Coexistence of malignant ovarian Brenner tumor and borderline mucinous cystadenoma, combined with primary uterine corpus endometrioid carcinoma: A case report and literature review

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Abstract. Malignant Brenner tumor (MBT) of the ovary is a rare malignant ovarian tumor, whereas uterine corpus endometrioid carcinoma (UEC) constitutes one of the most common malignant tumors of the female reproductive system. The present study reported on a case of the coexistence of ovarian MBT and borderline mucinous cystadenoma combined with primary UEC. Therefore, the present case is a synchronous primary cancer of both ovary and endometrium. Although synchronous primary cancers of the endometrium and ovary are relatively uncommon, they are not rare; however, due to the rarity of MBT, this case was considered singular. To the best of our knowledge, this was the first-ever reported case of the coexistence of an ovarian MBT and borderline mucinous cystadenoma combined with primary UEC. Based on a review of the literature associated with the present case, its clinicopathological features, immunohistochemical phenotype, differential diagnosis, molecular changes, prognosis and treatment were summarized and discussed. The aim of the present study was to improve the understanding of this rare synchronous primary cancer of the ovary and endometrium so as to avoid future misdiagnosis.

Introduction

Contemporaneous primary cancers of the endometrium and ovary comprise the most common synchronous gynecologic malignancies; they are detected in 3-5% of all patients with endometrial cancer and in 3-10% of all patients with ovarian cancer (1). Endometrioid endometrial carcinoma (EEC) is the most common histological subtype of synchronous endometrial and ovarian carcinoma, while other comorbidities are rare (2). In addition, the coexistence of ovarian Brenner tumor (BT) and mucinous neoplasm is not uncommon, accounting for ~16% (3). However, to the best of our knowledge, no previous study exists on the coexistence of ovarian malignant (MBT) and borderline mucinous cystadenoma combined with primary uterine corpus endometrioid carcinoma (UEC). Therefore, the present study reported on this current rare case of synchronous primary ovarian MBT with borderline mucinous cystadenoma complicated with primary UEC encountered at our hospital. Furthermore, a literature review was performed and the overall clinicopathologic features, immunohistochemical phenotypes, differential diagnosis, molecular changes and the prognosis and treatment of the disease were summarized. The purpose of this case report was to alert clinicians and pathologists that they may encounter similar cases in clinical practice. In order to reach an accurate pathologic diagnosis of this type of synchronous endometrial-ovarian primary cancer, it is recommended that the pathologist aggregates and closely examines the patient's clinical history, imaging data, morphologic characteristics and immunohistochemical and molecular testing results, and ultimately performs a comprehensive analysis.

Case report

Case presentation. A 50-year-old female patient presented at the Women and Children's Hospital of Chongqing Medical University (Chongqing, China) in May 2021 with an eight-month history of abnormal uterine bleeding, lower-abdominal-distension pain with lumbar pain and swelling for three months, as well as increased vaginal discharge for four days. The patient had been physically healthy in the past and medical history was unremarkable. Tumor-marker levels were as follows: CA19-9, >12,000.00 U/ml; CA-125, 256.3 U/ml; and CEA, 19.7 ng/ml. Magnetic resonance imaging of the abdomen and pelvis indicated that the uterine cavity was dilated and exhibited a lumpy mass with slightly long T1 and T2 signals. The mass size was ~8.4x3.5 cm, with slight enhancement upon

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Figure 1. Gross features of left attachment, presenting the cystic solid tumor where the solid portion was gray-white, tender and sticky (as displayed in the red circle) (scale bar is in cm).

enhanced-scan imaging. Multilocular cystic-solid occupying masses were uncovered in both left and right appendages, with sizes of 6.2x3.2x5.7 and 15.1x15.2x9.1 cm, respectively. The solid portion of the masses was located in their lower aspects and protruded into the respective cavity in papillary- and cauliflower-like shapes. Enhanced scanning indicated that the solid components, capsule wall and septum were also significantly enhanced. Hysteroscopy indicated that the uterine cavity was filled with abnormal endometrium with fragile tissue structures and a large number of abnormal blood vessels were also observed in the endometrium, with the neoplasm having invaded the cervical canal. Curettage was performed under hysteroscopy and the specimen was sent for pathologic examination. Microscopically, the atypical endometrioid glands fused with each other in the tissues collected from the cervix and uterine cavity, and the cancer cell atypia ranged from mild to moderate, with pathologic mitoses noted. The pathologic diagnosis based on cervical and uterine cavity curettage was endometrioid carcinoma [Federation of Gynecology and Obstetrics (FIGO) grade I]. Due to the pathological diagnosis and imaging anomalies, the patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and bilateral pelvic lymph node dissection.

Gross specimen characteristics. The samples included the whole uterus, bilateral adnexa, parauterine tissue and resected lymph nodes. In the left adnexa (Fig. 1), a cystic-solid mass of 9.0x8.0x4.5 cm with a smooth surface was noted; the mass had been cut open and the cystic content was lost. The wall thickness of the cyst was 0.2-0.5 cm and the size of the solid component was 5.0x3.0x3.0 cm. The cut surface of the solid portion was gray-white, adhesive and delicate in texture. A fallopian tube with a length of 6.0 cm and a diameter of 1.0 cm was attached to the surface of the mass and no oviductal umbrella was

observed. A cystic-solid mass of 12.0x8.0x4.0 cm in size in the right adnexa was also noted; the mass had been incised and the cavity's content was also missing. The wall thickness of the cystic component was 0.2-0.5 cm and the size of the solid component was ~9.0x6.0x3.0 cm. The cut surface of the solid portion was gray-white, adhesive and soft and delicate in texture, and the papilla protruded into the cyst. The uterine cavity was filled with grayish-white and fragile tumorous tissue and the endometrium was diffusely thickened to ~0.5-1.0 cm. The tumors infiltrated half-way into the muscle wall layer and extended into the cervical canal. The section of the cervical canal wall included a 2.0x1.8x1.5 cm grayish-white mass of medium texture and unclear boundary and a biopsy was taken. Besides, the serosa of the cervix was slightly coarse (Fig. 2A).

