

Case Report

Adult Granulosa Cell Tumor: A Sinister Differential for Clomiphene-resistant Infertility

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ABSTRACT

Granulosa cell tumors (GCTs) are rare sex cord–stromal tumors of the ovary. They may present with features of hyperestrogenism. We present a case of a 29-year-old nulliparous female, with infertility and oligomenorrhoea, initially managed with a provisional diagnosis of polycystic ovarian syndrome. She did not respond to multiple cycles of ovulation induction with clomiphene citrate. Later, an ovarian mass was detected, and she was initially planned for laparoscopy. Magnetic resonance imaging pelvis revealed a solid-looking mass in the ovary, with increased vascularity. Fine-needle aspiration cytology from the mass suggested GCT. She underwent staging laparotomy with fertility-preserving surgery. Thereafter, she conceived on first cycle of clomiphene citrate. She delivered twins and is presently 8 months postpartum. Thus, a high index of suspicion for underlying androgen- or estrogen-secreting tumor in cases of clomiphene-resistant infertility with ovarian cysts is advisable.

KEYWORDS: Clomiphene, follow-up, granulosa cell tumor, infertility

INTRODUCTION

Granulosa cell tumors are one of the rare tumors of ovary.^[1] These sex cord stromal tumors of ovary are characterized by affection at younger age group and good prognosis with early detection and treatment.^[2] They are estrogen secreting tumors and commonly present with menstrual disturbances and features of hyperestrogenism in the reproductive age women.^[1] We present a case of a 29 year old female who presented with infertility and ovulated with clomiphene citrate, after surgical excision of the tumor.

CASE REPORT

A 29-year-old nulliparous female presented to our outpatient department with the inability to conceive for 4 years. She also complained of amenorrhea, with menstruation occurring only after progesterone withdrawal. There were no associated complaints of acne, hirsutism, weight gain, or galactorrhea. She had been evaluated at a local private hospital and was being treated as a case of polycystic ovarian syndrome. She had received multiple cycles of ovulation induction with clomiphene citrate as well as gonadotropins

but did not ovulate. There was no significant family history. At our institute, she was prescribed tablet metformin and given clomiphene citrate for ovulation induction, with no success. After 3 months of treatment, pelvic sonography revealed bulky left ovary with hemorrhagic/endometriotic cyst. She was thus planned for laparoscopy. She returned after 3 months, and a magnetic resonance imaging pelvis was done, which reported a large (5.7 cm × 5.3 cm × 5.3 cm) mass in left adnexa with increased vascularity likely sclerosing stromal tumor. Ultrasound-guided fine-needle aspiration was done, which revealed granulosa cell tumor (GCT). By this time, cystic mass was palpable anterior to uterus on bimanual examination. Her serum anti-Müllerian hormone (sAMH) was >20 ng/mL, whereas inhibin B was >1122 pg/mL (normal range 14–362 pg/mL). Endometrial biopsy showed proliferative endometrium. She underwent staging laparotomy with

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Access this article online

Quick Response Code:



Website:
www.jhrsonline.org

DOI:
10.4103/jhrs.JHRS_142_17

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How to cite this article: Gainer S, Kaur J, Siwath S, Gupta N. Adult granulosa cell tumor: A sinister differential for clomiphene-resistant infertility. J Hum Reprod Sci 2018;11:190-2.

left salpingo-oophorectomy and multiple peritoneal and omental biopsies. Intraoperatively, there was 6 cm × 6 cm left ovarian mass with surgical spill, right ovary and tube was normal, no evidence of metastasis, and no palpable lymphadenopathy. Histopathology report showed adult GCT limited to left ovary. Her final diagnosis was adult GCT Stage IC1. Postoperative period was uneventful. She had normal menstrual cycles from the next month. She was advised clomiphene citrate as she was apprehensive and eager to conceive and there was no contraindication for its use. She conceived twins in her first clomiphene cycle. She went into preterm labor at 32-week period of gestation and delivered twins weighing 1.8 and 1.9 kg. Three months postpartum, her clinical examination was unremarkable. Inhibin levels were 15 pg/mL at 6-month follow-up. She was asymptomatic at her last follow-up visit at 8-month postpartum.

