Case Report

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A case of a vaginal Brenner tumor without a gland mimicking a borderline tumor: unusual morphology and diagnostic pitfalls

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Abstract

Brenner tumor is a rare neoplasm of the vagina. This tumor is diagnosed according to the criteria of ovarian tumors. We report here a 64-year-old postmenopausal woman with a 2.0-cm sessile vaginal polyp for 9 years. Microscopic examination showed unusual features of no gland appearing in the tumor, but the other two characteristic components of transitional islands and dense fibrous stroma were observed. The tumor was diagnosed as a vaginal Brenner tumor on the basis of the definition proposed by the World Health Organization classification of female reproductive organ tumors. In our case, part of the epithelial nests of the Brenner tumor showed basaloid cell differentiation with peripheral palisading, and irregular papillary hyperplasia was observed around the epithelial nests similar to a borderline tumor. However, no mitotic activity or nuclear atypia was present in either the epithelial or stromal components. The presence of epithelial nests requires attention in the medical history of the patient. Our patient did not have a history of primary urothelial carcinoma. Our patient's benign vaginal Brenner tumor with different morphological characteristics supports the current notion that Walthard nests might act as possible precursor lesions.

Keywords

Vaginal Brenner tumor, gland, borderline tumor, Walthard nest, squamous polyp, ovary

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Introduction

Brenner tumor is a rare primary tumor of the ovary and is an epithelial-derived tumor.[1] The diagnostic criteria and differentiation between benign, borderline, and malignant tumors remain problematic, causing confusion. Brenner tumor outside the ovary, such as in the vagina, is rarely seen, increasing the difficulty of diagnosis. Brenner tumor is defined as a tumor that consists of nests of bland, transitional-type cells (resembling urothelial cells) within a fibromatous stroma according to the World Health Organization classification of tumors of female reproductive organs (2014), instead of the usual three features of transitional islands, a gland, and a dense fibrous stroma.[2,3] Therefore, the diagnostic criterion of a vaginal Brenner tumor should consist of the above-mentioned two pathological characteristics. A borderline Brenner tumor is defined as displaying epithelial proliferation beyond that found in a benign Brenner tumor, but lacking stromal invasion.[4,5] The degree of differentiation of borderline tumors is between benign and malignant, and therefore, diagnosis of these tumors remains difficult. Attention should be paid to the differential diagnosis between a borderline tumor and a benign or malignant tumor. We report here a case of a benign vaginal Brenner tumor with a controversial morphological structure.

Case report

Patient

A 64-year-old women with a history of a vaginal mass for 9 years showed swelling 2 months before hospital admission without causing any discomfort on a gynecological examination. A pelvic examination showed that the mass was $2.0 \times 1.5 \times 0.5$ cm and arose from the vaginal wall. No bleeding or infection was noted. The lesion was excised under general anesthesia with no other complications. The patient was followed up for 3 months with no recurrence.

Pathology

The excised specimen was a solid mass that was $1.5 \times 1.5 \times 0.5$ cm with a smooth external surface. The cut surface was white-tan with minute cystic spaces.

Microscopically, the surface was lined by normal squamous epithelium and underlying numerous irregular epithelial nests that were embedded in a fibroid stroma (Figure 1a). The epithelial nests were similar to that of transitional epithelium with a clear or eosinophilic granular cytoplasm and oval in shape, with frequently grooved nuclei (Figure 1b). Some epithelial nests showed cystic spaces with a pink amorphous secretion. A few nests showed basaloid cell differentiation with peripheral palisading. There were small cysts in the center of the transitional nests that were lined by flat attenuated epithelia (Figure 1c). Occasional budding and irregular papillary hyperplasia were observed around the epithelial nests (Figure 1d). However, no gland was found in the whole tumor area. No mitotic activity or nuclear atypia was present in either the epithelial or stromal components.

