

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS COMPLICATING DIABETIC NEPHROPATHY

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Abstract: *Background:* Renal diseases other than diabetic nephropathy can be found in diabetic patients who have undergone renal biopsy. Various forms of primary and secondary glomerular diseases were reported, but membranoproliferative glomerulonephritis was rare.

Methods: Analyzing data at our Department for the past three years, we noted 18 patients with primary membranoproliferative glomerulonephritis and 4 associated with diabetic nephropathy.

Results: Nodular glomerulosclerosis with diffuse membranoproliferative glomerulonephritis was registered in two patients and a diffuse form of diabetic nephropathy with a combination of segmental and diffuse changes characteristic of membranoproliferative glomerulonephritis in the other two patients.

Conclusions: Analyzing what can be common for these two diseases we can conclude that they are at least three disorders: 1. hyperperfusion injury, hallmark for the diabetic nephropathy, but also with the highest incidence in membranoproliferative glomerulonephritis than in the other glomerulonephritides; 2. mesangial matrix expansion, and; 3. thickening of all extracellular membranes.

Key words: membranoproliferative glomerulonephritis, diabetes, diabetic nephropathy

Introduction

Diabetes mellitus is often complicated by nephropathy with progression to renal failure [1, 2]. Various forms of glomerulonephritis have been associated

with diabetes, sometimes resulting in more rapid deterioration in renal function, occasionally dictating alternative management of these patients in an attempt to reverse or contain nephrosis or renal failure [3, 4, 5, 6]. Membranoproliferative glomerulonephritis (MPGN) is a chronic progressive renal disease and a major cause of renal failure in older children and young adults, but also frequently seen in older adults. MPGN type I, the most common form, is characterized by mesangial proliferation, duplication of the glomerular basement membrane and subendothelial electron-dense deposits. The complement system is known to be closely related to the pathogenesis of this disease. MPGN may be caused by a variety of diseases that result in glomerular immune complex localization, such as autoimmune, neoplastic, infectious and hereditary disorders [7, 8, 9, 10, 11, 12]. MPGN type I, primary form, was documented by percutaneous renal biopsy at our department in 18 patients during the past three years and in 4 patients with insulin-dependent diabetes mellitus. This is a very rare association, only 4 cases were reported during the past 20 years [13, 14]. We would like to present our patients with diabetes and MPGN tip I, diagnosed during the past three years.

Subjects and methods

This is the retrospective study. We analyzed the patients undergoing renal biopsy at our Department for the past three years. Membranoproliferative glomerulonephritis was documented in 18 patients and, as was mentioned previously, 4 of them were with insulin-dependent diabetes mellitus. Histological examinations included optical and immunofluorescence microscopy using standard procedures, as well as semi-thin sections. Standard clinical features were also taken into consideration.

Results

Clinical findings

Table 1 – Табела 1

Clinical data of the patients with diabetes and MPGN type I
Клинички податоци на пациенти со дијабетес и МПГН тип I

Age	47±8,1 (26–64) years
Diastolic blood pressure	102,5±7,5 (90–120) mmHg
Serum creatinine	186,25±43,46 (90–221) μmol/l
Proteinuria	7,53±2,02 (3,63–13) g/24h
Serum albumins	26±2,82 (18–30) g/l

All patients were on insulin treatment for more than three years. All patients were nephrotic and only one was with a normal renal function. Percutaneous renal biopsy was performed in all of them.

Histopathological findings

Two of the patients presented enlarged glomeruli due to hypercellularity (mesangial and endocapillary) with characteristic lobular configuration. Intraglomerular cells consisted of mononuclear monocytes, mesangial and endothelial cells, and rare neutrophils. The mesangial matrix was enlarged with focal hyaline-sclerotic areas (blue staining on Trichrome-Mason). Hyaline, nodular, acellular widening of the mesangium was noted focally. Staining with silver methenamine (Jones) presented reduplication of the glomerular basement membrane. The visceral epithelium was hypertrophic with adhesions with the parietal epithelium. Interstitial edema with slight interstitial fibrosis was visible. Intrarenal blood vessels presented hyaline insudative changes. These histopathological changes were followed with deposition on immunofluorescence of granular deposits of IgA (+2+3), IgM (+2), IgG (+3), C3 (+2,+3), C4 (+1), Fib (+3). The whole histopathology in these two patients suggested a nodular form of diabetic nephropathy with diffuse membranoproliferative glomerulonephritis.

