Granulosa cell tumors of the ovary: a clinicopathologic and immunohistochemical study of 21 cases

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Summary

Purpose: To further study the clinicopathologic and immunohistochemical features of ovarian granulosa cell tumors (GCTs). *Methods:* We retrospectively studied all cases of GCTs diagnosed in our laboratory over the last 10-year period. Immunohistochemistry for inhibin, vimentin, cytokeratin, Ki-67 and p53 was performed on archival paraffin blocks. Pathologic and immunohistochemical findings were correlated with the clinical records of the patients. *Results:* Twenty-one cases (15 of the adult and 6 of the juvenile type) were retrieved. All patients were FIGO Stage I at the time of diagnosis. Recurrent disease was detected in four patients (19 %) during a median follow-up of 36 months (range 2-26 years). Pathology revealed a concomitant theca-cell component in three cases, a Sertoli-Leydig component in one case, and a thecoma in one case. Archival tissue material was available in 12 cases. Immunohistochemistry was positive for: β-inhibin in 12/12 cases (100%), vimentin in 11/12 cases (91.7%), cytokeratin in 3/12 cases (25%), CD34 in 0 cases (0%), and p53 in 2/12 cases (16.7%). The Ki-67 index was < 5% in 12/12 cases (100%). No significant correlations were observed between the pathologic and immunohistochemical parameters examined and the clinical outcome. *Conclusions:* Despite the relatively indolent nature and favorable prognosis of most GCTs, late recurrences are not a rare event even in Stage I patients, necessitating a close and long-term follow-up. The identification of novel prognostic markers, in addition to our traditional staging parameters such as clinical staging, is needed in order to more accurately predict probabilities of recurrence in these patients.

Key words: Adult; Juvenile; Granulosa cell tumor; Ovary.

Introduction

Granulosa cell tumor (GCT) of the ovary is a relatively uncommon sex-cord-stromal neoplasm comprising approximately 2-5% of all ovarian cancers. [1, 2]. GCT is subdivided in two types, known respectively as adult and juvenile, which differ with regard to their clinical and pathologic features [1, 2]. The more frequent adult type of this tumor is usually – but not exclusively – diagnosed in women of reproductive age, while approximately 80% of juvenile GCT cases are diagnosed in the first two decades of life [1]. Both types are often associated with excessive secretion of estrogens and endometrial pathology, leading to symptoms of menstrual irregularities, menorrhagia, or postmenopausal bleeding, although juvenile GCTs may also present with isosexual precocity or abdominal pain due to the presence of a large ovarian mass [1-3].

Despite the tendency of GCTs to recur, often several years after their initial diagnosis, they are characterized as relatively indolent neoplasms. However, the favorable prognosis seems to be largely dependent on the clinical staging at the time of the initial diagnosis [1]. Most previous studies have demonstrated a greater than 90% 5-year survival rate for patients with Stage I disease [2, 4-8]. On the other hand, an aggressive clinical course has been strongly correlated with disease presentation at an advanced stage, and 5-year survival rates for Stage III/IV cases range from 22-50% [5, 7]. Apart from stage, additional prognostic factors, including age, tumor size, tumor rupture and degree of nuclear atypia have also been described in some series [4-6, 9, 10]. However, the accurate identification of novel prognostic indicators which will aid in better evaluating prognosis and designating appropriate treatment for each individual case remains to be established.

The aim of the present study was to further investigate the clinical, pathologic and immunohistochemical features of GCTs and briefly review the existing literature.

Materials and Method

A retrospective study of patients with adult and juvenile GCT of the ovary was carried out. All cases diagnosed at the pathology laboratory of our hospital over a 10-year period (from 1996 to 2005) were included. Histological diagnosis was determined during routine pathologic assessment. The relative clinical and pathology reports as well as representative slides for each case were retrieved.

The clinical data, including patient age, presenting symptoms, menopausal status, treatment received, and the final clinical outcome were correlated with the pathologic data and immunohistochemistry results. The pathologic data included the following parameters: tumor size and location, histological type, degree of nuclear atypia and mitotic rate of tumor, associated endometrial abnormalities and disease stage at the time of diagnosis. For the purposes of staging, all patients had been submitted to peritoneal washings and pelvic lymphadenectomy.

Immunohistochemistry, formalin-fixed paraffin-embedded tissue blocks were retrieved from the archives of our laboratory.

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Additional sections were obtained for the application of a streptavidin-biotin immunohistochemical method. The specimens were stained using the Ventana automated immunostainer, with the following primary antibodies: vimentin (mabVg, Euro-Diagnostica), pan-cytokeratin (mono clone 80, Monosan), β-inhibin (mono E4, Serotec), Ki-67 (mono MIB-1, Dako), p53 (mono D07, Dako), CD34 (mono QBend/10, Novocastra).

