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Synchronous endometrial and ovarian cancer: A case report

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Abstract

BACKGROUND

Synchronous endometrial and ovarian cancer (SEOC) is a rare genital tract tumor. Precise diagnosis is crucial for the disease management since prognosis and overall survival differ substantially between metastatic endometrial cancer (EC) or OC. In this review we present 2 cases of women who were diagnosed with SEOC, and discuss the clinical characteristic of SEOC, diagnostic and molecular profiling issues. Next generation sequencing of 10 gene panel was performed on cancerous tissue and uterine lavage samples.

CASE SUMMARY

In our report patients with SEOC had endometroid type histology with early stage and low-grade histology for both EC and OC. They underwent surgical treatment and staging. Next-generation sequencing of 10 gene-panel identified *CTNNB1*, *PIK3CA*, and *PTEN* gene mutations in ovarian tissue in one case, while none of these genes were mutated in other case. Literature review in support to our data suggest a good prognosis for SEOC diagnosed at early stage.

CONCLUSION

Accurate diagnosis of SEOC is essential for disease management and gene mutation analysis can be helpful as a complementary diagnostic and prognostic tool.

Key Words: Ovarian cancer; Endometrial cancer; Synchronous primary cancer; Uterine lavage; Case report

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Core Tip: Synchronous gynecological tumors are a rare entity. The most common synchronous tumor is synchronous endometrial and ovarian cancer (SEOC). The importance of distinguishing SEOC from either isolated endometrium or ovarian cancer with metastasis is crucial, as it determines management and prognosis. When molecular testing was carried out for SEOC cases, a large proportion was found to be metastatic disease. Testing of vimentin, molecular analyses of gene mutation of *CTNNB1*, *Paired box gene 8*, *β-catenin* expression may be helpful to categorize SEOC in cases where clinical and pathological parameters are inconclusive.

INTRODUCTION

Synchronous gynecological malignant tumor is a rare entity. Synchronous endometrial and ovarian cancer (SEOC) is the most common, accounting for 50%-70% of all synchronous tumors. SEOC is described as the simultaneous presence of ovarian cancer (OC) and endometrial cancer (EC) at the same time of diagnosis. The rate of SEOC is approximately 3%-10%, 5% occur in patients with EC and 10% in patients with OC. Endometrioid histological type of EC is significantly associated with increased risk of secondary primary OC with endometrioid histology. Also, OC with endometroid histology diagnosed under the age of 50 can be associated with loss of mismatch repair genes expression, Lynch syndrome and other genetic mutations. In these patients, the risk of synchronous primary malignancy is higher. Up to 86% of SEOC have concordant endometrioid histology in the two cancer sites[1-4].

For more than 20 years histological criteria by Ulbright and Roth have been used to distinguish metastatic cancer from double primary cancer[5]. Criteria for SEOC diagnosis were first documented in 1981 and refined substantially in 1998[6,7]. The Scully criteria are based on histologic similarity, size, the presence of precursor lesions, location, and invasion pattern. Later, several authors have proposed methods of molecular analysis for precise SEOC diagnostic, but no consensus has been reached yet. Sometimes it is complicated to distinguish between SEOC and metastatic cancer (metastasis from endometrium to the ovary or ovary to the endometrium), but it is highly significant for proper treatment strategy selection. As SEOC is uncommon, it can be misdiagnosed as FIGO stage III of EC or FIGO stage II of OC. When histology of two tumors is discordant, the diagnosis of SEOC is less complicated, but dilemma occurs for concordant histologic types. The treatment management and overall survival differs significantly from SEOC and metastatic disease. Recent evidence has suggested that criteria by Ulbright and Roth for SEOC diagnostics may not always be applicable. When molecular testing was carried out for SEOC cases, a large proportion was found to be metastatic disease[8-12]. Molecular analyses of gene mutation of *CTNNB1*, *TP53*, *KRAS*, *PIK3CA*, and *PTEN* as well as microsatellite instability, β-catenin expression may be helpful to categorize SEOC in cases where clinical and pathological parameters are inconclusive[13]. In problematic cases molecular analysis of tumor foci may facilitate the precise diagnosis and identify the cell of origin, while mutation analysis in liquid biopsy has potential for early cancer detection.

