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Thin Glomerular Basement Membrane Disease (TGBM) in Bahrain– Light and Electronmicroscopic Study

KS Ratnakar, MBBS, MD* Sameer Al Arrayed, MRCP**
Sara Mathew George, MBBS, MD***
S Rajagopalan, MBBS, MD**** Fayek Al-Hilli, PhD*

Objective: To study clinicopathological (CP) and light and electromicroscopic (EM) characteristics of Thin Glomerular Basement Membrane (TGBM) Disease.

Method: Renal biopsies of six patients diagnosed between 1996-2000 as having TGBM disease.

Results: The age of patients ranged from 27-50 years with female predominance. There is family history of renal disease, haematuria, proteinuria and hypertension in two patients. One patient terminated in end stage renal disease. Light microscopy showed normal glomerular and tubulointerstitial compartment. Immunofluorescence studies were negative. EM confirmed the clinicopathological diagnosis showing diffuse attenuation of the glomerular basement membrane.

Conclusion: TGBM is uncommon disorder of unknown aetiology presenting as asymptomatic haematuria and/or proteinuria affecting young patient. CP correlation and Light and EM studies are essential to confirm the diagnosis.

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Asymptomatic haematuria with or without proteinuria in young is generally considered to be due to Alport's or IgA nephropathy. Not uncommonly, family history without Alports stigmata or total absence of family history and negative immunofluorescence is associated with similar clinical manifestations and essentially normal glomeruli on biopsy[1-4]. These cases show characteristic thin glomerular basement membrane (<320 nm) ultrastructurally. Pathobiology is obscure. We encountered six cases of thin membrane disease at Salmaniya Medical Complex, a tertiary care hospital in the State of Bahrain. Light and electronmicroscopic studies have been carried out. The details with relevant review are placed on record.

* Consultant Pathologist
*** Senior Registrar
Pathology Department
** Consultant Nephrologist
**** Chief Resident
Nephrology Unit
Salmaniya Medical Complex
Kingdom of Bahrain

METHODS

A retrospective study was carried out at the Department of Pathology, Salmaniya Medical Complex, Bahrain on renal biopsies received from patients belonging to all age groups complaining of haematuria during the five year period, 1996 to 2000. The renal biopsy specimen were processed for light microscopic, immunofluorescent and ultrastructural studies. The light microscopic examination included study of sections by Haematoxylin and Eosin, PAS (Periodic Acid Schiff), Masson's trichrome and Jones (Reticulin). The immunofluorescence was carried out to check the presence and location of IgG, IgA, IgM, C3, C4 and fibrin. Ultrastructual study was conducted as per standard procedure after epoxy resin embedding and stained by uranyl acetate.

The cases selected for study of Thin glomerular basement membrane disease fulfilled the criteria of haematuria (macro/microscopic), with or without family history, consistently negative for all immunofluorescent markers and uniformly thin glomerular basement membrane(<250nm).

The clinical features, biochemical profiles were analysed along with structural data.

RESULTS

The results are given in Tables I-IV, Figures 1,2,& 3.

Table 1. **Age and sex distribution of cases belonging to thin glomerular basement membrane nephropathy (TGBM) (1996-2000).**

Total number of biopsies (1996-2000)	239
Total number of TGBM	6
Percentage	2.51
Males – TGBM	1
Females – TGBM	5

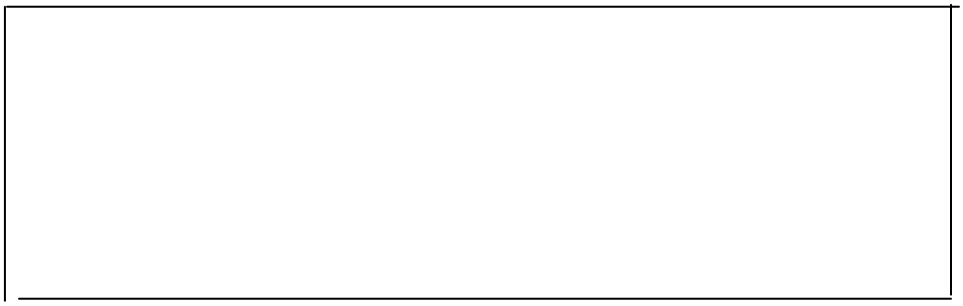

Figure 1. Renal Biopsy shows normal glomerular morphology from a case of TGBM. H&E x 400.

