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Case report

Successful yolk-sac tumor treatment with fertility-sparing partial oophorectomy

Timothy N. Dunn[a,*], Kamyar Khazaeian[c], Donna M. Coffey[c], Jan Rohozinski[b,e], Ertug Kovanci[d], Creighton L. Edwards[b], Celestine S. Tung[b]

[a] Department of OB/GYN, University of Alabama-Birmingham, 1700 6th Ave S, Woman & Infants Center Rm 5328, Birmingham, AL 35233, USA
[b] Department of OB/GYN, Division of Gynecologic Oncology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA
[c] Department of Pathology and Genomic Medicine, Houston Methodist Hospital, 6565 Fannin Street, Houston, TX 77030, USA
[d] Houston Fertility Specialists, 7900 Fannin Street, Suite 4400, Houston, TX 77054, USA
[e] Wake Forest School of Medicine, Institute for Regenerative Medicine, Winston-Salem, NC 27157, USA

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ABSTRACT

Yolk-sac tumors account for about 20% of ovarian germ cell tumors and occur predominantly in women below 35 years of age. Modern evidence-based treatment strategies have ensured long term post-treatment survival, but with increased survival, attention has been turned to an urgent need for developing fertility sparing treatment strategies. In this report we describe the successful treatment of a young woman who was able to conceive and deliver two children, in spite of the loss of one ovary two years prior to being diagnosed with an ovarian yolk-sac tumor on the remaining ovary.

1. Introduction

Malignant ovarian germ cell tumors are relatively rare and account for 2–3% of all ovarian tumors, with yolk-sac tumors accounting for 20% of these malignancies (Brown et al., 2014; de La Motte Rouge et al., 2008). 81% of yolk-sac tumors occur in women at or below 35 years of age, encompassing prime reproductive years for many patients (Nasioudis et al., 2017a). When treated early (Stage I and II), prognosis is good with stage-specific long term survival rates of 94.8% and 97.1% respectively (Nasioudis et al., 2017a). There is thus an urgent need to develop fertility-sparing surgical and treatment strategies for this patient group to minimize damage to their potential fertility (Aviki and Abu-Rustum, 2017; Nasioudis et al., 2017b). A report by de La Motte Rouge et al published in 2008 recorded that 21% of women presenting with yolk-sac cancers underwent radical surgery (bilateral salpingo oophorectomy with or without total abdominal hysterectomy) and 79% underwent conservative surgery (unilateral salpingo oophorectomy, unilateral oophorectomy or unilateral cystectomy) (de La Motte Rouge et al., 2008). More recent survey data published in 2017 indicates that the use of conservative fertility-saving surgical strategies may have actually decreased during the ten years separating the 2008 and 2017 surveys (Nasioudis et al., 2017a). Of particular note is the increased reported incidence of hysterectomies (38.2% of patients) in the 2017 report.

Herein we report the rather unique case of a 24 year old woman who had previously had a left oophorectomy to treat a mature teratoma two years prior to presenting with a solid pelvic mass on the right side. The mass was diagnosed as a stage IIB yolk-sac tumor at the time of surgery. Due to her age it was decided to proceed with a fertility sparing strategy to save as much of the healthy unaffected ovary as possible. She underwent pelvic mass resection but a portion of morphologically normal-appearing ovary, her fallopian tube, and her uterus were left in place. In addition, a portion of apparently unaffected ovary was collected for cryopreservation and future oocyte utilization. Post treatment menstruation resumed, and with the aid of in vitro fertilization (IVF), the patient was able to conceive and deliver two healthy children 6.5 and 10 years after successful surgery and treatment for the yolk-sac tumor.

2. Case

2.1. Medical history and diagnosis

In 2005 a 24-year old nulliparous female presented for evaluation of a recently discovered solid pelvic mass that had been identified by ultrasound. Two years before presentation she had undergone a left oophorectomy for a mature teratoma. The patient had experienced increased dysmenorrhea along with abdominopelvic pain, with

* Corresponding author.
E-mail address: timothydunn@uabmc.edu (T.N. Dunn).

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examination revealing a large pelvic mass extending to 6 cm below the umbilicus. Laboratory tests showed elevated AFP of 31,994.9 ng/ml (normal < 10 ng/ml) and slightly elevated CA125 of 40 U/ml (normal < 35 U/ml). Inhibin B and hCG (human chorionic gonadotropin) levels were normal. Ultrasound, when done by her referring provider, revealed a solid and cystic mass measuring at least 10x12cm. Surgery was scheduled due to concern for the possible presence of a malignant germ-cell tumor.

2.2. Treatment

Due to her age, desire for future child-bearing, and surgical history, a unique fertility sparing strategy was chosen. The operative plan included laparotomy and tumor reduction, with possible ovarian salvage for oocyte preservation prior to bleomycin-etoposide-cisplatin (BEP) chemotherapy.

