

Case Report

Low Grade Endometrial Stromal Sarcoma: Report of a Rare Uterine Malignancy

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ABSTRACT

Endometrial stromal sarcoma represents a very rare pathological entity occurring as a malignant disease in women genital sphere, frequently in the age group of 40-50 years. Low grade endometrial stromal sarcoma (LGESS) is a rare uterine sarcoma constituting 0.2% of all the uterine malignancies with a good prognosis despite a tendency to recur. We report a case of 42 yr old woman presented with menorrhagia, dysmenorrhoea, anemia and rapidly enlarging mass in uterus clinically diagnosed as leiomyoma, underwent a hysterectomy. Histological examination revealed cells with ovoid to short, spindle shaped nuclei resembling endometrial stromal cells proliferating in a space occupying manner and compressing and partially infiltrating the myometrium, rendered the diagnosis of LGESS. Our case emphasizes the inevitability for high index of skepticism and proper preoperative diagnosis in this rare tumor.

Keywords: Endometrial Stromal Sarcoma

Introduction

First reported in 1908, endometrial stromal sarcoma (ESS) is a rare uterine tumor known for its slow growth. Originally, known as interstitial endometrioma,

endolymphatic stromal myosis and low grade endometrial stromal sarcoma (LGESS) are very rare malignant uterine tumors that constitute 10% of all the uterine sarcomas but only 0.2% of all the uterine malignancies (1). ESS were

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previously subdivided into low or high grade categories depending upon mitotic index but now the latter are termed poorly differentiated or undifferentiated uterine sarcoma due to its aggressive clinical course. LGESS has infiltrating margins, typically show extensive worm like invasion with indolent growth and a tendency of late recurrence (2).

Distinguishing LGESS from benign smooth muscle proliferations like cellular leiomyoma can be challenging, but because of differing treatment and prognosis this distinction is important. Its clinical recognition may be difficult and the diagnosis is often made postoperatively after histopathological examination. Preoperative diagnosis is mostly a uterine fibroid.

Ultrasound and magnetic resonance imaging are inconclusive. Preoperatively it could be diagnosed by endometrial aspirate examination. Geetha *et al.* (3) reported a case of LGESS in a young patient clinicoradiologically presented as fibroid uterus and was advised myomectomy. But in view of rapid enlargement of uterus within the last 4 months, endometrial aspiration was performed which showed endometrial glands in the secretory phase with neoplastic cells suggestive of LGESS. Therefore, the treatment plan was shifted from a conservative myomectomy to a laprotomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy. Thus, if the diagnosis is known, the extent of surgery should be planned accordingly.

We are documenting a case of a 42 year old woman, presented with rapidly enlarging mass in uterus, clinically diagnosed as leiomyoma and subsequently diagnosed as LGESS on histopathological examination.

Case Report

A 42-years-old woman (gravid2, para1), referred

to our hospital with menorrhagia, pelvic pain, dysmenorrhea and anemia since six months earlier. Her menstrual cycles had been normal until six months back when she developed intermenstrual and postmenstrual bleeding per vaginum. But for one month she was having bleeding per vaginum on and off which was not controlled even after treatment.

She was not using any contraception. There was neither history of exogenous hormone use nor history of drug intake like tamoxifen. Ten months old ultrasonograph showed normal sized uterus with a fibroid measuring 3x3 cm for which no action was taken. Physical examination showed the patient to be obese with severe pallor. The rest of the general and systemic examination was normal.

Abdominal examination showed a suprapubic mass corresponding to 18 weeks size uterus. Per speculum examination showed mild cervicitis and normal vagina. Per vaginum examination revealed a soft, mobile, 18 weeks size anteverted uterus with clear bilateral fornices. Haemoglobin level was 5.4g/dL. An ultrasound scan carried 2 months back showed enlarged uterus (10x7x4cm) with diffuse coarse myometrial echoes.

Ultrasound scan showed further an isoechoic and hypoechoic mass measuring 104mm x 90mm in the uterus suggestive of intramural fibroid. Pap smear was negative for intraepithelial lesion or malignancy. With the clinical diagnosis of leiomyoma uterus with cystic degeneration she underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy.

