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Electron Microscopic Study of the Cases of Minimal Change Nephrotic Syndrome with Mesangial IgA Deposition

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Twenty-five cases of minimal change nephrotic syndrome(minimal change disease, MCD) with mesangial IgA deposition were evaluated electron microscopically. The thickness of the glomerular basement membrane(GBM) was 3875±1271 Å and 3056±1201 Å in adults and children, respectively. Alteration of the GBM was noted in 3 adults and eight children: splitting in 4, focal thinning in one, widening of the lamina rara interna in 10, and widening of the lamina rara externa in 4 cases. Minimal mesangial electron dense deposits were found in all but one adult, and an increase of the mesangial matrix and minimal mesangial proliferation were observed in 8 and 6 cases, respectively. Electron microscopic findings show representative findings of MCD in our cases. A relationship between the GBM alterations in these cases and frequent association of hematuria is suggested and discussed.

Key Words: Minimal change nephrotic syndrome, mesangial IgA deposit, electron microscopy

Minimal change nephrotic syndrome (minimal change disease, MCD) associated with mesangial IgA deposition has been regarded as a variant of IgA nephropathy (IgAN) and was known to be steroid responsive (Mustonen *et al.* 1983; Wu *et al.* 1985). However, there also have been several reports that it might be a variant of MCD (Choi *et al.* 1990) or an overlap syndrome of MCD and IgAN (Sinnassamy and O'Regan 1985; di Belgiojoso *et al.* 1986; Lai *et al.* 1986). These two different points of view yielded confusion in terminology, accordingly in pathogenesis and possible different outcome. In Korea, both MCD and IgAN are the major primary glomerulonephritis and this combination can be more frequently found than in western countries. We reported light and immunofluorescent microscopic findings of 60 cases previously (Choi *et al.* 1990), which showed a minimal degree (less than one positive) of IgA deposition with frequent codeposition of IgG or IgM in most cases, which raised questions of a role of IgA both in these cases and especially in terms of glomerular injury. Sinniah (1983) reported a 4% incidence of IgA deposits in a control necrospy population. There also has been an argument concerning the significance of minimal IgA with regard to the diagnosis of IgAN (Jennette 1988). Moreover, the cases of MCD with IgA deposition showed frequent association with hematuria, which may suggest, in an another view point, a variant of IgAN. For this reason, an investigation of the GBM alteration electron microscopically may be worthwhile to evaluate the possible relation to hematuria rather than hematuria in IgAN itself, and also to clarify whether or not our cases show the findings of MCD electron microscopically.

With increasing interest on electron microscopic findings of IgAN, several types of GBM alterations such as GBM lysis (Yoshikawa *et al.* 1986), attenuation and lytic changes of GBM (Sakaguchi 1987; Nomura *et al.* 1989) have been reported. However, we do not know whether these studies exclusively

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included advanced cases with loop deposits or contained cases with mild pathologic lesions like ours. Although there seems to be no link between mesangial IgA deposition and GBM changes, we tried to search any positive findings characteristic of this combination, or because of frequent association of hematuria, aimed to search interesting findings to assess the GBM alteration in these cases in relation to hematuria.

MATERIALS AND METHODS

Twenty five cases among sixty cases of MCD with mesangial IgA deposition which were previously reported (Choi *et al.* 1990) were selected for electron microscopic study. These cases had more than one whole glomerulus in blocks for electron microscopy. They showed minimal alteration or minimal mesangial proliferation by light microscopy and IgA positivity in all cases, but the degree was less than one positive in a 0 to 3 scale in 81.6% by immunofluorescent microscopy.

For electron microscopic examination, the fresh tissue was double fixed in 2.5% glutaraldehyde and OsO4, embedded in an epon mixture, ultrathin sectioned and stained with uranyl acetate and lead citrate, and examined with a Hitachi H-500 transmission electron microscope.

