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Original Article

Sertoli–Leydig cell tumors of the ovary: A Taiwanese Gynecologic Oncology Group study

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Abstract

Objective: To report the natural history and prognosis of the uncommon Sertoli–Leydig cell tumor (SLCT) of the ovary.
Materials and Methods: A 20-year retrospective review was conducted by the Taiwanese Gynecologic Oncology Group (TGOG), including nine tertiary medical centers from different regions in Taiwan. The medical records for 40 cases of ovarian SLCT were collected. Pathology reviews were carried out by a panel of expert pathologists.
Results: After pathological review, 17 patients were subsequently excluded because the pathology slides were unavailable in five cases, and discrepant results from the initial diagnosis were found in 12 cases (34%). For the remaining 23 patients, the median age was 41 years. The most common symptom was irregular vaginal bleeding followed by an abdominal mass or amenorrhea. Most of the tumors were unilateral and confined to the right ovary, with an average size of 8.2 cm. Preoperative serum markers were available for 12 patients and were elevated for three patients. All patients underwent primary surgery. Six patients accepted adjuvant chemotherapy, and bleomycin, etoposide, and cisplatin were used in four of them. Clinical follow-up information was available in 21 patients with a median of 19 months. Eighty-two percent of patients were alive and free of disease up to the date of the last follow-up. Two patients died of the disease.
Conclusion: This study demonstrates the extreme rarity of ovarian SLCT in Taiwan. Histological discordance between the diagnosis and central review proves the need for expertise review before treatment. For an improved understanding of the biological behavior and treatment strategy for this unique tumor, international collaboration is imperative.

Keywords: chemotherapy; ovary; Sertoli–Leydig cell tumor; sex cord-stromal tumors; Taiwanese Gynecologic Oncology Group (TGOG) study

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Introduction

Sex cord-stromal tumors account for approximately 7% of all malignant ovarian neoplasms, and Sertoli–Leydig cell tumors (SLCTs) represent <0.5% of all ovarian tumors [1]. They are categorized as tumors of low malignant potential, or low-grade malignancies, with indolent growth patterns. SLCT occurs most frequently in the second and third decades of life and typically produces androgens; clinical virilization is noted in 40% of patients. The androgenic symptoms include oligomenorrhea followed by amenorrhea, breast atrophy, acne, hirsutism, clitoromegaly, a deepening voice, and receding hairline.

Surgical resection is considered the cornerstone of treatment, and the disease is often diagnosed by pathology following surgery. The disease stage, histologic differentiation, mitotic index, presence of heterologous elements, and tumor rupture have all been reported to predict recurrence [2]. However, the role of the standard staging procedure including lymphadenectomy [3], choice of optimal adjuvant therapy [4], and efficient treatment in relapse remain perplexing due to the extreme rarity of this tumor. Here we report the natural history and prognosis of this uncommon ovarian tumor obtained from a Taiwanese Gynecologic Oncology Group (TGOG) study.

Materials and methods

A retrospective multi-institutional review of patients with ovarian SLCT was conducted by the TGOG, including nine tertiary medical centers from different regions in Taiwan. We collected the data from 40 cases with ovarian SLCTs diagnosed between January 1989 and December 2009. The medical records were reviewed and the clinical manifestations, demographic and pathological features, treatment strategies, and outcomes were documented. The hematoxylin and eosin (H&E) stained slides of the patients were reviewed by a panel of senior gynecologic pathologists, S.M. Jung (Chang Gung Memorial Hospital, Taoyuan), C.R. Lai (Taipei Veteran General Hospital, Taipei), M.C. Lin (National Taiwan University Hospital, Taipei), and T.Y. Wang (Mackay Memorial Hospital, Taipei). The pathologic diagnostic criteria were based on the WHO classification [5]. Every slide was reviewed by four pathologists to reach diagnostic consensus. Slides with discrepancies between the pathologists were then reviewed by another pathologist for a majority decision. The clinical and pathological data were then analyzed. Fisher's exact test for analysis of the survival and prognostic factors was used. The retrospective multicenter study was approved by the Institutional Review Boards of the attendant hospitals. Informed consent was obtained following Taiwanese regulations.

