

Original Article

Clinicopathological characteristics and incidence of mixed inverted urothelial papilloma and exophytic urothelial carcinoma of the urinary bladder: a single center retrospective study

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Abstract: Mixed inverted urothelial papilloma (IUP) and exophytic urothelial carcinoma (EUC) of the urinary bladder are a rare feature consisting of benign IUP with areas typical of exophytic carcinoma. Reports guiding the pathological diagnosis and treatment of these urothelial neoplasms are limited. Here, we examined three cases of mixed IUP and EUC to better establish the clinicopathological features of this disease. We reviewed 3206 transurethral resection of bladder tumor cases from the Sun Yat-sen Cancer Center between January 2001 and December 2014. We identified three cases of typical mixed IUP and EUC (3/3206), giving an incidence of 0.09% at the single center. All of the three patients, a 41-year-old male, a 69-year-old male and a 74-year-old male, presented with hematuria. In addition to typical IUP of the urinary bladder, 3 cases showed areas of exophytic neoplasms. One of the cases with exophytic neoplasms was high-grade papillary urothelial carcinoma of the urinary bladder, while the other two were low-grade papillary urothelial carcinoma. All the three patients showed symptomatic relapse at follow-up. Our study reports for the first time the incidence at a single center of mixed IUP and EUC, and identifies morphological features to help guide pathological diagnosis and clinical treatment.

Keywords: Clinicopathological characteristics, inverted urothelial papilloma, exophytic urothelial carcinoma

Introduction

Inverted urothelial papilloma (IUP) of the bladder is an uncommon tumor, generally considered benign, with an inverted growth pattern and normal to minimal cytologic atypia of the neoplastic cells [1-5]. Mixed IUP and exophytic urothelial carcinoma (EUC) of the bladder are a rare feature describing benign IUP with areas typical of exophytic urothelial neoplasms [6]. To the best of our knowledge, to date there have been few reports concerning mixed IUP and EUC to guide pathological diagnosis and clinical treatment.

To better understand mixed IUP and EUC, a literature search was performed using Pubmed. We reviewed all the available literature focused on mixed IUP and EUC, but identified only three

relevant articles [7-9]. A single report by Albores-Saavedra and colleagues described the features of inverted urothelial papilloma of the urinary bladder with a distinctive focal papillary growth pattern in the two cases [7]. But this is not the case that mixed IUP and EUC. Moreover, according to the 2004 WHO classification system, an initial diagnosis of inverted urothelial papilloma should be challenged if progression is observed, as many cases of recurrence or progression are diagnosed as papillary urothelial carcinoma with inverted growth at the initial biopsy [10]. The reference cited in this study, however, focused on urothelial transitional cell carcinoma with endophytic growth patterns instead of mixed IUP and EUC [11-13]. We further reviewed "Biopsy Interpretation of the Bladder, Second Edition", written by Epstein et al., which states that mixed

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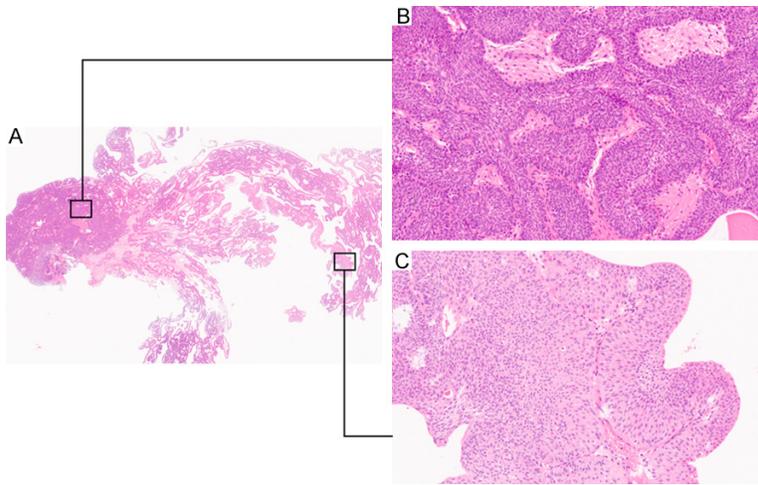


Figure 1. Morphological features of mixed inverted urothelial papilloma (IUP) and exophytic urothelial carcinoma (EUC) from Case 1. A. Low magnification image of the bladder tumor showing distinct morphological features. B. High magnification image of a tumor section showing inverted urothelial papilloma. No nuclear atypia or mitotic figures are observed. C. High magnification image of exophytic papilloma showing low-grade papillary urothelial carcinoma of the urinary bladder.

inverted and exophytic urothelial neoplasms should be followed with repeat periodic cystoscopic examinations. However, there is no further information on the hybrid lesions in their article [14].

