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Proliferative Brenner tumor of the ovary. Clinicopathological study of two cases and review of the literature

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Summary

Background: Ovarian Brenner tumors are rare epithelial tumors that account for 1%-2% of all ovarian neoplasms. They can be subdivided into benign, borderline or proliferative, and malignant neoplasms. In the vast majority of cases, these lesions are benign. Tumors of borderline malignancy are less frequent and only about 1% of Brenner tumors are malignant. We present two cases of Brenner tumors with borderline malignancy which were treated in our Department together with a review of the literature. *Cases:* A 50-year-old, gravida 1, para 1, patient was admitted for abnormal vaginal bleeding. Clinical examination, abdominal ultrasound (US), and computed tomography (CT) revealed a cystic multilobulated tumor of the right ovary with solid elements measuring 20 x 19 x 15 cm in diameter. In the other case a 70-year-old, gravida 2, para 2, patient presented with severe urinary difficulties. Palpation revealed a mobile abdominopelvic tumor 10 x 15 in diameter. US and CT exhibited a cystic tumor with multiple solid elements and calcifications of the left ovary. Both patients underwent exploratory laparotomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and total omentectomy were performed in both cases, while pelvic lymphadenectomy was decided only in the second case. Histologically, in both cases the diagnosis confirmed borderline Brenner tumor. *Conclusion:* Although Brenner tumors are rare and the majority of them are benign, the correct histological diagnosis at frozen section with identification of the small proportion of malignant tumors, allows the extent of the operation to be adapted if needed.

Key words: Ovarian Brenner tumor; Borderline ovarian tumor; Ovarian cancer.

Introduction

Ovarian Brenner tumors are rare epithelial tumors that account for 1%-2% of all ovarian neoplasms. They are usually unilateral, while a bilateral appearance of Brenner tumors is reported in about 7-15% of the cases [1]. Previously they were called transitional cell tumors because of their similarity to urothelial epithelium. Proliferating Brenner tumor of the ovary was first described in 1971 by Roth and Sternberg [2]. This entity was confirmed by Miles and Norris in 1972, who referred to a similarly defined group of cases as proliferative Brenner tumors [3].

The terms of borderline malignancy and proliferating in reference to Brenner tumors were equated in the World Health Organization (WHO) publication of 1973 Histologic Typing of Ovarian Tumors [4]. It is a separate category of Brenner tumor which is intermediate in its histologic appearance and biologic aggressiveness as compared with the benign and malignant types of Brenner tumors [2, 5]. We present two cases of borderline Brenner tumors treated with surgery in our department in order to study correlations with symptoms, tumor markers, imaging findings, treatment methods, histological differential diagnosis and prognosis.

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Case Reports

The first patient, a 50-year-old gravida 1, para 1 Greek woman presented with a complaint of abnormal vaginal bleeding. She had a history of thrombocythemia and obesity, while her past surgical history was unremarkable. Physical examination of the pelvis revealed a large, mobile tumor in the right lower abdomen. CT and US of the abdomen showed a large cholelith 2.5 cm in diameter, splenomegaly, multiple uterine fibromyomas, and an almost entirely cystic tumor but with solid elements and papillary projections of the right ovary 20 x 19 x 15 cm in diameter. Preoperative CA-125 levels were within normal ranges (21.4 U/ml, nr < 35.0).

The second patient, a 70-year-old gravida 2, para 2, Greek woman presented with urine retention. She had a history of hypertension and osteoporosis, while her past surgical history was unremarkable. Physical examination of the pelvis, CT and US of the abdomen showed a large 14 x 11.5 x 10 cm, multilocular cystic tumor with multiple solid elements and calcifications of the left ovary, with synchronous dislocation of the bladder from this mass. The preoperative serum tumor markers were mildly elevated in this case (CEA 4.7 ng/ml, CA-125 40.7 U/ml, CA 19-9 108.6 U/ml).

