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Familial Glomerulopathy with Giant Fibrillar Deposits

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Summary. Proteinuria and microhaematuria were observed in three siblings and one first-degree cousin. Histological examination of three kidney biopsies and one autopsy specimen shows the same diffuse glomerular lesions in all patients, characterized by mainly subendothelial but frequently transmembranous and mesangial deposits of a unique fibrillar structure, visible by electron microscopy.

Examination by immunfluorescence gave inconstant findings. No serological abnormalities could be established. To our knowledge, such a pecular form of familial glomerulopathy has not been described so far.

Key words: Glomerulonephritis – Familial – Pathology.

Introduction

It is well established that many nephropathies, especially glomerular lesions, exist in a familial or hereditary form (Bernstein 1979). Apart from glomerular involvement in systemic diseases (Kopelman et al. 1964; First 1973; Barsky et al. 1977; Chevet et al. 1978) there are numerous reports on idiopathic glomerulopathies. Whereas some forms show characteristic clinical symptoms and specific morphological glomerular lesions as for example Alports disease (Grünfeld et al. 1973), others are associated with non specific forms of glomerulonephritis (Habib and Gubler 1973; Schaerer et al. 1974; Bolton et al. 1976; Schwarz et al. 1976). We observed a familial glomerulopathy in three siblings and one first-degree cousin. All had microhaematuria and mild to severe proteinuria. Kidney tissue examination revealed glomerular lesions of an unique pattern. We could not find a similar form of glomerulopathy in the literature.

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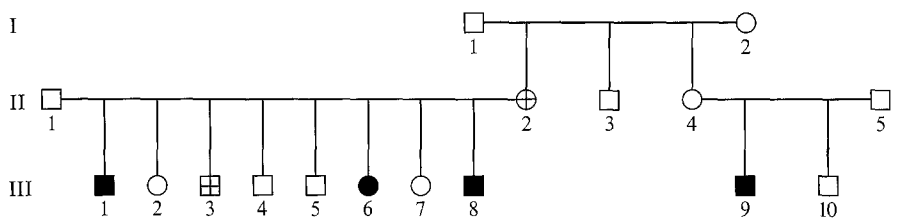
Case Reports

Case 1. B.L., a 44 year old truck driver was well until age 42 when hypertension, proteinuria and microhaematuria were first observed. 6 months later nephrological work-up including renal biopsy was done. On physical examination, no abnormal findings were observed. Blood pressure 140/95 mmHg. No oedema. Laboratory data is given in Table 3. During the following $1^1/_3$ years blood pressure rose to 170/110 mmHg requiring antihypertensive treatment. Serum creatinine increased to 1.5 mg/100 ml.

Case 2. F.-B.B., a 37 year old housewife had several gynaecological examinations (excision of ovarian cysts, salpingeal ligation), appendectomy and tonsillectomy. For the last 8 years recurrent urinary tract infection had occurred. Proteinuria was present for 4 years and microhaematuria for 8 years. Blood pressure 140/90 mmHg. At age 37, the patient commited suicide. An autopsy was performed.

Case 3. B.H., 33 year old policeman. Tonsillectomy at age 27. At age 32, proteinuria and microhaematuria were first diagnosed. On physical examination no pertinent abnormalities. Blood pressure 130/80 mmHg. No fluid retention. Laboratory data see Table 3. Excretory urogramm within normal limits. During follow up for $1\ ^1/_2$ years no progression of renal symptoms. Blood pressure always within normal limits

Table 1. Pedigree of kindred reported. *Square:* males, *circles:* females. Renal tissue obtained by biopsy (cases III/1, 8 and 9) or autopsy (case III/6) was examined in 4 cases. Case II/2 died at age 34 because of renal failure, case II/3 died at age 55 due to cerebrovascular accident. Case III/3 has mild proteinemia and microhaematuria



⊞ ⊕ Nephropathy
■ ● Nephropathy, histologically examined

Table 2. Summary of clinical data

Case	Sex	Age years	Age nephropathy first diagnosed	Hyper tension	Nephrotic syndrome	Oto-sclerosis
1.	M	43	42	present	present	absent
2.	F	37	29	absent	absent	absent
3.	M	33	32	absent	absent	absent
4.	M	44	31	present	present	present

