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Case report

Two cases of extragonadal malignant transformation of endometriosis after TAH/BSO for benign indications

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1. Introduction

Endometriosis is the estrogen-dependent growth and proliferation of endometrial glands and stroma outside of the uterine cavity. This can result in inflammation, dysmenorrhea, infertility, and/or chronic pelvic pain. Despite the ability of endometriosis to invade and metastasize, the disorder is considered benign. However, recent evidence suggests that endometriosis can progress in a step-wise manner from benign to borderline, and finally to malignancy (Wei et al., 2011). Endometriosis-associated epithelial ovarian cancer is frequently reported in the literature, but extragonadal cases are rare (Heaps et al., 1990). Here we describe two cases of extragonadal malignant transformation of endometriosis after total abdominal hysterectomy and bilateral salpingo-oophorectomy for benign indications.

2. Case reports

2.1. Case #1

A 58 year-old obese (BMI 32) G3P3 initially presented with bilateral ovarian masses in 2010. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and appendectomy. Final pathology showed cystadenofibromas with rare foci of glandular crowding arising in the setting of endometriosis with no borderline features or evidence of malignancy. The patient re-presented in 2016 with abdominal pain, fever and hematochezia. Workup revealed a large pelvic mass, and pelvic exam demonstrated a mass at the top of the vagina compressing but not invading the rectosigmoid. MRI revealed a multiseptated, nodular mixed cystic and solid mass lesion inferior to the rectosigmoid junction, a second complex lesion superior to the rectosigmoid junction, prominent wall thickening and left hydronephrosis. CT demonstrated the mass as well as two small liver lesions. Labs were notable for a normal CA-125, AFP, CEA, and HCG, but an elevated CA 19-9. She underwent an ultrasound-guided biopsy which showed endometrioid adenocarcinoma, FIGO grade 1, without loss of expression of MMR proteins. Given her history, this was presumed to be extragonadal malignant transformation of endometriosis.

As the mass was felt to be unresectable, the patient underwent five cycles of chemotherapy with carboplatin and paclitaxel followed by an attempted surgical debulking. Intraoperatively the mass was felt to be unresectable with extension to the pelvic sidewall and involvement of the bladder, rectosigmoid, and rectum. Biopsies were taken and surgery was aborted. She then underwent 6 cycles of monthly liposomal doxorubicin followed by a repeat CT scan which showed progression. She then received 56 Gy of pelvic radiation. Following radiation the patient was taken to the operating room for exam under anesthesia, cystoscopy, sigmoidoscopy, vaginal tumor excision, and biopsy of the right pelvic sidewall. Findings at time of this surgery confirmed a large cystic mass that was completely filling the vagina. The patient also had tumor that was invading into the rectum. On cystoscopy, the patient did not have tumor involving the bladder mucosa. Given rectal involvement, there was concern for fistula formation with bevacizumab, and the patient was started on megestrol acetate alternating with tamoxifen. A subsequent CT scan showed progression. She was then started on weekly carboplatin and paclitaxel, which was discontinued due to persistent

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profound anemia and thrombocytopenia. More recently, the patient was started on bevacizumab, which she is tolerating well with stable disease.

2.2. Case #2

An obese (BMI 37) 58yo G2P1011 underwent an uncomplicated total abdominal hysterectomy and bilateral salpingo-oophorectomy in 1997 for abnormal uterine bleeding. Intraoperative findings were notable for endometriosis and final pathology was benign. After surgery she was started on estrogen replacement. She then re-presented in 2016 with vague low back discomfort and was diagnosed with lumbar arthritis and multiple UTIs. In November 2016 she presented with acute onset abdominal pain and CT revealed moderate left hydronephrosis and ureteral dilation secondary to a 3 cm soft tissue mass occluding the distal left ureter. A biopsy was performed which showed endometrioid adenocarcinoma. The patient then underwent exploratory laparotomy, lysis of adhesions, resection of left pelvic sidewall mass, left radical pelvic dissection, bilateral pelvic lymphadenectomy, left periaortic lymphadenectomy, omentectomy, distal left ureterectomy, ureteral neocystostomy with psoas hitch and ureteral stent placement. Final pathology showed endometrioid adenocarcinoma with focal squamous differentiation 5.1 cm in greatest dimension. The lymph nodes and all other specimens were negative for malignancy. Mismatch repair protein expression was retained. Estrogen and progesterone receptor expression was uniformly positive. Given her history of endometriosis and hormonal replacement therapy, this was presumed to be malignant transformation of endometriosis. Postoperatively she received external beam radiation with 54 Gy to the left pelvis. Following completion of therapy, she underwent surveillance. After developing increasing pelvic symptoms, a follow up MRI showed a new 2.5 cm mass near the ureteral reimplantation site at the bladder. A CT scan showed small pulmonary nodules slightly increased in size from prior. She was recommend to start hormonal treatment with alternating Megace and tamoxifen, with subsequent regression of the pelvic mass.