Table 2. **Clinical Manifestations in the six cases of TGBM**

Case No.	Age	Sex	Clinical manifestations
1. 2716-96	50	F	Hypertension with proteinuria, haematuria.
2. 318-97	35	F	Family history of ESRD in two sisters. Hypertension+, Patient presented with chronic renal disease.
3. 6099-97	27	F	Haematuria with mild proteinuria.
4. 1589-98	36	M	Oedema, puffiness, haematuria.
5. 2082-98	41	F	Left flank pain, haematuria, proteinuria, ANA +, ADNA - negative, ANCA,antiGBM-negative.
6. 7756-98	34	F	Microscopic haematuria, hypertension

Table 3. **Biochemical profile in TGBM nephropathy cases 1996-2000**

Case No.	Serum Creatinine	S.urea	Calcium	Uricacid	Urinary protein	SLE immunoprofile (IgG, M,A,C3,C4) ADNA,ANA, AntiGBM, etc)
1. 2716-96	147	10.8	2.23	537	2.03	Negative
2. 318-97	302	10.1	2.30	352	0.37	Negative
3. 6099-97	59	3.5	2.4	188	1.0	Negative
4. 1589-98	68	3.6	1.88	168	<0.05	Negative
5. 2082-98	69	6.6	2.4	346	0.08	ANA Positive
6. 7756-98	82	5.2	2.03	301	--	Negative

NORMAL VALUES: Serum Creatinine 62 – 140 mol/L, S.Urea 3-7 mmol/L Calcium 2.13-2.63 mmol/L, Uricacid 150-350 µmol/L, Protein 24 hrs 0.05-0 1g

The total number of cases encountered during the five year period were six (2.5%) (out of 239 renal biopsies), age group varied from 27-50 years with female preponderance (5:1). In two cases, there was family history of renal disease with hypertension. In three cases, haematuria was accompanied by proteinuria, significant (>1 gm/24 hrs) in two. Renal dysfunction with serum creatinine of 286-302 micromol/L was noticed in one case. Though ADNA and other parameters including complement levels were negative, ANA was positive in one patient. The uric acid levels were high (>350 micromol/L) in two and upper normal (300-340) in two cases. However, serum calcium levels were normal.

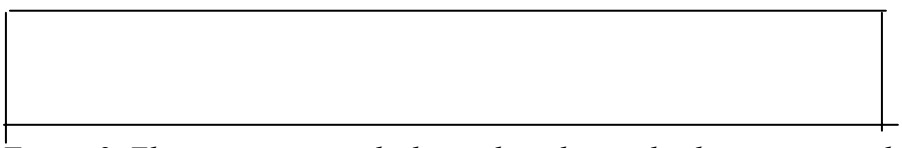

Figure 2. Electronmicrograph shows thin glomerular basement membrane with normal

podocyte, endothelial and mesangial components from a case of TGBM x 3000.

Table 4. **Summary of morphological changes in TGBM cases**

Case No.	LM	Immuno-Fluorescence	Ultrastructual
1. 2716-96	Normal glomeruli Intraluminal red cells in proximal and distal tubules.	Nil	Patent capillaries. Normal endothelial cells. Gl basement membrane is 180nm. Segmental foot process effacement. No deposits.
2. 318-97	Normal glomeruli. Tubular lumina are occluded by casts with red cells. Mild intertital focal fibrosis.Mild arteriolar hyalinization.	Nil	Capillary loops are open with normal endothelium. Glomerular basement membrane is thin 200 nm
3. 6099-97	Normal glomeruli. Widely open capillary lumen. Tubulointerstitial compartment showed focal tubular atrophy with fibrosis. Slight hyaline vascular change.	Nil	Lamina densa is markedly attenuated 200nm. Endothelial, epithelial and mesangial cells are unremarkable.
4. 1589-98	Normocellular glomeruli. Capillary lumina are patent. Tubules and vessels are normal.	Nil	Abnormally thin lamina densa of GBM.160nm. Foot processes are partly effaced. Endothelial and mesangial cells are unremarkable.
5. 2082-98	Glomerular tufts are normal. No capillary wall thickness. Tubules show focal Atrophy.	Trace positivity for IgA, others C3, negative.	Single layered thin lamina dense of GBM 120nm. Epithelial and endothelial cells considered are normal. No deposits in Vessels nonspecific. Mesangium show mild sclerosis.
6. 7756-98	Normocellular glomeruli with patent capillary lumina. Tubules and vessels are normal.	Weakly positive mesangial IgG, IgM, IgA,C3, considered non-specific.	Extensively abnormally thin GBM 180 nm. The lamina densa is single layered. Occasional effacement of foot processes. No electron

dense deposits.

Light microscopically, all cases showed normal glomerular morphology and tubulo-interstitial compartment (Figure 1). In two cases, there was mild renal vascular hyperplasia. Proximal tubular epithelium showed hemosiderin granules in some. No distinct casts were noticed. Immunofluorescence for all the immunoglobulins and complement were negative. The glomerular basement membrane ultra structurally was uniformly thin (200-250nm) (Figure 2 & 3).

