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Case Report

Rapidly growing ovarian endometrioid adenocarcinoma involving the vagina: A case report

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Abstract

Objective: We present a rare case of a very rapidly growing stage IV ovarian endometrioid adenocarcinoma involving the uterine cervix and vagina without lymph node involvement.

Case Report: A 43-year-old woman visited the hospital with complaints of lower abdominal discomfort and vaginal bleeding over the previous 3 months. Serum levels of tumor marker CA 125 and SCC antigen (TA-4) were normal. On magnetic resonance imaging, a 7.9×9.7 cm heterogeneous mass with intermediate signal intensity was observed in the posterior low body of the uterus. Two months ago, a computed tomography scan revealed an approximate 4.5×3.0 cm heterogeneously enhanced subserosal mass with internal ill-defined hypodensities. A laparotomy, including a total abdominal hysterectomy with resection of the upper vagina, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, appendectomy, total omentectomy, and biopsy of rectal serosa was performed. A histological examination revealed poorly differentiated endometrioid ovarian adenocarcinoma with vaginal involvement. The patient had an uncomplicated post-operative course. After discharge, she completed six cycles of adjuvant chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (300 mg/m^2) and has remained clinically disease-free until June 2010.

Conclusion: Epithelial ovarian cancer may grow very rapidly. The frequent measurement of tumor size by ultrasonography may provide important information on detection in a subset of ovarian carcinomas that develop from preexisting, detectable lesions.

Keywords: Endometrioid adenocarcinoma; Vaginal involvement

Introduction

Ovarian cancer is the leading cause of death from gynecological malignancy in most developed countries, although it is still relatively infrequent in developing countries. In the USA, ovarian cancer is the fifth leading cause of cancer-related death among women and the leading cause of gynecological cancer deaths, accounting for nearly 16,000 deaths in 2008 [1]. Over 90% of all ovarian cancers are epithelial in type histologically [2]. Endometrioid carcinoma of the ovary is a specific histopathological entity that accounts for 16–25% of epithelial ovarian cancer.

Generally, epithelial ovarian cancer grows rapidly and presents as advanced disease at the time of diagnosis because patients do not experience symptoms in the early stages [3, 4]. However, it generally takes about 3–6 months for a cancer to double in volume [5]. A previous study developed models for the growth, progression, and detection of occult serous cancers based on a comprehensive analysis of published data on serous cancers discovered by prophylactic bilateral salpingo-oophorectomy (PBSO) in BRCA1 mutation carriers [6]. However, to our knowledge, no report has been published on rapidly growing endometrioid ovarian cancer. In this study, we report a case of an endometrioid carcinoma of the ovary, which grew very rapidly and caused metastases to the uterine cervix and the vagina without lymph node involvement.

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Case report

On December 9, 2009, a 43-year-old woman (gravida 2, para 2) presented to the Department of Obstetrics and Gynecology in Kangwon National University Hospital with complaints of lower abdominal discomfort and vaginal bleeding over the previous 3 months. Her usual menstrual cycle was regular at 30 days, and her menstruation was moderate. Although she had mild dysmenorrhea, she had not taken any pain medication. She had her first period at the age of 13. Her medical and family histories were not significant.

She had previously visited a private obstetric and gynecologic clinic with complaints of spotting and abdominal distention on September 3, 2009. She underwent a screening examination including a pelvic examination and transvaginal ultrasonography (USG). An approximately 2.4×2.0 cm mixed echogenic density was observed on the left side of the posterior cervix of the uterus, which was suspicious of a cervical myoma (Fig. 1), but no other abnormalities were found in the uterus or either ovary. A Pap smear of the cervix was conducted, and the results were normal. Two days later, because symptoms persisted, she underwent an explorative pelviscopic operation, which revealed an adhesion between the left ovary and the posterior wall of the uterus and an approximate 3.5×2.0 cm cystic mass in the left ovary. No other gross abnormality was observed in the pelvic cavity, including the right ovary. A pelviscopic left ovarian cystectomy was performed, and the cyst was pathologically diagnosed to be an endometrioma. Two days later, she was discharged without any events. On the 7th day after the operation, a postoperative follow-up transvaginal USG showed nothing abnormal.

