Epithelial ovarian tumors and CA125 in premenarchal girls

Z. Stankovic[1], S. Djuricic[1], M. Djukic[2], D. Jovanovic[1], M. Vasiljevic[2]

[1]Department of Pediatric and Adolescent Gynecology, Surgery and Pathology, Mother and Child Health Institute of Serbia
[2]University Clinic of Gynaecology and Obstetrics Narodni Front, Belgrade (Serbia)

Summary

Purpose: This is a review of our 18-year experience with premenarchal girls with epithelial ovarian tumors. Special attention was focused on the predictive value of CA125 serum levels.

Methods: Analysis of premenarchal patients with resected or biopsied ovarian masses from 1988 to 2005 was performed. Patient age, clinical presentation, operative procedures, histologic type of tumor, treatment and outcome were obtained.

Results: Six premenarchal girls (aged from 6 to 14 years) were surgically treated for epithelial tumors, representing 13% of all ovarian tumors at this age. Histological findings revealed cystadenoma in four girls, one with a mucinous borderline tumor and one with undifferentiated carcinoma. Tumor volume was higher than 400 cm^3 in four girls. Sensitivity, specificity and positive predictive value of CA125 level for ovarian malignant epithelial tumors were 0.50, 0.50, and 0.33, respectively. The premenarchal girl with undifferentiated carcinoma in Stage III died after six months in spite of chemotherapy.

Conclusion: Ovarian epithelial tumors in premenarchal girls show important growth potential and a relatively high malignancy rate with great influence of borderline neoplasms. CA125 is a tumor marker with low sensitivity and specificity for detection of epithelial ovarian malignancy in this age group.

Key words: Ovarian carcinoma; Premenarchal girls; CA125 tumor marker.

Introduction

Less than 50% of childhood ovarian masses are of neoplastic nature and the majority of them arise from germ cells [1, 2]. As opposed to adults, ovarian tumors of epithelial origin represent less than 20% of childhood ovarian tumors and are very rare before menarche [2, 3]. Malignant epithelial tumors represent 5-33% of ovarian malignancy in childhood [4, 5] and may be either truly invasive or have characteristics of borderline tumors. Tumor marker CA125 is currently the most widely used tumor marker for ovarian epithelial cancer and it is recommended even in the pediatric population [1]. Because only a few cases or small series have been published, there is not enough information about the behavior, serum levels of CA125 and management of epithelial tumors in childhood, especially in premenarchal girls [2, 3, 6].

The aim of this study was to present a series of premenarchal patients with ovarian epithelial tumors, with special attention focused on the predictive value of CA125 levels.

Materials and Methods

Patients with epithelial ovarian tumors were collected via a search of the hospital surgical pathology database. All patients were diagnosed and surgically treated in university-affiliated pediatric institutions from January 1988 to December 2005. At the time of surgery patients' age was less than 19 years. Analyzed data comprise symptoms at presentation, serum level of tumor marker CA125, histopathological type, treatment and outcome. This review follows the World Health Organization (WHO) pathohistological classification of ovarian tumors and International Federation of Gynaecology and Obstetrics (FIGO) staging criteria [7]. Statistical analysis was carried out using SPSS for Windows (Version 10.0, SPSS Inc., Chicago, IL, USA). The diagnostic accuracy of CA125 was assessed using sensitivity, specificity and positive predictive value.

Results

There were 45 premenarchal girls with ovarian tumors in the analyzed period. Six had tumors of ovarian epithelial origin. The mean age of these six patients was 11.8 ± 2.9 years; range 6.1 to 13.7 years. Important clinical and pathological data are shown in Table 1. Family history of gynecological malignancy was negative in all patients. One patient had had a previous appendectomy. Symptoms and signs that led to clinical investigation were nonspecific, such as abdominal swelling, discomfort, abdominal pain, abdominal mass and frequent micturition. Two patients had tumors of the right ovary, three of the left ovary and one patient had a bilateral tumor. Histopathological analyses revealed benign tumors in four patients, one patient had a mucinous borderline tumor and one had undifferentiated carcinoma. On ultrasonography three benign tumors had a cystic appearance and four other tumors were semisolid. The tumor weight was more than 1,000 g in three girls. Bilateral tumor was found only in one patient with initially frequent micturition, previously reported as a case of rapidly growing serous cystadenoma. The other five premenarchal girls were in the second decade of life. One girl was surgically treated five days before menarche for serous cystadenoma and two girls had mucinous cystadenomas, with menarche occurring in both within the next 12 months. Past medical history was conspicuous only in a 12 and a half-year-old girl with a borderline mucinous cystadenoma weighing

