INTRODUCTION

Endometriosis is a common gynaecological condition characterised by the presence of endometrial glands and stroma outside the uterus. It is estimated to be present in 5–15% of women in the reproductive age group, 25–80% of infertile women, 2–5% of postmenopausal women, and 40–80% of women with pelvic pain.2

Although endometriosis is considered to be a benign condition, this condition shares many pathological characteristics with malignant tumours, including tissue invasion and damage,

ORIGINAL ARTICLE

Malignant extra-ovarian endometriosis: A case series of ten patients and review of the literature

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Background: The malignant transformation of endometriosis within the ovary is a recognised condition. There is less literature surrounding the malignant transformation of extra-ovarian endometriosis (MEOE).

Aims: We report our experience with MEOE in ten patients and present a review of the literature regarding this rare malignancy.

Materials and Methods: For this retrospective case series, patients were identified from a practice-based database. Where required, operative notes and pathology reports were reviewed.

Results: Ten patients diagnosed with MEOE between 1991 and 2014 were identified. In each case, the tumour was localised to the pelvis and centred on the pouch of Douglas, broad ligament, obturator fossa, parametrium and rectovaginal septum. Tumour histology was endometrioid adenocarcinoma (six), clear cell carcinoma (two), and adenosarcoma (two). Five patients had a history of endometriosis and four had received oestrogen-only hormone replacement therapy after hysterectomy and bilateral salpingo-oophorectomy. Treatments included surgery (one), surgery and radiotherapy (one), surgery and chemotherapy (one), surgery, radiotherapy and chemotherapy (three), and radiotherapy and chemotherapy (four). Maintenance hormonal therapy was also used in three patients. Curative doses of radiotherapy 45 Gy or more resulted in in-field control in five patients. Six patients had no evidence of disease at a mean follow up period of 15 years (5.5–24 years). Severe G3 long-term bladder morbidity occurred in three patients after radical surgery and radiotherapy.

Conclusion: MEOE is a rare condition for which treatment needs to be individualised. Multicentre studies and registries will hopefully define optimal treatment.

KEYWORDS
endometriosis, endometriosis-associated cancer, endometriosis-associated ovarian cancer, malignant endometriosis, malignant extra-ovarian endometriosis, malignant transformation of endometriosis
Malignant extra-ovarian endometriosis

Information was collected regarding the patient's age, parity, past medical history including history of endometriosis, family history, past or present use of hormone replacement therapy (HRT), operative findings, pathology results, further management and follow up. All patients gave informed consent for their treatment and had pathology review and presentation at a multi-disciplinary team meeting.

Radiotherapy (RT) intent was curative when the planned external beam dose was 45 Gy or more. Recurrence was defined as the diagnosis of cancer after a cancer-free interval. Progression was defined as worsening disease, when there was no cancer-free interval after diagnosis. Recurrence and progression were measured from the date of diagnosis of MEOE. In-field control was defined as permanent control of tumour within the treated RT field. Complications were graded according to the Radiation Therapy Oncology Group / European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema.

A review of the literature was performed using Medline/ PubMed and EMBASE. This search was conducted by using the keywords ‘malignant endometriosis’, ‘extra-ovarian endometriosis’ and ‘endometriosis-associated cancer.’

RESULTS

Ten patients with MEOE were identified. These cases were diagnosed during the years 1991–2014. Table 1 summarises the patient and tumour characteristics. The mean age at diagnosis was 45.3 years (range 34–56). Six patients were nulliparous and five had undergone prior treatment for endometriosis. Four had undergone a hysterectomy and bilateral salpingo-oophorectomy (total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO)) for the management of endometriosis (cases 4, 7, 8 and 9) all four of whom had taken oestrogen-only HRT following their TAH and BSO. The interval from completion of TAH and BSO to MEOE was 4, 12, 3, 9 years respectively.

Pain was the most common presenting symptom, occurring in the pelvis, buttocks and hips. Severe neurological pain (from compression on the obturator nerve and sciatic nerve) occurred in six cases and it was elevated in five. In all ten patients, the malignancy was confined to the pelvis at initial diagnosis and distant extra-pelvic spread was not detected. The most common location was the pouch of Douglas (POD), followed by the broad ligament and obturator foramen. Other locations include the parametrium and rectovaginal septum. Tumour sizes ranged 6–13 cm (median 9 cm).