Table 3. Summary of pertinent laboratory Data at time of renal biopsy or autopsy

	Case 1	Case 2	Case 3	Case 4		
				1st biopsy 1966	2nd biopsy 1971	3rd biopsy 1979
Urinalysis						
Leucocytes/HPF	5–10	10–20	1–5	5–10	5–8	30–40
Erythrocytes/HPF	4–8	10–20	20–40	1–5	1–3	5–10
Proteinuria g/24 h	4.7	0.7	1.0	2.1	5.8	10.2
Totalserumprotein g%	6.4	7.4	6.6	7.2	5.7	5.9
Serumcreatinine mg%	1.6	0.9	1.0	1.0	1.3	10.5
Paraproteinemia	absent	absent	absent	absent	absent	absent
Cryoglobulinemia	absent	not examined	absent	not examined	not examined	absent
Antinuclear antibodies	1:20	<1:10	1:10			<1:10
Immuncomplexes (C_{1q} fixation)	absent	absent	absent	–	–	absent
C_3 mg%	120	192	103	–	–	103
C_4 mg%	81	17	23	–	–	35
Total haemolytic complement (CH_{50})	166%	not examined	105%	–	–	120%

Case 4. W.E., a 44 year old construction worker was well until age 31 when proteinuria and haematuria were noticed and a first renal biopsy was performed. At age 35 mild otosclerosis with conduction deafness was diagnosed. At that time, blood pressure rose to 150/100 mmHg with persistent moderate hypertension ever since, controlled by drug treatment. At age 36 proteinuria rose to 5.8 g/24 h, not influenced by a course of prednisolone and azathioprin. Renal function slowly deteriorated and at age 45 chronic intermittent haemodialysis was started due to preterminal renal failure. Nephrotic syndrome and hyperlipaemia were present for 10 years. Urinalyis persistently showed mild leucocyturia (10–20 cells/HPF) and erythrocyturia (5–10 cells/HPF). For further laboratory data see Table 3.

The clinical data of the 4 patients examined are summarized in Table 2.

Material and Methods

Light microscopy was performed on renal biopsies of three patients and on one autopsy specimen. The following routine and special stains were used: H.E., PAS, Chromotrop-Aniline-Blue, Perjodic-Acid-Silver-Methenamine, Kongored and Thioflavine.

Immunofluorescence: Direct and indirect immunofluorescence was done in one patient, direct immunofluorescence only in the second. The presence of IgM, IgG, IgA, IgE (one patient), Bence Jones kappa and lambda, C_3, C_{1q}, C_4 and fibrinogen were sought.

For electron microscopy the tissue was cut into 1–2 mm^3 fragments, fixed in 2,5% glutaraldehyde (0,1 M cacodylate buffer, pH 7,25; 3 h at 4° C) and post-fixed with 1% OsO_4 (0,1 M cacodylate buffer, 3 h at room temperature). The samples were dehydrated through an up-graded ethanol

series and embedded in EPON 812. Ultrathin sections were contrasted with uranyl acetate and lead citrate. Survey and photography of the sections were performed with a ZEISS EM 9-S 2 electron microscope.

Results

Light Microscopic Examination. In all patients glomeruli show large subendothelial and mesangial deposits and focal segmental mesangial hypercellularity (Fig. 1). Intramembranous and extramembranous deposits are also constant findings, but less frequent. Segments of some glomeruli are lobulated with "double contours" of the capillary walls (Fig. 2). Degenerative lesions such as focal-segmental or global sclerosis and/or hyalinosis are variably frequent. Hyaline PAS positive deposits are found in a few arterioles. Focal tubular

