Int J Clin Exp Pathol 2020;13(5):1053-1059
www.ijcep.com /ISSN:1936-2625/IJCEP0107496

Original Article

Borderline ovarian tumor in the pediatric and adolescent population: a clinopathologic analysis of fourteen cases

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Received January 7, 2020; Accepted February 7, 2020; Epub May 1, 2020; Published May 15, 2020

Abstract: Borderline ovarian tumors (BOTs) are rare among children and adolescents. This study was to probe into the clinicopathologic characteristics and prognosis in children and adolescents with BOT. A retrospective investigation was performed on 14 adolescents younger than age 21 years diagnosed with BOT. Clinical presentation, preoperative characteristics, surgery, tumor stage, histology, and recurrence were collected. The results showed that median age at diagnosis was 17.5 years, mostly after menarche. Abdominal mass/pain were the most common presenting symptoms. Median tumor size was 14 cm. Cancer antigen-125 (CA-125) in the blood serum was elevated by 41.67% (5/12), and CA-199 was elevated by 16.67% (2/12). All patients had fertility-preserving surgery: 66.67% (8/12) via laparoscopy (LSC) and cystectomy, 33.33% (4/12) via laparotomy and unilateral salpingo-oophorectomy (USO), and 1 case recurred, and underwent panhysterectomy and bilateral salpingo-oophorectomy. 4 out of 14 tumors (28.57%) had serous and 10 of 14 (71.43%) had mucinous histology. Five tumors showed histological microinvasion. Median follow-up time was 52 months. 10 of 14 cases were alive at last follow-up without disease, and 4 of 14 cases were at lost visit. Thus BOTs in children and adolescents are very rare tumors which have excellent prognosis even in advanced stages, when managed with fertility-preserving procedures. Close follow-up is important because of the high recurrence rates many years after diagnosis.

Keywords: Borderline ovarian tumor, pediatric, adolescent

Introduction

Ovarian tumors are rare in children and adolescents. The incidence increases with age, from 0.43/100,000 cases at 1 year of age to 152/100,000 cases in 35-year-old patients [1]. The diagnosis of ovarian tumors in pediatrics and adolescents is often difficult and delayed due to non-specific symptoms. The World Health Organization has classified these tumors into three main groups according to whether they develop from epithelial cells, germ cells, or sex cord stromal tumors. Germ cell tumors represent more than 70-80% of ovarian tumors [2, 3], which are the most common types in children and adolescents. Benign epithelial tumors of the ovary are far more common in older women, but uncommon in childhood and adolescence, representing almost half of ovarian epithelial tumors in these ages [4].

Among all ovarian epithelial tumors in childhood and adolescents, about 10-30% were considered as borderline ovarian tumors (BOTs), also called "low malignant potential" [4-6]. BOTs are neoplasms of epithelial origin characterized by up-regulated cellular proliferation and the presence of slight nuclear atypia but without destructive stromal invasion [7]. There are few reports on BOTs in childhood and adolescents, current knowledge on those deriving from case-reports and small single institution case-series. The aim of this study was to investigate the unique clinicopathologic characteristics and outcomes of BOTs in children and adolescents.

Materials and methods

This study was approved by the ethics committee for the First Affiliated Hospital of Xinjiang Medical University, Xinjiang, China. A retrospective investigation was performed on 14 female

Table 1. General characteristics

Characteristic	Total
Median age (range), years	17.5 (12-21)
Median follow-up (range), months	52 (28-102)
Presenting symptoms	
Pain	5 (41.67)
Mass	11 (91.67)
Mass on imaging	12 (100)
Ascites	2 (16.67)
Menarche	
Premenarchal	1 (8.33)
Menarchal	11 (91.67)
Sex	
Yes	2 (16.77)
No	10 (83,33)
Median tumor size (range), cm	14 (5-30)
Elevated CA-125	5 (41.67)
Elevated CA-199	2 (16.67)
Surgery	
Cystectomy	8 (66.67)
USO	4 (33.33)
Laterality	
Right	11 (78.57)
Left	2 (14.29)
Bilateral	1 (7.14)
Histology type	
Mucinous	10 (71.43)
Serous	4 (28.57)
Microinvasion	
Yes	5 (35.71)
No	9 (64.29)
Stage	
IA	11 (91.67)
IB	1 (8.33)
Recurrence	1 (8.33)
Vital status	
Alive without disease	10 (83.33)
Alive with disease	NA

Data are presented as n (%), except where otherwise noted. CA-125, carcinoma antigen 125; CA-199, carcinoma antigen 199; USO, unilateral salpingo-oophorectomy; NA, not available.

adolescents younger than the age of 21 years who were diagnosed with BOT during a 7-year study period from Jan. 2011 until Dec. 2017. Diagnosis of BOTs was not performed before 2011 in the First Affiliated Hospital of Xinjiang Medical University before 2011.

