

## Case report

## Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy for recurrent adult granulosa cell tumor: A case report

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## ABSTRACT

**Background:** Adult granulosa cell tumor of the ovary (AGCT) is a rare functional sex-cord-stromal ovarian neoplasm characterized by low malignant potential and late relapse. Evidence-based management options for women with recurrent AGCT are limited.

**Case report:** We present the case of a 60-year-old woman with the fifth recurrence of AGCT initially diagnosed 19 years ago. After initial surgery in 1996, the patient underwent four additional surgical interventions for recurrent disease in 2005 (abdominal wall), 2009 (abdominal wall), 2010 (paravesical), and 2011 (paravesical). In 2011, she underwent pelvic irradiation with 50.5 Gray. In 2015, another recurrence was diagnosed based on an increase of serum inhibin and a tumor seen on CT scan in the right upper abdomen. The patient underwent cytoreductive surgery (CRS) with complete cytoreduction followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin 50 mg/m<sup>2</sup> and doxorubicin 15 mg/m<sup>2</sup>. No intra- or post-operative complications occurred. Final histology revealed recurrent AGCT with 6 cm in the largest diameter. Subsequently, antihormonal treatment with anastrozole 1.5 mg per day was prescribed. With a follow-up of six months, the patient is well and alive.

**Conclusion:** CRS and HIPEC are a reasonable treatment option for selected women with recurrent AGCT limited to the abdomen.

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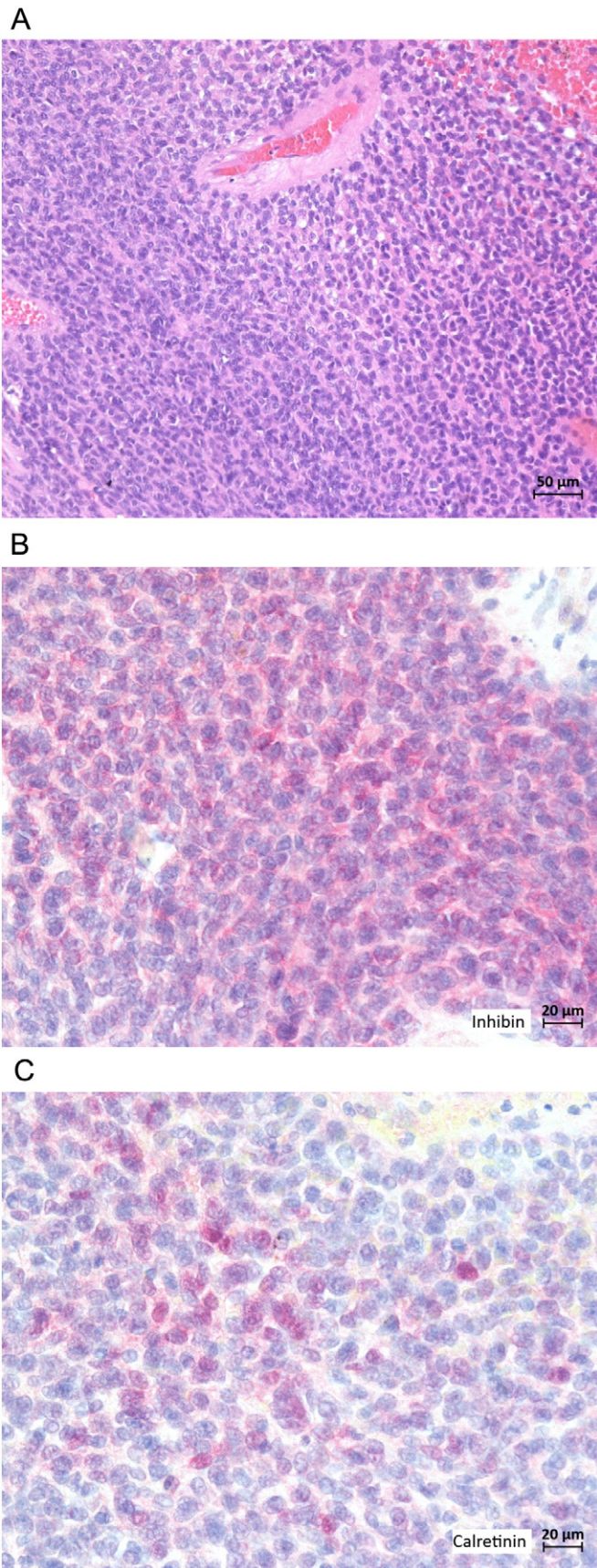
## 1. Introduction

Sex-cord-stromal tumors are rare ovarian neoplasms accounting for less than 5% of ovarian malignant tumors (Ugianskiene et al., 2014). Granulosa cell tumor (GCT) is the most common form of ovarian sex-cord-stromal tumors presenting in two histopathologically different forms, as common adult granulosa cell tumor (AGCT), and as the less frequent juvenile granulosa cell tumor (JGCT) (Ugianskiene et al., 2014; Bryk et al., 2015). In addition to morphological variation, these two tumor types differ regarding their prognosis and clinical course. Typically, AGCT are detected at an early stage and often have features of hyperestrogenism and subsequent menorrhagia and metrorrhagia. Other presenting symptoms are nonspecific such as abdominal pain and swelling. AGCT often follow an indolent course and are characterized by a low malignant potential and late relapses (Ugianskiene et al., 2014; Bryk et al., 2015). Although AGCT has a favorable prognosis with overall survival rates of 87% and 76% after 5 and 10 years, respectively, (Sehouli et al., 2004) there is a subset of patients with biologically aggressive tumors developing recurrence and ultimately leading to death.

