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Case Reports

Do we understand the pathophysiology of endometrial cancer?

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Summary

Endometrial carcinoma is the fourth most common cancer in UK women. Previous literature describes local, haematological or lymphatic dissemination to common sites including vaginal vault, lungs, liver, bones and brain. The authors present two unusual cases of endometrial cancer metastases to the psoas major muscle and laparoscopic port sites. Case 1 involves a 71-year-old female who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and peritoneal washings (TAH, BSO, PW) for Grade 1 endometrial cancer, Stage 1B. Three years later she represented with lower back and right hip pain, with MRI imaging revealing psoas muscle metastases. Case 2 describes a 60-year-old female who underwent laparoscopic-assisted vaginal hysterectomy (LAVH), BSO+PW for Grade 1 endometrial cancer, Stage 1B. Three years postoperatively she presented with a lateral abdominal mass overlying the laparoscopic port site scar, which was Grade 1 endometrial cancer on biopsy. These rare metastatic locations question our traditional understanding of the pathophysiology of endometrial carcinoma.

Key words: Endometrial cancer; Dissemination; Psoas major muscle; Laparoscopic port site.

Introduction

Endometrial carcinoma is historically associated with local, haematological or lymphatic dissemination to structures including the vagina, lungs, liver, bone, and brain [1]. Studies have shown that one-fifth of patients with endometrial carcinoma have extra-uterine disease in these sites, while 10% of those with confined endometrial disease have positive pelvic lymph nodes at diagnosis [2]. The present case reports detailing unusual endometrial carcinoma metastases to the psoas major muscle and anterior abdominal wall associated with laparoscopic port sites question our current understanding of endometrial cancer spread and raise the possibility of alternative dissemination mechanisms. This would have significant implications upon both surgical approach (eg: open versus laparoscopic) and treatment regimes.

Case Report

Case 1

A 71-year-old female, para 2 (normal deliveries) presented to Gynaecology Fast Track Clinic with a two-week history of postmenopausal bleeding per vagina, having gone through menopause at age 50. She had never taken hormone replacement therapy (HRT) and underwent routine recall for cervical smears. She suffered from essential hypertension and her examination findings were unremarkable. She was a non-smoker and had no family history of breast or gynaecological malignancy.

Transvaginal ultrasound (US) revealed a raised endometrial thickness of 17.3 mm with a right ovarian cyst measuring 2.3 cm. There were no adnexal masses or free fluid. CA-125 tumour marker was normal. Hysteroscopy showed an area of suspicious, vascular endometrium and endometrial biopsy revealed moderate dysplasia and intraepithelial neoplasia. The diagnosis was endometrial adenocarcinoma of likely endometrioid subtype. The patient underwent TAH, BSO+PW. Histology revealed Grade 1 endometrial carcinoma, Stage 1B. Adjunctive endometrial radiotherapy was administered.

Postoperatively, the patient received regular follow-up according to national guidelines; every three months for the first year then six monthly for five years. Three years postoperatively the patient's general practitioner requested urgent review due to worsening lower back and right hip pain. CT and MRI scans were arranged to exclude recurrence and bony metastases. Imaging revealed a well-defined abnormality within the right psoas muscle measuring 7 x 4 cm beginning at the level of L3 and extending down the psoas muscle with scalloping of L4 vertebra. (Figure 1) There was no significant lymphadenopathy and no evidence of disease elsewhere. Provisional differential diagnoses included haematoma, abscess or sarcoma.