The other two patients presented diffuse diabetic glomerulosclerosis. Besides these changes, inflammatory cellular mesangial proliferation with intracapillary influx of neutrophils was present with reduplication and partial destruction of the glomerular basement membrane. 7/12 glomeruli in one patient, and 5/15 in the other presented diffuse changes and a lobular glomerular configuration, and 5/12 segmental in the first and 10/15 in the second patient. The tubular epithelium showed degenerative and partially necrotic changes, the interstitium was edematous with diffuse mononuclear cell infiltration. Changes of intrarenal blood vessels were not severe in these two cases, affecting only vascular poles. IgA deposition was granular, +1, +2, IgM +3, +1, IgG +1,+2, C3 +3, C4 +2, Fib +2, +3, C1q +2,+3 on immunofluorescence.

Summarizing the histopathological findings we can conclude that nodular diabetic glomerulosclerosis with diffuse membranoproliferative glomerulonephritis was present in two patients and diffuse diabetic glomerulosclerosis with a combination of diffuse and segmental glomerular changes of membranoproliferative glomerulonephritis in the other two patients.

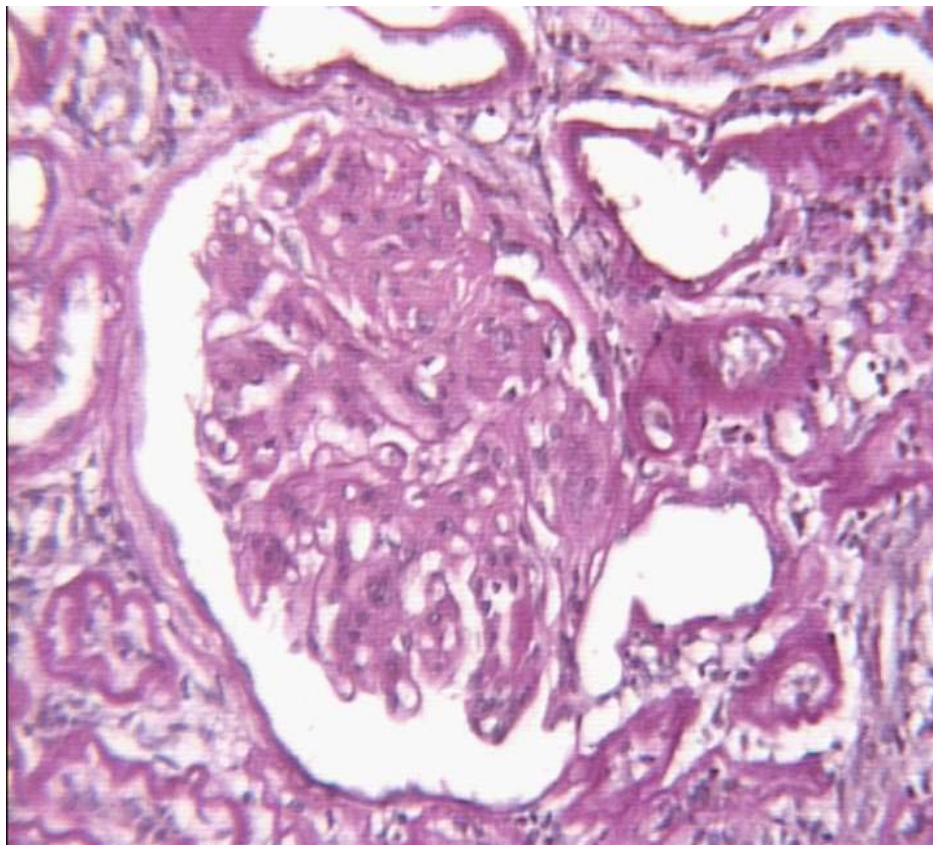


Figure 1 – *Glomerulus with visible nodular changes
(diabetic nodular glomerulosclerosis)
and lobular glomerulonephritis
(PAS 40X10X1,25)*

Слика 1 – *Гломерул со видливи нодуларни промени
(дијабетична нодуларна гломерулосклероза)
и лобуларен гломерулонефриитис
(PAS 40X10X1,25)*

