Endometrial stromal neoplasia: An uncommon tumor at a tertiary health centre in coastal India

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ABSTRACT

Introduction and Aim: Stromal malignancies of uterus are rare and accounts for 1-3% of all female genital tract malignancies. They are known to pose a diagnostic challenge to the clinicians and the pathologists. They show non-specific clinical features, gross appearance, varying histological and immunohistochemical features. This study highlights the important clinical, morphologic and immunohistochemical features of these tumors.

Methodology: Histopathologically diagnosed cases of endometrial stromal neoplasia over a period of 5 years from 2013 to 2017 were retrieved. The cases were analysed based on age, tumor size and histological types. Immunohistochemistry (IHC) was done whenever feasible.

Results: During the study period, we found 25 cases of endometrial stromal neoplasia. They were composed of four cases of endometrial stromal nodule (ESN), six cases of low grade endometrial stromal sarcoma (ESS) and three cases of ESS with smooth muscle differentiation. Twelve cases of carcinosarcomas and adenosarcomas and a single case of undifferentiated uterine sarcoma were seen. The mean age at presentation of Mixed epithelial stromal sarcoma (Carcinosarcoma) was 61 years while that of ESS and ESN was 46 and 47 years respectively. The mean size of ESN was 3.6 cm (1.5-6 cm), ESS was 4.5 cm (2.9-9.9 cm) and carcinosarcomas was 4.9 cm (2.5-16 cm).

Conclusion: Endometrial stromal neoplasia should be diagnosed after proper evaluation of gross morphology, histological features and immunohistochemical findings in correlation with the clinical presentation. In addition, genetic profiling is useful as an ancillary test. The spectrum of endometrial stromal neoplasia is a beginner’s ordeal if not aware of.

Keywords: Endometrial stromal neoplasia; undifferentiated uterine sarcoma; CD10; Carcinosarcoma.

INTRODUCTION

Stromal malignancies of the uterus are rare and account for 1-3% of all female genital tract malignancies. They are known to pose a diagnostic challenge to the clinicians and the pathologists. They show non-specific clinical features, gross appearance, varying histological and immunohistochemical features. World health organization (WHO) has classified the endometrial stromal tumors into four main categories such as endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (ESS-LG), high-grade endometrial stromal sarcoma (ESS-HG) and Undifferentiated Uterine Sarcoma (UUS). Mixed epithelial mesenchymal sarcomas are also seen (1, 2). This study documents the important clinical, morphologic and immunohistochemical expression of these tumors in our setup.

MATERIALS AND METHODS

Histopathologically diagnosed cases of endometrial stromal neoplasia received in the department of Pathology of a tertiary care hospital over a period of 5 years from 2013 to 2017 were retrieved. The gross and microscopic features were analysed. The clinical data was collected from the medical records department. The cases were classified into ESN, ESS-Low grade, ESS-High grade, Undifferentiated sarcoma, and mixed epithelial mesenchymal sarcomas as per WHO classification of tumors. Frequency of such histological subtypes were analysed. Immunohistochemistry (IHC) was done whenever feasible.

RESULTS

During the study period, we found 25 cases of endometrial stromal neoplasia (Table 1). They are composed of four cases of ESN, six cases of low-grade ESS, three cases of ESS with smooth muscle differentiation and
differentiation and one case of undifferentiated uterine sarcoma. Twelve cases of high grade mixed epithelial and mesenchymal sarcoma composed of carcinomas and adenosarcomas were seen.

