MALIGNANT BRENNER TUMOR OF THE OVARY: A CASE REPORT

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ABSTRACT Malignant Brenner tumour is a rare disease entity comprising only <1% of all ovarian neoplasms, hence, individual case reports, small case series, or recently, retrospective population-based studies provide the only accessible information about how to treat these patients. Presenting a case of a 41-year-old, G5P4 who came in due to increasing abdominal girth and a finding of a complex abdominopelvic mass on ultrasound. Ca-125 was only slightly elevated and CEA is within normal limits. Complete surgical resection of the tumour with complete staging was done. The specimen was submitted for histopathology and were found to have features consistent with Brenner tumour along with moderate to severe cytologic atypia which is indicative of malignancy. Upon diagnosis, the patient was immediately started on adjuvant chemotherapy with Carboplatin and Paclitaxel in 3-week dosing for 6 cycles. Surveillance Ca-125 levels were done post-chemotherapy and were found to return to normal levels. The patient has no evidence of disease for 6 months now.

Herein, is a case of MBT successfully treated with complete surgical resection of the tumour with extensive staging and adjuvant chemotherapy with Carboplatin and Paclitaxel. Consistent with the literature, remission was achieved noted through serial Ca-125 level determination. Our patient’s response supports that the said regimen should be considered as first-line adjuvant chemotherapy in patients with advanced disease given the good response of the tumour to this treatment. Nonetheless, as this represents a singular case of successful treatment, generalizations about treatment protocols cannot be suggested.

KEYWORDS Malignant Brenner Tumor, Ovarian neoplasm, CA-125, Carboplatin-Paclitaxel, Cytologic atypia

Introduction

An ovarian mass is a common gynecologic problem. Ovarian masses are a diverse group of tumours classified into an epithelial, germ cell, and sex cord-stromal based on tissue differentiation. Of these, ovarian epithelial carcinomas comprise 90 to 95% of all cases[1]. The ovarian Brenner tumour (BT) represents a rare epithelial ovarian neoplasm and accounts for 1-2% of all ovarian neoplasms[2]. BT is now subcategorized as benign, borderline (proliferative), or malignant. Malignant BT (MBT) is first reported by von Numer in 1945. This is an extremely rare subcategory, comprising only <5% of all BT. Due to the rarity of MBT, optimal management remains unclear. Clinical practice guidelines for diagnosis and management are not available yet. Individual case reports, small case series, or recently, retrospective population-based studies provide the only accessible information about treating these patients. In this paper, a case
of MBT is described, and review of current literature on these tumours is presented.

**Case report**

A 41-year-old, G5P4 (4-0-1-4) with no known co-morbidities and no prior surgeries presented for gynecologic consultation due to an increasing abdominal girth. Past medical, family and social history are non-contributory. The patient has an OB score of G5P4 (4-0-1-4). The first four pregnancies were all carried to term and delivered by normal spontaneous delivery. She had one spontaneous abortion at 12 weeks age of gestation and was completed via curettage.

History started three months prior to admission, when she noted a palpable mass at the right side of her abdomen, measuring approximately 5x5 cms., firm, movable, non-tender. There was no associated change in the amount, duration, or frequency of menstrual cycles. There were no associated constitutional symptoms at the time of onset of symptoms. No consult was done, nor medications are taken.

In the interim, the patient noted a progressive increase in abdominal girth, noted by difficulty in buttoning previously loose-fitting pants and trousers. She also noted easy fatigability, bloatedness, early satiety, weight loss (from 65 kgs. to 54 kgs. in two months), and dyspareunia—no associated changes in the pattern of menses or post-coital bleeding. The progression of symptoms prompted consult.

On physical examination, the patient was seen conscious, comfortable, and not in distress, with stable vital signs, and a BMI of 20 kg/m2. The abdomen was non-distended. Dull on percussion at the hypogastric area. There is a large pelvoabdominal mass measuring 15 x 15 cms., which is firm, slightly movable, with indistinct borders; the mass was slightly tender on deep palpation. There were no noted rigidity, guarding, or any signs of ascites. On speculum examination, there were smooth vaginal walls, and the cervix is midline, firm, smooth, with no lesions, or bleeding.

On internal examination, there was a note of parous introitus, smooth vaginal walls. Cervix is midline, closed, firm, non-tender. There a large pelvoabdominal mass measuring 15x15 cms., firm, slightly moveable, with indistinct borders, slightly tender on deep palpation. The adnexa cannot be assessed accurately due to the presence of the large pelvoabdominal mass. On recto-vaginal examination, there were no perirectal lesions or fissures. External sphincter tone is intact. There were no palpable masses on the rectal vault. Posterior cul de sac was full. A large mass palpated in the posterior cul de sac with limited mobility—no stool or blood per examining finger.

