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Case report

Malignant Brenner tumor of the ovary: Review and case report

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ABSTRACT

Ovarian neoplasms are a heterogeneous group of tumors with varying incidence in the general population. The most common are the surface epithelial tumors which include transitional cell tumors. Transitional cell tumors include both transitional cell carcinoma and Brenner tumor. The vast majority of Brenner tumors are benign, often incidental findings; however, malignant Brenner tumors (MBT) do occasionally occur. MBT present similarly to other ovarian neoplasms with abdominal pain and bulk symptoms. On imaging, these tumors demonstrate nonspecific findings. Microscopically, they demonstrate areas of conventional benign Brenner tumor juxtaposed with regions of frank malignancy showing marked cytologic atypia and infiltration. There is no consistent tumor marker for these tumors, but CA-125, CA 72-4 and SCC have been reported in singular instances. Tumors express several immunohistochemical markers of urothelial differentiation including uroplakin III, thrombomodulin, GATA3, p63, as well as cytokeratin 7. The primary treatment modality is surgical excision. Due to their rarity, the precise role and regimen of adjuvant chemo-radiation therapy for MBT has not been established. We herein review a case of MBT with emphasis on primary treatment and treatment of recurrent disease, including the use of adjuvant pelvic radiation, discuss the current state of the literature and standards of practice regarding this malignancy.

1. Introduction

Ovarian neoplasms are a heterogeneous group composed of tumors showing epithelial, germ cell, and sex cord stromal differentiation. The ovarian Brenner tumor (BT) represents a rare epithelial ovarian neoplasm and accounts for 1–2% of all ovarian neoplasms. Identified in 1907 by Fritz Brenner, BT are now subclassified into benign, borderline (proliferative) or malignant categories (Speert, 1956). Malignant BTs (MBT) are extremely rare, comprising < 5% of all BT. MBT was first reported by von Numers in 1945 (von Numers, 1945). Given the rarity of this tumor, individual case reports, small case series, or recently, retrospective population-based studies provide the only available information about how to treat these patients, and the optimal adjuvant management remains unclear (Gezginç et al., 2012; Nasioudis et al., 2016; Verma et al., 2014). Herein we describe a case of MBT and review the current literature on these tumors.

2. Case report

A 77-year-old G1 with a past medical history of hypertension, acquired hypothyroidism after radioiodine thyroid ablation for Grave's disease, and hysterectomy presented for gynecologic consultation due to a pelvic mass incidentally discovered during evaluation for recurrent UTI.

Computerized Tomography (CT) of the abdomen and pelvis showed a 9.2 × 9.6 × 10.8 cm heterogeneous mass in the right hemipelvis likely arising from the ovary. No lymphadenopathy was identified. Small solitary pulmonary nodules were seen in the bilateral lower lobes, but were not consistent with metastatic disease patterns. Tumor markers were normal (CA 125 = 14 U/mL and CEA = 2.4 ng/mL), on initial evaluation. Interval time from initial consultation to surgery was 11 days.

During surgical exploration, a > 10 cm right ovarian mass was visualized. The mass was friable, fleshy and densely adhered to the right pelvic sidewall. However, there was no evidence of other metastatic disease. Initial frozen pathology returned as sex cord stromal versus epithelial ovarian neoplasm. Bilateral pelvic and paraaortic lymph node dissection was performed for staging.

Pathologic examination revealed a biphasic proliferation of epithelial cells with areas of solid, well-formed nests immediately juxtaposed with regions of infiltrative cord-like and single cell growth (Fig. 1). Cytologically, the tumor showed only mild atypia even in the

