Diabetic nephropathy with primary membranous nephropathy: A case report

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Abstract
Diabetic nephropathy (DN) is one of the most common microvascular diseases in diabetes. Primary membranous nephropathy (PMN) is one of the most common causes of nephrotic syndrome (NS) in adults. Incidence of DN and PMN are increasing. DN complicated with PMN is rarely reported. We report a case of DN with PMN. Early diagnosis is very important, and appropriate treatment can often achieve good results.

Keywords
diabetic nephropathy • primary membranous nephropathy • kunxian capsule

1. Introduction
Diabetic nephropathy (DN) is one of the most common microvascular diseases in diabetes, and is the leading cause of end stage renal disease worldwide [1, 2]. It is characterized by basement membrane thickening, mesangial expansion and stromal hyperplasia, glomerulosclerosis and arteriolar hyalinosis in renal tissue, microalbuminuria, massive proteinuria, and renal function injury in clinical manifestation [3]. Primary membranous nephropathy (PMN) is one of the most common causes of nephrotic syndrome (NS) in adults, accounting for 30%-40% of all NS cases. Its incidence is rapidly increasing, especially in younger patients [4–6]. The incidences of DN and PMN are increasing. DN complicated with PMN is rarely reported. We report a case of DN with PMN.

2. Case Report
2.1. Clinical presentation
A 40-year-old woman with a medical history of type 2 diabetes mellitus (T2DM) for 6 years was evaluated at the nephrology clinic of this hospital because of lower extremities’ edema and a proteinuria positive status for 4 d. Six years ago, the patient had been diagnosed with T2DM, which was accompanied by polydipsia, polyuria, thirst, and a blood glucose level of 12 mmol/L, and had received metformin-with-glipizide therapy. Blood glucose, renal function, and urine routine were not monitored regularly. Four days ago, she developed mild edema of both lower limbs without obvious cause, and routine urine examination conducted at the local hospital indicated protein 3+ and sugar 1+. She had no hematuria, no oliguria, no symptoms of heart failure, no urinary tract irritation, and no fatigue or gastrointestinal symptoms. She denied hypertension, heart disease, and cerebrovascular disease, and she also denied a history of kidney problems or a family history of kidney disease. She had been diagnosed with tuberculosis 10 years ago and had recovered after formal treatment.

On physical examination, her temperature was 36.2°C, heart rate was 89 beats/min, blood pressure was 126/97 mmHg, height and weight were 156 cm and 99 kg, respectively, and the oxygen saturation was 100% while she was breathing ambient air. There was bilateral lower extremity pitting edema. There were no other findings on physical examination.

Her lab data showed a serum creatinine of 75.2 μmol/L, a serum albumin level of 42.1 g/L, and a 24-h urine protein of 1.56 g, while urine analysis showed urine blood 2+, an RBC count of about 2–3/high-power field (HPF), and no red cell casts. Laboratory tests also revealed poorly controlled diabetes with a fasting blood glucose level of 6.48–9.83 mmol/L, and an HbA1c level of 7.4%. Her M-type phospholipase A2 receptor (PLA2R) was 2.5 RU/mL.

Coagulation function, thyroid function, myocardial enzyme spectrum, and plasma complement C3 and C4 were normal. hepatitis B virus (HBV), hepatitis C virus (HCV), anti-nuclear antibody, extractable nuclear antigen (ENA) antibody spectrum, ENA antibody spectrum, anti-neutrophil cytoplasmic antibody, antiphospholipid antibody, rheumatoid factor, and tumor marker detection were all negative.

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The volume of the left kidney was 112 mm × 45 mm, and that of the right kidney was 115 mm × 41 mm. Chest computed tomography showed old pulmonary tuberculosis in the upper lobe of the left lung. The clinical differentials at the time of the biopsy included DN and other primary glomerulonephritides, especially membranous nephropathy, and focal segmental glomerulosclerosis. So, renal biopsy was performed to confirm the pathological diagnosis.

2.2. Pathological findings

The renal biopsy contained 19 glomeruli, and 2 were globally sclerotic.

