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Primary Endometrial Stromal Sarcoma arising from Cervix

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Abstract:*Endometrial stromal sarcomas are rare malignant tumors of the uterus (0.2% of all uterine malignancies). The primary tumor can occur in extra-uterine sites like ovary, fallopian tube, cervix, vulva, vagina, omentum and retro peritoneum. There are only 18 cases reported in literature of ESS arising from cervix till date. Primary tumor arising in the cervix mimics a fibroid polyp and poses a diagnostic dilemma. A pre-operative diagnosis of ESS is difficult and the diagnosis is retrospective from histopathology of a hysterctomy specimen done for presumed benign disease. We report a case of 48 years old perimenopausal lady who presented with irregular bleeding per vaginum and retention of urine. Clinical examination was suggestive of degenerated fibroid polyp. She gave history of removal of similar mass nine months earlier, the details of which were not known. In view of her age and recurrence of symptoms, total hysterectomy with bilateral salpingo-oophrectomy was done. The diagnosis was established on gross findings, cut section, histopathology and immunohistochemistry. The case report emphasises the need to include ESS in the differential diagnosis of cervical polyp.The role of adjuvant hormone therapy, chemotherapy and radiation is discussed.*

Key words*:Cervical polyp, Cervix , Endometrial Stromal Sarcoma, Extra uterine.*

I. Introduction

Endometrial stromal sarcoma was first reported in 1908. It is a malignant mesenchymal tumor arising from the uterus. The incidence is 0.2% of uterine malignancies[1].The primary tumor arising from cervix is very rare and there are only 18 cases reported in literature till date.

The tumor usually occurs in peri-menopausal women between 42-55 years of age. It presents as a polypoidal pelvic mass mimicking a fibroid polyp or with vaginal bleeding and poses a diagnostic dilemma. Diagnosis is mostly retrospective following hysterectomy for a presumed benign disease. The patients have long disease free interval after primary surgery. However local recurrence and distant metastasis have been reported after this long disease free interval. Efficacy of adjuvant therapy is not proven. Recurrent ESS is treated with progestins, GnRH agonists or aromatase inhibitors but there is no consensus regarding treatment. Chemotherapy and radiotherapy may be used for systemic metastasis while surgical excision is recommended for local recurrences.

The case report emphasises the need to include ESS in the differential diagnosis of cervical polyp.

II. Case Report

A 48 year oldlady was refered from district hospital with History of irregular bleeding per vaginum for 15 days and retention of urine.

Clinical examination revealed a polypoidal mass in vagina measuring 10X12 cms arising from cervix with well-circumscribed margins and irregular surface and surface bleeding. The cervix was effaced, thinned out and the mass was arising at 5O'clock position just below the internal os. She gave history of removal of similar mass eight months back, the histopathology of which was unavailable.

On ultrasound imaging, the uterus was normal size with normal central endometrial echo. Awell-circumscribed mass, measuring 11X13 cms in the region of cervix distending the endocervical canal was noted. She had previous two cesarean deliveries. In view of recurrence of polypoidal mass presumably degenerated fibroid, TAH with BSO was done.

Gross examination showed body of uterus to be normal size, and a polypoidal mass with a stalk 1.5 cms in length arising from 5O'clock position near internal os and distending the cervical canal (FIGO stage 1B). (FIG1)The cut section was fleshy, greyish, and smooth and was easily cut. Microscopic examination showed well-circumscribed lesion with spindle cells arranged in whorls and interlacing fashion. The cells having moderate amount of cytoplasm and oval spindle shaped nucleus exhibiting low mitotic activity(less than 10 mitotic figures per 10 high power fields)were present. (FIG2, 3) Tumour also showed increased vascularity and cells arranged in concentric fashion around blood vessels forming perithelioma pattern.

Immunohistochemistry showed CD 10 to be strongly positive and the cervical mass was reported as low grade endometrial stromal sarcoma arising from cervix. Body of uterus and endometrium was unremarkable.