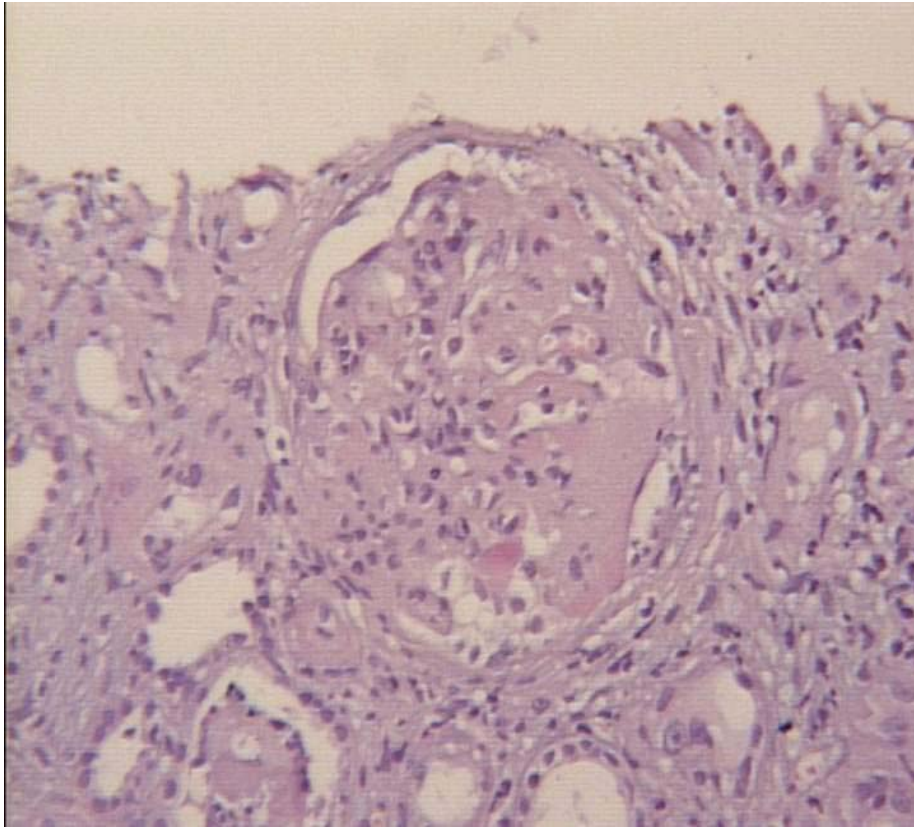


Figure 2 – *Hyaline insudative changes of intrarenal blood vessels, diffuse diabetic glomerulosclerosis and capillary changes due to membranoproliferative glomerulonephritis (Silver methenamine 100X10X1,25)*

Слика 2 – *Хиалини инсудативни промени на интјрареналнијте крвни садови, дифузна дијабетична гломерулосклероза и капиларни промени поради мембранојролиферативниотј гломерулонефритјис (Silver methenamine 100X10X1,25)*

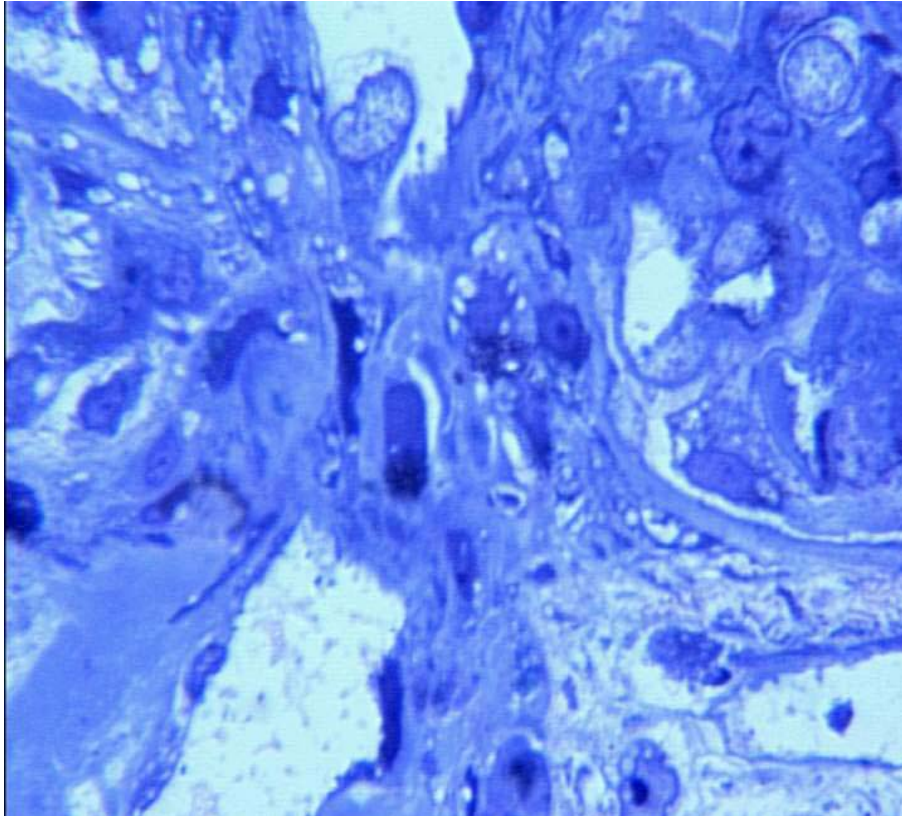


Figure 3 – *Semi-thin section of vascular pole of the glomerulus affected by both diseases. Hyaline insudative changes of afferent arteriole and capillary changes of membranoproliferative glomerulonephritis are visible*

