Endometrial Stromal Tumors of the Uterus: A Retrospective Clinico-Morphological Analyses of 15 Patients

Uterusun Endometrial Stromal Tümörleri: 15 Vakalık Kliniko-Morfolojik Retrospektif Çalışma

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ABSTRACT Objective: Tumors of the endometrial stroma are very rare mesenchymal tumors of the uterus with cytological and architectural features reminiscent of endometrial stromal cells. The aim of this study is to review our experience with endometrial stromal tumors, to analyze their clinical and histopathological features, and to compare our findings with previously published data. **Material and Methods:** A retrospective analysis was performed involving 15 patients between the years of 2005 to 2012, of cases of endometrial stromal tumors diagnosed at the Department of Pathology, Ankara University. **Results:** In the 7 year period, 15 cases of endometrial stromal tumor have been diagnosed in our department. The study included 1 endometrial stromal nodule, 8 endometrial stromal sarcoma and 6 undifferansiye stromal sarcoma. Patients' mean age at the time of diagnosis was 47,9 years. Vaginal bleeding was the most common presenting symptom. In 12 patients, definitive diagnosis of sarcoma was achieved only after surgical specimen analysis and in only 3 of them, physical examination combined with pelvic ultrasonography had suspected malignancy. All of the patients underwent surgery, myometrial invasion was noted in 14 of cases. **Conclusion:** We insist on the fact that endometrial stromal nodule is a rare disease to be carefully differentiated from other endometrial stromal tumors especially from endometrial stromal sarcoma, and for differing endometrial stromal sarcoma from undifferentiated endometrial sarcoma, marked cellular atypia and abundant mitotic activity is important clues.

Key Words: Endometrial stromal tumors; sarcoma, endometrial stromal

ÖZET Amaç: Endometrial stromanın tümörleri uterusun çok nadir görülen mezenşimal tümörleridir. Tümör hücreleri endometrial stromal hücrelere benzerler. Çalışmadaki amacımız merkezimizde değerlendirilen endometrial stromal tümörlerin, histopatolojik bulgularının klinik özellikleri ile korele edilerek değerlendirilmesi ve mevcut literatür ile karşılaştırılmasıdır. **Gereç ve Yöntemler:** 2005-2012 yılları arasında Ankara Üniversitesi Patoloji Anabilim Dalında endometrial stromal tümör tanısı almış 15 olgu çalışmaya dahil edilmiştir. **Bulgular:** Yedi yıllık sürede saptanan endometrial stromal tümör olgularının biri endometrial stromal nodül, 8'i endometrial stromal sarkom, 6'sı ise andiferansiye stromal sarkom olmak üzere 15 olgu saptanmıştır. Hastaların yaş ortalaması 47,9 yıl olarak saptanmıştır. Endometrial stromal sarkom olgularında yaş ortalaması 38,8 yıl bulunurken, andiferansiye stromal sarkom olgularının yaş ortalaması 60 yıl bulunmuş ve istatistiksel olarak anlamlı farklılık tespit edilmiştir. Vajinal kanama en sık semptom olarak saptanmıştır. Olguların 12'sinde tanıya cerrahi sonrasında ulaşılırken, 3 olguda pelvik muayene ve radyoloji ile malignite şüphesi belirmiştir. Tüm hastalar cerrahiye gitmiş, 14 olguda miyometrial invazyon saptanmıştır. **Sonuç:** Biz, nadir bir hastalık olan endometrial stromal nodüllerin diğer endometriyal stromal tümörlerden, özellikle de endometriyal stromal sarkomalardan ayırdedilebilmesi için ve endometriyal stromal sarkomaların andiferansiye endometrial sarkomalardan farkının anlaşılabilmesi için belirgin selüler atipi ve aşırı mitotik aktivitenin önemli ipuçları olduğunu ileri sürmekteyiz.