However, her symptoms continued and brought her to the Chuncheon Sacred Heart Hospital on September 30, 2009. Diagnostic procedures, including a pelvic examination, tumor marker (AFP, CA 19-9, and CA 125) analysis, gastroscopy, colonoscopy, chest X-ray, and an abdominal and pelvic computed tomography (CT) scan were conducted. The pelvic examination, tumor markers, endoscopy, and chest X-ray revealed nothing abnormal. The CT scan showed an approximate 4.5×3.0 cm heterogeneously enhanced subserosal mass with internal ill-defined hypodensities and a circumferential rim in the posterior wall of the uterus (Fig. 2), suggesting a degenerated uterine myoma, an endometrioma, or, less likely, an exophytic growing cervical cancer. The right adnexa adhered to the uterine mass so closely, that it was difficult to draw clear lines of demarcation between the right adnexa and the uterine mass. The CT scan failed to show any other specific findings in the abdominal or pelvic cavities, including the left adnexa. Because the spotting had stopped, she was discharged without any therapeutic procedures.

One month later, vaginal bleeding restarted and continued for 1 month, so she visited Kangwon National University Hospital. She appeared chronically ill, and showed a weight loss from 53.0 to 50.4 kg over the previous 3 months. No gross abnormal findings in the chest and abdomen were noted. On pelvic examination, she had a large, hemorrhagic, friable mass that seemed to originate from the anterior fornix and extended to the upper vaginal wall. A rectovaginal exam was negative. Colposcopically, a 3–4 cm sized exophytic mass covering the right side of the upper vagina and cervix was found (Fig. 3). Because the mass was friable and highly vascular, with multiple bleeding foci, it was difficult to identify the tumor origin. A punch biopsy of the tumor showed massive tumor

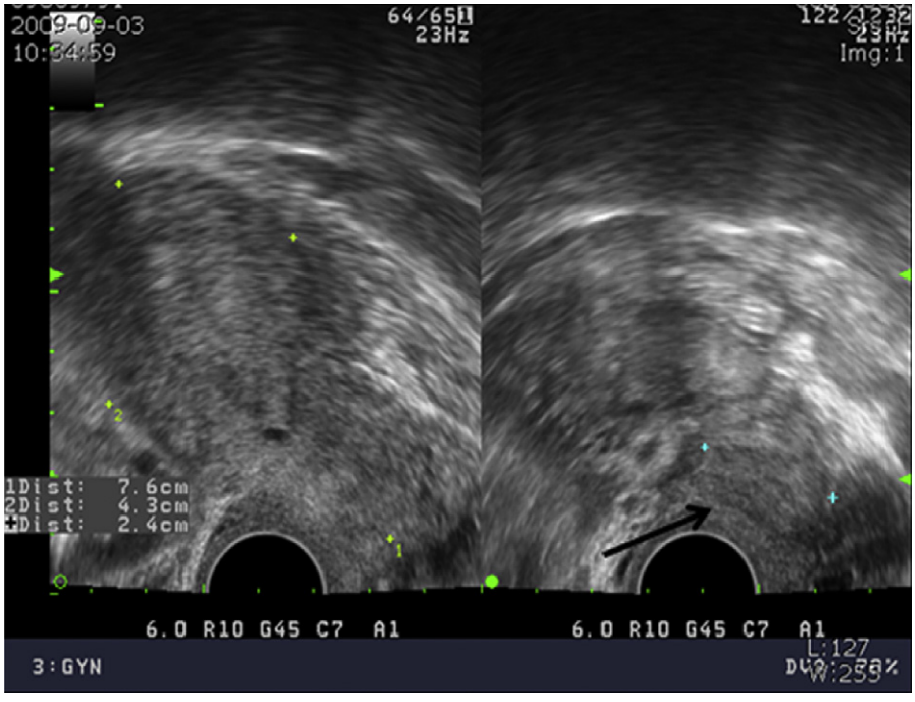

Fig. 1. Transvaginal ultrasonography finding on the first visit. An approximate 2.4×2.0 cm mixed echogenic density observed in the left side of the posterior cervix of the uterus is suspicious of a cervical myoma (arrow).

