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Research Letter

Long-term survival in a patient with an advanced ovarian juvenile granulosa cell tumor with para-aortic lymph node metastasis

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Dear Editor,

Granulosa cell tumors (GCTs) are uncommon, accounting for 3–5% of all ovarian malignancies. Juvenile-type GCTs (JGCTs) are rare, representing only 5% of all GCTs, and occur mostly in prepubertal girls. The majority of JGCTs confined to the ovary as International Federation of Gynecology and Obstetrics (FIGO) Stage I are associated with a favorable outcome [1–3]. Advanced cases, which account for 3% of JGCTs, are more aggressive and result in relapse and death within 3 years [2,3]. Favorable outcomes and late recurrence in advanced JGCTs are extremely rare.

The patient was a 12-year-old virgin with menarche at age 11 years presenting with an abdominal mass and metrorrhagia. Computed tomography scans revealed a 21 cm × 18-cm abdominopelvic tumor with multicystic and solid components (Figure 1A). The patient underwent laparotomy in 2001, with findings of a huge right, intact ovarian tumor and an enlarged para-aortic lymph node adjacent to the right renal artery. The surgical procedures included peritoneal washing cytology, right salpingo-oophorectomy, partial omentectomy, resection of the para-aortic lymph node, and peritoneal biopsies. There were no residual tumors postoperatively. Pathological examinations revealed tumor cells with hyperchromatic ovoid nuclei and eosinophilic cytoplasm containing vacuoles in the ovarian tumor and para-aortic lymph node, consistent with a diagnosis of FIGO Stage IIIC ovarian cancer (Figures 1B and 1C). Immunohistochemical staining of alpha-inhibin was positive. Call–Exner bodies and nuclear grooves were absent. The patient received four cycles of adjuvant chemotherapy with cisplatin 75 mg/m^2 on Day 1, bleomycin 15 mg on Days 1–2, and etoposide 75 mg/m^2 on Days 2–4, at 4-week intervals. She regained menstruation a few months after the last cycle of chemotherapy. She was followed-up regularly for 15 years without recurrence.

Because JGCT generally occurs during childhood and the disease is commonly unilateral, the primary management is through fertility sparing surgery (unilateral oophorectomy). Only a few advanced-stage JGCT patients with long-term survival have been reported: four patients survived 46–84 months [1,4], and one patient had a disease-free survival after recurrence for 17 years [5]. The outcomes of advanced JGCTs are reviewed in Table 1. The long-term survival of our patient is the result of complete surgical resection of the primary and metastatic tumors, the lack of peritoneal disease, and a good response to chemotherapy. The absence of peritoneal metastasis is the major favorable prognostic factor, which contributed to the success of the treatment, as it allowed us to completely excise the primary and metastatic tumors without residual lesions postoperatively [6].

Lymph node metastasis in GCTs is rarely reported. Ayhan et al [7] evaluated 60 cases of adult GCTs including lymphadenectomy in 18 patients, and found metastasis in an external iliac node in one patient. Abu-Rustum and associates [8] reviewed 68 cases: 64 adult-type and four juvenile-type. No nodal metastasis was identified at the initial operation in 16 patients, suggesting that nodal metastasis is very unusual. There is no standard treatment for patients with advanced or recurrent JGCTs due to their rarity. Among the adjuvant therapies reported, chemotherapy with cisplatin-based regimens has been the most effective, inducing response rates of 63–90% [3,9,10]. However, cytotoxic chemotherapy may variably affect ovarian function and menstruation depending on the type of chemotherapy, the patient's age, and ovarian reserve at time of diagnosis. Alkylating agents have extremely damaging effects on the ovary; platinum-based compounds, such as cisplatin and carboplatin, carry a medium risk of amenorrhea; the impacts of anthracycline antibiotics and plant alkaloids on fertility have variously been categorized as medium-to-low risk [11].

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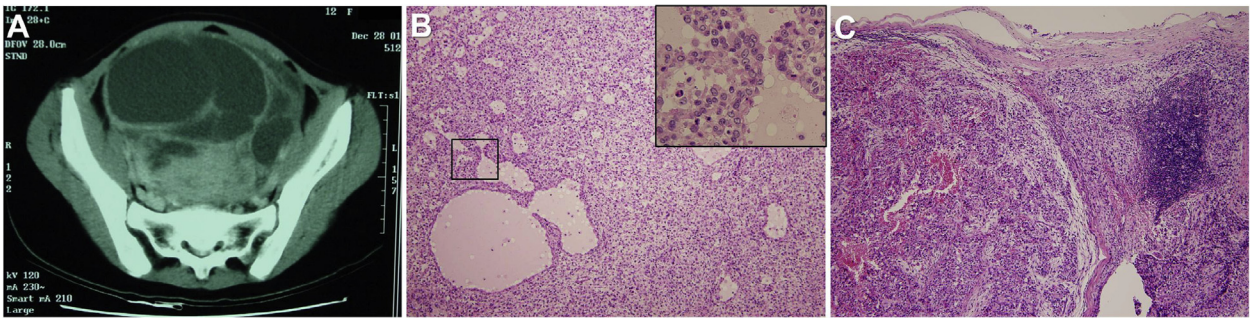

