

# GnRHa as a Treatment for Letrozole-Resistant Recurrent Adult Granulosa Cell Tumors: A Case Report and Literature Review

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## Case report

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# Abstract

**Background:** The optimal management of Recurrent Ovarian granulosa cell tumors was still unknown, Hormone therapy maybe an alternative for chemotherapy-resistant cases. the reaction rate for aromatase inhibitors was highest, how to treat the progressed case after aromatase inhibitors was challenging.

**Case presentation:** Here we report a case of Recurrent Ovarian granulosa cell tumors treated with Diphereline and achieved clinical cure. A 46-year-old woman presented with third recurrence after primary treatment. She developed tumor progression and drug-induced nephritis after 6 cycles of combined treatment of cisplatin and paclitaxel for the second recurrence and failed to benefit from chemotherapy ,after the third Optimal cytoreduction and tumor progression after 6 months Letrozole treatment. The implementation of experimental treatment with Diphereline achieved Good therapeutic effect.

**Conclusion:** Hormone therapy maybe an alternative to recurrent granulosa cell tumors, Gonadotropin-releasing hormone agonists maybe a rescued treatment for Aroatase inhibitor-resistant cases

## Highlights

1. There is no optimal treatment for recurrent GCTs. For this patient, we tried to use hormone therapy instead of chemotherapy and radiotherapy.
2. Considering the different mechanisms of action of Letrozole and GnRHa, We chose GnRHa treatment after letrozole resistance.
3. Though the literature reported that letrozole had the highest response rate, this patient still benefited from GnRHa even after letrozole resistance. As far as we know, no similar case has been reported

## Introduction

Ovarian granulosa cell tumors(GCTs) constitute less than 5 % of all ovarian tumors. Unlike epithelial ovarian tumors, they occur in a younger age group, are usually detected in an early stage. They follow an indolent course and are characterized by a long natural history. Due to the chance of recurrence even years after apparent clinical cure of the primary tumor, lifelong follow up is recommended. About 25 % GCTs develop recurrence and the median time of recurrence is usually 4–5 years<sup>[1]</sup>. Most recurrences are intraperitoneal and usually complete debulking of the disease is feasible even in cases with recurrent. Postoperative chemotherapy (platinum based) is usually given after surgery in cases with widespread disease or after sub-optimal cytoreduction. Recurrent chemoresistant, progressive non-responding GCTs or patients with high surgical risk are ideal candidates for targeted therapy<sup>[2]</sup>. During the last decade, our understanding of the molecular pathogenesis of adult GCTs has significantly improved, whereas the developments of chemotherapeutic regimens and targeted therapies have remained modest. Here we report a case of Recurrent adult Granulosa cell tumors, after three times of cytoreduction, we administered letrozole as postoperative treatment for 6 mouths. Recurrence was proved by radiographic findings and

letrozole resistance was considered. Then we administered Gonadotropin-releasing hormone agonists (GnRHa) treatment and achieved clinical cure.