Clinico-pathologic data were searched such as age, menarchal status, diagnosis, clinical presentation, tumor markers, surgical procedure performed, pathology, tumor stage, treatment, follow-up, and recurrence. Information derived from the pathology reports was applied to determine whether lymph node (LN) sampling/dissection was performed, the exact number of LNs removed and the precise number of LN positive for metastasis.

Results

14 patients were diagnosed with BOT during the study period, 2 of whom were consultation cases with incomplete information. A summary of the general characteristics for 12 cases with complete information is outlined in **Table 1**. Median age at diagnosis was 17.5 years (range, 12-21 years), 11 of 12 (91.67%) were menarchal, and 10 of 12 had no sexual life history. Median follow-up time was 52 months (range, 28-102 months). 91.67% (11 of 12) presented with abdominal mass on examination, 41.67% (5 of 12) with abdominal pain, and 16.67% (2 of 12) with ascites. Median tumor size was 14 cm (range, 5-30 cm). Preoperative cancer antigen 125 (CA-125) was elevated by 41.67% (5 of 12), and CA-199 was elevated by 16.67% (2 of 12). All patients had fertility-preserving surgery: 8 of 12 (66.67%) by laparoscopy (LSC) and cystectomy, 1 of which recurred after first operation and underwent panhysterectomy and bilateral salpingo-oophorectomy again, and 4 of 12 (33.33%) by laparotomy and unilateral salpingo-oophorectomy (USO).

13 of 14 BOTs were unilateral, 11 of which involved the right ovary, 2 of which involved the left ovary, and 1 of 14 BOTs was bilateral. Based on pathologic diagnosis, 4 of 14 tumors (28.57%) had serous (**Figure 1**) and 10 of 14 (71.43%) had mucinous histology (**Figure 2A**). Five tumors showed histological microinvasion (**Figure 2B**). In case 10, microinvasion appeared after recurrence. 11 of 12 cases were at stage IA, and 1 of 12 was at IB (case 3) with bilateral BOT and serous histology. Only one patient received cytotoxic chemotherapy because of recurrence. Tumor staging was not carried out for 2 consultation cases with incomplete information.

Table 2 shows the clinical characteristics, and outcome for each of the 14 patients with BOT. 1 out of 12 patients had recurrence at 17 months after initial diagnosis, and 2 consultation ones were lost to follow-up. 5 out of 12

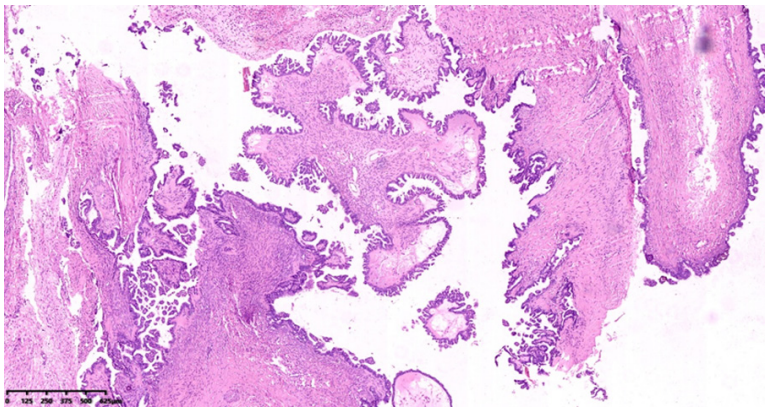

Figure 1. Serous borderline ovarian tumor: hierarchically branched papillae, covered by a single-layered or multilayered epithelium with serous differentiation. hematoxylin and eosin stain.

