Case Report

Extragonadal Giant Endometrial Cyst with Endometrioid Borderline Tumor

Hiroyuki Yazawa[1]*, Karin Imaizumi[1], Asami Kato[1], Kaoru Takiguchi[2]

[1]Department of Obstetrics and Gynecology, Fukushima Red Cross Hospital, [2]Department of Obstetrics and Gynecology, Ohta Nishinouchi Hospital, Fukushima, Japan

Abstract

We describe an extremely rare case of a borderline tumor arising from an extragonadal giant endometrial cyst. A 41-year-old woman complaining of abdominal pain was referred to our hospital with a diagnosis of large ovarian tumor. Magnetic resonance imaging revealed a large cystic tumor approximately 27 cm × 9 cm in area. The cyst contents were largely removed by suction, and then the tumor was resected laparoscopically. Both adnexa were normal in size and location. The tumor did not originate from the ovaries, and it was adherent only to the bilateral uterosacral ligaments and uterine body. The postoperative histopathological evaluation confirmed the presence of endometrioid borderline tumor with transition from endometriosis. Staging laparotomy was performed, and no remnant tumor was detected. This case is extremely unusual because such a large cystic tumor originating from extragonadal endometriosis is very rare, as is endometrioid borderline tumor arising from endometriosis.

Keywords: Atypical endometriosis, endometrioid borderline tumor, endometriosis-related ovarian neoplasm, extragonadal endometriosis

Introduction

Endometriosis is a common condition and is estimated to affect 5%–15% of women of reproductive age and 25%–50% of women with infertility,[1] and several possible theories about the pathogenesis of endometriosis have been documented.[2] Epidemiologically, endometriosis has been reported to increase the risk of ovarian neoplasms, resulting in a condition known as endometriosis-related ovarian neoplasm (ERON) or endometriosis-associated malignancy (EAM). Recently, numerous studies of ERON or EAM have reported details about its epidemiology, pathogenesis, genetic alterations, diagnosis, and prognosis. Herein, we present an extremely rare case of the extragonadal endometrial cyst with endometrioid borderline tumor, and then discuss endometriosis and ERONs in recently published reports. This case report is a retrospective study and was exempt from the Institutional Review Board at our institute.

Case Report

A 41-year-old woman, para 3, with abdominal and back pain was referred to our hospital for the evaluation and treatment of a large cystic tumor. Magnetic resonance imaging (MRI) confirmed the diagnosis; the tumor was approximately 27 cm × 9 cm in area with a solid component inside the cyst [Figure 1]. Tumor markers for epithelial ovarian cancer were elevated as follows: Carbohydrate antigen (CA) 125, 150 U/ml; CA 19-9, 220 IU/ml. Ovarian tumor was suspected and the laparoscopic operation was performed using three port insertions. Based on the surface characteristics of the tumor,

Article History:
Received 11 December 2018
Received in revised form 7 March 2019
Accepted 3 April 2019
Available online 24 October 2019

Access this article online

Quick Response Code:

Website: www.e-gmit.com

DOI: 10.4103/GMIT.GMIT_85_18

Address for correspondence: Dr. Hiroyuki Yazawa, Fukushima Red Cross Hospital, Yashima-cyo 7-7, Fukushima 960-8530, Japan.
E-mail: ikyoku12@fukushima-med-jrc.jp

How to cite this article: Yazawa H, Imaizumi K, Kato A, Takiguchi K. Extragonadal giant endometrial cyst with endometrioid borderline tumor. Gynecol Minim Invasive Ther 2019;8:179-84.

