

Finding of pathological thrombomodulin gene variant in a patient with idiopathic nodular glomerulosclerosis and chronic thrombotic microangiopathy-like changes

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Ramy Hanna¹ , Jonathan E Zuckerman², Antoney Ferrey¹,
Everado Arias Torres³, Sam Tonthat¹, Marina Barsoum⁴,
Lena Ghobry⁵, Olivia Wassef⁶ and Kamyar Kalantarzadeh¹

Abstract

Idiopathic nodular glomerulosclerosis is an unusual histopathological finding that has commonly been observed in male smokers with hypertension. It has remained an enigmatic condition and is best described as a diabetic pattern of glomerular injury seen in non-diabetic patients. It is also one of the few nicotine (smoking)-associated/smoking-associated patterns of renal injury. We present an even more unusual manifestation of this pathological finding in a 59-year-old Hispanic female who presented with chronic kidney disease approaching need for renal replacement therapy. The patient had idiopathic nodular glomerulosclerosis on kidney biopsy, despite no prior history of diabetes, nor smoking history, including no secondhand smoking exposure. The patient did have hypertension. The renal biopsy also showed evidence of chronic thrombotic-microangiopathic changes within arteries and arterioles. Genetic testing of the alternative pathway revealed an unusual and likely pathological variant of thrombomodulin supporting complement dysfunction as having a role in the presentation.

Keywords

Idiopathic nodular sclerosis, thrombotic microangiopathy, thrombomodulin mutation, alternative pathway activation, hypertension

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Introduction

Idiopathic nodular glomerulosclerosis (ING) is an unusual pathological entity that is best described as diabetes like nodular glomerulosclerosis in non-diabetic patients.¹ This was first recognized nearly 20 years ago as a lesion linked to non-diabetic smokers with hypertension.² Tobacco smokers seem to be at highest risk for this presentation;³ however, users of THC (tetrahydro-cannabinoid) usually derived from marijuana have been reported to develop this pattern of renal pathology as well.⁴ The reported mechanism is postulated to be due to arteriolar injury induced by inhaled metabolites from tobacco smoking.⁵ The typical pathologic presentation resembles Kimmelstiel-Wilson nodules that are typically found on biopsy.^{6,7}

There are now increasing numbers of ING presentations where the patients are nonsmokers,⁸ some series estimate about 15% of ING patients were nonsmokers.⁸ Some of these patients were also noted to not be hypertensive.⁹ We present

a case of a 59-year-old female who presented with hitherto undiagnosed chronic kidney disease (CKD; at stage V), who was found to have ING on renal biopsy. The patient was a

¹Division of Nephrology, Hypertension and Kidney Transplantation, University of California Irvine, Irvine, CA, USA

²Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

³Department of Medicine, University of California Irvine, Irvine, CA, USA

⁴School of Pharmaceutical Sciences, Chapman University, Orange, CA, USA

⁵University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA

⁶Division of Nephrology, Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Corresponding Author:

Ramy Hanna, Division of Nephrology, Hypertension and Kidney Transplantation, University of California Irvine, 333 The City Drive, Suite #400, Orange, CA 92868, USA.
Email: Rhannamd81@yahoo.com



never-smoker, and genetic analysis revealed a rare likely pathological variant of the thrombomodulin (THBD) gene involved in the alternative pathway of complement. A role for complement has not been conclusively demonstrated previously, but a clinical-pathological series showed 80% of a 10 biopsy series with evidence of healing thrombotic microangiopathy (TMA).¹⁰

Case report

A 59-year-old female with at least 2-year history of CKD stage 3 with an estimated glomerular filtration rate (eGFR) of 48 mL/min was presented to our center due to worsening shortness of breath. She was found to have a 15-pound (lbs) weight gain and severe bilateral lower extremity edema. Her serum creatinine on admission was 4.4 mg/dL with an eGFR of 10 mL/min. She was a non-diabetic and had never needed medications for glycemic control (hemoglobin A1C was 6%). The patient also was severely hypertensive with a blood pressure of 220/110 upon admission, which was worrisome for a hypertensive emergency. The patient had been on anti-hypertensive therapy with amlodipine, metoprolol, and losartan chronically.

