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The Case | Diabetic nephropathy in a nondiabetic smoker?

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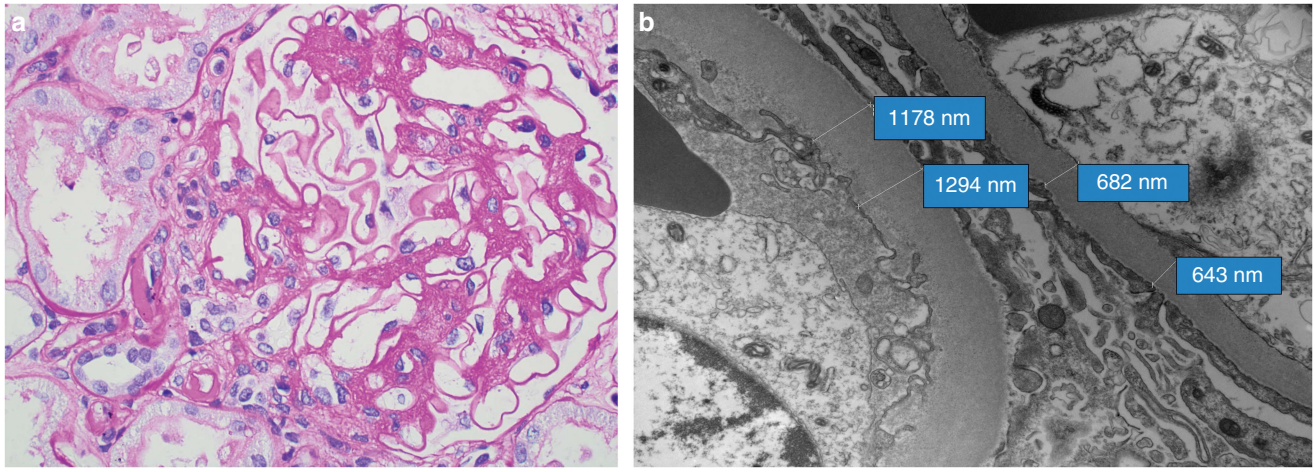

Figure 1 | Renal biopsy. (**a**) Light microscopy shows increased mesangial matrix with early nodule formation, capillary wall thickening, and arteriolar hyalinosis (periodic acid–Schiff). (**b**) Electron microscopy shows lamina densa thickening (up to 1290 nm), irregular subendothelial space widening, and focal foot process effacement (no amyloid-type fibrils noted).

A 58-year-old Caucasian man experienced leg swelling and weight gain, lasting for 3 weeks. Proteinuria on urinalysis prompted nephrology referral. He had an 18-year history of hypertension and proteinuria, with a 24-h urine protein level of 2.85 g noted 8 years ago. Medical history included hypertension, obesity, hyperlipidemia, and myocardial infarction. His medications included metoprolol, amlodipine, olmesartan, hydrochlorothiazide, rosuvastatin, and aspirin. He smoked one pack of cigarettes daily for more than 20 years. Physical examination was notable for a weight of 102 kg, body mass index of 36 kg/m^2, blood pressure of 140/60 mm Hg, and bilateral pedal edema.

Urinalysis showed 300 mg/dl protein, no glucose, two red blood cells per high-power field, one white blood cell per high-power field, and 24-h urine protein level of 5 g. Serum creatinine was 0.95 mg/dl (79.56 µmol/l), blood urea nitrogen 31 mg/dl (11 mmol/l), fasting glucose 90 mg/dl (4.5 mmol/l), albumin 3.4 g/dl (34 g/l), cholesterol 213 mg/dl (5.5 mmol/l), triglycerides 155 mg/dl (1.75 mmol/l), hemoglobin A1C 5.8% (39.9 mmol/mol), antinuclear antibody and hepatitis profile negative, and serum and urine protein electrophoresis, and serum-free kappa and lambda light chains normal. A renal ultrasound was normal. A kidney biopsy showed increased mesangial matrix with vague nodularity, a sclerotic pattern for IgM and C3 on immunofluorescence, and basement membrane thickening (Figure 1).

