CASE REPORT

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Smoking-associated nodular glomerulosclerosis, a rare renal pathology resembling diabetic nephropathy: case report

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Abstract

Introduction: Smoking is an important risk factor not only for cardiovascular and pulmonary diseases, but also for the progression of chronic kidney disease of different etiologies. Nodular glomerulosclerosis is a renal pathology pattern, which was described in different kidney conditions, especially diabetic nephropathy. A very rare association among smoking, hypertension and nodular mesangial glomerulosclerosis has been recently described. *Case presentation*: In this paper, we present the case of a non-diabetic male patient referred to our Department for advanced chronic kidney disease and nephrotic syndrome. After excluding different causes of secondary nephrotic syndrome, a kidney biopsy was performed. The patient was diagnosed with smoking associated nodular glomerulosclerosis, with a histological aspect closely resembling diabetic nephropathy. A low protein and low salt diet was started, accompanied by smoking cessation, the administration of diuretics, of antiproteinuric treatment with angiotensin receptor blocker and antihypertensive therapy. Under this therapy, after six months, the patient evolution was good with a clear improvement of kidney function and important reduction of proteinuria. *Discussion*: We also present the possible factors that could be involved in the deleterious effects of smoking upon kidney structure endothelial dysfunction, angiogenesis, altered intrarenal hemodynamics, nervous sympathetic system, increased oxidative stress and, very important, the generation of advanced glycation end products, which are also implicated in the development of diabetic nephropathy. *Conclusions*: Although a rare condition, smoking associated nodular glomerulosclerosis is a diagnosis not to be missed when dealing with a heavy smoker patient, especially when hypertensive, and sometimes associating nephrotic syndrome and this diagnosis should be considered together with much more frequent causes of nephrotic syndrome.

Keywords: nodular glomerulosclerosis, smoking, diabetic nephropathy.

Introduction

Smoking is not only one of the most important risk factor for cardiovascular diseases (as well as for many other conditions), but is also involved in renal function impairment, being associated with development of micro-albuminuria or even gross proteinuria (especially in patients who are also hypertensive, diabetics or obese) [1], and a more rapid progression of chronic kidney disease (CKD) toward end-stage renal disease (ESRD) [2]. There are many studies showing a close relationship between smoking and progression of many kidney diseases, including autosomal dominant polycystic kidney disease, different glomerulonephritis (especially IgA nephropathy), lupus nephritis, Goodpasture syndrome, diabetic and hypertensive nephropathy, chronic kidney allograft injury, or renal artery stenosis [2]. Deleterious effects of smoking on renal structure are mediated not only by endothelial dysfunction, accelerated atherosclerosis and nicotine, but also by oxidative stress, generation of advanced glycation end products (AGE) and sympathetic stimulation [3]. As a result, several pathological changes were described in kidney biopsies from actual or former heavy smokers, especially atherosclerosis and arteriosclerosis, and chronic tubular and interstitial lesions. Nevertheless, another pattern of injury, yet very rare, was recently described in long-standing smokers or ex-smokers, who are also associating essential hypertension and often peripheral artery disease (PAD), *i.e.*, nodular glomerulosclerosis (very similar to diabetic nephropathy) in the absence of diabetes mellitus [4].

We present the case of a non-diabetic patient with smoking-associated nodular glomerulosclerosis, presenting with nephrotic syndrome and advanced CKD.

Case presentation

The patient is a 46-year-old white male, who was referred to Department of Nephrology from "Fundeni" Clinical Institute, Bucharest, Romania, for a possible nephrotic syndrome. He was in his usual health status until few months before admittance in the Hospital, when he progressively noticed lower limbs swelling, early morning periorbital edema, foamy urine and difficulties in obtaining a good blood pressure (BP) control with his usual medication. The patient had a 30-pack years history of smoking and also performed a passive smoking activity (he works as a bartender). He was diagnosed with high

BP due to essential hypertension 15 years ago (a maximum systolic BP of 220 mmHg) and with stage IIB Leriche–Fontaine PAD four years ago, but he had no history of diabetes.

During the physical examination, we found poorly controlled BP, pale skin and mucosa and 3+ peripheral pitting edema. The patient was obese (body mass index – BMI 31.1 kg/m^2).

Blood tests showed mild normocytic-normochromic anemia (hemoglobin 10.9 g/dL), severely impaired kidney function (urea 183 mg/dL, creatinine 4.7 mg/dL with a decreased glomerular filtration ratio of 13 mL/min/1.73 m^2 estimated by modification of diet in renal disease (MDRD) study equation, value corresponding to stage V CKD), raised triglycerides (209 mg/dL) with normal total cholesterol, and mild inflammatory syndrome (fibrinogen 489 mg/dL). Fasting glucose and hemoglobin A1c levels were normal.

