Thin Basement Membrane Disease and Acute Renal Failure Secondary to Gross Hematuria and Tubular Necrosis

Arthur B. Abt, MD, Laurence E. Carroll, MD, and J. Harold Mohler, MD

• **A patient with thin basement membrane disease (TBMD), macroscopic hematuria, and acute renal failure is described. A renal biopsy showed massive occlusion of renal tubules by red blood cells and casts. This was accompanied by tubular cell damage consistent with acute tubular necrosis. The patient was receiving warfarin because of a history of deep venous thrombosis at the time he developed the acute renal failure. The possible relationship of the warfarin therapy to the TBMD, intratubular hemorrhage, and acute renal failure are discussed.**

INDEX WORDS: Thin basement membrane disease (TBMD); hematuria; tubular necrosis.

THIN BASEMENT membrane disease (TBMD), also referred to as familial benign hematuria, is a relatively common cause of microscopic or, infrequently, macroscopic hematuria in both children and adults.[1-4] A study from the Netherlands by Tiebosch et al[5] concluded that TBMD was as frequent as immunoglobulin A (IgA) nephropathy,[5] and a study from Australia documented TBMD in 11% of their nontransplant biopsies.[2] The disease is not X linked, and it is usually inherited as an autosomal dominant trait. Definitive diagnosis of this entity requires electron microscopic study of the renal biopsy specimen.

The disease has an excellent prognosis, and only a few patients progress to renal failure. Disease progression appears to be more common in patients with a history of hypertension and proteinuria.[6] We had the opportunity to see a patient with a family history of thin basement membrane disease, gross hematuria, and acute renal failure after therapy with warfarin for deep venous thrombosis. Acute renal failure has not been reported as a complication of TBMD. The possible relationship between the glomerular basement membrane lesion, massive renal hemorrhage, tubular necrosis, and warfarin are reviewed.

CASE REPORT

A 59-year-old man with a long history of microscopic hematuria (thought to be secondary to benign prostatic hypertrophy) and a serum creatinine of 1.0 mg/dL in the past year presented to his family physician with complaints of flank pain and gross hematuria. He was treated with ciprofloxacin for a suspected urinary tract infection. When after 10 days, this failed to resolve, he was referred to a urologist whom he had previously seen for microscopic hematuria and prostatic hypertrophy.

His medical history is also significant for chronic hypertension and a 1-year history of recurrent deep vein thrombosis of the left lower extremity treated with warfarin. A coagulation evaluation performed 1 year ago, including anti-thrombin III and proteins C and S, showed no abnormality.

When seen by the urologist, his blood urea nitrogen was 50 mg/dL, and his serum creatinine was 5.4 mg/dL. A nephrologist was consulted, and subsequent urinalysis demonstrated 3+ proteinuria, numerous red blood cells, and a questionable red cell cast. Angiotensin-converting enzyme inhibitor therapy, quinapril (Accupril, Parke-Davis, Morris Plains, NJ), was discontinued, and amlodipine besylate (Norvasc, Pfizer, New York, NY) was added to terazosin (Hytrin, Abbott Laboratories, Chicago, IL) for his hypertension. Warfarin was continued until his admission 4 days later when his blood urea nitrogen was 78 mg/dL and serum creatinine 8.4 mg/dL. His prothrombin international normalized ratio (INR), which previously had been within a low therapeutic range at 1.7 to 1.8, was 3.6. Because of an initial presumptive diagnosis of rapidly progressive glomerulonephritis, he received 1 g intravenous methylprednisolone daily for 3 days before the biopsy procedure, which was delayed by the elevated INR and the need for several doses of vitamin K.

After the biopsy, he was maintained on dialysis for 6 weeks without further steroid therapy. During this time, his gross hematuria cleared and urine flow increased. When seen 6 months postbiopsy, his serum creatinine was 1.3 mg/dL. His urinalysis continues to show numerous red blood cells and 3+ proteinuria. A 24-hour urine specimen contained 708 mg of protein.

