Virchows Arch (1997) 430:489–494 © Springer-Verlag 1997

CASE REPORT

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Diffuse mesangial sclerosis associated with Kawasaki disease: an analysis of alpha chains (α1–α6) of human type IV collagen in the renal basement membrane

Received: 6 June 1996 / Accepted: 6 January 1997

Abstract A case of diffuse mesangial sclerosis (DMS) associated with Kawasaki disease is reported. A previously healthy Japanese girl, aged 4 months, presented with clinical features of Kawasaki disease. At week 10 of the illness, she developed the nephrotic syndrome, which was refractory to steroid therapy. Renal biopsy demonstrated a diffuse mesangial proliferative glomerulonephritis with microcystic tubular dilatation and, ultrastructurally, marked thinning of the lamina densa in the glomerular basement membrane (GBM) and the tubular basement membrane (TBM) of the proximal tubule. She went into chronic renal failure and died at the age of 11 months. At autopsy, the kidney revealed DMS. Histologically, we found Finnish microcystic disease in its early stages in the biopsy. Using a newly developed monoclonal antibody, we analysed the alpha chains (α1–α6) of type IV collagen in the GBM and TBM. There was no defective constitution of alpha chains on the thin GBM, but the thin TBM of the microcystic proximal tubule showed a weak or discontinuous reactivity for α1 and α2 chains, suggesting faulty formation of the basement membrane. The sclerosing glomeruli of the DMS did not depend on collapse of the GBM, which was positive for α3–α5 chains, but mainly on the proliferation of mesangial matrix, which was positive for α1 and α2 chains.

Key words Infantile nephrotic syndrome · Diffuse mesangial sclerosis · Kawasaki disease · Type IV collagen

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Introduction

Kawasaki disease is a self-limiting inflammatory disease affecting multiple vessels. Severe kidney complications are rare. Data on only one patient with nephrotic syndrome associated with Kawasaki disease, who responded to steroid therapy, have been reported previously [8]. The present patient is the first with Kawasaki disease associated with infantile nephrotic syndrome (INS). The early histological lesion was similar to the Finnish-type congenital nephrotic syndrome (CNS) at biopsy [7], but within 4 months the patient revealed diffuse mesangial sclerosis (DMS) at autopsy [6]. Analysis of the renal basement membrane by means of newly developed rat monoclonal antibody for the human alpha chains (α1–α6) of type IV collagen was performed to investigate the possibly defective constitution of alpha chains in the glomerular basement membrane (GBM) and in the tubular basement membrane (TBM) [11, 16].

Clinical history

A previously healthy 4-month-old Japanese girl was admitted to our hospital with a high spiking fever and diarrhoea. She was the second child of 39-year-old mother who had no infectious disease. She had no family history of renal disease and did not have familial C1q deficiency. She had no abnormality of gestation, birth weight, or placental weight. Alpha fetoprotein was not measured in the maternal serum or amnionic fluid. She had no deafness or eye abnormalities. After admission, haemothorax of the left pleura was found, but it disappeared after several days. Fever did not respond to antibiotics and she subsequently developed the classic features of Kawasaki disease, with generalized erythematous maculopapular rash, erythema of the oral mucosa, bilateral nonpurulent conjunctivitis, and desquamation of the fingertips. Significant lymphadenopathy was absent. Leucocytosis (white cell count 17,300/ml), elevated erythrocyte sedimentation rate (42 mm/h), and strongly positive c-reactive protein (more than 20 mg/dl) were seen. Blood pressure was in the normal range (96 mm Hg/38 mm Hg). Urinalysis was normal. Bacterial cultures of the blood, cerebrospinal fluid, urine, and stool were negative. The diagnosis was Kawasaki disease, and she was treated with aspirin. Clinical symptoms disappeared and abnormal laboratory findings improved to almost normal ranges in 3 weeks; aspirin was discontinued. Dur-

