

Ovarian clear cell adenocarcinoma revealed in a young patient during hormone therapy: a case report

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Abstract

Ovarian cancer arising from an ovarian endometriotic cyst is frequently encountered; however, this condition has rarely been reported in young patients. We herein report a case of malignant transformation of an ovarian endometriotic cyst in a 26-year-old woman (gravida 0, para 0). During the initial examination at our hospital, ultrasound revealed an endometriotic cyst in the right ovary measuring 49×44×29 mm and an endometriotic cyst in the left ovary measuring 59×53×32 mm with no marked mural nodules on either side. The patient was followed up every 3 months while receiving hormone therapy. At the 6-month follow-up, ultrasound revealed 10-mm mural nodules within the endometriotic cyst of the left ovary. At 10 months, ultrasound revealed that these the mural nodules had enlarged to 15 mm. Pelvic magnetic resonance imaging revealed that the tumor in the left ovary was 64×63 mm in size, which was slightly larger than in the previous scan. The patient underwent laparotomy because of the potential for malignant transformation. Pathological examination revealed clear cell adenocarcinoma. Although malignant transformation of this cancer is rare in women in their 20s, its possibility should be considered; this is true even when cyst enlargement can be controlled during hormone therapy. Magnetic resonance imaging is extremely useful in the diagnosis of malignant transformation.

Keywords: Clear cell adenocarcinoma, Endometriosis, Malignant transformation

Introduction

Ovarian endometriotic cysts form secondary to proliferation of endometrium-like tissue in the ovaries and accumulation of menstrual blood. Ovarian endometriotic cysts can progress to ovarian cancer. At least two potential scenarios could result in the development of ovarian cancer from endometriosis. In the first scenario, extracellular hemoglobin, heme, and iron cause cellular oxidative damage by promoting the formation of reactive oxygen species, which results in DNA damage and mutations. In the second, cancer progression may be associated with persistent antioxidant production favoring a protumoral microenvironment.¹ However, the underlying mechanism of malignant transformation from endometriosis is unclear.

Kobayashi et al.² reported that the overall rate of malignant transformation of ovarian endometriotic cysts was approximately 0.72% (46/6398 patients). According to the literature, the risk of ovarian cancer is increased among patients with a long history of ovarian endometriotic cysts.³ Furthermore, in postmenopausal women, ovarian endometriotic cysts are associated with the risk of developing endometrioid carcinoma.⁴ A literature search revealed only one case report involving malignant transformation in a patient in her 20s.⁵ We herein report our experience with a young patient in her 20s who presented with an endometriotic cyst and developed clear cell carcinoma during hormone therapy.

Case report

A 26-year-old woman (gravida 0, para 0) was diagnosed with bilateral ovarian endometriotic cysts 2 years earlier, and oral administration of dienogest (Dinigest[®]; Mochida Pharmaceutical, Tokyo, Japan) was initiated. However, the patient experienced intensified lower abdominal pain and was referred to our facility (Fujita Health University Hospital, Aichi, Japan) for further medical care. The previous physician noted that the patient's serum cancer antigen 125 (CA125) level was 44.1 U/ml. During the initial examination at our hospital, ultrasound revealed an endometriotic cyst in the right ovary measuring 49×44×29 mm and an endometriotic cyst in the left ovary measuring 59×53×32 mm with no marked mural nodules on either side. The lower abdominal pain subsequently intensified; therefore, the medication was changed from dienogest to a low-dose oral contraceptive and the patient was followed up every 3 months. At the 6-month follow-up, ultrasound revealed 10-mm mural nodules within the endometriotic cyst of the left ovary. Pelvic magnetic resonance imaging revealed a monolocular cystic tumor measuring 51×42 mm in the left ovary. The tumor exhibited high signal intensity on T1-weighted imaging and low signal intensity on T2-weighted imaging. It contained papillary mural nodules showing high signal intensity on T2-weighted imaging and slightly high signal intensity on diffusion-weighted imaging (Figure 1). Because the potential for malignant transformation could not be ruled out, we followed up the patient every 2 months. At 10 months, ultrasound revealed that the mural nodules in the cyst of the left ovary had enlarged to 15 mm; pelvic magnetic resonance imaging revealed that the tumor in the left ovary was 64×63 mm in size, which was slightly larger than in the previous scan. The mural nodules within the cyst revealed a tendency to increase in size, and new mural

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nodules had also appeared (Figure 2). The serum level of the tumor marker CA125 was high at 65.2 U/ml, although this change was not significant.