Microscopic characteristics on pathologic examination. No normal ovarian tissue was found in the left and right adnexa. In the cystic area, the cystic wall was lined with mucinous epithelium and goblet cells were observed (magnification, x100) (Fig. 3A). Over 10% of the mucous epithelium of the cyst wall was stratified and part of the epithelium was fused into a papillary or cribriform structure (Fig. 3B). Cell atypia ranged from mild to moderate and mitotic figures were clearly recognizable. Fig. 3C indicates the coexistence of mucous epithelium with the urothelium, while Fig. 3D displays a typical urothelial tumor area. The tumor cells exhibited nest-like infiltration in the solid area of the mass. Certain nests had a central glandular cavity that was lined with mucous epithelium that contained eosinophilic mucus or that exhibited necrosis (Fig. 3E). In the poorly differentiated area, the tumor cells infiltrated into the stroma with cord-like, trabecular and gland-like structures (Fig. 3F), and they had moderate to severe atypia. The shape of the nuclei was round, oval, irregular or vacuolar, with smudged chromatin and obvious nucleoli. The cytoplasm was clear or eosinophilic
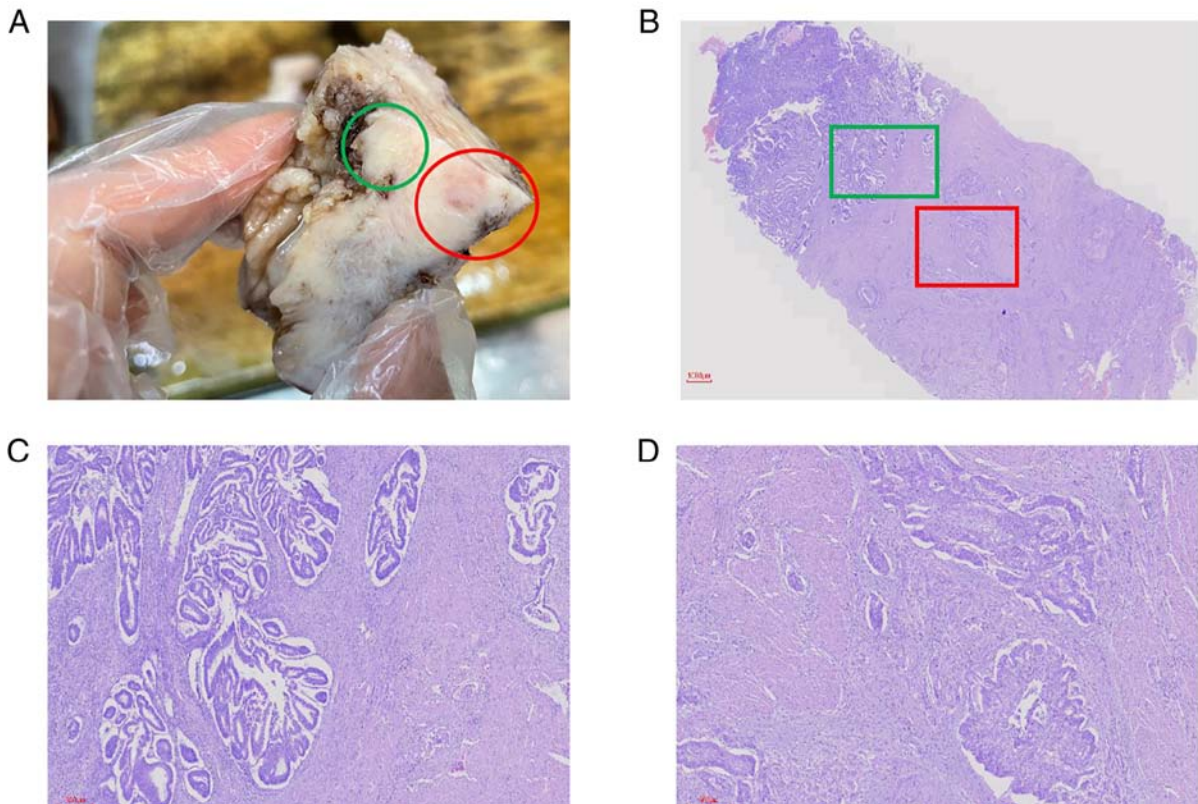
Figure 2. (A) Gross photographic and (B) photomicroscopic images of the synchronous tumor (scale bar, 1,000 μm). Green areas represent endometrial cancer of the uterus and red areas indicate ovarian cancer involving the uterus. (C and D) Partial enlargements of the (C) green and (D) red boxes in B (scale bars, 300 μm). C designates a well-differentiated endometrioid carcinoma with a partial microcystic, elongated and fragmented infiltrating myometrium. (D) The histomorphology of the mass observed on a section of the cervical canal wall was identical to that of an adnexal solid mass.
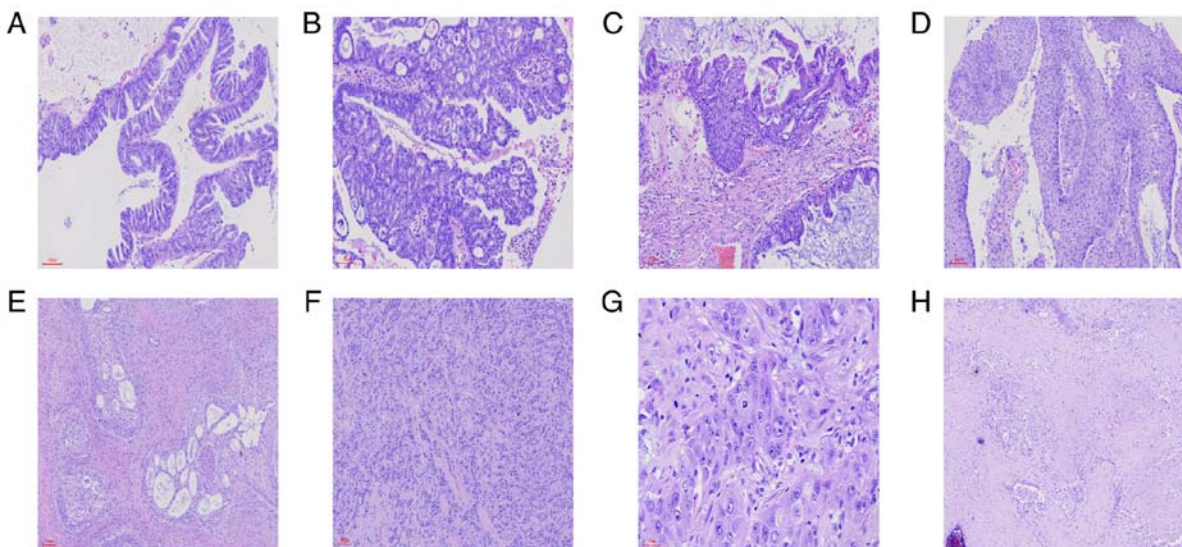