III. Discussion

ESS is a malignant mesenchymal tumor arising from the uterus. They contribute to 0.2% of all uterine and cervical malignancies[1].Microscopically, they resemble endometrial stromal cells in the proliferative phase.

The tumor frequently occurs in 40-55 years of age though few cases in younger age group are described[1]. In our case the age was 48 years.

3.1Classification

The classification and pathogenesis of endometrial stromal tumors (EST) is widely debated. The new World Healh Organization 2014 classification[2] describes four types of ESTs. Endometrial stromal nodule (ESN), low grade endometrial stromal sarcoma (LG-ESS), high grade endometrial stromal sarcoma (HG-ESS) and undifferentiated uterine sarcoma (UUS). LG-ESS comprises 50-60% of ESS and may arise in extra uterine sites arising in foci of endometriosis[3].The extra uterine sites include ovary, fallopian tube, cervix, vagina,vulva, omentum, sigmoid colon, round ligament and retroperitoneum.The differentiation between endometrial stromal nodule and ESS is based on well-circumscribed lesion in ESN while there is infiltrating margin in ESS[1]. Therefore the diagnosis of ESS is retrospective on histopathology of hysterectomy specimen.

3.2 Cytogenetics

The origin and biology of stromal sarcomas are not well understood. There is a relation between chromosomal aberrations and endometrial sarcomas. Chromosomal deletion on 7p was the most common finding (55.6%) in ESS and may play a role in tumor development and progression. These tumors are diploid with a low S-phase fraction. Recently, a specific translocation t(7;17) (p15;q21) with involvement of two zinc finger genes juxtaposed with another zinc finger protein 1(JAZF1) and joint juxtaposed with another Zinc protein 1(JJAZ1) was described in ESS[4]. YWHAE-FAM22 translocation identifies HG-ESSs[2]. HG-ESSs have a prognosis intermediate between LG-ESS and UUS. UUS exhibits no specific translocation pattern

The exact etiology is not known but association with estrogen use, polycystic ovarian syndrome and tamoxifen therapy is reported[4].Boardman CH[5] reported a case of ESS of ectocervix after goserelin therapy for breast cancer. In our case no associated factor was present.

3.3Diagnosis

25% of patients are asymptomatic.Most patients present with abnormal vaginal bleeding, polypoidal vaginal mass and dysmenorrhoea.The other symptoms could be urinary urgency, retention urine or constipation. Jaffe R[6] reported a case of ECSS in 1985 in the form of cervical polyp as in our case. Hasiakos D[3] reported low grade ESS of endocervix with clinical diagnosis of degenerated myoma. Olusola B[7] reported a case of endocervical stromal sarcoma in a 50 year old perimenopausal woman in whom clinical symptoms were suggestive of invasive cervical carcinoma. Recurrence is seen in about one third of patients.The recurrence is seen in pelvis and abdominal region. AmrSS[8] described a case of recurrent endocervical polyp (six times) in span of 28 months.Less commonly metastasis occur in lungs, liver and bones. Orbital metastasis was reported by Mehmet Metin Seker et al in 2014[9].

The differential diagnosis of polypoidal mass arising from cervix may be cervical polyp, leiomyomatous polyp, cervical carcinoma, sarcoma botrioydes, mixed mullerian adenosarcoma and rarely ESS. Diagnosis is not possible based on history and clinical findings.

Ultrasonography is not reliable and can lead to incorrect diagnosis of adenomyosis or uterine leiomyoma. Trans vaginal color Doppler shows low impedance flow compared to other benign tumors. Magnetic resonance imaging feature suggestive of ESS is the presence of bands of low- signal intensity within the area of myometrial invasion[4]. This is due to the worm-like permeation of tumor cells into the myometrium. Another feature is continuous extension of the lesion into the adjacent structures along the vessels, fallopian tubes, ligaments, and the ovaries.

