A Clinicopathological Study on Stage I Ovarian Adult Granulosa Cell Tumors with Recurrence within 5 Years

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To the Editor: Adult granulosa cell tumor (AGCT) of the ovary is a low-grade malignant, sex cord-stromal tumor with an indolent course and late recurrence. Recurrences usually occur more than 5 years after the first treatment.[1] However, a few cases of aggressive AGCT have been reported.[2,3] We retrospectively reviewed all 213 AGCT patients at Peking Union Medical College Hospital between 2000 and 2018 and identified six Stage I cases with recurrence <5 years. The Ethics Committee of Peking Union Medical College Hospital specifically approved this study (No. S-K413), and all included patients provided written informed consent to participate in the study.

The six patients’ ages ranged from 33 to 52 years. One patient underwent puncture of the cyst and drainage of cystic fluid before surgery. All tumors were unilateral and confined to the ovary on initial surgery. The tumors’ maximum diameters ranged from 5.7 to 12.0 cm [Figure 1a], and two tumors ruptured. Microscopically, five tumors exhibited diffuse growth pattern, four showed prominent mitotic activity (6–40/10 high-power fields [HPFs]), one had sarcomatous components, and one was mixed with mucinous cystadenoma components [Figure 1b]. Two patients with ruptured tumor received chemotherapy. The time to first relapse ranged from 20 to 51 months. Five tumors recurred in the pelvic cavity, and two tumors were identified during cesarean section. One tumor had metastasized to the lung [Figure 1c]. Immunohistochemically, the tumors were positive for α-inhibin (5/6) [Figure 1d], calretinin (5/6), CD99 (6/6), and forkhead box L2 (FOXL2, 6/6) [Figure 1e] and negative for epithelial membrane antigen (0/6). The Ki-67 labeling index ranged from 5% to 40%. Five cases had the point mutation in FOXL2 [Figure 1f]. Four patients received chemotherapy after the second resection. All patients were alive after 57–121 months (average, 82 months) of follow-up. The clinicopathological details are summarized in Table 1. To our knowledge, approximately 10–15% of Stage Ia AGCT patients and 20–30% of all patients will develop metastasis or recurrence, and relapses are often detected more than 5 years after the initial treatment.[1] Most AGCTs harbor a unique somatic C134W (c.402C>G) mutation of the FOXL2 gene, and this is a relatively specific and sensitive marker for AGCT.[4] Identifying FOXL2 mutation may be helpful for differential diagnosis, especially in mixed tumors with AGCT-like components.[5] In our series, FOXL2 mutations were detected in 5 (83%) cases. We were able to summarize some features of our cases. First, all patients were Stage I and had unilateral tumors, and the tumor diameter was <13 cm. Second, two tumors ruptured during the surgery, and one patient underwent puncture and drainage of cystic fluid, suggesting that operations on half of the series might have caused tumor cells to spread or reside. Third, most cases had a high mitotic activity. Fourth, two patients were found to have relapsed on later cesarean section; both had multifocal recurrences. Fifth, one tumor had sarcomatous components and another mixed with mucinous components. Were these features related to recurrence? According to the World Health Organization,[1] unfavorable prognostic factors in AGCT include advanced stage, large size (>15 cm), bilaterality, and tumor rupture. Rupture is associated with residual tumor tissue. In the study, half of the patients received the high-risk operation that may cause tumor cells to spread or reside, which should be avoided. Furthermore, two patients were found to have relapsed when they underwent cesarean section, and both of them had multifocal recurrences. Pregnancy is accompanied by physiological changes and can exert an undesirable effect by allowing a hormone-responsive tumor to expand rapidly.[6] High mitotic activity should be paid attention to, although the relationship between mitotic activity and prognosis is controversial.[7] Our data suggest that there might be a relationship between high mitotic activity and recurrence of AGCT. Interestingly, sarcomatous or sarcomatoid changes are seldom seen in AGCT.[2,3] When present, the tumor cells exhibited significant morphological polymorphisms, significant nuclear atypia, and high mitotic counts (more than 10/10 HPFs) on a classic AGCT background. It is extremely rare for ovarian AGCT and mucinous...
adenocystoma to occur simultaneously in the same patient. Only a few cases have been reported,[5,8] whose long-term outcomes are not known. However, two cases were followed for 5.6 and 8.4 years, respectively,[5] and showed no evidence of tumor recurrence or

