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Original contribution

Invasive high-grade urothelial carcinoma of the bladder, renal pelvis, ureter, and prostatic urethra arising in a background of urothelial carcinoma with an inverted growth pattern: a contemporary clinicopathological analysis of 91 cases☆,☆☆

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Summary Urothelial carcinoma with an inverted/endophytic growth pattern can occasionally mimic inverted urothelial papilloma and pose diagnostic challenges when assessing the presence or absence of invasion. Making these distinctions is critical for guiding appropriate treatment and improving patient outcomes. Here we conducted one of the largest studies to date of invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern. Primary sites examined included bladder, renal pelvis, ureter, and prostatic urethra. Clinicopathological parameters including extent of invasion, variant histology, presence of urothelial carcinoma in situ, and clinical follow-up were obtained. Ninety-one cases from 82 patients were included in the study. Lamina propria invasion was present in 81% of bladder, 60% of ureter, 20% of renal pelvis, and 100% of prostatic urethra cases. Muscularis propria invasion was identified in 19% of bladder, 14% of ureter, and 20% of renal pelvis cases. Urothelial carcinoma invaded periureteric fat in 29% of ureter cases and invaded the renal parenchyma in 60% of renal pelvis cases. Clinical follow-up was available for 77 of 82 (94%) patients with a mean duration of 18 months. Recurrent urothelial carcinoma persisted in 63 of 82 (77%) patients, 16 of 82 (19%) progressed with metastatic disease, and 20 of 77 (26%) patients with bladder involvement died of disease. This study further emphasizes the importance of distinguishing these tumors from benign mimickers of urothelial carcinoma. Recognition of invasive foci is also critical in view of the potentially high frequency of recurrence and the possibility of advanced disease in a subset of these patients.

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1. Introduction

Like several other genitourinary tumors, urothelial carcinoma is known to portray a wide spectrum of morphologic and architectural patterns. One particularly challenging entity along this continuum is urothelial carcinoma with an inverted or endophytic growth pattern. In 1959, the United States Armed Forces Institute of Pathology illustrated some of the challenges caused by this group, such as their propensity to mimic benign lesions and confound the presence or absence of invasion [1]. The histologic features and issues associated with this particular growth pattern were further elucidated in 1997 [2]. It was initially described as a subset of urothelial carcinoma with prominent endophytic growth that consisted of 2 main histologic patterns: one with interanastomosing cords and trabeculae resembling inverted papilloma (inverted papilloma-like pattern) and the other with broad bulbous borders pushing into the lamina propria (broad-front pattern) [2-4]. One or both of these patterns may be present within a lesion, yet both are equally capable of obfuscating invasion. Architectural features that may prompt concern for invasion include extensive bulbous projections into the lamina propria or interlacing of neoplastic cords with fibers of muscularis mucosae. Assessing for invasion thus becomes a more onerous task when the aforementioned is present in bladder biopsy or transurethral resection of bladder tumor specimens with tangential sectioning, cautery artifact, and/or crush artifact [2,5].

An additional challenge associated with urothelial carcinoma with an inverted growth pattern is that it can often be confused with inverted urothelial papilloma, a relatively uncommon benign tumor that can occur anywhere along the urinary tract and lacks the potential for malignant transformation [6]. The primary cause for confusion is largely attributed to their overlapping morphologies. Both can be described as trabecular lesions with inverted growth and anastomosing cords of urothelium. Further complicating the issue is the recently broadened morphological features of inverted urothelial papilloma which, in rare cases, may also exhibit vacuolated or foamy cytoplasm and focal papillary features, as seen in urothelial carcinoma [6-9]. Despite their morphological commonalities, urothelial carcinoma with inverted growth and inverted urothelial papilloma are distinctly different clinicopathological entities whose treatment protocols and expected clinical outcomes are antithetical to one another. Inverted urothelial papilloma is a benign entity with little risk of recurrence and malignant potential, whereas urothelial carcinoma with inverted growth is malignant and may warrant invasive therapy or surveillance depending on the presence or absence of associated invasion [6,7]. Misdiagnosing one for the other would thus cause significant errors in management and may lead to poorer patient outcomes.

