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CASE REPORT

High Grade Endometrial Stromal Sarcoma Tumor Recurrence

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Background

Endometrial stromal sarcomas (ESS) are very rare type of malignant uterine tumors, making up around 0.2-1% of all uterine neoplasms and less than 10% of uterine sarcomas.

Clinical Case

59 year old lady, previously treated for grade III invasive ductal breast carcinoma with surgery, anthracycline chemotherapy and external beam radiotherapy to the pelvis to ablate the ovaries, presented with postmenopausal bleeding. A transvaginal ultrasound scan (TVUS) showed a 4.5cm by 5.1cm heterogeneous area in the endocavity, suspicious of haematometria. Hysteroscopy, dilation and curettage (D&C) noted multiple clots as well as a mass, suspicious of a fibroid or tumour arising from the endometrium. An MRI of the uterus reported a pedunculated intracavitary fibroid. A total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH + BSO) was performed in view of worsening symptoms. Histology reported high grade endometrial stromal sarcoma, limited to the uterus, measuring 75mm in greatest dimension, pT1b Nx (FIGO IB). Six months later the patient presented again with pv bleeding. Upon examination a polypoid exophytic mass was noted in the vaginal vault. A sample was taken and sent for histology, which reported features in keeping with recurrence of the previous endometrial stromal sarcoma. An MRI of the pelvis showed vaginal vault stump recurrence and a 1.7cm serosal nodule on the mid sigmoid colon. CT of the abdomen and pelvis showed no evidence of extra pelvic disease. Patient was scheduled for a resection of the upper vagina including the vault nodule and adjacent sigmoid colon. Histology of the resected specimens reported recurrence of the high grade uterine stromal sarcoma in the vaginal vault, which invaded the sigmoid colon.

Conclusion

The mainstay treatment for ESS is a TAH + BSO. This case demonstrates that although complete remission can be obtained, recurrence can still happen. Clinicians should follow these patients closely, even when disease free. Early diagnosis and surgical removal of recurrence is of utmost importance to survival of these patients.

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Postmeopausal bleeding (PMB) is defined as vaginal bleeding that occurs at least twelve months after a woman's last period. It is a common complaint with a broad differential diagnosis but endometrial cancer must be excluded. About 4-11% of postmenopausal women report vaginal bleeding. Only 10% of those that present to their gynaecologist have endometrial cancer.[1]

Endometrial stromal sarcomas are a very rare type of malignant uterine tumors, making up around 0.2-1% of all uterine neoplasms and less than 10% of uterine sarcomas. The age of women affected by this type of malignancy ranges between 42 to 58 years, with an incidence of 1-2 per million women.[2]

CASE REPORT

We present a case about a 59 year old lady who presented with postmenopausal bleeding in 2022. Her past medical history included antithrombin III deficiency and left breast grade III invasive ductal carcinoma, the latter treated in 2002. The breast cancer was oestrogen receptor positive (ER+) and was treated with curative intent in 2002 with a wide local excision and axillary clearance, followed by adjuvant anthracycline based chemotherapy, external beam radiotherapy (RT) and tamoxifen. Tamoxifen was stopped due to recurrent deep vein thrombosis (DVTs) – on background of anti-thrombin III deficiency. At the time she received pelvic irradiation to a dose of 14Gy/4 fractions (EQD2 20Gy) to induce ovarian suppression as part of her breast cancer treatment. This was followed by secondary amenorrhoea.

She complained of brownish/pinkish vaginal discharge. Speculum and vaginal examination was normal. A transvaginal ultrasound scan (TVUS) showed an anteverted uterus with a 4.5cm by 5.1cm heterogeneous area in the endocavity, suspicious of haematometria.

