

Clitoral Metastasis In Poorly Differentiated Endometrial Adenocarcinoma

S Mandal, J Lowe, M George

Citation

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Abstract

Endometrial cancer is the commonest gynaecological malignancy and accounts for 6% of cancers in women. It can spread through direct extension to the cervix and peritoneal surfaces, through the bloodstream to the lungs, liver, bones, brain and vagina and via lymphatics to the supraclavicular lymph nodes. This case report describes vulval metastasis of endometrial cancer to the clitoris, an occurrence which has not often been documented in the literature and treatment with a combination of chemotherapy and radiotherapy. Histology also excluded primary vulval carcinoma of the clitoris.

INTRODUCTION

Endometrial cancer is the commonest gynaecological malignancy and accounts for 6% of cancers in women. Its aetiology is related to oestrogen excess or the action of unopposed oestrogen. It can spread through direct extension to the cervix and peritoneal surfaces, through the bloodstream to the lungs, liver, bones, brain and vagina and via lymphatics to the supraclavicular lymph nodes. This case report describes vulval metastasis of endometrial cancer to the clitoris, an occurrence which has not often been documented in the literature and treatment with a combination of chemotherapy and radiotherapy. Histology also excluded primary vulval carcinoma of the clitoris.

CASE

The patient, a 73 year old woman was referred by her GP to the gynaecological outpatients department in January 2005 complaining of a pink vaginal discharge for the previous 4 weeks and nausea. She had stopped hormone replacement therapy 2 years prior to presentation and was on bendrofluazide and ramipril for hypertension which had been diagnosed in 2001, thyroxine for hypothyroidism, diclofenac and coproxamol for osteoarthritis of both hips since 2001 and long term lansoprazole (30 mg/d) for gastro-oesophageal reflux since 2000. She also had a past history of a pharyngeal web diagnosed by oesophagoscopy biopsy in 2001 which had revealed benign changes. She had always had normal cervical smears, the last one having been taken in 1996, had had 4 normal deliveries and went through the menopause at the age of 53 years. There was no family

history of gynaecological cancers.

On presentation at outpatients, general examination revealed a body mass index (BMI) of 31 and a blood pressure of 208/108 mmHg while abdominal examination showed an abdomino-pelvic mass palpable to the size of a 12-13 week gravid uterus. Vaginal examination confirmed the mass to be of uterine origin and a hard clitoral swelling was also noted.

A transvaginal ultrasound scan done the same day in clinic could not give further information as poor images were obtained and a plan was made to bring the patient to the Day Case Unit for an examination under anaesthesia, vulval biopsy and diagnostic hysteroscopy with endometrial biopsy. She was also referred back to her GP for stabilisation of her blood pressure.

Pre-operative investigations revealed a slightly raised urea level (8.8mmol/L), a normal haemoglobin level of 11.5 g/dl, normal white cell and platelet counts and normal liver function.

Examination under anaesthesia revealed an enlarged, hard and friable clitoris and friable 'tumour' seen protruding through the external os. The uterus was enlarged to the size of a 12-13 week pregnancy but was mobile while the adnexa and parametria felt normal on palpation. Rectal examination revealed no abnormality. The 'tumour' was removed from the cervix and this was followed by drainage of a large volume of pus from a pyometra. Endometrial curettage was performed after which more tissue could be felt in the uterus

on digital examination through the open external os. Hysteroscopy was abandoned because of the pyometra but a clitoral biopsy was taken. Specimens sent for examination were pus for culture and sensitivity, clitoral tissue for histopathological examination and endometrial tissue for histopathology .

The patient was admitted overnight for IV cefuroxime and IV metronidazole treatment for the pyometra and was discharged the next day on a 1-week course of oral cephadrine and metronidazole. She was followed up in outpatients 5 days later. Haematology and biochemistry on the day revealed a normal full blood count, a urea concentration of 8.6 mmol/L and elevated alkaline phosphatase (175 u/l) and gamma-GT(244u/l) levels. The pus grew anaerobes sensitive to metronidazole.

Vulval biopsy showed widespread infiltration of anastomosing broad cords of undifferentiated carcinoma separated from the overlying normal squamous epithelium by a 2 mm tumour-free zone (Figure 1). There was no architectural or cytological differentiation with the presence of brisk mitotic activity in the tumour of up to 7 mitotic figures per high power field (Figure 2). There was no evidence of VIN or atypia in the squamous epithelium.

