OBSERVATIONS

Role of Anti-Phospholipase A(2) Receptor Antibodies in the Differential Diagnosis of Diabetic and Membranous Nephropathy

Diabetic nephropathy and membranous nephropathy can both present with nephrotic syndrome. Here, we report on a 43-year-old female patient suffering from type 1 diabetes, diabetic retinopathy, arterial hypertension, and nephrotic syndrome. Blood glucose levels were poorly controlled by a basal-bolus insulin regimen as shown by an HbA_{1c} of 15.9% (150 mmol/mol). The concomitant antihypertensive medication consisted of an angiotensin-2 receptor blocker, a β-blocker, a calcium antagonist, and furosemide. In March 2012, her serum creatinine and urine albumin-to-creatinine ratio were 1.06 mg/dL and 7 g/g, respectively. Until December 2012, both serum creatinine and albuminuria increased to 1.9 mg/dL and 11 g/g urinary creatinine, respectively. The estimated glomerular filtration rate via the MDRD-2 formula (Modification of Diet in Renal Disease) declined from 56 to 28 mL/min/1.73 m^2. Furthermore, she presented with aggravated leg oedemas, hypoalbuminemia of 2.4 mg/dL, hypertriglyceridemia, and hypertension reflecting nephrotic syndrome. Urinary cytology showed acanthocytes and granulated cylinders, and ultrasound of the kidney revealed both kidneys to be within normal range. The most prevalent renal diagnosis in long-term poorly controlled type 1 diabetes is diabetic nephropathy with Kimmelstiel-Wilson nodular glomerulosclerosis. Therefore, kidney biopsy is often avoided because of the high bleeding risk. Because of the progressive deterioration of renal function and the pathological urinary sediment, we searched for other causes of the nephrotic syndrome. In order to differentiate diabetic from membranous nephropathy, we measured anti-phospholipase A(2) receptor (PLA2R1) antibodies and found high PLA2R1 serum titres (4+), which have a high sensitivity and specificity for idiopathic membranous nephropathy (1,2). Surprisingly, kidney biopsy did not confirm the diagnosis of idiopathic membranous nephropathy. Rather, kidney histology showed extensive glomerular and vascular sclerotic changes attributable to diabetes and hypertension (Fig. 1*A* and *B*). There were no spikes on the glomerular basement membrane detectable in the silver stain (Fig. 1*C*). Immunofluorescence was negative for IgG (data not shown), IgG4 (Fig. 1*C*), and IgA as well as C3, C4d, and C1q (data not shown). In line, electron microscopy did not show subepithelial immune complex deposits reflecting membranous nephropathy (Fig. 1*D* and *E*). This result had a significant impact on the therapy of our patient. Firstly, we did not treat the patient with immunosuppressive agents such as calcineurin inhibitors or rituximab, which are used for the treatment of idiopathic membranous nephropathy (rev. in 3). In contrast, we tried to optimize antihypertensive and insulin treatment regimens. Secondly, we listed our patient for combined kidney and pancreas transplantation. Idiopathic membranous nephropathy has been shown to relapse in 40–50% of kidney transplant recipients with idiopathic membranous nephropathy (4,5). Thus, it is of major importance

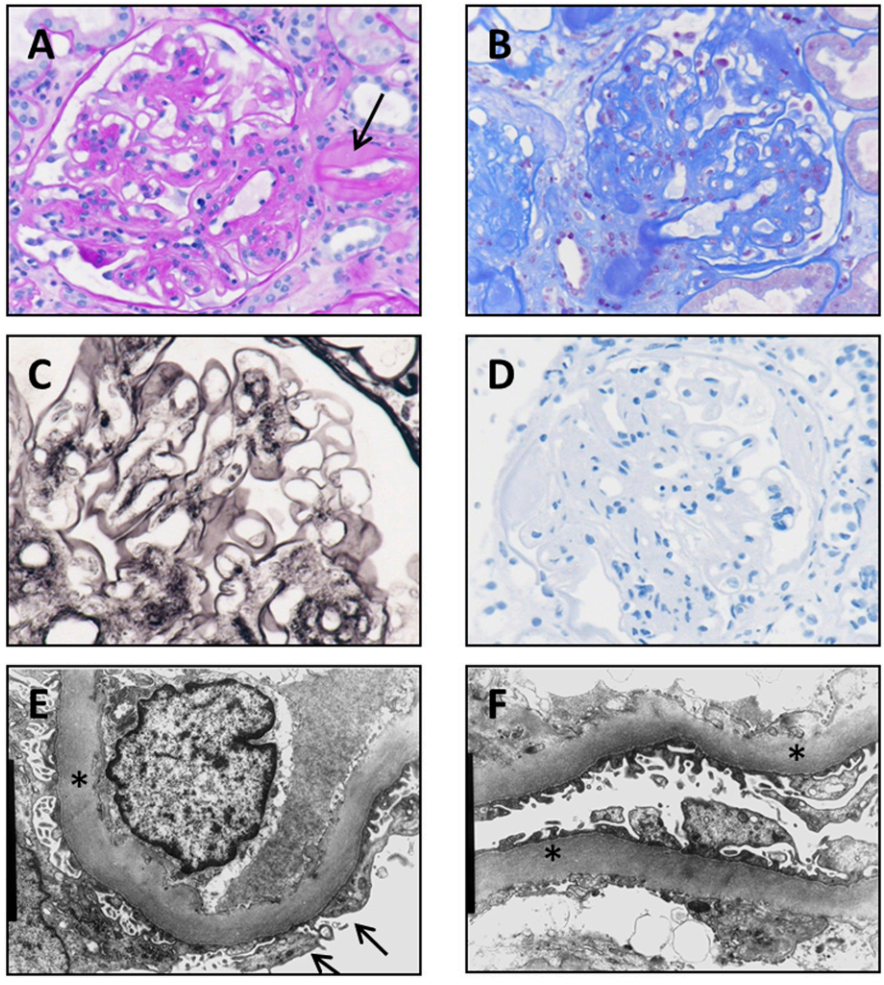

Figure 1—*Histological evaluation of the kidney biopsy.* A*: Kidney biopsy showed mesangial matrix accumulation, a slight increase in mesangial cellularity, and capillary basement membrane thickening. The arteriole shows marked hyalinosis of the wall (arrow).* B*: Extensive glomerular sclerosis is shown in the acid fuchsin orange G stain.* C*: There are no spikes on the glomerular basement membrane seen in the silver stain.* D*: IgG4 staining remained negative.* E *and* F*: Electron microscopy shows a nonspecific, uniform thickening of the basement membranes (*) and only focally attenuated podocyte foot processes (arrow). No subepithelial deposits in the sense of membranous nephropathy were detectable.*

to differentiate whether the patients suffer from diabetic nephropathy or idiopathic membranous nephropathy.

In summary, this case of diabetic nephropathy with high PLA2R1 titres puts the specificity of PLA2R1 antibodies for membranous nephropathy into perspective. Thus, kidney biopsy is still mandatory in the differential diagnosis of diabetic and membranous nephropathy, since PLA2R1 testing might lead to false positive results. Further studies are needed to evaluate whether patients suffering from type 1 diabetes are prone to display false positive results in PLA2R1 testing owing to interacting antibodies.

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