

Glomeruloesclerosis nodular en un tabaquista hipertenso no-diabético con dislipidemia

Nodular glomerulosclerosis in a non-diabetic hypertensive smoker with dyslipidemia

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ABSTRACT

Nodular glomerulosclerosis may be idiopathic or develop associated with diabetes mellitus, membranoproliferative glomerulonephritis, light or heavy chain deposits, amyloidosis, fibrillary or immunotactoid disease, and Takayasu's arteritis. Histological features of idiopathic nodular glomerulosclerosis are similar to the Kimmelstiel-Wilson changes. Recent evidence points to the role of hyperglycemia, hyperlipidemia, hypertension and smoking in the mechanisms of this uncommon condition.

The case study of a 65-year-old male presenting recent arterial hypertension and nodular non-diabetic glomerulosclerosis is described, and the possible role of heavy smoking in the pathogenesis of this condition is emphasized.

Key words. Nodular glomerulosclerosis. Smoking. Hypertension.

RESUMEN

La glomeruloesclerosis nodular puede ser idiopática o desarrollarse asociada con diabetes mellitus, glomerulonefritis membranoproliferativa, depósitos de cadenas leves o pesadas, amiloidosis, enfermedad fibrilar o inmunotactoides, y arteritis de Takayasu. Los aspectos histológicos de la glomeruloesclerosis nodular idiopática son similares a las alteraciones de Kimmelstiel-Wilson. Recientes evidencias indican el papel de la hiperglicemia, la hiperlipidemia, la hipertensión y el tabaquismo en los mecanismos de esta entidad rara.

Se presenta el estudio del caso de un hombre con 65 años que presentó hipertensión arterial reciente y glomeruloesclerosis nodular no diabética, y se da énfasis al posible papel de excesivo tabaquismo en la patogénesis de esta condición.

Palabras clave. Glomeruloesclerosis nodular. Tabaquismo. Hipertensión.

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INTRODUCTION

Nodular glomerulosclerosis is found in association with conditions like diabetes mellitus, membranoproliferative glomerulonephritis, light/ heavy chain deposits, amyloidosis, fibrillary/ immunotactoid disease, and Takayasu's arteritis^{1,2}. Idiopathic nodular glomerulosclerosis (ING) refers to histological features of glomerular lesions similar to the Kimmelstiel-Wilson changes, in patients without evidence of underlying disease¹⁻⁵.

Tobacco use constitutes a major worldwide problem, which is related with increased indices of morbidity and mortality, years of potential life lost, and productivity losses⁶. Smoking is related to microalbuminuria in healthy people and may impair renal function by diverse mechanisms, including the genesis of advanced glycation end products (AGEs), oxidative stress, angiogenesis, intrarenal hemodynamic disorders, and hypertensive effects of hypoxia on the sympathetic and the rennin-angiotensin systems².

ING has been associated with hypertension, smoking and hypercholesterolemia, which show similar prevalence (95.7%, 91.3% and 90%, respectively)⁴. The role of heavy smoking is highlighted in the patient here described with diagnosis of nodular glomerulosclerosis.

CASE REPORT

A 62-year old white man presenting with peripheral oedema for 4 months was admitted because of progressive loss of renal function. There was antecedent of high blood pressure (systolic: 130-139 mmHg and diastolic: 85-89 mmHg) and irregular use of ACE inhibitors during 12 years. Periodic evaluations about albuminuria and creatinine clearance had been unremarkable until near two years before admission. He was a cigarette smoker (pack-year: 40), and despite of heavy smoking, he had not chronic obstructive pulmonary disease (COPD) or sleep apnoea syndrome. Two of his brothers had hypertension, and his father had chronic renal failure; they were heavy cigarette smokers, but

the patient had no information about the exact etiology, type and severity of his father renal disease. There was no family history of consanguineous marriage or diabetes mellitus. His fasting blood glucose, glycated haemoglobin (HbA1c), and glucose tolerance tests were all within the normal ranges.

