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Non-endometrioid Synchronized Endometrial and Ovarian Carcinoma: Report of Two Rare Cases

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Abstract

Objectives: Synchronized endometrial and ovarian cancer (SEOC) is a condition in which there is both primary endometrial and primary ovarian cancer at the same time in a patient. These tumors have a better prognosis than metastatic ones. Most of them are diagnosed in the early stages and are low-grade tumors. So differentiation of this kind of rare tumor from others is essential. No adjuvant chemotherapy seems to be reasonable in cases with low-grade tumors both in endometrioid and non-endometrioid types. High-grades tumors have been described less, but, in some studies, genetic mutations were found in these tumors, which have been the basis of targeted therapy after surgery.

Case Presentation: In this report, two rare non-endometrioid types of SEOC cases are discussed. The first case is a low-grade papillary serous carcinoma of the ovary and uterus endometrium. In contrast, the second case is a clear cell carcinoma of the ovary and endometrioid adenocarcinoma of the uterus. We also review the literature in this field.

Conclusion: We conclude that in these cases, chemotherapy with routine regimens does not seem to be helpful in early stages with low-grade tumors. Also, in high-grade tumors, targeted therapy may be more effective than adjuvant chemotherapy.

Keywords: Papillary serous carcinoma, Clear cell carcinoma, synchronized endometrial, Ovarian cancer

Introduction

Synchronized endometrial and ovarian cancer (SEOC) is uncommon. But it is important to differentiate this special cancer category from metastatic types since most SEOC tumors have a better prognosis than metastatic forms (1). When the simultaneous and secondary involvement is due to metastasis of the primary tumor, the primary tumor is a high-risk type that can spread. There are diagnosis criteria which used to differentiate synchronized primary tumors and metastatic tumors, including dissimilar histopathology of the two tumors (ovary and ondometer), no invasion or superficial invasion to the myometrium layer, no vascular invasion, unilateral involvement of the ovary, no ovarian surface involvement, no evidence of extra ovarian implantation, evidence of endometriosis accompanying with tumoral tissue, evidence in favor of endometrial hyperplasia accompanying with tumoral tissue, no molecular similarity of the tumors and no similarity in DNA ploidy of the tumors (2,3). Although all SEOC tumors do not fill all of the diagnostic criteria, more than 60% of them have the diagnostic concordance (4). The most common spreading pattern of ovarian cancer is the transcoelomic way, through which the cancer cells spread and fill all of the peritoneal cavity. Endometrial cancer cells tend to spread to the surrounding tissue as a local invasion (5). So adjuvant modalities after surgery are recommended to prevent a recurrence. But in SEOC, the spreading pattern is different and almost like what is seen in borderline ovarian tumors. Cells in SEOC are removed from the primary tumor and enter into the other microscopic spaces without apoptosis, which is spread to an exclusive micro-environment.

Recently, only surgery and removal of all microscopic tumor tissue is enough to control cancer in SEOC (6). Therefore, differentiation between SEOC and metastatic types is significant. But there has not been any unique guideline so far for treating this specific tumor. On the other hand, there are rare cases whose treatment faces a considerable challenge.

In this study, two cases of SEOC with controversial treatments are presented. In the first case, we will introduce a scarce case of Low-grade papillary serous carcinoma of the endometrium. Although all of the serous papillary tumors of the endometrium are high grades tumors and poor prognosis that need to be immediately treated with aggressive adjuvant chemotherapy, having a papillary serous carcinoma of the endometrium does not always mean that a papillary serous carcinoma of the end a poor prognosis and does not reduce the survival. The effect of this tumor on the prognosis is related to the grade of cancer, not necessarily if there is a papillary

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serous sub-type. In our case, we will present a low-grade one with no need for chemotherapy.

The second case is a rare case of SEOC. This case includes primary endometrioid adenocarcinoma and primary ovarian clear cell carcinoma in patients with endometriosis lesions. Two adjuvant treatments, chemotherapy, and target therapy have been suggested for primary ovarian clear cell carcinoma. We use adjuvant chemotherapy for this case.