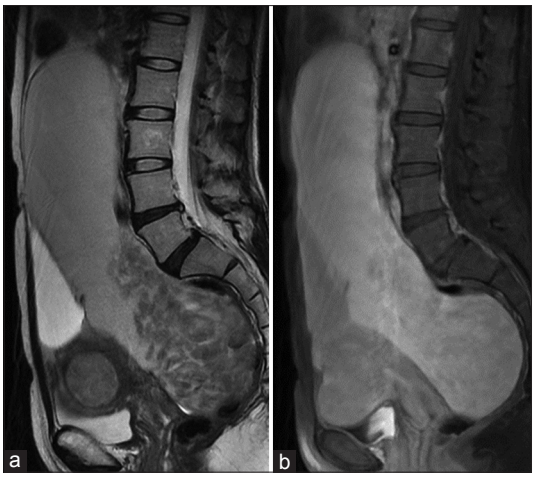

Figure 1: Noncontrast (a) and contrast-enhanced (b) T2-weighted sagittal magnetic resonance images showing a giant cystic tumor measuring approximately 27 cm × 9 cm, with a solid, nonenhancing component inside the cyst

it seemed more likely to be peritoneal rather than ovarian in origin [Figure 2a]. The tumor was connected to the uterine body by a narrow, 3-cm long band [Figure 2b]. The tumor capsule ruptured easily when gently touched with forceps. Brown chocolate-like fluid and coagulative tissue leaked from the tumor [Figure 2c and d]. Most of the cyst contents were removed by suction. Tumor attachments to surrounding structures were severed and then the tumor was packed into a specimen bag in the peritoneal cavity [Figure 2e], cut into small pieces inside the bag, and removed through the port site. Both adnexa were normal in size and shape, without any connections to the tumor [Figure 2f]. Two intramural uterine myomas 5 cm in each diameter were located on the anterior wall of the uterine body, and myomectomy was performed laparoscopically [Figure 3a]. We ultimately determined that the tumor had been connected only to the uterine body [Figure 3b] and to portions of the left [Figure 3c] and right [Figure 3d] uterosacral ligaments. There were no findings of another adhesions or endometriosis in the pelvic cavity. Since intraoperative frozen sections of the cystic tumor resulted in a histopathological diagnosis of the endometrial cyst without malignancy, the laparoscopic operation was concluded.

Although the solid component was not clearly identified macroscopically inside the tumor, subsequent postoperative histopathological examination confirmed the presence of the tumor epithelium, showing an increased nuclear-to-cytoplasm ratio, several mitotic cells, papillary changes, stratification, and metaplastic alteration to squamous cells without necrosis or invasive growth into the stroma [Figure 4A-E and e]. Immunohistochemical staining was negative for HNF1β [Figure 4F], p53, and MIB-1 and positive for ER. The postoperative histopathological diagnosis of the tumor was confirmed as the endometrioid borderline tumor in an

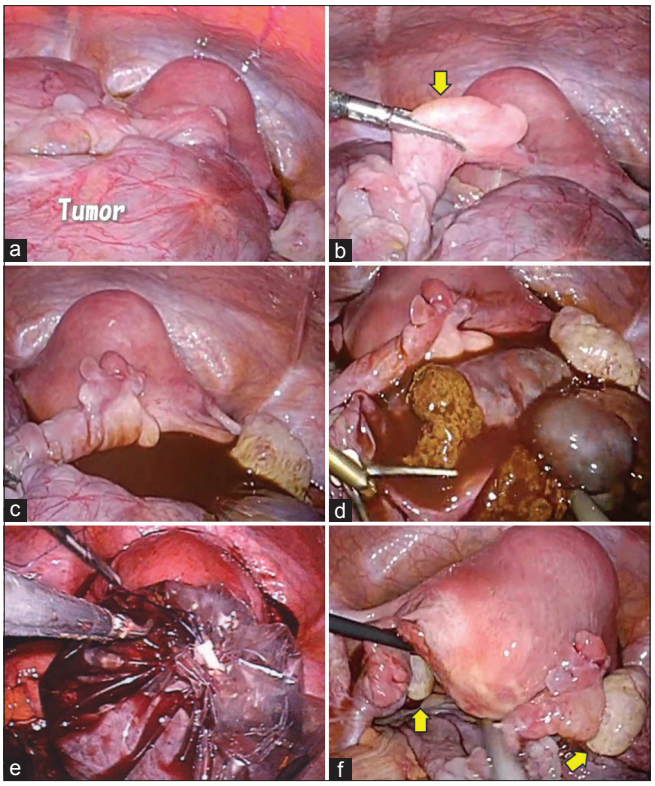

Figure 2: During laparoscopy, the giant cystic tumor was found in the center of the abdominal cavity. The characteristics of the tumor surface suggested that the tumor arose in the peritoneum rather than the ovary (a). The tumor was connected to the posterior uterine body by a narrow band approximately 3 cm in length (arrow) (b). The tumor capsule ruptured when gently touched with a forceps, and a brown chocolate-like fluid and coagulative tissue leaked from the tumor (c and d). The tumor contents were extracted by suction, packed into a specimen bag in the peritoneal cavity (e), then removed. Both adnexa (arrows) were normal in size and shape, without any connections to the tumor (f)

