Case Series

A Case Series of Endometrial Stromal Sarcomas : A Relook at a rare kind of Uterine Malignancy

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Endometrial Stromal Sarcomas (ESS) exhibits a very rare breed of uterine malignancy which comprises 10% of all uterine sarcomas but only around 0.2% of all uterine cancers. Depending on mitotic activity, vascular invasion or clinical outcome, broadly there are three varieties of Endometrial Stromal Tumours : Endometrial Stromal Nodule, Low-grade Endometrial Stromal Sarcoma, High-grade Endometrial Stromal Sarcoma. Our small series consists of five cases of ages ranging from 28 to 48, all of whom have been histologically and immunohistochemically diagnosed with low grade endometrial stromal sarcoma. The most common symptom out of all cases that warranted patient's attention was Abnormal Uterine Bleeding (AUB) bringing them to clinician and all underwent total hysterectomy and their specimen was finally diagnosed with low grade endometrial stromal sarcoma. Data from prospective or large randomized studies are still lacking due to the rarity of these tumours. Surgery represents the standard treatment for this disease. For uterus-limited disease (early stage), the en bloc resection of the tumour is strongly recommended which more or less necessitates total hysterectomy which is curative for early diseases. While all cases had nonspecific symptoms, underwent total hysterectomy as for presumed benign diseases and the eventual diagnosis in favour of stromal sarcoma were incidental, the principal purpose of this presentation is to evoke a sense of high degree suspicion of such rarity in the arena of uterine malignancy and an interest towards making an algorithm of diagnosing such malignancy known to have varied spectrum and outcome.

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Endometrial Stromal Sarcoma (ESS) is a rare mesenchymal neoplasm of uterus with occurrence of 10% of all uterine sarcomas and approximately 0.2% of all uterine malignancies[1]. Thanks to this rarity, sources of most of the relevant information are small series or case reports as available in online literature. With most clinical symptoms and other presentations being nonspecific, proper pre-operative diagnosis is unlikely and most cases are diagnosed in pathological laboratory after Histopathological Examination (HPE) and Immuno-histochemistry (IHC)[2].

For uterus-limited disease, en bloc removal of the tumour without morcellement is strongly recommended. Total hysterectomy with bilateral salpingo-oophorectomy (TAH & BSO) is the main line of management and complete cure is a reality for early cases. For advanced-stage disease, the standard surgical treatment is adequate cytoreduction with metastatectomy. Although endometrial sampling, ultrasound and magnetic resonance imaging can provide diagnostic clues but in most cases final diagnosis is made over hysterectomy specimen done for a presumed benign disease.

The WHO has broadly classified endometrial stromal tumour into benign Endometrial Stromal Nodule (ESN) and malignant Endometrial Stromal Sarcoma . Again malignant ESS can be Low-grade and High-grade. Here, we present a small yet significant series of 5 cases of low grade endometrial stromal sarcoma as diagnosed in our institution in last three years (2018-2021).

Editor's Comment :

- While the symptoms of per vaginal bleeding or uterine mass, points towards uterine fibroid or adenocarcinoma in most of the cases, endometrial stromal sarcoma is rarely suspected, specially when it is confined to the uterus. So, to avoid misdiagnosis and delay in treatment, importance of high degree suspicion, total hysterectomy with staging of the tumour and confirmation by IHC is paramount.Thus, despite the rarity or infrequent occurrence, case reporting or case series publication should be encouraged to avoid under-reporting of such cases.

Case Series

All five cases in our series fell in the age group of 28-48 years and they presented themselves to the gynaecology Outpatient Department (OPD) with cardinal complaint of Abnormal Uterine Bleeding (AUB) mostly. Suprapubic mass was often the presentation. Clinico-radiologically, all cases were diagnosed as fibroid, none of them had any features of extra uterine or metastatic disease and total abdominal hysterectomy with bilateral salpingo-oophorectomy had been successfully done in all cases. Surgical Specimens of them were sent to our pathology department for histopathological examination.