Results

The chart recording system of nine tertiary medical centers were searched for eligible cases, and 40 patients were found with SLCT diagnosed between January 1989 and December 2009. Five patients we subsequently excluded because their tissue slides were not available for pathologic review. There were discrepancies between the initial histological results and our subsequent results in 12 (34%) of the remaining 35 patients. The expert pathologists revised the diagnosis to endometrioid adenocarcinoma ($n = 1$), poorly differentiated carcinoma ($n = 1$), carcinosarcoma ($n = 1$), and granulosa cell tumors [granulosa cell tumor (GCT), $n = 9$]. Finally, total concordance between the initial diagnosis and the panel review was achieved in 23 patients (66%). The median age at diagnosis for these 23 patients was 41 years (range, 16–75 years). More than 70% of the patients were aged <50 years old at the time of diagnosis. As shown in Table 1, the most common symptom was irregular vaginal bleeding (44%), followed by an abdominal palpable mass (17%) or amenorrhea (17%). All of the patients were diagnosed after surgery, and most of the tumors were unilateral and confined to the ovary. The average size of the tumors was 8.2 cm (range, 2–22 cm) with 60% involving the right ovary. Some of the serum tumor markers were checked preoperatively, such as cancer antigen-125 (CA-125), carcinoembryonic antigen, α-fetoprotein(AFP), inhibin, β-human chorionic gonadotropin, and testosterone in 12 patients, and elevated levels of CA-125, testosterone, and AFP in three patients. The serum inhibin level assay was not available in most of the nine tertiary hospitals.

Table 1
Patient characteristics ($n = 23$).

Characteristics	*n*	(%)	*p**
Age (y)			
Median	41		
Range	16–75		
Major symptom			
Pain	1	4	
Abdominal distention	2	9	
Palpable mass	4	17	
Irregular vaginal bleeding	10	44	
Acne	1	4	
Deepening voice	1	4	
Amenorrhea	4	17	
FIGO stage			
I		78	
IA	16		
IC	2		
II	0	0	
III	0	0	
IV	1	4	
Not applicable	4	18	
Tumor size (cm)			
Mean	8.2		
Range	2–22		
Laterality			
Left	5	22	
Right	14	61	
Not applicable	4	17	
Tumor differentiation			
Well	3	13	0.04*
Intermediate	15	65	
Poor	5	22	

*p value of Fisher's exact test of overall survival for combined well and intermediate differentiation versus poor differentiation.

Table 2
Treatment modalities and prognosis.

Items	*n*	(%)
Operative methods		
Ovarian biopsy	1	4
Unilateral oophorectomy	6	26
TAH + BSO	5	22
Fertility-sparing staging operation	5	22
Staging operation	6	26
Adjuvant treatment		
No	18	78
Yes	5	22
Radiation therapy	1[a]	
Chemotherapy	5	
BEP	3	
Other regimen	1	
Unknown	1	
Prognosis		
Alive without disease	19	82
Died of disease	2	9
Loss of follow-up	2	9

BEP = bleomycin, etoposide, and cisplatin; BSO = bilateral salpingo-oopherectomy; TAH = total abdominal hysterectomy.
[a] Palliative radiation therapy for pathologic fracture at recurrence.

All patients underwent primary surgery (Table 2); 11 (48%) had a complete staging operation, six had optimal debulking surgery, and five had a fertility-sparing staging operation. The median number of lymph nodes removed was 18 (range, 0–36), and none of them showed metastasis. Six patients (four with stage IA disease and poorly differentiated tumors, one with stage IC, and one with stage IV disease) accepted adjuvant chemotherapy. Four patients received bleomycin, etoposide, and cisplatin (BEP). Follow-up information was available for 21 patients, with a median of 19 months (range, 4–156 months). Nineteen patients (82%) were free of disease up to the date of the last follow-up. Two patients died of the disease (DOD) and their clinical features are shown in Table 3. The first DOD case underwent a unilateral salpingo-oophorectomy for a poorly differentiated tumor and four cycles of adjuvant chemotherapy with BEP. The patient suffered from pelvic recurrence 2 years after the primary treatment and then underwent a second debulking surgery and salvage chemotherapy with BEP. She died 30 months after the initial diagnosis. The second DOD patient, with bony metastasis stage IV disease, underwent optimal debulking surgery and five courses of chemotherapy with BEP. The chemotherapy was switched to weekly paclitaxel due to poor response, and she died 13 months after her initial diagnosis. The two DOD cases were in the category of poorly differentiated tumors, and none of the patients with well differentiated or moderately differentiated tumors died of the disease. Using Fisher's exact test for analysis, poor differentiation was found to be a statistically significant poor prognostic factor as compared to the well and intermediate differentiations ($p = 0.04$).

Discussion

SLCT is a rare histologic type of ovarian cancer. Studies on the topic have always enrolled too few cases to provide clinical relevance and treatment modalities, as is the case with the 23 women included in this retrospective multi-center TGOG study. SLCT comprised diverse pathologic characteristics that can complicate the efforts of the pathologist and gynecologist to make correct diagnoses, including primary and metastatic ovarian cancers (Table 3) [4,5]. In a study for rare malignant ovarian tumors conducted by the GINECO [Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (France)] group, discrepancies between the initial diagnosis and central review occurred in 37% of their cases [6]. Similarly, the diagnosis was changed after pathologic review in 12 (34%) of our cases, with the majority of them shifting to GCTs. Among these 12 patients with inconsistent diagnoses, seven were initially designated with poorly differentiated SLCTs. Our results remind pathologists to use more caution in reaching the correct diagnosis to enable proper subsequent treatment planning.