Although several decades have passed since it was initially described, urothelial carcinoma with an inverted growth pattern continues to befuddle pathologists because it can easily be mistaken for its benign mimicker, inverted urothelial papilloma, and cases with invasion can often seem equivocal. Despite such known diagnostic challenges, little has been added to the literature to better define this problematic entity. Here we conducted what is likely the largest study to date following a review of the current English literature of invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern to further characterize its clinicopathological features and impact on patient outcomes.

2. Materials and methods

2.1. Case selection

Cases of invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern arising from the bladder, renal pelvis, ureter, and prostatic urethra were obtained through our urologic pathology files and the senior author's consults. Clinicopathological parameters including extent of invasion, variant histology, presence of urothelial carcinoma in situ, and clinical follow-up were obtained. This study was completed following the guidelines of and with approval from the Institutional Review Board of our institution.

3. Results

Ninety-one cases from 82 patients were included in the study. The mean patient age was 69 years (range: 38-95 years), and 65 patients were male (80%). The distribution of the primary sites included bladder (n = 77; 84%), ureter (n = 7; 8%), renal pelvis (n = 5; 6%), and prostatic urethra (n = 2; 2%) (Figs. 1-6). Several cases had mixed patterns of inverted growth including broad-front pushing patterns, large nests, and interanastomosing cords/trabeculae.

Lamina propria invasion was present in 62 of 77 (81%) bladder cases, 4 of 7 (60%) ureter cases, 1 of 5 (20%) renal pelvis cases, and 2 of 2 (100%) prostatic urethra cases. Muscularis propria (detrusor muscle) invasion was present in 15 of 77 (19%) bladder cases, 1 of 7 (14%) ureter cases, and 1 of 5 (20%) renal pelvis cases. Urothelial carcinoma invaded periureteric fat in 2 of 7 (29%) ureter cases and invaded the renal parenchyma in 3 of 5 (60%) renal pelvis cases. An exophytic component was present in 82 of 91 (90%) cases, and adjacent urothelial carcinoma in situ was present in 39 of 91 (43%) cases.

Variant/divergent histology was present in 17 of 91 (19%) cases, primarily from bladder (n = 15), and included micropapillary (n = 5) (Fig. 6), glandular (n = 2), clear cell (n = 4), squamous (n = 7), neuroendocrine (n = 1), plasmacytoid (n = 1), and nested (n = 1) variants. Tumors arising from the renal pelvis and ureter each had a case with squamous differentiation. Of the 2 cases involving prostatic urethra, neither demonstrated variant histology. Conversely, several cases involving the bladder demonstrated more than 1 variant within the same tumor. This was more commonly seen when 1 of the