Figure 3. Pathological images of bilateral ovarian tumors. (A) The cystic wall was lined with mucinous epithelium and goblet cells were present. (B) >10% of the lining epithelia was stratified and exhibited papillary or cribriform patterns. (C) Contemporaneous presence of mucous epithelium and urothelium. (D) A typical urothelial tumor area. (E) The tumor cells in the solid areas exhibit nest-like infiltration; in contrast, (F) in the poorly differentiated portion, the tumor cells exhibited a cord-like and trabecular structure that infiltrated the stroma. (G) The cells had moderate-to-severe atypia, the nuclei were irregular or vacuolar with obvious nucleoli and pathologic mitoses were easily observed. (H) Necrosis, squamous cell metaplasia and psammoma bodies were present (scale bars, 100 μm).

and pathologic mitoses were readily observed (magnification, x400) (Fig. 3G). Necrosis, squamous cell metaplasia and psammoma bodies were also observed (Fig. 3H). The mass from the uterine endometrium exhibited well-differentiated EEC

that infiltrated the uterine myometrium to <1/2 the muscle layer (Fig. 2B), and the cervical wall was invaded to a depth of ~2/3 the layer. A proportion of the carcinomatous tissues featured microcystic, elongated and fragmented (MELF)

Table I. Immunohistochemical findings of various carcinoma components.

Antibody	Borderline mucinous epithelium region	Malignant Brenner tumor region	Uterine corpus endometrioid carcinoma
Pan-CK	P	P	P
EMA	P	P	P
ER	Focal P	N	P
PR	Focal P	N	P
VIM	P	P	P
CK7	P	P	P
CK5/6	N	P	N
P16	N	N	Focal P
CEA	N	N	Focal P
P53	Focal P	Focal P	Focal P
WT-1	N	N	N
UP-III	N	P	N
SF-1	N	P	N
P63	N	Weak P	N
PAX2	N	P	N
PAX8	N	P	P
CK20	N	N	N
SATB2	N	N	N
CDX2	N	N	N
SALL4	N	N	N
MDM2	N	P	N
C-myc	N	P	N
CyclinD1	N	P	N
EGFR	N	P	N
Ki67, %	20	70	50

P, positive; N, negative; Weak P, immunohistochemical staining was moderately positive; Focal P, positivity in <10%; Pax-2, paired box 2; SALL4, spalt-like transcription factor 4; SATB2, stabilin-2; SF-1, steroidogenic factor 1; EMA, epithelial membrane antigen; CK, cytokeratin; CDX2, caudal type homeobox 2; WT-1, Wilms' tumor protein-1; VIM, vimentin; UP-III, uroplakin III; MUC2, mucin 2; ER, estrogen receptor; PR, progesterone receptor.

myometrial invasion (Fig. 2C). It is important to note that the histomorphologic appearance of the mass on the cut surface of the cervical canal wall was identical to that of the adnexal mass (Fig. 2D) and the serosal surface was also infiltrated by the tumor. Although the right parauterine tissue and one lymph node from 15 resected right pelvic lymph nodes exhibited MBT metastasis, no tumor metastasis was detected in the resected lymph nodes from other regions.

