Malignant ovarian germ cell tumors: Analysis of 32 cases

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Summary

Objective: In this study, some clinicopathologic characteristics and the outcome of patients with malignant ovarian germ cell tumors (MOGCT) were evaluated.

Materials and Methods: The clinical charts and pathologic reports of 32 patients with MOGCT treated at the Department of Obstetrics and Gynecology, and diagnosed at the Department of Pathology, Medical Faculty of Dicle University, Turkey from 1983 to 1999 were reviewed.

Results: Thirteen patients (40.6%) had dysgerminoma, nine (28.1%) had immature teratoma (four grade 1, three grade 2, and two grade 3), eight (25%) had endodermal sinus tumor, and two (6.3%) patients had mixed germ cell tumors. Site of involvement was unilateral in 30 (19 on the right and 11 on the left) and bilateral in two. All patients underwent primary surgery and 26 patients combination chemotherapy. There seemed to be a relationship between pathologic findings and clinical outcome, and MOGCT histologic types may affect the prognosis.

Conclusion: Dysgerminoma had a better prognosis than the nondysgerminomatous group ($p < 0.05$). This study provides additional data in confirmation of previous reports that management of MOGCT with fertility preservation is safe.

Key words: Malignant ovarian germ cell tumors; Chemotherapy; Treatment; Fertility.

Introduction

Malignant ovarian germ cell tumors (MOGCT) account for 5% to 10% of all malignant ovarian tumors and usually affect women of childbearing age. They are derived from primordial germ cells that migrate into the gonadal ridge at six weeks of embryonic life. Consequently, OGCT might exhibit a spectrum of histologic differentiation that mimics a primitive developing embryo [1-5]. Histologically these can be grouped as dysgerminomas and nondysgerminomatous OGCT. The latter group is comprised predominantly of immature teratomas, endodermal sinus tumors, and mixed tumors and also includes the uncommon histologies of embryonal carcinoma, polyembryoma and choriocarcinoma [6]. The prognosis for some types of MOGCT remains unsatisfactory; endodermal sinus tumor, mixed germ cell tumor, embryonal carcinoma, and polyembryoma have poor prognoses compared with immature teratoma and dysgerminoma [3].

The aim of the study was to evaluate some clinicopathologic characteristics, as well as the clinical outcome of our patients with MOGCT.

Patients and Methods

This clinicopathologic study was performed through the evaluation of the medical charts of 265 patients having malign ovarian cancer, treated at the Department of Obstetrics and Gynecology, and diagnosed at the Department of Pathology, Medical Faculty of Dicle University, Turkey, from 1983 to 1999. We selected 32 (12%) patients with MOGCT. The diagnosis of MOGCT and classification into one of the following categories were done according to WHO criteria [7]; dysgerminoma, endodermal sinus tumor, embryonal carcinoma, immature teratoma and mixed germ cell tumor. The tumors were then assigned to one of two groups: dysgerminoma or nondysgerminomatous tumor. Clinical staining was performed according to the International Federation of Gynecology and Obstetrics (FIGO). The grading system of Norris *et al.* [8] was used for immature teratomas. The operative reports and histology slides of patients were reviewed. After physical examination, abdominal and pelvic ultrasonographic assessment, serum tumor markers and chest X-rays, the patients underwent laparotomies for diagnosis, staging and cytoreduction, when appropriate. Variables such as surgical staging, histologic type, age, type of surgery, the presence of ascites, residual tumor after surgery, and second-look laparotomy were analyzed by comparing patients with dysgerminoma and nondysgerminomatous tumors. Intraoperative frozen section was performed in all cases. Chi-squared and Fisher's exact tests were used for statistical analysis.

Results

Thirteen patients (40.6%) had dysgerminoma, nine (28.1%) had immature teratoma (four grade 1, three grade 2, and two grade 3), eight (25%) had endodermal sinus tumor, and two (6.3%) patients had mixed germ cell tumors.

Site of involvement was unilateral in 30 (19 on the right and 11 on the left) and bilateral in two. The age distribution was 15 to 40 years (mean 21.5 years), and 10/13 patients with dysgerminoma and 18/19 patients with nondysgerminomatous tumors were younger than 25 years of age (Table 1).

