Simultaneous endometrioid ovarian and uterine carcinoma diagnosed after an in vitro fertilization procedure - Case report and review of the literature

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Summary

Background: The presence of simultaneous carcinomas involving both the ovary and uterus is relatively uncommon, while the possible link between fertility drugs and carcinogenesis still remains controversial.

Case: The case of a 40-year-old patient with simultaneous aggressive endometrioid carcinoma of the ovary and uterus a few months after the sixth attempt of in vitro fertilization is presented. The patient had de novo lung disease at surgery and diffuse metastatic spread to adjacent bone, subcutaneous tissue and the central nervous system (CNS) soon after a spectacular response to the primary paclitaxel/carboplatinum chemotherapy and while on maintenance and second-line chemotherapy, respectively.

Conclusion: The fulminating course of our patient might in part be attributed to the existence of advanced disease at presentation. Definite conclusions about the possible association with the previously performed assisted reproduction cannot be drawn but close clinical surveillance of such patients before, during and after infertility treatment is strongly warranted.

Key words: Endometrioid carcinoma; Ovarian cancer; Uterine cancer; In vitro fertilization.

Introduction

The presence of simultaneous carcinomas involving both the ovary and uterus is relatively uncommon and occurs in about 10% of patients with epithelial ovarian or uterine cancers [1]. However, these synchronous tumors represent a diagnostic and therapeutic challenge, particularly if they have similar histology.

The possible link between fertility drugs and carcinogenesis still remains controversial because most prior epidemiologic investigations have had serious methodological limitations, including small sample sizes, short follow-up times and absence of information on other predictors of cancer risk [2, 3].

In this report we describe the case of a patient who presented with metastatic endometrioid carcinoma of the ovary and uterus after the completion of six attempts of in vitro fertilization (IVF). This case had an unusually aggressive natural history, which is thoroughly discussed.

Case Report

A 40-year-old female was referred to her gynecologist in July of 2003 because of urine incontinence and vaginal discomfort for the prevous two months. From her family and personal medical history only infertility to diffuse simple endometrial hyperplasia without atypia was reported. Between 2000 and 2002 the patient underwent six unsuccessful attempts of IVF with the use of gonadotropin-releasing hormone analogues. A full hematological and radiological pre-IVF evaluation revealed no pathology, and hysteroscopic evaluation during IVF procedures was also normal.

On the basis of appearance, the patient seemed well. Abdominal and pelvic examination revealed a firm palpable vaginal lesion 2 cm × 3 cm. Histological examination of the lesion showed vaginal epithelium with widespread invasion from adenocarcinoma of moderate to poor differentiation. Peripheral blood count, coagulation studies, and biochemical profile were all within normal limits, while CA125 was 85 U/ml. Abdominal and transvaginal ultrasonography showed a solid lesion in the right ovary (maximum bipolar diameter 8 cm). Chest X-ray was normal, while computed tomography (CT) of the chest revealed multiple small-sized nodular lesions in both lungs strongly suspected as metastatic.

Despite the suspected spread to the lungs the patient underwent total hysterectomy and bilateral salpingo-oophorectomy with debulking intent. Sample tissues were obtained from the omentum and diaphragm, while peritoneal washings were also collected. Pathologic examination revealed a moderately differentiated endometrioid carcinoma in the right ovary with carcinomatous emboli into the blood and lymph vessels (Figure 1A), endometrioid carcinoma of the uterus body in the background of atypical endometrial hyperplasia with superficial invasion of the myometrium (Figure 1B), while the omentum, diaphragm and cytologic evaluation of peritoneal washings were normal.

Following surgery, the patient was admitted to our hospital and received six 3-weekly cycles of paclitaxel 175 mg/m^2 and carboplatinum AUC 5 with acceptable toxicity, and a partial remission. Clinical, laboratory and radiological post-chemotherapy evaluation showed complete remission of the vaginal lesion (CA125 = 7.5 U/ml), while chest CT revealed only two remaining lesions (7 mm and 3 mm) in the right middle lobe.

In order to make a decision as to further treatment, a physical examination and a positron emission tomography (PET) scan along with a spiral CT scan was performed. Abnormal uptake close to the pubic symphysis in the right pubic ramus was seen. A CT-directed needle biopsy was thereafter performed revealing a carcinoma compatible with the primary tumor.