Anahtar Kelimeler: Endometriyal stromal tümörler; sarkom, endometriyal stromal

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Endometrial stromal tumors (ESTs) of the uterus are second most common mesenchymal tumors of the uterus even though they account for <10% of all such tumors.[1] The classification of endometrial stromal tumor is difficult and complicated.[2,3] The recent World Health Organization of tumors of the breast and female genital organs divides the uterine stromal neoplasms in to three groups: benign endometrial stromal nodules (ESN), low-grade endometrial stromal sarcoma (LGESS) or ESS, and undifferentiated endometrial sarcoma (UES).[4] The ESN fall in the lower end of the spectrum of this group of tumours. Both are typically composed of a diffuse growth of small blue cells with scant cytoplasm, and oval to spindle nuclei that resemble the endometrial stromal cells of the proliferative endometrium.[5,6] At the other end of the spectrum is stromal sarcoma of the uterus. Stromal sarcoma of the uterus is a rare neoplasm,which is clasically divided into ESS and UES.[7] The diagnosis of endometrial stromal sarcomas is reached after excluding other high-grade tumours of the uterus with a sarcomatous component.[8] While UES tends to have poor prognosis, ESS usually have excellent short- term prognosis.[9] Since myometrial and vascular invasion are the two features that help us to differentiate ESS from ESN and the UES resembles the sarcomatous component of carsino sarcoma, extensive sampling of the tissues is required for confirmation of diagnosis.[10]

The usual clinical presentation of ESS is abnormal uterine bleeding that occurs in about 90% of women and 70% cases show uterine enlargement. They can present with pelvic pain and dysmenorrhoea.[4] Immunohistochemistry will help in the detection of tumor markers specific for ESS. Strong and/or diffuse positivity for CD10 is found in ESS, which are helpful in distinguishing these tumors from histological mimics like cellular leiomyoma that are generally negative.[11] Also immunomarkers such as desmin, h-caldesmon, oxytocin receptors, and inhibin are useful in distinguishing cellular leiomyoma. They express h-caldesmon, desmin, and oxytocin receptors while CD10 and inhibin expression is a feature of ESS.[12]

In this study 15 cases with EST, who were diagnosed at the Ankara University Medical School, are presented and an overview of the current literature concerning EST is given.

MATERIAL AND METHODS

This study included 15 patients with endometrial stromal tumors between 2005 and 2012 in the department of Pathology of Ankara University College of Medicine. Data were retrospectively reviewed and included age at the time of diagnosis, patient demographics, clinical presentation, extent of surgery performed were noted. One ESN, 8 ESS and 6 UES were identified. Surgical staging was based retrospectively on the 2009 FIGO guidelines for cancer of the uterine corpus.[13] FIGO grade could not evaluate for 4 consultation case and 2 metastatic case. Total hysterectomy and removal of as much tumor as possible was performed as surgical procedures. Informed consent was taken from the patients.

IMMUNOHISTOCHEMISTRY

Formalin-fixed, paraffin-embedded 4 mm sections were mounted on "superfrost plus" slides. After air-drying at 37°C for 20 hours, the slides were deparaffinized in xylene and rehydrated through a graded alcohol series to distilled water. The slides were pretreated for 20 minutes in a microwave oven before incubation with primary antibodies for 30 minutes. Endogenous peroxidase activity was blocked. Staining was performed with a peroxidase labeled polymer (EnVision, DAKO, Glostrup, Denmark). Appropriate immunoreactive tissue samples were used as positive controls with each round of staining. Sections without the primary antibody were used as negative controls. All the sections were counterstained with hematoxylin, dehydrated, and mounted with Cytosel XYL. The tissue sections were immunostained with 6 antibodies considered to be of diagnostic value in endometrial stromal tumors (ER, PR, CD10, SMA, desmin, h-caldesmon).

STATISTICAL ANALYSES

Data was analyzed using SPSS statistical package version 15. Numerical data were expressed as fre-

quency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between the histopathologic diagnose with all other parameters including age, clinic, surgical procedure and FIGO grade of the patients.

