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Case Series

Pure dysgerminoma of the ovary: a study of 31 cases

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ABSTRACT

Malignant germ cell tumors of the ovary are rare tumors characterized by their heterogeneity and occurring mostly in young women. Dysgerminoma is the most common type of these tumors. This was a retrospective study of 31 patients with pure dysgerminoma of the ovary diagnosed in Salah Azaiez institute of Tunis in Tunisia between 1970 and 2012. The median age was 22 years old. Abdominal pain was the most complaint in 45.1% of cases. An abdomino-pelvic mass was found in 83.8% of cases. Surgery was performed in all patients. The median tumoral size was 13.7 cm. Sixty four-point five percent of the patients underwent a conservative surgery. The tumor was classified stage I in 51.6% of the cases, stage II in 9.7% of the cases, stage III in 35.5% of the cases and stage IV in 3.2% of the cases. Fourteen patients received platinum-based adjuvant chemotherapy, and 10 patients had a radiotherapy. We have noticed 2 cases of recurrence and 2 cases of metastasis. Five-year and ten-year overall survival was 89.4%. Five-year disease free survival was 85.2% and ten-year disease free survival was 66.3%. Dysgerminomas of the ovary have a good prognosis. The two significant prognostic factors are the stage and the postoperative residual disease.

Keywords: Ovary, Germ cell, Tumor, Malignant, Dysgerminoma

INTRODUCTION

Malignant ovarian germ cell tumors are a rare form of gonadal malignancy that are most prevalent in adolescents and young adults. The most common type of these tumors is dysgerminoma that accounts for 38.2% of germ cells tumors and for 3 to 5% of all primary ovarian malignancies. [1]Dysgerminomas can be pure or mixed being one of several components of a germ cell tumor such as malignant teratoma or choriocarcinoma.[2] It is derived from primordial germ cells of the sexually undifferentiated embryonic gonad and affects predominantly younger women being less than 30 years old.[3] Nearly 50% of dysgerminomas occur before the age of 20 but they are rare before the age of 10.[3]

The majority of dysgerminomas are diagnosed at an early stage with unilateral involvement affecting one ovary that's why they respond well to conservative fertility-sparing treatment consisting of unilateral salpingo-oophorectomy. The oncologic safety of this procedure was confirmed for an early -stage disease and is currently the gold standard.[4]

Ovarian dysgerminomas, like their male counterpart the seminoma, are extremely radio- and chemo sensitive, therefore an excellent prognosis is usually expected and they are generally considered of low-grade malignancy but they may spread.[3]

CASE SERIES

Thirty-one patients were found to have a pure dysgerminoma of ovary between 1970 and 2012 and are the subject of this study. Patients with dysgerminoma combined with other germ cell tumors were excluded.

Staging was carried out according to FIGO recommendations. Patients demographic and disease characteristics were summarized using descriptive statistics.

Table 1: Surgical procedures.

Case	Age	FIGO stage	Surgical procedure out of ISA	Surgical procedure	Type of surgery	Residual tumor
1	12	IIIC	Right salpingooophorectomy+ lymphnode biopsy	0	Conservative	+
2	32	IIIC	Total hysterectomy+ salpingoophorectomy	0	Radical	+
3	15	IIA	Right salpingooophorectomy+ lateroaortic lymphnode biopsy (-)	Complete staging	Radical	-
4	22	IA	0	Complete staging	Radical	-
5	15	IA	Left ovariectomy	0	Conservative	-
6	27	IIIC	Right ovariectomy	Right salpingooophorectomy+omentectomy+appendicectomy+ left oophoropexy + lateroaortic lymphnode biopsy (+)	Conservative	+
7	15	IA	Left ovariectomy + right ovarian biopsy	0	Conservative	-
8	21	IA	Right ovariectomy	Right salpingoophorectomy +appendicectomy + left Ovarian biopsy (-) + lateroaortic lymphnode biopsy (-)	Conservative	-
9	60	IIIC	0	Bilateral salpingooophorectomy +omentectomy+ appendicectomy	Radical	+
10	32	IIIC	Right salpingooophorectomy	Left salpingoophorectomy +omentecomy +resection of a douglassian nodule (+)	Radical	+
11	13	IIIC	Right salpingoophorectomy	Omentectomy+appendicet+lateroaortic lymphnode biopsy(+) + left ovarian biopsy and left oophoropexy (-)	Conservative	+
12	29	IA	Left salpingoophorectomy	Omentectomy+right ovarian biopsy (-)+ right oophoropexy	Conservative	-
13	17	IA	Right salpingooophorectomy	0	Conservative	-
14	14	IA	Left ovariectomy	Conservative staging + lateroaortic lymphadenectomy (-)	Conservative	-
15	31	IV foie	Right salpingoophorectomy + omentectomy	0	Conservative	+
16	17	IIIC	Ful staging + lateroaortic lymphadenectomy (+)	0	Radical	-
17	17	IIIC	Full staging + lateroaortic lymphadectomy (+)	0	Radical	-

Continued.

