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Thin Basement Membrane: An Underrated Cause of End-Stage Renal Disease

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Abstract
The term "thin basement membrane" (TBM) refers to a glomerular disorder characterized by diffuse uniform thinning of the glomerular basement membrane (GBM) on electron microscopy. Patients with TBM usually show an isolated hematuria with excellent renal prognosis. However, some patients can develop proteinuria and progressive kidney dysfunction in the long term. Most patients with TBM are heterozygous for pathogenic variants in genes encoding for both the α3 and α4 chains of collagen IV, a major constituent of GBM. Such variants are responsible for a wide range of clinical and histological phenotypes. The differential diagnosis between TBM and autosomal-dominant Alport syndrome and IgA nephritis (IGAN) may be difficult in some cases. Patients who progress to chronic kidney disease may show clinicopathologic features similar to those of primary focal and segmental glomerular sclerosis (FSGS). Without a shared classification of these patients, the risk of misdiagnosis and/or underestimation of the risk of progressive kidney disease is real. New efforts are needed to understand the determinants of renal prognosis and recognize the early signs of renal deterioration, allowing a custom-made diagnosis and therapeutic approach. For this purpose, a practical and simple clinical approach is supplied.

Introduction

Thin basement membrane (TBM) is a histologic disorder, characterized by diffuse uniform thinning of GBM on electron microscopy and hematuria, usually microscopic, on clinical ground. The renal prognosis has been considered excellent for many years, but recent studies have shown that a significant percentage of patients who initially present with isolated hematuria may later develop proteinuria, renal function impairment, and end-stage renal disease (ESRD) at an advanced age.

Thin basement membrane disorder is often discovered incidentally. About 50% of cases of TBM show familial aggregation, most often in an autosomal dominant pattern. Although the disease is known with many different names, TBM is the most used, as it refers to a renal disorder associated with observable structural changes in the

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GBM. In most cases, TBM is caused by a disorder of type IV collagen (COLIV), a major constituent of GBM, that arises from variants of *COL4A3/COL4A4* genes, responsible for the synthesis of the α3-α4 chains of COLIV.

Pathology

The pathognomonic feature of TBM is a uniform thinning of GBM. *On light microscopy*, the glomeruli appear normal or show mild mesangial cellular proliferation and matrix expansion. An increased number of small glomerular capillary lumens were noted with the infiltration of inflammatory cells and foam cells [1]. Slight attenuation of the GBM can sometimes be observed by Jones methenamine silver or periodic acid-Schiff stains, suggesting GBM thinning.

Immunofluorescence is usually negative. No specific positivity for IgM or C3, and rarely IgG or IgA can be detected.

Electron microscopy reveals a uniform thinning of the GBM. There is not a standardized value defining GBM thinning, with a wide variability in different centers. The GBM thickness varies with age, gender, methods of tissue preparation, and measurement [2]. The GBM thinning in TBM is uniform, appearing as a trilaminar structure made up of a central lamina densa, an inner lamina rara interna, and an outer lamina rara externa (Fig. 1). The mean thickness in male adults is 370 ± 50 nm, and in female adults, it is 320 ± 50 nm [3]. In children, the GBM thickness is 150 nm at birth, 200 nm at 1 year, approaching adult thickness at 11 years [4]. The criteria for TBM in adolescents and adults vary from 200 nm [5] to 264 nm [6]. This range may be partly explained by the technical differences in tissue processing. The World Health Organization has proposed a threshold of 250 nm for adults and 180 nm for children between 2 and 11 years of age [7]. Sometimes, rare regions with laminations, microgranular formation, or regional thickening are described. Those features are typically observed in Alport syndrome, a genetic disorder characterized by renal, cochlear, and ocular involvement caused by an inherited defect in collagen IV (COLIV) due to variations in genes encoding the *COLIV* α3, α4, or α5 chains, for both X-linked [8] and autosomal recessive [9] or dominant [10] forms of Alport syndrome.

