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ORIGINAL ARTICLE

Is a consistent cytologic diagnosis of low-grade urothelial carcinoma in instrumented urinary tract cytologic specimens possible? A comparison between cytomorphologic features of low-grade urothelial carcinoma and non-neoplastic changes shows extensive overlap, making a reliable diagnosis impossible

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Introduction The ability to consistently diagnose low-grade urothelial carcinoma (LGUC) in urinary tract cytology (UTCy) specimens remains controversial, as the reported sensitivity of UTCy in the detection of LGUC is as low as 10%. To determine whether a consistent cytologic diagnosis of LGUC is possible, we assessed the presence and frequency of previously described cytomorphologic features of LGUC in UTCy from patients with LGUC and a negative control group.

Materials and methods Biopsy-proven cases of LGUC from June 1, 2010 to January 31, 2014 were identified; UTCy obtained within 3 months prior to biopsy composed the study group (n = 98). The negative control group consisted of UTCy obtained from patients with negative cystoscopy and biopsy (n = 53). All specimens were masked and reviewed in random order to evaluate 17 cytomorphologic parameters.

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Results Univariate statistical analyses demonstrated that the prevalence of paired cells, clumpy chromatin, and cytoplasmic homogeneity was higher in the study group; however, multivariate analysis did not show these features as significant predictors of LGUC.

Conclusions No cytomorphologic feature was statistically significant in the LGUC group versus the negative control group. The presence of 3-dimensional papillary structures with fibrovascular cores is diagnostic of LGUC, but it is only seen in a small minority (2 of 98) cases. Our results reemphasize the fact that urinary tract cytology has a low sensitivity for the diagnosis of LGUC and suggest that, instead of striving to detect LGUC in urine specimens, we should concentrate on the clinically relevant goal of urine cytology—the detection of high-grade lesions.

Introduction

The ability to consistently diagnose low-grade urothelial carcinoma (LGUC) in urine cytologic specimens remains controversial. Although cytomorphologic criteria to diagnose LGUC in urine cytology have been described, the reported sensitivity of urine cytology in the detection of LGUC ranges from 10% to 70%.[1-4] To determine whether a consistent cytologic diagnosis of LGUC is possible, we assessed the presence and frequency of previously described cytomorphologic criteria of LGUC in urine specimens from patients with biopsy-proven LGUC and control patients without urothelial neoplasms.

Materials and methods

The anatomic pathology database for Loyola University Medical Center was searched for urinary tract biopsy specimens diagnosed as LGUC in the period from June 2010 to January 2014. Once the institutional review board's approval was received, all the corresponding clinical information, including cystoscopy, urinary tract cytology and biopsy results obtained at the time of biopsy and during follow-up were obtained from electronic medical records. During the study interval, all urinary tract cytology specimens were diagnosed by 1 of 6 board-certified cytopathologists with interest and experience in urinary tract cytopathology, and all biopsies were signed-out by 1 of 3 pathologists covering a subspecialty genitourinary pathology service.

Patients who had an initial LGUC diagnosis, who had a high-grade urothelial carcinoma diagnosis in any follow-up biopsy, were excluded from the study. All corresponding ThinPrep (Hologic Inc, Bedford, MA) Papanicolaou-stained urine specimens obtained within 3 months prior to biopsy were selected as a study group. The mean follow-up time for the study group was 21 months (range 4 months to 4 years).

Selection criteria for the negative control group were as follows: (1) no evidence of urothelial carcinoma on cystoscopy/imaging studies performed for hematuria or irritative symptoms; (2) non-neoplastic findings on follow-up biopsies, if biopsies were performed; or (3) if no cystoscopy or biopsies were performed, negative cytologic follow-up for 6 months to 7 years (mean 31 months).

Of note, our study and control groups consisted of only instrumented urine specimens. No voided urine or ileal conduit specimens were selected for review.

All specimens were masked, intermixed, and reviewed in a random order. No attempt to subclassify these specimens was made. Out of all cytomorphologic parameters previously described in the literature, 17 were chosen for evaluation including:

- overall cellularity;
- presence of mostly single cells, mostly groups of cells, or mixed;
- presence of irregular clusters;
- presence of 3-dimensional papillary structures with and without fibrovascular cores;
- number of cells in groups/clusters;
- nuclear crowding/overlapping;
- the degree of anisonucleosis;
- uniformity of cells in a specimen;
- presence of paired cells (also known as "cannibalism");
- presence of cercariform cells;
- nuclear-cytoplasmic (N/C) ratio;
- presence of nuclear grooves;
- irregularity of nuclear membrane;
- chromatin pattern;
- presence of nucleoli;
- cytoplasm character; and
- presence of cytoplasmic collars.[2,3,5-9]

Cellularity was assessed subjectively as low, moderate, and high, based on the total number of cells on a slide, regardless of type of cell (umbrella or nonumbrella). Three-dimensional papillary structures were defined as smooth contoured clusters of cells with nuclear overlap, forming "papillae." Irregular cell clusters were defined as irregular contoured clusters of cells with nuclear overlap, not forming papillae (Fig. 1). The number of cells in groups/clusters was assessed as <10, 10 to 50, and >50. The N/C ratio was assessed as <0.5, 0.5 to 0.7, and >0.7. The cytoplasm was described as either frothy or homogeneous. Nuclear chromatin was described as homogeneous, clumpy, or hyperchromatic. The presence of a nucleolus, as well as its size, was recorded as seen or not seen, and, when seen, as small or large. If a feature was present, the