

Thin Basement Membrane Nephropathy Associated With Other Glomerular Diseases

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Many reports confirm that thin basement membrane nephropathy (TBMN) commonly occurs together with other glomerular diseases such as minimal change glomerulonephritis, diabetes, membranous nephropathy, immunoglobulin (Ig)A glomerulonephritis, and focal segmental glomerulosclerosis. We postulate 3 explanations for these observations. The association of minimal change glomerulonephritis with TBMN probably is artifactual whereas the association with diabetes and membranous glomerulonephritis probably is coincidental. However, the link between TBMN and IgA disease and focal segmental glomerulosclerosis may be pathogenetic. Clinical evidence indicates that the presence of an associated glomerulopathy significantly worsens the prognosis of TBMN. Thus, patients with TBMN and another glomerular lesion usually have more marked proteinuria, and are more likely to have hypertension and renal insufficiency. The frequency of another glomerulopathy in patients with TBMN means that all patients in whom TBMN is suspected but who have heavy proteinuria or renal insufficiency should undergo a renal biopsy examination. However, there is no evidence that TBMN alters the prognosis of another glomerulopathy, and, in particular, patients with TBMN and IgA disease do not have different clinical features or a worse prognosis than those with IgA disease alone.

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Thin basement membrane nephropathy (TBMN) is a common glomerular abnormality encountered in up to 7% of otherwise normal individuals.¹ Clinically, TBMN is a frequent cause of microscopic hematuria in both children² and adults,³ although it also often is asymptomatic.⁴ Since its original description,⁵ TBMN has been considered a benign clinical condition with an excellent prognosis. However, sporadic reports suggest that some patients with TBMN can progress to kidney failure.^{6,7} This article focuses on another area of potential concern regarding the prognosis of TBMN: the reported association between this glomerular abnormality and other glomerulopathies.

Associations Between TBMN and Other Glomerulopathies

The nature of the publications describing the associations between TBMN and other glomerulopathies can be classified as follows: (1) individual case reports (for example,⁸⁻¹⁰); (2) analysis of the incidence of TBMN in groups of patients with

particular glomerular diseases;^{7,11-13} and (3) analyses of the incidence of TBMN in native kidney biopsy databases.^{14,15} All of these reports suggest there may be associations between TBMN and many other glomerular diseases. However, these associations probably result for several different reasons. In Table 1 we have attempted to classify these associations according to what we believe is the most likely mechanism behind the association. We recognize that this classification is hypothetical but we believe that it is reasonable based on our clinical experience as well as the nature of the available literature reports. The first proposed group of associations (Table 1) may be related to either artifactual or acquired thinning of the glomerular basement membrane (GBM) in patients with another glomerulopathy. Thus, focal thinning of the GBM has been described in patients with many different kidney diseases.^{16,17} The researchers of these reports presumed that these anomalies were acquired, which indeed is a reasonable speculation. However, those studies do not include an analysis of the patient's clinical presentations or their family history. Consequently, we cannot be certain whether the histologic findings described in those reports truly represent acquired focal GBM thinning or the presence of a glomerulopathy in patients with TBMN. A more recent study reported an artifactual thinning of the GBM in some patients with minimal change glomerulonephritis.¹⁸

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Table 1 Reported Associations Between TBMN and Other Glomerulopathies

Likely Mechanism*	Associated Glomerulopathy	References
Artifactual/acquired	Minimal change disease	18
	Several glomerulopathies (isolated cases)	17,22
Coincidental	Membranoproliferative glomerulonephritis	10
	Diabetes	12
	Membranous nephropathy	13
Possible pathogenic link	IgA nephropathy	11,14
	FSGS	7,15
	Mesangial proliferative glomerulonephritis	14,15

*The classification used here to explain the association between TBMN and other glomerulopathies is based on reported cases in the literature.