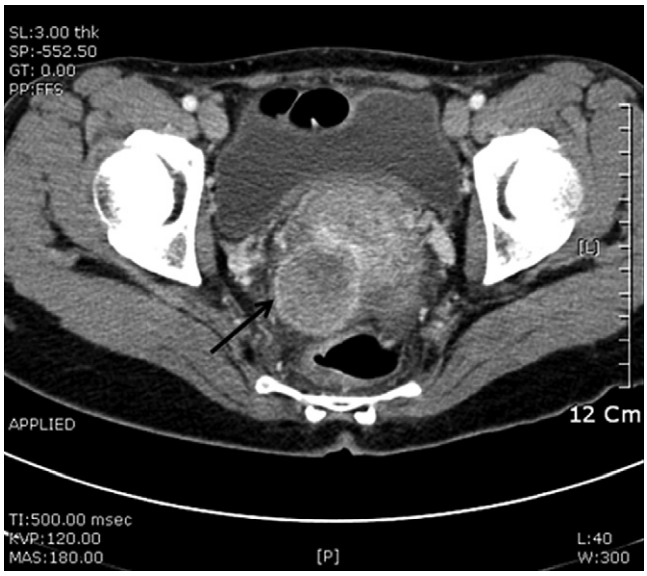

Fig. 2. Computed tomography findings of September 30, 2009. Arrow shows an approximate 4.5 × 3.0 cm heterogeneously enhanced subserosal mass with internal ill-defined hypodensities and a circumferential rim in the posterior wall of the uterus.

cell nests with squamoid differentiation (Fig. 4). The tumor appeared more likely to be a non-keratinizing invasive squamous cell carcinoma originating from the cervix, but carcinoma from the ovary could not be excluded. Because the origin of the tumor was unclear, the final diagnosis was pending at that time.

Serum levels of tumor marker CA 125 and SCC antigen (TA-4) were 14.3 U/mL and 1.02 ng/mL, respectively. Her chest radiograph was normal. A magnetic resonance image revealed a 7.9 × 9.7 cm heterogeneous mass, with intermediate signal intensity in the posterior lower body of the uterus (Fig. 5). The uterine cervical structure had no well-defined features, and the center of the mass was located in the posterior lower body of the uterus. The mass seemed to involve the proximal rectum and abutted the vagina. A

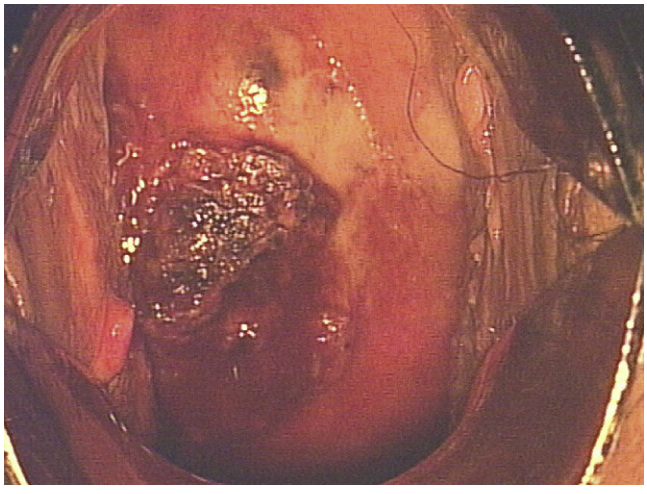

Fig. 3. Colposcopic finding on December 9, 2009 shows a 3–4 cm exophytic mass covering the right side of the upper vagina and cervix.