RESULTS

PATIENT DEMOGRAPHICS

The age range of the 15 patients was 30-68 years, with a mean age of 47.9 years (SD±13.3 years) and was significantly different between the two groups: 38.8 and 60 years for ESS and UES, respectively (p=0.01). Seven patients were postmenopausal (46.6%) and 8 premenopausal (53.3%). Vaginal bleeding was the most common presenting symptom, being present in 10 patients (%67). Just one patient who was diagnosed ESN had pelvic pain (6.6%), two patients had pelvic mass (13.2%) , and we could not reach the symptom of two consultation case (13.2%) (Table 1).

FIGO-CLASSIFICATION AND TUMOR GRADING

From the 14 patients (8 ESS and 6 UES) one patient (7.1%) had a primary tumour FIGO Stage I, 1 patient (87.1 %) had FIGO stage II, 5 patients had FIGO stage III (35.7%), 1 patients had FIGO stage IV (7.1%), and in 6 patients the tumour stage was not assessed. One patient (7.1%) had metastatic disease at the time of the first diagnosis. The localisation of the metastas was lung. In 12 patients (80%), definitive diagnosis of sarcoma was achieved only after surgical specimen analysis and in only 3 of them (30%), physical examination combined with pelvic ultrasonography had suspected malignancy.

SURGICAL TREATMENT

All of the patients (100%) underwent surgery: total hysterectomy with bilateral salpingo-oophorectomy in all of them and pelvic lymphadenectomy in 5 of them (35.7%) and omentectomy 2 of them (14,3%). Pelvic lymphadenectomy and omentectomy had been performed to any of the consultation cases, and we could not reach the reason of this procedure. The mean tumor size was 6.3 cm with std dev ±2.9 (range: 3-12 cm) (Figure 1).

MICROSCOPIC FINDINGS

In the study we have only one cases of ESN, at the currethage specimen of this case we saw mostly atipic stromal cells and high mitotic index and as a result we reported the case as high grade endometrial stromal sarcom, the patient went total hysterectomy with bilateral salpingo-oopherectomy and pelvic lymphadenectomy and on microscopic examination it showed oval to spindle shaped picture of cells, which resemble the stromal cells of a proliferating endometrium (Figure

TABLE 1: Clinic documantation of the patients.

Case [n]	Age [years]	Reasons for consulting	Surgery	FIGO grade	Histology
1	64	Pelvic pain	THBA+LN	-	ESN
2	68	Metrorrhagia	THBA	III	UES
3	58	Metrorrhagia	THBA	II	UES
4	49	Pelvic mass	THBA	I	ESS
5	51	Metrorrhagia	THBA	III	UES
6	48	Metrorrhagia	THBA	-	ESS
7	30	Unknown	THBA	-	ESS
8	39	Metrorrhagia	THBA	-	ESS
9	42	Unknown	THBA	-	ESS
10	68	Metrorrhagia	THBA	-	UES
11	30	Metrorrhagia	THBA+LN+O	III	ESS
12	39	Pelvic mass	THBA+LN+O	IV	ESS
13	67	Metrorrhagia	THBA+LN	III	UES
14	48	Metrorrhagia	THBA+LN	III	UES
15	34	Metrorrhagia	THBA	-	ESS

THBA: Total hysterectomy+bilateral adnexectomy; LN: Lymphadenectomy; O: Omentectomy; ESN: Endometrial stromal nodule; ESS: Endometrial stromal sarcoma; UES: Undifferentiated endometrial sarcoma.

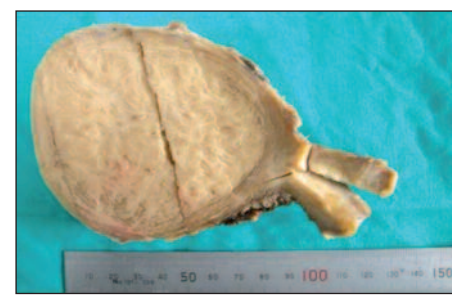

FIGURE 1: The gros inspection of total hysterectomy specimen revealed a well- circumscribed yellow tumor measuring 7.5 cm.
(See color figure at http://jinekoloji.turkiyeklinikleri.com/)

2a). There was focal marginal irregularity in the form of finger-like projections that measured 1,5 mm (Figure 2b). Diffuse and strong positivity both with ER and PR was observed . The tumor cells were CD10 positive, desmin and SMA negative.With this morphologic and immunohistochemical findings we reported the case as ESN. In the ESS cases we mostly observed infiltrating growth in to the myometrium, and densely cellular tumor composed of uniform, oval to spindle shaped cells of endometrial stromal type (Figure 3). Significant atipia and pleomorphism were absent. UES cases generally lacks specific differentiation and bears no histological resemblance to endometrial stroma which show marked cellular atypia and abundant mitotic activity (Figure 4).