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Table 1. — *Patient distribution regarding age, presence of ascites, stage and residual disease according to histologic group.*

	Dysgerminoma	Non-dysgerminoma	p value
Age (yrs)			
≤ 18	3	6	
19 to 25	7	12	
> 25	3	1	0.33
Ascites			
Present	4	6	
Absent	7	10	
Not available	2	3	0.63
Stage			
I	7	12	
II	3	3	
III	3	2	
IV	0	2	0.68
Residual disease			
≤ 2 cm	5	4	
> 2 cm	1	5	0.23
Total	13	19	

Information on tumor markers was available in 22 patients for αFP of whom 17 were normal, and seven elevated. ßHCG was available in 25 patients of whom 15 were normal, and ten elevated. These levels fell to normal range after surgery.

Intraoperative frozen-section was performed in all cases. Twenty-nine cases were diagnosed as malign (13 dysgerminoma, 6 immature teratoma, 8 endodermal sinus tumor, and 2 mixed germ cell tumors), two cases as suspicious for malignancy (immature teratoma), and one case as benign (immature teratoma).

Dysgerminoma (DYS)

Thirteen cases were DYS, which formed the biggest single subgroup. The ages ranged from 16 to 28 years (median 21.6). All 13 patients underwent primary surgery. Six (46.1%) of the patients with DYS presented residual disease after the primary surgery. The nine DYS patients underwent combination chemotherapy (CT).

As for staging, seven, three and three patients with DYS were classified as Stage I, II and III, respectively. Five of 13 patients with DYS tumors underwent fertility-sparing surgeries with preservation of the uterus and contralateral ovary. Four of the five fertility-preserved had regular menstruation, but one did not. Of the four cases with regular menses, three became pregnant and delivered normal full-term babies with no congenital anomalies.

Grossly, tumor dimensions were < 10 cm in two, 10-20 cm in eight, > 20 cm in three and two cases were bilateral. Tumors usually had a smooth serosal surface. The sectioned surfaces were soft, fleshy, lobulated, cream-colored or gray with some areas of cystic degeneration and hemorrhage. Nine cases had capsule rupture, ascites containing malignant cells, expansion to the uterus, tubes or pelvic tissues.

Microscopically, cells were arranged predominantly in diffuse, insular, or trabecular patterns. The uniform, rounded tumor cells had clear to eosinophilic cytoplasm, which had discrete cell membranes and a central, large, rounded nucleus and numerous mitotic figures. Three cases had focal syncytiotrophoblastic giant cells.

Immature teratoma (IT)

Nine cases were IT. The ages of the nine patients ranged from 15 to 40 years (median age 22.5 years). All nine patients underwent primary surgery. Six presented surgical Stage I disease and three had pelvic metastases (Stage II). Postoperative combination CT was administered to seven women, including high risk profile IT. Five women are alive without evidence of disease. Six cases of IT tumors underwent fertility-sparing surgeries. Three of the six patients had pregnancies and two of them had healthy children without any complications.

Macroscopically, the dimension of the tumors ranged from 9 to 23 cm. The median tumor diameter was 15 cm. Typically, the ITs were encapsulated and lobulated and contained both solid and cystic areas. The solid areas were firm and grayish white, pink, or tan. Cystic areas contained bloody fluid, gelatinous material, or sebaceous debris and hair. All cases were unilateral.

Histologically, elements of all germ cell layers were represented. Gut epithelium, respiratory epithelium, squamous epithelium, glial tissue, bone and cartilage were common mature components. Immature tissues were usually neuroepithelial, including neurotubules and neuroepithelial rosettes. The histologic grade distribution among them included grade 1 (n = 4), grade 2 (n = 3) and grade 3 (n = 2). Three patients had metastatic lesions. One of them was composed only of mature glial tissue (gliomatosis peritonei) and the others were composed of grade 2 and 3 immature ovarian teratoma.

Endodermal sinus tumor (EST)

Eight cases were EST. The ages ranged from 17 to 25 years (median 20.8) and all patients had primary surgical treatment. All cases were administered postoperative combination CT. Three of the EST cases underwent fertility-sparing surgeries with preservation of the uterus and contralateral ovary. All of the three fertility-preserved cases did not have regular menstruation. Five EST cases presented residual disease after the primary surgery.

Grossly, ESTs were large, with a median diameter of 17 cm. The external surface was usually smooth and glistening. The sectioned surfaces were composed of soft, friable, yellowish to grayish tissue often containing cysts. Extensive areas of hemorrhage and necrosis were common. All cases were unilateral.

