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Case Report

Non-invasive low-grade papillary urothelial carcinoma with whorled features: a report of two cases

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Abstract: Non-invasive papillary urothelial carcinomas present as cytoarchitectural disorders without invasion through the basement membrane. They are divided into low-grade and high-grade categories on the basis of the extent of cytologic atypia and architectural disarray. Notably, divergent differentiation (such as squamous and glandular differentiation) and variants (such as nested, micropapillary, plasmacytoid, and sarcomatoid) are reported primarily in invasive and high-grade urothelial carcinomas. We present two cases of low-grade non-invasive papillary urothelial carcinoma with recently described whorled features (urothelial eddies). Both patients were 77-year-old males with small papillary lesions in the bladder. Histopathologic examination revealed low-grade non-invasive papillary urothelial carcinoma with a sporadic whorled pattern. Patient number 1's tumor exhibited cytokeratin (CK) 20 immunopositivity, up to 5% Ki-67 labeling, and wild-type p53 staining. Patient number 2's tumor was negative for CK20 with wild type p53 staining in portions with whorls, but demonstrated diffuse CK20 and extensive p53 staining (possible mutation) in tumor portions lacking whorls. Patient number 1 experienced a 14-month recurrence and a second possible recurrence 43 months after the initial diagnosis. Patient number 2 experienced recurrence of low-grade papillary urothelial carcinoma with focal whorls in one location and subsequently a distinct low-grade papillary urothelial carcinoma with whorled features in a different part of the bladder. Our limited study supports the reported association of rare whorled features with non-invasive low-grade papillary urothelial carcinoma, albeit with a diverse immunophenotype. Evaluation of both whorled and non-whorled areas in the histology along with CK20 and p53 staining may be helpful for complete diagnostic and prognostic evaluation of these cases.

Keywords: Non-invasive papillary urothelial carcinoma, low-grade, whorled, urothelial eddies

Introduction

Urothelial carcinoma is the most prevalent type of urinary bladder cancer, which is the sixth most common type of cancer in the United States. Bladder cancer can be classified into 3 main clinically significant categories with different prognoses and management strategies: non-muscle-invasive bladder cancer (NMIBC) (approximately 75% of newly detected cases); muscle invasive, non-metastatic disease; and metastatic bladder cancer [1]. Non-invasive papillary urothelial carcinoma (NIPUC) presents as a cytoarchitectural disorder without invasion through the basement membrane [2]. These tumors constitute 70-75% of newly diagnosed urothelial carcinomas, with a median patient age of 70 years. These patients are at high risk of recurrence, but less than 15% develop invasive disease. Urothelial carcinomas are divided into low-grade (LG) and high-grade (HG) on the basis of the extent of cytologic and architectural alterations [2].

Histologic grade is an important prognostic parameter for NMIBC. In fact, tumor grade is considered the second most important variable affecting progression after the presence of carcinoma-in situ (CIS) [3]. While most NMIBCs are classified in a binary fashion as pure LG or HG, grade heterogeneity can be observed and there is a lack of consensus on its prognostic and therapeutic implications [4]. A recent study of transurethral resection specimens of NMIBCs reported comparable recurrence-free survival with worse 36-month progression-free survival