**Table 1: Characteristics of endometrial stromal neoplasia**

<table>
<thead>
<tr>
<th>Types</th>
<th>N (%)</th>
<th>Mean age (years)</th>
<th>Mean size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESN</td>
<td>4 (16)</td>
<td>47.5</td>
<td>3.6 (1.5-6 cm)</td>
</tr>
<tr>
<td>ESS</td>
<td>9 (36)</td>
<td>46.5</td>
<td>4.5 (2-9.9 cm)</td>
</tr>
<tr>
<td>Undifferentiated uterine sarcoma (UUS)</td>
<td>1 (4)</td>
<td>36</td>
<td>6.0</td>
</tr>
<tr>
<td>Mixed epithelial and mesenchymal tumor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adenosarcoma</td>
<td>3 (12)</td>
<td>46.5</td>
<td>7.8 (5-13 cm)</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>8 (32)</td>
<td>61</td>
<td>4.9 (2.5-16 cm)</td>
</tr>
<tr>
<td>Total</td>
<td>25(100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1:** AB: Endometrial stromal nodule (ESN) is composed of cells resembling a proliferative phase of endometrium with uniform nuclei of round to oval shape and scanty cytoplasm. Nuclear atypia is minimal. These neoplastic cells are arranged around thin-walled blood vessels (B). CD: Endometrial stromal sarcoma (ESS) low grade shows tumor islands of atypical endometrial stromal cells with extensive invasion of the myometrium. The nuclei are often oval to spindle shaped and mitotic activity being low (<5/10 hpf) with absence of necrosis. The vascular network is rich in the stroma with tumor cells arranged around these vessels. The vessels may be hyalinized. EF: Immunohistochemical expression of CD10 (E) and smooth muscle actin (SMA)(F) in ESS.

**Endometrial stromal sarcoma**

ESS was the most common endometrial stromal neoplasia encountered in our study (9 cases, 36%). The mean age of presentation was 46.5 years ranging from 40-57 years. Most of the cases presented with endometrial poly (66.7%) while others showed presence of intramural nodule (33.3%). The size ranged from 2 cm to 9.9 cm. Three cases showed ESS with smooth muscle differentiation which was proved by immunohistochemical expression of CD10, smooth muscle actin (SMA), and desmin in tumor cells. These cases had associated lesions such as bilateral low grade mucinous cystadenocarcinoma, Brenner tumor and endometriosis of the ovary and leiomyoma of the uterus (Fig. 1 AB).

**Endometrial stromal nodule**

We encountered 4 cases (16%) of endometrial stromal nodules. The mean age of presentation was 47.5 years. These patients did not have significant clinical symptoms of menorrhagia. They were incidentally detected in hysterectomy specimens. Two cases showed presence of intramural nodule while other 2 cases presented with polyp. The size of the nodule ranged from 1.5 cm to 6 cm. These cases had associated lesions such as mucinous cystadenoma and borderline mucinous tumor of the ovary and leiomyoma of the uterus (Fig. 1 AB).

**Fig. 2:** A-D. Carcinosarcoma shows tumours comprising hyper and hypocellular areas with morphology of high-grade tumour cells. The high-grade cells exhibit nested to cord-like growth patterns. Round epithelioid cells, eosinophilic cytoplasm, irregular nuclear contours with pleomorphic vesicular nuclei and some with nucleoli were seen. Mitosis of >10/10 hpf was evident. EF: Adenosarcoma consisting of atypical stromal cells giving a pseudo papillary and glandular appearance. GH: Undifferentiated uterine sarcoma revealed sheets of atypical medium sized cells having vesicular to hyperchromatic nuclei with brisk mitosis of >2/hpf with extensive areas of necrosis.
Undifferentiated uterine sarcoma

We encountered one case of undifferentiated uterine sarcoma in a 26-year-old female who presented with menorrhagia. Her initial biopsy was done 9 months before which showed stromal hyperplasia with few mitotic figures. After 9 months she developed severe bleeding and this time the curetting’s showed a high-grade uterine sarcoma. Immunohistochemical analysis showed positivity for INI-1, vimentin and MIB (50%) and negative IHC for CD10, CD45, SMA, desmin, CD34, CK, ALK, S100, CD31, EMA and myogenin (Fig. 2 GH).

