Idiopathic nodular glomerulosclerosis: Report of two cases and review of literature

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ABSTRACT

Nodular glomerulosclerosis, a pathological finding characterized by areas of marked mesangial expansion with accentuated glomerular nodularity can be seen in a number of conditions including diabetic nephropathy, amyloidosis, light chain deposition disease, fibrillary and immunotactoid glomerulopathy, collagen type III disease, nodular membranoproliferative glomerulonephritis, and Takayasu's arteritis. Idiopathic nodular glomerulosclerosis is a diagnosis of exclusion and is reported in patients with hypertension, smoking, chronic obstructive pulmonary disease, obesity, metabolic syndrome, etc. We report two cases of idiopathic nodular glomerulosclerosis, one in obese hypertensive male and the other in nonhypertensive, nonobese female patient.

Key words: Nodular glomerulosclerosis, hypertension, obesity, smoking

Introduction

Nodular glomerulosclerosis is a pathological finding characterized by areas of marked mesangial expansion with accentuated glomerular nodularity on renal biopsy. It was originally described by Kimmelstiel and Wilson as a pathognomonic feature of diabetic nephropathy.[1] However, nodules can also be seen in amyloidosis, light chain deposition disease (LCDD),[2] fibrillary and immunotactoid glomerulopathy,[3,4] collagen type III disease,[4] nodular membranoproliferative glomerulonephritis,[5] and Takayasu's arteritis.[6] If the presence of nodules is not associated with any of these disorders, it is labeled as being "idiopathic." The pathogenesis of this disorder is unclear and is known to occur in patients with hypertension, hypercholesterolemia, history of chronic smoking, chronic obstructive pulmonary disease with chronic hypoxemia, obesity, etc.[7,8] Despite the growing epidemic of metabolic syndrome, this entity is grossly underreported in India. In this report, we present two cases of idiopathic nodular glomerulosclerosis, one in an obese and hypertensive male and the other in an underweight nonhypertensive female.

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Case Reports

Case 1

A 46-year-old nondiabetic male presented with pedal edema of 1-month duration. He was hypertensive taking amlodipine 5 mg/day for last 1-year. He denied the history of smoking or alcoholism. Past history was insignificant except for an appendicectomy, 20 years back. On examination, he was normotensive, obese Class II (body mass index [BMI]-42). Fundus was normal. Systemic examination was unremarkable.

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The evaluation revealed proteinuria (3.032 g/day), bland urinary sediment, and a serum creatinine of 1.3 mg/dl. Serum albumin was 3.8 g/dl. Lipid profile was abnormal with high total cholesterol (213 mg/dl) and low-density lipoprotein (153 mg/dl) values. Thyroid profile was normal. Immunological markers were negative, and complements were normal. In view of significant proteinuria, a renal biopsy was performed with a provisional diagnosis of membranous nephropathy.

Renal biopsy included 13 glomeruli, all enlarged in size and showed variably sized nodules, which were cellular and were Periodic-acid-Schiff (PAS) and silver positive. Vessels and tubulointerstitium were unremarkable except for focal lymphocytic infiltrates. Immunofluorescence was negative for IgM, IgA, IgG, C3C, C1q, k, and λ. With the above findings being consistent with diabetic nephropathy, he was reevaluated, and diabetes mellitus was ruled out. HbA1C was 5.2%, and glucose tolerance test was within normal limits. Workup for other causes including amyloidosis, LCDD, and immune deposition diseases was negative. Electron microscopy (EM) which revealed diffuse flattening of foot processes with marked widening and ill-defined lobularity of the mesangium without any electron dense deposits. The negative features on EM and immunofluorescence rule out other differentials of nodular glomerulosclerosis including monoclonal immunoglobulin deposition disease, fibrillary and immunotactoid glomerulonephritis, fibronectin glomerulopathy, and collagenofibrotic glomerulopathy [Figures 1-3].

