

Hematuria in Thin Basement Membrane Nephropathy

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Thin basement membrane nephropathy (TBMN) often is diagnosed clinically when there is persistent dysmorphic or glomerular hematuria, but minimal proteinuria, normal kidney function, and no other obvious cause. This study investigated hematuria in patients with TBMN. A total of 112 patients with biopsy examination-proven TBMN were studied. All had hematuria at the time of presentation, with a mean urinary red blood cell (RBC) count of $256 \pm 250 \times 10^3/\text{mL}$. Seventy-five (67%) patients attended for review over a median of 48 months (range, 3-120 mo) and provided a total of 485 urine specimens. Twenty-one patients (28%) had no hematuria by phase-contrast microscopy on at least 1 occasion. These corresponded to 32 urine specimens (7% of total). Of the 21 patients, the most recent urinary RBC counts were within the normal range in 11 (52%), but hematuria had recurred in the other 10 (48%). Hematuria is persistent in most patients with TBMN, but occasionally it resolves or is intermittent.

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Microscopic hematuria with minimal proteinuria and normal renal function is the characteristic finding in thin basement membrane nephropathy (TBMN),¹ and TBMN is the commonest histologic abnormality in adults with microscopic hematuria undergoing a renal biopsy procedure.²⁻⁴ In TBMN, the urinary red blood cells (RBCs) have the characteristic dysmorphic appearance of glomerular bleeding and escape through transient gaps in the glomerular capillary endothelium and thinned basement membrane into the urinary space.^{5,6} Macroscopic hematuria is uncommon,⁷ and some patients with biopsy examination-proven disease have no hematuria at all.⁸

The hematuria in TBMN usually is described as persistent but long-term data on whether it sometimes resolves is sparse and conflicting.⁹⁻¹¹ In this study, we reviewed the findings of repeated urinary phase-contrast microscopy tests in a large cohort of patients with biopsy examination-proven disease who were followed-up for up to 10 years to determine whether the hematuria resolved.

Methods

The clinical records of all patients who presented between 1991 and 2004 to a consultant nephrologist in private prac-

tice and in whom TBMN was diagnosed on renal biopsy examination were reviewed.

In this practice, occasionally patients with isolated microscopic hematuria and RBC counts of less than $100 \times 10^3/\text{mL}$ underwent a biopsy examination, usually to satisfy employment, visa, or insurance requirements. Mostly patients who underwent biopsy examinations had isolated microscopic hematuria with 100×10^3 or greater glomerular RBCs/mL on phase-contrast microscopic examination of uncentrifuged urine, 1 or more episodes of macroscopic hematuria but with persisting microscopic hematuria less than $100 \times 10^3/\text{mL}$, or persisting microscopic hematuria less than $100 \times 10^3/\text{mL}$ with significant proteinuria ($\geq 0.5 \text{ g}/24 \text{ hr}$) or renal impairment.

All renal biopsy material was processed for light, immunofluorescent, and electron microscopic examination. The diagnosis of TBMN was made on the basis of widespread basement membrane thinning on electron microscopy, and the absence of other significant glomerular or interstitial abnormalities on light microscopy and immunofluorescence examination.

The patients' age, sex, any history of macroscopic hematuria, and the presence of renal impairment (serum creatinine level $>0.12 \text{ mmol/L}$) were recorded.

Unspun midstream urine specimens were examined by phase-contrast microscopy by an experienced technician at presentation, and at 3 months, 6 months, 1 year, and then annually. Normal urinary RBC counts were less than $18 \times 10^3/\text{mL}$. Glomerular RBCs were characterized by their variation in size, shape, and hemoglobin content.⁵ Nonglomerular

