Commentary
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The indispensable role of urinalysis for patients undergoing treatment for nonmuscle invasive bladder cancer

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Abstract

Despite several efforts in the search for noninvasive biomarkers to provide prognostic information for noninvasive muscle bladder cancer, none have shown significant potential. In this context, standard urinalysis is still necessary to provide many data. This method is an inexpensive, simple, and easy-to-repeat tool to follow-up patients over time. Urinalysis does not fall within study protocols and allows evaluation of the immune activation/response (even if indirectly). As such, this method can certainly provide useful information for prognosis.

Keywords: Urinalysis; Immune system; Bacteriuria; Prognosis; Inflammatory response; Microbiome

Despite significant efforts to identify noninvasive biomarkers able to provide prognostic information for nonmuscle invasive bladder cancer (NMIBC), no undisputable biomarkers have yet been identified.[1]

Standard urinalysis might still provide a lot of information, including evidence of both systemic[2] and intravesical[3] inflammation factors: this aspect is very important because the neoplasm stimulates an immune response that also involves the release of inflammatory factors at both the systemic and local level, and this release is stimulated by the recruited neutrophils. Macrophages are instrumental in the response to both infectious and noninfectious diseases, and their role in the bladder has been frequently and widely studied, because of the prevalence of illnesses, such as urinary tract infection and bladder cancer.

Notably, bladder tissue macrophages are among the most populous resident immune cells in this organ, and several studies have supported the idea that resident macrophages and infiltrating monocytes play nonredundant roles in response to infection, immunotherapy, and inflammation. Advancing the understanding of macrophage behavior in the bladder is complicated by the difficulty in obtaining tissue-resident cells. Surmounting this challenge to obtain a greater understanding of macrophage ontology, impact on innate and adaptive immunity, and regulation of homeostasis will ultimately contribute to the development of better therapies for common afflictions of the bladder.[3]

The role of polymorphonuclear neutrophil granulocytes (PMNs) displays a surprising dichotomy in antitumoral immune responses: PMNs have alternatively been shown to both promote tumor growth and progression under inflammatory conditions, and exert important antitumor functions, especially in the context of therapeutic interventions. Polymorphonuclear neutrophil granulocytes therefore play an immunoregulatory role: they represent a major source of the chemokines interleukin 8, growth-related oncogene α, and macrophage inflammatory protein 1α, as well as of inflammatory cytokine migration inhibitory factor. They further induce T-cell chemotaxis via the accessory function of activated monocytes, which is indispensable for effective tumor immunotherapy.[4]

The antibacterial immune responses activated by activation and release of PMNs are similar to the anticancer inflammatory responses induced by bacillus Calmette-Guerin (BCG), suggesting that patients with bacteriuria might better respond to BCG treatment and achieve longer disease-free intervals than patients without activation of the immune response by bacteriuria.

Herr[5] evaluated the issue of asymptomatic bacteriuria and investigated how this could affect the response to intravesical BCG. Both bacteria colonizing the bladder and the intravesical immunotherapy activate the immune response to destroy urothelial cancer cells.[5] Bacteria in the bladder activates the immune system to protect the host against acute infection and may also inhibit early tumor formation.[6] On the basis of this concept, the use of BCG for the prevention of recurrence of high risk nonmuscle invasive tumors has been proposed.[7]

Moreover, studies of the urinary microbiota identified remarkable differences between healthy populations and those with urologic diseases. Microorganisms are likely to have a profound effect on urologic health, both positive and negative, because of their metabolic output and other contributions. In addition, bacteria are also used in the prevention of bladder cancer recurrence.[8] However, this has only been demonstrated in few small sampled studies where specific probiotics were given to patients with NMIBC recurrence: this is definitely not the standard of care, nor is it recommended by any clinical guidelines.

In a retrospective study, Herr et al.[9] showed that patients with chronic bacteriuria, with or without BCG, seemed to have a lower rate of bladder tumor recurrence than uninfected patients. The innate immune response against microbes is initiated by cytokine

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recruitment of neutrophils to the affected urothelium.[10] Neutrophils can destroy tumor cells directly or indirectly[11,12]; patients with bacteriuria have more neutrophils in the blood than uninfected patients, and recent studies have demonstrated the number of circulating neutrophils as an independent prognostic parameter of cancer outcomes.[13,14] Yu et al.[15] showed that elevated absolute neutrophil counts and the presence of pyuria are signs of local immune activity in patients with chronic asymptomatic bacteriuria.