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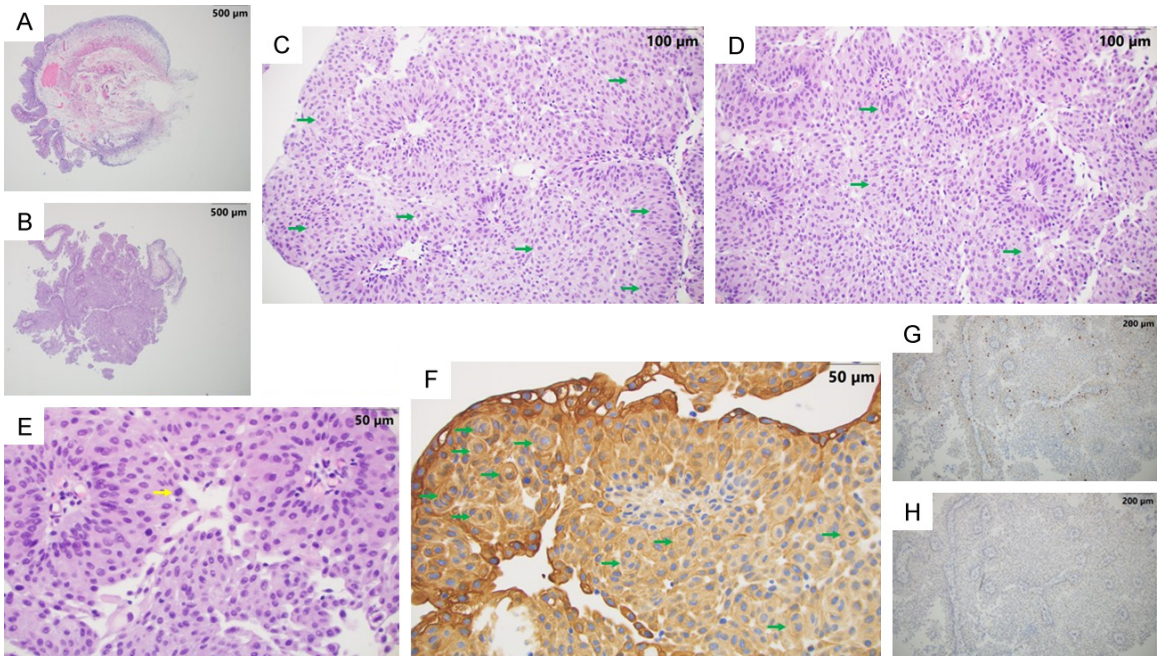

Figure 1. Histopathologic and immunohistochemical features in patient number 1. A and B: H&E-stained sections at low magnification of a bladder biopsy showing non-invasive papillary urothelial carcinoma (H&E ×40). C and D: H&E-stained sections showing low-grade urothelial carcinoma with a scattered whorled pattern (green arrows) (H&E ×200). E: H&E-stained section showing low-grade urothelial carcinoma with a rare superficial mitosis (yellow arrow) (H&E ×400). F: CK20 immunopositivity in low-grade urothelial carcinoma, including foci with a whorled pattern (green arrows) (CK20 ×400). G: Ki-67 immunostained section showing a low labeling index in tumor cells (< 5%) (Ki-67 ×100). H: p53 immunostained section showing wild-type staining in tumor cells (p53 ×100).

in HG patients than in mixed-grade (MG) patients, indicating that the impact of grade is greater on progression than on recurrence [4]. In contrast, most invasive urothelial carcinomas are HG. Nonetheless, grading is recommended for all invasive carcinomas (particularly those infiltrating the lamina propria), as significant outcome differences have been reported between low- and high-grade invasive tumors [2].

Divergent differentiation (such as squamous, glandular, or trophoblastic differentiation) and histologic subtypes (such as nested, micropapillary, plasmacytoid, sarcomatoid, and lymphoepithelioma-like) are reported primarily in invasive and HG urothelial carcinomas [2, 5-7]. There are no World Health Organization (WHO)-recognized histologic subtypes of LG NIPUC, except for a rare subset that can have an inverted growth pattern without stromal invasion and another rare subset with micropapillary processes that is not classified as micropapillary carcinoma [2, 5, 6].

A histologic pattern seen in LG urothelial carcinomas rarely mentioned in the literature is the whorled pattern. This pattern is characterized by concentrically organized small nests of ovoid to spindled cells in an onion skin pattern ("urothelial eddies"), without morphologic evidence of keratinization [8, 9]. Two studies have shown that the low tumor stage (Ta in 9/10 cases [8] and 12/12 cases [9]) and status of patients at follow-up support the low level of aggressiveness of these tumors [8, 9]. We present two cases of LG NIPUC with whorled features and discuss its possible relevance to prognosis.

