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Endometrial Stromal Tumors. A Ten Year Study of Clinical, Morphological and Immunohistochemical Aspects.

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Summary

During a ten year study period from January 1988 to January 1998, a total of twenty-six tumours were diagnosed as being of endometrial stromal origin, out of a total of 69,935 specimens received by the division of surgical pathology of this institute. Patients ranged in age from 29 to 54 years. The tumour was confined to the uterine corpus in 19 patients and was extracorporeal in the remaining seven cases (ovarian in 3, cervical in 1, vaginal in 1, parametrial in 1, and peritoneal in 1 case). Of the 26 cases, 22 were diagnosed as Low-grade Endometrial Stromal Sarcomas (LGSS), one case as High-grade Endometrial Stromal Sarcoma (HGSS) and three as Stromal Nodules – one of which showed sex-cord like areas.

Immunohistochemical staining for Vimentin, Cytokeratin, and Desmin was carried out in 10 of the 26 cases. Vimentin was positive in four cases and cytokeratin in five. Six cases showed focal desmin positivity. The epithelial cell component of stromal tumour with sex-cord like areas showed positive staining with both vimentin and cytokeratin.

Introduction

Endometrial stem cells of Mullerian origin have the potential to differentiate into epithelial cells, stromal cells or both (Fox 1995). Tumours derived from such cells may be purely epithelial, purely mesenchymal or mixed. Tumours pursuing the mesenchymal pathway can differentiate not only into endometrial stroma but also into mesenchymal elements not normally present in the uterus. Non-epithelial purely mesenchymal tumours may be pure or mixed and tumours with mesenchymal components may further be classified as homologous or heterologous. Pure homologous non-epithelial tumors are formed of cells which to a greater or lesser degree resemble the stromal cells of normal proliferative endometrium.

Norris and Taylor (1966) in their classical study in 1966 defined endometrial stromal neoplasms to be "composed of cells identical to or closely resembling those of endometrial stroma". The cells should be uniform in size, shape and staining character. The classification proposed by Norris and Taylor (1966) is still considered as standard. Endometrial stromal neoplasms are classified as non-invasive stromal nodules, and invasive stromal sarcomas-the latter being further grouped as low-grade and high grade on mitotic activity. Endometrial stromal nodules are by far the least common of the stromal neoplasms (Silverberg and Tabbara 1997), are clinically benign and are of interest mainly by virtue of problems in diagnosis.

Most studies deal mainly with endometrial stromal tumors confined to the female genital tract. Few reports have dealt exclusively with extra-uterine tumours. Ulbright and Kraus (1981) report three extra uterine tumours unassociated with endometriosis of which two occurred in the retroperitoneum and one in the vagina. This study deals exclusively with endometrial stromal tumours ie. pure homologous non-epithelial tumours of uterus and extrauterine sites and is aimed at highlightin

the varied clinical and morphological aspects of endometrial stromal tumours. A brief review of relevant literature is also included.

Material and methods:

The study was partly retrospective and partly prospective in nature. Cases which were coded as endometrial stromal tumours in our files were extracted from January 1988 to January 1998. All cases were reviewed and classified on the basis of clinical data, morphological aspects and any other relevant information which was available. Clinical information was abstracted from patient's charts and the referring physician was contacted for additional information wherever possible. Slides were stained with H & E stain. Special stain to demonstrate the reticulin pattern was applied whenever necessary. Immunohistochemical staining for vimentin, desmin and cytokeratin was done in 10 cases using the Enhanced Polymer One Step (EPOS) staining kit from Dakopatts Denmark. All slides were viewed first independently and then collectively by three of the authors (NJ, SRP, ST).

Results

Most cases were seen in the age group of 30-50 years and low-grade stromal sarcoma was the most common neoplasm encountered (84.62%). Stromal nodules presented as tan-yellow nodules averaging 3 cms in greatest diameter. Low-grade stromal sarcomas varied in appearance from nodular tan-yellow masses to diffuse myometrial thickening (fig. 1), to poorly delineated yellow areas. The clinical and morphological details are described in tables I to IV.