Case	Age	FIGO stage	Surgical procedure out of ISA	Surgical procedure	Type of surgery	Residual tumor
18	21	IIIC	Right salpingoophorectomy	Conservative staging + lateroaortic lymphadectomy (+)	Conservative	-
19	16	IC	0	Conservative staging	Conservative	-
20	41	IA	Right salpingoophorectomy	0	Conservative	-
21	18	IIIB	0	Bilateral salpingoophorectomy+omentectomy	Radical	-
22	15	IA	Right salpingoophorectomy	0	Conservative	-
23	14	IA	0	Right ovariectomy	Conservative	-
24	18	IIA	0	Full staging+ pelvic lymphadenectomy	Radical	-
25	11	IA	Right salpingoophorectomy	0	Conservative	-
26	14	IA	Left cystectomy	Left salpingoophorect+oment+appendictomy+pelvic and lateroaort lymphnode biopsy (-)	Conservative	-
27	33	IA	0	Full staging	Radical	+
28	10	IA	0	Left ovariectomy+ lateroaortic lymphnode biopsy (-)	Conservative	-
29	25	IC	Left salpingoophorectomy	0	Conservative	-
30	61	IIA	Full staging+ pelvic (-) +lateroaortic lymphadectomy (+)	0	Radical	+
31	18	IC	0	Right salpingoophorectomy +appendicectomy+ pelvic (-) + lateroaortic lymphadenectomy(+)	Conservative	-

Overall survival time was calculated from the time of diagnosis to the date of death or last of follow-up date. Recurrence-free survival time was calculated from the time of diagnosis to the date of recurrence. The overall survival and recurrence free survival curves were constructed using Kaplan-Meier method. Statistical analysis was performed using Statistical package for social sciences (SPSS).

Between 1970 and 2012, 31 patients were diagnosed with pure dysgerminoma of ovary at Salah Azaiez Institute, Tunis, Tunisia. Median age was 22 years-old (ranges from 12 to 60 years old).

Twenty-three patients (76 .6%) were under 30 years old (FIG1).

From these patients, seven women were married that five of them were multiparous and two patients were menopaused.

Clinical presentation was abdominal-pelvic pain in 45.1% of cases, an increased abdominal volume in 41.9% of cases, an abdominal mass in 12.9% of cases and an amenorrhea in 12.9% of cases. An acute symptomatology was observed in one case (3.2%): annex twist. Only one patient was asymptomatic.

On physical examination, most patients had abdominopelvic mass (26 patients) and three patients had ascites. Gynecologic examination was performed for seven patients and it revealed a suspicious mass in digital examination in one patient but the cervix, the vagina and the rectovaginal septum were normal.

Ultrasound examination was performed in 18 patients (58%). it showed pelvic mixed solido-cystic mass in 12 cases (38%) and ascites in four cases (12.9%). Ultrasound examination was normal in 2 patients. CT scan was made for 7 patients and findings were similar to ultrasound

examination in 6 patients but it showed for the 7th patient metastatic liver with peritoneal carcinomatosis.

Table 2: Type of chemotherapy (VAB: Vinblastine-Cyclophosphamide- Actinomycin- Bleomycin-Cisplatin/ BEP: Bleomycin- Etoposide-Cisplatin/ EP: Etoposide- Cisplatin).

Case	FIGO stage	Type of chemotherapy	Number of cycles
1	IIIC	VAB	6
2	IIIC	VAB	6
3	IA	BEP	4
4	IA	BEP	3
5	IIIC	BEP	3
6	IIIC	BEP	3
7	IIIC	BEP	4
8	IC	BEP	3
9	IA	BEP	4
10	IA	EP	3
11	IIA	EP	6
12	IIIB	EP	6
13	IC	EP	6
14	IA	BEP	5
15	IC	EP	4

Seven patients had intravenous urography that found 2 cases of mute kidney, 1 case of hydro nephrosis, 1 case of mass syndrome and it was normal in the other case. All patients had chest X-ray that was pathological in one case showing mediastinal adenopathy. Cystoscopy and rectoscopy were performed for two patients and it revealed signs of bladder and colorectal compression.