## Case Presentation

46-year-old female patient was undergoing the third recurrence after primary treatment for adult GCTs. Total abdominal hysterectomy, bilateral salpingo-oophorectomy with pelvic and abdominal para-aortic lymph node dissection was performed under open surgery for the Ia stage of left ovarian granulosa cell tumor in 2005. During the 10 years of postoperative regular follow-up, the tumor marker (including CA12-5, CA19-9, CEA, CA153, AFP, AMH, inhibinA) were normal as well as imaging evaluation. In February 2017, with the complaint of lower abdominal pain with abdominal distension, no nausea, vomiting, bloody stool and other discomfort, she was referred to the Gynecology of the Fifth Affiliated Hospital of Sun Yat-sen University. A mass of 73 x 62 mm was found during pelvic midline region by total abdominal MRI scan. Local recurrence of granulosa cell tumor was considered, and laparoscopic pelvic mass resection was performed. Intraoperative exploration revealed a mass of about 8.0 x 6.0 cm was found in the middle pelvic cavity with unclear boundary, adhesion to the bowel, small intestine and sigmoid distorts. Part of the intestinal serous layer is invaded by tumors, the surgeons completely removed the mass without excising intestines. Postoperative pathology confirmed the recurrence of ovarian granulosa cell tumor. Immunohistochemistry showed tumor cells: Vimentin(+), CD99(+), inhibin(+). However, postoperative chemotherapy was refused. In May 2018, CT scan showed: Multiple masses located in retroperitoneum, liver and kidney recess (Figure 1A), peritoneum and pelvic cavity (Figure 1B, 1C). Considering metastatic tumor with partial bleeding, no significant changes in pelvic and abdominal tumors were assessed after treatment with combined paclitaxel 240 mg and cisplatin 100 mg for 6 cycles. The level of serum creatinine elevated, was diagnosed with drug-induced interstitial nephritis, symptomatic treatment was given. In July 2019, MRI scan found: multiple metastatic tumors of liver and kidney recess, pelvic wall peritoneum and pelvic cavity with partial hemorrhage. The lesion was slightly enlarged (Figure 1D), the third optimal cytoreduction to no residual disease was performed on 16 July 2019. Intraoperative exploration revealed 2.0 x 3.0 x 2.0 cm metastatic neoplasm located in the right pelvic cavity, 1.5 x 2.0 x 3.0 cm metastatic neoplasm in the left pelvic cavity, about 8.0 x 7.0 x 7.0 cm metastatic neoplasm transposed the anterior wall of the sigmoid rectum, encapsulated by the gut, infiltrated growth. Multiple localized tumors located in the peritoneum. A localized tumor mass of about 5.0 x 5.0 x 4.0 cm, was seen in the peritoneum of the hepatic and renal recess, no enlarged lymph nodes were found. No significant tumor was found on the surface of liver and diaphragm, the surgeons completely removed all visible metastatic tumors with partial sigmoidectomy and intestinal anastomosis. Postoperative pathologic findings: Metastatic ovarian granulosa cell tumor, D99(+), CD56(+), Ki67(10%+) (Figure 1D). Postoperative adjuvant treated with the regimen of Letrozole 2.5 mg qd. A total abdominal CT scan was reviewed in November 2019, no abnormality was found (Figure 2A). Continued to be treated with letrozole. But in February 2020, the MRI scan showed a 3.0 x 2.5 cm metastatic neoplasm located abdominal para-aorta (Figure 2B). Letrozole resistance was diagnosed. After MDT consultation, we try to experimental treatment with Diphereline 3.75 mg im q28d for 3 cycles, the size of metastatic neoplasm reduced to 1.3 x 0.5 cm under the CT scan.

in August 2020(Figure 2C), Continued to be treated with Diphereline ,In February 2021, CT scan showed the Metastatic neoplasm disappear (Figure 2D),achieved clinical cure, So far, PFS reached 12 months, Proposed continued the current programme treatment

## Discussion

GCTs have a tendency for late recurrence., and lead to fatal ending in 82% cases. The longest reported survival time after recurrence is 40 years. About 21 % cases developed recurrence and the median time to relapse was 57.6 months (2-166 months) according to previous reports [3].The optimal management of Recurrent GCTs has never been determined by randomized trials.A combined modality of treatment, usually involving debulking of the disease followed by radiation or chemo-therapy is the norm and may prolong the DFS. Response rates for the most common combination of bleomycin, etoposide and cisplatin vary from 37–83% in older studies [4].but in the most recent series the responses are only moderate, reaching 22–35% [5]. It must be noted the current evidence is based on mostly retrospective studies on non-validated GCTs cohorts, presenting as a potential confounder when evaluating these responses. Combination chemotherapy with paclitaxel and carboplatin has also been used, providing with the same efficacy albeit less toxicity compared with bleomycin, etoposide and cisplatin.The role of adjuvant chemotherapy in adult GCTs is also obscure; reasonably high response rates to platinum-based combination therapies have been reported [6]. However ,adjuvant chemotherapy does not seem to significantly affect patient outcomes[7],This patient developed tumor progression and drug-induced nephritis after 6 cycles of TP chemotherapy for the second recurrence and failed to benefit from chemotherapy. So after the third Optimal cytoreduction, no more adjuvant chemotherapy was given.

