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Case report

Vaginal epithelioid angiosarcoma: A literature review of a rare entity in an unusual site

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ABSTRACT

We describe an extremely rare case of a 66-year-old woman with a vaginal epithelioid angiosarcoma. She presented with constitutional symptoms, pelvic pain, vaginal bleeding, and a violaceous vaginal lesion. A thorough gynaecological examination, tissue biopsy and imaging were crucial to establish an accurate diagnosis. With only 3 other cases reported in the literature, epithelioid angiosarcoma of the vagina seem to present late due to their nonspecific presentation and secluded location. Once diagnosed, optimal treatment is difficult to determine and together with the overly aggressive behaviour of these tumours, they are associated with a poor prognosis. To our knowledge, our case study and systematic literature review is the first to compare the management outcomes of epithelioid subtype angiosarcomas of the vagina. The rarity of this pathology contributes to diagnostic difficulties and lack of consensus regarding treatment of angiosarcomas of the vagina.

1. Introduction

Angiosarcomas are aggressive endothelial-comprised malignant neoplasms with vascular or lymphatic origin, making up less than 1% of all soft tissue sarcomas (McAdam et al., 1998). These tumours have a predilection for skin, breast, and deep soft tissue and account for 5.4% of all skin sarcomas (McAdam et al., 1998; Avancini et al., 2016). The first case of a vaginal angiosarcoma was presented in 1983 (Prempree et al., 1983). Fifteen years later McAdam reported the distinctive and rare vaginal epithelioid angiosarcoma variant. Here we present the fourth case of this rare tumour subtype and review the management of all vaginal angiosarcomas reported in the literature.

2. Case

A 66-year-old, para 1, presented to her general practitioner with a 3 months history of constitutional symptoms, including fatigue, drenching night sweats and weight loss. She also described light intermittent vaginal bleeding for 3 weeks. There were no other significant medical co-morbidities or previous surgical history.

As part of the patient's work up, a chest, abdomen, and pelvis computed tomography (CT) and transvaginal ultrasound were performed. They reported a bulky uterus with a normal endometrial thickness of 1 mm, and a rounded 2.5 cm lesion with some calcification located at the right lower uterine segment, most likely representing a pedunculated exophytic fibroid or dermoid cyst (Fig. 3).

The patient was referred to a local gynaecology unit for further assessment and an initial examination under anaesthetics (EUA), cystoscopy and hysteroscopy with endometrial sampling were performed. A 2–3 cm, ulcerating lesion was identified at the right upper third of the vagina and biopsied. The cervix appeared normal. On cystoscopy, no bladder invasion was identified, although an extrinsic mass effect was seen at the right bladder wall.

Microscopically, the vaginal wall biopsy showed the stratified squamous epithelium overlying the surface appearing intact and lacking dysplastic features. However, several fragments of neoplasia were identified in the subjacent tissue. These consisted of sheets of atypical cells associated with blood, fibrin, neutrophil polymorphs, but no necrosis. The atypical cells were enlarged with pleomorphic nuclei, multiple irregular nucleoli, and ample eosinophilic cytoplasm.

The immunostaining showed the atypical cells to be negative for cytokeratins (AE1/3, CAM5.2, CK5/6). SOX10 and CD34. Desmin and lymphoid markers (CD20, CD3) also appeared negative. Weak reactivity for CD68 was observed and there was focal reactivity for P16. Additional markers were assessed and strong reactivity for ERG was found in the tumour cells (Fig. 2), while a range of other markers including S100,

