

## DIABETIC NEPHROPATHY WITH FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Krešimir Galešić<sup>1</sup>, Danica Ljubanović<sup>2</sup>, Josip Pavan<sup>3</sup> and Ivana Račić<sup>1</sup>

<sup>1</sup>University Department of Medicine, <sup>2</sup>Department of Pathology and <sup>3</sup>Department of Ophthalmology, Dubrava University Hospital, Zagreb, Croatia

**SUMMARY** – The association of diabetic nephropathy with primary glomerulonephritis in type 1 diabetes is rare. Several reports have shown that primary glomerulonephritis can be superimposed on diabetic nephropathy. These glomerulonephritides include idiopathic membranous glomerulonephritis, IgA glomerulonephritis, Henoch-Schönlein nephritis, membranoproliferative glomerulonephritis, lupus nephritis, minimal change disease, postinfectious glomerulonephritis and rapidly progressive glomerulonephritis. Because some of these disorders can alter the management and prognosis of renal disease in diabetic patients, the appearance of urinary abnormalities or deterioration in renal function inconsistent with the natural history of diabetic nephropathy raises the possibility of a nondiabetic renal disease and should lead to a more detailed evaluation. We report on a patient with type 1 diabetes that underwent renal biopsy because of heavy proteinuria and nephrotic syndrome. Renal biopsy showed diabetic nephropathy coexistent with focal segmental glomerulosclerosis. To the best of our knowledge, this is the first reported case of primary focal segmental glomerulosclerosis associated with diabetic nephropathy and diabetic retinopathy, with excellent therapeutic response.

**Key words:** *Glomerulosclerosis, focal – complications; Glomerulosclerosis, focal – diagnosis; Glomerulosclerosis, focal – therapy; Diabetic nephropathies – diagnosis; Diabetic nephropathies – immunology; Diabetic nephropathies – therapy; Kidney, glomerules – pathology*

### Introduction

Immune complex glomerulonephritis can occur in patients with diabetic nephropathy. Idiopathic membranous nephropathy, IgA nephropathy, lupus nephritis, Henoch-Schönlein nephritis, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis and rarely rapidly progressive glomerulonephritis superimposed on diabetic nephropathy have been reported in the literature<sup>1-4</sup>. Primary focal segmental glomerulosclerosis associated with diabetic nephropathy is very rare<sup>2,5</sup>. We report on a patient with type 1 diabetes that underwent renal biopsy because of heavy proteinuria and

nephrotic syndrome. Renal biopsy showed diabetic nephropathy coexistent with focal segmental glomerulosclerosis. To our knowledge, this is the first reported case of concomitant diabetic nephropathy, diabetic retinopathy and primary focal segmental glomerulosclerosis. The present case as well as the cases reported in the literature indicate that diabetic nephropathy is not always the sole cause of proteinuria in diabetic patients. Detection of nondiabetic renal lesions in a patient with diabetic nephropathy may alter therapy for renal disease.

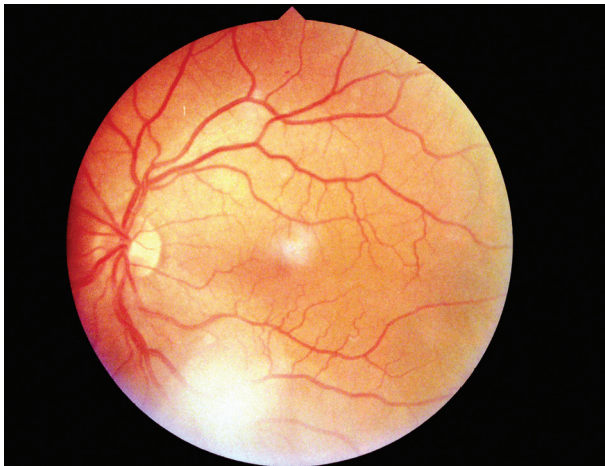
### Case Report

A 46-year-old man with nephrotic syndrome was admitted to our hospital in June 2005. The patient had a past history of diabetes mellitus type 1 of 25 years and hypertension of two months. He was seen in another hospital for resistant nephrotic syndrome and swelling