Table 1: Clinical and pathological features of six ovarian adult granulosa cell tumor patients

| Parameters                        | 1   | 2   | 3   | 4   | 5   | 6   |
|-----------------------------------|-----|-----|-----|-----|-----|-----|
| Age (years)                       | 37  | 33  | 31  | 52  | 36  | 49  |
| Location                          | Right ovary | Right ovary | Left ovary | Left ovary | Left ovary | Right ovary |
| Symptoms                          | Menoxenia and amenorrhea | Menoxenia and amenorrhea | Menoxenia | Lower abdominal pain | Menoxenia | Menoxenia |
| History                           | No  | No  | No  | Hysterectomy for uterine leiomyoma; puncture and drainage of cystic fluid | No  | No  |
| Initial surgery                   | Right LASO | Right LAOC, then right LASO after 30 days | Left LAOT | EL + BSO | Left LAOC | Right LASO + left LAO + LAH |
| Rupture                           | No  | Yes | No  | No  | Yes | No  |
| Number/gross/sizes (cm)           | Solitary/solid/6 | Solitary/cystic and solid/5.7 | Solitary/cystic and solid/10.0 | Diffuse/2 | Diffuse/10 | Diffuse/40 |
| Growth pattern/mitotic figures (10 HPF) | Diffuse/6 | Cord and trabeculae/1 |   |   |   |
| Other pathological features       |   |   |   | With mucinous cystadenoma | With sarcomatous components | No  |
| CHT                               | No  | Yes | No  | Yes | No  | No  |
| Following pregnancy               | No  | Yes | Yes | No  | No  | No  |
| First relapse time (months)       | 33  | 27  | 28  | 42  | 20  | 51  |
| First relapse sites               | Peritoneum | Peritoneum, left ovary, omentum, peritoneum, mesentery, Douglas pouch | Left ovary, omentum, peritoneum, mesentery | Middle lobe of the right lung | Left ovary | Omentum, mesoigmoid, splenic surface, intestinal surface, mesocolon, retroperitoneum, mesentery |
| Surgery after first relapse        | EL + cytoreduction | TAH + USO + PLND + cytoreduction | TAH + BSO + PLND + cytoreduction after 30 days | Wedge resection of the lung | Left LAO + left LAO + LAH | Secondary cytoreduction |
| CHT after second surgery          | No  | No  | Yes | Yes | No  | Yes |
| Second relapse time (months/sites) | 43/anterior uterus and vesical peritoneum | 54/omentum, peritoneum, mesentery | Yes | Yes | Yes | Yes |
| Surgery after second relapse       | TAH + USO + PLND + cytoreduction | Secondary cytoreduction | TC (3 cycles) | TC (3 cycles) | TC (3 cycles) | TC (2 cycles) |
| Third relapse time (months/sites)  | 91  | 66  | 93  | 64  | 121 | 57  |
| Surgery after third relapse        | Survival without tumor | Survival without tumor | Survival with tumor | Survival with tumor | Survival with tumor | Survival without tumor |
| Total follow-up time (months)      | 91  | 66  | 93  | 64  | 121 | 57  |
| Current situation                  | Survival without tumor | Survival without tumor | Survival with tumor | Survival with tumor | Survival with tumor | Survival without tumor |

PEB: Cisplatin + etoposide + bleomycin; PAC: Cisplatin + doxorubicin + cyclophosphamide; PC: Cisplatin + cyclophosphamide; TC: Taxol + carboplatin; CHT: Chemotherapy; TAH: Total abdominal hysterectomy; LAH: Laparoscopic-assisted hysterectomy; BSO: Bilateral salpingo-oophorectomy; LASO: Laparoscopic-assisted salpingo-oophorectomy; LAOC: Laparoscopic-assisted ovarian cystectomy; LAOT: Laparoscopic-assisted ovarian tumorectomy; EL: Exploratory laparotomy; USO: Unilateral salpingo-oophorectomy; PLND: Pelvic and/or para-aortic lymphadenectomy; HPF: High-power field.
metastases. Unfortunately, our case with coexisting mucinous adenocystoma had metastasized to lung at 42 months after the initial treatment. The rare case could be suggestive of the metastatic potential of its entity. Despite the early rapid relapse observed in our series, long-term outcomes were favorable.

Our data suggest that combining aggressive surgery with chemotherapy was an effective treatment for these patients. The study also suggested that Stage I ovarian AGCT could recur within 5 years although they rarely do. Some features, such as tumor rupture, high mitotic activity, tumor with a sarcomatous or mucinous components, and subsequent pregnancy, may be associated with tumor recurrence. However, the associations need to be established with more cases. Some high-risk surgical procedures should be avoided.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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