3. Discussion

Malignant transformation of endometriosis was first described by Sampson in 1925 (Sampson, 1925) In 1953 Scott et al. established the following criteria for the diagnosis of endometriosis-associated ovarian carcinoma, the most common site for malignant transformation of endometriosis: (i) evidence of endometriosis close to the tumor; (ii) exclusion of invasion from other sources; (iii) presence of tissue resembling endometrial stroma surrounding characteristic epithelial glands; and (iv) histological proof of transition from the benign changes that characterize endometriosis to the malignant changes of cancer (Scott, 1953).

Malignant transformation of endometriosis is an extremely rare phenomenon, with an estimated risk of approximately 1% for premenopausal women with endometriosis, and 1–2.5% for postmenopausal women (Van Gorp et al., 2004). This risk increases with increasing age, increasing duration of endometriosis, a genetic predisposition to endometriosis, and an abnormal inflammatory response (Brinton et al., 1997). However, Pearce et al. found in a meta-analysis of 13 case-control studies including nearly 8000 women that women with a history of endometriosis have a threefold increased risk of clear cell epithelial ovarian cancer and a twofold increased risk of endometrioid or low grade serous ovarian cancer (Pearce et al., 2012).

While ovarian malignancy is the most common site for endometriosis associated carcinoma, accounting for approximately 75% of cases, there are a number of patients, like the two cases above, who develop extragonadal disease. Brooks et al. reviewed 45 cases of extragonadal malignancies associated with endometriosis and found that the rectovaginal area was the next most common site, accounting for 36% of the cases, followed by the colorectal area, the bladder and the vagina (Brooks and Wheeler, 1977). In a separate study, postmenopausal status and a history of hormone replacement were associated with extragonadal cancers arising in endometriosis (Modesitt et al., 2002). Given the estrogen-driven nature of endometriosis, it is biologically plausible that a history of hormone replacement therapy, in particular unopposed estrogen, could increase the risk of endometriosis-associated cancers. In fact, a recent review of the literature found 14 published case reports of endometriosis-associated endometrioid adenocarcinoma in patients with a history of HRT. The majority of the patients were on unopposed estrogen therapy at the time of diagnosis, with duration of therapy ranging from 15 months to 20 years (Ronga et al., 2009). Accordingly, the European Menopause and Andropause Society (EMAS) recommends either continuous combined estrogen–progestogen therapies or tibolone in women with a history of endometriosis, regardless of hysterectomy status (Moen et al., 2010). Interestingly, the patient in case #1 had no history of HRT use, indicating the potential for residual endometriosis after TAH and BSO to undergo spontaneous malignant transformation with only stimulation from endogenous estrogen.

Due to the rarity of this type of cancer, there are no guidelines on the optimal management. Because this type of cancer is mostly low-grade, the efficacy of chemotherapy is called into question. However, Davis et al. found no difference in response to chemotherapy between EAOC and papillary serous ovarian cancer (Davis et al., 2014). Expert consensus recommends complete surgical resection when technically feasible followed by some form of adjuvant therapy, generally per standard ovarian cancer guidelines (National Comprehensive Cancer Network, n.d.). Heaps et al. reviewed 205 cases of endometriosis-associated cancers, including 44 cases of extragonadal disease, and found that radiation therapy was often able to completely control disease confined to the pelvis. They suggested that for extragonadal disease surgery followed by radiotherapy might be more effective. Those patients treated with progestins had a 77% five-year survival rate while only one patient responded to chemotherapy. Given this, they recommend surgical resection followed by radiation if disease is localized to the pelvis, with progestin therapy for metastatic or recurrent disease (Heaps et al., 1990). In the above cases, both patients were treated with progestins, but only the second case responded to the therapy. In reviewing the histopathology, the first case was only focally ER and PR positive while the second case was uniformly ER and PR positive. This subtle but key difference in receptor status could explain the disparity in treatment response and highlights the importance of evaluating hormone receptor status when devising a treatment plan for these patients.

4. Conclusion

In conclusion, endometriosis-associated cancers are rare but can occur even after hysterectomy and bilateral salpingo-oophorectomy for benign indications. It is important to consider a history of endometriosis when counseling patients regarding the risks and benefits of estrogen replacement therapy. When considering treatment options for this type of cancer, surgical resection, radiation and progestins may be beneficial, and evaluation of ER and PR status may play a role in predicting the response to hormonal treatment. The role of chemotherapy is not well defined in these patients.

Conflict of interest statement

There are no conflicts of interest to report for Dr. Katrin Eurich, Dr. Barbara Goff or Dr. Renata Urban.

Author contribution section

KE drafted and revised the manuscript. RU and BG revised the manuscript. All authors have given final approval of the version to be

published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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