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Original Article

Clinical presentation and outcome of adult-type granulosa cell tumors: A retrospective study of 30 patients in a single institute

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Abstract

Background: Ovarian adult-type granulosa cell tumors (GCTs) are characterized as low-malignant and late-recurrent ovarian tumors. Although some clinical and pathological prognostic factors have been reported, other factors have yet to be sufficiently investigated for necessary confirmation. The aim of this study was to test the correlation between clinical factors and outcome, based on patients seen in a single institute.
Methods: Thirty patients with pathologically confirmed adult-type GCTs between 1984 and 2010 were reviewed retrospectively. Among them, eight (26.7%) had recurrence, which subsequently contributed to two mortalities.
Results: In a comparison of the clinical characteristics of the premenopausal and postmenopausal women with GCT, all of the postmenopausal women had symptoms (100% vs. 63.6%, $p = 0.01$). With regard to disease recurrence, only abnormal preoperative serum cancer antigen 125 level ($\geq$35 U/mL) was significant (50% vs. 11%, $p = 0.03$), and residual tumor showed a borderline trend (100% vs. 21.4%, $p = 0.06$). Other factors, including International Federation of Gynecology and Obstetrics stage, tumor size, tumor rupture prior to or during operation, body mass index, parity, serum estrogen level, and adjuvant therapy, were not statistically significant.
Conclusion: Physicians should be alert to the difference in the symptom presentation of GCTs between pre- and postmenopausal women, giving particular attention to the usefulness of the preoperative serum level of cancer antigen 125 in patients with GCTs. More evidence is needed to confirm this observation.

Keywords: adult-type granulosa cell tumor; cancer antigen 125; ovary; recurrence

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1. Introduction

Adult-type granulosa cell tumors (GCTs) of the ovary account for 1−2% of all ovarian tumors, and are derived from ovarian sex-cord stromal hormone-secreting tumors.[1] GCTs are characterized as low-malignant and late-recurrent ovarian tumors,[2] but it is evident that patients with this illness have recurrent disease, which typically is the eventual cause of death.[3] Although most symptoms are nonspecific, the clinical symptoms of GCTs may include abdominal pain or distention, and abnormal bleeding or palpable pelvic mass.[4] Due to the rarity of GCTs, the prognostic factors of tumor recurrence are uncertain, although some clinical or pathological factors, such as advanced stage (Stage II−IV), large tumor size, high mitotic index, tumor rupture, and the presence of residual tumor after initial surgery have been reported.[2,3] The potential conventional tumor marker of GCTs is inhibin,[5] although it is used for follow-up. Because the serum level of cancer antigen 125 (CA125) might be elevated in advanced stage and tumor rupture, in theory, and advanced stage and tumor rupture are reported to be correlated with tumor recurrence, it is rational to suppose that the preoperative serum level of CA125 might also contribute to recurrence. The aim of this study was to test the correlation between clinical factors and outcome.

2. Methods

Thirty patients with pathologically confirmed GCTs between 1984 and 2010 at Taipei Veterans General Hospital were reviewed retrospectively. Approval for the study was obtained from the local ethics committee (VGHIRB 98-11-02). The characteristics assessed included age, gravidity, body mass index (BMI), menopausal status, preoperative serum levels of CA125 and estrogen, tumor size, tumor rupture prior to or during operation, surgical method, pathological finding, International Federation of Gynecology and Obstetrics (FIGO) stage, and adjuvant therapy. Survival probabilities were plotted using the Kaplan−Meier life table, and survival differences were tested for significance using the log-rank test. Statistical analysis was conducted using SPSS version 18 (SPSS Inc., Chicago, IL, USA), including Chi-square tests and Fisher's exact test. A p value < 0.05 was defined as statistically significant and all tests were two-tailed.

3. Results

GCTs occurred in the premenopausal status of 19 of the 30 patients. Clinical factors, with the exception of clinical symptoms, of both menopausal and postmenopausal status were similar without a statistically significant difference (Table 1). All premenopausal women had symptoms, but nearly 40% of postmenopausal women were asymptomatic ($p = 0.012$). Abdominal pain or distention (40%, $n = 12$) was most common, followed by bleeding disorder (30%, $n = 9$). Four patients were asymptomatic and the GCT was found accidentally, and all were postmenopausal. The mean age at diagnosis was 48.7 years (range, 32−77 years), and the mean follow-up period was 101.8 months (range, 26−316 months). Mean size of the GCTs was 10.4 cm (range, 5−20 cm). Seventeen of the 30 patients underwent an incomplete surgery (56.7%). The majority of the patients were Stage IA (73.3%, $n = 22$; Table 1). Eight patients (26.7%) underwent adjuvant therapy, and all were treated with multiagent chemotherapy with bleomycin, etoposide, and cisplatin (Table 1).

