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Case report

Intramembranous fine deposit disease associated with collagen disorders: a new morphological entity?

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Summary. A distinct, hitherto unknown renal histopathological appearance, consisting of diffuse thickening of the glomerular basement membrane (GBM) with fine intramembranous electron-dense deposits, was observed in the renal biopsies from three patients with collagen diseases. In each case, proteinuria was mild with normal urinary sediment. On light microscopy there were no particular abnormalities but a mild thickening of the glomerular capillary wall. Immunofluorescence studies revealed faint linear or extremely fine granular IgG deposition along the capillary wall. On electron microscopy, the GBM was diffusely thickened with fine intramembranous electron-dense deposits without spike formation. No other deposits were seen in the glomerulus. These histological features resembled those of membranous glomerulonephritis (MGN), although the possibility of the early change of MGN is excluded by specific findings in these cases. Other GBM-thickening diseases such as diabetic glomerulosclerosis were ruled out clinically and histologically. Our cases have a singular renal histopathology which differs from any of the previously established classifications of glomerular lesions. It may be a specific change associated with some type of collagen disease.

Key words: Glomerular basement membrane – Intramembranous deposit – Membranous glomerulonephritis – Collagen disease – Systemic lupus erythematosus

Introduction

In the collagen diseases, renal involvement is very common, and various histological changes have been demonstrated in renal biopsies. In systemic lupus erythematosus (SLE), deposits of various sizes are often observed throughout the glomerulus with or without cellular proliferation and mesangial sclerosis. Moreover, characteristic glomerular lesions such as "wire loop" or "haematoxylin bodies" are known to appear in the active stage of the disease.

In this paper, we describe another histological feature observed in three cases of collagen disease, in which the most remarkable change was a diffuse thickening of the glomerular basement membrane (GBM) accompanied by fine intramembranous electron-dense deposits without spike formation.

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Case reports

Clinical and laboratory findings are summarized in Table 1. Antibody to double-stranded DNA (ds-DNA) was measured by the passive haemagglutination and haemolysis tests (Sasaki et al. 1978). Complement components C3 and C4 were measured by a single radial immunodiffusion method. Circulating immune complex was measured by the Clq solid phase assay (Fukuda et al. 1985a) and by the anti-C3 immune complex assay (Fukuda et al. 1985b).

Case 1

A 20-year-old female with a slight fever and reticular erythema on the palms and fingers was admitted in May 1985. She had been noted to have proteinuria for 3 years. On admission, she had no oedema. The 24-h excretion of urinary protein was 1.4 g. There were no particular abnormalities in the urinary sediment. Antinuclear antibody (ANA) titre was elevated ($\times 320$). Antibody to extractable nuclear antigen or to ds-DNA was negative. According to the 1982 revised criteria for the classification of SLE (Tan et al. 1982), only three items (persistent proteinuria >0.5 g/24 h, leucopenia, and abnormal titre of ANA) were positive. Therefore the diagnosis of SLE was not certain, but probable.

On light microscopy (LM), the biopsy contained 20 glomeruli, 6 of which were globally sclerotic. In the other glomeruli, no significant changes were observed except for a mild thickening of the capillary wall. On immunofluorescence studies (IF), fine granular deposits of IgG were faintly observed along the capillary wall. Other immunoglobulins or complement components were not positively stained. On electron microscopy (EM), the main change was a diffuse thickening of the GBM (800–1000 nm in thickness), with fine intramembranous electron-dense deposits (Fig. 1A, B). Most of the deposits were located just in the midst of the GBM. Some