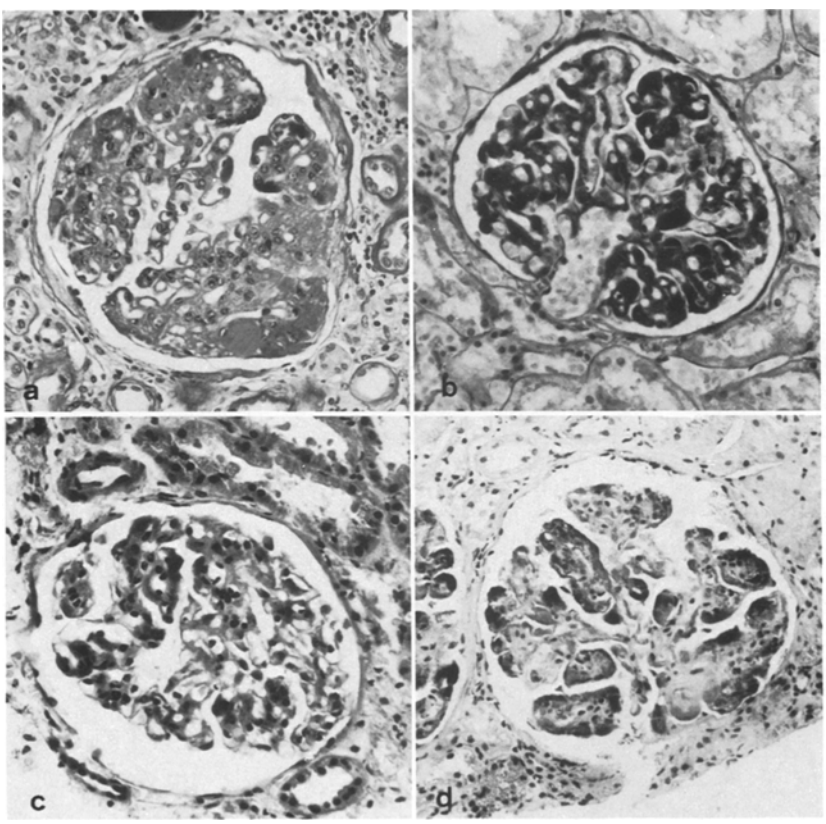


Fig. 1a–d. Altered glomeruli from each of the four patients described (**a** = case 1, **b** = case 2, **c** = case 3, **d** = case 4). Enlargement of capillary wall by mainly subendothelial deposits. Slight increase of mesangial matrix. Slight mesangial hypercellularity with lobular pattern (**a, c**). Segmental sclerosis and hyalinosis and capsular synechia (**c**). Paraffin section, PAS stain. Objectif ×10 (**a**), ×20 (**b, c, d**). Occular ×10

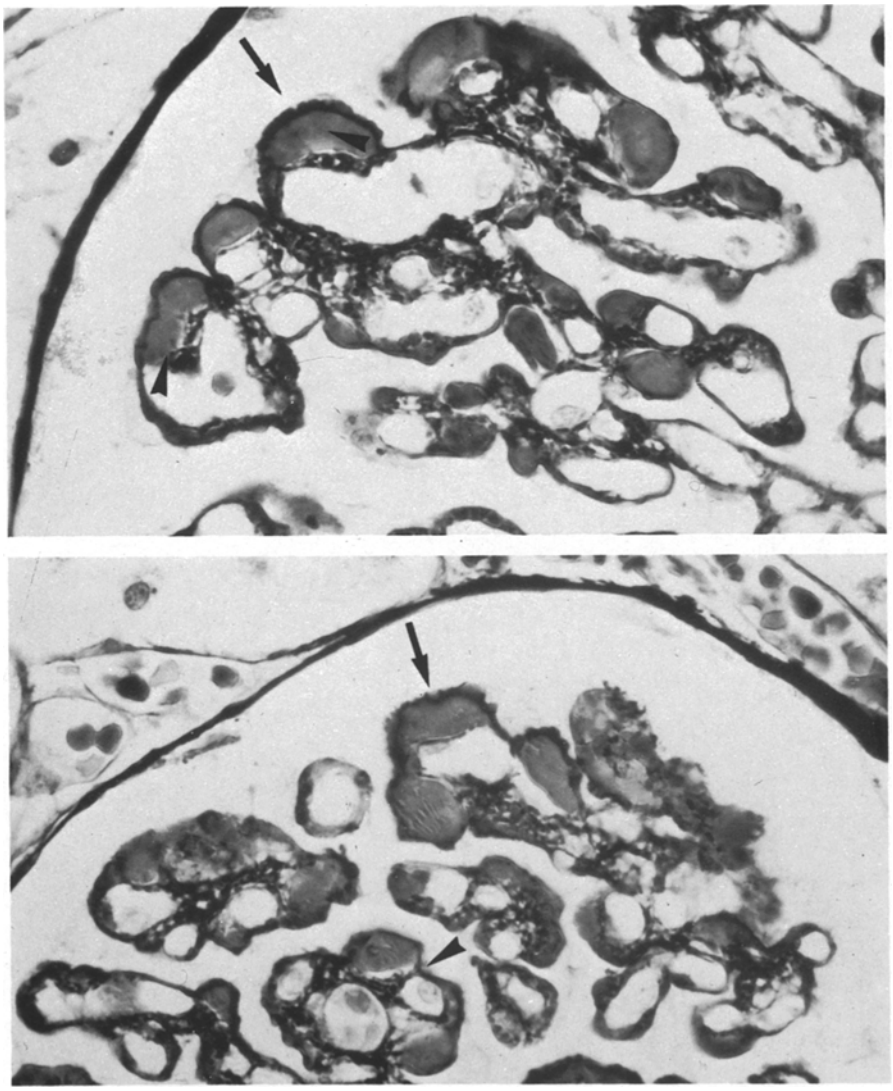


Fig. 2. Two glomerular segments of case 2. Increased mesangial matrix. Small mesangial deposits. Big subendothelial deposits with spikes formation of basement membrane (→). "Double contour" of capillary wall (▶). Paraffin section, PAS stain. Objectif × 100. Ocular × 10

atrophy and interstitial fibrosis are observed in two patients. The findings are summerized in Table 4.

