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Review

Investigating Microscopic Haematuria – the Role of Renal Biopsy

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Introduction

The investigation and management of isolated microscopic haematuria (mH) present a practical challenge to nephrologists. The correct approach to investigation of patients presenting in this way, the role of renal biopsy, and the need for urological evaluation, continue to be debated. There is wide variation in clinical practice.

Detection and definition of microscopic haematuria

For the purpose of this article I will define isolated mH as an abnormal number of erythrocytes in the urine in the absence of detectable proteinuria with normal GFR and normal blood pressure.

There is no agreement on a working definition of mH. Values of 1-5 red blood cells per high power field on urine microscopy, and 1,000-14,000 red blood cells per ml of urine by cell counting have all been used in the literature. In clinical practice of course microscopic haematuria is nearly always identified by dipstick testing of the urine rather than urine microscopy. Dipsticks do not detect haematuria but the presence of haemoglobin in the urine. Dipstick testing is reported to have a sensitivity of 96-100% and a specificity of 65-99% for haematuria. Identification that a patient has significant mH requires that the stick test should be positive ("trace" can be ignored because of the great sensitivity of the stick test). The urine test should be non-menstrual in a female and should be collected at least 24 hours after strenuous exercise or sexual intercourse.

A negative stick test with positive urine microscopy occurs occasionally in people taking a large dose of ascorbic acid. There has been uncertainty whether mH detected by dipstick testing should always be confirmed by urine microscopy. A positive urine stick test with negative urine microscopy can occur with haemoglobinuria and myoglobinuria, but much more commonly it occurs because of red cell lysis when the urine is hypotonic or of relatively high pH, and especially if the urine remains standing before microscopy is undertaken. Urine microscopy is therefore only useful in the investigation of stick-positive mH if the urine is examined very soon after voiding by an experienced operator. Urine microscopy performed by laboratory technicians after urine has taken some time to be transported to the laboratory is of little value. This probably explains why at least one study demonstrated that the likelihood of identifying significant glomerular disease in patients with mH was no higher in those with positive urine microscopy than those with a positive dipstick alone [1]. Urine microscopy as well as identifying red cells may also be helpful in the evaluation of red cell morphology (see below). The search for other diagnostic particles, for example urinary casts, is in practice rarely helpful in the absence of proteinuria or other symptoms or signs of kidney disease. Casts are a very uncommon finding in isolated mH.

Prevalence of microscopic haematuria

Prevalence of mH increases significantly with age in both men and women, and is more common in women in all age groups. Variations of reported prevalence differ greatly according to age of study population and definition of haematuria. The prevalence of a single positive test in the general population varies from 2- 20% and of persistent positive tests from 1-13%.

Causes of microscopic haematuria

As well as parenchymal renal disease, other causes of haematuria must always be considered in the differential diagnosis including infection, renal tract stones, trauma, tumours, and coagulation disorders. In patients with isolated mH, a major concern is the identification of cancers in the renal and urinary tract. There are data suggesting that over the age of 40 years up to 8% of men and 5% of women with isolated microscopic haematuria will have cancer; on the other hand below the age of 40 the cancer is found in <2% of men and is almost never found in women [2]. For this reason most clinical algorithms recommend cystoscopy for individuals over the age of 40 years with asymptomatic mH and normal renal imaging, but do not recommend cystoscopy under the age of 40 years. However when there is a history of macroscopic haematuria the risks differ – 24% of men and 6% of women over the age of 40 years will have a malignancy, and 6% of men, although very few women age less than 40 years [2]. All patients with a history of macroscopic haematuria should have a cystoscopy except those under the age of 40 years in whom the history is absolutely characteristic of glomerular rather than epithelial bleeding [brown rather than red urine coinciding with mucosal infection (most commonly in the upper respiratory tract)]. From the published literature it is not always straightforward to identify the relative proportions of parenchymal renal disease and "urological" causes of mH, since many such studies which report parenchymal disease as a rare cause of mH are based on 'haematuria' clinics run by urologists in which parenchymal renal disease will not be pursued if urological findings are negative. One study with full evaluation suggested that 10% of those with mH and also 10% of those with macroscopic haematuria had 'a nephrological cause' [2].

