Case Report

Failed Conservative Treatment of Synchronous Primary Cancer of Endometrium and Ovary in a Young Thai Woman: A Case Report

Komsun Suwannarurk MD*,
Kornkarn Bhamarapravatana PhD**, Yudthadej Thaweekul MD*,
Karicha Mairaing MD*, Yenrudee Poomtavorn MD*,
Naree Warnnissorn MD***, Pisit Wattanaruangkowit MD****

** Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of medicine, Thammasat University, Klongluang, Pathumthani, Thailand*
*** Department of Preclinical Science, Faculty of medicine, Thammasat University, Klongluang, Pathumthani, Thailand*
**** Department of Pathology, Faculty of medicine, Thammasat University, Klongluang, Pathumthani, Thailand*
***** Department of Radiology Faculty of Medicine, Thammasat University, Pathumthani, Thailand*

A case of well differentiated endometriod adenocarcinoma of the endometrium with a synchronous endometriod and clear cell adenocarcinoma of both ovaries was reported.
Recently, a 28-year-old woman presented with vaginal bleeding was diagnosed to have only FIGO stage IaG1 (FIGO 2000) cancer of the endometrium.

After 3 months of high dose progestin treatment, 15 cm bilateral ovarian tumors later diagnosed as FIGO stage IIIa ovarian cancer (mixed endometriod and clear cell adenocarcinoma) were detected, and later surgically removed. The patient then was started on Placitaxel/Carboplatin combination chemotherapy for 6 cycles after surgery.

The synchronous cancers of endometrium and ovary are usually presented in woman with median age of 50 with obesity, diabetes, and hypertension. These low grade tumors and better prognosis are the norm in contrast to the authors' case with clear cell component and higher stage of ovarian cancer in young lean Thai woman.

***Keywords**: Endometrial cancer, Ovarian cancer, Synchronous tumor of endometrium and ovary.*

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Synchronous cancer is the condition when two independent primary cancers occur simultaneously. Overall incidence of synchronous cancer in gynecologic cancer is only 1-2%[1]. Synchronicity of endometrial and ovarian cancer is a rare but well-recognized phenomenon[1]. Its occurrence is 5 and 10% in the patients with endometrial and ovarian cancer respectively[2].

In Thailand, endometrial cancer is the third most common of gynecologic cancer after cervical and ovarian cancer[3]. The differential diagnosis in this phenomenon is either low-stage double primaries cancer or cancers which have metastasized from one site to another. When histopathology of both cancers are different, synchronous cancer is easily diagnosed. However, when the histopathology of both endometrial and ovarian cancer are identical, the possibility of the diagnosis could be one of the three situations: primary ovarian cancer with endometrial metastasis, primary endometrial cancer with ovarian metastasis or synchronous cancer of both endometrium and ovary. The criteria for distinguishing between synchronous cancer and metastatic lesions were described by Scully et al[4].

Correspondence to:
Suwannarurk K, Gynecologic Oncology Unit,Department of Obstetrics and Gynecology, Faculty of medicine, Thammasat University, Klongluang, Pathumthani 12120, Thailand.
Phone: 08-1499-0231
E-mail: k_suwannarurk@yahoo.com

Case Report

The authors report the case of a 28-year-old woman (para 0-0-0-0), 1.65 m in height and 54 kg in weight, who was seen in the gynecology clinic Thammasat University Hospital regarding her abnormal

period. The patient was a healthy-looking, non-smoker and sthenic female. She had a healthy medical history and there were no reports of diabetes, hypertension andcancer in her family history.

The patient's pelvic examination was normal. An endometrial aspiration biopsy (Endocell®, Wallach, CT) was then taken. The histopathological report was of a complex hyperplasia with cellular atypia (Fig. 1A, B).

After 3 months of hormonal treatment of high dosed progestin (medoxy progesterone acetate 30 mg/day), repeated endometrial aspirations were performed. The pathological reports showed a case of well differentiated endometriod adenocarcinoma of the endometrium. No evidence of myometrial invasion was detected on abdomen-pelvis CT (Fig. 2A). The provisional diagnosis for this patient was stage IAG1 endometrial cancer (FIGO 2000). She was then counseled to choose between standard treatment of endometrial cancer (surgical staging surgery) or optional conservative treatment by high dose progestin and a close follow-up. The patient elected conservative treatment. She then underwent a dilatation and curettage. The report showed a well differentiated endometriod adenocarcinoma of the endometrium (Fig. 1C). High dose hormonal therapy (oral megrestol 320 mg/day) was then prescribed.