The second group of associations between TBMN and another glomerulopathy (Table 1) we believe is attributed more likely to the serendipitous coincidence of 2 diseases. This occurrence may not be surprising considering the high incidence of TBMN in the general population.¹ One of these studies¹³ describes TBMN in 2% of a large group of patients with idiopathic membranous nephropathy. This association is indeed of interest but unlikely to be caused by a predisposition of patients with TBMN to membranous nephropathy. Indeed, if that were the case one would expect that the incidence of TBMN among patients with membranous nephropathy (2%)¹³ would be higher than reported in native kidney biopsy examinations (5% to 8%),^{14,15} and that is not the case. Also notable is the presence of TBMN in a significant number of patients with diabetes.¹² Of interest, patients with both TBMN and diabetes were more likely to have microscopic hematuria than patients with diabetes alone.

Finally, Table 1 includes a third group of associations between TBMN and other glomerulopathies that we postulate may be related to an interaction between TBMN and the pathogenesis of another glomerulopathy. Included in this group are the associations between TBMN and immunoglobulin (IgA) nephropathy, mesangioproliferative glomerulonephritis, and focal glomerulosclerosis.^{7,14,15} The association between TBMN and IgA nephropathy first was reported in isolated clinical cases.^{8,9} Subsequent analyses of native kidney biopsy databases confirmed this association and showed that the incidence of TBMN in patients with IgA nephropathy is significantly higher than expected for the population.¹⁴ Furthermore, those patients with TBMN and IgA nephropathy had familial microscopic hematuria whereas patients with IgA nephropathy alone did not.^{11,14} This latter information provides strong support to the hypothesis that these patients had familial TBMN. Other studies reported that up to 39% of patients with IgA nephropathy also have TBMN.¹¹ There is no information available about the possible role of TBMN in the pathogenesis of IgA nephropathy. However, of interest, 1 study showed that the abnormal glycosylation of the IgA molecule that occurs in IgA nephropathy is absent in patients with combined TBMN and IgA nephropathy. These investigators suggest that the mechanism of IgA deposition in the mesangium may differ in patients with TBMN and in patients with uncomplicated IgA nephropathy.¹⁹

Other studies suggest that focal glomerulosclerosis (FSGS) is more common than expected in patients with TBMN.⁷

However, this association may represent premature glomerular obsolescence rather than an association between TBMN and idiopathic FSGS. Analyses of biopsy databases unfortunately do not provide consistent data regarding this association. Thus, in 1 study there was no increased incidence of TBMN among patients with FSGS¹⁴ whereas in another study there was an increase.¹⁴ Finally, TBMN also is found more commonly in patients with mesangial proliferative glomerulonephritis than in other native kidney diseases,¹⁴ although this association has not been confirmed in another series.¹⁵

In 2 studies, between 73% and 76% of native kidney biopsy specimens with TBMN had an associated glomerular pathology.^{14,15} However, these findings should be interpreted with caution. Most patients with TBMN do not undergo a renal biopsy examination. Thus, we do not know accurately how often patients with TBMN have an associated glomerulopathy. Nevertheless, it is likely that this association is very common. This impression is supported by our observation that kidney biopsy examinations of potential kidney donors with isolated microscopic hematuria most often show uncomplicated TBMN. Still, the reported associations between TBMN and other glomerulopathies in patients with clinically significant kidney disease suggest potentially clinically relevant questions such as: are patients with TBMN at particular risk for acquiring certain glomerulopathies, such as IgA nephropathy? And, does the combination of TBMN and another glomerulopathy alter the expected prognosis of either condition? Unfortunately, at present, there is insufficient evidence to fully answer these questions.

