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Endometrial stromal tumors – a report of 5 cases

Sahande Elagoz[1], Fügen Kıvanc[1], Handan Aker[1], Sema Arici[1], Hatice Ozer[1] Tevfik Güvenal[2], Ömür Erden[2]

Departments of Pathology[1] and Obstetrics and Gynecology[2], Faculty of Medicine, Cumhuriyet University, Sivas, Turkey

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Objective: We aimed to present five endometrial stromal tumor cases because of their rare existence and difficulties in establishing histological diagnosis.

Study Design: Five endometrial stromal tumors (EST) retrieved from pathology department archieve from 1994 to 2004. Immunohistochemical analyses performed for CD10, CD117, CD34, desmin, smooth-muscle actine (SMA), and estrogen/progesterone (ER/PR) in formaline fixed paraffine-embedded archival material.

Results: Three of the tumors were endometrial stromal nodules (ESN), and two were low-grade endometrial stromal sarcomas (LGESS). In ESN cases, desmin, CD34, CD117 and ER/PR immunoreactivity were not observed. All of them were positive strongly for CD10 and one was strongly positive for actin. In LGESS cases, all immunomarkers were negative except CD10. In addition, two LGESS and one ESN cases were positively stained with CD117 in sex-cord differentiation areas. Our cases have been followed-up from ten months to fourteen years. Except for a case, no recurrences was observed.

Conclusion: Specific immunohistochemical markers has not been established yet for the diagnosis of endometrial stromal tumors. Especially in younger women, to make a correct diagnosis for mesenchymal tumors of uterus, endometrial stromal tumors must be kept in one's mind.

Keywords: Endometrial stromal tumor, immunohistochemical features and sex-cord like differentiation.

Introduction

Mesenchymal tumors of the uterus with cytological and architectural features reminiscent of endometrial stromal cells are classified as endometrial stromal tumors (EST). The classification of endometrial stromal tumor is difficult and complicated.[1,2] Olive et al. suggested that dividing endometrial stromal sarcomas (ESS) into low grade and high-grade lesions is no longer favored and the term ESS should only be reserved for LGESS.[3] However, since high grade stromal sarcomas (HGSS) failed to show obvious differentiation, many of these tumors might not be of endometrial stromal origin, it has been proposed that these tumors represent monomorphic variants of malignant mixed müllerian tumors. Even, some authors prefer the term of poorly differentiated endometrial sarcoma rather than HGSS for these lesions.[1,2] Thus, the recent World Health Organization Classification of Tumors of the Breast and Female Genital Organs divides the uterine stromal neoplasms into three groups:[4] (i) benign endometrial stromal nodule (ESN); (ii) low-grade endometrial stromal sarcoma (LGESS); (iii) undifferentiated endometrial sarcoma. While LGESS is a clinically indolent malignant neoplasm which shows minimal cytological atypia, infrequent mitotic figures, and numerous thin–walled small arteriolar type vessels, the undifferentiated endometrial sarcoma is a highly agressive tumor that lacks a plexiform vasculature,

features severe cytological atypia, and has frequent and often atypical mitotic figures.[5,6]

ESTs are morphologically heterogenous. When LGESSs show prominent smooth muscle or fibroblastic differentiation, the distinction can be problematic between LGESS and cellular leiomyoma.[2,5] Although distinctive criteria are present, experience with EST is limited, and publicated series are not common.

In this study we presented five EST cases to discuss the diagnostic problems of these rare tumors.

Material and methods

In this study, we obtained five cases from archive of the Department of Pathology of Cumhuriyet University School of Medicine. Total abdominal hysterectomy and bilateral salphingooopherectomy (TAH + BSO) was performed for four cases, and probe curettage (PC) was performed for one case**.** Gross examination notes were found in the surgical pathology reports and clinical information was obtained from the Department of Obstetrics and Gynecology.. We examined every slide available from each case and new HE-stained slides generated from formaline-fixed, paraffin-embedded tissue were reviewed to confirm the diagnoses. Endometrial stromal differentiation was recognized as small cells with scant cytoplasm and round to ovoid nuclei. The accompanying vasculature included spiral arteriole-like vessels, and staghorn vessels**.** Diagnosis of LGESS were based on infiltrative margin and/or vascular invasion, while all ESNs were well circumscribed without an infiltrative margin. Selected representative formalin-fixed, paraffin-embedded sections were used in immunohistochemical studies. Monoclonal antibodies against desmin (clone D33; Dako, Carpinteria, CA, USA), smooth muscle actin (clone 1A4; Sigma, St. Louis, MO, USA), CD34 (class I, clone BI-3C5, Dako, ME USA), CD117/c-kit (clone 104D2, Dako, Carpinteria, CA, USA), CD10 (clone 56C6; Novocastra, Newcastle upon Tyne, UK) and estrogen/progesterone (ER/PR) (clone 6F11 and 16, Novocastra, UK) were applied. All antibodies were ready-to-use for immunohistochemical staining. Avidin-Biotin-Peroxidase complex (ABC) method was performed for IHC staining and AEC (Lab Vision, TA-125-HA) was used as chromogen substance.

