Thin-Glomerular-Basement-Membrane Nephropathy: Is It a Benign Cause of Isolated Hematuria?

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ABSTRACT: Thin-glomerular-basement-membrane (TGBM) nephropathy is among the most common causes of isolated hematuria. This autosomal dominant disorder is characterized by diffuse thinning of the GBM and is diagnosed by electron microscopic examination of renal biopsy tissue. A study of an affected kindred has revealed a mutation in the α chain of type IV collagen, resulting in abnormal basement membrane synthesis. Although the exact prevalence and prognosis is unclear, TGBM is usually regarded as a benign cause of hematuria and not associated with any untoward effect on renal function. We report a case of TGBM nephropathy, with associated proteinuria and progressive renal insufficiency. Other studies similarly contend that TGBM nephropathy may not be so benign. On the basis of these findings, we suggest that in some patients with TGBM nephropathy, progressive renal insufficiency may develop. We recommend a more vigilant approach in patients with TGBM nephropathy, especially if proteinuria is present.

MICROSCOPIC HEMATURIA, a common clinical problem, has been reported to affect 4% to 13% of the adult population, and more than half of these patients have no detectable urologic disease.[1] When renal biopsies have been done in patients with isolated hematuria and normal results of urologic evaluation, glomerular abnormalities have been reported in up to 78% of patients.[2,3] IgA nephropathy is considered to be the most common cause of idiopathic glomerulonephritis and glomerular hematuria.[4,5] However, recent studies[6,7] suggest that thin-glomerular-basement-membrane (TGBM) nephropathy may equal or exceed the prevalence of IgA nephropathy as the leading cause of glomerular hematuria. A largely familial disorder with autosomal dominant inheritance pattern, TGBM nephropathy is probably an underrecognized cause of isolated asymptomatic hematuria and is thought to have a benign prognosis. However, as illustrated by the following case report, some patients may have progressive renal insufficiency.

CASE REPORT

A 65-year-old Filipino man was first noted to have microscopic hematuria 6 years earlier during a hospital admission for evaluation of chest pain. Urinalysis during that admission showed trace proteinuria and 2+ blood on the urinary dipstick, with 20 to 50 red blood cells (RBCs) per high-power field on microscopic examination. The serum creatinine value was 1.2 mg/dL with a creatinine clearance of 90 mL/min and protein excretion of less than 150 mg per 24 hours. Findings on intravenous pyelogram (IVP) and cystoscopy were normal. During the subsequent clinic visits, the patient continued to have microscopic hematuria. Another IVP 2 years later again showed no abnormality. A year later, the patient's primary physician found microscopic hematuria with RBC casts and 1 to 2+ proteinuria on the urinary dipstick. The serum creatinine value was 1.3 mg/dL with a creatinine clearance of 78 mL/min and protein excretion of 0.59 g per 24 hours. A chemistry panel 3 years later showed a serum creatinine value of 1.9 mg/dL. At this point, the patient was referred to the renal clinic at San Francisco General Hospital for nephrology consultation.

The patient never reported flank pain or gross hematuria. His medical history included hypertension for more than 20 years, gastroesophageal reflux disease, chronic hyperamylasemia, benign prostatic hypertrophy, cataracts of both eyes, colonic polyps, occasional chest pain with a negative cardiac workup, and positive results of a tuberculin skin test, which led to a 6-month course of isoniazid. The patient's medications on referral to the renal clinic

KEY POINTS

- Thin-glomerular-basement-membrane disease is a common cause of hematuria.
- Histopathology is often unremarkable, except for diffuse thinning of the glomerular basement membrane.
- In one kindred, a mutation in the COL4A5 gene, resulting in abnormal type IV collagen formation, caused the underlying membrane defect.
- Although most patients have a benign course, proteinuria and hypertension increase the risk of renal insufficiency.