After 3 months of high dose megrestrol treatment, complex adnexal cystic mass was detected from current pelvic examination of the patient. A cervical cytology investigated during this visit showed negative result. Chest x-ray, hemogram and liver enzyme profile were all normal. The patient underwent the second abdomen-pelvis CT showing multiloculated ovarian cyst not seen in previous CT scan (Fig. 2B).

This is a case of suspected high risk ovarian cancer. After a prompt counseling, the patient elected to proceed with hysterectomy and bilateral adnexectomy. Exploratory laparotomy was performed via a midline incision. A peritoneal cytology examination was performed. Intraoperative gross examination of the uterus showed uterine normalcy and the absence of myometrial invasion and cervical involvement. The right ovary measured 6 x 7 x 8 cm solid cystic mass containing serous fluid. The left ovary was an endometriotic cyst measuring 3 x 3 x 4 cm. No metastatic lesions were detected grossly in the rest of the abdominal cavity. Bilateral pelvic lymph node dissection and infracolic omentectomy were then performed.

Final histopathological report of the uterus confirmed endometrial cancer. The uterus had minimal residual endometriod adenocarcinoma (G1). No myometrial invasion was seen (Fig. 3D). Mild

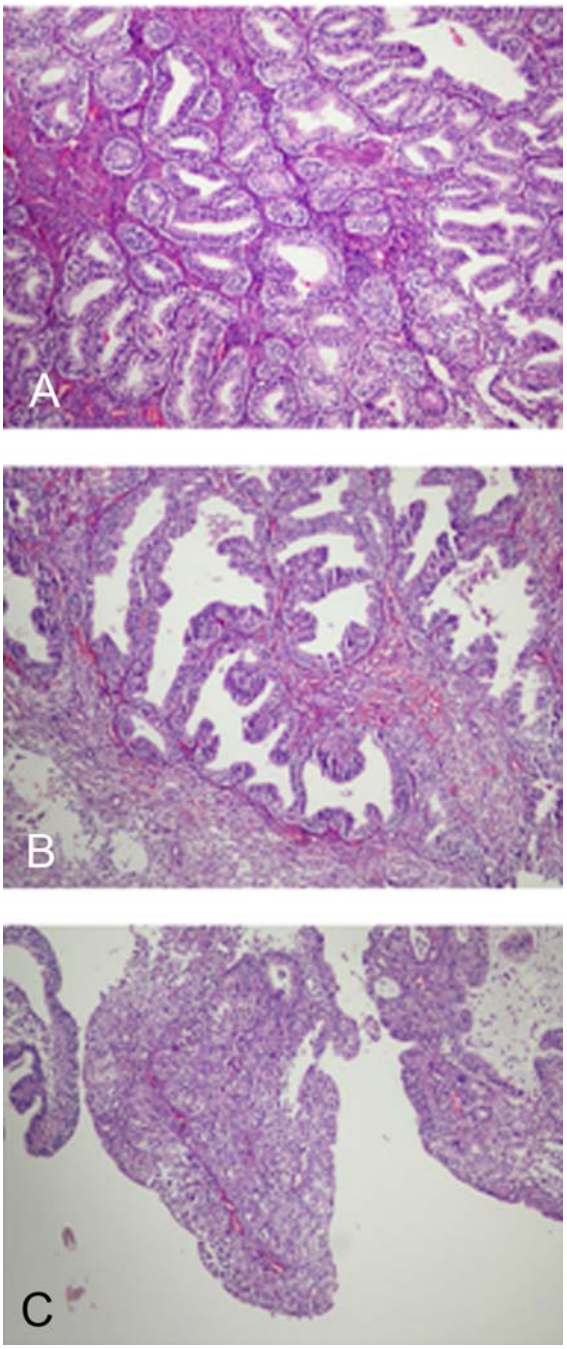

Fig. 1 Complexed endometrial hyperplasia of endometrium (A), with cellular atypia (B) and endometriod adenocarcinoma of endometrium from fractional curettage (hematoxylin and eosin; original magnification, x 100 (A), x 100 (B) and x 50 (c))