On first vision, tumour location, size, and gross appearance were noted and corroborated with operative notes. After conventional haematoxylin and eosin-based

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staining and fixing, we applied the proposed 2003 World Health Organization Classification criteria for the diagnosis of primary uterine ESS: oval or round, uniform cells resembling those of proliferative-phase endometrial stroma accompanied by a distinct vascular pattern (ie, small vessels resembling spiral arterioles of the endometrium), with an infiltrative border (finger-like projections extending >3 mm from the border of the mass into surrounding tissue) and/or vascular invasion. The following histopathologic characteristics were recorded: tumour contour (mostly well circumscribed vs. mostly infiltrative), presence of typical ESS vascular pattern and its extent (focal *versus* diffuse), presence or absence of pleomorphism (variation of nuclear shape and size that could be detected at intermediate magnification), fibroma-like stroma (absent, focal, or diffuse), presence or absence of vascular invasion, Mitotic Index (MI) obtained in the most mitotically active area by counting 10 consecutive High-power Fields (HPF), sex cord elements (absent *versus* present and extent), smooth muscle differentiation (absent *versus* present and extent) and the presence or absence of nuclear grooves, prominent myxoid change, edema, necrosis, hyaline plaques, endometriosis, foamy cells, cytoplasmic clearing, epithelioid features, calcifications, glandular differentiation and other unusual features[3].

All specimen were staged pathologically according to FIGO classification, IHC were done to all cases for ER receptor and CD 10 & vimentin. Apart from active participation and supervision by two senior pathologists, we collected relevant information from clinicians, medical records and attending oncologists.

Case 1

A 28 years old P(2+1) female attended Gynaecology OPD with complaint of gradual distension of abdomen for 6 months and her radiological investigations (CECT and USG) revealed a large predominantly solid abdomino-pelvic mass measuring (21.7×17.4×11.3) cm. Uterus and ovaries were not seen separately. After TAH & BSO, the received specimen revealed on gross examination, a tumour mass in the right side of uterine fundus measuring (25×23×12) cm. Cut section of tumour mass showed solid, cystic and haemorrhagic areas. Cervix and bilateral adnexa appeared free on gross (Fig 1a).

On microscopic examination, endo-myometrium showed histopathological features of proliferative stroma with tumour arising from it and invading myometrium (>50%). Irregular, densely cellular Islands of tumour cells with diffuse growth were seen permeating the myometrium in a classical tongue like pattern (Fig 1b). No lympho-vascular invasion was seen. Tumour cells had uniform, oval to fusiform nuclei with mild atypia with scanty cytoplasm with low mitotic activity. Tumour cells were seen whorled around the spiral arterioles.

According to the new 2009 FIGO Staging, it was stage IB disease and AJCC 8th edition PT1bNx. Immuno-histochemistry (IHC) for CD10 showed diffuse cytoplasmic positivity (Fig 1c) while oestrogen receptor showed patchy nuclear positivity (Fig 1d) Postoperative period was uneventful. Patient was discharged after 5 days. On follow-up patient, patient was on tamoxifen therapy and there was no evidence recurrence on further follow-up.

Case 2

The USG of this 45years old female patient revealed a large intramural fibroid. Gross examination of her TAH BSO specimen showed one large intramural fibroid projecting into the endometrial cavity and extending up to cervical canal measuring (11x10x5) cm. Cut section revealed solid whitish whorling pattern. On microscopy, endometrium showed features of non-secretory

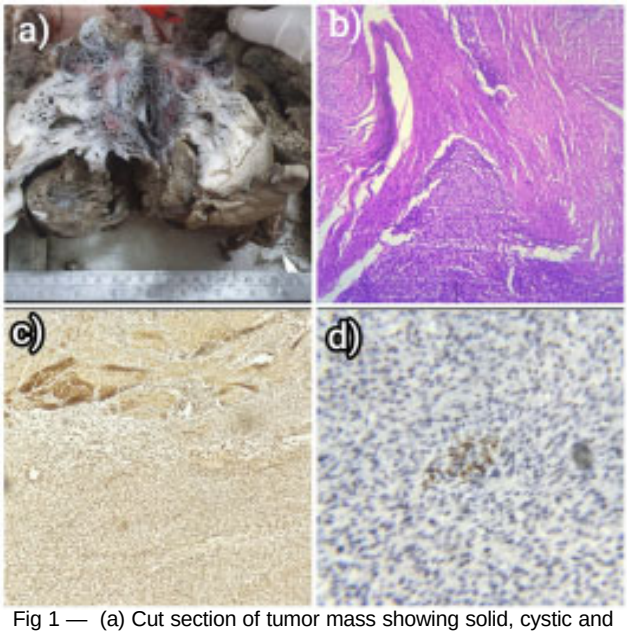

Fig 1 — (a) Cut section of tumor mass showing solid, cystic and haemorrhagic areas. (b) Tumor cells permeating into myometrium (H&E stain, 100x). (c) Diffuse Cytoplasmic CD10 positivity of tumor cells (100x). (d) Patchy nuclear ER positivity of tumor cells (100x).

