

CASE REPORT ARTICLE

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Rapidly Growing Ovarian Granulosa Cell Tumor Following Complete Debulking for Suspected Ovarian Cancer with Histopathology Result of Benign Ovarian Cyst

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Ovarian granulosa cell tumor (GCT) is a rare low-grade malignancy condition. One type of GCT is adult GCT (AGCT), which has the tendency for late recurrence. AGCT is clinically palpable and focally cystic and solid. In this case report, a condition of recurrent ovarian cancer after laparotomy debulking surgery was reported. A 57-year-old woman, who was diagnosed with AGCT, had a history of laparotomy debulking three months prior and complained of abdominal pain and enlargement, along with significant weight loss. Ultrasound examination revealed a solid cyst, raising suspicion of recurrent ovarian cancer. Laboratory results indicated elevated CA-125 levels. Histopathology results confirmed metastasis of AGCT, after the second laparotomy debulking was done. Recurrence of GCT is uncommon within three months of debulking. In this rare condition, we suggested a laparotomy debulking and adjuvant chemotherapy as a treatment. Effectiveness of treatment of recurrent disease is an independent risk factor to reduce the risk of another relapse and increase the survival rate.

Keywords: granulosa cell tumor, ovarian cancer, debulking

Introduction

The prevalence of ovarian malignancy is currently rising.¹ Ovarian granulosa cell tumor (GCT) is a rare, low-grade malignant tumor, accounting for 70% of the sex cord-stromal tumors. It has two histopathologic types: adult GCT (AGCT) and juvenile GCT (JGCT).

AGCTs are uncommon cases, representing approximately 2-5% of all ovarian malignancies.^{2,3} They occur more often in mid middle-aged and post-menopausal women, usually between 50 and 55 years of age.^{4,5} The most common symptom of AGCT is vaginal bleeding due to the abnormal endometrium. Abnormal vaginal bleeding and a unilateral ovarian mass are the most prominent clinical

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manifestations in postmenopausal patients. Larger masses may cause abdominal distention or pain. Ascites presents as a symptom in 18.6%-21% of the patients. A realistic or cystic mass may be observed on ultrasound, which helped to diagnose AGCT.⁵ AGCT is clinically palpable and focally cystic and solid. AGCTs often secrete hormones, particularly estrogen, leading to endometrial alterations, like hyperplasia and endometrial cancer, and irregular vaginal bleeding. While they are mostly low grade and diagnosed at an early clinical stage, they have a tendency for late recurrence.^{6,7} The majority of women with AGCTs are diagnosed at stage I disease.^{2,8}

In overall ovarian cancer, about 80% of patients who have tumor residual disease after surgery and receive platinum based combination chemotherapy, will have a median of 18-month disease-free survival rate.⁴ Nevertheless, the main clinical characteristic of AGCT tumors is the tendency for late recurrence. Around 20% of patients with early-stage AGCTs can expect recurrence. The 5-year survival rate is 97-98%, and recurrence usually occurs within five years of surgical treatment, but instances of recurrence after 20 to 30 years have been reported.^{7,9} Managing relaps of ovarian granulosa-cell tumor might be challenging due to the ineffective therapy.²

In this case report, a recurrent GCTs after three months of laparotomy debulking surgery was reported. At the previous surgery a multiple mass suspected malignancy was found which was arising from the ovary, with multiple intraperitoneal seeding. Meanwhile, the second laparotomy debulking results found a receding mass with ascites of serous haemorrhage, which is suspected metastasis of the pelvic and abdominal region. Laparotomy debulking and adjuvant chemotherapy is required for effective treatment in reducing risk of another relapse.

