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Bryan, Rik; Kockelbergh, Roger

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Asymptomatic microscopic haematuria and significant urinary tract disease

Richard T Bryan^{1,2} & Roger C Kockelbergh^{2,3}

¹ Institute of Cancer & Genomic Sciences, University of Birmingham, Birmingham, UK

² Action Bladder Cancer UK

³ Department of Urology, University Hospitals of Leicester NHS Trust, Leicester, UK.

Asymptomatic microscopic haematuria (AMH), or non-visible haematuria (NVH), remains a conundrum to primary and secondary care alike; is it a sign of significant urinary tract disease, and does it require urgent investigation? The wide variation in international guidelines in defining who and when to refer adds further to this confusion [1].

In this edition of *Bladder Cancer*, Ghandour et al present their evaluation of haematuria in a large public health care system in the USA [1] - Parkland Health and Hospital Systems, comprising a central hospital, 12 outpatient centres, 12 school-based clinics, and 5 mobile vans. They retrospectively studied a cohort of 11,422 patients ≥ 18 years of age and with ≥ 3 red blood cells (RBCs) per high power field (HPF) on urinalysis (UA) (some of whom had visible haematuria) in the outpatient clinic or emergency room between January 2015 and April 2018; they excluded patients with prior visits to any urology, nephrology, or oncology clinics prior to the date of the positive UA, patients with UA performed as an inpatient, and patients with previous renal transplantation. Their primary analysis excluded those patients initially diagnosed with a UTI. Their findings should be considered in the context of the American Urological Association (AUA) guidelines, defining microscopic haematuria as ≥ 3 RBCs/HPF and strongly recommending evaluation with cross-sectional imaging using multiphasic computed tomography (CT) along with cystoscopic evaluation of all patients aged ≥ 35 years without explained benign causes of the haematuria [2]. In the current study, over 83% of patients were aged ≥ 35 years.

Only 11.4% of patients were referred to urology and, of those referred, only 35% received complete evaluation of haematuria (upper tract imaging and cystoscopy). With regard to referral patterns, older age, higher counts of RBCs/HPF on UA, hypertension, and repeated UA were all significant independent predictors of referral to a urologist, whereas female gender was a significant independent predictor failure to refer (OR=0.31, $p<0.001$). Only 35% of referred patients underwent complete evaluation; females, younger patients, black patients, and those patients with 3-19 RBCs/HPF (with the latter group representing 87% of the cohort, or 9,933 patients) were less likely to undergo complete evaluation.

Looking at the whole cohort, both referred and not referred, urinary tract disease was subsequently identified in 30% of patients; 3.7% of these patients were diagnosed with malignancy ($n=130$, 1.1% of the whole cohort): 106 prostate cancers, 20 bladder cancers, 3 kidney cancers and one upper tract urothelial carcinoma (UTUC). All malignancies, except 53 prostate cancers, were diagnosed in the referred group, giving a cancer detection rate of 5.9% in those patients referred to urology, and a diagnosis of significant urinary tract disease in a further 72%. Focusing on the 24 cases of bladder cancer/kidney cancer/UTUC, we see that 17 (71%) were diagnosed in patients 35-65 years of age and 12 (50%) were diagnosed in patients with 3-19 RVCs/HPF on UA; 17 of the 21 urothelial cancers (81%) were high grade.

Secondary analyses by the authors in UTI patients with haematuria ($n=3241$) identified a further 13 cases of bladder cancer (0.4% of UTI patients with haematuria), 9 of which occurred in patients <65 years of age (69%) and 7 of which occurred in patients with 3-19 RBCs/HPF on UA (54%); 11 of these 13 cancers (85%) were high grade.

Aside from the key points made by the authors, we note the poor rate of referral, despite clear guidelines from the AUA [2]. This is further accentuated in female patients which, disappointingly, may demonstrate entrenched assumptions of UTI as the cause of haematuria (instead of significant other urinary tract diseases, including malignancy), thus leading to delayed diagnoses of malignancy

[3]. Such delays may result in the stage migration observed in female bladder cancer patients compared to male patients [4], and worse survival [5]. And as the Parkland data also show, haematuria accompanying UTI does not exclude the possibility of malignancy.

Given the differences in referral guidelines between the UK and USA relating to age cut-offs for the investigation of AMH, and the similarities between the Parkland Health and Hospital System and the "average" UK National Health System (NHS) hospital and its network, the cancer detection rate of 5.9% in referred patients is comparable to 10.0-12.1% from UK data (13.8-18.9% for VH and 3.1-4.8% for NVH) [6;7]. In line with the Parkland data presented here, Tan et al observed that in the bladder cancers diagnosed following NVH, 59.4% were high-risk cancers, with 31.3% being muscle-invasive [7]. Importantly, in the Parkland cohort, a further 72% of referred patients were diagnosed with significant urinary tract disease ranging from hydronephrosis to urolithiasis (albeit considerably higher than observed in UK cohorts [6;7]). Thus, urology referral identified significant disease (including malignancy) in the majority of patients, the vast majority of whom had been referred due to AMH and the majority of whom were <65 years old. This is a clear message for primary care practitioners and guideline committees.

Having established that AMH requires urological referral and complete evaluation, what is the urgency of referral and investigation? Bladder cancer patients already experience considerable delays in their diagnostic and treatment pathways [8]; whether such delays significantly influence outcomes remains complex and controversial (although the findings of pathway delays and worse outcomes for female patients remain consistent) [4]. In this regard, haematuria risk scores may permit us to bridge the gaps between primary care considerations, urological cancer concerns, and patient preferences [7]; as Ghandour et al highlight, such risk scores exist and appear to have clear utility [9;10]. In an era of stratified and personalised medicine, surely such risk scores must now become *de rigeur* [11]?

Perhaps in the near future, accessible, affordable, sensitive and specific non-invasive diagnostic biomarkers may solve this conundrum and transform haematuria referral decisions and subsequent treatment and surveillance pathways [11-15]?

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