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Endometrial Stromal Sarcomas: Case Series of Rare Mesenchymal Uterine Tumour

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Abstract

Endometrial stromal sarcoma (ESS) is a rare malignant tumor of endometrium compromising 10 % of all uterine sarcomas occurring in perimenopausal age group. Patient's mainly present with symptoms of abnormal vaginal bleeding, abdominal pain and rapid enlargement of abdomen. They are usually mistaken as leiomyoma, adenomyosis or intrauterine polyps and majority of time they are diagnosed postoperatively on histopathology. These tumours are mostly positive for both estrogen and progesterone receptors (ER/PR). Here we describe seven cases of ESS and their clinical course.

Keywords: Endometrial stromal sarcoma, rare tumour, leiomyoma

Introduction

Uterine sarcomas make up about 2% to 5% of all uterine cancers. The annual incidence of ESS is 1-2 per million women. It affects younger women and the mean age is 42-58 years. Diagnosis is mostly confirmed post-operatively after histopathological examination. Sarcomas of the uterus may arise from smooth muscle, connective tissue or the endometrial stroma. Based on tumour margin and cytological characteristics WHO has classified endometrial stromal tumour into benign endometrial stromal nodule (ESN) and endometrial stromal sarcoma. ESS can be divided into: - low grade and high grade depending on the cell morphology and mitotic count[1]. Certain risk factors like pelvic irradiation, unopposed estrogen exposure, tamoxifen and polycystic

ovarian syndrome can be causative agents[2].Magnetic resonance imaging (MRI) is useful for a preoperative diagnosis[3]. The important imaging feature that suggests ESS is the presence of bands of low-signal intensity within the area of myometrial invasion,

Total Abdominal Hysterectomy with Bilateralsalphino-oopherectomy (TAH-BSO) is considered as the standard surgical treatment. Radiotherapy helps in high risk cases to prevent local recurrences. Adjuvant hormone therapy in the form of progesterone, gonadotropin releasing hormone (GnRH) analogues and aromatase inhibitors are effective to prevent local recurrence and distant metastasis.

Case Report 1

A 48year old P_1L_0 female presented with complaints of pelvic mass which was rapidly increasing in size and abnormal vaginal bleeding since five months. On examination abdomen was tense and a large globular uterine mass was felt. An impression of leiomyoma was made. MRI pelvis revealed a 12.2 x 13.5 x11 cm of mass in endometrial cavity.

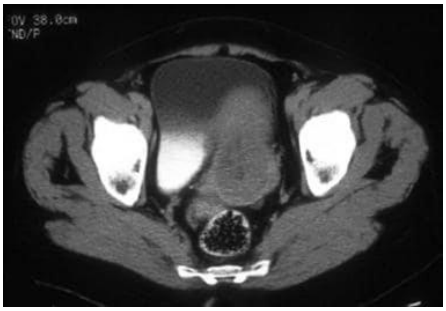

Figure 1(A): MRI Pelvis- 12.2 x 13.5 x 11 cm of mass in endometrial cavity

Laboratory tests showed CA125 was raised to 190U/ml; patient was planned for TAH-BSO with bilateral lymph node dissection and omentectomy. Post of period was uneventful. Histological examination reported low grade endometrial sarcoma involving myometrium, paratubal tissues and omentum. No lymphovasular invasion and perineural invasion seen and no lymph node were positive. Immunohistochemistry (IHC) study reported WT 1, CD10, Desmin, H caldesmon, ER, PR positive confirming diagnosis of LG-ESS.

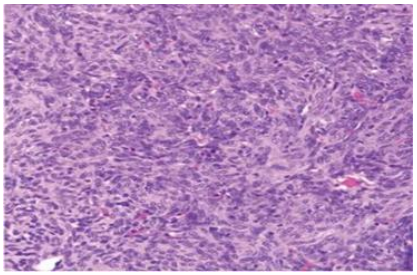

Figure 1(B): H&E Staining -fascicles of spindle cells with nuclei and fine chromatin network.

Hormonal therapy with Tablet Tamoxifen 20mg daily started and patient is now on follow up.