Multi-disciplinary team (MDT) discussion advised CT guided aspiration of the psoas mass, with two aspirations revealing inflammatory changes with no evidence of malignancy. Progressive back and hip pain prompted a repeat MRI scan which confirmed right psoas muscle metastases with para-aortic lymphadenopathy. The patient underwent radiotherapy (50 Gy in 25 factions) to the psoas mass but the disease progressed clinically and radiologically with an enlarging para-aortic/retroperitoneal mass. Further paraspinal radiotherapy (ten Gy in five fractions) and two cycles of chemotherapy (carboplatin and paclitaxel) yielded little bene-

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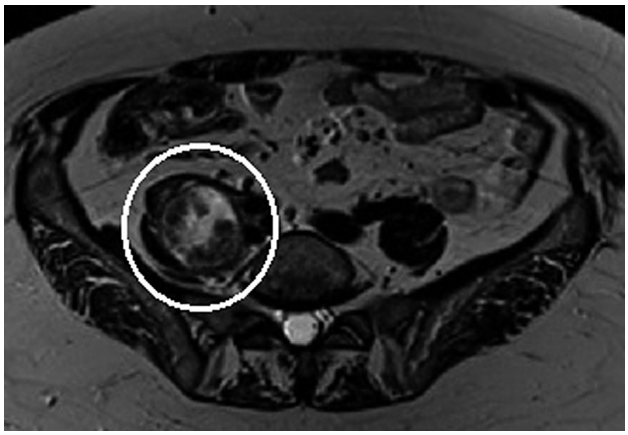

Figure 1. — A well-defined abnormality within the right psoas muscle measuring 7 x 4 cm beginning at the level of L3 and extending down the psoas muscle with scalloping of L4 vertebra.

fit. The patient was commenced on medroxyprogesterone 200 mg BD and died in a hospice shortly after developing malignant spinal cord compression.

Case 2

A 60 year-old female who had been post-menopausal for 8 years presented to the Gynaecology Fast Track clinic with a 2 week history of bleeding per vagina. She had never taken HRT, had always received routine cervical smears and had no significant family history. She suffered from type two diabetes mellitus, hypertension and mild osteoarthritis. She was a non smoker and her examination was unremarkable.

Transabdominal US revealed thickened, echogenic endometrium measuring 17 mm with normal appearances of the ovaries, with no pelvic mass or free fluid.

Hysteroscopy showed areas of atypical and vascular endometrium with no polyps or fibroids. Endometrial biopsy revealed atypical endometrial hyperplasia. Invasive adenocarcinoma could not be excluded.

The patient underwent an uncomplicated LAVH, BSO+PW. Histological examination diagnosed Grade 1 endometrial adenocarcinoma, Stage 1B. Intraoperatively, a 12-mm midline port and 2 5-mm lateral ports were utilized with a peritoneal drain placed for 12 hours postoperatively. Uterus delivery was not difficult. The fascial layer of the midline port was closed with vicryl and glue applied to the lateral incisions.

Regular postoperative follow up commenced every four months for two years then six monthly for five years. Three years postoperatively the patient was referred with a possible hernia overlying the left laparoscopic port site (created during LAVH). A CT was arranged to exclude malignancy, either a new primary or recurrence. Imaging revealed a 3.7 x 3.8 cm mass arising from the left anterior abdominal wall with no evidence of recurrent pelvic or lymphatic disease (Figure 2). MDT advised needle core biopsy of the mass, which concluded metastatic endometrioid adenocarcinoma. The anterior abdominal wall lesion was excised with clear margins.

One year later, a suspicious vaginal vault area was biopsied and revealed recurrent Grade 1 endometrial adenocarcinoma of papillary type. CT imaging additionally revealed lymph node recurrence, with a 2.6 x 2cm soft tissue mass near the external iliac node. Radiotherapy (45 Gy in 25 fractions) and brachytherapy (selectron treatment) was administered to the vaginal vault. This yielded a mixed response; reducing the size of the lymph node and vaginal vault lesions but growth in the rectus lesion (not incorporated into the field). The patient was diagnosed with incurable disease and medroxyprogesterone 200 mg BD commenced.