The patient's serological workup showed a normal kappa/lambda free light chain ratio 1.65, normal C4 complement but with C3 complement level (80 g/L) at the lower limit of normal. Her anti-nuclear antibody was a positive at 1:320 speckled pattern, but ribonucleoprotein antibody (RNP), Smith antibody (anti-Smith), double-stranded DNA antibody (anti-dsDNA), anti-nuclear cytoplasmic antibodies (ANCA), total complement, human immunodeficiency virus (HIV), rapid plasma reagin (RPR), *Treponema pallidum* particle agglutination antibody (TPPA), rheumatoid factor (RF), Sjogren's syndrome A/B (SSA/SSB), hepatitis panel (Hepatitis A, B, C), cryoglobulin level, and hepatitis C virus polymerase chain reaction (HCV PCR) were all negative. Cardiolipin testing was indeterminate with 37 IgG GPL and <9.4 IgM GPL. Anti-phospholipid antibody testing was negative, erythrocyte sedimentation rate (ESR) was 19 s, and C-reactive protein was not drawn during her initial hospitalization.

A 24-h urine protein was 4.05 g of protein/24h, and a urine protein to creatinine ratio was about 9.5 g/g creatinine. Hemoglobin was 9 g/L, platelets were 128,000–148,000/ μ L, reticulocytes were low at 0.5%, vitamin B12 (cyanocobalamin) levels were 724 pg/mL, and there was no iron deficiency (iron saturation of 25%). No evidence of hemolysis was present on peripheral smear. Prothrombin time (PT) was 14 s, international normalized ratio (INR) was 1.04, and activated partial thromboplastin time (aPTT) was 28 s. Direct Coombs and indirect Coombs antibodies were negative. A disintegrin and metalloproteinase motif #13 member #1 (ADAM TS 13) was >94%. Lactate dehydrogenase was 196 U/L (in normal range), and haptoglobin was 180 mg/dL (within normal range). Shiga toxin testing was negative.

Renal ultrasound showed a 10.2-cm right kidney and a 10.2-cm left kidney.

The patient's renal function continued to worsen, with persistence of fluid overload with sCr elevation to 5 mg/dL. Initially the blood pressure was treated by substituting amlodipine for increasing doses of nifedipine. The patient was started on hemodialysis (HD) via an inserted right chest tunneled dialysis catheter, given ongoing worsening of renal function and expectation for prolonged need for HD. A renal biopsy was obtained after the patient's blood urea nitrogen levels and blood pressure were stabilized, and the results are displayed (Figure 1).

The renal biopsy contained approximately 36 glomeruli (26 globally sclerotic). The glomeruli were enlarged and exhibited diffuse nodular mesangial sclerosis and thickened capillary loops. There was no significant endocapillary or mesangial hypercellularity. Well-developed glomerular capillary loop double contours were not present. There were no glomerular thrombi. At least one glomerulus exhibited segmental sclerosis. There was extensive interstitial fibrosis and tubular atrophy involving >80% of the sampled cortex. There was minimal interstitial inflammation. Arteries exhibited moderate intimal sclerosis as well as focal subintimal mucoid intimal edema. Arterioles exhibited muscular hypertrophy and marked and frequently occlusive intimal hyalinosis associated with occasional foam cells and occasional red blood cell fragments. Definite active arterial/arteriolar thrombi were not present. A Congo red stain was negative for amyloid deposition. Immunofluorescence studies demonstrated glomerular and tubular basement membrane pseudolinear staining with IgG and albumin and segmental smudgy glomerular capillary tuft staining with IgM, C1q, and C3 in areas of segmental sclerosis. Significant fibrinogen staining in glomeruli was not present. Smudgy staining with IgM, C1q, C3, and fibrinogen was present in areas of arteriolar hyalinosis. There was no evidence for any immune complex deposition or light chain deposition disease. Electron microscopic studies demonstrated thickened glomerular basement membranes due to homogeneous expansion of the lamina densa as well as markedly expanded mesangial matrix. Minimal glomerular basement membrane duplication was present and was associated with mild subintimal electron lucency and mild endothelial cell swelling (the specificity of these findings was uncertain due to adjacent capillary loop segmental sclerosis). Luminal platelet aggregates or fibrin tactoids were not present. Podocytes were extensively effaced. Endothelial cells were otherwise unremarkable without tubuloreticular inclusions. There were no immune complex type deposits or any fibrillary, microtubules, or other deposit types present.