Immunohistochemical findings. The immunohistochemical findings are summarized in Table I. Components of the MBT from the left and right adnexa (Fig. 4) were positive for the epithelial markers cytokeratin (CK), epithelial membrane antigen (EMA) and CK7, and for the urothelial marker Uroplakin III (UP-III). Tissues stained positive for steroidogenic factor 1 and weakly positive for p63, positive for CEA in a portion of the tumor, and positive for the molecular genetics-related proteins MDM2, C-myc, cyclin D1 and EGFR. The Ki67 hotspot index with respect to tumor cells was ~70% and tissues were negative for estrogen receptor (ER) and progesterone receptor (PR). Tissues were unreactive toward P16, P53 protein expression

was wild-type, and they were negative for the Müllerian duct markers paired box 2 (Pax-2), Pax-8 and germ cell source marker spalt-like transcription factor 4 (SALL4), as well as for the gastrointestinal markers stabilin-2, CK20, caudal type homeobox 2, mucin 2 (MUC2) and MUC6.

Components of the borderline mucinous tumors from the left and right adnexa were positive for EMA, CK7 and PAX8, and all markers for MBT were negative.

Regarding UEC components, ER, PR and vimentin antibodies reacted positively; furthermore, CK7 was positive with CEA being locally positive. In contradistinction, P16 and Wilms' tumor protein-1 (WT-1) markers were negative and P53 protein exhibited wild-type expression. The mismatch repair gene-related proteins MutL homolog 1 (MLH1), postmeiotic segregation increased 2 (PMS2), mutS homolog 2 (MSH2) and MSH6 were positive.

Pathologic diagnosis. The following observations were considered in the diagnosis: i) Bilateral ovaries: MBT with borderline mucinous tumor, invasion of uterine serosal surface, and cervical stroma and infiltration of vessels; ii) UEC grade I, invasion of
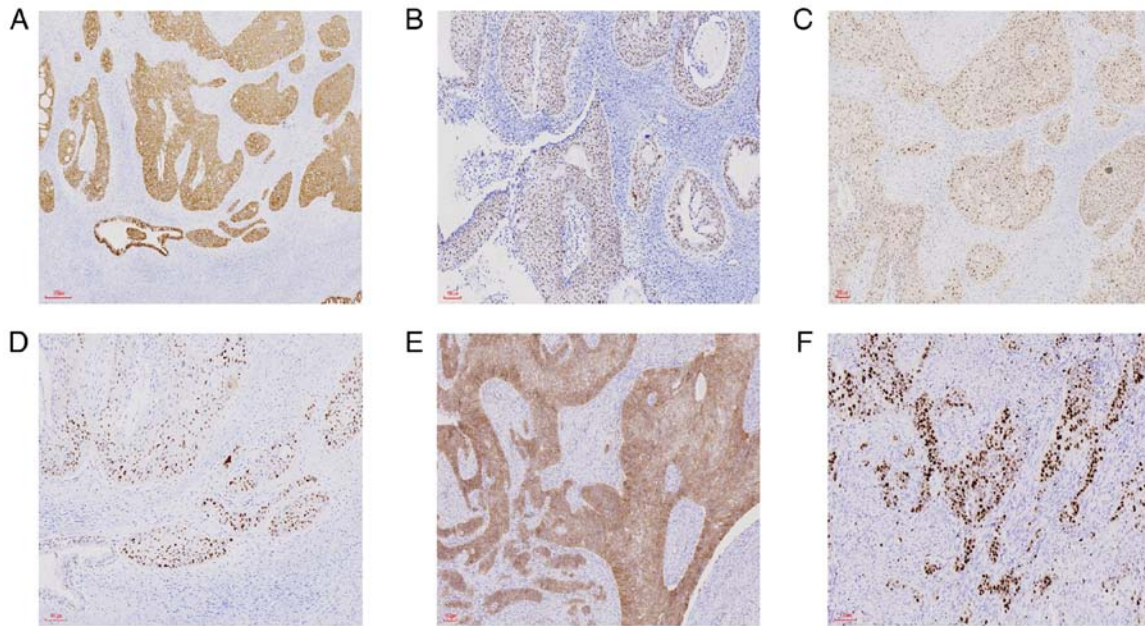
Figure 4. Immunohistochemical findings of bilateral ovarian malignant Brenner tumor components. The tissue stained positive for (A) epithelial marker cytokeratin 7 and (B) urothelial marker uroplakin-III. Molecular genetics-related proteins that included (C) MDM2, (D) cyclin D1 and (E) EGFR also reacted positively. (F) The Ki67 hotspot index for the tumor cells was ~70% (scale bars, 100 μm).

uterine wall <1/2 into the muscular layer, part of the tumor infiltrated the muscle layer in a MELF pattern, the cervical epithelium and stroma were involved and the cervical wall was infiltrated to a depth of <2/3 its thickness; iii) right parauterine tissue: MBT metastasis; iv) right pelvic lymph nodes: MBT metastasis (1/15).

The staging of the tumors was based on the American Joint Committee on Cancer (4) and the FIGO (5,6), as follows: i) MBT of ovary: pT3cN1M0, stage IIIC; and ii) UEC: T2N0M0, stage II (G1).

Postoperative treatment and follow-up. As MBT has a high degree of malignancy and metastasizes to parauterine tissues and pelvic lymph nodes, postoperative treatment is primarily focused on the MBT. The US 2021 National Comprehensive Cancer Network guidelines (7) recommend the use of paclitaxel + carboplatin or paclitaxel + carboplatin + bevacizumab for maintenance as the initial systemic treatment regimen for epithelial ovarian cancer stages II-IV. As bevacizumab may affect wound healing if applied less than two months after the operation, systemic treatment with paclitaxel + carboplatin regimen was initially adopted as an intravenous chemotherapeutic regimen. Follow-up by telephone was implemented with the patient for four months, the patient was treated at the hospital with chemotherapy twice and the patient is now undergoing radiotherapy and exhibiting disease-free survival for nearly one year.

