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Idiopathic nodular glomerulosclerosis in a chronic marijuana user; a case report and review of the literature

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ABSTRACT

Background: Nodular glomerulosclerosis is a characteristic histological finding of diabetic nephropathy (DN) with thickened glomerular basement membrane (GBM) and hyalinized arterioles. Idiopathic nodular glomerulosclerosis (ING), a rare distinct clinicopathologic entity, is the term used to denote classic DN confirmed by light microscopy, immunofluorescence, and electron microscopy in the absence of diabetes mellitus (DM). ING has been linked to heavy tobacco smoking, chronic hypertension, obesity and insulin resistance. Its association with marijuana use is unknown.

Case Presentation: We report a case of biopsy-proved ING in the absence of pre-existing history of DM and heavy smoking. This report addresses the possible accentuation of tobacco use risk by marijuana.

Conclusions: This report addresses the possible accentuation of tobacco use risk by marijuana.

Case Report

Implication for health policy/practice/research/medical education:
Idiopathic nodular glomerulosclerosis (ING) is a rare distinct clinicopathologic entity that has been linked to heavy tobacco smoking, chronic hypertension, obesity and insulin resistance. Its association with marijuana use is unknown. We report a case of biopsy-proved ING in the absence of pre-existing history of diabetic nephropathy (DN) and heavy smoking. This report addresses the possible accentuation of tobacco use risk by marijuana.

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1. Introduction

Nodular glomerulosclerosis, a histologic pattern of nodular mesangial sclerosis with glomerular lobularity, is the classic lesion of diabetic nephropathy (DN) (1). The differential diagnosis for nodular glomerulosclerosis is broad and includes membranoproliferative glomerulonephritis, amyloidosis, monoclonal immunoglobulin deposition disease, fibrillary or immunotactoid glomerulonephropathy, glomerulopathy associated with a chronic hypoxic state (e.g., Takayasu's arteritis), and idiopathic nodular glomerulosclerosis (ING). ING is rare and remains a diagnosis of exclusion (2). The defining pathological features of ING are diffuse and nodular mesangial sclerosis accompanied by glomerular basement membrane (GBM) thickening, glomerulomegaly, and arteriolosclerosis. It is strongly associated with hypertension and heavy smoking. We report a case of ING in a chronic marijuana user with insignificant history of tobacco use and no history of DM.

2. Case Report

A 36-year-old African-American female with insignificant medical history presented to the emergency room with chief complaint of daily vomiting for one week, poor appetite, and unintentional weight loss of 35 kg over one year. She also had been experiencing migraine headaches and was taking ibuprofen chronically. Nine years earlier, she had taken antihypertensive medication for six months after her last pregnancy with no history of preeclampsia or chronic hypertension (HTN) known prior to the pregnancy. Despite systolic blood pressure (BP) readings of 150-170 mm Hg recorded 5 months prior to this admission; she was on no anti-

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hypertensive medication. She had no diabetes mellitus (DM). Her family history was negative for autoimmune diseases, but her mother and sister both had HTN and DM. She had no allergies and denied the use of any herbal remedies. She had started smoking tobacco cigarettes socially at age 25 and smoked up to five cigarettes per day before quitting a year ago. She had significant history of using marijuana starting 10 years ago and had been smoking twice a day for the last five years prior to admission. She denied use of other illicit drugs or heavy drinking.

On examination, she was afebrile and her BP measured 195/103 mm Hg with a regular pulse of 103 beats/minute. Oxygen saturation was 100% on room air. Her body mass index was 29 kg/m^2. Physical examination was otherwise unremarkable except for pale conjunctiva. Laboratory parameters showed microcytic anemia with hemoglobin of 4.9 g/dL and iron saturation of 4% with a ferritin level of 13 ng/mL. Stool was negative for occult blood. Erythrocyte sedimentation rate was 66 mm/h. Her urine and blood culture were both negative. Her renal function was as follows: blood urea nitrogen 87 mg/dL; creatinine 10.9 mg/dL (1.0 mg/dL 5 years earlier); bicarbonate 12 mEq/L; potassium 5.1 mEq/L. Phosphorus was 8.3 mg/dL with elevated parathyroid hormone of 1,729 pg/mL. Urinalysis showed 3+ protein at specific gravity of 1.008 without any red blood cells. Spot random urine revealed a protein to creatinine ratio of 384/77 mg/dL with a serum albumin of 3.6 g/dL. Total cholesterol was 151 mg/dL with low-density lipoprotein being 82 mg/dL. Anti-neutrophil antibody, serum complement levels, hepatitis and HIV screening were all negative or normal. Fasting blood glucose was normal, and Hgb_{A1c} was 5.3%. Urine drug screen was positive for cannabinoid (delta-9-tetrahydrocannabinol [TCH], and other derivatives). Renal ultrasound demonstrated a right kidney size of 10.4 cm and left kidney of 10.8 cm in length with increased cortical echogenicity without hydronephrosis. Her echocardiography showed moderate concentric left ventricular hypertrophy, normal ejection fraction, and moderate pulmonary hypertension. Renal biopsy was done for unchanged renal function despite volume resuscitation with packet red blood cell transfusions and blood pressure control.