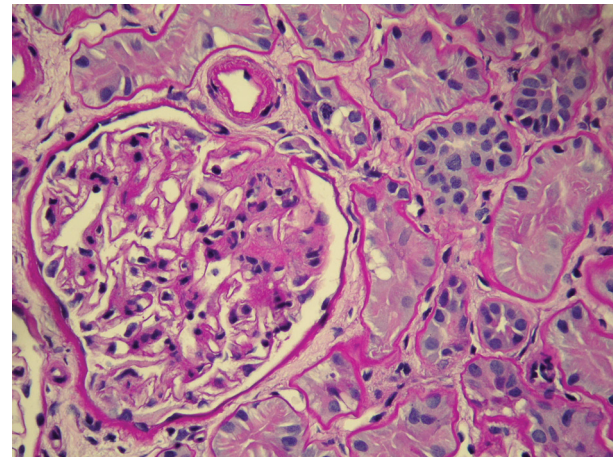
Correspondence to: *Krešimir Galešić, MD, PhD*, University Department of Medicine, Dubrava University Hospital, Av. Gojka Šuška 6, HR-10040 Zagreb, Croatia

E-mail: kresog@kdb.hr

Received March 28, 2007, accepted in revised form September 4, 2007



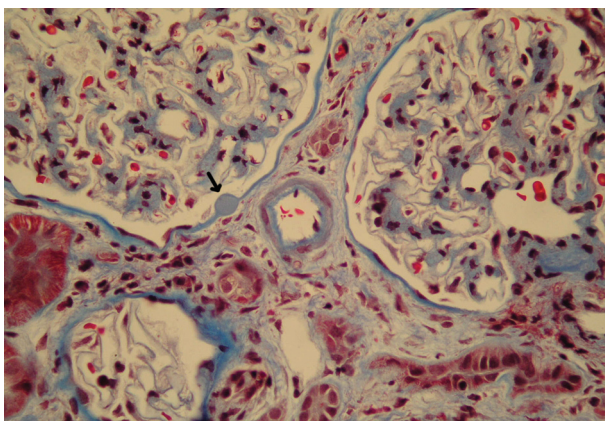
*Fig. 1. Nonproliferative diabetic retinopathy with discrete microaneurysms, hemorrhages and hard exudates.*



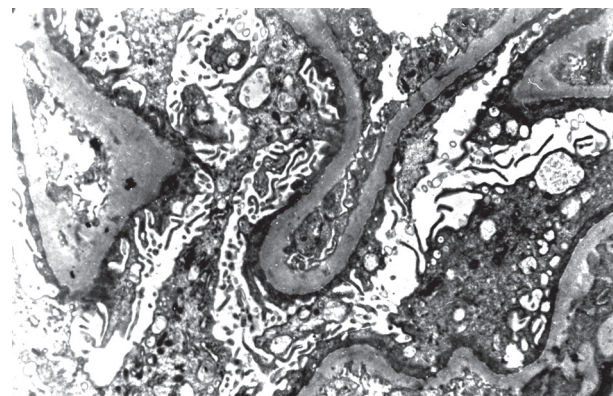
*Fig. 2. Focal segmental glomerulosclerosis. A glomerulus showing perihilar segmental sclerotic lesion (periodic acid Schiff stain, X400).*

of the lower extremities, and later was referred to our hospital for further evaluation of nephrotic syndrome. There was no history of fever, hemophthisis, joint pain, or skin rash. Previous medical history, except for diabetes, was unremarkable. On admission, the patient was pale, weight 105 kg, had elevated blood pressure (160/100 mm Hg), bibasilar lung crackles and generalized edema. He had the following laboratory results: anemia was present with a hemoglobin level of 86 g/L, hematocrit 0.33, and mean corpuscular volume 85.3 fl. Urinary dipstick showed protein + + +, trace red cells; microscopy showed a few granular casts. Liver enzymes were normal and creatinine was 130  $\mu\text{mol/L}$  (reference range

64-109  $\mu\text{mol/L}$ ). The following tests were negative or normal: antinuclear antibody (ANA), hepatitis B surface antigen (HbsAg), hepatitis B core antibody (HbcAb), human immunodeficiency virus antibody (HIV) and prothrombin time (PT). Serum C3 and C4 were in the normal range. Serum protein electrophoresis was abnormal, with low total serum protein (36g/L) and albumin (19 g/L). Protein urine excretion was 20.2 g/day (normal value <0.2 g/day). Ultrasound showed kidneys of normal size with echogenic cortex. Examination of ocular fundus showed nonproliferative diabetic retinopathy with several discrete microaneurysms, dot and blot hemorrhages, and hard exudates (Fig. 1).



