Endometrioid adenocarcinoma 13 years after total abdominal hysterectomy and bilateral salpingo-oophorectomy

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ABSTRACT

يعد التحول الخبيث كمضاعفات غير متكررة للانتباذ البطاني الرحمي. نتيجة لكون بطانة الرحم منتبذة، قد تسبب زيادة هرمون الإستروجين تحوله إلى السرطان. نصف هنا حالة لامرأة تبلغ من العمر 68 عاماً قد خضعت لعملية استئصال الرحم بالكامل عبر البطن واستئصال البوق والمبيض على الجانبين لانتباذ بطانة الرحم. وضعت المريضة على العلاج البديل على الإستروجين فقط. حضرت المريضة وهي تعاني من وجود كتلة في الجانب الأيسر من الحوض وصعوبة في التنفس. أظهرت نتيجة الأشعة المقطعية للصدر والحوض والبطن وجود انصباب بجانب غشاء الرئة اليمنى وكتلة نسيج طري في الحوض. تم تصريف الانصباب بجانب الرئة وتم اخذ عينة من الكتلة عبر البريتون وأظهرت نتيجة فحصها وجود ورم غدي سرطاني منتشر. تمت معالجة المريضة بست دورات من العلاج الكيميائي (كاربوبلاتين/باكليتاكسيل) وقد استجابت للعلاج بشكل جيد. قد يؤدي تحفيز الإستروجين غير العكسي إلى ما قبل الإصابة بالخباثة أو التحول الخبيث لبؤرات انتباذ بطانة الرحم. لذلك، يجب أخذ إضافة العلاج البديل بروجيستين للإستروجين بعين الاعتبار لدى النساء اللواتي خضعن لعملية استئصال الرحم مع المبيض نتيجة لانتباذ بطانة الرحم.

Malignant transformation is an infrequent complication of endometriosis. As endometriosis is an ectopic endometrium, hyperestrogenism may cause hyperplasia or transformation into cancer. We describe a case of a 68-year-old woman who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis. She was subsequently placed on estrogen-only replacement therapy. She presented with left-sided pelvic mass and shortness of breath. Computed tomography of chest, pelvis, and abdomen, demonstrated right-sided pleural effusion and soft tissue mass in the pelvis. Pleural effusion was tapped and biopsy from the peritoneal mass showed metastatic adenocarcinoma; immunohistochemistry findings favored endometrioid adenocarcinoma. She was treated by 6 cycles of Carboplatin/Paclitaxel and responded well. Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestins to estrogen replacement therapy should be considered in women who have undergone hysterectomy with oophorectomy due to endometriosis.

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Endometriosis is a common gynecological disease in which endometrial tissue (glandular epithelium and stroma) is found at locations outside the uterine cavity. The ovary is the primary site in 79% of cases, and extragonadal sites are identified in 21%. The most common presenting symptoms or signs are abdominal and/or pelvic pain, pelvic mass, and vaginal bleeding. The growth and maintenance of endometriotic implants are dependent upon the presence of ovarian steroids. Therefore, endometriosis occurs during the active reproductive period. Endometriosis is rare before menarche and after menopause. Malignant transformation is an infrequent complication of endometriosis, and the risk of malignant transformation of ovarian endometriosis was estimated at 2.5%. As endometriosis is an ectopic endometrium, hyperestrogenism (either endogenous or exogenous) may cause hyperplasia or transformation into cancer. It has been suggested that estrogen replacement therapy (ERT) is associated with a risk of epithelial ovarian cancer of the clear cell and endometrioid type. The prevalence of endometriosis in clear-cell ovarian carcinoma is 35.9%, and 19% in endometrioid ovarian carcinoma.[1]

We are presenting a case of malignant transformation of endometriosis in a patient on unopposed ERT for 13 years, and we focused our discussion on recommendations for those patients who require hormone replacement therapy with history of endometriosis.