Endometrial histology was similar to that of the vulval tumour but with some glandular differentiation and no heterologous elements (Figure 3).

Figure 1

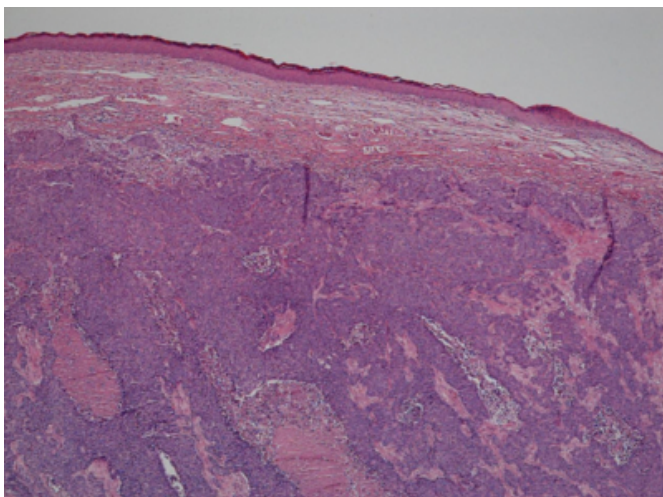


Figure 2

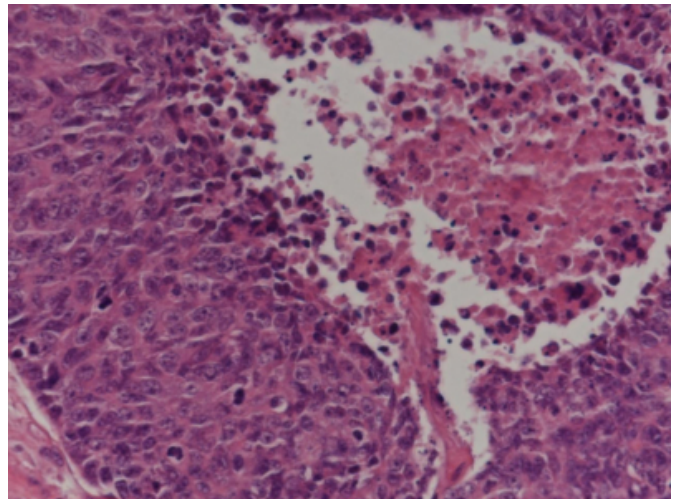
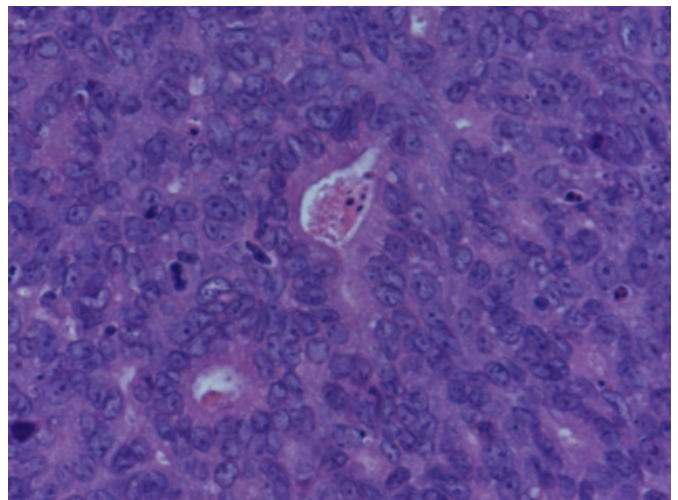


Figure 3



The histopathological diagnosis was extensively necrotic, poorly differentiated (grade 3) adenocarcinoma of the endometrium with undifferentiated carcinoma of the vulva consistent with metastasis from the endometrium.

A chest X-ray done the same day revealed multiple soft tissue nodules in both lung bases highly suggestive of metastatic disease. A computed tomography (CT) scan of the abdomen and pelvis done a week later to look for further metastases revealed an enlarged uterus with a distended endometrial cavity and irregular, nodular endometrium, no extrauterine soft tissue infiltration, normal liver, pancreas, kidneys, spleen, gall bladder and urinary bladder, small (<0.5 mm) lymph nodes in the aorto-caval and para-aortic regions, no pelvic lymphadenopathy, fibrosis of the medial lower lobe of the right lung and irregular, small, nodular opacities in the left lower lobe.