Слика 3 – Полућенок исечок на васкуларниот пол на гломерулој зафатен од двете болести. Се гледаат хиадини инсудативни промени на аферентната артериола и капиларни промени на мембранопролиферативниот гломерулонефритис

Discussion

As was mentioned previously, membranoproliferative GN is caused by a variety of diseases that result in glomerular immune complex localization, such as autoimmune (systemic lupus erythematosus, cryoglobulinemias), neoplastic, infectious (hepatitis B and C) and hereditary disorders [5, 6, 7]. Rare cases were reported associated with portosystemic shunt surgery, tuberculosis, cryptogenic organizing pneumonitis, hepatic hydatid disease, liver cirrhosis,

sickle cell disease, Turner's syndrome, congenital chloride diarrhea, etc. Chronic glomerulonephritides are frequent nondiabetic renal diseases complicating diabetic nephropathy including IgA nephropathy, membranous nephropathy, minimal change disease, mesangial proliferative glomerulonephritis, endocapillary proliferative glomerulonephritis and very rarely membranoproliferative glomerulonephritis [1, 2, 13, 14]. On the contrary, we found only association between diabetic nephropathy and membranoproliferative glomerulonephritis type 1 in our patients, the other biopsied patients with diabetes presented only changes characteristic for diabetic nephropathy.

What can be common to these two disorders: diabetic nephropathy and membranoproliferative glomerulonephritis? Hyperperfusion injury is common to both diseases, characteristic of diabetic glomerulosclerosis, it can be also found in different forms of glomerulonephritis with varying frequency [15, 16]. The highest incidence was found in patients with membranoproliferative glomerulonephritis. Renal structure and function in both diseases are also similar [17]. Renal pathological changes of diabetes include thickening of all renal extracellular basement membranes and the mesangial matrix. Mesangial expansion out of proportion to the size of the glomerulus is related to proteinuria, hypertension and declining GFR. Interstitial volume may be increased in insulin-dependent diabetes mellitus particularly in areas containing sclerotic glomeruli or marked tubular atrophy. Parallel findings were documented for type I membranoproliferative glomerulonephritis in which the increased mesangial volume fraction was related to decreased GFR, increased glomerular permeability to protein and hypertension. As in diabetes, the cortical interstitial volume fraction is correlated with functional abnormalities in membranoproliferative glomerulonephritis. Similarities between these two disorders are consequences of a primary process which is different and it is very difficult to explain the possible mechanism of association.

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Резиме

**ДИЈАБЕТСКА НЕФРОПАТИЈА КОМПЛИЦИРАНА
СО МЕМБРАНОПРОЛИФЕРАТИВЕН ГЛОМЕРУЛОНЕФРИТ****Л. Грчевска¹, Г. Петрушевска², С. Цикова¹, С. Костадинова²,
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Вовед: **Извадок:** Други ренални заболувања, покрај дијабетската нефропатија, можат да бидат најдени кај пациенти со дијабет кај кои е направена ренална биопсија. Разни форми на примарни и секундарни гломеруларни заболувања се регистрирани, меѓутоа мембранопрولیферативниот гломерулонефрит е редок.

Методи: Анализирајќи ги податоците на нашата клиника за изминатите три години, забележавме 18 пациенти со примарен мембранопрولیферативен гломерулонефрит, од кои 4 асоцирани со дијабетска нефропатија.

Резултати: Нодуларна гломерулосклероза со дифузен мембранопрولیферативен гломерулонефрит беше најдена кај два пациенти и дифузна форма на дијабетска нефропатија со комбинација на дифузни и сегментни лезии карактеристични за мембранопрولیферативен гломерулонефрит кај други два пациенти.

Заклучоци: Анализирајќи што може да биде заедничко за овие две заболувања можеме да заклучиме дека постојат најмалку три пореметувања: 1. хиперперфузија, заштитен знак на дијабетската нефропатија, но исто така со највисока инциденца кај мембранопрولیферативниот гломерулонефрит во споредба со другите гломерулонефрити; 2. експанзија на мезангијалниот матрикс, и 3. здебелување на екстрацелуларните мембрани.

Клучни зборови: мембранопрولیферативен гломерулонефрит, дијабет, дијабетска нефропатија.

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