Submitted: 20 September, 2022 Accepted: 25 November, 2022 Published: 15 February, 2023 DOI:10.22514/ejgo.2023.014

CASE REPORT

European Journal of Gynaecological Oncology

Endometrioid carcinoma associated with ovarian endometriosis: need for cautions during treatment

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Abstract

Although endometriosis could be associated with certain epithelial ovarian cancers and elevated serum cancer antigen (CA) 19-9 levels, it is difficult to diagnose endometriosis using this marker. We report an unusual case of endometriosis that evolved into endometrioid carcinoma in an asymptomatic 38-year-old woman with elevated CA 19-9 levels who presented to our clinic. Transvaginal ultrasound and computed tomography of the abdomen and pelvis revealed endometriosis of the right ovary. A laparoscopy was performed to evaluate for chocolate cysts. However, based on the postoperative pathological assessment, she was diagnosed with endometrioid carcinoma associated with endometriosis and was reoperated for surgical staging. This case indicates that sudden elevation of CA 19-9 level might be a sign of malignancy, small asymptomatic endometriosis should not be ignored, and incidental diagnosis of ovarian cancer should be carefully assessed by surgical staging.

Keywords

Endometrioid carcinoma; Endometriosis; CA 19-9; Surgical staging

1. Introduction

Endometriosis is a benign, gynecologic, estrogen-dependent disease characterized by the presence of endometrial glands and stroma outside the uterine cavity [1]. Endometriosis affects approximately 10% of women of reproductive age [2]. Although endometriosis is considered a benign condition, histological and molecular data from previous studies indicated possible risks for malignancy [1]. Endometriosis is more commonly associated with endometrioid and clear cell carcinoma subtypes of ovarian cancer than with serous or mucinous subtypes [1]. The absolute risk of developing ovarian cancer from ovarian endometriosis remains minimal despite the possibility of an increase in the relative risk of the disease. In a previous study, the investigators found that there were about two cases per 1000 patients with ovarian endometriosis upon comparing patients with and without ovarian endometriosis during a 10-year period [3].

Tumor markers are valuable for the differential assessment of ovarian masses. Cancer antigen 19-9 (CA 19-9) is a mucin protein commonly used to diagnose benign and malignant gastrointestinal, biliary tract and pancreatic diseases [4]. High CA 19-9 positivity rates have been reported in ovarian malignancies such as mucinous adenocarcinoma, endometrioid adenocarcinoma and mucinous borderline ovarian tumors. Patients with benign tumors, *i.e.*, ovarian endometriosis and mature cystic teratoma, have also been observed to have increased CA19-9 values [5].

However, the incidence of endometrioid cancer in patients with endometriosis and increased CA 19-9 levels associated is not well documented. Herein, report an unusual case of endometriosis that evolved into endometrioid carcinoma in a patient with elevated CA 19-9 level.

2. Case presentation

A 38-year-old female patient (gravida 2, para 1) was referred to the Gastroenterology department of our hospital after she was found to have elevated serum CA 19-9 level (61.8 IU/mL) but without specific findings on abdominal ultrasonography at a primary hospital. Therefore, a follow-up visit was scheduled for the next three months after the initial visit to examine the tumor maker levels. At the three-month follow-up, her serum CA 19-9 level had increased to 352.15 IU/mL, whereas other tumor marker levels, including CA 125, carcinoembryonic antigen, alpha-fetoprotein and beta-human chorionic gonadotrophin, were within normal limits.

She visited our Gynecology department for routine examinations as she had undergone a left ovarian cystectomy for mucinous cystadenoma in 2015 and a myomectomy in 2017 at our hospital. She came to our Gynecology department on the scheduled date, two months after undergoing the abdominal ultrasound examination at the primary hospital, and we performed transvaginal ultrasonography, which revealed a bilocular cystic mass measuring 3.8 cm × 3.3 cm, with diffuse, low-level echoes and a regular smooth cystic wall in the right ovary (Fig. 1A). Computed tomography (CT) of the abdomen and pelvis showed a 4.0 cm, low attenuation, thin-walled and unilocular cyst in the right ovary without any solid

