Non-diabetic metabolic nodular glomerulosclerosis

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Abstract. Nodular glomerulosclerosis is classically associated with diabetes. Nowadays, it is well known that this histologic pattern can be the presentation of different diseases, including dysproteinemias and amyloidosis. Most recently, the previously thought to be idiopathic nodular glomerulosclerosis has been associated with hypertension, smoking, and obesity. We present a clinical case of a non-diabetic 74-year-old man, with hypertension and heavy smoking history, who presented with nephrotic proteinuria and chronic kidney disease. We review the literature and propose a different nomenclature for this pattern of metabolic glomerulopathy.

Introduction

Nodular glomerulosclerosis is a histologic pattern historically associated with diabetic nephropathy. It was first described in 1936 by Kimmelstiel and Wilson [1] as intercapillary glomerulosclerosis related to diabetes. As with almost all the histologic patterns, these lesions are not pathognomonic, and the final diagnosis implies the integration of clinical data.

Nodular glomerulosclerosis has been associated with numerous other conditions, so it requires an extensive laboratory work-up and rigorous histologic evaluation of renal biopsy, including histochemistry, immunofluorescence, and electron microscopy.

In the past, when no cause was found to explain this diabetic-like nephropathy, it was called idiopathic nodular glomerulosclerosis [2]. In 1999, Herzenberg et al. [2] observed that hypertension and obesity were common among these patients, and in 2002, an association with smoking was suggested for the first time by Markowitz et al. [3]. Also, this type of lesion has been described in patients with impaired fasting glucose or impaired glucose tolerance, and in some cases was described as the initial diabetes manifestation [4].

We present a case of non-diabetic metabolic nodular glomerulosclerosis (NDMNG) and a review of the literature.

Case report

A 74-year-old Caucasian man was referred to nephrology consultation for poorly controlled hypertension (imprecise starting date) and kidney dysfunction, with a serum creatinine of 1.57 mg/dL (eGFR 53 mL/min/1.73m²).

Besides hypertension, his cardiovascular history included heart failure with left ventricular hypertrophy with preserved ejection fraction and moderate aortic insufficiency. Of note, there was an ongoing heavy cigarette smoking (60 pack-years). Other relevant data included asymptomatic benign
prostatic hyperplasia and nephrolithiasis, with episodes of renal colic in the past. He 
was under furosemide, perindopril, amlo
dipine, nebivolol, riminidine, simvastatin, 
and tamsulosin, but no regular NSAIDs use.

Physical examination revealed blood 
pressure of 178/57 mmHg and no peripheral 
edema, a weight of 58 kg, and a body mass 
index of 21 kg/m².

Urinalysis showed a protein-to-creati
nine ratio of 6,042 mg/g, an albumin-to-cre
atinine ratio of 4,603 mg/g, and microscopic 
hematuria. Hypercholesterolemia (total 
cholesterol 242 mg/dL) and hyperuricemia 
(serum uric acid 7.1 mg/dL) were present; 
sedimentation rate was 67 mm/h. Serum 
albumin was within the normal range. The 
serum free light chain ratio, total IgG IgA, 
and IgM were normal, serum protein elec
trophoresis showed no M spike, and immu
nofixation was negative. The immunologic 
study was also negative (complement, rheu
matoid factor, ANA’s, anti-dsDNA, ANCA), as 
were serologies for HIV, HBV, and HCV. He 
had no diabetes (fasting glucose 97 mg/dL, 
HbA1c 5.4%). On ultrasound, kidney size was 
normal, and there were no signs of obstruc
tion or lithiasis.

On renal biopsy findings, 7 of 16 glom
eruli were globally sclerotic; the remaining 
were hypertrophied with Bowman’s capsule 
thickening and hyaline expansion of the me
sangial matrix, forming nodules (positive 
periodic acid Schiff stain), accompanied by 
slight segmental mesangial proliferation and 
mesangiolysis. Two glomeruli showed le
sions of segmental sclerosis. There was se
vere interstitial fibrosis and tubular atrophy 
involving ~ 70% of the sample, accompanied 
by chronic inflammatory lymphocytic infiltrate. Arteries exhibited reduplication of the 
internal elastic lamina, and arterioles pre
sented exuberant hyalinosis of the wall, with 
almost complete occlusion of the lumen 
(Congo red negative). The immunofluores
cence study was negative.