On admission, he appeared chronically ill and body mass index was 23.5 Kg/m²; blood pressure: 150 x 90mm Hg, heart rate: 70 bpm, and respiratory rate: 18 rpm. Heart and lung examinations were unremarkable. Pitting oedema (3+) was found in lower limbs. Direct ophthalmoscopy did not disclose retinopathy. Laboratory data: haemoglobin: 11 g/dL, urea: 62 mg/dL (22 mmol/L), creatinine: 2 mg/ dL (176.8 µmol/L), triglycerides: 380 mg/dL, total cholesterol: 450 mg/dL, albumin: 3 g/ dL, total daily protein urinary loss: 3.8 g, complement CH50: 48 mg/dL (26-58 mg/dL), C3: 95 mg/dL (90-180 mg/dL), C4: 40 mg/dL (16-47 mg/dL); anti DNA and antinuclear factor were normal, tests for HIV and hepatitis B and C were negative, and serum protein electrophoresis did not detected monoclonal protein. Renal ultrasonography (US) showed normal symmetrical kidneys.

Diagnosis of nephrotic syndrome was established and US guided kidney biopsy was done. Renal specimen contained 23 glomeruli and 3 of them were globally sclerotic; the remaining glomeruli showed focal or diffuse expansion of mesangial area in a nodular pattern. There was mild tubular atrophy, and afferent and efferent arteriolar hyalinosis (Fig. 1). Immunofluorescence did not show immune deposits, and no amyloid was seen by Congo red stain (Fig. 2). Electron microscopy showed marked diffuse basement membrane thickening and some effaced podocytes. Peripheral capillary loops were uniformly thickened, without abnormal deposits. No fibrillary or micro tubular structure was observed (Fig. 1 C and D).

DISCUSSION

This 62-year old white male with ING was a heavy tobacco smoker and had diagnosis of arterial hypertension. Moreover, he presented with high triglycerides and cholesterol blood levels, but no disturbance in glucose metabolism was detected. ING patients with hypertension, hypercholesterolemia and smoking may show exaggerated glomerulovascular response due to higher

sensitivity to non-diabetic glycemic levels. Therefore, special attention has been paid to the follow-up of glucose tolerance to rule out eventual late-onset diabetes². Three of the main risk factors involved in the pathogenesis of ING are briefly commented.

Association between arterial hypertension and nodular glomerulosclerosis has been recently suggested, and Markowitz et al reported hypertension in about 96% of 23 cases studied⁴. The effects of uncontrolled hypertension on the progression of chronic nephropathy are well established, as well as the role played by the rennin-angiotensin-aldosterone system both on the progression of diabetic nephropathy and the development of glomerular nodular lesions. Contrary to most of the previous reports, hypertension was not severe in this patient and retinal examination was normal, suggesting a less conspicuous role of hypertension in the genesis of the nodular changes here reported. Although hypertension seemed not essential for the origin of nodular glomerulosclerosis in the present case study, smoking is a major risk factor for high blood pressure and for ING⁵. Hypertensive nephrosclerosis is considered the main precursor event for development of ING; and uncontrolled hypertension can adversely influence the outcome of glomerulosclerosis⁵.

High serum levels of glucose and cholesterol have influence on the pathogenesis of ING, and Markowitz et al found hypercholesterolemia in 90% of 23 patients with ING⁴. SHR/N-cp rats are a genetic model of spontaneous type 2 diabetes and obesity. In contrast with the STZ model, the animals develop marked increase in serum triglycerides and cholesterol, and lower levels of serum glucose. Despite of lower hyperglycemias, significant glomerular injury, resembling the Kimmelstiel-Wilson nodules was found after 3 months of induced diabetes in SHR/N-cp rats⁷. These findings strongly suggest that, at least in animal models, hyperglycemia itself is not enough to cause the development of the glomerular nodular change,

while hyperlipidemia constitutes an important synergistic factor.

There is growing evidence that cigarette smoking increases the risk of progression in diabetic and non-diabetic nephropathy. It has been recently proposed that the term ING should be replaced by smoke-associated nodular glomerulosclerosis, since virtually all reports of «idiopathic» nodular lesions were associated with high exposure to smoke¹⁻⁵. Unfortunately, there are no animal models of smoke-induced kidney damage to demonstrate nodular glomerulosclerosis. Furthermore, regression of these lesions with smoking cessation was never unequivocally showed. However, as almost all reported cases have been described in smokers, smoking is considered as the main risk factor for the development of ING. Moreover, smoke of cigarettes contains free radicals capable of directly inducing oxidative stress², which may increase the production of glomerular extracellular matrix by activation of TGF-and IGF receptor prosclerotic signalling pathways⁵. Although the age of onset of ING is more than 60 years, Kikuchi et al reported a 27-year-old male with nodular glomerulosclerosis and hypertension. The patient was tobacco smoker for more than 13 years, and was exposed to passive smoking for decades, because his parents were smokers at home¹. Markowitz et al. described data from 23 patients with ING: male 78.3%, mean age 68.2 years, longstanding hypertension 95.7%, heavy smoking 91.3% (active smoking 57%), renal failure (mean creatinine 2.4 mg/dl) 82.6%, proteinuria (more than 3 g daily) 69.6%, and dyslipidemia 90%⁴. Nasr and D'Agati reported a 70-year-old non-diabetic woman with longstanding hypertension, chronic renal failure and albuminuria, but without dyslipidemia. She was a reformed smoker with COPD due to a pack-year: 60, and the authors suggested that the designation idiopathic nodular glomerulosclerosis should be changed by «smoking-associated nodular glomerulosclerosis»⁵. Therefore, the acronym ING would be changed by SANG.