Making the differential diagnosis is a true conundrum, particularly for pediatricians. Electron microscopy analysis at the early stages of Alport syndrome can show uniform thinning of the GBM, similarly to TBM; as a result,

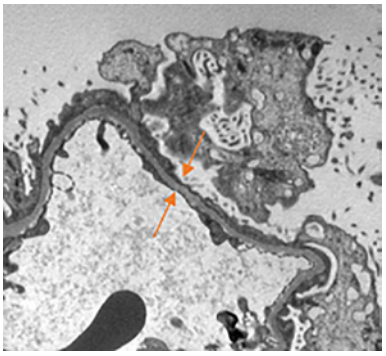

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Fig. 1. Electron microscopy reveals a regularly thin in an otherwise normal GBM that averages approximately 180 nm (magnification ×9,000).

there is significant hesitancy among renal pathologists about diagnosing TBM. Diffuse GBM thinning can be seen in TBM, in the earliest phase of Alport syndrome, and in female carriers with X-linked Alport syndrome too [11]. Three-dimensional evaluation by low-vacuum scanning electron microscopy (LV-SEM) may be useful for a differential diagnosis in these difficult cases. The GBMs show characteristic coarse meshwork appearances in Alport syndrome; instead, GBMs are thin with sheet-like appearances in TBM. At the cut-side view of the capillary wall, the GBMs in Alport syndrome appear as fibrous inclusions between a podocyte and an endothelial cell, while the GBMs in TBM show thin linear appearances [12]. Diffuse roughly etched images on the surface of the GBM with irregular-sized holes by LV-SEM are also described. However, this technique is not routinely available at most centers. Furthermore, immune-histochemical evaluation of the COLIV α3 to α5 chains in renal biopsy can help differentiating between TBM and early stages of Alport syndrome with thin GBM, as these chains are either absent or abnormally distributed in the latter. However, in a small number of Alport syndrome kindreds, the staining for COLIV α3 to α5 chains is normal [13]. The complete absence of COLIV α5 is considered a pathological characteristic in male patients with XLAS, but 20% of patients show a positive COLIV α5 staining [8]. In TBM, the expression of the GBM COLIV α5 chain is decreased, despite normal expression of COLIV α3 and COLIV α4. The role of the COLIV α5 chain in TBM pathogenesis is unknown [1, 14, 15]. The combined use of electron microscopy and immune-histochemical evaluation increases both sensitivity and specificity to TBM and Alport's diagnosis; however, the characteristic glomerular alterations

are not correlated with the degree of hematuria, proteinuria, or CKD [1, 13]. Healthy children and some patients with minimal-change nephropathy or other glomerulonephritis may also show thin GBM, but it is usually focal and not uniform as in TBM.

Etiology

In most cases, TBM is an inherited disorder of COL4. At least 50% of TBM cases show familial aggregation, most often in an autosomal dominant pattern. However, a negative family history cannot be reliable because patients are frequently unaware that they have relatives with hematuria. Usually, patients with TBM are heterozygous for pathogenic variations in either *COL4A3* or *COL4A4*; however, linkage to *COL4A3* or *COL4A4* has been excluded in other families. A missense variant in the fibronectin1 gene was identified in members of a Chinese family with hematuria and TBM; a male patient in this family progressed to ESRD [16].

Pathogenesis

Collagen IV is the major collagenous constituent of the mature mammalian GBM; there are six distinct COLIV isomeric chains, designated from α1 to α6, and each COLIV molecule is a heterotrimer made up of three α chains; triple helices form non-fibrillar networks which interact with laminin, making up basement membranes. The most common form of COLIV molecule contains α1 and α2 chains in a 2:1 ratio. In the GBM, the α1: α2 network is replaced after birth by the α3: α4: α5 one, whose chains are encoded respectively by genes COL4A3 and COL4A4 (on chromosome 2) and COL4A5 (on chromosome X). COLIV is essential for the GBM integrity, as well as for some other specialized basement membranes in the inner ear and lens capsule.

Autosomal dominant TBM usually involves heterozygous variants in either *COL4A3* or *COL4A4*; lots of variants have been identified in TBM, and most of them are single nucleotide substitutions, different in each family [17, 18]. Instead, *COL4A1/COL4A2* variations do not represent a further major genetic locus for TBM [19].