How to treat the insensitive tumor patients to chemotherapy is still a difficult problem. Granulosa cell tumor is hormone sensitive type. Compared with chemotherapy, hormone therapy has the advantages of high tolerance, long-term application and no serious side effects. At present, the study is limited to case reports. A recent systematic review[8] reviewed 31 patients from 19 studies with a total response rate of 71%, of which the complete response rate was 25.8% and the partial response rate was 45.2%. The effect of different types of hormone therapy was not the same, and the reaction rate of aromatase inhibitors was 100%, while that of tamoxifen was 0%.This patient developed tumor progression after Letrozole treatment for 6 months, There is no previous literature on the treatment of Letrozole resistant GCTs

Estrogen stimulates proliferation of granulosa cells by increasing the cells responsiveness to FSH. Hormonal manipulation of GCT arise from the surmise that suppression of endogenous estrogen will provide an anti-proliferative milieu which could be effective in treating GCT. Several mechanisms have been suggested for how hormone manipulation may inhibit tumor growth in GCT. These can be categorized as indirect action on tumors via suppression of gonadotropins or endogenous steroids and direct effects on the tumor via a local mechanism mediated by specific receptors in the GCT. Various drugs like medroxyprogesterone acetate, megestrol acetate, tamoxifen, aromatase inhibitors and GnRH agonists have been tried, but with varied rate of response[9]. Progestins act as chemopreventive agents by

inducing apoptosis pathway involving transforming growth factor (TGF- $\alpha$ ) in ovarian epithelium, a plausible local mechanism for inhibiting tumor growth. Malik et al<sup>[10]</sup> have documented prolonged remission (14–42 months) in patients having extensive disease treated with high doses of medroxyprogesterone acetate (100–300 mg thrice daily). Hardy et al<sup>[11]</sup> by alternating biweekly cycles of megestrol acetate (40 mg twice daily) with tamoxifen (10 mg twicedaily) in a patient with recurrent ER negative PR positive GCT documented a CR at 22 months and a DFI of 5 years. Continuous progesterone exposure leads to depletion and down regulation of PRs in target tissues while tamoxifen increases PR concentration. Thus, sequential therapy may prolong the antiproliferative effects of progestin by allowing regeneration and stimulation of PRs. steroidal aromatase inhibitors (anastrozole and letrozole) act by inhibiting the conversion of androstenediol to estriol and testosterone to estradiol. They cause up to 90 % reduction of aromatization of androgens and have few side effects. Freeman et al<sup>[12]</sup> have reported the use of anastrozole (1 mg/day) and letrozole (2.5 mg/day) in recurrent GCT and have documented remissions ranging from 12 to 54 months. There was reduction in size of disease, few cases had complete response and fall in inhibin levels were seen. Moreover there was an improvement in the performance status. GCTs express receptors for follicle stimulating hormone (FSH), which has been shown to support the growth of GCTs. Thus, hormonal therapies that can decrease gonadotropins may block the stimulatory effects on granulosa cells. Kim et al<sup>[13]</sup> have described PR with monthly GnRH agonists (leuprolide acetate 3.75 mg IM) lasting 3– 11 months. Think about the different mechanism of anti-proliferation between aromatase inhibitors and GnRH agonists ,A few other studies have shown partial response to GnRH agonists<sup>[14]</sup>. while other studies showed no response to GnRH antagonists<sup>[15]</sup>. Experimental treatment with Diphereline for this patient was impleted which has achieved good therapeutic effect. Prospective multicentric trial is needed to address the role of hormone therapy for management of these rare neoplasms.

## Conclusion

The surgical treatment of GCT should aim for optimal cytoreduction,Hormone therapy maybe an alternative to recurrent GCT. It is found difficult and time-consuming to make studies on new drugs and combinations in prospective clinical trials because of ttumor relative rarity and its prolonged disease course. Large international clinical trials are needed to validate new treatment strategies for patients with GCTs

## Declarations

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Not applicable.

### **Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

### **Authors' contributions**

All authors analyzed and interpreted the patient data according to the histological examination and the literature review. YH was a major contributor in writing the manuscript, and ZY was in charge of the final approval of the version to be published. ZY and YH performed the surgery, and ZY served as the endocrinology doctor who was responsible for the patient's treatment

throughout this process. All authors read and approved the final manuscript.

### **Competing interests**

The authors declare that they have no competing interests.

