Malignant Transformation of both Ectopic Glandular Epithelium and Stroma Arising from Different Endometriotic Sites: Case Report

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Abstract

Background: Malignant transformation of endometriosis is predominately adenocarcinoma and rarely adenosarcoma. Endometrioid adenocarcinoma and adenosarcoma occurring in an endometriosis patient after menopause is a rare event that has not been previously reported.

Case presentation: We report a case of a 57-year-old Chinese woman who was diagnosed with ovarian endometrioid adenocarcinoma 12 years after opting for expectant management for an “ovarian chocolate cyst.” She was diagnosed with pelvic adenosarcoma 16 months after the surgery.

Conclusion: This case shows that malignant transformation of endometriosis is worthy of attention. Furthermore, there may be an inherent molecular mechanism involved in the malignant transformation of endometriosis.

Key words: Endometriosis; Malignant transformation; Postmenopause.
**Background**

Endometriosis is a common gynaecological disease. The prevalence of endometriosis in pre-menopausal women is estimated at 15%. Approximately 0.7-1.0% of patients with endometriosis have lesions that undergo malignant transformation [1]. Development of adenocarcinoma from ectopic endometrial glandular epithelium which is usually found in ovarian endometriosis is more common than adenosarcoma developing from ectopic endometrial stroma, which is usually found in extra-ovarian endometriosis. The malignant transformation of both glandular epithelium and stroma successively occurring in the same patient has not previously been reported. We present the first published report of endometrioid adenocarcinoma and adenosarcoma secondary to postmenopausal endometriosis.

**Case Presentation**

A 57-year-old Chinese woman had been clinically diagnosed with a “left ovarian chocolate cyst,” which measured $4.1 \times 3.6$ cm, when she was 45 years old. She had no symptoms related to endometriosis except mild dysmenorrhea; therefore, she opted for expectant management in which both the symptoms and the size of the cyst were controlled. The patient experienced menopause at 51 years of age, resulting in relief of abdominal pain; she did not receive, hormone replacement therapy (HRT). Four years after menopause, a contrast-enhanced pelvic computed tomography (CT) revealed a $4.1 \times 3.6$ cm left adnexal cystic-solid mass, with thick, irregular
walls and papillary projections. The solid components were enhanced after contrast material administration. The level of CA19-9, used as a tumor marker, was 37.38 U/mL; other tumor markers, including serum CA125, AFP and CEA, were within normal limits. Based on the diagnosis of left ovarian endometrioma with suspicion of malignant transformation, the patient underwent surgery. Surgical indications were: (1) Four years post menopause, the cyst exhibited no signs of atrophy; (2) Contrast-enhanced pelvic CT imaged enhanced papillary projections, which were within the cyst; and (3) CA19-9 exceeded the normal value. At laparotomy, it was noted that the left ovarian cyst was $4 \times 4$ cm with a smooth external surface. A $0.5 \times 1$ cm chocolate-like cyst was also found in the right ovary. Both ovaries were attached to the posterior lobes of the broad ligament. The left ovarian cyst ruptured during dissection; it contained chocolate-like fluid and had cauliflower-like solid protrusions on the internal surface. Examination of the frozen section revealed malignancy. Under the impression that this was ovarian cancer, cytoreductive surgery was performed. Microscopically, the tumor cells were arranged in irregular glandular or cribriform structures and grew infiltratively (Figure 1). Transition from the glandular epithelium of the endometriosis to the endometrioid adenocarcinoma cells was detected in several slices. Using paraffin immunohistochemistry, the area of endometrioid adenocarcinoma was positive for both estrogen and progesterone receptors. The final pathologic diagnosis was a stage IC well-differentiated endometrioid
adenocarcinoma of the left ovary, arising from the ovarian ectopic endometria. The patient subsequently underwent six courses of intravenous adjuvant chemotherapy, consisting of paclitaxel and carboplatin, and underwent regular follow-up.

Sixteen months postoperatively, color Doppler ultrasound imaged a solid pelvic mass, measuring 5cm in diameter with low-level echo and irregular borders. A $6.1 \times 4.1$ cm soft tissue mass in the left pelvic cavity, with increased fluorodeoxyglucose (FDG) metabolism (maximal standardized uptake value of 5.1), was imaged by positron emission tomography (PET)/CT. All laboratory tests, including AFP, CEA, CA19-9, and CA125 were within normal limits. Intraoperatively, a 5 by 5 cm friable solid mass with a fish-like appearance without capsule was found between the extraperitoneal internal and external iliac arteries. Microscopic findings revealed a few tortuous glands with eosinophilic cytoplasm, surrounded by spindle or short spindle-like tumor cells arranged in a lamellar fashion; some had prominent nuclei, bleeding, and local necrosis. Some of the endometriotic glands were cuff ed by malignant stroma, which is a characteristic finding of adenosarcoma (Figure 2). Immunohistochemically, the tumor cells were focally positive for CD10 and diffusely positive for Vinmentin. Cytokeratin(CK), estrogen receptor(ER) and inhibin stains were all negative. All cells were consistent with adenosarcoma morphology. The patient was diagnosed with pelvic adenosarcoma (malignant transformation of ovarian endometriosis) and received five courses of
intravenous adjuvant chemotherapy with paclitaxel and carboplatin postoperatively; 18 months after the surgery, the patient died of tumor recurrence.