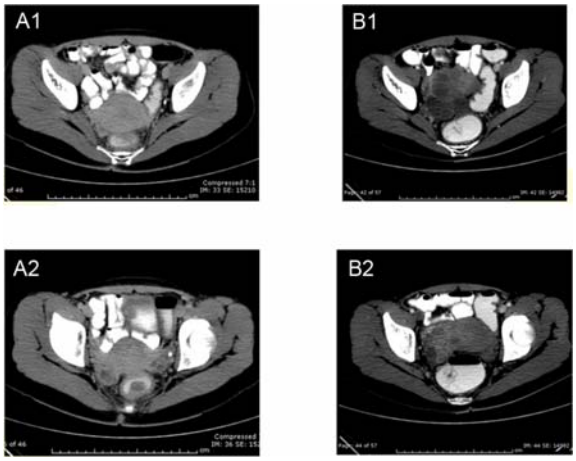

Fig. 2 Abdominopelvic CT after provisional diagnosis of endometrial cancer (A1, A2) and after 3 months of high dose progestin treatment (B1, B2)

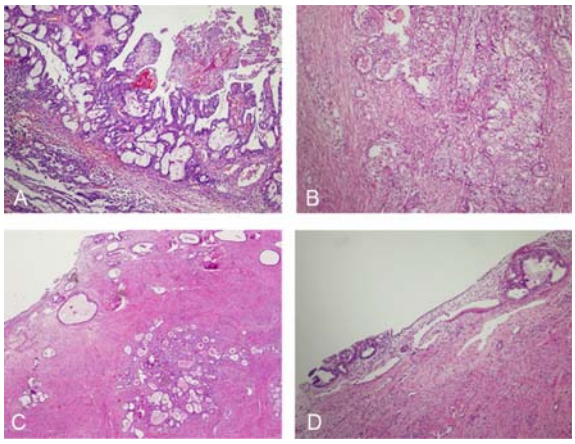

Fig. 3 Moderate differentiated endometriod carcinoma of the right ovary (A) with focal clear cell carcinoma (B), cervical stromal involvement of endometriod adenocarcinoma of endometrium (C) and minimal residual endometriod adenocarcinoma (G1) without invasion of myometrium (D) (hematoxylin and eosin; original magnification, x 100 (A), x 100 (B), x 50 (c) and x 50 (d))

adenomyosis and cervical stromal involvement of endometriod carcinoma were seen without angiolymphatic invasion (Fig. 3C).

The right ovary revealed a mixed grade 2 endometrioid adenocarcinoma (Fig. 3A). It had 30% component of clear cell carcinoma (Fig. 3B) with adhesion and uterine invasion. The left ovary had serosal endometriosis and an endometriotic cyst. Peritoneal biopsies were positive for tumor spread. The peritoneal washing, omentum and lymph nodes were negative for malignancy.

The endometrial carcinoma was staged as FIGO stage II, grade 1 endometriod adenocarcinoma. However, ovarian cancer was staged as FIGO IIIa, grade 2 endometriod adenocarcinoma with clear cell component. The diagnosis confirmed a case of synchronous cancers of endometrium stage IIb G1 and ovary stage IIIa.

The patient was started on Placitaxel/ Carboplatin combination chemotherapy right after surgery. She received continuing chemotherapy for 6 courses. After completing chemotherapy for 6 months, the patient developed fever complicated with edema of her right leg. A further investigation was done and we diagnosed a deep vein thrombosis of right thigh. Anticoagulant therapy was started for removal of venous thrombus in a deep vein of the thigh. The anticoagulant therapy was started with intravenous administration and then was changed to oral form. The patient was discharged from the hospital and then repeatedly re-admitted to the hospital due to partial gut obstruction that was treated by conservative and supportive methods.

Discussion

The synchronous cancer of endometrium and ovarian cancer is a well recognized incidence. The occurrence is rare. If histopathologic types of both cancer are unidentical, the coexistence of two primaries malignancy can be easy diagnosed[1]. If the histopathologic patterns are identical, the differential diagnosis then lies between synchronous carcinoma and one primary tumor with metastases to another site. The prognosis of synchronous cancers are usually better than single late stage of cancer.

The explanation of synchronous cancers of endometrium and ovary is still unclear[1]. Secondary Mullerian system theory mentioned that the epithelium of internal female genital organ and peritoneal surface have shared molecular receptors responding to carcinogenic stimulus. This process leads to the development of multiple primary cancers or synchronous tumors[1]. The hypothesis could explain only the same histopathology type of cancer. This explanation might not be used to explain the phenomenon of synchronous cancer of dissimilar histopathology. There should be a different mechanism underlying this interesting phenomenon that needed further studies.

