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Case report

Conservative management of stage IIB ovarian carcinoma with favorable oncology and fertility outcomes

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1. Introduction

Epithelial ovarian cancer (EOC) is the deadliest of all gynecologic cancers, and with the advancements in surgery and targeted treatment approach, 5-year survival is 48% (American Cancer Society, 2020). Over 75% of the cases are high grade serous carcinoma. About 20% of patients are women however diagnosed with endometrioid or clear cell ovarian carcinoma, subtypes frequently associated with endometriosis. Endometriosis has several malignant-like tendencies: local and distant foci of disease with the attachment and invasion of other tissues/organs, it exhibits recurrence, and it is characterized by unregulated cell proliferation and estrogen-dependent growth (Nezhat et al., 2014; Nezhat et al., 2015). These 2 cell subtypes of ovarian cancer are often diagnosed earlier and consequently have better prognosis than more frequent high grade serous ovarian cancer, with the overall 5-year survival of about 80% in early stages (Nezhat et al., 2014). Patients with these subtypes of ovarian cancer are usually younger women who have understandable desire to treat successfully both endometriosis associated infertility and ovarian cancer.

We present a case of a patient with long standing history of endometriosis and infertility who was found to have endometrioid ovarian carcinoma after exploratory laparoscopy. We discuss the conservative cancer treatment approach and dilemma of pursuing fertility treatment with ovarian stimulation and egg retrieval and embryo freezing prior to completion of ovarian cancer treatment.

2. Case report

A 38-year-old nulligravida with known history of severe endometriosis and infertility and prior unsuccessful IUI/IVF cycles was referred to gynecologic oncology center for surgical management of bilateral endometriomas. Patient was diagnosed with endometriosis at age 28 after laparoscopic ovarian cystectomy (side unknown). She started fertility treatments at age 35, however after several unsuccessful IUI cycles she underwent a laparoscopy for treatment of endometriosis followed by 3 additional unsuccessful cycles of IVF. Subsequently she was found to have bilateral endometriomas 4x3cm (left) and 3x3cm (right) on pelvic MRI. She was treated with Leuprolide for 3 months and referred to our gynecologic oncology service. A follow up MRI showed stable size of the right ovary, while the size of the left ovary increased to 6.7 cm. Several multiple subserosal and intramural uterine leiomyomas were also noted, the largest measuring 3.2 cm and a 4.7 cm. The patient was counseled about surgical management and she consented to undergo diagnostic hysteroscopy with endometrial biopsy, exploratory

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laparoscopy and treatment of endometriosis, bilateral ovarian cystectomies, and myomectomy.

During the exploratory laparoscopy, extensive pelvic adhesions and endometriosis lesions were lysed, excised, and sent to pathologic evaluation. Due to the dense adhesions, the left ovary ruptured spontaneously during dissection from the side wall. Upon further dissection of the left ovary, a lesion suspicious for carcinoma was identified, excised, and a frozen section revealed adenocarcinoma. At that time decision findings were discussed with the husband and the decision was made to proceed with a left salpingectomy, right ovarian cystectomy, and peritoneal biopsies with planned complete surgical staging at a later date when final pathology was known and after assuring detailed discussion about fertility treatments.

Final pathology revealed endometrioid carcinoma involving the left ovary and the left pelvic adhesion, while the right cystectomy, endometrial biopsy and the remaining excised pelvic adhesions were negative, leading to possible diagnosis of at least Stage IIB, Grade I endometrioid ovarian carcinoma arising in the background of endometriosis. Immunohistochemical studies were positive for estrogen and progesterone receptor 95%, 2–3+, 95%, 3+, respectively and negative stinging for WT1, p53, vimentin. Ki-67 was positive in 20–30% of cells. Post-operative day 10 PET CT revealed hyper metabolic uptake in the endometrial canal, bilateral adnexa, and several small foci at the superior aspect of the uterus. It was unclear if these areas with increased uptake were physiologic versus related to tumor involvement. A 5 mm solitary right lower lobe lung nodule was also identified with the recommendations for additional follow up. There was no evidence of suspicious lymphadenopathy or distant metastatic disease.

The case was discussed at multi-disciplinary tumor board conference with the recommendations for standard surgical staging and adjuvant chemotherapy. However, the patient and her husband, strongly desired pregnancy and fertility sparing cancer treatment. After extensive counseling including gynecologic oncologist, pathologist and reproductive endocrinologist it was agreed for the patient to undergo fertility treatment (single cycle of ovarian stimulation for egg retrieval) followed by neo-adjuvant chemotherapy and surgical staging to include: left oophorectomy, right salpingectomy, pelvic and *para*-aortic lymph node dissection, and omentectomy.

Patient underwent an ovarian stimulation protocol commencing on day 2 of her menstrual cycle with Menopur 150 I.U., Gonal-F 250 I.U., and Letrozole 5 mg orally daily. (Oktay et al., 2006; Azim and Oktay, 2007). After 6 days of this regimen, the GnRH antagonist Ganirelix (250ug subcutaneously) was added. After 11 days of stimulation, oocyte maturation was triggered with a single IM injection of hCG 10,000 I.U., and an egg retrieval was performed 35 h later under intravenous sedation with Propofol. Her stimulation response was consistent with low ovarian reserve, with a total of only three eggs being retrieved, all from her left ovary that was previously found to contain cancer cells. After 6 days in culture, two mid-grade expanded blastocysts were biopsied and vitrified. To avoid having a child with a hemoglobinopathy, PGD testing was performed, which determined there was one non-affected blastocyst.