Immunofluorescence. The biopsies of two patients were examined. One showed completely negative results by direct and indirect methods (Case 3), whereas in the other (Case 1) by the direct method, granular parietal fluorescence was seen for IgA, Bence Jones kappa and lambda and less intense for IgM, IgE and C_4. Fixation for IgG, C_3, C_{1q} and albumin was absent.

Table 4. Light microscopic findings

Patients	Case 1: III/1	Case 2: III/6	Case 3: III/8	Case 4: III/9	
Biopsy/Autopsy	B 1978	A 1979	B 1978	B 1966	B 1971
Mesangial	focal segmental	focal segmental	focal segmental	focal segmental	diffuse
Proliferation	+	+	+	+	+
Deposits					
mesangial	++	++	+++	++	++
subendothelial	+++	+++	+++	++	+++
intramembranous	+	++	+	+	+
subepithelial	+	++	+	+	+
Sclerosis/Hyalinosis	focal global/ segmental	focal global	focal segmental	–	–
Vascular deposits	+	+	+	–	+
Tubulointerstitial atrophy	zonal	–	zonal	–	–

Electron Microscopic Findings. Ultrastructural findings are comparable in all three kidney biopsies and in the autopsy case. All glomeruli examined show mainly giant subendothelial electron dense deposits (Fig. 4). Intramembranous, subepithelial and mesangial deposits are also frequently seen (Figs. 3, 5 and 6). Sometimes small or medium-sized deposits are found in the membrane of the Bowman-capsule. There is segmental sclerosis of capillary loops. Mesangial matrix is increased and extracellular spaces contain fine reticular filaments, no collagenous fibrils are seen. The basement membranes of the capillary walls occur as homogeneous structures varying in thickness only. The lamina rara externa is mostly seen as a clear space except where deposits are present. Endothelial cells appear slightly swollen and the cytoplasm extends as a thin mainly regular coating. In the capillary lumen some vesicles with amorphous material are present. Elements of the rough-surfaced endoplasmic reticulum are scattered throughout the cytoplasm of the podocytes. Sometimes lysosomes and autophagic vacuoles or vesicles are seen.

The dimensions of the electron dense deposits are the same in all glomeruli examined and show an unusual pattern with regularly shaped filaments (Figs. 7 and 8). The structure of the straight filaments is fine or medium granular, the lay-out is irregular. The deposits lack any complex- or bundle organization. No annular or curved cylindrical structures could be found. The same pattern and structure of the deposits can be established in all patients. The non-organized fine or medium granulated filaments are present in the deposit of each patient. The single filaments are 120 Å $\pm$ 8 Å wide and 1,250 Å $\pm$ 60 Å long (Table 5).