Microscopically, six cases of the eight ESTs had a reticular pattern, characterized by a loose meshwork of spaces lined by primitive tumor cells with clear cytoplasm. The hyperchromatic, irregular, large nuclei contained prominent nucleoli; mitotic figures were numerous. In many tumors a reticular pattern merged with a microcystic or macrocystic pattern where Schiller-Duval bodies were encountered. One case was a hepatoid and one was a polyvesicular vitelline pattern.

Mixed tumors (MIX)

Two cases were mixed germ cell tumors. One was composed of dysgerminoma and EST and the other one was composed of EST and immature teratoma.

One patient in the DYS group died and one patient relapsed. In the nondysgerminomatous group, 11 patients are alive, two with disease and nine disease-free, and eight of the patients died. Four patients with DYS and six patients with nondysgerminomatous tumors presented malignant ascites at the primary surgery. Second-look laparotomy was performed in eight patients with nondysgerminomatous tumors and two patients with DYS (Table 2). As for prognosis, the DYS group had a better prognosis than the nondysgerminomatous group ($p < 0.05$).

Discussion

The germ cell tumor (GCT) constitutes the second largest group of ovarian neoplasms after surface epithelial stromal tumors and comprises approximately 20% of all ovarian neoplasms observed in Europe and North America. In countries like Asia and Africa where the prevalence of surface epithelial stromal tumors is much lower, GCTs constitute a much larger proportion of ovarian neoplasms. In children and adolescents, more than 60% of ovarian neoplasms are of germ cell origin and one-third are malignant [4-6].

MOGCTs account for approximately 5% of all ovarian cancers in Western countries [6]. The rate of MOGCT, however, is as high as 10% to 15% in countries whose populations are largely oriental and black [2, 9, 10]. Most subtypes of MOGCT occur in a pure form, but approximately 8-10% are composed of two or more subtypes [6]. The patients in this study accounted for 12% of ovarian and 3.1% of all gynecologic malignancies. The age and histologic distribution in our study were similar to those reported previously by other investigators [2, 5].

For MOGCT, the risk of bilateral involvement is relatively low [1, 10]. DYS is usually unilateral. It tends to occur more often in the right ovary and bilateral involvement has been reported to occur in 10-17% [4]. Two of our cases with DYS were bilateral (15.4%). ESTs are almost always unilateral. Bilaterality typically is a manifestation of metastatic spread. EST shows a certain predilection for the right ovary [4]. It is usually unilateral [11], but may coexist with a mature cytic teratoma in the opposite ovary [4, 12]. In our study none of the IT, EST and mixed germ cell tumors had bilateral involvment.

Table 2. — *Characteristics of patients with dysgerminoma and nondysgerminomatous tumors.*

Case	Histology	Age (yrs)	Stage	Residual tumor	Fertility sparing surgery	Chemotherapy	Pregnancies	Second-look	Current status	Follow-up (motths)
1	DYS	18	IA	None	Y	None	Term [1]		NED	137
2	DYS	19	IA	None	Y	None	Term [1]		NED	120
3	DYS	23	IA	None	N	None			NED	98
4	DYS	22	IA	None	Y	None	Term [1]		NED	76
5	DYS	20	IC	None	Y	Y			NED	79
6	DYS	26	IC	None	N	Y			NED	68
7	DYS	27	IC	None	N	Y			NED	71
8	DYS	17	IIC	≤ 2 cm	N	Y			AWD	27
9	DYS	16	IIC	≤ 2 cm	Y	Y			NED	52
10	DYS	19	IIC	≤ 2 cm	N	Y		Y	DOD	49
11	DYS	25	IIIC	< 2 cm	N	Y			NED	17
12	DYS	21	IIIC	< 2 cm	N	Y			NED	63
13	DYS	28	IIIC	> 2 cm	N	Y		Y	NED	24
14	IT	21	IA (G1)	None	Y	None	Abortion		NED	63
15	IT	40	IIC (G2)	None	N	Y		Y	DOD	36
16	IT	25	IA (G2)	None	Y	Y		Y	DOD	40
17	IT	24	IIB (G3)	≤ 2 cm	N	Y		Y	DOD	22
18	IT	19	IA (G1)	None	Y	Y			NED	76
19	IT	22	IA (G1)	None	Y	Y	Term [1]		NED	41
20	IT	15	IIA (G3)	≤ 2 cm	N	Y		Y	AWD	38
21	IT	20	IA (G1)	None	Y	None	Term [1]	Y	NED	67
22	IT	17	IA (G2)	None	Y	Y			NED	82
23	EST	18	IA	None	Y	Y			NED	22
24	EST	25	IA	None	Y	Y			DOD	34
25	EST	17	IA	None	Y	Y			NED	40
26	EST	19	IC	> 2 cm	N	Y		Y	NED	15
27	EST	25	IC	> 2 cm	N	Y		Y	AWD	37
28	EST	23	IV	> 2 cm	N	Y			DOD	8
29	EST	22	IIIC	≤ 2 cm	N	Y			DOD	6
30	EST	18	IIIC	≤ 2 cm	N	Y		Y	DOD	14
31	MIX	17	IC	> 2 cm	N	Y			NED	35
32	MIX	22	IV	> 2 cm	N	Y			DOD	10