With the above findings, the diagnosis of idiopathic nodular glomerulosclerosis was made, and the patient was discharged on telmisartan. Further follow-up of the patient at 3 monthly intervals revealed a progressive decline in proteinuria to <1 g/day.

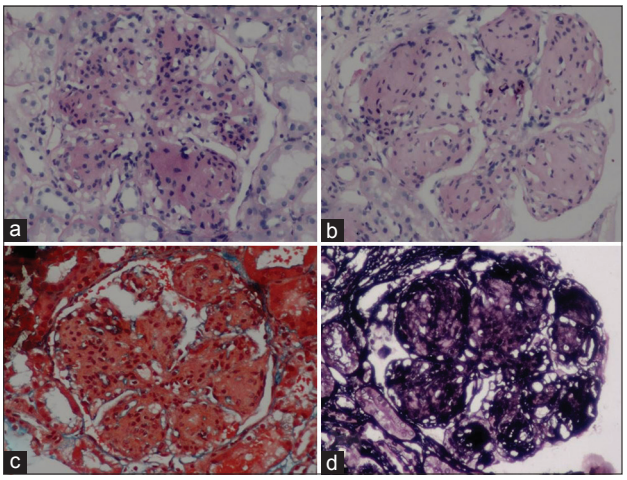

Figure 1: (a and b) The glomeruli showing nodules which are cellular and variable in size with Periodic-acid-Schiff (PAS) positivity (c) The nodules did not show matrix material (Masson trichrome, ×100). (d) The nodules were brightly positive on silver stains (SM-PAS, ×100)

Case 2

A 45-year-old female presented with myalgias, decreased appetite, and mild pedal edema of 15 days' duration. She was moderately built and underweight. BMI was 16.5. Systemic examination was unremarkable. Investigations revealed serum creatinine 8.9 mg/dl and 24 h urinary protein excretion 710 mg/day. Serum albumin was 3.4 g/dl. Urine microscopy revealed bland urinary sediment without any microscopic hematuria. Ultrasound showed normal-sized kidneys with increased echotexture and maintained corticomedullary differentiation. She was given 3 sessions of hemodialysis, and a renal biopsy was performed. Renal biopsy showed 12 glomeruli, all glomeruli were enlarged with nodules and were PAS and silver positive. Vessels and tubulointerstitium were unremarkable. Immunofluorescence was negative for IgM, IgA, IgG, C3C, C1q, κ, and λ. EM did not show any electron dense deposits and was suggestive of nodular glomerulosclerosis. Her HbA1C was 5%. Fundus examination was normal. Blood sugars were normal. Autoimmune workup was negative. Workup for other causes of nodular glomerulosclerosis such as amyloidosis, LCDD, and immune deposition diseases was negative. Lipid profile was normal except for a mildly decreased high-density lipoprotein level (38 mg/dl). She remained dialysis dependent.

Discussion

We report two cases of nodular glomerulosclerosis resembling diabetic nephropathy in nondiabetic patients. Less than 50 cases of idiopathic nodular glomerulosclerosis have been reported in the literature and none from India. Markowitz *et al*., in 2002 have published the largest series of this entity including 23 cases.[9] This could be because of the nonavailabilty of advanced diagnostics like EM in the past. Idiopathic nodular glomerulosclerosis was described previously as diabetic like nodular glomerular lesions occurring in a nondiabetic patient. Baradhi *et al*., in 2012 reported a case of diabetic nephropathy in a nondiabetic smoker in which they have detailed about various causes of nodular glomerulosclerosis including idiopathic nodular glomerulosclerosis.[10] This rare disease entity was thought to be strongly associated with long-standing hypertension, chronic smoking, hypercholesterolemia, etc.[7] A study from China reported the clinicopathological profile of 20 cases of idiopathic nodular glomerulosclerosis. Male preponderance was noted, and overweight (in 95% patients), cigarette