ing the 10th week of the illness, a coronary aneurysm was detected by echocardiography. Cardiac angiography (CAG) revealed one aneurysm on the left coronary artery and three on the right coronary artery. On the 2nd day after CAG, she suddenly developed massive proteinuria with microscopic haematuria and generalized oedema, all of which persisted. Nephrotic syndrome was confirmed by the presence of severe proteinuria (3.5 g/day), hypoproteinaemia (4.6 g/dl), hypoalbuminaemia (2.5 g/dl), hypercholesterolaemia (346 mg/dl), and oedema. C3 (64 mg/dl) and C1q (19.2 mg/dl) were almost in normal ranges. Assays for cytomegalovirus and syphilis were negative. Antinuclear antibody and anti-dsDNA antibody were negative. A renal venogram showed no evidence of renal vein thrombosis. Renal biopsy was performed during week 13 of the illness. The child was treated with aspirin, a thrombolytic agent, and a corticosteroid. The nephrotic state did not respond to therapy, and renal function gradually worsened. Blood pressure was elevated to 164/98 mmHg. Ascites and anasarca developed. Peritoneal dialysis was performed for chronic renal failure (creatinine clearance 30 ml/min, creatinine 1.0 mg/dl, blood urea nitrogen 57 mg/dl) during the 26th week of the illness. She died from respiratory disturbance during the 30th week of the illness at the age of 11 months. An autopsy was performed.

Materials and methods

For light microscopy, kidney tissues from the biopsy and the autopsy were fixed in 0.1 M phosphate-buffered 10% formalin. Paraffin sections (2 μm thick) were stained with periodic acid–Schiff (PAS), Masson's trichrome, and periodic acid–methenamine silver (PAM). For electron microscopy, biopsy kidney tissue was fixed in phosphate-buffered 1.2% glutaraldehyde, postfixed in 1% osmium tetroxide, and embedded in Epon 812. Ultrathin sections were double-stained with uranyl acetate and lead citrate. For immunohistochemical studies, paraffin-embedded sections were processed by the peroxidase–antiperoxidase method. Antisera against IgG (1:1600), IgM (1:1600), IgA (1:2500), C3 (1:1600), C1q/C4 (1:1600), and CD68 (PG-M1, 1:50) (DAKO Japan, Kyoto, Japan) were used to treat the sections after digestion for 15 min at 37°C by 0.05% protease type 8 (Sigma, St. Louis, Mo.). Antiserum against Leu M1 (1:30; Becton Dickinson Immunocytometry Systems, San Jose, Calif.) was used to treat the section without digestion.

Immunohistochemical detection of the alpha chains (α1–α6) of type IV collagen was performed as previously described [11, 16]. In brief, the paraffin-embedded sections were heated in acidic media (pH < 1.0) at 121–127°C for 6 min, then incubated with the primary rat monoclonal antibodies against α1 chain (H11), α2 chain (H22), α3 chain (H31), α4 chain (H43), α5 chain (H53), and α6 chain (H63) at room temperature for 1 h . After incubation, they were washed three times with phosphate-buffered saline (PBS) and were incubated with the secondary antibody, peroxidase-conjugated, affinity-purified goat anti-rat IgG for 1 h (DAKO LSAB Kit). A kidney from an 8-month-old Japanese girl who died from postoperative complications following surgery for patent ductus arteriosus was used as the normal control.

Pathological findings

Renal biopsy revealed 27 glomeruli. The diameter of Bowman's capsule of the glomeruli measured from 90 μm to 130 μm. Global sclerosis, adhesions, and crescent formations were not found. Almost mature glomeruli showed moderate proliferation of mesangial cells with an increased PAS-positive mesangial matrix (Fig. 1a). Immature-looking glomeruli were found focally showing a condensed tuft lined with a continuous layer of visceral epithelial cells with or without a dilated urinary space. Leu M1-positive proximal tubules showed focal microcystic dilatation. The inner diameter of the tubules measured 100–150 μm (Fig. 2a). The proximal tubular epithelium was hypertrophic containing fine granular droplets. Distal tubules were mildly dilated and contained regional hyalin casts. Tubulointerstitial lesions were not prominent. No cytomegalic inclusions were present in the nuclei or in the cytoplasm of glomerular endothelial cells and tubular epithelial cells.