Urine analysis revealed hyaline, granular and fatty casts and no active sediment or cellular casts. A 24-hour urine collection showing 4.3 g of protein combined with reduced serum albumin (2.9 g/dL) confirmed the presence of nephrotic syndrome.

Renal ultrasound showed reduced size of both kidneys with hyperechoic and smaller than normal cortical area, suggesting the diagnosis of CKD.

A lab workup was performed in search for secondary causes of nephrotic syndrome. Serology for hepatitis B and C viruses and HIV were negative. Complement C3 and C4 titers were normal and so were antistreptolysin O antibody levels. The serological panel for antinuclear antibodies, double-stranded DNA, rheumatoid factor, cryoglobulins, anti-neutrophil cytoplasmic antibodies (ANCAs), anti-glomerular basement membrane antibodies, and antiphospholipid antibodies were all negative.

Workup for myeloma (serum protein electrophoresis and immunofixation and serum and urinary free light chains immunoglobulins) was also negative. Thyroid function tests results were normal.

Detailed patient's history found no signs of nephrotic syndrome secondary to drugs. No signs of solid organ neoplasia were found.

All these investigations raised awareness about an idiopathic nephrotic syndrome and for this reason, a kidney biopsy was performed. It consisted of one core of renal cortex and medulla (Figure 1).

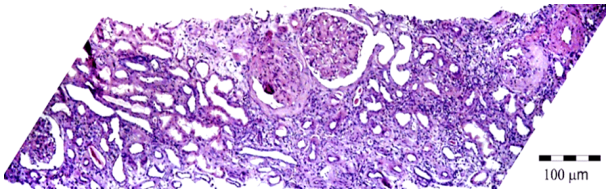

Figure 1 – ***Core biopsy. Glomeruli with various lesions. Periodic Acid–Schiff (PAS) staining, ×10.***

Some glomeruli were globally sclerosed (Figure 2a). Other glomeruli showed moderate to marked mesangial expansion because of Periodic Acid–Schiff (PAS) positive matrix hypertrophy and only mild increase in mesangial cellularity, with mesangial sclerosis forming focally large nodules narrowing the capillary lumen with obvious resemblance of diabetic glomerulosclerosis (Figure 2b). Some glomeruli presented glomerular hyaline deposits and capsular adherences of the glomerular tuft. Large hyaline deposits on the arteriolar wall should also be noted (Figure 2c). Mesangial nodules were PAS-positive (Figure 2b); they stained with Masson's trichrome blue, suggesting matrix expansion (Figure 2d). There was a diffuse thickening of the glomerular basement membrane (GBM) due to the subendothelial expansion of the mesangium (Figure 2, b and d). An important process of arteriosclerosis was noticed in arteries and arterioles, with intima hyalinization (Figure 2, a–e). Moderate tubular atrophy together with thickening of the tubular basement membrane (TBM) and interstitial fibrosis were seen. Congo red staining for amyloid was negative. Immunofluorescence was negative for immune deposits (IgG, IgA, IgM, C1q, C3, κ and λ) inside glomeruli (results not shown).

Electron microscopy showed thickening of both the GBM and the tubular membrane through the excessive deposition of collagen, proliferation of mesangial matrix and mesangial cells hypertrophy and focal effacement of foot processes; no electron-dense deposits were seen (results not shown).

Nodular mesangial sclerosis, together with thickening of GBM and TBM and hyaline sclerosis of both afferent and efferent arterioles are highly suggestive of diabetic nephropathy, but because history lack of diabetes in our patient the final histological diagnosis was smoking-associated nodular glomerulosclerosis. Thickening of GBM with a double contour and expansion of mesangial area are also found in membranoproliferative glomerulonephritis, but in this condition there is an important proliferation of mesangial cells, in immunofluorescence there are immune deposits in the GBM corresponding to dense deposits found in electron microscopy.

Renal amyloidosis is also characterized by mesangial nodules, but these stain weakly with PAS and amyloid fibrils are usually easily identified by their aspect in electron microscopy and by their ability to stain positive with Congo red.

Other rare diseases (Table 1) in which mesangial nodules and occasionally a double contour for GBM are seen are diagnosed by their characteristic appearances in electron microscopy, or, in some cases (such as light chain deposition disease, fibronectin and collagenofibrotic glomerulopathies) by immunofluorescence or immunohistochemical analysis.