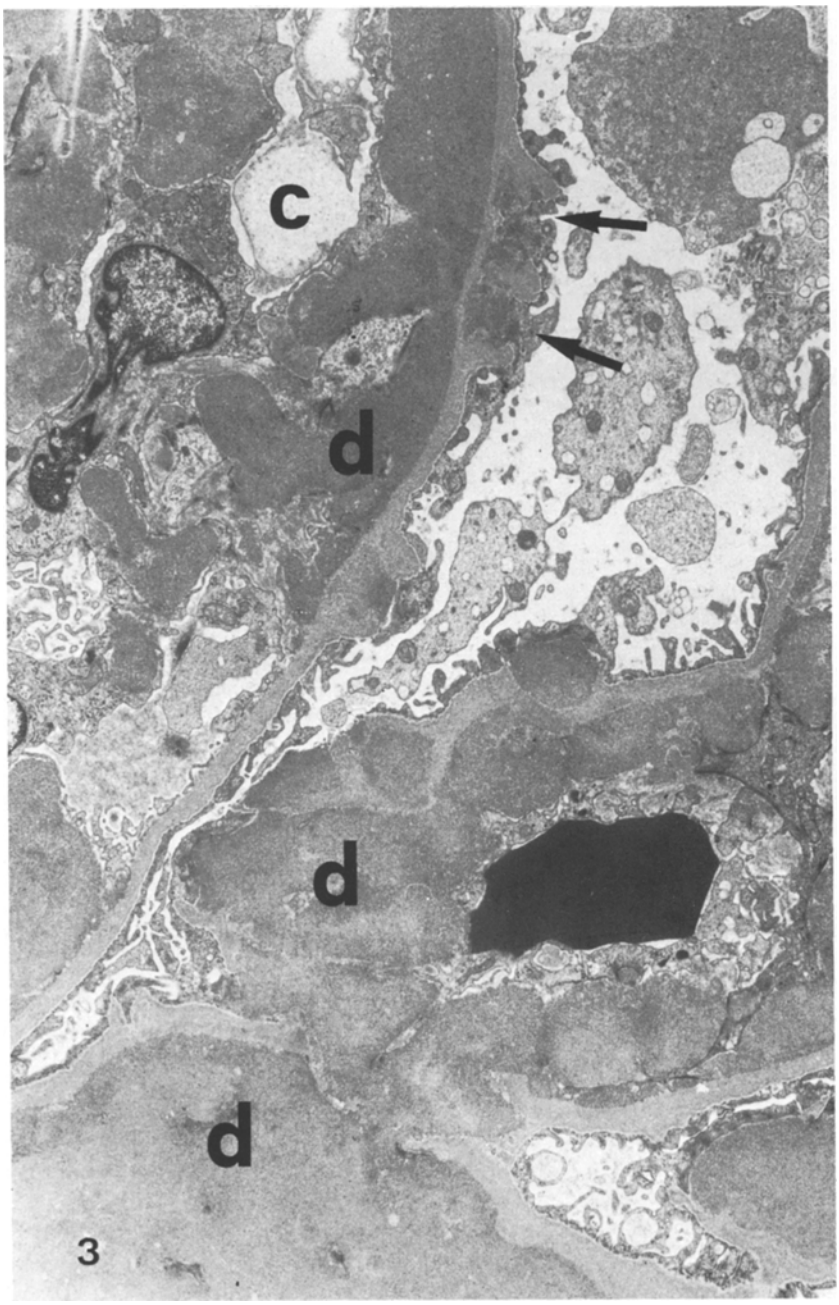


Fig. 3. Case 4: Electron micrograph shows part of a glomerulus. Note the giant electron dense subendothelial, intramembranous and subepithelial deposits (*d*). *Arrows* show what we interpret to be a rupture of the basement membrane and spike formation. *C*, capillary lumen. Magnification ×6,500

