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Kanda, Masatoshi  
Ojima, Yojiro  
Kizaki, Tomohiko  
Ohara, Noriyuki

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## (Citation)

The Kobe journal of the medical sciences, 61(4):109-114

## (Issue Date)

2015

## (Resource Type)

departmental bulletin paper

## (Version)

Version of Record

## (JaLCD0I)

<https://doi.org/10.24546/81009222>

## (URL)

<https://hdl.handle.net/20.500.14094/81009222>



## Aggressive Granulosa Cell Tumor of the Ovary with Rapid Recurrence: a Case Report and Review of the Literature

AYAKO SONOYAMA<sup>1\*</sup>, MASATOSHI KANDA<sup>1</sup>, YOJIRO OJIMA<sup>1</sup>,  
TOMOHIKO KIZAKI<sup>2</sup> and NORIYUKI OHARA<sup>1</sup>

<sup>1</sup>*Department of Obstetrics and Gynecology, Sanda Municipal Hospital, Sanda, Japan;*

<sup>2</sup>*Department of Pathology, Sanda Municipal Hospital, Sanda, Japan*

Received 4 September 2015/ Accepted 10 December 2015

**Key words:** aggressive granulosa cell tumor, rapid recurrence, ovary, immunohistochemistry,  $\alpha$ -inhibin, Ki-67

**Aggressive adult granulosa cell tumor (AGCT) of the ovary remains uncommon. We report a case of aggressive AGCT of the ovary who had rapid recurrence at two months after surgery. A patient was referred for further examination of a pelvic tumor. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. In the areas showing a sarcomatoid pattern, the mitotic count were 25/10 HPFs, and the mitoses were most prominent in foci composed of pleomorphic cells with enlarged and bizarre nuclei. In some areas, tumor cells with relatively uniform nuclei proliferated in a trabecular pattern. The mitotic count was 4/10 HPFs. Tumor cells were diffusely positive for  $\alpha$ -inhibin. She was diagnosed as having aggressive AGCT. The Ki-67 labeling index in the sarcomatoid AGCT was higher (40%) than that in the areas of typical AGCT (3%). Immunostaining for p53 in the sarcomatoid AGCT was almost strongly positive, but that in typical AGCT was negative. Two months later after the initial surgery, a recurrent abdominal 12 cm-sized mass developed after performing adjuvant chemotherapy consisting of paclitaxel and carboplatin. She died of the disease at 3 months after initial surgery. A markedly higher mitotic count, a higher Ki-67 labeling index, and strong immunoreactivity of p53 in AGCT suggests highly malignant potential. In such a case, a careful follow-up is warranted due to the possibility of rapid recurrence.**

### INTRODUCTION

Granulosa cell tumor (GCT) belongs to sex-cord stromal tumor and is classified into adult type and juvenile type. Adult GCT (AGCT) usually has an indolent clinical course with delayed recurrence and good overall survival for early stage (14). However, a few cases with aggressive AGCT have been reported (5,17). Pathologically, aggressive GCTs were characterized by brisk mitotic activity with equal or more than 10/10 high power fields (HPFs) (17) or high Ki-67 labeling index more than 60% (5). Jozwicki et al. reported a patient with AGCT who had a very aggressive course and rapid recurrence despite radical surgery and chemotherapy, and a short time of survival (5). Pathologically, the proliferating patterns of tumor cells in aggressive GCT were varied, including a cord-like or alveolar configuration (17), and fibrothecomatous and sarcomatoid patterns (5).

We report a case of aggressive AGCT of the ovary who had rapid recurrence at two months after surgery.

### CLINICAL CASE

A 66-year-old woman visited an antecedent clinic with a complaint of abdominal bloating of two weeks' duration. A computed tomography (CT) of the pelvis showed a multilobular mass in the pelvis. She was referred to us for further examination of a pelvic tumor. A magnetic resonance imaging displayed a 30 cm-sized multilobular cystic tumor (Figure 1). Scattered low intensity lesions were noted on T2-weighted images (Figure 1). Serum CA125 levels were elevated at 274 U/ml (normal range; 0 – 35 U/ml). A putative preoperative diagnosis was a mucinous cystadenocarcinoma of the ovary.

