

Minimal Change Nephrotic Syndrome Superimposed on Type 2 Diabetic Glomerulosclerosis

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Introduction

Diabetic nephropathy is one of the most important causes of end-stage renal disease that requires renal replacement therapy and accounts for more than 40% of the new cases in Japan and Western countries [1]. In particular, the prevalence of type 2 diabetic nephropathy in end-stage renal failure has rapidly increased [2]. Patients with type 2 diabetes are also known to have non-diabetic glomerular diseases with a reported incidence of 25–35% [3]. Stoycheff et al. [4] reported that 44% of patients with type 2 diabetic nephropathy and proteinuria greater than 0.9 g/day had nephrotic-range heavy proteinuria. However, the exact prevalence of nephrotic syndrome in patients with macroalbuminuric diabetic nephropathy and non-diabetic glomerular disease associated with nephrotic syndrome in patients with type 2 diabetes mellitus remains uncertain.

Unlike type 1 diabetes, clinical progression to diabetic nephropathy is not apparent in type 2 diabetes because of the difficulty in determining the acute onset of diabetes itself [5]. In addition, diabetic nephropathy does not usually cause hematuria, similar to minimal change nephrotic syndrome (MCNS) and membranous nephropathy (MN) [6-8], which are representative glomerular diseases known to cause nephrotic syndrome [9]. Therefore, it is sometimes difficult to differentiate MCNS and MN from diabetic nephropathy, especially in middle- to advanced-aged patients with type 2 diabetes; even nephrologists occasionally overlook patients with MCNS or MN, or incorrectly diagnose them with diabetic nephropathy.

Minimal change nephrotic syndrome superimposed on histologically diagnosed type 2 diabetic glomerulosclerosis

MCNS is a major cause of idiopathic nephrotic syndrome in children and adults [9,10]. The onset of disease is usually rapid, and it is characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, generalized edema, and, as visualized by light microscopy, minimal glomerular changes [11]. Generalized foot process effacement can also be observed under electron microscopy. Clinically, nephrotic syndrome shows a favorable response to steroid therapy. Overt diabetic nephropathy caused by diabetic glomerulosclerosis (DGS) first appears 10–15 years after the onset of type 1 diabetes and 5–10 years after the onset of type 2 diabetes [12]. In the early stages of the disease, the glomeruli appear normal under light microscopy, but electron microscopy reveals basement membrane thickening. As time passes, diffuse mesangial expansion appears to be associated with an increase in Periodic Acid Schiff (PAS)-positive matrix material. This material is central to the tuft, but it later expands and effectively obliterates the capillaries, leading to global glomerulosclerosis. Nodules, which were the first glomerular pathologic abnormality described by Kimmelstiel and Wilson [13], seldom appear before 15 years of duration of diabetes. Although these nodules are considered diabetes-specific for practical purposes, they are also occasionally observed in other renal diseases, such as monoclonal immunoglobulin deposition disease, membranoproliferative glomerulonephritis, and idiopathic nodular glomerulosclerosis [14,15].

In a review of a literature, Stokes [16] referred to 22 cases of MCNS in diabetic patients, all of which had sufficient clinical and/or pathologic data to support a diagnosis of MCNS in the setting of diabetes. He concluded that majority of the reported MCNS cases of diabetics were children, who presented with nephrotic syndrome either simultaneously with, shortly after, or prior to the diagnosis of insulin-dependent type 1 diabetes mellitus. To our knowledge, only four cases of MCNS have been reported in patients with adult-onset type 2 diabetes to date [17-20]. We reported five other cases in addition to these [21]. Table 1 shows the clinical and histological characteristics of these nine patients. They were 57.4 ± 8.9 (mean \pm SD) years of age with 9.1 ± 6.9 years of diabetes, and a glycated hemoglobin assay (HbA1c) score of $7.3 \pm 2.0\%$. All the patients achieved complete remission. Six of them were treated with prednisolone (PSL), while two were treated with cyclosporine A (CsA) alone. One patient (Patient 5) was initially treated with CsA alone but showed no response; accordingly, the treatment was switched to PSL alone instead of CsA. Three patients (Patients 5, 6, and 9) diagnosed with mild DGS also had diabetic retinopathy. Three other patients (Patients 1, 3, and 4) were undergoing treatment with insulin. All nine patients showed a sudden increase in proteinuria or a sudden appearance of edema during the clinical course. These observations indicate that the presence of diabetic retinopathy should not always be considered as a factor to exclude non-diabetic glomerular diseases, especially when the sudden onset of nephrotic syndrome is evident; however, diabetic retinopathy has been reported to correlate well with overt diabetic nephropathy [22,23].

