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Case Report

OVARIAN BRENNER TUMORS REVISITED: DO WE HAVE SPACE FOR MALIGNANT TUMORS?AND METHANOL

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Summary

We present a case of a 75-year-old female who underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy for an ovarian tumor. Hematoxylin-eosin-stained slides from tumor specimen revealed 1) focci of benign Brenner tumor; 2) mucinous cysts and 3) intracystic papillary projections resembling low-grade papillary transitional cell carcinoma (Grade 1-2) with squamous differentiation and comedo-type necrosis; 4) focal areas resembling noninvasive papillary transitional cell carcinoma Grade 3. Immunohistochemical investigation with a panel of antibodies (p63, p53, Ki-67, Wilms Tumor 1 - WT1, p16) was initiated. Areas resembling urothelial carcinoma showed diffuse nuclear positive reaction for p63 and wild-type expression of p53. Ki-67-nuclear positivity varied from less than 5% up to 30% in areas resembling high-grade urothelial carcinoma. WT1 expression was not seen. Weak but still exceeding background staining was observed in predominantly cytoplasmic fashion with few scattered positive nuclei in transitional cell nest of the benign component. No reactivity, however, was seen within the proliferative component. The histopathological diagnosis was a borderline/atypical proliferative Brenner tumor.
The patient has been regularly followed up and is at present disease-free 5 years after diagnosis. In this paper, the authors describe the morphological characteristics of Brenner tumors and address some debatable issues in the light of recent immunohistochemical and molecular studies.
Key words: borderline/atypical proliferative Brenner tumor, histology, immunohistochemistry

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Introduction

Ovarian tumors containing epithelial cells resembling histologically those of the urothelium were recognized as ovarian transitional cell tumors up to the revised 4th edition of World Health Organization (WHO) Classification of Tumors of Female Reproductive Organs, 2014 [1]. Transitional cell ovarian neoplasms accounted for 1% to 2% of all ovarian tumors and included Brenner tumors and transitional cell carcinomas. The new classification expectedly and grounded on solid body of evidence changed the concept by re-classifying transitional cell carcinomas as variants of high-grade serous and

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to a lesser extend high-grade endometrioid cancer [2-8]. Nowadays, Brenner tumors are classified as benign, borderline/atypical proliferative and malignant [1]. Most benign Brenner tumors are small and are incidentally found in oophorectomy specimens. In contrast, the borderline and malignant entities are rare and pose diagnostic challenges in routine practice.

Case Report

A 75-year-old female (menopause at age 55, gravida 3, para 1) presented with a history of progressive abdominal enlargement due to a growing mass and lower abdominal pain. Ultrasound examination showed a tumor in the region of the right ovary with heterogeneous echogenicity. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy were performed.

On gross examination, the tumor was cystic with whitish, solid, firm areas measuring 150x170 mm (Figure 1A). Some of the cystic spaces were filled with mucinous material (Figure 1B), and friable papillary masses projecting into cyst were found elsewhere (Figure 1C).

Hematoxylin-eosin-stained slides from a tumor specimen (solid areas) revealed sharply demarcated nests of transitional epithelial cells with cyst formation in a fibromatous ovarian stroma. The cells were round to polygonal with well-defined cell borders and eosinophilic to clear cytoplasm. Some nuclei had longitudinal grooves, giving the nuclei a coffee bean appearance. Cysts of variable size, lined with mucinous epithelium and small areas of spiculated calcification were present. Intracystic papillary projections on microscopic examination resembled low-grade papillary transitional cell carcinoma (Grade 1-2) with squamous differentiation and comedo-type necrosis (Figure 1 D, E). Some areas resembled noninvasive papillary transitional cell carcinoma