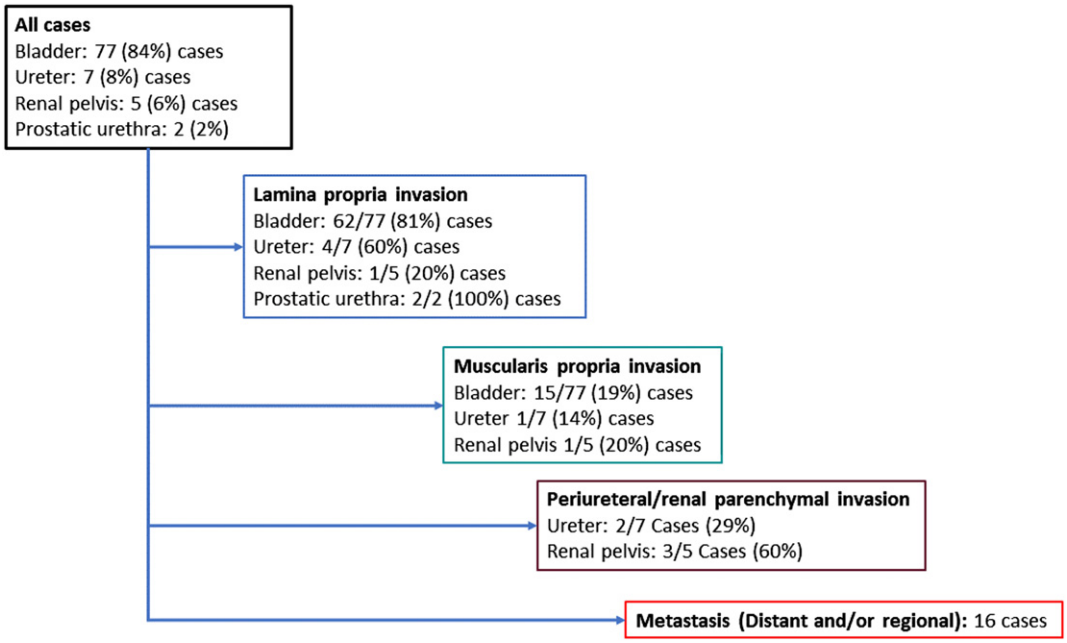

Fig. 1 Flowchart summarizing clinicopathological findings.

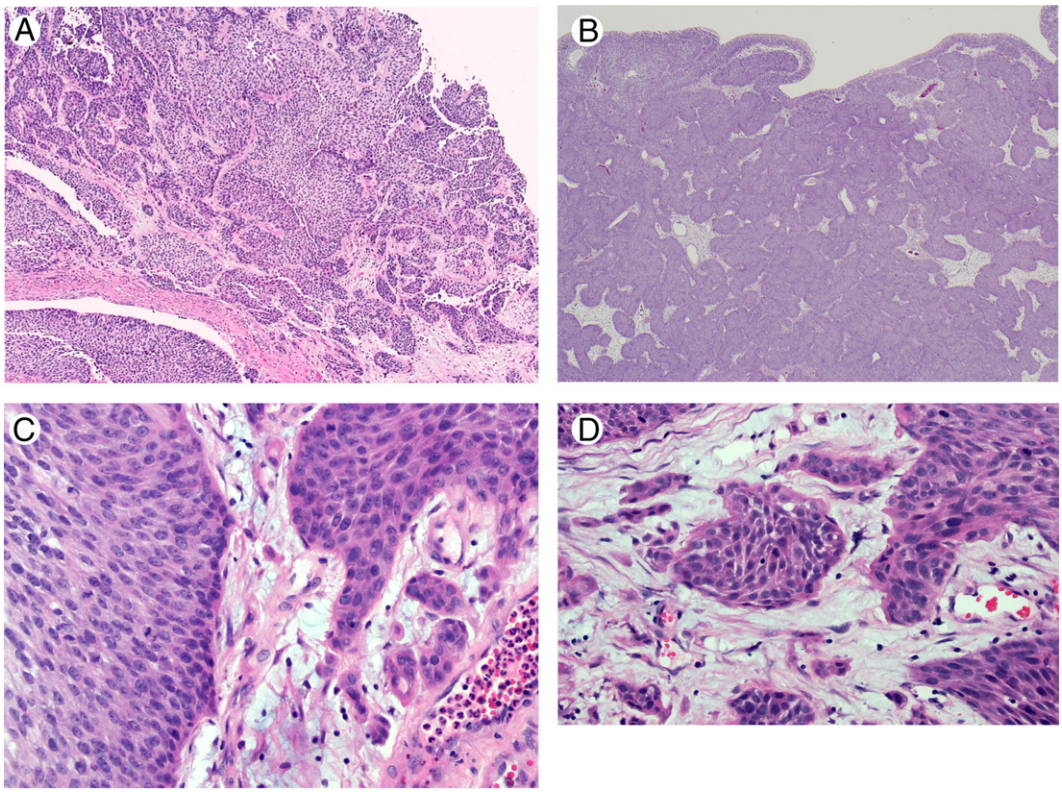

Fig. 2 A, Bladder with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern. Note invasive nests with irregular borders (hematoxylin and eosin [H&E], original magnification ×4). B, Bladder with inverted papilloma. Note absence of invasive nests and presence of smooth borders (H&E, ×4). C, Bladder with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×20). D, Bladder with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×20).

