INTERNATIONAL JOURNAL OF MEDICAL AND APPLIED SCIENCES
E-ISSN:2320-3137

Case study

LOW GRADE ENDOMETRIAL STROMAL SARCOMA WITH SEX CORD LIKE DIFFERENTIATION- A RARE ENTITY AND A DIAGNOSTIC DILEMMA WITH REVIEW OF LITERATURE.

Manisha Makkar, Jashan Sandhu*, Vijay Suri, V. K. Dubey

Department of Pathology,Adesh Institute of Medical Sciences and Research Bathinda, Punjab, India.

CORRESPONDING AUTHOR: Dr Jashan Sandhu, MD (Pathology),1101/1, Tagore Nagar, Ludhiana-141001

ABSTRACT

Endometrial stromal sarcoma is a very rare pathological entity occurring as a malignant disease in women genital sphere that occurs in the 40-50 years age group. Low grade endometrial stromal sarcoma is a rare uterine sarcoma constituting 0.2% of all the uterine malignancies. It has a good prognosis despite a tendency to recur. We are documenting a case of low grade endometrial stromal sarcoma with sex cord like differentiation presenting with well circumscribed mass in uterus diagnosed on clinical examination and ultrasonography as a leiomyoma but later diagnosed as a low grade endometrial stromal sarcoma with sex cord like differentiation on histopathological examination.
KEYWORDS: Cellular leiomyoma, endometrial stromal sarcoma, sex cord stromal tumor

INTRODUCTION

Endometrial stromal sarcoma (ESS) is a rare, slow growing uterine tumor that was first described in 1908. It is known by other names like as interstitial endometrioma, endolymphatic stromal myosis or 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] LGESS with sex cord like differentiation is an even rarer entity and poses a diagnostic dilemma and has to be distinguished from uterine tumor resembling ovarian sex cord stromal tumor (UTROSCT). ESS were previously subdivided into low or high grade categories based on the mitotic index but are now classified on the basis of histological similarity to endometrial stromal cells.[2] LGESS has infiltrating margins with extensive worm like invasion into the myometrium.

Its clinical recognition may be difficult as it resembles a leiomyoma clinically and on ultrasonography and its diagnosis is often made postoperatively after histopathological examination.

We are presenting a case of LGESS with sex cord like differentiation in a 45 year old female who presented with mass in uterus clinically diagnosed as leiomyoma which was later diagnosed as LGESS on histopathological examination.

CASE SUMMARY

A 45 year old female patient, gravid 2 para 2, presented with menorrhagia, pelvic pain and dysmenorrhea since one year. Her last child birth was 8 years back and there was no

history of contraceptive use. A pelvic ultrasound scan carried out showed enlarged uterus (9.5x8x6cm) with an intramural fibroid. On physical examination, she was found to have an enlarged uterus. Ultrasound scan showed further enlargement of uterus with intramural fibroid. The clinical diagnosis of leiomyoma uterus was made. Total hysterectomy was performed and the specimen was sent to Department of pathology for histopathologic examination.

GROSS EXAMINATION

We received a total abdominal hysterectomy specimen measuring 12x9x6cm. On cut section endo/myometrium measured 0.2/3 cm. On serial slicing multiple fibroids were identified measuring 0.6 cm to 1.2 cm in diameter. One well circumscribed nodular lesion measuring 1.3cm in diameter was seen. It was friable grey brown in colour. (Figure1) The histological sections were taken from the endomyometrial junction, fibroids, the friable lesion and the cervix.