Tumor markers levels were raised in some patients: Beta HCG was made for 10 patients and it was positive in 5 of them, LDH serum level was markedly elevated in 3 cases. Finally, Ca125 was pathologic in two cases from seven.

The initial management was surgical for all patients with radical intent in 11 patients (35.5%) having a complete staging procedure and conservative intent in 20 patients (64.5%) having fertility-sparing surgery (Table 1).

Surgery was optimal in 22 patients (70.96%) of which four were at stage III. Five patients with advanced stage underwent fertility-sparing surgery. Among them, 4 were single with stage IIIC dysgerminomas and 1 had metastatic liver.

A 60 years old woman diagnosed with stage IIIC dysgerminoma had a big douglassian nodule and detachment between the bladder and the uterus was so difficult that why hysterectomy was not possible. She underwent bilateral salpingoophorectomy with omentectomy and appendicectomy. Then, she had hysterectomy after chemotherapy.

A 32 year-old woman diagnosed with stage IIIC dysgerminoma on right salpingoophorectomy performed out of our institute. She had internal iliac lymphnodes blocking the pelvis with a douglassian nodule and a normal uterus so that, surgical procedure was resumed at left salpingoophorectomy with omentectomy and resection of the douglassian nodule. She underwent hysterectomy after chemotherapy.

Pelvic lymphnode sampling was performed in 7 patients and it was positive in 3 cases.

Seven patients underwent pelvic and lateroaoartic lymphadenectomy that was positive in 5 cases. Therefore, the rate of lymph node involvement was 51.1% in these cases of dysgerminomas.

Twelve patients (38.7%) were classified as stage IA and they underwent conservative surgery. Three of them (9.6%) had contralateral ovarian biopsy that was negative in all cases.

The median tumor size was 13.7 cm (ranges from 8 to 30 cm). Tumor size was upper than 10 cm in 29 cases (93.5%) and upper than 20 cm in 9 cases (29%).

The tumor was on the right side in 16 patients (51.6%), on the left side in 6 patients (19.3%) and bilateral in 9 patients (29.1%).

According the FIGO stage: sixteen patients were classified stage I (51.6%), three patients stage II (9.7%), eleven patients stage III (35.5%) and one patient stage IV (3.2%).

Adjuvant chemotherapy was indicated in 15 patients (Table 2). It was performed in 5 cases (16.1%) with FIGO stage IA having a tumor size that ranged from 15 to 18 cm.

Adjuvant radiotherapy was indicated in 10 patients (32.2%) with a dose that ranged between 16 and 55 Gy. It generally began 2 months after surgery. (Table 3)

Two patients (6 .4%) with FIGO stage IIIC had sub-optimal radical surgery with residual disease. Therefore, they received second look surgery after adjuvant chemotherapy.

The first one had six curses of VAB without residual tumor. She underwent second look surgery consisting on total hysterectomy.

The second one had six curses of VAB with residual disease. Total hysterectomy with tumoral resection was performed as second look surgery.

Residual disease after completion of treatment was noted in three patients (9.6%): 2 of them were classified as stage IIIC and the third one as stage IC. Initial treatment was radical surgery for the first two patients with residual tumor in both cases, one of them received adjuvant

chemotherapy and the other one had adjuvant radiotherapy. The patient with FIGO stage IC had conservative surgery without residual tumor than adjuvant chemotherapy was performed. Second line treatment was chemotherapy performed in the two patients.

Table 3: Dose and irradiation field according to FIGO stage.

Case	FIGO stage	Type of surgery	Irradiation field	Dose of radiotherapy (Gy)
1	IIIC	Conservative +mesenteric lymphnode biopsy	Abdominopelvic+mediastinal + supra clavicular	30 + 20
2	IIIC	Radical	Abdominopelvic+ iliac and lateroaortic lymphnodes	20 + 35
3	IIA	Radical+ lateroaortic lymphnode biopsy (-)	Abdominopelvic+ iliac and lateroaortic lymphnodes	30 + 20
4	IA	Radical	Iliac and lateroaortic lymphnodes	30
5	IA	Conservative	Abdominopelvic	20
6	IIIC	Conservative+ lateroaortic lymphnode biopsy(+)	Iliac+ lateroaortic lymphnodes+ supraclavicular+mediastinal	40 + 16
7	IIIC	Conservative+ lateroaortic lymphnode biopsy(+)	Abdominopelvic	30
8	IA	Conservative	Iliac and lateroaortic lymphnodes	25
9	IIIC	Conservative	Iliac and lateroaortic lymphnodes	50
10	IC	Conservative	Abdominopelvic	36

Table 4: Site and management of recurrences.

