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Clinical Report

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Idiopathic nodular glomerulosclerosis in a never-smoking, normotensive, non-obese, normal-glucose-tolerant middle-aged woman

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Abstract

A 53-year-old woman with a history of dyslipidemia presented with medium-grade proteinuria and several years of progressive renal dysfunction. Renal biopsy showed diffuse and global Kimmelstiel–Wilson nodule like nodular mesangial sclerosis, but she had no history of diabetes mellitus, no diabetic retinopathy and normal oral glucose tolerance. Congo red staining was negative, and immunofluorescence staining showed no immunoglobulin deposition including kappa or lambda light chains. Electron microscopy showed no electron dense deposits or organized deposits. Thus, we diagnosed idiopathic nodular glomerulosclerosis (ING). ING is a recently established clinicopathologic disease entity linked to longstanding cigarette smoking and hypertension. Obesity is also listed as a contributing factor. However, none of these factors was documented in this case. This is a valuable case of ING that suggests the existence of as-yet unknown causative factors of ING other than smoking, hypertention or obesity.

Keywords: CD34; diabetic nephropathy; idiopathic nodular glomerulosclerosis; vascular endothelial growth factor

Background

Kimmelstiel and Wilson [1] originally described nodular glomerulosclerosis as a lesion pathognomonic of diabetic nephropathy (this lesion is now known as Kimmelstiel–Wilson nodule), but nodular glomerulosclerosis has been known to occur in many other diseases. Alpers and Biava [2] first reported nodular glomerulosclerosis as a distinct disease entity, and Herzenberg *et al.* [3] then coined the term idiopathic nodular glomerulosclerosis (ING). Alsaad and Herzenberg [4] described how to distinguish diabetic nephropathy from ING.

Characterized by diffuse and global nodular glomerulosclerotic lesions closely resembling Kimmelstiel–Wilson nodule, ING is a rare disease in non-diabetic patients. Some regard this disease as a phenotype of arteriosclerotic renal disease without diabetes mellitus (DM) [5]. It is diagnosed by excluding DM and other diseases that cause nodular glomerulosclerosis, is closely associated with longstanding cigarette smoking and hypertension [6] and seems to be linked to obesity [7].

We report here a rare case of ING in a middle-aged woman for whom no previously reported causative factors had been documented, thereby suggesting the existence of as-yet unknown causative factors.

Case report

A 53-year-old Japanese woman first showed renal dysfunction [(serum creatinine = 96.4 μmol/L (1.09 mg/dL)] at a medical checkup in 2007. Her serum creatinine level had gradually increased since then and was 203 μmol/L (2.30 mg/dL) in 2010, when (3+) proteinuria was also found and she was referred to our Renal Department. She had a 10-year history of dyslipidemia, for which she was taking a statin, but no history of DM or hypertension. She had never smoked and was not exposed to passive smoking. There was no family history of DM. Physical examination showed no peripheral edema, that her blood pressure was 104/66 mmHg and that she was not obese (her body mass index was 19.3 kg/m^2).

Her complete blood count was within normal range. Serum creatinine was 194 μmol/L (2.19 mg/dL); urea nitrogen, 10 mmol/L (29 mg/dL); TP/Alb, 63/39 g/L (6.3/3.9 g/dL); glucose, 5.3 mmol/L (95 mg/dL). Total cholesterol was 8.92 mmol/L (345 mg/dL); triglycerides, 3.12 mmol/L (276 mg/dL). Antinuclear antibody titer was negative. Hypocomplementemia was absent. No M peak was detected on serum protein electrophoresis. Urinalysis showed proteinuia (3+) and occult blood (±). Microscopic

examination showed several fatty casts, otherwise inactive sediments. Proteinuria was quantified at 2.1 g/day.

A percutaneous renal biopsy showed that 13 of 36 glomeruli in light microscopic sections were globally sclerotic, and that the others had Kimmelstiel–Wilson nodule like nodular mesangial sclerosis (Figure 1A). Congo red staining was completely negative.