Case Reports

Case 1

The case was a 54-year-old, gravida 3, menopaused women for 4 years, referred to the Gynecology Oncology Department of our teaching Hospital, Tehran, Iran with pelvic pain. Her past medical history had no specific points, and there was no cancer in her family history. On the pelvic examination, the fullness of the right adnexa was found. Doppler ultra-sonography and magnetite resonant imaging (MRI) revealed a solid cystic mass in the right ovary with 65 & 102 mm in the largest diameter and thickening of the endometrial layer of the uterus (Figure 1A). Serum level of cancer antigen 125 was 17 U/mL, (normal range: <35 U/mL). After pre-operation preparation, staging via laparotomy was performed, and the mass was resected and sent for frozen section examination. Borderline serous tumor of the ovary had been discovered. So total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy were done. On the 5th day of her hospitalization, the patient was discharged without any remarkable post-operation complications. The permanent microscopic findings were interesting: Low-grade papillary serous carcinoma of the right ovary, with no surface involvement, no vascular invasion accompanying three endometrial polyps with low-grade papillary serous carcinoma on the surfaces of the polyps. There was no myometrium invasion (Figure 1B-D). Therefore, the ovarian cancer was stage 1 and graded 1 papillary serous carcinoma, and the endometrial cancer was also staged 1 and grade 1 papillary serous carcinoma. Immunohistochemistry (IHC) staining was positive for P 16, negative for TP53, and negative for instability of microsatellites. No adjuvant therapies were considered, and after 1-year survival time, she is recurrence-free.

Case 2

A 63-year-old woman, nulliparous, was referred with heavy vaginal bleeding and abdominal mass. On admission time, serum level hemoglobin was 4.2 g/dL. So she received four units of packed cells, and after stabilization, imaging was performed. Sonography and computerized tomography scan revealed a huge solid cystic mass about 30 cm as the largest diameter, probably originating from the left adnexa. Omentum and para-aortic lymph nodes were shown to be involved by tumoral tissue. The serum level of cancer antigen 125 was 296 U/mL (normal range: < 35 U/mL), she underwent laparotomy, and there was a vast mass reported as a malignant ovarian carcinoma in frozen section examination. For this case, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic, and lymph node dissection were done. The post-operation period was acceptable. The final pathological report revealed clear cell carcinoma of the left ovary with 25 cm in size, without ovarian surface involvement and vascular invasion, accompanying endometrioid adenocarcinoma grade 2 of the endometrium with deep endometrial invasion: omentum and para-aortic lymph nodes involved by clear cell carcinoma. There were endometriosis lesions on both the anterior and posterior surfaces of the uterus. So the ovarian cancer was clear cell carcinoma stage 3, and the endometrial cancer was endometrioid carcinoma grade 2 stage 1b (Figure1 E-G). IHC staining showed loss of immune-reactivity for ARID1 and was negative for TP53 and negative for instability of microsatellites. Adjuvant chemotherapy with taxol and carboplatin for six sickles with the interval of every three weeks was considered due to the stage and grade of ovarian cancer. Although targeted therapy with temsirolimus had not been established as an adjuvant modality in clear cell carcinoma, we planned to prescribe it after the completion of chemotherapy. The disease progressed during the chemotherapy period and she could not complete her treatment. She died after a short time due to severe ascites and cardiorespiratory arrest.

Discussion

Women with endometrial cancer have an increased risk of SEOC, which must be diagnosed through an accurate pathological assessment of the ovaries. SEOC tumors are included in 3.5%-5% of endometrial cancers and 2.7%-10% of ovarian cancers (7,8). The average age of diagnosis is 47 years old, which is lower than metastatic ones (9). Case 1 was a 54-year woman, and case 2 was 63-year woman old, which was higher than the average age. The most common histopathology in SEOC is the endometrioid type with lower grades. Other histologic subtypes, such as clear cell and papillary serous, are extremely rare in SEOC tumors, and almost all of the studies have been done in endometrioid SEOC tumors (10). Case 1 had a low-grade papillary serous carcinoma of the ovary and low-grade papillary serous endometrial carcinoma. Based on the diagnostic criteria, the ovarian surface was free of tumor, the vascular invasion was not seen, both of the two tumors were low grade, myometrium invasion was not found, extra ovarian tissues were free of the tumor, and there was stage 1 of ovarian cancer, and stage 1 of endometrial cancer with low-grade papillary serous carcinoma. Although papillary serous carcinoma of the ovary can be a low-grade or high-grade (11). Papillary serous cancer in endometrial tumors is always