endometrial cyst. Moreover, atypical endometriosis showing cytological atypia and architecturally, complex proliferative lesions were also identified [Figure 4B and C].

Because the patient did not desire future childbearing, hysterectomy, bilateral adenectomy, partial omentectomy, and pelvic lymph node biopsy were subsequently performed as a staging laparotomy for ovarian borderline tumor. No remnant tumor cells were detected on postoperative histopathological examination. Based on laparoscopic findings, the large endometrial cyst was thought to have arisen in the peritoneum, whereas pathological findings indicated that the endometrioid borderline tumor probably originated from endometriosis. The patient provided informed consent for this case report and associated images.

Discussion

Endometriosis is defined as the growth of endometrial-like tissue (glands and stroma) outside the uterine cavity and is estimated to affect 5%–15% of women of reproductive

age and 25%–50% of women with infertility.[1] There are several theories regarding the pathogenesis of endometriosis, including the following: (1) implantation of endometrial cells derived from retrograde menstrual bleeding into the peritoneum, so-called Sampson's theory;[2,3] (2) coelomic metaplasia, in which the mesothelium turns into endometrial tissue through metaplasia, so-called Meyer's theory;[2,4] and (3) development by metaplasia from müllerian-type epithelium located outside the cavity of the original müllerian ducts, referred to as a "secondary müllerian system" by Lauchlan.[5] Nisolle and Donnez reported that peritoneal, ovarian, and rectovaginal endometriotic lesions must be considered as three separate entities with different pathogenetic origins.[6] Peritoneal endometriosis can be explained by the transplantation theory. Red peritoneal lesions are the most active and most highly vascularized lesions and are considered to be the first stage of early endometrial tissue implantation.[6] The formation of ovarian, endometrial cysts is caused by metaplasia of the coelomic epithelium, which then invaginates into the ovarian cortex.[7] The deeply infiltrating endometriosis of the rectovaginal septum corresponds to an adenomyotic nodule originating from müllerian remnants by the process of metaplasia. In our case, the cystic tumor was adherent only to portions of the bilateral uterosacral ligaments and the uterine body by narrow bands that were histopathologically identified as granulation tissue. Because there was no other peritoneal or ovarian endometriosis in the peritoneal cavity, the endometrial cyst most likely arose in the uterosacral portion of the peritoneum from müllerian remnants by the process of metaplasia.

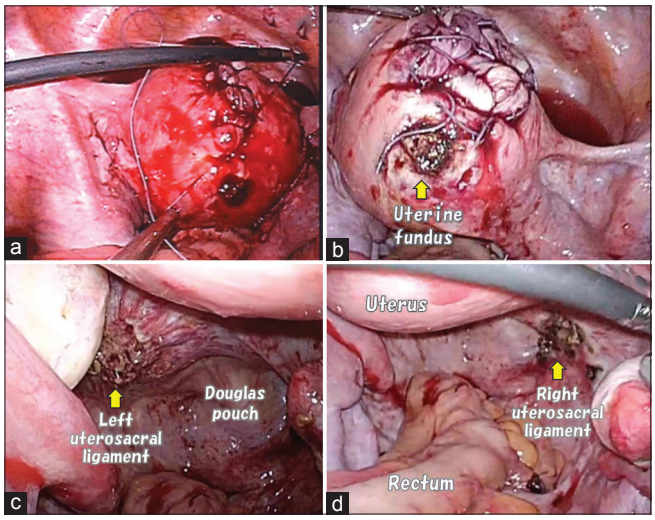

Figure 3: Laparoscopic myomectomy was performed (a). The tumor was only connected to the uterine body (arrow in b) and the bilateral uterosacral ligaments (arrows: left side in c, right side in d). No endometriosis was identified in the pelvic cavity