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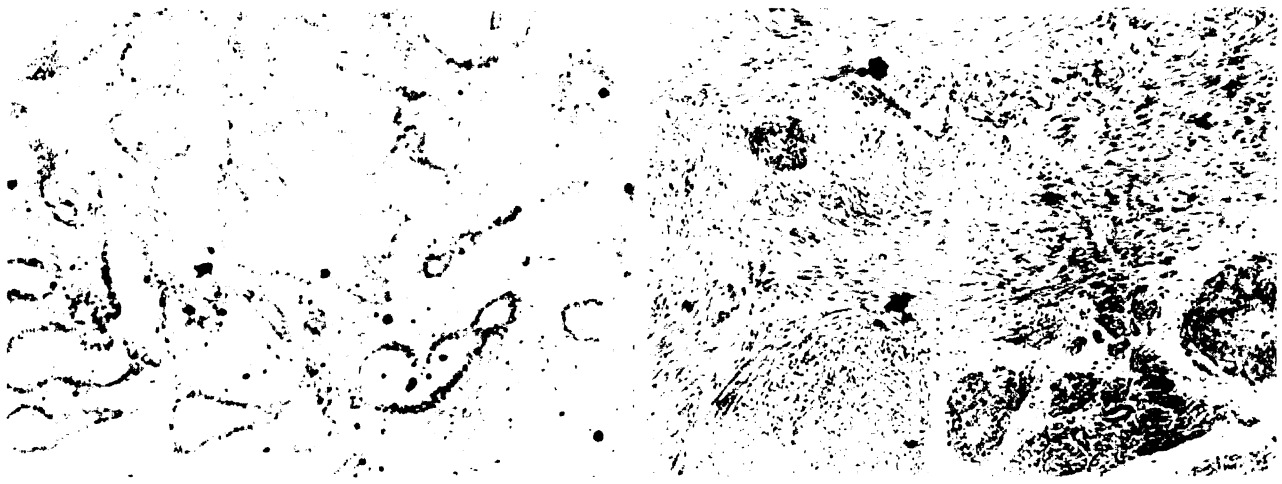

1A Fig. 1B

Figure 1. — **A)** Endometrioid carcinoma of moderate differentiation in the right ovary with carcinomatous emboli into the blood and lymph vessels. **B)** Endometrioid carcinoma of the uterus body in the background of atypical endometrial hyperplasia with superficial invasion of the myometrium.

The patient received 30 Gy in 3 Gy fractions to the above area and started single-agent chemotherapy with Paclitaxel 175 mg/m^2. Soon after the second cycle of chemotherapy the patient was admitted to our hospital with headache, dysarthria, neurological deficits, gait unsteadiness and mental state changes; moreover, physical examination revealed a subcutaneous 2 cm nodule on the upper left arm. Brain CT revealed multiple metastatic foci and cytology by fine needle aspiration of the nodule was positive for adenocarcinoma. Corticosteroids were initiated and the patient received whole brain radiotherapy (30 Gy in 10 - 3 Gy fractions), with rapid improvement of symptoms.

A few days later the patient initiated second-line chemotherapy with topotecan. After the second cycle of chemotherapy the patient was admitted again to our hospital with intense dyspnea and cough. Chest X-ray revealed diffuse pulmonary lesions; while the solitary subcutaneous metastasis was almost doubled in size. Pegylated liposomal doxorubicin (PLD, Caelyx®) was then added to the chemotherapy regimen. However, after the first cycle of the topotecan/PLD combination the patient experienced rapid deterioration of her pulmonary function. Chest X-ray showed further worsening of the lung disease. No further chemotherapy was therefore attempted. The patient died from respiratory failure two weeks later, eight months after the initial diagnosis.

Discussion

Ovarian cancer represents 4% of all female cancers. Epithelial ovarian cancer comprises four major histological subtypes (serous, mucinous, clear cell and endometrioid), and it is now becoming clear that the developmental pathways for these subtypes are fundamentally different [4]. Endometrioid tumors represent approximately 20% of common epithelial ovarian tumors. In about 20% of individuals, these cancers are associated with endometrial carcinoma. Endometrioid ovarian cancers probably arise via the malignant transformation of ectopic endometrial implants called endometriosis and not the ovarian surface epithelium [5]. The majority (about 80%) of these tumors are malignant, and the remainder (roughly 20%) usually are of borderline malignancy. Endometrioid tumors occur primarily in women who are between 50 and 70 years of age [6].