Table 1. Clinical and laboratory findings of the patients

	Case 1	Case 2	Case 3
Age/sex	20/F	30/F	31/F
Clinical diagnosis	(SLE)[a]	MCTD	SLE
Blood pressure (mm Hg)	140/80	110/60	100/60
Urinary protein (g/day)	1.4	0.3	0.5
BUN (mg/dl)	25	14	12
Serum creatinine (mg/dl)	1.6	0.9	0.9
Creatinine clearance (ml/min)	66	92	77
Total protein (g/dl)	7.8	6.3	6.4
Haemoglobin value (g/dl)	11.1	11.6	10.9
White cell count (/mm^3)	3500	2100	4700
Platelet count (X10^4/mm^3)	16.0	14.2	<1.0
ESR (mm/h)	91	24	26
Antinuclear antibody	×320	×2560	×40
Anti-native DNA antibody[b]	Negative	Negative	×320
CH50 (units/ml)	25.0	28.2	25.2
C3 (mg/dl)	87	64	ND
C4 (mg/dl)	33	18	ND
Circulating immune complex[c]			
C1q-SP (μgAHG/ml)[c]	Negative	Negative	Negative
Anti-C3 (μgAHG/ml)[c]	3.6	Negative	Negative
Therapy at biopsy	None	PSL 15 mg/day	PSL 20 mg/day

BUN, Blood urea nitrogen; ESR, erythrocyte sedimentation rate; MCTD, mixed connective tissue disease; PSL, prednisolone; SLE, systemic lupus erythematosus

[a] Probable SLE satisfying three items of the 1982 revised criteria

[b] Anti-native DNA antibody was measured by the passive haemagglutination and haemolysis test (Sasaki et al. 1978)

[c] Circulating immune complex was measured by the C1q solid phase assay (Fukuda et al. 1985) and by the anti-C3 immune complex assay (Fukuda et al. 1985)

deposits were covered with electron-lucent lacunae that were extended from the deposits to minute notches of subepithelial surface of the thickened GBM (Fig. 1C). Each deposit was 40–80 nm in diameter. A number of membrane degradation products were also observed in the GBM. Spike formation was not observed on the GBM.

Case 2

A 30-year-old female was admitted in September 1984 with swollen hands and polyarthralgia. Urinalysis revealed mild proteinuria (0.3 g/24 h) with normal sediment. ANA titre was significantly elevated (×2560, speckled pattern) with extremely high titre of anti-ribonucleoprotein (RNP) antibody (×10240). She was diagnosed as having mixed connective tissue disease (MCTD) based on typical clinical features, high titre of antibody to RNP, and the absence of antibody to Sm antigen or ds-DNA.

Thirty glomeruli were obtained. On LM, the only glomerular abnormality was a mild thickening of the capillary wall without spikes. No significant changes were observed in the tubules, interstitium, or vessels. If showed faint linear IgG deposition along the capillary loop. IgA, IgM, Clq, C3 and fibrinogen were all negative. On EM, there was a diffuse thickening of the GBM with intramembranous fine deposits and membrane degradation products. Each deposit was 40–80 nm in diameter. No other deposits were observed in the glomerulus (Fig. 2).