Epidemiologically, endometriosis has been reported to increase the risk of ovarian neoplasms by 0.3%–1.6%,[8] a phenomenon known as endometriosis-related ovarian neoplasm (ERON) or EAM. Several studies have assessed the risk of ovarian cancer in patients with endometriosis.[9] Kobayashi *et al*. reported that during follow-up of 6396 women with ovarian endometrial cyst up to 17 years in Japan, 46 incident ovarian cancer (0.72%) were identified and demonstrated marked increase in ovarian cancer risk (standardized incidence ratio [SIR] = 8.95, 95% confidence interval [CI], 4.12–15.3).[10] Brinton *et al*. demonstrated that

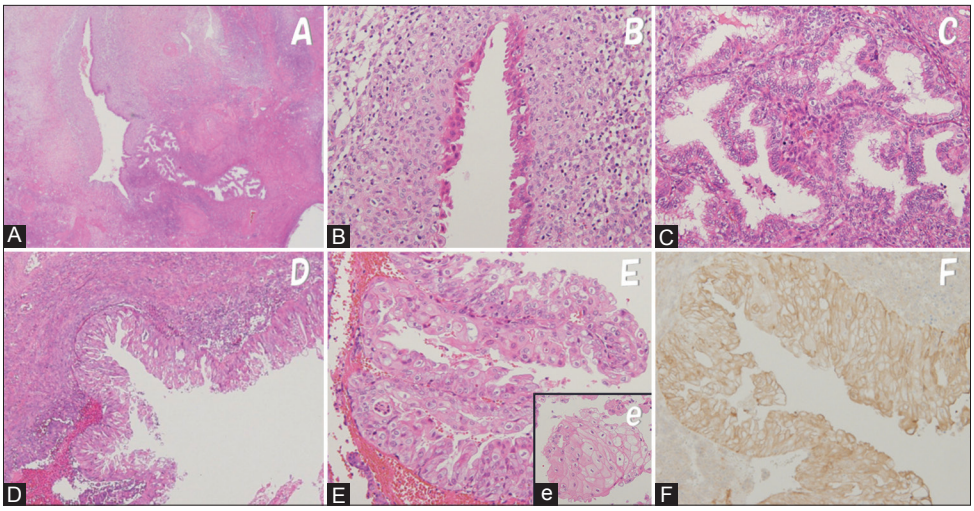

Figure 4: Low magnification of the cystic epithelium showing endometrial glands and stroma with hemosiderin-laden macrophages, leading to the diagnosis of an endometrial cyst (A). Transition of normal endometrioid epithelium to atypical epithelium showing cytological atypia (B). Atypical endometriosis with architecturally complex proliferative lesions (C). Low magnification of endometrioid borderline tumor (D). High magnification of endometrioid borderline tumor with findings of increased nuclear-to-cytoplasmic ratio, several mitotic cells, papillary changes, stratification, and metaplastic alteration to squamous cell without necrosis or invasive growth into the stroma (E, e). Immunohistochemical examination showing negative staining for HNF1 β (F)

the ovarian cancer risk in women with endometriosis was twice as high (SIR = 1.98, CI, 1.4–2.6) as that in the general population,[11] while the risk was even higher (SIR = 2.48, CI, 1.3–4.2) in infertile women.[12] Aris also demonstrated a high incidence (1.63%, relative risk = 1.69) of ERONs in a 10-year cohort study in Canada.[13] The most common malignant tumors in this setting are clear-cell carcinoma (CCC) and endometrioid carcinoma, each accounting for approximately 10% of all ovarian carcinomas in Western countries[14] and approximately 25% and 18%, respectively, in Japan.[15] The third major category of ERON is seromucinous borderline tumor, also known as müllerian mucinous/mixed epithelial tumor, whereas borderline endometrioid and clear-cell tumors are much less common.[16]

