

SYNCHRONOUS PRIMARY OVARIAN AND ENDOMETRIAL CANCER WITH A FAIR PROGNOSIS IN A YOUNG WOMAN

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Synchronous primary ovarian and endometrial cancers are quite unusual based on our previous experience [1,2]. Confirmative diagnosis depends on the pathologic recognition of different histologic patterns. Although some researchers have tried to determine the underlying mechanisms for the development of synchronous tumors using advanced molecular or clonal analysis, the etiologies of such tumors remain unclear [3–6]. A recently proposed hypothesis suggests that the etiology of synchronous cancers is related to the embryologically similar organs that develop synchronous neoplasms when they are simultaneously subjected to carcinogens.

However, the overall prognosis of patients with synchronous primary ovarian and endometrial cancers was reported to be better than those with metastatic tumors [1,2,7,8]. Conservative preservation of fertility is often considered for young premenopausal women [9]. In this case report, we discuss the management of a young female patient with synchronous primary ovarian and endometrial cancers, with fair prognosis, at our hospital.

We present a 31-year-old, gravida 0, para 0, married woman who visited our outpatient clinic because of an incidental finding of elevated CA-125 (300 U/mL) during a routine health examination in April, 2006. She was in good health before this admission and received regular Papanicolaou tests at a local hospital. Her menstrual cycle was regular without dysmenorrhea, and the interval was about 35–40 days with a moderate amount of blood. Only one episode of intermenstrual vaginal spotting was noted 3 months before this admission. She visited her local hospital, and transvaginal sonography revealed an endometrial hyperplasia, which

resolved spontaneously without any medication. At presentation to our obstetrics/gynecology clinic, transvaginal sonography showed one heterogeneous tumor of $6.8 \times 6.6 \times 5.2$ cm in size in the right ovary, one small tumor in her left ovary, and heterogeneous endometrium with a thickness of 17 mm.

The patient was admitted on May 5th, 2006 to the National Taiwan University Hospital (NTUH), where a right ovarian tumor (5.9×3.9 cm) with a small amount of ascites and one 2.8-cm hepatic hemangioma in the S7 lobe were detected by abdominal and pelvic computed tomography. The CA-125 concentration was rechecked and was 1,944.61 U/mL. The hemogram showed anemia (hemoglobin, 9.5 g/dL). After a thorough explanation and discussion, she decided to undergo exploratory surgery. However, she also strongly wished to preserve her uterus for future reproductive potential.

During the operation performed on May 9th, 2006, the right ovarian tumor was removed and frozen for pathologic assessment. In addition, a small solid component was detected on the surface of her left ovary but was not enlarged, and there were no indurated lymph nodes. The pathologic analysis of the excised right ovarian tumor specimen revealed the potential for low-grade malignant changes. A conservative staging operation, which involved bilateral salpingo-oophorectomy, omentectomy and bilateral pelvic lymph nodes dissection, was conducted via a low vertical incision. Meanwhile, fractional dilatation and curettage was also performed because of the ultrasound finding of a thickened endometrium. One closed wound vacuum drain tube was inserted at the cul-de-sac for drainage with a slight amount of discharge. The postoperative course was good, and a small amount of light-pink-colored fluid was drained.

The final pathology report revealed right ovarian endometrioid adenocarcinoma and left ovarian mixed endometrioid adenocarcinoma with clear cell adenocarcinoma. Ascites cytology was positive for malignant cells. Furthermore, the endometrial curetting showed



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low-grade endometrioid adenocarcinoma. After discussion with our pathologist, early-stage synchronous primary ovarian (stage Ic) and endometrial (stage Ia, grade I) cancer was diagnosed. This patient underwent the second stage of the total abdominal hysterectomy on May 19th, 2006.

On May 27th, 2006, adjuvant chemotherapy of paclitaxel and carboplatin was prescribed based on our own experience [2]. A portacath insertion was completed via the right subclavian vein on June 20th, 2006, and her treatment regimen was switched to cyclophosphamide and carboplatin because of a severe allergic skin reaction that was possibly induced by paclitaxel.

The five courses of cyclophosphamide and carboplatin therapy were completed on October 15th, 2006. Follow-up examination results revealed that CA-125 had decreased to a normal level since the second course of chemotherapy (Figure 1). Her general condition was good, except for postsurgical menopausal syndromes, which resolved after treatment with 17 β -estradiol gel (transdermal) and dydrogesterone (oral) as hormone replacement therapy. A positron emission tomography scan performed on February 14th, 2007 showed no evidence of abnormal fluorodeoxyglucose metabolic lesions. In addition, a computed tomography scan performed on April 16th, 2008 revealed no local recurrence. The following Papanicolaou test results were within normal range.

