*The Korean Journal of Pathology 2011; 45: 223-226*
*DOI: 10.4132/KoreanJPathol.2011.45.2.223*

# Cytologic Distinctive Features of Brenner Tumor

**Jung-Sik Jang · An Na Seo**
**Seon Jae Lee · Ji-Young Park**

Department of Pathology, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu, Korea

**Received:** June 22, 2010
**Accepted:** March 15, 2011

**Corresponding Author**
Ji-Young Park, M.D.
Department of Pathology, Kyungpook National University Hospital, Dongin-dong 2-ga, Jung-gu, Daegu 700-422, Korea
Tel: +82-53-420-5247
Fax: +82-53-426-1525
E-mail: jyparkmd@knu.ac.kr

Herein, we present two cases of Brenner tumor, a rarely occurring neoplasm in the ovaries, obtained via intraoperative fine needle aspiration. The borderline Brenner tumor exhibited marked squamous metaplasia, characterized by individually distributed atypical squamous cells. A benign Brenner tumor associated with mucinous cystadenoma evidenced typical mucinous metaplastic features and transitional foci. These distinctive features may prove helpful in differential diagnosis of varied ovarian tumors, and particularly for intraoperative consultation.

**Key Words:** Ovary; Cytology; Brenner tumor; Cystadenoma, mucinous

Ovarian Brenner tumors are an uncommon epithelial tumor, accounting for 1.5% to 2.5% of all ovarian neoplasms; only 3-5% of Brenner tumors are borderline malignant. The histologic features of those cases were relatively well established, but the cytologic features were not. We experienced two cases of Brenner tumor obtained via intraoperative fine needle aspiration. One was a borderline Brenner tumor with marked squamous metaplasia, and the other was a benign Brenner tumor associated with mucinous cystadenoma. Evaluating the cytologic features of Brenner tumor will aid in improving the accuracy and efficiency of the differential diagnosis of ovarian tumors during intraoperative consultation.

## CASE REPORTS

### Case 1

A 51-year-old female suffered from dull lower abdominal pain and distention. Abdominal ultrasonogaphy revealed a 17.5 cm-sized multilobular cyst, with multiple septation and hyperechoic mural nodules. Upon abdomen-pelvic computed tomography, the 19×16 cm-sized huge cystic mass was located in the lower abdomen and pelvic cavity. The mass had an irregular wall and evidenced septal thickening with an enhancing solid component; it was initially regarded as an ovarian malignancy. In the peritoneum, mild thickness was also detected. The cancer antigen-125 level was elevated to 35.94 U/mL (normal, <35 U/mL) and the carcinoembryonic antigen level was within normal limits. A bilateral salpingo-oophorectomy and intraoperative fine needle aspiration of ovary was conducted. The aspirated material was directly smeared onto glass slides and fixed for 20 minutes in 95% ethanol, then stained via the Papanicolaou method.

#### Cytologic findings

The epithelial tumor cells were arranged in a sheet-like formation or as single cells on a clear background without hemorrhage or necrosis. The cytoplasm was pale or clear, and the cytoplasmic border was distinct, resulting in a honeycomb-like appearance in some of the nest. The nuclei were round or oval-shaped with fine chromatin and one or more conspicuous nucleoli (Fig. 1A). Some of the epithelial cells contained grooved nuclei with a 'coffee-bean' appearance. These epithelial nests were regarded as transitional cell epithelium. One notable feature was an abundance of individual keratinized squamoid cells mingled with the tumor nest or individual tumor cells. The cytoplasm was deeply orangeophilic, and evidenced an oval to caudate mor-

phology. The nuclei evidenced increased N/C ratio, irregular and angulated membrane, hyperchromatism, and a coarsely granular chromatin pattern. They corresponded to atypia of high-grade squamous intraepithelial lesions in uterine cervical cytology (Fig. 1B).

The cytologic features were suggestive of Brenner tumor, due to the characteristic 'coffee-bean appearance' transitional cell epithelium. Cytologically, the lack of a distinct papillary tumor nest or marked atypia in transitional cells precluded the possibility of borderline or malignant Brenner tumor.

### Histologic findings

The tumor evidenced a uniformly distributed transitional cell nest within the spindle fibromatous stroma, arranged in a whorled or short fascicle pattern. The transitional cells evidenced pale or eosinophilic cytoplasm with oval or rentiform nuclei and conspicuous nucleoli. The grooved 'coffee-bean' nuclei were more prominent.

The tumor also exhibited a greater degree of typical fibrovascular papillae surfacing on the transitional epithelium protruding into the cystic space (Fig. 1C). In the papillary portion, the tumor cells evidenced more cytologic atypia and increased N/C ratio and pleomorphism. These features were reminiscent of papillary urothelial neoplasm in the bladder. However, no definite evidence of invasion or severe atypia that might be applicable to malignancy was detected. Marked squamous metaplasia was also detected. At the luminal portion of the papillary lesion, the epithelial cells were highly keratinized and exfoliated into single cells (Fig. 1D). This might be the reason that individual dysplastic squamous cells were observed upon cytology. No necrosis or hemorrhagic focus was observed in the tumor. Based on the histologic findings, a final diagnosis of borderline Brenner tumor was rendered.