Several risk factors for ERONs have been reported, and a recent review article demonstrated that older age at endometriosis diagnosis (≥45 years), large size (>9-cm diameter), solid endometrial cysts component, nulliparity, hyperestrogenism (endogenous or exogenous), and postmenopausal status were all associated with an increased risk of malignant transformation of ovarian endometrioma, whereas complete surgical excision of endometriotic tissue with concomitant unilateral oophorectomy and use of oral contraceptives may be associated with a lower risk of ovarian cancer in women with endometriosis.[17] Tanase *et al*. recently determined that several preoperative factors independently distinguish ERON from benign ovarian endometrial cyst, namely the height (>1.5 cm) and height/width ratio (>0.9) of mural nodules, the maximum diameter of the cyst (>7.9 cm) on MRI findings, and patient age at diagnosis (>43 years).[18] They also reported that the presence of various signal intensities on T1-weighted imaging (WI), a lower proportion of shading on T2-WI, and nodules located on the abdominal side may be useful in the proper diagnosis of malignant transformation.[18]

The prognosis of ovarian cancer in women with endometriosis has also been demonstrated. Aris reported that the mean age of women with ERON was 5.5 years younger than in those without ERON,[13] and Orezzoli *et al*. found that the mean age of women with CCC arising in ERON was 10 years younger than those with CCC not arising in ERON.[19] ERON is commonly a low-stage and low-grade disease and is associated with significantly better prognosis.[8,20] In a meta-analysis by Kim *et al*., ERON was associated with better overall survival than non-ERON, although progression-free survival did not differ between the two.[8] After controlling for stage, age, grade, and treatment, no difference in overall survival between these two patient groups could be identified, and therefore, the better clinical outcome of ERON than non-ERON might be explained by a high rate of well-differentiated, early-stage tumors rather than by an association with endometriosis *per se*.[20,21] ERONs were significantly more frequently diagnosed at an early stage, perhaps due to symptoms or follow-up related to endometriosis.[22]

Recently, evidence has accumulated demonstrating the carcinogenicity of ERON. Due to periodic hemorrhage and hemolysis associated with ovarian endometrial cysts, significant amounts of cell-free hemoglobin are released from erythrocytes into the cyst fluid, leading to iron-induced oxidative stress and thus triggering carcinogenic genetic alterations.[21,23] Iwabuchi *et al*. reported that the balance of oxidants and antioxidants is important for cell death and carcinogenesis in ovarian endometrial cysts, and upregulation of antioxidant functions may be involved in the pathogenesis of malignant transformations.[23] Genetic alterations such as *K-RAS*, *PTEN*, *BLC-2*, and *ARID1A* in ERONs have been studied extensively,[21,24] and Ishikawa *et al*. recently demonstrated that *ARIDIA* mutations were the most common (95% of ERONs), suggesting that this gene plays a critical role in ERON carcinogenesis.[24]

While ovarian endometriosis most frequently results in cystic tumors, extraovarian endometriosis (e.g., peritoneal, rectovaginal, intestinal, urinary bladder, or uterine adenomyosis) is associated with nodular tumors. Moreover, extragonadal malignant tumors arising from endometriosis (MTAE) are very rare entities.[25] According to a literature search performed by Ulrich *et al*., the most common site of extragonadal MTAE was the bowel (29%), followed by the rectovaginal septum (13%) and uterine adenomyosis (8.6%).[25] Regarding the pathogenesis of malignant transformation arising from extragonadal endometriosis, Gemmell *et al*. recently reviewed 25 patients with postmenopausal status and a history of hormone replacement therapy, and reported that endometrioid adenocarcinoma was the most common histology (18 patients), followed by adenosarcoma (two patients).[26] Modesitt *et al*. also reviewed 21 patients with the same status and reported that the most common histological tumor type was endometrioid carcinoma (6 patients).[27] Other pathologies, such as endometrial stromal sarcoma, adenosquamous carcinoma, and müllerian carcinosarcoma, were also listed, and only one case of the endometrioid borderline tumor was reported.[26,28]