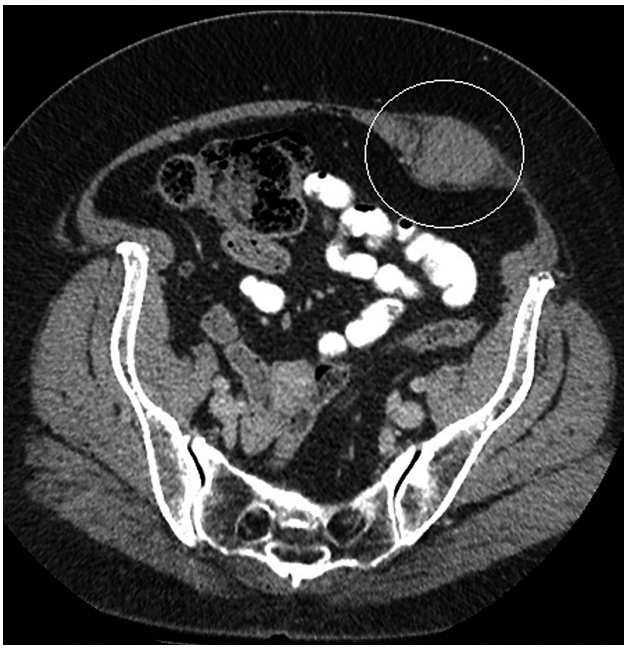

Figure 2. — A 3.7 x 3.8 cm mass arising from the left anterior abdominal wall with no evidence of recurrent pelvic or lymphatic disease

The rectus sheath lesion continued to progress reaching 8 x 7 cm, likely aided by the patient's use of tamoxifen, which she was advised to cease. Due to the associated pain, palliative radiotherapy (45 Gy in 25 fractions) was administered yet the mass continued to increase in size. She developed a pulmonary embolus and underwent community palliative care.

Discussion

Endometrial cancer accounts for 5% of new cancer diagnoses in UK women with an incidence of 26 cases: 100,000 females, steadily increasing since the 1970s [3]. Contributing factors include increased obesity, use of HRT, and changes in reproductive behaviour (nulliparity/fewer children). Ninety percent of females are >50 years at diagnosis and 10% patients with post-menopausal bleeding have endometrial cancer [3]. Bohkman described two distinct types of endometrial cancer; type 1 (80% cases) associated with obesity and endometrial hyperplasia, with a five-year survival rate of 85%. Type 2 endometrial cancer (eg: serous, clear, small cell) has a poorer prognosis (50% five-year survival), metastasize early, and are not estrogen-associated [4].

Type 1 endometrial cancer characteristically spreads locally (vaginal vault) and via the lymphatic system, with

disease generally localised to the pelvic nodes [5, 6]. Further lymphatic spread involves the common iliac and para-aortic nodes (8% incidence), with the latter having a poor prognosis [6]. Hepatic and pulmonary metastases occur by haematological or lymphatic (three-times more commonly) spread [7]. Type 2 endometrial carcinoma has a greater predilection for lymphatic dissemination, with resultantly higher rates of extra-uterine disease at presentation [5].

There are few literature reports on laparoscopic port site endometrial cancer metastases (PSM) [8,19], yet these reports highlight deficiencies in our understanding of endometrial carcinoma pathophysiology. In 1961 Thomas *et al.* [20] described the principle of tumour cell contamination of surgical wounds yet little advance has been made in our understanding of the exact mechanisms. Factors encouraging spread include incision of the tumour; blood vessels or lymphatics, or direct contact between the tumour and abdominal wall intraoperatively. These principles were surmised by the tumour cell entrapment theory of 1989 [21], recognising the potential for tumour cell spread via:

- Free intraperitoneal tumour emboli.
- Fibrin entrapment of intra-abdominal tumour emboli on traumatised peritoneal surfaces.
- Blood clots containing viable cancer cells remaining in the abdomen postoperatively.
- Growth of viable cells encouraged by growth and tissue repair factors involved in wound healing.