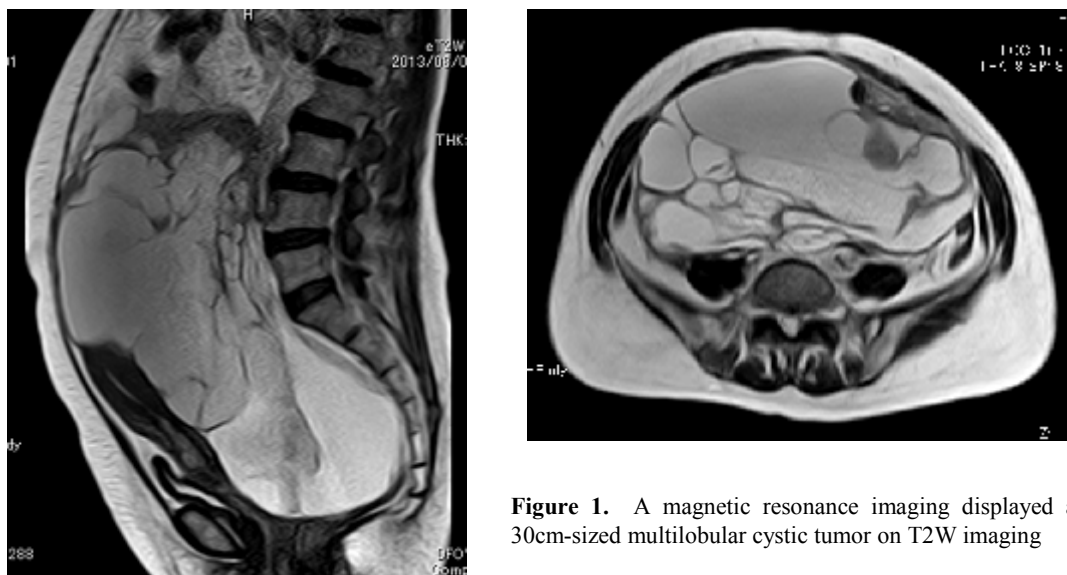
At laparotomy, the tumor originated from the left ovary and was adherent to the cul-de-sac. No peritoneal dissemination was noted. An intraoperative frozen section of the tumor revealed non-epithelial malignant ovarian tumor. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy.

Macroscopically, the left ovarian tumor consists of multiple cysts of various sizes and solid yellowish tissue, with areas of necrosis and hemorrhage (Figure 2). Nineteen blocks of neoplastic lesions were assessed histologically. Tumor cells proliferated predominantly in a sarcomatoid diffuse pattern and focally in a trabecular pattern. Histological features in a trabecular pattern revealed typical AGCT. Tumor cells had relatively uniform

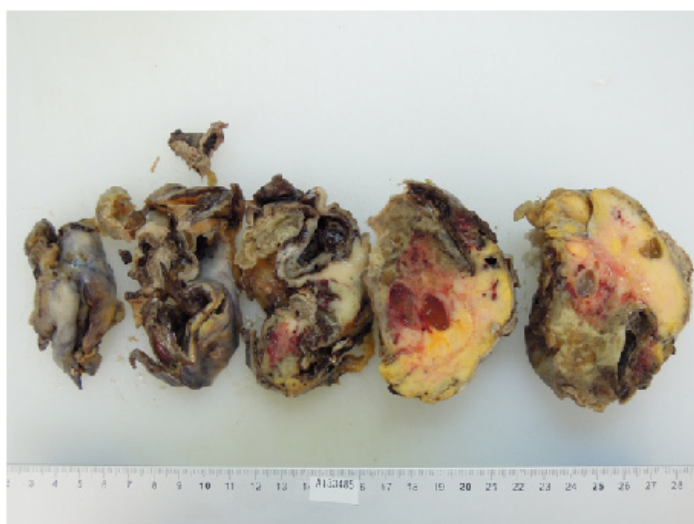
nuclei. Nuclear grooves and a few Call-Exner bodies were observed (Figure 3A). The mitotic count was 4/10 HPFs. The area percentage of typical AGCT was about 10% of tumor. The rest of tumor cells showed a sarcomatoid pattern. They were composed of relatively enlarged nuclei without nuclear grooves. In the most sarcomatoid areas, pleomorphic cells with bizarre nuclei proliferated diffusely, and no border between tumor cells was present (Figure 3B). The fibrous stroma and hemorrhagic necrosis were scattered. The mitotic count was 25/10 HPFs and the mitoses were most prominent in pleomorphic cell areas (Figure 3B).