Five patients (Patients 2, 3, 5, 6, and 9) were diagnosed with DGS by light microscopy. The case of Patient 5 was particularly interesting because of the presence of nodular lesions despite a segmental distribution pattern (Figure 1). Pabico et al. [24] reported a case, also in a patient with type 1 diabetes, of nodular DGS who underwent spontaneous remission in the clinical course. These observations suggest that nodular glomerular lesions in diabetic patients are not necessarily always associated with proteinuria. In seven of the nine patients, electron microscopy revealed diffuse foot process effacement. In all patients diagnosed with DGS by light microscopy, the glomerular basement membrane (GBM) was diffusely and markedly thickened, measuring >850 nm in thickness (Figure 2) compared with 300–400 nm in normal adults [15]. Four patients (Patient 1, 4, 7, and 8; Table 1) were diagnosed with minor glomerular abnormalities by light microscopy,

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Patient	1	2	3	4	5	6	7	8	9
Gender	M	M	M	M	M	F	M	F	M
Age ^a (years)	38	62	67	62	55	61	51	65	56
Duration of diabetes ^a (years)	15	4	2	10	Not known	15	5	2	20
HbA1c ^a (%)	n.a.	5.6	n.a.	7.7	6.0	5.9	8.6	6.2	11.2
Retinopathy ^a	n.a.	n.a.	-	-	+	+	-	-	+
Insulin therapy ^a	+	-	+	+	-	-	-	-	-
Increase in proteinuria and/or appearance of edema	sudden	sudden	sudden	sudden	sudden	sudden	sudden	sudden	sudden
Therapy	PSL	CsA	CsA	PSL	CsA → PSL	PSL	PSL	PSL	PSL
Outcome	CR	CR	CR	CR	CR	CR	CR	CR	CR
LM	MGA	DGS	DGS	MGA	DGS	DGS	MGA	MGA	DGS
EM	GBM thickening	GBM thickening	Mesangial matrix ↑ GBM 850 nm	n.a.	No glomeruli	Mesangial matrix ↑ GBM 1000 nm	GBM 600 nm	GBM 600 nm	Mesangial matrix ↑ GBM 800 nm
Reference	[16]	[17]	[18]	[19]	[20]	[20]	[20]	[20]	[20]

^aAt the time of renal biopsy.

CsA, cyclosporine A; PSL, prednisolone; CR, complete remission; DGS, diabetic glomerulosclerosis; MGA, minor glomerular abnormalities, GBM, glomerular basement membrane; n.a., not available

Table 1: Clinical and pathologic findings in patients with minimal change nephrotic syndrome superimposed on diabetic glomerulosclerosis.

but electron microscopy performed in three of these patients showed a diffusely thickened GBM (Figure 3), which is a characteristic finding in early diabetic nephropathy [25].

With regard to distinguishing MCNS superimposed on diabetic nephropathy from nephrotic syndrome caused by diabetic nephropathy; it takes 10–15 years for microalbuminuria (30–300 mg/day) to progress to overt proteinuria (>300 mg/day), and additional years to achieve nephrotic-range proteinuria, in diabetic nephropathy. In addition, proteinuria in patients with diabetic nephropathy increases “slowly and gradually” over time [26], unlike in MCNS. In type 2 diabetes, however, this argument is occasionally unreliable, because the onset of the disease is frequently obscure. Renal biopsy is a diagnostic option in such a situation [27]. Recently, it was reported that urinary concentration of β 2-microglobulin (β 2-MG), a recognized marker of renal tubular damage or dysfunction, was high in diabetic patients with micro- and macroalbuminuria, and reliably differentiated diabetic nephropathy from non-diabetic glomerular diseases [28–30]. We compared the urinary β 2-MG concentrations among MCNS Patients 5–9 (Table 1) and selected patients with nephrotic syndrome caused by DGS (n = 7) from our institute whose serum creatinine levels and ages were similar to Patients 5–9 (MCNS Patients 5–9 versus new group:

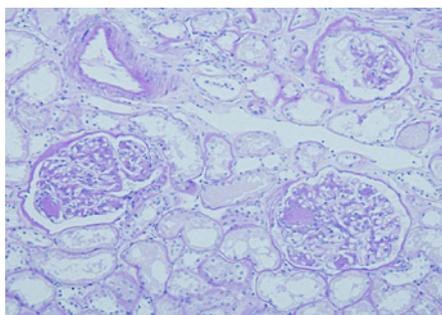


FIGURE 1: Light microscopy findings in Patient 5 diagnosed with diabetic glomerulosclerosis (Table 1). Note the segmental distribution of multiple, small nodular lesions, together with a mild mesangial matrix expansion. PAS staining; original magnification: 100 \times .

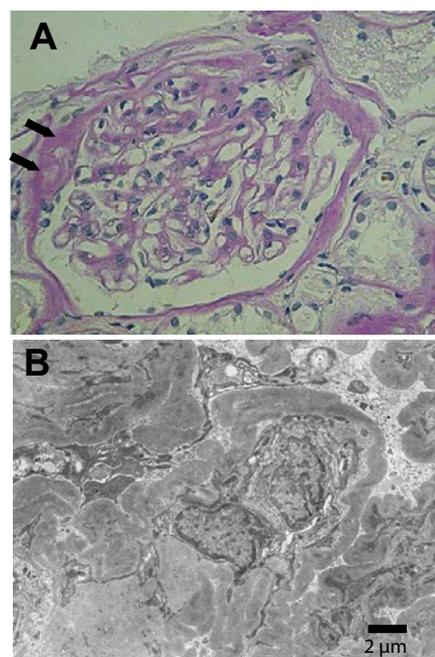


FIGURE 2: Light and electron microscopy findings of Patient 2 diagnosed with diabetic glomerulosclerosis (Table 1). (A) Note the slight increase in mesangial matrix and irregular thickening of the capillary walls, and also, the capsular drop on the thickened Bowman’s capsular epithelium (arrow). (B) Electron microscopy showing a diffuse and marked thickening of the glomerular basement membrane (around 1000 nm); mesangial matrix expansion; and diffuse effacement of the podocytes of foot processes. (A): PAS staining; original magnification: 300 \times .