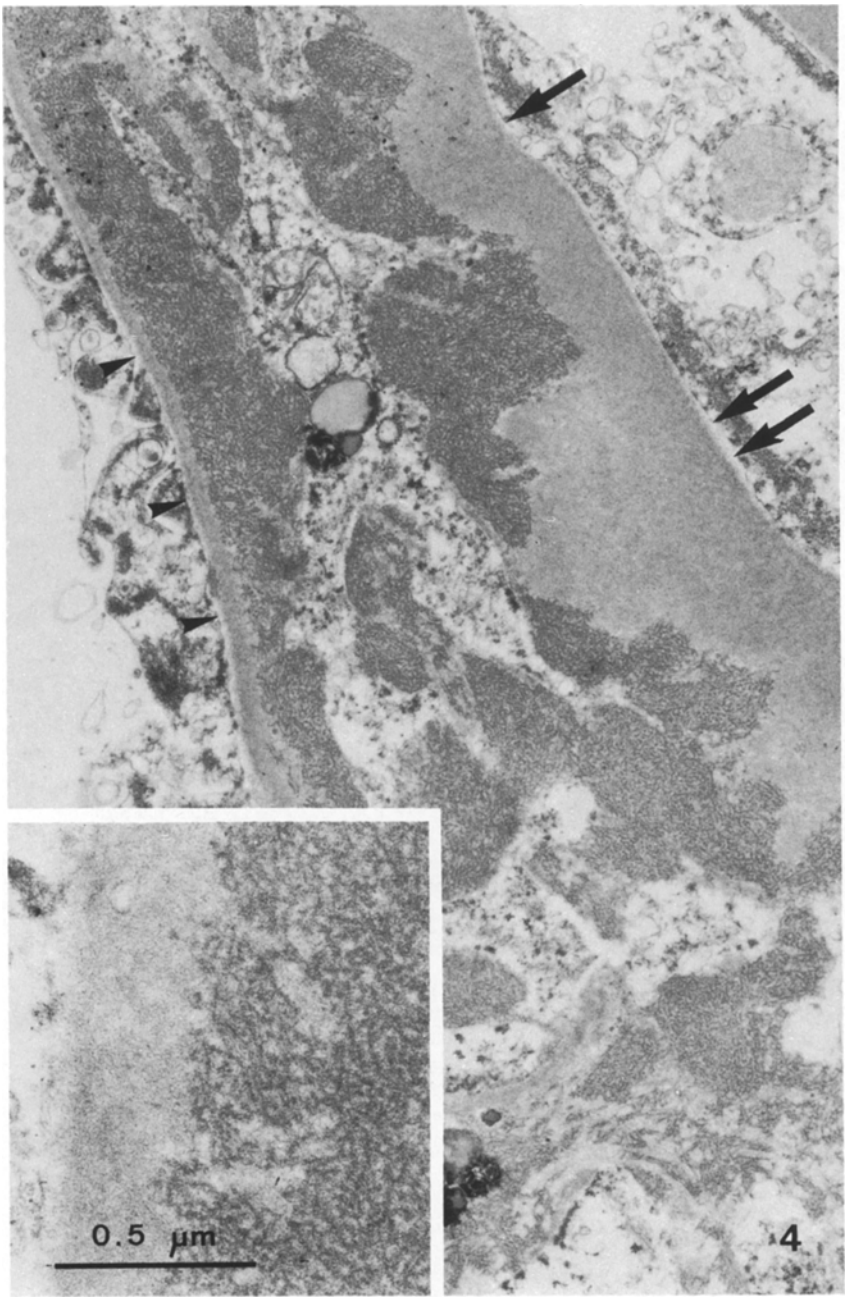


Fig. 4. Case 2: Electron micrograph shows a normal lamina densa (►) and one thickened (→) and giant subendothelial fibrillar deposits in a collapsed glomerular loop. Magnification ×18,000

