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Case Report

Uterine Sarcoma; An Unusual Presentation - Case Report and a Literature Review

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Abstract

Uterine sarcomas are a rare heterogeneous group of tumours accounting for approximately 1% of all female genital tract malignancies and 8% of all uterine malignancies, a notably higher proportion than previous estimates of 2 - 3% [1]. This increased incidence may be explained by improved diagnostics, accompanied by a true increase of incidence in the ageing population [1]. We present a case of uterine sarcoma in a 49-year-old woman, mother of three, who presented initially with menorrhagia. Her examination under anaesthesia (EUA), hysteroscopy, and dilatation and curettage (D and C) revealed no significant abnormalities. The endometrium looked unremarkable and a Mirena coil was inserted. She continued to have persistent symptoms and a pelvic ultrasound scan revealed a 5 cm fibroid.

Ten months later, the patient presented again with heavy bleeding per vagina. An urgent pelvic ultrasound showed a significant increase in the fibroid size, now measuring 10.3 x 11.3 x 10 cm. No other pelvic or abdominal abnormalities were noted, with the Mirena coil remaining in situ. The patient agreed to start LHRHa injections for symptomatic management, however this had little impact and she presented again three months later, still in significant pain. Her abdomen was distended with a large pelvi-abdominal mass reaching the level of the umbilicus. She was considered for an urgent laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). Laparotomy revealed an enlarged uterus reaching the umbilical level, with multiple metastatic lesions covering the uterine surface, bowel, and omentum. The planned surgical intervention was abandoned, and multiple biopsies were taken. CT-TAP was performed and revealed distant widespread metastases. Palliative treatment was decided after discussion with the multidisciplinary team (MDT), patient, and immediate family.

Keywords: *Uterine Sarcoma; Endometrial Stromal Sarcoma; ESS; Leiomyoma; Fibroid; Laparotomy; Bleeding*

Background

Uterine sarcomas are a rare subset of cancer that account for approximately 3 - 7% of uterine malignancies [2]. Although the clinical presentation is non-specific and dependent on the histological subtype, classically a rapidly growing pelvic mass, with or without vaginal bleeding and abdominal/pelvic pain, is noted [1,3]

Historically, the International Federation of Obstetrics and Gynaecology (FIGO) staged uterine sarcomas according to the 1988 system developed for carcinomas [4]. FIGO presented a new classification system specific to uterine sarcomas in 2009 to better reflect their unique biological behaviours [2,4]. The Gynaecological Oncology Group currently classifies uterine sarcomas into two distinct groups, epithelial and mixed epithelial-nonepithelial, based on the type of cancerous cells and their presumed tissue of origin [2]. Epithelial sarcomas include leiomyosarcomas (arising from the smooth muscle of the myometrium), endometrial stromal sarcomas (ESS), and undif-

ferentiated endometrial sarcomas (UES) (both arising from the endometrium), whilst adenosarcomas are classified as mixed epithelial-nonepithelial malignancies [5].

A notable absence from this list is the uterine carcinosarcoma, which has recently been reclassified as a metaplastic carcinoma and is therefore no longer considered among the uterine sarcomas [2]. This reclassification has left leiomyosarcoma as the most common histological variant of uterine sarcomas. Leiomyosarcoma is an aggressive tumour; 5 - year survival has been estimated to be 25 - 76%, dropping to only 10 – 15% in patients with metastatic disease [6]. In contrast, ESS is far less aggressive. Patients with stage I ESS have a 5 - year overall survival rate of >90%, falling to 50% for patients with stage III-IV. Patients with late-stage disease are also likely to relapse earlier and have a higher overall mortality rate [7].

Clinical Case

We present a case of uterine sarcoma in a 49-year-old woman, parity 3, who presented initially to the gynaecology outpatient clinic with menorrhagia. The patient had trialled a non-hormonal treatment for six months with no benefit and was on a multi-drug painkiller regimen while awaiting an elective hip replacement procedure. Her cervical smears to date had been normal. She underwent examination under anaesthetic (EUA), hysteroscopy, and dilation and curettage (D and C). Hysteroscopic findings showed a bulky, retroverted uterus with a thickened, suspicious looking endometrium. A thorough curettage was performed, and the endometrial sample was sent for urgent histological review. A Mirena coil was also inserted during this procedure. The histology report showed a proliferative phase endometrium, with no endometritis, hyperplasia, or malignancy. The patient's pelvic ultrasound confirmed a retroverted uterus and noted a 5 cm fibroid at the uterine fundus.

The patient presented back to clinic ten months after the initial procedure with heavy menorrhagia. An urgent pelvic ultrasound was arranged, which showed a significant increase in the previous 5 cm fundal fibroid. A large, solid fibroid mass measuring 10.3 x 11.3 x 10 cm was seen, with no adnexal cysts. No other pelvic or abdominal abnormalities were noted, with the Mirena coil still *in situ*. Following a lengthy consultation, the patient was started on LHRHa injections to manage her bleeding.

At her 6-week follow-up, the patient reported a significant reduction in her bleeding but was experiencing significant pain in her hips. No pelvic/abdominal examination was performed, but another follow-up was arranged to re-evaluate her in 8 weeks' time. At this following appointment, the patient was in a significant pain. Her abdomen was distended with a large pelvic-abdominal mass reaching the level of her umbilicus.

Following this consultation, the patient was referred for an urgent laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy (TAH-BSO).