Electron microscopy revealed marked attenuation of lamina densa of the GBM, measuring 140–180 nm. The mesangial matrix was increased and loose, but no dense deposits were seen. Podocytes were immature, showing a few organelles in the relatively narrow cytoplasm. Foot process effacement was extensive (Fig. 3a). The basement membrane of the proximal tubules, containing many lipid-like droplets, showed marked attenuation, measuring 120–150 nm, whereas the basement membranes of distal tubules and Bowman's capsule were normal in thickness, measuring 800 nm and 800–1000 nm, respectively (Fig. 3b). In immunohistochemistry, glomeruli demonstrated mild deposition of IgM and C1q in a diffuse mesangial pattern.

At autopsy, about 75% of all glomeruli were characterized by diffuse expansion of the sclerosing mesangial matrix with obliteration of the capillary lumina and the transformation of the glomerular tufts into avascular, shrunken, sclerotic masses surrounded by coronas of partly hypertrophied and vacuolized podocytes (Fig. 1b). One third of all glomeruli were adhering to the Bowman's capsule, forming a septal bridge. Twenty-five percent of the glomeruli remained and showed diffuse proliferative glomerulonephritis. Cystic dilatation of the proximal tubules was found. The distal tubules were also dilated and contained hyalin casts. The diameter of the inner surface of the ectatic tubules varied from 100 μm to 200 μm. Interstitium was focally oedematous but did not contain foam cells. CD68-positive cells, probably macrophages, were prominent in the oedematous interstitium. Such cells were also found in the Bowman's space and in the glomeruli (Fig. 2b). The degree of infiltration of CD68-positive cells into the interstitium and glomeruli was the same as in the earlier biopsy.

Alpha chains (α1–α6) of type IV collagen were detected immunohistochemically in the renal basement membrane of the biopsy specimens and at autopsy (Table 1). The α1 and α2 chains in the biopsy specimen and in the control were distributed mainly in the mesangial matrix and the basement membrane of Bowman's capsule (BCBM), whereas the GBM showed weakly positive staining for these antibodies. The sclerosing glomeruli of DMS at autopsy were strongly positive for α1 and α2 chains (Fig. 4a). The α1 and α2 chains on the TBM of the dilated proximal tubules were weakly positive in the biopsy specimen. At autopsy, the TBM of the dilated proximal tubules showed discontinuous or equivocal staining for α1 and α2 chains, whereas the basement membrane of the distal tubule stained positively for these chains (Fig. 4a). In the control kidney, the basement