The items checked for the glomerular basement membrane alteration were GBM thickening or thinning with measurement of the thickness, splitting of the lamina densa, electron dense deposits or incorporation of abnormal material. The measurement of the GBM was performed under the printed photographs, from epithelial foot processes to the endothelial cytoplasm, and the arythmetic mean was corrected by a factor of $4/\pi$ to compensate for the overestimation of thickness. Approximately 80 GBM measurements were made for each patient. In addition, endothelial, mesangial and epithelial cell changes, if present, were recorded.

Table 1. GBM alterations in patients with MCD with mesangial IgA deposition

Case No.	Age	Sex	Thickness of GBM(Å, mean±SD)	Splitting	Thinning	Widening l.r.i.	Widening l.r.e.	Deposit	Granulation
1	59	f	2873± 482	−	−	−	−	−	+
2	43	m	4361±1922	−	−	+	−	−	−
3	39	f	4578±1499	−	−	−	−	−	−
4	36	m	3908± 651	−	−	−	−	−	−
5	36	f	4633±1121	−	−	+	−	−	−
6	32	m	4900±1213	−	−	−	−	−	−
7	27	m	4506±1374	−	−	−	−	−	−
8	27	m	2923± 644	−	−	−	−	−	−
9	25	m	3588± 777	−	−	−	−	−	−
10	24	m	3658± 629	−	−	−	−	−	−
11	24	m	3286± 539	−	−	+	−	−	−
12	23	m	3324± 868	−	−	−	−	−	−
13	20	m	3445± 734	−	−	−	−	−	−
14	18	m	3034± 935	−	−	−	−	−	−
15	18	m	4528±1396	−	−	−	−	−	−
16	14	m	3001±1112	−	−	+	−	−	−
17	13	m	4320±1379	−	−	−	−	−	−
18	11	m	2286± 450	+	−	+	−	−	−
19	10	m	2658± 939	−	+, focal	−	−	−	−
20	9	m	3366±1266	−	−	+	−	−	−
21	8	f	3376± 616	+	−	+	+	−	+
22	8	m	1931± 512	+	−	+	+	−	−
23	7	m	2864± 648	+	−	+	+	−	−
24	5	f	3606± 838	−	−	−	−	−	−
25	5	f	3644± 867	−	−	+	+	−	−

l.r.i.: lamina rara interna, l.r.e.: lamina rara externa

RESULTS

Glomerular basement membrane

The average thickness of the GBM was 3876 A in adults and 3056 A in children. Splitting of the lamina densa was found in 4 children, present in long segments in a few loops. The GBM was thinned focally in one case. Electron dense deposits were not found in all cases. The laminal rara interna was widened in 3 adults and 7 children, irregularly bordered by endothelial cells. The lamina rara externa was mildly widened in 4 cases (Table 1).

Mesangium

Electron dense deposit, though minimal in amount, was found in the mesangium in 14 adults and 10 children. Mesangial cell proliferation was found in 6 cases (2 adults and 4 children), and in 8 cases (3 adults and 5 children) the mesangial matrix was increased (Table 2).

Epithelial and endothelial cells

Effacement of epithelial foot processes, either diffuse or focal, was noted in all cases, associated with microvillous transformation. Arcade formation of endothelial cytoplasm was found in 13 adults. Myeloid body was observed in 4 cases, in endothelial, mesangial, epithelial cytoplasm or in the urinary spaces.

Relationship between GBM alteration and hematuria

The incidence of microscopic hematuria was higher in adults, whereas gross hematuria was more frequently found in children. GBM alteration tended

Table 2. Mesangial, epithelial and endothelial changes in patients with MCD with mesangial IgA deposition