Metastatic and independent cancers can be

distinguished using immunohistological staining and DNA flow cytometry[5]. The conventional clinico-pathologic criteria still relies on Scully work[4] that developed from Ulbright and Roth[6]. Major criteria for identification of the synchronous primary cancers included different histologic types (major criterion). Minor criteria are (1) both tumors confined to primary sites, (2) no direct extension between tumors, (3) no lymphvascular tumor emboli, (4) no or only superficial myometrial invasion and (5) no distant metastasis[6].

Endometrial carcinoma is commonly found in overweight, nulliparous and postmenopausal women with personal history of diabetes mellitus or hypertension[7]. However, patients with dual primary carcinoma tend to be 10-20 years younger than their counterparts with ovarian or endometrial carcinoma[7]. According to several previous reports, the median age of dual primary cancer ranged from 41-54 years[7]. In Thailand, median age in synchronous cancer of endometrium and ovary was 47 years old compared to 56 for metastatic group[8].

Endometrial neoplasia is uncommonly in young patients. It occurs in less than 5% of all cases[9]. Manchana et al reported up to 10% of endometrial adenocarcinoma patients age were lower than 40[10]. Shamshiraz et al reported a case of synchronous ovarian malignancy in a 21 year old US patient. This patient had an early endometrial cancer and a serous ovarian tumor of low malignant potential[11].

The authors' patient was 28 years old and the presence of co-malignancy suggests the presence of a systemic risk factor, such as null para. The prognosis of endometrial carcinoma that arises as a second cancer appears to be more favorable than for endometrial carcinoma in general. She was much younger than the typical median age of synchronous carcinoma patient. An aggressive histopathologic type of ovarian synchronous cancer of endometrium and ovary are known to have a good prognosis because they are normally low grade and are diagnosed at early stage[1]. There were no recurrences in grade 1 endometriod endometrial cancer who received only surgical procedure[7]. In contrast, patients with higher graded ovarian tumors are usually treated with adjuvant radiation or chemotherapy .

When the diagnosis of endometrial cancer is made in young woman, her child bearing requirement will be considered together with the treatment. For patient who wants more children, the first criterion for conservative treatment is a confirmed diagnosis of a well differentiated endometrial carcinoma by an expert pathologist[12]. The second criterion is the clinical absence of myometrial invasion. When the two criterion are met (FIGO stage IaG1 endometrial cancer) conservative treatment is then considered.

Well differentiated endometrial carcinoma has the highest chance of showing positive progesterone receptors (PR) necessary to respond to medical treatment[12]. However, it is necessary to ensure that the whole lesion is well differentiated cancer before hormonal treatment is given. Standard fractional uterine curettage or hysteroscopic examination should be used for confirming low grade cancer histopathology and maximum removal of tumor. That was what the authors did for our patient, because an office endometrial aspiration or biopsy were not considered to be an adequate representative of the whole lesion[13].

It is very difficult to determine invasion of cancer by biopsy, curettage of hysteroscopy. CT scan was then used to confirm the absence of myometrial invasion before beginning conservative treatment for early stage endometrial cancer begun. CT scan was utilized here so as to conserve child bearing ability for the patient, who would otherwise have received hysterectomy as the standard treatment for intraoperative evaluation of myometrial invasion.

Merisio et al reported that complexed endometrial hyperplasia in Italy had silent endometrial cancer between 16-62%[14]. Provisional stage 1 disease in patients younger than 45 years of age are more likely to have low-grade disease localized to the endometrium confirmable by CT scan. However, the authors' case was an unusual one in terms of the extremely young age (28) of the patient. The following treatment given was megrestrol acetate (320 mg/day) for consolidation that resembled Mazzon's work in year 2010[15]. Successful high dose hormonal therapy is used as an alternative treatment for selected early-stage and low grade cancer in young women who desire further childbearing[16].

For the young women who require fertility preservation, regression was found in 80% of cancer cases with progestin treatment[17]. However, after 3 months of high dose megrestol treatment, the complex mass of the right adnexa was found via pelvic examination of the authors' subject. Abdominopelvic CT was then performed to evaluate the details of the mass. Current CT image showed that the normal right adnexa had changed to a complex mass. This complex mass was not an obvious development from the former CT scan.