PSM occur in 1-1.9% of surgery for gynaecological malignancies [11,15], typically presenting 21 months postoperatively (range 7-48 months) [8,13]. PSM and intra- or retroperitoneal tumour spread is not exclusively associated with advanced or high-grade malignancies [13] as supported by the present case reports. In agreement with other studies [9] the lateral port at which PSM occurred in the present case report was not used for specimen retrieval. It is improbable that haematological, lymphatic or direct contact is solely responsible for these metastatic sites. Wang *et al*. [19] concur that haematological dissemination cannot underly PSMs, considering that the lungs receive most venous drainage from the gynaecological organs, and the abdominal wall receives only a small percentage of cardiac output. Consequently, isolated abdominal wall recurrence without pulmonary metastases is unlikely.

One proposed etiological mechanism involves trans-tubal spread into the peritoneal cavity, a theory strengthened by Cressman *et al.* [2] who reported that 52% patients with positive PW had no evidence of extra-uterine disease. Stewart *et al.* [22] described a strong correlation between intra-luminal tumour cells within the fallopian tubes and positive PW and peritoneal metastases. Trans-tubal spread is certainly important for the dissemination of type II endometrial carcinoma [23, 24]. Some suggest that retrograde, trans-tubal dissemination may occur as early as diagnostic hysteroscopy, with Revel *et al.* advising fluid-based hysteroscopy should be avoided if the TVUS is highly suspicious of malignancy [25-28].

Diurdievic *et al.* [29] describe the only other case of psoas muscle endometrial cancer metastases, additionally reporting metastases in the anterior and lateral pelvic wall. Lonnefors *et al.* reported PSMs to most commonly occur in the specimen retrieval port [11].

At laparoscopic surgery, tumour cells may directly seed on the damaged rectus sheath at the port site, encouraged by repeated changes of instruments with traumatic movement into and out of the abdomen; specimen retrieval and the pneumoperitoneum itself seeding tumour cells [8-19]. Small incisions (eg: laparoscopy) are proposed to promote tumour growth more successfully than larger incisions [9,12]. Suggestions to overcome PSM include gas-free laparoscopic surgery; avoidance of power cutting devices; use of retrieval bags; correct trochar placement with minimal trauma; suturing ten- to 12-mm trochar sites; instrument and port-site lavage with iodine or chemotherapeutic agents; initiating adjuvant therapy promptly and including the port sites within the radiation field [8-19,30].

Laparotomy wound recurrences of endometrial cancer are extremely rare, yet conflicting data exists comparing open and laparoscopic surgery [9-14, 31]. A Cochrane review [32] compared the two approaches and found no difference in wound recurrence. However the included studies involved only early endometrial cancer, so these findings may not be generalizable for more advanced disease. Some authors argue that systematic closure of the abdominal wall layers in open surgery produces lower wound recurrences [14]. It is proposed that data showing no difference between open and laparoscopic surgery is skewed by non-uniform trial designs, small sample sizes, inadequate representation of all endometrial cancer grades/stages, and short follow up durations which miss presentations of wound recurrence [14, 17, 33].

A multi-factorial etiology for PSM including the tumour type is most likely responsible, considering that gallbladder adenocarcinoma is well reported to recur at primary port sites [10,11]. Equally, colorectal adenocarcinomas have been linked to PSM, with 50% occurring at the specimen retrieval site [9]. However, similar to endometrial cancer, a Cochrane review of 2008 found no difference in wound recurrence rates comparing open and laparoscopic surgery for early (non-metastatic) colorectal cancer [34].

Conclusion

In conclusion, the present case reports highlight deficiencies in our understanding of endometrial cancer dissemination mechanisms with significant implications on surgical approach.