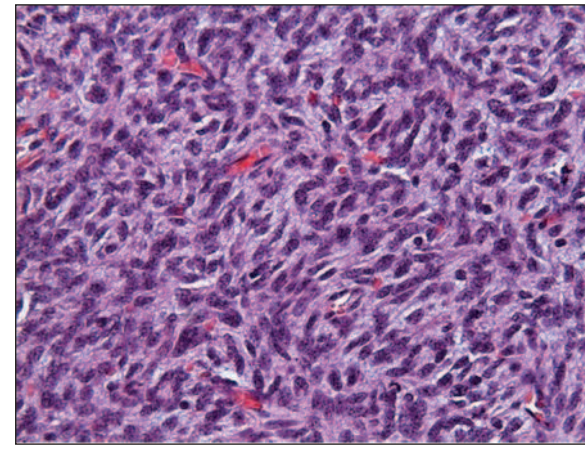

FIGURE 3: ESS. The tumor resembles normal stroma of proliferative endometrium, characterized by generally uniform cells with minimal nuclear pleomorphism and cytologic atypia, hyalinized connective tissue, and a rich, vascularized background (H&EX100).
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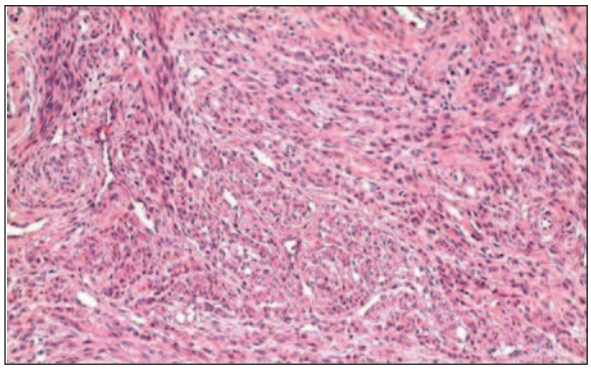

FIGURE 2a: ESN cells resemble normal stroma of proliferative endometrium (H&Ex100).
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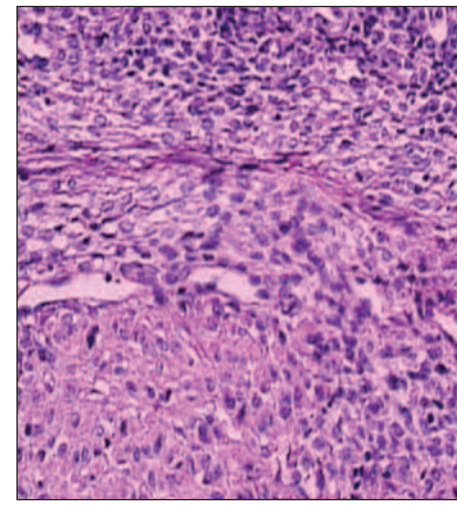

FIGURE 4: UES. The tumor is composed of anaplastic spindle cells that have a high mitotic index and frequently encountered abnormal mitotic figures (H&Ex200).
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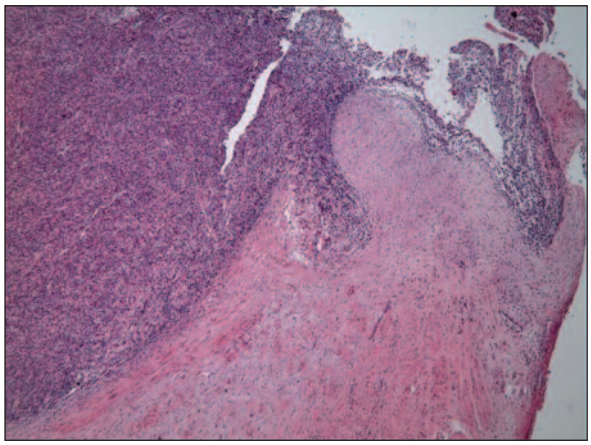