Case Report. A 68-year-old woman presented with left-sided pelvic mass and increasing shortness of breath in February 2006. Her history included total abdominal hysterectomy (TAH), and bilateral salpingo-oophorectomy (BSO) for multiple large fibroids and endometriosis (**Figure 1**), and 2 ileostomies for small bowel torsion (1993). She was subsequently placed on estrogen-only replacement therapy. Her weight was 120 kg, and her height was 157 cm, body mass index (BMI) of 48.7. Her gynecologic history was unremarkable. She had never been pregnant. On physical examination, there was decreased air entry on the right lung, and a left sided pelvic mass felt deep in the pelvis. Computed tomography of chest, pelvis, and abdomen, demonstrated right sided pleural effusion (**Figure 2**), and soft tissue mass in the pelvis, 5 cm in diameter, and another small one on the peritoneal surface with thickness noted around the distal sigmoid. Carcino Embryonic Antigen (CEA) was normal, Cancer Antigen 125 (CA125) was 929. Endoscopic examination revealed no abnormalities of the colon. Mammogram, and a bone scan were normal. Pleural effusion was tapped and revealed metastatic adenocarcinoma. Biopsy from peritoneal mass revealed poorly differentiated adenocarcinoma, by immunohistochemistry the tumor was positive for cytokeratin 7 (CK7), CA125, CD10, and estrogen receptors. It was negative for cytokeratin 20 (CK20), CEA, thyroid transcription factor-1 (TTF1), and progesterone. The findings favor an endometrioid adenocarcinoma. The case was discussed at the tumor board, due to her previous history of 2 ileostomies and her prognosis due to advanced disease, it was decided to start her on chemotherapy. She responded well to the treatment of 6 cycles of Carboplatin/Paclitaxel noted during chemotherapy and follow up of CA125, which decreased to normal level after the third cycle of chemotherapy. Follow-up CT scans showed disappearance of the pleural effusion (**Figure 3**) and shrinkage of the pelvic mass. She was followed regularly in the oncology clinic every 2 months, and she was asymptomatic and CA125 was normal for 14 months. She is alive and well until this report was completed.

Discussion. In the last decade, based on epidemiological and biological studies, endometriosis has been associated with a definite increase in risk of various malignancies.[2] This aspect has important clinical implications, requiring modifications in

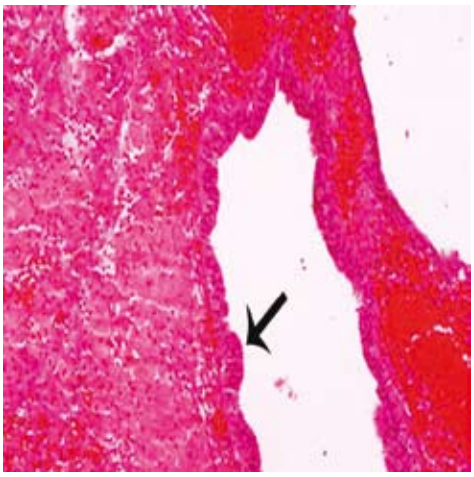

Figure 1 - Endometriosis: histological appearance.

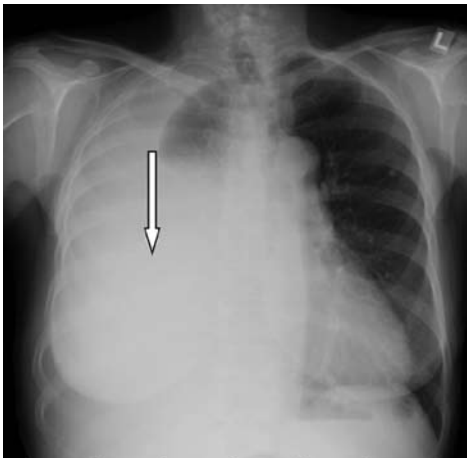

Figure 2 - Complete obliteration of the right lung by malignant pleural effusion (arrow).

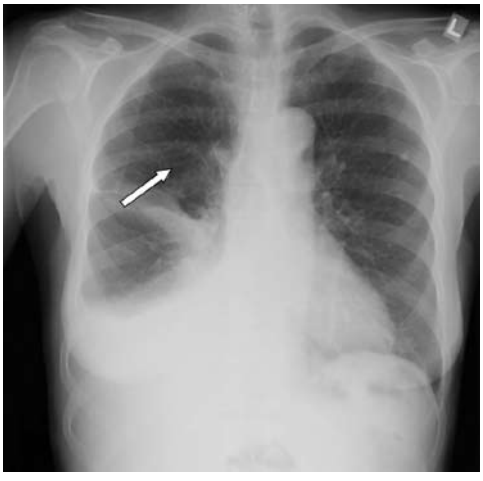

Figure 3 - Disappearance of pleural effusion after chemotherapy (arrow).