His family history is significant for a son and daughter with microscopic hematuria. His daughter had a renal biopsy at age 17, demonstrating thin basement membrane disease. She remains in good health 20 years postbiopsy. The son has not had any further medical evaluation.

From the Department of Pathology, Milton S. Hershey Medical Center, Penn State Geisinger Health System, Hershey, PA; and the Department of Internal Medicine, Lancaster General Hospital, Lancaster, PA.

Received June 28, 1999; accepted in revised form September 3, 1999.

Address reprint requests to Arthur B. Abt, MD, Department of Pathology, H083, M.S. Hershey Medical Center, PO Box 850, Hershey, PA 17033. E-mail: aabt@psghs.edu

0272-6386/00/3503-0022$3.00/0

Renal Pathology

The biopsy specimen contained renal medulla and cortex with nine glomeruli. One glomerulus was globally sclerotic, and the others appeared normal by light microscopy (Fig 1). There was no evidence of crescent formation or mesangial proliferation. Many renal tubules (approximately 60%) were distended by intratubular red blood cells, and this was most prominent in the medulla (Fig 2). Some tubules were dilated with flattened or degenerate epithelial cells. Rare tubular cells showed mitotic figures. There was no interstitial hemorrhage, fibrosis, or inflammation, and tubular basement membranes were intact. Afferent arterioles showed hyalinization, and intralobular arteries were within normal limits. The immunofluorescent specimen contained two glomeruli, and they showed no significant staining.

Ultrastructural studies showed glomerular capillary basement membranes of varying thickness, and many membrane segments were markedly thinned (Fig 3). The glomerular basement membrane thickness varied from 142 to 214 nm, with an arithmetic mean of 179 nm. There were no areas of basement membrane splitting and no immune complex–type deposits, and epithelial foot processes showed focal areas of effacement.

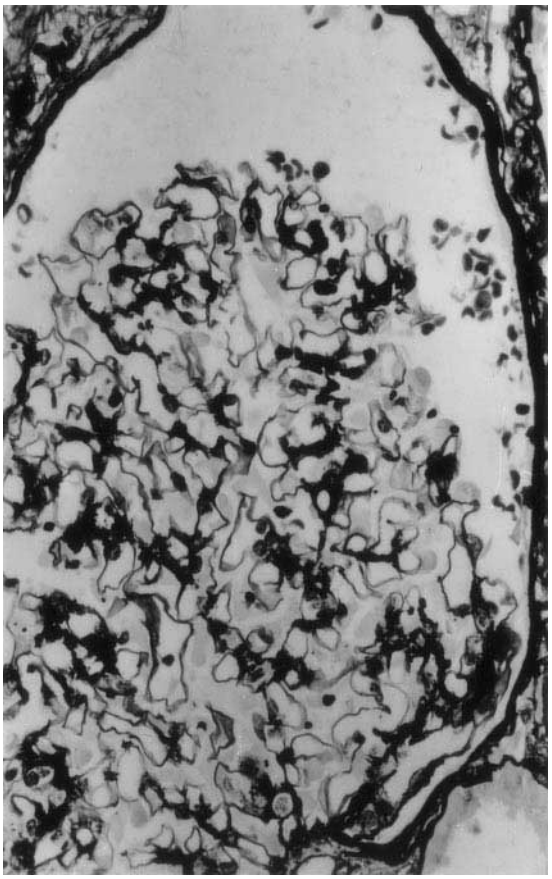

Fig 1. A glomerulus shows normal architecture. Erythrocytes are apparent in Bowman's space (Methenamine-silver stain, original magnification ×500).