Case report

A 57-year-old with recurrent ovarian cancer referred to the oncology polyclinic. She experienced abdominal pain and enlargement, along with significant weight loss of almost 10 kg within the last 2 months. Three months prior, she had been diagnosed with AGCT and underwent laparotomy debulking surgery on October 4, 2022. Figure 1 showed the resected tissue from this laparotomy. The histopathology results showed chocolate cyst, endometrial polyps, adenomyosis, nabothian cysts, and chronic cervicitis. The

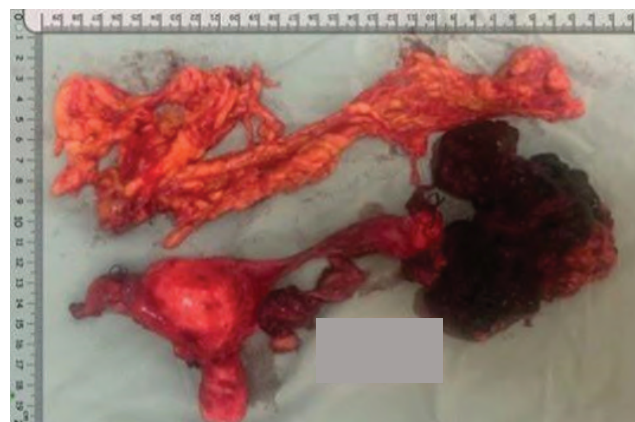


Figure 1. Resected tissue from the first laparotomy debulking surgery.

subject received gonadotropin releasing hormone (GNRH) injection therapy once a month for three months to prevent endometriosis.

However, three months after the surgery, she complained of abdominal pain and increased abdominal size, with no history of vaginal discharge. The subject does not smoke nor use alcohol or drugs. Physical examination was unremarkable except for an enlarged abdomen. Gynecological examination revealed a calm uterus without vaginal bleeding. Ultrasound examination revealed a solid cyst measuring 5.68 x 5.8 x 7.46, which raised suspicion of recurrent ovarian cancer (Figure 2, Figure 3).

Laboratory results of CA-125 levels from the first surgery performed was 30 μ mL. After the secondary surgery it was elevated into 89.78 μ mL. A review of the first anatomical pathology slide confirmed AGCT, leading to a diagnosis of suspected recurrent ovarian malignancies (Figure 4). On February 16, 2023, laparotomy debulking was performed, we found a receding mass in pelvic size about ± 10 cm with severe adhesive bowl grade 3. We also found ascites with ± 600 mL serous haemorrhage. Additionally, multiple peritoneal seeding less than 1 cm with left pelvic lymphadenopathy at left rectoiliacca communis, which was suspected metastasis in abdominal pelvic. The histopathology results revealed metastasis of AGCTs (Figure 5). Then, adjuvant chemotherapy was intended to be given. This case report was approved by Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Andalas (ethical clearance No. 209/UN16.2/OBGYN/VIII/2023).

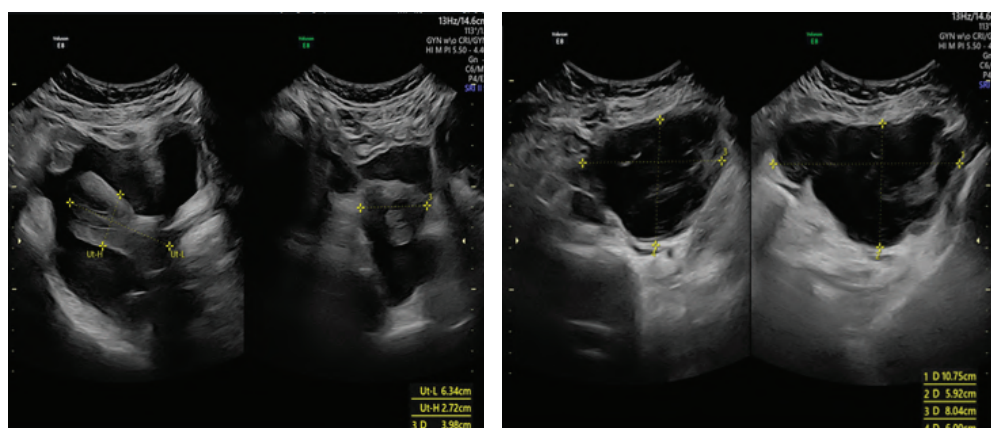


Figure 2. Ultrasound results before the first laparotomy debulking surgery.