Case Report 2

A 48 year old P_4L_4 woman presented with progressive mennorhagia and abdominal pain. The patient was pale with haemoglobin of 6.8gm/dl. Her vitals and systemic examination was unremarkable. Abdominal examination revealed a soft firm tender mass with smooth margins arising from pelvis. On vaginal examination 5x6 cm of mass was felt involving cervix and upper 1/3rd of vagina. MRI of abdominopelvic region reported 4.3x5.9x7.4cm T1weighted isointense, T2 weighted hyperintense lesion along the anterior wall of uterus and cervix. There was bilateral external iliac lymph node largest 6x3.9x6.6cm on left side.

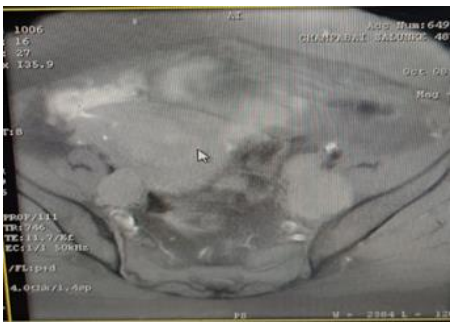

Figure 2(A): MRI Pelvis shows an enhancing lesion involving endometrial cavity.

TAH with BSO was planned but patient was unwilling for surgery hence only biopsy of the lesion was taken, Histological examination with IHC results showed CD10,Vimentin,Cyclin D1,CD-99,C-Kit diffuse positive ,focal positive for SATB2 and BCL2 , while negative for SMA , Desmin, S100, Pan CK. The Ki67 labelling index was 60- 70%. Findings favoured a diagnosis of HG- ESS. Patient is now planned for pelvic RT 50GY/25# /5 weeks with concurrent Cisplatin 40mg/m^2 weekly. Six weeks post RT patient is now on chemotherapy with Adriamycin 60mg/m^2 repeated every three weekly. Long term disease free survival is under assessment.

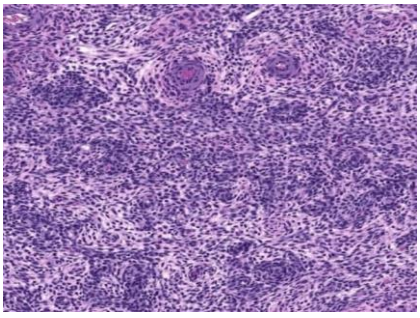

Figure 2 (B): H&E–Cells showing hyperchromatic nucleus with intervening stromal tissue

Case Report 3

A 46year old female P_3L_3 presented with a four-month history of prolonged bleeding per vagina and underwent TAH with BSO after endometrial curettage about 10 years ago. Pathological report revealed LG-ESS of endometrium with extensive myometrial invasion and vascular thrombi. Based on this report she received adjuvant chemotherapy with Cisplatin and Ifosfamide given every three weeks for three cycles and pelvic RT-50Gy/25#/5weeks.

Patient defaulted for further treatment and on presentation to our hospital she was found to have a pelvic mass with abdominal pain. Per vaginal examination revealed an exophytic mass. MRI of abdominopelvic region showed a lobulated retroperitoneal soft tissue mass of size 18x13x17cm causing mass effect on adjacent structures. Intraabdominal lymphadenopathy and ascites in the pelvic cavity were seen suggestive of recurrent neoplastic lesion.

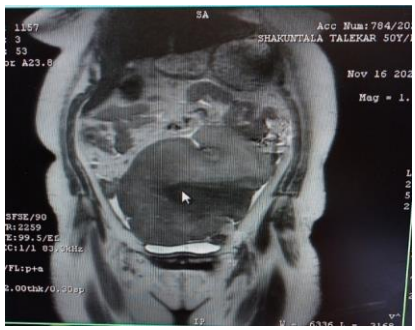

Figure 3 (A): MRI Pelvis – Enhancing mass -10 x 17 x 15.4 cm abutting Urinary bladder