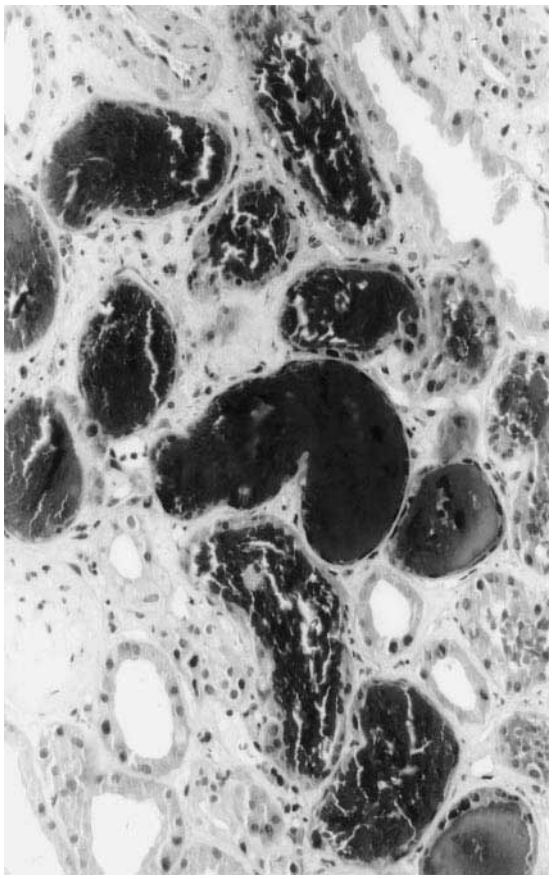

Fig 2. Renal tubules are distended by numerous erythrocytes. The adjacent epithelial cells appear flat (hematoxylin-eosin stain, original magnification ×240).

DISCUSSION

Thin basement membrane disease was first recognized by Rogers et al in 1973.[7] They described a kindred with persistent microscopic hematuria and no evidence of deafness or nephritis. All members of the family were asymptomatic, and there was no morbidity. Dische et al[8] described 14 patients with TBMD presenting with hematuria or proteinuria. Several had abnormal renal function, and one had end-stage renal failure. They concluded that TBMD can be a progressive disease. A study from the Netherlands noted a higher incidence of hypertension in TBMD as compared with controls, and several of their patients developed proteinuria and mild renal insufficiency.[6] The proteinuria was most often of the nonselective type.

Some of the features seen in our patient overlap with the loin pain–hematuria syndrome.[9]

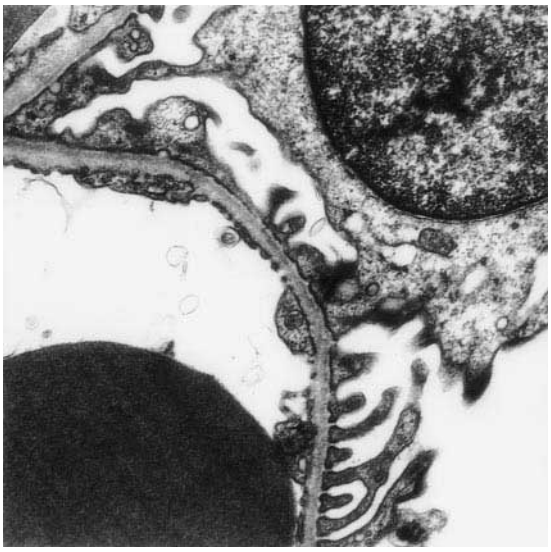

Fig 3. An electron microscopic photograph shows a portion of a thin glomerular capillary basement membrane. The foot processes are relatively well preserved (original magnification ×14,000).

This condition is most frequently reported in women, and it is has been associated infrequently with TBMD. The glomeruli are normal in most patients, and hyalinization of small renal arteries has been the most constant pathological abnormality. Hebert et al[9] described seven patients with TBMD, gross hematuria, and loin pain.[9] They concluded that occlusion of renal tubules by blood could cause the renal pain.

