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CASE REPORT

A CASE OF THIN BASEMENT MEMBRANE NEPHROPATHY NOT UNCOMMON BUT REMAINS A DISEASE OF UNDERDIAGNOSIS: CLINICO-PATHOLOGICAL STUDY OF HEMATURIA WITH PAIN ABDOMEN IN A YOUNG MALE

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Abstract:-

We report a case of a 14 year old male who presented with lower abdominal pain and passing grossly red urine intermittently for 20 days, having no history of sore throat, skin lesions,blurring of vision, hearing loss and similar family history.A full serology and urology workup was negative for any abnormality. Kidney biopsy revealed uniform thin and slender appearing GBM without any other structural abnormality.Though Immunohistochemistry (IHC) and genetic analysis were not done, a diagnosis of thin basement membrane nephropathy (TBMN), a genetically benign hematuria without kidney failure progression is made. Skin biopsy histopathological examination also revealed finding of thin basement membrane this needs to be differentiated from Alport's syndrome (AS) which has worse prognosis. Probably this is the first case reported from India with descriptive investigations and findings. Due to rarity of this disease and non-availability of laboratory facility especially for kidney biopsy examination, diagnosis is often missed or delayed at primary health care centers especially when no associated proteinuria has yet developed.

***Keywords*:-** *hematuria, glomerular basement membrane, thin basement membrane nephropathy.*

INTRODUCTION

Thin basement membrane nephropathy (TBMN) is one of the important and common cause of persistent hematuria in children and adults, other causes include IgA nephropathy and AS. TBMN, which affects at least 1% of the population, is a lifelong non-progressive disorder associated with family history [1-3].

It is a major clinical challenge to differentiate between TBMN characterized by non-progressive hematuria and AS with progressive hematuria as the main symptom. The typical histopathological feature of TBMN, i.e., uniform thinning of the GBM, could also be found at the early stages of AS, which suggested that the patho-mechanisms of the two diseases might overlap. This connection was verified at the gene level during the early 1990s, when the type IV collagen genes COL4A3 and COL4A4, were discovered and shown to be mutated in TBMN [4]. At present, 40% of TBMN cases have been associated with the COL4A3 and COL4A4 genes. In principle, DNA-based diagnosis of TBMN is possible, but such tests are not commercially or easily available.

At present, the clinical diagnosis still is made mainly on the basis of persistent hematuria with minimal proteinuria and normal renal function, combined with EM examination of biopsy showing thinned GBM; the use of immunologic examination of the type IV collagen III-V chains and gene analysis still are not being used extensively as these tests are not readily available or very costly. Therefor majority of TBMN cases are still considered to be undiagnosed or underdiagnosed.

CASE REPORT

A 14 year old boy presented to us with dull aching, non-colicky lower abdominal pain for 20 days .It was associated with an episode of passing grossly red urine (hematuria) ,which was intermittent and it varied from frank to minimal over a period of 10 days. There is no history of preceding episode of sore throat, skin lesion, arthralgia, oral ulcers, trauma, decreased urine output and fever.

Antepartum, postpartum, neonatal, childhood, family past history of hematuria, deafness, ocular disease or chronic kidney disease (CKD) were unremarkable.

General and systemic examination were unrewarding. Blood pressure, pulse rate were within normal limits. Thorough eye examination including fundoscopy and slit lamp examination were normal,although audiometry was suggestive of left mild sensorineural deafness.

(Table 1) Investigations including basic metabolic panel were normal, and extensive serology and urology workup to rule out other causes of hematuria was negative. 24 hour urinary protein was insignificant while patient had persistent hematuria with 3-10 % dysmorphic RBCs. All radiology findings were normal. Later USG guided kidney biopsy was done and sent for examination.

Light microscopy (LM) findings were unremarkable in renal cortical parenchymal area containing up to 37 glomeruli. There was no evidence of segmental sclerosis, tuft necrosis, subendothelial / Congophilic deposits or crescent formation in the visualized glomeruli. [Fig 1a, 1b]. No evidence of tubular atrophy and interstitial fibrosis. Arteries and arterioles sample appear unremarkable.

DIF showed negative staining for any significant immune deposits.

Electron microscopy (EM) was suggestive of thin and slender appearing GBM and without significant effacement of visceral epithelial cell foot processes. GBM thickness measured at several locations varied from 138.9 to 365.2 nm (mean of 231.5 nm). No evidence of any other GBM abnormalities, splitting, basket weaving or significant alteration of collagen distribution. No any electron dense deposits seen in any area. No tubuloreticular inclusions seen [Fig 2a, 2b, 2c]

IHC evaluation of the type IV collagen □3 to □5 chains in renal biopsy and genetic analysis was not done due to nonavailability of the test and financial constraints.

Skin biopsy was also done which revealed a thin basement membrane that was an important notable finding and added in diagnosis. .

Based on the clinical features of hematuria with no proteinuria and normal renal function, other laboratory & kidney biopsy finding, a diagnosis of TBMN was made.