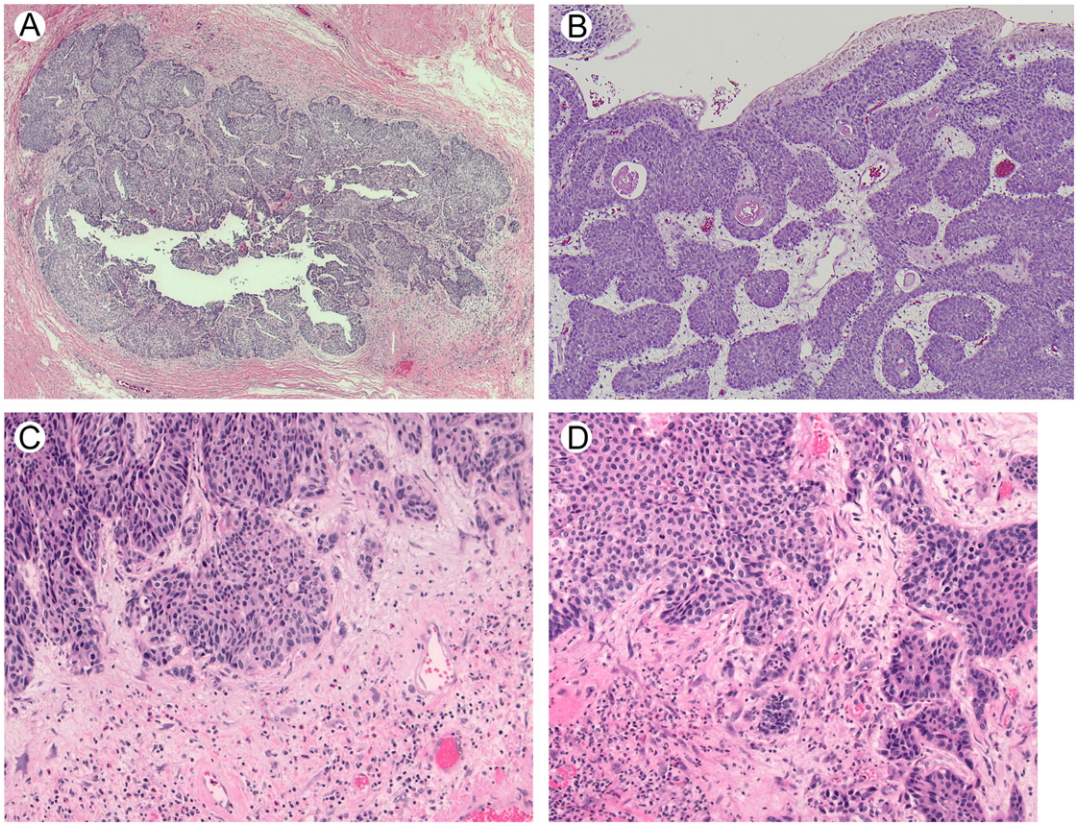

Fig. 3 A, Ureter with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern. Note invasive nests with irregular borders (H&E, ×2). B, Ureter with inverted papilloma. Note absence of invasive nests and presence of smooth borders (H&E, ×4). C, Ureter with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×10). D, Ureter with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×10).

variants was either glandular or squamous. Including all sites, squamous differentiation was the most common variant detected (7/91; 8%), followed by micropapillary (5/91; 6%).

