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ORIGINAL ARTICLE

Cytomorphologic features and differential diagnosis of neoplasms with small cell features in liquid-based urinary tract cytologic specimens

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Introduction Urinary tract cytology (UTCy) allows the accurate diagnosis of high grade urothelial carcinoma. Rare malignancies characterized by the presence of small cells may be more difficult to recognize, however. The aim of this study was to review our experience with liquid-based (ThinPrep) UTCy specimens showing small atypical cells and characterize their cytomorphology, potential differences from previously reported morphologic features, and discuss their differential diagnostic considerations.

Materials and methods Among 18,859 UTCy specimens reviewed during a 13-year period (2001-2012), we identified 13 cases corresponding to surgical pathology specimens diagnosed as small cell carcinoma (6), melanoma (3), lymphoma (3), and leukemic involvement of the urinary tract (1). We recorded the original diagnoses made on these cases and 10 cytomorphologic features that could aid in their diagnosis.

Results We identified 13 cases in UTCy of 7 men and 6 women; 11 of which were diagnosed as positive or suspicious for malignancy. In 8 out of 13 cases (62%) the type of malignancy was correctly reported. Of the 10 recorded features, cellular clustering and nuclear molding were seen only in small cell carcinoma, whereas prominent nucleoli and an inflammatory background or diathesis were noted in lymphoma and melanoma cases. Intracellular pigment and multinucleation were recorded in melanoma cases.

Conclusion The presence of small atypical cells in liquid-based UTCy should raise the suspicion of underlying malignancy involving the urinary tract. Cell clustering, nuclear molding, and hyperchromasia

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are helpful hints for the diagnosis of small cell carcinoma and the presence of small atypical cells with prominent nucleoli raises the possibility of lymphoma or melanoma.
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Introduction

The use of urinary tract cytology (UTCy) for the diagnosis and follow-up of tumors involving the urinary tract has a long history, starting from the pioneering work of Vilém (Wilhelm) Dušan F. Lambl (1824-1895), who recommended it as a bedside diagnostic tool as early as 1856,[1] and the works of George N. Papanicolaou, who established its diagnostic utility and laid the scientific foundations of modern urinary tract cytodiagnosis in the 1940s.[2,3] The reported sensitivity and accuracy of UTCy for high-grade urothelial carcinomas and non-urothelial malignancies involving the urinary tract is moderately high.[4,5] The diagnostic performance of UTCy is dependent on the type of specimen (voided urine versus bladder and upper urinary tract washings and brushings) and the method of cytopreparation. During the last decades liquid-based cytopreparatory methods (ThinPrep and SurePath), which have the advantage of limiting the negative impact of cellular degenerative changes and obscuring factors, have become the cytopreparatory methods of choice for UTCy specimens.[6-8] Despite these obvious advantages over the previously used cytopreparatory methods (sediment smears, filter preparations, and cytocentrifugation preparations), however, liquid-based cytology also affects the morphology of cellular and background elements present in the sample[9] and may alter the previously described cytologic diagnostic criteria. Cytologists (cytotechnologists and pathologists) are already familiar with the cytologic features of urothelial cells and commonly encountered malignancies in various liquid-based preparations, as attested by the more accurate diagnosis of high-grade urothelial carcinomas in these preparations.[7] Nevertheless, experience with the liquid-based cytologic features of uncommon conditions and malignancies of the urinary tract is limited, and the criteria that are useful to diagnose these conditions in conventional preparations may not be entirely applicable to liquid-based preparations. Because of the immediate alcohol fixation of the cellular sample, cells tend to acquire a rigid globular shape, and thus appear smaller than in conventional preparations in which they are flattened by smearing or cytocentrifugation. This apparent shrinkage affects the cytoplasm more than the nucleus, and makes cells with small amounts of cytoplasm appear even smaller. These differences in cytologic appearance in liquid-based preparations may therefore have a higher impact on the diagnosis of conditions and neoplasms characterized by the presence of small atypical cells. In addition, other differences between conventional cytologic preparations and liquid-based preparations that may affect their diagnostic features considerably include the fragmentation of true cellular clusters, artifactual clustering, reduction of hyperchromasia, better visualization of chromatin details and nucleoli, and the absence or reduction of diagnostically useful background elements. The aim of this study was to review our experience with liquid-based (ThinPrep) urinary tract cytologic specimens showing small atypical cells and to characterize their cytomorphology, describe potential differences from previously reported morphologic features, and discuss the differential diagnostic considerations.

Materials and methods

The electronic records of our institution were searched for cases diagnosed as small cell carcinoma, lymphoma, leukemia, and melanoma on either UTCy or urinary tract surgical pathology from January 1, 2001 to December 31, 2012. For cases diagnosed on urinary tract surgical pathology material, the records were searched for any UTCy specimens obtained within the previous 6 months of the index diagnosis. UTCy specimens from all patients identified by this search, as well as all corresponding surgical pathology material and, when available, diagnostic cytologic material from other sites, were retrieved and reviewed. Patient age, sex, final diagnosis, diagnostic comments, ancillary studies, previous malignancy history, and other related clinical data were recorded for each case. The presence of following cytomorphologic parameters was documented in all UTCy Thin Prep slides: necrotic/inflamed background, presence of cell groups, hypercellularity, single naked nuclei, nuclear pleomorphism/anisonucleosis and nuclear molding, karyorrhectic/mitotic nuclei, and prominent nucleoli. Presence of pigment, binucleation/multinucleation, degenerative changes, intranuclear inclusions, and tingible body macrophages were recorded in the category of "Other findings".

UTCy specimens were processed by the ThinPrep (Hologic, Inc., Bedford, Mass) technique using a standardized methodology: submitted samples were centrifuged at 2000 revolutions per minute for 10 minutes, the pellet so obtained was resuspended in CytoLyt solution, transferred into a PreservCyt vial, and run on a ThinPrep 2000 processor and then stained with the Papanicolaou method. Grossly bloody samples were first admixed with an equal amount of CytoLyt solution to remove erythrocytes. Cell block preparations were performed by the thrombin method when grossly visible tissue fragments were identified in the UTCy sample or at the cytopathologist's request. Cell block sections were stained with hematoxylin and eosin and with

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