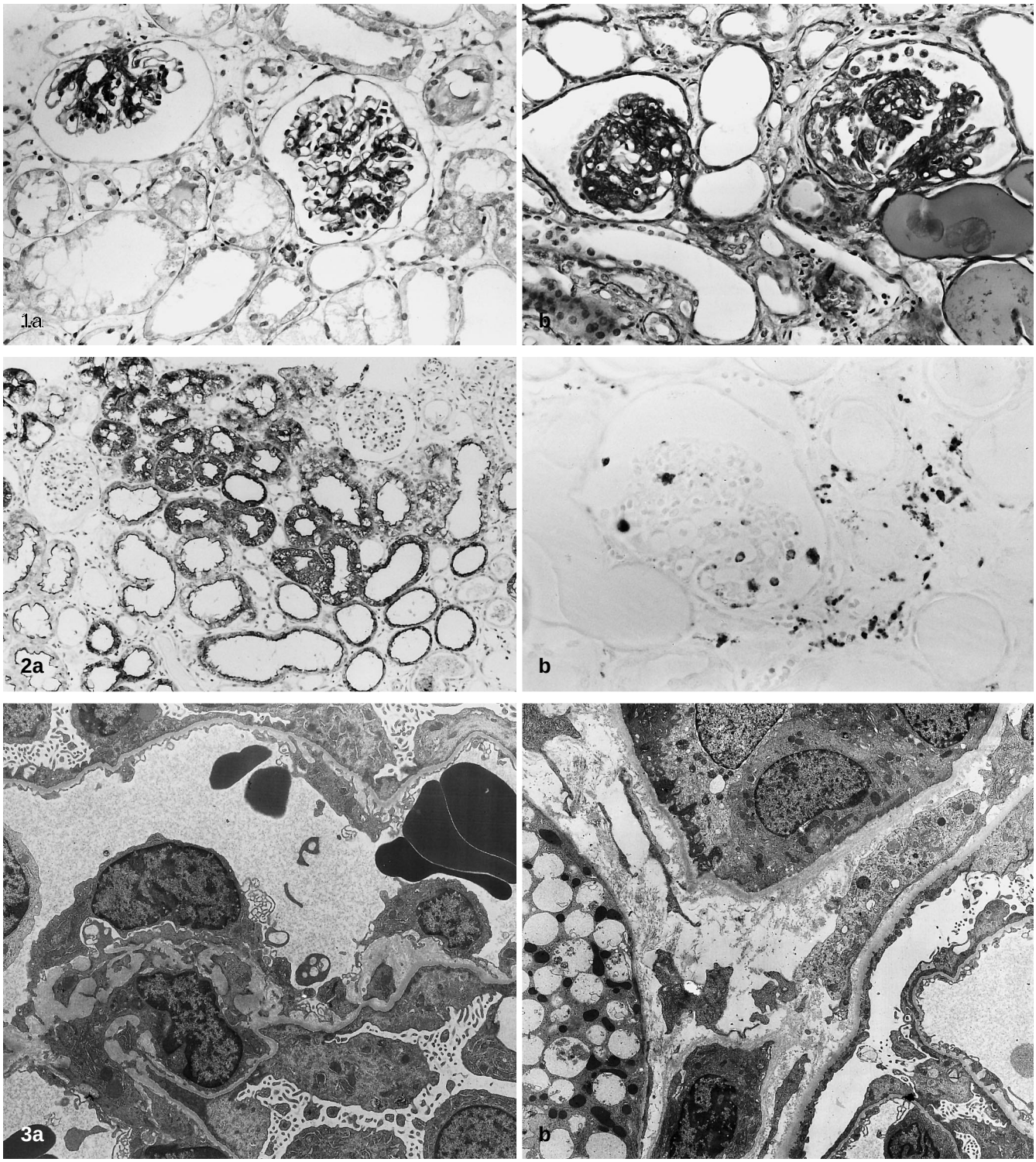

Fig. 1 a, b Light microscopy of the kidney biopsy and autopsy specimens. **a** Almost mature glomeruli show moderate proliferation of mesangial cells with increased PAS-positive mesangial matrix in the biopsy specimens. PAS, ×200. **b** Glomeruli were characterized by diffuse expansion of sclerosing mesangial matrix with obliteration of the capillary lumina and the transformation of the glomerular tuft into avascular, shrunken, sclerotic masses surrounded by coronas of partly hypertrophied and vacuolized podocytes. PAS, ×200

Fig. 2 a, b Immunohistochemistry on the microcystic lesion and macrophages in the kidney. **a** Leu M1-positive proximal tubules of the biopsy show focally microcystic tubular dilatation with 100–150 μm inner diameter. PAP with anti-Leu M1 antibody, ×100. **b** CD68-positive cells in Bowman's space in the glomerular tuft and in the oedematous interstitium (at autopsy). PAP with anti-CD68 antibody, ×400