Discussion

While synchronous primary cancers of the endometrium and ovary are common and endometrioid cancer may manifest in both areas (1,2), synchronous primary cancers of the UEC and ovarian MBT are relatively unusual (1,8). Furthermore, the coexistence of ovarian MBT and borderline mucinous cystadenoma combined with primary UEC is even rarer and no similar cases have been reported in the literature, to the best of our knowledge.

Abnormal uterine bleeding (particularly post-menopausal uterine bleeding) is etiologically associated with endometrial cancer in 10-30% of cases (9), and the clinical manifestations of MBT are similar to those of other malignant ovarian tumors, including abdominal distension, abdominal pain, ovarian mass and abnormal vaginal bleeding (10). The present case was clinically uncovered due to abnormal uterine bleeding and increased vaginal discharge, likely caused by endometrial cancer with potential involvement of MBT. Although UEC may be readily further examined by hysteroscopy and diagnosed by fractional curettage, MBT has nonspecific features (mostly cystic-solid masses of the ovary) and the diagnosis of MBT thereby requires surgical excision and detailed pathologic observations (10).

It is difficult to distinguish synchronous primary cancers from metastatic cancers, particularly for synchronous primary carcinomas of the same histologic subtype. In 1985, Ulbright and Roth (11) delineated a set of pathologic criteria to distinguish metastatic disease from synchronous primary tumors and Scully *et al* (12) subsequently described more detailed clinicopathologic features to differentiate the metastatic origin between the ovary and the endometrium. If the pathologic findings of the tumors in different bodily regions favor the characteristics of independent primary cancers, a diagnosis of synchronous primary cancers may then be made. In the present case, the diagnosis was straightforward, since the histologic tumor types between the ovaries and endometrium were distinct.

Identification of histologic tumor types is principally dependent upon histomorphologic characteristics of the tumors. Endometrioid carcinoma is the most common histotype of endometrial carcinoma and its histologic characteristics are well known (13). Endometrioid carcinoma is characterized by glandular structures lined by columnar/cuboidal cells with round/ovoidal pseudostratified nuclei and a smooth luminal surface; nuclear atypia is most commonly of low grade; and such histologic features were duly noted in the present case.

Furthermore, altered differentiation such as mucinous, squamous or morular are common and are used as confirmatory features of the endometrioid histotype (13). It is worth noting that the present endometrioid carcinoma case exhibited the typical pattern of MELF infiltration, which refers to the patterns of microencapsulated, elongated and fragmented infiltration in endometrioid carcinoma; however, its incidence is low and it is frequently observed in certain low-grade endometrial carcinomas with deep myometrial infiltration (14). Investigators have ascertained that MELF infiltration is frequently accompanied by lymph node invasion (15); thus, if this pattern of infiltration is observed, special attention should be paid to determine whether there is vascular involvement and lymph node metastasis (LNM). Benign BT, borderline BT and MBT microscopically resemble urothelium and its neoplasms (16), and <5% of all BTs are malignant and microscopically characterized by destructive stromal invasion (17). In 1963, Idelson (18) postulated diagnostic criteria to diagnose an MBT, which stipulated the following: i) The tumor cells conform to Brenner's morphologic characteristics; ii) benign and borderline Brenner areas are present, preferably exhibiting transitional changes; iii) the possibility of pseudomucinous cystadenocarcinoma or teratoma may be excluded; and iv) metastasis of urothelial carcinoma may also be excluded. It may be suggested that stromal invasion by epithelial elements of MBT is demonstrated and this is a current prerequisite according to the most recent World Health Organization (WHO) classification (17,19).

While UEC frequently arises from atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia [its recognized precancerous lesion (20)], the histologic origin of ovarian BT remains controversial. The historically proposed origins of BT have included ovarian surface epithelium, mesonephric remnant, rete ovarii, mucinous tumor and teratomas (3). However, more recent evidence indicates that ovarian BT is derived from a Walthard cell nest (a type of urothelial metaplasia) that is usually found within the normal ovaries and fallopian tubes (21); with Walthard nests located in 50% of patients with BT and 59% of patients with mucinous tumor (3). The ultrastructural presence of tumor cell cilia also indicates that BT is more likely to originate from Walthard cell nests (16). Thus, in clinical practice, if the mucous component is observed in the tissue slice, it may augur a diagnosis of BT.

Immunohistochemically, low-grade UEC normally expresses ER, PR, vimentin, CK7 and CEA; whereas p16 and WT-1 were not expressed and P53 protein exhibited wild-type expression (22). In addition, since MLH1, PMS2, MSH2 and MSH6 were all positive in the present case, this indicated that the function of mismatch repair proteins was not lost and that the patient was not a case of Lynch syndrome-associated endometrial carcinoma. BT features urothelial differentiation and reflects immunophenotypes similar to those of normal urothelium and Walthard cell nests, i.e. positivity for UP-III, CK7, GATA3 and S100 calcium binding protein (23). Although tumor stromal cells surrounding epithelial nests express calretinin, α-inhibin and SF1 in most benign BTs, there is a lack of expression of Müllerian markers such as PAX8 and PAX2 and reproductive markers such as SALL4. Of note, p63 protein that is required for urothelial differentiation is diffusely expressed in benign and borderline BT, but it is frequently weakly positive or negative in MBT, indicating that p63 is involved in the malignant transformation of MBT (19). Several studies suggested that p16 was expressed in benign BT and absent in atypical proliferative (borderline) BT, which may be associated with homozygous deletion of CDKN2A in atypical proliferative BT (24,25). In addition, malignant BT was strongly positive for cyclinD1, RAS and EGFR (corresponding with the molecular changes), and molecular expression rose commensurately with the degree of BT malignancy. It has been proposed that the combination of EGFR, RAS, cyclin D1, p16, Rb and p53 may be employed to distinguish benign BT from borderline/malignant BT (26).