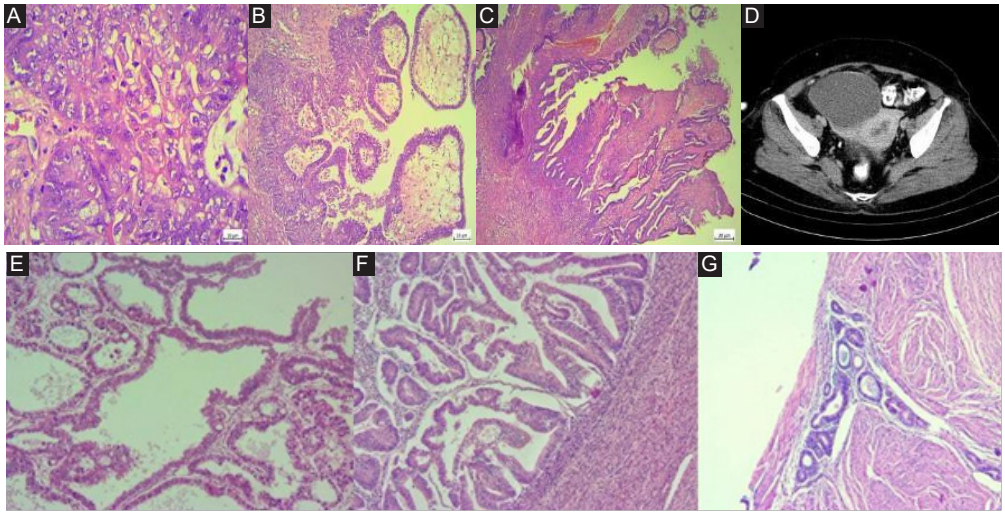

Figure 1. (A) solid cystic mass in right ovary, (B) serous carcinoma of the endometium, (C) serous carcinoma of the ovarry, (D) low grade papillary serous carcinoma of the endometrium, (E) clear cell carcinoma of the ovarry, (F) endomrtrioid adenocarsinoma and (G) endometriosis on the serous of the uterus. **(A)** A solid cystic mass in the right ovary with 65 & 102 mm in largest diameter and thickening of the endometrial layer of the uterus. **(B)** Serous carcinoma of the endometrium: there is a low-grade papillary serous carcinoma of the endometrium, lying on the polyps. **(C)** Serous carcinoma of the ovary: haphazard infiltrative glandular pattern and large papillae surrounded by thin micro papillae. **(D)** In this high power field view of low-grade papillary serous carcinoma of the endometrium, the mitotic index is low (up to 10 mitosis), and the nuclear atypia is mild. **(E)** Clear cell carcinoma of the ovary, solid and glandular pattern composed of cells with clear cytoplasm and tubules lined by a single layer of epithelium containing many hobnail cells. **(F)** Endometrioid adenocarcinoma: conflict glandular and papillary proliferation with infiltrative growth. **(G)** Endometriosis on the serous of the uterus, cystically dilated endometrial glands with a cuff of endometrial stroma surrounded by numerous pigment-laden histiocytic cells.

high-grade, which is very aggressive and has a high recurrence. This carcinoma causes death in 40% of cases (13) due to a mutation in tumor suppression gene TP53, with a terrible outcome for the patient (11). So when we discovered a low-grade papillary serous carcinoma of the endometrium, we suspected SEOC and requested IHC staining. The result was not in favor of TP53, positive for WT1 and P 16, confirming our SEOC tumor diagnosis. Most of the SEOC tumors are sporadic, but since the patients are young and have synchronized cancer of the endometrium and ovary, it is essential to confirm or rule out hereditary non-polyposis colorectal cancer by IHC study (12). IHC staining in our case did not prove the instability of the microsatellites, which become positive in hereditary non-polyposis colorectal cancer cases. A somatic single nucleotide variant has been introduced in a recent study in SEOC tumors with endometrioid histology, but this test has not been recommended in diagnosis yet (4).

The prognosis of SEOC tumors is better than metastatic ones. Treatment in high-grade papillary carcinoma is a combination of surgery and chemotherapy (13). Most studies have reported high degree endometrial or ovarian serous papillary cancer (13-15). So, in these studies, adjuvant chemotherapy after surgery was a significant factor in reducing recurrence and increasing survival. Unlike previously published studies, prospective data on the role of adjuvant therapy in the early stages of serous endometrial cancer is limited (14). In these cases, the main part of treatment is surgery. The role of adjuvant therapy in the early stages of serous carcinoma is not well established. Prospective data on the role of adjuvant therapy as a major component in the early stages of endometrial serous cancer is limited (15). In our case, serous carcinoma papillary in the uterus and ovaries was low. Therefore, surgery and staging were selected as the main component of treatment, and no adjuvant treatment such as chemotherapy or radiotherapy was used. Although we did not use any adjuvant therapy in this case, the patient is now alive after a year without recurrence. So, adjuvant treatment such as chemotherapy and radiotherapy is not recommended in patients with ovarian and endometrial cancer in stage 1 of the disease with low-grade tumors.