Case reports

Patient 1

A 77-year-old male was first diagnosed with LG papillary urothelial carcinoma (PUC) on the left posterior wall of the urinary bladder focally involving subepithelial connective tissue (lamina propria; stage pT1) in August 2020. Focal whorls were noted. On follow-up cystoscopy, the patient was noted to have two small papillary tumors. A cold cup biopsy was performed in October 2021. Histopathologic examination revealed LG NIPUC (**Figure 1A**, **1B**) with a sporadic whorled pattern (**Figure 1C**, **1D**). Rare

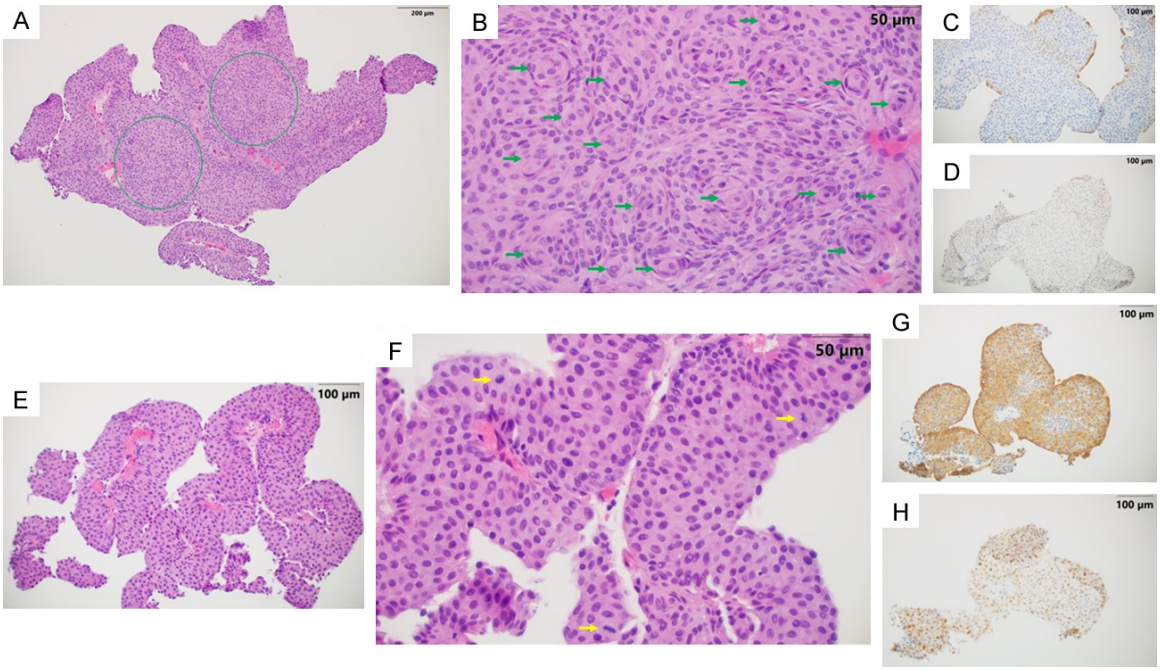

Figure 2. Histopathologic and immunohistochemical features in patient number 2. (A and B) H&E-stained sections of a bladder biopsy sample showing non-invasive papillary urothelial carcinoma with numerous foci of whorled pattern (A, green circles highlighting areas with prominent whorls; B, green arrows highlighting whorls) (A: H&E ×100; B: H&E ×400). (C) CK20 immunostained section showing the absence of staining in urothelial carcinoma with foci of a whorled pattern (except staining of a few umbrella cells) (CK20 ×200). (D) p53 immunostained section showing wild-type staining in urothelial carcinoma with foci of a whorled pattern (p53 ×200). (E and F) H&E-stained sections of a bladder biopsy sample showing non-invasive papillary urothelial carcinoma component without a whorled pattern, focally with occasional superficial mitoses (F, yellow arrows) (E: H&E ×100; F: H&E ×400). (G) CK20 immunostained section showing positive staining in urothelial carcinoma component without a whorled pattern (CK20 ×200). (H) p53 immunostained section showing increased staining in urothelial carcinoma component without a whorled pattern, suggesting possible p53 mutation (p53 ×200).