Patient was counseled about the disease, its prognosis and the need of regular follow up.

Patient is under regular follow up with us. At the time of reporting this case patient was asymptomatic. However, microscopic hematuria was persisting.

Table 1: Investigations

Parameter	Range	Patient's value
Hemoglobin (gm/dl)	13-16	13.8
Total leucocyte count (x10^3 /µl)	4-10	5.1
Platelet count (x10^5 /µl)	1.5-4.5	1.84 x 10^5
Serum sodium (mEq/L)	136-145	142
Serum potassium (mEq/L)	3.5-5.5	4.4
Serum urea (mg/dl)	15-50	41
Serum creatinine (mg/dl)	0.5-1.0	0.7
Serum uric acid (mg/dl)	2.6-6.0	7.5
Serum calcium (mg/dl)	8.5-10.1	9.6
Serum phosphorous (mg/dl)	2.5-4.9	4.5
Total bilirubin (mg/dl)	0.2-1	0.6
SGOT (IU/L)	15-37	31
SGPT (IU/L)	16-63	26
ALP (IU/L)	54-369	301
Total protein (gm/dl)	6-7.8	7
Serum albumin (gm/dl)	3.8-5.4	4.2
ANA		Negative
Anti DNA		Negative
RA/CRP		Negative
ASLO titre	<200	<200
Anti-DNAse B Antibody	<200	134
HIV – I & II		Non-Reactive
HBsAg		Non-Reactive
AntiHCV		Non-Reactive
C3 (g/L)	0.9-1.8	1.21
C4 (g/L)	0.1-0.4	0.22
Urine examination (R/M)		
Specific gravity	1.001-1.035	1.020
Protein	Nil	Nil
Glucose	Nil	Nil
Blood	Nil	3+
RBCs	0-2/hpf	Numerous
Pus cells	0-2/hpf	1-2/hpf
Casts	Nil	Nil
Bacteria	Nil	Nil
Urine Free Hemoglobin	Negative	Positive
Urine for dysmorphic RBCs	Nil	3% dysmorphic RBCs seen
Urine culture	No growth after 48hrs of incubation	
24 hr urine protein	<150mg/24hr	40mg/24hr
X – RAY KUB	No any obvious abnormalities	
USG ABDOMEN	Right kidney-9.6x4 cm, Left Kidney-9.6 x5.6cm,CMD maintained, no calculus no HDUN is noted.	
CT KUB WITH UROGRAPHY	Normal kidneys. No mass, calculus or	
	hydronephrosis on either side. Normal excretion of contrast in the pelvicalyceal system and ureter on each side.	

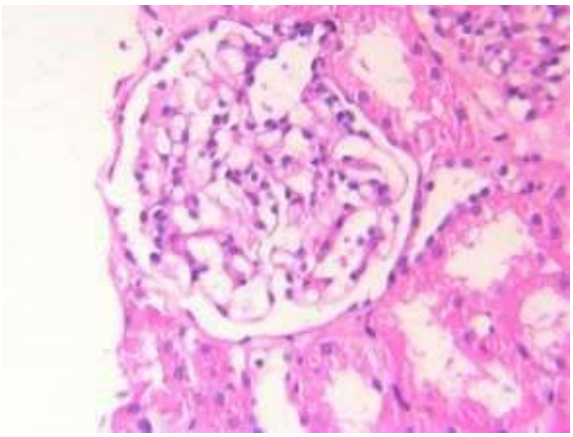


Figure 1a: 160 x H&E stain

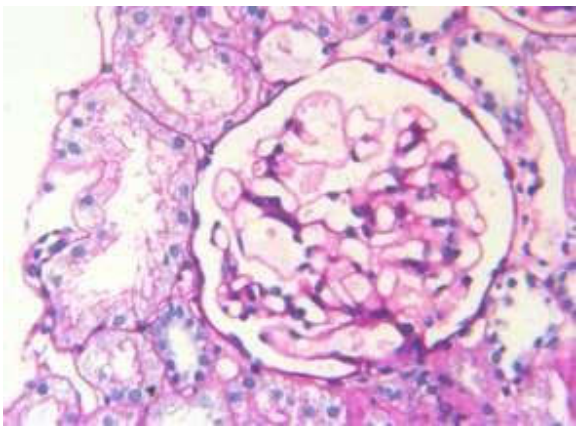


Figure 1b: 160 x PAS stain

Fig 1a, 1b: Light Microscopy (LM) images shows morphological unremarkable glomeruli

Fig 2a, 2b, 2c: Electron microscopy (EM) show uniform thin and slender appearing GBM and without significant effacement of visceral epithelial cell foot