COL4A3-COL4A4-COL4A5-Related Nephropathies

Variations in the *COL4A3* and *COL4A4* genes could affect the synthesis, assembly, deposition, or function of the COLIV molecule. These variations are associated with a wide spectrum of nephropathies, with clinical findings ranging from microscopic hematuria to progressive renal disease leading to ESRD and with extra-renal manifestations such as sensorineural deafness and ocular anomalies [20]. Recently, *Gibson* et al. [21] examined the frequencies of predicted pathogenic *COL4A3-COL4A5* variants in sequencing databases of populations without known kidney disease. Predicted pathogenic *COL4A5* variants were found in at least one in 2,320, while heterozygous predicted pathogenic *COL4A3* or *COL4A4* variants were found in about one in 106 individuals. The high frequency of those variants suggests that other genetic and environmental factors may interfere with the corresponding clinical manifestations.

The X-linked Alport syndrome (XLAS), caused by variations in *COL4A5* gene, is the most typical form of Alport disease. Patients who are homozygous or combined heterozygotes for *COL4A3* or *COL4A4* genes develop autosomal-recessive Alport syndrome (ARAS). XLAS and ARAS are progressive diseases; the rate of progression to ESRD and the timing of extrarenal manifestations are linked to genotype [20]. Some exceptions remain in which heterozygous patients for *COL4A3* or *COL4A4* variants develop autosomal-dominant Alport syndrome (ADAS) [22]. ADAS is a milder form of the disease with a later age of onset and without classical symptoms. The clinical counterpart of heterozygous pathogenic variants in *COL4A3* and *COL4A4* is a wide spectrum of phenotypes too, ranging from complete absence of urine abnormalities to progressive renal disease and extra-renal symptoms (autosomal dominant Alport syndrome) [23].

According to the recent "Guidelines for Genetic Testing and Management of Alport Syndrome," the variations in the genes *COL4A3, COL4A4, and COL4A5* are associated with a spectrum of nephropathy, from microscopic hematuria to progressive renal disease leading to ESRD, an event more frequent than generally estimated [24]. In contrast, although Alport syndrome is characterized by progressive nephropathy with lamellation of the GBM, few patients with GBM thinning diagnosed as ADAS from a family history of ESRD only suffer from hematuria, without developing other symptoms [25]. The "Alport Syndrome Classification Working Group" stated that the GBM thinning should not be recognized as a clinical entity in the absence of other clinical, pathological, and genetic data because of the risk of misclassification and underestimation of the risk of progressive kidney disease. Kasthan et al. [20] proposed to incorporate into autosomal dominant Alport syndrome patients with hema-

turia, thin GBMs, and heterozygous variants in *COL4A3* or *COL4A4* genes, eliminating TBM nephropathy as a diagnostic entity. As a result, the consensus document does not endorse the use of the term TBM nephropathy. Advances in genetic analysis allowed to find genotype-phenotype correlations and mechanisms of onset in some male X-linked Alport syndromes that lead to milder phenotypes of late-onset ESRD [26].

According to Savige et al. [27, 28], some studies suggest that 10–20% of *COL4A3* or *COL4A4* heterozygotes have kidney failure by the age of 70, but most reports came from hospital-based series with severe disease. Although *COL4A5* variants are usually less common than *COL4A3* and *COL4A4* variants (1:20), their prevalence in patients with kidney failure is similar to that of other variants, suggesting that the risk of kidney failure with pathogenic heterozygous variants is much less than with *COL4A5* variants. *COL4A3* and *COL4A4* genes can also be involved in hereditary focal segmental glomerulosclerosis (FSGS). This entity, characterized by podocyte detachment and loss, ma occur in both children and adults with persistent proteinuria >500 mg per day or steroid-resistant nephrotic syndrome [29–32]. In 116 patients from 13 Cypriot families with microscopic hematuria, mild proteinuria, and variable degrees of renal impairment, a dual diagnosis of FSGS and TBM was made in 20 biopsied cases. Out of 236 family members genetically studied, 127 (53.8%) carried a heterozygous variant of *COL4A3* or *COL4A4* genes. None of heterozygous patients had extrarenal manifestations. During a 3-decade follow-up, 31 of 82 patients (37.8%) developed chronic renal failure, and 16 (19.5%) reached ESRD. The next-generation sequencing technique on these patients failed to reveal a second variation in any of *COL4A3-A4-A5* genes, supporting that true heterozygosity for *COL4A3-A4* variations predisposes to FSGS and chronic renal failure [30, 31].