superficial mitoses were noted (**Figure 1E**). No invasion was identified. Immunohistochemical staining revealed full-thickness immunopositivity for cytokeratin (CK) 20 (**Figure 1F**), a Ki-67 labeling index of up to 5% (**Figure 1G**), and wild-type p53 staining (**Figure 1H**), indicating LG histology. After the biopsy, the patient began periodic surveillance cystoscopies. Upper tract imaging in July 2022 was negative. The patient completed BCG induction in December 2022. Transurethral resection of a potential bladder tumor performed at another institution in August 2023 was reportedly negative for neoplasia. Cystoscopy in February 2024 revealed an approximately 1 cm papillary mass on the posterior wall concerning for recurrence, and fulguration was planned.

Patient 2

A 77-year-old male experienced painless gross hematuria for two years. A CT scan revealed asymmetric irregular mural thickening of the left posterolateral urinary bladder wall. Cystoscopy revealed multiple small papillary masses (approximately 3 cm in tumor burden and low-grade in appearance) along the left lateral and posterior walls in June 2019. He underwent transurethral resection of a bladder tumor (TURBT) and was subsequently diagnosed with LG NIPUC. Focal whorls were noted. He completed induction with gemcitabine/docetaxel in September 2019 and completed monthly instillations in May 2020. In March 2021, the patient was noted to have a 2 cm papillary growth along the left lateral wall consistent with recurrence. On TURBT this lesion was found to have similar histology to the initial resection sample. On subsequent surveillance cystoscopy, the patient was noted to have a sub-centimeter solitary mass on the right bladder dome. Histopathologic examination of this mass revealed LG NIPUC (**Figure 2A**, **2E**) with a sporadic whorled pattern (**Figure 2B**). Rare superficial

mitoses were noted in non-whorled areas (**Figure 2F**). No invasion was identified. Immunohistochemical staining of the whorled areas revealed essentially absent CK20 staining (except umbrella cell staining) (**Figure 2C**) and wild-type p53 staining (**Figure 2D**), supporting LG histology. Notably, in some areas lacking a whorled appearance the tumor showed diffuse CK20 (**Figure 2G**) and extensive p53 staining (possible mutation) (**Figure 2H**). The patient then began surveillance cystoscopies. In October 2021, the patient was noted to have a papillary growth on the left lateral wall consistent with recurrence and underwent TURBT. This revealed LG NIPUC without whorls. A CT urogram in November 2021 was negative for upper tract lesions or filling defects. Cystoscopy in December 2023 revealed prior resection scars and a small subcentimeter papillary lesion on the left posterior bladder wall that was fulgurated. Voided urine cytology was negative for HG urothelial carcinoma through March 2024. Cystoscopy in March 2024 revealed prior resection scars but no evidence of recurrence.

Discussion

LG PUCs have delicate papillae with extensive branching, some loss of polarity at medium magnification, mild nuclear pleomorphism and irregularity, and rare typical mitoses that can be present away from the basement membrane [2]. LG PUC is characterized by activating mutations in FGFR3, tends to be otherwise genomically stable, and is often preceded by urothelial hyperplasia [10]. The recurrence rate is 48-71%, and the progression rate to invasive cancer and death is < 5% [2]. LG papillary carcinomas that invade only the lamina propria constitute up to 13% of cases and have not been extensively studied [11, 12].

In contrast, HG PUC may have fused papillae and more complex or solid exophytic growth [2]. It has moderate to marked cytoarchitectural disorder (including nuclear atypia), pleomorphism notable at low to medium magnification, crowded/overlapping cells, prominent nucleoli, and brisk mitotic activity including atypical mitoses [2]. Notably, heterogeneity in histologic grade is common in PUC [2]. The prevailing approach is to grade the tumor on the basis of the highest-grade component. However, the minimum amount of HG tumor varies from 5% to 10% and therefore experts recommend including the proportion of the HG component in the pathology report [2]. Moreover, pure HG urothelial carcinomas may be more aggressive than mixed low- and high-grade carcinomas. HG PUC is genomically unstable, with TP53 mutations as its hallmark molecular alteration and urothelial dysplasia as its premalignant lesion [10]. HG NIPUC has a recurrence rate of 60% and a 25% rate of progression to invasive disease [2].