*Fig. 3. Diffuse form of diabetic glomerulosclerosis with widespread hyalinization of the mesangial region. Capsular drop is seen (arrow) (Masson trichrome stain; X400).*



*Fig. 4. Focal segmental glomerulosclerosis. There is extensive foot process effacement, cytoplasmic vacuolization and microvillus transformation of podocytes (transmission electron microscopy, X5600).*

### Biopsy findings

Light microscopy: the renal biopsy specimen contained 23 glomeruli, three of which were globally sclerotic. Eight glomeruli showed segmental sclerosis with hyalinosis and foam cells. In five glomeruli involved, perihilar sclerosis was observed (Fig. 2). All other glomeruli had mild to moderate expansion of mesangial matrix (diffuse glomerular sclerosis). Capsular drops were seen in two glomeruli (Fig. 3). Small areas of interstitial fibrosis and tubular atrophy were associated with global glomerular sclerosis. However, the majority of tubules were back to back and had normal morphology. Mild to moderate hyaline arteriosclerosis was affecting both afferent and efferent arterioles.

On immunofluorescence (23 glomeruli), there was focal segmental mesangial positive staining for IgM (+). C3 was positive (++) in Bowman's capsule, blood vessel walls and focally in tubular basement membranes. The reaction for all other antibodies (IgG, IgA, C1q, fibrinogen, kappa and lambda chains) was negative.

On electron microscopy, one glomerulus available for study presented diffuse thickening of the glomerular basement membrane (measuring 550-850 nm, average 700 nm) and slight increase in mesangial matrix. Small mesangial immune deposits were noticed. There was extensive foot process effacement, cytoplasmic vacuolization and microvillous transformation of podocytes (Fig. 4).

According to light, immunofluorescence and electron microscopy findings, a diagnosis of mild to moderate diabetic nephropathy and focal segmental glomerulosclerosis was made. Therapy with corticosteroids, cyclophosphamide, albumin infusion and furosemide, and an angiotensin 2 receptor inhibitor (valsartan) was initiated. Within one month of the introduction of methylprednisolone and cyclophosphamide, the patient experienced massive diuresis and remission of nephrotic syndrome. In October 2005, during evaluation of the disease, the patient was well, without edema, his blood pressure was normal without therapy, and his body weight was 75 kg. His renal function improved (creatinine clearance was normal) and proteinuria was 0.8 g/day. Other laboratory findings were within the normal range.

### Discussion

Glomerulonephritis has been recognized as a rare complication of diabetes mellitus. Once a history of long-standing diabetes has been elicited in patients with renal disease, abnormalities in renal function and struc-

ture are often attributed to diabetic nephropathy, without consideration of further diagnostic possibilities. However, in some diabetic patients a concurrent renal lesion may be superimposed on diabetic nephropathy<sup>1-3,5-9</sup>. Also, it appears that a wide spectrum of nondiabetic renal lesions can occur in patients with diabetes and without diabetic nephropathy<sup>6,9</sup>. Both situations present a diagnostic challenge to clinicians and pathologists. These situations most often occur when primary glomerulonephritis develops in a diabetic patient.