By performing the next-generation sequencing on 70 families with hereditary FSGS, Malone et al. found out rare or novel variants of the *COL4A3* or *COL4A4* genes in 7 of these families [32]. The predominant clinical findings in these families were proteinuria and hematuria. In another study, 22% of patients with FSGS and a familial history of renal disease showed variation of *COL4A3-5* genes [29]. An unexplained coexistence of IgA nephropathy (IgAN), with TBM or *COL4A3-COL4A4* variants was described, frequently when other family members had hematuria [5, 33, 34].

Finally, cases of kidney cysts associated with TBMN or *COL4A3-COL4A4* variants have been reported. The mono or bilateral cysts present from the age of 35 and are often associated with proteinuria, FSGS, and chronic kidney disease (CKD); however, cysts alone do not impair kidney function. If other clues of *COL4A3-COL4A4* variant nephropathies are absent, genetic test is not recommended [35, 36].

In summary, different variants of *COL4A3*, *COL4A4*, and *COL4A5* may cause a wide range of different clinical entities. However, testing for *COL4A3* and *COL4A4* variations is difficult because of the frequent polymorphism of these genes and the likelihood of a further gene locus. From a practical point of view, simultaneous next-generation sequencing of all three *COL4A3-COL4A4-COL4A5* genes may be recommended as the most expedient approach to diagnose COLIV-related GBM nephropathies.

Epidemiology

TBM is a common cause of persistent glomerular bleeding in children and adults. However, the exact prevalence of the disease is difficult to appreciate as not all the patients have persistent microscopic hematuria, many of them are not submitted to renal biopsy, and electron microscopic analyses are performed only in a limited number of cases.

Moreover, TBM may be detected in association with various types of glomerulonephritis. This is one of the main reasons why it cannot be classified as a separate nephropathy but rather as a histological lesion. TBM may occur in all geographic regions of the world and in all ancestries, but most cases have been reported in developed countries. Hematuria has been diagnosed at all ages. It is still uncertain whether the disease is, or not, more frequent in females.

Clinical Presentation

TBM typically presents in children and young adults with persistent microscopic hematuria, no or mild proteinuria, and no other renal or extra-renal abnormalities. Most erythrocytes are dysmorphic, meaning that they are distorted and crenated due to the passage through the GBM gaps. Some of them, called acanthocytes, are ring-shaped cells with one or more protrusions (Fig. 2). Many patients have relatives with isolated microscopic hematuria. At least a single episode of macroscopic hematuria is observed in 5–22% of patients, usually manifesting after exercise or during infection and simulating poststreptococcal glomerulonephritis or immunoglobulin A (IgA)

nephropathy. Gross hematuria can be associated to flank pain. Exceptionally, in patients with macroscopic hematuria, erythrocyte casts may cause tubular obstruction and acute kidney injury [37]. Sometimes hematuria disappears with age, but about 10% of patients develop proteinuria and CKD associated with hypertension. Such a clinical picture is suggestive for Alport syndrome: the differential diagnosis is sometimes difficult and could require a detailed family history, clinical assessment, renal biopsy, especially genetic tests. The predominant forms of Alport syndrome are usually inherited as an X-linked or autosomal recessive trait while TBM is usually autosomal dominant. Extra-renal symptoms are rare in TBM, and in most cases, the underlying disease is slowly progressive.