Results

Clinical features

The mean patient age was 43 years for ESN and 40 years for LGESS cases. All of the patients had presented abnormal uterine bleeding. Clinical presentation of three cases were submucosal and intramural myoma, one of which has been carried out by PC and other two by TAH + BSO, with bilateral external iliac and obturator lymph node dissection in one. Two of the cases were found incidentally after TAH+ BSO performed for other reasons.

Gross features

For the ESN, the tumors ranged from 1 to 2 cm (mean 1.5 cm) in maximal dimension and were well circumscribed. In two cases of LGESS, the tumor ranged 4 to 6 cm (mean 5 cm) in maximal dimension and both of them grossly presented well-circumscribed mass and resembled leiomyoma macroscopically. Three tumors (2 ESN, 1 LGESS) were polypoid, projected into the endometrial cavity, and described as "submucosal" masses. Two cases (1 ESN and 1 LGESS) were described as "intramural"mass. The cut surfaces were fleshy and uniformly yellow-white**.** None of them had hemorrage, necrosis, cyst and ulceration.

Microscopic features

Microscopically three neoplasms diagnosed as ESN were entirely well circumscribed with a smooth expansile margin. One neoplasm focally had two tongue-like projections and detached satellite nodules expanding into or lying within the adjacent myometrium. These foci were not >3 mm beyond the main border of the tumor. There was no vascular and/or myometrial invasion and mitotic figures**.** Diffuse growth of small cells closely resembling those of the normal proliferative endometrial stroma was the characteristic feature of these tumors. The tumor cells were typicially oval to spindle shaped and small or medium with scant to occasionally more appreciable cytoplasm. The nuclei were uniformly oval to fusiform with inconspicuous nucleoli. No bizarre nuclei and

mitotic figures were detected. Typical arterioles were numerous in two neoplasms. The tumor cells occasionally exhibited a tendency to make whorls around the arteioles (Figure 1). Thick-walled blood vessels were seen in one of ESNs. None of them included smooth muscle and myxoid and hyalinized collagen. Having non-infiltrative margins and showing no vascular invasion and mitotic activity, these tumors were considered as ESN.

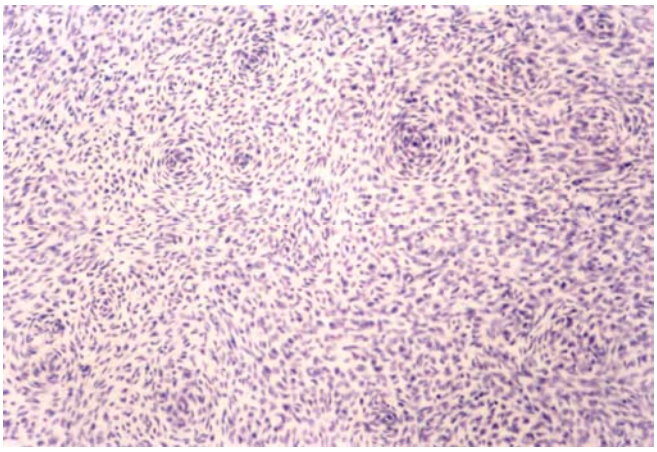

Figure 1. A more prominent network of small vessels surrounded by stromal cells in endometrial stromal nodule (HE; x50)

Two LGESS cases were similar to ESN morphologically, despite showing myometrial and vascular invasion (Figure 2) and mitotic activity in one case. In the latter, obturator lymph node was also involved by tumor and mitotic rate ranged from 3 to per 10 HPFs. In the other case lymph node dissection was not performed and no mitotic figures was found. As there are endometrial stromal differentiation in addition to above-mentioned features they considered as LGESS. Sex-cord like differentiation was also observed in both of the LGESS cases and one of the ESNs. In these areas, the tumor cells were arrenged in anastomosing cords and trabeculae, and showed strong positive immunoreactivity for CD117 and SMA (Figures 3 and 4). Smooth muscle differentiation areas not exceeding 30% of the tumor were shown in two cases and and these areas were positively stained for SMA. In tumor cells, no immunoreactivity for desmin, SMA, CD34, CD117 and ER/PR was detected, howewer, they stained positively for CD10 (Figure 5). Four of the all cases were followed-up for recurrence and metastases, except for the ESN case diagnosed with PC. This patient did not accept operation at our