Cases	FIGO stage	Type of surgery	Residual tumor	Chemotherapy (CT)	Radiotherapy (RT)	Time of recurrence	Site	2nd line treatment
1	IA	Conservative	0	0	0	18 months	Abdomino-pelvic	RT: adominopelv+ supraclav+mediastinal
2	IIIB	Radical	0	+	0	12	Pelvic	CT : VIP

Two recurrences were noted (6.4%) and it occurred within 20 months of diagnosis. Their FIGO stage was IA and IIIB. These two patients relapsed in the pelvis or the abdomen and their management was either chemotherapy or radiotherapy (Table 4).

Two patients presented distant metastases within 12 months of diagnosis. FIGO stage was IA for one of them and IC for the second one. Initial treatment consisting on optimal conservative surgery without residual disease was performed in two patients and one of them received adjuvant chemotherapy.

The first patient presented distant metastases in the mediastinum and supraclavicular lymph nodes. She received radiotherapy with a total dose of 48Gy in the abdominopelvic area and the metastatic site.

Metastatic spleen was noted in the second patient. Second line treatment was splenectomy with chemotherapy.

Median follow-up was 57 months (ranged from 1 to 256 months). 26 patients (83.9%) were free of disease with a follow up that ranged from 7 to 182 months.

The patients who presented recurrences were free of disease after a median follow up period of 119 months. Among the patients who still have residual disease after treatment: one of them died at 12 months after surgery and radiotherapy.

The second patient had second line surgery consisting on hysterectomy with tumor reduction and chemotherapy. Complete remission was noted after a follow-up period of 104 months.

The third one had a second line chemotherapy.

Among distant metastatic cases, the patient who had metastatic supraclavicular lymph nodes respond well to chemo and radiotherapy. She was free of disease at 73

months after treatment completion. The other one who had metastatic spleen died 6 months after surgery.

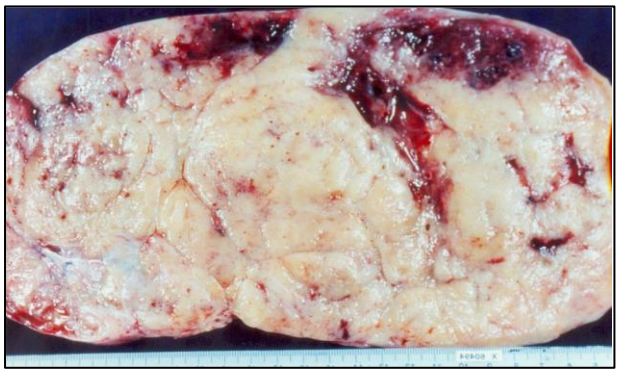

Figure 1: Dysgerminoma- lobulated and whitish macroscopic appearance.

Therefore, we noted four deaths including 3 deaths related to the disease.

Five years and ten years overall survival rate was 89.4%. Neither age nor tumor size or type of surgery was significantly associated with overall survival. Although, FIGO stage and residual tumor after surgery were significantly associated with overall survival at 5 years and 10 years.

Five years event free survival rate was 85.2%, and the ten years one was 66.3%. It was significantly different when associated with residual tumor after surgery but age, FIGO stage, type of surgery and tumor size had no impact on event free survival.

DISCUSSION

Ovarian Dysgerminomas are malignant germ cell tumors that affects mostly children and young women.[5] In our series, the median age of patients was 22 years old and 76.6% of them were less than 30 years old. These tumors are histologically equivalent to testicular seminoma due to their origin. The most common clinical presentation is a young woman with a subacute lower quadrant pain and a pelvic mass found by physical examination.[6] In fact, our series illustrate 31 cases of dysgerminomas with abdominal distention as the most common symptom of nearly 42% of cases.

Diagnosis can be made by pelvic ultrasound imaging which found in 59% of cases a highly vascularized, large, solid, lobulated adnexel mass with irregular internal echogenicity.[6] In addition, pelvic MRI can be suggested to confirm the diagnosis: it showed typically a multi-lobulated solid mass with lobules divided by fibrovascular septa.[6] However, the final diagnosis of dysgerminoma is confirmed by anatomopathological study on surgical specimen. In our cases, ultrasound examination was the reliable imaging technique and MRI was not made for any patient. Tumor markers may help to establish the diagnosis but they are especially a tool for postoperative monitoring to detect any recurrence. Diagnosis is established generally at an early stage with disease limited to one ovary, which suggest a good prognosis. Indeed, in the literature, 70% of dygerminomas were stage I at the time of diagnosis and only 10% involved both ovaries.[7]

