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

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

Parameters	Patient number					
	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 LASO + LAH
Rupture	No	Yes	No	No	Yes	No
Number/gross/sizes (cm)	Solitary/solid/6	Solitary/cystic and solid/5.7	Solitary/solid/10.0	Solitary/cystic and solid/11.9	Solitary/cystic and solid/6.0	Solitary/cystic and solid/12.0
Growth pattern/mitotic figures (10 HPF)	Diffuse/6	Cord and trabeculae/1	Diffuse/9	Diffuse/2	Diffuse/10	Diffuse/40
Other pathological features				With mucinous cystadenoma	With sarcomatous components	
CHT	No	Yes TC (3 cycles)	No	No	Yes PEB (1 cycle) PAC (1 cycle) PC (1 cycle)	No
Following pregnancy	No	Yes	Yes	No	No	No
First relapse time (months)	33	27	28	42	20	51
First relapse sites	Peritoneum	Perimetrium, left ovary, omentum, peritoneum, mesentery, Douglas pouch	Left ovary, omentum, peritoneum, mesentery	Middle lobe of the right lung	Left ovary	Omentum, mesosigmoid, splenic surface, intestinal surface, mesocolon, retroperitoneum, mesentery
Surgery after first relapse	EL + cytoreduction	TAH + USO + PLND + cytoreduction	TAH + BSO + PLND + cytoreduction	Wedge resection of the lung	Left LASO	Secondary cytoreduction
CHT after second surgery	No	No	Yes TC (3 cycles)	Yes TC (3 cycles)	Yes TC (3 cycles)	Yes TC (2 cycles)
Second relapse time (months)/sites	43/anterior uterus and vesical peritoneum		54/peritoneum, and mesentery		53/right anterior uterus and vesical peritoneum	
Surgery after second relapse	TAH + USO + PLND + cytoreduction		Secondary cytoreduction		TAH + USO + PLND + cytoreduction	
Third relapse time (months)/sites					20/pelvic wall and omentum	
Surgery after third relapse					Secondary cytoreduction	
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.

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

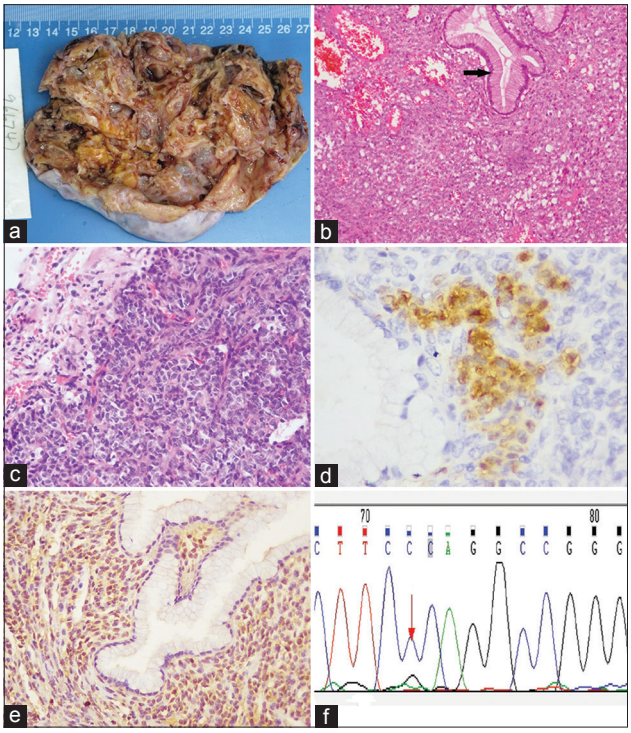

Figure 1: The morphology, immunophenotype, and *FOXL2* gene mutation status of case 4. (a) The cut surface of the ovarian tumor revealed a yellow-tan solid area and several smooth-lined cysts, each contained mucinous fluid. (b) The tumor consisted of both mucinous (black arrow) and granulosa cell components, and the two components were mixed in most areas (Haematoxylin and Eosin [H&E] staining, ×40). (c) The pulmonary metastatic tumor was composed of granulosa cell components only, and the mucinous components were absent (H&E staining, ×200). (d) Calretinin was partially positive in the granulosa cell components, but negative in the mucinous components (Immunohistochemistry staining, ×400). (e) FOXL2 was positive diffusely in the granulosa cell components (immunohistochemistry staining, ×200). (f) A C134W (c.402C>G) point mutation in the *FOXL2* gene was found by Sanger sequencing (red arrow).

metastasis. 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.

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Conflicts of interest

There are no conflicts of interest.

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