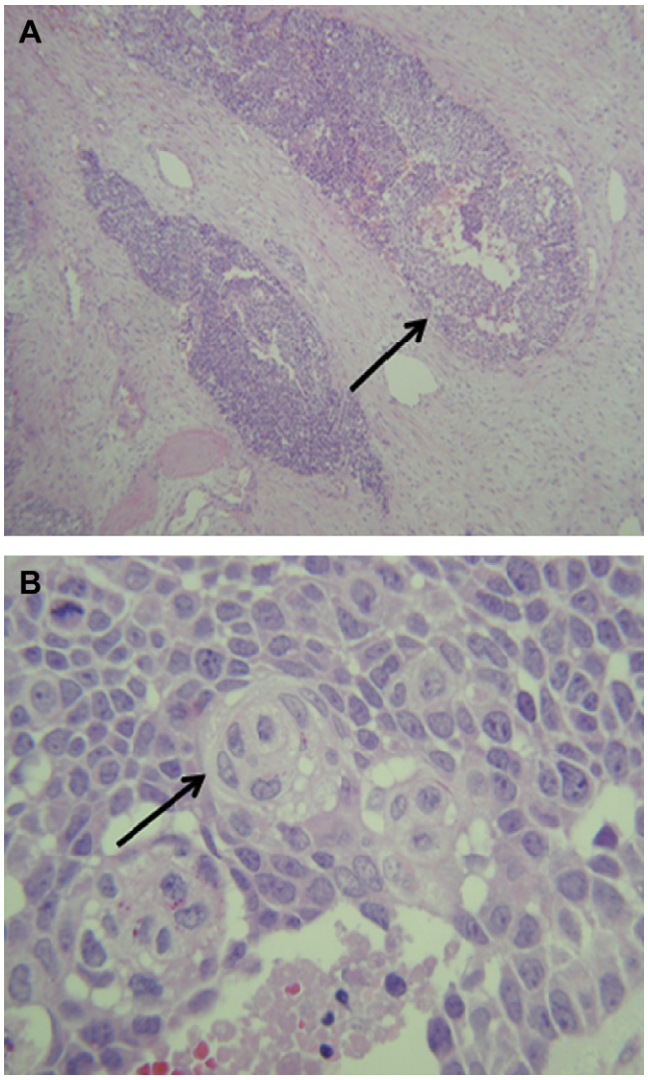

Fig. 4. Microscopic findings of the tumor showing: (A) tumor cell nests (arrow) and (B) squamoid differentiation (arrow).

sigmoidoscopy detected no abnormality in the mucosa, but extrinsic compression was seen in the left lateral wall of the rectum. An intravenous pyelogram showed no radiopaque lesion or filling defect in the bilateral opacified renal pelvocalyces, bilateral ureters, or the opacified bladder.

A laparotomy was performed on December 14, 2009. A small amount of ascites was found in the peritoneal cavity. An approximate 6 cm right ovarian mass was adhered to the posterior aspect of the lower uterine segmental mass, which was estimated to be about 10 cm in size. This mass perforated the lumen of the upper right side of the vagina (Fig. 6.). The transformation zone of the cervix and cervical canal seemed to be grossly intact. The pelvic mass had adhered to the rectum, but no involvement of the omentum, intestines, or pelvic cavity peritoneum was observed. A total abdominal hysterectomy, including resection of the upper vagina, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, appendectomy, total omentectomy, and biopsy of the rectal serosa, was conducted. The ascites cytology showed no tumor cells.