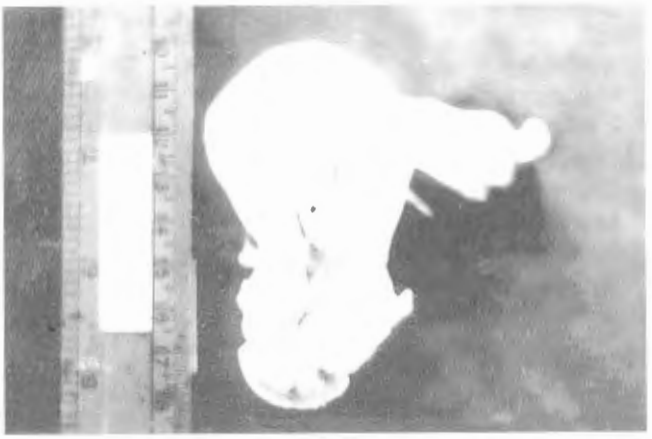

Fig. 1 Gross photograph of low grade endometrial stromal sarcoma showing thickening of myometrium along with pale yellow nodular areas.

Immunohistochemical staining was performed

Table I. Endometrial Stromal Tumours. Age-wise distribution of different lesions.

Age (yrs)	No. of Cases	Stromal Nodule	LGSS	HGSS
< 30 yrs	2	1	1	-
30-50 yrs	18	2*	15	1
> 50 yrs	6	-	6	-
Total	26	3	22	1

Sex-cord like areas seen in one case.

Table II. Endometrial Stromal Tumours. Anatomical Location.

Site	Stromal Nodule	LGSS	HGSS	Total
Uterus	3	15	1	19
Cervix	-	1	-	1
Vagina	-	1	-	1
Ovary	-	3	-	3
Parametrium	-	1	-	1
Peritoneum	-	1	-	1
Total	3	22	1	26

Table III. Endometrial Stromal Tumours. Gross Appearances.

Uterine Corpus:	
Nodular tan-yellow mass (4 LGSS, 3 stromal nodules)	7
Diffuse myometrial thickening	10
Poorly demarcated yellow-white areas	2
Ovary: Well demarcated yellow-white areas with cystic spaces	3
Cervix: Polypoid Yellowish white growth	1
Vagina: Yellowish nodular mass	1
Parametrium & Peritoneum : Grey-yellow nodule with hemorrhages	1 each.

Table IV. Endometrial Stromal Tumours. Microscopic features.

Stromal Nodule:	
Uniform spindle cells with evenly distributed blood vessels	2
Uniform spindle cells with tubular and cord-like areas	1
LGSS:	
Uniform spindle cells with low mitotic index	22
Lymphatic invasion	22
Prominent vascular pattern	20
Star-burst hyalinisation	11
Foam cell aggregates	1
HGSS:	
Plump cells with high mitotic index and areas of necrosis	1

in 10 of the 26 cases. Desmin was positive at least focally in six cases, cytokeratin in five and vimentin in four cases. The epithelial like areas of endometrial stromal nodule with sex-cord like areas showed positive reaction to both vimentin and cytokeratin.

Discussion

Endometrial stromal tumours are rare neoplasms (Silverberg and Tabbara 1997). They are best classified according to the classic study by Norris and Taylor (1966). The stromal nodule is a benign proliferation of cytologically bland endometrial stromal cells in which the margins of tumour are pushing (Tavasolli and Norris 1981). No evidence of lymphatic invasion should be present. They are the least common of endometrial stromal tumours. Only three stromal nodules were encountered among 26 cases of endometrial stromal tumours (11.54%). All these tumours were limited to the uterus, averaged 3 cms in diameter and had tan-yellow appearance on cut surface. Similar features were noted by Norris and Taylor (1966), and Tavasolli and Norris (1981). Histologically, the stromal nodule closely resembles normal endometrial stroma with evenly distributed blood vessels. The endometrial stroma can at times form a variety of gland like structures some of which can mimic ovarian sex-cord elements. Silverberg and Tabbara (1997) quote an incidence of 25%. If these predominate, the term "Uterine tumour resembling ovarian sex-cord tumour" has been used. The epithelial component of these neoplasms usually stains positively for vimentin and cytokeratin (Clement and Scully 1988). We report one case of endometrial stromal nodule with sex-cord differentiation in a 29 year old woman who underwent hysterectomy for severe cervicitis and a bulky uterus. The gross appearance was that of a tan yellow nodule in the myometrium measuring around 4 cms in maximum diameter. Microscopically, uniform spindled cells were seen closely admixed with tubular and cord like structures of rounded cells (fig. 2). The cells comprising these cord like areas stained positively for both vimentin and cytokeratin.