Diagnosis of an Associated Glomerulopathy

The diagnosis of TBMN often is presumed in patients with persistent microscopic hematuria, no proteinuria, and normal renal function. These patients either do not come to medical attention or, if the hematuria is discovered during a routine medical examination, often do not undergo a kidney biopsy examination. Based on our clinical experience with potential kidney donors, we do not think that it is necessary to perform a kidney biopsy examination in patients with isolated microscopic hematuria for the purpose of excluding an associated glomerulopathy. How-

ever, routine clinical follow-up evaluation of these patients is warranted.⁷

Patients with TBMN and a glomerulopathy are more likely to have higher levels of proteinuria, hypertension, and renal insufficiency compared with those with uncomplicated TBMN.^{4,14,15,20} However, overlap in the clinical presentations of these 2 groups of patients may prevent accurate prediction of the glomerular pathology. Conversely, the clinical presentation of patients with IgA nephropathy is similar whether the patient has coexistent TBMN or not.¹¹ Thus, the diagnosis of TBMN associated with a glomerulopathy requires a kidney biopsy examination with electron microscopy which, in our opinion, should be performed in patients with microscopic hematuria associated with proteinuria of more than 2 g/24 h and/or renal insufficiency.

Examination of kidney biopsy tissue may not resolve the question of whether TBMN is associated with a glomerulopathy or not. Earlier studies have shown that GBM abnormalities, including focal thinning, are not uncommon in patients with acquired glomerulopathies.^{17,21} Whether these GBM changes are secondary to the glomerular disease or indicate the presence of TBMN cannot be resolved on histologic grounds alone but requires additional clinical information. In these patients, a family history of microscopic hematuria is most important to establish the correct diagnosis. It should be noted that the initial encounter with a patient with TBMN frequently provides a negative family history of urinary abnormalities. We and others have noted that it is only on more careful scrutiny that familial hematuria is discovered.^{7,14}

Another issue frequently encountered in interpreting the pathology of patients with a glomerulopathy and basement membrane thinning relates to the extent of the latter abnormality. It frequently is stated that the diagnosis of TBMN requires the presence of diffuse basement membrane thinning. However, in our experience, biopsy specimens from patients with familial hematuria more often have focal rather than diffuse areas of membrane thinning. In fact, it is of historical interest that the first family of TBMN described had focal thinning of the GBM.⁵ In previous studies we showed that patients with focal thinning of the basement membrane usually had familial hematuria, supporting the contention that this actually is TBMN.¹⁴ It would seem more accurate and reasonable to diagnose TBMN when the average thickness of the GBM based on multiple measurements, performed in several capillary loops from more than 1 glomerulus, is less than that expected for the laboratory (usually <250 nm). We would suggest that the demonstration of abnormal GBM thinning, even when focal, should prompt careful scrutiny for the presence of familial microscopic hematuria. Throughout this discussion we have not considered the potential difficulties in distinguishing, clinically or pathologically, TBMN from Alport syndrome. The recent recognition that some cases of TBMN and the autosomal-recessive form of Alport syndrome have a common genetic background adds to the diagnostic difficulties.^{4,22,23}

Prognostic Implications of the Association Between TBMN and Another Glomerulopathy

The available clinical evidence indicates that the presence of an associated glomerulopathy significantly worsens the prognosis of TBMN. This evidence is not based on longitudinal studies but rather on the observation that patients with both TBMN and another glomerulopathy have a clinically more aggressive disease with higher levels of proteinuria, hypertension, and renal insufficiency.^{4,14,15} In contrast, there is no evidence that TBMN alters the progression of another glomerulopathy. Thus, although the presence of TBMN somewhat alters the clinical presentation of patients with another glomerulopathy,^{11,12,15} those alterations generally are not associated with a worse prognosis than expected for patients with a particular glomerulopathy and normal basement membrane thickness.

Conclusions

The described associations between TBMN and other glomerulopathies are clinically relevant. Patients with this combination of pathologies have a guarded renal prognosis and warrant careful monitoring and follow-up evaluation.⁷ Furthermore, the discovery of this association should warn us of the possibility that the patient has a familial nephropathy. Of concern, 1 previous study has shown an increased incidence of end-stage kidney disease in relatives of patients with TBMN.⁷ The associations reviewed here do not necessarily dissuade us from the concept that TBMN is generally a benign clinical condition. At the same time, in patients with a clinical presentation involving more than isolated microscopic hematuria, we should consider the presence of an associated glomerulopathy and, at least in some cases, consider performing a diagnostic kidney biopsy examination.

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