In present study, next generation sequencing of 10 genes in DNA from uterine lavage and ovarian tissue samples from two cases with SEOC was performed aiming at improved understanding of the molecular profile of these rare tumors and evaluation of rationality of uterine lavage based genetic in SEOC diagnostics.

CASE PRESENTATION

Chief complaints

I clinical case: A 54-year-old, menopausal (gravida 0, para 0) woman presented with lower abdominal pain.

II clinical case: A 45-year-old woman (gravida 1, para 1) arrived to National Cancer Institute of Lithuania with histologically confirmed uterine cancer with no complaints.

History of present illness

I clinical case: The complaints lasted for last six months.

II clinical case: Hysteroscopy was performed because endometrial polyp was detected by ultrasound. Final histology confirmed well differentiated (G1) endometrioid endometrial cancer.

History of past illness

I cinical case: There were no other comorbidities, body mass index (BMI) 22.4 kg/m^2.

II clinical case: There were no comorbidities, she had a BMI of 27.8 kg/m^2.

Personal and family history

I clinical case: Her medical and family histories were unremarkable for any type of cancer.

II clinical case: There were no history of malignancy in the family.

Physical examination

I clinical case: The clinical examination revealed mobile pelvic mass 15 cm in diameter which was extended till the umbilicus. Pelvic ultrasound examination identified: Thickened endometrium up to 11 mm and left adnexal multilocular cystic tumor with papillary structures. Computed tomography (CT) scan of the thorax, abdomen and pelvis revealed left cystic ovary mass approximately 136 mm × 114 mm × 114 mm in size with several septum and papillary component.

II clinical case: On clinical examination left adnexal mass was identified. Transvaginal ultrasound showed normal sized uterus with endometrial thickness of 6 mm, and 7 cm × 8 cm left adnexal solid mass with mixed echogenicity and cystic inclusion, right ovary cyst up to 3 cm is likely to be functional cyst. Magnetic resonance imaging of the abdominal and pelvis showed irregularly shaped, solid, left adnexal mass up to 60 mm × 77 mm × 80 mm, suspected paraaortic and iliac lymph nodes.

Laboratory examinations

I clinical case: Cancer antigen 125 was evaluated 209 U/mL (normal range < 35 U/mL).

II clinical case: Cancer antigen 125 was not evaluated 32 U/mL (normal range < 35 U/mL).

Imaging examinations

I clinical case: Figure 1 shows hematoxylin-eosin stains of the endometrial and Figure 2 shows ovarian tumor specimens. Peritoneal cytological washing and additional peritoneal biopsies, as well as lymph nodes, were negative for malignant cells. Haematoxylin and eosin (H&E)-stained slide at low power (lens objective × 4) shows closely packed irregular glandular structures. H&E-stained slide at medium power (lens objective × 14) shows columnar epithelium with oval, stratified nuclei and visible nucleoli (Figure 1A and B). H&E-stained slide at low power (lens objective × 4) shows closely packed irregular glandular structures and focal solid growth. H&E-stained slide at medium power (lens objective × 14) shows tumor composed of moderate amount of eosinophilic cytoplasm with slightly polymorphous nuclei and visible nucleoli (Figure 1C and D).

II clinical case: Figure 2A and B shows hematoxylin-eosin stains of the endometrial and Figure 3A and B shows ovarian tumor specimens. H&E-stained slide at low power (lens objective × 4) shows closely packed irregular glandular structures. H&E-stained slide at

medium power (lens objective × 14) shows tall columnar epithelium with oval, stratified nuclei with visible nucleoli (Figure 2A and B).