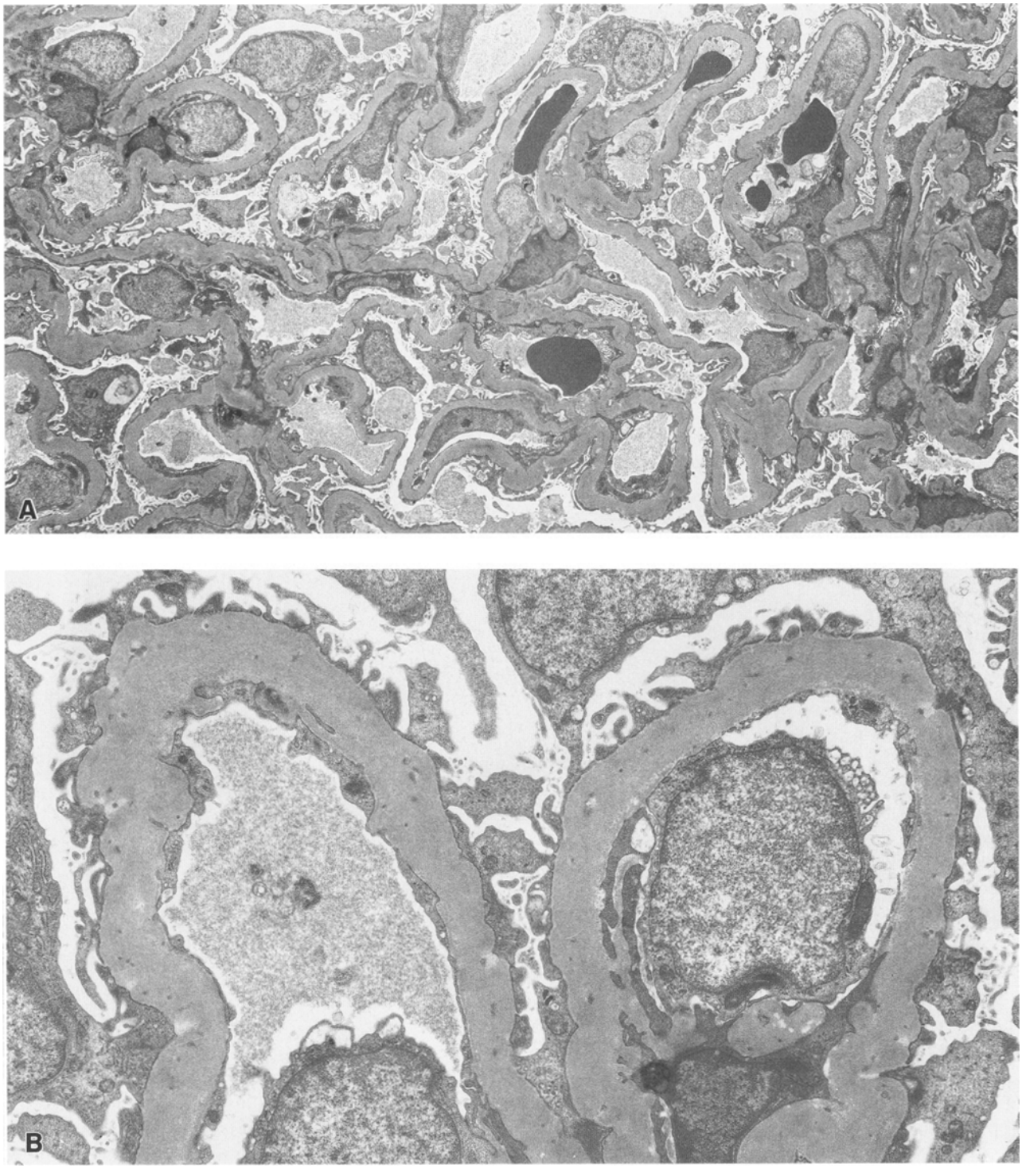
Case 3

A 31-year-old female was admitted in April 1982 with a slight fever and polyarthralgia. She had butterfly rash on the face and multiple ulcers in the oral cavity. Laboratory studies revealed thrombocytopenia (<10000/mm^3) and high titre of ANA. These findings indicated the presence of SLE, and steroid therapy (prednisolone 20 mg/day) was started. In March 1984, she exhibited psychic disorder (manic state) and mild proteinuria (0.5 g/24 h). Urinary sediment showed no particular abnormalities. Renal biopsy was performed in September 1984.

On LM, 25 glomeruli were observed. Each glomerulus showed slight mesangial proliferation with a mild thickening of the capillary wall. On IF, fine granular deposits of IgG were present along the capillary loop. On EM, the main changes were confined to the GBM, which was thickened with intramembranous fine deposits (Fig. 3).

Discussion

The renal pathology described in this report might be included in a category of membranous glomerulonephritis (MGN) because of the diffuse thickening of the GBM with IgG deposition. However, the glomerular ultrastructure was quite different from that of typical MGN in following three points. First, the deposits observed in these cases were extremely small (40–80 nm in diameter) in comparison with those in typical MGN. The average diameter of the epimembranous deposits in idiopathic MGN was reported to be 300–1100 nm (Zollinger and Mihatsch 1978). Secondly, the deposits were buried deep in the GBM, far from the subepithelial surface of the membrane, but retaining the electron density. Thirdly, spike formation was absent in these cases. With regard to the cause of the histological difference from typical MGN, we speculate that the deposits in these cases were