Light microscopy showed mesangial cells and stroma proliferated slightly, segmental aggravation, and capillary loops opened well (Figure 1A). Renal tubular and interstitial lesions were moderate with multifocal tubular atrophy, tubular epithelial cell detachment, and interstitial inflammatory cell infiltration and fibrosis, and protein tube type can be seen in the small lumen (Figure 1B). The arteriole wall was highly thickened and arteriolar hyalinosis was also observed (Figure 1C).

Immunofluorescence showed slightly thin linearly staining in the glomeruli with IgG+, C3±, κ+, and λ+ (Figure 1D and E). Electron microscopy showed that the glomerular basement membrane was segmental uniformly thickened, the inner loose layer was thickened, the electron density under the epithelium and in the glomerular basement membrane was deposited about 30%, and the epithelial foot process segments were fused (Figure 1F and G). The overall findings documented PMN (I stage) and early diabetic glomerulopathy.

2.3. Treatment and outcome

At commencement of treatment, the patient was started on metformin, glimepiride, acarbose to monitor and control blood glucose, and metoprolol and atorvastatin to control blood pressure and blood lipid level. Half a month later, the serum creatinine was 96.3 μmol/L, the serum albumin level had decreased to 32.6 g/L, and the 24-h urine protein had increased to 2.37 g; we gave the patient a low-dosage steroid therapy (prednisone 20 mg/d) and a traditional Chinese medicine, Kunxian capsule (KXC) (0.6 g/time, 3 times/d). Serum creatinine, serum albumin, and 24-h urinary protein level had significantly improved. Post-follow-up for 1 year, the prednisone and KXC administration were tapered off gradually, while the above parameters maintained stable (Figure 2).

3. Discussion

DN is one of the common complications of diabetes mellitus (DM) and one of the main causes of death in DM patients [7]. The pathogenesis of DN is extremely complex. The patient in the present case has remained with a diagnosis of DM for 6 years with poor blood glucose control. Fundus examination suggested diabetes retinopathy (DR) with scattered patchy hemorrhage and exudation in the retina. It was considered...
that the fundus changes are caused by DM [7]. DN and DR are 50% synchronous [8], and so this patient cannot be directly diagnosed with DN.

PMN is an autoimmune disease that is characterized by the production of autoantibodies. Within the total study population reflected in the literature, 80% shows NS, whereas 20% non-nephrotic proteinuria or chronic nephritis [9]. PLA2R is found in 70%–80% of PMN patients and correlated with clinical evolution, response to treatment, and renal survival [10]. The PLA2R level of this patient was normal, and so we need renal biopsy to further clarify the diagnosis.

In the patient’s biopsy report, there were not found the typical features of Kimmelstiel–Wilson nodules, but there existed mesangial cells and stroma proliferated slightly, interstitial inflammatory cell infiltration, arteriolar hyalinosis, thickened glomerular basement membrane, and the electron density in the basement membrane; accordingly, the final diagnosis was PMN (I stage) and early diabetic glomerulopathy.

In recent years, a prominent scholarly opinion has been that DN is a chronic inflammatory disease caused by metabolic and immune factors [11,12]. Anti-inflammatory and anti-immune therapy is gradually applied to DN [13]. KXC is a plant of the same family of *Tripterygium wilfordii* (*T. Wilfordii*), which has anti-inflammatory and anti-immune effects, but its toxicity is less than that of *T. Wilfordii*. Some scholars used KXC in the treatment of DN, IgA nephropathy, and lupus nephritis and found that it can significantly reduce proteinuria and improve clinical symptoms, and this effect is related to reduction in the expression of inflammatory factors and inhibition of inflammatory response [14,15].

For this patient, because of increasing serum creatinine, increasing proteinuria, and interstitial inflammatory cell infiltration, she received a small dosage of prednisone but a full dosage of KXC. Resultantly, there was a perceptible improvement in the patient’s renal function and proteinuria, thus allowing us to conclude the efficacy of this treatment regime. We speculate that the treatment’s effectiveness is related to the mechanism of anti-inflammation and immune regulation made available by prednisone and KXC. The patient is still being followed-up and the prognosis still needs further evaluation.

4. Conclusion

DN with primary glomerulonephritis is not uncommon. Early diagnosis is very important, and appropriate treatment can often achieve good results.

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Ethics Approval and Consent to Participate

The research was approved by the Ethics Committee of The First Affiliated Hospital of Xinxiang Medical University (EC-021-172) and the patient signed consent to participate.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References