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Table 1. — *Clinical and histopathological findings in pre-menarchal girls with ovarian surface epithelial neoplasms .*

Histology	Age (yrs)	Stage	Symptoms	CA125 (U/ml)	Volume (cm^3)	Treatment	Follow-up (yrs)
Serous cystadenoma n = 2	6.1	–	Frequent micutrition	12	25	Bilateral cystectomy	2.1
	13.7	–	Abdominal mass	49	400	Left cystectomy	12.7
Mucinous cystadenoma n = 2	13.3	–	Abdominal swelling	21	4000	Left salpingo-oophorectomy	16.2
	13.4	–	Abdominal pain, torsion	44	40	Left oophorectomy	3.6
Mucinous borderline tumor n = 1	12.5	IA	Abdominal swelling	24	4100	Right salpingo-oophorectomy	1.1
Undifferentiated carcinoma n = 1	11.9	III	Discomfort, Abdominal swelling	634	850	Right salpingo-oophorectomy, Chemotherapy	Died after 0.5

4,700 g and with normal CA125 values. She had celiac disease diagnosed at age two years. In one patient with serous cystadenoma and in one with adnexal torsion elevated levels of CA125 (> 37 U/ml) were registered (Table 1). A highly elevated serum level of CA125 (634 U/ml) was found only in one patient with undifferentiated carcinoma in Stage III of disease. Postoperatively this patient received three cycles of etoposide, cisplatin and bleomycin at 3-week intervals. Three months later local recurrant tumor was revealed and the serum level of CA125 had increased to 1341 U/ml. She underwent a second surgery comprising resection of the large recurrant tumor, left salpingo-oophorectomy and hysterectomy. Despite subsequent polychemotherapy (cisplatin, bleomycin, paclitaxel, holoxan) she succumbed to metastatic disease six months after the primary diagnosis.

One 15 and a half-year-old premenarchal girl with a normal serum level of CA125 and a primary diagnosis of peritoneal pseudomyxoma based on analysis of a bioptic specimen was excluded from this study. Subsequent biopsy of the large abdominal tumor mass showed mucinous adenocarcinoma of probable ovarian origin, strong and diffuse CK7 and variable CK20 immunopositive tumor cells. The reason for exclusion was that recent morphological, immunohistochemical and molecular genetic studies [16] have provided compelling evidence that virtually all cases of peritoneal pseudomyxoma are of gastrointestinal, usually appendiceal, origin but in our patient appendectomy had not been performed.