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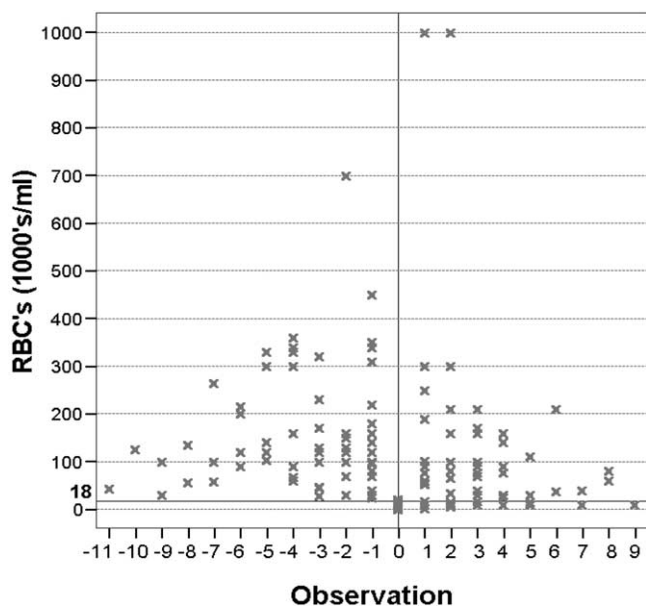


Figure 1 Urinary RBC counts in patients with TBMN who had at least 1 normal count ($<18,000$ RBCs/mL, solid horizontal line). The zero observation point (solid vertical line) represented the first time a normal urinary red cell count was recorded, with all preceding and subsequent readings shown.

cells generally were uniform in appearance. This study did not examine for urinary casts.

All statistical analyses were performed using SPSS (Chicago, IL), and results in different groups were compared using the Student *t* test.

Results

A total of 112 patients were diagnosed with TBMN on the basis of their renal biopsy findings. Eighteen (16%) were male and 94 (84%) were female. One (1%) had renal impairment (creatinine level, $.13$ mmol/L). All 112 patients had hematuria on at least 1 occasion, and 6 (5%) reported macroscopic hematuria. In all cases the hematuria was glomerular in nature.

At presentation, the patients' mean urinary RBC count was $256 \pm 250 \times 10^3$ mL. Twenty-seven (24%) patients had less than 100×10^3 RBC/mL, and 6 (5%) had more than $1,000 \times 10^3$ RBC/mL. Thus, most patients (71%) had urinary RBC counts between 100 and $1,000 \times 10^3$ RBC/mL. The mean urinary RBC count was 319×10^3 /mL for men and 244×10^3 /mL for women (*P* is not significant).

The 112 patients had a total of 522 urine examinations (mean, 4.7 ± 3.1). Thirty-seven patients (33%) attended only for their initial and postbiopsy visits. The other 75 (67%) patients thus provided a total of 485 urine specimens over a median duration of 48 months (range, 3-120 mo).

Twenty-one patients of the 75 (28%) who had more than 1 urine test had a urinary RBC count within the normal range on at least 1 occasion (Fig. 1). However, these accounted for only 32 of the total number of urine examinations (6%). Of these 21 patients, the most recent urinary RBC counts were

within the normal range in 11 (52%) patients but hematuria had recurred in the other 10 (48%). One patient had an initial result of 340×10^3 RBC/mL followed by 5 consecutive readings within the normal range. Another patient had 3 results in the range of 20 to 40×10^3 RBC/mL followed by 2 normal readings. The other 9 patients all had increased urinary RBC counts followed by a final normal level.

Discussion

These data suggest that patients with TBMN usually have urinary RBC counts between 100 and $1,000 \times 10^3$ /mL at the time they come to medical attention. Macroscopic hematuria corresponding to $5,000 \times 10^3$ RBC/mL was reported uncommonly. However, the policy of not performing a biopsy examination routinely on patients with urinary RBC counts of less than 100×10^3 /mL may have biased toward higher RBC counts in this study. Unlike Aarons et al,⁸ who found that 8% of patients with biopsy examination–proven TBMN had no urinary bleeding, all our patients had hematuria at presentation. Again, this partly may reflect the reluctance to perform a biopsy examination on patients with low urinary RBC counts, but on the other hand all those with high levels of proteinuria without another obvious cause usually underwent this procedure.