Several reports have shown that immune complex glomerulonephritis can be superimposed on diabetic nephropathy. These glomerulonephritides include idiopathic membranous glomerulonephritis, IgA glomerulonephritis, Henoch-Schönlein nephritis, membranoproliferative glomerulonephritis, lupus nephritis, postinfectious glomerulonephritis, and rapidly progressing glomerulonephritis<sup>1-4,6-10</sup>. Glomerular diseases such as minimal change disease and amyloidosis have also been described with diabetic nephropathy<sup>2,7</sup>. There are only few reports of focal segmental glomerulosclerosis in diabetic patients<sup>2,5,6,11</sup>. Yum *et al.* retrospectively analyzed 18 consecutive renal biopsies from diabetic patients. Eight of these patients were found to have primary glomerulonephritis in addition to diabetic nephropathy. One patient had primary focal segmental glomerulosclerosis in the absence of diabetic retinopathy. In this case, there were no data on immunosuppressive therapy and clinical course of focal segmental glomerulosclerosis either<sup>2</sup>. Izzedine *et al.* also retrospectively analyzed the incidence of diabetic nephropathy in 21 diabetic patients who underwent renal biopsy for microscopic hematuria and/or proteinuria. Six of these patients had focal segmental glomerulosclerosis but without diabetic retinopathy. Again, there are no data on patient treatment with focal segmental glomerulosclerosis<sup>10</sup>. Shimamura *et al.* report on the coexistence of focal segmental glomerulosclerosis and diabetic glomerulopathy. The authors could not exclude focal segmental glomerulosclerosis secondary to advanced diabetic glomerulopathy and/or hypertension. The patient described in this case did not have diabetic retinopathy<sup>5</sup>.

In comparison with all these reports, our patient had primary focal segmental glomerulosclerosis associated with diabetic nephropathy and diabetic retinopathy. The diagnosis of diabetic nephropathy was based on diffuse and nodular glomerulosclerosis on renal biopsy<sup>12</sup>. In the study by Mauer *et al.*, the critical early lesion of diabetic nephropathy was an increase in the volume frac-

tion of mesangium<sup>4</sup>. Capsular drop (a round, eosinophilic accumulation of material between the basement membrane and parietal epithelial cells of Bowman's capsule) is seldom seen in conditions other than diabetes<sup>11,12</sup>. On the other hand, the hyalinosis lesion (the so-called exudative lesion or fibrin cap) that often presents in diabetic patients is not specific for diabetic nephropathy. It is identical to the lesion characteristic of focal and segmental glomerulosclerosis with hyalinosis and may be seen nonspecifically in various forms of glomerulonephritis and reflux nephropathy. Global glomerulosclerosis (scarring) is common in diabetic patients. There are at least two types of glomerular scarring in diabetic patients. The first type has relatively large glomeruli that have accumulated huge amounts of matrix and basement membrane-like material as well as hyaline exudative changes. This type of glomerular scarring always occurs in the context of severe, diffuse or nodular glomerulosclerosis in other glomeruli. The second type has the appearance of small, shrunken, relatively acellular glomeruli with collapsed tufts and wrinkled glomerular basement membrane (the so-called ischemic changes) and is related to arteriolar hyalinosis that in diabetic patients affects both afferent and efferent arterioles<sup>4,12,13</sup>. Although diabetes mellitus is a known cause of secondary focal segmental glomerulosclerosis<sup>14</sup>, according to Mauer *et al.* focal segmental glomerulosclerosis is a rare lesion in diabetic patients<sup>4</sup>. On immunofluorescence, a typical finding in diabetic nephropathy is the occurrence of linear staining along the glomerular capillary walls, usually with immunoglobulin G (IgG) and albumin<sup>11</sup>. The earliest change on electron microscopy is the increase in the thickness of glomerular basement membrane. The epithelial cells show variable effacement of the foot process. There is variable increase in mesangial matrix and deposits of hyalin<sup>12,13</sup>.

Focal segmental glomerulosclerosis is a clinicopathologic entity that takes both primary and secondary forms. It is characterized morphologically by segmental areas of sclerosis in some glomeruli. The sclerotic areas often contain hyalin and foam cells<sup>13</sup>. There are five subtypes of primary focal segmental glomerulosclerosis: 1) focal segmental glomerulosclerosis, not otherwise specified; 2) perihilar variant; 3) cellular variant; 4) tip variant; and 5) collapsing variant<sup>14,15</sup>. On immunofluorescence, in the segmental sclerotic area, IgM is commonly seen, usually in combination with C3. In the unaffected glomeruli, and in the unaffected parts of the tuft with segmental sclerotic lesions, there is no evidence of ei-

ther immunoglobulins or complement other than sporadic weak mesangial staining for IgM. On electron microscopy, the foot process effacement is typically seen. The extent of this change is variable; in some instances it is patchy, and in others widespread. Complete foot process effacement is typically seen in idiopathic focal segmental glomerulosclerosis<sup>16</sup>.