The patient promptly quit smoking after diagnosis. He was put on a low protein (30 g protein/day, together with ketoanalogs) and low salt diet (maximum 2 g salt/day). He started treatment with an angiotensin receptor blocker (Candesartan 16 mg/day) with antihypertensive, antiproteinuric and nephroprotective effects. He received 40 mg/day of Furosemide for edema relief and also as antihypertensive therapy. Dyslipidemia was treated with a statin (Atorvastatin 20 mg/day). He obtained good BP control (with a BP target of less than 125/75 mmHg due to presence of nephrotic-range proteinuria) with Amlodipin 10 mg/day, Nebivolol 5 mg/day, together with Candesartan and Furosemide. After six months, the proteinuria dropped to 1.2 g/day, the peripheral edema disappeared and the renal function significantly improved to an estimated glomerular filtration rate (GFR) by MDRD formula of 22 mL/min/1.73 m^2 (corresponding to stage IV CKD, and a serum creatinine of 3.2 mg/dL).

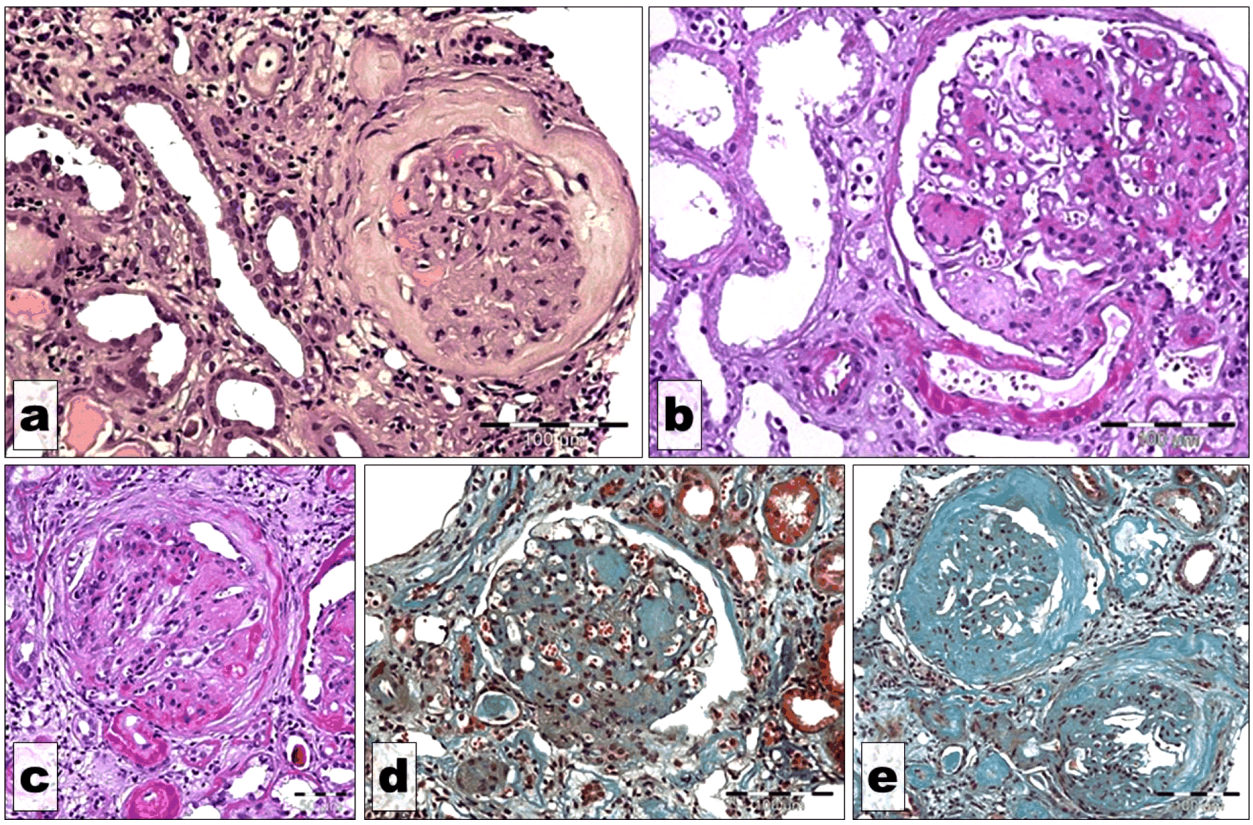

Figure 2 – ***Morphological aspects: (a) Global sclerotic glomerulus with peripheral hyaline deposits and closed glomerular arterioles (HE staining, ×200); (b) Glomerulus with diffuse mesangial expansion and nodular glomerulosclerosis (PAS staining, ×200); (c) Sclerotic glomerulus with adhesions between the Bowman's capsule and the glomerular tuft (PAS staining, ×200); (d) Glomerulus with segmental nodular glomerulosclerosis and diffuse mesangial expansion (Masson's trichrome staining, ×200); (e) Sclerotic glomeruli with tuft adherences on Bowman's capsule. Glomerular arterioles with thickened wall and narrowed lumen. Atrophic tubules with thickened basement membranes (Masson's trichrome staining, ×200).***