Biopsy of the mass was done and pathological examination showed metastatic sarcoma of uterine origin. Immunohistochemistry studies showed positive staining for vimentin, weakly positive for CD 56, ER positive. Tumor was negative for EMA, CD10, Cyclin-D and SMA with low Ki67 index Diagnosis of recurrent ESS was made and patient was started on chemotherapy with Adriamycin 60mg/m^2 given every three weeks. After receiving three courses of chemotherapy MRI pelvis was suggestive of partial response but the patient was not willing for further intra-venous chemotherapy nor surgery. Hormonal therapy with Tablet Letrozole 2.5mg daily was started and after three months assessment CT Scan revealed progressive disease. Patient is now planned for chemotherapy with Docetaxel 70mg/m^2 (d1) and Gemcitabine 1gm/m^2 (d1& d8) three weekly three cycles. Long term disease free survival is under assessment.

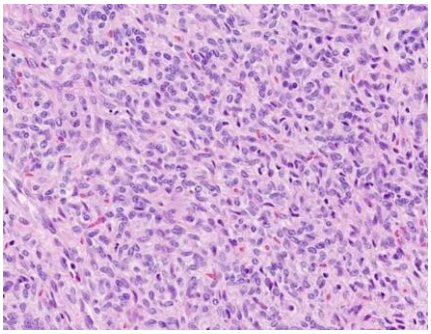

Figure 3 (B): H&E- cells showing diffusely scattered hyperchromatic nuclei with abundant stromal connective tissue.

Case report 4

A 29 year old P_1L_1woman presented with a two months history of menorrhagia, her past history was unremarkable. Pelvic ultrasound showed a small intraluminal leiomyoma 3x3 cm in lower uterine body. Cervical polypectomy with endometrial curettage was done. The polyp was friable and globular measured around 5x3cm.

Figure 4(A): Specimen of resected endometrial polyp.

On histopathological examination diagnosis of ESS-HG was made. Immunohistochemical studies showed positive staining for SMA and focally positive for ER and PR. Tumor cells are immunonegative for C-Kit, H caldesmon, cyclin D and CD10. The diagnosis of high grade ESS was established. Patient underwent total laproscopic hysterectomy with bilateral salphingo-oopherectomy. Post operative period was uneventful. Macroscopically an ulceroproliferative tumor in the fundus and body of the uterus measuring 1.8x1.5x0.5cm invading less than half of myometrium was seen. Lymphovascular emboli were present. Histologically diagnosis of residual component of HG-ESS of endometrium was made. Adjuvant hormone therapy Tab Megestrol 160mg daily was started.

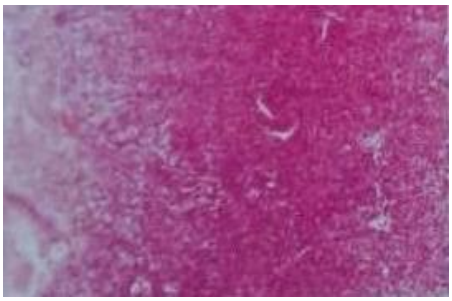

Figure 4(B): Microscopic examination-round cells with hyperchromatic nuclei mixed with stromal cells,

There was a progression free survival (PFS) of 13 months following which the PET -CT scan revealed metabolically active metastatic lesion in left lobe of liver 1.5x1.6cm , left adrenal gland 20x24 mm , focal mass lesion in right iliac bone and subpleural nodule in left upper lobe of lung. The patient was started on chemotherapy with Adriamycin 60mg/m^2 (d1) and Ifosfamide 2gm/m^2 (d1-d4) given every three weeks. After four courses chemotherapy partial response was noted. Patient was then planned for SBRT (Stereotactic Body Radiotherapy) 30Gy/5# to left adrenal lesion and RFA (Radiofrequency Ablation) for hepatic lesions. Post procedure patient was started on Tablet Anastrazole 1mg daily. Review PET-CT revealed complete resolution of hepatic metastasis. Patient is now on follow up and long term survival is under assessment.