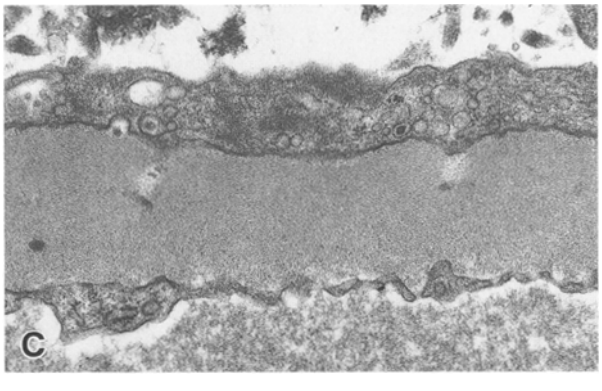


Fig. 1 A–C. Case 1. **A** Electron micrograph of the glomerulus showing a diffuse thickening of the basement membrane. ×2000. **B** Segments of two glomerular capillaries. There observed are very fine electron-dense deposits inside the glomerular basement membrane (GBM), together with membrane degradation products. The thickness of the GBM amounts to approximately 900 nm. ×7800. **C** Epithelial side of the deposits is covered with electron-lucent areas extending to a minute notch on subepithelial surface of the membrane. ×20000. The diameter of the deposits was 40–80 nm

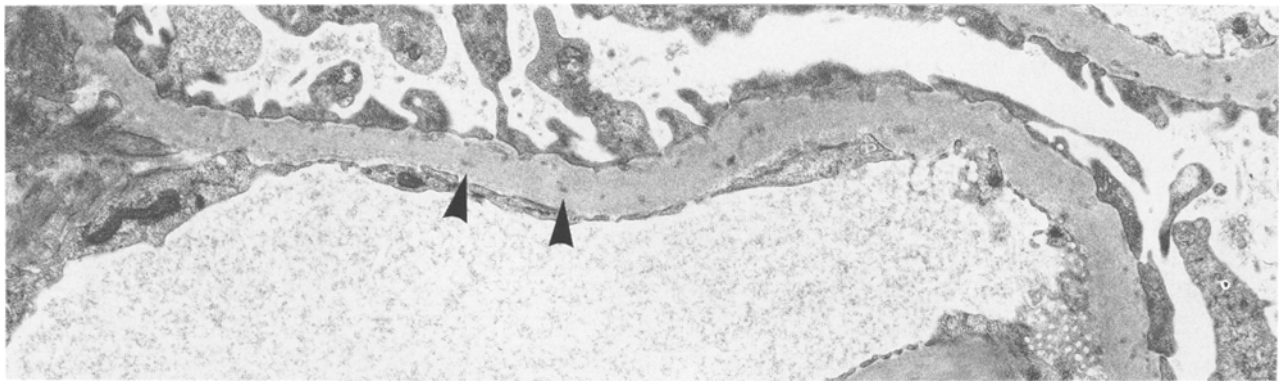


Fig. 2. Case 2. Diffuse thickening of the GBM is observed with intramembranous fine deposits (*arrowheads*) and membrane degradation products. The GBM thickness measures approximately 600 nm. × 7800