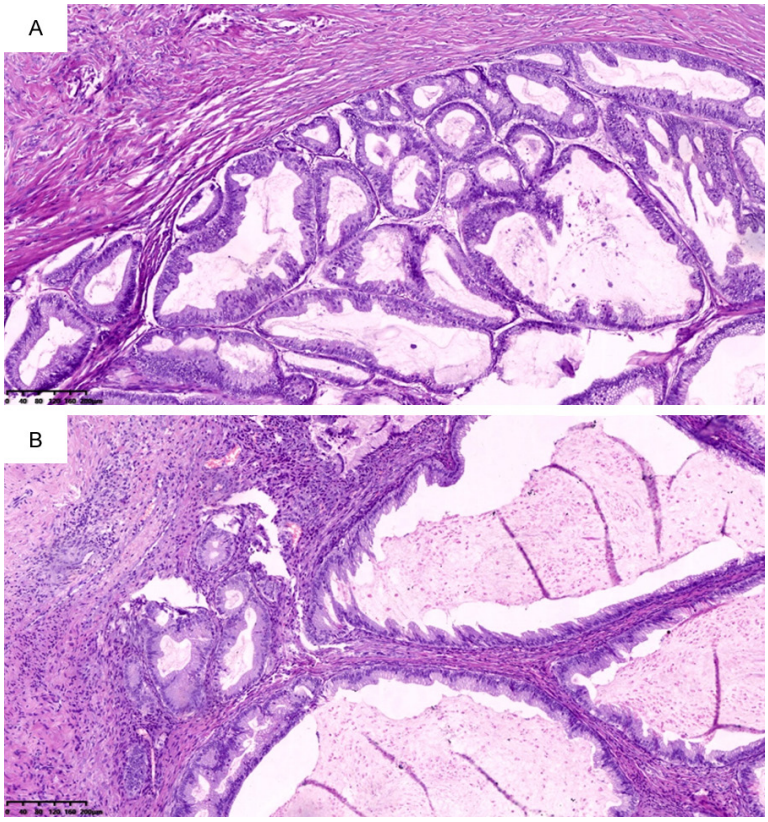

Figure 2. Mucinous borderline ovarian tumor. A. Papillary infoldings, columnar cells with abundant cytoplasmic mucin, admixed with goblet cells of variable degrees of maturation, with basally located nuclei with no considerable nuclear atypia. B. Mucinous borderline tumor with microinvasion. It was characterized by small cell groups and glands with a normal ovarian stroma without desmoplastic change.

patients had elevated CA-125, including 4 cases of mucinous histology and 1 case of serous histology. 2 out of 12 had elevated CA-199 which were mucinous histology, and 1 of those showed normal CA-199 at initial diagnosis and the elevation of CA-199 when relapse 17 months after surgery (case 10). Case 10 had an initial laparoscopy, right ovarian cystectomy, followed by an ipsilateral mucinous borderline tumor recurrence and contralateral serous cystadenoma and treated with panhysterectomy and bilateral salpingo-oophorectomy. Case 10 received a chemotherapy with paclitaxel and carboplatin after second surgery. Case 7 had the elevation of both CA-125 and CA-199 with mucinous histology. On the basis of surgical records, 7 of 12 cases were greater than 10 cm, and 5 of 12 were less than 10 cm. 10 of 14 cases were alive at last follow-up without disease, and 4 of 14 cases were lost to follow-up.

Of 14 cases, case 2, 5, 8, 10, and 12 underwent immunohistochemical analysis showed in **Table 3**. The 5 cases had immunohistochemical results of CK7 (+) and CK19 (+). The positive rate of Ki-67 was more than 10% in 3 out of 5 cases. In recurrent case 10, the positive rate of Ki-67 was 20%.

Discussion

In this series, we collected a total of 14 BOT cases younger than the age of 21 years from the First Affiliated Hospital of Xinjiang Medical University, Xinjiang, China ranging from Jan. 2011 to Dec. 2017. For two consultation cases out of of 14 cases with incomplete information, we only counted their histological types. From our report, BOTs are rare in childhood and adoles-

Table 2. Clinical characteristics, management, and outcome of 14 patients with BOT