Uterine curettings are also not helpful for diagnosis as the tumor mass is always intramyometrial.On histopathology, cervical polyps show endocervical glands and thick walled blood vessels, endometrial polyp has presence of endometrial glands. Mixed mullerian tumors show presence of glands and are seen in older age group. Spindle cell tumors are leiomyoma, rhabdomyosarcoma and ESS. Rhabdomyosarcoma occurs in young age with presence of rhabdomyoblasts. Sarcoma botryoides has cambium layer and myxoid stroma[1]. The differential diagnosis of ESS is from leiomyoma which is done on the basis ofconsistency of tumor, increased vascularity and mitotic activity. The cells are arranged in concentric fashion around blood vessels forming perithelioma pattern. There are less than 10 mitotic figures per high power field.

Immunohistochemistry: CD10 is a cell-surface neutral endopeptidase, seen originally on immature lymphoid cells.Neoplastic endometrial stromal cells are immunoreactive for CD10 while cellular leiomyomas are negative for CD10.Inhibin is also expressed in ESS. Desmin, h-caldesmonand**β**-catenin areImmuno-markers

characteristic of smooth muscle tumors and are present in cellular leiomyomas[4].ESS is positive for both estrogen and progesterone receptors.

ESS is a slow growing tumor with favorable prognosis. The prognosis depends on stage of tumor at the time of detection, grade, surgical margins, number of mitoses and vascular and lymphatic invasion[9].

3.4Treatment

The mainstay of treatment is surgery. The efficacy of adjuvant therapy is not proven.

3.4.1Surgery

ESS is a slow growing tumor and they are usually diagnosed at early stage, therefore in younger patients local excision is done[1]. The standard surgical treatment is TAH with bilateral salpingo-oophrectomy. As the tumor is hormonally responsive,Hormone replacement therapy containing estrogenand tamoxifen is contraindicated postoperatively[4].

According to Li AJ[10]bilateral salpingo-oophorectomy did not appear to affect time for recurrence or overall survival in stage-I ESS. Therefore he recommended preservation of ovaries in premenopausal women with stage-I ESS to prevent adverse effects of early surgical menopause.

Also routine lymphadenectomy does not improve overall survival rates[11]. Lymph node metastases was reported in 10% of cases who underwent lymph node dissection by Chan et al[12]and they recommend lymphadenectomy for both prognostic and treatment purposes of ESS. In addition, patients with positive nodal metastasis at the time of lymphadenectomy had significantly poorer survival (35.3%) compared with those with negative nodes (80.1%).

3.4.2Adjuvant therapy

For stage-IESS, only observation is required. Hormones, chemotherapy and radiotherapy may be used for stage II-IV, or recurrence. Due to the rarity of ESS, it is difficult to conduct prospective randomized clinical trials for determining the optimal treatment regimen. Treatment has been defined by the experience gained from retrospective case series and case reports.

3.4.2.1Hormone therapy

Reich O[13] described hormonal therapy in ESS.Hormone therapy is effective in ESS due to positive expression of steroid receptors. Hormones include megestrol acetate/medroxy progesterone, gonadotropin releasing hormone (GnRH) analogues, and aromatase inhibitors.The mechanism of action of progestins is to bind progesterone receptors and down regulate gene transcription leading to decreased endometrial gland and stromal proliferation[11].GnRH agonists down regulate GnRH receptors in the anterior pituitary leading to hypo-estrogenic state. The new generation aromatase inhibitors such as letrazole, when given orally, inhibits peripheral conversion of androgens to estrogen causing a reduction in circulating estrogens, and can be used as adjuvant treatment in ESS.In a study by Chu and colleagues[14], 75% of patients with stage-I disease did not recur if treated with adjuvant megestrol compared to 29% of similarly staged patients who did not receive adjuvant megestrol. They recommend adjuvant megestrol 160 mg daily.Dupont[11] reported disease free interval of 10 years by using megesterol acetate40 mg twice daily with weekly injection of 3.75mg leuprolide in a case with lung metastasis. Monthly intramuscular injections of leuprolide 7.5 mg can be given either alone or in combination with progesterone[4].