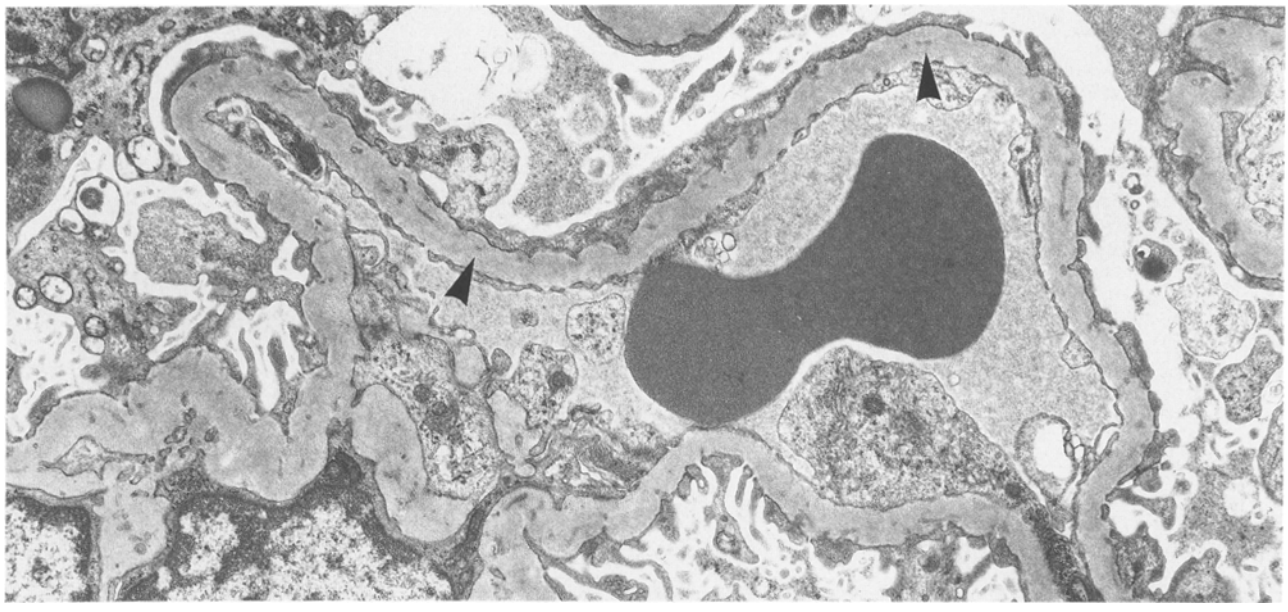


Fig. 3. Case 3. The GBM is diffusely thickened (approximately 500 nm in thickness) with intramembranous fine deposits (*arrowheads*) and membrane degradation products. Foot processes of the epithelium are diffusely effaced. × 7800

so small that they were easily taken into the GBM with no spike formation, but causing a reactive diffuse thickening of the GBM itself. Electron-lucent lacunae covering the epithelial side of the intramembranous deposits, typically observed in case 1 (Fig. 1C), seem to show morphological traces of the deposits which had passed from the epimembranous surface of the GBM into the membrane. The reason why the deposits remained small is unknown. Some unidentified biological or immunochemical properties of immune complexes may prevent the formation of large deposits.

The biological properties of immune complexes are related to the properties of antigen and antibody molecules forming the lattice of complexes, as well as the number of each reactant and the nature of the antigen-antibody union (Mannik 1980). The lattice of immune complexes influences their tissue deposition. For instance, large-latticed complexes are deposited in mesangial and subendothelial areas, and relatively small-latticed complexes formed under conditions of antigen excess are localized in the subepithelial area of the glomerular capillary loops (Mannik 1982). As for the latter, another interpretation might be more likely, namely that the subepithelial deposits are locally formed in situ, independent of circulating immune complexes (Couser et al. 1978; Van Damme et al. 1978; Couser and Salant 1980; Mannik 1980; Makker and Moorthy 1981; Couser 1985). However, the relationship between the biological properties of immune complexes and the size of the deposits recognized on EM remains unclear.

Clinically it is noteworthy that all the cases reported herein were non-nephrotic (proteinuria was 0.3–1.4 g/24 h) with normal renal function and normal urinary sediment. Another characteristic is that all cases were clinically diagnosed as SLE, MCTD, or their incomplete form. Among 284 cases whose renal ultrastructure was completely examined by EM in our institute (including 31 cases of SLE, 2 of Sjögren syndrome, 1 of MCTD,

and 1 of periarteritis nodosa) only 3 cases, reported herein, have shown this type of renal histology. The same histology has never been observed in primary glomerular diseases. In the literature, similar renal histology was observed in a case of scleroderma (Churg and Sobin 1982), also included in the collagen diseases. Thus the present histology could be defined as a specific glomerular response to some type of collagen disease. It appears possible that some biological properties of immune complexes, which are related to antinuclear auto-antibody and/or its relatives, may have an effect on this peculiar glomerular morphological change.

Further histological studies and immunochemical examinations are needed to confirm our assumption of the cause of this morphological change.

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