Case Series

Brenner tumors of the ovary: A case series in a teaching institute center

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Abstract

Brenner tumors of the ovary are very rare, and mostly benign. Borderline Brenner tumors are rare and malignant Brenner tumors are even much rarer with a worse prognosis. This study was carried out in the Department of Pathology, VSSIMSAR, Burla, Odisha over a period of 3 years. A histopathology study was done in all the cases, while immunostaining was done in selected cases only. A total of seven cases were studied, out of which four (57.14%) cases were diagnosed as benign Brenner tumors, two (28.57%) cases as borderline Brenner tumors, and one (14.28%) case as malignant. Histopathology study is the gold standard for diagnosis of Brenner tumor, with the aid of immunostain whenever necessary.

Keywords: Brenner tumors, histopathology, ovary

Introduction

Brenner tumor is an uncommon neoplasm of the ovary first reported by MacNaughton-Jones in 1898.[1] However, Fritz Brennerin 1907 described the ovarian tumor that now bears his name.[2] The malignant variant was not documented until Von Numers described an example with both benign and malignant elements in 1945.[3]

Brenner tumors are relatively rare fibroepithelial tumors composed of transitional-type cells, resembling urothelial cells, and account for 1.4–3% of all ovarian tumors with a mean age of 51.4 years (16–82 years).[4] The World Health Organization (2014) classifies them into benign, borderline/atypical proliferating, and malignant Brenner tumors based on proliferation and invasion.[5] Benign Brenner tumors comprise 95%. Malignant cases are extremely rare and account for 2% of all cases, whereas borderline tumors are less than 5%.[6] Our study aims to analyze the clinicopathological features of this rare tumor for early diagnosis and treatment.

Materials and Methods

This retrospective study was undertaken in the Department of Pathology, Veer Surendra Sai Institute of Medical Science and Research, Burla, Sambalpur, during the period from May 2017 to April 2020. A total number of seven cases of Brenner tumors, which were histopathologically proven, were included in our study. The surgical procedure adopted was a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The clinical data were retrieved from histopathology records. Being a retrospective study, the original slides and recuts from the original blocks were available. The histological diagnosis was reviewed by a group of pathologists. Immunostains were done in a few cases only.

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Benign Brenner Tumor

Clinical data

A total of four cases of benign Brenner tumors were diagnosed. The age of patients varied from 35 to 65 years with a mean age of 52 years. Only one case was in the postmenopausal age group. The common symptoms were abdominal pain and menstrual abnormalities. In two cases, it was an incidental finding.

Gross

Grossly, the specimens showed circumscribed, bosselated masses covered by the smooth serosal lining. The largest tumor measured 8 × 6 × 4 cm, while the smallest tumor measured 1.5 × 1.5 × 1 cm. The cut surface appeared solid gray-white and whorled. Two cases showed small cysts containing mucinous fluid. A bilateral Brenner tumor was found in one case only. In three cases, the tumor was in the right ovary, and in one case, it was in the left ovary. The cancer antigen 125 (CA 125) varied from 6.40 to 15 U/ml (normal < 35.0 U/ml).

Microscopy

Microscopic examination shows nests and cords of epithelial cells resembling transitional cells within a dense fibromatous stroma. Cells were uniform, polygonal with pale cytoplasm, regular oval nuclei, and longitudinal grooving (coffee-bean appearance). The microcysts were lined by columnar mucinous cells.

Borderline Brenner Tumor

Clinical data

Two cases of borderline Brenner tumors presented with abdominal pain. Age of the patients was 48 years and 60 years. One case had slightly elevated CA125 (42 U/ml).

Gross

The tumors were unilateral measuring 15 × 8 × 6 cm and 8 × 8 × 4 cm. Both the tumors had a smooth outer surface with uni-loculated or multi-loculated cystic and solid areas. The cyst had focal thickening with papillary areas containing watery fluid.