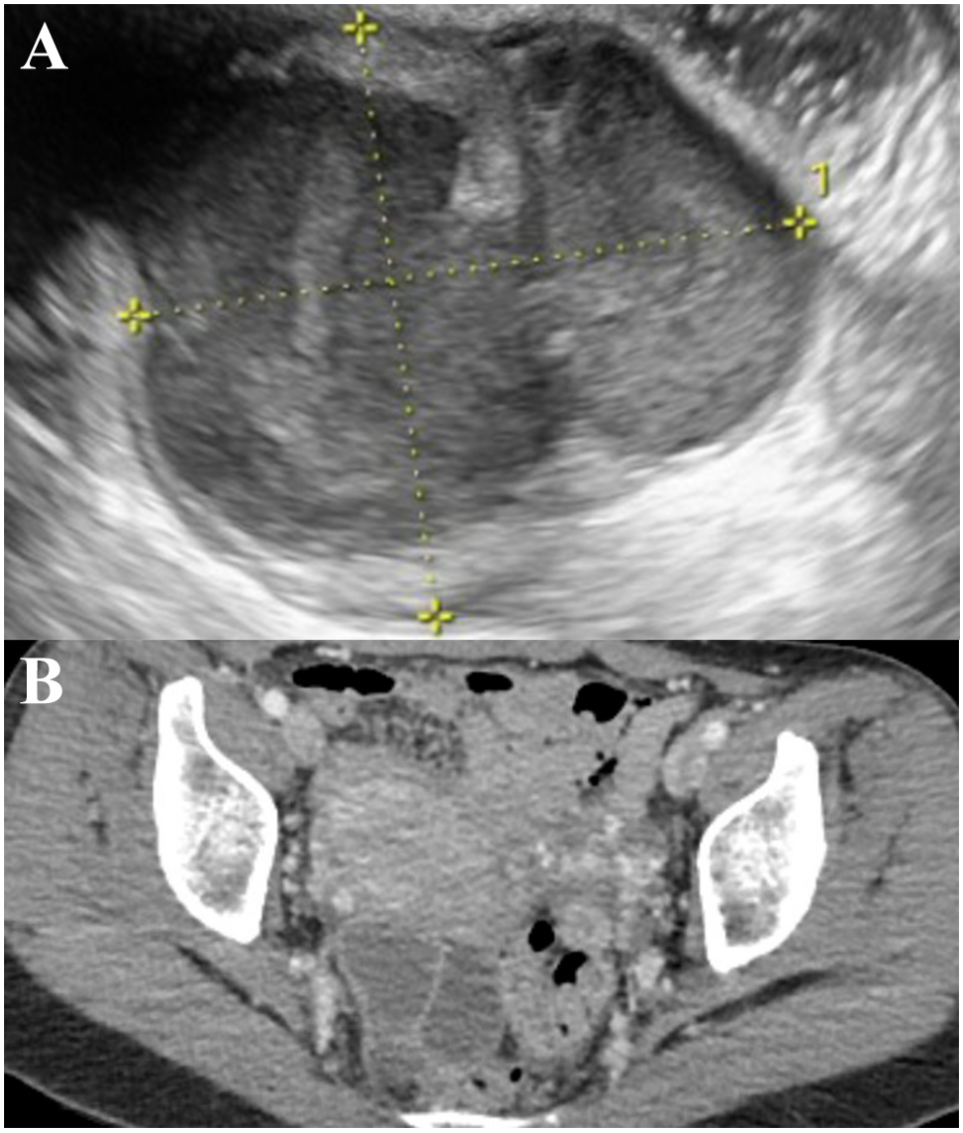

FIGURE 1. Imaging of the right ovarian cystic mass. A. Transvaginal ultrasound image of the 3.8 × 3.3 cm right ovarian cystic mass. The tumor was homogeneous, composed of low-level echoes, and the cyst wall was regular and smooth. B. Abdominal and pelvic computed tomography of the 3.5 cm right ovarian cystic mass showed that the tumor was a low-attenuation, thin-walled, unilocular cyst without solid components.

component (Fig. 1B). Her laboratory test results were within normal ranges.

The patient underwent laparoscopic right ovarian cystectomy, following which we observed a smooth-walled cyst that contained chocolate-like fluid with severe pelvic adhesions (Fig. 1B). Contrary to expectations, postoperative pathology revealed an International Federation of Gynecology and Obstetrics (FIGO) grade 1 endometrioid carcinoma associated with endometriosis (Fig. 2). Imaging tests, including pelvic magnetic resonance imaging, chest CT and positron emission tomography, were also performed and the results showed a mild hypermetabolic lesion in the right pelvic cavity. However, no other abnormal findings, such as lymph nodes or distant metastases, were noted. In addition, the patient's serum CA 19-9 level returned to the normal range after surgery. Thereafter, she was reoperated for surgical staging. Pathological examination confirmed the presence of residual endometrioid carcinoma in the right ovary (Fig. 3), which was confirmed to be a FIGO stage IC1 tumor, and she underwent paclitaxel plus carboplatin as adjuvant chemotherapy.