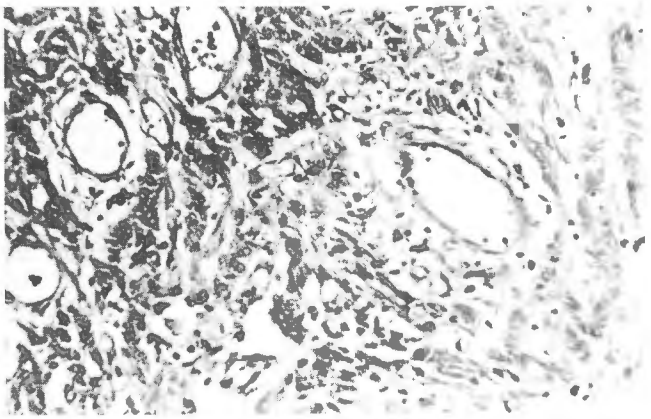

Fig. 2 Endometrial stromal tumour with sex-cord like areas showing cords of epithelial like cells (H & E stain) (x 400)

In our series, the predominant endometrial stromal tumor was the low-grade stromal sarcoma which was found in 22 of the 26 cases (84.62%). This is in concurrence with the observations of Chang et al (1990), Mahmood and Thomas (1988), and Hart and Yoonesi (1977). In our study, LGSS occuring in the uterus varied in gross appearance from tan yellow nodules (4 cases) to diffuse myometrial thickening (10 cases) to poorly demarkated yellow areas (1 case). All the cases of LGSS showed presence of lymphatic invasion (fig. 3). Mitotic index was between 3 and 6. Around 90% of LGSS showed prominent blood vessels (fig. 4), and 50% showed "star-burst" hyalinisation (fig. 5). Chang et al (1990) note the incidence of hyalinisation to be 42%, while it was 44% in the series of Hart and Yoonesi (1977). The only case of high grade stromal saracoma in our study showed a mitotic index of 12 and the cells were pleomorphic with coarse chromatin and prominent nucleoli. Areas of necrosis were also seen. Similar observations were made by Tao (1993).

Endometrial stromal tumours can also be extra-uterine in location. We report seven cases occuring primarily outside the uterine corpus of which three were in the ovary, one in the cervix, one vaginal and one each

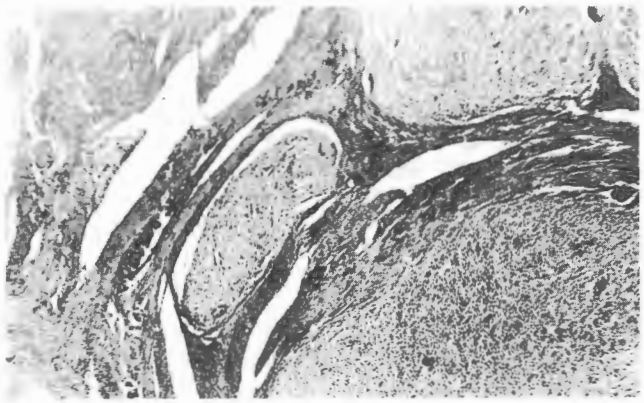

Fig. 3 Low grade stromal sarcoma showing tumor islands inside lymphatic channels in the myometrium. (H & E stain) (x 100)

