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(CASE REPORT)

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Recurrent malignant Brenner tumor of the ovary with involvement of the urinary bladder: Case report and a brief review of the literature

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Abstract

Brenner tumors (BTs) are an uncommon type of ovarian surface epithelial neoplasm that are mostly benign. Malignant Brenner tumors (MBTs) are rare tumors that makeup < 5% of those of BTs. Recurrence is relatively rare, primarily in the advanced stage. Pelvic organ metastasis or lymph node metastasis is also seen, although less frequently than for other high-grade ovarian carcinomas. We report a 72-year-old woman who presented with lower abdominal pain, vomiting, and gross hematuria. There was also urgency, dysuria, pelvic pressure, and right lower quadrant pain. She had a history of surgical resection of localized MBT without adjuvant therapy. At the current presentation, malignant cells were identified in the urine cytology and ascitic fluid. Imaging studies showed the presence of a solid cystic mass at the site of prior surgery. Surgical staging with optimal cytoreduction was performed with an intraoperative confirmation of the diagnosis of MBT. The tumor was graded as FIGO IIIA1 (T2 N1 M0). The patient was administered adjuvant chemotherapy (carboplatin + paclitaxel and bevacizumab), and close surveillance was carried out. She was alive with no evidence of disease at 28 months of follow-up. This case illustrates an uncommon, yet aggressive pattern of MBT recurrence, underscoring the importance of close long-term monitoring and the value of a multidisciplinary team approach for evaluation and management.

Keywords: Brenner tumor; Benign; Malignant; Ovarian carcinoma; Transitional cell carcinoma

1. Introduction

BT is a rare kind of ovarian surface epithelial tumor that comprises about 1-2% of all ovarian tumors. [1] Histologically, it is of transitional cell type, closely resembling urothelium, with a very dense collagenous stroma. [2] [3] Most BTs are benign, and the frequency of malignancy in BTs is less than 5%; hence, MBTs are uncommon in the field of gynecologic oncology. [4] MBT occurs most commonly in postmenopausal women, with an average age of 60 at diagnosis. [1] The clinical features are typically nonspecific, including abdominal bloating, pelvic pain, or pressure symptoms. [5] Although rare, compared to their other counterparts, MBTs demonstrate an invasive loco-regional growth and metastatic potential.

The etiology of MBTs is still uncertain, and they are assumed to arise through the malignant transformation of benign or borderline Benner tumors. [6] [7] [8] The histomorphology of transitional cells in MBT frequently presents a diagnostic challenge, particularly in distinguishing it from metastatic urothelial carcinoma. [9] Thus, histopathologic

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and immunohistochemistry (IHC) evaluations are necessary for definitive diagnosis. The management of MBTs is also like that of other ovarian cancers; primary debulking surgery and staging surgery are the mainstays of the treatment. [10] [11] The benefit of adjuvant chemotherapy is not well established due to a lack of data, and the application of the principles of adjuvant therapy is to use the same for similar-stage cases of epithelial ovarian carcinoma (EOC). [2] The prognosis of MBTs is regarded as good, with a five-year survival rate in the early stages of over 80% for stage I disease. [4]

MBT recurrence is rare, and when it does occur, it is generally associated with intraperitoneal dissemination, as is the case with other ovarian carcinomas. [12] However, the recurrence pattern can differ, and local invasions and lymph node metastases are extremely rare. Recurrence management is extremely challenging owing to the lack of standardized treatments. [1] As MBTs are rare, and aggressive recurrent disease is even rarer, case reports are crucial in helping to describe the various clinical presentations, responsiveness to treatment, and inevitable outcomes. Understanding these rare recurrence patterns is crucial for establishing effective monitoring protocols and treatments for patients with MBTs.

We describe a case of recurrent malignant Brenner tumor in a 72-year-old woman with an aggressive presentation in the form of bladder invasion and pelvic lymph node metastases, which is a rare and alarming pattern of recurrence, emphasizing the importance of close long-term follow-up and a multimodality treatment strategy for patients with MBTs.