Microscopy

Microscopic examination showed papillae of low-grade transitional cells surrounded by fibrous stroma. The cells have a uniform, mildly atypical nucleoli with a slightly increased nuclear-to-cytoplasmic ratio. One case showed epithelial proliferation without stromal invasion, while the other case showed a greater degree of nuclear atypia without stromal invasion. Foci of benign Brenner tumor were also present. One of the tumors showed a serous cyst lining (serous cystadenoma). Mitotic activity was not conspicuous [Figure 1]. Immunohistochemistry was performed, which showed strong CK positivity, P63 focally positive, and CK20 negative [Figure 2].

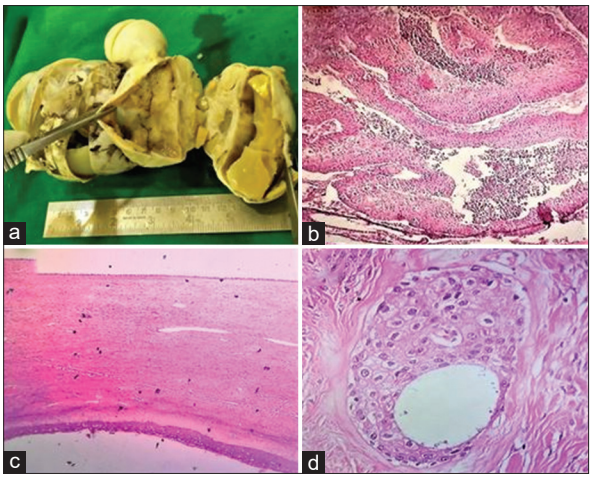

Figure 1: a) Gross of borderline Brenner tumor showing solid to cystic spaces and cysts filled with mucinous materials, b) microsection shows proliferative epithelial cells of urothelial type. H and E × 100, c) one of the cystic cavities is lined by cuboidal epithelium (serous cystadenoma of the ovary). H & E × 100, and d) microsection shows nests of benign urothelial cells with nuclear grooving. H & E × 400

Malignant Brenner Tumor

Clinical data

Only one case of bilateral malignant Brenner tumor was reported in a 65-year-old postmenopausal woman. She presented with abdominal distension and pain. CA125 was markedly raised (449.2 U/ml). Examination of the urinary tract revealed no abnormality.

Gross

A total hysterectomy with bilateral salpingo-oophorectomy specimen was received. The larger ovarian mass measured 18 × 10 × 10 cm, while the smaller mass measured 16 × 12 × 8 cm. Cut section was solid, fleshy, and friable.

Microscopy

Microscopy revealed atypical transitional cells arranged in solid nests and infiltrative cord-like patterns showing high-grade nuclear morphology. The mitotic figure was high (10/10 HPF). Borderline Brenner component, stromal invasion, and calcification were noted [Figure 3]. Immunohistochemistry was done for CK7, CK20, p63, and WT1. Based on the microscopic presence of borderline Brenner component, stromal invasion, and calcification along with CK7 positivity and P63 and CK 20 negative results, the final diagnosis of bilateral Brenner tumor, high-grade, FIGO stage IB was made [Figure 4].

Discussion

Brenner tumors are usually asymptomatic and often an incidental pathological finding. Common symptoms are abnormal vaginal bleeding, perceptible lumps, and pain associated or not with the pelvic masses.[5] In our study, patients presented with abdominal pain, with 40% of benign tumors incidental at the time of the

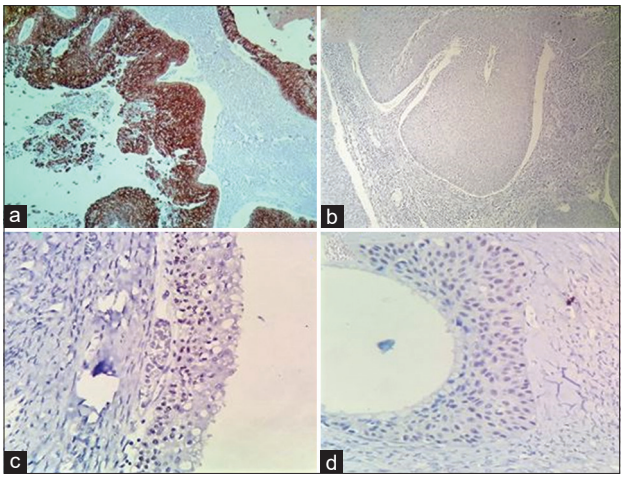

Figure 2: Immunohistochemistry of borderline Brenner tumor showing a) Strong CK7 positivity, b) CK20 negative, c) focal P63 positivity, and d) WT1 negative