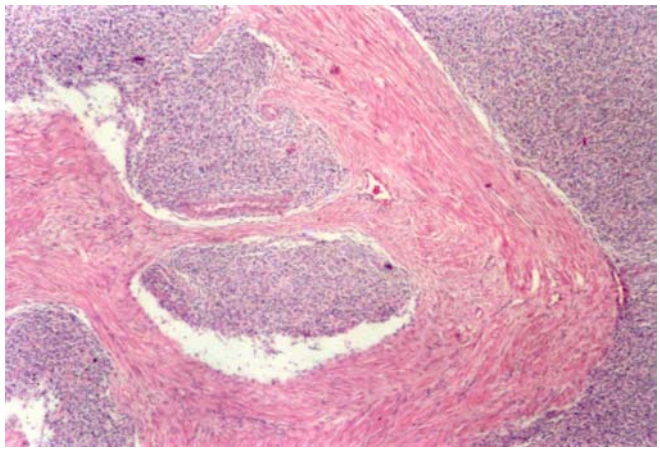

Figure 2. Broad bands of tumor cells diffusely invading the myometrium in LGESS (HE; x10)

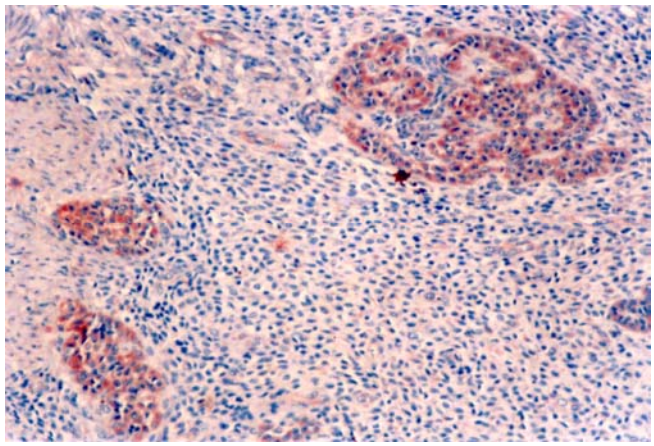

Figure 3. CD117 staining in sex-cord like areas. There is no staining in the tumoral cells (AEC; x50)

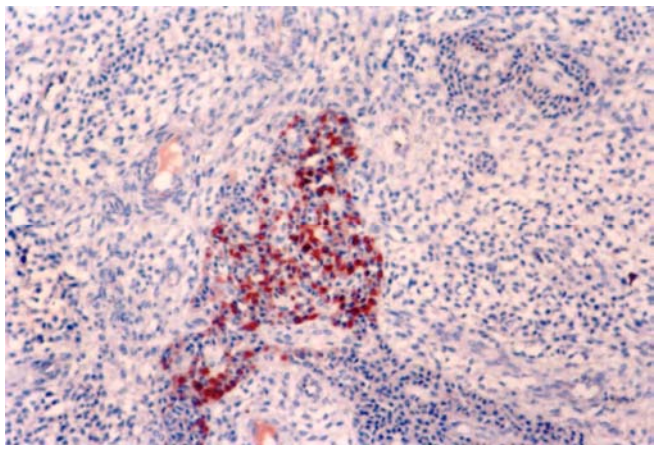

Figure 4. Focal SMA staining in sex-cord like areas in LGESS (AEC; x25)

institution and showed recurrence 10 years after the initial diagnosis. In the other cases, recurrences and metastases have not been observed after treatment.

Discussion

Endometrial stromal tumors are among the least common neoplasms of the uterine corpus, with an

annual incidence of about 2 per million women.[1,2,4] LGESS is a rare tumor of the uterus accounting for only 0,2% of all genital tract malignant neoplasms.[4]