Preoperative chest X-ray, mammography, and vaginal swab/cervical smear of both patients were negative for abnormal findings. The second patient also underwent preoperative colonoscopy and urethrocystoscopy without signs of invasion, but with signs of pressure on the bladder from the tumor.

Both patients underwent exploratory laparotomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and total omentectomy was performed in both cases, while pelvic lymphadenectomy was decided in the second case. In both cases there was no presence of ascetic fluid and there were

Fig. 1

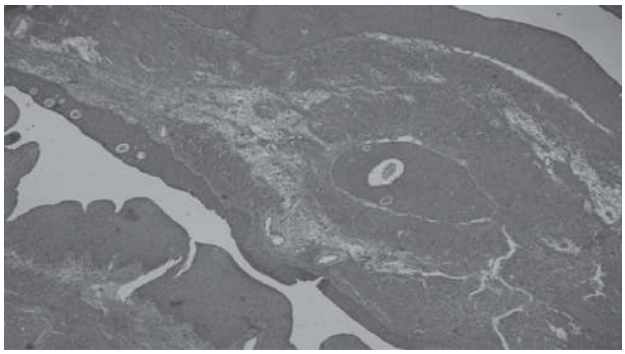

Fig. 2

Figure 1. — Cystic areas of the tumor, filled with serous fluid and gelatinous material, coexisting with solid areas of white-yellow color.
Figure 2. — HEx40 Intracystic papillary configuration composed of transitional type epithelium similar to a low-grade non invasive papillary transitional cell neoplasm of the urinary tract.

no peritoneal implants, adhesions or metastases to other abdominal organs. In both cases the peritoneal washings were negative for malignant cells.

Both patients had a normal postoperative recovery without any complications. The diagnosis of borderline Brenner ovarian tumors in both cases was established from the histopathologic examination. The gross section revealed in both cases a large, multicystic component containing a polypoid mass and foci of white-yellowish solid areas. The cysts were lined by broad papillae with fibrovascular cores covered by transitional cells resembling low-grade papillary transitional cell carcinoma of the urinary tract. In the first case tumor cells showed mild atypia, nuclear grooves and sparse mitoses while in the second one severe atypia as well as squamous and mucinous metaplasia. No invasion was demonstrated in either case. The tumor immunoprofile was positive for CK7, pankeratin, EMA, EGFR, CEA, P63 and negative for CK20, S100, Vimentin, SMA, estrogen, progesterone, CA-125, and p53. In both cases histology showed that the uterus, the contralateral ovary, omentum and the pelvic lymph nodes that were removed in the second case, were negative for malignancy.

The patients were treated with surgery only. They remain disease-free, 21 and 23 months after diagnosis and surgical treatment, respectively. Follow-up with physical examination, US of the abdomen and serum marker CA-125 is performed every six months, without signs of persistent disease or recurrence.

Discussion

The histogenesis of Brenner tumors has provoked considerable debate. Origin from granulosa cells [6], Walthard cell nests [7], rete ovarii [8], teratomas of the ovary [9], or stromal cells [10] has been proposed. However, it is now generally accepted that Brenner tumors derive directly from the epithelium of the ovarian cortex or from celomic inclusion cysts, which are formed by invaginations of the ovarian celomic epithelium [11-13].

The majority of benign Brenner tumors of the ovary occur between ages 30 and 59 years [14]. The peak incidence of borderline and malignant Brenner tumors, between ages 45 and 60 years, is older than their benign counterparts [5]. Our patients were 50 and 70 years old, respectively.

Patients with proliferative Brenner tumors usually present with abdominal masses or abnormal vaginal bleeding because of irregular estrogen synthesis [11]. One of our patients presented with abnormal vaginal bleeding, while in the other case urine retention was the main symptom. In both cases physical examination and US, CT revealed large abdominal masses. Benign Brenner tumors usually measure less than 5 cm in diameter. On the other hand borderline and malignant Brenner tumors are larger, measuring 8 to 10 cm in diameter [5, 15]. In both cases, borderline Brenner tumors were too large, measuring 20 and 14 cm in maximum diameter, respectively.