MICROSCOPIC EXAMINATION

The hematoxylin and eosin (H&E) stained sections from the circumscribed nodule showed a tumor composed of uniform oval to spindle shaped cells closely resembling endometrial stromal cells possessing small, round to ovoid, darkly staining nuclei with finely granular cytoplasm and inconspicuous nucleoli. (Figure2) At places, the tumor cells showed sex cord like differentiation and several of the nuclei showed grooving. (Figure 3) Mitotic count was 3-4/ 10HPFs. A diagnosis of endometrial stromal nodule with sex cord like differentiation was initially being considered on the basis of the gross discrete circumscribed appearance but on further more extensive sampling of the nodular lesion areas were seen where the tumor was seen infiltrating the adjoining myometrium as well as deeply in tongue like projections. (Figure 4) The tumor cells also exhibited prominent concentric arrangement around the blood vessels. The tumor cells were separated by abundant myxoid stroma at places. Reticulin stain showed positive staining around individual tumor cells.(Figure 5) Immunohistochemically, CD 10 was found to be positive. Endometrium showed hyperplasia and cervix showed chronic cervicitis with squamous metaplasia and nabothian follicles. The histopathological diagnosis of LGESS with sex cord like differentiation was thus made.

DISCUSSION

ESS is characterized by proliferations composed of cells with endometrial stromal cell differentiation. ESS is a rare disease comprising 10% of all uterine sarcomas but only around 0.2% of all uterine malignancies. Some of the cases of LGESS may also show sex cord like differentiation.[3]

In the latest 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).[4]ESS was divided in low and high grade tumors previously according to cell morphology and mitotic count. Boardman CH et al defined LGESS from HGESS by cellular uniformity, less frequent mitosis (<3/10 HPF versus >10/10HPF), and lack of hemorrhage and necrosis.[1] However, mitotic count is no longer considered as a main criteria in distinguishing between low and high grade ESS. If the tumor has the typical features of an EST it should be classified as a low grade ESS despite higher mitotic counts as the mitotic count has no bearing on the prognosis. Resemblance to the endometrial stromal cells is the most important feature in

distinguishing high grade from low grade ESS. If a component of low grade ESS is recognizable, only then is the tumor classified as a high grade ESS, otherwise a diagnosis of UES should be considered and that too after ruling out possibility of high grade leiomyosarcomas or rhabdomyosarcomas.[5] The division of ESS into low and high grade categories has fallen out of favor and the term ESS now considered is best restricted to neoplasms that are formally regarded as LGESS. [2]

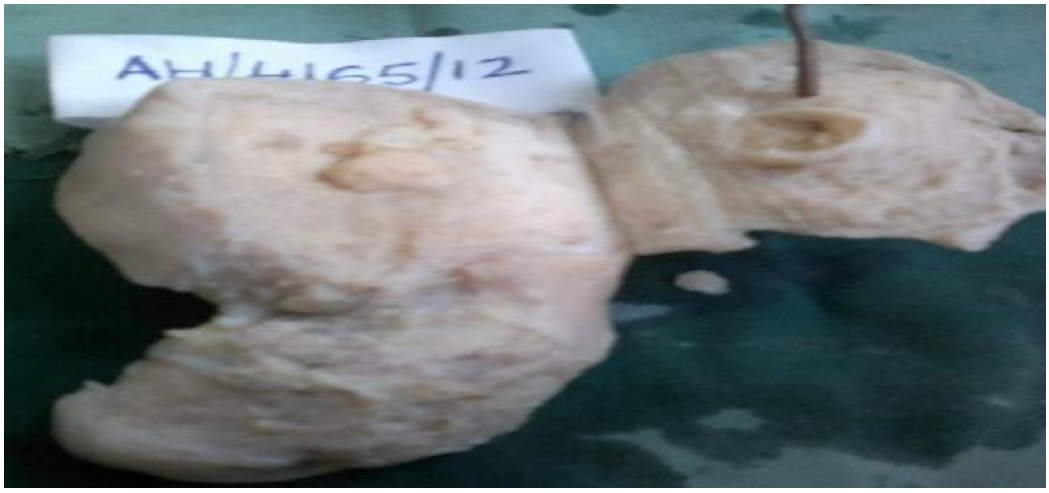

Figure 1- Gross specimen of uterus showing well circumscribed grayish brown nodular lesion.

