CASE REPORT

Idiopathic nodular glomerulosclerosis (ING) in an African American (AA) man with hepatitis C

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SUMMARY

Idiopathic nodular glomerulosclerosis (ING) in a non-diabetic patient is uncommon. Nodular glomerulosclerosis is hallmark sign of diabetic nephropathy. ING is a very rare clinicopathological disease associated with smoking, obesity and hypertension, chronic obstructive pulmonary disease and metabolic syndrome. A 68-year-old non-obese African American man with hypertension, smoking and history of hepatitis C presented to the clinic with progressive worsening of lower extremity oedema and declining renal function over few months. Renal biopsy demonstrated nodular glomerulosclerosis. In this case, ING is hypothesised to be associated with hepatitis C along with smoking and hypertension (HTN). We present this case to speculate the existence of yet unknown aetiologies of ING.

BACKGROUND

Kimmelstiel and Wilson,¹ described findings of nodular glomerulosclerosis as a pathognomonic of diabetic nephropathy. But it is also associated with other diseases like amyloidosis, light chain disease, nodular membranoproliferative glomerulonephritis and takayasu's arteritis. Nodular glomerulosclerosis as distinct entity was first reported by Alpers *et al.*² The term ING (idiopathic nodular glomerulosclerosis) was coined by Herzenberg *et al.*³ The distinguishing features of diabetic nephropathy from ING was described by Alsaad and Herzenberg.⁴ Herein, we report a 68-year-old non-obese African American man with hypertension for 10 years, active smoking and hepatitis C presenting with ING. Most of the case reports published in the literature showed a predilection in the Caucasian population compared with the African American population and increased body mass index (BMI). We report this case to suggest the existence of yet unknown aetiologies of ING other than previously known.

CASE PRESENTATION

A 68-year-old African American man with hypertension for 10 years and active smoking presented to the clinic with progressive worsening of lower extremity oedema and declining renal function. He denied any non-steroidal anti-inflammatory drugs (NSAID) use, contrast exposure, recent antibiotic usage, dysuria, haematuria. His medications include amlodipine, Lisinopril, furosemide and potassium chloride. Physical examination was unremarkable except for BMI of 25, elevated blood pressure (156/96) and 4+ pedal oedema.

INVESTIGATIONS

His laboratory workup included normal haemogram with low platelets 117, creatinine 2.4, Urea 25, albumin 2.5, HbA1c of 5, 24 hours urine protein 7.7 g, reactive hepatitis C antibody, quantitative HCV RNA PCR of 149 000, HCV viral log 5.173, 1b genotype and non-reactive HIV 1 and 2. Vasculitis workup included antinuclear antibody titre of 1:160 and speckled pattern, negative anti-neutrophil cytoplasmic antibody, double stranded DNA antibody, complement c3 and c4 levels. On immunoelectrophoresis, no free kappa light chains were seen. Protein electrophoresis showed non-specific increase in Alpha 2 globulins and monoclonal protein seen in gamma fraction.

As our patient presented with significant anasarca and renal insufficiency, our differentials were Focal segmental glomerulosclerosis (FSGS), membranous nephropathy and hepatitis C related renal diseases. We pursued further with a renal biopsy which demonstrated nodular glomerulosclerosis with severe tubular atrophy, interstitial fibrosis and arterio-arteriolo sclerosis. On light microscopy, two renal cortex fragments visualised showed up to nine glomeruli of which five are globally sclerotic. Non-sclerotic glomeruli were normocellular with marked mesangial matrix expansion forming mesangial nodules. No crescents were seen (figure 1). Congo red staining was negative. Immunofluorescence microscopy with human IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, kappa and lambda immunoglobulin light chains were negative except for linear staining along capillary walls with IgG(1+) and albumin(2+). Ultrastructural studies revealed markedly increased mesangial matrix with thickened and wrinkled glomerular basement membranes. No electron dense deposits and tubuloreticular structures were seen (figure 2).

DIFFERENTIAL DIAGNOSIS

- ▶ Diabetic nephropathy.
- ▶ Amyloidosis.
- ▶ Light chain disease.
- ▶ Fibrillar and immunotactoid glomerulopathy.
- ▶ Collagen type 3 disease.
- ▶ Nodular membranoproliferative glomerulonephritis.
- ▶ Takayasu's arteritis.

TREATMENT

Aggressive management of hypertension with statin, ACE inhibitors along with other antihypertensive medications and abstinence from smoking.

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Figure 1 Non-sclerotic glomerulus with marked mesangial matrix expansion forming mesangial nodules without crescent formation.

OUTCOME AND FOLLOW-UP

During recent follow-up visit after 3 months, 24-hour protein improved from 7.7 g to 4 g and creatinine 3. He was referred to gastroenterologist for treatment of hepatitis C. Long-term follow-up is needed to see if his renal function improves after treatment of hepatitis c.

DISCUSSION

ING is a diagnosis of exclusion. Following are the various theories that have been postulated to explain the pathophysiology in the development of diabetic kidney disease in patients with hypertension, smoking, obesity and hyperlipidaemia: (1) exaggerated glomerulo-vascular response and increased sensitivity to a non-diabetic range blood glucose levels; (2) free radicals from cigarette smoking induce oxidative stress, activate transforming growth factor and also insulin-like growth factor leading to increased glomerular extracellular matrix production. It also causes sympathetic activation thereby altering the intrarenal haemodynamics. Reactive glycation products from the smoking rapidly interact with proteins to form advanced glycation end products. Chronic hypoxia activates the sympathetic nervous system in turn stimulating renin angiotensin system and promoting extracellular matrix deposition.⁵ Some authors

Figure 2 Mesangial matrix expansion forming mesangial nodules with thickened and wrinkled glomerular basement membranes on Electron Microscopy (EM).

consider ING as spectrum of arteriosclerotic renal disease without diabetes mellitus (DM).⁶

To our surprise, the renal biopsy findings resembled nodular glomerulosclerosis which is the hallmark sign of diabetic nephropathy, usually marked by areas of mesangial expansion with accentuated glomerular nodularity that can be seen in amyloidosis, light chain disease, fibrillar and immunotactoid glomerulopathy, Collagen type 3 disease, nodular membranoproliferative glomerulonephritis and takayasu's arteritis.⁷ In our patient, workup for vasculitis was negative. We hypothesised ING in our patient to be associated with hepatitis C along with smoking and HTN.

A case of diabetic nephropathy with delayed onset of DM which was 9 years after the onset of nephropathy was reported by Siraj *et al* suggesting that undetected diabetes might have been present before but not at the onset of nephropathy. Long-term follow-up is therefore needed in the present case to see if his renal function and symptoms improve after treatment of hepatitis c and also with regular follow-up on A1c as he may develop DM later.⁸

In summary, we present this uncommon case of ING in non-obese non-diabetic African American to speculate the existence of yet unknown aetiologies of ING. Critical analysis of the other unknown causes and pathological mechanisms are further required.

Learning points

- ▶ Idiopathic nodular glomerulosclerosis (ING) is a very rare clinicopathological disease associated with smoking, obesity, hypertension, chronic obstructive pulmonary disease and metabolic syndrome.
- ▶ Diabetic nephropathy, amyloidosis, light chain disease, fibrillar and immunotactoid glomerulopathy, Collagen type 3 disease, nodular membranoproliferative glomerulonephritis and takayasu's arteritis are the differential for nodular glomerulosclerosis.
- ▶ Aggressive management of hypertension with statin, ACE inhibitors along with other antihypertensive medications and abstinence from smoking is the reported treatment for this disease.
- ▶ Long-term follow-up is needed with A1c to see if patients with ING develop DM later.

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