Discussion

AGCT is a relatively uncommon gynecologic malignancy, with an incidence of less than 3.7 per 100,000 persons. Meanwhile, AGCT is more common than JGCT, which is about 95% of all GCTs.⁵ AGCT mainly occurs in peri- and post-menopausal women and features low-grade malignant biological behavior, followed by late and multiple recurrence. There are 25-30% of patients that experience recurrences. Age at recurrence, therapeutic approach, and adjuvant chemotherapy have been identified as key prognostic factors for recurrent AGCT.⁴

In previous literature, three cases were observed in post-menopausal women. The clinical manifestations range from abdominal pain and distention, menstrual abnormalities such as menorrhagia, intermenstrual bleeding, post-menopausal bleeding, or amenorrhea.^{5,10} Endocrine manifestations are related to estrogen hypersecretion, resulting in endometrial hyperplasia, leiomyomas, and irregular menstrual abnormalities.^{5,10,11} In this case, the subject experienced

abdominal pain and abdominal distention, without vaginal bleeding. Larger masses may cause abdominal pain and distention. However, in asymptomatic patients, coincidental clinicoradiological examinations play a role in the diagnosis.^{5,10,11} Radiologically, both JGCT and AGCTs present as large solid masses measuring up to 12 cm in diameter.^{10,11} Ultrasound examination in our case revealed a solid cyst measuring about 8 cm, which raised suspicion of recurrent ovarian cancer.

There are two recurrence patterns, such as unifocal/local and multifocal/distant. These patterns were defined according to the site and number of lesions. Unifocal recurrence refers to a lesion at only one site, while multifocal recurrence is defined upon ≥ 2 lesions; and local recurrence refers to pelvic location of the lesion, while distant recurrence occurs when the lesion is located beyond the pelvis, in the abdomen or thorax.^{5,12} The definitive diagnosis is made through histopathological analysis. This showed a microfollicular pattern, which is the most common diagnostic histopathological feature. The adult form of

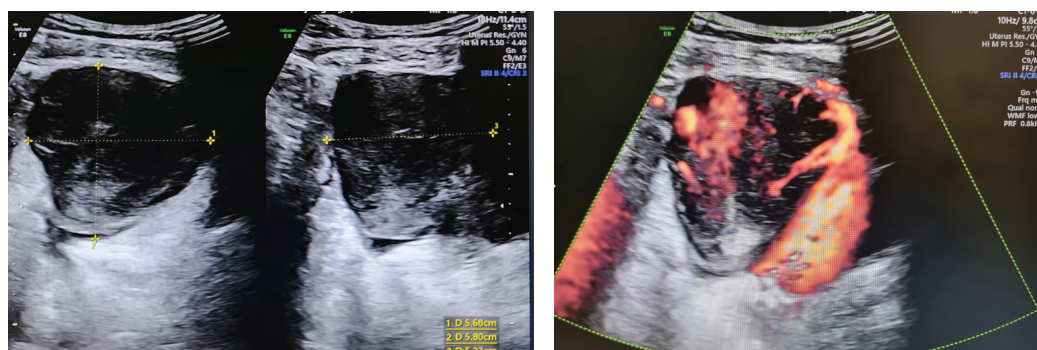


Figure 3. Ultrasound results after five months of laparotomy debulking surgery.

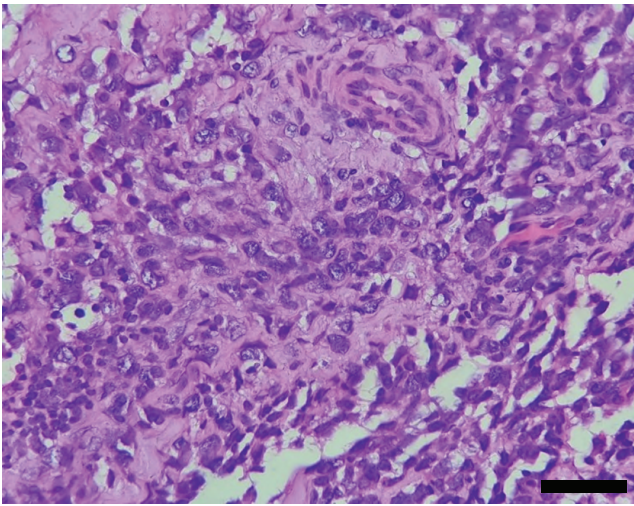


Figure 4. The anatomical pathology slides after the first laparotomy debulking surgery results showing GCT. Black bar: 200 μ m.