In the absence of diabetes and with the finding of completely negative immunofluorescence (making systemic lupus erythematosus (SLE) unlikely), negative Congo red, and the absence of any organized deposits, a diagnosis of ING was rendered as well as subacute to chronic microangiopathic changes within arteries/arterioles consistent with severe

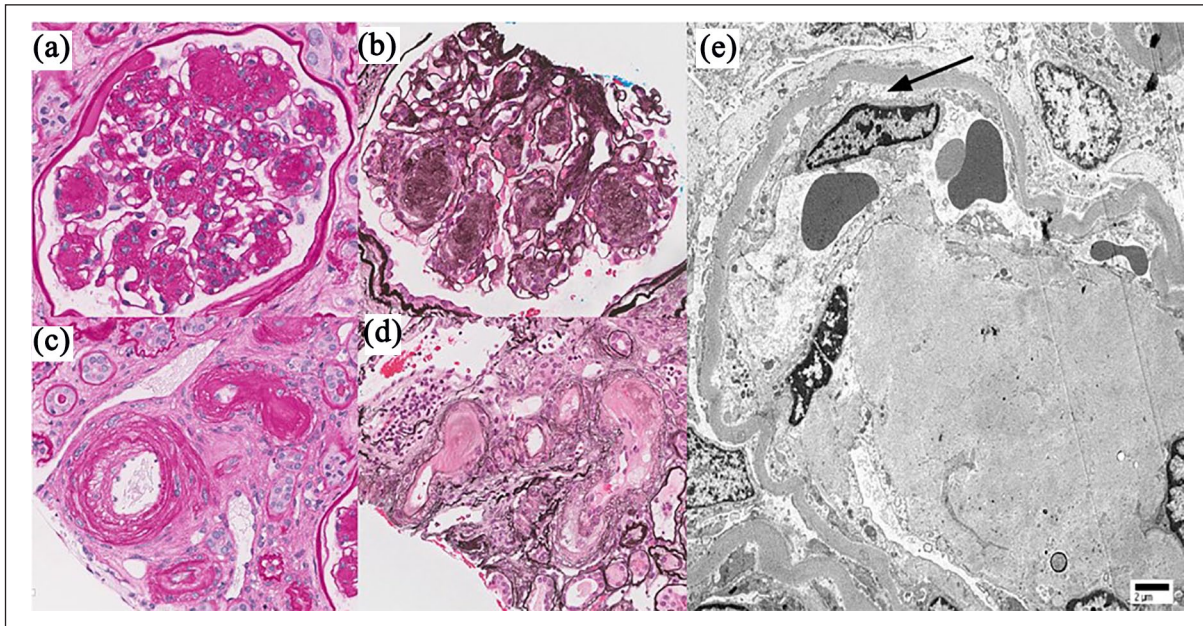


Figure 1. Renal biopsy findings. Glomeruli exhibit diffuse nodular mesangial sclerosis and thickened glomerular basement membranes: (a, c) periodic acid Schiff stain, 400 \times and (b, d) Jones' silver stain, 400 \times . Arteries exhibit mild subintimal edema and arterioles exhibit severe intimal hyalinosis with occasional foam cell accumulation. (e) Electron micrograph of the nodular glomerulosclerosis. Rare subendothelial lucency with thin strip of subendothelial neomembrane was present (arrow) and was associated with mild endothelial cell swelling.