Sometimes, it is unclear whether patients are affected by TBM caused by heterozygous *COL4A3* or *COL4A4* variations, by a disease caused by variants of other genes, or by coexistent glomerular diseases. Indeed, in about two thirds of cases, TBM is associated with IgAN or FSGS. A differential diagnosis with initial phases of IgAN may be difficult; a renal biopsy with ultramicroscopic and immunohistochemical evaluation is necessary.

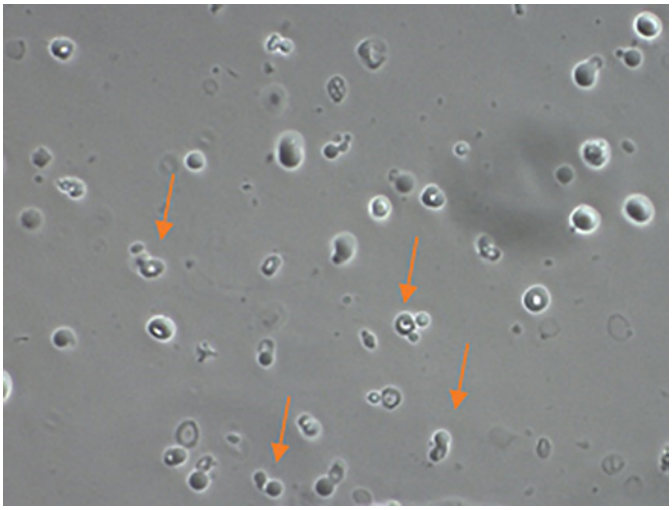

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Fig. 2. The urinary sediment reveals dysmorphic erythrocytes; some of them are acanthocytes (some of them indicated by arrows).

Natural History

TBM is often considered a benign disorder; the first description of the disease was done in the 1960s, when several families with isolated hematuria were classified as "benign familiar hematuria." Most patients do not progress and maintain persistent hematuria for up to 30 years. However, other patients may develop proteinuria and CKD in the long term. A prospective regional study carried out in the Netherlands showed that most patients with TBM had chronic microscopic hematuria, frequently associated with hypertension in the older ages; about 15% of TBM patients also had substantial proteinuria, mainly associated with FSGS lesions. The 5% of patients had nephrotic syndrome, occasionally associated with FSGS tip lesions [38]. In an Italian multicenter study, over a follow-up time of 12–240 months, 8 out of 38 adults with TBM (21%) showed disease progression or hypertension [39]. In the already mentioned study on Cypriot families with 127 variant carriers, microscopic hematuria was the only urinary finding in patients under 30 years. The prevalence of patients with isolated hematuria fell to 66% between 31 and 50 years, to 30% between 51 and 70 years and to 23% over 70 years. Chronic renal failure developed in 8% of variant carriers between 31 and 50 years, in 25% between 51 and 70 years, and in 50% over 70 years. Altogether, 18 of these 127 patients (14%) developed ESRD at a mean age of 60 years [30]. Accordingly, Voskarides et al. [40] concluded that some *COL4A3-COL4A4* variants either predispose some patients to FSGS and CKD or are caused by another genetic modifier that is responsible for FSGS and CKD. In a retrospective study, 1/3 of patients with TBM not associated to other glomerular diseases had advanced chronic kidney disease at diagnosis [41]. A systematic review comparing the long-term course of *COL4A3*- and *COL4A4*-related nephropathies found a high risk of developing CKD in 199 patients (30%) and ESRD in 104 patients (15%), with a clear age dependent penetrance for ESRD; only 4 patients reached ESRD before 30 years of age [42]. From a clinical point of view, it can be difficult to separate FSGS associated with TBM from primary FSGS. Podocyte foot process effacement, while helpful in discriminating between primary and maladaptive FSGS, may be of little help in detecting genetic forms of FSGS. Genetic analysis should be done in doubtful cases.