Mixed epithelial and stromal sarcoma

We encountered 11 cases of mixed epithelial stromal tumor, composed of 3 cases of adenosarcoma (Fig. 2 EF) and 8 cases of carcinosarcoma (Fig. 2 A-D). The mean age of presentation of carcinosarcomas was 61 years while that of adenosarcoma was 46.5 years. The mean size of carcinosarcomas was 4.9 cm (2.5-16 cm) and adenosarcoma was 7.8 cm (5-13 cm). One case of adenosarcoma showed positivity for CD 10, Vimentin, ER and PR.

DISCUSSION

Endometrial stromal tumors are currently categorized by WHO 2014 as endometrial stromal nodule (ESN), endometrial stromal sarcoma, low-grade (ESS-LG), endometrial stromal sarcoma, high-grade (ESS-HG), and undifferentiated uterine sarcoma (UUS). Mixed epithelial and stromal tumors are classified as adenomyoma, adenofibroma, adenosarcoma and carcinosarcoma (2). These main categories of stromal tumors have been documented and evident in the present study.

The ESN comprised 3 cases with 2 cases in postmenopausal age group and one in the young adult and were mainly polyoid masses in the uterine cavity in 2 cases and one older patient of 60 years had intramural mass of 3.5 cm size. As described in literature, these nodules are well circumscribed, tan to yellow in color and have soft consistence. Histologically these nodules have circumscribed borders with occasional lobulated projections into adjacent myometrium. The criteria followed is less than 3 in number with ≤ 3 mm in size. The stromal nodule is composed of cells resembling the proliferative phase of endometrium with uniform nuclei of round to oval shape and scanty cytoplasm. Nuclear atypia is minimal. These neoplastic cells are organized around thin-walled vascular channels. These vessels are uniform in calibre and are evenly spaced in the neoplasm. A few foci of thick-walled blood vessels may be evident occasionally. IHC for CD10 is often positive. These patients usually have a good prognosis; however, it is important to extensively sample the interphase between the endometrium and stroma to look for a permeative pattern and lymphovascular invasion to rule out a low-grade sarcoma lurking behind (1,2).

ESS-LG is the second most common uterine stromal tumor with clinical manifestation of abnormal uterine bleeding or lower abdominal mass extending into the pelvis or symptoms of extra-uterine spread. The tumor often presents with multiple, ill-defined, irregular, yellow to soft tan nodules within the uterus. Tumor plugs within the vessels can be seen in parametrial soft tissue. Microscopically the tumor is composed of islands of atypical endometrial stromal cells with extensive invasion of the myometrium. The nuclei are often oval to spindle shaped and mitotic activity being low (<5/10 hpf) with absence of necrosis. The vascular network is rich in the stroma with tumor cells arranged around these vessels. The vessels may be hyalinized. Foci of histiocytes and collagen bands are also evident in the stroma. This tumor can show varied histological features. Few tumors show smooth muscle differentiation, often seen as nodules with central core of hyalinization. The peripheral radiating collagen bands encircle the tumour cells giving it a ‘starburst’ pattern. These tumors may show epithelioid or rhabdomyosarcoma like differentiation, endometrioid glands, sex cord tumor like differentiation resembling granulosa cell and Sertoli cell tumours, fibroblastic proliferation and myxoid change in the background. Immunohistochemically, the tumor cells are typically positive for smooth muscle actin (SMA), CD10 and occasionally for desmin. Genetic profile of most of these tumours exhibits t (7,17) (p15; q21) which results in a fusion of SUZ12 and JAZF1 genes. This translocation is seen in most of ESN and ESS-LG tumours. Involvement of two zinc finger genes at the specific translocation t (7,17) is described in most of the ESS (1,2,3,4).

Landreat et al., (5) evaluated ten cases of ESS-LG over a period of seventeen years and documented the mean age of presentation was 50 years in their study. The clinical presentations were similar to the present study. This low-grade tumour had frequent recurrences in his series (70%). The risk factors of obesity, hypertension and diabetes were documented. IHC expression for CD10 helped in resolving the diagnostic dilemma between smooth muscle tumor such as leiomyoma and endometrial sarcoma. Further, desmin and h-caldesmon will be negative in ESS. ESS-LG shows progesterone receptor isoform expression. This hormone dependant tumors was earlier treated with surgical castration. This has been documented by Gloor et al., and Li et al., (6,7). High positivity of hormone receptors such as progesterone and estrogen are indications for adjuvant hormone therapy for preventing recurrences of the tumor. Aromatase inhibitors and progestins are recently prescribed in stage I and II tumor (5).