FIGURE 2b: Focal marginal irregularity in the form of finger-like projections that measured 1,5 mm (H&Ex40).
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Vascular invasion was seen in a ESS case (Figure 5) and invasion of leiomyoma nodule in a ESS case was determined (Figure 6). ESS cases showed mean 4.6±2.38 mitos; however, UES cases showed mean 9±6.03 per 10 hpf. Myometrial invasion was noted in 14 of cases (93.3%). Mitotic activity was considered mean 6.5 with std-dev±4.7 (range:1-20). Necrose was observed in just 4 patients (28.6%).

Immunohistochemical studies showed that the neoplastic cells in ESS were immunreactive to CD10

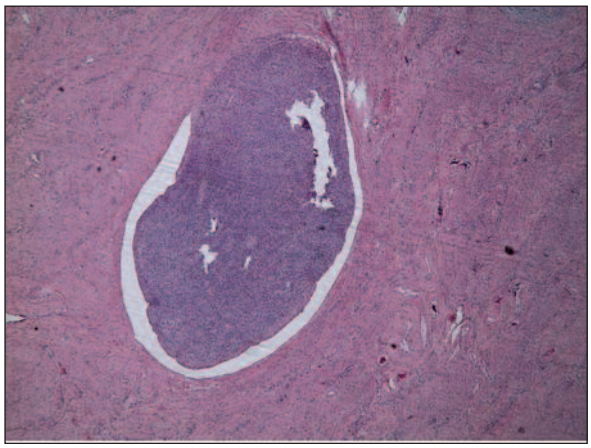

FIGURE 5: ESS. Nests of neoplastic endometrial stromal cells are present in vascular spaces (H&Ex100).
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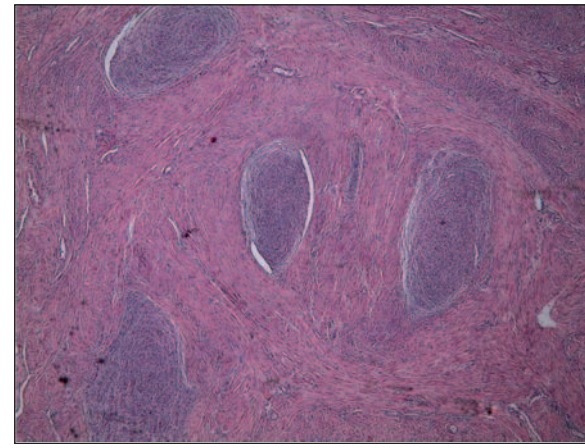

FIGURE 6: Leiomyoma nodule invasion of a UES case (H&Ex100).
(See color figure at http://jinekoloji.turkiyeklinikleri.com/)

however the UES focus were slight positive. Desmin and h-caldesmon were negative for all cases and just 2 UES cases showed weak SMA positivity. Microscopic features and immunohistochemical findings of all patients were documanted in Table 2 (Figure 7a-d).

DISCUSSION

Endometrial stromal tumors are among the least common neoplasms of the uterine corpus, with an annual incidence of about 2 per million women.[4,14] ESN is a rare subtype that accounts for about one