A number of histopathological studies have demonstrated the coexistence of atypical endometriosis and neoplasms. ERON may arise from atypical endometriosis, which is defined by large hyperchromatic or pale nuclei with moderate to marked pleomorphism; an increase nuclear-to-cytoplasmic ratio; and cellular crowding, stratification, or tufting.[21,29] According to a study by Fukunaga *et al*., atypical endometriosis was identified

in 67% of cases of CCC and 54% of cases of endometrioid carcinoma among 27 and 13 cases of ERONs, respectively.[30] Ogawa *et al*. also demonstrated that 29 of 37 (78%) cases of ERONs exhibited atypical endometriosis.[31] These studies support the hypothesis that atypical endometriosis is a premalignant condition, but there are still insufficient data to form a definite conclusion.[21] In our case, the existence of typical and atypical endometriosis and the transition from atypical endometriosis to endometrioid borderline tumor were pathological confirmed.

Regarding the secondary surgery of our patient, although there is no standardized treatment for extragonadal borderline tumor, we selected hysterectomy, bilateral adenectomy, partial omentectomy, and pelvic lymph node biopsy as secondary staging laparotomy with informed consent in accordance with the statement of the Treatment Guidelines for Ovarian Cancer, 2015 Edition, in Japan,[32] which recommends above secondary laparotomy in patients who do not wish to bear children in future.

Conclusion

The extragonadal giant endometrial cyst in our case was thought to have arisen in the uterosacral portion of the peritoneum, originating from müllerian remnants by the process of metaplasia. The borderline malignant tumor was pathologically diagnosed with arising from endometriosis. This case is extremely unusual because giant cystic tumors originating from extragonadal endometriosis are very rare, as endometrioid borderline tumor arising from endometriosis is very rare.