The action of neutrophils and macrophages has been extensively evaluated directly on histological specimens. Jallad et al.[16] analyzed the prognostic value of inflammation/granuloma in 215 BCG-treated NMIBC patients over a 5-year period, and the correlations between histopathological results and disease recurrence and progression were assessed. The mean recurrence-free survival rates were higher in the granuloma and inflammation groups (65 and 56 months, respectively) than in the normal histology group (20 months; log-rank $p = 0.001$). The same trend was seen for progression-free survival, with higher rates in granuloma and inflammation groups (75 and 82 months, respectively) compared with the normal histology group (33 months) (log-rank $p < 0.001$). Moreover, the absence of inflammation/granuloma was significantly associated with recurrence on multivariate analysis (log-rank $p < 0.001$). The authors highlighted how inflammation/granuloma in histology samples after intravesical BCG treatment for NMIBC could be considered as a positive marker of response, while their absence increased the risk of recurrence and progression.

In an apparent contradiction, Herr et al.[9] demonstrated how BCG treatment had a destructive role against the urinary microbiome, up to eradicate bacterial infection. The authors reported how intravesical BCG therapy was associated with clearance of uropathogens in NMIBC patients, possibly because of augmented innate host immunity.[16]

These studies also allowed some evidences in clinical practice and management for patients in follow-up for NMIBC.[7,17] Urologists often insist on the patient having sterile urine before undergoing invasive outpatient urological procedures, and urine culture and antibiotics are usually given before cystoscopy or BCG instillation, especially in patients with a positive urine cultures. This evidence-based experience suggests that cystoscopy and induction BCG therapy can be performed safely, even in patients with asymptomatic bacteriuria, without pretreatment or prophylactic antibiotics. Pretreatment antibacterial therapy further does not seem to be necessary before these 2 outpatient urological procedures in patients with bladder cancer. Such strategy facilitates timely interventions and reduces the possibility of antibiotic resistance.[18]

With this in mind, it is always recommended to ask the patient about any urinary symptoms; this aspect is always very challenging because the symptoms that the patient complains of can also be related to the neoplasm (such as in cases of carcinoma in situ)[19]; an in-depth analysis of symptoms, however, can exclude the potential risks due to intravesical treatment.[20]

The word "prognostic" has been variably applied to urinary biomarkers. Most urinary biomarkers increase in concentration with both stage and grade of disease and could therefore be considered as prognostic indicators.[21] However, very few studies have directly investigated whether urinary biomarkers could provide prognostic information over and above that provided by standard clinicopathological factors.[22] Indeed, bladder tumor antigen, carcinoembryonic antigen, matrix metalloproteinase-9, tenascin-C, cystatin-B, and the soluble extracellular domains of epidermal growth factor receptor and epithelial cell adhesion molecule have been reported as independent prognostic indicators, although these data require independent validation. Moreover, Shariat et al.[23] reported that the pretreatment urinary nuclear matrix protein 22® levels slightly improved the ability of nomograms to predict later recurrence. Moreover, benign conditions and previous BCG instillations may influence the results of many urinary marker tests.[24]

Nevertheless, positive results of cytology, UroVysion, nuclear matrix protein 22®, fibroblast growth factor receptor 3/telomerase reverse transcriptase, and microsatellite analysis in patients with negative cystoscopy and upper tract workup may be used to identify patients more likely to experience disease recurrence and possible progression.[25,26]

Finally, the economic benefit, in terms of reducing the times of recovery and reorganization of resources, should be taken into full consideration.[27]

This method is an inexpensive, simple, and easy-to-repeat tool to follow-up patients over time. Urinalysis does not fall within study protocols, and allows evaluation of the immune activation/response (even if indirectly). As such, this method can certainly provide useful information for prognosis.

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Statement of ethics

Not applicable.

Conflict of interest statement

No conflict of interest has been declared by the authors.

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Author contributions

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