2.1. Renal biopsy

On light microscopy, the glomeruli showed extensive diffuse and nodular glomerulosclerosis (Figure 1). Several of the GBM appeared thickened with a few glomeruli contained intra-capillary hyaline. There was no mesangial/endocapillary cell proliferation or double contouring, and no immune complex deposits were identified. One glomerulus showed wrinkling of the GBM consistent with ischemic change. There was diffuse interstitial fibrosis and tubular atrophy extending throughout the cortex. Several arterioles showed hyaline arteriolosclerosis. Immunofluorescence was only positive for segmental IgM in 2/8 glomeruli, but otherwise negative for human IgG (heavy and light chains), IgG (gamma chain), IgA, kappa light chain, lambda light chain, C1q, C3, C4, albumin, and fibrinogen. Electron microscopy of two of glomeruli showed widening of the mesangial areas by mesangial matrix (diffuse glomerulosclerosis) and areas of nodular glomerulosclerosis. The GBM was thickened with a mean thickness of 616 ±- 50 nm. The visceral epithelial cells showed large areas of foot processes effacement (Figure 2). There was no immune complex deposition or deposits compatible with light chain seen. There was no fibrillary material compatible with amyloid or fibrillary glomerulonephritis.

3. Discussion

Once considered a diagnosis of exclusion, ING is a rare distinct clinicopathologic entity (2). It is predominantly described in elderly Caucasian individuals and

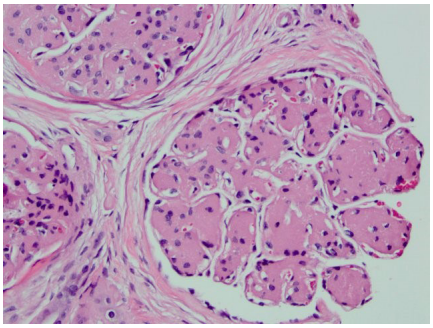

Figure 1. Light microscopy of idiopathic nodular glomerulosclerosis (H&E original magnification × 200): The glomerulus shows extensive diffuse nodular glomerulosclerosis.

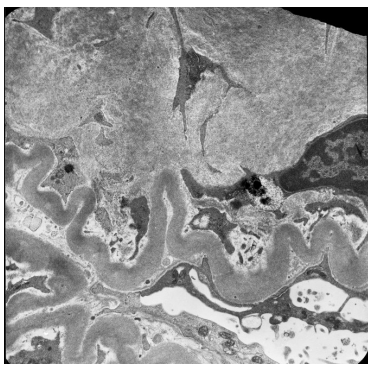

Figure 2. Electron microscopy of idiopathic nodular glomerulosclerosis (original magnification × 14300): There is widening of the mesangial areas by increased mesangial matrix and thickened glomerular capillary basement membrane. There is diffuse foot process effacement.

is linked to heavy smoking, hypertension, and obesity (3,4). Patients usually present with renal insufficiency and proteinuria of variable degrees. The pathogenesis involves the interplay of hypertension, heavy smoking, increased glomerular extracellular matrix (ECM) and angiogenesis (5).

Tobacco smoking has a negative impact on renal function, particularly in a patient with hypertension, DM, and primary renal disease (6). It increases the risk of albuminuria, progression to proteinuria, and renal functional impairment, particularly in men and the elderly. The pathophysiologic mechanisms include the formation of advanced glycation end-products (AGEs) by glycotoxins, induction of oxidative stress, angiogenesis, and altered intrarenal hemodynamics (7,8). Induction of oxidative stress by free radicals contained in cigarette smoke and directly by AGE increases ECM. AGE alters ECM by promoting mesangial cell synthesis of fibrogenic cytokines, platelet-derived growth factor, insulin growth factor (IGF) and transforming growth factor-beta (TGF-β) (9). Furthermore, smoking directly and indirectly, through chronic hypoxia, leads to sympathetic activation and stimulation of the renin-angiotensin aldosterone system; it promotes increased renal vascular resistance, decreased renal plasma flow, hypertension, and ECM production. In addition, AGE interacts with its receptor RAGE, which is predominantly expressed in podocytes. Podocytes play a crucial role in the pathogenesis of glomerulosclerosis and prevent proteinuria through a complex regulation of actin cytoskeleton in their foot processes. They are insulin responsive cells and their function, structure, and survival are under the control of insulin stimulation (10). Respectively, podocyte-specific insulin resistance is considered a potential mechanism of glomerular kidney damage (11).