Eight cases of high grade carcinosarcomas were seen at the mean age of 61 years in the present study, of
which two were collected as endometrial curetting’s and other cases had hysterectomy performed. The tumour manifested as a polypoid intra cavity mass with myometrial invasion. Microscopically, the tumour comprises of hyper and hypocellular areas with morphology of low grade and high-grade tumour cells. The high-grade cells had nested to cord-like growth patterns. Round epithelioid cells, eosinophilic cytoplasm, irregular nuclear contours with pleomorphic vesicular nuclei and some with nucleoli were seen. Mitosis of >10/10 hpf was evident. The hypocellular areas showed similar morphology of low-grade sarcomas with focci of fibroblastic and myxoid areas. On IHC, CD10 was positive in the low-grade years and cyclin D1 showed strong and diffuse positivity in high grade areas with negativity for CD10 and hormone receptors. To distinguish high grade stromal sarcomas from low grade ESS, destructive myometrial invasion with necrosis and presence of both morphologically low- and high-grade areas favour the diagnosis of high-grade stromal sarcoma. The high-grade areas have a distinct larger population of epithelioid cells in nested or corded patterns. The vascular pattern of the stroma of these larger cell areas is delicate and arborized. Mitotic activity is high. Molecular testing of high-grade ESS is characterized by t (10;17). Epithelioid leiomyosarcoma is another diagnostic dilemma to be distinguished from high grade ESS. The morphology of the cells varies from large to spindle component in epithelioid leiomyosarcoma. IHC is positive for desmin, caldesmon and negative for cyclin D1(1-3). The discovery of t (10;17) results in fusion of YWHAE and NUTM2 genes (8,9).

UUS occurred in a young female of 26 years with polypoidal masses in the uterine cavity and endocervix. Though it occurs in post-menopausal women, our case is unusual for the early presentation. The endometrial curettings received on first biopsy showed stromal hyperplasia with few mitotic figures, a year later she manifested with persistent bleeding and the biopsy sample revealed poorly differentiated endometrial sarcoma with sheets of atypical medium sized cells having vesicular to hyperchromatic nuclei with brisk mitosis of >2/hpf, extensive areas of necrosis. Myometrial invasion and vascular invasion was evident. The IHC revealed diffuse strong positivity for vimentin, INI-1& Ki67 of 50%. The other immune stains commonly done for endometrial sarcomas were all negative. However, she was lost to follow up. The two histological appearances of UUS are uniform and pleomorphic type (10). The uniform type has overlap with high grade ESS with a translocation of t (10;17), the pleomorphic type shows destructive infiltration of myometrium with pattern less tumour growth. It comprises highly pleomorphic cells with positivity for CD10, cyclin D1 and p53. The prognosis for UUS-pleomorphic type is survival <2 years (1-3).

Uterine sarcomas at the regional cancer centre of North India found the median overall survival to be 7.67 months and 1-year actuarial survival of 45.4%. Median survival in patients with ESS and UUS were 18.7 and 9.38 months (11). The differential diagnosis of endometrial neoplasia encompasses benign lesions such as adenomyosis, cellular leiomyoma, cellular endometrial polyp, and malignant lesions such as low-grade Mullarian adenosarcoma (12).

CONCLUSION

Endometrial stromal neoplasia should be diagnosed after proper evaluation of gross morphology, histological features and immunohistochemical findings in correlation with the clinical presentation. In addition, genetic profiling is useful as an ancillary test. The spectrum of endometrial stromal neoplasia is a beginner’s ordeal if not aware of.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

REFERENCES