### **Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### **Ethics approval and consent to participate**

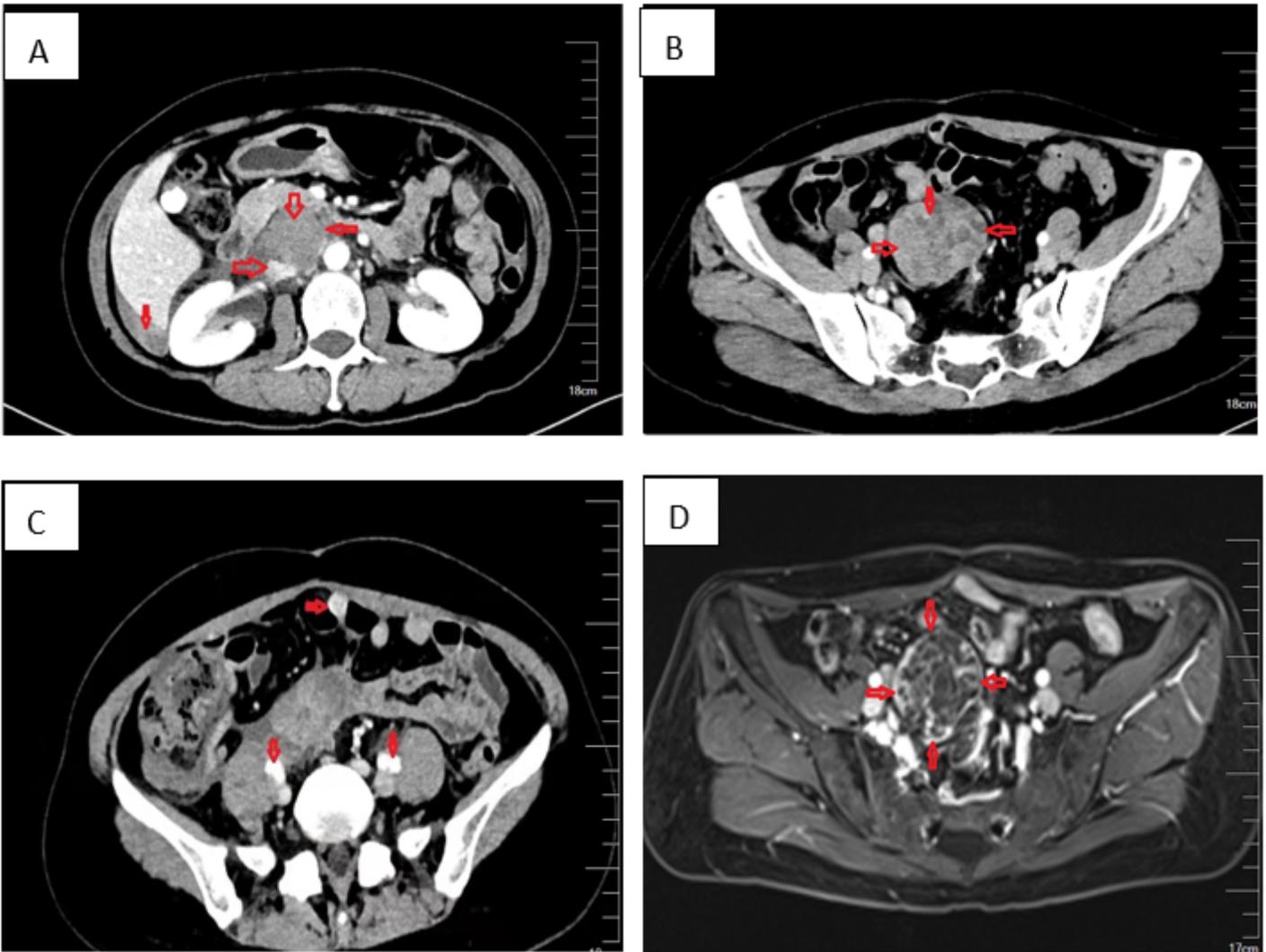
Approval was obtained from the Institutional Review Board (IRB) of The Fifth Affiliated Hospital of Sun Yat-sen University for publishing this case report.