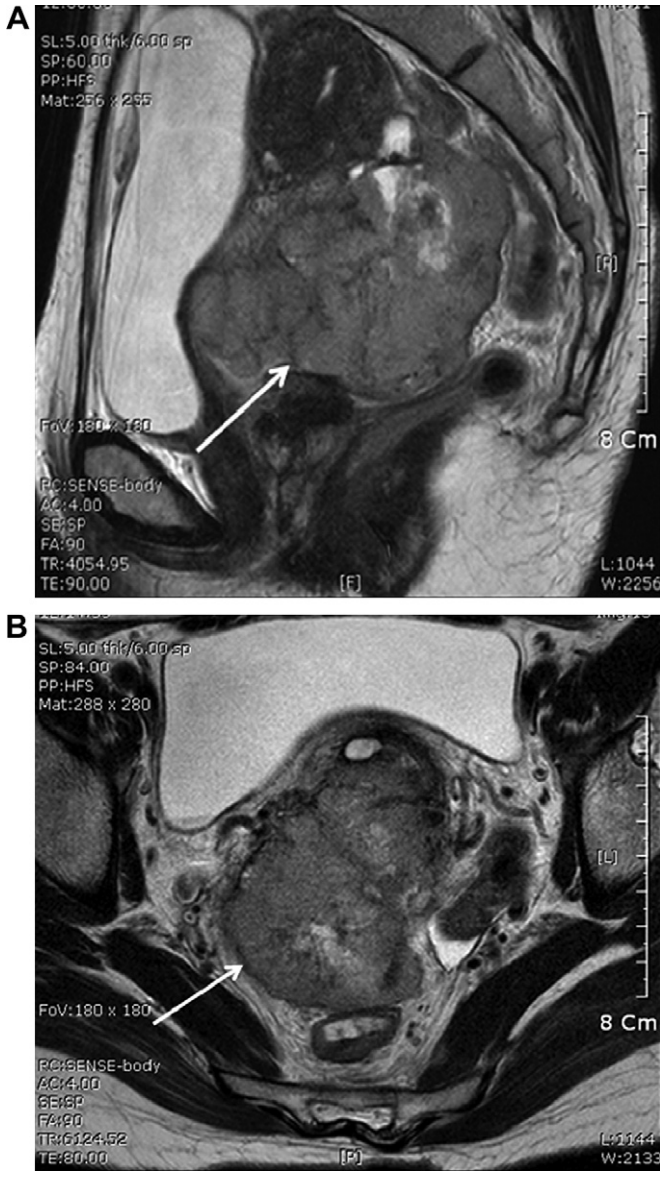

Fig. 5. MR (A) sagittal and (B) axial images on December 10, 2009. A 7.9 × 9.7 cm heterogeneous mass with intermediate signal intensity is seen in the posterior low body of the uterus (arrows). The uterine cervical structure has poorly defined features, and the center of the mass is located in the posterior low body of the uterus.

A histological examination revealed that the tumor had extended to the lower uterine segment, the uterine cervix, the vaginal wall, and the rectal serosa, but no involvement of the left ovary, fallopian tube, or the uterine endometrium was found. Metastases were not found in any of the 38 retrieved lymph nodes. Immunohistochemical examinations to determine the tumor origin were performed. Cytokeratin staining was positive, whereas staining for cytokeratin-7/20, inhibin, calretinin, smooth muscle actin (SMA), and carcinoembryonic antigen (CEA) were negative. Epithelial membrane antigen (EMA) and vimentin staining were focally positive. The final diagnosis was poorly differentiated endometrioid ovarian adenocarcinoma, with focal squamoid differentiation.

