CASE REPORT

Primary malignant mixed Müllerian tumour (MMMT) of the vagina and review of the literature

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SUMMARY

Primary malignant mixed Müllerian tumour (MMMT) of the vagina is a rare entity. We report a case of a 62-year-old woman who presented with a fixed and hard anterior vaginal wall mass with contact bleeding. She proceeded to have an anterior infralevator pelvic exenteration with urethrectomy and anterior vaginectomy, creation of an ileal conduit and bilateral lymph node dissection. Histopathological examination and immunohistochemistry confirmed the diagnosis of primary MMMT of the vagina. The patient was stage IVA at diagnosis. Despite chemotherapy and radiotherapy, she had progressive disease and eventually passed away at the age of 65 years.

BACKGROUND

Primary malignancies of the vagina are very uncommon. Most vaginal tumours are histologically classified as squamous cell carcinomas, but melanoma, sarcoma, adenocarcinoma and other histological types also rarely occur. Malignant mixed Müllerian tumour (MMMT) is a rare biphasic neoplasm. Primary MMMT of the vagina is extremely uncommon with only 11 documented case reports in the published literature. We present the 12th case report of primary MMMT of vagina.

CASE PRESENTATION

A 62-year-old postmenopausal woman presented with a history of intermittent postmenopausal bleeding. On vaginal examination of the patient, there was a fixed and hard lower anterior vaginal mass with contact bleeding. A vaginal smear showed a few severely dyskaryotic epithelial cells with features suspicious of invasive malignancy. An anterior vaginal biopsy showed poorly differentiated subepithelial carcinoma, and histopathology was unable to determine if this was a primary or metastatic carcinoma.

Subsequently, a vaginal core biopsy showed lymphatic obstruction likely secondary to underlying tumour. Urine cytology showed marked acute inflammation and occasional atypical squamous cells suspicious for malignancy. Immunohistochemistry stains queried a possibility of primary urethral cancer.

CT urogram showed bilateral mild-moderate hydronephrosis and moderately dilated ureters to the level of the vesicoureteric junctions. MRI showed a 3.7×3.2 cm irregular mass lesion involving the anterior vaginal wall, with involvement of the posterior bladder base. There was neither cervical, rectal nor lateral extension. A small urinary

bladder diverticula and subcentimetre calculus was seen.

Consequently, the patient underwent anterior infralevator pelvic exenteration with urethrectomy and anterior vaginectomy, creation of an ileal conduit and bilateral pelvic lymph node dissection. Intraoperative findings showed a hard 5 cm tumour between the anterior vaginal wall and urethra, and possible involvement of the posterior bladder wall. The cervix was not involved, the right ureter was normal and left ureter dilated, and a palpable lymph node found near the left internal iliac artery and the rest of the pelvic organs seemed unremarkable.

Histological sections of the tumour showed tubulopapillary architecture with epithelioid cells featuring nuclear enlargement, irregularity and anisonucleosis (figure 1). Some of the tubules showed hobnailing of the lining tumour cells, while in other areas, the tubules featured slit-like spaces. In large areas of the tumour, the cells formed sheets and single cells infiltrating adjacent tissue. Foci of sarcomatoid change were evident (figure 2).

On immunohistochemistry, the tumour cells were strongly and diffusely positive for CK7 variably positive for CA-125 and showed variable nuclear staining for p53. They were negative for CK20, CD10, calretinin, WT-1, CD31, CD34, p16, ER and 34BE12. Lymphovascular invasion was seen in the tumour, with an anterior soft tissue margin. Final histology revealed a malignant mixed Müllerian tumour (MMMT) involving the vagina, bladder and urethra, with lymphovascular involvement.

One left internal iliac lymph node out of 37 pelvic nodes removed was involved with metastatic

Figure 1 Epithelioid cells featuring nuclear enlargement, irregularity and anisonucleosis.

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Figure 2 Epithelial cells are seen transiting to spindle-shaped cells, indicating sarcomatoid transformation.

carcinoma. The tumour was less than 1 mm from the anterior soft tissue margin and involved the left lateral vaginal margin. The rest of the surgical margin was clear of disease. The patient was eventually diagnosed as having stage IVA primary cancer of the vagina.

OUTCOME AND FOLLOW-UP

The patient underwent five cycles of chemotherapy with cisplatin and ifosfamide, complicated by hallucinations. She was then referred for radiotherapy and completed external pelvic radiotherapy and vaginal vault brachytherapy. Despite treatment, a rising CA125 trend was noted following completion of radiotherapy. Repeat CT abdomen pelvis (CTAP) 6 months later showed lung metastasis. No soft tissue mass was seen in the pelvis to suggest local recurrence. Since the patient was asymptomatic, a follow-up CTAP was arranged several months later.

Unfortunately, the patient developed left lower limb deep vein thrombosis and a necrotic lesion in the right upper thigh, representing disease recurrence 2 months later. The patient was then treated with subcutaneous clexane for the deep vein thrombosis. CT of the thorax carried out 2 months later showed progressive disease with further pulmonary metastasis.

Options of chemotherapy versus basic support care were discussed in length with the patient and her family, and they opted

for basic support care. The patient subsequently received home hospice care and eventually passed away at the age of 65 years.