Treatment

Most patients with TBM and isolated hematuria do not require any specific treatment. Proteinuria (or microalbuminuria) may precede the development of CKD, and it is the earliest event that can be clinically measured. Pa-

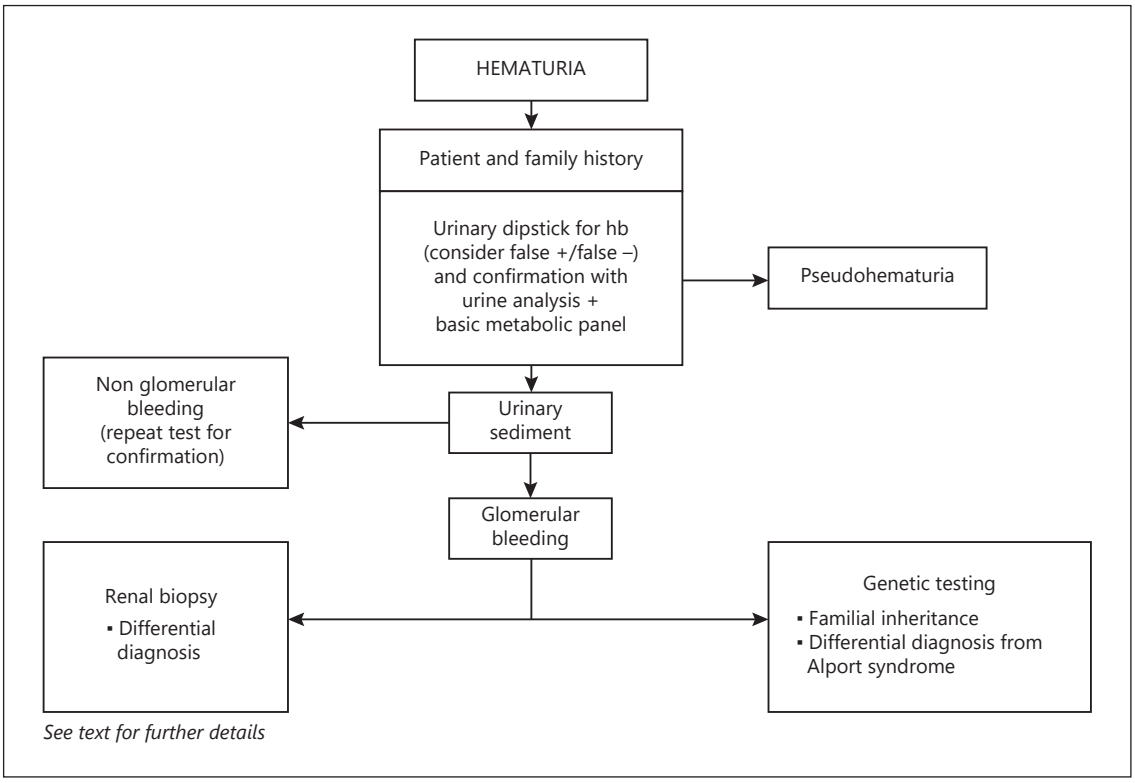

Fig. 3. Algorithm for TBM diagnosis. Renal biopsy is indicated in case of doubt about possible glomerulonephritis or Alport syndrome.

tients showing signs of progressive renal disease may benefit from treatments that may reduce proteinuria such as renin-angiotensin system inhibitors (RASi), finerenone, and vitamin D. Interestingly, the off-label use of RASi has been associated with significant delay in the development of ESRD in patients with Alport syndrome [43, 44]. Thus, all patients with proteinuria and/or arterial hypertension should receive the maximum tolerated dose of a RASi, mineralocorticoid antagonists, and vitamin D unless clinically contraindicated.

Specific therapy for concurrent glomerulonephritis is suggested. In the exceptional cases of anti-GBM disease with concurrent TBM, plasmapheresis, corticosteroids, and cyclophosphamide can be recommended.

Practical Recommendation

The first challenge for the nephrologist who comes across a patient with persistent microscopic hematuria is to assess the diagnosis (Fig. 3). The patient's personal and familiar history is essential; any extrarenal manifestations or recurrent familiar symptoms could help with the differential diagnosis.