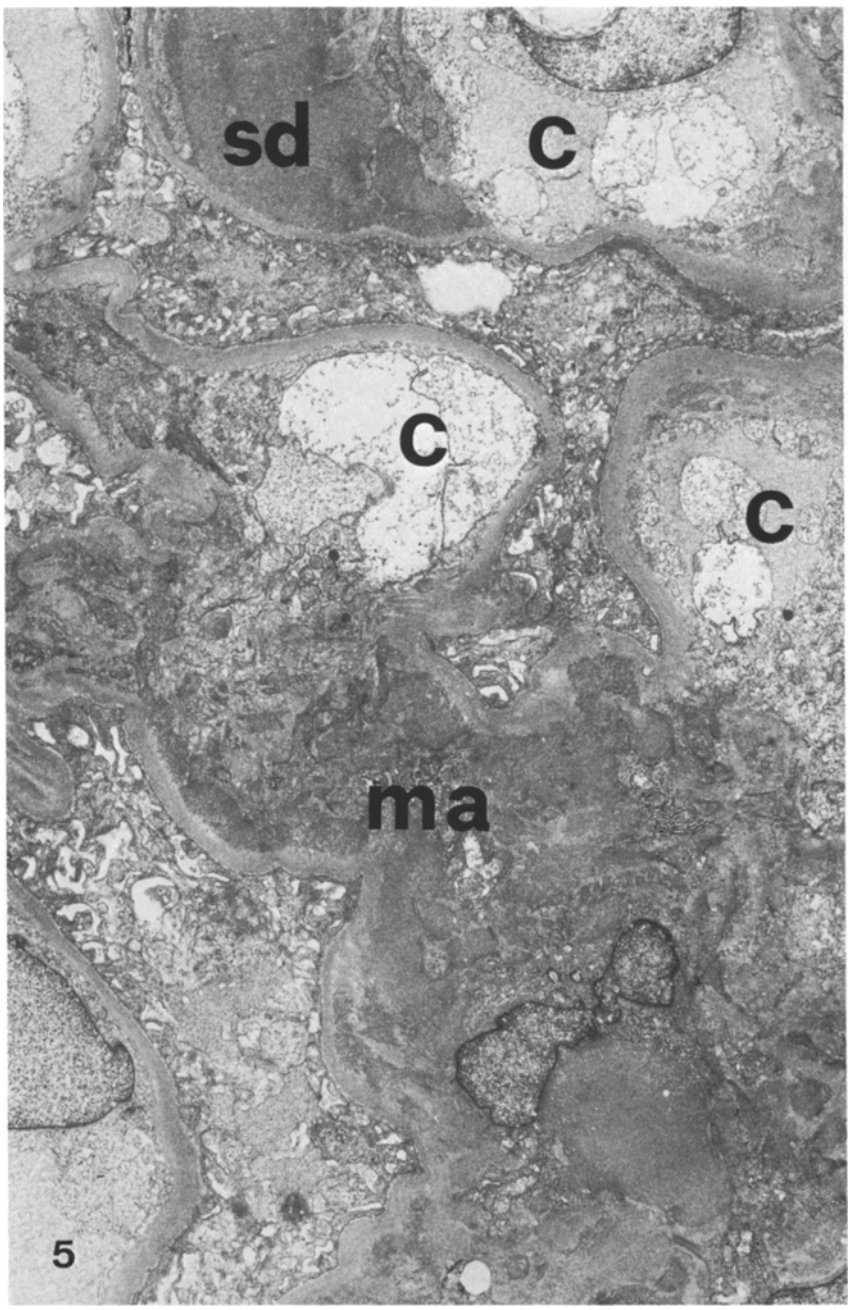


Fig. 5. Case 3: Mesangial area (*ma*) with more prominent deposits. *C*, capillary lumen; *sd*, subendothelial deposits. Magnification ×6,500

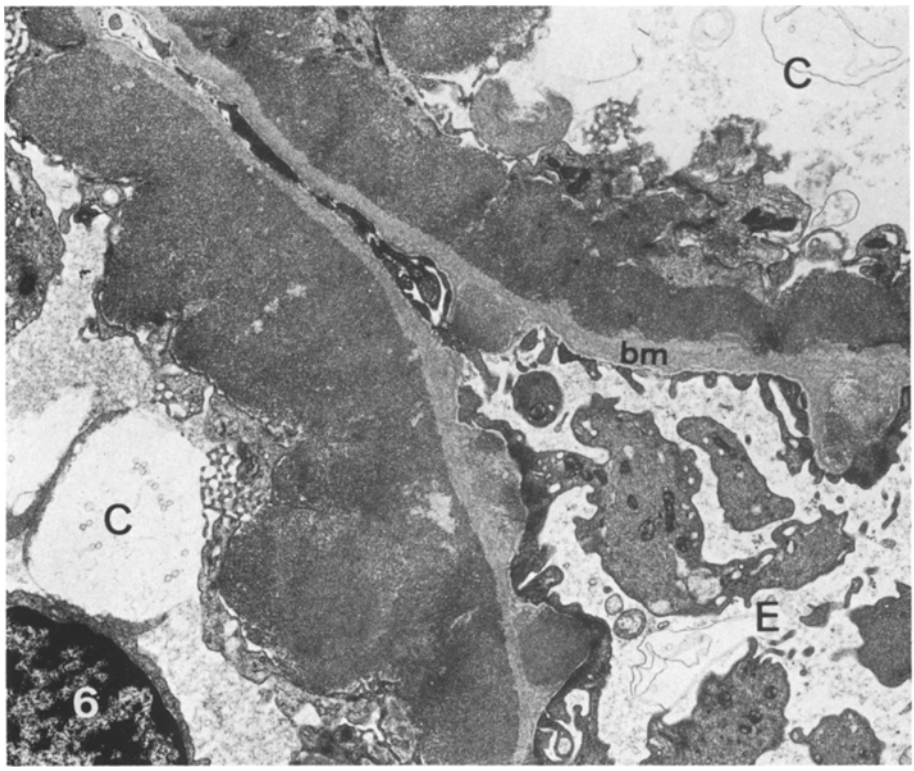


Fig. 6. Case 1: Impressive electron dense, mainly subendothelial and transmembranous fibrillar deposits. *C*, capillary lumen; *bm*, basement membrane, *E*, epithelial side of basement membrane. Magnification × 7,500