H&E-stained slide at low power (lens objective × 4) shows closely packed irregular glandular structures with focal necrosis. H&E-stained slide at medium power (lens objective × 14) shows columnar epithelium with oval, stratified nuclei, and visible nucleoli (Figure 2C and D).

FINAL DIAGNOSIS

I clinical case

On final histological result: Pathological findings revealed a well-differentiated (G1) endometrioid carcinoma of the uterus without myometrial invasion and a moderately-differentiated (G2) endometrioid tumor limited to left ovary. Figure 1A and B shows hematoxylin-eosin stains of the endometrial and Figure 1C and D shows ovarian tumor specimens. Peritoneal cytological washing and additional peritoneal biopsies, as well as lymph nodes, were negative for malignant cells. Lymphovascular invasion was not seen. The final diagnosis of synchronous FIGO IA endometrioid grade 2 ovarian carcinoma and FIGO IA grade 1 endometrial carcinoma was made.

II clinical case

Histological examination confirmed well-differentiated endometrioid (G1) tumor limited to left ovary and a well-differentiated (G1) endometrioid carcinoma of the uterus without myometrial invasion. Figure 2A and B shows hematoxylin-eosin stains of the endometrial and Figure 2C and D shows ovarian tumor specimens. Peritoneal cytological washing and biopsies, as well as lymph nodes, were negative for malignant cells. The final diagnosis of synchronous FIGO IA endometrioid grade 1 ovarian carcinoma and FIGO IA grade 1 endometrial carcinoma was made. Lymphovascular invasion was not seen.

TREATMENT

I clinical case

The patient underwent an exploratory laparotomy, frozen section of ovarian tumors was highly suggestive of malignancy. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, omentectomy, selective peritonectomy were conducted.

II clinical case

The patient underwent surgical staging: Hysterectomy with bilateral salpingo-oophoarectomy, peritoneal biopsy, pelvic and para-aortic lymph node dissection.

OUTCOME AND FOLLOW-UP

I clinical case

To gain insight into the tumor biology, uterine lavage and ovarian tissue samples were sequenced using custom targeted 10 gene panel which included genes commonly associated with ovarian and endometrial cancers: *TP53*, *BRCA1*, *BRCA2*, *PIK3CA*, *KRAS*, *PTEN*, *ARID1A*, *CTNNNB1*, *FBXW7*, and *PPP2R1A*. No pathogenic mutations were detected in uterine lavage or tissue sample. After surgery, six cycles of chemotherapy of Carboplatin were performed. Patient was disease-free at 44 mo of follow-up.

II clinical case

As in previous case, uterine lavage and ovarian tissue samples were sequenced using custom targeted 10 gene panel. In ovarian tissue sample, somatic mutations of *PIK3CA* and *PTEN* were detected. Moreover, tumor sample had a mutation in β-catenin gene *CTNNB1.* No mutations were found in uterine lavage sample, showing low spread of cancerous cells. Mutation profile for both cases are shown in Table 1 No adjuvant treatment was considered. The patient is disease-free at 42 mo of follow-up.

DISCUSSION

SEOC is a rare variant of gynecological cancers. Usually, SEOC appears with different clinical characteristics compared to patients with EC or OC alone. SEOC is observed

among the younger age women under 55 years and 40% of them are nulliparous. In most cases it can be diagnosed at an early stage and is associated with low-grade disease. The endometrioid subtype of the primary tumors is the most common histological finding with the rate of 50%-70% of cases. In our report, both women with SEOC had endometrioid histological type. The most common symptom of SEOC is abnormal uterine bleeding and pelvic pain due to the pelvic mass[9,11].