Intraoperative abdominal exploration identified a 12 cm right ovarian mass with a thin rim of ovarian tissue that appeared normal and was thought to be uninvolved by the neoplasm. Given no gross disease on the uterus or fallopian tube, those structures were left in place. The ovarian mass was dissected away from the apparently normal ovarian tissue by visual inspection from which an additional 1 × 2 cm sample was collected for cryopreservation. Remaining vascularized ovarian tissue was remodeled into an ovary and left in situ in the pelvis.

Gross pathology of the removed tumor is shown in Fig. 1. Clear surgical tumor margins were observed under microscopic examination. Histological analysis (see Fig. 2) revealed a tumor with an admixture of histological patterns. The predominant pattern was reticular with areas of solid or microcystic architecture. Hyaline globules were also present, as were Schiller-Duvall bodies, all three features consistent with yolk sac tumor histology. In addition, areas of cells with clear to eosinophilic cytoplasm, pleomorphic nuclei with prominent nucleoli and brisk mitotic activity were also observed. The only positive staging biopsy was on the rectosigmoid serosa, giving a final diagnosis of stage IIB yolk-sac tumor.

Chemotherapy treatment was started 27 days postoperative and consisted of four BEP cycles. Therapy cycles lasted 3 days with cisplatin (75 mg/m^2) given on day 1, and etoposide (100 mg/m^2) and bleomycin (10 units) given on day 1, 2 and 3 at three weekly intervals. After surgery, AFP levels dropped to 731.6 ng/ml measured prior to beginning chemotherapy. Subsequent AFP levels decreased to 39.6 ng/ml before cycle two, 3.3 ng/ml before cycle three, and 1.6 ng/ml prior to her fourth and final cycle. Surveillance AFP levels have all been in the normal range since that time. The patient is now without recurrence for 13 years.

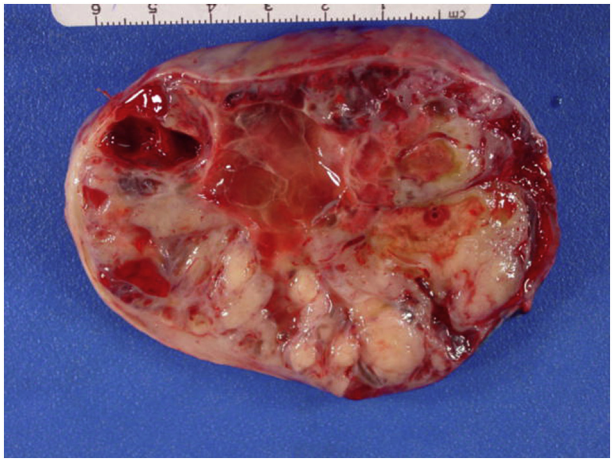

Fig. 1. Gross Morphology.
Cross section of the patient's right adnexal mass revealed a heterogeneous cut surface with predominant solid and focal cystic areas. Hemorrhage and focal necrosis were noted.

2.3. Post treatment reproductive health

Four months after completing chemotherapy, a regular 28 day pattern of menstrual cycles was reestablished, and the patient married three years post treatment. Spontaneous conception was attempted for over a year before referral to an infertility specialist for assisted reproductive treatment. At age 31, and six years after chemotherapy, her Anti-Müllerian Hormone (AMH) was < 0.08 with a day three Follicle-Stimulating Hormone (FSH) of 11.8.

2.4. Pregnancy 1

After testing her partner for male factor infertility and establishing a normal sperm count it was decided to proceed with IVF due to diminished ovarian reserve. After a single cycle of stimulation in May 2011, eight eggs were retrieved. Six were mature (Metaphase II) and underwent intracytoplasmic sperm injection (ICSI). Five were fertilized and 3 reached blastocyst stage. Two blastocysts were transferred which resulted in a healthy, full term 6 lb. 12 oz. baby girl via successfully vaginal delivery in February 2012.

2.5. Pregnancy 2

A second attempt at pregnancy in 2013 using the frozen blastocyst remaining from the IVF cycle in 2011 was unsuccessful. Therefore 3 cycles of stimulation for IVF were performed in 2014 which yielded 5 eggs in total. Two day 3 embryos were obtained and frozen. These two embryos were transferred in February 2015 resulting in another singleton pregnancy. A healthy full term boy was delivered without complications in October 2015.