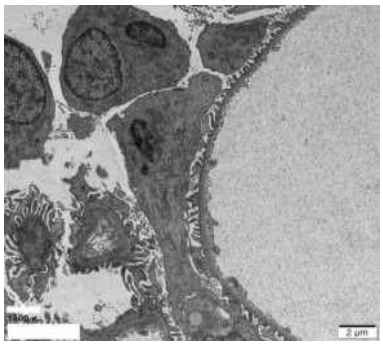


Figure 2a

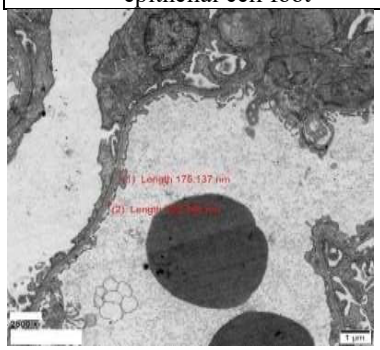
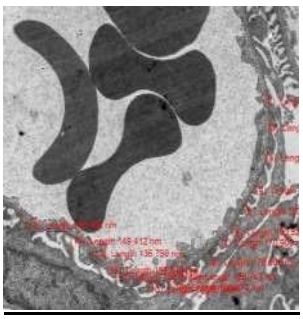


Figure 2b

Figure 2c



DISCUSSION

TBMN seems to be a disease of the adult without gender predominance, and affects GBM type IV collagen trimer □3-5. It usually presents with painless intermittent gross hematuria followed by persistent microscopic hematuria. Hematuria can be either gross or microscopic, and may or may not be associated with dysuria. Colicky abdominal pain may occur in some individuals who developed clots in genitourinary tract. Diagnosis is made mostly on the basis of persistent hematuria usually combined with nil or minimal proteinuria. Though our case presented with hematuria associated with lower abdominal pain but there was no any evidence of clot or infection noted and that was an unusual presentation. Persistent hematuria in TBMN is defined as hematuria which is observed on at least two occasions 2 years apart [5]. This feature of TBMN, distinguishes it from other more acute renal disorders such as hematuria of post streptococcal infections. Most patients remains asymptomatic and the condition is usually incidentally detected during health control [3].

Kidney biopsy reveals the findings suggestive of thin GBM. World Health Organization has proposed a threshold of 250 nm for adults and 180 nm for children between 2 and 11 yr of age [6]. According to Vogler et al.[7], the criteria for TBMN in children vary between 200 and 250 nm, and in adults from 200 nm and 250 nm or up to 264 [8]. In our case mean of GBM thickness was 231.5 nm. This variation in recommendations is due to difficulties in standardizing the technical methods. This means that the morphologic criteria for thin GBM have to be evaluated carefully by the pathologist, and one has to take into account that the width of the GBM varies according to age and gender of the patient and also between different laboratories as a result of technical differences in sample preparation. Individual criteria should be established for each histologic laboratory.

In TBMN, the cardinal findings are that the GBM is thinned in most of the glomerular capillaries and that there is absence of other significant glomerular pathology. These finding were present in our case. Sometime a typical feature of lamellation or regional thickening though rare if seen is suggestive of AS [1], that was absent in our case. This feature may pose a problem in differentiating between TBMN and AS, as EM analysis at early stages of AS can reveal similar uniform thinning of the GBM (see below for differential diagnosis). IHC evaluation of the type IV collagen 3 to 5 chains in renal biopsy has become of major importance as a method to differentiate TBMN from early stages of AS.

Similar to AS, familial TBMN is manifested by chronic hematuria, but it differs clinically from AS in several important aspects: (1) extrarenal abnormalities are rare though present in our case as there was left mild sensory neural deafness in audiometry examination without clinical deafness was present in patient; (2) proteinuria, hypertension, and renal deterioration are unusual; (3) gender differentiation of TBMN are not apparent; and (4) transmission is autosomal dominant. For early diagnosis of AS, it very important to clarify family history [9].

Therefore, differential diagnosis from X-linked or autosomal recessive AS is extremely important. This should include IHC analysis of the type IV collagen 3 to 5 chains. Genetic analyses can verify the diagnosis, unfortunately IHC & DNA analysis is not readily available and there is financial constraints too.

Here we are reporting this case probably the first case from India as no any case has been reported with descriptive biopsy findings as per our best knowledge. We have seen only one case reported from India [10], but descriptive kidney biopsy images were not available. TBMN must be under registry to find out exact prevalence in India. Still in periphery complete biopsy evaluation facility is not readily available due to which many cases remains undiagnosed or unregistered.

Currently, no clear evidence-based treatment protocols are available for TBMN. In any case, patients with TBMN should be monitored for the appearance of hypertension, proteinuria, or renal insufficiency.

CONCLUSION

TBMN is one of the most common disorders of the kidney although undiagnosed or underdiagnosed due to constraints. Presentation is usually painless hematuria but dysuria without any clot in genitourinary tract and infection may be present as uncommon presentation. TBMN and AS must be differentiated at earlier stage during evaluation as AS has severe outcome. Counselling and monitoring have important role to play in the management of TBMN.

Although clinical presentation with family history and kidney biopsy especially EM findings are helpful for diagnosis of TBMN; IHC examination of expression of the type IV collagen α3 to α5 chains is the most informative method. Availability of IHC & gene analysis would be of utmost importance. Financial aspect of the tests should also be sought for.

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