Clinical follow-up was available for 77 of 82 (94%) patients, with a mean duration of 18 months (range: 0.2-74 months). Urothelial carcinoma recurred in 63 of 82 (77%) patients, 16 of 82 (19%) experienced disease progression with metastasis (14 patients had metastasis with/without regional lymph node involvement, and 2 patients had only regional lymph node involvement), and 20 of 77 (26%) patients with primary bladder cancer died of disease.

4. Discussion

Inverted urothelial neoplasms of the genitourinary tract are relatively uncommon, typically occurring in the urinary bladder and less frequently in the upper urinary tract [7,10]. However, familiarity with these lesions (an assortment of benign and malignant neoplasms) is important because they occasionally bear semblance to one another, thus increasing the likelihood for diagnostic errors. This is a common issue associated with urothelial carcinoma with an inverted growth pattern and its benign mimicker, inverted urothelial papilloma. Correctly distinguishing between the two warrants recognition of subtle histological differences and the presence of invasion. Inverted urothelial papilloma, a benign tumor, typically has a smooth or dome-shaped surface with cords and trabeculae made up of orderly, monotonous cells with occasional peripheral palisading growing endophytically beneath the surface. Urothelial carcinoma with an inverted growth pattern, on the other hand, may show an exophytic papillary lesion at its surface and, beneath, thickened trabeculae with endophytic growth made up of cytologically atypical cells with increased mitotic figures [11,12]. On occasion, distinguishing between the two can become inordinately challenging especially when these features are obscured, such as in limited biopsy specimens with extensive crush or cautery artifact, or tangential sectioning.

Urothelial carcinoma with an inverted growth pattern was initially described decades ago, notable for its overlapping morphological features with inverted urothelial papilloma and potential for obfuscating invasion as a result of its deceptive growth pattern [2]. However, it has since faded into obscurity, as little has been added to the literature to enhance

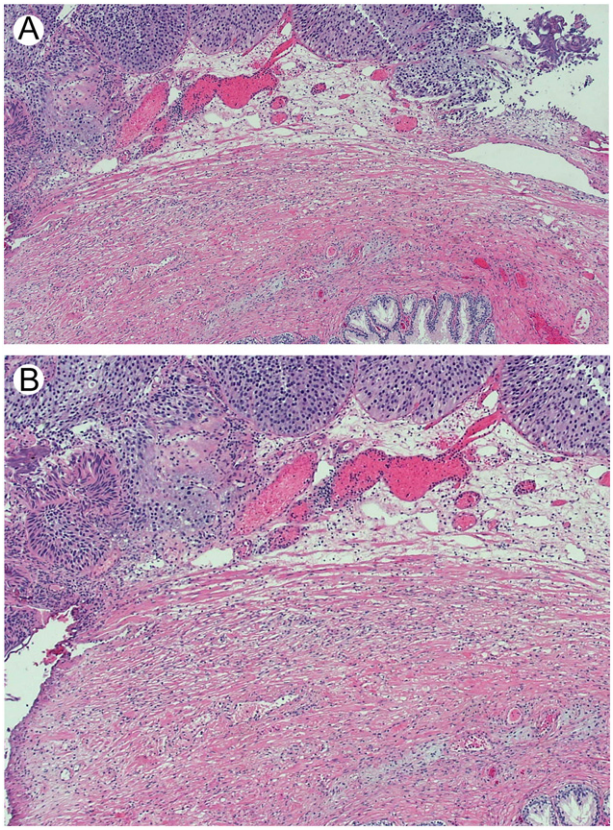

Fig. 4 A, Prostatic urethra with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×2). B, Prostatic urethra with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×4).