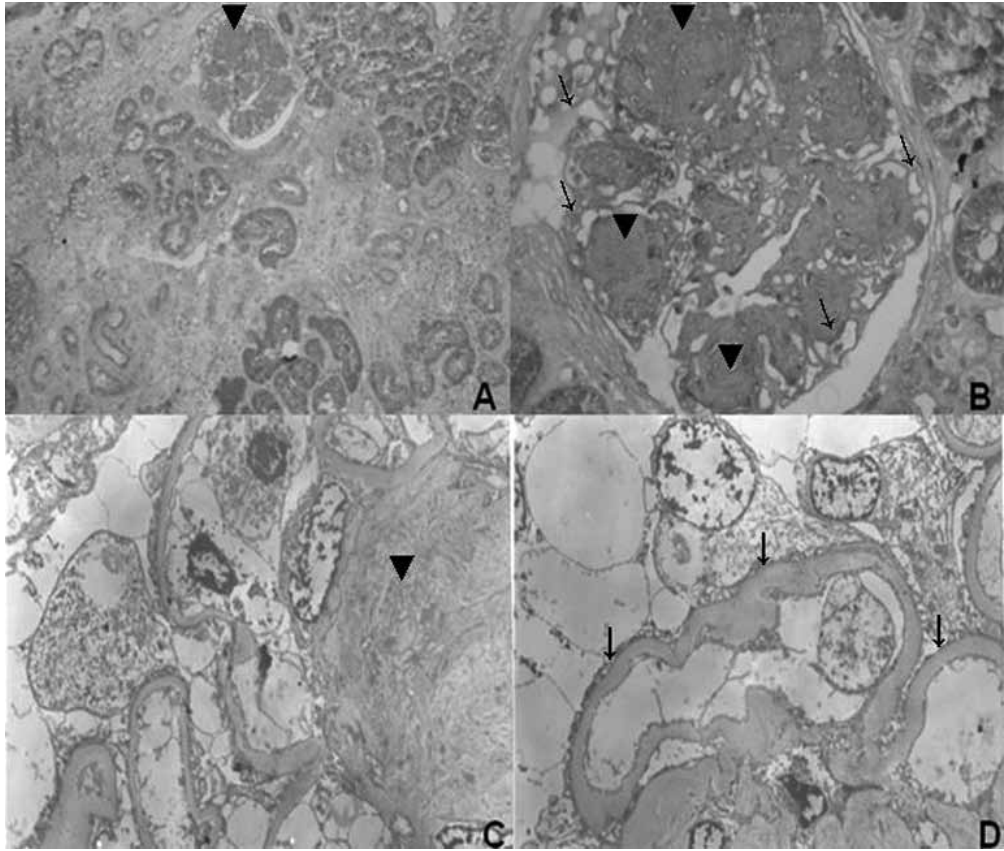


Figure 1. A and B (Masson's Trichrome stain; A: 10x and B: 20x): Nodular glomerulosclerosis represented by diffuse thickening of the basal membrane (arrows) in association with sclerotic mesangial nodules in the glomerulus (arrow head). C and D (Transmission electron microscopy). C: Ultrastructural images of nodular glomerulosclerosis with mesangial cell proliferation and sclerotic mesangial nodules (arrow head). D: Thickened glomerular basal membrane and mesangial cell proliferation (arrows).

