Malaysian J Pathol 2017; 39(1) : 89 – 93

CASE REPORT

Vaginal Brenner tumor with literature review: does this tumour originate from Walthard nests?

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Abstract

Vaginal Brenner tumor is extremely rare. Only five cases have been reported in the English literature to date. Here we report a vaginal Brenner tumor in a 76-year old postmenopausal woman, who presented with a 2.5cm-sized sessile vaginal polyp. Microscopically, it showed characteristic features of Brenner tumor consisting of three components; transitional islands, glands, and dense fibrous stroma. The epithelial tumor cells were positive for GATA-3, p63 and ER, but negative for PAX8. The origin of Brenner tumors in the vagina is unclear, but previous reports suggested of Müllerian origin. However, our case revealed that vaginal Walthard nests could be possible precursor lesions based on their immunohistochemical staining results.

Keywords: Brenner tumour, vagina, Walthard nest

INTRODUCTION

Brenner tumours (BTs) are composed of epithelial cell nests, similar to urothelial epithelium surrounded by dense fibromatous stroma. It is believed that BTs originate from ovarian surface epithelium through transitional cell metaplasia (TCM), but other theories have been proposed as to their origin. Walthard nests (WNs), teratomas, and fallopian tube epithelium have been suggested as other origin sites because BTs do not show a Müllerian phenotype.[1-4] BTs and most WNs do not stain for the Müllerian marker PAX8, therefore, a probable link between BTs and WNs has been suggested because of similar morphology and immunoprofile.[2]

Extraovarian BTs are extremely rare. They can arise in the broad ligament,[5-8] uterus[9] and testicular and paratesticular tissues.[10-14] In the English literature, only five vaginal BT cases have been reported, and most reports suggested that vaginal BTs arose from TCM within the Müllerian epithelium.[15-18] However, evidence of a Müllerian origin is not compelling because the vaginal BT immunoprofile is not known yet.

Here, we report a rare case of vaginal BT with literature review with emphasis on immunohistochemical results, suggesting a WN origin.

CASE REPORT

Clinical course

A 76-year-old woman was admitted for rectal adenocarcinoma surgery and was found to have an asymptomatic vaginal polyp during a routine gynecologic examination before surgery. A 2.5 cm sessile vaginal polyp was resected during low anterior resection. No disease was seen during a seven-month follow-up period.

Pathologic findings

The excised specimen was a smooth-surfaced polyp, measuring 2.5 cm (Fig. 1A). The tumour was covered by vaginal mucosa (Fig. 1B, arrow), relatively well-circumscribed, and comprised of variably-sized epithelial nests surrounded by dense, hyalinized fibromatous stroma (Fig. 1B). Some epithelial nests showed cystic spaces with a pink amorphous secretion (Fig. 1B). Most epithelial cell nests showed urothelial-like epithelium with clear, pink, or granular cytoplasm. This cytoplasm showed elongated nuclei with frequent nuclear grooves (Fig. 1C). The fibromatous stroma showed a higher cellularity compared to non-neoplastic vaginal subepithelial stroma, with peritumoral stromal cell accentuation (Figs. 1B-C). No mitotic figures or significant nuclear atypia were noted.

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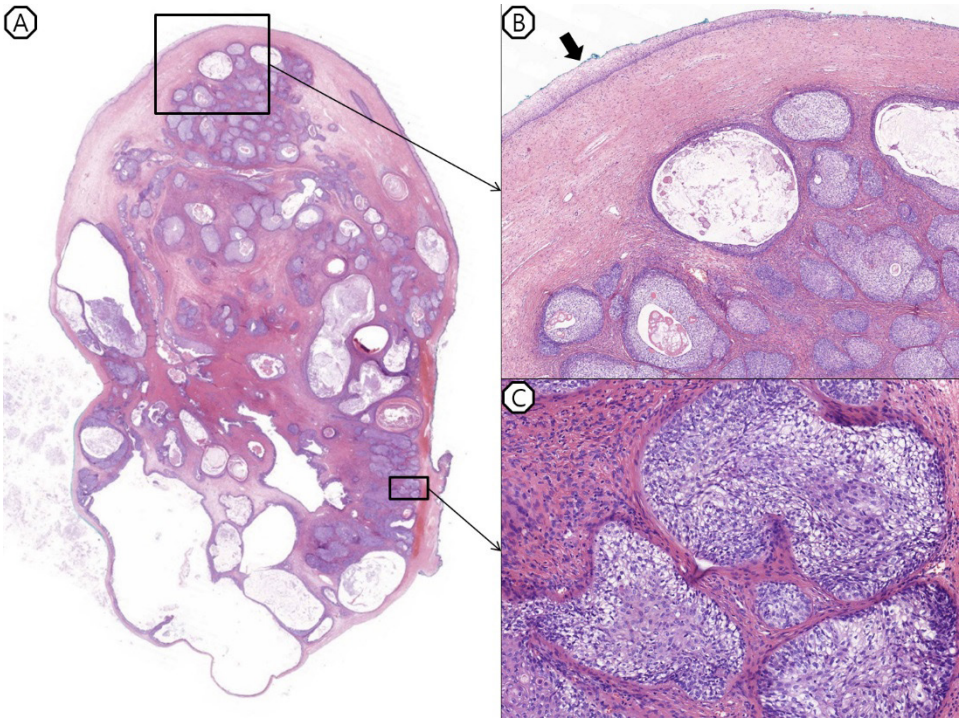