2. Case presentation

A 72-year-old female was admitted to the surgical emergency department due to a 1-month history of lower abdominal pain, vomiting, and gross hematuria. She also had constitutional symptoms, including weight loss, loss of appetite, and fatigue for the last four months. She had dysuria, frequency, urgency, incomplete bladder voiding, and intermittent urinary retention. In addition, she had generalized pelvic fullness and pressure. Physical examination revealed a firm, palpable mass of the right lower abdomen, swelling of the right lower limb, and clinical features of abdominal ascites.

The patient had previously undergone a right salpingo-oophorectomy for localized malignant borderline tumor (MBT) of the right ovary six years prior to the current presentation. At that time, the patient refused a major surgery and opted for only the right salpingo-oophorectomy. Histologically, the prior tumor was an MBT with positive surgical margins and five uninvolved regional lymph nodes. There was no reference to the presence or absence of benign or borderline components of BT in the available reviewed reports. The patient refused additional surgery for adequate margins and refused adjuvant chemotherapy or radiotherapy. She had no family history of cancer, and she was negative for BRCA mutations.

At the current presentation, tumor markers indicated an elevated CA-125, but CEA and CA 19-9 were within the normal range. Cytologic examination of the urine and ascitic fluid showed malignant cells. On transvaginal ultrasound, the patient's right adnexal region (the site of the prior surgery) showed a predominantly lobulated solid cystic mass, measuring 8 × 5 cm in its largest dimension, with irregular margins. Contrast-enhanced CT revealed a heterogeneous, mixed solid-cystic mass in the right adnexal region, extending into the lateral wall of the urinary bladder and contiguous uterine structures, with foci of calcification. MRI revealed a mass with an intermediate signal on T1-weighted images and a high signal in hemorrhagic regions. On T2-weighted images, the mass exhibited heterogeneously intermediate to low solid, high cystic, and low fibrous stromal signal intensity. The scan also revealed mild ascites, pelvic and para-aortic lymphadenopathy, and multiple peritoneal implants, each less than 1 cm, with involvement of the right pelvic sidewall and urinary bladder. No lesions were observed in the uterus or opposite ovary.

The case was discussed at a multidisciplinary tumor board, and the most likely diagnosis was a recurrent MBT with local invasion. It was decided to perform en bloc excision for full surgical staging and optimal debulking to remove the pelvic mass, surrounding soft tissue, uterus, left ovary/fallopian tube, and partial cystectomy, as well as the urinary fistula forming part of the tumor. In addition, peritoneal nodules were also decided to be removed. Debulking was followed by a careful closure in two layers of the bladder wall, encompassing both the inner mucosa and submucosa, as well as the outer muscular layer. Satisfactory performance of bladder preservation surgery was achieved through meticulous intraoperative management and planning. Preoperative indwelling of Foley catheterization promoted good bladder decompression and allowed good exposure during surgery. The chromogenic agent methylene blue facilitated the precise localization of tumor involvement by maintaining controlled bladder filling during cystotomy and evaluating the degree of invasion of the bladder wall. Postoperative care was crucial for achieving successful healing and optimal functional results. A Foley catheter for two weeks after surgery ensured appropriate healing of the bladder suture line and minimized complications. A cystogram was necessary before the catheter was removed to assess the integrity of

the repair and rule out the development of a fistula or urine leak. There were no complications due to careful monitoring for hematuria, urinary tract infections (UTIs), urine retention, and extremely low-yield complications, such as the formation of vesicovaginal or vesicoenteric fistulas.

The removed tumor was a solid, fleshy, polypoid mass that measured 8 x 5 cm and protruded into cystic cavities. Microscopically, the tumor consisted of solid and papillary nests of malignant epithelial cells of the transitional type protruding into cystic spaces. Comedo-type necrosis and stromal invasion were visible. The tumor cells exhibited high-grade nuclear atypia, pleomorphism, and high mitotic activity (more than 10 mitoses per 10 high-power fields). The tumor exhibited mixed histological features, comprising papillary carcinoma components, foci of squamous differentiation, and regions resembling transitional cell carcinoma. Nuclear grooves and the absence of mucin formation were also observed in the foci of borderline Brenner tumor elements. (Figure 1A, B, C, and D) In immunohistochemistry (IHC) studies, the tumor cells were focally and weakly positive for WT1 and strongly positive for CK7, CK5/6, thrombomodulin, and p63 (signaling epithelial differentiation). The tumor cells showed negative staining for TTF-1, CDX2, estrogen, progesterone, and CK20 (which helped distinguish it from primary bladder transitional carcinoma). Four out of eleven dissected pelvic and para-aortic lymph nodes had metastatic involvement. These results were in line with a recurrent MBT, given her clinical course, histomorphology, and IHC studies. The body survey showed no evidence of metastases at other body locations. FIGO IIIA1 (T2, N1, M0) was the stage of the tumor.