As shown in Figure 1B and C, small vascular lumens surrounded by CD34-positive endothelial cells (Figure 1D) were seen at the center of the nodular lesions. Vascular endothelial growth factor (VEGF) was also found in these lesions (Figure 1E). Thickening of the glomerular basement membrane and moderate arteriosclerosis were seen. Tubular atrophy and interstitial fibrosis were found focally. Immunofluorescence staining showed no immunoglobulin deposition including kappa or lambda light chains (Figure 2A), and electron microscopy showed no electron dense deposits (Figure 2B) or organized deposits.

Because of the renal biopsy findings, we re-evaluated her glucose metabolism. The glycosylated hemoglobin level was 5.5%. Oral glucose tolerance testing re-evaluated a normal fasting glucose and a normal glucose tolerance. Fundoscopy did not reveal evidence of diabetic retinopathy (In addition, hypertensive retinopathy was not

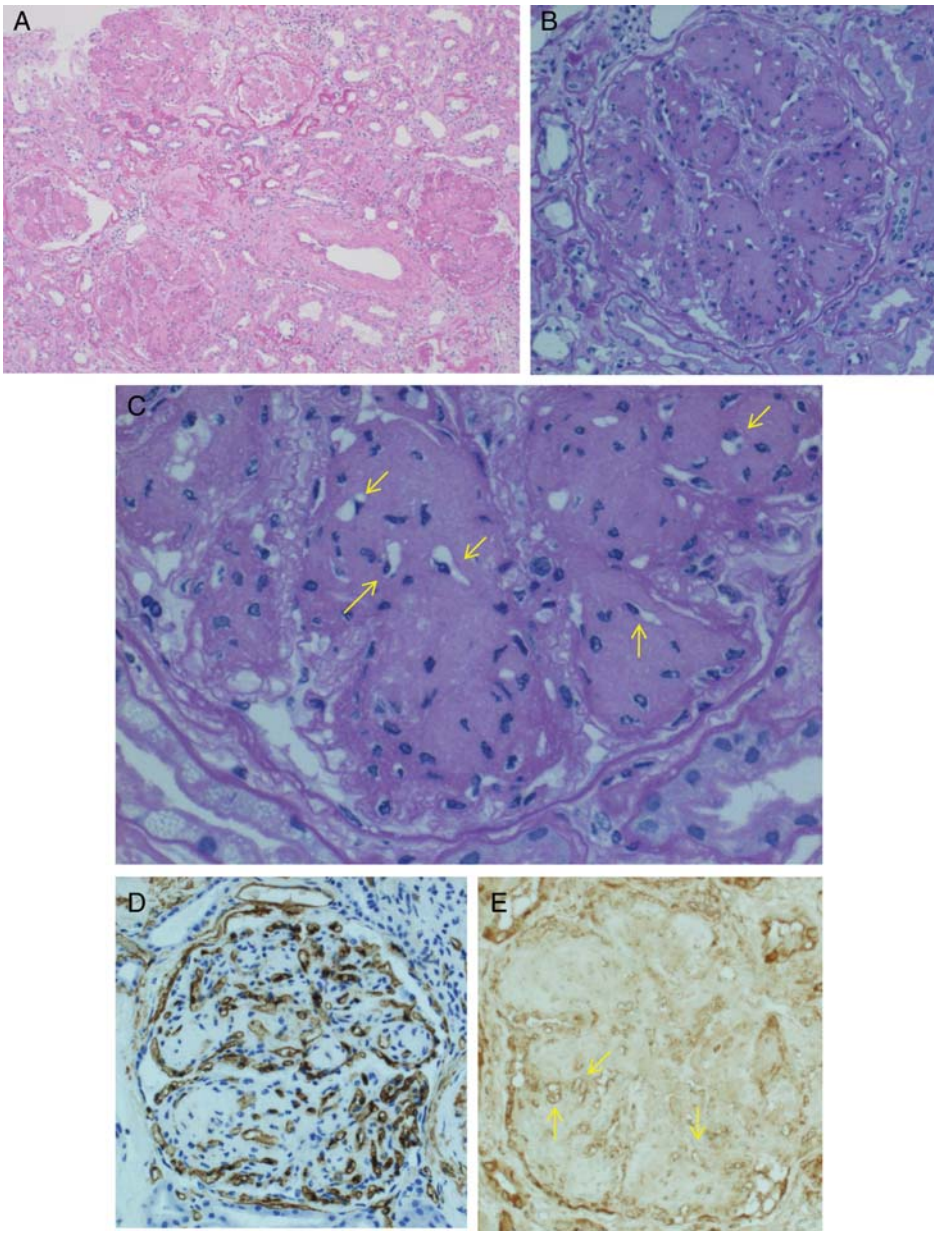

Fig. 1. Representative light microscopic photographs of the renal biopsy tissue. (**A**) Glomeruli showed diffuse nodular mesangial sclerosis resembling the Kimmelstiel–Wilson nodule (hematoxylin and eosin stain). (**B**) Higher magnification of a representative glomerulus that showed periodic acid-Schiff stain (PAS stain) positive nodular mesangial sclerosis. (**C**) At further higher magnification, small vascular lumens (arrows) were seen at the center of the nodules (PAS stain). (**D**) 3-μm thick paraffin section of the renal biopsy tissue was stained for CD34 by usual indirect immunoperoxidase staining with mouse anti-human CD34 monoclonal antibody (Dako, Glostrup, Denmark). The small vascular lumens were surrounded by CD34-positive endothelial cells. (**E**) These lesions were also positive for vascular endothelial growth factor (VEGF, arrows) (Indirect immunoperoxidase staining for VEGF with mouse anti-VEGF monoclocanl antibody, abcam, Tokyo, Japan) [(Original magnification (A) ×130; (B), (D), (E) ×260; (C) ×520)].