Endometrioid carcinomas are typically associated with microsatellite instability and mutations in phosphatase and tensin homolog, β-catenin, K-RAS and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA) (27). With respect to BT, fluorescence *in situ* hybridization analysis identified CDKN2A (p16 coding gene) as homozygously deleted in the epithelial components of all borderline BT cases, but that CDKN2A remained in all patients with benign BT (24). The deletion of CDKN2A may thus have a critical role in the progression from benign BT to borderline BT (24). In addition, several somatic mutations in KRAS and PIK3CA were observed in ~30% of cases of borderline BT (24). The amplification of MDM2 and the cyclin D1 (CCND1) gene was confirmed by sequencing analysis in malignant BT (25).

In the present case, ovarian MBT was complicated by borderline mucinous cystadenoma. Studies have indicated that 25% of mucinous tumors contain Brenner components, 16% of BTs contain mucinous components and that Walthard nests have been detected in 50% of BTs and 59% of mucinous tumors (3). Furthermore, mucous epithelial components are frequently localized in BT nests and transitional cell components may be observed beneath the mucous epithelium; both exhibit similar patterns of calcification and distribution. The BT and mucinous tumors share similar immunohistochemical findings that include diffuse positivity for GATA3, and a lack of Müllerian-tube staining for PAX8 and PAX2 and the germ cell tumor marker Sall4 (28). These immunohistochemical changes are also consistent with the molecular genetic changes. Wang *et al* (29) performed a clonal analysis of two components of 10 tissues that contained synchronous BT and mucinous tumors by utilizing the human androgen receptor gene and found that in 8 out of 10 cases, the pattern of X-chromosome inactivation was identical between the two tumor components, revealing that they were of monoclonal origin (29). Tafe *et al* (30) also indicated that there was a 40-75% overlap between the BT and mucinous tumors, including a mutation in RAS and CDKN2A or an amplification of MYC, CDK4 or CCND1. Pejovic *et al* (31) demonstrated that both well-differentiated ovarian mucinous carcinoma and its coinciding BT featured 12q 14-21 amplification. In conclusion, it is likely that a specific relationship exists between the two cancers in terms of morphological, immunohistochemical and molecular changes, and it is indicated that mucinous carcinoma and BT may be monoclonally related. Certain authors have proposed that mucinous tumors may be formed by the transitional epithelium of the BT consolidating into mucinous epithelium through metaplastic modifications and the further proliferation of mucinous epithelium (32).

The primary differential diagnosis of low-grade endometrioid carcinoma is serous carcinoma; distinction between the two is important, as they differ in terms of prognosis and therapy (33). While patient features and tumor histology are useful in making a differential diagnosis, serous and low-grade endometrioid carcinomas may exhibit similar growth patterns, including glandular, papillary, micropapillary and solid forms; in addition, immunohistochemical staining (including that for p53 and p16) may be conducive to making this distinction (33). Loss of mismatch-repair proteins in cancer tissue or in Lynch syndrome-associated adenocarcinoma suggests EEC. In the 2020 classification from the WHO (34), increased emphasis is now put on The Cancer Genome Atlas molecular typing of endometrial cancer so as to predict prognosis rather than only its histologic type. When the histologic tumor type remains uncertain, application of Gilks' binary grading system may provide more useful prognostic information compared with FIGO grading (33). The primary differential diagnosis with respect to MBT is transitional cell carcinoma (TCC), and while they reflect similar morphologic features and immunohistochemical phenotypes, the two grading systems also possess numerous disparities. In a previous study, imaging and gross examination suggested that TCC lacked the common calcification of MBT and that MBT was more commonly expressed at stage I without extraovarian spread, while ~69% of ovarian TCC was diagnosed in the advanced stage (35). Microscopically, although TCC was not accompanied by benign BT or borderline BT components, it exhibited obvious malignant features. TCC usually has diffuse strong immunoreactivity for p16, Rb and p53, while MBT is negative. In BT, the expression of EGFR, RAS and CCND1 is concomitantly elevated with the increase in the degree of malignancy, but this phenomenon is lacking in TCC. There are also numerous differences in molecular changes; for instance, a p53 gene mutation is prominently observed in TCC (36).

Determining the appropriate treatment modality for patients diagnosed with synchronous primary endometrial and ovarian cancer depends upon the grade and stage of tumors in each topographic location (37). In the present study, surgery was first performed, followed by adjuvant treatment in the form of chemotherapy or radiotherapy according to tumor stage. If diagnosed as stage IA, no additional treatment was required after surgery; if diagnosed as IIIA or II, additional treatment was required (37). The final diagnosis of the present case was stage IIIC of MBT in the ovary and stage II of UEC, and therefore, radiotherapy was performed after chemotherapy. It was previously demonstrated that the use of a platinum-based chemotherapeutic agent plus paclitaxel post-operatively improved patient survival (38). In the present study, it was indicated that MDM2 amplification was associated with MBT and that MDM2 may therefore be selected in the future as a drug target for patients with MBT (39).