Due to an unexpected four-week delay in the planned chemotherapy, the couple was counseled to proceed with laparoscopic surgical staging. At the time of exploratory laparoscopy, no evidence of intra-peritoneal metastasis was noted. Surgical procedures included peritoneal washings, left oophorectomy, right salpingectomy, pelvic and *para*-aortic lymph node dissection, and omentectomy. Myomectomy also was performed since the deep intramural myoma was impinging the uterine cavity. Final pathology revealed Stage IIB Grade 1 endometrioid adenocarcinoma of the left ovary. Following the laparoscopic surgical staging, she then received adjuvant 6 cycles of Carboplatin and Taxol without complications. Follow-up PET CT scan showing no evidence of disease. She continued strict surveillance with gynecologic oncologist, hematologic oncologist, and infertility specialist. One year after completing adjuvant chemotherapy, the patient underwent a successful natural frozen embryo transfer and subsequently delivered a healthy baby boy via cesarean section, about 2 years after her initial diagnosis of cancer. The patient continues to do well without evidence of disease now over 5 years after her cancer diagnosis and 3 years after cesarean delivery. Her child is healthy and developing properly.

3. Discussion

Although ovarian cancer is usually the disease of postmenopausal women, about 12% of women with ovarian cancer are younger than 44 year old (Kim and Lee, 2016). Moreover, ovarian cancer associated with endometriosis is more likely to be found in younger patients, and it is likely to be diagnosed earlier as stage I-II, leading to improved outcomes (Paik et al., 2018). It is understandable that young women with ovarian cancer desire both preservation of fertility and successful ovarian cancer treatment.

The current guidelines recommend conservative treatment of ovarian cancer Stage IA (grade 1/2) and Stage IB lesions when fertility is desired (NCCN, 2020). The strategies aimed at preserving fertility in such cases include both fertility-sparing surgery and oocyte/embryo cryopreservation prior to undergoing cytotoxic chemotherapy (Taylan and Oktay, 2019).

However, the data is not available on safety of conservative treatment approach in ovarian cancer beyond stage I. Women with stage II epithelial ovarian cancer (EOC) have reduced 5 -year survival when compared with women with stage I disease, 70% vs 95% respectively. Nonetheless, our review of the literature discovered a total of 10 cases of stage II EOC treated conservatively in order to preserve fertility (Table 1). Four of the 10 cases were stage IIB carcinomas, however the histology and outcomes in terms of recurrences, survival and pregnancy outcomes have not been shown systematically for the 10 cases (Table 1).

Our case is unique in that our patient underwent ovarian stimulation after fertility sparing surgery with both ovaries remaining in situ until after the oocyte retrieval was completed. The viable oocyte was retrieved from the cancer containing ovary. Few prior reports described oocyte retrieval after hyperstimulation in ovarian cancer. Devesa described a series of 7 patients with ovarian cancer who underwent oocyte retrieval. (Devesa et al., 2014). Porcu et al. reported a case of healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer (Porcu et al., 2008). However, the reported oocyte cryopreservation was not from the ovary containing cancer. To our knowledge, this is the first report of a successful pregnancy and delivery using a frozen embryo generated via an oocyte retrieval from an ovary containing invasive cancer. Unlike BRCA1 and BRCA2 germline mutations, which are be transmitted in an autosomal dominance pattern, the perceived risk of transferring cancer cells by egg

Table 1
Stage II epithelial ovarian cancer conservatively managed.

Stage	Histology	Recurrence	Time to recurrence	Reference
II C	Ns, grade 2	Yes	Ns	Colombo et al. (2005)
II	Ns	Ns	Ns	Colombo et al. (2005)
II A	Ns	Yes	Ns	Morice et al. (201)1
II B	Ns	Ns	Ns	Park et al. (2008)
II B	Ns	No	Ns	Muzii et al. (2009)
II	Serous	No	N/A, NED at 50 months	Hu et al. (2011)
IIC*	Endometriod, G2	No	N/A	Petrillo (2014)
II B	Ns	Ns	Ns	Cromi et al. (2014)
II C*	Mucinous	Yes	Ns	Lee et al. (2015)
II B	Ns	Yes	5 months	Yin et al. (2019)

Abbreviations: Ns – not shown; *old staging.

retrieval from a cancer containing ovary does not exist because maternal cancer cells cannot enter the embryo. Neither the patient nor her husband were carriers of a germline cancer gene mutations.

In summary, the complexities of this case illustrate that fertility treatment and fertility preserving options are important for women with ovarian cancer and must carefully tailored individually. The multidisciplinary team of gynecologic oncologists, reproductive endocrinologists and embryologists is paramount to assure that both cancer treatment and fertility preservation are considered in young women with ovarian cancer.

Author contribution

Study Design: FN
Study implementation: AB, MW, DT
Data analysis and review: FN
Manuscript writing and editing: AB, TP, FN.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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