Fig. 3 a, b Electron microscopy. **a** The GBM showed marked attenuation of the lamina densa, which measured 140–180 nm with extensive foot process effacement. There were no dense deposits in the mesangial matrix. Immature podocytes contained vacuole. ×3,000. **b** The TBM of the proximal tubule containing many vacuoles showed marked attenuation (120–150 nm), whereas the basement membrane of the distal tubule (800 nm) and Bowman's capsule (800–1000 nm) were normal in thickness. ×2,000

Table 1 An Analysis of α Chains of Type IV Collagen (*MAb* monoclonal antibody, *GBM* glomerular basement membrane, *MM* mesangial matrix, *BCBM* basement membrane of Bowman's capsule, *TBM* tubular basement membrane, – negative, +-equivocal, –/+ negative or positive, + positive, ++ strongly positive, –* positive only on the region close to vascular pole, +** positive on the collecting tubule)

α–Chains	Material	MAb	GBM	MM	BCBM	TBM
α1	Biopsy	H11	+–/+	+	++	+
	Autopsy	H11	+–/+	+/++	++	–/+
	Control	H11	+–/+	+	++	++
α2	Biopsy	H22	–/+	+	+/++	+
	Autopsy	H22	–/+	++	+/++	–/+
	Control	H22	–/+	+	++	++
α3	Biopsy	H31	++	–	–*	–/+–
	Autopsy	H31	++	–	–*	–
	Control	H31	++	–	–*	–/+
α4	Biopsy	H43	+	–	–*	–/+–
	Autopsy	H43	+/++	–	–*	–
	Control	H43	++	–	–*	–/+
α5	Biopsy	H53	+/++	–	+	–/+**
	Autopsy	H53	+/++	–	+	–/+**
	Control	H53	++	–	+	–/+**
α6	Biopsy	H63	–	–	+	–/+
	Autopsy	H63	–	–	+	–/+–
	Control	H63	–	–	+	–/+

membrane of the tubules covering the proximal, distal, and collecting tubules were extensively positive for α1 and α2 chains. Staining for the α3 and α4 chains was positive on the GBM and on the BCBM of the region close to the vascular pole, but was completely negative on the mesangial matrix. There was no difference in the staining pattern among the biopsy, autopsy, and control specimen. An interesting finding was that the sclerosing glomeruli at autopsy contained α3-, α4-, and α5-positive glomerular tufts with a noncollapsed and normal appearance, buried in the proliferating mesangial matrix (Fig. 4b). Staining in the TBM was equivocal or negative for α3 and α4 chains in the biopsy and autopsy specimens, whereas the TBM in the control was regionally weakly positive. Localization of the α5 chain in the glomeruli was the same as that of the α3 and α4 chains, but was extensively positive in the BCBM. The TBM was weakly positive for the α5 chain only in the collecting tubules. There was no localization of the α6 chain in the glomeruli, but it was found extensively on the BCBM and in parts of the TBM. There was no difference in the staining pattern among the biopsy, autopsy and control specimens for the α5 and α6 chains. The perimyocytic matrix of the small renal artery was positive for the α1, α2, α5, and α6 chains.

Congenital anomalies, such as cleft palate, microcephaly, ventricular septal defect, and eye changes, were not found. Pathological findings suggesting Kawasaki disease were found in the coronary arteries, with one aneurysm in the left coronary artery, measuring 4 × 6 mm, and three in the right coronary artery, measuring 5 × 5 mm, 4 × 5 mm, and 4 × 4 mm. Each showed severe stenosis with marked intimal thickening. Pericardial fibrous thickening containing a few lymphocytes was found along the coronary arteries. No fibrosis was apparent in the myocardium. Chronic periarteritis showing adventitial fibrosis but no inflammatory cells was found in the lung and the spleen. Lymph nodes measured 9 × 4 mm in the retroperitoneum, in which lymphocytic depletion was found.