Compared to Scully criterion, this case

showed different histopathology in ovarian and endometrial cancer. The subject had superficial invasion of endometrium. However, she had minimal cervical stromal involvement which elevated the cancer staging from IA to II. In the Scully criteria, unilateral ovarian cancer was usually found with endometriosis[4]. The authors subject matched both Scully characteristics.

This patient at the first provisional diagnosis was as an early stage of endometrial cancer, but after conservative treatment the later diagnosis was found to be ovarian metastasis of endometrial cancer. After surgery and pathological review, the criteria for diagnosis of synchronous tumor of both endometrium and ovary was met. The further treatment of this case after surgery was adjuvant chemotherapy.

Before conservative treatment of endometrial cancer was performed with the subject, an accurate stage diagnosis and grading of the tumor were performed by expert pathologist and radiologist. The routine investigation for myometrial invasion by CT imaging alone was insufficient for this case. Her rapid progression was not expected because the patient did not fit typical endometrial patient profile. Endocervical curettage showed no malignant tissue. However, this case yielded an unfavorable result.

This was a very atypical case. The experience from this case suggests that if a conservative course of treatment is considered, a more aggressive investigation should be employed for patients with this profile regardless of the patient's age. In the literature, the radiologic imaging such as CT, MRI or PET CT should be the tool for myometrial invasion assessment[17]. In a developing country, it is uncommon to have access of full option sophisticated imaging tools found only at tertiary health care institutions. Hysteroscopic exam to ensure accurate cancer staging is then recommended. The laparoscopic examination of internal abdominal organ should be performed to confirm cancer staging and provide additional information to rule out any minimal metastasis of cancer tissue.

When the diagnosis of early and low grade endometrial cancer in the young was made, the conservative treatment should be strictly selected for the patient with a very close follow-up. The invasive diagnosis of the disease is justified if it can detect an atypical case before conservative treatment. If conservative treatment is planned without comprehensive investigation, the diagnosis could be missed. Good opportunity for early treatment and a better quality of patient's life will then be lost.

Potential conflicts of interest

None.

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ความล้มเหลวของการรักษาแบบอนุรักษ์ในมะเร็งเยื่อบุโพรงมดลูกร่วมกับมะเร็งรังไข่ในสตรีไทยอายุน้อย: รายงานผู้ป่วย

คมสันติ์ สุวรรณฤกษ์, กรการณ์ ภมรประวัติธนะ, ยุทธเดช ทวีกุล, กริชา ไม้เรียง, เย็นฤดี ภูมิถาวร, นารี วรรณณิสสร, พิศิษฐ วัฒนเรืองโกวิท

รายงานผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกชนิด differentiated endometriod adenocarcinoma ร่วมกับมะเร็งรังไข่ชนิด endometriod และ clear cell adenocarcinoma ในผู้ป่วยสตรีไทยอายุ 28 ปี มาพบแพทย์ด้วยอาการเลือดจากช่องคลอดผิดปกติได้รับการวินิจฉัยว่าเป็นมะเร็งเยื่อบุโพรงมดลูกระยะ IaG1 (FIGO 2000) ภายหลังการรักษาด้วยฮอร์โมนโปรเจสตินขนาดสูงนาน 3 เดือน ตรวจพบเนื้องอกรังไข่ขนาดเส้นผ่าศูนย์กลาง 15 เซนติเมตร ทั้งสองข้างได้รับการวินิจฉัยว่าเป็นมะเร็งรังไข่ระยะ IIIa ชนิด endometriod และ clear cell adenocarcinoma ผู้ป่วยได้รับการผ่าตัดและได้รับเคมีบำบัดด้วยยา placitaxel และ carboplatin จำนวน 6 รอบ ภายหลังผ่าตัด การเกิดร่วมกันระหว่างมะเร็งเยื่อบุโพรงมดลูกและมะเร็งรังไข่มักจะพบในสตรีอายุมัชฌิม 50 ปี ที่มักพบร่วมกับโรคอ้วน เบาหวาน และความดันโลหิตสูง โดยทั่วไปมักจะเป็นมะเร็งที่มีความรุนแรงน้อยและมีพยากรณ์โรคที่ดีแต่ในรายงานนี้พบมะเร็งที่มีความรุนแรงสูง และระยะของโรคที่มากในสตรีไทยที่อายุน้อยและผอม