Letrazole is used in a dose of 2.5 mg daily for recurrent cases.Aromatase inhibitors and Gonadotropin releasing hormones are new effective alternatives for first line and second line treatment as progestins are poorly tolerated due to side effects[13].

The effective duration of preventive hormonal therapy is still undetermined. Various factors have been shown to influence hormone responsiveness. These are concentration of the sex steroid receptor, and relative expression of the progesterone receptor (PR) isoforms (PR-A and PR-B). The receptor concentration and the predominant isoform may vary in ESS originating in the uterus versus extra uterine sites, such as to make the latter less hormone responsive.

3.4.2.2Chemotherapy

The survival benefit of radiation therapy and chemotherapy in adjuvant setting is not clear[11].In case report of cervical polyp by Jaffe[5], the patient died one year after surgery due to abdominal metastasis. In case report of Amr SS[9] the patient was disease free nine years after surgery without chemotherapy or radiotherapy. Malgorzata[15] described adjuvant chemo with doxorubicin and cisplatinfor 3 cycles every 4 weeks and radiotherapy after local excision with patient being disease free after 57 months of treatment. Mehmet[10] reported adjuvant chemotherapy with ifosfamide, mesna and doxorubicin for 3 cycles followed by orbital radiotherapy with partial response in a case of orbital metastasis.Khosla D et al[16]reported the role of adjuvant chemo and

radiotherapy in stage IB2 and stage IIIB with patients being disease free at follow up.

3.4.2.3Radiotherapy

After adjuvant radiotherapy, local recurrence was less frequent as reported by Reed et al[17].Radiotherapy in the form of brachytherapy with or without pelvic radiation can be used as adjuvant therapy.

3.4.3Recurrent disease

Recurrences develop in one-third to one-half of patients with ESS and usually are limited to the pelvis and lower genital tract.The recurrence is more in patients with retained ovaries after hysterectomy or who receive estrogen replacement therapy. Distant metastasis may occur after several years[11]. There is no standard treatment protocol for recurrence. Local recurrences are treated with surgical re-excision or radiotherapy while systemic metastasis are treated with hormones or chemotherapy or a combination of these modalities.

3.4.4 Follow-up and survival rates

The 5-year survival rate for ESS is 54% to nearly 100% in FIGO stage I, and at stage-IIit is 30%. For advanced disease (stage III and IV) the survival is only 11%[4]. These tumors have a tendency for late recurrence;therefore long-term follow up is essential.

Follow up is once in 3 months for the first year and half-yearly for next 4 years. Annual follow up is recommended after that. Routine asymptomatic surveillance imaging is not recommended after primary treatment.

The relapse free survival depends on the tumor stage, myometrial invasion, adjuvant treatment, and bilateral salpingo-oophrectomy.