Due to the diagnosis controversy, a new category system was developed by the World Health Organization [7]. In addition to the new consensus on the pathologic features of H&E staining, immunohistochemical (IHC) studies had proven useful in differentiating tumors. Negative staining for epithelial membrane antigen and positive staining for inhibin and calretinin were the most remarkable for SLCT [8]. CD56, FOXL2, DICER-1, WT1, and CD10 were also reported as helpful for differentiating tumors [9–13]. A combination panel of IHC stains and H&E stains is believed to be the best method for correctly diagnosing SLCTs.

The average age of the women in our study was 41 years, much older than the 25 years previously reported [2,14,15]. Thirty-five percent (8/23) of our patients were younger than 30 years. In the largest case study of ovarian SLCT published by Young and Scully [2], the average age of the patients with well-differentiated tumors was 10 years higher than the overall

Table 3
Clinical features of the 2 patients who died of Sertoli–Leydig cell tumor (SLCT) of the ovary.

Patient (age, y)	Symptoms	Tumor size	Stage	Differentiation	Surgery	Recurrence site	Adjuvant therapy after recurrence
1 (21)	Abdominal palpable mass	22 cm	IA	Poor	Unilateral oophorectomy	Peritoneal cavity	Chemotherapy with bleomycin, etoposide, cisplatin
2 (53)	Abdominal palpable mass, back pain	12 cm	IV	Poor	Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic/para-aortic lymphadenectomy	Bone metastasis initially	Chemotherapy with bleomycin, etoposide, and cisplatin, then changed to weekly paclitaxel; radiation for bony metastasis

average. Similarly, the average age of our patients with well-differentiated tumors was 50 years, and for patients with tumors of intermediate and poor differentiation the ages were 40.7 years and 31.8 years, respectively.

Ovarian SLCTs may secrete androgens, but only 25% of our study patients presented with androgenic symptoms because clinical data for this item was lacking, which might be due to differences in clinical practice at the various medical centers. Elevation of serum CA-125 did not help diagnose or detect SLCT because it occurred in only one out of seven patients. Most of the SLCTs were confined to a unilateral ovary, especially the right-side ovary as shown in our study (61%). Bilateral involvement was as low as 1.5% in Young and Scully's report and there were none in our patients. For most of the previously reported cases with bilateral tumors [16–19], Young and Scully suggested the possibility of other diagnoses, such as Krukenberg tumors or luteinized thecomas. Therefore, the diagnosis of ovarian SLCT should be made cautiously for those women with high-stage and bilateral occurrences. Likewise, in our discordant diagnosis group, in spite of the nine GCTs, which are also more likely to be present in early stage disease, the carcinosarcoma and poorly differentiated tumors had bilateral involvement and were present with advanced disease.

Surgical resection is the primary treatment for ovarian SLCT. Since most of the patients were diagnosed at reproductive ages with early stage disease, fertility-sparing surgery was considered appropriate due to the prospect of good outcomes. In recent published studies, it has been suggested that the routine lymphadenectomy might be unnecessary for sex-cord stromal tumors [20,21]. Eleven of our patients had nodal evaluations and all of them were negative for metastasis.

The indications and regimen for postoperative adjuvant chemotherapy could not be determined due to the limited number of cases in our study, except that tumors with poor differentiation were found to be related to worse outcome. Aggressive treatment and intensive surveillance may be needed for poorly differentiated tumors. Furthermore, studies have shown that a high disease stage, poor tumor differentiation, high mitotic index, presence of heterologous components, and tumor rupture were poor prognostic factors that required adjuvant chemotherapy [2,14,15]. As for chemotherapy, platinum-based chemotherapy had been widely used for sex cord-stromal tumors [22]. In a prospective clinical trial for sex cord-stromal tumors where BEP was used, the overall response rate was high, but the relapse rate was >50% [23]. Six of our patients underwent chemotherapy for poorly differentiated tumors or extraovarian spread, and four of them had the BEP regimen. One case was refractory to BEP and another developed recurrent disease 2 years later. A large scale study is needed to define the best regimen.

Our study of 23 patients with ovarian SLCT over a 20-year period demonstrates the rarity of this type of ovarian cancer in Taiwan. The high discrepancy rate between initial diagnosis and central review suggests the necessity of pathological attention, using both H&E and IHC stains for correct diagnosis. Conservative surgery is suggested for women in early stages and in need of fertility, with unchanged prognoses. Adjuvant chemotherapy may be considered when tumors with poor differentiation or advanced stage are encountered, although the best regimen could not be determined in our study. International cooperation is warranted to improve our understanding of the biological behavior and treatment strategies for this unique tumor.

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