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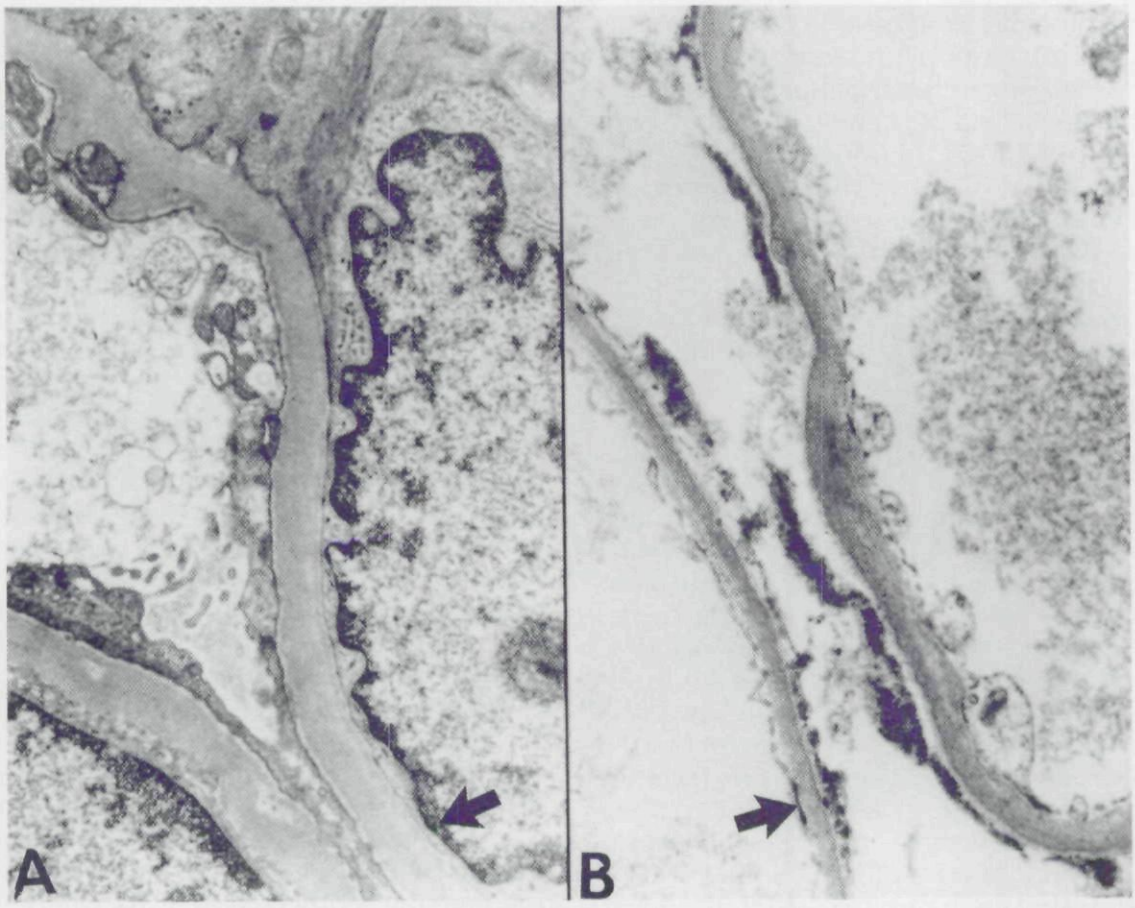

Electron micrographs show (A) normal glomerular basement membrane (GBM) (arrow) and (B) glomerular basement membrane from patient with thin GBM nephropathy (arrow). Diameter of normal GBM is 370 nanometers and diameter of patient's GBM (B) is 130 nm. (Original magnification x 8000 for both A and B)

included diltiazem, famotidine, quinine, and oxybutynin chloride (ditropan). The patient had one brother with asymptomatic hematuria.

Physical examination was essentially unremarkable except for mild prostate enlargement. His blood pressure was 139/76 mm Hg, and he had no pedal edema. The serum creatinine level was 1.9 mg/dL with a 24-hour urine collection showing a creatinine clearance of 60 mL/min. Results of extensive laboratory investigations including serum complement levels, antinuclear antibody, antineutrophil cytoplasmic antibody, and serologic tests for hepatitis B and C were normal or negative. Renal ultrasonography showed kidneys of normal size and echogenicity, without evidence of hydronephrosis. Because of persistent hematuria and worsening renal function, renal biopsy was done.

Light microscopy examination showed five normal glomeruli without any evidence of glomerulosclerosis or hypertensive changes and one glomerulus that was obsolescent. Immunofluorescence study was negative for immunoglobulins and complement. Electron microscopy evaluation showed generalized thinning of the basement membrane (120 to 140 nm; normal 373 ± 42 nm) (Figure). The final pathologic diagnosis was TGBM nephopathy.

DISCUSSION

Thin-glomerular-basement-membrane nephropathy is a familial disorder with an autosomal dominant pattern of inheritance, characterized histologically by diffuse thinning of GBM and clinically by microscopic hematuria. It has also been termed "benign familial hematuria," "benign hereditary nephritis," and "basement laminal nephropathy,"[8-10] and it may be the first or second most common cause of glomerular hematuria.[6,11,12] Initial studies suggested an excellent prognosis with stable renal function,[6,13,14] but more recent reports have shown evidence of progressive renal insufficiency associated with glomerular sclerosis and renal dysfunction in some patients.[6,11,15]

Benign hematuria was first described by Baehr[8] in 1926 as a "benign and curable form of hemorrhagic nephritis." Later, McConville et al[16] noted that there were kindreds with benign hematuria that showed an autosomal dominant pattern of inheritance. In a landmark study, Rogers et al[9] made the seminal observation that patients with so-called benign familial hematuria had thinning of the GBM. This association between benign familial hematuria and attenuation of the thickness of the GBM has been confirmed by subsequent studies,[11,17] and thus the terms benign familial hematuria and TGBM nephropathy are often used interchangeably.