Acute renal failure secondary to intratubular hemorrhage and tubular necrosis is well documented, and it has been reported in patients with IgA nephropathy[10] and focal necrotizing glomerulonephritis.[11] Lee et al[10] postulate that tubular damage may be secondary to products released by fragmented phagocytized red blood cells, but red blood cell phagocytosis was not a prominent feature in our patient. Duflot, Cohen, and Adler[12] have described macroscopic hematuria as a presenting sign of acute tubular necrosis in the absence of other organic lesions.[12] The authors suggest that the hemorrhage might be secondary to tubulovenous herniations, although these were not seen in their patient. In our patient with TBMD and gross hematuria, the massive obstruction of renal tubules by blood and acute tubular necrosis were thought to be responsible for both the flank pain and the acute renal failure. Our patient's renal function gradually improved over a period of 6 months, and when last seen his serum creatinine was 1.3 mg/dL. His urinalysis continued to demonstrate large amounts of blood and 3+ protein.

Microscopic hematuria, the most common side effect of warfarin, has been reported in 20% of patients, and it is unrelated to the INR.[13] Warfarin is a frequently employed anticoagulant known to exaggerate bleeding tendencies, and TBMD is a common cause of hematuria. The absence of prior reports noting massive renal hemorrhage or acute renal failure in patients with TBMD receiving warfarin suggests that this is either a very rare complication or an unfortunate coincidence.

We conclude that the differential diagnosis of acute renal failure in patients with TBMD must be broadened to include massive intratubular hemorrhage with tubular necrosis in addition to crescentic glomerulonephritis and other known causes of acute renal failure. The possible relationship of the warfarin therapy to massive hematuria in this patient with TBMD remains unknown and in need of further documentation.

REFERENCES

1. Dische FE, Anderson VER, Keane SJ, Taube D, Bewick M, Parsons V: Incidence of thin membrane nephropathy: Morphometric investigation of a population sample. J Clin Pathol 43:457-460, 1990

2. Aarons I, Smith PS, Davies RA Woodroffe AJ, Clarkson AR: Thin membrane nephropathy: A clinico-pathological study. Clin Nephrol 32:151-158, 1989

3. Yoshikawa N, Hashimoto H, Katayama Y, Yamada Y, Matsuo T: The thin glomerular basement membrane in children with haematuria. J Pathol 142:253-257, 1984

4. 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

5. Tiebosch ATMG, Frederik PM, van Breda Vriesman PJC, Mooy JMV, van Rie H, van De Wiel TWM, Wolters J, Zeppenfeldt E: Thin-basement-membrane nephropathy in adults with persistent hematuria. N Engl J Med 320:14-18, 1989

6. Nieuwhof CMG, De Heer F, De Leeuw P, Van Breda Vriesman PJC: Thin GBM nephropathy: Premature glomerular obsolescence is associated with hypertension and late onset renal failure. Kidney Int 51:1596-1601, 1997

7. Rogers PW, Kurtzman NA, Bunn SM, White MG: Familial benign essential hematuria. Arch Intern Med 131: 257-262, 1973

8. Dische FE, Weston MJ, Parsons V: Abnormally thin glomerular basement membranes associated with hematuria, proteinuria or renal failure in adults. Am J Nephrol 5:103-109, 1985

9. Hebert LA, Betts JA, Sedmak DD, Cosio FG, Bay WH, Carlton S: Loin pain-hematuria syndrome associated with thin glomerular basement membrane disease and hemorrhage into renal tubules. Kidney Int 49:168-173, 1996

10. Lee HS, Pyo HJ, Koh HI: Acute renal failure associated with hematuria in IgA nephropathy. Am J Kidney Dis 12:236-239, 1988

11. Fogazzi GB, Banfi G, Ponticelli C: Acute tubular necrosis caused by gross hematuria in a patient with focal and segmental necrotizing glomerulonephritis. Nephron 61: 102-105, 1992

12. Duflot J, Cohen AH, Adler S: Macroscopic hematuria as a presenting manifestation of oliguric acute tubular necrosis. Am J Kidney Dis 22:607-610, 1993

13. Goodman SG, Langer A, Durica SS, Raskob GE, Comp PC, Gray RJ, Hall JH, Kelley RP, Hua TA, Lee RJ, Fuster V: Safety and anticoagulation effect of a low-dose combination of warfarin and aspirin in clinically stable coronary artery disease. Am J Cardiol 74:657-661, 1994