current therapeutic management if endometriosis is recognized as a cancer precursor lesion. Historically, in 1925, Sampson[3] presented a lengthy report entitled "Endometrial Carcinoma of the Ovary, Arising in Endometrial tissue of that origin." He further theorized that menstrual blood escaping into the peritoneal cavity may cause 2 groups of lesions, those arising from the growth of implanted endometrial tissue, known today as "endometriosis" and those developing from metaplasia of peritoneal mesothelium and surface epithelium of the ovary. He reported 7 cases of carcinoma that he attributed to an origin in endometriosis. Following Sampson's original report, confirmation was slow and surprisingly few cases are found in the literature. Vogt[4] reported a case with carcinoma in the posterior cul-de-sac and Hanser[5] had a similar case. In 1951, Bacher and Hertzog[6] concluded there were only 11 acceptable cases in the literature, which demonstrated carcinoma developing in or from endometriosis. In 1966, Gray et al[7] reviewed the literature on 141 cases of carcinoma of the ovary of the Mullerian type, he found that endometriosis was directly or possibly involved in 18 cases, 7 of them were found in endometrioid cyst. He concluded that tumor stimulus first might promote benign endometriosis, then atypical changes, and finally malignant disease. Several investigators have reported endometrial malignancies arising in endometriotic foci following unopposed estrogen stimulation. Estrogen monotherapy in obese patients significantly increases the risk of malignant extra-gonadal endometrial transformation. A large series of 793 patients with ovarian cancer found that unopposed ERT was associated with a significant increase in the risk of endometrioid and clear cell epithelial ovarian cancer (odds ratio [OR] 2.56; 95% confidence interval [CI] 1.32-4.94). In addition, the risk associated with ERT was much larger in women with an intact genital tract than those with a history of hysterectomy or tubal ligation (OR 3.00; 95% CI 1.54-5.85).[8] Hyperestrogenism has been implicated as a risk factor for the development of cancer from endometriosis. Zanetta et al[9] reported that when obesity and the use of unopposed estrogen are considered together, there is significant risk for the development of cancer from endometriosis. In this study, the median duration of estrogen used was 10 years. The patient in our case has been receiving unopposed estrogen for 13 years and was obese. Tamoxifen is a nonsteroidal triphenyl ethyl compound that is widely used as adjuvant therapy in the treatment of breast cancer. The efficacy of tamoxifen in breast cancer is a result of its antiestrogen properties, but tamoxifen may also exert a weak estrogenic effect. Two cases of tamoxifen-associated endometrioid adenocarcinoma arising within endometriosis have been reported, one of which involved ovarian endometriosis,[10,11] suggesting that women with a history of endometriosis and who are taking tamoxifen may be at increased risk of malignant transformation within the endometriosis. Some authors[12] suggest that ERT does not stimulate recurrence of symptoms related to endometriosis, but others[13] advocate delaying the initiation of ERT for up to 18 months after surgery. The use of progestins in replacement therapy may reduce the risk of malignancy arising in endometriosis. Hickman et al[14] advocate the use of postoperative continuous adjunct medroxyprogesterone with ERT for patients undergoing TAH with BSO for endometriosis in an effort to reduce the incidence of pain recurrence and malignant transformation of residual endometriosis.

In a recent retrospective cohort study, 95 women underwent TAH with BSO for endometriosis and subsequently received ERT within 6 weeks after surgery and those who delayed for more than 6 weeks to start ERT. They found that patients who begin ERT immediately after TAH with BSO are at no greater risk of recurrent symptoms indicating recurrence of endometriosis.[14] A short period of estrogen stimulation after surgical menopause for treatment of endometriosis can lead to recurrence of either endometriosis or symptoms. This was found in a retrospective study of 123 women with endometriosis after definite surgery TAH, BSO that were followed for 2 years in the Gynecologic Endocrinology and Menopause clinics. There was one (2%) case of recurrent endometriosis and 3 (6%) cases of recurrent symptoms in the estrogen only group.[15]

In conclusion, although unopposed estrogens are commonly administered to women who have undergone hysterectomies, physicians are urged to bear in mind the original indications for the procedure. Endometriosis is a hormone-dependent disease and ERT can be associated with a risk of recurrence or malignant transformation. Unopposed estrogen appears to carry a higher risk than combined preparations. Delay in starting ERT after pelvic clearance is not of any benefit. After radical surgery for severe endometriosis, women often have much to gain from ERT, particularly in the early years. Benefits of ERT in terms of control of menopausal symptoms, prevention of urogenital atrophy and loss of libido and bone protection are of particular importance. Although there is no firm evidence, the addition of progestins to ERT should be considered in women who have undergone hysterectomy with oophorectomy due to of endometriosis.

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