0.87 ± 0.22 (mean \pm SD) versus 0.81 ± 0.25 mg/dl of serum creatinine and 57.6 ± 5.5 versus 55.0 ± 13.3 years of age). The concentration of urinary β 2-MG was significantly lower in the MCNS group than the DGS group (Figure 4; $p < 0.01$) (unpublished data). These results suggest that urinary β 2-MG concentration is a useful diagnostic tool to distinguish patients with MCNS superimposed on early diabetic nephropathy from those with nephrotic syndrome caused by diabetic nephropathy.

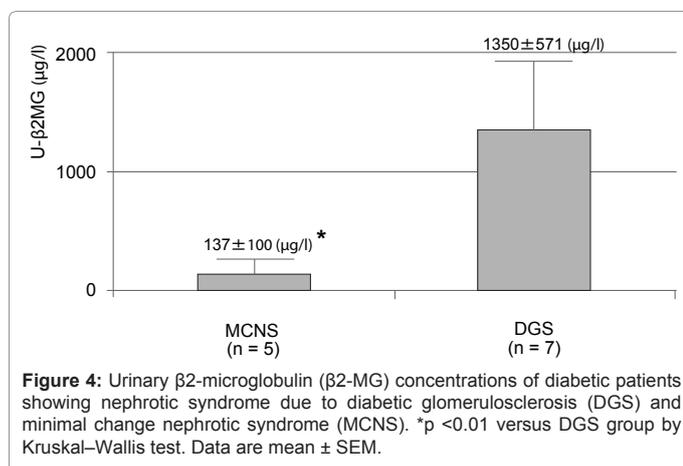
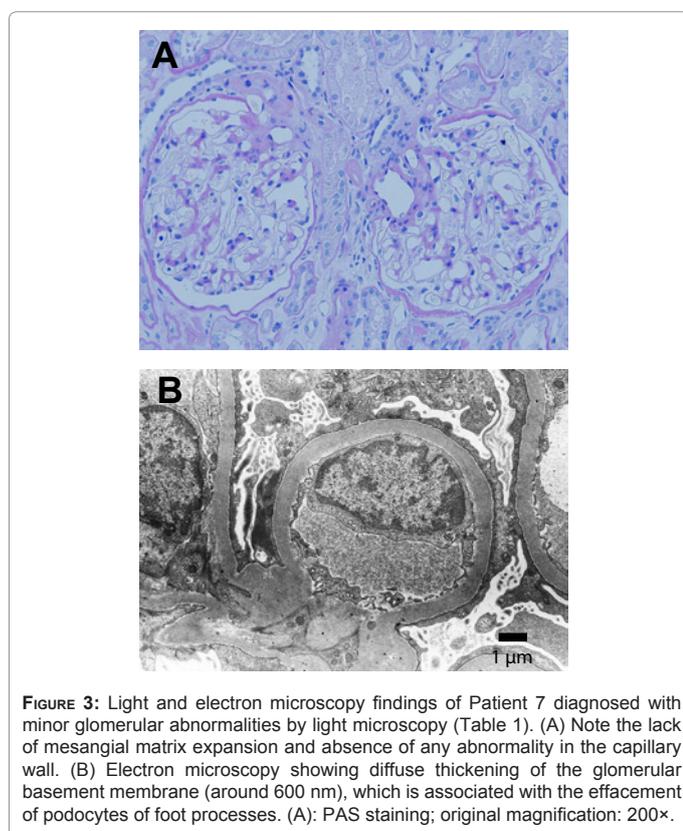
Conclusion

It is important to differentiate MCNS from nephrotic syndrome caused by diabetic nephropathy, because MCNS responds well to steroid or immunosuppressant therapy but the differential diagnosis is occasionally difficult. We should take into consideration the time course of the appearance of heavy proteinuria or edema (sudden or gradual) and the speed of increase in proteinuria in patients with type 2 diabetes mellitus showing nephrotic syndrome, and appreciate that proteinuria in patients with diabetic nephropathy increases slowly and gradually over time. When the time course of diabetes mellitus or the appearance of proteinuria is uncertain, renal biopsy should be considered. However, nephrologists should bear in mind that renal biopsies in a few cases of MCNS show nodular lesions. We propose

measuring urinary β 2-MG concentration as a helpful laboratory method to differentiate MCNS from nephrotic syndrome caused by DGS in diabetic patient.

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