3. Discussion

Ovarian endometriosis, which occurs when tissues similar to the endometrium grow within the ovaries, is the most common form of endometriosis, accounting for 67% of all cases [6, 7]. Although endometriosis is usually considered a benign disease, it can be associated with malignancy. In 1925, Sampson first proposed the following criteria for the diagnosis of ovarian malignancy associated with endometriosis: (i) evidence of endometriosis in proximity to the tumor, (ii) presence of cancer within an ovary with endometriosis but not elsewhere, and (iii) histological appearance consistent with the origin of endometriosis [8]. In 1953, Scott further expanded the criteria by adding histological evidence of the transition from endometriosis to neoplasm [9], raising the question of whether

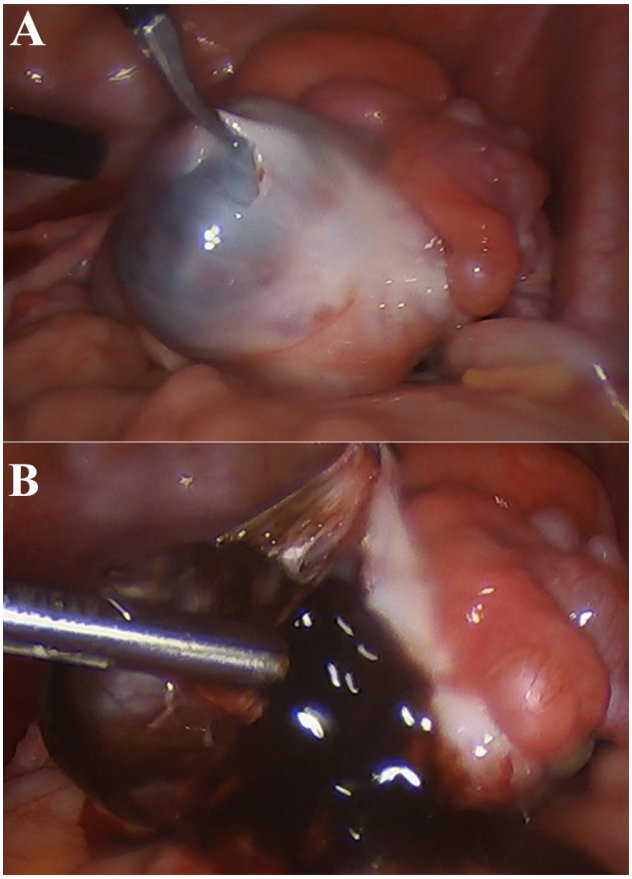

FIGURE 2. Surgical depiction of the right ovarian cyst. A. The laparoscopic image of the right ovarian cyst. B. The right ovarian cyst contained a chocolate-brown fluid.

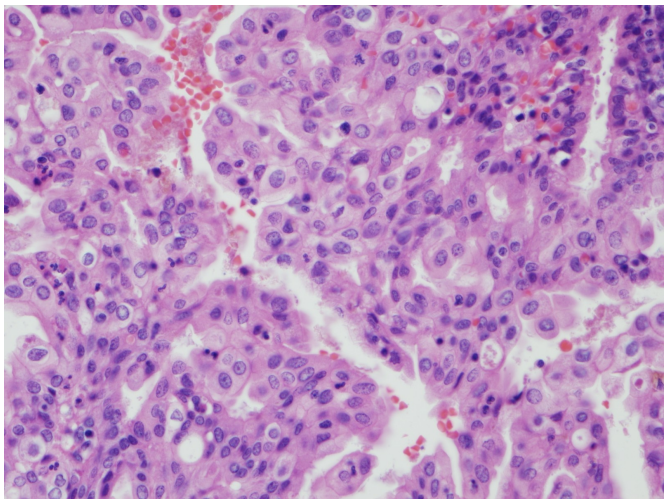

FIGURE 3. The histological section of the endometrioid carcinoma shows loss of glandular architecture and stroma (hematoxylin and eosin; ×400).

endometriosis is a pre-malignant condition.