Case Report 5

A 40 year old P_2L_2woman presented with four months history of abdominal pain and excessive vaginal bleeding. Her past history was unremarkable. CECT of the abdominopelvic region showed a heterogenous enhancing pelvic lesion on left side of size 5.8x9.7x8.1

cm ,left moderate HUN due to mass effect and enlarged left common iliac lymphnodes. Her CA125 was normal.

TAH with BSO was done with resection of enlarged pelvic nodes. On histopathology a large mass of size 8x6x3cm was seen in the endometrial cavity invading more than half of myometrium. Microscopic examination showed malignant spindle cell tumour with areas of cartilaginous degeneration and calcifications in the stroma with brisk mitosis .IHC studies revealed positive staining for NKX 2.2, NK X3.1, Cyclin-D1 and negative for SMA ,Desmin ,PR,S-100,CK, CD10,C-Kit,HMB-45 .MiB-1 proliferative index was 40%.Based on these findings a diagnosis of HG-ESS was made.

Post operative period was unremarkable. Adjuvant pelvic radiation 50Gy/25#/5weeks was given and patient is now planned for chemotherapy with Adriamycin 60mg /m^2 (d1) and Ifosfamide 1.5gm/m^2 (d1-d4), three weekly six cycles. Long term survival is under assessment.

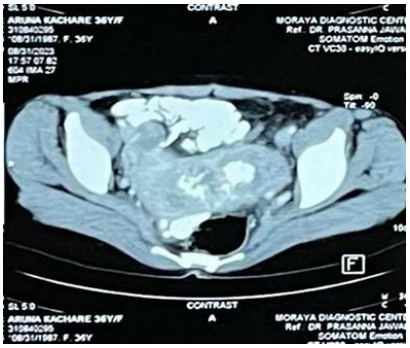

Figure 5: CECT pelvis- enhancing lesion– 5.8x9.7x8.1 cm in endometrial cavity

Case Report 6

69 yrs old P_5L_5 post menopausal woman presented with complaints of vaginal bleeding since five months. On speculum examination large cervical mass was felt. MRI pelvis showed heterogeneously enhancing soft tissue lesion of size 6.3x7x6.2 cm with necrotic areas arising from cervix and multiple hyperintense lesions in right lobe of liver-could suggest metastasis. FNAC of hepatic lesions was not possible as they were tiny to approach.

PET CT revealed heterogeneously enhancing soft tissue mass lesion of size 6.8 x 6.3 x 6.6 cm involving the cervix. Inferiorly lesion is seen extending to lower 1/3rd of vagina. No significant abdomino-pelvic lymphadenopathy. There were non -FDG avid hypodense lesions in right lobe of liver and upper lobe of right lung-reported less likely metastatic. Cervical biopsy revealed high grade undifferentiated neoplasm. IHC studies revealed positive staining for BCOR ,NKX 2.2, SAT B2 ,CD56 and negative forCD34,ERG.Ki-67 index was70-75%.Based on these findings a diagnosis of HG-ESS was made.

Patient is planned for chemotherapy with Doxorubicin 60mg/m^2 (d1)and Ifosfamide1.5 mg/m^2 (d1-d4) three weekly three cycles. Long term disease free survival is under assessment.

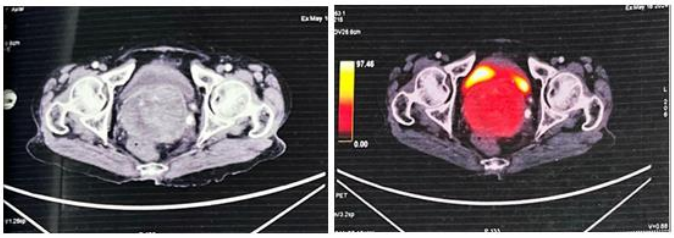

Figure 6: PET CT showing lesion of size 6.8 x 6.3 x 6.6 cm involving cervix.

Case Report 7

37 year old P_3L_3 woman presented with three months history of excessive vaginal bleeding and abdominal pain. On examination a large cervical mass was felt. . Her past history was unremarkable.