Ultrastructural evaluation: globally thick
ened basal membrane; podocytes with ex	ensive foot process effacement. Mesangial 
matrix segmental expansion, with no in
crease of cellularity. No electron-dense de
posits or fibrils were found.

The patient never quit smoking, and de
spite blood pressure control with a maximum 
tolerated dose of perindopril, he progressed 
to stage G5A3 chronic renal disease within 3 
years and was started on hemodialysis.

Non-diabetic metabolic nodular glomerulosclerosis

Definition

NDMNG is a histologically based exclu
sion diagnosis, after ruling out: chronic 
membranoproliferative glomerulonephritis, dysproteinemia-related glomerular involve
ment, fibrillary or immunotactoid glomeru
lonephritis, fibronectin glomerulopathy, col
lagen III glomerulopathy, chronic hypoxic or 
ischemic conditions, and cystic fibrosis [3, 5, 
6]. This pattern of glomerular lesion is a rare 
finding in the absence of diabetes, described 
in only 0.45 – 0.5% of biopsies [3, 7]. The so
far biggest meta-analysis described in the 
literature included only 95 cases [4].

Most recently, there has been discus
sion about the right nomenclature for this 
disease. After the established association 
between this histologic pattern with cardio
vascular risk factors, the term “idiopathic 
nodular glomerulosclerosis” is no longer ap
propriate. “Diabetic nephropathy without 
diabetes”, “smoking-related glomerulopa
thy”, and “smoking-associated nodular glo
merulosclerosis” are some of the proposed 
terminologies [4, 6, 8]. Since smoking is not 
the only predisposing identified risk factor 
for this condition, we consider that the term 
“non-diabetic metabolic nodular glomerulo
sclerosis” should instead be used.

Clinical presentation and outcomes

NDMNG is more frequent among men, 
with a mean age of 60-years at biopsy (Table 1) 
[3, 4, 7, 8, 9, 10].

Patients usually present advanced kid
ney dysfunction, with serum creatinine 
ranging from 2.4 to 4.2 mg/dL. Urinalysis 
typically shows proteinuria and microhema	turia ranges from absence to 75% in one se
ries. The mean proteinuria at kidney biopsy 
is 1.9 – 4.2 g/day, and 22 – 53% may present 
with full nephrotic syndrome [3, 7, 8, 9, 10].

Studies have shown that these patients 
have a poor prognosis, with 30 – 35% reach
ing end-stage renal disease (ESRD) less than

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3 years after biopsy [4]. On the other hand, smoking cessation and therapy with renin-angiotensin-aldosterone system inhibitors have been associated with better prognosis [3].

**Biopsy findings**

Nodular glomerulosclerosis presents histologically as an increase in the mesangial matrix, with nodule formation and glomerulomegaly, accompanied by thickening of the glomerular basal membrane, indistinguishable from diabetic nephropathy. More than 80% of patients show moderate to severe arteriolar hyalinosis and sclerosis [3, 4, 6]. Glomerular hyalinosis, mesangiolysis, and microaneurysms may be also observed (Figure 1). Tubulointerstitial fibrosis and tubular atrophy as well as arteriolar hyalinosis have been described as prognostic factors [3, 4].