On histologic evaluation of TGBM nephropathy, light microscopy and immunoflourescence microscopy of the renal parenchyma are typically unremarkable. Electron microscopy shows diffuse or focal thinning of the GBM and the lamina densa. Width of the GBM varies with the laboratory technique used to measure it[18-20]; thus, the definition of what constitutes a "thin" GBM has not been consistent in the literature.[21] Generally, a GBM diameter of less than 250 nm in adults and 200 to 250 nm in children has been suggested as indicative of TGBM nephropathy.[22]

Thinning and attenuation of the GBM may also be seen early in the course of Alport's syndrome, another glomerular disorder associated with hematuria. In comparing the glomerular basement abnormalities in patients with familial hereditary nephritis (Alport's syndrome) and TGBM nephropathy, Piel et al[23] in 1982 suggested the possibility that Alport's syndrome and TGBM may be variations in the spectrum of inherited abnormalities in the formation of the GBM. Advances in techniques in recombinant molecular biology and linkage analysis have now validated this earlier speculation. Alport's syndrome is classically an X-linked disorder manifested by hematuria, high-tone sensorineural hearing loss, ocular defects, and often progression to renal failure. The primary abnormality appears to be due to mutations in the COL4A5 gene on the X chromosome that codes for the α-5 chain of type IV collagen, resulting in abnormal GBM formation. In addition, there are rare autosomal recessive forms of Alport's syndrome due to mutations in the α-3 and α-4 chains of type IV collagen. Recently, linkage and mutation analysis in a kindred with TGBM nephropathy has demonstrated a missense mutation in the COL4A4 gene that codes for the α-4 chain of type IV collagen, resulting in a glycine to glutamic acid substitution.[24] The abnormal gene product produces a defect in collagen that interferes with the normal meshwork architecture of the GBM. Thus, the genetic defects in Alport's syndrome and TGBM nephropathy are similar, resulting in abnormal GBM formation; however, the clinical sequelae are different, since patients with Alport's syndrome have progressive renal insufficiency, whereas patients with TGBM are thought to have a more benign course.

Thin-glomerular-basement-membrane nephropathy may account for almost 30% of the cases of glomerular hematuria[6] and may be the most common cause of microscopic hematuria in asymptomatic patients with normal findings on urologic evaluation.[3,6] The frequency of TGBM nephropathy may be as high as 5% to 9% of the general population, according to studies on kidneys used for renal transplantation.[15,25] This may contribute to the prevalence of microscopic hematuria that has been observed in 4% to 13% of healthy adults.[1,12] Since TGBM nephropathy/familial hematuria is such a common cause of microscopic hematuria and is an autosomal dominant disorder, it has been argued that when evaluating a patient with microscopic hematuria, the family members of the affected patient should be screened for the presence of hematuria before embarking on a costly and invasive urologic evaluation.[12] In addition, patients with isolated microscopic hematuria without proteinuria or renal insufficiency and a strong family history of hematuria may not require a renal biopsy to confirm this disorder, given the usually benign course.

Although patients with TGBM nephropathy are usually asymptomatic, some patients may have unilateral or bilateral flank pain (loin pain syndrome). This has been described mainly in young women and may be the result of intratubular hemorrhage.[26] It has been suggested that the hematuria observed in TGBM nephropathy may be a result of an exaggeration of the normal minimal leak of red blood cells across the GBM.[6]

The long-term prognosis for most patients with TGBM nephropathy remains excellent. A recent study, however, reported proteinuria, hypertension, premature glomerular obsolescence, and progressive renal insufficiency in some patients with TGBM nephropathy,[27] and similar findings were seen in our patient. Thus, in a subset of patients, TGBM nephropathy, a benign familial hematuria disorder, may not be so benign. In the absence of significant proteinuria and renal dysfunction, patients can be reassured and safely followed up by periodic measurements of blood pressure, urinary protein excretion, and renal function. Proteinuria and hypertension in patients with TGBM nephropathy appear to be risk factors for the development of progressive renal insufficiency. Thus, the management of these patients should include close monitoring of renal function and achieving good antihypertensive control.

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