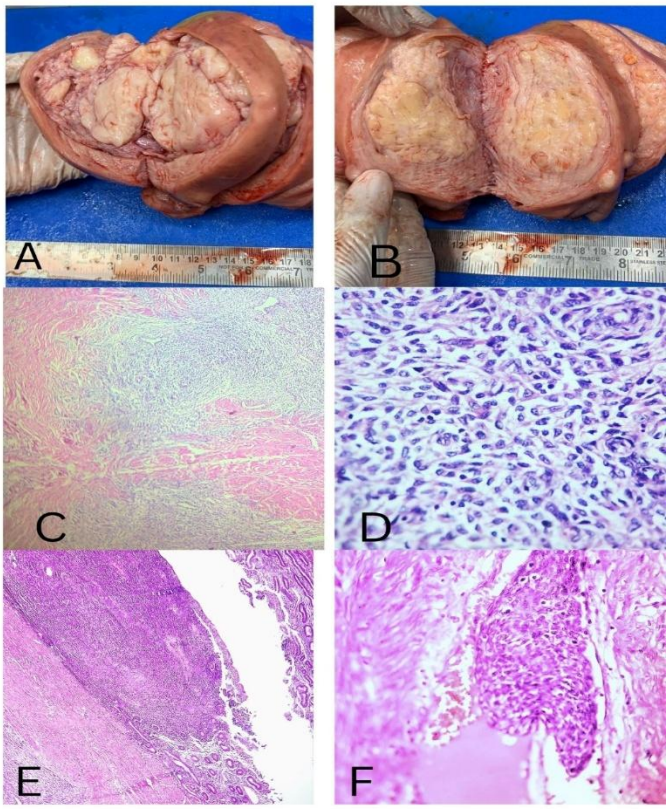

FIGURE 2

CASE 3:

50 year old female presented with abnormal uterine bleeding and abdominal discomfort. Ultrasound revealed multiple intramural fibroid. The patient underwent total abdominal hysterectomy. Gross examination showed uterus with cervix measuring 10x7x5 cm. on cut section two lesions were noted intramurally one measuring 1x1 cm located near the endometrium, another measuring 4x3 cm with yellowish areas. Histopathology reveled a low grade ESS along with a small leiomyoma. [FIGURE 3]

FIGURE 3:

Fig A: Gross specimen of the uterus showing yellowish nodule on one side on cut surface

Fig B: on serial sectioning cut surface of uterus showing a leiomyoma along with yellowish nodule.

Fig C: shows a cellular neoplasm arranged in interlacing fascicles consistent with leiomyoma.

Fig D &E : Shows endometrial stromal neoplasm.note the tumour whorl around the arteriole.

Fig F: Shows CD10 positivity in the endometrial stromal tumour.

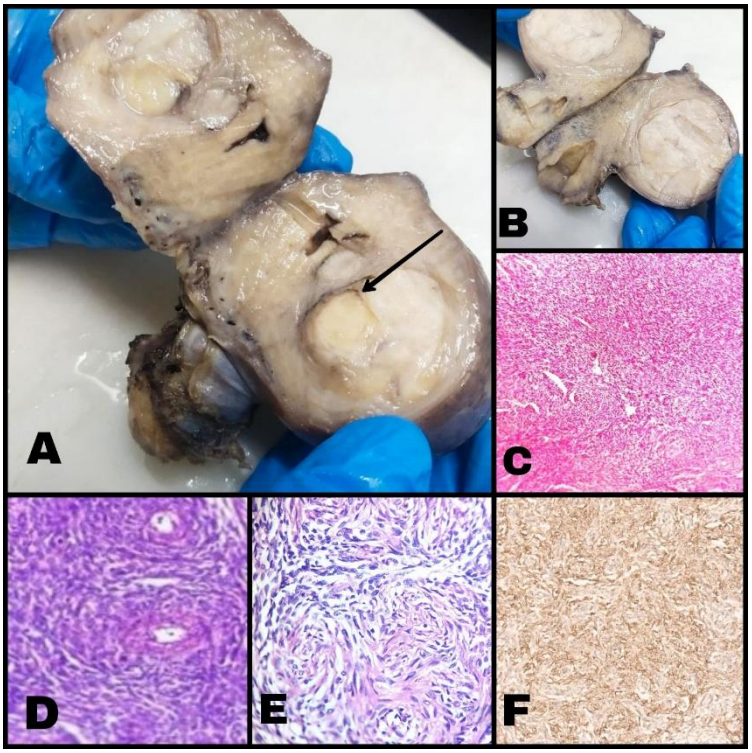

FIGURE 3

3. DISCUSSION

The two main forms of uterine mesenchymal tumors are uterine smooth muscle tumors and ESTs, with the latter being rather rare. In most instances, normal histological examination is typically adequate to distinguish between ESTs and smooth muscle tumors. ESTs and CL can exhibit marked similarity in architectural and cytological characteristics, thereby creating a diagnostic dilemma which is furthermore exaggerated by ESS with smooth muscle differentiation.