The importance of distinguishing SEOC from either isolated endometrium or ovarian cancer with metastasis is crucial, as it determines adjuvant treatment strategy and prognosis. The prognosis of patients with synchronous EC and OC is better than the patients with single-organ cancer with ovarian or endometrial spread. Median 5-year progression free survival rate is reported to be 65% for SEOC but is less than 50% for FIGO stage IIIA EC with ovarian spread. If SEOC is diagnosed in early stage the overall survival rate is excellent- up to 90%, in contrast to the poor prognosis noted in metastatic disease[1,2,4,13]. Both patients in our report were diagnosed with low grade endometrioid carcinomas of the ovary and uterus and are still alive more than 2 years after treatment. Based on histological findings alone, concurrent uterine and ovarian endometrioid carcinomas are considered synchronous primaries, when all of the following criteria are met: Both tumors are low grade (FIGO 1 or 2); less than 50% of myometrial invasion is present; ovarian tumor is unilateral, limited to parenchyma and no other site is involved in a malignant process; extensive lymphovascular invasion is absent at any location.

To determine cancer origin accurately, advancement of immunohistochemistry andmolecular testing is needed. According to literature it is suggested that immunohistochemistry testing of vimentin can be carried out. Desouki *et al*[14] suggested that a negative stain has a sensitivity and specificity to predict primary OC at 97% and 82%, while positive vimentin staining had an 82% sensitivity and 97% specificity in predicting EC. Another study used different antibodies (ER, PR, HER2, p53, and Ki-67) and they found that ER, PR, BCL2 showed different immunostaining patterns between EC and OC and suggested that they can be used as a surrogate marker in the distinction of these tumors[15]. However, the practical meaning of immunohistochemistry in this

setting is still the matter of debate due to SEOC heterogeneity and clonality. Immunohistochemical analysis of hormone receptors and markers is not always helpful, because they did not allow a comprehensive evaluation and comparison of possible clonal origin.

Molecular studies of SEOC used variable approaches-mutation analysis of single or group of genes, microsatellite instability (MSI), loss of heterozygosity[16-20]. Clonality of SEOCs can be confirmed by sequencing different genes using next-generation sequencing. Paired box gene 8 (*PAX8*) is a marker that can be useful in distinguishing between EC and OC, because primary OC express *PAX-8* but not EC metastases[18]. Nuclear localization of β-catenin and presence of *CTNNB1* mutations are associated with SEOC. Irving *et al*[21] identified that *CTNNB1* mutations were restricted to SEOC and were absent in all the metastatic tumors, providing direct evidence for a divergence of molecular oncogenetic mechanisms in the subset of SEOC. Genetic classification of SEOC *vs* metastatic tumors based on β-catenin expression/mutation correlates with clinical outcome, but screening of the tumor suppressor genes may be labor-intensive and expensive. Other studies analyze the DNA mismatch repair protein (MMR) expression in SEOC in comparison with the expression of these proteins in Lynch syndrome. The results of these studies showed that majority of SEOCs are sporadic cancers, but patients with endometrioid or clear cell OC under the age of 53 have higher risk for loss of MMR (MLH1, MSH2, MSH6) expression and Lynch syndrome[16,22]. Kobayashi *et al*[23] reported that the frequency of MSI in SEO was 24%, which is comparable to the frequency of endometrial cancer. In our report, none of the patients had a medical history of Lynch syndrome or other hereditary cancers.

Molecular profiling also can be beneficial for prognostic and predictive meaning. Studies analyzing SEOC mutational profiles identified *PI3KCA*, *PTEN*, *KRAS*, *CTNNB1*, and *ARID1A* gene mutations can be helpful for diagnostic of SEOC[16,22-28]. The study by Reijnen *et al*[22] comparing 50 SEOC cases with metastatic EC, OC and TCGA mutation data, showed that mutational profile of SEOC harbored a profoundly different molecular profile compared to metastatic disease. SEOC were enriched for *PTEN* and *CTNNB1*