There were eight cases of recurrence (26.7%) during the follow-up period (Table 2). Recurrence was associated with elevated preoperative serum levels of CA125 (≥35 IU/mL), to a statistically significant degree (50% vs. 11%, $p = 0.03$). Other factors, including FIGO stage, tumor size, tumor rupture prior to or during operation, body mass index, parity, serum estrogen level, complete staging surgery, or adjuvant therapy were not statistically significantly associated with disease

Table 1
Characteristics of the 30 patients with granulosa cell tumors of the ovary.

	All patients ($n = 30$)	Premenopausal ($n = 19$)	Postmenopausal ($n = 11$)	p
Symptoms				0.039
No symptom	4 (13.3)	0 (0)	4 (36.4)	
Bleeding disorder	9 (30)	7 (36.8)	2 (18.2)	
Abdominal pain/ distension	12 (40)	8 (42.1)	4 (36.4)	
Palpable mass	5 (16.7)	4 (21.1)	1 (9.1)	
Symptoms				0.012
No	4 (13.3)	0 (0)	4 (36.4)	
Yes	26 (86.7)	19 (100)	7 (63.6)	
Operation				0.806
USO	9 (30)	5 (26.3)	4 (36.4)	
TH + BSO	8 (26.7)	5 (26.3)	3 (27.3)	
Complete staging surgery	13 (43.3)	9 (47.4)	4 (36.4)	
Tumor rupture				0.104
No	22 (73.3)	16 (84.2)	6 (54.5)	
Yes	8 (26.7)	3 (15.8)	5 (45.5)	
FIGO stage				0.110
IA	22 (73.3)	16 (84.2)	6 (54.5)	
IC	5 (16.7)	3 (15.8)	2 (18.2)	
II	0	0	0	
III	2 (6.7)	0	2 (18.2)	
IV	1 (3.3)	0	1 (9.1)	
CA125 IU/mL				0.266
<35	18 (60)	13 (68.4)	5 (45.5)	
≥35	12 (40)	6 (31.6)	6 (54.5)	
Body mass index kg/m^2				1.000
<25	17 (56.7)	11 (57.9)	6 (54.5)	
≥25	13 (43.3)	8 (42.1)	5 (45.5)	
Adjuvant treatment				0.104
No	22 (73.3)	16 (84.2)	6 (54.5)	
Chemotherapy	8 (26.7)	3 (15.8)	5 (45.5)	
Residual tumor after treatment				0.126
Absence	28 (93.3)	19 (100)	9 (81.8)	
Presence	2 (6.7)	0	2 (18.2)	

Data are presented as n (%).
BSO = bilateral salpingo-oophorectomy; CA125 = preoperative serum level of cancer antigen 125; complete staging surgery = washing cytology, TH, BSO, omentectomy, pelvic and para-aortic lymphadenectomy, and multiple randomized biopsies; TH = total hysterectomy; USO = unilateral salpingo-oophorectomy.

Table 2
Prognostic factors of the 30 patients with granulosa cell tumors of the ovary.

	Total patients $n = 30$	Recurrence $n = 8$	No recurrence $n = 22$	p
FIGO stage				0.166
I	27	6	21	
II–IV	3	2	1	
Body mass index				0.242
<25	17	3	14	
≥25	13	5	8	
Parity				1.000
Nullipara	7	2	5	
Multipara	23	6	17	
CA125 (IU/mL)[a]				0.034
<35	18	2	16	
≥35	12	6	6	
Estrogen (mU/mL)[b]				0.338
<60	8	1	7	
≥60	11	4	7	
Estrogen (mU/mL)[c]				0.545
<35	6	1	5	
≥35	5	2	3	
Size of tumor				1.000
<10 cm	13	3	10	
≥10 cm	17	5	12	
Tumor rupture[d]				0.158
Yes	8	4	4	
No	22	4	18	
Complete surgery				0.698
Yes	13	4	9	
No	17	4	13	
Residual tumor				0.064
Yes	2	2	0	
No	28	6	22	
Adjuvant therapy				0.158
Yes	8	4	4	
No	22	4	18	

FIGO = International Federation of Gynecology and Obstetrics.
[a] Preoperative serum cancer antigen 125 level.
[b] Preoperative serum estrogen level of premenopausal women.
[c] Preoperative serum estrogen level of postmenopausal women.
[d] Rupture of tumor prior to and during operation.

Table 4
Analysis of the patients with granulosa cell tumors who died of disease.