The mural nodules that had developed within the endometriotic cyst in the left ovary indicated malignant transformation. The differential diagnoses included a Müllerian mucinous papillary borderline tumor, polypoid endometriosis, and dienogest therapy-induced decidualization. However, the duration of dienogest therapy was short (approximately 8 months), indicating that malignant transformation had likely occurred; thus, the patient underwent left ovarian cystectomy. During surgery, a frozen section of the cyst revealed a borderline malignant tumor or atypical endometriosis. Therefore, we decided to perform left adnexectomy, right ovarian cystectomy, and partial omental resection. The postoperative pathological findings included an endometriotic cyst with hemosiderin deposition and clear cell adenocarcinoma in the mural nodule portion (Figure 3); these findings ultimately led to a diagnosis of stage IA clear cell adenocarcinoma. However, because the patient was young and unmarried, we obtained informed consent regarding the possibility of recurrence and withheld any additional surgery to preserve fertility. The patient received paclitaxel and carboplatin therapy postoperatively. No recurrence has been observed at the time of this writing (11 months postoperatively).

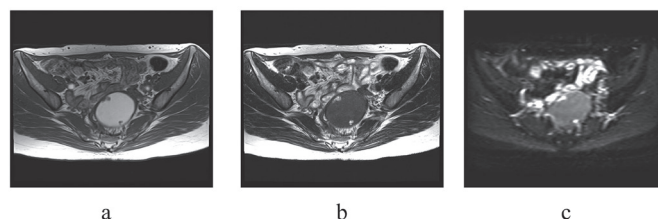
Discussion

Endometriosis is a condition in which endometrium-like tissue ectopically proliferates; it reportedly affects 4% to 13% of women of reproductive age.⁶ Ovarian endometriotic cysts form secondary to the accumulation of blood from endometrium-like tissue that proliferates in the ovaries, and the cysts may eventually progress to ovarian cancer. Ovarian cancer arising from endometriotic cysts is often endometrioid adenocarcinoma or clear cell adenocarcinoma.⁷

The onset of malignant transformation of ovarian endometriotic cysts commonly occurs around the time of menopause. Kawaguchi et al.⁸ reported that malignant transformation arising from an ovarian endometriotic cyst occurred before menopause in 78% (14/18) of their patients (mean age, 45.2 years; range, 33–66 years). Furthermore, Scarfone et al.⁹ reported that among 73 patients with ovarian clear cell adenocarcinoma, those with ovarian clear cell adenocarcinoma arising from endometriosis were predominately younger than those without endometriosis (mean age, 51.4 vs. 58.4 years; $p = 0.02$). Thus, the mean age of 51.4 years is consistent with the occurrence of malignant transformation of ovarian endometriotic cysts at menopause. In contrast, few reports have described malignant transformation in patients in their 20s; therefore, the incidence remains largely unknown. Kobayashi et al.² conducted a cohort study of 6398 patients with ovarian endometriotic cysts and reported that the overall rate of malignant transformation of ovarian endometriotic cysts was approximately 0.72% (46/6398 patients). In the same study, malignant transformation occurred in only 2 of 926 patients in their 20s; this indicates that the incidence of malignant transformation in patients in their 20s is low.

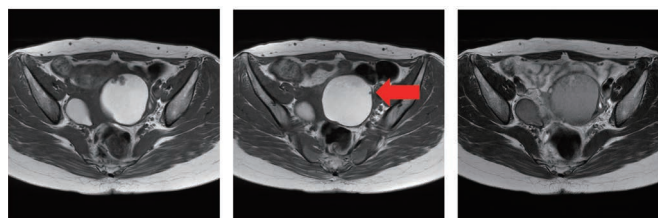
The serum CA125 level is a useful tumor marker of ovarian cancer, and elevated serum CA125 levels are frequently encountered in patients with endometriosis. Tagashira et al.⁵ reported a case involving a 27-year-old patient with endometrioid adenocarcinoma arising from an ovarian endometriotic

Figure 1.