When it comes to curetting or myomectomy specimens, this differentiation is more crucial but even more challenging because of the scanty material. While a hysterectomy might be seen as curative for a CM, an ESS necessitates careful monitoring and follow up to rule out any metastases or recurrence.

Clinically, patients with ESS present with abnormal uterine bleeding, pelvic pain, or dysmenorrhea. Patients with CL have chief complaints of menstrual irregularities, pelvic mass, abdominal pain and pelvic pressure[10]. Here, our patient presented with menstrual irregularities and abdominal pain.

ESS usually occurs in the 4th to 5th decade[11]. Uterine imaging in case of ESS is not reliable and can lead to faulty diagnosis of adenomyosis or uterine leiomyoma[10]. There is ongoing debate over the histogenesis of ESTs. Numerous immunohistochemical and ultrastructural investigations have suggested that it is the differentiation of smooth muscle, sex cord and epithelial components.[13] The endometrial stroma occasionally gives rise to neoplasm that may resemble stromal cells cytologically and architecturally. The authors have found that ESTs are composed of cells that have a resemblance to endometrial stromal cells of proliferative endometrium.[10,15]

Grossly, CL are well-circumscribed, tan, or yellow nodules that tend to have a softer consistency than the usual type of leiomyoma[11] and thereby confused with ESts. LG-ESS usually involves myometrium, and sometimes it can be tan to yellow polyp, which may be infarcted or hemorrhagic[12]. However, our cases presented with grey yellow nodule one in the myometrium.

The main lesion of ESS is always intramural, but most of them involve endometrium and uterine curettage may be helpful in such cases, however, definitive diagnosis can only be made on histopathological examination of the entire lesion along with immunohistochemical examination.[10]

It is even more challenging when EST and leiomyoma coexist since endometrial stromal cells have a propensity to differentiate into fully formed smooth muscle cells also.[14]

CL is a benign smooth muscle tumor composed of densely cellular fascicles of smooth muscle with scant intervening collagen with the presence of large thick-walled blood vessels. In contrast, Endometrial stromal tumours show predominantly delicate

arborizing vessels. Oliva et al.[16] emphasized large thick-walled blood vessels as an important feature to distinguish CL from stromal tumours. However, the presence of many thin- and thick-walled vessels may lead to the confusion as in the present cases.

ESTs show heterogeneous morphological features, with LG-ESS being a clinically indolent malignant neoplasm with minimal cytological atypia, infrequent mitotic figures, and numerous thin-walled small arteriolar type vessels.[13]. Our cases also showed sparse minimal atypia along with presence of thick and thin walled vessels. This created a dilemma on histopathological examination which was later resolved on studying the more paraffin sections and CD 10 immunohistochemistry marker (IHC), later.

IHC plays a major role in distinguishing CL and ESS. Strong and/or diffuse positivity of CD10 favors ESS in our cases. ESSs are almost always positive for both estrogen receptor and progesterone receptor (PRs). [11]

Thus, Distinction of ESS and CL is essential in view of different prognosis and treatment plan.

4. CONCLUSION

Among the mesenchymal tumors of the uterus, leiomyomas are very common and ESTs are rare and often more aggressive and it can be misdiagnosed as a benign condition, especially when it is adjacent to the leiomyoma. Imaging techniques like MRI or Ultrasound may not clearly differentiate these two lesions and histopathological analysis is essential for the definitive diagnosis.

The co-existence of leiomyoma and endometrial stromal sarcoma in the same uterine specimen further emphasizes the importance of careful grossing to offer the accurate pathological diagnosis. Also, a thorough inspection of every lesion is essential, especially in any unusual or heterogeneous areas to make sure that malignant elements like low grade and high grade ESS are not missed. Therefore, thorough sampling along with Immunohistochemical markers also comes to the rescue in some indecisive cases and proves to be of great value in arriving at a definitive diagnosis.

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