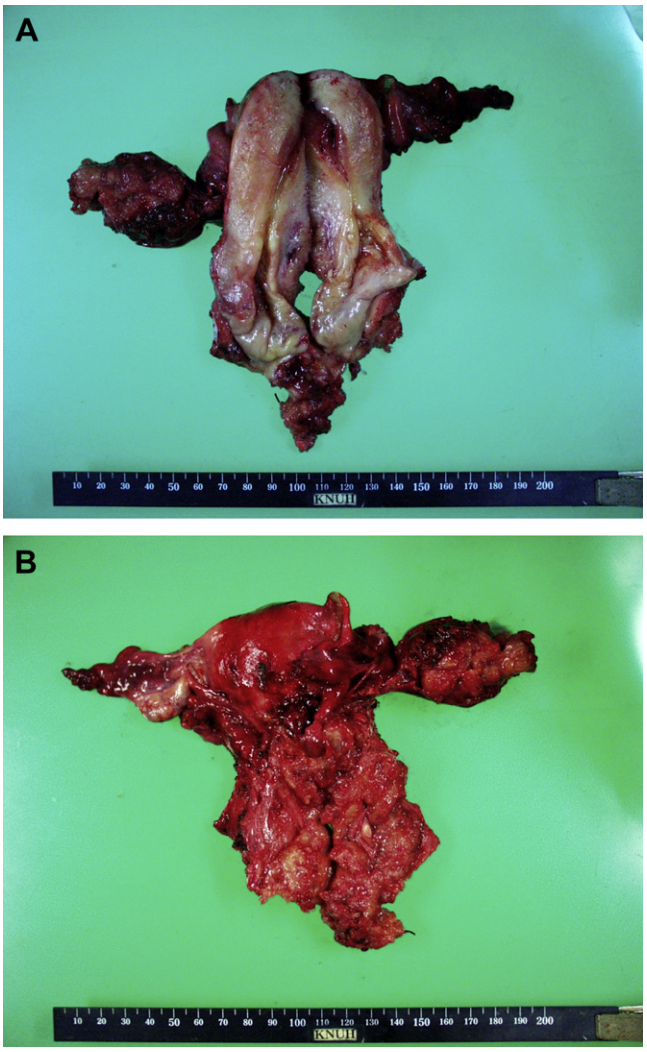

Fig. 6. (A) Anterior and (B) posterior gross findings of the specimen. An approximate 6-cm right ovarian mass was adhered to the posterior aspect of the lower uterine segmental mass, which was estimated to be about 10 cm. This mass perforated the lumen of the upper right side of the vagina.

She had an uncomplicated post-operative course. After discharge, she completed six cycles of adjuvant chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (300 mg/m^2). After treatment, she remained clinically disease-free until June 2010. The clinical course of the patient is summarized as a flow chart (Fig. 7).

Discussion

It is generally believed that solid tumors such as ovarian cancer start from a single malignant cell, and exponential growth occurs early in the history of the tumor. Some factors influence the rate of tumor growth. For example, advanced stage tumors grow more rapidly than early stage tumors, and metastatic lesions generally have a faster doubling time than primary lesions [5]. Histological type can also influence the growth rate; germ cell tumors, lymphomas, and malignant mesenchymal tumors are relatively fast-growing tumors (doubling time,