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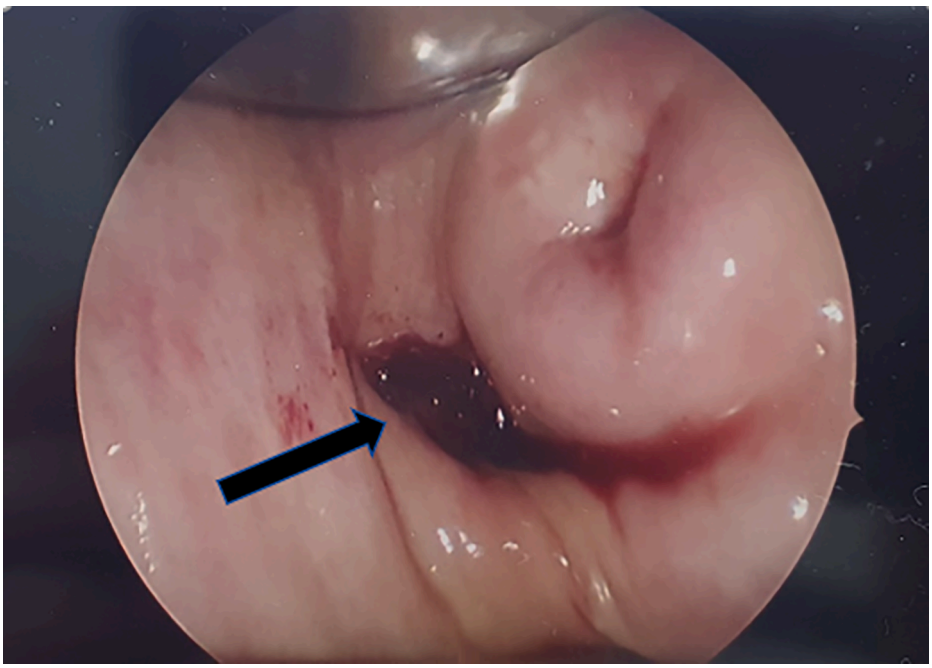

Fig. 1. A colposcopic image of the violaceous plaque in the right posterior vaginal fornix (black arrow).

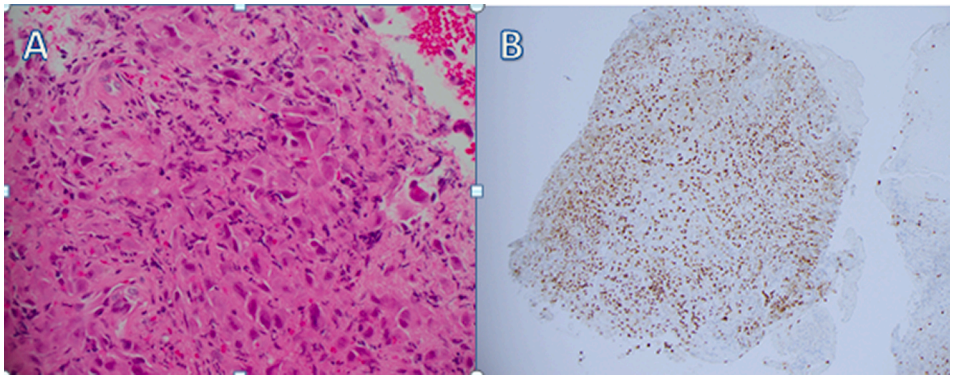

Fig. 2. A. Vaginal wall biopsy histopathology demonstrating the microscopic view of the undifferentiated epithelioid angiosarcoma. **B.** The immunostain ERG, an endothelial marker.

Glypican 3, and P63 were negative. There was weak and nonspecific reactivity for CD30. The morphological and immunohistochemical assessment of the vaginal biopsy confirmed an undifferentiated epithelioid angiosarcoma.

The case was discussed at the gynaecological oncology and sarcoma multidisciplinary team meetings (MDT), and it was decided to determine the local extent of disease, potential metastasis and/or a potential different primary by magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging. The pelvic MRI described a 30 × 15 mm right-sided vaginal mass, parametrial involvement and enhancement of the adjacent right pelvic sidewall tissue. There was no pelvic lymphadenopathy or free fluid seen (Fig. 3). The whole-body PET/CT scan showed an FDG-avid right-sided pelvic lesion and FDG avid right external and common iliac lymph nodes, highly suspicious for lymphadenopathy (Fig. 3).

