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Immunoglobulin A Nephropathy in Patients with Non-Insulin Dependent Diabetes Mellitus

The occurrence of immunoglobulin A nephropathy (IgAN) in patients with non-insulin dependent diabetes mellitus (NIDDM) is a rare event and of pathogenetic interest. It is not clear whether this is merely coincidence. We report here five patients with IgAN in NIDDM associated with or without diabetic glomerulosclerosis. All of the patients were Korean males. In three patients, diabetes mellitus was diagnosed at the same time with diagnosis of IgAN, and the known duration of the diabetes in the other two patients were three and seven years, respectively. There was no evidence of diabetic retinopathy in four patients, but it was found in one patient. In all cases, the diagnosis of IgAN was made by immunohistology.

Key Words: *Glomerulonephritis, IgA; Diabetes mellitus, non-insulin dependent*

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INTRODUCTION

First described in 1968 by Berger and Hinglais (1), immunoglobulin A nephropathy (IgAN) is now recognized as the most common primary glomerulonephritis in the world (2). Since the original description of the glomerulopathy, idiopathic IgAN has received the bulk of attention in medical literature, and many diseases have been reported which are sporadically associated with mesangial IgA deposition (3). Diabetic nephropathy is a form of glomerulopathy commonly seen in patients with longstanding diabetes mellitus (DM). However, in some patients a sudden onset of proteinuria, atypical urinary sediment or rapid deterioration of renal function may occur, suggesting that non-diabetic renal disease may be superimposed on diabetic nephropathy (4). Until now, IgAN in DM has rarely been reported (4-7). Therefore we report here five patients with IgAN in non-insulin dependent diabetes mellitus (NIDDM).

MATERIALS AND METHODS

Between 1992 and 1998, 475 renal biopsies were performed in our department and 22 NIDDM patients were identified (4.6%). The diagnosis of NIDDM was made when basal C-peptide $\geq$1.0 ng/mL, age of the onset of NIDDM $\geq$30 years and no known history of diabetic ketoacidosis (8). Renal tissues in all patients studied were examined for light, immunofluorescent, and/or electron microscopies by standard methods. The diagnosis of IgAN was made when solely or predominantly IgA-containing immune complexes were detected in the mesangium by immunofluorescent microscopy.

CASE REPORTS

Case 1

A 58-year-old Korean male presented with gross hematuria and generalized edema. There was no known history of NIDDM, diabetic ketoacidosis or hypertension, but he had old pulmonary tuberculosis. On physical examination, the patient appeared puffy and had pretibial pitting edema was noted. Laboratory findings were as follows (Table 1): serum creatinine 1.4 mg/dL, albumin 2.7 g/dL, cholesterol 307 mg/dL, aspartate aminotransterase 47 IU/L, alanine aminotransferase 72 IU/L, fasting blood glucose 119-228 mg/dL, and basal C-peptide 3.7 ng/mL. Urinalysis revealed protein (+++), specific gravity 1.020 with many red blood cells, granular, hyaline and fatty casts per high power field. Twenty-four hr urinary protein excretion was 6,113 mg. A kidney biopsy showed the presence of mesangial hypercellularity and focal or global cellular crescents in four of 15 glomeruli. Immu-

Table 1. Summary of clinical and laboratory findings

Patient No.	Age/Sex (years)	Duration of DM (years)	Creatinine (mg/dL)	IgA (mg/dL)	Proteinuria (mg/day)	Hematuria (/HPF)
1	58/M	0	1.4	328	6,113	Many
2	43/M	0	1.2	389	796	Many
3	36/M	0	0.9	527	3,588	Many
4	56/M	3	2.0	423	2,530	Many
5	47/M	7	2.8	268	11,450	Many

nofluorescent microscopy showed fine granular mesangial deposits composed of IgA (+++), IgM (+), C3 (+) and fibrinogen (++). After the administration of steroid, the edema disappeared, but urinalysis continued to reveal persistently protein (+++), specific gravity 1.020 with many red blood cells per high power field.