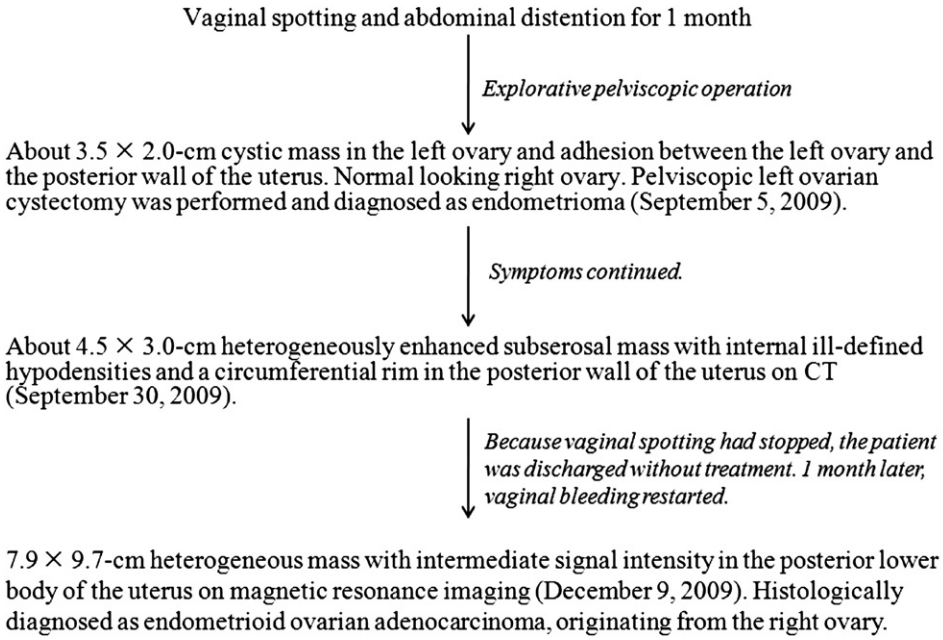

Fig. 7. A flow-chart showing the clinical course of the patient.

20–40 days), whereas adenocarcinomas and squamous carcinomas grow more slowly (doubling time, 50–150 days) [5].

Data from the literature concerning the growth rate of ovarian carcinoma are scarce. Brown and Palmer estimated the growth rates of early-stage and late-stage (stage III and IV) serous ovarian tumors using the Monte Carlo method. According to their analyses, early stage ovarian cancers double in volume approximately every 4 months, whereas advanced-stage tumors double in volume approximately every 2.5 months [6]. If a tumor grows faster, it is more likely an infection than a cancer, and if it grows slower, the possibility that it is a cancer is low. In this study, we reported on a very rapidly growing endometrioid ovarian cancer. Although we could not find a previous study reporting the growth rate of endometrioid ovarian carcinomas, we assumed that it might be similar to that of serous ovarian cancer, because both are epithelial in origin.

In the present case, the right ovarian mass, suspected as a degenerated uterine myoma on the CT scan, seemed to grow to a 4.5 × 3.0 cm tumor in 1 month, as the right ovary was macroscopically normal on a previous laparoscopy. Furthermore, about 2 months later, the tumor had enlarged to 10 cm, which was an increase of about three times in diameter, comparable to a 20–30 fold increase in volume. Considering that typical advanced-stage ovarian tumors double in volume approximately every 2.5 months, the growth rate of our case was extraordinary, more than 10-fold the normal growth rate. Kobayashi et al reported on an ovarian tumor that grew from 5 to 14 cm in diameter in only 4 weeks [7]. Compared with our case, the growth rate of that tumor seemed to be more rapid. But we still believe that our case is worth reporting, because their patient developed the tumor during pregnancy. Because the levels of gonadotropins and steroid hormones change markedly during pregnancy, a malignant neoplasm can grow much more rapidly under such a condition [7]. Cuesta et al suggested that an endometrioid adenocarcinoma coexisting with endometriosis has a favorable prognosis [8]. The presence of pelvic endometriosis may contribute to the early diagnosis of ovarian cancer because of symptoms, including pain and dysmenorrhea. Another study suggested that the coexistence of an endometriotic lesion might serve as a negative influence on the intraperitoneal spread of the localized cancer cells in the ovary [9]. Nevertheless, our patient was diagnosed as stage IV due to direct invasion to the vaginal lumen, which may be additional evidence of the extraordinarily rapid growth of the tumor in this case.

It is not clear whether the ovarian cancer originated from endometriosis or de novo. In fact, the coincidence of endometriosis and endometrioid ovarian cancer has been mentioned in several reports since 1928 [10]. Endometriosis is found in approximately 10% of premenopausal women, but is present in 10–15% of patients with ovarian cancer [11, 12]. Endometrioids, clear-cell carcinomas, and mixed subtypes are pathologically common in neoplasms arising from endometriosis [13]. The incidence of ovarian endometrioma in ovarian cancer occurs as follows: 3.3%, serous type; 3.0%, mucinous type; 21.2%, endometrioid type; 39.2%, clear-cell adenocarcinoma [9]. A malignant transformation of endometriosis is thought to occur in 0.7–1.0% of all cases [14]. Sampson, who first described a possible association between endometriosis and carcinoma of the ovary, defined the following criteria for diagnosing a malignant transformation of endometriosis: (1) a clear example of the endometriosis in proximity to the tumor must be found; (2) no other primary site for the tumor can be found; and (3) the histological appearance must be consistent with an origin from endometriosis [13]. Based on this perspective, it seems difficult to conclude that malignant transformation occurred in this case, as endometriosis was initially diagnosed on the left side, whereas the cancer was

