

**Original contribution**

Invasive low-grade papillary urothelial carcinoma: an immunohistochemical study of 26 cases^{☆,☆☆}



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Received 28 May 2015; revised 27 July 2015; accepted 29 July 2015

Keywords:

Urothelial carcinoma;
PTEN;
Ki-67;
E-cadherin;
p53

Summary Invasive low-grade papillary urothelial carcinoma (LGPUC) is rare. We studied the immunohistochemical (IHC) expressions of CK20, p53, E-cadherin, phosphatase and tension homolog (PTEN), and Ki-67 in both noninvasive and invasive components in 26 cases. In the noninvasive component of LGPUC, 81% showed CK20 expression, and 50% showed p53 labeling. There was a wide range of Ki-67 labeling from less than 5% to 70%. All cases had intact PTEN except 1 that showed focal clonal PTEN loss in both noninvasive and subjacent invasive components. All cases had preserved strong and diffuse E-cadherin expression in both noninvasive and invasive components. There was no significant change between the noninvasive and invasive components in the IHC labeling of these markers, although 7 (33%) of 21 cases showed decreased CK20 expression to a certain extent in the invasive component. Only 2 cases showed significant increase of p53 expression in the invasive component compared with the noninvasive component. Two cases showed increase of Ki-67 labeling from less than 5% in the noninvasive to 20% and 40%, respectively, in the invasive component. High Ki-67 labeling was present in a significant portion of invasive LGPUC cases in both noninvasive and invasive components, much higher than in previous studies of noninvasive LGPUC. Whether higher Ki-67 in these cases is associated with more aggressive disease warrants further study. In general, it is not very helpful to use immunostains in diagnosis and predicting prognosis. This is the largest series to study the IHC characteristics of this entity.

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1. Introduction

Bladder cancer is the second most common genitourinary tract malignancy, and urothelial carcinomas (UCs) represent 90% of all primary bladder cancer. UCs carry significant

mortality and morbidity. The clinicopathological parameters such as grade, stage, and lymph node status are the most important prognostic factors to predict recurrence, progression, and survival. Low-grade papillary UC (LGPUC) has a recurrence rate of 34% to 72%, which is slightly lower or similar to that of high-grade UC (HGPUC) (43%–74%). However, LGPUC has lower disease progression rate (4%–18% compared with 28% in HGPUC) and lower disease mortality (0%–4%), whereas HGPUCs account for most of the cancer-related deaths among papillary carcinomas [1–9].

As most of the LGPUCs lack invasion (pTa), there are scant data on potential differences in the noninvasive and

[☆] Competing interests: The authors disclose no significant relationship with, or financial interest in, any commercial companies pertaining to this article.

^{☆☆} Funding/Support: There are no funding disclosures.

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invasive components. Given the rarity of finding invasion associated with LGPUC, we have noted in our consult material that pathologists often have difficulty in establishing the diagnosis of invasion in this setting. Pathologists, when they do recognize invasion, tend to diagnose it as high grade despite overlying low-grade noninvasive papillary cancer and similarly low-grade morphology in the invasive component. The primary aim of this study was to investigate the immunohistochemical (IHC) expression of various biomarkers that, based on either their expression in flat lesions of the bladder or what is known about the markers in general, had the potential to be useful diagnostically if they were different in the invasive component. In addition, if differentially expressed, would these biomarkers have any prognostic value in helping to further understand the clinical behavior of this rare entity?

2. Materials and methods

This study was approved by the Johns Hopkins Medicine Institutional Review Boards. A search using the Hopkins Pathology Database System from 2000 to 2014 identified 66 cases of invasive LGPUC (Inv LGPUC), of which 26 cases had tissue available for IHC studies, including 21 cases from the genitourinary pathology consult service and 5 from the Johns Hopkins Hospital. Criteria for diagnosing Inv LGPUC included low-grade cytology (low nuclear/cytoplasmic ratio and lacking pleomorphism/hyperchromasia/mitotic figures) with the usual morphologic features of invasion including single cells, small nests, retraction artifact, stromal reaction, and paradoxical differentiation. Variants of UC with low-grade morphology, such as nested variant and large nested variant of UC, were not included in the study. Cases with only a minute focus of invasion not amenable to IHC analysis were excluded. Many of the cases were included in our previous study for morphologic and clinical characteristics of this entity by Toll and Epstein [2]. The materials were recollected for the current study.