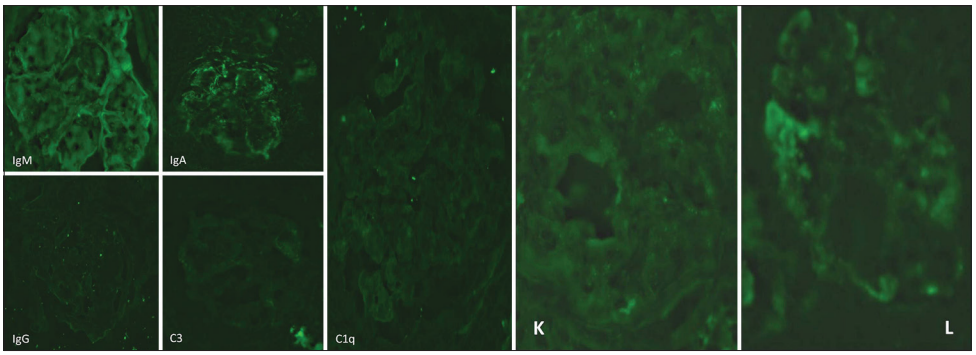

Figure 2: The immunofluorescence panel included IgM, IgG, IgA, C3, C1q, and kappa and lambda light chains. There was no evidence of linear or granular positivity along the basement membrane or mesangium for any of the immunoglobulins or complement or light chains

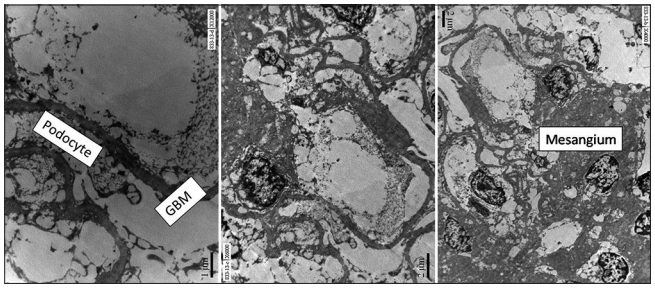

Figure 3: Absence of electron dense deposits in the mesangium, subepithelial or subendothelial region. Fibrils were also not identified

smoking (in 85%), and hypertension (in 90%) were the risk factors strongly associated.[11]

Various hypotheses postulated explaining the occurrence of nodular glomerulosclerosis in the setting of hypertension, hypercholesterolemia, smoking, and obesity include: increased sensitivity to a nondiabetic range of blood glucose levels resulting in exaggerated glomerulovascular response. Cigarette smoke contains free radicals that induce oxidative stress, increasing the glomerular extracellular matrix (ECM) production by activating transforming growth factor and insulin-like growth factor prosclerotic signaling pathways. Tobacco smoke also contains reactive glycation products which can react rapidly with proteins to form advanced glycation end product. Cigarette smoking alters intrarenal hemodynamics by sympathetic activation. Chronic hypoxia activates the sympathetic nervous system in turn stimulating renin-angiotensin system and promoting ECM production.[8] Though long-term hypertension and smoking were considered causative in the pathogenesis of this disease entity, in our first patient, hypertension was only of a short duration which was well-controlled with a single drug, and he was not a smoker, and our second patient was nonhypertensive and never smoked. Apart from this, our patient had obesity which has not been described solely as a risk factor in association with idiopathic nodular glomerulosclerosis in literature. We attribute our finding of idiopathic nodular glomerulosclerosis to obesity, a component of metabolic syndrome, which might add to hyperfiltration injury in our first patient. We advised our patient weight reduction along with ARB (telmisartan) which would otherwise help in hypertension control and reduce hyperfiltration injury. Our second patient is neither obese nor hypertensive but has a severe form of the disease with dialysis dependence. The above findings from the two cases show that idiopathic nodular glomerulosclerosis might not be single disease entity and needs further investigation into its etiopathogenesis. Idiopathic nodular glomerulosclerosis should be suspected in any nondiabetic with a histopathological description of diabetic nodular glomerulosclerosis after ruling out other causes of nodular glomerulosclerosis and EM is a must in these cases.

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Conflicts of interest

There are no conflicts of interest.

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