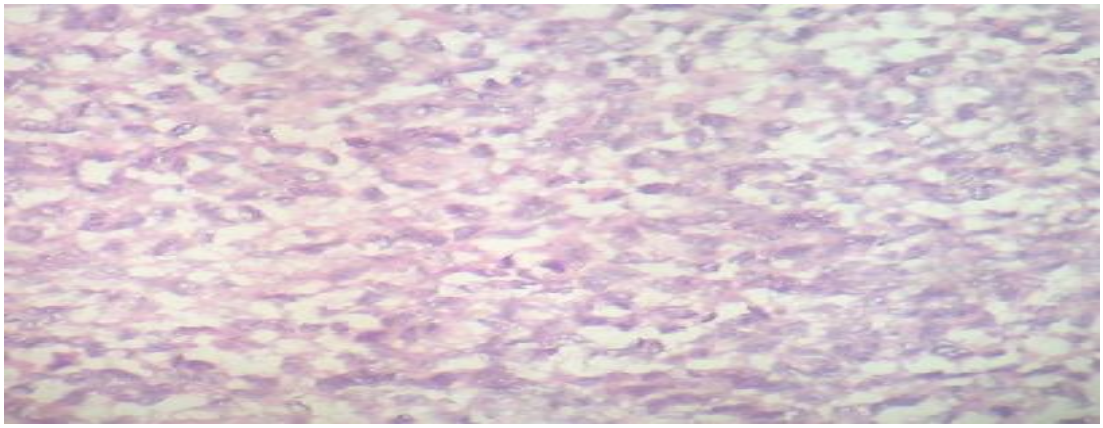

Figure 2- Photomicrograph showing tumor composed of oval to spindle cells with ovoid nuclei resembling endometrial stromal cells. (H & E; 400X)

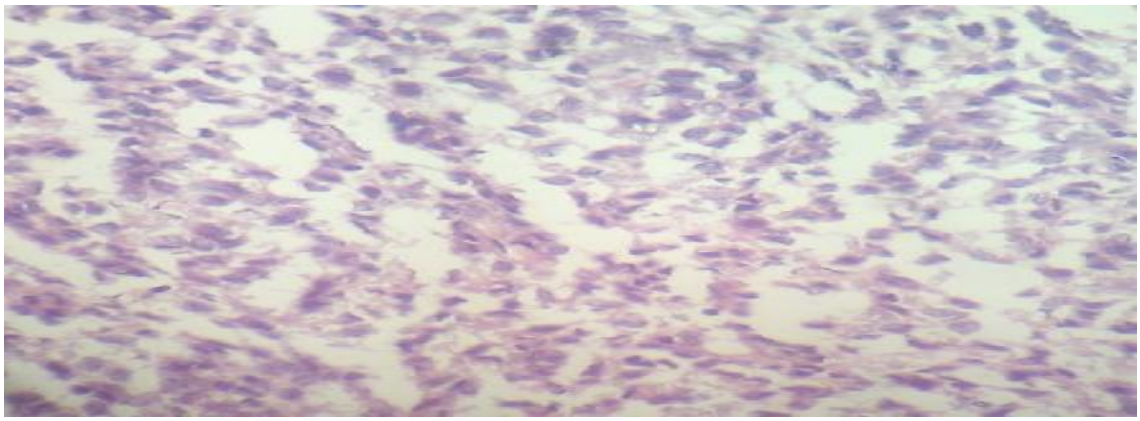

Figure 3- Photomicrograph showing endometrial stromal tumor with sex coed like differentiation and nuclei showing grooving. (H & E; 400X)