Postoperative treatment included six courses of adjuvant chemotherapy with paclitaxel and carboplatin every three weeks. She was also treated with anti-vascular endothelial growth factor (anti-VEGF) agent bevacizumab for the high-risk features of her tumor. The patient was monitored with active surveillance, including interval imaging and clinical follow-up, every three months. Postoperative care of the urinary bladder included pelvic floor physiotherapy and recording voiding diaries in the few months following surgery. Special care was taken to prevent overdistention of the bladder and early removal of the catheter, which can lead to leakage or fistula formation. The patient tolerated the surgery well without complications, and at 28 months after treatment, she continued to respond to clinical remission, with no local or systemic recurrence before she was lost to follow-up.

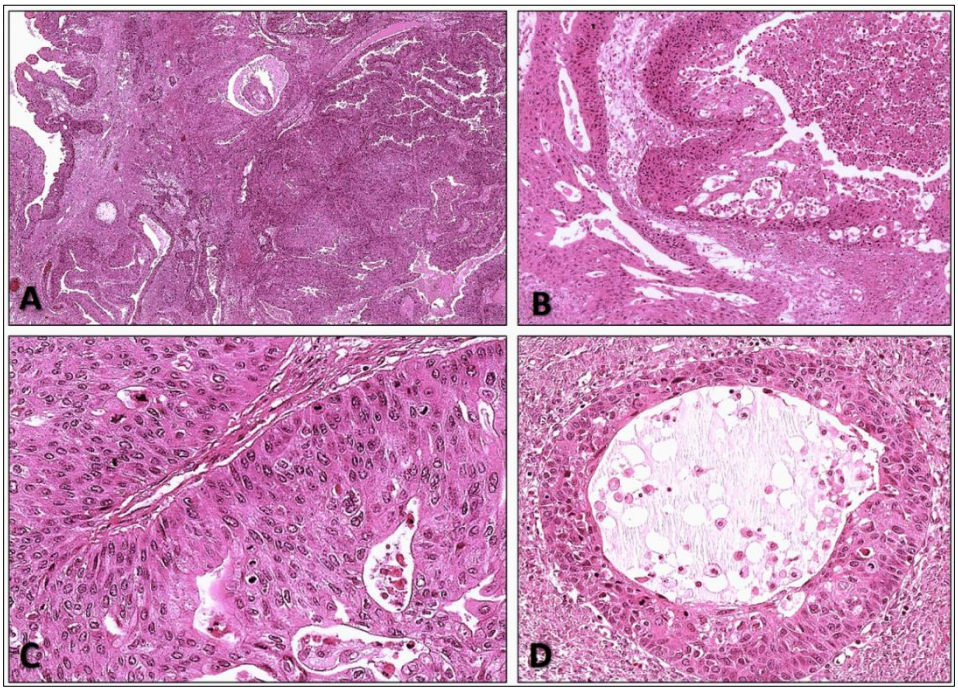

Figure 1 Histomorphologic features of the excised malignant Brenner tumor (MBT)

- 1A Low power view showing solid and papillary nests of malignant epithelial cells of the transitional type protruding into cystic spaces (H&E stain X20)
- 1B: Intermediate power view showing comedo-type necrosis and stromal invasion (H&E stain X40)
- 1C: High power view showing the tumor cells exhibiting high-grade nuclear atypia, pleomorphism, and high mitotic activity (H&E stain X60)
- 1D: High power view showing foci of borderline Brenner tumor elements with nuclear grooves without invasion of the stroma (H&E stain X40)