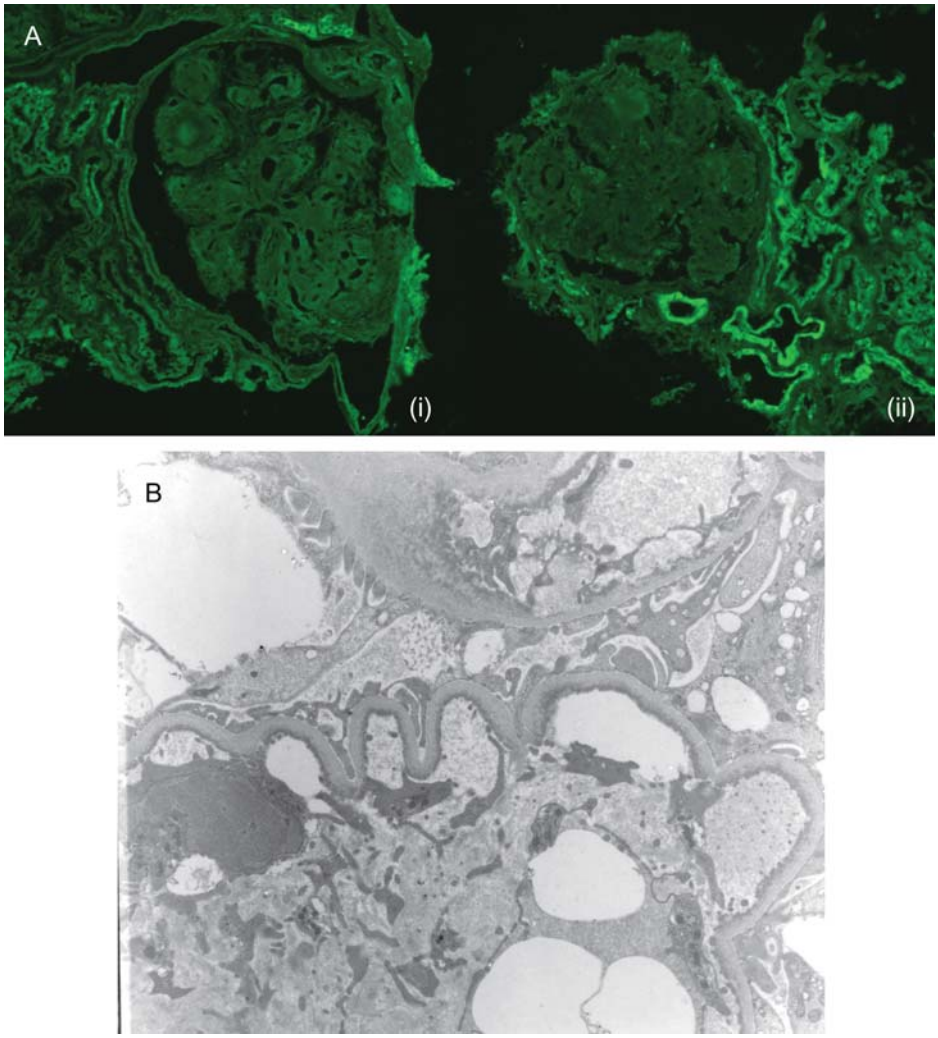

Fig. 2. Immunofluorescence (IF) and electron microscopy (EM) findings of the renal biopsy. (**A**) IF staining showed no deposition of (i) kappa (left) or (ii) lambda (right) light chains. (**B**) EM showed no electron dense deposits or organized deposits [Original magnification, (A) ×260].

found). In light of these findings, we diagnosed ING by exclusion. She is now under close observation while being treated with an angiotensin II Type 1 receptor blocker and an increased statin dose.

Discussion

Long-standing cigarette smoking and hypertension have been regarded as strong causative factors in the development of ING, and some grade obesity as a possible risk factor. In this case, however, these factors were absent. Dyslipidemia was also reported to be a common comorbidity in ING [8]. One report of ING in a patient with a history of dyslipidemia suggested that dyslipidemia was important in the development of ING [9], but the patient had a long history of smoking and hypertension and the dyslipidemia was well-controlled. We therefore believe that although the patient reported here had a history of uncontrolled dyslipidemia for ∼10 years, one cannot conclude that dyslipidemia alone caused her ING.

The glucose threshold required for the development of diabetic nephropathy may differ between individuals. In one reported case of diabetic nephropathy, clinically evident DM was absent at the time of renal biopsy but appeared 9 years later [10]. As suggested in that report, undetected DM might have been present before but not at the time of the onset of nephropathy. Long-term follow-up is therefore needed in the present case because DM may occur later.