Immunohistochemical stains for vimentin,  $\alpha$ -inhibin, calretinin, CD56, WT1, AE1/AE3, EMA, CA125, CD34, CD10,  $\alpha$ -smooth muscle actin, desmin, h-caldesmon, Ki-67(MIB1), and P53 were performed. The immunohistochemical results of typical AGCT areas were compared with those of sarcomatoid areas (Table I). Tumor cells were negative for CA125, CD10,  $\alpha$ -smooth muscle actin, desmin, h-caldesmon, and CD34. Tumor cells were diffusely positive for  $\alpha$ -inhibin (Figure 3C), and calretinin was focally positive in the sarcomatoid areas (Figure 3D). The Ki-67 labeling index was 3% in the typical AGCT, but that in the sarcomatoid areas was amounted to 40%. Immunoreactivity of p53 was almost strongly positive in the sarcomatoid areas, while that in the typical AGCT was negative (Figure 4A, B).

She received adjuvant chemotherapy consisting of paclitaxel ( $175 \text{ mg/m}^2$ ) and carboplatin ( $\text{AUC}=5$ ). However, she felt an abdominal mass after finishing two courses of chemotherapy. A CT of the abdomen revealed a 12cm-sized tumor in the abdomen. She also presented with pleural effusion. She was diagnosed as having recurrence at two months after the initial surgery. We recommended the introduction of palliative care to the patient and her family due to the unresponsiveness to the chemotherapy. However, they desired a further chemotherapy, and she was transferred to a university hospital. She received additional chemotherapy consisting of bleomycin, etoposide, and cisplatin, but died of DIC and respiratory failure next month.

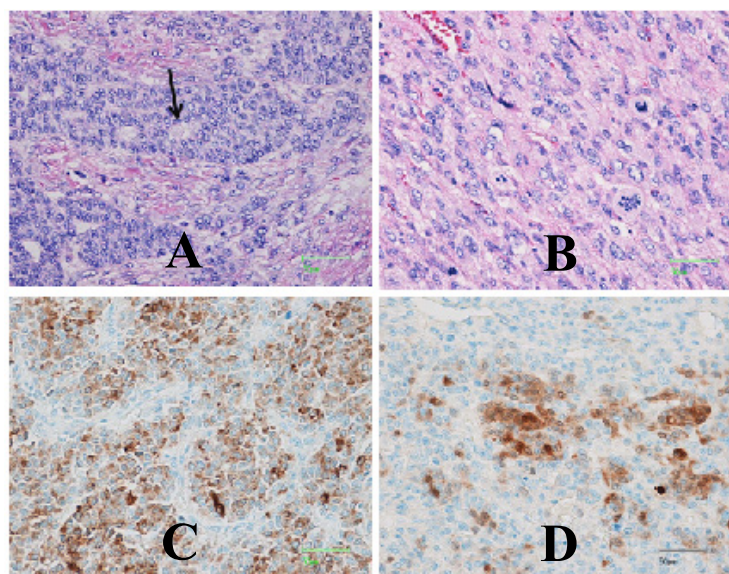


**Figure 1.** A magnetic resonance imaging displayed a 30cm-sized multilobular cystic tumor on T2W imaging

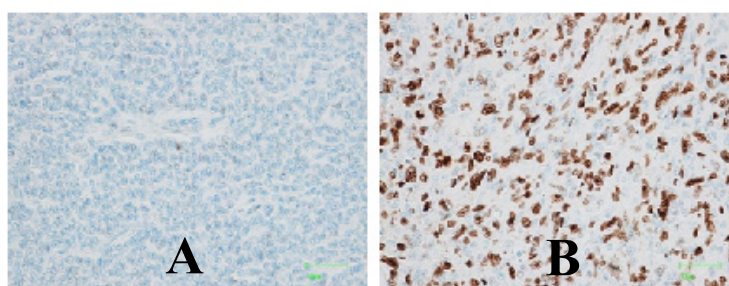


**Figure 2.** The cut surfaces are cystic and solid with necrosis and hemorrhage.

## SARCOMATOID OVARIAN GRANULOSA CELL TUMOR



**Figure 3.** Histological features of adult granulosa cell tumor. Tumor cells typical for a classic adult granulosa cell tumor in a trabecular pattern and a Call-Exner body (arrow), HE stain (A), Pleomorphic cells proliferating in a sarcomatoid diffuse pattern. Many mitotic figures are present, HE stain (B), Immunohistochemistry of  $\alpha$ -inhibin diffusely positive (C) and calretinin focally positive (D) for sarcomatous pleomorphic cells, original magnification x200 (A),(B), (C), and (D)



**Figure 4.** Immunohistochemistry of p53 in typical AGCT area, showing focal weak staining (A), and that in sarcomatous area, showing diffuse intense nuclear staining (B), original magnification x200 (A) and (B),

## DISCUSSION

Our case was an uncommon aggressive AGCT which recurred at two months after the initial surgery despite administration of adjuvant chemotherapy. AGCT is classified as borderline-malignancy of the ovarian tumor according to the FIGO classification (17). However, several cases of AGCT have been reported to have an aggressive clinical course as shown in Table II. These patients recurred between 1.5 and 23 months. Susil *et al.* reported a case which had a component of sarcomatous change and died at 3 months (16).