hypertension. The consideration for other etiologies of chronic TMA was also raised in the diagnostic comment. It should be noted that the morphologic features of the marked arteriolar intimal hyalinosis in this case were at the very severe end of which we typically see in our biopsy practice in the setting of advanced renal chronic changes due to any etiology. While to some degree these changes may have been reflective of secondary changes in the near end-stage kidney disease setting, they were sufficiently conspicuous to raise the possibility of a superimposed microangiopathic process.

The patient required transition to maintenance of HD treatment as renal replacement therapy (RRT), given the low platelets and a TMA like picture, complement genetics were sent. A complement genetic panel showed a heterozygous mis-sense variant (c1456 guanine to thiamine, protein 486 aspartate to tyrosine substitution) in the thrombomodulin (THBD) gene; this variant was previously seen in association with atypical hemolytic uremic syndrome and was not seen in any healthy controls without alternative pathway dysfunction. This suggested a role for alternative pathway dysfunction in the TMA observed in this patient, as such a trial of eculizumab for C5 blockade was attempted. Thus far, it has not been successful, but this was a likely outcome given that the findings on biopsy were predominantly chronic indicating long-standing chronic damage and arterial injury. The patient's pre-diabetes was considered as a possible "second hit" that may have contributed to the patient's TMA presentations. The equivocal cardiolipin tests may have also

been a potential exposure that leads to this presentation, but the serologies obtained were equivocal.

Discussion

In this report, we review a rare condition reminiscent of diabetic nephropathy in a patient with no diabetes and only with long-standing hypertension. The noteworthy features of this case include the finding of features of chronic TMA on biopsy which prompted genetic analysis of complement genes. This is the first reported case of any confirmed complement gene mutations associated with the ING pattern of injury. The thrombomodulin mutation identified is a recognized pathogenic variant of alternative complement pathway dysfunction.^{11,12} The lack of peripheral hemolysis suggests a renal limited TMA presentation, despite the finding of low platelets systemically. It is important to note that the lack of systemic hemolysis does not preclude the existence of TMA, and the finding seen in this case is reminiscent of Timmermans et al.¹³ about arteriolar injury and complement dysfunction in patients with chronic hypertension. The lack of efficacy of eculizumab was disappointing, but probably given the advanced degree of chronicity in the renal biopsy.

This report, along with rising concern that hypertension-related TMA may in some cases be complement mediated,¹⁴ suggests the need for deeper study into ING. Table 1 lists the characteristics of published cases and studies of ING

Table 1. Clinical characteristics of reported idiopathic nodular sclerosis patients.