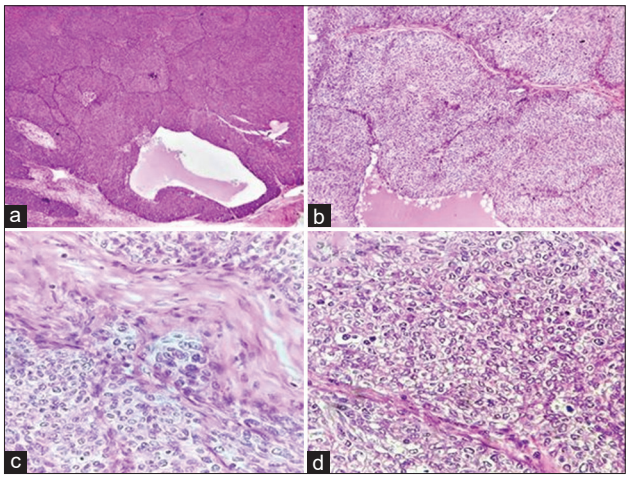

Figure 3: Microsections of malignant Brenner tumor a) H and E x40, b) H and E x100, c) microsection shows invasion into stroma (H&E × 400), and d) microsection shows mitotic figures (H&E × 400)

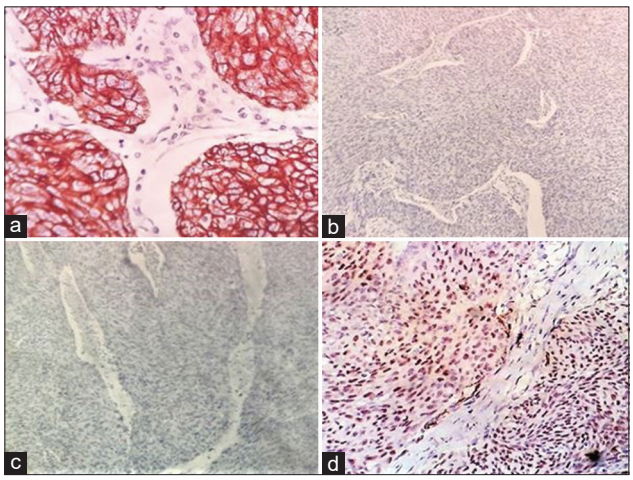

Figure 4: Immunohistochemistry of malignant Brenner tumor shows a) strong CK7 positivity, b) CK 20 negative, c) P63 negative, and d) WT1 positive

study. During a 3-year period, we found only seven (1.8%) cases of Brenner tumors out of 388 ovarian tumors, which is correlated well with the study by Kondi-Pafiti *et al.*[4] They found 30 (1.5%) cases of Brenner tumors among 1,680 cases of ovarian tumors during a 9-year period.

The histogenesis of the Brenner tumor is not well understood. Some studies suggest that Brenner tumors have a tubal origin, arising from tubo-peritoneal junction cells (the junction between the tubal fimbria and the mesothelial serosa). It is suggested that these cells undergo transitional cell metaplasia and invaginate into the paratubal or ovarian surface, forming nests termed Walthard cell nests.[7]

Imaging studies like sonography and CT, which show nonspecific findings, are often mistaken for other solid ovarian masses.[8]

The average age of presentation in our series was 56 years with the age of borderline Brenner tumor as 48 and 60 years and malignant tumor as 65 years. The study correlated well with other studies by Yüksel *et al.*[9] who reported median age of 52 (22–75) years. Green *et al.*[8] also showed the average age as 58 years (32–78 years).