It has been reported that tumors with endometrioid histologic features at both sites have a favorable prognosis, while non-endometrioid tumor morphologies at both sites share a poor prognosis (2). In one study, the histopathologic type of the ovarian cancer component, stage of endometrial cancer and level of CA125 at diagnosis have been observed to have a great influence on the development of recurrence and survival of synchronous primary carcinomas of the endometrium and ovary (40). Therefore, it may be posited that MBT in ovaries is a primary determining factor of prognosis with respect to the present case. It is generally conjectured that the prognosis of MBT is favorable, with a five-year survival rate of MBT confined to the ovaries of 94.5%; however, the rate involving extraovarian tissues was determined to be 51.3% (19). It was also reported that in patients with extrauterine metastasis, such as that to the dura mater, lung, peritoneum, omentum, skin and bone, the recurrence rate was 28% (19), and the average recurrence time for MBT was 11 months (41). LNM of MBT is not common and it is revealed in only 5.1% of patients, and when it does occur, lymphadenectomy exerts no effect on the improvement in the five-year survival rate of MBT (19). Although CA-125 is not specific and its concentration is not related to the malignant degree of a tumor, ~70% of patients with MBT have elevated CA-125 levels. Therefore, CA-125 remains the most important tumor marker for the post-treatment monitoring of disease recurrence (19,41).

Availability of data and materials

All of the data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YC and CZ conceived and designed the study and wrote the original manuscript. QL and JZ analyzed data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. YC , CZ and QL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and its accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Matsuo K, Machida H, Blake EA, Holman LL, Rimel BJ, Roman LD and Wright JD: Trends and outcomes of women with synchronous endometrial and ovarian cancer. Oncotarget 9: 28757-28771, 2018.