The pertinent hematoxylin and eosin-stained slides for all cases were reviewed by both authors, and diagnosis of Inv LGPUC was confirmed according criteria described in our prior study on this entity [9]. The following IHC analysis was performed at our institution using 4- μ m-thick sections obtained from formalin-fixed, paraffin-embedded tissue (monoclonal antibodies ready to use unless specified): CK20 (KS20.8, prediluted; Dako, Carpinteria, CA), p53 (BP53-11, prediluted; Ventana, Tucson, AZ), E-cadherin (EP700Y, prediluted; Ventana), phosphatase and tension homolog (PTEN) (6H2.1, 1:100; Biocare, Concord, CA), MIB-1 (30-9, 1:1000; Ventana). Ki-67 labeling index was measured using the MIB-1 proliferation marker. IHC stains were performed on a Ventana BenchMark XT automated stainer (Ventana), with appropriate positive and negative controls.

Immunostains were scored using a semiquantitative system considering extent and intensity of staining. Extent was graded as follows: 0, 0%; focal (F), 1% to 10% positive

cells; patchy (P), 10% to 50% positive cells; diffuse (D), greater than 50% positive cells. For intensity, points were assigned as follows: 0, negative; 1+, weakly positive; 2+, moderately positive; 3+, strongly positive.

p53 and CK20 were scored as follows: 0, negative; 1, weak (1+) and patchy (10% to <50%); 2, moderate (2+) and patchy (<50%) or weak (1+) and diffuse (>50%); and 3, moderate (2+) or strong (3+) and diffuse (>50%). For p53, we required score 2 and higher to be considered positive. Only moderate to strong Ki-67 nuclear stains were counted as positive.

3. Results

There were 23 males and 3 females with a male predominance (88%). The median age at diagnosis was of 65 years (range, 45-92 years). The specimens consisted of 23 transurethral resection of the bladder tumors, 2 nephrectomies involving the renal pelvis, and 1 cystoprostatectomy. Two cases had definite muscularis propria invasion, 22 cases had lamina propria invasion, and 2 had muscle invasion indeterminate between muscularis mucosae and muscularis propria invasion. Diagnostic criteria for Inv LGPUC were described in our previous study (Fig. 1A) [2].

In the noninvasive component of LGPUC, CK20 expression was present in 21 cases (81%), of which 16 (61%) scored 2 and 3 ($n = 7$ and 9 , respectively). In the invasive component, 11 (42%) scored 2 and 3. Comparing CK20 expression in the invasive versus noninvasive component, the results were as follows: unchanged ($n = 18$), decreased ($n = 7$) (Fig. 1B), and slightly increased ($n = 1$).

For p53 labeling, 13 cases in the noninvasive component were scored 2 to 3 and considered positive (50%, score 2, $n = 9$; score 3, $n = 4$). Fifteen in the invasive component were positive (58%, score 2, $n = 9$; score 3, $n = 6$). Comparing p53 expression in noninvasive versus invasive component, the results were as follows: unchanged ($n = 24$) and significantly increased ($n = 2$) (Fig. 1C) (Table). Only a few cases (8%) showed significant gain of p53 in the invasive component.

There was a wide range of Ki-67 labeling from less than 5% to 70%: Ki-67 less than or equal to 5% ($n = 11$, 42%), 6% to 30% ($n = 8$, 31%), 31% to 70% ($n = 7$, 27%). Two cases showed increased Ki-67 labeling (from <5% in the noninvasive to 20% and 40%, respectively, in the invasive component) (Fig. 1D); 2 showed a decrease (20%-10%, 50%-30% respectively) (Table), both with small foci of invasion.

All cases had intact PTEN expression (Fig. 1E) except 1 that showed focal clonal PTEN loss in both the noninvasive and subjacent invasive components (Fig. 2A and B). All cases had preserved strong and diffuse E-cadherin expression in both the noninvasive and invasive components. The strong E-cadherin signals did spotlight the invasive nests or single cells in some difficult cases (Fig. 1F).

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