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

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Yang H, Zhuang Y these authors are equally contributed to this work.

1. Abstract

Ovarian Granulosa Cell Tumors (GCTs) are the most common type of ovarian sex cord-stromal tumor. They follow an indolent course and are characterized by a long natural history The optimal management of Recurrent GCT has never been determined by randomized trials , Hormone therapy maybe an alternative here we report a case of Recurrent GCT treated with GnRHa and achieved clinical cure.A 46-year-old woman presented with third recurrence after primary treatment for adult granulosa cell tumor. She developed tumor progression and drug-induced nephritis after 6 cycles of TP chemotherapy for the second recurrence and failed to benefit from chemotherapy, after the third Optimal cytoreduction and tumor progression after Letrozole treatent for 6 months. we try to Experimental treatment with Diphereline achieved Good therapeutic effect.

2. Highlights

- There is no optimal treatment for recurrent granulocell tumor. For this patient, we tried to use hormone therapy replace of chemotherapy and radiotherapy.
- Considering the different mechanisms of action of Letrozole and GnRHa, we tried GnRHa treatment after letrozole resistance.
- The literature reported that letrozole had the highest response rate, but this patient still benefited from GnRHa even after letrozole resistance, as we know, no similar case has been reported.

3. Introduction

Granulosa cell tumors 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 % GCT develop recurrence and the median time to recur is usually 4–5 years [1]. Most recurrences are intraperitoneal and usually a complete debulking of the disease is feasible even in the recurrent setting. Postoperative chemotherapy (platinum based) is usually given after surgery more so in cases with widespread disease or after sub-optimal cytoreduction. Recurrent chemoresistant, progressive non-responding GCT or patients with high surgical risk are ideal candidates for targeted therapy [2]. During the last decade, our understanding of the molecular pathogenesis of AGCTs 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 use letrozole as postoperative treatment for 6 mouths, Radiographic findings showed recurrence, and letrozole resistance was considered. We tried GnRHa treatment and achieved clinical cure.

4. Case Presentation

The patient is a 46-year-old female with the third recurrence after primary treatment for adult granulosa cell tumor. 15 years ago, 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. During the 10 years of postoperative regular follow-up. the tumor marker(including CA12-5, CA19-9, CEA, CA153, AFP, AMH, inhitbinA) were normal, No abnormality was found in imaging evaluation .In February 2017, She complained lower abdominal pain with abdominal distension, no nausea, vomiting, bloody stool and other discomfort, was referred to the Gynecology of the Fifth Affiliated Hospital of Sun Yat-sen University .under Total abdominal MRI scan ,A mass of 73 x62mm was found during pelvic midline region , the local recurrence of granulosa cell tumor was Considered, Laparoscopic pelvic mass resection was performed. Intraoperative explored reveal A mass of about 8.0 x6.0cm was found in the middle pelvic cavity with unclear boundary, Adhension to the bowel, small intestine and sigmoid distorts, Part of the intestinal serous layer is invaded by tumors, completely remove the mass during the surgery. Postoperative pathology confirmed the recurrence of ovarian granulosa cell tumor, Immunohistochemistry showed tumor cell :Vimentin(+), CD99(+), inhibi(+), the Patient refused Postoperative chemotherapy, In May 2018,CT scan found : 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 100mg 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 reveal 2.0 x3.0x2.0cm Metastatic neoplasm located in the right pelvic cavity, 1.5 x2.0x3.0cm Metastatic neoplasm in the left pelvic cavity,about 8.0x7.0x7.0 cm Metastatic neoplasm transposited 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 5.0x5.0x4.0 cm, was seen in the peritoneum of the hepatic and renal recess, no enlarged lymph nodes was found, No significant tumor was found on the surface of liver and diaphragm, Postoperative pathologic findings: Metastatic ovarian granulosa cell tumor, D99(+), CD56(+), Ki67(10%+) (Figure 1D), Postoperative Adjuvant Treated with the regimens of Letrozole 2.5mg 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 x2.5cm Metastatic neoplasm located abdominal para-aorta (Figure 2B), Letrozole resistance was diagnosed,after MDT consultation,we try to Experimental treatment with Diphereline 3.75mg im q28d for 3 cycles, the size of Metastatic neoplasm Reducted to 1.3 x0.5cm 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.