DYS, dysgerminoma; IT, immature teratoma; EST, endodermal sinus tumor; MIX, mixed germ cell tumor; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

Surgery with adequate staging remains the cornerstone of management of these cancers. Treatment results that advocate the feasibility of conservative management in MOGCT have been reported to date [9, 13-15]. This is because of fertility issues associated with the young age of these patients coupled with the excellent responses to combination CT [16]. According to Gershenson's review article [1], unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus can be performed in most patients, thus maintaining the potential for fertility because of the rarity of bilateral ovarian involvement with tumor. It is also described that, when the contralateral ovary and the uterus are free of disease, sustained remission rates with unilateral salpingo-oophorectomy are at least equivalent to those with bilateral salpingo-oophorectomy with or without hysterectomy. If the opposite ovary contains tumor, then bilateral salpingo-oophorectomy is recommended [1]. In our study, fertility-sparing surgery was performed in five patients with dysgerminoma and in nine patients with nondysgerminomatous tumors. Our experience suggests that conservative surgery will not adversely affect the outcome.

Schwartz *et al.* [13] in their series of 81 patients reported 88% alive with no evidence of disease with a minimum follow-up of two years. They emphasized the importance of stage in treatment planning and the role of conservative surgery. Cheung *et al.* [17] in their series of 37 patients with a median follow-up of 48 months report 94% alive with no evidence of disease, and comment on the vital role of CT in the management.

Prior to the multiple-agent CT era, MOGCT patients carried a poor prognosis, with the possible exception of pure DYS and low-grade IT [2, 3, 14, 18]. The introduction of combination CT in the last two decades has not only improved the survival of patients, but has also modified treatment strategies, making it possible to perform less radical and fertility-sparing surgery [19]. In the DYS group in this study, nine patients underwent combination CT. Of these, seven cases had had a good response to CT, one case progressed and one died. The CT regimen was used in 17 of the 19 patients with nondysgerminomatous tumors. Of these, nine cases had a good response to CT. Of the nondysgerminomatous group, ten cases progressed during the treatment and eight cases died of the disease. In a study carried out by Kusamura *et al.* [2], in 14 patients with nondysgerminomatous tumors treated with CT, half of them did not have a good response to the therapy and progressed during the treatment. CT has become the treatment of choice for MOGCT in our medical faculty.

Since MOGCT is a disease of women of child-bearing age, fertility is an important consideration in the management. This has been shown to be feasible at all stages of the disease [20]. The safety of conservative surgery and CT was demonstrated in this study. Ezzat *et al.* [9] reported that of 44 women eligible to conceive, 16 had successful pregnancies. None of the chil-dren born subsequent to CT have been reported to have any congenital abnormalities. The other major issue in cured patients is a second malignancy induced by CT. WiIliams *et al.* [21] reported on two patients with leukemia and lymphoma, following combination CT. In our study, five women became pregnant, delivering a total of five normal full-term babies with no congenital anomalies. None of the patients in our series have had second malignancies as yet.

Since there is little place for second-look laparotomy, the procedure is not performed as a routine step in the management of patients with MOGCT in our faculty. This is mainly restricted to malignant teratoma with persistent radiologic abnormalities following CT, where it may help to avoid systemic CT in patients who no longer have viable tumor. Also, it may be of benefit for a subset of patients with incompletely resected disease or with teratomatous elements in the primary tumor [22, 23]. It is rarely beneficial in patients with completely resected tumors who receive combination CT [9].

In conclusion, this study provides additional data in confirmation of previous reports that management of MOGCT with fertility preser-vation is safe. There also seemed to be a relationship between pathologic findings and clinical outcome, and MOGCT histologic types may affect the prognosis. We conclude that the dysgerminoma group had a better prognosis than the nondysgerminomatous group ($p < 0.05$).

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