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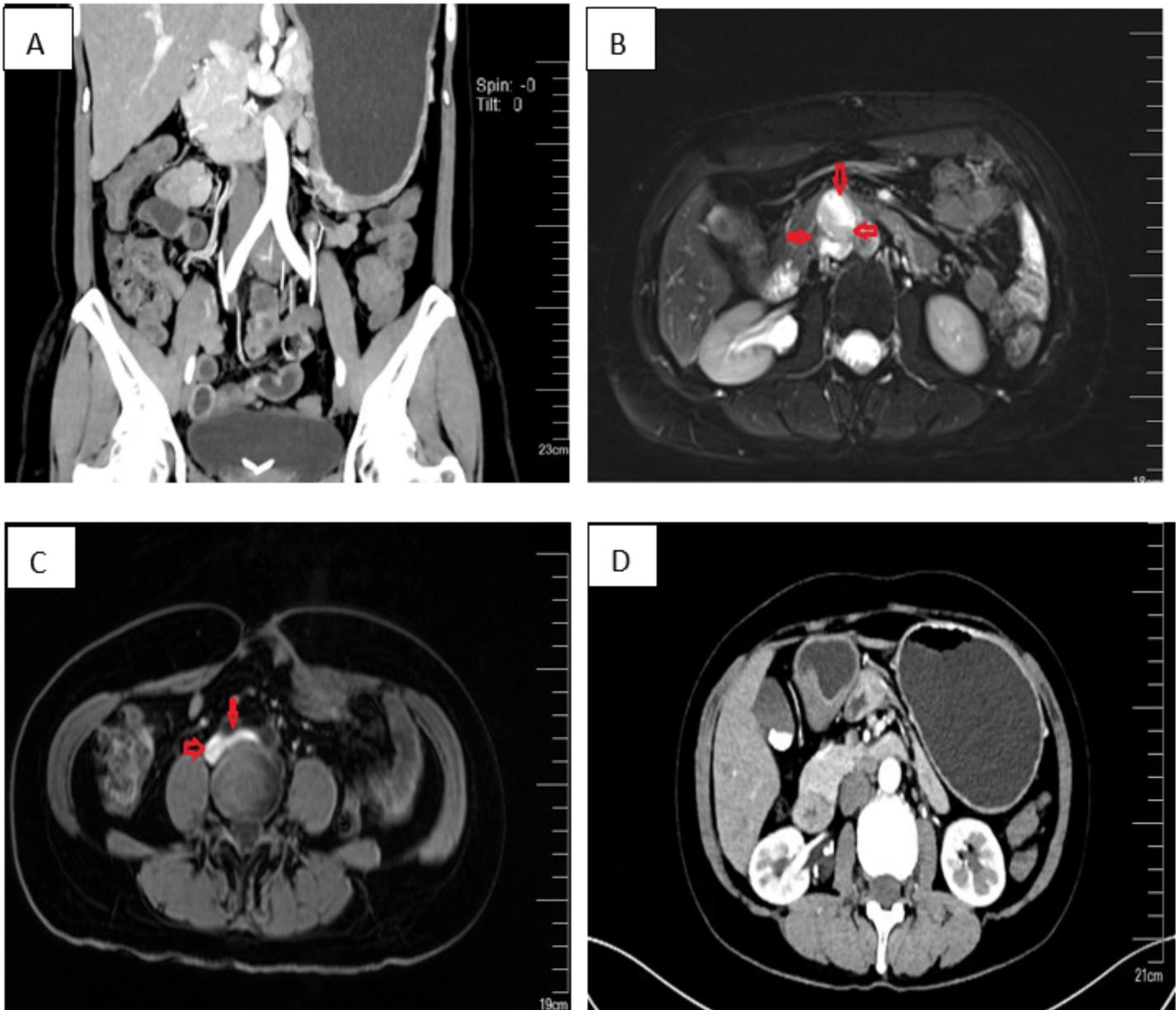
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## Figures



**Figure 1**

In May 2018,CT scan found : Multiple masses Located in liver and kidney recess(A), peritoneum and pelvic cavity(B,C) . In July 2019,MRI scan found metastatic tumors of pelvic cavity was slightly enlarged(D)



**Figure 2**

in November 2019, No abnormality was found; in February 2020, The MRI scan showed a 3.0 x 2.5cm Metastatic neoplasm located abdominal para-aorta(B); in August 2020, the size of Metastatic neoplasm Reduced to 1.3 x 0.5cm (C), In February 2021, CT scan showed the Metastatic neoplasm disappear (D)