According to the cancer registration record (from 1977 to 1994) at the NTUH, of the 322 patients with endometrial cancer and 421 patients with ovarian cancer, only six patients had synchronous primary endometrial and ovarian cancers [1]. According to other data from the NTUH (from 1977 to 2005), the incidence of synchronous endometrial and ovarian cancers was 2.7% in patients with ovarian cancer and 3.3% in patients with endometrial cancers [2]. By comparison, in the Gynecologic Oncology Group Study (from 1985 to 1991) [8], the incidence of synchronous endometrial and ovarian cancers was much higher, being 10% in patients with ovarian cancer and 5% in patients with endometrial cancers. This may be related to the fact that the findings reported by Chiang et al [2] represent cases encountered at a single institute (NTUH) and only included cases with a confirmed pathologic diagnosis. Racial differences may offer another reason for these discrepancies [2].

According to the pathologic findings, endometrioid adenocarcinomas with similar histologic characteristics were the most common types to be reported. Until now, very few researchers have reported patients with synchronous primary endometrial and ovarian cancer with different or mixed histologic types, which may be related to their worse prognosis compared with

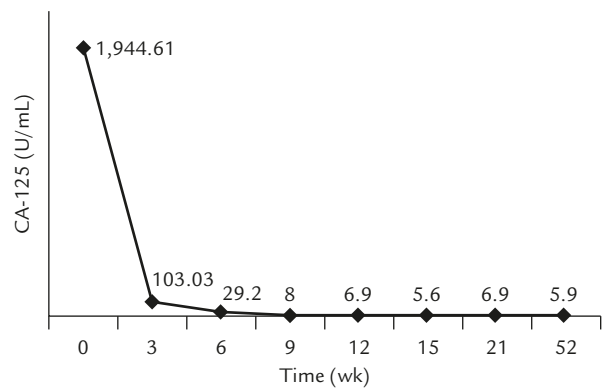


Figure 1. Levels of the tumor marker CA-125 before and after surgery, and after chemotherapy.

endometrioid cancers [10–12]. The average disease-free interval for patients with synchronous tumors was around 35–144 months (median, 94.2 months) [1]. The outcomes at our institute were similar to those reported elsewhere [7,8], and the estimated 5-year and 10-year survival rates were 85.9% and 80.3%, respectively, according to the previously published statistics for our hospital [8]. Until now, no statistical analyses have provided strong evidence indicating age, stage of ovarian cancer or grade of endometrial cancer as significant prognostic factors.

When the pathologic findings reveal two different histologic types, the confirmatory diagnosis of synchronous tumors is not difficult. However, when the pathologic study reveals similar types, the differentiation between the two separate primary cancers or one single advanced cancer with metastasis is much more difficult. Based on the clinical observations and pathologic and molecular analysis (including immunohistochemical and DNA analysis), most synchronous primary tumors can be diagnosed correctly and definitively. Furthermore, by applying standardized criteria [10] [(1) both tumors are confined to primary sites; (2) no direct extension between the tumors; (3) no lymphovascular tumor emboli; (4) no or only superficial myometrial invasion of the endometrial lesion; and (5) no distant metastasis], we could still differentiate the two cancers. According to the pathologic report, there was endometrioid adenocarcinoma in the presence of atypical hyperplasia; therefore, the diagnosis should favor primary endometrial cancer (Figure 2). In our experience, ovarian endometrioid adenocarcinoma coexisting with clear cell carcinoma (Figure 3) is relatively common. In the present case, we noted endometriosis in the left ovary, which might explain the primary ovarian cancer in our patient (Figure 4).

By applying the criteria above and the pathologic findings, our patient was diagnosed with synchronous

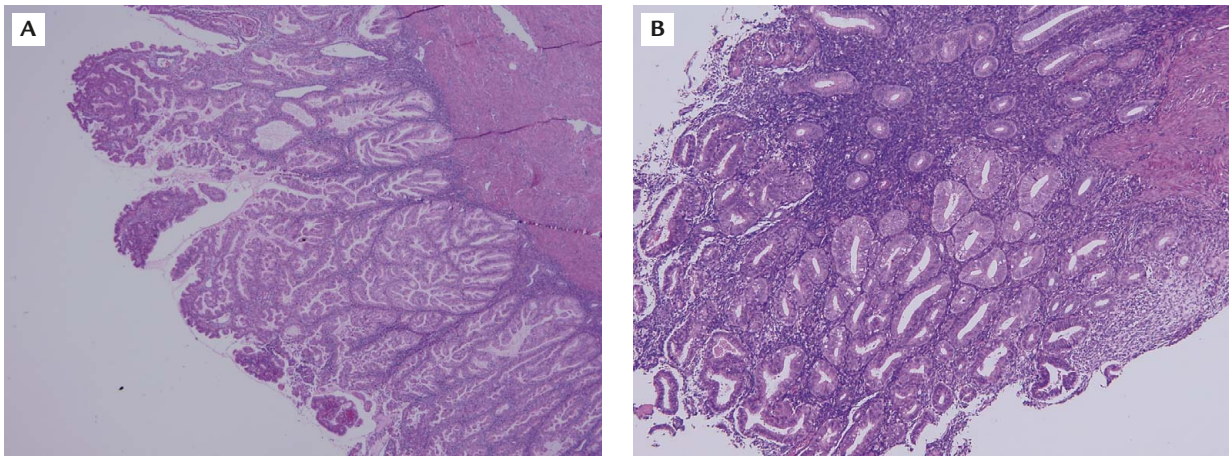


Figure 2. (A) The endometrium showing a International Federation of Gynecology and Obstetrics grade 1 endometrioid adenocarcinoma characterized by a complex glandular architecture without myometrial invasion (hematoxylin and eosin, 40×). (B) Atypical endometrial hyperplasia lesion near the endometrioid adenocarcinoma, which is a sign for primary endometrial cancer (hematoxylin and eosin, 100×).