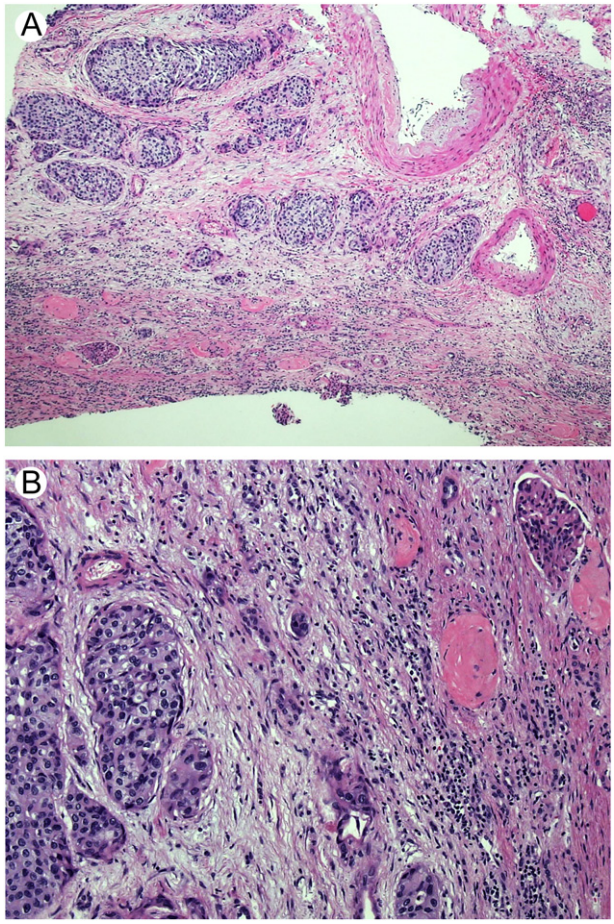

Fig. 5 A, Kidney/renal pelvis with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×4). B, Kidney/renal pelvis with invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×10).

our understanding of this ambiguous growth pattern. We thus chose to carry out what is likely the largest study to date following a review of the current English literature of invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern. This is also likely the largest study to analyze the clinicopathological features of urothelial carcinoma with an inverted growth pattern arising from multiple different primary sites.

Given the relatively uncommon nature of inverted neoplasms arising in the upper urinary tract, most of our cases of invasive urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern originated from the bladder (n = 77), with significantly fewer cases arising from the ureter (n = 7), renal pelvis (n = 5), and prostatic urethra (n = 2). There were clear distinctions between all 4 groups regarding the extent of invasion, variant histology, presence of urothelial carcinoma in situ, and clinical outcomes. However, the mean age for all 4 groups was similar and consistent with the literature for the peak incidence of urothelial carcinoma occurring during the seventh decade of life with a strong male predilection [4,13]. Each group averaged between 67 and 73 years of age and consisted primarily of male patients with a male to female ratio of 3.8:1.

There were distinct differences in the stage at presentation for patients in each of the 4 groups. All patients with involvement of prostatic urethra were categorized as pT1 on initial presentation. Similarly, patients in the bladder group also presented at earlier stages of disease, with 81% initially categorized as pT1. Conversely, patients with upper urinary tract urothelial carcinoma (renal pelvis and ureter) were more likely to present at higher stages (categorized as pT2 or more) than patients with urothelial carcinoma of the bladder or prostatic urethra. In our study, 80% and 43% of renal pelvis and ureter cases were categorized pT2 or higher at presentation, respectively. This is in keeping with the current literature which suggests that 50% of patients with upper urinary tract carcinoma will present with superficial disease (pTis, pTa, pT1) and the remaining half will present at stages pT2 or greater, in contrast to only 25% of patients with bladder carcinoma which typically present at stages pT2 or greater [13].

However, earlier stage at presentation did not confer a significantly better prognosis for patients in the bladder group. Similarly, patients with involvement of the renal pelvis also