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Microscopic haematuria caused by parenchymal renal disease

Causes of mH identified by abnormal renal imaging include a number of cystic renal diseases, papillary necrosis, medullary sponge kidney, and tuberculosis. When mH occurs with normal renal imaging, it may be occasionally be due to interstitial nephritis but in practice the most common differential lies between glomerulonephritis, most commonly IgA nephropathy, and various hereditary nephropathies affecting the basement membranes including Alport syndrome and thin basement membrane nephropathy (TBMN).

In children with isolated mH, TBMN is the commonest cause of mH reported in 20-50% of cases followed by Alport syndrome (8-40%) and IgAN (8-35%). In adults IgAN is commonest (12-28%) followed by TBMN (6-42%). 17-62% of adults with isolated mH are reported to have a normal renal biopsy, but in some series this included patients in whom electron microscopy was unavailable, and therefore evaluation was incomplete. Older people with mH are still likely to have glomerular disease and in one study up to 10% of patients over the age of 50 years were found to have parenchymal renal disease on renal biopsy performed when urological evaluation did not identify a cause for mH [1]. Although renal disease may be identified, any chance of progressive kidney disease in a relevant time frame is much smaller in this age group. The distinction between Alport syndrome and TBMN is often straightforward especially in Alport patients when the characteristic deafness is prominent and if the family history is clearly X-linked. It should not be forgotten that Alport syndrome may occasionally be autosomal recessive and rarely autosomal dominant. TBMN on the other hand is typically autosomal dominant. Emerging data are finding a range of genetic defects in type IV collagen chains in both Alport syndrome and TBMN with some evidence that there may be overlap [5]. It is likely that genetic analysis will in due course refine further our understanding of the pathogenesis of these conditions, and eventually provide useful clinical testing. In practice glomerular morphology on light microscopy may be entirely normal in the early stages of both Alport syndrome and TBMN and electron microscopy is mandatory for accurate differential diagnosis. Even with EM however, changes in young people with Alport syndrome (and in female carriers) may not be diagnostic, showing little more than variable GBM thickness, and none of the architectural disruption with basket-weave patterning seen in more advanced Alport syndrome. Immunostaining for the alpha chains of type IV collagen can also be informative [6] but unfortunately specific antibodies for such staining are only infrequently available in routine pathology laboratories. In most cases, there is still no worthwhile substitute for electron microscopy in a complete evaluation of a renal biopsy from a patient with mH.

Other causes that should always be considered in "unexplained" mH include hypercalciuria which may cause mH in the absence of overt stone disease especially in children [3], and in children and young adults the "nutcracker syndrome" in which haematuria occurs only with upright posture because the left renal vein is compressed between the aorta and the superior mesenteric artery; this is a benign condition [4]. It is also important to remember that in a significant proportion of patients no cause will be found for haematuria.

Investigation of microscopic haematuria

Urine microscopy

Identification of red cell morphology by urine microscopy has been widely discussed as an investigative tool in mH. The presence of dysmorphic erythrocytes, especially acanthocytes, is associated with glomerular haematuria [7] and is reported therefore to be a useful early investigation directing whether it is appropriate for a patient to have a renal biopsy or to undergo urological evaluation including cystoscopy. There have been only two studies in which urine microscopy has been used prospectively to investigate patients with isolated mH of unknown origin. In these studies sensitivity of 60% and specificity of 85% in distinguishing between glomerular and non-glomerular haematuria was reported [8,9]. Urine microscopy is markedly operator-dependent; it is clear that nephrologists expert in phase contrast microscopy of urine find it an extremely valuable tool, but it is not useful in clinical practice when undertaken by routine laboratory staff.