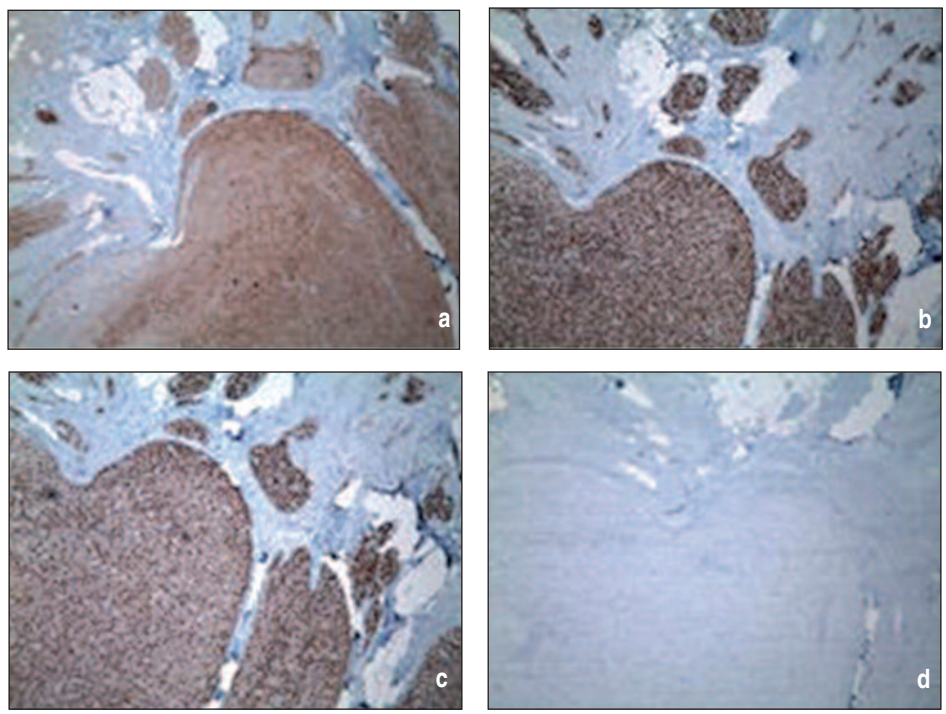

FIGURE 7: Immunohistochemical findings. **a.** CD10 positivity of an ESS case (CD10 x100). **b.** ER positivity of an ESS case (ERx100). **c.** PR positivity of an ESS case. (PRx100). **d.** Desmin negative in an ESS case (Desminx100).
(See color figure at http://jinekoloji.turkiyeklinikleri.com/)

TABLE 2: Microscopic features and immunohistochemical findings of all patients.

					Immunohistochemistry				
Case [n]	**Diagnose**	**Myometrial invasion**	**Mitosis [n]**	**Necrose**	**ER**	**PR**	**CD10**	**SMA**	**Desmin**	**h-caldesmon**
1	ESN	Absent	3	Absent	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
2	UES	Extensive invasion	8	Focal	Weak positive	Weak positive	Weak positive	Negative	Negative	Negative
3	UES	Extensive invasion	10	Focal	Weak positive	Weak positive	Weak positive	Weak positive	Negative	Negative
4	ESS	Finger like projections	>9mm 1	Absent	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
5	UES	Extensive invasion	8	Absent	Weak positive	Weak positive	Weak positive	Negative	Negative	Negative
6	ESS	Finger like projections	>9mm 8	Focal	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
7	ESS	Finger like projections	>9mm 6	Absent	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
8	ESS	Extensive invasion	4	Absent	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
9	ESS	Extensive invasion	5	Absent	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
10	UES	Extensive invasion	20	Absent	Weak positive	Weak positive	Weak positive	Weak positive	Negative	Negative
11	ESS	Extensive invasion	2	Absent	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
12	ESS	Extensive invasion	4	Absent	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative
13	UES	Extensive invasion	2	Focal	Weak positive	Weak positive	Weak positive	Negative	Negative	Negative
14	UES	Extensive invasion	6	Absent	Strong positive	Strong positive	Weak positive	Negative	Negative	Negative
15	ESS	Finger like projections	>9 mm 7	Focal	Strong positive	Strong positive	Strong positive	Negative	Negative	Negative

ESN: Endometrial stromal nodule; ESS: Endometrial stromal sarcoma; UES: Undifferentiated endometrial sarcoma.

fourth of the endometrial stromal tumors which constitute less than 5% of uterine tumors.[15,16] Recently, Dionigi et al. published a series of 50 cases including EST that had an entirely circumscribed margin or had limited focal infiltration at their periphery, and he retained onyl four ESN.[17] In our study we detected just one ESN. Endometrial stromal nodule has been defined as a well-circumscribed endometrial stromal tumor; however, focal irregularities or finger-like projections into the adjacent myometrium are acceptable if none of them exceed 2 to 3 mm.[18,19]