Table 2 summarises the pathology, management and outcomes. Six malignancies were endometrioid adenocarcinoma (two G1, one G2, and three G3), two were low-grade adenosarcoma, and two were high-grade clear cell.

MATERIALS AND METHOD

This study was approved by the Ethics Committee of Epworth HealthCare (EH 2017-211). The practice-based prospectively maintained database of a gynaecological oncologist was searched for all patients with a diagnosis of MEOE. We included patients who had an extra-ovarian malignancy amid a background of benign endometriosis, and patients with an extra-ovarian malignancy of endometrial origin and a history of endometriosis, and/or a history of endometriosis for whom no other primary tumour site had been found.
<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>History of endometriosis (and treatment) and other gynaecological history</th>
<th>Past medical history</th>
<th>HRT</th>
<th>Parity</th>
<th>Symptoms, signs and CA125 level at diagnosis</th>
<th>Location of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>No</td>
<td>None relevant</td>
<td>Nil</td>
<td>P2</td>
<td>Abdominal bloating and mass. CA125 not done</td>
<td>Right pelvis; 9.5 cm</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>No</td>
<td>None relevant</td>
<td>Nil</td>
<td>P3</td>
<td>Pelvic pain. CA125 not done</td>
<td>POD</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>Later developed breast DCIS aged 62 years</td>
<td>None relevant</td>
<td>Nil</td>
<td>P0</td>
<td>Vaginal bleeding and discharge; ulcer in L vaginal fornix; CA125 not done.</td>
<td>POD and parametrium; 6 cm</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>TAH/BSO aged 52 years for benign endometriosis in L ovary, residual endometriosis in POD Removal of benign endometrioma in POD, anterior resection and loop ileostomy aged 53 years. Treated with Zoladex × 6 months</td>
<td>None relevant</td>
<td>Oestrogen only for 1.1 years</td>
<td>P0</td>
<td>L iliac fossa pain and L sacro-iliac pain. CA125 57 units/mL</td>
<td>POD; mostly cystic; fluid cytology positive; 13 cm</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>TAH/BSO aged 42 years for fibroids and adenomyosis. Endometriosis was not noted</td>
<td>None relevant</td>
<td>Oestrogen only for 9 years</td>
<td>P4</td>
<td>Pelvic pain. CA125 84 units/mL</td>
<td>RV septum; 6 cm</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>Infertility</td>
<td>Nil</td>
<td>P0</td>
<td>Constipation and pelvic pain CA125 243 units/mL</td>
<td>POD and RV septum; 9 cm</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>Long history of endometriosis and infertility. TAH/BSO aged 31 years for severe endometriosis</td>
<td>None relevant</td>
<td>Oestrogen only for 3 years</td>
<td>P0</td>
<td>Pelvic pain</td>
<td>POD; 8 cm</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>Laparotomy, exploration of right obturator fossa, drainage of endometrioma excision of endometriosis right USL aged 29 years. Treated with Zoladex × 6 months. Then progestogen</td>
<td>None relevant</td>
<td>Nil</td>
<td>P0</td>
<td>Pain R hip. CA125 19 units/mL</td>
<td>R broad ligament, obturator foramen, bony pelvis; &gt;10 cm</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>Hormonal treatment from age 26 years with progestogen. RSO for endometrioma aged 30 years. LSO aged 35 years. TAH aged 40 years</td>
<td>Breast DCIS aged 46 years, Myeloma aged 49 years</td>
<td>Oestrogen only for 11 years</td>
<td>P0</td>
<td>Pelvic pain CA125 42 units/mL</td>
<td>POD; 6 cm</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>CT guided drainage of endometriosis from obturator internus aged 39 years</td>
<td>None relevant</td>
<td>Nil</td>
<td>P2</td>
<td>Pain L buttock CA125 548 units/mL</td>
<td>L hemipelvis, obturator foramen, bony pelvis; partly cystic; 13 cm</td>
</tr>
</tbody>
</table>

BSO, bilateral salpingo-oophorectomy; CT, computed tomography; DCIS, ductal carcinoma *in situ*; HRT, hormone replacement therapy; LSO/RSO, L and R salpingo-oophorectomy; POD, pouch of Douglas; RV, rectovaginal septum; TAH, total abdominal hysterectomy; USL, uterosacral ligament.
### Table 2: Pathology, treatment and outcomes after the diagnosis of malignant endometriosis