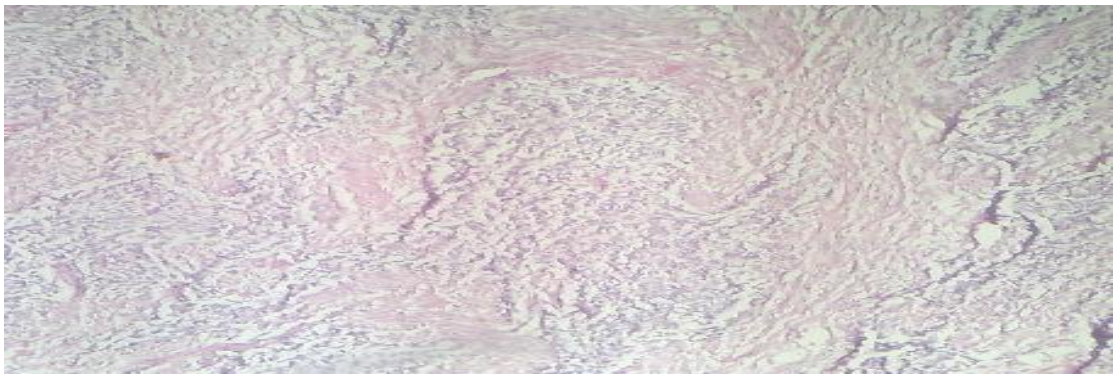

Figure 4- Photomicrograph showing invasion of tumor into adjoining myometrium as tongue like projections. (H & E; 100X)

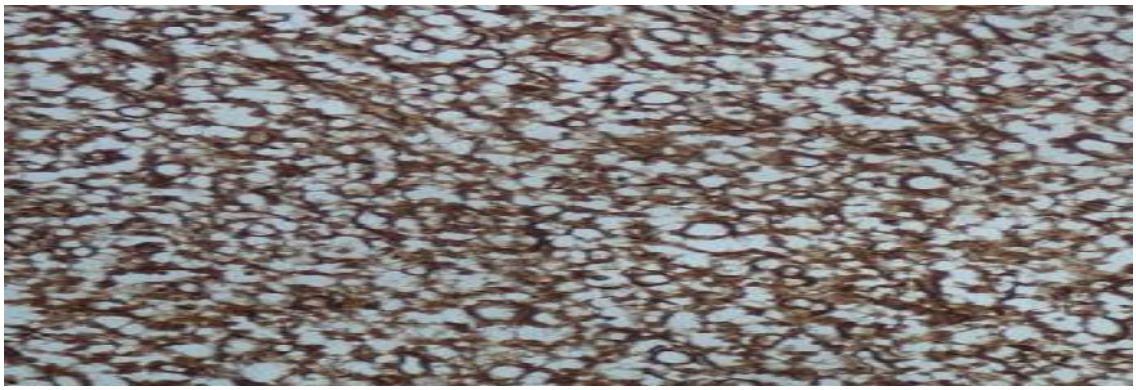

Figure 5- Photomicrograph showing positive reticulin staining around individual tumor cells. (H & E; 400X)

Uterine sarcomas generally affect postmenopausal females. Women with LGESS present at a younger age (45- 57 yrs) than women with other uterine sarcomas. Symptoms at presentation include abnormal vaginal bleeding, progressive menorrhagia and abdominal pain as seen in our case.[6] Approximately one third of the females with LGESS may present with extrauterine disease. The pathogenesis of these lesions is still uncertain, but exposure to tamoxifen and unopposed estrogens or prior irradiation have been implicated in some cases.

The typical gross appearance of ESS is a poorly demarcated tumor which may be pink, tan or yellow. Cords and nodules of tumor with diffuse myometrial permeation by worm like masses may be seen. It may also form soft, tan, smooth surfaced polyps that are occasionally infarcted and hemorrhagic. In our case uterus showed a solitary discrete well circumscribed nodule which was friable on cut section, leading to suspicion of endometrial stromal nodule.