### Table 1. Case series of non-diabetic metabolic nodular glomerulosclerosis – clinical characteristics.

|                          | Markowitz et al. (2002) [3] | Li and Verani (2008) [9] | Wu et al. (2013) [7] | Salvatore et al. (2015) [8] | Hamrahian et al. (2018) [10] |
|--------------------------|-------------------------------|--------------------------|----------------------|-----------------------------|-----------------------------|
| Number of patients       | 23                            | 15                       | 20                   | 4*                          | 17                          |
| Male, %                  | 78                            | 33                       | 80                   | 100                         | 76                          |
| Race                     |                               |                          |                      |                             |                             |
| White, %                 | 74                            | 73                       | 100                  | 41                          |                             |
| Black, %                 | 26                            | 20                       | 0                    | 41                          |                             |
| Asian, %                 | 0                             | 0                        | 0                    | 6                           |                             |
| Hispanic, %              | 0                             | 7                        | 0                    | 6                           |                             |
| Media age, years (min – max) | 68 (47 – 80)          | 64 (48 – 76)              | 56 (16 – 71)         | 62 (48 – 72)                 | 60 (27 – 81)                |
| Hypertension, %          | 96                            | 93                       | 90                   | 100                         | 100                         |
| Duration of hypertension, years | 15                            | 14                       | 4                    |                             |                             |
| Smokers, %               | 91                            | 67                       | 85                   | 100                         | 65                          |
| Cumulative cigarette intake, pack-years | 53                            | 54                       | 20                   | 23 years                    |                             |
| Obesity (BMI > 30), %    | 13                            | 60                       | 55                   |                             |                             |
| Overweight (BMI 25 – 29), % | 27                            | 40                       | 35                   |                             |                             |
| Hypercholesterolemia, %  | 90                            | 50                       | 50                   |                             |                             |
| Median creatinine at the diagnosis, mg/dL (min – max) | 2.4                           | 2.8 (1 – 6.8)             | 4.2 (1.1 – 8)         | 1.9 (1.3 –3.0)              | 2.35                        |
| Median proteinuria, g/day (min – max) | 4.7                           | 5.6 (1 – 11.3)            | 2.85 (1.26 – 6.11)   | 3.0 (1.75 – 5.5)            | 3.58 g/g (0.8 – 12.3)       |
| Nephrotic-range proteinuria, % | 70                            | 73                       | 35                   |                             |                             |
| Nephrotic syndrome, %    | 22                            | 53                       | 25                   |                             |                             |
| Microhematuria, %        |                               |                          |                      |                             |                             |
| ESRD, %                  | 35                            | 30                       | 25                   |                             |                             |

*Six patients were excluded for nodular glomerulosclerosis pattern absence. ESRD = end-stage renal disease.
Immunofluorescence is negative for immune deposits but can show IgG, IgM, C3, or albumin in an unspecific pattern [4, 6, 7, 9]. The ultrastructural evaluation shows thickened glomerular basement membrane (GBM) (> 400 nm in females, > 450 nm in females).
Discussions

NDMNG is a rare disease that has been associated with smoking and hypertension, among other cardiovascular risk factors.

Hypertension is not only one of the most common etiologies of end-stage renal disease, but it is also present in more than 90% of NDMNG patients at the time of biopsy [3, 7, 8, 9, 10].

In patients with NDMNG, a high prevalence of smokers is noted – more than two-thirds of patients with a history of tobacco use and high cumulative intake of cigarettes, median 20 – 54 pack-years [3, 7, 9]. Smoking is a well-recognized risk factor for chronic kidney disease and even in non-diabetic and non-hypertensive patients, an association with microalbuminuria can be found [11]. The proposed mechanism by which smoking can lead to proteinuria and renal damage is through tobacco-sourced advanced glycation end product interaction with serum proteins [3, 6]. Cigarette smoking also produces free radicals that induce oxidative stress and activate the sympathetic nervous system, which induces activation of the renin-angiotensin-aldosterone system [3, 6, 7, 11]. Thus, smoking alters intrarenal hemodynamics, through vasoconstriction and blood flow reduction [6, 11]. All these mechanisms converge to produce a nephrotoxic effect that can be responsible for nodular glomerular lesions.

NDMNG has been associated with several cardiovascular risk factors besides smoking and hypertension, such as obesity and hypercholesterolemia, which are also well-known vasculopathy promoters [3, 4, 5, 7, 8, 9]. We postulate that this lesion might arise in the presence of different combinations of cardiovascular risk factors and that it represents a severe form of metabolic microvasculopathy.

The clinical case presented here is another example of the complex integration of risk factors, such as hypertension, smoking, and dyslipidemia, in the etiology of this lesion pattern, and consequent rapid progression to ESRD. More studies are needed to further improve knowledge about this entity and to clarify what is the best approach to prevent these patients from progressing to ESRD.

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Conflict of interest

The authors declare that there are no competing interests regarding the publication of this article.

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