<table>
<thead>
<tr>
<th>No.</th>
<th>Pathology</th>
<th>Hormonal treatment</th>
<th>Chemotherapy</th>
<th>Recurrence/clinical course</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Endometrioid ca; G1</td>
<td>None</td>
<td>None</td>
<td>No further problems</td>
<td>Patient well with NED at 10.4 years</td>
</tr>
<tr>
<td>2</td>
<td>Adenosarcoma, low-grade</td>
<td>TAH/BSO, ovaries normal, not removed</td>
<td>Carboplatin, paclitaxel, carboplatin after RT</td>
<td>Treated with MPA, progressive disease over 3 months. Then carboplatin, paclitaxel, carboplatin after RT</td>
<td>Died after 14.3 years from lung and liver. Treated with MPA, progressive disease over 3 months. Then carboplatin, paclitaxel, carboplatin after RT. Complications: radiation cystitis, non-functioning bladder managed by ISC. G3</td>
</tr>
<tr>
<td>3</td>
<td>Endometrioid ca; G3</td>
<td>G3</td>
<td>Carboplatin, paclitaxel after RT</td>
<td>PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection and Martius flap. Residual endometriosis but no cancer.</td>
<td>Patient well with NED at 15.0 years</td>
</tr>
<tr>
<td>4</td>
<td>Clear cell ca</td>
<td>None</td>
<td>None</td>
<td>No further problems</td>
<td>Patient well with NED at 11.5 years</td>
</tr>
<tr>
<td>5</td>
<td>Endometrioid ca; G1</td>
<td>None</td>
<td>Carboplatin, paclitaxel, carboplatin after RT</td>
<td>PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection and Martius flap. Residual endometriosis but no cancer.</td>
<td>Patient well with NED at 24.0 years</td>
</tr>
<tr>
<td>6</td>
<td>Endometrioid ca; G3</td>
<td>None</td>
<td>Carboplatin, paclitaxel, carboplatin after RT</td>
<td>PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection and Martius flap. Residual endometriosis but no cancer.</td>
<td>Patient well with NED at 23.5 years</td>
</tr>
<tr>
<td>7</td>
<td>Adenosarcoma; low-grade</td>
<td>Debulking tumour mass</td>
<td>Carboplatin, paclitaxel</td>
<td>PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection and Martius flap. Residual endometriosis but no cancer.</td>
<td>Patient well with NED at 24.0 years</td>
</tr>
<tr>
<td>8</td>
<td>Endometrioid ca; G3</td>
<td>None</td>
<td>Carboplatin, paclitaxel, carboplatin after RT</td>
<td>PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection and Martius flap. Residual endometriosis but no cancer.</td>
<td>Patient well with NED at 24.0 years</td>
</tr>
<tr>
<td>9</td>
<td>Clear cell ca</td>
<td>None</td>
<td>Carboplatin, paclitaxel, carboplatin after RT</td>
<td>PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection and Martius flap. Residual endometriosis but no cancer.</td>
<td>Patient well with NED at 24.0 years</td>
</tr>
<tr>
<td>10</td>
<td>Endometrioid adenocarcinoma; G2</td>
<td>None</td>
<td>Carboplatin, paclitaxel, carboplatin after RT</td>
<td>PET scan after 4 months showed possible persistent disease in the RVS. Vaginectomy, anterior resection and Martius flap. Residual endometriosis but no cancer.</td>
<td>Patient well with NED at 24.0 years</td>
</tr>
</tbody>
</table>

BSO, bilateral salpingo-oophorectomy; BTO, bilateral total oophorectomy; BTO-PL, bilateral total oophorectomy-paraaortic lymph node dissection; BT, brachytherapy; EBRT, external beam radiotherapy; NACT, neoadjuvant chemotherapy; MPA, medroxyprogesterone acetate, usual dose 200 mg twice daily; ISC, intermittent self-catheterisation; LN, lymph node; R, right; RT, radiotherapy; RVS, rectovaginal septum; SBO, SAH, subtotal abdominal hysterectomy.
Treatment was individualised according to the location and size of their disease. Six patients underwent surgery with the objective of complete removal of the tumour. There was no macroscopic residual tumour in one (case 1), macroscopic residual disease in four (cases 2, 5, 7 and 9) and involved margins in one case (case 3).