The specimen consisted of enlarged uterus with cervix and bilateral adnexae, measuring 16x10x4cm. Cut section revealed thickened and irregular endometrium and an obliterated endometrial cavity by friable grayish brown polypoidal growth measuring 8x4 cm, attached to the cavity (Fig. 1). The histological sections were

taken from the growth, endomyometrial junction, cervix and bilateral adnexal structures. Paraffin-embedded sections prepared from different parts of the tumor were stained by hematoxylin and eosin (H&E) and reticulin stains.

Microscopically, showed a densely cellular tumor composed of uniform oval to spindle shaped cells closely resembling endometrial stromal cells. The tumor cells were of relatively uniform size and shape, imparting a monotonous appearance and possessing uniform round to ovoid nuclei with finely granular dispersed chromatin, small inconspicuous nucleoli and scanty amphophilic cytoplasm with ill-defined cell borders. The tumor was paucimitotic (5 mitotic figures per 10 high power fields) with mild cytologic atypia. The tumor was seen infiltrating the adjoining myometrium, as well as deeply, in tongue like projections (Fig. 2).

A rich network of delicate small arterioles resembling the spiral arterioles of the late secretory endometrium was seen. The arterioles tend to be uniformly distributed among the stromal cells, and capillaries and small veins were often conspicuous as well.

The tumor cells also exhibited prominent concentric arrangement around the blood vessels (Fig. 3). At places, plugs of tumor grow within lymphovascular spaces in the myometrium was appreciated. In between, the tumor cells were separated by abundant myxoid stroma. An occasional focus of necrosis was noted. Reticulin stain showed a dense network of fibrils around individual tumor cells. Cervix and adnexa were histologically normal.

The histopathological diagnosis of LGESS was conferred for appropriate management. Immunohistochemical stains were not done in our case because of economic limitations.

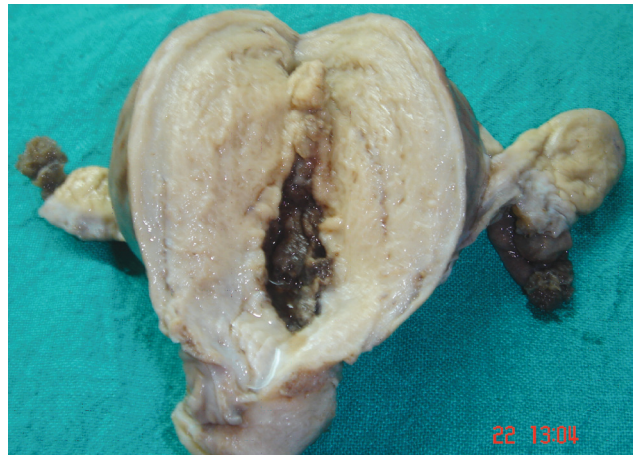


Fig.1- Endometrial cavity full of friable grayish brown polypoidal growth

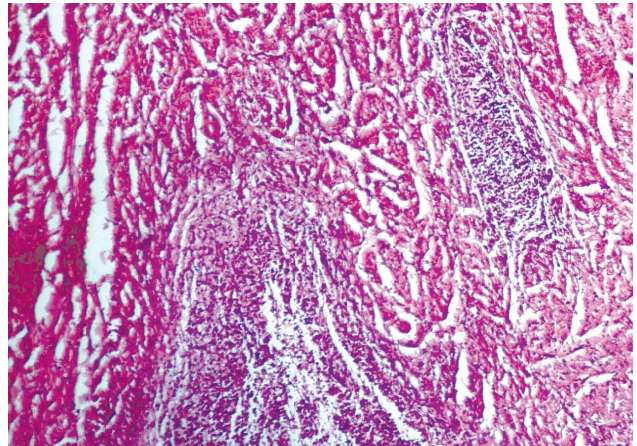


Fig.2- Photomicrograph showing tumor cells infiltrating the adjoining myometrium in tongue like projections (H&E; $\times 100$)