Further investigation included a hysteroscopy, dilation and curettage (D&C). During the procedure, multiple clots were noted as well as a mass, suspicious of a fibroid or tumour arising from the endometrium. An MRI of the uterus was also performed and confirmed a 6.0 x 4.9 x 4.3 cm heterogeneously enhancing intracavitary mass connected by means of a peduncle to the left side of the uterine wall, in keeping with a pedunculated intracavitary fibroid (Figure 1). The fibroid showed areas of devascularization/infarction with early sloughing into the endometrial cavity.

A total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH + BSO) was carried out as her primary treatment. Histology from this revealed a high grade endometrial stromal sarcoma, limited to the uterus, measuring 75mm in greatest dimension with clear resection margins, pT1b Nx (FIGO IB). Her case was discussed at the gynae-oncology multi-disciplinary team meeting with no adjuvant treatment indicated.

Six months later, the patient had a repeat vault smear that was normal. Three months after a normal vault smear the patient presented again with pv bleeding. On examination a polypoid exophytic mass was noted in the vaginal vault. This was biopsied and histology confirmed local recurrence of endometrial stromal sarcoma.

An MRI of the pelvis was performed to plan further management. This was suggestive of recurrence within the right lateral aspect of the vaginal vault stump measuring 1.6cm with likely involvement of

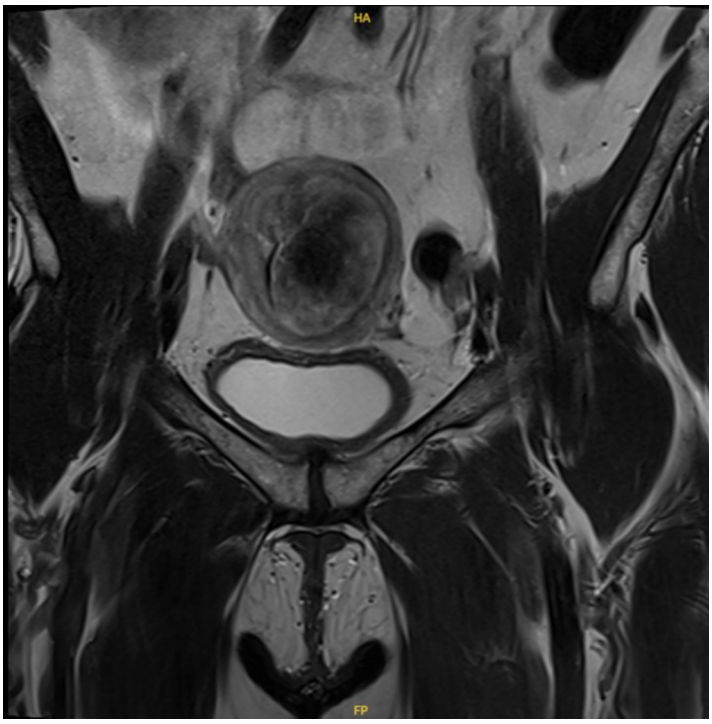

Figure 1 *Cross-sectional T1 weighted MRI of patient's pelvis showing a 6.0 x 4.9 x 4.3 cm heterogeneously enhancing pedunculated intracavitary mass, in keeping with a pedunculated intracavitary fibroid. The fibroid shows areas of devascularisation/ infarction with early sloughing into the endometrial cavity.*