Initial management was surgical in six patients. After surgery, one patient received no further treatment (case 1) as they had an encapsulated tumour with negative surgical margins. Case 9 received postoperative chemotherapy and had a complete response lasting nine years. Four patients received postoperative external beam pelvic RT either alone (case 7) or combined with cisplatin-based concurrent chemotherapy (cases 3 and 5). In three cases the dose of RT ranged from 45 to 59 Gy in 22–30 fractions, but in case 2 the RT was ceased before 45 Gy because of acute toxicity.

Initial management was non-surgical in four patients in whom the diagnosis had been made by core biopsy. Case 4 received neo-adjuvant chemotherapy (NACT) followed by RT after showing a partial response to caelyx and case 6 showed a complete response to chemo-RT. Response in each case was determined clinically and by positron emission tomography / computed tomography imaging. Two patients with advanced local disease (cases 8, 10) received platinum-based chemotherapy and palliative RT but neither showed a definite response to this treatment. Case 10 also received hormonal treatment with medroxyprogesterone acetate (MPA dose 200 mg twice daily but had progressive disease).

Six patients had no evidence of disease (NED) 5.5–24 years after initial diagnosis (mean 15 years). All four patients with grade 1 or low-grade tumours are NED compared with two of the six with grades 2, 3 or high-grade tumours. Four have remained free of recurrence. Their initial treatment had been surgery only (case 1), concurrent cisplatin chemo-RT (cases 5, 6), and postoperative RT only (case 7). Both patients with low-grade adenosarcomas (cases 2, 7) received long-term hormonal maintenance therapy with MPA (200 mg twice daily). Case 7 also received tamoxifen (20 mg daily). They are NED after 23.5 and 24 years respectively.

Two patients developed a late recurrence at the vaginal vault (case 2) and in a para-aortic lymph node (case 4) and both are currently NED 14 and three years after treatment of the recurrence. Two patients who developed late recurrence in the upper abdomen and liver (case 3) and POD (case 9) were treated with chemotherapy. Case 3 had a partial response lasting six months and case 9 had a further complete response lasting nine months; however, both subsequently died of their disease.

In-field control was achieved in the five (cases 3–7) who received 45 Gy or more of RT of whom three (cases 3, 5, 6) had also received concurrent cisplatin-based chemo-RT. Case 2 had not received a curative dose of RT and suffered a late in-field recurrence at the vaginal vault after 10 years. In-field control was not achieved in the two patients with extensive local disease (cases 8, 10) who received palliative RT and chemotherapy.

Three patients who had undergone complex/radical surgery followed by RT experienced late radiation cystitis (G3). One patient has had multiple hospital admission for subacute small bowel obstruction (G3) probably due to adhesions and radiation enteritis but surgical intervention has not been required. One patient developed a disease-related colovesical fistula.

**DISCUSSION**

While endometriosis is a common condition, endometriosis-associated malignancies are relatively uncommon, and the ability of the clinician to predict which patients will go on to develop a malignancy within endometriosis and the management of these patients remains elusive.5 Nezhat et al.21 suggest that some characteristics of women with endometriosis that warrant ongoing follow up includes women with a long-standing history of endometriosis, endometriosis-associated infertility or infertility treatment, or women with ovarian endometrioma. Our study supports this recommendation, as six of our patients had a long history of endometriosis with prior treatment, and six were nulliparous.

The management of patients with benign endometriosis may include observation, hormonal treatment or surgical excision. Nezhat et al.2 advocate complete surgical resection of all endometriotic foci in women undergoing surgical treatment, with tissue evaluation of ovarian endometriomas to rule out malignancy. The benefits of serial surgery to excise visible lesions needs to be balanced by the risks of major operative morbidity due to adhesions and other anatomical distortions. Furthermore, there are no definitive data that demonstrate early surgical treatment of limited implants is associated with a reduced risk of disease progression and malignancy.22 Nezhat et al.5 also recommend ongoing hormonal treatment aimed at reducing the risk for recurrent endometriosis and endometriomas, as oral contraceptive use is associated with 80% lower occurrence of ovarian cancer in women with endometriosis who use the drug for more than ten years;23 however, its efficacy in reducing malignant transformation in extra-ovarian endometriosis is speculative.

Caution should be taken when prescribing unopposed oestrogen HRT in women with a history of endometriosis as there has been an association noted between women with malignant endometriosis and unopposed oestrogen HRT, even in those women who have had a TAH or BSO.24 This risk factor was evident in our case series as four of six patients with known endometriosis had received unopposed oestrogen HRT.