IV. Figures

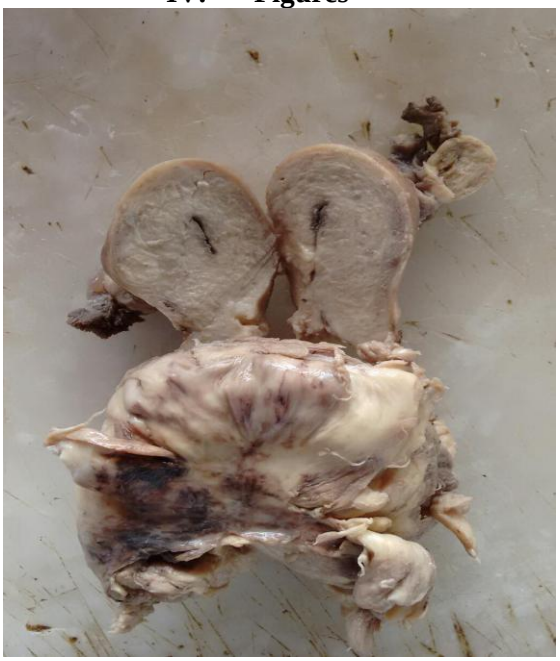

Fig 1 Gross photograph of Normal uterus with cervical polypoidal mass

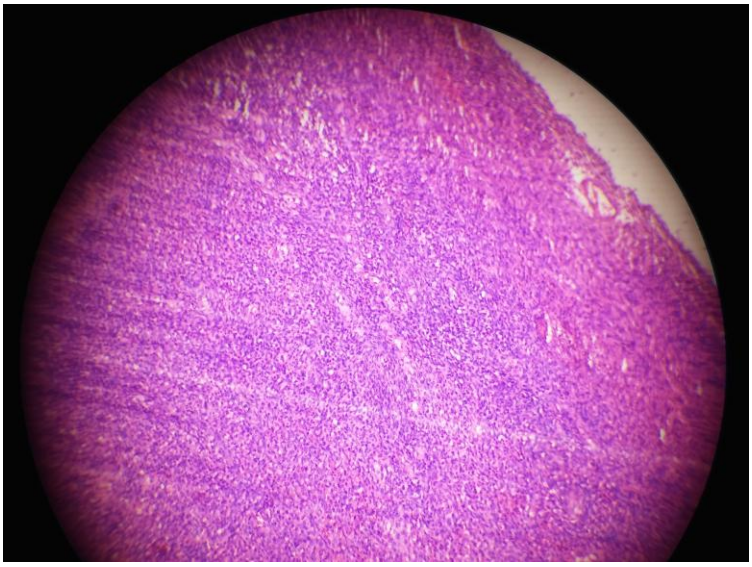

Fig 2 Photomicrograph showing cellular tumor composed of small uniform looking cells with dark staining round to oval nuclei (H and E ×10)

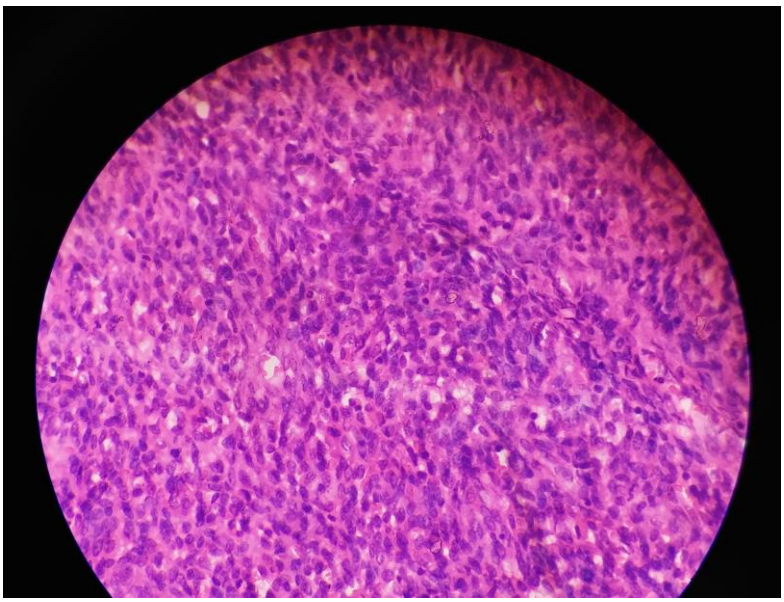

FIG 3 Photomicrograph ESS (H and E X 40)

V. Conclusion

The report describes a rare case of extrauterine ESS arising from cervix. To the best of our knowledge to date there are 18 cases reported in literature arising from cervix .

The aim is to report low grade ESS in an unsusal location.

The presentation was in the form of vaginal bleeding and polypoidal mass which was treated with surgery. The diagnosis was made retrospectively.

The diagnostic challenge is to differentiate ESS from leiomyoma. ESS should be kept as a differential diagnosis when polypoidal lesions present arising from cervix.

Since there are very few cases reported,treatment has been defined by the experience gained from retrospective case series and case reports. Main stay of treatment is surgery. Local recurrences are treated with excision or radiotherapy while distant metastasis are treated withprogestins or chemotherapy.Prospective studies are required to determine prognostic factors and optimal treatment modality.

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