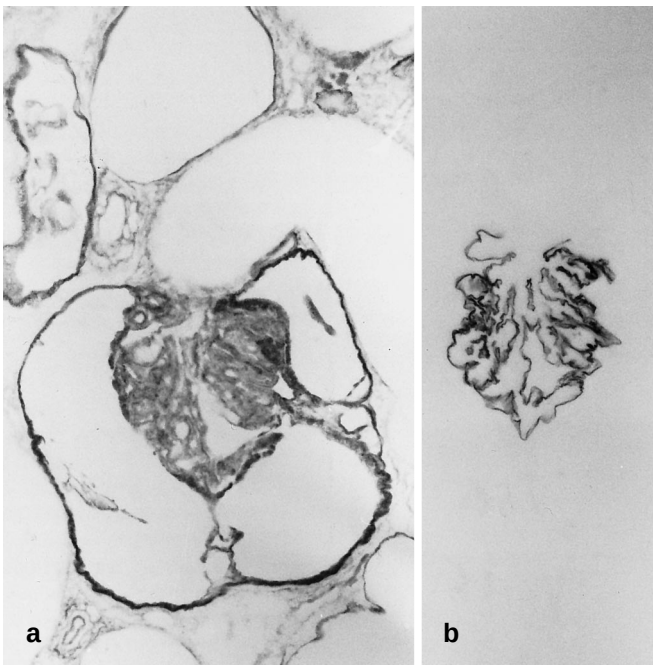

Fig. 4 Immunohistochemistry on the renal basement membrane using antibodies against α1 and α4 chains of human type IV collagen. **a** The sclerosing glomerular tuft and the basement membrane of Bowman's capsule of DMS at autopsy was positive for anti-α1-chain antibody. The antibody against α1-chain on the TBM of the dilated proximal tubules was negative or equivocal, whereas the basement membrane of the distal tubules stained positively for these chains. PAP with anti α1 chain antibody, ×400. **b** The same sclerosing glomeruli on the serial section was positive for α4 chain, showing a noncollapsed, normal glomerular tuft. PAP with anti α4 antibody, ×400

Discussion

Habib and Bois first described a distinct clinicopathologic entity of DMS [6]. Most patients have severe proteinuria between 4 and 12 months of age and experience rapid progression to end-stage renal disease before 3 years

of age. The present patient was healthy in the first 3 months of life before the onset of Kawasaki disease. The proteinuria was discovered just after admission for treatment for Kawasaki disease at the age 4 of months. Nephrotic syndrome developed at the 10th week after admission. The patient had no family history and no perinatal abnormality, a clinical history not consistent with the diagnosis of CNS. This is a recessive inherited disease, associated with premature birth, low birth weight, or placental enlargement, and shows proteinuria soon after birth [7, 18, 19]. The progression seen here, which does not occur in CNS, suggests the clinical diagnosis of INS [5]. However, the histological finding at biopsy was of diffuse mesangial proliferative glomerulonephritis with microcystic tubular dilatation, corresponding to Finnish-type CNS (Finnish microcystic disease) [7, 18, 19]. Clinical criteria of CNS and INS do not correspond with the histological criteria of Finnish microcystic disease or DMS, respectively [17]. According to Sibley and Striegel [18], CNS with congenital onset (less than 3 months) was Finnish-type CNS (Finnish microcystic disease) in 286 of 396 cases (72%) and DMS in 46 of 396 cases (12%). INS with infantile onset (more than 3 months) is Finnish microcystic disease in 12 of 106 cases (11%) and DMS in 50 of 106 cases (47%). The present patient had an infantile onset and revealed Finnish microcystic disease histologically in the biopsy specimen, followed eventually by histology showing the typical features of DMS at autopsy 4 months later [5, 6].

The early lesion of DMS is not yet well documented [6, 18, 19], and it is not known whether the late stage of Finnish-type CNS is similar to DMS or whether early lesions of DMS are similar to Finnish microcystic disease. Morphological differentiation between the two forms is not possible, and this case is a unique variant of Finnish-type CNS or DMS. The histological finding of DMS at autopsy might correspond to a chronologically late stage in the evolution of the nephropathy, where morphological similarity of the tubules to Finnish microcystic disease in the biopsy corresponds to the progressive clinical outcome [4].