Low-grade ESS displays infiltrative growth pattern, and less than 10 mitoses/10 HPF.[17] However, recent studies presented strong evidence that mitotic index did not correlate with the prognosis of ESS.[20] In the study we observed that ESS cases showed mean 4.6±2.38 mitosis; however, UES cases showed mean 9±6.03 per 10 hpf. EST often express both oestrogen and progesterone receptors.[21-23] The amounts of these receptors are higher than in other uterine sarcomas, higher than the mean found in normal endometrium during the proliferative phase and much higher than during the secretory phase.[24] ESSs are richer in oestrogen and progesterone receptors than UESs.[21,25] In the study we observed that our unique case ESN showed strong and diffuse ER and PR positivity, similarly all EES cases and just one UES case showed strong positivity of ER and PR.

In defining the diagnosis histopathologically, the distinction between smooth muscle and the endometrial stroma-derived neoplasms is often a problem. Smooth muscle neoplasms are thought to be distinguishable from endometrial stromal tumours by the expression of conventional muscle

markers, such as smooth muscle actin or desmin.[25] Other immunohistochemical studies, however, have revealed that ESS, like normal myometrium, may express both epithelial and/or muscle-related antigens.[26,27] These findings could reflect a common mesodermal-Mullerian derivation and demonstrate an intimate relationship between the endometrial stromal cells and the endometrial glands and myometrium. H-Caldesmon, an actin- and tropomyosin-binding protein, as well as staining of the smooth muscle myosin heavy chain and calponin has been shown to be helpful in distinguishing between benign cellular leiomyoma (CL) and ESS, but not between uterine leiomyosarcoma and ESS.[12] In the present study we stained all cases with h-caldesmon, desmin and SMA and all our cases, except a UES showing weak and focal SMA, were negative with these antibodies. The CD10 antigen has been shown to be an immunohistochemical marker of normal endometrial stroma. Positivity was also found in endometrial stromal nodules and LG ESS.[12] Therefore, it has been suggested that it is used to distinguish these tumours from histological mimics, such as cellular leiomyoma or adult granulosa cell tumour, which are generally negative. Positive staining with CD10 in a high-grade uterine sarcoma, which is negative with muscle markers, might indicate endometrial stromal differentiation and can be helpful in identifying HGESS in a group of undifferentiated uterine sarcomas.[28,29] All our UES cases showed weak positivity of CD10 while the others showing diffuse and strong CD10 positivity.

The median age at primary diagnosis of uterine sarcomas is quoted to be between 39 and 65 years.[30] In our patients, the median age was 47.9 years, with a range from 30 to 68 years. Mean age was significantly different between the two groups: 38.8 and 60 years for ESS and UES. One study group reported 11 cases, with only one patient with ESS older than 50 years, but all 7 patients with a UES were older than 50 years.[31,32] The disease can occur both in premenopausal and postmenopausal women. This results show that the UES is observed in older women than ESS. In most malignancies of the uterus, the first symptom is often abnormal vaginal bleeding. Hence, as in many other reports, most of our patients clinically presented with abnormal bleeding.[33,34] However, the patients also suffer from abdominal swelling or pain, back pain or weight loss.[35]

Therefore, a pre-operative curettage is a common step towards arriving at a diagnosis.[36,37] Due to the great similarity of ESS with normal endometrium, it may be impossible to diagnose ESS with certainty on curretage fragments, and the definitive diagnosis can be made only on a hysterectomy specimen. Carrying on this study we reported a case from curretage specimen as high grade stromal tumor, but seeing the histerectomy material we change the diagnose as ESN because there was minimal myometrial invasion that measured 1,5 mm.

This is the first study which was carried on by pathologists about the histomorphologic features of ESTs with demographic and clinical results so far. We insist on the fact that ESN is a rare disease to be carefully differentiated from other ESTs especially from ESS, and for differing ESS from UES, marked cellular atypia and abundant mitotic activity is important clues.

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