Table 1 – ***Differential diagnosis of nodular mesangial sclerosis [5]***

Diabetic nephropathy		
Smoking-associated nodular glomerulosclerosis		
Glomerulopathies with fibrillar deposits	*Congo red positive*	Renal amyloidosis
	Congo red negative	Fibrilar glomerulonephritis and immunotactoid glomerulopathy
		Light chain deposition disease
		Fibronectin glomerulopathy
		Collagenofibrotic glomerulopathy
Membranoproliferative glomerulonephritis		
Takayasu's arteritis		

Discussion

This case is a good example of important deleterious effects of smoking upon renal histology, with major impact on kidney function and long-term patient's outcome. Smoking is not only a well-known risk factor for cardiovascular and pulmonary diseases and malignancies, but is also involved in progression of kidney diseases of different etiologies.

Smoking is associated with development of microalbuminuria in otherwise healthy individuals, without diabetes, hypertension or other known kidney conditions, and this effect is in close relationship with endothelial dysfunction at the level of glomerular tuft [6, 7]. In the same time, smoking aggravates the albumin to creatinine ratio in patients who are already microalbuminuric because of diabetes or hypertension [8, 9]. The HOPE (Heart Outcomes and Prevention Evaluation) study found smoking as an independent risk factor for microalbuminuria in both diabetic and non-diabetic patients [10]. Long-term cigarette smoking is also involved in a faster progression of chronic kidney disease (especially in diabetic and hypertensive nephropathies) [2], but is also a significant risk factor for *de novo* future kidney failure, while smoking cessation decreases this risk, especially in male patients [11]. It is also a noxious factor to the renal allograft, being associated with chronic graft injury and decreased graft survival [12].

Nodular glomerulosclerosis is a pathological pattern of mesangial sclerosis accentuating glomerular lobularity. The most characteristic features of nodular glomerulosclerosis are seen in diabetic nephropathy and were first described in 1936 by Kimmelstiel & Wilson [13]. Different other conditions may also involve mesangium with sclerosis at this level and these entities need to be evaluated when a diagnosis of nodular glomerulosclerosis is established after a kidney biopsy (Table 1). Idiopathic nodular glomerulosclerosis is a diagnosis of exclusion, after all these diseases are eliminated after proper analysis of kidney sample by optical and electron microscopy, and by immunofluorescence. Alpers & Biava used the term "idiopathic nodular mesangial sclerosis",

in 1989 [14], which was replaced by "idiopathic nodular glomerulosclerosis", in 1999 [15]. However, during the past 10 years, there are emerging evidences that this pathological kidney condition is not so "idiopathic" as it was first thought, since it is associated in most of the cases with longstanding smoking and usually hypertension. The group of Nasr, from Columbia University, was the first who described, in 2002, this smoking-associated clinicopathologic renal entity (closely resembling diabetic nephropathy) in the largest series published so far, with 23 patients [4]. However, it is a very rare histological finding, since only 45 cases were reported until 2007 in the English medical literature [3, 5], and only few more cases were added thereafter. In the study of Nasr, it was noted a high prevalence of hypertension (95.7%) and dyslipidemia (90%), and more than 40% of patients associated peripheral artery disease, like in our patient reported here [4]. The clinical findings at presentation were chronic kidney disease in more than 80% of patients and gross proteinuria in almost 70% of them, with full nephrotic syndrome in an important percentage of patients – 21.7% [4]. Unfortunately, this histological aspect on renal biopsy caries a poor prognosis for the patient, since average time from biopsy to ESRD is only 26 months; negative predictors are continuation of smoking, lack of angiotensin II blockade, degree of arteriosclerosis, tubular atrophy and interstitial fibrosis [3].