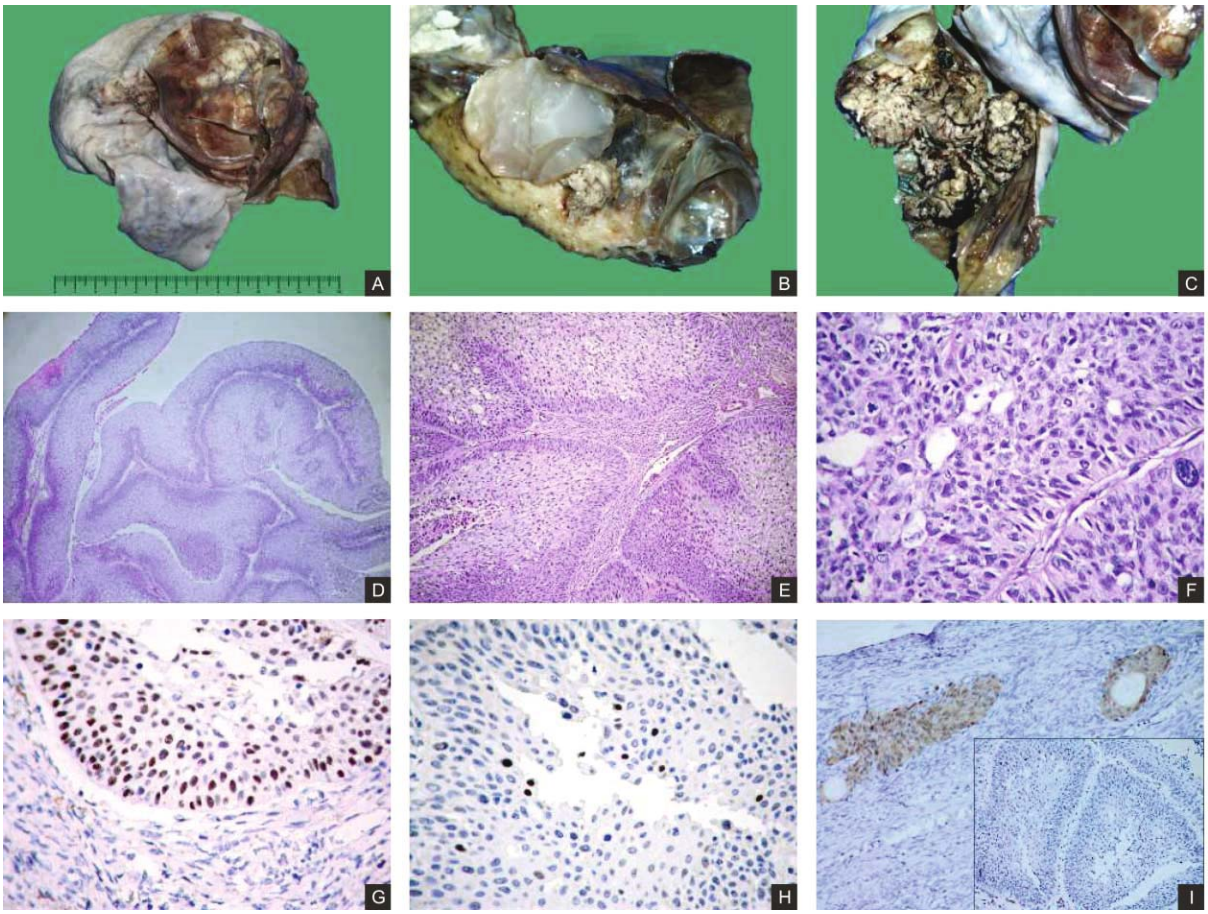

Figure 1. A, B, C – gross specimen. D, E, F – Hematoxylin-eosin-stained areas from proliferative component. G, H, I – immunohistochemical expression of p63, p53 and p16, respectively

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Grade 3 (Figure 1 F). Unequivocal stromal invasion was absent. The mitotic rate was heterogeneous, with some spots reaching up to 15 mitotic figures per 10 high power fields.

Other pathological findings from histological examination of the left ovary, left fallopian tube and uterus included corpora albicantia, severe fibrosis of the tubal plicae, intramural uterine leiomyoma with focal hyalinization, and non-atypical endometrial hyperplasia with partial cystic dilation of glands.