Case No.	Mesangium			Epithelium			Endothelial arcades	Myeloid body
	Matrix increase	Hypercellularity	Deposit	Foot process fusion	Hypertrophy	Others		
1	–	–	+	–	+		+	U, Mes, Cap
2	+	–	+	focal	–		+	
3	–	–	+	diffuse	–		+	
4	–	–	+	focal	–	P.D.	+	End
5	–	–	+	diffuse	–		+	
6	–	–	+	diffuse	–	P.D.	+	
7	–	–	+	diffuse	–		+	
8	+	–	+	focal	–	P.D.	+	U, Cap
9	–	–	+	diffuse	–		+	
10	–	–	+	focal	–	P.D.	+	
11	+	+	+	diffuse	+	P.D.	–	End
12	–	+	+	diffuse	–	P.D.	+	
13	–	–	–	diffuse	–		+	
14	–	–	+	diffuse	–		+	
15	–	–	+	diffuse	–		–	
16	–	–	+	diffuse	–		+	
17	+	+	+	diffuse	–		–	
18	+	–	+	focal	–	P.D.	+	
19	–	–	+	diffuse	–		+	
20	–	–	+	diffuse	–		+	
21	+	+	+	diffuse	–		+	
22	–	+	+	diffuse	–		+	
23	–	–	+	–	–		–	
24	+	–	+	focal	–		+	
25	+	+	+	focal	–		+	

P.D.: protein droplet, U: urinary space, End; endothelial cell, Mes: mesangial cell, Cap; capillary lumen

Table 3. Relationship between GBM alteration and hematuria

Hematuria / GBM alteration	Gross		Microscopic		Absent	
	A	C	A	C	A	C
Total number of cases	0	3	14	3	1	4
GBM splitting	0	2	0	1	0	1
GBM thinning	0	0	0	0	0	0
Widening of lamina rara interna	0	3	3	3	0	1
Widening of lamina rara externa	0	3	0	0	0	1
Incorporation of granules	0	1	1	0	0	0

A: adults, C: children

to be more frequently found in children and under the presence of gross hematuria (Table 3).

DISCUSSION

MCD is characterized by minimal glomerular alteration and essentially no immunoglobulin deposit. However, a minimal amount of immunoglubulins, mostly IgM or IgG, can be deposited in the mesangium (Kim *et al.* 1982). IgA deposition is rarely encountered in patients with MCD, however, most cases have been reported as IgAN referring to the definition of IgAN (Mustonen *et al.* 1983; Rambausek *et al.* 1987; Wu *et al.* 1985).

We hypothesized that these cases included 2 categories: coincidence of MCD and IgAN, and a variant of MCD. We tried to avoid the concept of a variant of IgAN because these clinical and pathological features did not fit well with classical IgAN. Late appearance of mesangial IgA deposit in steroid responsive nephrotic syndrome in a report from Southwest Pediatric Nephrology Group in an otherwise typical MCD patient suggests coincidence of two disease entities. However there is also evidence favoring the concept of a variant of MCD. First, there were a few patients presented with nephrotic syndrome without episodes of hematuria, and remitted spontaneously or by steroid treatment (Abreo and Wen 1983; di Belgiojoso *et al.* 1986). Second, the degree of IgA deposits were decreased or lost during follow up in a few patients (Cheng *et al.* 1989). According to our recent collective review of 60 cases (Choi *et al.* 1990), most of the cases showed the features of MCD by light, immunofluorescent and electron microscopy, which leads to confusion in terminology and pathogenesis. There is no consensus between the degree of IgA and clinical severity (Costa *et al.* 1987).

These cases have mostly been reported in Orientals, in whom IgAN and MCD are the most frequent primary GN. We believe that there are cases of MCD and IgAN developing simultaneously or concomittantly. It was reported that IgAN developed later in MCD patients. However, to our knowledge, there has not been a report of a case in a reverse sequence. If a patient with IgAN becomes nephrotic, the disease can be easily considered as a manifestation of progression to renal insufficiency, because it is hardly reasonable for a patient to have another primary renal disease with different pathogenesis. We also strongly believe that there are even more cases featuring a variant of MCD as in our report (Choi *et al.* 1986). In these circumstances, IgA has no or little, if any, role. We are not sure that all IgA deposits are nephritogenic, which was supported by Sinniah who reported spontaneous deposition of IgA in a control necropsy population with no renal disease. In an experimental model the size of the IgA immune complex and the nature of the antigen played a critical role (Rifiai 1988). In an experimental study of IgAN with ddy mice by oral and parenteral administration of the poliomyelitis vaccine, mesangial IgA deposition could be prevented by concurrent use of sodium cromoglycate (SCG), but mesangial IgA deposits already present could not be cleared by the late administration of SCG (Jin and Choi 1990). Disapperance of mesangial IgA deposits following steroid induced remission is against the role of IgA. IgA in IgAN might be different from IgA in these cases. IgA deposits related to various stimuli including infectious agents or food may be heterogenous and have different structural configuration and some might do no harm to the kidney. We experienced minimal IgA deposi-