A diagnosis of stage IV adenocarcinoma of the endometrium with clitoral and pulmonary metastases was made with no definite intra-abdominal metastases below the diaphragm. The patient was then referred to the Regional Cancer Centre after a multidisciplinary meeting and was seen there in February 2005.

A plan was made for chemotherapy and radiotherapy and the patient received 4 cycles of cisplatin and adriamycin between March and May 2005. A chest X-ray performed after 2 cycles of chemotherapy showed marked regression of the pulmonary nodules and she was prescribed dexamethasone for anorexia and nausea and diazepam for anxiety.

The patient complained of visual disturbances, unsteady gait and agitation after completion of chemotherapy but a CT scan of the brain did not reveal any cerebral metastases and her symptoms were attributed to the chemotherapy. She went on to receive radiotherapy with 30 Gy in 10 fractions and this was completed in June 2005.

Megestrol acetate in the dose of 160 mg/d was prescribed for its antiemetic and antianorexic effects and her GP was advised to continue this.

The patient was followed up in the Regional Cancer Centre by the clinical oncologist. A chest X-ray showed continued clearance of the pulmonary nodules and the impression was that she had had a good partial response to treatment. She complained of profound depression after radiotherapy but had had a slight increase in appetite with megestrol acetate and increased exercise tolerance.

DISCUSSION

Endometrial cancer is the commonest gynaecological malignancy and accounts for 6% of all cancers in women.[¹] The peak incidence is between the ages of 50-60 years with < 4% of cases occurring below 40 years.[²]

The main risk factor for the development of endometrial cancer is the presence of unopposed oestrogen. This could be due to polycystic ovarian syndrome, nulliparity, late menopause, obesity, unopposed oestrogen therapy, anovulation or oligoovulation or the effect of oestrogen-producing tumours. Obesity can itself increase the risk by 3-10 times[²] while unopposed oestrogen treatment increases the risk sixfold after 5 years of use.[³] Adding progestogens for 10-12 days per cycle for sequential HRT or as a part of continuous combined HRT decreases the relative risk to

1.5.[³] Tamoxifen, used for the treatment and secondary prophylaxis of breast cancer increases the risk of endometrial cancer fourfold after 5 years of use [³] and endometrial cancer in long-term users of tamoxifen has a poorer prognosis.[³] Other risk factors include hypertension and diabetes while the life-time risk of developing endometrial cancer in women who carry the mutations for the autosomal dominant syndrome of hereditary non-polyposis colorectal cancer (HNPCC) is 42-60%.[³]

Endometrial cancer can extend through direct spread from the surface of the uterine cavity to the cervical canal, through the myometrium to the serosa and into the peritoneal cavity or through the lumen of the fallopian tube to the ovary, broad ligament and peritoneal surfaces.[²] Haematogenous spread is known to occur to the liver, lungs, bones, brain and vagina while lymphatic spread can ultimately occur to the supraclavicular lymph nodes. Lymphatics from the fundus pass with the ovarian vessels to the paraaortic nodes and some to the external iliac lymph nodes while those from the cornua follow the round ligaments to the superficial inguinal lymph nodes. Lymphatics from the body traverse the broad ligaments to the external iliac nodes while those from around the cervix drain into the internal iliac and sacral nodes.

Eighty percent of endometrial cancers are adenocarcinomas. More than 90% of patients present with abnormal bleeding, usually postmenopausal bleeding or pre-menopausal recurrent metrorrhagia.[²] Seventy percent of patients present with Stage I disease.[⁴] Staging of endometrial cancer is based on the FIGO classification (see Table 1) and is a combination of surgical and histological staging.