References

[1] National Cancer Institute: "Endometrial cancer treatment PDQ; General information about endometrial cancer; 2014". Available at: http://www.cancer.gov/cancertopics/pdq/treatment/endometrial/HealthProfessional/page1

[2] Creasman W.T., Odicino F., Maisonneuve P., Quinn M.A., Beller U., Benedet J.L., *et al.*: "Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer". *Int. J. Gynaecol. Obstet.,* 2006, *95*, S105.

[3] Cancer Research UK: "Cancer statistics; Endometrial Cancer". London: Cancer Research U.K, 2011.

[4] Bokhman J.V.: "Two pathogenetic types of endometrial carcinoma". *Gynecol. Oncol.,* 1983, *15*, 10.

[5] Amant F., Moerman P., Neven P., Timmerman D., Van Limbergen E., Vergote I.: "Endometrial cancer". *Lancet,* 2005, *366*, 491.

[6] AlHilli M.M., Mariani A.: "The role of para-aortic lymphadenectomy in endometrial cancer". *Int. J. Clin. Oncol.*, 2013, *18*, 193.

[7] Morgan-Parkes J.H.: "Metastases: mechanisms, pathways, and cascades". *AJR Am. J. Roentgenol.*, 1995, *164*, 1075.

[8] Faught W., Fung Kee Fung M.: "Port site recurrences following laparoscopically managed early stage endometrial cancer". *Int. J. Gynecol. Cancer*, 1999, *9*, 256.

[9] Kadar N.: "Port-site recurrences following laparoscopic operations for gynaecological malignancies". *Br. J. Obstet. Gynaecol.*, 1997, *104*, 1308.

[10] Kim B., Huh S.J., Kim B.G.: "Port site metastasis after robotic-assisted laparoscopic hysterectomy for uterine cervical cancer: a case report and literature review". *Taiwan J. Obstet. Gynecol.*, 2013, *52*, 558.

[11] Lönnerfors C., Bossmar T., Persson J.: "Port-site metastases following robot-assisted laparoscopic surgery for gynecological malignancies". *Acta Obstet. Gynecol. Scand.*, 2013, *92*, 1361.

[12] Martínez A., Querleu D., Leblanc E., Narducci F., Ferron G.: "Low incidence of port-site metastases after laparoscopic staging of uterine cancer". *Gynecol. Oncol.*, 2010, *118*, 145.

[13] Muntz H.G., Goff B.A., Madsen B.L., Yon J.L.: "Port-site recurrence after laparoscopic surgery for endometrial carcinoma". *Obstet. Gynecol.*, 1999, *93*, 807.

[14] Nagarsheth N.P., Rahaman J., Cohen C.J., Gretz H., Nezhat F.: "The incidence of port-site metastases in gynecologic cancers". *JSLS*, 2004, *8*, 133.

[15] Ndofor B.T., Soliman P.T., Schmeler K.M., Nick A.M., Frumovitz M., Ramirez P.T.: "Rate of port-site metastasis is uncommon in patients undergoing robotic surgery for gynecological malignancies". *Int. J. Gynecol. Cancer*, 2011, *21*, 936.

[16] Rauff S., Ng J.S.: "Port-site recurrence in a patient undergoing robot-assisted gynecologic cancer surgery for endometrial cancer - A case report". *Gynecol. Oncol. Case Rep.*, 2012, *2*, 127.

[17] Sanjuán A., Hernández S., Pahisa J., Ayuso J.R., Torné A., Martínez Román S., *et al.*: "Port-site metastasis after laparoscopic surgery for endometrial carcinoma: two case reports". *Gynecol. Oncol.*, 2005, *96*, 539.

[18] Wang P.H., Yen M.S., Yuan C.C., Chao K.C., Ng H.T., Lee W.L., *et al.*: "Port site metastasis after laparoscopic-assisted vaginal hysterectomy for endometrial cancer: possible mechanisms and prevention". *Gynecol. Oncol.*, 1997, *66*, 151.