3. Discussion

BTs are rare ovarian epithelial neoplasms first reported by Fritz Brenner in 1907. [13] The World Health Organization (WHO) classifies BTs into benign, borderline (also referred to as proliferative), and malignant tumors. [14] MBTs typically possess transitional (urothelial-like) epithelial elements in a dense fibrous stroma. This malignant form of BTs accounts for <5% of all BTs and for <0.05-1.0 % of all ovarian neoplasms, thus being extremely rare. [15] MBTs usually affect postmenopausal women, and the average age at diagnosis is 50–70 years [2]. MBTs are histologically characterized by the development of clearly invasive carcinoma within benign or borderline carcinomatous elements. [5]

The precise mechanism of MBT development remains unclear. However, like other epithelial ovarian tumors, a long duration of nulliparity, low parity, and hormonal effects have been postulated [4]. They are thought to arise from the ovarian surface epithelium or Walthard cell nests (WCNs) and undergo metaplastic change to transitional-type epithelium. WCNs are hamartomatous groupings of transitional (urothelial-like) epithelium that are mostly seen in the para-ovarian region, fallopian tube serosa, mesosalpinx, and less frequently on the surface of the ovary or pelvic peritoneum. [7] [8] Histologically, they present as small aggregates or nests of eosinophilic, polygonal cells with clear cytoplasm and typically elongated nuclei with grooves running parallel to their long axes— so-called "coffee bean"-shaped nuclei. [5] WCNs derive from Müllerian or mesothelial cells and are often seen in adult fertile women. Although they are non-neoplastic, their morphology and immune profile mimic the epithelial elements of BTs [7] [8] Such transitional-type epithelium is seen in both structures, supporting this hypothesis. [8] IHC studies support the association because both WCNs and BTs epithelium are frequently positive for CK7, p63, GATA3, and uroplakin, and are typically negative for CK20, allowing differentiation from primary urothelial carcinoma of the bladder. [16]

MBTs present as one of the most difficult diagnoses in gynecologic pathology because of their extreme rarity, nonspecific symptomatology, and close histologic resemblance with other ovarian and urothelial malignancies. [1][17] Diagnosis is primarily based on careful histopathologic assessment, supported by adequate immunohistochemical (IHC) studies, to differentiate MBT from its many mimics [5] underscoring a high level of suspicion needed for patients with a history of prior benign Brenner tumor [3]

The pathology of the resected tumor, characterized by its distinctive microscopic features, ensures an accurate histological diagnosis. The malignant component is characterized by the proliferation of transitional-type epithelial cells arranged in solid nests, papillary structures, or cribriform patterns, exhibiting high-grade nuclear atypia with numerous mitoses. Invasion of the interstitium is a prerequisite for malignancy. [5] [18] As in our case, the recognition of coexistent benign or borderline BT components strongly favors the theory that the MBT represents a malignant progression from a preexisting BT lesion and may help differentiate MBT from other primary ovarian tumors and metastatic disease; [1] Although the added advantage of frozen section evaluation is only a provisional diagnosis, a permanent section with complete IHC work routinely helps establish a definitive diagnosis. [18]

The differential diagnosis of MBT is extensive, and various morphological mimics must be excluded. Metastatic or direct extension of high-grade urothelial carcinoma from the bladder to the ovary is the most significant differential consideration. [4] Primary ovarian non-Brenner-type transitional cell carcinoma, now incorporated in contemporary diagnostic designations, may also show these features. [18] Furthermore, endometrioid carcinoma may have components that closely mimic transitional cells, and serous carcinoma sometimes shows pseudo-transitional foci that mimic MBT. [19] Immunohistochemically, CK20 negativity is crucial for differentiating MBT from primary bladder urothelial carcinoma, which is typically diffusely strongly positive for CK20 expression. Patterns of WT1 expression are also useful for diagnosis, where serous carcinomas are consistently diffusely positive for WT1, and MBTs are consistently focally positive or negative, as in our case. [2] [16] Novel molecular profiling methods remain unexplored but may soon provide new insights into the diagnostic genetic signature of MBTs. [2] [18] The mutations commonly observed in serous carcinomas, including those involving BRCA1/2 or PIK3CA, and the characteristic FGFR3 mutations in urothelial carcinomas are not generally seen in MBTs. [6] [9] MBTs do not often possess TP53 mutations, as seen in high-grade serous ovarian carcinomas (with TP53 mutations in >90%). This is diagnostically relevant as TP53 mutations are frequent in urothelial carcinomas as well, and therefore, their lack aids differentiation between metastatic bladder cancer and MBT [18]. These molecular differences offer a potentially useful approach to definitively rule out morphologic mimics when classic diagnostic modalities are equivocal; however, additional studies are required to validate their diagnostic utility in routine practice.