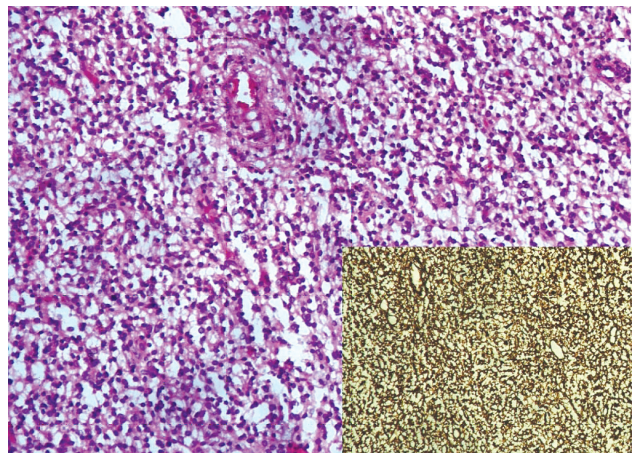


Fig.3- Photomicrograph showing perivascular whorling proliferation of plump and spindle cells with scant cytoplasm and indistinct cell borders. Reticulin stain revealing positive staining around individual tumor cells (inset) (H&E; $\times 200$; inset, $\times 200$)

Postoperative period was uneventful. She received adjuvant pelvic radiotherapy with 45Gy in 23 fractions followed by chemotherapy with four courses of adriamycin and cyclophosphamide. She has had no complication or local recurrence after two year of follow up.

Discussion

ESS is a rare disease with probably less than 700 new cases in USA or Europe per year (4). ESS is characterized by proliferations composed of cells with endometrial stromal cell differentiation. According to the 2003 World Health Organization classification, endometrial stromal tumors (EST) are divided into – endometrial stromal nodule (ESN), low grade endometrial stromal sarcoma (ESS) and undifferentiated endometrial sarcoma (UES) (5). Boardman *et al.* differentiated low grade ESS from high grade ESS by cellular uniformity, less frequent mitosis (<3/10 HPF versus >10/10HPF), and lack of hemorrhage and necrosis (1). However, there are controversies surrounding the separation of ESS into high and low grade based on mitotic activity and at present mitotic counts are no longer used to differentiate high and low grade lesions. The division of ESS into low and high grade categories has fallen out of favor and the term ESS is now considered best restricted to neoplasm that are formally regarded as LGESS.

Uterine sarcomas usually affect post menopausal females. Women with LGESS are younger with a median age being 45 and 57 years. Symptoms at presentation include abnormal vaginal bleeding, progressive menorrhagia and abdominal pain as seen in our case (6). Around 30% of females with LGESS have extrauterine disease at presentation. The pathogenesis of these lesion remains unknown, but exposures to tamoxifen and unopposed estrogens or prior irradiation have been implicated in some cases.

Grossly LGESS reveals a poorly demarcated pink, tan or yellow cords and nodules of tumor having infiltrating margin with diffuse myometrial permeation and typically show extensive worm-like vessel extension. It may form soft, tan, smooth surfaced polyps that are occasionally infarcted and hemorrhagic. Microscopically, LGESS permeate the myometrium in irregular tongues (>3 in number) and often invade myometrium (>3mm), as well as extrauterine veins and lymphatics (2). LGESS show neoplastic stromal cells resembling those of proliferative endometrium. The tumor cells are monotonous with uniform size and shape having round to ovoid nuclei with fine granular chromatin, small inconspicuous nucleoli and small amount of amphophilic cytoplasm with indistinct cell borders. Numerous thin walled small arteriolar types of vessels are characteristically present. Reticulin fibres surround individual cells in basket weave pattern. Plaques and zones of hyaline fibrosis are common and aggregates of foam cells or foci of necrosis are occasionally present. Rarely, abundant myxoid stroma widely separates tumor cells.

The neoplastic cells of LGESS are immunoreactive for vimentin, CD10 and at least focally for actin. They are usually, but not always negative for desmin and h-caldesmon. LGESS is almost always positive for hormone receptors (estrogen and progesterone receptors). Stromal sarcoma cells are typically nonreactive to antibodies against CD117, smooth muscle actin (SMA) and cytokeratin. A recent study has shown that among the cases of ESS that were examined, all cases were immunoreactive to anti-CD10 (5/5 cases) and anti-progesterone receptor (10/10 cases) antibody, most reacted with anti-estrogen receptor antibody (9/11 cases), 5/9 and 3/7 were focally positive for smooth muscle actin and desmin, respectively, and all were negative for CD34 (0/7 cases) (7). It is now widely

accepted that diffuse CD10 immunoreactivity is a very useful positive predictive marker of LGESS, but evaluating CD10 immunoreactivity alone is often not helpful for differentiating ESS from its mimics. With regard to the progesterone receptor, while LGESS show high sensitivity to antibodies against this antigen, this immunostain is less specific for differentiating LGESS from other mesenchymal tumors. Therefore, a panel of immunohistochemical stains may be more helpful for diagnosis (8).