The management of urothelial neoplasia is based on multiple factors. Patients are categorized by risk: low- (only one Ta tumor, low-grade, < 3 cm in size, without concomitant CIS), intermediate- (between low-risk and high-risk categories), and high-risk (high-grade, T1, > 3 cm, multiple recurrent Ta tumors, CIS) [11, 13, 14]. Most invasive urothelial carcinomas are high grade. Grading is recommended for all tumors, particularly those infiltrating the lamina propria, because significant outcome differences have been reported between low- and HG invasive tumors [2]. A large study reported a 5-year recurrence-free survival of 56% for T1 LG tumors and 55% for T1 HG tumors, a 5-year progression-free survival of 94% for T1 LG tumors and 68% for T1 HG tumors, and a 5-year cancer-specific survival of 97% for LG T1 tumors and 76% for HG T1 tumors [11, 12].

The dual pathway model for bladder carcinogenesis combining molecular-genetic and pathologic data shows that FGFR3 alterations are a feature of genetically stable LG papillary carcinomas while TP53 mutations are the hallmark alteration of genetically unstable HG urothelial carcinomas. Of note, TP53 and FGFR3 are thought to be mutually exclusive [10, 11]. Immunohistochemical stains are not recommended for grading urothelial carcinomas in routine cases. However, a simple 2-cytokeratin panel (CK20, CK5/6) was recently found to delineate luminal (CK20+, CK5/6-) and basal (CK5/6+, CK20-) phenotypes in both muscle-invasive and non-muscle-invasive urothelial carcinoma [11, 15, 16]. This finding is significant as tumors with the same histologic grade, but different biomarker profiles showed significant differences in recurrence-free, progression-free, and cancer-specific survival rates [11, 15, 16]. In addition, these differences may also extend to sensitivity to chemotherapy as well as immunotherapy [11, 15, 16]. The lumi-

nal category includes tumors with a predominantly papillary pattern, whereas the basal category includes tumors with squamous differentiation [5, 17]. Moreover, the basal-squamous subtype is also enriched in TP53 mutations and shows increased lymphocytic infiltrates and strong immune gene signature expression [17].

Divergent differentiation (such as squamous, glandular, or trophoblastic differentiation) and histologic variants (such as nested, microcystic, micropapillary, plasmacytoid, lymphoepithelioma-like, giant cell, lipid-rich, clear cell, and sarcomatoid variants) are reported primarily in invasive and HG urothelial carcinomas [2, 5-7]. The plasmacytoid, sarcomatoid, and micropapillary subtypes are considered high-risk factors for NMIBC, and current National Comprehensive Cancer Network (NCCN) guidelines recommend early cystectomy for these lesions [6, 18]. Nested and microcystic histologic variants of T1 urothelial carcinoma appear to be morphologically LG but demonstrate aggressive clinical outcomes similar to those of conventional HG urothelial carcinoma [11]. Notably, there are no WHO-recognized variants of LG NIPUC, except for a rare subset that can have an inverted growth pattern without stromal invasion or reaction and another rare subset with micropapillary processes that is not classified as micropapillary carcinoma [2, 5, 6]. Understanding these distinctions is important for the evaluation of heterogeneous lesions in order to aid in their risk stratification and guide their management. Current practice includes an arbitrary but generally accepted approach to grade a lesion on the basis of its highest grade component as long as it represents ≥ 5% of the tumor [2]. However, the 2022 consensus opinions of the International Society of Urological Pathology (ISUP) recommend that pathologists always report divergent differentiation/histologic subtypes regardless of proportion (even < 5%), and include enumeration of the volume of each type [6]. Tumor metastases often retain the primary variant morphology, therefore accurate recognition and reporting of histologic variations at the primary site could help pathologists make the correct diagnosis at metastatic sites [7].