Our patient presented with advanced renal insufficiency, nephrotic range proteinuria, and untreated hypertension of unknown duration. Her renal function remained impaired despite volume resuscitation with packed red blood cells and blood pressure control. Kidney biopsy findings of diffuse and nodular glomerulosclerosis, GBM thickening, and arteriolar hyalinosis favored a diagnosis of diabetic glomerulosclerosis, but there was no evidence of diabetes or impaired glucose tolerance on biochemical testing and available records from the past. There were no immune deposits on immunofluorescence and no fibrillar or microtubular structures on electron microscopy. The patient's negative serology tests led us to diagnose ING with features of hypertensive vascular changes. Interestingly, though she was not a heavy tobacco smoker, she used marijuana daily.

Cannabis is the most widely used illicit drug after tobacco and alcohol. There is a rising interest in its therapeutic use for chemotherapy-induced nausea and vomiting, HIV-associated anorexia, neuropathic pain in multiple sclerosis, pain associated with rheumatoid arthritis, fibromyalgia, and cancer (12). Respectively, its safety is an emerging source of concern. Marijuana is an ill-defined conglomerate of chemicals. Its short- and long-term adverse effects are difficult to evaluate because often there is a concurrent consumption of tobacco and alcohol. Delta-9-tetrahydrocannbinol (TCH) is mainly metabolized in the liver by cytochrome P-450 and appears to be responsible for the principle toxicological effect. Its effects are dose dependent and range from serious psychological to somatic disorders, including tachycardia and dyspnea progressing to apnea and death. Excessive use of marijuana, as experienced by our patient, could result in a cyclic vomiting, a condition called 'cannabinoid hyperemesis syndrome' (13). The long-term cardiovascular effects and associated health risks with chronic use of marijuana remain unknown. Acutely, there is a dose-dependent tachycardia and modest increase in blood pressure via centrally mediated beta-sympathetic stimulation and reduced parasympathetic activity (14). Decreased vascular resistance associated with increased blood flow to the extremities may cause postural hypotension and even syncope (15). Although it is difficult to determine the effect of marijuana in our patient's renal pathology and the diagnosis of ING, her insignificant smoking history strongly suggests that chronic use of marijuana has played a significant role or may have accentuated the risk of development of ING associated with tobacco use. Smoking causes carbon monoxide-induced hypoxia and, compared to one tobacco cigarette, a marijuana cigarette increases the carboxyhemoglobin levels by fivefold resulting in tissue hypoxia (16). Moreover, cases of arteritis associated with marijuana use leading to ischemia have been described (17). Finally, marijuana produces oxidative stress increasing ECM via TGF-beta and IGF as outlined above (18).

Our case is unique in that the patient was a young African American female with relatively insignificant tobacco smoking history but chronic daily marijuana use for over 10 years. This contrasts with the two biggest case series reported by Columbia University (1996-2001) (4), where most patients were old, white, heavy-smoking males and the University of Texas/Houston (1998-2007) (3) where most patients were females. This gender distribution in the two biggest case series could be due to the sampling period with smoking becoming more prevalent among females over the last decades.

4. Conclusions

The pathogenesis of ING remains unclear and the

prognosis is poor. It involves the interplay of hypertension, obesity, insulin resistance and heavy smoking. Chronic use of marijuana may accentuate the tobacco risk. Although illegal in many countries, marijuana use is widespread, especially among the adolescents and young adults, for its euphoric effects. With the rising therapeutic use of cannabis-based medicine, it is important that physicians be equally vigilant about the possible long-term renal toxicity effects of marijuana beyond the acute kidney injury seen with cannabinoid hyperemesis syndrome.

Authors' contribution

MM reviewed pathology literature and wrote the first draft. SAS reviewed nephrology literature and helped with first draft. TF edited the manuscript and took care of the patient after hospital discharge. MH did take care of the patient during the hospitalization and is the senior author.

Conflicts of interest

Authors have no relevant conflict of interest to disclose.

Informed consent

A written informed consent was obtained from the patient to report this case.

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