The differential diagnosis of LGESS includes ESN, cellular leiomyoma, cellular intravenous leiomyomatosis, cellular endometrial polyp and various soft tissue neoplasms. ESN is a tumor composed of cells closely resembling those of endometrial stroma having non-infiltrative border with minimal cytologic atypia and without vascular invasion. Hence, extensive sampling of tumor margins and detecting vascular invasion are extremely important in distinguishing between the two (9).

Fascicular areas, thick walled blood vessels and cleft-like spaces in cellular leiomyoma, more often seen at the periphery of the tumor are the features which differentiate it with LGESS. In uncertainty, antibodies to smooth muscle myosin-heavy chain, CD10, calponin, smooth muscle actin and desmin can reliably distinguish ESS from cellular leiomyoma (9).

ESS may be a diagnostic challenge especially when they are present in an extrauterine site. Owing to the presence of an arborising vasculature and cells with an undifferentiated appearance, ESS can be confused with several soft tissue neoplasms like hemangiopericytoma, solitary fibrous tumor and synovial sarcoma. Most ESS are CD10 positive combined with antiestrogen receptor and CD34 (10).

The clinical presentation of intravenous leiomyomatosis (IVL) is nonspecific, however

as with LGESS, this lesion is present outside the uterus at the time of diagnosis in at least 30% of the patients. Grossly, because of its prominent intravascular growth, a soft tan to yellow cut surface and frequent association with conventional leiomyoma; it may be misinterpreted as ESS. Microscopically, dense cellularity resembling highly cellular leiomyoma may increase confusion with LGESS. Helpful distinguishing morphological features in IVL are clefted or lobulated contour of intravascular masses, focal fascicular architecture, cells with blunt ended nuclei and prominent thick walled vessels (11).

EST should also be distinguished from perivascular epithelioid cell tumors (PEComa) which show tongue like infiltrative growth resembling infiltrating pattern seen in LGESS. PEComas also show predominantly nested growth which is often associated with focal fascicular growth of cells with elongated nuclei and the cells tend to be arranged in radial fashion around the vessels which is not encountered in EST and furthermore EST will show focally some areas resembling the normal endometrial stroma with arterioles. Also, EST donot express human melanoma black 45, Melan A or microphthalmia factor (12, 13).

Surgery is the final resort for primary treatment of LGESS consisting of total abdominal hysterectomy with bilateral salpingo-oophorectomy. Regardless of patient's age, preservation of ovarian tissue is not recommended because of likelihood of ovarian metastasis. In addition, since ESS has steroid receptors the possibility exists that estrogen production by retained ovaries may stimulate any residual disease, oophorectomy is recommended. Due to high recurrence risk even with localized tumors, many clinicians advocate use of adjuvant chemotherapy, radiation therapy and/or hormonal therapy to suppress

tumor growth. Hormone therapy with medroxy-progesterone, tamoxifen, gonadotropin releasing hormone analogues (GnRH) and aromatase inhibitors are suggested for LGESS and for recurrent disease (14). Uterine sarcomas have a poor prognosis and survival is much worse than that reported for endometrial adenocarcinoma, with an overall survival of less than 50% at 2 years, even when presenting at an early stage. A higher survival is reported with LGESS as compared to other uterine sarcoma (15, 16).

Because of rarity of this tumor, diagnosis of LGESS is not frequently encountered in gynecological practice and hence awareness is essential. Frequently it could be mistaken for a fibroid with conservative management in perimenopausal women. As our patient had a short duration of menorrhagia with radiological findings suggestive of degenerated leiomyoma uterus. This shows that high index of suspicion is required to make preoperative diagnosis of LGESS particularly in fibroids with any abnormal presentation such as rapid enlargement or, leiomyoma with degenerative changes. Therefore, this case highlights the inevitability for high degree of skepticism and proper preoperative diagnosis in this rare type of tumor. An attempt is made to document the histologic features of LGESS with discussion of the differential diagnoses and to contribute in the spectrum of uterine neoplasia.

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