PET CT of the patient revealed heterogeneously enhancing large lobulated complex soft tissue mass lesion of size 11.4 x 19.2 x 19.5cm involving bilateral adnexae extending intrapelvically reaching upto lower abdominal wall. Intra-abdominal lymphadenopathy and ascites in the pelvic cavity were noted. Her CA125 was raised to 484.40 U/ml.

A biopsy of the cervical mass was performed and pathological examination showed sheets of moderately pleomorphic oval to spindle cells with fine to coarse chromatin. IHC studies showed positive staining for CD10, cyclinD1, CD99, BCOR and Ki -67-80%, findings suggestive of HG-ESS.

Patient was planned for chemotherapy with Doxorubicin 60mg/m^2 three weekly three cycles. Despite treatment patient experienced rapid progression of disease and succumbed two months later.

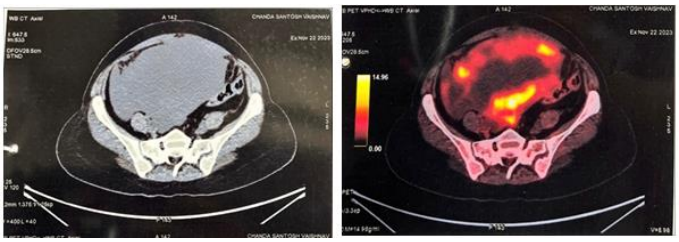

Figure 7: PET CT showing intrapelvic lesion of size 11.4 x 19.2 x 19.5 cm involving bilateral adnexae.

Discussion

According to the National Cancer Database, which is a nationwide, facility-based, comprehensive database established by the American Cancer Society and Commission on Cancer of the American College of Surgeons, survival in patients with HG-ESS remains poor[5]. The median overall survival was 19.9 months (95% CI, 17.1–22.1 months), and the five-year overall survival was only 32.6% (95% CI; 30.1- 35.3%). Prognostic factors negatively associated with survival include patients age, tumor size, omission of lymphadenectomy, pathologically positive resection margins, and distant or nodal metastasis[5].

Endometrial stromal sarcoma affects postmenopausal age group women. Majority of patient present with abnormal genital bleeding, abdominal pain and pelvic mass. They are differentiated between low grade and undifferentiated tumor is made on basis of nuclear pleomorphism and necrosis. Early diagnosis is essential because patient survival is directly related to tumor stage. IHC will help in detection of tumor marker specific ESS. Immunomarker such as desmin , H-caldesmon , oxytocin receptors while CD 10 and inhibin expression is feature of ESS[6]. Differential diagnosis includes several soft-tissue neoplasms demonstrating arborizing vasculature, highly cellular leiomyoma, cellular endometrial polyp, low-grade mullarianadenosarcoma, and adenomyosis[7]. Extra-genital ESS may be confused with gastrointestinal stromal tumors, hemangiopericytoma, lymphangiomyomatosis, or mesenchymal cystic hamartoma of the lung[8,9]. ESS of the ovary is difficult to distinguish from sex-cord stromal tumors. Primary line of management is surgery –TAH-BSO and excision of grossly detected tumor. Post operative radiotherapy and hormonal therapy help in preventing recurrence. Hormonal therapy has shown to be effective in ESS because of estrogen and progesterone receptors in it. Hormones include megestrol/ medroxyprogesteroneacetate, gonadotropin releasing hormone analogues and aromatase inhibitiors[10,11.] Few cases of recurrent ESS was treated with etoposide, cyclophosphamide and doxorubicin, ifosphamide and gemcitabine. Newer treatment options to prolong the survival of patients are being explored. 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. Final diagnosis and treatment however depends on histopathological and IHC report. 5 year survival rate for ESS is 54% to nearly 100 % for stage I, for advanced disease the survival is only 11%[12, 13].

Conclusion

Large variation in pathologic characteristics with rare appearance of the disease. ESS is difficult to find in

population. IHC may help in diagnosis and planning therapeutic strategies. Vascular targeted agents combined with traditional chemotherapy are expected to become treatment of choice for ESS to improve the overall survival and improve QOL in these patients.

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