Reference	Age	Race	Gender	Diabetic?	Smoker	Hypertensive?	Thrombotic microangiopathy	Obese	HL	Mutation?	Other
Andronesi et al. ¹⁵	46	Caucasian	M	N	Y	Y	N	Y	Y	NC	
Araujo et al. ¹⁶	64	Hispanic	M	N	Y	Y	N	Y	Y	NC	
Balafa et al. ¹⁷	58	Caucasian	M	N	Y	Y	N	N	Y	NC	FHx ESRD
Baradhi et al. ¹⁸	58	Caucasian	M	N	Y	Y	N	Y	Y	NC	
Batal et al. ¹⁹	28–77 n = 3	2 Caucasian 1 Hispanic	2M, F	N × 3	Y × 3	Y × 3	N × 3	Unk	Unk	NC	3 anti-GBM antibodies
Chandragiri et al. ²⁰	45, 46 n = 2	2 Indian	M, F	N × 2	N × 2	Y × 2	N × 2	Y, N	Y, N	NC	HIV
Costa et al. ²¹	62	Caucasian	M	N	Y	Y	N	Y	Y	NC	
Cunha et al. ²²	45	Caucasian	M	N	Y	Y	N	Unk	Y	NC	Overweight
Herlitz ²³	49	AA	F	N	Y	Y	N	N	Unk	NC	
Kuppachi et al. ⁶	77	Caucasian	F	N	Y	Y	N	Unk	Y	NC	Pancreatic mass
Kuppachi et al. ⁶ (reviewed cases)	51.3 mean age n = 22	41% Caucasian	82% M	100% N	Unk	Unk	Unk	Unk	Unk	NC	Range 0.2–10 g/g proteinuria
Kuri et al. ²⁴	34	Hispanic	F	N	N	N	N	Y	Unk	NC	
Li and Verani ³	64.2 mean age n = 15	73% Caucasian 27% other	67% F 33% M	100% N	67% Y	93% Y	N	60% obese		NC	
Markowitz et al. ²	68.2 mean age n = 23	74% Caucasian 26% other	78% M 22% F	100% N	91% Y	96% Y	N (endothelial changes noted in few cases)	NK	90% HL 10% not HL	NC	
Mollae et al. ⁴	36	AA	F	N	Y	Y	N	N	Y	NC	THC use NSAID use
Nakamura et al. ⁵	59	Japanese	M	N	Y	Y	N	N	Y	NC	Overweight Measured AGE-high levels
Nasr and D'Agati ²⁶	70	Caucasian	F	N	Y	Y	N	N	N	NC	NSAID use
Onteddu et al. ²⁷	68	AA	M	N	Y	Y	N	N	N	NC	HCV
Revuelta et al. ¹	53, 74 n = 2	Caucasian	2M	N × 2	Y × 2	Y × 2	N × 2	50% obese	100% HL	NC	HIV 1, Case 2
Salvatore et al. ¹⁰	62 mean age n = 10	Caucasian	10 M	100% N	100% Y	100% Y	N	20% obese	NK	NC	8/10 biopsies e/o TMA
Uchida et al. ⁹	53	Japanese	F	N	N	N	N	N	NK	NC	No risk factors
Wu et al. ⁸	55.5 mean age n = 10	Chinese	80% M 20% F	100% N	85% Y	90% Y	N	N	NK	50% HL	95% overweight (BMI > 25)
Current case	59	Hispanic	F	N	N	Y	Y	N	Y	Y, THBD	Overweight

AA: African American; AGE: advanced glycosylation end products; BMI: body mass index; e/o: evidence of; ESRD: end-stage renal disease; F: female; FHx: family history; GBM: glomerular basement membrane; g/g: gram protein per gram creatinine; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HL: hyperlipidemia; M: male; n: number of patients; N: no; NC: not checked; NSAID: non-steroidal anti-inflammatory drugs; THBD: thrombomodulin; THC: tetrahydrocannabinoid; TMA: thrombotic microangiopathy; Unk: unknown; Y: yes.

including interesting pathological correlations with TMA, hypertension, and smoking status. The finding of a TMA and a thrombomodulin mutation in this report may be a fortuitous discovery that sheds light on a possible connection between the alternative pathway of complement and ING.^{1–10,15–27} The connections of ING to hyperlipidemia, obesity, and atherosclerosis are also interesting since they all represent inflammatory states, and this could be suggestive of a role for complement as well.² Studies of the coagulation cascade may be useful in ING and TMA presentations given that the coagulation cascade and the complement system interact.

Ultimately many more elegant translational and basic science studies are needed to unravel the etiology of ING. We recommend routine complement testing in ING, especially in cases where the classical risk factors of obesity, hyperlipidemia, and hypertension are not apparent.⁹ Evaluation of classical coagulation pathways may also be warranted. Most importantly, given the possibility of an underlying genetic complement disorder in these patients, avoidance of living-related donation in this setting might be prudent. Careful monitoring of these patients for recurrent TMA in the allograft setting may also be appropriate.

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Informed consent

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ORCID iD

Ramy Hanna  <https://orcid.org/0000-0003-1807-8909>

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