3. Discussion

The majority of yolk-sac tumors occur in women at or below 35 years of age during preadolescent or prime reproductive years when fertility conservation is of prime concern to both the patient and treating clinicians (Nasioudis et al., 2017a). As chemotherapy has improved patient survival, there has been a resurgence of interest in pursuing fertility sparing strategies due to the age of the patients affected most commonly by these diseases (Aviki and Abu-Rustum, 2017; Nasioudis et al., 2017b). There are many factors that influence the utilization of fertility-sparing treatment of gynecological malignancies (Shah et al., 2017). A shortage of reports describing successful cases of fertility preservation has led to a lack of consensus on treatment strategies. In the case of germ cell tumors this has been partially addressed at a conceptional level by Nasioudis et al (Nasioudis et al., 2017b) but there is still a need for the development of consensus at the level of clinical practice. With the focus on fertility-preserving surgery, however, a patient such as this with a prior oophorectomy now with a malignancy in her only remaining ovary presents a conundrum for the treating clinician. The standard of care regarding these malignancies is a USO, which would obviously leave a similar patient destined for surgical menopause and the inability to have her own genetic children. While there have been reports of cystectomy alone for an immature teratoma, this is the first case of partial oophorectomy for a yolk-sac tumor. With the success of chemotherapy as previously described, in situ ovarian preservation could be explored as a means to maintain some viable ovarian tissue for fertility in similar patients. In light of this, some women might benefit from the involvement of fertility specialists in the development of pre-treatment fertility-preserving strategies, especially as certain medical therapies exist that can help preserve ovarian function (Anderson et al., 2017). An example of this is the recent increasing consensus that using gonadotropin-releasing hormone antagonists during chemotherapy might minimize ovarian damage

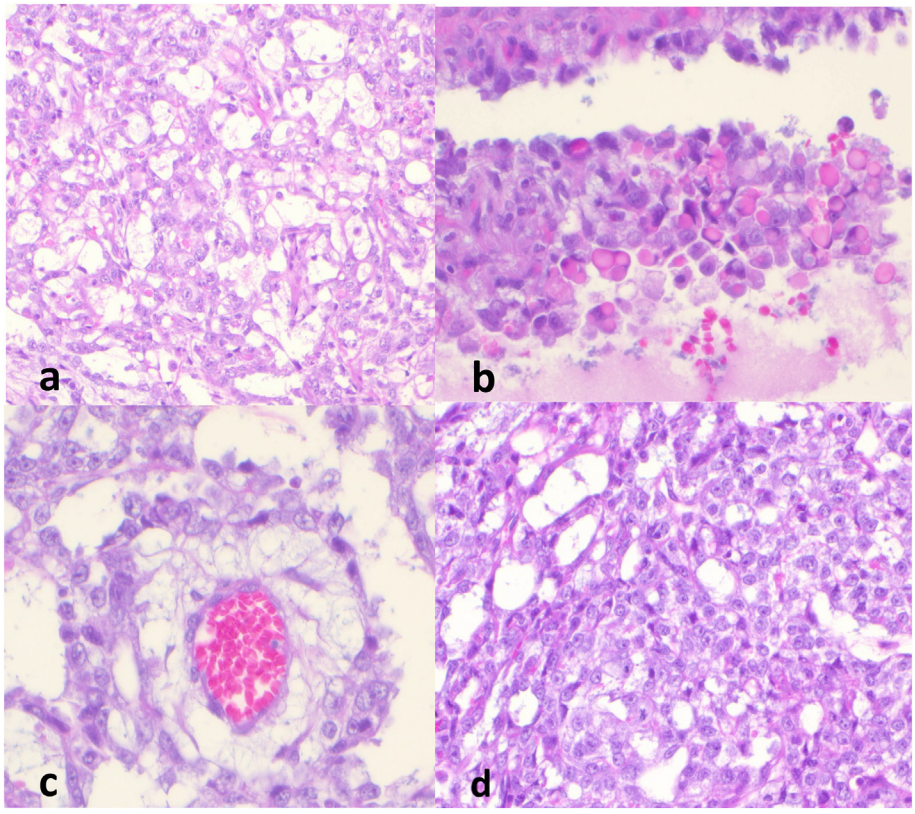

Fig. 2. Microscopic Findings.
a. Yolk Sac tumor has an admixture of different patterns. The most common pattern is the reticular pattern characterized by lace like pattern with interanastomosing channels or spaces.
b. Intracellular or extracellular hyaline globules are often present. Hyaline globules are PAS diastase positive.
c. Shiller- Duval bodies are pathognomonic of yolk sac tumor; however they are only found in one-third of cases. Shiller Duval bodies have a central capillary surrounded by loose stroma and an outer layer of neoplastic cells.
d. Cytologic features of yolk sac tumor: Cells with clear to eosinophilic cytoplasm, pleomorphic nuclei with prominent nucleoli and brisk mitotic activity.

(Hickman et al., 2016). Overall, as seen in this patient's case, in situ preservation of morphologically normal ovarian tissue via partial oophorectomy followed by chemotherapy can potentially result in both a durable cure and fertility.

4. Conclusions

Because of the very high long term survival rates observed in women treated for yolk-sac tumors during their reproductive years, there is a continued need for approaches to fertility preservation. In situ conservation of ovarian tissue unaffected by tumor growth can be considered as part of the patient's management should she have a prior history of contralateral oophorectomy. Restoration of normal menses post treatment may occur spontaneously, but when strategies that utilize ovarian tissue conservation are employed, fertility specialists should be part of the clinical team to aid these patients in their attempts for normal reproductive and endocrinologic function.

Conflict of interest

The authors have no financial disclosures to declare.

Author contribution

Dr. Timothy Dunn created the initial draft of the manuscript. All authors were involved in reviewing, editing, and contributing to reference information. Drs. Coffey and Khazaeian were primarily responsible for histopathology.

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