In our patient, because of the development of the severe nephrotic syndrome resistant to albumin infusion and intensive therapy by furosemide, we decided to perform renal biopsy, which showed mild to moderate diabetic nephropathy and focal segmental glomerulosclerosis. Diffuse glomerular sclerosis, capsular drops, hyaline arteriosclerosis affecting both afferent and efferent arterioles, and thickening of the glomerular basement membrane on electron microscopy seen in the biopsy specimen are changes characteristic of diabetic nephropathy. On the other hand, segmental sclerosis with hyalinosis and foam cells in 35% of the glomeruli in the absence of advanced diabetic glomerulosclerosis in our case made it possible to recognize this as a complicating second glomerular disease rather than as part of diabetic glomerulosclerosis, i.e. hyalinosis lesion. The focal segmental mesangial positive staining for IgM on immunofluorescence and extensive foot process effacement on electron microscopy also supported this diagnosis. The excellent response to methylprednisolone and cyclophosphamide confirmed it.

Primary focal segmental glomerulosclerosis accounts for up to 20% of glomerular lesions in adults presenting with proteinuria. Over the last 20 years there has been a marked increase in the incidence of this lesion<sup>17</sup>. This is the reason why we could expect in the future an increased rate of the association of this type of glomerulonephritis with diabetic nephropathy because the incidence of diabetes mellitus in the world is also increasing. The effect of the nondiabetic renal disease on the prognosis depends on the nature of that lesion and the time of its occurrence in the natural history of diabetic nephropathy. We believe that when proteinuria or any other abnormality in renal function appears in a diabetic patient, it deserves close scrutiny rather than being dismissed as diabetic nephropathy. The occurrence of red blood cell casts and hematuria as well as heavy proteinuria are not usual in diabetic nephropathy and require further evaluation. Deterioration of renal function either earlier in the course of diabetes or at a more accelerated pace, such as a decline in glomerular filtration rate exceeding 1 mL *per minute per* month should also

arouse suspicion of a nondiabetic renal disease<sup>6</sup>.

It is generally agreed that renal biopsy should not be performed routinely in diabetic patients who have abnormal urinary test findings or renal function. However, our case and the review of the literature attest to the usefulness of the biopsy in patients carefully selected according to the following criteria: 1) premature appearance of the nephrotic syndrome with a history of diabetes of less than ten years; 2) presence of gross or persistent microscopic hematuria; 3) sudden or rapid deterioration of renal function; and 4) nephrotic syndrome or renal insufficiency in the absence of retinopathy and hypertension<sup>2</sup>.

In conclusion, renal biopsy with complete evaluation (light, immunofluorescence and electron microscopy) remains the only means for detecting a second glomerular disease in diabetic patients, which might alter the natural course, therapeutic approach and prognosis in patients with diabetes mellitus.

