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Original contribution

Significance of a minor high-grade component in a low-grade noninvasive papillary urothelial carcinoma of bladder☆

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Summary To assess the clinicopathological features and prognostic significance of the presence of 5% or less high-grade component in otherwise low-grade noninvasive bladder urothelial carcinoma, referred to as mixed-grade (MG) urothelial carcinoma, we reviewed all archival cases with such diagnosis between 2005 and 2014. Clinicopathological and outcome parameters were compared to those in our previously reported low- and high-grade noninvasive bladder urothelial carcinoma cohorts (LGUC and HGUC, respectively). The study included 31 MG urothelial carcinomas. Mean patient age was 67.6 years, and mean follow-up was 39.7 months. Intravesical treatment was administered in 15 patients (48.4%). Recurrence occurred in 14 cases (45.2%): 10 as LGUC and 4 as HGUC; there was no stage progression. Mean time to progression was 9 months (5-17 months), and there was no death of disease. MG urothelial carcinoma stage progression and dead of disease rates were comparable to that of LGUC. MG urothelial carcinoma stage progression was significantly lower than that of HGUC, $P = .002$, using Pearson χ^2 test. MG urothelial carcinoma patients with no intravesical treatment had higher incidence rate of grade progression (25%) compared to LGUC patients (7.9%); however, the difference was not statistically significant. MG urothelial carcinoma had a prognosis closer to "pure" LGUC than "pure" HGUC. Untreated MG urothelial carcinoma may have a higher rate of grade progression than LGUC, although more data are needed before this issue can be definitively addressed. Until such data are available, it is reasonable to keep MG urothelial carcinoma as a distinct grade category with potential management implications.

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1. Introduction

Bladder urothelial carcinoma is the fourth most common cancer in men and the tenth in women. Non–muscle-invasive bladder cancer represents the majority (≈75%) of bladder malignancies [1].

The current World Health Organization/International Society of Urological Pathology (2004 WHO/ISUP) classifies noninvasive carcinoma based on the highest grade in a pathologic specimen [2]. Although such approach might yield better interobserver reproducibility, it does not reflect the inherent heterogeneity of urothelial neoplasms [3]. Despite the prognostic and biologic implications of accurate grading, a consensus on the minimal amount of high-grade component required to classify a tumor as high grade has not been reached.

Previously, we reported our institutional experience with low- and high-grade noninvasive bladder urothelial carcinoma cohorts (LGUC and HGUC, respectively) as categorized using the 2004 WHO/ISUP grading system [4,5]. The aim of the current study is to assess the clinicopathological features and prognostic significance of the presence of less than or equal to 5% high-grade component in an otherwise low-grade noninvasive bladder urothelial carcinoma, referred to as mixed-grade (MG) urothelial carcinoma in comparison to "pure" LGUC and HGUC cases.

2. Materials and methods

Our institutional review board approved the study.

2.1. Study population and clinicopathological data

Noninvasive (pTa) papillary urothelial carcinomas where less than 5% of the totally examined tumor tissue satisfy the histologic criteria for HGUC has been noted in the pathologic report as MG urothelial carcinoma in our institution in the last decade. The diagnosis of MG urothelial carcinoma is based on the focal presence of morphologic features of HGUC including architectural disorganization, nuclear enlargement, and pleomorphism, occasionally with increased mitotic activity in a tumor that otherwise fully displays histologic features of LGUC (orderly architecture with preserved polarity and low nuclear-to-cytoplasmic ratio). See Fig. 1. The estimation of a "5%" component was done in a similar measurement approach to the simplified method that we currently use in assessing percent amount of prostate cancer in transurethral resection of prostate (calculated percentage of number of positive/total number of chips adjusting for chips size) [6].

All bladder transurethral resection (TUR) cases between 2005 and 2014 with a diagnosis of MG urothelial carcinoma were identified in our electronic surgical pathology system.

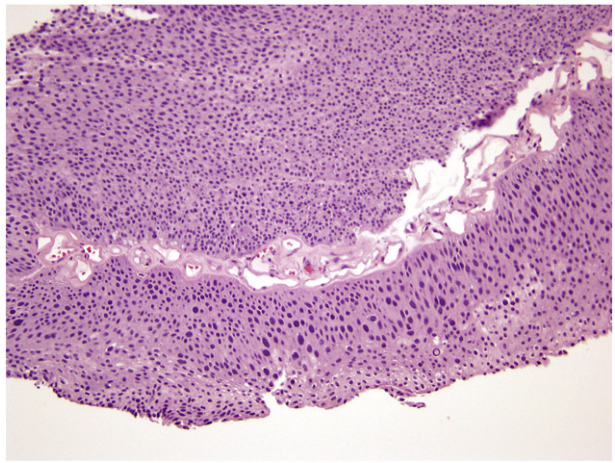

Fig. 1 Papillary urothelial carcinoma, low-grade component displaying orderly architecture with preserved polarity and low nuclear-to-cytoplasmic ratio in lining urothelial cells (top). High-grade component (≤5% of the tumor) with architectural disorganization, nuclear enlargement, and pleomorphism (bottom). Hematoxylin and eosin, original magnification ×200.

The initially found 99 cases included inpatient (34) and outside (65) cases that were sent to our urologic pathology consultation service. Clinicopathological and follow-up data were successfully retrieved in 47 patients with initial (de novo) diagnosis of bladder MG urothelial carcinoma. Patients with upper urinary tract tumors or close subsequent (≤3 months) diagnoses of higher grade (Urothelial Carcino-

Table 1 Patient demographics, clinicopathological features, and outcomes for MG urothelial carcinoma cohort

Variables	Mean ± SD (range) or as specified
Age (y)	67.6 ± 12.7 (36-88)
Sex (male)	23/31 (74.2%)
Race	
White	25 (80.6%)
Black	2 (6.4%)
Unknown	4 (12.9%)
Tobacco use	
Yes	16 (51.6%)
No	8 (25.8%)
Unknown	7 (22.6%)
Tumor size (cm)	3.31 ± 1.56 (0.6-6.5)
Multifocal tumor	7/31 (22.6%)
Intravesical treatment BCG and/or mitomycin	15 [a]/31 (48.4%)
Follow-up (mo)	39.7 ± 35 (3-144)
Recurrence	14/31 (45.16%)
No. of recurrences	2 ± 1.67 (1-6)
Time to recurrence (mo)	18 ± 18.44 (3-57)
Grade progression	4/31 (12.9%)
Stage progression or death of disease	0
Time to progression (mo)	9 ± 5.48 (5-17)

Abbreviations: MG, mixed grade; BCG, bacillus Calmette-Guérin.
[a] Eighty percent at first diagnosis.