Case 2

A 43-year-old Korean male was admitted for microscopic hematuria and proteinuria evaluation. Three years ago, he had been treated for renal tuberculosis. There was no known history of NIDDM, diabetic ketoacidosis or hypertension. Physical examination was unremarkable. Laboratory findings were as follows (Table 1): serum creatinine 1.2 mg/dL, albumin 4.5 g/dL, fasting blood glucose 216 mg/dL, and basal C-peptide 5.9 ng/mL. Urinalysis revealed protein (+), specific gravity 1.020 with many red blood cells per high power field. A kidney biopsy showed mesangial hypercellularity and mesangial matrix widening. Immunofluorescent microscopy showed moderate mesangial deposits composed of IgA, IgG and C3. No specific therapy was instituted.

Case 3

A 36-year-old Korean male presented with peripheral edema. There was no known history of NIDDM, diabetic ketoacidosis or hypertension. On physical examination, pretibial pitting edema was noted. Laboratory findings were as follows (Table 1): serum creatinine 0.9 mg/dL, albumin 2.7 g/dL, cholesterol 328 mg/dL, fasting blood glucose 249 mg/dL, and basal C-peptide 5.7 ng/mL. Urinalysis revealed protein (+++), specific gravity 1.020 with many red blood cells per high power field. Twenty-four hr urinary protein excretion was 3,588 mg. There was no evidence of diabetic retinopathy on funduscopic examination by an ophthalmologist. There was no evidence of peripheral polyneuropathy on nerve conduction velocity. A kidney biopsy showed mesangial widening with irregular mesangial cell proliferation. A few glomeruli were globally (4/12) or segmentally (1/14) sclerotic. There were mild focal interstitial infiltrations with focal tubular atropy. Immunofluorescent microscopy revealed granular mesangial IgA deposit with trace perivascular C3 deposits. Treatment including glycemic control, angiotensin converting enzyme (ACE) inhibitor and antiplatelet agent was advised. Two years later, urinalysis revealed protein (±), specific gravity 1.020 with 10-29 red blood cells per high power field.

Case 4

A 56-year-old Korean male was presented for evaluation of microscopic hematuria and proteinuria. Three years ago, he was admitted due to a thalamic infarct, and he was diagnosed with NIDDM and hypertension. There was no history of diabetic ketoacidosis. Physical examination was unremarkable. Laboratory findings were as follows (Table 1): serum creatinine 2.0 mg/dL, albumin 3.1 g/dL, and basal C-peptide 9.7 ng/mL. Urinalysis revealed protein (+++), specific gravity 1.015 with many red blood cells per high power field. There was no evidence of diabetic retinopathy on funduscopic examination by an ophthalmologist. There were findings compatible with peripheral polyneuropathy on nerve conduction velocity. A kidney biopsy showed strong granular mesangial IgA deposit with perivascular C3 and IgM deposits, consistent with IgA nephropathy. Treatment including glycemic control and ACE inhibitor was advised. Hemodialysis was initiated in February 1997.

Case 5

A 47-year-old Korean male was presented for evaluation of rapid deterioration of renal function. He had NIDDM for seven years and suffered from diabetic retinopathy and polyneuropathy. There was no history of diabetic ketoacidosis. There was pretibial pitting edema on physical examination. Laboratory findings were as follows (Table 1): serum creatinine 2.8 mg/dL, albumin 2.3 g/dL, and basal C-peptide 3.3 ng/mL. Urinalysis revealed protein (+++), specific gravity 1.015 with many red blood cells and granular cast per high power field. A kidney biopsy showed generalized nodular and diffuse mesangial sclerosis, displacing the mesangial cells toward

the periphery and fibrin caps. A few glomeruli showed mesangial hypercellularity compatible with IgA nephropathy superimposed on diabetic nephrosclerosis. Treatment including glycemic control and ACE inhibitor was advised. But this patient was lost to follow-up.