Moreover, aggressive AGCT is reported to show distinct histological features unlike conventional AGCT.

In our case, tumor was characterized by the composition of both sarcomatoid AGCT and typical AGCT. Several authors reported aggressive AGCTs with high mitotic count or rapid progression (5,17). Jozwicki *et al.* reported a patient with a very aggressive AGCT, composed of granulosa, sarcomatoid, and fibrothecomatous tissues. The tumor recurred rapidly, and the patient died 16 months later (5). In our case, the mitotic count in the areas of sarcomatoid AGCT amounted to maximum 25/10 HPFs, which was corresponding to the result of a previous report (17). Aggressive AGCTs were shown to display diverse histological findings. In the presented case, tumor cells proliferated predominantly in a sarcomatoid diffuse pattern, whereas other reports demonstrated that tumor cells proliferated in a cord-like or alveolar configuration (17), and fibrothecomatous or sarcomatoid patterns (5). A diagnosis of aggressive AGCT has been made on the basis of the high mitotic count.

To make a precise diagnosis and distinguish our case from sarcomas, immunohistochemical profiles were examined. Tumor cells showed diffusely positive immunoreactivity for  $\alpha$ -inhibin and vimentin, but negative for EMA, CA125, CD10,  $\alpha$ -smooth muscle actin, desmin, h-caldesmon, and CD34.

Nofech-Mozes *et al.* reported that EMA, CD10, and melan-A were universally negative in all AGCT (9). These results indicated that the tumor was of mesenchymal origin and that endometrial stromal sarcoma or

leiomyosarcoma was deniable. In our patient, immunopositivity for  $\alpha$ -inhibin established a diagnosis of AGCT. Shah *et al.* demonstrated that 12 cases of sarcomas including one gastrointestinal stromal tumor and 11 leiomyosarcomas were immunonegative for inhibin except for one case of endometrial stromal sarcoma with sex cord-like areas (15). The authors demonstrated that although sarcomatoid AGCT may be misinterpreted as a sarcoma,  $\alpha$ -inhibin was useful immunomarker to distinguish sarcomatoid AGCT from other spindle cell neoplasms (15).

In our case, although immunostaining for vimentin,  $\alpha$ -inhibin, CD56, and AE1/AE3 was similar between typical AGCT areas and sarcomatoid areas, the Ki-67 labeling index and p53 expression were higher in the areas of sarcomatoid AGCT than those in the areas of the typical AGCT. In a sarcomatoid AGCT, the Ki-67 labeling index was higher compared with typical AGCT, and immunostaining for p53 expression was almost strongly positive while negative in typical AGCT. The finding of strong immunoreactivity of p53 in the sarcomatoid AGCT is indicative of morphologically higher malignant potential of tumor cells. Similarly, Jozwicki *et al.* reported that in a patient with AGCT who had a very aggressive course, the Ki-67 labeling index was more than 60% (5).

In contrast, several authors reported immunohistochemical profiles of classical GCTs. Kondi-Pafiti *et al.* reported that in 21 cases of AGCT and juvenile GCT, GCT was shown to be positive for p53 in 2/12 cases (16.7%) and the Ki-67 labeling index was less than 5% in 12/12 cases (100%) (6). In our case, the findings of p53 overexpression and the higher Ki-67 labeling index were in agreement with those described by Kondi-Pafiti *et al.* (6).

The mitotic count of GCT was reported to be associated with a poor prognosis (13), and the Ki-67 labeling index was shown to increase the risk of recurrence (10). High p53 expression was also reported to be associated with a poor prognosis (1). Our patient had a rapid recurrence in the abdomen despite adjuvant chemotherapy. Thus, our case was confirmed to have clinically aggressive propensity on histological and immunohistochemical basis.