The basic pathogenic defect in this disorder is not known. The observation of complete remission of nephrotic syndrome following renal transplantation in patients with CNS indicates, as in the case of Alport syndrome, a genetic disturbance of the GBM structure and its formation [10]. Disturbed metabolism of type IV collagen in the GBM of the CNS has also been suggested [14]. There have been a few reports documenting the electron microscopic data of the GBM of Finnish-type CNS or DMS. The width of the GBM, especially of the lamina densa in Finnish-type CNS, is 124–144 nm, which is thinner than the control for the same age (200 nm) [1, 2]. The GBM of DMS is thickened and highly irregular, with a cloudy pattern of alteration, and the changes reminiscent of Alport syndrome [18, 20] suggest a disturbance of GBM development [15]. The widths of the GBM and the TBM of the proximal tubules of the biopsy specimen in the present case was 140–180 nm and 120–150 nm, respectively, and revealed marked attenuation, similar to the GBM of thin membrane disease or Alport syndrome. However the thin GBM of the present patient was positively stained with antibodies against each of the six α-chains of human type IV collagen. The result of the biopsy was similar to that of thin membrane disease without any defect of the six α-chains (personal data), but was different from X-linked Alport syndrome with defective staining for the α3, α4, and α5 chains [11, 13].

The sclerosis in the glomeruli of the DMS was produced mainly by deposition of α1 and α2 chains, which were components of the mesangial matrix, and not by the collapse of the GBM. The α3–α5 chains in the sclerosing glomeruli were localized on the apparently normal glomerular tuft, which was buried in the proliferating mesangial matrix. CD68-positive cells, presumably macrophages, had infiltrated both the glomeruli of the biopsy specimen and the sclerosing glomeruli. These cells may be associated with mesangial cell proliferation and the subsequent overproduction of α1 and α2 chains in the mesangial matrix. These immunohistochemical findings cannot be generalized and regarded as representative of those in typical CNS or DMS. Nerlich et al. [12] investigated the localization of the extracellular matrix component in Finnish-type CNS and DMS using polyclonal antibodies against collagen type IV. Finnish type CNS showed a normal basement membrane localization and composition, whereas DMS revealed the accumulation of collagen type I, III, and V within the sclerosing glomeruli, together with a complete loss of basement membrane collagen type IV and laminin. This report supports the result of the biopsy resembling Finnish microcystic disease, but contrasts with the result in the glomeruli of DMS at autopsy.

The TBM of the microcystic proximal tubules at the biopsy was weakly stained with anti-α1- and -α2-chain antibodies, which corresponded to the abnormally thin TBM seen in electron microscopy, and showed weak or discontinuous reactivity for these antibodies at the autopsy. Localization of the α1 and α2 chains in the control was extensive on the TBM covering the proximal, distal, and collecting tubules. Results for anti-α3- and -α4-chain antibodies were negative or equivocal in the biopsy and autopsy specimens, whereas these antibodies were partially positive on the TBM of the control kidney. These results may indicate that faulty formation of the TBM of the proximal tubules is one of the causes of microcystic tubular dilatation if relatively high amounts of collagen type IV are required for proper folding against the pressure in the urinary space.

There may be no direct correlation between Kawasaki disease and DMS. Because CNS and INS have a predisposition for infection [5] and Kawasaki disease is an infectious disease, an acquired factor may be the common basis of the two diseases. In the present patient, we excluded congenital cytomegalic inclusion disease [3], familial C1q deficiency associated with renal and cutaneous disease [9], and congenital syphilis-associated glo-

merulopathy. Positive IgM and C1q deposition in a diffuse mesangial pattern may be associated with nonspecific trapping in the mesangial matrix in this case, as there were no electron-dense deposits in the area.

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