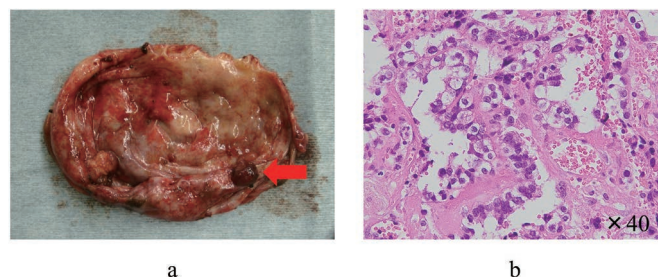
Magnetic resonance imaging 6 months after the initial examination. (a) T1-weighted image, (b) T2-weighted image, and (c) diffusion-weighted image. The left ovarian tumor is a monolocular cystic tumor measuring 51×42 mm. It exhibits high signal intensity on the T1-weighted image and low signal intensity on the T2-weighted image. It contains papillary mural nodules showing high signal intensity on the T2-weighted image and slightly elevated signal intensity on the diffusion-weighted image.

Figure 2.



Magnetic resonance imaging 10 months after the initial examination. (a) T1-weighted image, (b) T1-weighted image, and (c) T2-weighted image. The tumor in the left ovary is 64×63 mm, indicating growth. The mural nodules in the tumor are also enlarged. New mural nodules (←) have appeared.

Figure 3.



Pathological findings of the resected specimen. (a) Resected specimen: a papillary solid portion (←) can be seen in the wall of the left ovarian endometriotic cyst. (b) Hematoxylin- and eosin-stained specimen. Histopathological findings of the endometriotic cyst include the characteristics of clear cell adenocarcinoma with enlarged atypical nuclei and clear cytoplasm.

cyst. They emphasized that in patients with endometriosis accompanied by a high serum CA125 level, it is necessary to consider the possibility of the onset of ovarian cancer even if the patient is young. However, it has also been reported that the serum CA125 level is not an indicator of malignant transformation of ovarian endometriotic cysts.^{10,11} Furthermore, Taniguchi et al.¹⁰ stated that the appearance of mural nodules and rapid enlargement of the cyst diameter should be noted when diagnosing malignant transformation.

In the present report, we describe our encounter with a relatively rare case of malignant transformation occurring in a patient in her 20s. Although the cyst grew from 50 to 60 mm, this change was insufficient to be considered rapid enlargement of the cyst. Furthermore, although the serum CA125 level increased from 44.1 to 65.2 U/ml, this change was low relative to previous reports; thus, we believe that this change could not be used as an indicator of malignant transformation. The appearance of mural nodules led us to

suspect malignant transformation. However, 6 months after the initial visit to our hospital, when the mural nodules appeared, diagnosis was difficult because of the patient's young age and the fact that the cyst had grown slightly in size. Because oral dienogest or low-dose oral contraceptives usually suppress endometrial proliferation and are both expected to reduce the size of endometriotic cysts, it is unlikely that these drugs cause tumor enlargement. Sugimoto et al.¹² reported on the tumor-reducing effects of dienogest. They observed the tumor-reducing effects even after a few months of oral intake. In the present case, slight enlargement in the tumor diameter was still observed, although oral dienogest was only administered for a short duration of approximately 8 months. It is possible that oral treatment with dienogest or low-dose oral contraceptives actually suppressed a dramatic enlargement in cyst diameter that would have occurred as a result of malignant transformation. Our patient was diagnosed with an endometriotic cyst and treated with hormone therapy. We believe that the rapid growth of the cyst was repressed by the hormone therapy. Substantial incremental growth of the cyst was not observed; however, this resulted in difficulty determining whether malignant transformation of the endometriotic cyst had occurred. Therefore, we considered that the most important indicator of malignant transformation was the appearance of mural nodules. When cyst enlargement occurs, the presence or absence of hormone therapy should be duly noted. Furthermore, although the incidence of malignant transformation is low in young individuals, the possibility of transformation should be kept in mind.

In this case report, we describe our experience with a young patient who developed ovarian clear cell adenocarcinoma secondary to malignant transformation of an ovarian endometriotic cyst during the follow-up observational period. Although mural nodules appeared, there was little change in the cyst diameter or serum CA125 level. Moreover, because the patient was relatively young, it was difficult to diagnose malignant transformation or determine the optimal timing for surgery. Our search of the literature revealed only one case report of malignant transformation in a patient in their 20s.⁵ Malignant transformation in women in their 20s is rare. However, because ovarian endometriotic cysts can become malignant, even in young individuals, regular and careful follow-up is necessary.

Acknowledgments

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Conflicts of interest

The authors have no conflicts of interest to declare.

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