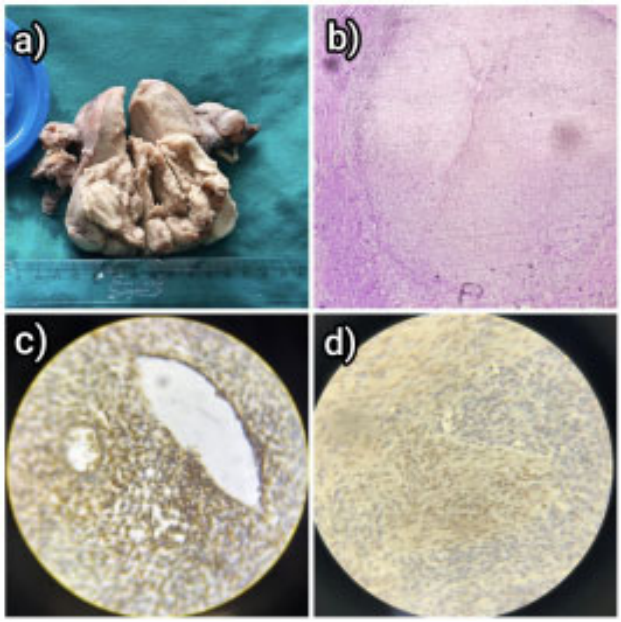

Fig 2 — (a) Fibroid like mass arising from lower endometrium extending upto cervix. (b) "Tongue" like extension of tumor cells into myometrium (H&E stain, 100x). (c) Strong CD10 positive tumor cells around blood vessels (100x). (d) ER positivity of tumor cells (100x).

endometrium with cystic changes and tumour arising from its stroma. Oval to spindle shaped tumour cells with fusiform nuclei and scanty cytoplasm were seen invading more than 50% myometrium. Lympho-vascular space invasion was absent. Cervix, bilateral adnexa were free from any tumour process.

According to the new 2009 FIGO Staging, it was stage IB disease and AJCC 8th edition stage was PT1bNx and IHC was confirmatory (Fig 2).

Case 3

There was one heterogenous irregular friable area identified in the operated surgical specimen at uterine fundus measuring (2.5 x 2 x 1.5) cm. Multiple intramural fibroids are also discovered on cut section. On microscopic examination, endometrium again showed features of non-secretory endometrial glands and stroma. Tumour arising from endometrial stroma invades less than 50% of myometrium (Fig 3a). Tumour cells are spindle shaped with scanty cytoplasm with oval to fusiform nuclei and inconspicuous nucleoli. There is focal whorling of tumour cells around the small arterioles (Fig 3b). Focal smooth muscle differentiation, fibrosis, glandular elements and focal sex cord elements also noted. No lympho-vascular space invasion noted.

Sections from fibroids showed histopathological features of atypical epithelioid leiomyoma. Histopathological examination and immuno-histochemical study confirmed the diagnosis of low grade endometrial stromal sarcoma with focal muscle differentiation and focal sex cord elements.

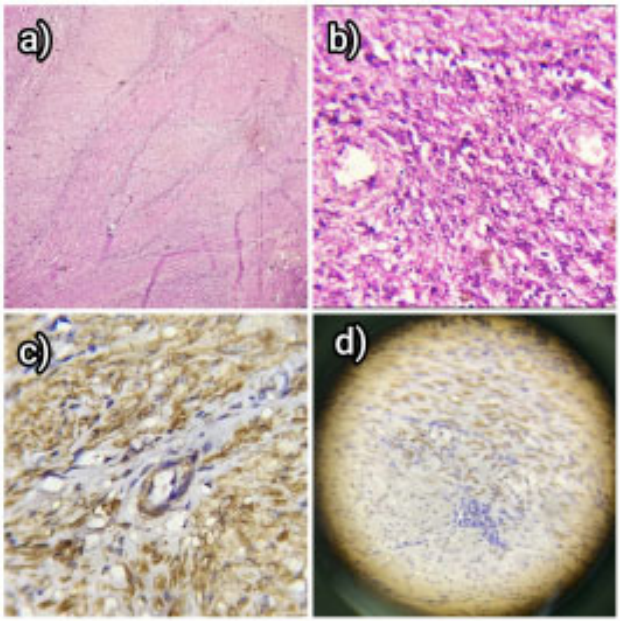

Fig 3 — (a)Tumor cells invading myometrium (H&E stain, 100x). (b) Whorling of tumor cells around arterioles (H&E stain, 100x). (c) Strong CD10 positive tumor cells (100x). (d) Patchy nuclear ER positivity of tumor cells (100x).