## References

- AHUJA TS, VELASCO A, DEISS W, INDRIKOV AJ, RAJARAMAN S. Diabetic nephropathy with anti-GBM nephritis. *Am J Kidney Dis* 1998;31:127-30.
- YUM M, MAXWELL DR, HAMBURGER R, KLEIT SA. Primary glomerulonephritis complicating diabetic nephropathy. *Hum Pathol* 1984;15:921-7.
- BERTANI T, APPEL GB, D'AGATI V, NASH MA, PIRANI CL. Focal segmental membranous glomerulopathy associated with other glomerular diseases. *Am J Kidney Dis* 1983;2:439-48.
- MAUER SM, BILIOUS RW, ELLIS E, HARRIS R, STEFFES MW. Some lesson from the studies of renal biopsy in patients with insulin-dependent diabetes mellitus. *J Diabetes Complications* 1988;2:197-202.
- SHIMAMURA T, LeFAVOUR GS, EISINGER RP. Coexistence of focal segmental glomerulosclerosis and diabetic glomerulopathy. *Pathol Int* 1995;45:257-8.
- KASINATH BS, MUJ AIS SM, SPARGO BH, KATZ AI. Non-diabetic renal disease in patients with diabetes mellitus. *Am J Med* 1983;75:613-7.
- BERTANI T, OLESNICKY L, ABU-REGIABA S, GLASBERG S, PIRANI CL. Concomitant presence of three different glomerular diseases in the same patient: report of a case and review of the literature. *Nephron* 1983;34:260-6.
- CHIHARA J, TAKEBAYASHI S, TAGUCHI T, YOKOYAMA K, HARADA T, NAITO S. Glomerulonephritis in diabetic patients and its effect on the prognosis. *Nephron* 1986;43:45-9.
- OLSEN S, MOGENSEN CE. How often is NIDDM complicated with non-diabetic renal disease? An analysis of renal biopsies and the literature. *Diabetologia* 1996;39:1638-45.
- IZZEDINE H, FONGORO S, PAJOT O, BEAUFILS H, DERAY G. Retinopathy, hematuria, and diabetic nephropathy. *Nephron* 2001;88:382-3.
- OLSON JL. Diabetes mellitus. In: JENNETTE JC, OLSON JL, SCHWARTZ MM, SILVA FG, eds. *Heptinstall's Pathology of the kidney*. 5<sup>th</sup> ed. Philadelphia, New York: Lippincott-Raven Publishers, 1998; pp. 1247-86.
- HEPTINSTALL RH. Diabetes and gout. In: HEPTINSTALL RH, ed. *Pathology of the kidney*. 3<sup>rd</sup> ed. Boston, Toronto: Little Brown and Company, 1983; pp. 1397-454.
- OLSON JL, SCHWARTZ MM. The nephrotic syndrome: minimal change disease, focal segmental glomerulosclerosis and miscellaneous causes. In: JENNETTE JC, OLSON JL, SCHWARTZ MM, SILVA FG, eds. *Heptinstall's Pathology of the kidney*. 5<sup>th</sup> ed. Philadelphia, New York: Lippincott-Raven Publishers, 1998; pp. 187-257.
- D'AGATI VD, FOGO AB, BRUIJIN JA, JENNETTE JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004;43:368-82.
- ROSSINI M, FOGO AB. Interpreting segmental glomerular sclerosis. *Curr Diagn Pathol* 2004;10:1-10.
- AZIZ SA, COHEN AH, WINER RL, LLACH F, MASSRY SG. Diabetes mellitus with immune complex glomerulonephritis. *Nephron* 1979;23:32-37.
- KORBET SM. Primary focal segmental glomerulosclerosis. *J Am Soc Nephrol* 1998;9:1333-40.



## Sažetak

## DIJABETIČNA NEFROPATIJA S FOKALNOM SEGMENTNOM GLOMERULOSKLEROZOM

K. Galešić, D. Ljubanović, J. Pavan i I. Račić

Udruženost dijabetične nefropatije s primarnim glomerulonefritisom rijetka je kod šećerne bolesti tip 1. Nekoliko izvješća pokazuje da se primarni glomerulonefritis može razviti na osnovi dijabetične nefropatije. Ovi glomerulonefritisi obuhvaćaju idiopatski membranski glomerulonefritis, IgA glomerulonefritis, Henoch-Schönleinov nefritis, membranoproliferacijski glomerulonefritis, lupus nefritis, bolest minimalne promjene, postinfekcijski glomerulonefritis i brzo progredirajući glomerulonefritis. Kako neke od ovih bolesti mogu promijeniti liječenje i prognozu bubrežne bolesti kod dijabetičnih bolesnika, patološki nalaz u mokraći ili pogoršanje bubrežne funkcije koji nisu u skladu s naravom dijabetične nefropatije ukazuju na mogućnost nedijabetične bubrežne bolesti i zahtijevaju detaljniju procjenu. Opisuje se bolesnik sa šećernom bolešću tip 1 kod kojega je napravljena biopsija bubrega zbog teške proteinurije i nefrotskog sindroma. Biopsija bubrega je pokazala dijabetičnu nefropatiju, ali i fokalnu segmentnu glomerulosklerozu. Prema našim saznanjima, ovo je prvi objavljeni slučaj primarne žarišne segmentne glomeruloskleroze udružene s dijabetičnom nefropatijom i dijabetičnom retinopatijom, s izvrsnim odgovorom na terapiju.

**Ključne riječi:** *Glomeruloskleroza, fokalna – komplikacije; Glomeruloskleroza, fokalna – dijagnostika; Glomeruloskleroza, fokalna – terapija; Dijabetične nefropatije – dijagnostika; Dijabetične nefropatije – imunologija; Dijabetične nefropatije – terapija; Bubrež, glomeruli – patologija*