The rest of the physical examination was unremarkable. Transvaginal ultrasound showed normal-sized anteverted uterus (6.32 x 4.23 x 4.97 cms), intact endometrium with an endometrial stripe of 0.97 cms. Abdominopelvic complex mass measuring 14.14 x 13.82 x 13.38 cms, to consider and ovarian new growth. No fluid detected at the posterior cul-de-sac. Ca-125 was slightly elevated at 139.3 u/Ml. CEA was within normal limits.

During surgical exploration, the bilateral ovaries were enlarged, right ovary measures 14x13x13 cm. Left ovary measures 10x9x8 cm, multiloculated with solid components. On cut section, serosanguinous fluid was noted with yellowish solid components within the locules (Figure 1). The uterus was unenlarged. The appendix was noted to be slightly enlarged measuring 6x1x1 cm with prominent vascularities. Liver and subdiaphragmatic surfaces were smooth. Residual tumour with an aggregate of 5 cms was noted on the pelvic sidewalls, cul de sac, and urinary bladder. The initial consideration was serous cystadenocarcinoma of the bilateral ovaries. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal fluid cytology, infracolic omentectomy, bilateral lymph node dissection, and appendectomy were done for complete surgical staging.

Gross pathologic examination of the ovaries revealed cystic masses with solid areas and capsular irregularities. The recognizable fallopian tubes have irregular serosal surfaces. Microscopic examination showed biphasic proliferation of epithelial cells with areas of solid, well-formed nests immediately juxtaposed with regions of infiltrative cord-like and single-cell growth. Cytologically, the tumours showed moderate to severe atypia. Tumour extension was noted in the bilateral fallopian tubes, myometrium, and omentum. Pelvic lymph nodes were negative for tumour. Based on the presence of urothelial differentiation with conventional BT morphology adjacent to frankly infiltrative malignancy, this tumour was classified as MBT. It was considered moderately to poorly differentiated based on moderate to severe cytologic atypia. This was staged as IIIC based on the involvement of the bilateral ovaries with histologically confirmed omental metastasis greater than 2 cm in diameter (Figures 2, 3, 4).

The patient received an aggressive therapeutic strategy and was treated with carboplatin and paclitaxel every three weeks dosing for a total of 6 cycles. Surveillance Ca-125 was done on the 1st and 3rd months after the last cycle of chemotherapy. The values were within normal limits, as follows: 3.70 and 5.40, respectively. The patient has no evidence of disease for six months now.

**Discussion**

MBT presents similar symptoms to other ovarian cancers such as abdominal distension, abdominal pain, bulk symptoms and relative vague symptomatology[2]. Patients typically present with disease confined to the ovary or surrounding tissue with the lymphatic spread being less common[2]. One patient was reported to have experienced an initial symptom of hematuria due to the presence of the large pelvoabdominal mass. On recto-vaginal examination, there were smooth vaginal walls. Cervix is midline, closed, firm, non-tender.

![Figure 1: Gross specimen of bilateral ovaries. Grossly, malignant Brenner tumors are large and may be cystic with mural nodules or entirely solid.](image-url)
Figure 2: Histopathology of the ovaries. Malignant Brenner tumors show cytologically malignant areas (usually resembling high-grade urothelial carcinomas of the urinary tract) with stromal invasion. The tumor cells are arranged in solid sheets, irregularly shaped nests, or branching trabeculae. They usually have high-grade features, including pleomorphic hyperchromatic nuclei, brisk mitotic activity, central necrosis producing comedocarcinoma-like pattern, and desmoplastic stromal response. The appearance of the malignant component may be transitional (seen here), squamous, glandular, undifferentiated or mixed. [2]

Figure 3: Moderate to severe cytologic atypia indicate high-grade features, including pleomorphic hyperchromatic nuclei, brisk mitotic activity.

Figure 4: The transitional-type differentiation necessary for the diagnosis of BT/MBT is characterized by the presence of nuclei with distinct nuclear grooves (so-called “coffee-bean” shapes) seen in this figure.

Computed Tomography and Magnetic Resonance Imaging can demonstrate this Brenner tumour as a cystic mass with solid mural components. The benign component contained dense calcifications on computed tomography and showed very low intensity on T2-weighted images, whereas the malignant component showed high intensity. The admixture of 2 components may well reflect the pathological feature and maybe a diagnostic clue to malignant Brenner tumour [5]. The clinical utility of CT and MR imaging is unclear, as MBT does not have pathognomonic imaging features. Imaging more readily contributes to the assessment of tumour location, size, and burden and surgical planning. As with other ovarian tumours, diagnosis can only be made by histologic evaluation [2].