The hypertensive heavy smoker here described was also a passive smoker at home. Epidemiological and experimental studies have disclosed relationships between smoking, hypertension and dyslipidemia, both in diabetic and in non-diabetic individuals^{8,9}. Smoking is associated with dyslipidemia, increased glicated haemoglobin, and metabolic syndrome⁹. Nicotine can increase proteinuria, glomerular hypertrophy, and mesangial area in diabetic mice, in association with increased NADPH oxidase⁴, nitrotyrosine, and Akt expression⁸. Non-diabetic mild-to-moderate hypertensive patients may have microalbuminuria (MA), a marker

of endothelial dysfunction, and dyslipidemia may play a role in the origin of MA¹⁰. Data about initial MA of this patient are lacking because he was firstly followed elsewhere.

In Spain, like in Brazil, smoking poses a heavy social and economic burden despite of official campaigns against the tobacco consumption^{6,11-13}, which is related with diverse malignancies, bronchopulmonary and arterial diseases, dyslipidemia, and hypertension^{6,9}. Worth of note are some high rates of tobacco-smokers among nurses (36%) and physicians (28%)⁶, who should be opinion makers against this worldwide and still uncontrolled epidemy.

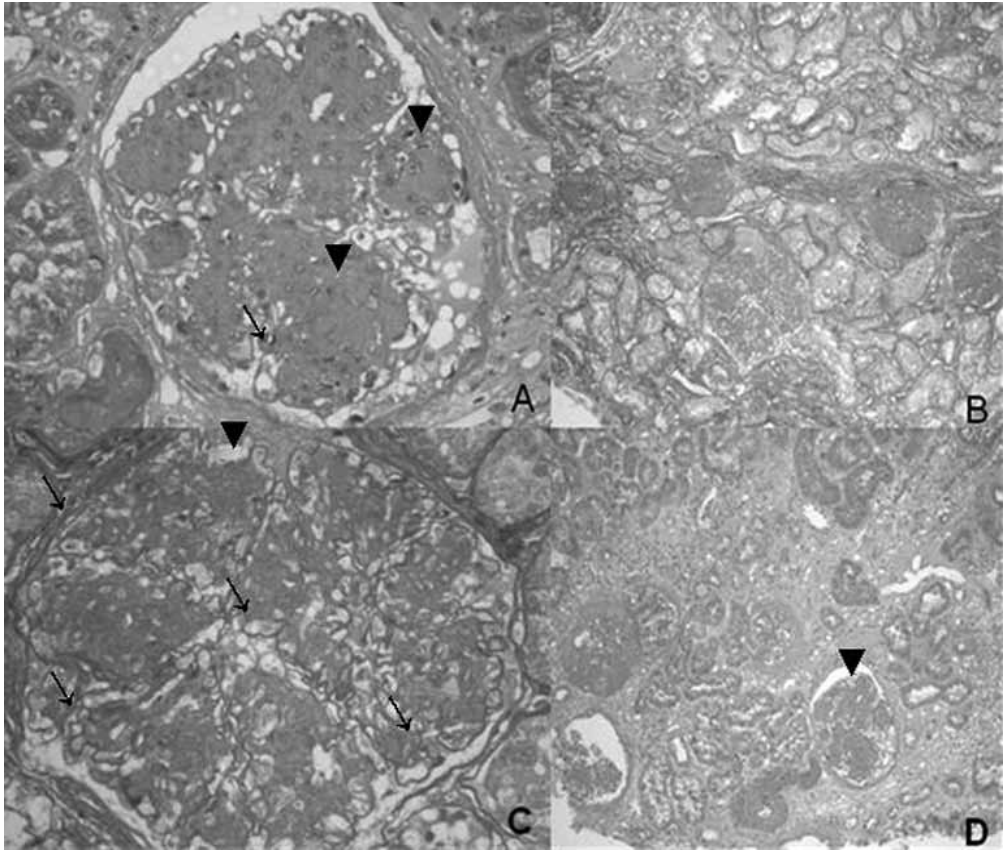


Figure 2. A, C and D (H&E stain, 20x, 40x and 5x, respectively) and B (PAS stain, 10x): Nodular glomerulosclerosis represented by diffuse thickening of the basal membrane (arrows) in association with sclerotic mesangial nodules in the glomerulus (arrow head). Clinical course on ambulatory surveillance has been uneventful, including control of blood pressure, urinary protein loss, creatinine clearance, and fasting glycaemia.

This case study seems to strengthen the association between heavy smoking and nodular glomerulosclerosis, and may contribute to enhance the interest about further experimental studies to better clear the role of tobacco smoking on the development of ING.

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