Case 4

In this case of 35 years old female, USG of the abdomen revealed a proliferative growth in uterus and her post operative surgical specimen showed on grossing an irregular proliferative growth measuring (7.5 x 2 x 2) cm. almost obliterating the uterine lumen. Cut section revealed solid, soft, whitish multiple polypoidal growth (Fig 4a).

On microscopic examination, sections from the growth showed tumour cells infiltrating myometrium up to serosa (>50% of myometrium). Spindle tumour cells have fusiform nuclei with scanty cytoplasm with minimal atypia. Sections from left fallopian tube and left ovary and left parametrium showed infiltration by tumour process. Lymphovascular space invasion is noted. Staging was PT2aNxMx. Histopathological examination and immuno-histochemical study confirmed diagnosis of low grade endometrial stromal sarcoma.

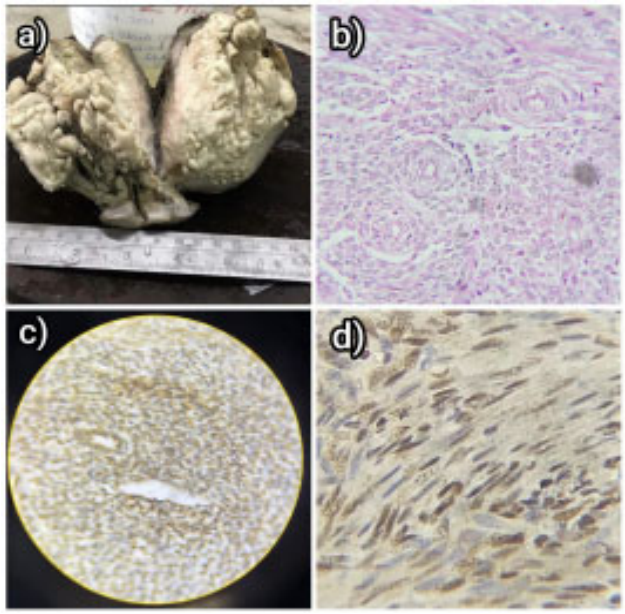

Fig 4 — (a) Solid and irregular, multiple polypoidal uterine growth on gross examination. (b)Tumor cells whorling around arterioles (H&E stain, 100x). (c) CD10 positive tumor cells around arterioles (100x). (d) Strong ER positivity (400x).

Case 5

On gross examination of this 48 years old patient's surgical specimen, a tumour mass was noted in the uterine fundus measuring (12cm×7cm×5cm). Cut section of tumour mass was heterogenous with solid, cystic and hemorrhagic elements. Cervix and bilateral adnexa appeared free on grossing.

On microscopic examination, endo-myometrium showed histopathological features of non-secretory endometrial glands and stroma. Tumour arising from endometrial stroma invades more than 50% of myometrium in tongue like fashion. Tumour cells are oval cells with scanty cytoplasm with oval to fusiform nuclei and inconspicuous nucleoli. There is focal whorling of tumour cells around the small arterioles. Mitotic count was <3/10 high power fields. Patchy areas with high mitotic count, focal necrosis and focal xanthogranulomatous changes were also noted. Lymphovascular spaces were seen uninvaded (staging PT1bNxMx). IHC again stamped diagnosis of ESS of low grade (Fig 5).