Due to the limited amount of research and reports on mixed IUP and EUC, we reviewed all of the transurethral resection of bladder tumor (TURBT) cases of the urinary bladder diagnosed at the Sun Yat-sen Cancer Center between January 2001 and December 2014.

The aim of this article is to enrich our knowledge of mixed IUP and EUC and help guide pathological diagnosis and clinical treatment.

Methods

This study was approved by the Institute Research Medical Ethics Committee of Sun Yat-sen University, and the informed consent (written or verbal) was obtained for use of retrospective tissue samples from the patients within this study. All samples were anonymized.

To extract all studies around mixed IUP and EUC, we performed a sensitive search in PubMed web of knowledge from the commencements until June 2016. The search was carried out using keywords “Inverted urothelial

papilloma”, “exophytic urothelial papilloma”, “inverted urothelial neoplasm”, “exophytic urothelial neoplasm”, “urothelial carcinoma”, “urothelial papilloma”, with Boolean “OR” between them combining “Polymorphism” with Boolean “AND”.

All TURBT samples were available for review by hematoxylin and eosin stained sections.

Results

The incidence of mixed inverted and exophytic urothelial neoplasms of the urinary bladder at a single center

For this study, we identified all TURBT cases of the urinary bladder diagnosed at the Sun Yat-sen University Cancer Center,

Guangzhou, China, between January 2001 and December 2015. Two genitourinary pathologists reviewed the hematoxylin and eosin-stained slides from all cases. We identified three typical Mixed IUP and EUC (3/3206), resulting in an incidence of this mixed lesion of 0.09% at a single center.

Clinical cases

Case 1: A 41-year-old man presented with intermittent hematuria. Color Doppler ultrasound examination showed a 2.3 cm × 1.4 cm hypoechoic lesion located on the trigone of the urinary bladder. The tumor was completely excised by TURBT. Twenty-four months after the complete excision of the tumor, the patient is symptomatic relapse.

Case 2: A 69-year-old man presented with gross hematuria and dysuria. Color Doppler ultrasound examination showed a 4.0 cm × 2 cm hypoechoic lesions located on the trigone of the urinary bladder. The tumors were completely excised by TURBT. The patient has remained disease free for 12 months.

Case 3: A 74-year-old man presented with gross hematuria. Color Doppler ultrasound examination showed two 3.3 cm × 2.5-cm and 3.0 cm × 2.5 cm hypoechoic lesions located on the trigone of the urinary bladder. The tumors were

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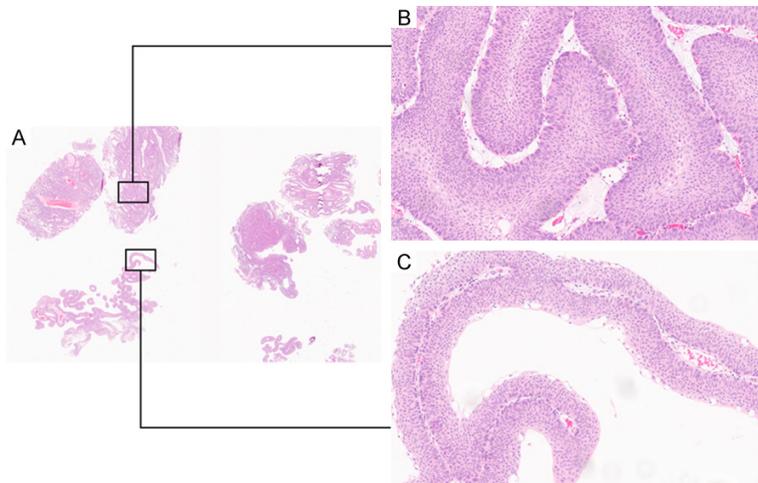


Figure 2. Morphological features of mixed inverted urothelial papilloma (IUP) and exophytic urothelial carcinoma (EUC) from Case 2. A. Low magnification image of the bladder tumor showing distinct morphological features. B. High magnification image of a tumor section showing inverted urothelial papilloma. No nuclear atypia or mitotic figures are observed. C. High magnification image of exophytic papilloma showing low-grade papillary urothelial carcinoma of the urinary bladder.