LGESS has infiltrating margins and typically shows extensive worm like vessel extension. They permeate the myometrium in irregular tongues (>3 in number) and often invade myometrium (>3mm) as well as extrauterine veins and lymphatics.[2] Microscopically, LGESS show neoplastic stromal cells resembling those of proliferative endometrium. The tumor cells are monotonous with uniform size and shape. The nuclei are round to ovoid with fine granular chromatin and small inconspicuous nucleoli. Small amount of amphophilic cytoplasm with indistinct cell borders are seen. Mitotic activity is low (<3/10HPF). Numerous thin walled small arteriolar type 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. Immunohistochemically, endometrial stromal tumors are positive CD10, h-caldesmon, histone deacetylase 8, and smooth muscle myosin.

ESTs may show different types of differentiation including smooth muscle, fibrous or myxoid change, sex cord-like elements, glandular differentiation, epithelioid, rhabdoid or clear cells, rhabdomyoblastic differentiation, and granular change. Fatty metaplasia and bizarre nuclei have recently been reported in these tumours. Our case showed sex cord like differentiation and so the main differential diagnosis was Uterine tumor resembling an ovarian sex cord stromal tumor (UTROSCT). [5]

UTROSCT has been defined as a tumour with prominent sex cord-like differentiation in which there is no conspicuous endometrial stromal background. The age and clinical presentation for patients with UTROSCT and for those with ESTs are almost the same except for the fact that the patients with UTROSCT very rarely present with metastases. Grossly, the appearance of UTROSCT may be similar to an ESN as it typically presents as a circumscribed myometrial or submucosal mass that is soft and ranges from grey to tan to yellow, as was in our case.

On microscopic examination, both ESN and low-grade ESS may show sex cord-like differentiation, and the histological appearance of some UTROSCTs may merge imperceptibly with that of ESTs. The histological patterns should resemble those of ovarian sex cord tumors, especially granulosa-cell and Sertoli-cell tumors, alone or in combination, and these should be the only elements present in the tumor to label it as an UTROSCT. Immunohistochemical analysis may be of help in this differential diagnosis. Inhibin, the most specific marker for sex cord stromal tumors of the ovary, is negative in pure ESTs, but often positive in areas of sex cordlike differentiation in ESTs and in UTROSCTs. Calretinin, CD99 and Melan A may also stain normal sex cord elements as well as UTROSCTs, but they are negative in pure endometrial stromal areas. CD10 which is typically positive in ESTs, has

also been recently reported to be positive in UTROSCTs.[5] Thus correlation of immunohistochemical findings with the diverse morphological areas of a given tumor is very important.

It is also very important to differentiate UTROSCT from low grade ESS, as UTROSCT typically behaves in a benign fashion, whereas patients with low-grade ESSs have frequent recurrence. Positivity for any marker of sex cord differentiation may falsely lead to a diagnosis of UTROSCT making it necessary to sample the tumour extensively to rule out any endometrial stromal component before labeling it as an UTROSCT. The distinction of an EST with sex cord differentiation from a UTROSCT can be made only in a hysterectomy specimen and not in curetting's. [5]

The main differential diagnosis of a typical 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 with minimal cytologic atypia and without vascular invasion. The microscopic appearance of ESS and ESN are identical. Infiltrative margins (>3mm and >3 in number) and distinctive growth as worm like cords are seen in LGESS whereas margins are well demarcated in ESN. Hence, extensive sampling of tumor margins and detecting vascular invasion are extremely important in distinguishing between the two. [5]

ESS can be mistaken for cellular leiomyoma. Its clinical recognition may be difficult and the diagnosis is often made post- operatively after histological examination. Cellular leiomyomas are composed of spindle shaped cells with spindly nuclei and fascicular growth pattern, thick muscular walled blood vessels, cleft like spaces and showing focal merging with adjacent myometrium contrasting LGESS which contains monotonous population of cells with round to ovoid nuclei with fine chromatin. Large thick muscular walled blood vessels throughout the tumor are present in leiomyomas in contrast with arterioles of endometrial stromal neoplasm. When there is difficulty in diagnosis, antibodies to smooth muscle myosin-heavy chain, CD10, calponin, smooth muscle actin and desmin can reliably distinguish ESS from cellular leiomyoma.[5]