tion in a case of typhoid fever and had doubts whether it bore the same pathogenesis and outcome as primary IgAN.

By electron microscopy, MCD conventionally shows effacement of epithelial foot processes as a sole abnormal finding. However, uncommon findings such as breaks or gaps (Spiro 1959), widening of the lamina rara interna (Duffy *et al.* 1970; Pollak *et al.* 1968) or curved striated bodies or round bodies (Yoshikawa *et al.* 1981) were reported. Recently a variety of GBM alterations were described in IgAN in addition to mesangial deposits, such as thinning and splitting (Shigematsu *et al.* 1982; Southwest Pediatric Nephrology Group 1982), GBM lysis (Yoshikawa *et al.* 1986), or various attenuation patterns (Sakaguchi 1987; Morita and Sakaguchi 1988). The frequency was reported to be from 38% (Nomura *et al.* 1989) to over 90% (Morita and Sakaguchi 1988). However, the significance is uncertain. This might represent the resorption of electron dense deposits previously present in loops but it might reflect primary GBM alteration and play a role in the pathogenesis of IgAN. Among GBM alterations in our cases, widening of the lamina rara interna was the most frequent and focal thinning the least, which might be regarded as nonspecific. However, considering the more frequent association of hematuria with MCD than usual, especially gross hematuria in children, these changes might be related to hematuria, even though we could not tell that this was not a sign for IgAN. GBM changes might be a genetic or developmental defect of GBM, through which red blood cells escape from the capillary lumen or the sequelae of nonspecific GBM damage. The possibility of resorption of electron dense deposits can be discarded because loop deposits are usually related to massive mesangial electron dense deposits and mesangial proliferation.

In summary, we conclude that most of our cases of MCD with mesangial IgA deposition are a variant of MCD. The electron microscopic findings in these cases showed GBM alteration in the forms of widening of lamina rara interna and externa and splitting of lamina densa and might have a relation with hematuria. Long term follow up will be required to clarify the evolution of GBM changes especially in children with gross hematuria and much attention will be paid to this combination for determination of clinical course.

REFERENCES

Abreo K, Wen SF: A case of IgA nephropathy with an unusual response to corticosteroid and immunosuppressive therapy. *Am J Kidney Dis 3: 54-57, 1983*

Cheng IKP, Chan K-W, Chan M-K: Mesangial IgA nephropathy with steroid-responsive nephrotic syndrome: disappearance of mesangial IgA deposits following steroid-induced remission. *Am J Kidney Dis 5: 361-364, 1989*

Choi IJ, Jeong HJ, Kim PK, Lee JS, Kim KS, Lee HY, Chung SH, Kim DS: A study of glomerular minimal lesion and minimal mesangial proliferation with or without nephrotic syndrome; pathologic, immunopathologic and clinical correlation. *Yonsei Med J 27: 17-24, 1986*

Choi IJ, Jeong HJ, Lee HY, Kim PK, Lee JS, Han DS: Significance of mesangial IgA deposit in minimal change nephrotic syndrome. *Yonsei Med J 31: 258-263, 1990*

Costa RS, Droz D, Noel LH: Long-standing spontaneous clinical remission and glomerular improvement in primary IgA nephropathy (Berger's disease). *Am J Nephrol 7: 440-444, 1987*

di Belgiojoso GB, Mazzucco G, Casanova S, Radaelli L, Monga G, Minetti L: Steroid-sensitive nephrotic syndrome with mesangial IgA deposits: a separate entity? observation of two cases. *Am J Nephrol 6: 141-145, 1986*