Discussion

Primary ovarian tumors are uncommon in pediatric patients with an annual incidence of 2.6 cases per 100,000 girls [4, 8] and less then one fifth of them have an epithelial origin [2, 4, 5]. In childhood there is a gradual increase in the incidence of epithelial ovarian tumors with age, and most occur after menarche [4, 8]. The present analysis comprises six cases of ovarian epithelial tumors, representing 13% of all ovarian tumors in premenarchal girls in our group. Cystadenoma is the most common type of epithelial ovarian tumor in adults and children, and it is more commonly serous rather than mucinous [1, 2, 4, 8]. In our study cystadenomas represent 83% of all analyzed tumors, which is very similar to the study by Norris *et al.* (88%) [9], but mucinous cystadenoma predominates over serous with a ratio of 3:2. A literature review made by Deprest *et al.* presented almost 30 common epithelial neoplasms, representing 5% of ovarian tumors in girls less than ten years old [3]. In a 6-year-old patient with bilateral tumors, we quantified the rate of growth using volume-doubling time of the ovarian masses, which was two weeks. The other epithelial tumors had a tumor volume up to 400 cm^3 with no specific symptoms of disease, and expected torsion of mucinous cystadenoma with a volume under 50 cm^3. Reported malignancy rate, including malignant and borderline tumors, among epithelial ovarian tumors in girls under 20 years of age ranges from 7.5 to 30% [2, 3, 4, 10]. We did not find references on malignancy rate in premenarchal girls. In our study, the malignancy rate for epithelial ovarian tumors in premenarchal girls was 33%. In the 14-year-long study of Morowitz *et al.*, among 19 epithelial ovarian tumors in girls only one was in a premenarchal girl and had a malignant histology [2]. Shankar *et al.* reported ovarian adenocarcinomas in three premenarchal girls but they did not find any borderline tumors in this age group [6]. Histologically malignant epithelial ovarian tumors in premenarchal girls reported so far have been serous and mucinous adenocarcinoma, undifferentiated carcinoma and endometrioid carcinoma [6, 11]. In most premenarchal girls, epithelial ovarian malignancy has been diagnosed in an advanced stage and outcome of disease has been fatal, despite surgery and chemotherapy, with no reported long-term survivors [6]. The course of disease in one of our cases was unfavorable and rapid. Histopathological analysis of a malignant ovarian tumor in a premenarchal girl in our series resulted in a diagnosis of the undifferentiated ovarian carcinoma. Tsai *et al.* concluded that 70% of adolescents had borderline ovarian tumors, but they did not find any in premenarchal patients [13]. Borderline tumors represented 50% of the

malignant tumors in our study, with favorable outcomes. One girl with a serous borderline tumor was reported but most borderline epithelial neoplasms in premenarchal girls have been mucinous [14].

A diagnostic strategy for ovarian epithelial malignancy in the pediatric population includes the estimation of the serum level of CA125 tumor antigen, which is based on experience gathered from similar tumors in adults. Other studies in adults have reported that tumor marker CA125 has a high false-positive rate and poor sensitivity and specificity for epithelial ovarian malignancy, and is of little value in the detection of early ovarian cancer [15]. In our study of premenarchal patients, the sensitivity, specificity and positive predictive value of CA125 were 0.50, 0.50 and 0.33, respectively. We found that the serum level of CA125 in the girl with rapidly growing bilateral epithelial tumors was not elevated, such as in the patient with borderline mucinous cystadenoma. To our knowledge, there are only seven premenarchal patients with mucinous cystadenoma reported in the literature [3, 9, 14, 16]. Elevated levels of CA125 were noted in one mucinous and one borderline tumor [3, 16]. In two out of three patients with serous cystadenocarcinoma from the study of Shanker *et al.*, immunochemical analysis of the tumor cells showed positivity for CA125, but there was no evidence of elevated serum levels of that tumor marker in either of them [6]. However, it may be a useful tumor marker in identifying recurrent or residual disease in malignant epithelial ovarian neoplasms, such as in our patient. In two patients with serous cystadenomas in our group, we preserved the ovarian tissue, without recurrence of disease. Management of these patients with fertility-conserving treatment needs careful follow-up because of the possibility of recurrence in the remaining ovary.

Conclusions

This study of premenarchal girls with epithelial ovarian tumors comprised six patients. Ovarian epithelial neoplasms in premenarchal girls have an important influence on malignant and borderline tumors. A malignant ovarian epithelial tumor in a premenarchal girl is usually revealed at an advanced stage and has a high rate of mortality. The behavior of epithelial ovarian malignancy in premenarchal patients appears to be more aggressive than in adolescents. CA125 is a tumor marker with low sensitivity and specificity for detection of epithelial ovarian malignancy in this age group.

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Address reprint requests to:
M. VASILJEVIC, M.D.
Medical Faculty of Belgrade
Clinic of Gynecology and Obstetrics
Narodni Front
Omladinskih Brigada Street 7V
11000 Belgrade (Serbia)