A further EUA in theatre to assess the surgical resectability of the angiosarcoma by the gynaecological oncology team confirmed a 2 cm violaceous right vaginal lesion in the upper third of the vagina (Fig. 1). The right parametrium was thickened and the lesion was fixed to the right pelvic side wall. Based on the clinical and histopathological findings, the disease was staged as FIGO (International Federation of Gynaecology and Obstetrics) Stage III, T3N1M0 and determined to be unresectable. It was decided to treat the disease with systemic paclitaxel and carboplatin followed by external beam radiation to the pelvis and vaginal brachytherapy. The patient was thoroughly counselled by the gynaecological oncology, radiation oncology and medical oncology teams but decided against any conventional treatment and chose to pursue alternative natural therapies. Shortly after diagnosis, the patient presented to the emergency department with increasing vaginal bleeding and symptomatic anaemia, requiring multiple blood transfusions. She engaged with the palliative care service and died 6 months after initial diagnosis from disseminated disease.

3. Discussion

Primary vaginal cancers are rare and account for only 1 to 2% of all gynaecological malignancies. The vagina, however, can be a common site for metastatic gynaecological or secondary cancers. Most vaginal cancers are squamous cell carcinomas, followed by adenocarcinomas, melanomas, and various other rare malignancies (Ugwu et al., 2019). Most reported cases of gynaecological angiosarcomas have been reported in the uterus and ovaries (Yost and Bradish, 2017). Although

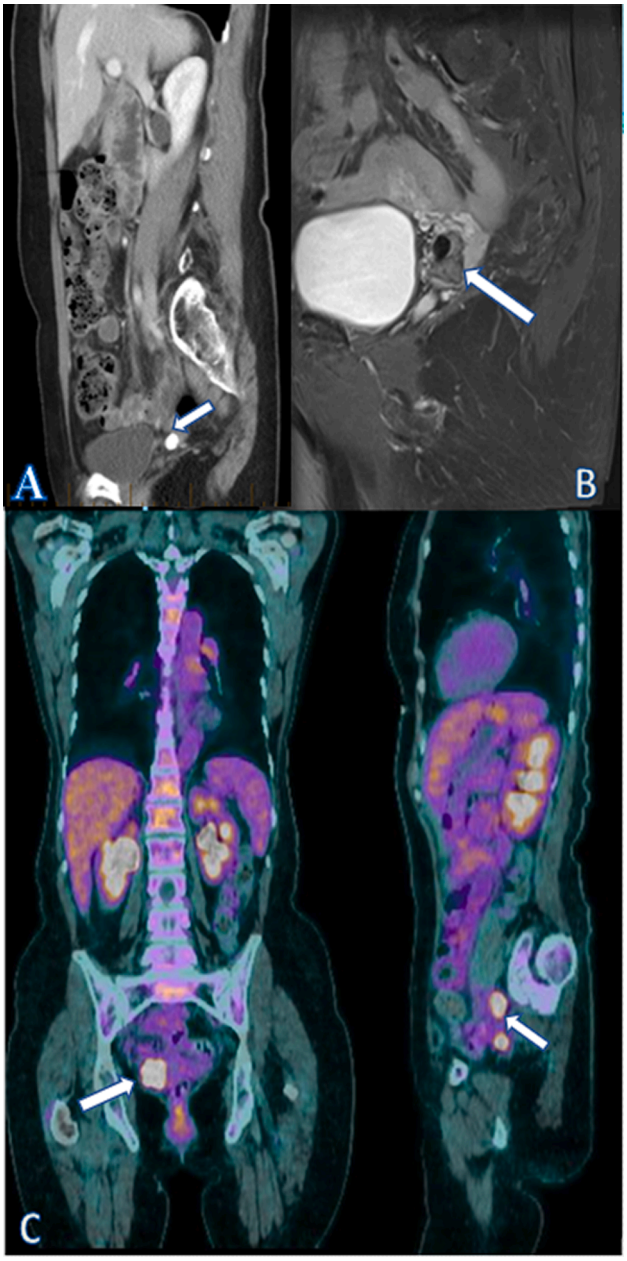

Fig. 3. A. CT scan of the pelvis showing a possible pedunculated cervical fibroid or right ovarian dermoid (white arrow). Further imaging and clinical correlation confirmed these findings to represent an angiosarcoma of the right vaginal fornix. B. Pelvic MRI describes a low signal serpiginous lesion immediately adjacent to the right lateral wall of the vaginal fornix in the right pelvis (white arrow) which correlated clinically to the vaginal angiosarcoma There is surrounding enhancement of the adjacent right pelvic tissues. Bilateral pelvic varices noted. Ovaries are not identified. C. Whole Body FDG PET/CT Scan showing FDG avid pelvic malignancy with right pelvic and middle common iliac nodal involvement (white arrows). No evidence of distant metastatic disease. The lymphadenopathy is not appreciated on the CT imaging in this case.