**Discussion and Conclusion**

The malignant transformation of endometriosis has always been an important topic of endometriosis research. The association between the malignant transformation of endometriosis and primary ovarian cancer, the possibility of endometriosis to increase the risk of ovarian cancer and the pathogenesis of the malignant transformation of endometriosis are attracting increasing attention. However, clinically, the scattered cases of malignant transformation of endometriosis, the misdiagnosis caused by strict pathological diagnostic criteria, and shortcoming of pathological examination have raised obstacles to basic research and hindered the progress of this research regarding malignant transformation of endometriosis. Endometriosis is a form of estrogen-dependent disease and loss of ovarian function was often regarded as a protective factor for endometriosis; therefore patients with mild symptoms, especially in menopause or post-menopause, were often managed with expectant therapy.

In this case, the mass was only $4.1 \times 3.6$ cm and the patient had been postmenopausal for four years; however, malignant transformation of endometriosis occurred, which challenged the traditional concept of the condition. This case illustrates the need for close observation of menopausal
or postmenopausal endometriosis patients. Therefore, pain and infertility merit clinical attention in young endometriosis patients, while for older endometriosis patients, malignant transformation is worth even more attention. Malignant transformation of endometriosis is a serious clinical event, and the high risk factors of malignant transformation include: (1) Age: Age positively correlates with the rate of malignant transformation, especially in women over 50 years. If the endometrial cyst does not shrink or persists for one year after menopause, malignant transformation should be considered. (2) Course of disease: The risk of malignant transformation will increase if the disease course is prolonged (i.e., >8 years); (3) High estrogen levels or use of hormone replacement therapy, especially in obese women. (4) Treatment with danazol; (5) Early menarche, short menstrual cycles, late menopause, low gravidity and parity are all risk factors for malignant transformation; and (6) Exposure to environmental toxin, such as dioxin.

In recent years, the long-term incentives of iron ions in the chocolate cyst[2] and abnormal expression of the candidate genes such as P53 [3], PTEN [4], K-ras [5] and VEGF [6] have been considered to be related to the malignant transformation of endometriosis. The patient in this case was postmenopausal and the lesion was small; however, malignant transformation of ectopic endometrial glandular epithelium of ovarian endometriosis and ectopic endometrial stroma of ex-ovarian endometriosis successively occurred. These findings cannot be solely explained by continuous stimulation of the iron ions.
Endometriosis may contain intrinsic carcinogenic factors, which are worth exploring. In addition, the correlation between malignant transformation of ectopic endometrium and endometrial cancer has become a subject of significant research [7]. Between malignant transformation of ectopic endometrium and eutopic endometrium, some common high-risk factors and characteristics exist. Research has shown that the rate of malignant transformation and histological type of the ectopic endometrium were comparable to that of the eutopic endometrium [4]. Endometriosis has been reported to occur in approximately 30% of patients with ovarian endometrioid adenocarcinoma and studies have reported that as many as 50% of women with ovarian endometrioid carcinoma will also have a coexisting endometrial adenocarcinoma [8], which indicates that under the same carcinomatous process, both ectopic and eutopic endometrium may simultaneously undergo malignant transformation. Our previous study reported that epigenetic inactivation of hMLH1 in eutopic endometria was synchronous with that of ectopic endometrium [9]. Therefore, malignant transformations of ectopic endometrium may be related to molecular mechanism abnormalities of the eutopic endometrium; this concept provides a new approach to research on the mechanism of malignant transformation of endometriosis. We stress that postmenopausal patients with endometriosis should be thoroughly evaluated, particularly if other risk factors are present.

Malignant transformation of ectopic endometrial glandular epithelium is
commonly found in ovarian endometriosis and the major pathological subtypes are endometrioid adenocarcinoma (55.1%) and clear cell carcinoma (21%) [10]. It is possible that ectopic endometrial stromal cells undergo malignant transform into adenosarcoma, which mainly occurs in the extra-ovarian endometriosis, including the pelvis, rectovaginal septum, and cesarean scar [11]. Therefore, for young endometriosis patients, pain and infertility are worthy of clinical concern; while for older endometriosis patients, malignant transformation warrants even more attention. Endometriosis is characterized by extensive lesions, even including lymph node involvement [12] as well as invasion around nerves [13] and vessels [14]. The second malignant transformation in this patient occurred in the retroperitoneal ectopic stroma, which further verified that the endometriotic lesions were extensive and the lesions with malignant transformation were also extensive. In addition, the case also suggests that malignant transformation of endometriosis was not a fortuitous event; rather, there might be an inherent molecular mechanism. The investigation on the candidate genes related to the malignant transformation of endometriosis should be helpful for screening the high-risk population for malignant transformation of endometriosis and provide us with the basis for the appropriate choice of treatment.

Consent

Written informed consent for publication of this case report and associated images could not be obtained from the patient, but the patient’s husband
provided the required consent. A copy of the written consent is available for review by the Editor of this journal.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

WDB designed the study and drafted the manuscript. WDB, CYH and LY treated and observed the patient including follow-up. YXH and XC performed the histopathological and immunohistochemical examinations. RF and GCS participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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**References**


Figure legends

Figure 1: H/E 40x Endometriosis malignant transformed to endometrioid
adenocarcinoma: the tumor cells were arranged in irregular glandular and grew infiltratively.

**Figure 2:** H/E 40x Endometriosis malignant transformed to endometrioid adenosarcoma: a few tortuous glands with eosinophilic cytoplasm, surrounded by spindle or short spindle-like tumor cells arranged in a lamellar fashion. The endometriotic glands were cuffed by malignant stroma, which is a characteristic finding of adenosarcoma.