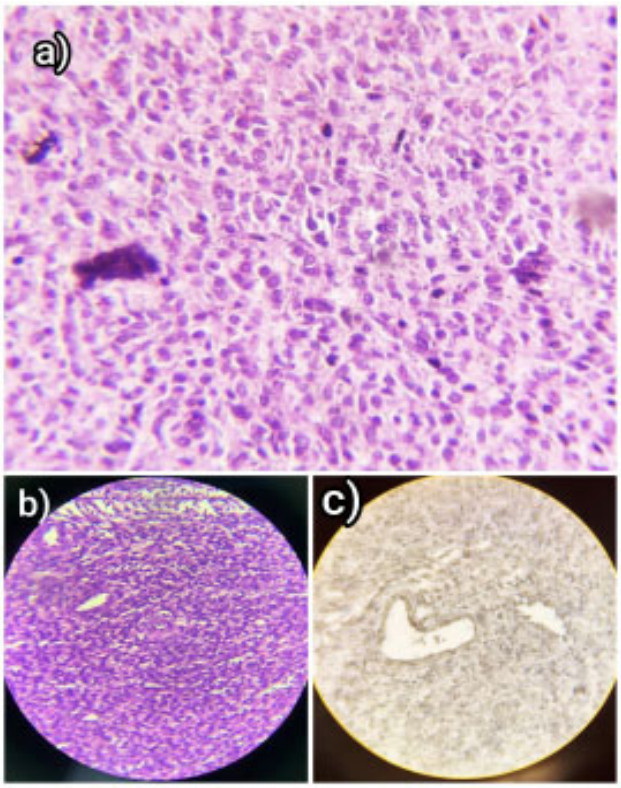

Fig 5 — (a) & b) Diffuse sheet of tumor cells (H&E Stain, 400x & 100x). (c) Weak CD10 positivity of tumor cells around arterioles (100x).

Discussion

The clinical behaviour and pathological features of uterine stromal cancers were studied in details for the first time in 1966[4]. This new kind of neoplasms were then divided morphologically into two groups: one with pushing margins (stromal nodules) and one with infiltrating margins (endolymphatic stromal myosis or stromal sarcoma). Stromal nodule was considered benign while tumours with infiltrating margins were further divided by their mitotic activity: tumours containing fewer than 10 mitotic figures in 10 High-power Field (endolymphatic stromal myosis-low grade), and those containing 10 or more mitotic figures in 10 HPF (stromal sarcoma-high grade). Over the time, different authors have expanded or curtailed to integrate the description and classification of this type of neoplasm on the basis of their experiences in terms of clinic-pathological characteristics and patient survival.

The few scattered experiences from pathologists hinted existence of intermediary or continuum between two aforesaid types or further expansion of the spectrum but nothing was well supported by sufficient empirical data (Evans, *et al*) till WHO committee stepped in.

Initially, WHO 2003 classification recognized only two categories of stromal sarcomas simply on the basis of cytologic atypia, namely, Low-grade Endometrial Stromal Sarcoma (LG-ESS) and Undifferentiated Endometrial Sarcomas (UES)[5]. The 'UES' category was then too broad, meant to include a wide range of heterogeneous tumours with different clinical behaviour and outcome, morphology and genetic features. In 2012, the improvement of cytogenetics and molecular biology further opened up the horizon which allowed the recognition another kind of ESS with more aggressive clinical picture and higher mitotic activity what led to their reinstitution in WHO classification (2014) as a distinct group of ESS, ie, High Grade ESS (HG-ESS), as defined as a malignant tumour of endometrial stromal derivation with high grade, round-cell morphology often associated with a low-grade spindle cell component and characterized by a t(10;17) leading to the YWHAE-NUTM2 rearrangement[6].

Later in 2018, the recognition of HG-ESS was further strengthened and hence re-instated in WHO classification as definite intermediate between LG ESS and UES was on basis of unique features of cells with uniform but definite nuclear atypia, permeative myometrial invasion and mixed clinical behaviour[7].

So the current WHO classification acknowledges four categories within the endometrial stromal family of tumours: Endometrial Stromal Nodule (ESN), Low Grade Endometrial Stromal Sarcoma (LG-ESS), High-grade Endometrial Stromal Sarcoma (HG-LSS) and undifferentiated uterine sarcoma (UES)[8].

After leiomyosarcomas, LG-ESS represents the most common stromal tumour by frequency. It usually affects perimenopausal women, but occasionally arises in young women and adolescents as we had one such of 28 years (Case 1). Risk factors for this neoplasm include obesity and diabetes, younger age at menarche, tamoxifen intake or oestrogen use and pelvic radiation[9]. Abnormal uterine bleeding, pelvic pain and dysmenorrhea are the most frequent symptoms of the patients. About one-third of patients present symptoms suggestive of extrauterine spread, while one fourth are asymptomatic[3]. This neoplasm principally arises from uterine corpus while ovary is the commonest organ involved in extra uterine variety[10]. Besides ovary, abdominal cavity, vulva and vagina are the rare sites of extra uterine ESS. Extrauterine pelvic extension of LG-ESS is frequently associated with endometriosis[11].