there are 9 cases of angiosarcomas arising in the vagina in the literature, a PubMed search of the English literature showed only 3 recorded vaginal cases of the epithelioid angiosarcoma variant to date. The information regarding the presentation, management, and outcome of the vaginal angiosarcomas in the literature are summarised in Table 1.

Cutaneous angiosarcomas have a non-specific presentation and generally present as a painless, violaceous plaque (Young et al., 2010), as in our patient who did not experience any discomfort from the vaginal lesion. Clinical diagnosis of vaginal angiosarcoma may be delayed and present at a late stage due to its asymptomatic nature and hidden location (Ugwu et al., 2019; Young et al., 2010). Most often angiosarcomas of the female genital tract (FGT) have an aggressive course with a 5-year overall survival of only 27–35% and a mean survival of 7 months (Brătilă et al., 2016).

Angiosarcomas appear to have no predisposing risk factors and occur sporadically with no specific primary angiosarcoma genetic aberration having been described and the overall genetics of angiosarcomas remaining poorly understood (Richer et al., 2014). However, due to an increase in reported numbers of angiosarcomas over the last few decades, several risk factors have been postulated, such as an increased use of radiotherapy in female genital tract cancer management and improved diagnostic methods (Avancini et al., 2016). Radiation is a well-recognised cause of angiosarcomas and over 200 cases have been reported in the literature (Morgan et al., 1989), irrespective of the anatomical site (Richer et al., 2014). Only a handful of epithelioid angiosarcomas were previously described and even fewer cases of gynaecological angiosarcomas have been presented in the context of prior radiotherapy (McAdam et al., 1998; Richer et al., 2014). Table 1 shows that 6 out of 9 reported cases of vaginal angiosarcomas indeed had a history of therapeutic radiation for a different gynaecological malignancy. This risk factor, however, is still to be associated with the uniquely rare epithelioid variant, as none of the reported cases had prior radiotherapy (Table 1).

An interesting finding is that 8 of the 12 reported cases of angiosarcoma of the vagina had a previous hysterectomy and 6 cases in the context of previous female genital tract malignancy management. In contrast, only 1 case of epithelioid angiosarcoma in the literature had a previous hysterectomy for a benign condition. Other rare potential risk factors identified in previous studies of gynaecological angiosarcomas include the use of a long-term vaginal ring pessary and other foreign bodies, including bullets and surgical sponge material from prior surgery (Avancini et al., 2016; Richer et al., 2014). There were no potential risk factors present in our case. Angiosarcomas have been described as being more common in elderly women (Avancini et al., 2016). However, in the cases from the literature the patients' age ranged from 22 years to 86 years.

The optimal management of vaginal angiosarcomas can only be extrapolated from reported angiosarcomas of the uterus, cervix, and pelvis, and remains mostly undefined. Complete resectability of the vaginal lesions seem to be the main prognostic factor, as prognosis of more advanced disease remains poor, regardless of the adjuvant treatment (Table 1). A study from 2014 by Kruse et al evaluated the survival of 51 patients with angiosarcomas of the female genital tract. The study demonstrated that most patients having had surgery as their primary intervention followed by adjuvant radiotherapy for angiosarcomas of the vulva, vagina, and uterus had an increased overall survival and improved local control. Chemotherapy for ovarian angiosarcoma or advanced metastatic angiosarcoma of the female genital tract may have a primary role for survival benefit. However, only 2 patients had an angiosarcoma of the vagina in the study (Kruse et al., 2014). Amongst vulvar angiosarcoma cases, treatment approach includes surgical excision in all cases with adjuvant radiotherapy and/or chemotherapy in most (Sheinis et al., 2016; Guirguis et al., 2007).