The simultaneous presence of carcinoma in the endometrium and ovary may indicate either metastatic disease or independently developing neoplasms [7]. The classification of these lesions either as two separate primary tumors or as a single primary tumor with metastasis has implications for patient prognosis and therapy recommendations. Some investigators have proposed that the coexistence of endometrioid histology in the ovaries and uterus represent two separate primaries and these patients may have a relatively favorable prognosis [8]. Patients with synchronous endometrioid tumors of the endometrium and ovary are generally younger than reported for either endometrial adenocarcinomas or ovarian epithelial adenocarcinomas. They tend to be of low grade and present at early stage while they are frequently associated with endometriosis. However, published data suggest that the survival of patients with synchronous primaries correlates with the stage of the individual tumors and that a second, synchronous primary does not adversely affect prognosis [9]. The distinction between two primary carcinomas on the one hand and a metastatic disease on the other in patients suffering from synchronous endometrioid carcinomas of the uterus and ovary is difficult. Exclusive histopathologic analysis appears to be insufficient and sometimes misleading.

More recently it has been suggested that molecular analysis might be useful in determining the relationship of synchronous uterine and ovarian endometrioid neoplasms. Loss of heterozygosity (LOH) at locus 10q23.3 and mutation of the PTEN tumor suppressor gene occur frequently in both endometrial carcinoma and ovarian endometrioid carcinoma [10]. The PTEN/MMAC gene on chromosome 10q23 is a tumor suppressor implicated in the pathogenesis of a wide variety of malignancies, but to date, somatic mutations in PTEN have not been iden-

tified in studies of predominantly serous ovarian cancers. In endometrial cancers, PTEN mutations are very common in tumors of the endometrioid type but have rarely been found in serous types. The identification of frequent somatic PTEN mutations in endometrioid ovarian tumors indicates that it plays a significant role in the etiology of this subtype. The absence of mutations in other histological subtypes is consistent with the hypothesis that epithelial ovarian cancers arise through different developmental pathways.

The case reported here had three separate tumor masses of the same histology in three areas closely involved in the procedure of IVF. One might hypothesize that tumor cells were implanted from an ovarian primary to both the vaginal wall and endometrial cavity or from the endometrial cavity to ovary through the vaginal wall. However, the presence of obviously preexisting atypical hyperplasia of the endometrium makes plausible the scenario of two synchronous primaries – one in the ovary and the other in the endometrium [11]; tumor cells were probably implanted in the vagina during IVF manipulations. A genetic analysis would be helpful to verify any of the above scenarios but it was not feasible.

The described case has once more aroused the frequently encountered concern of the possible correlation of assisted reproduction techniques and carcinogenesis. There are several theories concerning factors that may play a role in the development of ovarian cancer. Two theories in particular have prompted researchers to examine fertility drugs as a potential risk factor. The first is that an increased number of uninterrupted ovulations in a woman's lifetime increase her chance of developing ovarian cancer. This theory may explain why events that interrupt the constant cycle of ovulations, such as pregnancy, lactation, and oral contraceptives, are associated with a decreased risk of ovarian cancer. The second is that increased levels of certain hormones associated with ovulation, such as human chorionic gonadotropin, increase the risk of ovarian cancer. Fertility drugs can increase both the number of ovulations and the levels of hormones associated with ovulation.

Ovulation inducing agents have been available for clinical use for approximately 30 years and have helped many couples who might otherwise not have had children. At present there is no definitive answer in the concern that these drugs might increase the risk of developing ovarian cancer. Although there are data that support an association between fertility drugs and ovarian cancer, there are equally convincing data suggesting that there is no such association [3, 4, 12-16].

In conclusion, our patient presented with simultaneous ovarian and uterine endometrioid cancer without any clinical or histological evidence of endometriosis. The described aggressive clinical course might be attributed to the de novo advanced disease while the spread to the lungs might explain the involvement of the CNS. However, the preexisting six attempts of in vitro fertilization can not exclude the possibility of enhancement of such an aggressive phenotype. Definite conclusions can not be extracted but close clinical surveillance of such patients before, during, and after infertility treatment is strongly warranted.

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