Future avenues of research involve large, multi-institutional collaborations to accrue cases for in-depth genomic analysis, the exploration of therapeutic targets as discovered through molecular profiling, and the convergence of molecular diagnostic standards that can be applied in day-to-day pathologic workup. The combination of RNA

sequencing and methylation analysis may also provide new insights into the biology of these rare tumors. [4] Although molecular profiling of MBTs is relatively immature, available data indicate that they possess a unique molecular profile that could facilitate diagnosis and potentially direct treatment strategies. [6] As we learn more about them, molecular profiling is likely to gain importance also in the treatment of challenging cases.

3.1. What we learned from this case

The case highlights interesting clinical and pathological details of MBTs, particularly when they appear as an uncommon, recurrent, and aggressive neoplasm. First, it shows that solid-cystic components of MBTs initially managed with surgical excision and no adjuvant therapy may recur aggressively, involving adjacent structures such as the urinary bladder and pelvic wall. This emphasizes the need for long-term follow-up applications, even in cases that seem to be early-stage disease at onset. Secondly, it shows that patients with recurrent MBTs might present with unspecific symptoms such as hematuria, pelvic pain, urinary retention, and a palpable abdominal mass. This further supports the need for a high clinical suspicion of MBTs in patients with a history of MBTs. Radiological studies were very beneficial in evaluating the disease load, and cytology on urine and ascites was diagnostic. The aggressive histological features (transitional cell-like histology, high-grade atypia, stromal invasion, and lymph node involvement) in our case serve as powerful reminders of the significant malignant potential of these tumors when complete staging is not performed.

IHC was invaluable in differentiating MBT from transitional cell carcinoma of bladder origin and other mimickers. From a surgical perspective, this case demonstrated that it is possible to resect involved segments of the bladder wall surgically without compromising bladder function. Multidisciplinary surgical debulking ensured total cytoreduction with margins evaluation on frozen section pathology. Lastly, the prompt response to adjuvant platinum-based chemotherapy in combination with bevacizumab, along with no evidence of disease at 28 months status post-treatment in this patient, reiterates the benefit of aggressive multimodal therapy in the subset of recurrent MBT cases

4. Conclusion

Recurrent MBT is a rare, aggressive ovarian neoplasm that may show local invasion and regional lymphangitic spread. This case report highlights the diagnostic dilemma and therapeutic implications of such a recurrence in the urinary bladder. A multi-diagnostic approach, including imaging techniques, cytology, histopathology, and immunohistochemistry (IHC), was critical in establishing the correct diagnosis and determining further courses of action. Complete surgical tumor reduction with bladder-preserving resection and subsequent adjuvant chemotherapy, and targeted therapy achieved a good effect. This case highlights the importance of multi-institutional vigilance and a multidisciplinary team approach in the treatment of rare ovarian cancers.

Compliance with ethical standards

Disclosure of conflict of interest

All authors (Eseohe Imhansi-Jacob, Manon Djomani, Addison Mock, Atsek Wassimi, Anthony Bonilla, Leydi Filgueiras, Kaitlyn Aquino, Jessica Jahoda, and Mohamed Aziz) declare the following

Statement of Ethical approval

Ethical review and approval were not required for the study on human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Statement of informed consent

The patient was lost to follow-up, and all attempts to reach the family members were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

Payment/services information

All authors have declared that they received no financial support from any organization for the submitted work.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Other relationships

All authors have declared that no other relationships or activities could appear to have influenced the submitted work.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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