The pathogenesis of BT has not been unequivocally elucidated. Although BTs demonstrate transitional-type differentiation as is seen in bladder and ureters, most investigators favour that these tumours do not originate in the urothelial tract. Some reports suggested origin directly from ovarian surface epithelium; however, recent evidence shows these tumours derive from sites of transitional cell metaplasia within the adnexa [2], also known as Walthard cell nests, within normal ovaries and fallopian tubes. Interestingly, Walthard cell nests are more likely to be present in women with BT or another ovarian neoplasm than in controls [2].

The histologic diagnosis of MBT is made mainly by the criteria established by Hull et al. It requires (1) the concomitant presence of both the malignant and benign/borderline BT with clear stromal invasion by the malignant epithelial components, (2) associated tumour types (most commonly mucinous cystadenoma) must either be absent or geographically distinct from the MBT, (3) the transitional-type differentiation necessary for the diagnosis of BT/MBT is characterized by the presence of nuclei with distinct nuclear grooves (so-called “coffee-bean” shapes). All these microscopic details are seen on the histopathology of the patient’s ovaries (see Figures 2, 3, 4). These microscopic characteristics can be aided with an immunohistochemical demonstration of urothelial marker expression (GATA3, uroplakin III, thrombomodulin, and p63) [2].

Tumour markers of malignant neoplasms can be used for surveillance to monitor the effectiveness of therapy and to detect
Differential diagnosis

The primary differential diagnosis for MBT is Transitional Cell Carcinoma. Despite their shared transitional cell phenotype, there is enough evidence that these two tumours represent distinct pathologic and clinical entities. On imaging and gross examination, TCC lacks the calcifications typically seen in MBT. Furthermore, MBT has been shown to present more often in stage I without an extra ovarian spread and be less aggressive than primary TCC of the ovary, irrespective of tumour stage 2. Microscopically, TCC does not demonstrate a benign Brenner tumour component characterized by well-differentiated transitional cell nests; instead, TCC shows frankly malignant features throughout. The tumours have distinct immunophenotypes from each other: TCC demonstrates immunohistochemical overlap with high-grade serous carcinoma through the diffuse expression of WT1, ER, and p53; BT/MBT are typically negative (or only focally positive) for these markers. Furthermore, TCC shows overexpression of p16, and MBT shows loss of heterozygosity and silencing.

On the other hand, BT, benign and malignant have increased EGFR, Ras, Cyclin D, p63, and is also shown to possess TERT promoter mutation. However, there is a lack of study to date to analyze TERT promoter mutation in ovarian TCC. Specifically, the data favour these mutations in the urinary bladder and upper urinary tract TCC. Direct comparison is necessary and may warrant further exploration if sequencing for TERT mutations is to have true diagnostic utility in the future [2].

Management

The treatment for MBTs is essentially surgical. The surgical procedure has to be extended as in other epithelial ovarian malignancies for complete staging, to include omentectomy and removal of retroperitoneal lymph nodes. In this case, the patient underwent total abdominal hysterectomy-bilateral salpingo-oophorectomy, omentectomy, and lymph node dissection. The benefit of adjuvant therapy in the management of MBT is poorly defined as these are rare ovarian tumours and are infrequently encountered in clinical practice. The effect of platinum-based chemotherapy plus paclitaxel as post-surgical chemotherapy has shown some survival advantage. The current standard chemotherapy regimen for patients with ovarian epithelial neoplasms is carboplatin plus paclitaxel. While there are not, nor will there be, large clinical trials assessing the efficacy of chemotherapy in patients with MBT, the data from other epithelial ovarian tumours is extrapolated, and carboplatin/paclitaxel is an acceptable choice [2]. It would be reasonable to assess chemoresponsiveness after three therapy cycles with these agents given the data suggest there is no advantage to a 6-cycle regimen. Recently, the 5-year disease-specific survival of MBT with the extra-ovarian disease in this patient had a survival rate of 51.3%. Similar to other tumours, poorly differentiated tumours portend a worse prognosis than those which are well-differentiated. An analysis of rare ovarian tumours, including BT of unspecified benignity, established that the generalized recurrence rate of the said tumours was approximately 28%. There is evidence of improved progression-free survival among women with epithelial ovarian cancer who receive adjuvant chemotherapy [2].

Conclusion

Herein we describe a case of MBT successfully treated with complete surgical resection of the tumour with extensive staging and adjuvant chemotherapy with Carboplatin and Paclitaxel. Consistent with the literature, remission was achieved noted through serial Ca-125 level determination. Our patient’s response supports that the said regimen should be considered as first-line adjuvant chemotherapy in patients with advanced disease given the good response of the tumour to this treatment. Nonetheless, as this represents a singular case of successful treatment, generalizations about treatment protocols cannot be suggested.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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