GCT presents five histologic patterns: micro follicle, macro follicle, insular, trabecular, and spindle/sarcomatoid.¹⁰ Silver stain shows reticulin fibers around clusters of cells, suggestive of GCT. Although a focal thecal component was seen along with GCT, documented literature requires the presence of more than 25% of thecal cells to be considered a thecoma, which is a benign entity with a very good prognosis.¹⁰

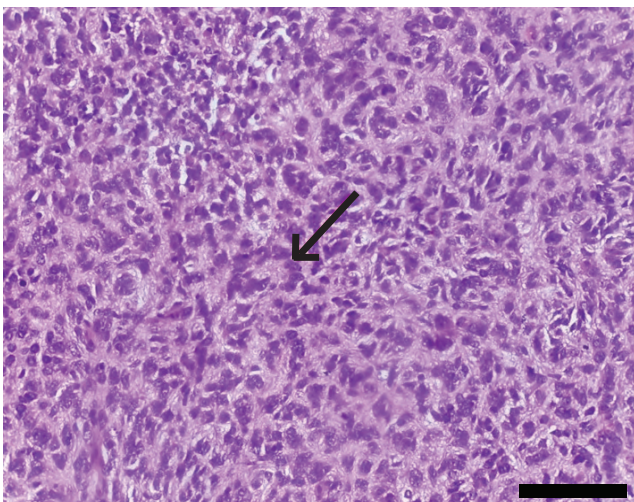


Figure 5. Pathological results show tumor cells sheets of ovarian GCT. Call-Exner bodies and nuclear grooves on the second debulking laparotomy. Black arrow: ovarian-tumor cells sheets. Black bar: 250 μ m.

Raised serum tumor markers in GCT include estradiol, inhibin, antimullarian hormone, and CA-125.^{10,11} In our case, there was an increase level of CA-125. CA-125 is a high molecular weight mucinous glycoprotein found on the surface of ovarian cancer cells. This antigen is then shed and quantified in serum samples of ovarian cancer patients. Serum CA-125 levels are elevated in 50% of early-stage tumors, which are mostly type I ovarian cancers and 92% of advanced-stage tumors, which are mostly type II ovarian cancers. Laboratory results of CA-125 levels from the first surgery performed were 30 μ mL. After the secondary surgery it was elevated to 89.78 μ mL. Elevations in CA-125 have been shown to detect recurrent cancer 2–5 months before clinical diagnosis. The specificity and sensitivity of CA-125 for predicting recurrent ovarian cancer were 91.3% and 85.9%, respectively. Early treatment based on CA-125 elevations vs. delayed treatment based on clinical symptoms was also investigated, and it was found that CA-125 can be used for monitoring when highly elevated preoperatively.¹³

The traditional treatment modalities include complete surgical excision of tumor with unilateral salpingo-oophorectomy in patients desiring fertility preservation. Occasionally, chemotherapy or radiotherapy is used as follow-up treatments.^{10,11} Premenarchal women or patients presenting in the reproductive years with early stage disease are often managed with unilateral salpingo-oophorectomy and appropriate surgical staging in an attempt to preserve fertility. In post-menopausal women and those who have completed childbearing, surgery consists of a total abdominal hysterectomy and bilateral salpingo-oophorectomy, along with standard surgical staging.⁴ However, these patients experienced a recurrence of ovarian neoplasm suspect malignancy three months after laparotomy debulking surgery. In this case, surgical treatment was chosen then followed by chemotherapy. Surgery is the standard initial treatment modality for all patients with AGCTs, and post-operative adjuvant chemotherapy of AGCT has changed and evolved over the past decades.¹⁴ The 2018 ESMO guidelines recommend debulking surgery with adjuvant therapy as the most effective treatment for recurrent disease.¹⁵ Treatment of recurrent disease was an independent risk factor of secondary relapse, compared with the surgery combined with adjuvant chemotherapy treatment, the risk of second recurrence were respectively, 10 and 15 times higher when only surgery or chemotherapy was performed.¹⁶ The patient received GNRH injection therapy once a month for three

months to prevent endometriosis. The GNRH receptor is also suitable as a target for therapies with improved anti-tumor effects and reduced side effects.¹⁴