To date, 3 previous studies have addressed whether the hematuria in TBMN resolves. Tiebosch et al⁹ followed-up 18 patients with biopsy examination–proven TBMN prospectively for a median of 50 months, and all of their patients continued to have microscopic hematuria. In contrast, Goel et al¹⁰ found that hematuria assessed on dipstick resolved in half of the 43 patients who were reviewed for a mean of 88 months. Finally, McGregor et al¹¹ performed phase-contrast microscopy on fresh uncentrifuged urine specimens and found that hematuria resolved in 3 of the 21 (14%) patients with biopsy examination–proven cases of TBMN who were followed-up for at least 38 months. However, none of these studies has confirmed the resolution of the hematuria in subsequent urine specimens.

In our series of 75 patients followed-up for a median of 48 months, 2 (3%) patients had hematuria that resolved and that was confirmed on subsequent urinalysis. A further 9 patients' last recorded urinary RBC counts remained within the normal range. Therefore, the maximum possible number of patients in whom hematuria had resolved in this series was 11 (15%).

Persistent microscopic hematuria is also a feature of immunoglobulin (Ig) A glomerulonephritis. Again resolution is uncommon. In the series of Nicholls et al,¹² clinical resolution occurred in 6% of patients followed-up for an average of 60 months. However, the disappearance of microscopic hematuria did not reflect resolution of the glomerular pathology. Five of 15 such patients underwent repeat renal biopsy examination and in all cases the histologic changes of IgA disease persisted. Repeated renal biopsy examinations understandably are rare in TBMN but in a previous report¹³ repeated examinations in 3 patients after intervals of 3 months to 5 years found no significant change in GBM thickness.

In summary, data from our cohort of patients indicates that microscopic hematuria occasionally resolves or is intermittent in TBMN, even when patients are reviewed over a relatively short period of time. It is unlikely that this corresponds to healing or thickening of the underlying and thinned glomerular membrane.

References

1. Savage J, Rana K, Tonna S, et al: Thin basement membrane nephropathy. *Kidney Int* 64:1169-1178, 2003
2. Blumenthal SS, Fritsche C, Lemann J: Establishing the diagnosis of benign familial hematuria. The importance of examining the urine sediment of family members. *JAMA* 259:2263-2266, 1988
3. Kincaid-Smith P: Thin basement membrane disease, in Massry SG, Glasscock RJ (eds): *Textbook of Nephrology*. Baltimore, MD, Williams & Wilkins, 1995, pp 760-764
4. Auwardt R, Savage JA, Wilson D: A comparison of the clinical and laboratory features of thin basement membrane disease and IgA glomerulonephritis. *Clin Nephrol* 52:1-4, 1999
5. Fairley KF, Birch DF: A simple method for identifying glomerular bleeding. *Kidney Int* 21:105-108, 1982
6. Collar JE, Ladva S, Cairns TDH, et al: Red cell traverse through thin glomerular basement membranes. *Kidney Int* 59:2069-2072, 2001
7. Abt AB, Carroll L, Mohler JH: Thin basement membrane disease and acute renal failure secondary to gross haematuria and tubular necrosis. *Am J Kidney Dis* 35:533-536, 2000
8. Aarons I, Smith PS, Davies RA, et al: Thin membrane nephropathy: A clinico-pathological study. *Clin Nephrol* 32:151-158, 1989
9. Tiebosch ATMG, Frederik PM, Van Breda Vriesman PJC, et al: Thin basement membrane nephropathy in adults with persistent hematuria. *N Engl J Med* 320:14-18, 1989
10. Goel S, Davenport A, Goode NP, et al: Clinical features and outcomes of patients with thin and ultrathin glomerular membranes. *QJM* 88:785-793, 1995
11. McGregor DO, Lynn KL, Bailey RR, et al: Clinical audit of the use of renal biopsy in the management of isolated microscopic hematuria. *Clin Nephrol* 49:345-348, 1998
12. Nicholls KM, Fairley KF, Dowling JP, et al: The clinical course of mesangial IgA associated nephropathy in adults. *QJM* 210:227-250, 1984
13. Saxena SM, Davies DJ, Kirsner RLJ: Thin basement membranes in minimally abnormal glomeruli. *J Clin Pathol* 43:32-38, 1990