

Review article

Urinary immunocytology—Promise or nonseller? A review with an opinion

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Abstract

Urine cytology is considered a valid diagnostic method of urological and nephrological diagnosis and follow-up, whereas immunohistochemistry is an indispensable adjunct to histopathology. The combination of both—urinary immunocytology—has, so far, only attained a marginal role. This review gives a state-of-the-art update of urinary markers and relevant epitopes, elucidates some methodological pitfalls, and gives an outlook on the promise of urinary immunocytology today. It suggests that morphological urine cytology should be amended by immunology in a mutual quest of urologists and pathologists to improve the diagnostic power of urine cytology. The cost-effectiveness of the method is considered. This review also sheds light on the age-old dispute among pathologists about the nature of urothelial carcinoma that is reflected in the frequent and controversial reclassifications of the disease.

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1. Introduction

When Papanicolaou and Marshall [1] introduced urine cytology as a diagnostic procedure in cancers of the urinary tract, they initiated a development that rendered urine cytology a valid diagnostic method of urological and uro-oncological diagnosis and follow-up. Panurothelial assessment, high specificity and sensitivity, cost-effectiveness, and a stable and easy workflow are some of its advantageous features. When Köhler and Milstein [2] described the first monoclonal antibody, they sparked an explosion in the field of immunology. A wide variety of diseases became understandable and immunological analysis has become an indispensable adjunct to histopathologic diagnosis. The combination of these 2 approaches—urinary immunocytology—however, has a marginal role only so far. This review gives a state-of-the-art update of relevant epitopes, elucidates

some reasons and methodological pitfalls, and gives an outlook on the promise of urinary immunocytology today.

2. The urologist's approach to urinary immunocytology

Clinical experience suggests that urothelial carcinomas are—unlike colorectal carcinomas, e.g.—not well characterized as a continuum from benign to undifferentiated carcinoma. They can rather be divided into 2 groups. Although a larger (>70% of patients) group of low-grade tumors have a tendency to recur but progress rarely, a smaller group of high-grade carcinomas progress and metastasize early and are fatal if not diagnosed and treated early and with determination. The second group is the one that deserves and attracts most scientific attention.

Morphological urine cytology has stood the test of time and is consistently considered the gold standard of urine-based diagnosis of urothelial carcinoma with unmatched specificity and sensitivity for the detection of high-grade tumors [3]. Its value in various clinical settings has

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frequently been evaluated and corroborated, and the World Health Organization classification of 2004 has been taken into account [4]; for more recent reports see Refs. [5,6]. The limitations of conventional morphology-based urine cytology have been lined out (for reviews see Refs. [5–9]), and responsible cytologists have formulated clear guidelines for its use [10]. Morphometric approaches can add some diagnostic information [11], but they are time consuming or expensive (Quanticyt) and have thus been implemented in few centers only.

For high-grade tumors, the quest for additional powerful markers has been virulent in urology for many years. Many promising markers have been suggested to complement or replace urine cytology, so far with little or no additional diagnostic power. The hype of the 1990s has long cooled down because published results were difficult to reproduce. So far, no urine marker has been able to achieve the specificity of urine cytology let alone replace it. Some urine markers gained Food and Drug Administration approval on the basis of studies designed to highlight their performance and major drawbacks, such as excessive false-positive rates were sometimes ignored as was the case with nuclear matrix protein 22 (NMP22). The sobering criticism that ensued has not deterred some urine markers from being widely marketed, and caution is warranted when employing a new diagnostic test [12].

Several immunocytology-based urine tests are commercially available that rely on antibodies against cell surface antigens that are commonly expressed by urothelial carcinoma cells. The immunocytological urine test with the widest distribution is the Immunocyt/uCyt⁺. For the remainder of cases, urinary immunocytology has largely been limited to detect and identify rare and episodic tumors of the genitourinary tract.

3. The pathologist's approach to urinary immunocytology

In pathology, immunocytology is an established adjunct to morphology in many disorders, both malignant and benign, which improves the diagnostic accuracy and also allows the identification of markers both for prognosis and for targeted therapy.

Its use in detecting metastatic carcinoma [13] or neuroblastoma [14,15] cells in blood or bone marrow is established while being aware of methodological limitations. In the diagnosis of effusions that often contain few and distorted cells, immunocytology is an accepted pivotal tool [16,17].

Current cytopathology textbooks attribute immunocytology only a marginal role when diagnosing urothelial carcinoma [9,16,18]. Current reviews on immunocytochemistry [19] and on urothelial immunohistochemistry [20] also do not specifically mention urinary immunocytology.

It appears that immunocytology of urine, however promising from a theoretical point of view and however

much is being published on the issue, has not (yet) gained much influence, neither in urology nor in pathology.

4. What is the bottom line?

When reviewing the literature, it appears that the markers, genes, and immunological epitopes considered relevant for urothelial cancer are differently viewed by pathologists and urologists (author [P = pathology, U = urology]): Netto (P) [21], Gakis et al. (U) [22], Burger et al. (U) [23], Lindemann-Docter et al. (P) [24], Nawroth et al. (P,U) [25], Skoog and Tani (P) [19], Sullivan et al. (P) [26], Protzel and Hakenberg (U) [27], Bolenz and Loten (U) [28], van Rhijn et al. (U) [29], and Vrooman and Witjes (U) [30]. These reviews are discussed in Ref. [31], and partly in Refs. [32,33].

5. Commercially available tests using urinary immunocytology

ImmunoCyt/uCyt⁺ uses 2 fluorescein-coupled antibodies, M344 and LDQ10, directed against 2 sulfated glycoproteins and Texas Red-coupled antibody 19a211 directed against glycosylated high-molecular-weight carcinoembryonic antigen. When using it as a reflex test in patients with atypical urine cytology, a negative result of ImmunoCyt predicts a negative cystoscopy [34]. Schmitz-Dräger et al. [36] published several studies on the value of ImmunoCyt in patients with asymptomatic hematuria [35,36].

Although not an immunological technique, fluorescence in situ hybridization can detect genetic instability in urothelial carcinomas that correlates with a more aggressive behavior of the tumor. The UroVysion test uses centromeric DNA probes of chromosomes 3, 7, and 17 plus a probe of chromosomal region 9p21, which are labeled with distinct fluorescent dyes. With the UroVysion test, additional diagnostic information can be expected in some carcinomas of the upper urinary tract, admittedly a difficult field to tackle [24,37].

Both ImmunoCyt/uCyt⁺ and UroVysion perform well and have been recommended as confirmatory tests [19,26,34,38,39]. If cystoscopy is negative or equivocal, this approach can avoid biopsies and thus save money [40]. Nonetheless commercially available immunocytological urine systems have not gained widespread acceptance in clinical routine. This is attributed to costs as well as the considerable time consumption associated with their use.

Calculation of the cost of the various tests depends—among others—on the viewing angle and the system of remuneration. Estimates are from several hundred USD for the UroVysion (of which 90 USD are for reagents), approximately 100 USD for the bladder tumor antigen (BTA)/bladder tumor antigen stat (BTA stat) (30 USD for reagents), and 60 USD for urine cytology (approximately 5

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