Renal biopsy

Renal biopsy remains a useful diagnostic tool although its exact role is open to debate. On the one hand proponents of renal biopsy in the evaluation of mH argue that it is a safe day case procedure with very low risks; that it will allow a precise diagnosis, in particular may establish a family diagnosis avoiding the need for further biopsies in other family members; and that by identifying parenchymal renal disease, unnecessary urological investigation can be avoided. Furthermore in up to 50% of patients an entirely normal renal biopsy may be found in which case the patient can be reassured and discharged. Renal biopsy provides the kind of precise information which is sometimes required by insurance companies, employers, or immigration authorities.

On the other hand those who are more cautious about renal biopsy argue that it is an invasive procedure; that in the vast majority of patients with isolated mH the prognosis is excellent; and that clinical follow up will in any case be required, and therefore it may be unimportant to make a precise morphological diagnosis.

Available information suggests that in these asymptomatic, normotensive, non-proteinuric individuals with normal renal function the risks of renal biopsy are extremely low. The incidence of macroscopic haematuria is reported as 2-5%, and significant peri-renal haematoma 2-3%. Infection, nephrectomy or death following a renal biopsy are rarely, and did not occur in most recent series. A further significant risk of renal biopsy however is that the biopsy is inadequate either because the number of glomeruli for light microscopic evaluation are insufficient, or because no electron microscopy is available.

Another argument in favour of renal biopsy rests upon evidence that glomerular disease presenting with isolated mH is less benign than has previously been thought, an especially important point since many of these patients are young adults in whom lifetime renal risk must be considered. These risks are best documented in IgAN: data from the Toronto Registry indicates a ten year risk of deterioration in renal function of zero in IgAN presenting with isolated mH [10]. On the other hand a cohort of IgAN from Hong Kong had a significant risk of proteinuria,

hypertension or renal impairment during a seven year follow up (44% had such an event) after presenting with mH and very low grade proteinuria [11]. Three large series have followed adults with mH regardless of the exact diagnosis and report a 5-11% risk of proteinuria over approximately five years of follow up, and a 13-16% risk of new hypertension [9, 12, 13]. On the other hand 17-36% of patients in those cohorts had complete regression of mH during the same follow up period [14-16]. One small study of individuals with isolated mH and a normal renal biopsy indicated that 60% lost haematuria within ten years.

Can non-invasive testing distinguish between TBMN and IgA nephropathy?

A family history may be useful. TBMN is characteristically autosomal dominant, although in many families there will have been no systematic urine testing of other family members. While in some parts of the world urine abnormalities in relatives of individuals with IgAN are common this pattern is not consistent, and in Northern Europe only a small minority of those with IgAN have relatives with an abnormal urine test.

It is well known that asymptomatic proteinuria occurring with mH significantly increases the risk of substantial glomerular disease. In one study of patients presenting with mH and proteinuria <2.5g/day 46% of patients had IgAN, only 7% TBMN, and 26% other patterns of GN. Whereas in isolated mH in the same series 20% had IgAN and 43% TBMN with no other GN identified [12].

It may be that microalbuminuria is predictive in this setting. In a study of 169 patients with isolated mH who had a renal biopsy, microalbuminuria was to some extent predictive of renal biopsy findings [14]. Among patients with no microalbuminuria [urine albumin excretion <30mg/24 hours]) 81% had TBMN and only 11% IgAN. On the other hand among those with microalbuminuria [urine albumin excretion 30-300mg/24 hours] but not detectable proteinuria on conventional stick testing only 46% had TBMN and 48% IgAN.

Algorithm for the investigation and management of mH

A possible for the investigation and management of mH is shown in Figure 1. It is important to emphasise that this algorithm is only clinically appropriate if electron microscopy is available; without electron microscopy renal biopsy should not be routinely offered for evaluation of isolated mH.