Figure 1. (A) Contrast computed tomography of ovarian juvenile-type granulosa cell tumors showing a large abdominopelvic tumor with cystic and solid components. Hematoxylin and eosin images of (B) a low power view (×100) of juvenile-type granulosa cell tumors of the ovary (insert: high power view, ×400) and (C) para-aortic lymph node.

Table 1
Literature review of the patients with advanced ovarian juvenile-type granulosa cell tumors.

Author	Age (y)	Diameter (cm)	FIGO stage	LN metastasis	Primary treatment			Remission	Recurrence			Pregnancy (after CT)	Current status
					Surgery	Adjuvant	Cycle		Localization	Treatment	Survival		
Young et al 1984 [2]													
#1	22	14.5	IC		TAH, BSO	RT, bleo, cis, vinb		6 mo	Rectum, liver, om	bleo	3 mo		DOD
#2	22	20	IC		USO			5 mo	Ovary, intestines, om, liver, ut	S, 5-FU, act, cyclo, dox, hex, cis	11 mo		DOD
#3	23	20	IIC		TAH, BSO	cis		7 mo	Vagina, supraclavicular LN	S, 5-FU, cyclo, mito, chromo	6 mo		DOD
#4	12	17	IIB		USO	act, cyclo, vinc	7						
					2nd look	5-FU, act, cyclo	12	1 y	Pelvis, supraclavicular area	S, bleo, cis, vinb, RT	4 mo		DOD
#5	7	12	IIB		USO	bleo, cis, vinb	3	3 mo	Pelvis, liver	act, cyclo, dox, vinc	4 mo		DOD
Colombo et al 1986 [3]													
#1	20		III		USO	bleo, cis, vinb	6	7 mo					NED
#2	7		IV		USO	bleo, cis, vinb	3	7 mo					DOD
Powell et al 1993 [4]	13	17.5	IIIB	No	[a]USO								
					[b]restaging	act, chlora, met	3	7 y				1	NED
Wessalowski et al 1995 [12]	3	11	IC		USO, staging	dox, ifo, vinc	5	10 mo	Liver, om	H (liver), S, carbo, eto, ifo, RT	1 y		NED
Powell and Otis 1997 [13]	13	19	IIIC	No	USO, staging	carbo, eto	6	39 mo					NED
Hirakawa et al 2008 [14]	37		IIC	No	TAH, BSO, LND, D	bleo, cis, eto	3	3 mo	Abdomen	carbo, pac, doc, RT	5 mo		DOD
Powell et al 2014 [5]	17	17	IIIC	No	USO, D	carbo, eto	6	13 mo	Liver, spleen	S, bleo, pac	17 y	2	
									[c]Liver, pancreas, stomach	S, bleo, carbo, pac	1 y		NED
Karalök et al 2014 [15]	21	12	IC	No	USO, LND, staging	bleo, cis, eto	4	67 mo				1	NED
Our case	12	21	IIIC	Yes	USO, LND, staging	bleo, cis, eto	4	15 y					NED

5-FU = 5-fluorouracil; act = actinomycin-D; bleo = bleomycin; BSO = bilateral salpingo-oophorectomy; carbo = carboplatin; chlora = chlorambucil; chromo = chromomycin; cis = cisplatin; CT = chemotherapy; cyclo = cyclophosphamide; D = debulking; doc = docetaxel; DOD = died of disease; dox = doxorubicin (adriamycin); eto = etoposide; FIGO = International Federation of Gynecology and Obstetrics; H = hyperthermia; hex = hexamethylmelamine; ifo = ifosfamide; LND = lymph node dissection; met = methotrexate; mito = mitomycin; mo = month; NED = no evidence of recurrent disease; om = omemtum; pac = paclitaxel; RT = radiotherapy; S = surgery; TAH = total abdominal hysterectomy; USO = unilateral salpingo-oophorectomy; Ut = uterus; vinb = vinblastine; vinc = vincristine; y = year.

[a] Operation at 26 weeks of pregnancy.
[b] Operation at postpartum.
[c] Adult-type GCT.

In conclusion, our patient suffered from an advanced JGCT with para-aortic lymph node metastasis and has enjoyed a 15-year disease-free survival. Complete tumor resection and adjuvant chemotherapy can achieve long-term control of nodal metastatic JGCT.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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