mutations and *TP53* was mutated less frequently in SEO than in ovarian metastatic cases. Although, SEOC closely resembles endometrial EC, but with slightly less frequent *ARID1A* mutations. In the endometrioid SEO subgroup, *PTEN* mutations were identified in 72% of ovarian tissue and in 75% of endometrial tissue. In contrast, *PTEN* mutations are less common in endometrioid OC, with prevalence only 17%. In endometrioid endometrial carcinomas *PTEN* mutation was found in 67% of cases[22]. Other studies also found frequent mutation of *CTNNB1* in SEOC cases[22]. In our molecular analysis, one case was identified with mutations of the *CTNNB1*, *PIK3CA*, and *PTEN* genes, which are frequently detected in SEOC. Other case Mutation frequency from TCGA database and the crosstalk between PI3K/AKT and WNT pathways are visualized in Figure 3, showing possible molecular mechanism of SEOC development. No mutations were identified in other SEOC case in our study, showing further need of genome-wide analysis for improved understanding of molecular origins of these rare tumors.

CONCLUSION

SEOC predominantly occurs in younger premenopausal women. The identification of SEOC or metastatic endometrium/ovarian disease have great clinical significance, as the disease management, prognosis and overall survival differ. Precise diagnosis of SEOC may require additional molecular or IHC testing in addition to routine histopathologic assessment. According to literature review testing of vimentin, molecular analyses of gene mutation of *CTNNB1*, *PAX8*, and *β-catenin* expression may be helpful to categorize SEOC in cases where clinical and pathological parameters are inconclusive. Our two cases do not show that uterine lavage was suitable diagnostic test for SEOC, but further investigation is needed, and additional disease-specific biomarkers need to be discovered.

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Figure Legends

Figure 1 Haematoxylin and eosin staining in case I. A: Haematoxylin and eosin (H&E)-stained slide at low power (lens objective × 4) shows closely packed irregular glandular structures; B: H&E-stained slide at medium power (lens objective × 14) shows columnar epithelium with oval, stratified nuclei and visible nucleoli; C: H&E-stained slide at low power (lens objective × 4) shows closely packed irregular glandular structures and focal solid growth; D: H&E-stained slide at medium power (lens objective × 14) shows tumor composed of moderate amount of eosinophilic cytoplasm with slightly polymorphous nuclei and visible nucleoli.

Figure 2 Haematoxylin and eosin staining in case II. A: Haematoxylin and eosin-stained (H&E) slide at low power (lens objective × 4) shows closely packed irregular glandular structures; B: H&E-stained slide at medium power (lens objective × 14) shows tall columnar epithelium with oval, stratified nuclei with visible nucleoli; C: H&E-stained slide at low power (lens objective × 4) shows closely packed irregular glandular structures with focal necrosis; D: H&E-stained slide at medium power (lens objective × 14) shows columnar epithelium with oval, stratified nuclei, and visible nucleoli.

Figure 3 Crosstalk of PI3K/AKT and WNT pathways in synchronous endometrial and ovarian. Both pathways converge at glycogen synthase kinase-3 beta (GSK3β): In PI3K/AKT pathway, activation of PI3K is required for AKT activation and downstream signaling. PTEN acts as deactivator of PI3K pathway. AKT also phosphorylates and inactivates GSK3β. Meanwhile in WNT signaling GSK3β/Axin complex is required for β-catenin phosphorylation and degradation. The numbers indicate TCGA published mutation data form uterine (right side data) and ovarian (left side data) cancers. Figure generated using PathwayMapper tool. GSK3β: Glycogen synthase kinase-3 beta

Table 1 Mutational profile of synchronous endometrial and ovarian cancer case 2

Gene	Uterine lavage mutation	Tissue mutation	dbSNP	Amino acid change
PIK3CA	-	c.1093G>A	rs1064793732	p.Glu365Lys
PTEN	-	c.517C>T	rs121913293	p.Arg173Cys
CTNNB1	-	c.101G>A	rs28931589	p.Gly34Glu

dbSNP: Single-Nucleotide Polymorphism database.

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