DISCUSSION

The first case of vaginal MMMT was described in 1975,^{1 2} and there is a current total of 11 published cases in the literature.^{1–11} We present the 12th case of vaginal MMMT, added to [table 1](#).⁵ The diagnosis of primary MMMT of the vagina is based on the following four criteria which include ‘(1) location in the lower vagina without involvement of the cervix or vulva; (2) mixed histological appearance of glandular, squamous and spindle cell elements that show mitoses and atypia; (3) invasion and possible metastasis and (4) a lack of evidence of other primary malignancy that could lead to vaginal metastasis’.^{4 12}

The commonest site of MMMT in the female genital tract is the endometrium, followed by the other female reproductive organs such as ovaries, fallopian tube, cervix and vagina.^{5 8} MMMTs are very aggressive tumours composed of either epithelial and mesenchymal components. The epithelial component includes histological subtypes such as squamous cell, adenocarcinoma, adenosquamous or basal carcinoma, adenoid-cystic and undifferentiated carcinoma.⁵ The sarcomatous component may be homologous, which includes fibroblasts, smooth muscles or heterologous mesenchymal elements including cartilage, striated muscle and bone.^{5 10 11}

Of 11 published cases, the age of the patients ranged from 57 to 74 years. The commonest epithelial component in vaginal MMMT is squamous cell carcinoma, and it is usually diagnosed early, at stage 1–2. We report the 12th case of primary MMMT of the vagina and the third case to be diagnosed at stage 4 after Ahuja *et al* and Shibata *et al*. Ahuja *et al*⁵ also reported the youngest case, where a 48-year-old patient was diagnosed late with stage 4 adenocarcinoma. Among the 11 cases, 6 died of their disease and 3 had recurrent disease at 5, 6 and 8 months follow-up, respectively.⁵ Despite different therapeutic approaches, the course of the disease was abysmal with six deceased within a time range of 23 months from initial diagnosis and treatment.

In both previous reported cases of stage 4 disease, a total pelvic exenteration was the primary surgical treatment. Unlike Shibata *et al* and Ahuja *et al*, we did not perform a total pelvic exenteration but proceeded with an anterior infralevator pelvic exenteration instead. In the study by Shibata *et al*, the patient

Table 1 Primary MMMT of the vagina—morphological, clinical and treatment details of the reported cases⁵

Case	Age	Histology	Stage	Treatment	Outcome
Rutledge	?	?	4 cm diameter	RT	Alive, 12 months
Davis	61	?	Stage 2	Hysterectomy+vaginectomy	Alive, 60 months
Peters	62	Ep ¹ :SCC ² +AdCa ³ ;Sar ⁴ :SS ⁵	Stage 2	TPE	Dead, 12 months
Peters	70	Ep:AdCa;Sar:SS+CS ⁶	Stage 2	WLE	Dead
Peters	69	Ep:SCC;Sar:LMS ⁷ +CS+OS	Stage 2	WLE	Dead
Peters	62	Ep:SCC;Sar:LMS	Stage 1	Hysterectomy+vaginectomy	Dead
Neesham	74	Ep:SCC+AdCa;Sar:FS ⁸ ?	Stage 1	WLE+RT	Neck lymph node mets 6 months
Shibata	72	Ep:Anaplastic Ca;Sar:RMS ⁹ ,LMS,CS	Stage 4	TPE+RT	Dead
Sotiropoulou	74	Ep:SCC;Sar:LMS	Stage 2	WLE	Dead
Sebenik	57	Ep:SCCrecurrent	Stage 1	WLE+RT	Sar:UPS
Ahuja	48	Ep:AdCa;Sar:LMS+osteoid	Stage 4	TPE	Recurrence after 8 months
Present Case	62	Ep:AdCa;Sar:Unclassified	Stage 4A	APE+RT+C	Dead; Recurrence after 20 months

1: epithelial component; 2: squamous cell carcinoma; 3: adenocarcinoma; 4: sarcomatous component; 5: synovial sarcoma; 6: chondrosarcoma; 7: leiomyosarcoma; 8: fibrosarcoma; 9: rhabdomyosarcoma.

APE, anterior pelvic exenteration; C, chemotherapy; MMMT, malignant mixed Müllerian tumour; RT, radiotherapy; TPE, total pelvic exenteration; WLE, wide local excision.

received adjuvant radiotherapy whereas our patient had adjuvant chemotherapy followed by palliative radiotherapy instead. Unfortunately, the patient in Shibata *et al* died 3 years after treatment with radiotherapy. In Ahuja *et al*, the patient declined radiotherapy and had disease recurrence at 8 months post-surgery and was lost to follow-up. Our patient had recurrence 20 months after completing treatment and succumbed to the disease 6 months later.

The 5-year survival rate for vaginal MMT has been reported to be 17%⁶ and only one case of 5-year survival without disease has been reported—this patient was stage 2 at the time of diagnosis.^{1 2} The outcome of metastatic MMT in general is extremely poor, and Colombi *et al*¹³ reported that most patients died within 1 year of diagnosis. The prognosis of metastatic MMT might differ according to the origin and metastatic site. Despite aggressive therapy with surgical resection and adjuvant radiotherapy or chemotherapy, the prognosis of primary MMT of the vagina remains poor, as in the case of our patient.

Further research is required in order to determine appropriate treatment and evaluate the outcome of this rare type of tumour. Recently, a Harvard group identified PIK3CA mutations in 19% of gynaecological carcinosarcomas with mutations in the phos-

phatidylinositol 3-kinase (PI3 K) pathway mainly in the uterine carcinosarcomas.¹⁴ Preliminary studies on the PI3K pathway may lead to prospective clinical trials designed to target PIK3CA mutations.¹⁴

In retrospect, primary MMT of the vagina is extremely rare and occurs in elderly women. The prognosis remains poor and further research is needed to elucidate this tumour.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Primary malignant mixed Müllerian tumour (MMT) of the vagina is an extremely rare tumour and occurs mostly in elderly women.
- MMT is an aggressive neoplasm with extremely poor prognosis and 5-year survival in about 17% of patients.
- Surgery followed by radiotherapy is the current favoured management.
- Further research is required in order to determine appropriate treatment and evaluate the outcome for this rare cancer.

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