DISCUSSION

GCT is a type of sex cord–stromal tumor of ovary. With an incidence of about 0.58–1.6 per 100,000 women per year, it contributes to <5% of ovarian tumors.^[1]

Some characteristic features of GCTs in contrast to the more common epithelial tumors include affecting younger age group, features of hyperestrogenism, detection at early stage, and good prognosis with surgical cure.^[1] It is also a differential diagnosis of isosexual precocious puberty. Initial symptoms may be nonspecific like pain abdomen or distension. About 30% of patients in reproductive age group present with menstrual disturbances, as seen in our patient.^[1]

Adult variety of GCT is generally seen in the premenopausal or early postmenopausal women and the median age of diagnosis is 51 years, although it has been reported from 9 to 93 years, our patient being 29 years.^[2] Physical examination may reveal a pelvic mass, as was seen in our patient.

Ultrasonography is nonspecific and may show a unilateral echogenic cystic or solid mass, with no papillary projections and thickened endometrium.^[3] Serum inhibin B, sAMH, and 17β estradiol may help in indicating toward the underlying pathology. Inhibin B has a reported sensitivity of up to 89% and specificity of almost 100%.^[4] AMH is also a reliable tumor marker with sensitivity between 76% and 100%.^[5] Our patient also had high inhibin B and sAMH values. sAMH and inhibin B are also useful for posttreatment follow-up and detection of tumor recurrence. Preoperative workup must include endometrial biopsy as endometrial hyperplasia is found in 25%–50% of cases, whereas endometrial carcinoma has been seen in 5%–13% of cases.^[6] Final diagnosis is made on histopathology.

Surgery is the primary treatment modality. When fertility preservation is not desired, staging laparotomy through midline vertical incision involves total abdominal hysterectomy and bilateral salpingo-oophorectomy, exploration of peritoneal cavity, washings for cytology, multiple peritoneal biopsies, and omentectomy. Routine lymphadenectomy is not shown to improve survival.^[7] In young patients with Stage Ia tumor, unilateral salpingo-oophorectomy is a feasible option.^[8] As bilaterality is encountered in <2% patients, wedge biopsy of contralateral ovary is controversial. Complete surgery, although not imperative, can be considered after childbearing.^[8]

A decrease in 25-year survival from 86% in patients with Stage Ia disease to 60% in patients with Stage Ic has been reported.^[6] In a recent study by Park *et al.*, the 5-year disease-free survival and overall survival rates in early stage (Stage I and II) disease were 89% and 99%, respectively, whereas, in advanced stage (Stage III and IV) disease, it was 72% and 80%, respectively.^[9]

As patients with early stage disease (Stage I and II) have a very good prognosis, postoperative treatment is usually not required. Some studies have shown that patients with Stage Ic disease with poor prognostic factors such as large tumor size, high mitotic index, tumor rupture, or incomplete staging have a higher chance of relapse and may benefit with postoperative treatment.^[10] Platinum-based chemotherapy (bleomycin, etoposide, and cisplatin) for 6 cycles is most commonly used for adjuvant chemotherapy in advanced stage. The response rates have varied from 60% to 93% and duration of response 5–58 months.^[9] Radiation is not routinely recommended for treatment of primary tumor.^[11]

Lifelong follow-up with clinical examination, ultrasound, and inhibin measurement is recommended as recurrences are late. For recurrent disease, combined modality of treatment, usually involving debulking of the disease followed by radiation or chemotherapy, is the norm and may prolong the DFS.^[12] Hormonal therapies such as medroxyprogesterone acetate, megestrol acetate, tamoxifen, aromatase inhibitors, and gonadotropin-releasing hormone agonists have been tried for recurrent and advanced disease but with varied success.^[6]

CONCLUSION

GCT is indolent tumors which should be considered as differential diagnosis in infertility patients resistant to ovulation induction. Survival rates are high with primary treatment in early stages. Long-term surveillance is essential to detect late recurrences.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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