DISCUSSION

Several reports have shown that glomerulonephritis mediated by immune complexes can complicate diabetic renal disease. Reported types of glomerulonephritis that complicate diabetes mellitus include membranous glomerulonephritis, endocapillary proliferative glomerulonephritis, minimal change disease, membranoproliferative glomerulonephritis, rapidly progressive glomerulonephritis, and cryoglobulinemic glomerulonephritis. To our knowledge, IgAN in diabetes mellitus has rarely been reported (4-7). We report here five patients with NIDDM associated with or without diabetic glomerulosclerosis. All of the patients were Korean males. In three patients (case 1, 2 and 3), diabetes mellitus was diagnosed at the same time with diagnosis of IgAN, and the known duration of the diabetes in the other two patients were three and seven years, respectively. There was no evidence of diabetic retinopathy in four patients, but it was found in one patient (case 5). IgAN should be highly suspected in all patients who had one of two common presentations: (1) episodic macroscopic hematuria, often coinciding with an upper respiratory tract infection, less often with gastroenteritis or (2) asymptomatic with abnormal urine sediment findings containing erythrocytes, red blood cell casts and proteinuria. Microscopic hematuria was observed in all of our cases, but macroscopic hematuria in only one patient (case 1). Proteinuria and/or nephrotic syndrome were also observed in all of these cases. Renal failure was observed in two patients (case 4 and 5). Morphologic examination revealed the presence of mesangial hypercellularity and mesangial IgA deposits on immunofluorescence. In our cases, the diagnosis of IgAN was made by immunohistology.

The occurrence of IgAN in these patients with NIDDM is a rare event and of pathogenetic interest. Although the pathogenesis of IgAN remains uncertain, IgA-containing immune complexes are involved. Recently, the salivary IgA levels in DM patients were higher than normal control (9). However the mechanism of leading to the glomerular deposition of this mucosal IgA remains poorly known. The association with many of these secondary disorders may be coincidental because of the high prevalence of IgAN that is usually a long-term and chronic disease. Is the occurrence of IgAN in a diabetic patient just mere association or is there a causal relationship? Gans et al. (5) reported the observation of five cases of IgAN together with the possibility of an increased prevalence in patients with insulin-dependent diabetes mellitus (IDDM) who had celiac disease and dermatitis herpetiformis. Also they suggested that the coexistence of IgAN and IDDM was not mere coincidence. But there is no data concerning the relationship between IgAN and NIDDM in our study. As already discussed earlier, IgAN is associated with an immune complex mechanism, whereas NIDDM seems to be not associated with immune mechanism. Thus, each entity demonstrates a distinct pathogenesis and a lack of causal relationship. The patients in this study reveal that diabetic glomerulosclerosis may occur alone, or coexist with IgAN and more importantly may be proceeded by IgAN. These observations suggest that diabetic lesions share independent pathogenesis with IgAN. Apart from this small group of IgAN patients with clinical and pathological features of diabetes, none of the 126 patients with IgAN examined during the same period has manifestations of diabetes, a further argument against a common pathogenesis. And there were autopsy observations which indicate that there was no excess of IgAN in patients with diabetes mellitus (10).

The finding of IgAN and diabetes could be coincidental, but it is known that various immunologic abnormalities and infections predisposing to immune complex nephritis are common problems in diabetic patients. And, some features could involve immune complex deposition in the pathogenetic mechanisms. Irvine et al. (11) reported that immune complex nephritis was often associated with diabetic patients, managed by insulin or other antidiabetic drugs who might have developed immune complex nephritis through the formation of anti-insulin antibody (11). However, insulin treatment was not given to any of our patients before histologic diagnoses. Therefore, the role of insulin treatment may be excluded in the process of superimposed glomerulonephritis.

In summary, we report five patients with NIDDM who showed features consistent with IgAN associated with or without diabetic glomerulosclerosis. But we could not conclude whether this is merely coincidence or not. To clarify their relationship, we need more cases of IgAN with NIDDM. And also we suggest that the renal biopsy should be required for the search of non-diabetic glomerular disease such as IgAN, when red blood cells are found in the urine, especially in patients who have a short duration of the diabetes mellitus.

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