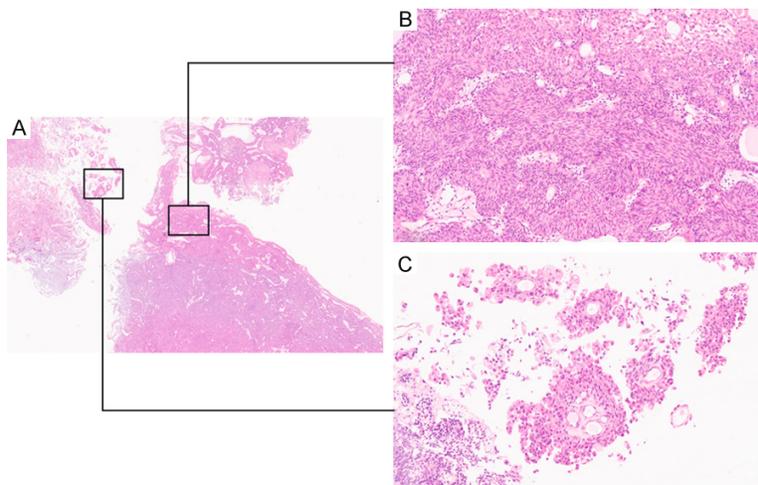


Figure 3. Morphological features of mixed inverted urothelial papilloma (IUP) and exophytic urothelial carcinoma (EUC) from Case 3. A. Low magnification image of the bladder tumor showing distinct morphological features. B. High magnification image of the tumor section showing inverted urothelial papilloma. No nuclear atypia or mitotic figures are observed. C. High magnification image of exophytic papilloma showing high-grade papillary urothelial carcinoma of the urinary bladder.

completely excised by TURBT. Eighteen months after the complete excision of the tumor, the patient is symptomatic relapse.

Morphological features

Microscopic examination of the three bladder tumors showed two distinct morphological fea-

tures (**Figures 1A, 2A, 3A**). The three cases showed similar features in the IUP, which consisted of a relatively smooth surface covered by histologically and cytologically normal urothelium. Long and short papillary fronds lined by three to eight layers of well-differentiated urothelial cells invaginated extensively from the surface urothelium into the subadjacent lamina propria. The urothelial cells showed no nuclear atypia or mitotic figures (**Figures 1B, 2B, 3B**). Typically, the IUP displayed a streaming pattern rather than a fibrovascular urothelial papillae.

Moreover, the three bladder tumors showed different features in the exophytic papillary section. Case 1 and 2 showed low-grade papillary urothelial carcinoma of the urinary bladder (**Figures 1C, 2C**), while Case 3 showed high-grade papillary urothelial carcinoma of the urinary bladder (**Figure 3C**).

Discussion

According to the 2004 WHO classification, exophytic urothelial neoplasms include exophytic urothelial papillomas, papillary urothelial neoplasms of low malignant potential, low-grade and high-grade urothelial carcinomas [8]. Previous studies have found that IUP accounted for less than 2% of all urothelial neoplasms and could be considered non-malignant [1, 15, 16]. Kunze and colleagues divided IUPs into two morphologically distinct variants: the trabecular and glandular IUPs [17]. Picozzi et al. reported that IUP appeared to be a risk factor for transitional cell carcinoma and careful follow-up was required if the histologic diagnosis of IUP was definitive or questionable [5]. In rare cases, IUP

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could be mixed with exophytic neoplasms, but there is no data regarding the incidence of mixed IUP and EUC.

Mixed IUP and EUC are IUP with areas typical of exophytic urothelial neoplasms. There were few case reports regarding mixed IUP and EUC in the existing literature. Moreover, neither the "Biopsy Interpretation of the Bladder", by Epstein et al. nor the WHO monograph on tumors of the urinary system and male genital organs have provided exact descriptions and definitions of mixed IUP and EUC [8, 11]. We reviewed all TURBT cases of the urinary bladder diagnosed at the Sun Yat-sen Cancer Center between January 2001 and December 2014, and interestingly, we found only three cases of mixed IUP and EUC. Our study reports for the first time the incidence of mixed IUP and EUC at a single center. For mixed IUP and EUC, the inverted papillary fronds display the typical histological features of IUP. The majority of urothelial cells lacked cytologic atypia and mitotic figures and did not extend beyond the lamina propria. The exophytic urothelial neoplasms displayed different morphological features, including papillary urothelial neoplasms of low-grade and high-grade urothelial carcinomas. Compared with IUP, mixed IUP and EUC should be treated according to the severity of the exophytic urothelial neoplasm [7, 8, 18, 19].

In conclusion, we have reported for the first time the incidence of mixed IUP and EUC at a single center and identified the morphological features to help guide the pathological diagnosis and clinical treatment of this disease.

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Disclosure of conflict of interest

None.

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