2. Soliman PT, Slomovitz BM, Broaddus RR, Sun CC, Oh JC, Eifel PJ, Gershenson DM and Lu KH: Synchronous primary cancers of the endometrium and ovary: A single institution review of 84 cases. Gynecol Oncol 94: 456-462, 2004.
3. Seidman JD and Khedmati F: Exploring the histogenesis of ovarian mucinous and transitional cell (Brenner) neoplasms and their relationship with Walthard cell nests: A study of 120 tumors. Arch Pathol Lab Med 132: 1753-1760, 2008.
4. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, *et al* (eds). AJCC cancer staging manual. 8th edition. Springer, New York, NY, 2017.
5. Zeppernick F and Meinhold-Heerlein I: The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. Arch Gynecol Obstet 290: 839-842, 2014.
6. Soslow RA, Tornos C, Park KJ, Malbica A, Matias-Guiu X, Oliva E, Parkash V, Carlson J, McCluggage WG and Gilks CB: Endometrial carcinoma diagnosis: Use of FIGO grading and genomic subcategories in clinical practice: Recommendations of the international society of gynecological pathologists. Int J Gynecol Pathol 38 (Suppl 1): S64-S74, 2019.
7. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Barroilhet L, Behbakht K, Berchuck A, Chen LM, Cristea M, DeRosa M, Eisenhauer EL, *et al*: Ovarian cancer, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 19: 191-226, 2021.
8. Krepinska E, Kriz JT and Laco J: Endometroid adenocarcinoma of the uterus, borderline tumor of the ovary and Brenner tumor of the contralateral ovary in a 63-year-old woman. Eur J Gynaecol Oncol 31: 584-585, 2010.
9. Izetbegovic S, Stojkanovic G, Ribic N and Mehmedbasic E: Features of postmenopausal uterine haemorrhage. Med Arch 67: 431-434, 2013.
10. King L, Gogoi RP, Hummel C and Smith A: Malignant Brenner tumor: Two case reports. Case Rep Womens Health 20: e00082, 2018.
11. Ulbright T and Roth L: Metastatic and independent cancers of the endometrium and ovary: A clinicopathologic study of 34 cases. Hum Pathol 16: 28-34, 1985.
12. Scully RE, Young RH and Clement PB: Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. In: Atlas of tumor pathology. Armed Forces Institute of Pathology, Bethesda, MD, 1998.
13. Santoro A, Angelico G, Travaglino A, Inzani F, Arciuolo D, Valente M, D'Alessandris N, Scaglione G, Fiorentino V, Raffone A and Zannoni GF: New pathological and clinical insights in endometrial cancer in view of the updated ESGO/ESTRO/ESP guidelines. Cancers (Basel) 13: 2623, 2021.
14. Stewart CJ, Brennan BA, Leung YC and Little L: MELF pattern invasion in endometrial carcinoma: Association with low grade, myoinvasive endometrioid tumours, focal mucinous differentiation and vascular invasion. Pathology 41: 454-459, 2009.
15. Pavlakis K, Messini I, Vrekoussis T, Panoskaltsis T, Chrysanthakis D, Yiannou P and Voulgaris Z: MELF invasion in endometrial cancer as a risk factor for lymph node metastasis. Histopathology 58: 966-973, 2011.
16. Kuhn E, Ayhan A, Shih IeM, Seidman JD and Kurman RJ: Ovarian Brenner tumour: A morphologic and immunohisto-chemical analysis suggesting an origin from fallopian tube epithelium. Eur J Cancer 49: 3839-3849, 2013.
17. Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, Hauptmann S and Sehouli J: The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Arch Gynecol Obstet 293: 695-700, 2016.
18. Idelson MG: Malignancy in Brenner tumors of the ovary, with comments on histogenesis and possible estrogen production. Obstet Gynecol Surv 18: 246-267, 1963.
19. Nasioudis D, Sisti G, Holcomb K, Kanninen T and Witkin SS: Malignant Brenner tumors of the ovary; a population-based analysis. Gynecol Oncol 142: 44-49, 2016.
20. Albertini AF, Devouassoux-Shisheboran M and Genestie C: Pathology of endometrioid carcinoma. Bull Cancer 99: 7-12, 2012.
21. Zheng R and Heller DS: Borderline Brenner tumor: A review of the literature. Arch Pathol Lab Med 143: 1278-1280, 2019.
22. Geels YP, van der Putten LJ, van Tilborg AA, Lurkin I, Zwarthoff EC, Pijnenborg JM, van den Berg-van Erp SH, Snijders MP, Bulten J, Visscher DW, *et al*: Immunohistochemical and genetic profiles of endometrioid endometrial carcinoma arising from atrophic endometrium. Gynecol Oncol 137: 245-251, 2015.
23. Kondi-Pafiti A, Kairi-Vassilatou E, Iavazzo Ch, Vouza E, Mavrigiannaki P, Kleanthis Ch, Vlahodimitropoulos D and Liapis A: Clinicopathological features and immunoprofile of 30 cases of Brenner ovarian tumors. Arch Gynecol Obstet 285: 1699-1702, 2012.
24. Kuhn E, Ayhan A, Shih IeM, Seidman JD and Kurman RJ: The pathogenesis of atypical proliferative Brenner tumor: An immunohistochemical and molecular genetic analysis. Mod Pathol 27: 231-237, 2014.
25. Wang L, Allison D and Shukla PS: Amplification of MDM2 and loss of p16 expression: Do they have a role in malignant transformation of ovarian Brenner tumor? Am J Clin Pathol 154: 133-141, 2020.
26. Albu DF, Albu CC, Gogănău AM, Albu ŞD, Mogoantă L, Edu A, DiŢescu D and Văduva CC: Borderline Brenner tumors associated with ovarian cyst-case presentation. Rom J Morphol Embryol 57 (Suppl 2): 893-898, 2016.
27. Llobet D, Pallares J, Yeramian A, Santacana M, Eritja N, Velasco A, Dolcet X and Matias-Guiu X: Molecular pathology of endometrial carcinoma: Practical aspects from the diagnostic and therapeutic viewpoints. J Clin Pathol 62: 777-785, 2009.
28. Roma AA and Masand RP: Different staining patterns of ovarian Brenner tumor and the associated mucinous tumor. Ann Diagn Pathol 19: 29-32, 2015.
29. Wang Y, Wu RC, Shwartz LE, Haley L, Lin MT, Shih IeM and Kurman RJ: Clonality analysis of combined Brenner and mucinous tumours of the ovary reveals their monoclonal origin. J Pathol 237: 146-151, 2015.
30. Tafe LJ, Muller KE, Ananda G, Mitchell T, Spotlow V, Patterson SE, Tsongalis GJ and Mockus SM: Molecular genetic analysis of ovarian Brenner tumors and associated mucinous epithelial neoplasms: High variant concordance and identification of mutually exclusive RAS driver mutations and MYC amplification. Am J Pathol 186: 671-677, 2016.
31. Pejovic T, Bürki N, Odunsi K, Fiedler P, Achong N, Schwartz PE and Ward DC: Well-differentiated mucinous carcinoma of the ovary and a coexisting Brenner tumor both exhibit amplification of 12q14-21 by comparative genomic hybridization. Gynecol Oncol 74: 134-137, 1999.
32. Rodríguez IM and Prat J: Mucinous tumors of the ovary: A clinicopathologic analysis of 75 borderline tumors (of intestinal type) and carcinomas. Am J Surg Pathol 26: 139-152, 2002.
33. Garg K and Soslow RA: Strategies for distinguishing low-grade endometrioid and serous carcinomas of endometrium. Adv Anat Pathol 19: 1-10, 2012.
34. Berek JS, Friedlander M and Hacker NF: Endometrial cancer. In: Berek and Hacker's gynecologic oncology. Berek JS and Hacker NF (eds). 7th edition. Wolters Kluwer Health, Philadelphia, PA, 2020.
35. Austin RM and Norris HJ: Malignant Brenner tumor and transitional cell carcinoma of the ovary: A comparison. Int J Gynecol Pathol 6: 29-39, 1987.
36. Cuatrecasas M, Catasus L, Palacios J and Prat J: Transitional cell tumors of the ovary: A comparative clinicopathologic, immunohistochemical, and molecular genetic analysis of Brenner tumors and transitional cell carcinomas. Am J Surg Pathol 33: 556-567, 2009.
37. Shin W, Park SY, Kang S, Lim MC and Seo SS: How to manage synchronous endometrial and ovarian cancer patients? BMC Cancer 21: 489, 2021.
38. Han JH, Kim DY, Lee SW, Park JY, Kim JH, Kim YM, Kim YT and Nam JH: Intensive systemic chemotherapy is effective against recurrent malignant Brenner tumor of the ovary: An analysis of 10 cases within a single center. Taiwan J Obstet Gynecol 54: 178-182, 2015.
39. Shetty S, Habeeb O, Rivera C, Astbury C, Przybycin C and Joehlin-Price AS: MDM2 amplification in malignant Brenner tumors may play a role in progression to malignancy and aid in separation from urothelial and other ovarian carcinomas. Hum Pathol 117: 42-50, 2021.
40. Sozen H, Vatansever D, Iyibozkurt AC, Topuz S, Ozsurmeli M, Salihoglu Y, Guzelbey B and Berkman S: Clinicopathologic and survival analyses of synchronous primary endometrial and epithelial ovarian cancers. J Obstet Gynaecol Res 41: 1813-1819, 2015.
41. Lang SM, Mills AM and Cantrell LA: Malignant Brenner tumor of the ovary: Review and case report. Gynecol Oncol Rep 22: 26-31, 2017.