	Total patients ($n = 30$)	Alive ($n = 28$)	Deceased ($n = 2$)	p
FIGO stage				0.193
I	27	26	1	
II–IV	3	2	1	
Body mass index				1.000
<25	17	16	1	
≥25	13	12	1	
Parity				1.000
Nullipara	7	7	0	
Multipara	23	21	2	
CA125 (IU/mL)[a]				0.152
<35	18	18	0	
≥35	12	10	2	
Estrogen (mU/mL)[b]				1.000
<60	8	8	0	
≥60	11	10	1	
Estrogen (mU/mL)[c]				1.000
<35	6	5	1	
≥35	5	5	0	
Size of tumor				0.492
<10 cm	13	13	0	
≥10 cm	17	15	2	
Tumor rupture[d]				0.469
Yes	8	7	1	
No	22	21	1	
Complete surgery				1.000
Yes	13	12	1	
No	17	16	1	
Residual tumor				0.131
Yes	2	1	1	
No	28	27	1	
Adjuvant therapy				0.469
Yes	8	7	1	
No	22	21	1	

FIGO = International Federation of Gynecology and Obstetrics.
[a] Preoperative serum cancer antigen 125 level.
[b] Preoperative serum estrogen level of premenopausal women.
[c] Preoperative serum estrogen level of postmenopausal women.
[d] Rupture prior to and during operation.

recurrence, although the presence of residual tumor after primary surgery showed a marginal association ($p = 0.06$).

The median time to recurrence was 83 months (range, 13–227 months), based on the imaging findings. Two patients underwent repeat surgical excision with pathological confirmation. Peritoneal recurrence was most common (75%, $n = 6$), and two cases had recurrence in the liver parenchyma. All patients with recurrent GCT were treated with chemotherapy with

Table 3
Clinical findings of patients who had recurrent disease.

Case	Age (y)	Stage	Primary treatment	Residual tumor	Pretreatment CA125 (U/mL)	DFS (mo)	Site of recurrence	Treatment for recurrence	Outcome	Follow-up after recurrence (mo)
1	32	IA	USO	No	42	134	Liver parenchyma	Surgery + C/T	Alive	206
2	56	IV	USO + C/T[a]	Yes	65	96	PC	C/T	Die	131
3	35	IA	USO	No	11	83	PC	Surgery + C/T	Alive	49
4	41	IA	TH + BSO	No	12	227	PC	C/T	Alive	70
5	73	IIIC	Staging surgery + C/T[a]	Yes	82.4	13	PC	C/T	Alive[b]	6
6	48	IC	Staging surgery + C/T[a]	No	56	58	PC	C/T	Alive	90
7	44	IC	Staging surgery + C/T[a]	No	76.3	99	Liver parenchyma	C/T	Die	28
8	38	IA	Staging surgery	No	37	46	PC	C/T	Alive	12

C/T = chemotherapy; DFS = disease-free survival; PC = peritoneal cavity; TH = total hysterectomy; staging surgery = complete staging surgery included total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, and multiple random biopsies; USO = unilateral salpingo-oophorectomy.
[a] Multi-agent chemotherapy with bleomycin, etoposide, and cisplatin.
[b] Alive status with presence of a tumor.

various kinds of regimens, and all patients were treated with cisplatin-based or paclitaxel-based chemotherapy (Table 3). Two patients finally died of the disease (Table 4). However, no single prognostic factor could predict the survival of the patients, whether recurrent patients ($n = 8$) or all patients (Table 4, $n = 30$). The 5-year and 10-year survival rates for all stages were 96.7%. Multivariate analysis did not show significance due to the small case number; however, based on univariate analysis, we found that low preoperative serum CA125 (<35 IU/mL) might benefit in survival, because recurrence rate was low in this group (Table 2).

4. Discussion

Ovarian adult-type GCTs account for 1−2% of all ovarian tumors, and present distinct hormonal behaviors and low-grade malignancies compared with common types of ovarian epithelial tumors. Ovarian adult-type GCTs commonly occur in the perimenopausal or early postmenopausal female; the median age at diagnosis was reported to be 46−54 years,[1−5] which was also supported by our current study. Ovarian CGTs are frequently functional, often with estrogen-secreting characteristics; therefore it is rational to suppose that bleeding disorder may be the most common symptom, especially for postmenopausal women.[6] This hypothesis has been supported in the literature.[7−9] For example, Auranen et al[7] reported that 27 of 35 patients had bleeding disorder, Chua et al[8] showed 40% of patients had GCT associated with endometrial hyperplasia, and Ohel et al[9] reported 6.4% and 11% of 172 patients were associated with breast cancer and endometrial cancers, respectively. All these studies confirmed the relationship between an excess of estrogen and ovarian GCT. However, 36% (4/11) of postmenopausal women with GCT in the current study were asymptomatic, which could easily be explained by the low serum levels of estrogen in nearly half of the postmenopausal patients (Table 2). A previous report mentioned that postmenopausal bleeding is a common presenting sign,[1] and that fewer than one-fifth of postmenopausal women had postmenopausal bleeding; however, one-third of the patients had irregular menstruation (Table 1). We did not find endometrial lesions in the current study. By contrast, nonspecific abdominal symptoms, including pain, distension, and mass, were most common and in nearly 60% (17/30) of all patients, which was related to the fact that GCTs are oftentimes large (>10−15 cm) and tend to hemorrhage.[2] In addition, many women have a palpable or pelvic mass[2]; one-fifth of patients in this study also described this symptom.