Immunohistochemical investigation was initiated in an attempt to confirm the tumor histogenesis and possibly predict malignant potential. The panel of antibodies utilized included: p63, p53, Ki-67, Wilms Tumor 1 (WT1). Areas resembling urothelial carcinoma showed nuclear positive reaction for p63 in 75% of the tumor cells (Figure 1G), and wild-type expression of p53 (less than 5% of the tumor cells were positive, Figure 1 H). Ki-67-nuclear positivity varied from less than 5% in areas with mucinous or squamous differentiation up to 30% in areas resembling high-grade urothelial carcinoma. WT1 expression was not seen.

Additional immunohistochemical search for p16 was inspired by the findings of Kuhn et al. [9] in a recent publication. Weak but still exceeding background staining was observed in a predominantly cytoplasmic fashion with few scattered positive nuclei in a transitional cell nest of the benign component (Figure 1I). No reactivity, however, was seen within the proliferative component (Figure 1I inset).

The original histopathological diagnosis was Brenner tumor of a low malignant potential, now re-classified as borderline/atypical proliferative Brenner tumor.

The patient has been regularly followed up and is at present disease-free 5 years after diagnosis.

Discussion

The first Brenner-like tumor was reported in 1898 by MacNaughton-Jones [10], and it was not until 1907 that Fritz Brenner detailed the description of the tumor and was credited the legacy of the tumor name [11]. Malignant transformation of the Brenner tumor first emerged in scientific publication authored by von Numers in 1945 [12]. Three decades later, a new category of Brenner tumor with features, intermediate between typical benign and malignant appeared, reported by Roth and Sternberg in 1971 [13]. Soon after, Halgrímsson and Scully introduced "borderline Brenner tumor" for a broader category of Brenner tumors and considered proliferating ones as a subcategory of the former [14]. In 1985, Roth et al. reviewed 14 unusual Brenner tumors, defying strict categorization as benign or malignant and proposed a 3-tier classification scheme of borderline cases, reflecting progressive epithelial abnormalities [15]. These included tumors that are metaplastic, proliferating, and of low malignant potential. Each of these categories corresponds to a particular urothelial abnormality or neoplasm.

The typical benign Brenner tumor has its corresponding urinary tract epithelial lesion known as Von Brunn cell nests.

What was earlier considered metaplastic Brenner tumor has shown an exuberant degree of cyst formation on gross and microscopic examination, accompanied by prominent mucinous metaplasia, often with a complex glandular pattern [15]. Nuclear atypia is not present; the corresponding urinary tract epithelial lesion is cystitis glandularis. Additionally, the difference between metaplastic variant and Brenner tumors with associated mucinous cystadenoma is stressed. Focci of typical Brenner tumor may be present, but are not a prerequisite for the diagnosis. Papillary fronds characteristic of proliferating Brenner tumors are not seen.

Proliferating Brenner tumor, as originally described by Roth et al., features an unusual degree of epithelial proliferation and morphologically resembles low-grade (Grade 1-2) papillary urothelial carcinoma, as hosted in the urinary bladder [15]. The papillary tumor tends to grow within cystic spaces, and the epithelial component is noninvasive. Focal necrosis is common. A typical Brenner tumor is always present in adjacent areas, but the amount may be small and its identification at the time was not considered essential for the diagnosis.

A Brenner tumor of low malignant potential was similar to proliferating Brenner tumors, but some areas displayed nuclear atypia greater than in proliferating Brenner tumors and mirrored the noninvasive high-grade papillary transitional carcinoma of the urinary bladder (Grade 3) or squamous cell carcinoma in situ. Areas of proliferating, metaplastic and/or typical benign Brenner tumor should invariantly be present, according to Roth et al. [15].