Figure 4

Table 1: Staging of Endometrial Cancer {after the International Federation of Gynaecology and Obstetrics (FIGO) and the American Joint Committee on Cancer (AJCC)}- Surgical and histological staging

| | |
|------------------|---|
| Stage I | Cancer confined to corpus uteri |
| IA | Tumour limited to endometrium |
| IB | Invasion to ≤ ½ of myometrium |
| IC | Invasion to > ½ of myometrium |
| Stage II | Cancer involves corpus and cervix but has not extended outside the uterus |
| IIA | Endocervical glandular involvement only |
| IIB | Cervical stromal invasion |
| Stage III | Cancer extends outside the uterus but is confined to the true pelvis |
| IIIA | Tumour invades serosa and/or adnexa and/or positive peritoneal cytology |
| IIIB | Vaginal metastasis |
| IIIC | Metastasis to pelvic and/or para-aortic lymph nodes |
| Stage IV | Cancer involves bladder or bowel mucosa or has metastasized to distant sites |
| IVA | Tumour invasion of bladder and/or bowel mucosa |
| IVB | Distant metastases, including intra-abdominal and/or inguinal lymph nodes |
| | Each stage is graded according to the degree of histological differentiation |
| G1 | 5% or less of a nonsquamous or nonmucinous growth pattern |
| G2 | 6% to 50% of a nonsquamous or nonmucinous growth pattern |
| G3 | More than 50% of a nonsquamous or nonmucinous growth pattern |

Over 63% of patients are cancer-free 5 years after treatment.[2] Overall survival rates for stages I and II vary between 70 and 95% but can be as low as 20-30% with high-grade cancer and ranges from 10-60% in stages III and IV.[2] Risk factors for spread include the degree of differentiation or grade, capillary-lymph space involvement and myometrial invasion. Higher the grade greater the likelihood of deep myometrial invasion, lymph node metastasis or extrauterine spread. Myometrial invasion can be a harbinger of lymph node involvement and distant metastasis independent of degree of differentiation.[1]

This case showed no evidence of direct extrauterine spread through the myometrium on clinical examination or CT scan

and clinical examination excluded vaginal spread. It is therefore very likely that the clitoral metastasis was a result of haematogenous spread. This is evident, too, from the histology report which showed carcinoma of the vulva consistent with metastasis from endometrial cancer in that there was a 2 mm tumour free zone between the metastasis and the surface squamous epithelium which also showed no signs of VIN or atypia, thus excluding a diagnosis of co-existent primary carcinoma of the vulva.

Case reports of early (stage IC) endometrial cancer treated by total abdominal hysterectomy and bilateral salpingoophorectomy presenting 2 years later with skeletal metastases to the 4th toe [5] and recurrent cerebral metastases treated successfully with stereotactic radiosurgery and chemotherapy [6] have been reported. Pulmonary metastasis is relatively common and vaginal recurrences are not unknown.[6, 7] However a search of the literature using Medline, Pubmed and the Cochrane Database of Systematic Reviews revealed only a few cases of vulval metastasis in endometrial cancer. [8, 9]

This patient was treated with 4 cycles of doxorubicin and cisplatin which caused regression of the pulmonary nodules, followed by pelvic radiotherapy and was prescribed megestrol acetate (160mg/d) for anorexia and nausea.[10] Most patients with stage IV disease are best treated with systemic chemotherapy and the commonest regime used is a combination of cisplatin and doxorubicin although the addition of paclitaxel to cisplatin/doxorubicin has been shown to improve response rates, progression-free survival and overall survival rates compared to doxorubicin/cisplatin alone [11] although with increased risk of neurotoxicity.[11] Chemotherapy followed by radiotherapy in advanced (stages III and IV) endometrial cancer has been found to be well tolerated.[12] Although progestogen therapy for advanced and recurrent endometrial cancer has been reported to lead to response in 35-40% of patients with pulmonary, vaginal and mediastinal metastases especially if progesterone receptor levels are >100, current evidence does not support the use of adjuvant progestogens in the primary treatment of endometrial cancer.[1, 2, 4]

CORRESPONDENCE TO

Address: Flat 41 Park View 176 Arrowe Park Road
Woodchurch Wirral UK CH49 5PG E-Mail-
docmandal@aol.com Phone- 00-44-(0)7789 683014 Fax -
00-44-(0) 151 604 7340

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Author Information

S. Mandal

Registrar, Department of Obstetrics and Gynaecology, Arrowse Park Hospital

J. Lowe

Consultant Pathologist, University Hospital of North Tees

M. George

Consultant Obstetrician and Gynaecologist, University Hospital of North Tees