Firstly, hematuria should be confirmed with both a dipstick and a urine analysis, and obvious causes should be excluded (urinary tract infections, menstruations, etc.). The specificity of red blood cell (RBC) testing with a dipstick can be limited by false-positive/false-negative results. In alkaline urine (pH > 7.0) or diluted urine (density <1.010), RBCs can be lysed with hemoglobin release. Ascorbic acid, hemoglobinuria, myoglobinuria, menstrual blood, concentrated urine, and strenuous exercise can cause a false-positive result on a dipstick test. On the other hand, low urine-specific gravity and a pH < 5.1 may end with false-negative results.

A study of the urine sediment by phase contrast microscopy showing ≥75–80% dysmorphic red blood cells is strongly suggestive of a glomerular disease. The finding of ≥4–5% acanthocytes allows the diagnosis of glomerular disease [45].

A kidney biopsy with ultrastructural examination may help with a differential diagnosis and TBM identification, especially in clinical settings where the genetic test is not

easily affordable. The differential diagnosis with Alport syndrome may be difficult, and the threshold for the definition of a thin GBM has been differently estimated and varies with age. Moreover, while TBM is historically characterized by a uniform thinning of GBM, some investigators have described a segmental GBM attenuation in a considerable number of patients [46–48]. Immunohistochemical evaluation of the COLIV α3-COLIV α4-COLIV α5 chains may help for the differential diagnosis, as these chains are usually absent or abnormally distributed in Alport syndrome. Some clinical features may help in the differential diagnosis: patients with typical Alport syndrome and their relatives are often affected by hearing loss, lenticonus, and/or retinopathy. Approximately 95% of the homozygous female carriers of X-linked Alport syndrome have hematuria, but a differential diagnosis with authentic TBM based on clinical findings could be difficult without other familiar, immunohistochemical, and genetic clues.

Sequencing of the *COL4A3* and *COL4A4* genes is possible in specialized laboratories: DNA sequencing of the *COL4A3*, *COL4A4*, and *COL4A5* genes for making an accurate genetically based diagnosis of TBM and the various forms of Alport syndrome is essential; furthermore, genetic testing allows an accurate evaluation of familiar inheritance.

Patients with TBM may develop symptomatic proteinuria and CKD, most often in the long term. Blood pressure, serum creatinine, and proteinuria should be monitored every year in patients with persistent hematuria.

Transplantation

Before defining microscopic hematuria as a sign of recurrence after transplant, it is essential to investigate whether the donor was affected by Alport syndrome or IgA nephropathy. Living kidney donation from individuals with TBMN and extensively with *COL4A3* and *COL4A4* variants remains controversial. Two small case series collected information about 13 living kidney donors with TBM: over a follow-up time ranging from 15 to 76 months, all the donors had a normal renal function, without hypertension or proteinuria [49, 50]. The 2022 Guidelines for Genetic Testing and Management of Alport Syndrome recommended that potential donors suspected of having *COL4A3–COL4A5* variants undergo genetic testing before kidney transplantation to confirm the diagnosis, determine the mode of inheritance, and detect possible variants with poor prognosis [24].

In contrast with the previous guidelines published in 2019, individuals with heterozygous *COL4A3* or *COL4A4* variants should not act as kidney donors because of their own risk of kidney impairment and further deterioration after donation [24, 27]. However, this limitation should be discussed with the family(ies) of the donor and recipient, considering the age and the clinical status of the potential donor.

Conclusions

Today, TBM can no longer be considered an independent disease. It is a histological finding that may be observed in different glomerulopathies, including the earliest form of Alport syndrome, females with X-linked Alport syndrome, FSGS, IgAN, and even cases of extracapillary glomerulonephritis. Initially, TBM is associated with isolated hematuria, but over time, proteinuria and hypertension may appear, heralding the possible development of CKD and ESRD. Thus, TBM cannot be considered a benign condition, particularly in aged patients and in those who develop proteinuria. RASi, nonsteroidal mineralocorticoid receptor antagonists, and vitamin D may be used to slow down the progression to ESRD.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Claudio Ponticelli and Gabriella Moroni conceived the study. Claudio Ponticelli, Gabriella Moroni, and Martina Uzzo conducted a review of the literature, drafted the manuscript, reviewed and edited the manuscript, and supported the study. All authors checked the final version of the manuscript.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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