An infrequently described pattern of LG urothelial carcinoma is the whorled pattern or "urothelial eddies" [8, 9]. A recent study described papillary urothelial neoplasms with "urothelial eddies" (resembling the squamous eddies of inverted follicular keratosis of the skin) in 10 of 756 (1.3%) TURBT samples from patients aged 45-79 years [8]. Among these patients, 7/10 were classified as having papillary urothelial neoplasms of low malignant potential (PUNLMP) and 3/10 as having LG urothelial carcinoma. A total of 9/10 patients presented with noninvasive tumors, whereas 1/10 presented with microinvasion. The authors defined urothelial eddies as small nests of ovoid to spindle cells arranged in an onion-skin pattern. The urothelial eddy area ranged between 10% and 95%. Their immunoprofile was similar to that of conventional urothelial carcinoma (high expression of GATA3, S100P, uroplakin III, and CK7; low expression of high-molecular-weight cytokeratin, Ki-67 and p53). Ultrastructurally, these tumors showed large intercellular spaces with numerous cytoplasmic microvillous projections. Although 4/10 patients (including those with microinvasion) experienced tumor recurrence the grade and stage remained the same without muscle invasion or death during the mean 88.7-month follow-up period, indicating that urothelial eddies in papillary urothelial neoplasms are associated with indolent behavior and do not reflect squamous differentiation [8]. Another recent study of 12 cases described a LG whorled variant of PUC on the basis of concentrically organized cell structures without morphologic features of keratinization (such as the whorls seen in transitional meningioma) present in at least 50% of the neoplastic urothelium [9]. These tight whorls create dense cellularity and mold the nuclei into a spiral arrangement inducing an onion-bulb-like configuration in the cells. Mitoses and necrosis are not present. Immunostaining for Ki-67 revealed a low proliferation index ranging from 1% to 20% with only one case of relatively high (20%) labeling, but there was no difference between areas with whorls and intervening neoplastic tissue. P53 immunoreactivity was low in most patients, except for high/abnormal (80%) p53 immunoreactivity in 3 patients. The low tumor stage (Ta in 12/12 patients), lack of progression after transurethral resection, and infrequent clinical recurrence (2/12 patients) support the low grade/low aggressiveness of these tumors [9].

The histologic relevance of the whorled pattern in LG PUC is twofold. First, it may give the low-

magnification impression of early squamoid differentiation and with it the associated prognostic implications. However, as these areas of the tumor have a small quantity of cytoplasm with scant eosinophilia, lack squamous pearls, and show uniform GATA3 staining similar to that of the intervening non-whorled tumor cells, the overall histologic findings argue against squamoid differentiation. Second, the loss of polarity and nuclear variability within the whorled portions may suggest a low-magnification impression of HG carcinoma. However, the sparsity of branching or fusion of papillae, low average nuclear size, and generally ordered growth all favor a LG neoplasm [8, 9].

In our study, we found that the distribution of the whorled pattern was patchy and occupied < 50% of the examined tumor tissue overall. Therefore, we believe that "whorled features" is a better term than "whorled variant" for the current cases. Patient number 1 presented with whorled features with CK20 immunopositivity but wild-type p53 staining. Interestingly, the second case had two fragments with diverse morphologies and staining patterns. One fragment showed a whorled pattern with wild-type p53 staining without CK20 staining, whereas the second fragment lacked the whorled pattern but had CK20 immunoreactivity and increased p53 staining. This latter finding indicates heterogeneity in the tumor of patient number 2. This supports the previously reported observation that p53 is generally wild-type in LG PUC with whorled features [9]. CK20-positive staining may or may not be present (found in one of two cases in this study), but when CK20 staining is present it can involve both whorled and non-whorled areas.

In summary, our study supports the reported association of rare whorled features (urothelial eddies) with non-invasive LG PUC (albeit with a diverse immunophenotype) but does not suggest that this feature indicates squamous differentiation. We suggest that the examination of both whorled and non-whorled areas with CK20 and p53 staining may be helpful for the complete diagnostic and prognostic evaluation of these patients.

Disclosure of conflict of interest

None.

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