Typically, these recurrences develop late and have been described up to 17 years after the initial diagnosis (Sehouli et al., 2004; Wilson et al., 2015). There have been efforts to characterize recurrent AGCTs and to identify prognostic markers associated with recurrence. For example, initial tumor stage, tumor size, degree of cellular atypia, and mitotic index have been reported to predict recurrence (Sehouli et al., 2004; Wilson et al., 2015). In addition, subcellular characteristics such as loss of ER-beta expression, high proliferating cell nuclear antigen (PCNA) expression, and aneuploidy have also been described as those features characterizing the subgroup of AGCT with poor outcome (Staibano et al., 2003).

Surgery is the mainstay of treatment for the initial management of women with AGCT with the goal of complete tumor resection (Ugianskiene et al., 2014; Bryk et al., 2015). There is no established role for adjuvant chemotherapy or adjuvant hormone therapy (Gurumurthy et al., 2014). In contrast, systemic chemotherapy is a commonly used therapy in women with recurrent or primary advanced AGCT. For example, in a literature review of 15 studies with 224 patients, van Meurs et al. assessed the response rate to chemotherapy among women with primary advanced or recurrent AGCT. They calculated a total response rate (including complete and partial responses) of 50% (95% confidence interval, 44–57%). Strict criteria of response, however, were not uniformly applied in the analyzed studies (van Meurs et al.,

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**Fig. 1.** Microscopic image of an adult granulosa cell tumor of the ovary. Black bar equals 50 µm (panel A) and 20 µm (panels B and C). Panel A depicts a hematoxylin/eosin staining of granulosa tumor cells. Panel B depicts an immunohistochemical staining showing expression of inhibin. Panel C depicts an immunohistochemical staining showing expression of calretinin.

2014a). Hormone therapy is also used in women with recurrent GCT. Van Meurs et al. analyzed 22 women with measurable recurrence or residual disease treated with hormonal treatment, i.e. tamoxifen or aromatase inhibitors (van Meurs et al., 2014b). The pooled objective response rate, defined as complete response or partial response, was 18% (4/22). In one patient (4%) a complete response and in three (14%) a partial response was described. Fourteen patients (64%) had stable disease. In the series of Wilson et al., surgery was the main therapeutic modality at relapse, but 86% of patients additionally received non-surgical treatments with a clinical benefit rate of 43% for chemotherapy, 61% for hormonal therapy and 86% for radiation (Wilson et al., 2015).

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a form of local intraperitoneal chemotherapy based on experimental evidence suggesting an enhanced anti-tumor effect of chemotherapeutic compounds at an elevated temperature  $>40^{\circ}\text{C}$  (Oseledchik and Zivanovic, 2015). Several studies have convincingly shown that hyperthermia can increase both tumor penetration of cisplatin as well as DNA crosslinking (Ansaloni et al., 2015). In addition to hyperthermia, HIPEC theoretically offers a number of further advantages, among them a high volume of chemotherapy, a homogenous distribution, no interval between cytoreduction and chemotherapy, high concentrations of chemotherapy in the intraperitoneal compartment with low systemic exposure. On the other hand, HIPEC requires intraoperative perfusion machines, elaborate logistics, and a high degree of organizational effort. In addition, the morbidity and mortality associated with CRS and HIPEC are considerable. For example, Voron et al. reported a 2.5% mortality rate and a major morbidity rate of 30% in a series of 204 patients treated with CRS and HIPEC (Voron et al., 2015). Based on the experience with HIPEC in other tumor entities, this treatment modality has been proposed for women with recurrent AGCT (Al-Badawi et al., 2014). The rationale for HIPEC in this indication is the high rate of intraabdominal tumor recurrence after surgical debulking suggesting the presence of microscopical residual tumor in many cases. HIPEC is intended to eradicate these microscopical intraabdominal tumor foci. We describe the case of a woman with recurrent AGCT, successfully treated with CRS and HIPEC in our institution.