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The case presented in this paper fulfills all of these histological criteria. The differential diagnosis with malignant Brenner tumor is based solely on the absence of stromal invasion. Stromal invasion is not as easy to interpret as it may seem since it may look like irregularities of epithelial nests, some degree of confluence with depletion of stroma, at times with large, crowded epithelial masses, and occasionally accompanied by desmoplastic stromal reaction [16]. Again, Roth et al., based on a modest number of 9 malignant cases, further elaborated and introduced slightly perplexing subtypes malignant Brenner tumors that corresponded to urinary tract epithelial lesion as invasive transitional cell carcinoma - low-grade in well differentiated malignant Brenner tumors, and high-grade transitional, invasive squamous cell or undifferentiated carcinoma in poorly differentiated ones [16].

The 4th edition of WHO Classification of Tumors of Female Reproductive Organs reduced all of above categories, based mainly on long-term survival data, reflecting benign behavior and collapsed the previous multitude of diagnoses into only three categories: benign, borderline/atypical proliferative and malignant Brenner tumors [1]. Transitional cell carcinomas of the ovary are no longer considered as a separate entity, though they were the most common and debated transitional cell ovarian tumors in the literature [2-3, 5-6]. The number of papers dealing with malignant Brenner tumors does not exceed 16 [2], accessible to the authors, and is obviously disproportionate relating to transitional cell ovarian carcinomas [5]. All current research employing new diagnostic modalities report 1 to 6 malignant Brenner tumors [6-8], the most recent one from 2014, included benign and borderline cases but not even a single malignant tumor [9]. As a consequence, we are now aware of the immunohistochemical profile of the former 2 categories (particularly p63 positivity) and it is consistent with true urothelial differentiation, which may not hold true regarding malignant Brenner tumors: in a single study by Liao et al. 2007 only one case out of six was reported positive [6]. Three contemporary studies address the p16 expression in Brenner tumors, yielding confusing results [7-9]. Still, the three papers are in agreement concerning the absence of p16 staining within the borderline group and the total of just 2 cases, originally diagnosed as malignant Brenner are p16 uniformly deficient [7-8]. It is the benign group that raises some discrepancies - Cuatrecasas et al. report significantly low to absent expression in benign tumors [7], while Ali et al. [8] and Kuhn et al. [9] found any type and level of expression in almost all (3/3 and 12/13) of the studied benign Brenner tumors. In the latter study, 2 out of 5 borderline cases that contained a benign component were focal positive in the benign tumor [9]. Our case shares the same expression profile, lacking any positivity throughout the proliferative component and positivity, though low, confined to the benign tumor tissue. In our opinion, p16 can be cautiously used as a potential marker to differentiate benign and atypical proliferations, but at present there is no enough evidence to support the use any immunohistochemical marker to differentiate borderline and malignant ones. The malignant group is obviously underrepresented in all studies and further observations are warranted to clarify the histological, immunohistochemical and molecular characteristics of these neoplasms and carefully correlated with clinical data based on long-term follow-up and outcomes. To the authors knowledge, not a single fatality was ever recorded within the borderline group, illustrated again by the long survival of our case. A few attempts were made to elucidate the molecular basis of benign-to-malignant transformation [7, 9]. Candidate genes, to name a few, so far are PIK3CA, KRAS and CDKN2A, but this could hardly be considered an exhaustive list and paves the way to placing these tumors in the more favorable group I ovarian cancers [17].

The histogenetic origin of ovarian Brenner tumors is still a matter of debate. Although the ovarian surface epithelium used to be viewed as the likely origin of Brenner tumors, more temptative is the recognition of Walthard cell nests as a precursor lesion [17-19]. The frequent co-existence of Brenner tumors and mucinous tumors has been well documented [19], partly explained with the notoriety of transitional epithelium for undergoing metaplasic changes to divergent epithelial populations, including mucinous ones [20]. This explores the possibility that mucinous and Brenner tumors share same origins from microscopic transitional cell nests at the tubal-mesothelial junction, named Walthard nests. When the mucinous component is established, it overgrows the diminishing transitional component, and the latter component frequently becomes occult. A genetic study found amplification of chromosome region 12q14-21

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in both a mucinous carcinoma and an associated Brenner tumor, suggesting a clonal relationship [21]. Additional molecular genetic studies, including next-generation techniques are necessary to prove or change the validity of this hypothesis.

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