Suspected pathogenic mechanisms involved in development of smoking-induced nodular glomerulosclerosis are endothelial dysfunction with altered intrarenal hemodynamics, oxidative stress especially through generation of reactive species of oxygen (ROS), sympathetic activation, angiogenesis and generation of AGE [3, 16]. Strikingly, in the review of Kuppachi *et al.*, of all the cases published so far, 80% of the patients were male, pointing towards a possible hormonal influence [5]. To be noted some common mechanisms with diabetic nephropathy, respectively angiogenesis and generation of AGE's, which may at least partially explain the striking resemblance between glomerulosclerosis because of cigarette-smoking and diabetic nephropathy. These two pathological entities share common features, such as nodular and diffuse glomerulosclerosis, mesangiolysis, afferent and efferent arteriolar hyalinosis, thickening of GBM and TBM, Bowman's capsular hyalinosis, and foot processes effacement. The only major difference between these two conditions is the way mesangial nodules are vascularized – in smoking-associated nodular glomerulosclerosis there is a process of angiogenesis, highlighted by new small endothelial-lined vessels inside the nodules (with positivity for CD34-immunostaining), while in diabetic nephropathy the nodules lack this neovascularization [3, 4].

Cigarette smoke, through some of its stable compounds (especially nicotine), induces generation of ROS by endothelial cells, with the final result of endothelial dysfunction [17]. Acrolein, another smoke compound, can cause endothelial dysfunction and atherosclerosis in experimental models [18]. Endothelial dysfunction induced by smoking is responsible for arteriosclerosis, including at the level of intrarenal vessels, with the final result of fixed narrowing of the renal arterioles with glomerular and tubular ischemia. Consequently, not only glomerulosclerosis and tubular atrophy are promoted, but also stimulation of rennin–angiotensin system.

One of the major active and stable compounds found in tobacco, which is involved in deleterious effects upon kidney structure, is nicotine, which can be acquired both through active and passive smoking. Nicotine mediates its effects *via* the activation of nicotinic acetylcholine receptors (nAChRs). These are transmembrane receptors made from five subunits and are found on the surface of different cells, both neuronal as well as non-neuronal cells, including mesangial, vascular smooth muscle and endothelial cells [16]. Of these subunits, the α7-nAChR subunit is the major mediator of negative effects of nicotine on renal function, and renal injury can be prevented by experimental blockade of the α7-nAChR subunit [19]. Nicotine has mitogenic effects and induces extracellular matrix production (especially *via* activation of transforming growth factor-beta – TGF-β and insulin-like growth factor signaling pathways), both directly (by stimulating nAChRs from mesangial cells surface) and indirectly, by generation of ROS [3, 4, 19]. Stimulation of nAChRs by nicotine also induces activation of receptors to AGE (RAGE), which in turn induces oxidative stress by cellular up-regulation of oxidative enzymes [19, 20]. Nicotine also stimulates angiogenesis *via* binding nAChRs on endothelial cells [21].

AGEs are an important factor involved not only in diabetes complications (including diabetic nephropathy), but also in aging, atherosclerosis, and increased vascular stiffness [22]. Noxious effects of AGE are mediated through binding to RAGE, found on different cells surfaces, including mesangial cells and podocytes. AGEs are found in significant quantities in plasma from heavy smokers [23], and also RAGEs are up-regulated in this situation [24]. Activation of RAGEs by AGEs stimulates matrix synthesis (including fibronectin, type IV collagen, laminin, and heparan sulfate) by mesangial cells through activation of different signaling pathways, including NF-κB (nuclear factor-κB) and JAK (Janus kinase) [25]. Chronic hypoxia (due to chronic obstructive pulmonary disease because of smoking) activates sympathetic nervous system, which in turn stimulates RAGE and also rennin–angiotensin system (through β_2-receptors found on *macula densa*), with the final result of amplification of matrix synthesis by mesangial cells [4, 26]. Sympathetic nervous system also mediates some of the negative effects of smoking upon kidney – in the lab animals, increase in glomerulosclerosis and interstitial fibrosis because of cigarette smoke was prevented by renal denervation [27].

As a final result of all these complex pathogenic mechanisms, a vicious circle is generated with a negative impact on kidney structure and function. The extremely high prevalence of hypertension among patients with smoking-associated nodular glomerulosclerosis raises the hypothesis of an additive effect between cigarette smoking and hypertension in this clinicopathologic condition. However, giving the rarity of this biopsy finding compared with the high prevalence of smoking in the general population, it still leaves place for many unanswered questions.

Conclusions

In summary, although smoking-related nodular glomerulosclerosis remains a rare entity, this diagnosis has to be taken into account in patients with a long history of smoking, hypertension and often established extra-cardiac vascular disease. While all these features were found in our patient, nephrotic syndrome – which was also a finding in our case, is not so common in this setting, and smoking-associated glomerulosclerosis has to be considered along with other, more common causes of nephrotic syndrome.

Conflict of interests

The authors declare that they have no conflict of interests.

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