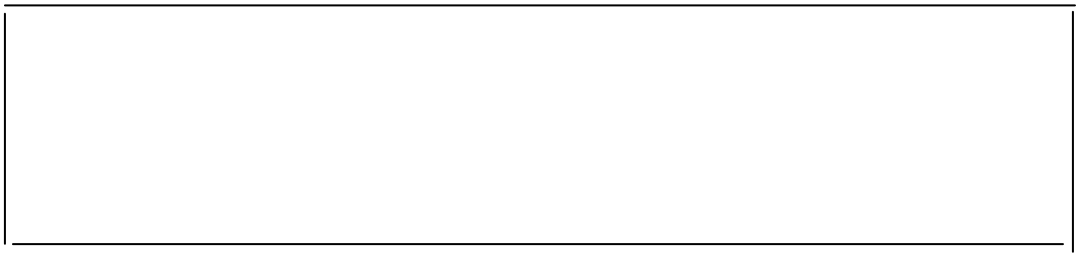

Figure 3. High Power electronmicrograph shows trilaminar basement membrane of extreme uniform thinness x 10000

DISCUSSION

The nosology related to haematuria in the young is increasingly interesting and confusing. Benign familial haematuria, benign recurrent haematuria, thin basement membrane disease are applied to denote one or other aspect of the disorder that affects young with family history in few and consistently associated with ultrastructural demonstration of thin glomerular basement membrane[1-4]. Clinicopathologic features help to distinguish often by exclusion, IgA nephritis and hereditary renal diseases such as Alport's syndrome. The disease is no longer a disorder of children, adults are being reported with increasing frequency[4].

The constellation of clinical manifestations other than micro and macro haematuria are variable. Loin pain, renal calculous disease particularly uricaemia are some to mention, to occur with variable frequency[5,6]. In this series, one patient primarily complained of loin pain. Uric acid levels are elevated or showed upper normal values in four cases. The relation between TGBM and hyperuricaemia is still not clear.

'Thin membrane' is an ultrastructural abnormality detected in several patients belonging to idiopathic haematuria and Alport's syndrome. Light microscopically, the glomerular size and morphology are within normal limits. The immunohistology is non-contributory. Alport's syndrome is characterized clinically by renal disorder with neural hearing impairment.

The thin glomerular basement membrane is associated with 'basket weave' lamina densa[7]. Further, collagen of GBM in Alport's syndrome does not possess Good Pasture antigen, whereas it is present in TGBM nephropathy[8]. All the cases in this report did not

reveal any 'basket weave' pattern and clinically no stigmata related to Alport's syndrome are noticed. Focal thinning or attenuation of GBM may be noticed in several glomerular disorders. Immunofluorescent or histochemical studies, laboratory tests along with ultrastructual studies need to be corroborated in order to understand the etiopathogenesis in this group of cases.

TGBM is often questioned regarding the 'thinness'. Methods of fixation, morphometric methodology and number of glomeruli examined are all known to influence the study[9]. However, uniform methodology regarding fixation, processing has been applied to all the samples in this study. No definite mathematical formulae or grids have been applied to measure but the comparative values in all the samples with controls (age and sex matched/ normal glomeruli) were evaluated concurrently. The normal GBM in adults always measured >250 (350 ± 43)nm. Tiebosch et al1 resolved that 264 nm as cut off point judging the thinness in adults when limited amount of tissue (one glomerulus) is available for study. In the current series, GBM thinness varied from 200-250 nm.

Loin pain-haematuria syndrome has been described by Little et al[10] in 3 young females associated with gross haematuria. Clinical setting similar to this has been recorded in one patient (case 5) in this series. Herbert et al6 in a recent report attributed TGBM as the basis of loin pain. It is suggested that the renal tubular occlusion with red cells may be responsible for flank pain. In the cases presented here (case 5), no tubular distension with red cells has been demonstrated. The flank pain, therefore cannot be attributed solely to tubular choking with red cells. Manuel Praga et al5 reported hypercalcemia, hyperuricosuria in over 44 percent cases of TGBM with flank pain. In the case 5, reported here the serum calcium and uric acid levels were in upper normal range but urinary excretion values have not been carried out which would have given a clue regarding the pathogenesis of Loin pain.

Prognosis is generally good and disease runs a benign course. However impaired renal function has been recorded in 3 out of 12 cases by Dische et al[11]. In our case only one case (case 2) showed features of end stage renal disease. Though, nonspecific, in one case (case 5) ANA was positive, the causal relationship of which is obscure.

The pathogenesis of haematuria in TGBM nephropathy continues to be speculative. The origin of red cells in urine, glomerular or tubular is still controversial. Many symptoms cannot be attributed to this sole structural glomerular abnormality. In view of these difficulties, possibly, WHO classification of glomerular diseases referred the disorder as 'thin basement membrane syndrome'. Long term follow up, molecular biology studies including genome understanding would clarify the TGBM disease in future.

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