[19] Wang P.H., Yuan C.C., Lin G., Ng H.T., Chao H.T.: "Risk factors contributing to early occurrence of port site metastases of laparoscopic surgery for malignancy". *Gynecol. Oncol.*, 1999, *72*, 38.

[20] Thomas C.G.: "Tumor cell contamination of the surgical wound: experimental and clinical observations". *Ann. Surg.*, 1961, *153*, 697.

[21] Sugarbaker P.H., Cunliffe W.J., Belliveau J., de Bruijn E.A., Graves T., Mullins R.E., *et al.*: "Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer". *Semin. Oncol.*, 1989, *16*, 83.

[22] Stewart C.J., Doherty D.A., Havlat M., Koay M.H., Leung Y.C., Naran A., *et al.*: "Transtubal spread of endometrial carcinoma: correlation of intra-luminal tumour cells with tumour grade, peritoneal fluid cytology, and extra-uterine metastasis". *Pathology*, 2013, *45*, 382.

[23] Soslow R.A., Pirog E., Isacson C.: "Endometrial intraepithelial carcinoma with associated peritoneal carcinomatosis". *Am. J. Surg. Pathol.*, 2000, *24*, 726.

[24] Abeler V.M., Vergote I.B., Kjørstad K.E., Tropé C.G.: "Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern". *Cancer*, 1996, *78*, 1740.

[25] Revel A., Tsafrir A., Anteby S.O., Shushan A.: "Does hysteroscopy produce intraperitoneal spread of endometrial cancer cells?" *Obstet. Gynecol. Surv.*, 2004, *59*, 280.

[26] Obermair A., Geramou M., Gücer F., Denison U., Graf A.H., Kapshammer E., *et al.*: "Impact of hysteroscopy on disease-free survival in clinically stage I endometrial cancer patients". *Int. J. Gynecol. Cancer*, 2000, *10*, 275.

[27] Takac I., Zegura B.: "Office hysteroscopy and the risk of microscopic extrauterine spread in endometrial cancer". *Gynecol. Oncol.*, 2007, *107*, 94.

[28] Zerbe M.J., Zhang J., Bristow R.E., Grumbine F.C., Abularach S., Montz F.J.: "Retrograde seeding of malignant cells during hysteroscopy in presumed early endometrial cancer". *Gynecol. Oncol.*, 2000, *79*, 55.

[29] Djurdjević S., Mladenović-Segedi L., Djolai M.: "Endometrical cancer metastases in the region of abdominal muscles and pelvic wall". *J. BUON.*, 2006, *11*, 75.

[30] Neuhaus S.J., Watson D.I., Ellis T., Dodd T., Rofe A.M., Jamieson G.G.: "Efficacy of cytotoxic agents for the prevention of laparoscopic port-site metastases". *Arch. Surg.*, 1998, *133*, 762.

[31] Santeufemia D.A., Lumachi F., Basso S.M., Tumolo S., Re G.L., Capobianco G., *et al.*: "Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy as salvage treatment for a late wound recurrence of endometrial cancer". *Anticancer Res.*, 2013, *33*, 1041.

[32] Galaal K., Bryant A., Fisher A.D., Al-Khaduri M., Kew F., Lopes A.D.: "Laparoscopy versus laparotomy for the management of early stage endometrial cancer". *Cochrane Database Syst. Rev.,* 2012, *9*. CD006655. doi: 10.1002/14651858.CD006655.pub2.

[33] Mo X., Yang Y., Lai H., Xiao J., He K., Chen J., Lin Y.: "Does carbon dioxide pneumoperitoneum enhance wound metastases following laparoscopic abdominal tumor surgery? A meta-analysis of 20 randomized control studies". *Tumour Biol.*, 2014, *35*, 7351. doi: 10.1007/s13277-014-1812-5. Epub 2014 Apr 18.

[34] Kuhry E., Schwenk W., Gaupset R., Romild U., Bonjer J.: "Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials". *Cancer Treat. Rev.*, 2008, *34*, 498.

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