Results

After reviewing the archival files of our laboratory, we were able to retrieve 21 cases of GCTs, 15 (71.4%) of the adult and six (28.6%) of the juvenile type, among 560 cases of malignant ovarian tumors, indicating an incidence of 3.75%. Follow-up data were available for all patients. The median follow-up period was 36 months (range 2-26 years). Archival tissue material was available for the performance of immunohistochemistry in 12/20 cases (60%).

Clinical data: Table 1 shows the clinical features of all patients included in the study. Patient age ranged from 17 to 73 years (mean: 47.8 years). The mean age of adult patients was 58.6 years (range 49 to 73 years) while in the juvenile group the mean age was 20.8 years (range 17-31 year). Eleven patients (52.4%) were postmenopausal, nine (42.9%) premenopausal, while one patient (4.8%) was pregnant. Among the adult group, most patients were postmenopausal (11/15 cases, 73.3%) and presented with abnormal postmenopausal bleeding. In the remaining four adult premenopausal cases the presenting sign was menstrual irregularities in three cases and abdominal pain in one. In the group of juvenile GCT, five of our patients presented with abdominal pain while a pregnant patient was asymptomatic at the time of diagnosis. Fourteen patients (14 cases, 66.7%) were submitted to total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO), and all remaining patients (7 cases, 33.3%) to unilateral salpingo-oophorectomy (USO). With regard to staging, all of our patients (21 cases, 100%) were Stage I at the time of diagnosis. Recurrences were noted in four cases (three of the adult and one of the juvenile type). Time elapsed between the initial operation and recurrence was two, six, 20 and 25 years (mean interval: 13.2 years). Two adult cases relapsed in the pelvis after a disease-free interval of two and 25 years, respectively, while one adult case presented with a liver metastasis 20 years postoperatively. The case of the juvenile GCT relapsed with distant metastasis in the lung after a disease-free period of six years. Local recurrences were treated with secondary surgical debulking, while chemotherapy was administered in patients with metastatic disease. All our patients were alive and disease-free at the time of the last follow-up.

Pathologic and immunohistochemical data: Table 2 shows the pathologic features of our studied material. Various histological patterns of growth were observed including mainly microfollicular, macrofollicular, trabecular, solid and diffuse patterns (Figures 1 and 2). In the majority of our cases the tumor was located in the

Table 1. — *Distribution of clinical characteristics in 21 patients with GCT.*

Characteristics (IGF-II concentration, application time)	Frequency/range (mean)*	Percent (%)
Age (years)		
– All	17-73 (47.8)*	
– Adult group	49-73 (58.6)*	
– Juvenile group	17-31 (20.8)*	
Menopausal status		
– Premenopausal	9/21	42.9
– Postmenopausal	11/21	52.4
– Pregnant	1/21	4.8
Presenting symptoms		
– Postmenopausal bleeding	11/21	52.4
– Menstrual irregularities	4/21	19.0
– Abdominal pain	5/21	23.8
– Asymptomatic	1/21	4.8
Stage		
I	21/21	100
II	0/21	0
III	0/21	0
IV	0/21	0
Recurrences		
– Local	2/21	9.5
– Distant metastases	2/21	9.5
Treatment		
1) Primary		
– TAHBSO	14/21	66.7
– USO	7/21	33.3
2) Adjuvant		
– Secondary debulking	2/21	9.5
– Chemotherapy	2/21	9.5

TAHBSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy.

Table 2. — *Distribution of pathological findings in 21 patients with GCT.*

Characteristics (IGF-II concentration, application time)	Frequency/range (mean)*	Percent (%)
Histological type		
– Adult type	15/21	71.4
– Juvenile group	6/21	28.6
Tumor location		
– Right	7/21	33.3
– Left	13/21	61.9
– Bilateral	1/21	4.8
Tumor size (cm)		
– All	3-30 (9.1)*	
– Adult type	3-19 (7.0)*	
– Juvenile	5-30 (14.4)*	23.8
Mitotic rate		
– Low	21/21	100.0
– Moderate	0/21	0
– High	0/21	0
Nuclear atypia		
– Low	20/21	95.2
– Moderate	0/21	0.0
– Severe	1/21	4.8
*Endometrial abnormalities***		
– Hyperplasia	6/14	42.9
– Polyps	3/14	21.4
– Adenocarcinoma	2/14	14.3
– None	3/14	21.4