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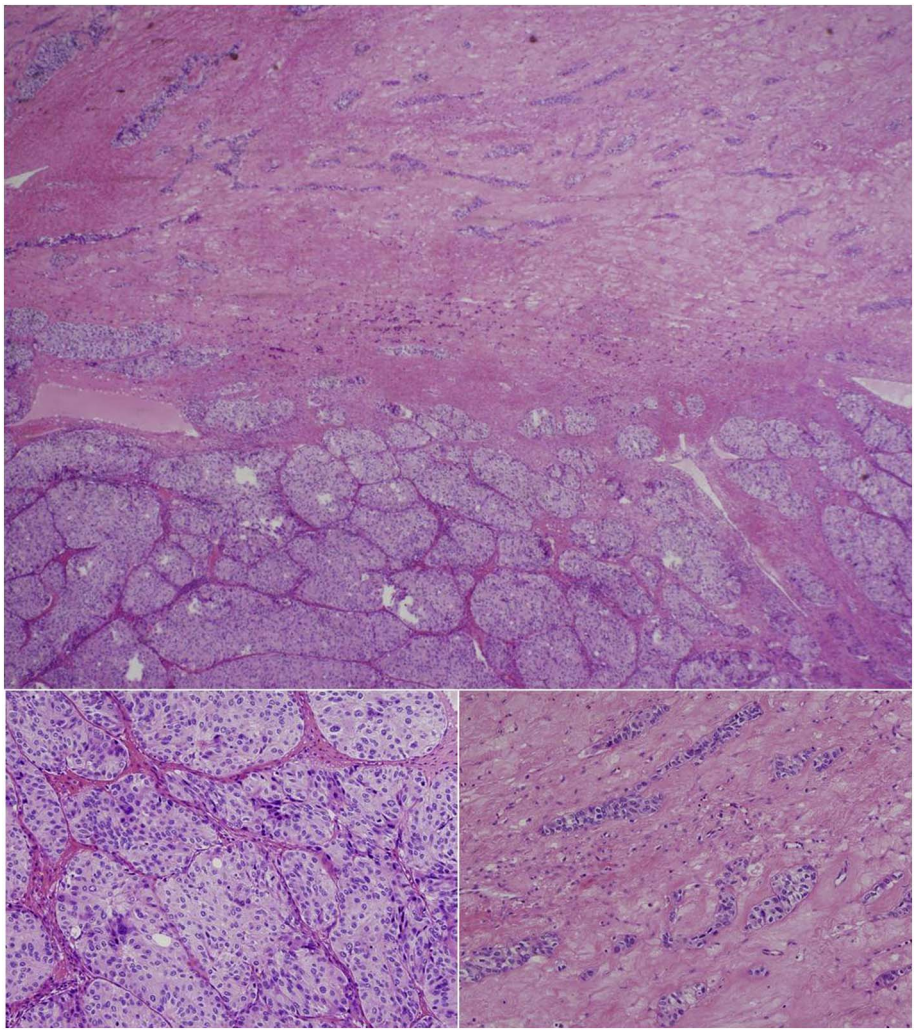

Fig. 1. Malignant Brenner tumor is characterized by the juxtaposition of areas of conventional Brenner tumor juxtaposed with infiltrative, frankly malignant cells. The interface between these two processes is illustrated here in the top image (Hematoxylin & eosin stain, 4 ×), which demonstrates well-demarcated nests of Brenner tumor at the bottom of the field [20 ×, bottom right image] and infiltrative cords and single cells percolating through the top portion of the field [20 ×, bottom left image].

infiltrative areas. Immunohistochemical studies showed positivity for cytokeratin 7 with focal GATA3 and p63 expression. Stains for the sex cord stromal marker inhibin, the neuroendocrine marker chromogranin, and the mesothelial marker calretinin were all negative. Based on the presence of urothelial differentiation with conventional BT morphology adjacent to frankly infiltrative malignancy, this tumor was classified as MBT and was considered low-grade on the basis of minimal cytologic atypia. The tumor was limited to the right ovary and was staged as pT2c on the basis of ascites fluid involvement and adhesions to the pelvic sidewall.

The patient desired an aggressive therapeutic strategy and was treated with carboplatin and paclitaxel every 3 week dosing for a total of 6 cycles. Disease recurrence was identified nearly 1 year later on CT with the appearance of a new right adnexal lesion measuring 2.5 × 1.9 cm and an enlarged left inguinal lymph node. Recurrence was biopsy confirmed in the lymph node. PET scan revealed multiple areas of increased uptake concerning for disease spread to the inguinal and external iliac lymph nodes and a second course of chemotherapy with carboplatin/paclitaxel was initiated. Interval CT after cycle 2 to assess efficacy showed mixed response and bevacizumab was added to the treatment regimen. Data showing increased progression free survival with Bevacizumab in epithelial ovarian tumors (GOG0218, ICON7) was extrapolated to MBT for treatment in this patient despite there being no data suggesting significant impact on overall survival (Burger et al., 2011; Oza et al., 2015). Favorable response was seen on PET after total cycle 12 and the patient continued bevacizumab for a total of 20 cycles. PET revealed local disease progression in the pelvis. The patient elected for removal of the pelvic mass and then received adjuvant radiation of 30 Gy in 10 fractions to the tumor bed. While limited information exists on radiation therapy in this tumor type, the family of epithelial ovarian neoplasms is known to be radiosensitive, and therefore was considered next line therapy as the patient had progressed through multiple chemotherapeutic options. She has been without evidence of disease since that time (24 months). To our knowledge this is the first report of a prolonged disease-free interval after treatment with debulking and radiotherapy in the setting of recurrent MBT.

3. Presenting symptoms

MBT presents similarly to other ovarian cancers (abdominal distension, abdominal pain, bulk symptoms and relative vague symptomatology) (Gezginç et al., 2012; Moon et al., 2000; Nasioudis et al., 2016). Patients typically present with disease confined to the ovary or surrounding tissue with lymphatic spread being less common (Nasioudis et al., 2016). < 10% of patients with MBT present with ascites, but MBT should be considered in patients with an ovarian mass and the presence of squamous cells in the peritoneal fluid (Driss et al., 2010). One case of MBT has been reported where the presenting symptom was intracranial hypertension from dural metastasis (Baizabal-Carvallo et al., 2010). While generally not hormone secreting, estrogen secreting MBTs have been reported leading to abnormal uterine bleeding, such as menstrual irregularity or postmenopausal bleeding (Joh et al., 1995; Kühnel et al., 1987).