Disappearance of Upper Urinary Tract Urothelial Carcinoma after Treatment of a Borderline Brenner Tumor: Case Report and Literature Review

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Established Facts
- Controversy remains about the potential association, common pathophysiology, and histologic similarities between Brenner tumors of the ovary and recurrent low-grade papillary urothelial carcinoma.

Novel Insights
- The particularity and originality of our case lies in the sustained disappearance, for more than 11 months, of a highly recurrent low-grade urothelial carcinoma of the lower urinary tract after ovarian tumor removal and the presumed disappearance of an untreated upper urinary tract urothelial carcinoma.

Keywords
Brenner tumor · Ovarian tumor · Urothelial carcinoma · Bladder cancer · Upper urinary tract

Summary
Background: Brenner tumors are relatively rare ovarian neoplasms with very few reported cases associating these tumors and urothelial carcinomas with different characteristics and particularities. Case Report: We report an unusual clinical case of borderline unilateral Brenner tumor of the ovary associated with a highly recurrent diffuse low-grade papillary urothelial carcinoma of the upper and lower urinary tract. The patient received a total cystectomy and resection of the Brenner tumor. Her clinical response was marked by the absence of recurrence of the urothelial carcinoma and the disappearance of an untreated tumor of the upper urinary tract.

The available literature in the association between these tumors was reviewed and their histologic appearance analyzed. Conclusion: The good prognosis of urothelial carcinoma in patients with Brenner tumors suggests different risk factors, physiopathologic features, and carcinogenesis than with typical urothelial carcinoma.

Introduction
Brenner tumors account for 2–3% of all ovarian tumors, and are derived from the ovarian surface epithelium or the pelvic mesothelium through transitional cell metaplasia [1]. They were originally known as transitional cell tumors of the ovaries due to their histologic similarities to the urothelium [2, 3]. In fact, the histologic findings in Brenner tumors are characterized by the intersection of
great numbers of branching fibro-vascular papillae covered by transitional epithelium that manifest the same spectrum of architectural and cytological features encountered in urothelial lesions of urinary tract [4]. Furthermore, the association between Brenner tumor of the ovary and papillary urothelial carcinoma has been described [5–8]. However, controversy remains about this potential association, common pathophysiology, and histologic similarities.

In the present article, we report an unusual case of borderline unilateral Brenner tumor of the ovary with a highly recurrent diffuse low-grade papillary urothelial carcinoma of the upper and lower urinary tract. In this report, the literature on the association of Brenner tumor with urothelial carcinoma of the urinary tract is reviewed and the histologic appearance of these tumors analyzed.

**Case Report**

In 2008, a 74-year-old woman (who gave informed consent for the reporting of her case) was diagnosed at our department as having diffuse papillary urothelial non-muscle invasive bladder tumors (NMIBT) of low grade and with no infiltration of the underlying connective tissue. No anomalies were noted on cytology and computed tomography (CT) scan of the upper urinary tract (UUT). During follow-up (2008–2014), the patient received transurethral resection of bladder tumor (TURBT) at a median interval of 4 months (18 times) following the same pattern each time. Cytology was always normal. In June 2013, a CT scan of the UUT showed a duplicate right collecting system and multiple bilateral suspicious lesions without infiltration of the ureter wall and the adjacent adipose tissue. Biopsy of these lesions by ureteroscopy confirmed the presence of multiple low-grade papillary urothelial tumors of the UUT that were treated conservatively by holmium laser fulguration. The endovascular instillations were not tolerated by the patient due to severe lower urinary tract symptoms, and she refused more radical treatment. However, after 18 extensive bladder tumor resections, the patient suffered from permanent urinary leakage and substantial alteration of her quality of life due to the development of a small-capacity atomic bladder. Moreover, surveillance of the UUT was rendered more hazardous because of technical difficulties surrounding catheterization of the ureteral orifices. Hence, the patient chose to undergo radical cystectomy. A preoperative magnetic resonance imaging scan revealed the presence of multiple gadolinium-enhanced lesions inside the 3 ureters and a small multilocular cystic mass with a solid component on the left ovary. The patient had no significant past gynecological history: G2P2A0, menarche at age 15, menstrual cycles regular, last mensturation at age 52.

A second flexible ureteroscopy with laser fulguration of the left ureter as well as the lower right ureter confirmed the presence of endoluminal papillary masses. Due to technical difficulties in finding the orifice, the upper left ureter was not explored, and lesions seen on CT scan were not treated at the same time. 1 month later, the patient underwent anterior pelvic exenteration with bilateral extended pelvic lymph node dissection. The upper right ureter was explored during the operation using a flexible cystoscope. 6 infracaventricular papillary tumors were noted and left untreated. The left ovarian tumor, seen on imaging, was removed with the specimen. Bricker-type ureterointestinal anastomosis was performed. The pathology report confirmed the diagnosis of low-grade diffuse urothelial papillary carcinoma of the bladder staged pTaN0, and contained the diagnosis of borderline Brenner tumor for the ovarian mass (fig. 1). Both tumors exhibited the same immunohistochemical profile: negative cytokeratin 20 (clone Ks 20.8, Dako Carpinteria, CA, USA), and positive cytokeratin 7 (clone OV-TL 12/30, Dako) and carcinoembryonic antigen (CEA) (polyclonal, Dako). 2 months after surgery, the double J stent of each ureter was removed, and diagnostic flexible ureteroscopy was performed under general anesthesia. The already treated ureters were totally free from recurrence. In the upper right ureter, the tumors had completely disappeared. After 14 months of follow-up, the patient is free from any recurrence.