** Only among women submitted to TAHBSO.

Fig. 1

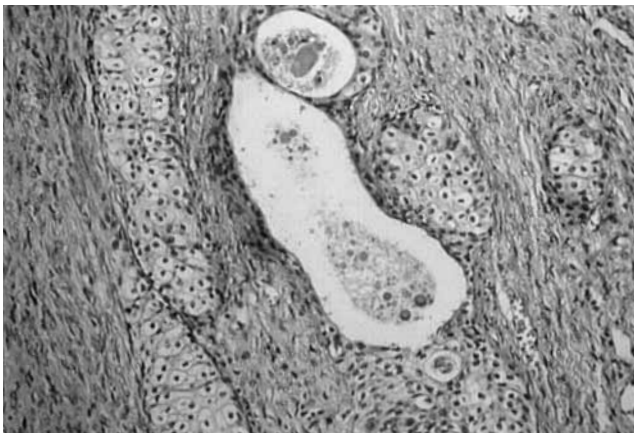

Fig. 2

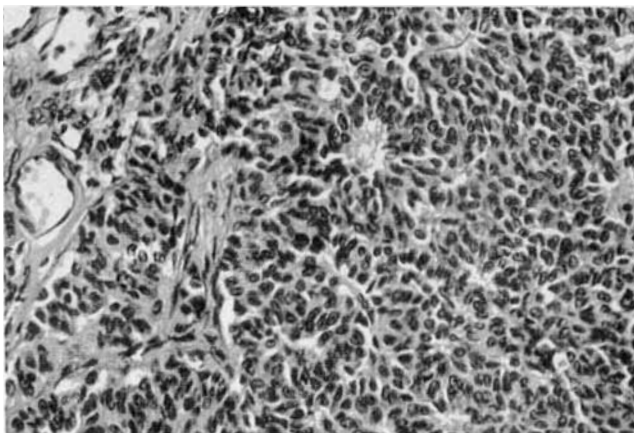

Fig. 3

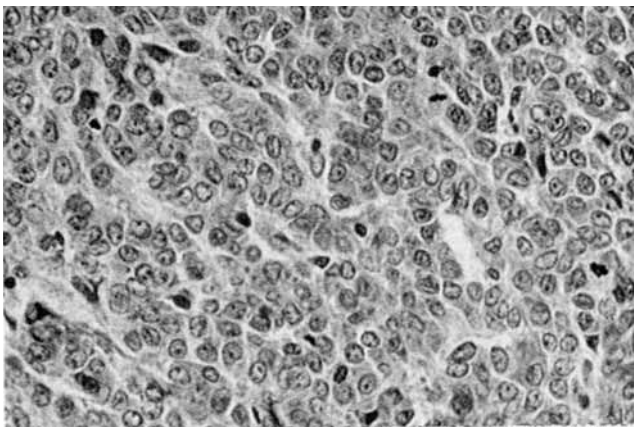

Figure 1. — Histological section of a juvenile granulosa ovarian tumor showing a cystic pattern (hematoxylin-eosin x 25).

Figure 2. — Histological section of a juvenile granulosa ovarian tumor showing a solid pattern with Call-Exner bodies (hematoxylin-eosin x 120).

Figure 3. — Histological section of the recurrent juvenile granulosa tumor with prominent mitotic activity (hematoxylin-eosin x 250).

left ovary (13 cases, 61.9%). In seven cases (33.3%) the right ovary was involved, while bilateral involvement was noted in one case (4.8%). Tumor size in all cases ranged from 3-30 cm (mean: 9.1 cm), with a mean size of 14.4 cm in the juvenile types and a mean size of 7 cm in the adult cases. With the exception of one case associated with distant metastasis, which displayed prominent mitotic activity (Figure 3), the mitotic rate was low (< 5 mitoses/10 HPF) and the degree of nuclear atypia was also low in all remaining cases. A theca-cell component was found in three (adult) cases while a Sertoli-Leydig component was found in the case of the juvenile type which recurred with metastatic disease. In 11 out of 14 patients (78.6%) who were submitted to TAHBSO, concomitant endometrial abnormalities were found as follows: endometrial adenocarcinoma was diagnosed in two cases, endometrial hyperplasia in six cases and endometrial polyps in three cases. An ovarian thecoma was also found in one (adult) case.

Immunohistochemistry was positive for β-inhibin in 12/12 cases (100%), vimentin in 11/12 cases (91.7%), cytokeratin in 3/12 cases (25%), p53 in 2/12 cases (16.7%) and CD34 in 0 cases. The Ki-67 index was < 5% in 12/12 cases (100%).

No significant correlations were observed between the pathologic and immunohistochemical parameters examined and the clinical outcome.

Discussion

Adult and juvenile GCTs are described as two histologically and clinically distinct neoplasms and are usually studied as separate clinicopathologic entities although they represent different subtypes of the same tumor [11]. In the present study we examined both subtypes to compare their features and investigate the differences with regard to their particular biological behavior.