detected only on the right side. However, even though a left ovarian cyst was diagnosed histologically as endometrioma on a previous laparoscopy, we cannot exclude the possibility that endometrioid ovarian cancer may have coexisted with the benign lesion. According to the patient's first time operation record, a left ovarian cyst, enlarged to 3−3.5 cm, was admixed with the small intestine and adhered to the lower posterior portion of the uterus. It is possible that the posterior cul-de-sac might have been at least partially obliterated. In such conditions, due to technical limitations, the surgeon might not open the surgical field enough for the proper diagnosis. It may be that only a benign lesion was included in the specimen for the histological exam. An adhesion between the left ovary and the uterus may have helped cryptic cancer cells to invade the uterus and right ovary directly. Incomplete first time surgery might debulk only the benign portion of the tumor and augment the growth rate of crypt cancer cells. De novo carcinogenesis is also possible in the development of endometrioids and the clear-cell type of ovarian carcinoma [15].

A distant metastasis (stage IV disease) is unusual, but it may occur at the time of diagnosis of ovarian cancer, or can arise during evolution of the disease. In a previous study, distant metastases were present in 8% of the patients at the time of diagnosis and in 22% of the patients during the disease course [16]. When these tumors metastasize, they usually initially metastasize to the retroperitoneal lymph nodes [17]. A distant metastasis is usually associated with widespread disseminated disease and poor performance status; the effects of this rare metastasis are devastating, and survival is usually very poor [17]. Distant metastases theoretically may occur anywhere; however, the pleura, liver, lung, central nervous system, spleen, skin, bone, and breast are, decreasing in order, the most commonly involved sites [16]. This case was diagnosed as stage IV, due to direct vaginal invasion. Ovarian cancer rarely metastasizes to the uterine cervix, vagina, or vulva. So, vaginal invasion is an interesting pattern of distant metastasis in this case of ovarian cancer. Bergman's autopsy series documented 11 cases of vaginal spread of ovarian carcinoma [18]. It was suggested that the lymphatics may convey tumors from the ovary to the vagina, as described by Willis [19]. However, in all of Bergman's cases, the pelvic peritoneum was involved with tumor masses in the pouch of Douglas, from which the carcinoma could infiltrate the vagina, which is a similar metastasis pattern to our case. Most cases of ovarian carcinoma spread through the retroperitoneal lymphatics. Ovarian cancer generally causes ascites or bowel adhesions, but peritoneal and distant metastases seldom occur in the absence of intra-abdominal disease [16]. Interestingly, in our case, direct vaginal invasion occurred without formation of malignant ascites or lymph node involvement. It seemed that the speed of extension was so rapid that cancer could invade the uterine cervix and vagina before metastasis to the lymphatics and blood vessels. Unfortunately, it is unclear what made the cancer grow and invade the neighboring organs so quickly. Further studies are needed.

In our case, the patient's tumor marker levels were within normal ranges, and the tumor showed nonspecific findings on the USG even 3 months before diagnosis. Although it is well known that serous or other histological types of ovarian carcinomas that appear to develop from a normal-appearing ovary cannot be detected even by careful examination using transvaginal USG [20], the frequent measurement of tumor size by USG may provide important information on detection in a subset of ovarian carcinomas that develop from preexisting, detectable lesions. Presently, no practical option seems to be available except frequent measurements of tumor size by USG and checking serum tumor marker levels for the management of a pelvic mass.

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