Duffy JL, Clinque T, Grishman E, Churg J: Intra-glomerular fibrin, platelet aggregation, and subendothelial deposits in lipoid nephrosis. *J Clin Invest 49: 251-258, 1970*

Jennette JC: Clinical and pathologic features of IgA nephropathy. The immunohistology of IgA nephropathy. *Am J Kidney Dis 12: 348-352, 1988*

Jin SY, Choi IJ: The effect of sodium cromoglycate on the induction of experimental IgA nephropathy. *Yonsei Med J 31: 33-48, 1990*

Kim PK, Kim NA, Kim KS, Choi IJ: Steroid effects on minimal lesion nephrotic syndrome with and without immune deposits. *Intern J Pediatr Nephrol 3: 257-261, 1982*

Lai KN, Lai FM-M, Chan KW, Ho CP, Leung ACT, Vallen-Owen J: An overlapping syndrome of IgA nephropathy and lipoid nephrosis. *Am J Clin Pathol 86: 716-723, 1986*

Morita M, Sakaguchi H: A quantitative study of glomerular basement membrane changes in IgA nephropathy. *J Pathol 154: 7-18, 1988*

Mustonen J, Pasternack A, Rantala I: The nephrotic syndrome in IgA glomerulonephritis: Respnse to corticosteroid therapy. *Clin Nephrol 20: 172-176, 1983*

Nomura Y, Ohya N, Shimada M: A histopathological study on the prognosis of childhood IgA nephropathy and glomerular basement membrane lesions. *Pediatr Nephrol 3: 242, 1989*

Pollak VE, Rosen S, Pirani CL, Muehrcke RC, Kark RM:

Natural history of lipoid nephrosis and of membranous glomerulonephritis. *Ann Intern Med 69: 1171-1196, 1968*

Rambausek M, Walherr R, Rauterberg W, Andrassy K, Ritz E: Mesangial IgA nephropathy and idiopathic nephrotic syndrome. *Nephron 47: 190-193, 1987*

Rifai A: Characteristics of nephritogenic IgA immune complexes. *Am J Kidney Dis 12: 402-405, 1988*

Sakaguchi H: Electron microscopic findings of glomerular changes in IgA nephropathy. *Proceedings of the Seventh Asian Colloquium in Nephrology*. Nov 25-28, 1987, Taipei, Taiwan *pp 188-189*

Shigematsu H, Kobayashi Y, Tateno S, Hiki Y, Kuwao S: Ultrastructural glomerular loop abnormalities in IgA nephritis. *Nephron 30: 1-7, 1982*

Sinnassamy P, O'Regan S: Mesangial IgA deposits with steroid responsive nephrotic syndrome: Probable minimal lesion nephrosis. *Am J Kidney Dis 5: 267-270, 1985*

Sinniah R: Occurrence of mesangial IgA and IgM deposits in a control necropsy population. *J Clin Pathol 36: 276-279, 1983*

Southwest Pediatric Nephrology Study Group: A multicenter study of IgA nephropathy in children. *Kidney Int 22: 643-652, 1982*

Spiro D: The structural basis of proteinuria in man: Electron microscopic studies of renal biopsy specimens from patients with lipoid nephrosis, amyloidosis, and subacute and chronic glomerulonephritis. *Am J Pathol 35: 47-73, 1959*

Wu G, Katz A, Cardella C, Oreopoulos DG: Spontaneous remission of nephrotic syndrome in IgA glomerular disease. *Am J Kidney Dis 6: 96-99, 1985*

Yoshikawa N, Cameron AH, White RHR, Stamdring DM: Curved striated and round bodies in glomerulopathies of children. An ultrastructural study. *J Pathol 135: 211-221, 1981*

Yoshikawa N, Yoshiara S, Yoshiya K, Matsuo T: Lysis of the glomerular basement membrane in children with IgA nephropathy and Henoch-Schönlein nephritis. *J Pathol 150: 119-126, 1986*