The CT appearance of Brenner tumors varies according to tumor type. Benign tumors are homogeneous, solid or unilocular cystic, borderline tumors and are usually multilocular cystic with solid elements and malignant tumors are heterogenous solid or multilocular cystic [16]. In both cases CT revealed cystic tumors with solid elements.

The gross appearance of borderline or malignant Brenner tumors differs from that of benign tumors. That is, borderline and malignant tumors are almost entirely cystic with solid papillary projections, described as mixed cystic and solid lesions, while benign are characterized by solid nodules with lobulated surfaces. Intracystic projections in benign tumors are rare, being much more common in borderline and malignant Brenner tumors.

Histologically, benign Brenner tumors have solid or microcystic epithelial cell nests surrounded by dense fibrous stroma. Borderline Brenner tumors resemble low-grade transitional carcinoma without stromal invasion, whereas malignant Brenner tumors resemble malignant invasive transitional carcinoma with stromal invasion. There is less intervening fibrous stroma in borderline and malignant Brenner tumors than in benign Brenner tumors [5].

Considering that Brenner tumors of different types

have common features it is suggested that the proliferative and malignant variants derive from their benign counterpart by cellular proliferation and malignant transformation [17]. Thus, benign Brenner tumors may be potentially malignant and must be excised completely [11, 18]. In cases of malignant Brenner tumors, the surgical procedure has to be extended as in other epithelial ovarian malignancies [19]. Thus, precise histological diagnosis at frozen section allows the extent of the operation to be adapted only if needed, in order to avoid unnecessary risky surgery as well as under-treatment of a malignant neoplasm [11].

The most important feature for distinguishing intermediate forms of Brenner tumors from malignant ones at frozen section is the presence of stromal invasion in the latter. This feature has generally been considered difficult to identify because of the fundamental fibroepithelial nature of Brenner tumors, and the fact that their stroma is derived from ovarian stroma. Even more, in proliferative Brenner tumors the degree of nuclear hyperchromatism is mild to moderate, the mitotic rate may be high, and tumor necrosis is often present [18]. Thus, these latter features are not helpful in distinguishing proliferative from malignant Brenner ovarian tumors.

In our second case the presence of tumor cells with severe atypia and the difficulty to identify the presence or abscence of stromal invasion at frozen section suggested that more extensive surgery, including pelvic lymph node sampling, was warranted. The absence of stromal invasion as well as immunohistochemistry established the diagnosis of atypical proliferative Brenner tumor at the final pathologic examination.

The prognosis of a borderline Brenner tumor is excellent. It is considered to be a tumor of very low risk for recurrence or metastases even many years after excision. Proliferative Brenner tumors presumably have a non-aggressive biologic behavior, possibly because treatment involves the complete removal of the papillary tumor which typically grows intracystically together with the involved ovary. Similar tumors in the urinary bladder, on the other hand, may persist after treatment, since the urinary bladder mucosa may give rise to new papillary tumors after their removal [18]. In one series of ten cases of borderline Brenner ovarian tumors, there was no evidence of recurrence or metastases up to eight years after excision [5, 18].

No therapy in addition to surgery is needed [20]. There is now convincing evidence in the literature that chemotherapy is indicated only for cases of serous borderline tumors associated with invasive implants [21]. Our patients were treated with surgery only and they remain well, without evidence of disease 21 and 23 months after surgery, respectively.

Conclusion

Although Brenner tumors are rare and the majority of them are benign, the correct histological diagnosis at frozen section, with identification of the small proportion of malignant tumors, allows the extent of operation to be adapted if needed. The prognosis of a borderline Brenner tumor is excellent and no adjuvant therapy is needed.

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