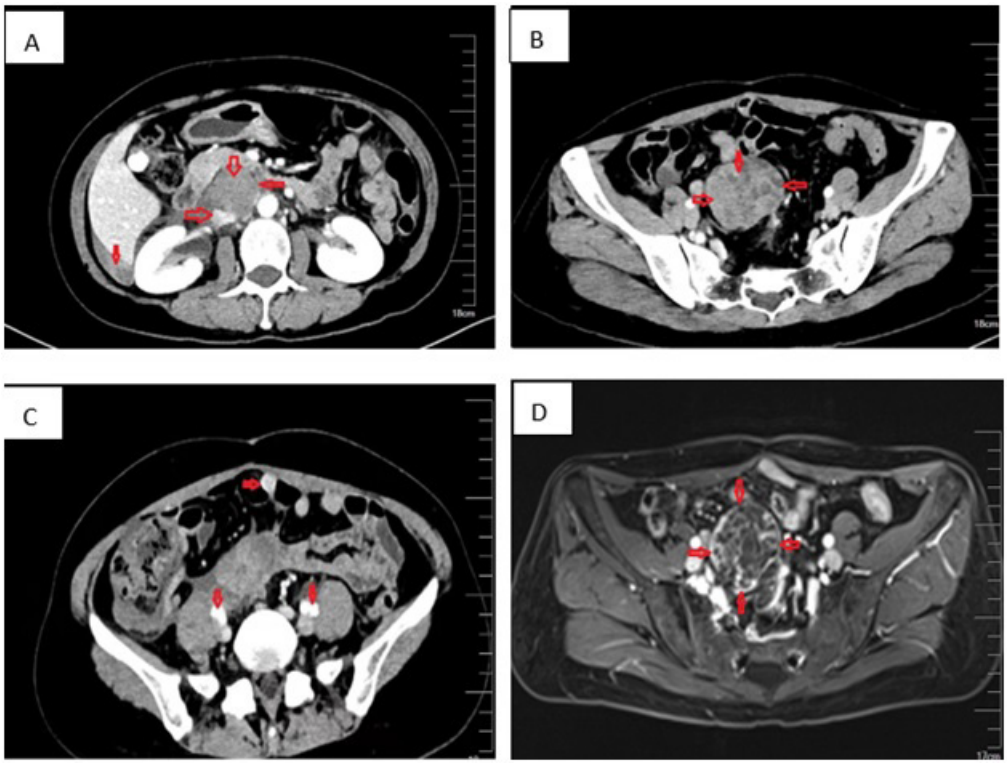

Figure 1: In May 2018,CT scan found : Multiple masses Located in liver and kidney recess(A), peritoneum and pelvic cavity(B,C) . In July 2019,MRI scan found metastatic tumors of pelvic cavity was slightly enlarged(D)

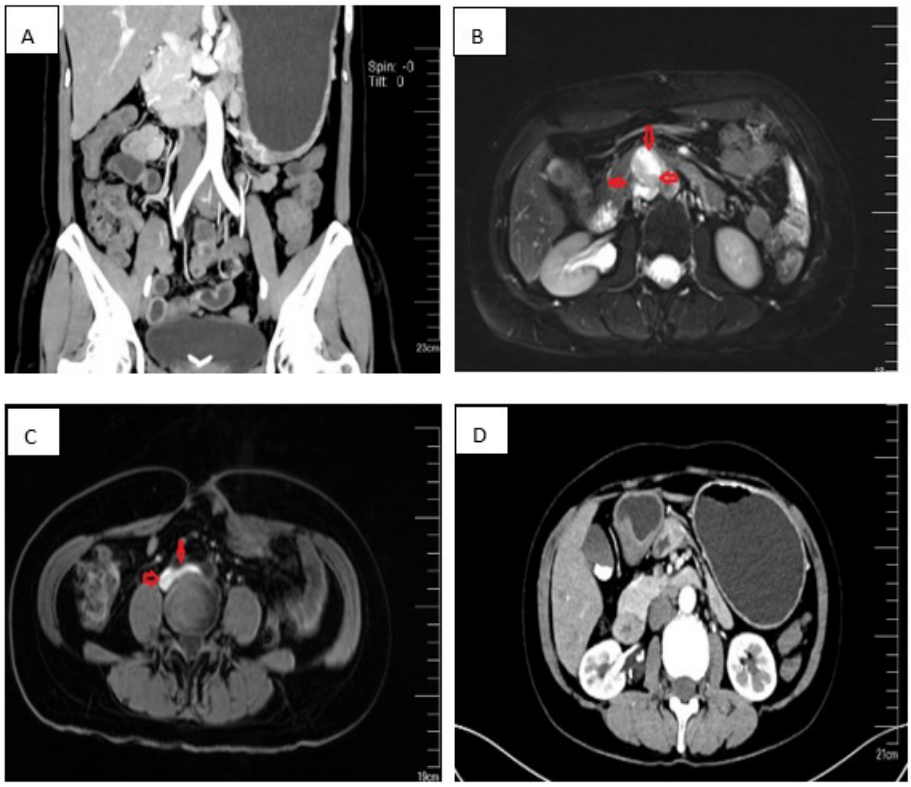

Figure 2: In November 2019, No abnormality was found（A）; in February 2020,The MRI scan showed a 3.0 x2.5cm Metastatic neoplasm located abdominal para-aorta(B); in August 2020, the size of Metastatic neoplasm Reducted to 1.3 x0.5cm (C), In February 2021, CT scan showed the Metastatic neoplasm disappear (D)

5. Discussion

GCT have a tendency for late recurrence. Once the tumor recurs, it's fatal in 80 % cases. The longest reported time to recurrence is 40 years. About 21 % develop recurrence and the median time to relapse was 57.6 months (2-166 months) as reported [3]. The optimal management of Recurrent GCT 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% to 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 GCT 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 AGCTs 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 with chemotherapy is still a difficult problem? Granulosa cell tumor is hormone sensitive type. Compared with chemotherapy, hormone therapy has the advantages of good 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 medroxyprogestrone 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-α) in ovarian epithelium, a plausible local mechanism for inhibiting tumor growth. [10] have documented prolonged remission (14–42 months) in patients having extensive disease treated with high doses of medroxyprogestrone acetate (100–300 mg thrice daily). [11] by alternating biweeky 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. [12] 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. More ever there was an improvement in the performance status too. 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. [13] 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 [14]. while other studies showed no response to GnRH antagonists [15]. we try to Experimental treatment with Diphereline for this patient achieved Good therapeutic effect. Prospective multicentric trial is needed to address the role of hormone therapy for management of these rare neoplasms.

6. Conclusion

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

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