Pathology

Both ESN & ESS can be submucosal or often growing into lumen (polypoidal form) or intramural. While ESN can exhibit expansible features but the absence of myometrial and lympho-vascular invasion is obligatory for diagnosis. In comparison, in ESS, the borders are defined and it usually presents specific pattern of permeation into the myometrium and parametrial tissue called 'worm like'[3,11]. Its polypoidal variety often gives positive yield in endometrial biopsy but not a single case in our small series had any such outcome. Macroscopically there might be areas of haemorrhage with necrosis and cystic degeneration (eg, Case 1) but pure cystic mass is unlikely. Often soft nodules can be recognized between the endometrium and the myometrium. Microscopically ,the myometrial and lympho-vascular invasion in 'tongue like' fashion is classical (as in Figs 1b, 2b & 3a) and is a key point for the distinction between LG-ESS and ESN[12].

Microscopically, LG-ESS resembles the proliferative phase of endometrial stroma featuring small cells with oval to spindle shaped nuclei arranged in sheet surrounded by spiral arterioles like vessels (Figs 3b & 4b). The mitotic index is usually low: about 5/10 per high power fields, but

in some cases it can be higher.

Although there is no single specific marker for ESS, the immune-stain panel should include CD10 and smooth muscle markers like desmin, vimentin as the latter two are important for the distinction between ESS and other tumours with overlapping immuno-phenotype[13]. LG-ESS cells express oestrogen and progesterone receptors and the tumours were seen to respond to administration of progestins.

Genetically, about 50% cases of Low grade Endometrial Stromal Sarcoma show translocation of t (7;17) with polycomb family genes fusion of JAZF1–SUZ12 (JJAZ1)[14]. These genetic findings can be utilized in aid of the diagnosis of Low Grade Endometrial Stromal Sarcoma by using FISH or RT-PCR, the facility our institution is unfortunately not equipped with[4,14].

The natural history of Low-grade Endometrial Stromal Sarcoma is characterized by indolent clinical course and occasional local recurrences and metastases. All available literatures are in support of favourable prognosis when surgery ,which is essentially hysterectomy and bilateral salpingo-oophorectomy is done early[15]. Cytoreduction is recommended in advanced tumours with extrauterine manifestations, however, in a study conducted by Leah, *et al*, the cytoreductive surgery did not seem to ensure any added benefit in survival[16,17]. The optimal adjuvant therapy remains unclear with options including observation without therapy, hormonal therapy, chemotherapy and radiation therapy, either alone or in varying combinations. Hormonal therapy with medroxyprogesterone, tamoxifen, Gonadotropin Releasing Hormone (GnRH) analogues and aromatase inhibitors are suggested for LGESS stage 3-4 and for recurrent disease.

Although, we have not encountered any recurrences during this study period of three years or less, the risk of recurrence is considered as high as 50% and often they can be very late[18]. In one large series, the interval before recurrence varied from three months to 23 years, with a median interval of three years[19]. In the largest clinicopathologic study to date on ESS, the median time between hysterectomy and relapse was 5.4 years and nine months for stages 1 and 3-4, respectively[20].

High grade endometrial stromal sarcoma are more aggressive, often shows extrauterine extensions and necrosis as reflected histopathologically with extensive myometrial invasion with mitotic figure >10/10hpf. Higer chances of recurrences are seen in successive follow ups[3].

Given the rarity of the pathology with few studies and Case Reports being available in electronic media, this presentation of 5 cases, however small, surely can help clinicians maintain an high degree of suspicion for such infrequent pathology, make a relook at its prospect of early diagnosis and management and improve its clinical outcome.

Conclusion

Low Grade Endometrial Stromal Sarcoma is an uncommon malignant stromal tumour of uterus, which occurs usually in perimenopausal women but can also occurs in young women. The clinical features or even gross pathology of endometrial stromal nodule, High Grade and Low Grade Endometrial Stromal Sarcoma often are nonspecific & overlapping and extra uterine element of latter two can make the diagnostic field more confusing, but knowledge of their existence, careful histopathological examination, immunohistochemistry and if possible genetic study can surely diagnose it with more surety.

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