Most studies report that the leading prognostic factors of GCTs were clinical and pathological parameters. The common clinical parameters include FIGO stage of the disease, tumor size (>10−15 cm), tumor rupture prior to or during operation, age at diagnosis, presence or absence of residual tumor after initial surgery, or even complete surgical staging without lymphadenectomy or postoperative adjuvant chemotherapy with a bleomycin, etoposide, and cisplatin regimen.[2,3,7−12] Common pathological parameters include nuclear atypia, mitotic index (mitotic index $\geq$ 4−10 mitoses/10 high-power fields), and some histopathological or serum markers.[1,13−15]

Because the majority of patients ($n = 27$) in this study were supposed Stage I, and the sample size was small ($n = 30$), the correlation between stage and recurrence seemed to be statistically insignificant, although the majority of studies show that the initial stage of GCT is the most important prognostic factor.[1−3] Preoperative serum parameters, including inhibin B, transforming growth factor family secreted by granulosa cells, and anti-Mullerian hormone and estradiol secreted by granulosa cells are also reported to be valuable.[2,16,17] However, we cannot comment on this issue, because we did not detect these parameters in the patients studied, although the preoperative serum levels of estrogen seemed not to be correlated with prognosis in the current study. By contrast, preoperative serum levels of CA125, which were conventionally considered an important prognostic factor for epithelial ovarian tumor,[18,19] seemed to be statistically significant to tumor recurrence. If the patients had a preoperative serum level of CA125 $\geq$ 35 IU/mL, half of them were recurrent; this compares with 10% of patients who had a preoperative serum level of CA125 < 35 IU/mL. This finding may be related to the vascular nature of GCT and the tendency to hemorrhage, and the peritoneal irritation might have contributed to the elevated serum level of CA125.[20,21] In addition, the presence of peritoneal irritation might hint at the possibility of tumor dissemination preoperatively, which is correlated with advanced stage, bigger tumors, tumor rupture, and a high possibility of residual tumor after primary surgery.

Complete staging surgery is emphasized in some published reports,[10,12] although the role of lymphadenectomy is highly controversial and the majority of published papers did not support the routine use of lymphadenectomy during complete staging surgery, based on the extremely low incidence of lymph node metastases in patients with GCT.[10,22−24] In this study, complete staging surgery seemed to be statistically insignificant, even for he Stage I patients. In the Taiwanese Gynecologic Oncology Group (TJOG) study, the 176 patients with GCT after primary surgical treatment also showed that complete staging surgery seemed to be insignificant.[3] By contrast, complete excision of the tumor seemed to be a more apparent prognostic factor in the TJOG study.[3] In a previous Korean study, residual tumor was also reported as the only significant factor of recurrence in multivariate analysis.[12] In this study, we also found that residual tumor after primary surgery might be important for prognosis, although without statistical significance. The possible explanation is the small size of the study population.

In this study, we only evaluated the correlation between the clinico-pathological factors and prognosis of adult-type GCTs, and failed to test the role of gene mutation or alteration of GCTs, such as the *FOXL2* gene [c.402C > G (C134W)].[25−27] This gene is now considered pathognomonic of GCTs, confirming a diagnosis of adult-type GCTs.[26] FOXL2 is a forkhead−winged helix transcription factor that is an evolutionarily conserved single-exon gene of 2.7 kb located at 3q23 that encodes for a 376 amino-acid protein belonging to the large family of forkhead transcription factors.[26] In addition, the prognostic significance of *FOXL2* mutations and mRNA expression has

also been reported in adult GCTs of the ovary by D'Angelo's group,[28] because the authors found that higher FOXL2 protein expression had worse overall survival and disease-free survival than those with negative or weakly immunoreactive tumors.

In conclusion, we found that some of the postmenopausal women with GCTs were diagnosed by routine physical examination in the current study. We also emphasized the possible value of an elevated preoperative serum CA125 level in these women with GCTs, because elevated preoperative serum levels of CA125 could predict future recurrence in patients with GCTs. More evidence is needed to confirm this observation.

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