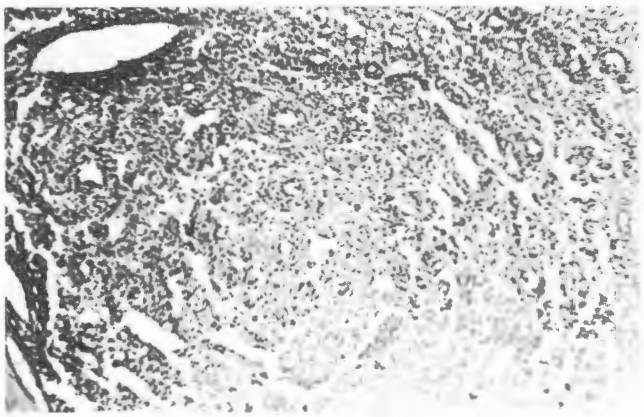

Fig. 4 Prominence of capillaries seen in endometrial stromal tumors. (H & E stain) (x 400)

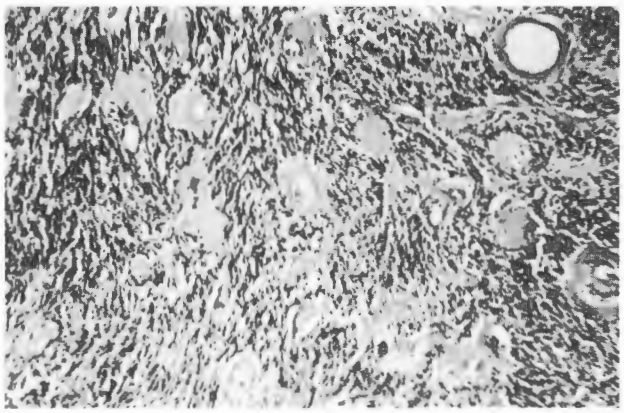

Fig. 5 Endometrial stromal tumor showing "star-burst" hyalinisation pattern. (H & E stain) (x 400)

in the peritoneum and parametrium. Ulbright and Kraus (1981) report 3 extra-uterine stromal tumours unassociated with endometriosis – two occuring in the retro-peritoneum and one juxta-vaginal. In our study, stromal tumours arising anatomically outside the female genital tract were detected incidentally when hysterectomy was performed for other reasons. The stromal tumour arising from the peritoneum showed aggregates of foam cells – a finding which has been noted with some consistency in endometrial stromal tumors (Ulbright and Kraus 1981, Hart and Yoonesi 1977). The vaginal nodule was sent as a growth which was excised from that area. The ovarian tumors were also detected incidentally on examination of hysterectomy specimens. None of the extra-uterine tumors had associated tumors in the uterus.

Reports on immunohistochemical staining properties of endometrial stromal tumours reflect inconsistency. While the normal stromal cells of endometrium were found to show a negative reaction for actin, desmin, vimentin, S-100 protein, and cytokeratin; stromal tumours have been found to give different positive reactions (Devany and Tavasolli 1991). Binder et al (1991) report positive staining for vimentin, cytokeratin in 50% of stromal tumours with consistently negative staining for desmin. Lin and Tan (1992) report myogenous rather than epithelial phenotype in stromal tumours with sex-cord like areas, whereas Clement and Scully (1988) report an epithelial phenotype. Our finding in one case concurs with that of Clement and Scully (1988). Focal desmin positivity was encountered in 60% of our cases. This probably reflects on focal myogenic differentiation of endometrial stromal tumors which is known to occur (Chang et al 1990).

Among the clinical features, abnormal uterine bleeding and pain were the most common presenting symptoms. Similar findings have been reported in other studies (Chang et al 1990, Hart and Yoonesi 1977, Sanyal et al 1994). Endometrial stromal tumours have been found most commonly in the age group of 30 to 50 years in our series – a much younger age group when compared to other reports from the west Dinh et al (1989). Cherian et al (1995) have reported occurrence at a younger age – a probable reflection of geographical variation. Presence of heterotopic Mullerian tissue outside the female genital tract may be possible intermediary and explain the occurrence not only of Mullerian neoplasms but also of teratomas at ectopic sites (Ulbright and Kraus 1981). In the present study, five cases of endometrial stromal tumors had associated endometriotic foci lending credence to this concept.

Conclusions:

Endometrial stromal tumours were found to be rare neoplasms and involved women more often between the ages of 30 and 50 years. Abdominal uterine bleeding and pain were the commonest clinical manifestations. Low grade stromal sarcoma was the commonest

neoplasm encountered in this group and all of these showed lymphatic invasion. A fair number (7/26) of tumours occurred primarily outside the uterine corpus.

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