Ethical statement

This study is approved by the ethics committee of Fukushima Red Cross Hospital (approval no. 2019-29 obtained on Sep. 19th, 2019) with the need of obtaining informed consent from the patient participants.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Giudice LC. Clinical practice. Endometriosis. N Engl J Med 2010;362:2389-98.
2. Vinatier D, Orazi G, Cosson M, Dufour P. Theories of endometriosis. Eur J Obstet Gynecol Reprod Biol 2001;96:21-34.
3. Sampson JA. Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation. Am J Pathol 1927;3:93-110.43.
4. Meyer R. The current question of adenomyositis and adenomyoma in general and particular seroepithelial adenomyositis and sarcomatoid adenomyometritis (Über des stand der frage adenomyositis und adenomatome im allgemeinen und insbesondere über adenomyositis serosoepithelialis und adenomyometritis). Zentralbl Gynakol 1919;43:745-50.
5. Lauchlan SC. The secondary müllerian system. Obstet Gynecol Surv 1972;27:133-46.
6. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril 1997;68:585-96.
7. Donnez J, Nisolle M, Gillet N, Smets M, Bassil S, Casanas-Roux F, *et al.* Large ovarian endometriomas. Hum Reprod 1996;11:641-6.
8. Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: A meta-analysis. Br J Cancer 2014;110:1878-90.
9. Siufi Neto J, Kho RM, Siufi DF, Baracat EC, Anderson KS, Abrão MS, *et al.* Cellular, histologic, and molecular changes associated with endometriosis and ovarian cancer. J Minim Invasive Gynecol 2014;21:55-63.
10. Kobayashi H, Sumimoto K, Moniwa N, Imai M, Takakura K, Kuromaki T, *et al.* Risk of developing ovarian cancer among women with ovarian endometrioma: A cohort study in Shizuoka, Japan. Int J Gynecol Cancer 2007;17:37-43.
11. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. Am J Obstet Gynecol 1997;176:572-9.
12. Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, *et al.* Ovarian cancer risk associated with varying causes of infertility. Fertil Steril 2004;82:405-14.
13. Aris A. Endometriosis-associated ovarian cancer: A ten-year cohort study of women living in the Estrie region of Quebec, Canada. J Ovarian Res 2010;3:2.
14. Gurung A, Hung T, Morin J, Gilks CB. Molecular abnormalities in ovarian carcinoma: Clinical, morphological and therapeutic correlates. Histopathology 2013;62:59-70.
15. Yamagami W, Nagase S, Takahashi F, Ino K, Hachisuga T, Aoki D, *et al.* Clinical statistics of gynecologic cancers in Japan. J Gynecol Oncol 2017;28:e32.
16. Matias-Guiu X, Stewart CJR. Endometriosis-associated ovarian neoplasia. Pathology 2018;50:190-204.
17. Thomsen LH, Schnack TH, Buchardi K, Hummelshoj L, Missmer SA, Forman A, *et al.* Risk factors of epithelial ovarian carcinomas among women with endometriosis: A systematic review. Acta Obstet Gynecol Scand 2017;96:761-78.
18. Tanase Y, Kawaguchi R, Takahama J, Kobayashi H. Factors that differentiate between endometriosis-associated ovarian cancer and benign ovarian endometriosis with mural nodules. Magn Reson Med Sci 2018;17:231-7.
19. Orezzoli JP, Russell AH, Oliva E, Del Carmen MG, Eichhorn J, Fuller AF, *et al.* Prognostic implication of endometriosis in clear cell carcinoma of the ovary. Gynecol Oncol 2008;110:336-44.
20. Davis M, Rauh-Hain JA, Andrade C, Boruta DM 2nd, Schorge JO, Horowitz NS, *et al.* Comparison of clinical outcomes of patients with clear cell and endometrioid ovarian cancer associated with endometriosis to papillary serous carcinoma of the ovary. Gynecol Oncol 2014;132:760-6.
21. Krawczyk N, Banys-Paluchowski M, Schmidt D, Ulrich U, Fehm T. Endometriosis-associated malignancy. Geburtshilfe Frauenheilkd 2016;76:176-81.
22. Bounous VE, Ferrero A, Fuso L, Ravarino N, Ceccaroni M, Menato G, *et al.* Endometriosis-associated ovarian cancer: A distinct clinical entity? Anticancer Res 2016;36:3445-9.
23. Iwabuchi T, Yoshimoto C, Shigetomi H, Kobayashi H. Oxidative stress and antioxidant defense in endometriosis and its malignant transformation. Oxid Med Cell Longev 2015;2015:848595.
24. Ishikawa M, Nakayama K, Nakamura K, Ono R, Sanuki K, Yamashita H, *et al.* Affinity-purified DNA-based mutation profiles of endometriosis-related ovarian neoplasms in Japanese patients. Oncotarget 2018;9:14754-63.
25. Ulrich U, Rhiem K, Kaminski M, Wardelmann E, Trog D, Valter M, *et al.* Parametrial and rectovaginal adenocarcinoma arising from endometriosis. Int J Gynecol Cancer 2005;15:1206-9.
26. Gemmell LC, Webster KE, Kirtley S, Vincent K, Zondervan KT,

Becker CM, *et al.* The management of menopause in women with a history of endometriosis: A systematic review. Hum Reprod Update 2017;23:481-500.
27. Modesitt SC, Tortolero-Luna G, Robinson JB, Gershenson DM, Wolf JK. Ovarian and extraovarian endometriosis-associated cancer. Obstet Gynecol 2002;100:788-95.
28. Powell JL, Connor GP, Henderson GS. Androgen-producing, atypical proliferating endometrioid tumor arising in endometriosis. South Med J 2001;94:450-3.
29. Worley MJ, Welch WR, Berkowitz RS, Ng SW. Endometriosis-associated ovarian cancer: A review of pathogenesis. Int J Mol Sci 2013;14:5367-79.
30. Fukunaga M, Nomura K, Ishikawa E, Ushigome S. Ovarian atypical endometriosis: Its close association with malignant epithelial tumours. Histopathology 1997;30:249-55.
31. Ogawa S, Kaku T, Amada S, Kobayashi H, Hirakawa T, Ariyoshi K, *et al.* Ovarian endometriosis associated with ovarian carcinoma: A clinicopathological and immunohistochemical study. Gynecol Oncol 2000;77:298-304.
32. Japan Society of Gynecologic Oncology, editor. Treatment Guidelines for Ovarian Cancer. 2015th ed. Kanehara & Co., Ltd.; 2015.