The standard treatment of ovarian dysgerminomas is surgery with or without adjuvant treatment. Traditionally, Full staging procedure including hysterectomy with bilateral salpingoophorectomy, omentectomy, appendicectomy and pelvic and lateroaortic lymphadenectomy was recommended for advanced stage even in young nulliparous patients.[3] Considering the young age of the majority of patients, fertility, shoud be taken into consideration to make therapeutic strategies. Currently, all authors in the literature agree on the indication of fertilty-sparing surgery to treat early stage ovarian dygerminomas or even advanced stage dysgerminomas in women wishing to retain their reproductive potential.[4] So that, extensive complete staging surgery should be avoided. In fact, conservative surgery consist on unilateral salpingoophorectomy with staging biopsies and preseving of the uterus and contralateral ovary but opinions varie on whether a biopsy should be done despite a normal appearance of the contralateral ovary.[6] In our series, 67.7% of patients underwent fertility-sparing surgery and 4 of them (19%) underwent contralateral ovarian biopsy that was negative in all cases. It didn't show any occult disease. There is evidence showing that conservative surgery for stage IA dysgerminoma is safe with a 10-year survival rate of 91% in the prechemotherapy era.[3] However, radical surgery still recommended only for old patients, dysgerminomas affecting both ovaries and dysgenesic gonads.[8]

Adjuvant treatment for stage I ovarian dysgerminomas include radiotherapy, chemotherapy or clinical, radiological and biological surveillance. There is no randomised trial, which studied these options. According to Sagaes et al postoperative abstention is conceivable only for stage IA. However, stage IB and IC require adjvant chemotherapy.[9]

Prophylactic radiotherapy of pelvic and lateroaortic lymphnodes for stage IA and IB dysgerminomas tend to vanish in favor of simple surveillance.

For advanced stage of dysgerminomas, chemotherapy is as effective as radiotherapy with less side effects.

The chemosensitivity of ovarian dysgerminomas has revolutionized their management and prognostic.[4] In fact, Bleomycin-etoposide-cisplatine (BEP) is the first line chemotherapy with treatment every 3 weeks for 3 or 4 courses.[3] Despite that, chemotherapy can have significant long-term side effects, but it spares fertility and keeps the possibility of a later pregnancy.[3]

Adjuvant chemotherapy after conservative treatment was recommended for stage IC, stage II and stage III dysgerminomas with 2 or 3 courses if residual tumor was noted and 4 courses if surgery was complete R0. For stage IV, 4 courses of BEP was indicated.[10] In our series, 15 patients (48.3%) received adjuvant chemotherapy. Among them, 5 cases were at stage IA, chemotherapy was indicated because tumor size was high in 4 cases and surgery was non optimum with residual tumor in one case. For 2 patients classified as stage IIIC, chemotherapy was not BEP regimen. It was VAB-6: Cyclophosphamide, vinblastine, bleomycin, dactinomycin, and cisplatin.

Chemotherapy is also indicated for recurrent or metastatic disease.

Whatever the stage of the tumor, dysgerminoma can recur. Recurrence rate after conservative treatment varied between 17 and 32 % in the literature.[11,12] In our study, the recurrence rate after conservative treatment was 5%. Alwin et al suggested a close follow up after conservative treatment because 15 to 25% of cases relapsed within two years of surgery.[13] Late recurrence over 2 years has been reported as a very rare phenomenon.[3] In our study, there was only 2 recurrences that occurred below 2 years from surgery. These recurrences were classified as stage IA and IIIB. They responded well to chemotherapy and radiotherapy and they remained disease free.

The spread of dysgerminoma is often locoregional to the contralateral ovary, the pelvis or mediastinal, supraclavicular or retroperitonal lymphnodes.[14] However, distant metastasis are uncommon and the most common site is liver in 90% of cases, followed by lung, bone and brain.[15] In our series, 2 patients developed distant metastasis: the first patient was stage IA dysgerminoma that developed supraclavicular and mediastinal metastasis within 14 months of surgery and it respond well to radio and chemotherapy, the second case was stage IC dysgerminoma which presented splenic metastasis within 10 months of surgery. She had splenectomy with chemotherapy and she died after 6 months.

CONCLUSION

Ovarian dysgerminomas are an uncommon disease that has a good prognosis. Its management is essentially surgical consisting on fertility sparing surgery that preserves the reproductive function. It relapses more often within 2 years of surgery and late recurrence over 2 years are rare. Considering their chemosensitivity, recurrences are salvageable but late side effects should be taken into account especially that patients are young.

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