Immunohistochemical staining of p63, cytokeratin-7, cytokeratin-20, CD34, prostate-specific antigen, vimentin (Shanghai Jiehao Biotechnology, Ltd., Shanghai, China), GATA binding protein 3 (GATA-3), p16, PAX-8, Ki-67, (Ascend Biotechnology Co., Ltd., Guangzhou, China), estrogen receptor (ER), and progesterone receptor (PR) (Roche Diagnostics, Shanghai, China) was performed according to the manufacturers' instructions. Briefly, 4 μm of formalin-fixed, paraffin-embedded tissue blocks were deparaffinized and then placed into the Ventana Medical Systems (Roche Diagnostics Ltd., Basel, Switzerland). The epithelial tumor

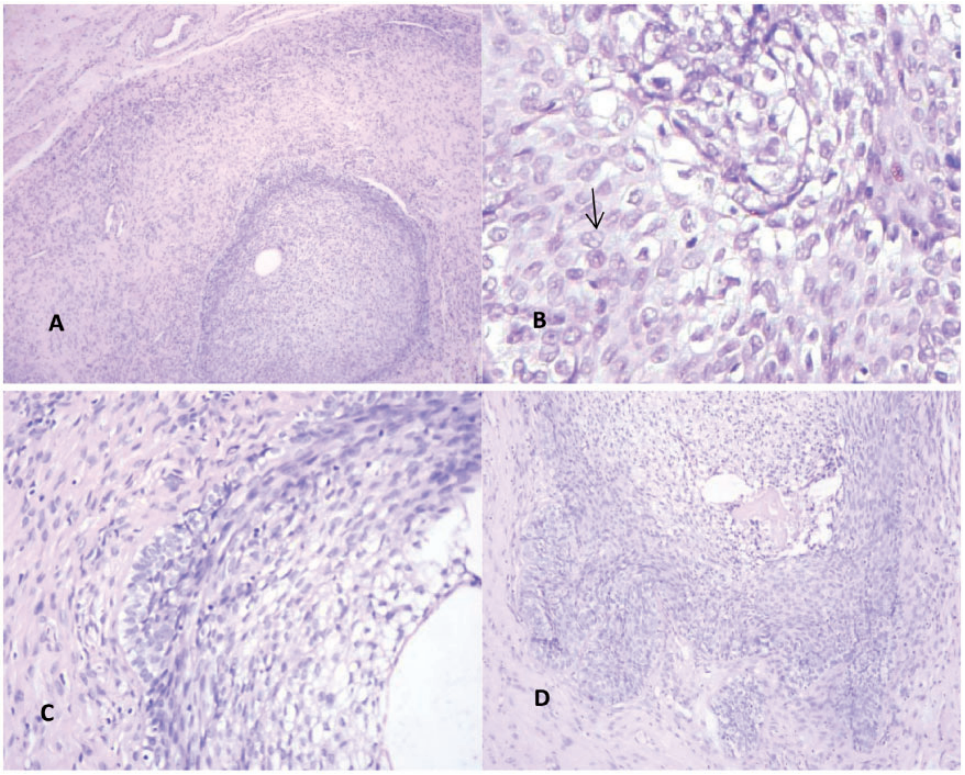

Figure 1. Microscopic features of a vaginal Brenner tumor. (a) Low-power view shows a classic Brenner tumor with solid and cystic epithelial nests with secretion and a fibroid stroma (hematoxylin and eosin, ×40). (b) Urothelial cells with a clear to eosinophilic cytoplasm and scattered grooved nuclei (arrow) can be seen (hematoxylin and eosin, ×400). (c) Part of the nests show basaloid cell differentiation with peripheral palisading. The cyst is lined with flat attenuated epithelium (hematoxylin and eosin, ×200). (d) Occasional budding and irregular papillary hyperplasia can be seen around the epithelial nests (hematoxylin and eosin, ×100).

component was immunoreactive with GATA-3, p63, cytokeratin-7, and ER (Figure 2a–d). The stromal component was immunoreactive with vimentin, ER, and PR. Ki-67 immunoreactivity was observed in <5% of tumor cells. No immunoreactivity was observed with cytokeratin-20, prostate-specific antigen, p16, and PAX-8.