Case 2 was 63-year-old, which was older than the average age of the SEOC tumors. She had a clear cell carcinoma of the ovary with stage 3 due to omental and para-aortic lymph node involvement, and grade 2 endometrioid cancer of the uterus with stage 1b because of the deep myometrium invasion of cancer. Our advanced search about SEOC with clear cell histology found that this variant is scarce in SEOC tumors. Clear cell carcinoma of the ovary does not usually need grading, and this cancer is always considered a high-grade tumor. In this case, although it was a SEOC tumor, due to the clear cell carcinoma component of the ovary, the overall behavior of the tumor was very aggressive, and involvement of the extra ovarian tissues such as omentum and para-aortic lymph nodes were involved present. A very uncommon condition in SEOC since most of them are endometrioid

types (16). It is known that clear cell carcinomas occur on previous endometriosis lesions in most cases (17).

The most common ovarian cancer that coincides with endometrial cancer is endometrioid (18-20). Less common types include clear cell carcinoma and serous types that. Clear cell type is a more common type with endometriosis (18,19). This type is usually resistant to chemotherapy and has a poor prognosis. According to studies, endometriosis is a risk factor for ovarian cancer (21,22). The European Society of Human Reproduction Embryology reports that the presence of oxidative stress around endometriosis lesions causes carcinogenic changes (19,23,24). The most common cancer in women with endometriosis lesions is clear cell carcinoma (9 times more than others). According to studies in clear cell cancer, surgery with adjuvant therapy are the main treatments. Surgical treatment includes complete hysterectomy + bilateral salpingo-oophorectomy + omentectomy (18,25). While in some other studies, target therapy has been recommended as an effective adjunctive treatment for this type of cancer (18). So far, no specific standard has been set for target therapy, and treatment is selected based on genes mutations (18). These types of cancers are generally resistant to systemic chemotherapy. So target therapy seems to be an important part of treatment. In principle, mutated genes in endometriosis lesions. Recent studies have shown that mutation of kinase domain of phosphatidylinositol three kinases, mutation AT-rich interactive domain 1A, and MET amplification oncogene receptor tyrosine kinase is the first happening event in the carcinogenic transformation of endometriosis cells to clear cell carcinoma (17). Inhibitors of these activated genes are used for target therapy (18,26). In our case, as in similar studies (25,27), chemotherapy treatment with the usual taxol and carboplatin regimen was selected. Unfortunately, the patient died despite receiving chemotherapy treatment. So IHC staining may be useful for diagnosis and, more importantly, targeted therapies instead of adjuvant chemotherapy in clear cell carcinoma.

Temsirolimus, a mammalian target of rapamycin, is a kinase enzyme inhibitor, which has been used as targeted therapy in clear cell carcinoma of the ovary (28-30). In our case, IHC staining showed loss of immune-reactivity of ARID 1a, so we had planned temsirolimus after completion of chemotherapy, but the patient died shortly after starting chemotherapy. Maybe for optimizing the outcome of patients with clear cell carcinoma, only targeted therapy after surgery is better than chemotherapy. Nevertheless, more studies have to be done in this regard.

Conclusions

SEOC tumors usually are endometrioid type histologically, and these are in early stages with a good prognosis. But there are also rare cases with non-endometrioid subtypes. In these cases, chemotherapy with routine regimens does not seem helpful in early stages and low-grade tumors. In high-grade tumors, targeted therapy may be more effective than adjuvant chemotherapy. The molecular study has shown a difference between the etiology of SEOC tumors and other tumors with the same pathological findings. So we suggest it is more appropriate to start targeted therapy than chemotherapy in such cases, to keep up time for the optimized outcome of the patient.

Authors' Contribution

SA participated in study design, data collection, evaluation, drafting. SN and ES conducted molecular experiments. All authors edited and approved the final version of this paper for submission, also approved the final draft and take responsibility for the integrity of the data.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The informed consent was obtained from patients, and the ethics committee of our hospital approved the publication of the history.

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