**Discussion**

Brenner tumor is a relatively uncommon ovarian neoplasm that is part of the surface epithelial group of ovarian tumors [9]. It is named after Fritz Brenner who characterized it in 1907 [10]. The term ‘Brenner tumor’ was first used by Robert Meyer in 1932 [11]. The average age at presentation is 50 years, with 71% of the patients being more than 40 years [12]. The majority of cases are benign without cell atypia and stromal invasion [13]. Proliferating and borderline tumors account for less than 5% of Brenner tumors [14, 15]. However, the histopathogenesis is not completely elucidated. Our literature search yielded 35 borderline Brenner tumors reported since 1945. These tumors are usually asymptomatic and often discovered incidentally during pathologic examination of surgical specimen [13].

Although Brenner tumors and urothelial carcinomas have many close histologic-morphologic similarities and some studies have considered them as having the same origin and pathophysiology, we found only 4 cases describing an association between Brenner tumor and urothelial carcinoma in postmenopausal women [5–8]. The only article found in the literature reporting an association between a benign Brenner tumor and muscle invasive urothelial carcinoma is published in Chinese [8]. The 3 remaining cases described an association between borderline, proliferating, and malignant Brenner tumors, respectively, and urothelial NMIBT. In the first case, a bilateral ovarian tumor was misdiagnosed as metastasis from a urothelial NMIBT. The patient was subsequently treated with chemotherapy and died due to side effects. However, when the authors reviewed their case, they found that the morphologic appearance and biological behavior of the ovarian tumors were more consistent with a proliferative Brenner tumor than with metastases. They were the first to suggest a possible common pathway.

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**Fig. 1.** Strikingly similar histologic appearance of bladder non-invasive low-grade papillary urothelial carcinoma (upper right: hematoxin and eosin (HE) ×50; upper left: HE ×200) and ovarian borderline Brenner tumor (lower right: HE ×50; lower left: HE ×200). Note ovarian corpus albicans on the left side of lower right.
but without further details [5]. In the second reported case, the authors described the appearance of an NMIBT several months after the presentation of a malignant Brenner tumor. The initial diagnosis of bladder metastasis was subsequently rejected based on the absence of malignant features [6]. In the third case report, which was published recently, a Brenner tumor appeared 13 years after the diagnosis of urothelial NMIBT. The authors suggested that the 2 tumors are most likely independent coincidental primary neoplasms. However, they could not reject the theory of a common physiopathologic pathway, and concluded that more cases needed to be reported to better understand this association [7].

Our case report is the first describing an association between a borderline Brenner tumor and diffuse highly recurrent urothelial NMIBT. The particularity and originality of our case lies in the sustained disappearance, for more than 14 months, of a urothelial carcinoma of the UUT after ovarian tumor removal and the presumed disappearance of a UUT urothelial carcinoma. One could easily argue that in the case of our patient removal of the Brenner tumor changed the natural history of the disease. This is suggested by the presumed disappearance of the UUT tumor and the absence of recurrence 14 months after surgery. In the case reported by Ziadi et al. [7], there was no urothelial carcinoma recurrence 7 months after ovarian removal. The presence of mediators between these 2 tumors could be suggested. In addition, the highly recurrent disease in their 30-year-old female patient without known risk factors is unusual, as is the pattern of recurrence, the diffuse location of the tumors, and the absence of progression over years of follow-up in our case. Furthermore, in these 2 recent cases, prognosis was good. All these features suggest different risk factors, physiopathologic features, and carcinogenesis compared to typical urothelial carcinoma. Consequently, treatment of urothelial carcinoma should be less aggressive in these patients. Although the association between the 2 tumors may be coincidental, a link in their physiopathology cannot be excluded. Their association could reflect a common initiating event that induces similar multifocal changes in the epithelium of both organs with similar origin. However, despite the apparent morphologic and immunologic similarities, Brenner tumors are immunophenotypically distinct from urothelial cell proliferation. CK20 could be positive in transitional cell neoplasm but is practically absent in all Brenner tumors of the ovary, while CK7 is positive for both tumors, and CEA may also be expressed by both tumors [16–18]. In our case, both tumors were positive for CEA and CK7 and negative for CK20. This constellation was not helpful because it is encountered in a wide variety of carcinomas including those affecting the urothelium and the female genital tract [19]. Finally, ultra-structural, molecular, and genetic studies of these 2 tumors are needed to better understand their carcinogenesis.

**Disclosure Statement**

The authors do not have any conflict of interest.

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**References**