Case	Age, years	Ethnic	Menstrual	Side	Symptoms	Size, cm	CA-125, Elevation (U/mL)	CA-199 Elevation (U/mL)	First Surgery	Histology	Stage	Recurrence, months	Recurrent Surgery	FU months	Vital Status
1	21	Han	Yes	R	Pain, distension	5	Yes (246.10)	No (8.92)	LSC, RSO, LOC	Mucinous*	IA	No	-	102	A
2	18	Hui	Yes	R	Pain, distension	5	Yes (76.70)	No (12.82)	LSC, ROC	Serous	IA	No	-	-	NA
3	15	Han	Yes	B	Irregular menstruation	8	No (15.10)	No (21.38)	LSC, LOC, RSO	Serous	IB	No	-	79	A
4	20	Han	Yes	R	Distension	30	Yes (52.50)	No (8.08)	XLAP, RSO	Mucinous	IA	No	-	-	NA
5	21	Han	Yes	R	Distension	6	No (18.6)	No (18.60)	LSC, ROC	Serous	IA	No	-	69	A
6	12	Han	No	R	Distension	20	No (12.60)	No (9.41)	XLAP, LOC, ROC	Mucinous*	IA	No	-	54	A
7	16	Xibe	Yes	R	Irregular Menstruation, pain, distension	18	Yes (120.90)	Yes (97.31)	XLAP, ROC	Mucinous	IA	No	-	53	A
8	17	Han	Yes	R	Pain, distension	9	No (11.50)	No (12.24)	LSC, RSO	Mucinous	IA	No	-	51	A
9	21	Han	Yes	R	Distension	14	No (29.70)	Yes (97.31)	XLAP, ROC, RS	Mucinous*	IA	No	-	50	A
10	20	Uygur	Yes	R	Irregular menstruation, distension#	17	1. No (27.95) 2. Yes (150.50)	1. No (4.150) 2. (24.60)	LSC, ROS	Mucinous*	IA	17	XLAP, BSO, PHR☆	48	A
11	16	Han	Yes	L	Distension#	18	No (17.90)	No (30.88)	LSC, LSO	Mucinous*	IA	No	-	42	A
12	16	Uygur	Yes	L	Distension	14	No (10.50)	No (9.62)	LSC, LOC	Mucinous	IA	No	-	28	A
13	15	Hui	Yes	R	NA	NA	NA	NA	NA	Serous	NA	NA	NA	NA	NA
14	19	Han	Yes	R	NA	NA	NA	NA	NA	Mucinous	NA	NA	NA	NA	NA

A, alive; BOT, borderline ovarian tumor; CA-125, carcinoma antigen 125; CA-199, carcinoma antigen 199; L, left; R, right; RSO, right salpingo-oophorectomy; LSC, laparoscopy; LOC, left ovarian cystectomy; ROC, right ovarian cystectomy; XLAP, exploratory laparotomy; RS, Right salpingectomy; BSO, bilateral salpingo-oophorectomy; PHR, panhysterectomy; FU, follow-up; A, available; NA, not available. *Microinvasion. #Ascites. ☆Adjuvant chemotherapy (paclitaxel and carboplatin).

Table 3. Immunohistochemical analysis

Case	Immunohistochemical analysis
1	-
2	ER (+), PR (+), Ki-67 (<5%+)
3	-
4	-
5	ER (+), PR (+), Ki-67 (<5%+)
6	-
7	-
8	ER (+), PR (-), Ki-67 (40%+)
9	-
10	Ki-67 (+20%), ER (+), PR (-), Ki-67 (+20%)
11	-
12	ER (-), PR (-), Ki-67 (+15%)
13	-
14	-

cents. This is consistent with some literature [8]. Höhne et al. reported that BOT are extremely rare in young children and only a few case reports exist [9]. 12 cases in our report were at FIGO stage I, 11 of those were at IA, 1 case was at IB with bilateral BOT, and 2 cases were lost to follow-up. 10 out of 14 cases are alive without disease, and 4 cases are uncertain. Thus BOTs have good prognosis. A similar report indicated that the majority of BOTs are limited to the ovary(ies) at presentation with 75% being diagnosed at FIGO stage I [10]. They generally have an excellent prognosis with a 10-year survival of 97% for all stages combined [11].

In our report, 11 out of 12 cases occurred after menarche in adolescents, only 1 case occurred in premenarche, with median age at diagnosis of 17.5 years. Thus the incidence of BOTs in children and adolescents increases with age, with most occurring after menarche. The higher occurrence of ovarian epithelial tumors in menarchal girls is believed to result from hormonal stimulation and repeated disruption and repair of the ovarian epithelium due to ovulation, which might lead to greater risk for spontaneous mutations as they age [12]. There are similar reports about most cases of epithelial ovarian tumors found in postmenarchal patients [6, 12]. To our knowledge, there are less than 20 cases of BOT in premenarchal girls reported in the literature. There was only one case of BOT in premenarchal girls in the present study who was 12 years of age and showed signs of puberty. In a report about a total of 114 cases of BOT, only 7/114 were younger than 13 years old, whereas the youngest reported cases of BOT were a 2-year-old girl and a 3-year-old girl [6, 9].