What is the diagnosis?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | Idiopathic nodular glomerulosclerosis (ING) (aka pseudodiabetic glomerulopathy)

Table 1 | Differential diagnosis of nodular glomerulosclerosis

Entity	Clinical	LM	IF	EM
ING	No history of DM	Nodules may be more frequent and isometric than DM	Negative	Fine fibrils in matrix, but no deposits
Nodular diabetic glomerulosclerosis	History of DM	Scattered non-isometric mesangial nodules (1–2 per tuft)	Negative	Fine fibrils in matrix, but no deposits
Membranoproliferative glomerulonephritis (primary or secondary)	Etiology dependent	Double contours and cellularity prominent	Positive for Ig and/or C3	Granular deposits
Amyloidosis (AL or AA)	Etiology dependent	Congo red positive	Monoclonal light chain in AL	Random non-branching fibrils (8–12 nm)
Monoclonal Ig deposition disease	Paraprotein in blood and/or urine	Nodules more uniform than DM and ING and show less Jones positivity	Monoclonal light and/or heavy chain	Finely granular deposits
Fibrillary glomerulonephritis	Usually unexpected	Congo red negative	Polyclonal IgG and C3	Fibrils (16–24 nm)
Immunotactoid glomerulonephritis	Paraproteinemia or lymphoproliferative disorder	Congo red negative	Monoclonal light and/or heavy chain	Microtubules (20–50 nm)
Fibronectin glomerulopathy	Family history	Mesangial deposits are PAS positive but Jones negative	Usually negative except for fibronectin	Massive electron-dense deposits (mostly amorphous) replacing mesangial matrix; GBM of normal thickness
Type III collagen glomerulopathy	Blood and urine N-terminal procollagen type III peptide	May be hypercellular	Negative	Fibers with characteristic 60 nm periodicity

Abbreviations: AA, amyloid associated; AL, amyloid light chain; DM, diabetes mellitus; EM, electron microscopy; GBM, glomerular basement membrane; IF, immunofluorescence; Ig, immunoglobulin; ING, idiopathic nodular glomerulosclerosis; LM, light microscopy; PAS, periodic acid–Schiff.

In 1989, Alpers and Biava first reported 'nodular mesangial sclerosis' as a distinct diagnostic entity, and later in 1999 Herzenberg *et al.*[1] coined the term 'idiopathic nodular glomerulosclerosis'. The major differential diagnosis is between diabetic glomerulosclerosis and ING. Both are characterized by glomerular basement membrane (GBM) thickening and nodular/rounded expanded and lamellated mesangial matrix (Kimmelstiel–Wilson nodules in diabetes). Nodular diabetic glomerulosclerosis typically has more severe GBM thickening and vascular disease than ING, and ING can have more nodules per glomerulus than diabetes, and the nodules are more likely to be isometric. However, these morphological nuances cannot reliably distinguish between ING and diabetes; rather, clinical correlation and a history of diabetes make the diagnosis. Other conditions that can produce mesangial nodules are more readily differentiated from ING, using their chief distinguishing characteristics (Table 1).

Patients with ING are typically older white men with a history of hyperlipidemia, long-standing hypertension, and smoking, who present with renal insufficiency and nephrotic-range proteinuria.[2,3] Li *et al.*[3] found a significantly higher incidence of obesity (60%) and overweight (27%) in patients diagnosed with ING. The pathogenesis of this process awaits elucidation. Markowitz *et al.*[2] hypothesized that ING results from the interplay of hypertension and smoking in increasing glomerular extracellular matrix production and angiogenesis. Given the histological similarity to diabetes, it is tempting to speculate that similar mechanisms, such as advanced glycation end products and oxidative stress, are involved. The findings in our patient of widening and rarefaction of the subendothelial space, as well as hyalinosis of the efferent arteriole, suggest chronic endothelial injury that may be pressure independent.[3]

Our patient was of course not diabetic and had a long history of hyperlipidemia, hypertension, and smoking, factors that are linked to this disease. His fasting plasma glucose levels and hemoglobin A1C were normal, protein electrophoresis and serum-free light chains did not show a paraprotein, and ultrastructural examination of renal biopsy did not reveal electron-dense deposits or amyloid-type fibrils. Careful clinical evaluation and follow-up may be necessary to fully exclude diabetes. Although data regarding prognosis are limited, progression to end-stage renal disease has been noted. Our management included aggressive control of blood pressure, hyperlipidemia, and cessation of smoking.

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