Endometriosis treatment options include pain relievers, hormone therapy such as a combination of oral contraceptive pills and progestins, and surgical resection. The severity of symptoms and infertility are crucial considerations when assessing the indications for surgical resection. The European Society of Human Reproduction and Embryology (ESHRE) 2022 guideline recommends surgeons to perform cystectomy rather than drainage and coagulation during the surgical treatment of women with ovarian endometrioma because cystectomy can decrease endometriosis-related pain and increase the likelihood of continued pregnancy. In addition, cystectomy has also been found to potentially reduce the recurrence of endometrioma [10].

Transvaginal ultrasonography is a crucial investigational technique for endometriosis. Typical benign endometriomas can be identified as unilocular or multilocular cystic lesions with consistent low-level echoes (ground glass appearance) [11]. The International Ovarian Tumor Analysis (IOTA) classification system is critical for distinguishing suspicious features as it can help differentiate benign from malignant endometriomas [12]. Malignant tumors are more likely to have solid mural nodules with Doppler flow showing vascularity. Additionally, malignant lesions are more likely to contain papillary projections than benign endometrioid cysts. Thus, clinicians should not neglect the risk of malignancy when communicating and treating endometriosis patients. On average, the risk of endometriomas developing into cancer is less than 0.8%. One study found that the risk of cancer increased with lesion size (>9 cm) and age (>45 years) [13]. Another study reported that the median maximum diameter of malignant endometriotic tumors was 10.7 cm, while the median maximum diameter of benign endometriomas was 5.8 cm ($p < 0.0001$), and that malignant endometriomas were more likely to be multilocular (47% *vs.* 9.7%) [14]. Comparatively, in our presented case, the ovarian cyst had a diameter less than 4 cm and the patient was younger than 45 years old, yet, she was diagnosed with cancer based on the final surgical biopsy. If conservative care rather than ovarian cystectomy had been performed, the latent early-stage cancer would have been missed.

Currently, there are no biomarkers that can reliably diagnose or differentiate endometriosis. Endometriosis is often associated with high levels of CA 125. Since serum CA 125 level is also elevated in ovarian malignancies, it is generally not useful for differentiating benign ovarian endometriomas from ovarian malignancies [15]. CA 19-9 is another biomarker associated with endometriosis. A limited number of studies showed a significant association between CA 19-9 level and endometrioma. The exact mechanism behind the increased serum level of CA 19-9 in patients with endometrioma remains unclear. However, a hypothesis proposed by some researchers suggests that fluid from a ruptured endometrioid could be absorbed into the body's blood circulation in serum exchange, resulting in a marked increase in CA 19-9 level [16]. Previous research indicates that CA 19-9 is a useful marker for distinguishing endometrioma from other cancers [15]. As in our study, a sudden increase in serum CA 19-9 level may indicate malignancy; hence, it should be carefully assessed and addressed. However, unusual increases in CA 19-9 levels can also be identified in benign conditions [17]. Consequently, it should be emphasized that the assessment of biomarker levels for ovarian mass could induce unnecessary stress in patients and increase overtreatment risks. However, it is challenging for clinicians to timely determine the risk of malignancy in ovarian endometriosis based on aberrant levels

of tumor markers.

Ovarian malignancies might be inadvertently diagnosed after surgical treatments. This present case emphasized the significance of surgical staging, despite the absence of abnormalities on additional imaging or blood tests even when a tumor of stage 1 is anticipated. In this study, after ovarian cystectomy, no residual lesions were discovered on imaging examinations; however, lesions were observed in the pathology reports, highlighting the need to treat patients in compliance with accepted clinical practice guidelines. The preoperative diagnosis of ovarian endometriosis is challenging. This present case highlighted some critical points that could help better manage endometriosis cases. First, asymptomatic endometriosis less than 4 cm in size should not be neglected. Second, although it is not suggested to use tumor marker levels such as CA 19-9 to diagnose endometriosis-associated malignancy, a sudden increase in CA 19-9 levels should be carefully evaluated. Lastly, surgical staging according to approved guidelines is crucial when ovarian cancer is inadvertently discovered after surgery.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

WYH—performed the investigation, writing, review & editing and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional Review Board of Kyung Hee University Medical Center approved a waiver of informed consent (approval number: KHUH 2022-11-071).

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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How to cite this article: Woo Yeon Hwang. Endometrioid carcinoma associated with ovarian endometriosis: need for cautions during treatment. European Journal of Gynaecological Oncology. 2023; 44(1): 115-118. doi: 10.22514/ejgo.2023.014.