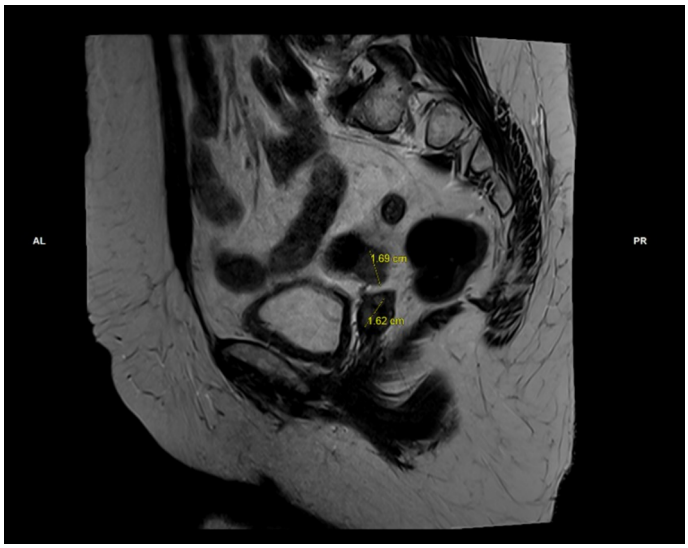

Figure 2 *Cross-sectional T1 weighted MRI of patient's pelvis showing a 1.7cm serosa nodule on the mid sigmoid colon – in very close proximity of the vaginal stump.*

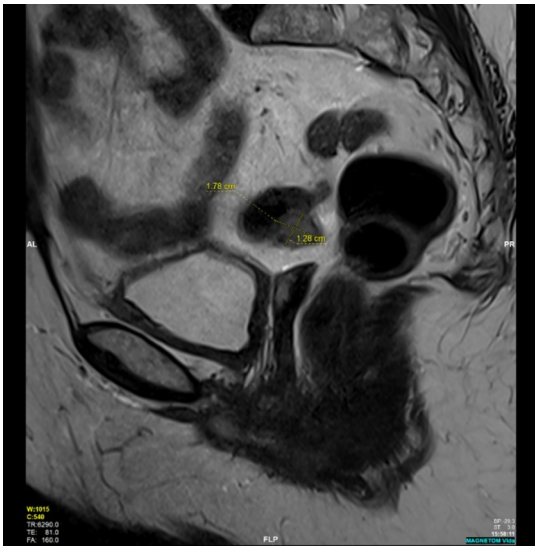

Figure 3 *Another cross-sectional T1 weighted MRI of patient's pelvis showing the 1.7cm serosa nodule on the mid sigmoid colon – in very close proximity of the vaginal stump. Its radiological characteristics are identical to those of the described vaginal mass thus its likely to represent another focus of disease recurrence.*

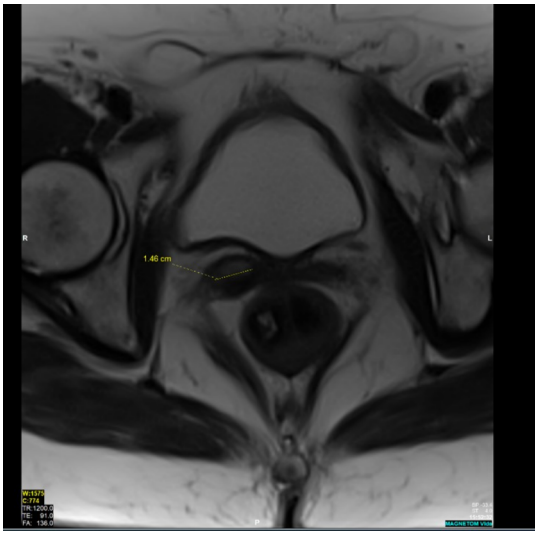

Figure 4 *A cross-sectional MRI of patient's pelvis showing a 1.46cm T2 hyperintense, T1 isointense mass on the right lateral aspect of the vaginal vault stump. This demonstrates restricted diffusion.*

the serosa within the midsigmoid colon (**Figure 2, 3 and 4**). Its radiological characteristics were identical to those of the described vaginal mass likely representing another focus of disease recurrence.

CT of the abdomen and pelvis showed no evidence of extra pelvic disease.

Patient was scheduled for a resection of the upper vagina including the vault nodule with the general surgeons. Part of the sigmoid colon, including the above described nodule, was resected using an end-to-end anastomosis. Urologist was also involved due to close proximity of the lesion to the bladder and the presence of adhesions due to previous abdominal surgery.

