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ORIGINAL ARTICLE

Significance of cytologic detection of low-grade squamous intraepithelial lesion in urine

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Introduction Cellular changes of low-grade squamous intraepithelial lesion (LSIL) are uncommon in urine cytology. There is limited data regarding the clinical aspects and follow-up of patients with such findings. The aim of this study is to examine the clinicopathologic correlates of LSIL in urine cytology.

Materials and methods A database search was conducted for urine cytology samples from January 1, 2000 to March 31, 2013 for the keywords "HPV," "LSIL," "koilocytes," and "atypical squamous cells genital tract." Thin Prep preparations (Hologic, Marlborough, MA) on the retrieved cases were reviewed. Cases with morphologically unequivocal LSIL were further analyzed.

Results Twenty-five cases—20 women (ages 17-65 years), 5 men (ages 70-84 years)—of voided urine cytology fulfilled the study criteria. History of genital tract squamous dysplasia and/or carcinoma was present in 10 patients (50%). Eight patients (30%) were immunosuppressed. Eleven patients had LSIL or atypical squamous cells on cytologic follow-up. One patient developed penile squamous cell carcinoma and another patient developed vulvar intraepithelial neoplasia 3, 5 years and 3 years from the index urine cytology, respectively. Ten women had human papillomavirus testing (Hybrid Capture 2; Digene Corporation, Gaithersburg, MD), of which 8 were positive (within 6 months to 4 years from the index urine cytology).

Conclusions Our study reveals that LSIL is an uncommon finding in urine cytology, and in most cases, it is associated with LSIL in the genital tract. However, occasionally, it may lead to the detection of high-grade squamous intraepithelial lesions or human papillomavirus–associated squamous cell carcinomas of the genital tract.

Introduction

Urine cytology is an important tool for the detection and surveillance of urothelial carcinomas, especially high-grade urothelial carcinomas.[1-3] Certain studies have emphasized the

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importance of the finding of atypical keratinizing squamous cells in urine cytology. These atypical squamous cells may represent a benign reactive process or metaplastic change or may signify the presence of an underlying urothelial carcinoma or squamous cell carcinoma of the urinary bladder or less likely, a squamous cell carcinoma originating from the genital tract or other sites.[4,5] There is, however, limited data as to the importance of the less frequent finding of squamous cells with features of low-grade squamous intraepithelial lesion (LSIL) or cellular changes consistent with human papillomavirus (HPV) infection in urine cytology.

In women, the majority of these LSIL cells are attributed to contamination from the genital tract. In men, these cells possibly originate in the penile urethra.[6-8] Rarely, *condylomata acuminata* of the urinary bladder may result in the exfoliation of LSIL cells in urine.[9] Some studies have highlighted that LSIL is more frequently seen in urine specimens from immunosuppressed patients, especially in specimens from renal transplant recipients.[10,11] The aim of this study is to examine the clinicopathologic correlates of LSIL in urine cytology with emphasis on outcomes and management.

Materials and methods

After obtaining approval from the Institutional Review Board at Cleveland Clinic, a database search was conducted for urine cytology samples (including voided and instrumented urine samples) from January 1, 2000 to March 31, 2013 for the keywords "HPV," "LSIL," "koilocytes," and "atypical squamous cells genital tract." Thin Prep (Hologic, Marlborough, MA) preparations on the retrieved cases were reviewed. Only cases with morphologically unequivocal LSIL were included for further analysis. Strict criteria were employed to recognize LSIL on morphologic grounds: intermediate-type squamous cells with a sharply defined halo with thickened cytoplasmic edges and either hyperchromatic irregular nuclei that are 3 times the size of an intermediate cell nucleus or variably enlarged nuclei with coarsely granular/smudgy chromatin. Cases with atypical squamous cells that fall short of a diagnosis of LSIL (atypical squamous cells of undetermined significance), cases with abnormally keratinized atypical squamous cells with abnormal nuclei (that raise the differential diagnosis of carcinoma with squamous differentiation), cases with cells suggestive of high-grade squamous intraepithelial lesion (HSIL) and cases with concomitant urothelial cell abnormalities were excluded from further analysis. We excluded these cases as it is difficult to distinguish HSIL reliably from high-grade urothelial carcinoma or urothelial carcinoma with squamous differentiation based on morphology alone. Our study is focused on the cellular changes of HPV infection in urine cytology that are easily recognizable on morphologic grounds. The clinical and follow-up data including any histologic and/or cytologic follow-up and high-risk (HR) HPV testing (Hybrid Capture 2; Digene Corporation, Gaithersburg, MD) results for the LSIL patients were recorded from the electronic medical record. The follow-up data that was recorded included: follow-up duration (time period between initial diagnosis of LSIL until the patient's relevant clinical exams or investigations were conducted), follow-up interval (time period between initial diagnosis of LSIL and the subsequent relevant clinical exam or investigation), cytologic follow-up (Papanicolaou [Pap] test or urine cytologic examination) and histologic follow-up (any colposcopic or urogenital tract biopsies or excisional procedures).

Results

A total of 61,112 urine cytology specimens (including voided urine, instrumented urine, bladder washings, and urethral washings) were accessioned at our institution during the study period. Of these, 25 cases were retrieved that fulfilled the study criteria. All showed the presence of LSIL in voided urine cytology specimens (Fig. 1). The patients

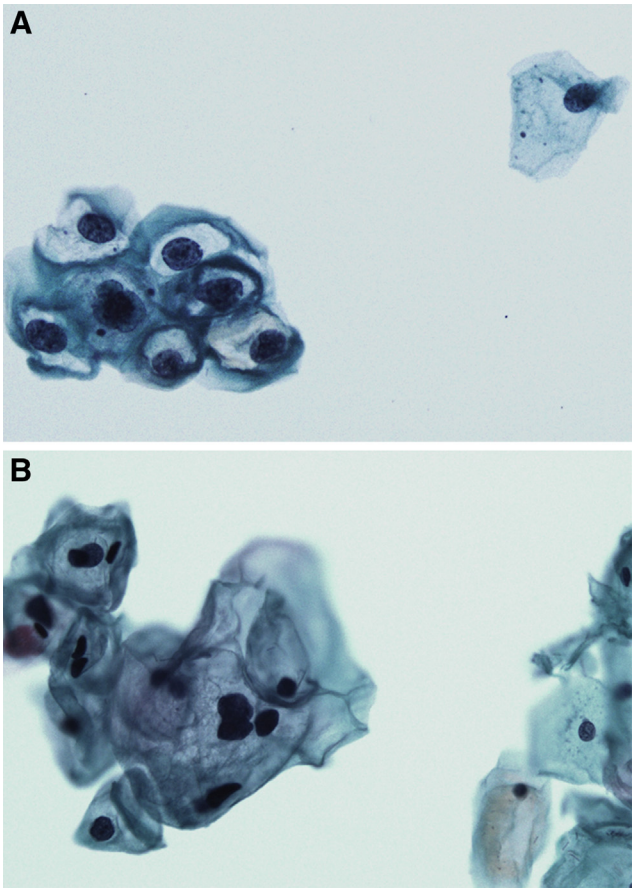

Figure 1 Cytomorphologic criteria of low-grade squamous intraepithelial lesion in urine cytology in our study. Koilocytes with sharply defined halo with thickened cytoplasmic edges and coarsely granular chromatin (A). Koilocytes with the characteristic halo, increased nuclear size, and smudgy chromatin (B). (Papanicolaou stain, Thin Prep, 400×.)