FIG. 1: Microscopical features of vaginal Brenner tumour. (A) A scanning image shows a relatively well-defined solid and cystic tumour. (B) Low-power view shows a classic Brenner tumour with overlying vaginal mucosa (arrow) and epithelial nests that are solid and cystic with secretion (HE, x52). (C) High-power imaging reveals solid epithelial nests with clear or eosinophilic cytoplasm surrounded by dense fibromatous stroma (HE, x200)

Immunohistochemistry

Immunohistochemical stains of formalin-fixed paraffin-embedded sections were performed by Bond Max Autostainer (Leica Biosystems, Melbourne, Australia) and Ventana autostainer using an Ultra View DAB procedure, Benchmark ULTRA IHC staining module from Ventana (Tucson, Arizona). The following antibodies were used: GATA-3 (1:100; Cell Marque, Corp, Rocklin, CA), p63 (1:100; Novocastra, Newcastle, UK), ER (prediluted; Ventana, Benchmark XT immunohistochemistry), and PAX8 (1:100; Cell Marque Corp, Rocklin, CA).

Epithelial tumour cells were positive for GATA-3, p63 and ER (Figs. 2A-C), but negative for PAX8 (Fig. 2D).

DISCUSSION

In this report, a rare vaginal BT case is presented. The clinicopathological data of the case presented here and of the previously reported cases are summarized in Table 1. Two patients presented with irritation or soreness, and one with vaginal bleeding, while the tumour was found incidentally in three patients. Patient ages ranged from 67 to 84 years (mean, 74 years), and tumour sizes ranged from 1.2 to 2.5 cm (mean 1.84 cm). Follow-up was available for five patients, in whom there was no evidence of disease. In three patients, concomitant tumours were identified. One patient had a uterine leiomyoma, one had an endometrial carcinoma, and one had rectal cancer. Immunohistochemistry was available for only two cases including the present case. Tumour cells were positive for CK7, p63, ER, GATA-3, but negative for CK20 and PAX8.

The differential diagnosis includes tubulosquamous polyp of the vagina. This shows enough histological and immunohistochemical similarities. Tubulosquamous polyp has expansile nests of epithelial cells, mainly of squamous type, with central bland round nuclei and abundant eosinophilic or clear cytoplasm, containing small tubules located usually at the periphery of the nests or completely surrounded by a paucicellular stroma.[19] On the contrary, the predominant epithelium was interpreted as transitional rather than squamous type in cases of BT of the vagina.[20] Tubulosquamous polyp of the vagina revealed diffuse expression of GATA-

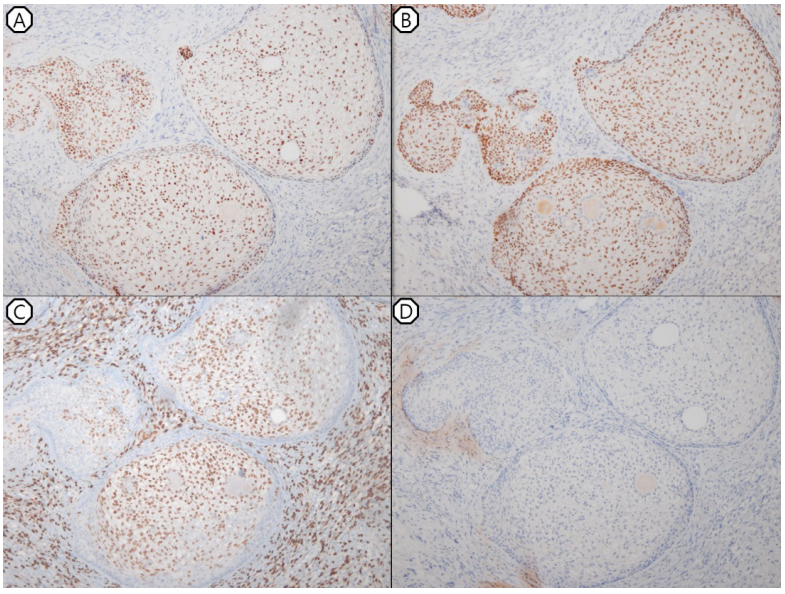

FIG. 2: Immunohistochemistry. (A) Epithelial tumour cells are diffusely positive for GATA-3 (x100). (B) Epithelial tumour cells are diffusely positive for p63 (x100). (C) Epithelial tumour cells and surrounding stromal cells are positive for ER (x100). (D) Epithelial tumour cells are negative for PAX8