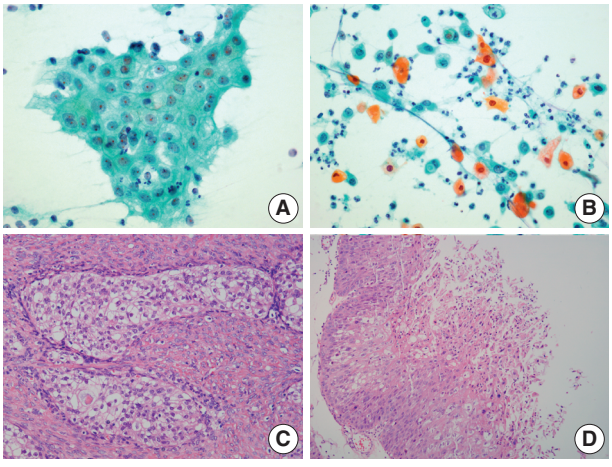


**Fig. 1.** The borderline Brenner tumor. (A) The features of tumor cells include prominent nucleoli and well-defined cytoplasmic border (Papanicolaou stain). (B) The individual typical grooved 'coffee-bean' nucleic tumor cells are mingled with the deep orangeophilic keratinized squamoid cells (Papanicolaou stain). (C) The Brenner tumor nest in dense stroma reveals mild to moderate cytologic atypia, but the basement membrane is well preserved. In the lower nest, the extracellular eosinophilic hyaline globule is observed. (D) The tumor shows the fibrovascular papillae surfacing in the transitional epithelium. In the apical portion, marked metaplasia to atypical squamous cell is observed.

## Case 2

A 61-year-old female suffered from urinary incontinence. In her past history, the patient had undergone a laparoscopic total hysterectomy due to leiomyoma. Transvaginal ultrasonography revealed a 10.9×9.1 cm-sized cystic mass within the left adnexa. The mass was regarded as malignant due to a solid portion. Grossly, the external surface of the salpingo-oophorectomy specimen was tan, soft, clear, and glistening. The mass harbored multiple variably-sized cysts with mucoid fluid and solid portions. Intraoperative fine needle aspiration of the ovary was conducted at the solid portion. The aspirated material was smeared directly onto glass slides and fixed for 20 minutes in 95% ethanol and stained via the Papanicolaou method.

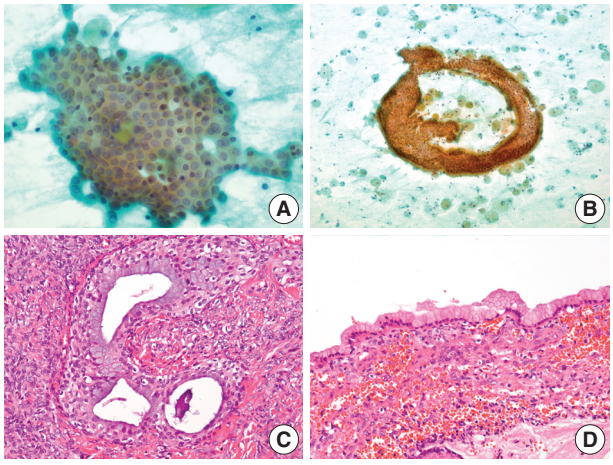


**Fig. 2.** Benign Brenner tumor. (A) Transitional cell nest. Occasionally, grooved or indented nuclei are detected (Papanicolaou stain). (B) The Brenner tumor nest with mucinous metaplasia shows the mucinous columnar cell lining and the underlying transitional cell epithelium (Papanicolaou stain). (C) The glands or microcysts are lined by a monolayer of mucinous cells on the luminal surface with underlying transitional cells. (D) One layer of mucinous columnar cells resembles mucinous cystadenoma.

### Cytologic findings

In a colloid-like background, a number of histiocytes were spread throughout the entire slide. The epithelial tumor cell nests were evenly scattered in solid nest, gland, and microcyst forms (Fig. 2A). The tumor cells contained fine granular chromatin, small prominent nucleoli, and moderate amounts of cytoplasm. Typical grooved 'coffee-bean' nuclei were detected in some tumor cells. These cells were considered transitional cells. A few nests were covered by mucinous columnar cells. The underlying epithelial cells were identical to the tumor cells (Fig. 2B). The cytologic features were suspicious for Brenner tumor with mucinous metaplasia.

### Histologic findings

In the cystic portion, the lining was mucinous columnar epithelium, with no invasion into the stroma. Cellular stratification was absent and the nuclei were basally located without atypia. This component was consistent with a mucinous cystadenoma. No evidence of this component was detected on cytology. The mucinous columnar cell-covered nests observed in the aspiration cytology did not come from this lesion, as the underlying cells were composed of transitional cells rather than ovarian stromal cells.