Histologically two major variants of BOTs exist, serous and mucinous type. For reasons that are still unclear, serous BOTs are more common in Europe, North America, and the Middle East, while the mucinous BOTs more common in East Asia [13]. Luchian et al. reported 54 patients with BOTs; the histological types were: mucinous (27 cases, 50%), serous (18 cases, 33.33%), other (9 cases) [14]. In the present 14 cases, 10 cases (71.43%) were mucinous BOTs, and only 4 (28.57%) cases are serous BOTs. Mucinous BOTs were more common, which is consistent with the above.

BOTs have variable symptom presentations which are nonspecific, abdominal pain and distension occurring frequently with ovarian masses. 5 (41.67%) of our 12 patients presented with abdominal pain, 11 cases (91.67%) presented with abdominal distension. Microinvasion was founded in 5 of our 14 cases including 2 consultation in which histological types were mucinous. Microinvasion has been reported in 4 to 18% of mucinous BOTs and has no adverse effect on prognosis [15]. By the end of follow-up date, 5 cases with evidence of microinvasion were alive without disease in our report. About one-third of serous BOTs are bilateral, while mucinous BOTs are usually large, and unilateral [16]. In our reported 14 cases, 13 cases were unilateral (11 cases are at right, 2 cases are at left) and 1 cases with serous type was bilateral, accounting for 25% of serous types in our report. The mean tumor size was 14 cm. Of 12 cases, 7 cases were larger than 10 cm in size which were mucinous, 2 of which were with ascites, and no tumor cells were found in ascites. Findings that raise concern for an ovarian malignancy include cyst size larger than 10 cm, and presence of ascites, [17]. The recurrence rate for BOT may be as high as 37.5% when fertility-sparing surgery is performed and the malignant transformation is not negligible [18, 19]. By the end of follow-up date, 7 patients larger than 10 cm in size are alive without disease and only one case recurred in our report. Due to the limited follow-up time, it is necessary to continue the follow-up.

Serum tumor marker examination such as CA-125, and CA-199 has some value in the diagnosis of BOTs. CA-125 increased in both serous and mucinous BOTs, and CA-199 increased more in mucinous BOTs. In this report, CA-125 was elevated in 5 of 12 patients including 4 cases with mucinous type (1 with elevated CA-125 after recurrence) and 1 case with serous type, and CA-199 was elevated in 2 of 12 patients with mucinous type. The case with elevated CA-125 after recurrence underwent panhysterectomy and bilateral salpingo-oophorectomy, and she is still healthy. However, in the case of chronic ovarian disease or gynecological inflammation including ovarian chocolate cyst rupture, peritonitis, cirrhosis, benign tumor, endometriosis, tuberculosis or pelvic inflammation, CA-125 will also be on the high side. Therefore, as opposed to the 35 U/mL threshold in postmenopausal women, the American Congress of Obstetricians and Gynecologists has used a CA-125 threshold of greater than 200 U/mL for referral of premenopausal women. In our report, only one case had a CA-125 value higher than 200 U/mL with alive without disease. Therefore, CA-125 and other clinical factors should be considered to determine together the risk of ovarian malignancy.

In our report, immunohistochemical tests for ER, PR, and Ki-67 were performed on some cases. ER expression in case 2, 5, 8 and 10 was positive. PR expression in case 8, 10 and 12 was negative. ER expression is a common feature of BOTs [20]. ER expression was more in malignant tumors than in borderline and benign. As compared to ER, PR expression was more in benign than borderline and malignant tumors [21]. Ki-67 positive rates in case 8, 10 and 12 in our study were more than 10%, and case 10 reoccured. Thus continuous follow-up is necessary. The positive rate of Ki-67 in case 10 was 20%. Recurrence occurred 17 months after the first operation, and the patient survived without disease after the reoperation. Immunohistochemistry marker report of ER, PR status, and Ki-67 in each pathology report will pave the way for better understanding of biologic behavior and modify treatment strategies for BOTs.

In conclusion, pediatric BOTs are very rare tumors which have an excellent prognosis even in advanced stages when managed with fertility preserving procedures. Histologically mucinous BOTs are more common than serous. Close follow-up is important because of the high recurrence rates many years after diagnosis. Due to limited literature on pediatric and adolescent BOTs, further research is necessary.

Acknowledgements

We thank Sayahat Bieerkehazhi for scientific editing of the manuscript. This study was supported by the Third Level program of Tianshan Talents at Xinjiang Medical University, China (to Yonghua Shi).

Disclosure of conflict of interest

None.

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