It is generally accepted that patients with a FIGO stage more than IA should receive optimal surgical treatment, *i.e.* total abdominal hysterectomy and bilateral salpingo-oophorectomy, plus adjuvant chemotherapy (2,11,12). Fertility preserving surgery with unilateral salpingo-oophorectomy is feasible in young patients with stage IA (7). The most used chemotherapy regimens were those with platinum-based combinations, *i.e.* BVP (bleomycin, vinblastine, and cisplatin) or BEP (bleomycin, etoposide, and cisplatin) (14). Paclitaxel alone or TC (paclitaxel, and carboplatin) is also reported as an effective tool in GCT. Brown *et al.* showed that a response rate of TC was 54% (4,7). In our case, we used TC as a first chemotherapy, but the tumor in our case was highly aggressive and rapid recurrence occurred. Although BEP therapy was used for recurrent tumor, it was not also effective and the patient died of pleural effusion and respiratory failure. For those aggressive cases, more efficacious chemotherapy needs to be established.

In conclusion, our case highlights an uncommon case of clinically aggressive AGCT. The immunoreactivity for  $\alpha$ -inhibin is useful in the differential diagnosis of AGCT from sarcomas. When AGCT shows highly proliferative potential histologically, a careful follow-up of patients is warranted due to the possibility of a rapid recurrence.

**Table I.** Immunohistochemical analysis in typical AGCT areas and sarcomatoid areas

| Antigen                    | Typical AGCT* areas | Sarcomatoid areas        |
|----------------------------|---------------------|--------------------------|
| vimentin                   | +                   | +                        |
| $\alpha$ -inhibin          | +                   | +                        |
| calretinin                 | +/-                 | +/-                      |
| CD56                       | +                   | +                        |
| WT1                        | -/+                 | -                        |
| AE1/AE3                    | -/+                 | -/+                      |
| EMA                        | -                   | -                        |
| Ki-67(MIB1) labeling index | 3%                  | 40%                      |
| p53 expression             | negative            | almost strongly positive |

\*AGCT indicates adult granulosa cell tumor.

+: almost positive, -: negative, +/-: focally positive, -/+: almost negative.

## SARCOMATOID OVARIAN GRANULOSA CELL TUMOR

**Table II.** Early recurrent adult granulosa cell tumor: clinicopathologic features.

| Author                                  | Age | Stage | Symptom                   | Size<br>(cm) | Therapy                          | Histological features                                 | Mitotic count<br>(per 10HPF) | Recurrence           |                                        | Follow-up               |
|-----------------------------------------|-----|-------|---------------------------|--------------|----------------------------------|-------------------------------------------------------|------------------------------|----------------------|----------------------------------------|-------------------------|
|                                         |     |       |                           |              |                                  |                                                       |                              | Interval<br>(months) | Treatment                              |                         |
| Susil <i>et al.</i> <sup>16)</sup>      | 66  | NR    | Lower<br>discomfort       | 12           | BSO+CAP                          | Sarcomatous change                                    | 21                           | 1.5                  | -                                      | Died at 3 months        |
| Ameryckx <i>et al.</i> <sup>3)</sup>    | 78  | Ia    | Postmenopausa<br>bleeding | 15           | ATH+BSO+OMT                      | No sarcoma components                                 | >5                           | 6                    | adhesiolysis+GnRHa                     | Enlargement of the mass |
| Pectasides <i>et al.</i> <sup>11)</sup> | 62  | Ic    | NR                        | 4            | ATH+BSO<br>+chemotherapy         | NR                                                    | >10                          | 10                   | chemotherapy                           | Died at 20 months       |
| Jozwicki <i>et al.</i> <sup>5)</sup>    | 35  | IV    | NR                        | 30           | radical hysterectomy<br>+BSO+BEP | Atypical fibrothecomatous<br>and sarcomatoid patterns | 28                           | 14                   | radiotherapy                           | Died at 16 months       |
| McNeilage <i>et al.</i> <sup>8)</sup>   | 52  | NR    | Menorrhagia               | 15           | ATH+LSO                          | Sarcomatoid<br>of the recurrent tumor                 | 12                           | 23                   | radiotherapy+resection<br>+carboplatin | Died at 97 months       |

NR, not reported; ATH, abdominal total hysterectomy;

BSO, bilateral salpingo-oophorectomy;

LSO, light salpingo-oophorectomy; OMT, omentectomy;

CAP, cyclophosphamide+adriamycin+cisplatin;

BEP, bleomysin+etoposide+cisplatin; TC, paclitaxel+carboplatin; GnRHa, gonadotropin-releasing hormone agonist

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