In our study, two cases were bilateral, one benign and the other malignant. Kondi-Pafitis showed unilateral Brenner tumor in 93% of cases and bilateral in 7% of cases.[4]

Brenner tumors may coexist with other tumors of the ovary.[4,10,11] Yüksel *et al.*[9] reported 13 (28.2%) cases of mixed ovarian tumors associated with Brenner tumors. They found mucinous cystadenoma of the ovary in seven (15.2%) patients, serous cystadenoma in two (4.3%), endometrioma in two (4.3%), struma ovarii in one (2.1%), and mature cystic teratoma in one (2.1%).

In our study, one of the cases of borderline Brenner tumor was associated with serous cystadenoma of the ovary. Size also correlates with histological grade with the benign tumor being the smaller size. In our study, the size varied from 1 cm to 18 cm. The smallest tumor was a benign Brenner tumor and the largest was a malignant tumor.

No reliable tumor markers for malignant Brenner tumor have been identified. cancer antigen 125 (CA125) is elevated in some patients only. Because of its low sensitivity (50–62% for early-stage epithelial ovarian cancer) and limited specificity (94–98.5%), CA125 is not recommended as a screening test in asymptomatic women.[12]

Microscopy

Histopathological examination remains the first tool in the diagnosis of these tumors and to exclude closely related tumors. Brenner tumors are formed of epithelial nests of transitional cells resembling those lining the urinary bladder on a dense

fibrous stroma. Complex cystic tumors contain varying amounts of stroma and are more commonly found with borderline or malignant histologic findings.[13] Borderline or low malignant potential Brenner tumors are associated with a greater degree of nuclear atypia [Figure 1]. Hull and Campbell in 1973 proposed four histopathology hallmarks to be present in malignant Brenner tumors as following are: (i) frankly malignant histological features (ii) intimate association between the malignant element and a benign Brenner tumor, (iii) mucinous cystadenomas preferably to be absent or completely separated from both the benign and the malignant Brenner tumor, and (iv) stromal invasion by an epithelial component of the malignant Brenner tumor to be present.[14]

Malignant Brenner tumor consists of sheets and anastomosing trabeculae of high-grade pleomorphic cells with enlarged hyperchromatic nuclei, prominent nucleoli, and increased mitotic activity [Figure 3].

Immunohistochemistry

Kondi-Pafiti *et al.*[4] studied 30 cases of Brenner tumor and found CK positive in all cases and CK20 negative in Brenner cell element but positive in the mucinous component in 5/7 cases of mixed Brenner tumor, Uroplakin positive in 23/30 cases, and focal positivity of WT-1 and chromogranin. Another study by Kuhn *et al.*[7] showed WT1 positive in 10% of cases of epithelial component and 32% of stromal component of benign Brenner tumor. But in atypical proliferative Brenner tumors, epithelial component was negative for all the three above-mentioned IHC markers and the stromal component was positive in all the cases for WT1. Our study was comparable to these studies. The borderline Brenner tumor showed CK7 positive, CK20 negative, p63 focally positive, and WT1 negative [Figure 2]. Malignant Brenner tumor was CK7 positive, CK20 negative, p63 negative, and WT1 positive [Figure 4] which distinguishes it from metastatic transitional cell carcinoma from the urinary tract (CK20 positive, WT1 negative), which is diagnosed based on the clinical history of tumor in the urinary system and immunohistochemical markers. In addition, transitional cell carcinoma lacks the calcification typically seen in malignant Brenner tumors, fails to demonstrate a benign/borderline Brenner tumor component, and shows frankly malignant features throughout.[15]

The primary treatment modality is surgical excision, and patient outcomes following chemotherapy are better than for other types of ovarian cancer. Therefore, raising awareness of this rare tumor among primary care providers and family physicians will aid in early detection and treatment, resulting in a better prognosis.

Conclusion

It is important to differentiate borderline Brenner tumors from malignant tumors because they differ in prognosis and management. Histopathological examination remains the gold standard for the diagnosis of this entity. Immunostain plays an important role as an aid to the final diagnosis and also in differentiating it from metastatic urothelial carcinoma from the urinary system.

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Conflicts of interest

There are no conflicts of interest.

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