Histology of the resected specimens showed recurrence of high grade uterine stromal sarcoma in the vaginal vault, invading the sigmoid colon - disease here having ulcerated through the vaginal vault epithelium and extended into muscularis propria layer of adjacent bowel. Resection was microscopically complete with clear margins.

Recovery was complicated by DVT of the right lower limb. Rivaroxaban was started as per haematologist advice. Her recovery was otherwise uncomplicated and she was discharged after a week. A new baseline post-operative CT showed no evidence of residual disease.

Adjuvant chemotherapy with gemcitabine and docetaxel was stopped after 3 cycles due to recurrent episodes of neutropenic sepsis and following chemotherapy she received radiotherapy and vaginal vault brachytherapy.

DISCUSSION

Background

Endometrial stromal sarcomas are rare tumors of the uterus. Diagnosis is difficult and in the majority of cases only confirmed after surgical resection of presumed benign disease, usually a polyp or fibroid. First line surgical management is a TAH + BSO. For early disease, surgery can achieve cure. Leaving the ovaries in situ does not affect survival and is an important consideration in young women. Adjuvant chemotherapy often follows surgery for high grade ESS. The role of adjuvant hormone therapy (such as progesterone and aromatase inhibitors) is established, though based on small retrospective studies[2], in low grade ESS in reducing the risk of

recurrence but is thought less effective in higher grade disease.[3] Local as well as distant metastasis can occur, even after 20 years from the initial diagnosis.

Pathology

Endometrial stromal tumors pose diagnostic dilemmas for pathologists as the classification and pathogenesis of these tumors has been debated for years. The latest classification system was issued by the World Health Organisation (WHO) in 2014. WHO categorises endometrial stromal tumors into 4 categories;

- Endometrial stromal nodule (ESN)
- Low-grade endometrial stromal sarcoma (LG-ESS)
- High-grade endometrial stromal sarcoma (HG-ESS)
- Undifferentiated uterine sarcoma (UUS)

The presence of distinct translocations, tumor morphology and prognosis define these categories.[4]

Diagnosis

90% of ESS present with abnormal uterine bleeding and up to 70% have uterine enlargement. Pelvic pain and dysmenorrhea may also be present. 25% of women are asymptomatic. The bulk of the tumour is most often localized to the myometrium, with involvement of the endometrium in the majority of cases, so uterine curettage may provide the diagnosis. Definitive diagnosis, however, is usually confirmed after TAH as ESS appears similar to normal myometrium histologically. Lesions might also be completely intramyometrial.[5]

TVUS alone is not accurate enough and may lead to an incorrect diagnosis of adenomyosis or leiomyoma. MRI may be helpful pre-operatively. Evidence of extension of the lesion into surrounding structures as well as presence of bands of low-signal intensity within the area of myometrium involved are highly suggestive features of ESS.[5]

Prognostic factors

Prognosis is primarily dependent on the initial stage of disease at the time of detection. International Federation of Gynaecology and Obstetrics (FIGO) staging (Table 1) for uterine sarcoma is used to stage ESS.[6]

Treatment

Surgery (TAH +BSO) is the most effective treatment for ESS. There is no evidence for adjuvant endocrine therapy in high grade ESS, but chemotherapy is used instead. Adjuvant endocrine therapy is, however, used in low grade ESS. The efficacy of adjuvant therapy is not proven but chemotherapy is often given due to high risk of recurrence, decision making often extrapolated from the management of leiomyosarcomas.[7]

In this patient, at time of initial ESS diagnosis, stage 1b disease was confirmed and clear resection margins were achieved. At this point, there was no indication for adjuvant treatment as per international guidelines – UK Soft Tissue Sarcomas (STS) guidelines.[8] Choice of adjuvant treatment would also be complicated by her history of previous treatment with anthracycline chemotherapy, which is the first line drug of choice in sarcoma. She had also received previous pelvic RT. There remains lack of evidence for improved long-term survival following adjuvant chemotherapy, mainly due to rarity of these cases. Data collected from the largest trial of adjuvant chemotherapy for STS, the EORTC 62, 931, failed to demonstrate any clear benefit from adjuvant chemotherapy in local control, relapse-free survival or overall survival.[9]