Discussion

Our case is the seventh case among all vaginal Brenner tumor cases in the English literature to date (Table 1). The age and clinical characteristics of our case are consistent with those of previous reports.[2,3,6–8] These tumors are usually found in postmenopausal women and are often small and present with no symptoms. The morphological features of vaginal Brenner tumors are similar to those of ovarian tumors. However, our case did not have a small gland and squamous cell metaplasia of the epithelial nests. Whether these two features are related to a long history requires further study.

The diagnosis of Brenner tumor mainly involves a mixed epithelial–stromal tumor

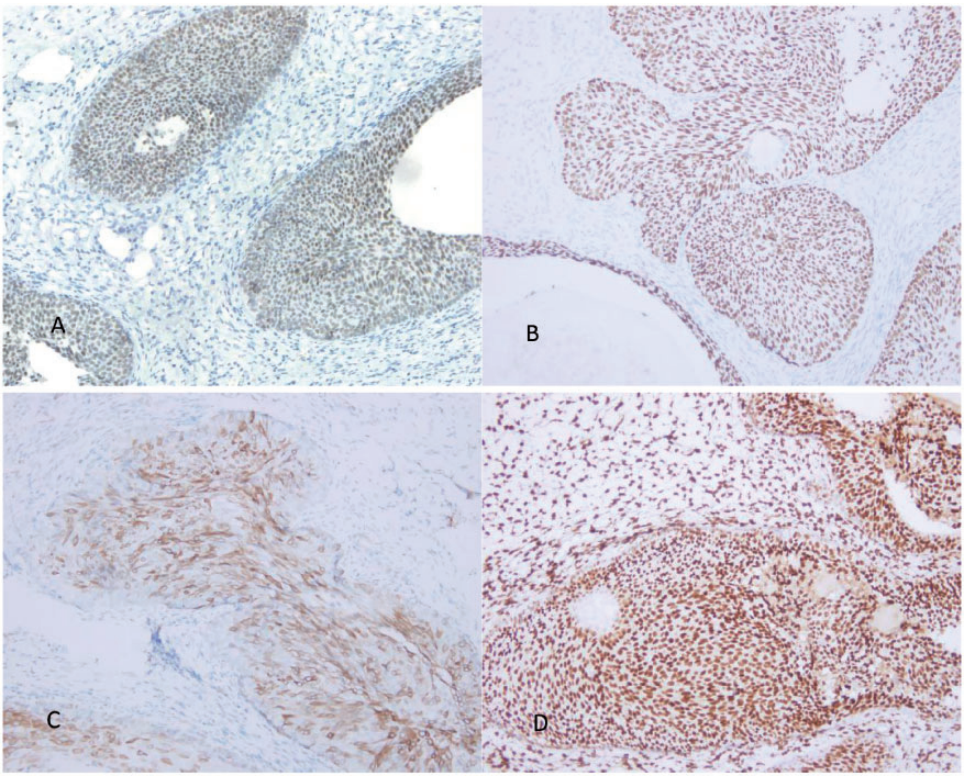

Figure 2. Immunohistochemistry findings. (a) Epithelial tumor cells are diffusely positive for GATA binding protein 3 (×100). (b) Epithelial tumor cells are diffusely positive for p63 (×100). (c) Epithelial tumor cells are positive for cytokeratin-7 (×100). (d) Epithelial tumor cells and stromal components are reactive to estrogen receptor immunostaining (×100).

and part of the tubulosquamous polyps of the vagina, and the diagnosis depends on whether these are real squamous nests. Mixed epithelial–stromal tumors always occur in younger women with a mean age of 30 years.[7] The epithelial component of Brenner tumor consists of squamous and mucinous glands, rather than urothelial-type islands, and involves stroma-type spindle cells, which have a more cellular stroma containing cytokeratin-reactive cells. These tumors are also positive for CD34, ER, PR, and CD10.[5,8] Tubulosquamous polyps include well-circumscribed nests of epithelial cells, mainly of the squamous type, with a central-bland appearance, round nuclei, and an abundant eosinophilic or clear cytoplasm. Tubulosquamous polyps consist of small tubules that are usually located at the periphery of the nests or completely surrounded by a paucicellular stroma.[9] Prostatic-type tissue can be found in the polyps, and glandular tissue is always positive for prostatic-specific antigen.[10,11]

An important characteristic of borderline Brenner tumors of the ovary is that areas of atypia coexist with benign components, but without stromal invasion. Cytological findings that confirm a Brenner tumor as proliferative or borderline are as follows: mucinous or squamous metaplasia in the transitional epithelium, the presence of small papillary processes, complex glandular formation, and nuclear

Table 1. Clinical features of vaginal Brenner tumors.