At laparotomy, a bulky uterus reaching the umbilical level was noted. The uterus had an irregular surface and multiple metastatic lesions covered the uterine surface, bowel, and omentum. Morbid adhesions were found in the abdomen, making it impossible to visualise other pelvic or abdominal organs. An omental biopsy was taken and an intraperitoneal drain was inserted due to bleeding from the metastatic foci, following which the abdomen was closed. Histopathology of the omental biopsy showed a high-grade ESS. There was diffuse staining with Cyclin-D1, although staining for cytokratins (AE1-3, CK5/6, CK14, Desmin, Calponin, SMA, CD34, WT1, Calretinin, Inhibin and HMB45) were all negative. CT-TAP was performed post-operatively and revealed multiple metastatic nodules in the lungs, liver and omentum. There were also extensive bony metastases with bilateral hydronephrosis correlating to stage IVB disease. A multidisciplinary team discussion of the case culminated in referral for palliative treatment.

Discussion

This case highlights the importance of considering uterine sarcomas as a differential for a presentation of vaginal bleeding with a uterine mass. ESSs are very rare; only comprising 0.2% of all uterine malignancies and less than 10% of all epithelial uterine sarcomas [8]. Clinical factors tend to be poor differentiators between ESS and benign leiomyoma – the age of onset is fairly similar in both diseases and symptoms largely mimic one another [9,10]. Although the rarity of ESS makes it an unlikely differential, a recent literature review has estimated that 90% of women with ESS present initially with uterine bleeding, and 70% present with uterine enlargement [9]. Although only 25% of ESS cases are asymptomatic, roughly 30-50% present with extra-uterine spread [8]. The presence of large and rapidly growing leiomyomas should therefore prompt investigation for ESS, as it has notably similar symptoms [11].

The patient's symptoms were investigated with a pelvic ultrasound on this occasion. Ultrasound diagnosis of ESS is often unreliable as it may suggest an incorrect diagnosis of adenomyosis or leiomyoma, with MRI also producing similar results [9,11]. Thus, there can be substantial difficulty in distinguishing between ESS and leiomyoma pre-operatively, as it can mimic both the physical appearance and imaging characteristics of benign leiomyoma. It is unsurprising that this has led to 75% of women with ESS receiving an incorrect leiomyoma diagnosis [12].

Peri-operative diagnosis of ESS is also very difficult due to an appearance that can often mimic highly cellular leiomyomas, although the presence of large, thick-walled muscular vessels would make ESS the more likely differential [11]. In this patient's case, extensive metastases and haemorrhagic lesions were clear signs of malignancy. Although the patient had undergone D and C on initial presentation, this unfortunately also has poor diagnostic reliability due to the similarity between ESS and normal endometrium [12]. ESS is also likely to grow through the intramural sections of the uterus, making histopathological diagnosis even more challenging [11].

It appears that immunohistochemistry is a better approach to accurately diagnose ESS. There are several disease-specific markers, including CD10, inhibin, and oestrogen/progesterone receptor positivity [8,11]. These immunological markers can also be useful to differentiate between ESS and leiomyosarcoma – ESS tends to be positive in CD10 and inhibin, while leiomyosarcoma tends to be positive in h-caldesmon, desmin, and oxytocin receptors [8,9]. Immunohistochemistry of our patient was negative for all markers except Cyclin-D1, which is an unusual presentation for ESS.

Treatment

As ESS is a rare malignancy, there is a lack of established treatment consensus and further clinical trials are needed to adequately establish the efficacy of different approaches [13]. One point of consensus is that TAH-BSO is the most effective treatment option for reducing recurrence of disease, regardless of stage of grading [14,15].

Adjuvant therapy can also provide effective treatment; studies have repeatedly demonstrated the efficacy of treating low-grade recurrent ESS with hormonal therapy, making this an important consideration for both the clinician and the patient [16-18]. Anti-oestrogen therapy, by way of an aromatase inhibitor or progestogen, can be considered in advanced disease, and has demonstrated promising results in this context [9,19,20].

In contrast, adjuvant radiotherapy is not often considered for low-grade ESS and is instead usually reserved for high-grade disease [19,21]. Patients who have previously attempted hormonal treatment or are unable to tolerate it may also be considered for systemic chemotherapy, with agents such as ifosfamide and doxorubicin as primary options [13,20,21]. Unfortunately, for patients with very advanced disease, as with our patient, palliative care may be the most appropriate option.

Prognosis

Although estimates on prognosis for ESS patients have been reported in literature, there is a lack of reliable data from large clinical trials. Current estimates are that patients with low-grade ESS have an impressive 5-year overall survival rate ranging from 54 - 100%, dropping to around 30% in patients with stage II and approximately 11% for stages III-IV [9]. These figures demonstrate the vital importance of early diagnosis and treatment to ensure the best prognosis possible for the patient.

The tendency for ESS to have a late recurrence makes long-term follow-up a priority; it is recommended to follow-up quarterly for the first year, every 6 months for the following 4 years, and annually thereafter [9]. The risk of recurrence is high enough to indicate such close monitoring as low-grade ESS has a recurrence rate of 25 - 31% [14,23]. The rate of lymph node metastases, which are an independent predictor of poor prognosis, has been estimated to be between 10 - 45% [24,25]. As ESS is a relatively rare malignancy, more research is needed to identify other important prognostic indicators, especially for high-grade disease.

Conclusion

ESS is a rare sub-type of uterine sarcoma, with poor consensus in literature on its treatment and prognosis. Data from large, randomised control trials is needed to enable better care for patients suffering from this disease. Although it is widely agreed that surgery is the best initial treatment, the role of adjuvant therapy is not well-described beyond some evidence for the use of hormonal therapies. The rarity of these tumours presents challenges for diagnosis, with cases often being misdiagnosed as benign leiomyoma and consequently delaying necessary treatment. Clinicians should have a low threshold for suspecting malignant disease and should be wary of the false confidence that can arise from a leiomyoma diagnosis.

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