There are a limited number of cases of MEOE in the literature, and its diagnosis is often based on circumstantial information. Most cases fulfil Sampson’s8 three criteria for the diagnosis of malignant change in ovarian endometriosis. Only a minority of cases demonstrate a dysplastic transition from benign to malignant endometriosis as required by Scott’s criteria.9 The literature review by Benoit et al.25 found that dysplastic transition is found in only 36–42% of cases. This led Mostoufizadeh26 to regard that...
the co-existence of a neoplasm and endometriotic tissue is sufficient to indicate an endometriotic origin. A history of endometriosis adds to the circumstantial evidence, especially when the malignancy has arisen in a site of known endometriosis. The issue is further confounded in patients who have received radiotherapy prior to surgical resection which can have a significant impact on tumour morphology as occurred in two cases (5 and 7) in which no residual malignancy was identified. We believe that it is time for Sampson’s and Scott’s criteria to be expanded to include patients with a history of endometriosis.

Due to the rarity of MEOE, therapeutic management has not been standardised. Primary surgical treatment should be performed when feasible which aims to completely resect all disease and obtain staging biopsies of peritoneal surfaces and lymph nodes. Surgical resection may be challenging especially when the malignancy is located deep in the POD or rectovaginal septum and its infiltrative nature often results in residual disease after surgery. Ulrich et al. advocate radical surgery followed by RT as the treatment of choice.

Radiation therapy is effective in this condition and in-field control of disease was achieved in all five of our patients whose total dose of RT was 45 Gy or more. We recommend that RT should be used when the surgical resection is incomplete.

The role of chemotherapy is less clear. Published reports such as that by Heaps et al. suggest that chemotherapy is ineffective in the treatment of ME, but most of their cases in their case series and literature review predated the introduction of cisplatin. In a literature review conducted by Benoit et al., they concluded that the effect of chemotherapy is minimal given its limited efficacy in endometrial cancer. In our series five patients with measurable disease received chemotherapy; there were one complete and two partial responses. Larger numbers are required before any conclusions about the effectiveness of chemotherapy can be drawn.

The place of chemo-radiotherapy is also not clear. It has been postulated that ME behaves more like endometrial carcinoma. The recently published PORTEC-3 phase III trial of women with high-risk endometrial cancer compared adjuvant chemotherapy during and after pelvic RT (chemo-RT) versus pelvic RT alone. In that study, chemo-RT did not improve five-year overall survival although it did increase failure-free survival, but it has some appeal in MEOE which is usually localised in the pelvis at the time of presentation. Two cases (5 and 6) in our series presented with large masses in the rectovaginal septum and/or POD and both had prolonged complete responses to concurrent platinum-based chemo-RT and are still alive with NED. Its role should be explored further as MEOE masses are usually large and localised in the pelvis at the time of presentation.

Heaps et al. recommended the use of progestin therapy in all cases of cancer arising in endometriosis. Hormone receptor testing to assess suitability for hormonal treatment was advocated by Brooks et al. and although this has theoretical appeal, there is currently no strong evidence that it is useful. In our study, two patients with adenosarcomas received long-term maintenance progesterone treatment following initial treatment and are long-term disease-free survivors, but again there is no high-level evidence to support its use.

There is a fine balance between aggressive treatment of primary disease and recurrent disease versus the risk of major therapeutic morbidity. In our series, four patients experienced serious complications to the bladder and/or bowel. These were often due to a combination of RT and surgery.

The prognosis for malignant transformation within MEOE confined to the genital tract correlates well with stage. In the literature, patients with isolated disease of endometrioid histology had an 82–100% five-year survival. However, disseminated intra-peritoneal disease has a very poor associated prognosis, with an 0–12% five-year overall survival. In our case series, none of our patients had tumour spread at the time of diagnosis and the five-year overall survival was 80%.

The limitations of this study relate to small sample size, accrual of patients over a long period of time and the individualisation and heterogeneity of treatments. Following these patients over a very long period has enabled us to report our long-term treatment outcomes. We cannot dogmatically define the optimal treatment of this rare disease and it would be very difficult for any one institution to accrue the necessary numbers. One way to progress would be to establish a multi-institutional registry of pathology, management and outcomes. More research needs to be done on this rare and challenging gynaecological malignancy.

REFERENCES