Table 1 *FIGO Surgical Staging of Uterine Sarcoma: Leiomyosarcoma and Endometrial Stromal Sarcoma*

Stage	Description
I	Limited to the uterus
IA	Tumor ≤ 5 cm in largest dimension
IB	Tumor > 5 cm
II	Extending beyond the uterus but within the pelvis
IIA	Involving the adnexa
IIB	Involving other pelvic tissues
III	Infiltrating abdominal tissues
IIIA	In one site
IIIB	> 1 site
IIIC	Pelvic and/or para-aortic lymph node metastasis
IVA	Invading bladder or rectum
IVB	Distant metastases

Adapted from staging established by the International Federation of Gynecology and Obstetrics (FIGO) and American Joint Committee on Cancer (AJCC), AJCC Cancer Staging Manual, ed. 8. New York, Springer, 2017.

Recurrent disease

Recurrences are common and occur in one-third to one-half of patients diagnosed with ESS. These are often local recurrences but distant metastasis (usually to the lungs) also occur after several years.[5]There is no standard therapy for recurrent disease. Hormone therapy, chemotherapy, radiation, surgical re-excision or a combination of these methods have been used. A few published case reports describe cases of recurrent ESS treated with doxorubicin, etoposide and cyclophosphamide as well as surgical re-excision of local recurrences. Our patient received gemcitabine and docetaxel chemotherapy, as she had previously received anthracycline chemotherapy (for breast cancer) followed by pelvic radiotherapy 45Gy/25 fractions and vaginal brachytherapy.

RT induced pelvic sarcomas

Previous RT may or may not have contributed to this patient's current disease. The median latency period for development of malignancy post RT is reported as approximately fourteen years. However, radiation induced sarcomas have also been described, after a far shorter period.[10] Examples of published cases include a case of pelvic sarcoma with rhabdomyoblastic differentiation 12 years after RT for cervical cancer and another case of an osteosarcoma 11 years after RT, also for cervical cancer. Though a history of pelvic RT may increase the risk of developing uterine sarcoma, this association appears to be stronger for carcinosarcoma.

There are no specific criteria for identifying whether a sarcoma arising in a previously treated RT field is primary or radiation induced. Histopathological features suggestive of radiation-related changes like atypical fibroblasts, alteration of vascular structure, dense fibrosis and fibrous stroma in the dermis adjacent to the sarcoma have been described but cannot definitely allude to causation.[11]

In 1948, Cahan proposed criteria to identify sarcomas as secondary, treatment-related tumor rather than sporadic. These criteria were later revised in 1971 and 1999 and include: [12]

- Radiation must have been administered in the area where the sarcoma arose. The area includes a five percent isodense line of the previously irradiated field.
- There should be a difference between the histological features of the original lesion and the sarcoma post radiation
- Patients must be excluded if they have inherited syndromes that predispose them to sarcomas, like Rothmund-Thomson and Li-Fraumeni syndrome.
- The minimal latency period i.e. period of exposure to RT and histological diagnosis, initially was five years but shorter times frames have been also reported.

The prognosis of patients with secondary radiation-associated sarcomas is poorer than that of patients with primary sarcomas, with most series reporting overall five-year survival rates in the range of 10 to 50 percent.

CONCLUSION

In this lady's case, it is possible that RT contributed to the recurrence of disease. Nowadays RT is no longer used for ovarian ablation. Pre-menopausal women who do not tolerate tamoxifen (as happened in this case due to recurrent DVT secondary to anti-thrombin III deficiency) would either be referred for BSO or suppressed medically with a goserelin acetate given in combination with an aromatase inhibitor. Surgery (TAH +BSO) is the most effective treatment for ESS.

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