References	Age (years)	Symptoms	Size	Concomitant lesion	Location in the vagina	Origin	IHC	Histopathology
Chen, 1981[6]	67	None	1.5	None	Mid third	Müllerian	None	Unclear
Rashid and Fox, 1995[7]	77	Irritation and soreness	2.0	None	Not exact	Wolffian or Müllerian	None	Transitional, glandular, and stromal
Ben-Izhak et al., 1998[8]	68	None	1.2	Uterine leiomyoma	Upper third	Müllerian	None	Nests of transitional epithelium with a cellular fibrous stroma
Ben-Izhak et al., 1998[8]	72	Bleeding	NA	Endometrial carcinoma	Mid third	Müllerian	None	
Shaco-Levy and Benharroch, 2013[2]	84	Irritation	2.0	None	Lower third	Müllerian	CK7(+) CK20(−) p63(+) ER(+)	Urothelial islands, glands, and fibrous stroma
Park and Cho, 2017[3]	76	None	2.5	Rectal adenocarcinoma	Not exact	Wolffian	GATA-3(+) p63(+) ER(+) PAX-8(−)	Transitional islands, glands, and dense fibrous stroma
Current case, 2019	64	None	2.0	None	Lower third	Wolffian	GATA-3(+) p63(+) ER(+) PAX-8(−) CK7(+) CK20(−) PSA(−)	Transitional islands and dense fibrous stroma. Stroma without glands. Occasional budding and irregular papillary hyperplasia around epithelial nests.

IHC: immunohistochemistry; CK: cytokeratin; ER: estrogen receptor; GATA-3: GATA binding protein 3; PSA: prostate-specific antigen.

atypia, including hyperchromatic nuclei, coarse chromatin clumping, prominent nucleoli, and increased mitotic activity.[12–14] In conclusion, the presence of characteristic epithelial nests, a fibromatous stroma, and marked cytological metaplasia without atypia provides important evidence for correct diagnosis of a benign tumor. The other differential diagnosis includes metastatic urothelial carcinoma, especially for budding and irregular papillary hyperplasia and epithelial nests. Therefore, epithelial cell dysplasia and the medical and family history should be focused on in diagnosis. This could be a challenge for an inexperienced pathologist.

The origin of vaginal Brenner tumors was considered to be Müllerian until a report by Park and Cho.[3] In a previous case,[2] urothelial islands expressed cytokeratin-7, ER, and p63, but lacked cytokeratin-20 and PAX-8, supporting the assumption that they were of Müllerian origin. However, Park and Cho[3] suggested that Walthard nests act as possible precursor lesions or the initial step of Brenner tumor formation because of GATA-3-positive findings. Walthard nests are mainly positive for GATA-3 and negative for other markers, except for focal expression of PAX-8 in the basal cells of some groups of Walthard nests and transitional metaplasia.[15] Transitional cell metaplasia resembles Walthard nests because of bland nuclei, longitudinal grooves, and urothelial-type differentiation, but transitional cell metaplasia is generally smaller than Walthard nests.[16] Transitional cell metaplasia is thought to be the probable source of Walthard nests, but the relationship between transitional cell metaplasia and Walthard nests still remains unclear. The immunophenotype and histopathological characteristics of vaginal Brenner tumors are similar to those of ovarian Brenner tumors. However, vaginal Brenner tumors need to be further studied in the future because of the small number of cases.

Authors' contributions

Qin Zhang and Can Tian were involved in data collection. Chuan-shan Zhang organized the discussion of diagnosis of the case. All authors participated in writing the manuscript. All authors approved the final manuscript.

Consent

The patient gave consent for publication of this report and accompanying images.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics

Our research was approved by the Ethics Committee of Tianjin Third Central Hospital, Tianjin, China.

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