Similar mechanisms may play a role in both ING and diabetic nephropathy because ING has histological features strikingly similar to those of diabetic nephropathy. Indeed, Markowitz *et al*. [8] reported that pentosidine, an advanced glycation end-product, accumulates in the glomerular nodules and renal interstitium both in ING and in diabetic nephropathy, and that vascular lumens in glomeruli were also increased similarly in ING and diabetic nephropathy. They also reported, however, a different pattern of CD34 staining in the nodular lesions of glomeruli: in diabetic nephropathy, positive CD34 staining was shown at the periphery of the nodules, while in ING it was at the center of the nodules [8]. The CD34-staining pattern in the present case was consistent with that seen by Markowitz *et al*. [8] in the ING cases. This difference may indicate that ING and diabetic nephropathy share

pathogenic mechanisms that are similar but not identical. In addition, we found positive VEGF staining in the nodular lesions where vascular lumens increased. Because VEGF is suggested to have a pathogenetic role in diabetic nephropathy [11], increased expression of VEGF may induce not only angiogenesis but also renal injury in ING.

In summary, we report a rare renal biopsy case of ING that suggests the existence of as-yet unknown causative factors of ING other than smoking, hypertension or obesity. Identification of the causes and pathogenic mechanisms of ING will require further accumulation and precise analysis of ING cases.

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Conflict of interest statement. None declared.

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