In the solid portion, many benign transitional cell nests were observed, scattered in the fibromatous stroma. These tumor cells had centrally grooved "coffee-bean" nuclei, abundant amphophilic-to-clear cytoplasm and distinct cell membranes. Some of the tumor nests harbored central or eccentric lumen lined with mucinous cells (Fig. 2C). Because of the severe mucinous metaplasia and cystic changes, some nests changed to partial cysts lined by monolayers of mucinous columnar cells. Furthermore, a few cysts resembled mucinous cystadenoma (Fig. 2D). In this case, the final diagnosis was benign Brenner tumor associated with mucinous cystadenoma.

## DISCUSSION

The cytological features of Brenner tumor have been described as sheets of epithelial cells of benign appearance with ovoid nuclei with a 'coffee-bean' appearance.[1,2] Extracelluar, large, hyaline globules are also reported as a characteristic finding in smears. The cytologic features of borderline or malignant Brenner tumor are polygonal cells in clusters or single cells with moderately pleomorphic nuclei harboring granular chromatin and multinucleate cells. Additionally, occasional but prominent grooving nuclei with many mitotic figures are detected.[3] The cytologic findings for case 1 also revealed hyperchromatic nuclei with an increased N/C ratio, which are not common in benign tumors; histology revealed syncytial clusters and papillae of epithelial cells with prominent atypia, features consistent with borderline Brenner tumor.

Although 'coffee-bean' nuclei are characteristic features of Brenner tumors, nucleic folds are also occasionally encountered in granulosa and mesothelial cells. The eosinophilic globules in the center of the epithelial nests and the spindle fibrous stromal nest are helpful in differential diagnosis. Granulosa cell tumors also harbor similar Call-Exner bodies, but the tumor cells form loosely cohesive syncytial aggregations, contrasting with the sheet arrangement and strict aggregation of Brenner tumor cells.

Squamous features or differentiation on cytology have been detected in several types of ovarian tumors, as well as Brenner tumors. Mature cystic teratomas evidence anucleate and nucleate squamous cells, benign columnar cells, and a few neutrophils, lymphocytes, and macrophages in a background of thick amorphous material.[4] Immature teratomas exhibit neuroendocrine features, immature glial-like cells, neuroectodermal rosettes, squamous cells, and ciliated epithelium.[5] In endometrioid carcinoma, squamous differentiation is commonly observed in the form of morules or larger sheets, occasionally with central necrosis. Cytologic features may reveal the nest form of squamous cells, rather than individual cells, mingled with sheets and clusters of small epithelial cells with hyperchromatic nuclei and scanty cytoplasm. Ovarian squamous cell carcinoma usually occurs as a component of benign cystic teratoma, Brenner tumors, or transitional cell carcinoma. In the case presented herein, the squamous components reveal high-grade atypia, but are limited to the focal luminal epithelium. Thus, squamous metaplasia is a more appropriate diagnosis than squamous cell carcinoma.

Nomura and Aizawa[6] previously reported that 6 cases of Brenner tumor involved transitions or intimate admixtures with mucinous tumors among the 458 ovarian mucinous tumors. In the case presented herein, a similar transitional focus was found. The pathogenesis of a co-existing mucinous tumor and a Brenner tumor remained unknown. Pejovic *et al.*[7] observed an amplification of the 12q14-21 segment in both tumors, suggesting that these tumors were clonally related.

Thus, in this paper we present and describe two cases of rare Brenner tumors in the ovaries. Opportunities to observe the cytologic features of this condition are rare, and our findings may prove helpful in differential diagnosis during the intraoperative

consultation of ovarian tumors, as well as contributing to our understanding of the cytopathology of Brenner tumors.

## REFERENCES

1. Wojcik EM, Selvaggi SM. Fine-needle aspiration cytology of cystic ovarian lesions. Diagn Cytopathol 1994; 11: 9-14.
2. Ramzy I, Delaney M, Rose P. Fine needle aspiration of ovarian masses: II. Correlative cytologic and histologic study of nonneoplastic cysts and noncelomic epithelial neoplasms. Acta Cytol 1979; 23: 185-93.
3. Khajuria A, Karmakar T, Srinivasan R. Fine needle aspiration cytology of a subcutaneous metastasis of a malignant Brenner tumor of the ovary: a case report. Acta Cytol 1995; 39: 246-8.
4. Punia RP, Bal A, Handa U, Mohan H. Aspiration cytology of dermoid cyst of the ovary in a pregnant woman. Diagn Cytopathol 2001; 25: 200-1.
5. Ramalingam P, Teague D, Reid-Nicholson M. Imprint cytology of high-grade immature ovarian teratoma: a case report, literature review, and distinction from other ovarian small round cell tumors. Diagn Cytopathol 2008; 36: 595-9.
6. Nomura K, Aizawa S. A histogenetic consideration of ovarian mucinous tumors based on an analysis of lesions associated with teratomas or Brenner tumors. Pathol Int 1997; 47: 862-5.
7. Pejovic T, Bürki N, Odunsi K, *et al.* Well-differentiated mucinous carcinoma of the ovary and a coexisting Brenner tumor both exhibit amplification of 12q14-21 by comparative genomic hybridization. Gynecol Oncol 1999; 74: 134-7.