GCT tends to have late and multiple recurrences.¹⁶ The recurrence rate of GCT is 20% in Stage IA and 43-48% in Stage II-IV. After initial surgery, the median time to relapse is about 4-6 years, and the recurrence interval can even extend to 20 years. Patients with recurrent disease have much shorter median overall survival (OS) than non-relapsed patients (26.5 vs. 30.6 years). JGCT often relapses within a few years, whereas AGCT can relapse decades after the initial diagnosis.^{15,16} In this case report, recurrence occurred after three months of laparotomy debulking. Based on the literature, the prognostic significance of recurrence risk factors including age, menopausal status, tumor size, surgical method, FIGO (International Federation of Gynecology and Obstetrics) stage, and adjuvant chemotherapy in patients with AGCT. Even though AGCT tends to late recurrences, about 18.4% of patients with stage I disease had recurrence from initial surgery to relapse in 7-12 months. It means a long-term follow-up of patient AGCT is important to detect recurrence cases.¹⁷

The pelvic region (30-45%) and upper abdomen (55-70%) are the most common sites of recurrence in AGCT.^{15,17} The same result was seen in this case report, the subject complained of abdominal pain and distention after 3 months of the first laparotomy debulking surgery. From the second laparotomy debulking results, we found a receding mass size with left pelvic lymphadenopathy in the pelvic region and ascites with ± 600 mL serous haemorrhage. It means there was a metastasis in the pelvic and abdomen region. In addition to the FIGO stage, other recurrence-related risk factors include age (>50 years), residual tumors, tumor rupture, CA-125 levels (≥ 35 IU/mL), tumor size, and diabetes.^{15,16} Patients with diabetes were found to be more susceptible to relapse and had a lower 5-year recurrence-free survival rate (hazard ratio 3.37, 95% CI 1.38-8.20).¹⁶

Various prognostic factors in GCT have been reported of which the staging is a traditional paramount variable. Other factors include intraperitoneal disease, tumor size, patient's age, histologic grade of differentiation, mitotic activity, and nuclear atypia.¹⁸ Practically, about 80-90% of patients with AGCTs are presented in FIGO stage I disease. The overall prognosis is very good. A retrospective study found all four cases of AGCTs presented with the early first stage (FIGO-Stage 1).¹⁴ Survival rates after ten years for stages 1,2,3, and 4 are 87.2%, 75%, 20%, and 0% respectively.^{8,11} Studies

have shown that tumors smaller than 10 cm have a better prognosis. However, smaller tumors may exhibit aggressive behavior, making tumor size an unreliable prognostic factor.⁸ Patients under 40 years of age are believed to have a better prognosis, but various authors differ in their opinion with regard to significance of patients age and survival.^{8,10,19} Histologic grade and mitotic figures demonstrate an inverse relation to survival rate.^{18,19} Routine follow-up of patients with AGCT includes standard gynecological examination and the detection of serum markers is required to detect relapse in early stage.⁵

Conclusion

A recurrence of AGCT in a post-menopausal woman occurred after three months of laparotomy debulking. After initial surgery, AGCTs tend to have late and multiple recurrences, which can be expected after an average of 5 years. But in this case, we found an early recurrence of AGCT. Laparotomy debulking and adjuvant chemotherapy are recommended to decrease the recurrence frequency significantly. Long-term follow-up is required, even in early-stage AGCT patients.

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Authors Contribution

SM, PAA, and RO were involved in the conception of the ideas, discussion of the results, manuscript drafting preparation, while AS was involved in manuscript drafting and revision.

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