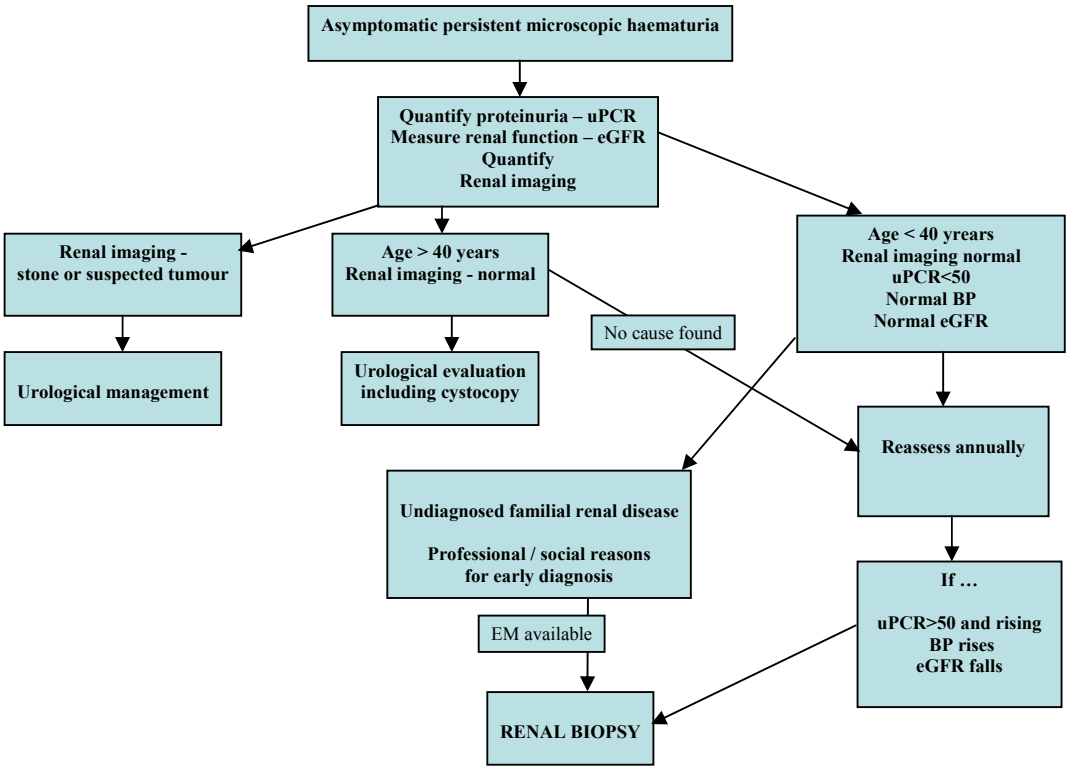

Fig. 1. Evaluation of asymptomatic microscopic haematuria

How should isolated mH be followed up?

Given the variability in outcome described above, there seems no doubt that all patients with mH should be recommended to have an annual review including urinalysis, blood pressure measurement and assessment of renal function by serum creatinine and estimated GFR. These reviews should continue as long as haematuria persists, which it will in a substantial proportion of cases; in others there will sooner or later be additional clinical evidence suggesting an increasing risk of progressive kidney disease. How such reviews are organised will be a

matter of local healthcare organisation. In the UK it is possible to delegate much of this follow up to family physicians with clear recommendations about triggers for referral back for specialist nephrology care. It is always important that advice and recommendations given both about referral and follow up of patients with mH should be realistic and agreed with family physicians. An additional very important point is the need for the patient themselves to take responsibility for the problem. It is unfortunately the case that many young individuals with isolated mH who feel entirely well are not easily convinced of the importance of an annual medical check up. It is still sadly not uncommon that patients identified in this way will be lost to follow up and will then return years later with proteinuria, hypertension and advancing renal failure which could undoubtedly have been slowed if not prevented by proper management.

Conclusion

Renal biopsy still plays a crucial role in the precise diagnosis of many patients with isolated microscopic haematuria. Nevertheless thorough evaluation can minimise the use of renal biopsy and can allow a diagnosis to be reached in a proportion of patients when renal biopsy is not appropriate. The should include a careful family history, thorough age-related evaluation for non-glomerular causes of haematuria, and urine examination including measurement of microalbuminuria, although probably only including urine microscopy in experienced hands. Even then the purpose of the biopsy and the value of the findings should be carefully discussed with the patient before proceeding. Finally, local health care arrangements and a variety of circumstances (including the availability of electron microscopy) will significantly affect renal biopsy policy in this setting.

Conflict of interest statement. The author declares no conflict of interest.

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