With regards to vaginal angiosarcomas, Table 1 shows that the 4 cases that underwent primary excision followed by adjuvant radiotherapy had a disease-free survival ranging from 36 to 52 months and the 4 patients having had primary chemotherapy followed by immunotherapy or targeted therapy had overall survivals ranging from 9 and 33 months. A recent cases series proposed weekly paclitaxel as the most effective treatment for angiosarcomas of the female genital tract if primary or adjuvant chemotherapy is indicated (Chinczewski et al., 2020). The potential role of interleukin-2 therapy in the suppression of the development of distant metastasis or in combination with irradiation in inoperable vaginal angiosarcoma is yet to be established (Takeuchi

Table 1
Reported cases of vaginal angiosarcomas in the literature.

Study (Primary author and year)	Clinical presentation	Age at Diagnosis (years)	Epithelioid angiosarcoma variant	Previous Hysterectomy	Post radiation for female genital tract malignancy	Primary angiosarcoma treatment and management course	Post treatment follow up and survival (months)
McAdam et al. (1998)	Vaginal mass	86	Yes	Yes†	No	Inoperable.Unfit for brachytherapy. External beam radiation. (Symptom control).	<4 months
Richer et al. (2014)	Vaginal mass	41	Yes	No	No	Weekly paclitaxel 6 cycles followed by whole pelvic radiation (45 *Gy* in 25 fractions), followed by brachytherapy boost(22Gr in 9 Fractions).	Disease free at 30 months
Brătilă et al. (2016)	Pelvic pain	22	Yes	No	No	Paclitaxel and cisplatin 6 cycles failed to control relapse. Radical hysterectomy with bilateral salpingo-oophorectomy followed by further chemotherapy 3 cycles.	Disease free after 9 months
Prempree et al. (1983)	Vaginal mass	49	No	Yes††	No	Excision and adjuvant brachytherapy and external beam radiotherapy.	Disease free after 36 months follow up
Morgan et al. (1989)	PV bleeding	72	No	Yes	yes	Inoperable. 3 cycles doxorubicin. Poor response.	7 months
Kruse et al. (2014)	PV Bleeding, vaginal mass	46	No	No	No	Excision and adjuvant radiation. Recurrence treated with paclitaxel. Further recurrence treat with palliative radiation and second line doxorubicin.	48 months
Chinczewski et al. (2020)	Nausea, vomiting, haematuria	34	No	Yes	yes	Weekly paclitaxel (total 21 days, 2 courses) followed by pazopanib.	33 months
Takeuchi et al. (2005)	Vaginal nodules during routine gynaecological check-up	–	No	Yes	Yes	Declined surgery (posterior exenteration); brachytherapy combined with adjuvant rIL-2 immunotherapy.	16 months
Tohya et al. (1991)	–	73	No	Yes	Yes	Excision and radiotherapy.	<51 months
Chan and SenGupta (1991)	–	–	No	Yes	yes	Excision.	Died post-operative from haemorrhage
Morimura et al. (2001)	–	61	No	Yes	yes	Combination chemotherapy (cyclophosphamide, vincristine, doxorubicin and dacarbazine) and interleukin-2.	15 months disease free
Mark et al. (1953)	–	–	No	–	–	Excision and radiotherapy.	<51 months

† Hysterectomy for uterine rupture followed by long term vaginal pessary use.
†† Hysterectomy for uterine prolapse.

et al., 2005).

While a wide surgical excision is recommended for resectable angiosarcomas of the vagina (Brătilă et al., 2016; Morgan et al., 1989); there is no available evidence supporting adjuvant radiotherapy. Similarly, the role of systemic chemotherapy and radiation therapy in the treatment of angiosarcomas of the vagina has yet to be established (Young et al., 2010). With no effective treatment available, prognosis in many cases remains poor, even with early intervention in this rare tumour entity (Sheinis et al., 2016).

4. Contribution of individual authors

Dr Jennifer Weishaupt:

- Conceptualisation
- Investigation and analysis
- Original draft, review and editing of manuscript.

Dr John Miller

- Review and editing of manuscript

Prof. Martin K Oehler

- Supervision
- Review and editing of manuscript

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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