GCTs may be detected in almost any age group, from the first to the tenth decade of life, with a mean age of 52 years at the time of diagnosis [11]. Nevertheless, juvenile GCTs in particular are more age-specific in comparison to their adult counterpart, occurring mostly in prepubertal girls and only rarely in older patients [11]. In this study the mean age of all patients was 48 years. The youngest patient with an adult type of tumor was 45 years old, while the oldest patient with a juvenile GCT was a pregnant 31-year-old woman. As regards the clinical presentation, major differences were noted not only between premonopausal and postmenopausal patients but also among adult and juvenile cases. More specifically, all postmenopausal women in our series presented with abnormal postmenopausal bleeding, while premopausal patients presented with menstrual irregularities or with abdominal pain. The latter symptom was far more common in cases with the juvenile type of tumor and was

directly related to the larger tumor size found in this group (mean size of 14.4 cm, versus a mean size of 7 cm in the adult cases). As previously described [2, 12] and as normally expected, larger tumors are much more likely to cause persistent , abdominal or pelvic pain or to be complicated with hemorrhagic rupture into the abdominal cavity, occasionally mimicking a ruptured ectopic pregnancy [4, 13]. Concomitant endometrial abnormalities may also be found, and are consistent with increased estrogen production by the tumor [2, 11]. In our series the most common endometrial pathology found in association with GCTs was endometrial hyperplasia, followed by endometrial polyps and adenocarcinoma.

The primary treatment for patients with suspected GCTs is surgery [2, 11]. The surgical procedure should be conservative unless there are obvious signs of advanced cancer, and should aim at establishing a definite histological diagnosis, completing the process of staging and achieving optimal tumor debulking [2, 11]. For patients presenting with Stage I disease, a total abdominal hysterectomy with bilateral salpingo-oophorectomy is typically performed in postmenopausal women or when childbearing is not an issue, while the more conservative approach of a unilateral salpingo-oophorectomy may represent a more appropriate option for younger premenopausal women who wish to retain their fertility [11]. Treatment options for recurrent or advanced-stage disease remain a controversial issue, and mainly include the performance of secondary surgical debulking and the administration of chemotherapy agents , either alone or in combination [2].

Although GCTs are considered to be of low-grade malignant potential, in a significant percentage (10-50%) of patients, late and/or several relapses tend to occur, often many years after the initial diagnosis [14]. The median time of relapse is approximately four to six years postoperatively, although in several previous reports relapses appearing more than 20 years later have been described [2, 6-8, 15, 16]. This fact necessitates a close, long-term follow-up of patients in order to detect recurrent disease in time and to intervene accordingly. For patient monitoring the measurement of serum levels of inhibin has been recommended [11, 17]. Although inhibin production is restricted neither to the ovary nor to GCTs (both the placenta and some epithelial ovarian cancers, especially of the mucinous type, also secrete this molecule), it seems that a consistently rising level of inhibin in a postmenopausal woman with a history of GCT is a strong predictor of recurrence and should warrant further investigation [2, 11, 17, 18]. A common site of recurrence is the pelvis, followed by disease spread to the upper abdomen [4, 6, 12]. Distant metastases involving the lung and bones may also be found but seem to be a rare event [2]. In our series, recurrences were noted in four patients: two cases relapsed in the pelvis, one case presented with liver metastasis and the remaining case relapsed with distant metastasis in the lung. Interestingly, the disease-free interval in two out of these four cases was 20 and 25 years, respectively, which further supports the described propensity of GCTs for late recurrences.

According to previous studies and literature reviews, mainly FIGO stage, and to a much lesser degree other parameters such as tumor size, tumor rupture and degree of nuclear atypia, seem to influence the clinical outcome of women with GCTs [4-6, 9, 10]. Some authors have further suggested that age, Ki-67 index, p53 and DNA ploidy may also significantly affect prognosis, but the clinical value of these markers remains to be validated [4, 19-22]. In the present study we also investigated the prognostic significance of some previously described yet still debatable factors, including but not limited to tumor size, mitotic index, nuclear atypia, Ki-67 index and p53 immunostaining in women with both adult and juvenile GCTs. Our failure to reach any significant correlations between the studied parameters and patient outcome could be due to the small number of cases included in our study. This is a common problem which has been reported by many authors and is normally attributed to the relative infrequent occurrence of this neoplasm [14, 23].

In conclusion, additional large scale prospective and retrospective studies are needed to further define the exact clinical significance of all previously described parameters in GCTs and provide further insight into the molecular pathways that regulate the development of these indolent neoplasms as well as their transformation to a metastatic and potentially life-threatening disease. Furthermore, as suggested by Auranen et al., recent advances in molecular genetics carry great promise for radical improvements in our understanding of the biological pathways that regulate granulosa cell proliferation, with the potential to significantly contribute as well in the development of novel prognostic and therapeutic markers for GCT patients [23].

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