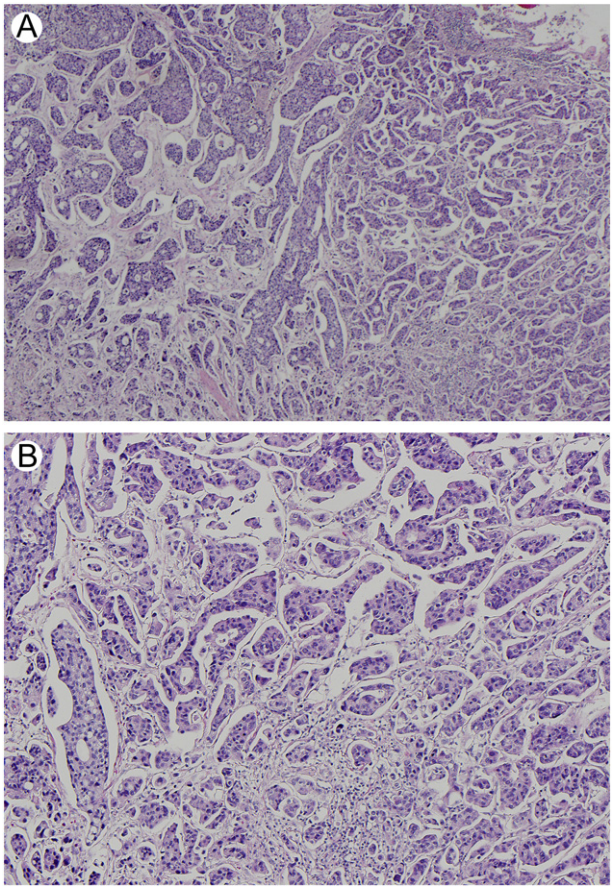

Fig. 6 A, Bladder with focus of invasive micropapillary urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×4). B, Bladder with focus of invasive micropapillary urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern (H&E, ×10).

had poor outcomes. Interestingly, both groups shared a similar proportion of cases with urothelial carcinoma in situ (~41%). Previous studies have suggested that patients presenting with invasive urothelial carcinoma and concomitant urothelial carcinoma in situ have a greater likelihood of disease progression and cancer-associated death than patients with carcinoma in situ alone [11].

Variant histology, another ominous prognostic indicator, was also present in about 20% of cases in both groups. They demonstrate an increased likelihood of distant metastasis and a greater propensity of locally aggressive disease, and are less likely to respond to chemotherapy or radiotherapy in the same manner as conventional urothelial carcinoma [3,14-16]. In addition, studies of upper urinary tract urothelial carcinoma with variant histology have shown an associated increased risk of recurrence, lymphovascular invasion, and propensity for diagnosis at a higher grade and stage [17]. In our study, these features likely contributed to disease progression in a subset of these patients. Of the 61 bladder patients with available clinical follow-up, approximately 20% developed metastasis and 26% died. Of the 5 patients with renal pelvis urothelial carcinoma, 2 (40%) developed metastasis and both subsequently passed away. It is also important to note that urothelial carcinomas with inverted growth in the upper tract may also be associated with microsatellite instability. Studies by Ehsani and Osunkoya [18] and by Harper et al [19] have demonstrated that mismatch repair protein loss of MSH2 and/or MSH6 occurs in patients with urothelial carcinoma with inverted growth in the upper tract, and these markers are relatively sensitive and specific for identifying patients with potential Lynch syndrome.

Cases with tumor arising in the ureter had slightly better outcomes. Variant histology was present in only 1 of 7 cases (14%), and urothelial carcinoma in situ was present in 4 (60%). Only 1 patient developed disease progression with metastasis, but all 7 patients were alive on clinical follow-up. Patients with involvement of the prostatic urethra had the most favorable outcomes of all 4 groups. Although urothelial carcinoma in situ was present in both cases, neither had variant histology, and both were categorized as pT1. Neither patient went on to develop disease recurrence, and both patients were alive on clinical follow-up.

In summary, this is likely the largest study to date following a review of the current English literature of invasive high-grade urothelial carcinoma arising in a background of urothelial carcinoma with an inverted growth pattern. This study further emphasizes the importance of accurately differentiating these tumors from benign mimickers of urothelial carcinoma with an inverted growth pattern. Recognition of invasive foci and variant/divergent histologic features is also crucial given the potential likelihood of recurrence and the possibility of advanced disease in a subset of these patients.

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