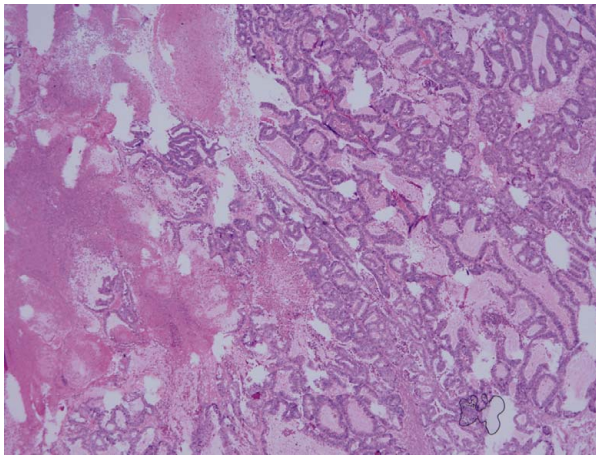


Figure 3. Right ovarian endometrioid adenocarcinoma with high-grade nuclei (hematoxylin and eosin, 40×).

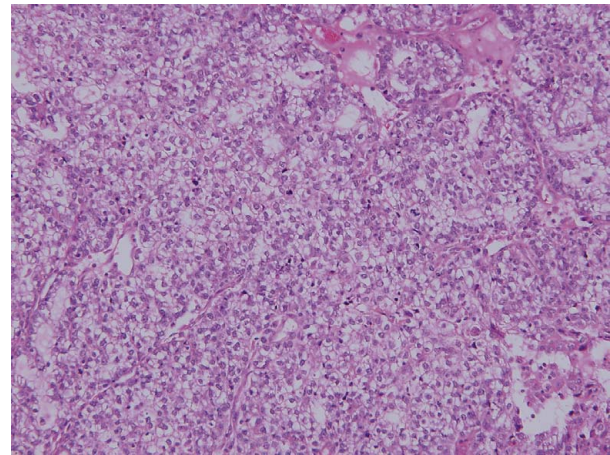


Figure 4. Left ovarian endometrioid adenocarcinoma mixed with clear cell carcinoma (hematoxylin and eosin, 200×).

primary ovarian and endometrial cancers. According to some case reports, up to 80–86% of patients with synchronous tumors were diagnosed after the initial presentation of abnormal vaginal bleeding [2,8]. The mean age for definite diagnosis was 47–49 years [2,8], which was younger than that of patients with either primary ovarian or endometrial cancers. The medical history of this patient revealed no evidence of previous polycystic ovarian syndrome, infertility or endometriosis. There was only one episode of intermenstrual vaginal spotting, which resolved spontaneously. She was quite thin with good nutrition and socioeconomic status. There was no family history of gynecologic cancers.

A two-stage operation was initially planned and conducted based on the patient's wish to preserve her reproductive function. Before this operation, we also consulted an infertility specialist. Because of the high potential of malignant changes and technical challenges,

we decided not to conduct oocyte or ovarian tissue cryopreservation and preferred to preserve her uterus. Except for one episode of vaginal spotting with slightly thickened endometrium, without significant evidence for an endometrial lesion, we did not perform a simple diagnostic dilatation and curettage before surgery to exclude endometrial cancer. After the first conservative staging surgery with the final confirmed pathologic report, this patient decided to undergo the second debulking operation to complete the staging and started adjuvant chemotherapy, even though the prognosis may be better for most patients with synchronous tumors than for those with metastasis. Overall, this patient completed six cycles of postoperative adjuvant chemotherapy because of the mixed histologic types of endometrioid/clear cell carcinoma of the left ovary; the patient experienced no significant side effects. At the time of writing, there was no evidence of recurrence in this patient.

Overall, a conservative staging operation is an acceptable option for young women with early-stage ovarian cancer who wish to preserve their reproductive function. However, the possibility of synchronous primary ovarian and endometrial cancers should be considered, and the patients must be well informed, particularly when history of abnormal uterine spotting is found. The patient in this case report underwent two-stage surgery for fertility preservation and adjuvant chemotherapy because of the mixed histologic types; the outcomes to date were good. We recommend that for young female patients who wish to preserve their reproductive function, even without high suspicion of endometrial lesions, diagnostic dilatation and curettage should be conducted preoperatively to aid treatment planning.

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