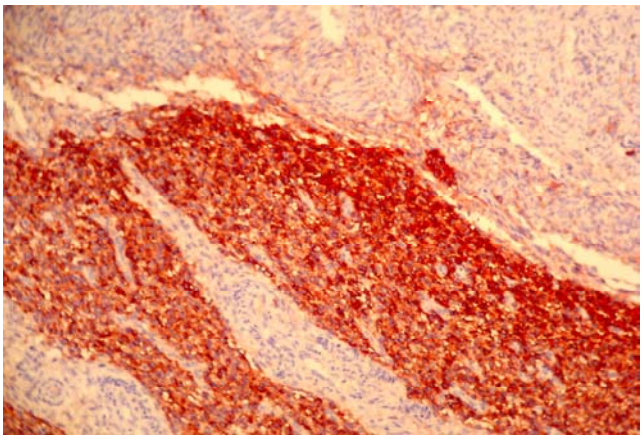

Figure 5. CD10 positivity in LGESS (AEC; x25)

Although a circumscribed and presumptively benign variant of EST was described in the first decade of the last century, it is only in the last few decades that this category of EST has been well-established.[6] Multiple changes in classification and nomenclature of ESTs over the past few years complicate the analysis of the literature. Tumors that were, previously called stromatosis, endolymphatic stromal myosis, stromal hyperplasia, stromaloma, or low-grade endometrial stromal sarcoma would still correspond to today's definition of LGESS.[2,6,7] Endometrial stromal sarcomas have been classified as low grade or high grade based on the mitotic rate, which was initially thought to affect the prognosis.[8] It has been since then recognized that mitotic rate is not prognostically significant and recently, it has been suggested that infiltrative tumors with bland, typical stromal-type cytology should be designated as low-grade stromal sarcoma, regardless of mitotic rate.[1,2,9] The histogenesis of these tumors is still a matter of controversy. Epithelial, sex-cord, and smooth-muscle differentiation have all been proposed by a variety of immunohistochemical and ultrastructural studies.[1,2,4]

Although grossly ESNs are well circumscribed and lack the typically overt permeative infiltration of an ESS, some of them have a little irregularity of the margin and even minimal invasive growth pattern.[2,3,6] Diagoni and associates recommended that these tumors should be dignosed as endometrial stromal tumors with limited infiltration and seperated from conventional ESNs and ESSs at least until knowledge of their behavior is established.[6] One of our cases has limited infiltration into myometrium but its prognosis was unknown. In microscopic examination, although typical vascularity of ESTs facilitates their differential diagnosis, this feature can be inconspicuous on initial examination.[1,2,7,8] Olive et al. emphasized the presence of large thick-walled muscular vessels as a feature that serve to distinguish a highly cellular leiomyoma from a stromal proliferation.[3] IHK is often not helpful because both neoplasms could express muscle actins and desmin. The addition of new immuno-histochemical marcers such as h-caldesmon and CD10 may solve the diagnostic problems. CD10, expressed by lymphoid cell precursors, is a cell-surface neutral endopeptidase and it stains endometrial stroma in the uterus but not glands. Strong and diffuse CD10 staining was observed in ESN and LGESS whereas most leimyomas were negative.[5,10,11] H-caldesmon was claimed as a more sensitive and spesific marker of smooth muscle differentiation in the uterus than desmin.[4,7,10] Between EST and leiomyomas, correct classification is important due to the differences in clinical behavior and treatment. In none of our cases tumoral cells have shown immunoreactivity for desmin, SMA, CD117 and ER/PR, but only sex-cord like spaces were positive for CD117. H-caldesmon could not be performed in this study.

In larger series, ESSs comprise less than 20% of uterine sarcomas and most are LGESS. Although the presence of an EST is sometimes established by curettage, a definitive diagnosis of LGESS can be made if myometrial and/or vascular invasion is identified in the tissue fragments. Nevertheless, a hysterectomy is usually required to permit the thorough evaluation of the tumor margin which is necessary to distinguish a stromal sarcoma from a benign stromal nodüle.[2,12] One of our ESN cases was diagnosed in PC material but the patient did not accept the TAH+BSO operation. In this patient, intrapelvic spread was observed after ten years in another hospital.

Although ESSs resemble nonneoplastic proliferative endometrial stroma, they are morphologically heterogeneous. Fibroblastic and smooth-muscle differentiation may be seen and may erroneously suggest myometrial infiltration. But in