## 2. Case report

We present the case of a 60-year-old woman with recurrent AGCT initially diagnosed 19 years ago. After initial surgery in 1996, the patient underwent four additional surgical interventions for recurrent disease in 2005 (abdominal wall), 2009 (abdominal wall), 2010 (paravesical), and 2011 (paravesical). In 2011, she underwent pelvic irradiation with 50.5 Gray. In 2015, another recurrence was diagnosed based on an increase of serum inhibin B and a tumor seen on CT scan in the right upper abdomen. At laparotomy, the tumor was located attached to the terminal ileum and the ascending colon. There was no peritoneal carcinomatosis and no disease in the pelvis or upper abdomen. The patient underwent cytoreductive surgery (CRS) including a right hemicolectomy, resection of the terminal ileum, a side-to-side (functionally end-to-end) ileotransversostomy, and a subtotal peritonectomy. A complete cytoreduction with no visible residual tumor (CCRO) was achieved. Surgery was immediately followed by HIPEC with cisplatin 50 mg/m<sup>2</sup> and doxorubicin 15 mg/m<sup>2</sup>. We used a continuous closed circuit abdominal procedure with 5 intraabdominal drains (two for inflow and 3 for outflow) and two temperature units in the lower and upper abdomen, respectively, for temperature monitoring during HIPEC. We used a Belmont® Hyperthermia Pump (Belmont Instrument Corporation, Billerica, MA), The duration of HIPEC was 1 h with an intraabdominal temperature maintained at 41 °C. Intraabdominal temperatures and the body's core temperature as well as urinary output were monitored during the procedure. No intra- or immediate post-operative complications occurred. On post-operative day 3 the patient reported nausea and

dizziness, which completely resolved after stopping the antiemetic metoclopramide. No other postoperative complication occurred and the patient was discharged on postoperative day 6. Final histology revealed recurrent AGCT with 6 cm in the largest diameter. Fig. 1 shows microscopic images of the tumor including immunohistochemical studies demonstrating the expression of calretinin and inhibin. After surgery, antihormonal treatment with anastrozole 1.5 mg per day was prescribed based on the recommendation of our institutional interdisciplinary tumor board. With a follow-up of six months, the patient is well and alive. Written informed consent for publishing these data was obtained by the patient.

### 3. Comment

In this case report, we discuss the clinical course of a patient with recurrent AGCT treated successfully with CRS and HIPEC. Based on this case and other reports in the literature (Al-Badawi et al., 2014; Gouy et al., 2013; Canbay et al., 2012; Hayes-Jordan et al., 2015), we conclude that CRS and HIPEC in women with recurrent AGCT is feasible and may be an effective treatment option.

AGCT is a rare entity characterized by high rates of recurrence and repeated surgical interventions. Although surgery at the time of initial diagnosis of AGCT is commonly accepted, there is no clear consensus on the optimal management of women with recurrent disease, which occurs in a third of patients. For example, in a large retrospective series of 160 FIGO stage I AGCTs, Wilson et al. observed recurrent disease in 32% (51/160) of cases over a follow-up period of 7 years (Wilson et al., 2015). The median time to relapse was 12 years underscoring the typical biological behavior of AGCT with late relapse. Due to the rarity of AGCT, treatment options for recurrent disease have not been rigorously tested in clinical trials. Therefore, evidence-based management options for recurrent AGCT are limited and treatment options have not been standardized. In a systematic review of the Cochrane Collaboration covering the literature until 2014, no comparative trial in women with recurrent AGCT was identified (Gurumurthy et al., 2014). However, in retrospective single-center and multi-center cohort studies, a variety of treatment options have been described, among them systemic chemotherapy, surgery, radiation, and hormonal treatment.

Based on the safety and efficacy of CRS and HIPEC in cancer entities such as colon cancer, gastric cancer, and mesothelioma, CRS and HIPEC have been used in women with recurrent AGCT. For example, Al-Badawi et al. performed CRS and HIPEC with cisplatin (50 mg/m<sup>2</sup>) and doxorubicin (15 mg/m<sup>2</sup>) in the abdominopelvic cavity for 90 min at 41.0–42.2 °C (Al-Badawi et al., 2014). Complete cytoreduction was achieved in all except one patient. Five patients had tumor recurrences in the abdomen and pelvis and one patient in the abdomen only. No grade V morbidity according to the Clavien–Dindo classification was observed. Two patients developed lung atelectasis, which was managed by mere chest physiotherapy (grade I). One patient developed urinary tract infection (grade II) and another patient developed pneumonia (grade II) – both of which were managed by antibiotics. One patient developed splenic bed and anterior abdominal wall collections requiring ultrasound-guided aspiration without general anesthesia (grade III). One patient developed pulmonary embolism requiring intensive care-unit management (grade IV). These data demonstrate that CRS followed by HIPEC is feasible in women with recurrent AGCT. In the absence of controlled comparative trials, it is unclear whether or not HIPEC has a therapeutic effect in addition to optimal debulking of recurrent AGCT. However, due to the rarity of this disease, it is very unlikely that there will ever be large trials comparing various treatment modalities in the recurrent setting. Therefore, the biological

rationale of HIPEC treating microscopic tumor foci left behind after debulking surgery may be used as an argument in favor of this therapy. In our case report, we found that CRS and HIPEC were feasible and safe in this situation.

Due to the rarity of recurrent AGCT, there is no consensus regarding the optimal therapy of this disease. Thus, it is important to identify additional safe and effective treatment strategies. Based on our case report and the data reported in the literature we suggest that for women with recurrent AGCT and disease localized to the abdomen, CRS and HIPEC may be considered. However, additional literature – ideally a formal prospective phase II safety and efficacy trial – should be undertaken, before this treatment can be regarded an accepted alternative.

### Conflict of interest statement

The authors report no conflict of interest.

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