TABLE 1: Cases of vaginal Brenner tumour

References	Age	Symptoms	Findings on clinical exam	Size (cm)	Follow-up (years)	Concomitant tumours	Suggested origin	IHC
Case 1 (Chen, 1981)[16]	67	None	Polyp	1.5	NED (7)	None	Müllerian	None
Case 2 (Rashid and Fox, 1995)[17]	77	Irritation and soreness	Polyp	2.0	NED (1.5)	None	Wolffian or Müllerian	None
Case 3 (Ben-Izhak *et al*, 1998)[15]	68	None	Polyp	1.2	NED (4)	Uterine leiomyoma	Müllerian (TCM)	None
Case 4 (Ben-Izhak *et al*, 1998)[15]	72	Bleeding	Polyp	NA	NA	Endometrial carcinoma	Müllerian (TCM)	None
Case 5 (Shaco-Levy and Benharroch, 2013)[18]	84	Irritation	Polyp	2.0	NED (0.5)	None	Müllerian (TCM)	CK7(+) p63(+) ER(+) CK20(-)
Case 6 (Present case, 2016)	76	None	Polyp	2.5	NED (7)	Rectal adenocarcinoma	Walthard nests	GATA3(+) p63(+) ER(+) PAX8(-)

Abbreviation: NED, no evidence of disease; TCM, transitional cell metaplasia; IHC, immunohistochemistry; CK, cytokeratin; ER, estrogen receptor; GATA-3, GATA binding protein 3; PAX-8, paired box 8

3, but negative staining for PAX8,[20] as seen in our case. Therefore, histological findings rather than immunostains would be more helpful for differential diagnosis.

Ovarian BT origin was suggested to be TCM or WNs.[1,2] However, vaginal BT origin was not clear due to a lack of cases. Previous reports have suggested a vaginal origin for BTs through TCM.[15-18] Egan *et al* demonstrated TCM distribution in the uterine cervix including the endocervical canal, transformation zone, native ectocervix, and vagina.[21] Outside the urinary tract, this type of epithelium (TCM) appears to be a potential carcinogenesis site.[22] TCM resembled WNs because the cells were identical to WNs with bland nuclei, often showing longitudinal grooves and urothelial-type differentiation, but TCM were generally smaller than WNs.[1] The relationship between TCM and WNs is not clear, but TCM has been thought to be the probable WN source.[22] However, the immunohistochemical profile is slightly different between TCM and WNs. PAX8 (a Müllerian-lineage marker) showed significantly decreased expression in WNs compared to TCM (7% vs. 40%).[1,2] Even in PAX8-positive WN cases, it was expressed mostly at transitional nest peripheries, as well as at the basal epithelium.[2] In ovarian benign and atypical proliferative BTs, PAX8 was negative in all recent studies.[1,2] WN focal and basal expression with PAX8 and complete loss in BTs suggest that WNs rather than TCM could be possible precursor lesions or initial steps to BT formation.[2]

In Egan's study, higher TCM patient mean age and the observation that over 80% of patients were postmenopausal suggest that an altered hormonal environment of the cervicovaginal mucosa was an important contributing factor.[21] In another study, a role of androgenic stimulation in BT pathogenesis was proposed based on immunohistochemical staining patterns.[1] In transsexual women, following androgen therapy, the vaginal mucosa showed histologic changes similar to TCM.[23] The mean age of six patients with vaginal BTs was 74 years (range 67 to 84), and all were postmenopausal. We hypothesize that vaginal BTs arise from WNs in cervicovaginal mucosa influenced by postmenopausal androgenic stimulation.

Conclusion

We report a sixth vaginal BT case with emphasis on its origin. Vaginal BTs usually present with a vaginal polyp and are often asymptomatic in postmenopausal elderly women. The origin is uncertain, but WNs could be possible precursor lesions based on their immunohistochemical staining pattern.

ACKNOWLEDGEMENT

Conflict of interest: The authors have no potential conflicts of interest to disclose. *Source of Funding*: This study was supported by intramural research promotion grants from Ewha Womans University School of Medicine.

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