ESTs the muscle cells were often arranged in nodules characterized by a prominent central area of hyalinization with collagen bundles radiating toward the periphery with tumor cells embedded among them (a peculiar form of smooth muscle differentiation in ESTs).[6] If this smooth muscle is misconstrued as myometrial muscle, misinterpretation for invasion and misdiagnosis for ESS could be made for these well-circumscribed tumors. So, correlation with the gross findings and knowledge of the exact site of the section aid in resolving this issue. The main feature that discriminates the ESN from LGESS is the well-delineated, expansile growth at its margine, which contrasts with the infiltrative pattern of LGESSs.[1–3,8] Although thick-walled vessels and the cleft-like spaces are features of cellular leiomyomas, these are not typical for these tumors. Howewer, thick-walled vessels could be shown in peripheral spaces.[2,6,8] If extensive smooth muscle differentiation is present (>30%), the tumor should be classified as a combined stromal-smooth muscle tumor.[1,2,4] Sex cord-like differentiation accounts 5–70% of these tumors. In three tumors of our cases, we observed similar areas and these areas showed positive immunoreactivity for CD117 and SMA but negative for desmin. CD117 system also plays a role in proliferation and differentiation of melanocytes, erythrocytes, germ cells, mast cells and Cajal cells.[13–15] Reviewing the literature, we could not find CD117 immunoreactivity in sex-cord like differentiation areas. In two cases presented by Pang et al., immunopositive staining of the sex cord like areas for desmin and ultrastructural findings may support the concept of smooth muscle differentiation and leading the claim that LGESS with sex-cord like elements might be a consequence of tamoxifen ingestion.[16]

The histogenesis of these tumors is still a matter of controversy. Immunohistochemical and ultrastructural studies have demonstrated epithelial, sex-cord, and smooth muscle differentiation.[4] A few LGESS patients have history of pelvic irradiation and tamoxifen treatment for breast cancer.[4,16] Some authors have claimed that CD117 is expressed by endometrial stromal sarcomas and same others have identified a favorable impact of CD117 expression.[13,15] Howewer, the others have observed that the median and disease-free survival appeared to be adversely affected by the presence of CD117 staining.[17] These contradictions may be explained by differences in antibody manufacturers, technical problems and clonal status of CD117. Mutations could enhance tyrosine kinase activity of CD117 in one of several exons of the c-kit gene resulting in ligand-independent kinase activity and subsequent stimulation of downstream signaling pathways. Exon 11 and 17 appear to be two of the more commonly mutated exons in c-kit tumors positive for KIT protein expression.[13–15] Because of absence of viable therapeutic alternatives for LGESS, some authors have been examined whether imatinib mesylat can be used. This tyrosine kinase inhibitor specifically targets c-Kit and claimed to be a potentially useful agent in the treatment of LGESS.[15] LGESS is charecterized by indolent growth and late recurrences; up to one-half of patients develop one or more pelvic or abdominal recurrences. Surgical stage is the best predictor of recurrences and survival for LGESS. TAH+BSO which is the standart treatment for stage I LGESS decreases recurrence risk.[1,2,4] Riopel et al suggested that the incidence of lymph node involvement in LGESS is higher than expected and more extensive sampling of lymph nodes in a larger number of patients may allow a better understanding of the frequency and prognostic significance of these metastases.[7] Ayhan et al. reported eight cases of endometrial stromal sarcoma of which four had lymph node sampling and none had lymph node metastases.[18] In one of our cases, we observed lymph node metastases and the patient is alive for two years.

Some authors recommend postoperative progestin therapy for LGESS with the hope of reducing the risk of the recurrence. The effectivity of radiotherapy is contraversial and chemotherapy tends to be ineffective.[1,2] Aromatase positive LGESS cases are offered new treatment modalites such as hormonal therapy with aromatase inhibitors.[19]

In summary, when a cellular mesenchymal proliferation is recovered in an endometrial sampling, three issues need to be considered in this setting. The first, what kind of differentiation does the proliferation exhibit (smooth muscle or endometrial)? The second, are the criteria of malignancy sufficient? The third, are there enough samples for accurate diagnosis? When

endometrial stromal differentiation and typically vascularity are present, the most important issue with these tumors is extensively sampling the margine with the adjacent myometrium to exclude the typical infiltrative pattern of an ESS. ESN and EST with limited infiltration must be followed-up in larger series. The important point is that not all cellular, spindle cell proliferations recovered in curettage are stromal sarcomas; the clinically innocuous cellular leiomyoma is a highly probable alternative. We still do not have an ancillary dignostic technique that allows positive identification of endometrial stroma variants which lack classical appearance of endometrial stroma. Immunohistochemistry seems to be a minor tool which confirms the diagnoses established on HE staining. The clinical behavior of the LGESS with sex-cord like differentiation is expected to be same with that of LGESS, and prolonged follow-up is advised. Expression of c-kit is common than expected in LGESS. Due to the limited benefits of adjuvant chemotherapy and radiation especially in CD117 positive cases, the role of tyrosine kinase inhibitors could also be examined as an alternative treatment.

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