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 e.g. hemangiopericytoma, solitary fibrous tumor and synovial sarcoma. Most ESS are CD10 positive combined with antiestrogen receptor and CD34.[7]

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, cellular IVL may be misinterpreted as ESS because of its prominent intravascular growth, a soft tan to yellow cut surface and frequent association with conventional leiomyoma. Microscopically, dense cellularity resembling highly cellular leiomyoma may increase confusion with LGESS. Helpful distinguishing morphological features are that in IVL there are clefted or lobulated contour of intravascular masses; focal fascicular architecture; cells with blunt ended nuclei and prominent thick walled vessels. [8]

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 do not express human melanoma black 45, Melan A or microphthalmia factor. [9, 10]

Surgery is fundamental in LGESS consisting of total abdominal hysterectomy with bilateral salpingo-oophorectomy. 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. 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. [11, 12]

CONCLUSION

Because of rarity of this tumor, ESS may not be familiar to gynecologists. In young patients it could be mistaken for a fibroid or as in this specific case it could be mistaken for a UTROSCT and management is planned accordingly. The case highlights the necessity for high degree of suspicion and proper preoperative diagnosis in this rare type of tumor.

REFERENCES

1. Boardman CH, Webb MJ, Jefferies JA. Low grade endometrial stromal sarcoma of the ectocervix after therapy for breast cancer. Gynecologic oncology 2000; 79:120-123.
2. Shafi M, Luesley DM, Jordan JA. Gynecological oncology. Churchil Livingstone, UK; 2001:120-121.
3. Pink D, Lindner T, Mrozek A, Kretzschmar A, Thuss-Patience PC, Dorkan B et al. Harm or benefit of hormonal treatment in metastatic in low grade endometrial stromal sarcoma: single centre experience with 10 cases and review of literature. Gynecol Oncol 2006; 101:464-469.
4. Hendrickson MR, Tavassoli FA, Kempson RL, et al. Mesenchymal tumors and related lesions. Pathology and genetics of tumors of the breast and female organs. Lyon: IARC Press, 2003:233-236.
5. Baker P, Oliva E. Endometrial stromal tumors of the uterus: A practical approach using conventional morphology and ancillary techniques. J Clin Pathol 2007; 60:235-243.
6. Livi L, Paiar F, Shah N, Blake P, Villanucci A, Amunni G. Uterine sarcoma: twenty-seven years of experience. Int J Radiat Oncol, Biol, Phys 2003; 57:1366-1373.
7. Bhargava R, Shia J, Hummer AJ, Thaler HT, Tornos C, Soslow RA. Distinction of endometrial stromal sarcomas from hemangiopericytomatous tumors using a panel of immunohistochemical stains. Mod Pathol 2005; 18:40-47.
8. Clement PB, Young RH, Scully RE. Intravenous leiomyomatosis of the uterus. A Clinicopathological analysis of 16 cases with unusual histologic features. Am J Surg Pathol 1988; 12:932-945.
9. Oliva E. CD10 expression in the female genital tract: does it have useful diagnostic applications? Adv Anat Pathol 2004; 11:310-315.
10. Folpe AL, Mentzel T, Lehr HA, et al. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol 2005; 29:1558-1575.
11. Husseiny GE, Bareedy NA, Mourad WA, Mohamed G, Shoukri M, Subhi J. Prognostic factors and treatment modalities in uterine sarcoma. Am J Clin Oncol 2002; 25:256-260.
12. Rovirosa A, Ascaso, Ordi J, Abellana, Arenas M, Lejarcegui JA, et al. is vascular and lymphatic space invasion a main prognostic factor in uterine neoplasms with a sarcomatous component? A retrospective study of prognostic factors of 60 patients stratified by stages. Int J Radiation Oncol Biol Phys 2002; 52:1320-1329.