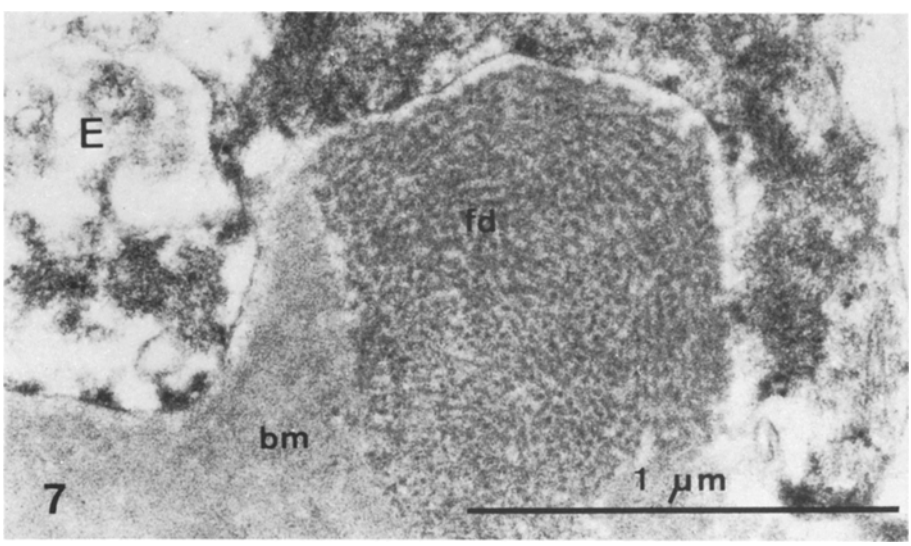


Fig. 7. Case 2: Subepithelial fibrillar deposit (*fd*). *bm*, basement membrane; *E*, epithelial side of basement membrane. Magnification × 56,000

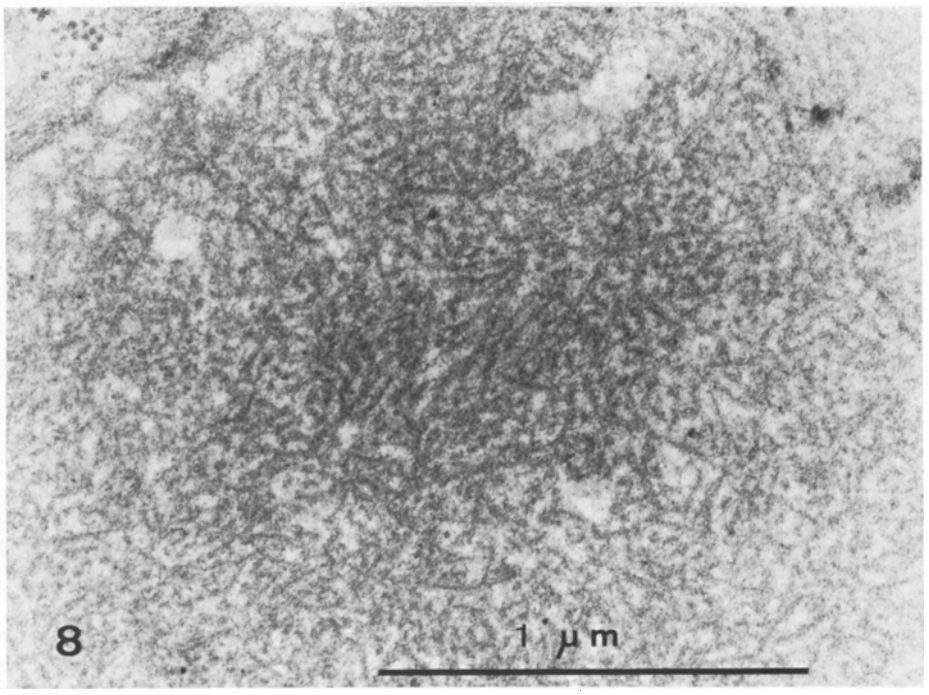


Fig. 8. Case 4: Note the unusual pattern of this deposit which is representative for all. The short and straight filaments appear fine to medium granulated, not aggregated into bundles, lack of any complex-organization, irregular lay-out. Measurements of the single filament give a mean length of 1,250 Å and a mean width of 120 Å. Magnification ×56,000

Table 5. Measurements of single finely granular filaments

	Case 1	Case 2	Case 3	Case 4
Number of micrographs	5	5	5	5
Number of filaments measured	100	100	100	100
Magnification	56,000	56,000	56,000	56,000
Average length in Å (standard error)	1,250	1,270	1,220	1,260
	(50)	(20)	(30)	(50)
Average width in Å (standard error)	123	121	120	118
	(5)	(4)	(2)	(6)

Discussion

Morphologically two groups of familial glomerulopathies can be distinguished: one characterized by glomerular deposits and the other without deposits (Table 6). Deposits are a striking feature in our cases.

IgA-Nephropathy is defined by dominant deposits of IgA in a mainly mesangial position, most frequently accompanied by C_3 and sometimes IgG and with a varying histological picture (Berger 1969; Werra et al. 1973; Zimmermann and Burkholder 1975). Familial forms of IgA nephropathies are known (Werra

Table 6. Familial or hereditary glomerulopathies

With glomerular deposits	Without glomerular deposits
IgA-nephropathy	Alport syndrome
Amyloidosis	Hyperprolinemia
Systemic lupus erythematodes	Benign haematuria
Immunological hereditary nephropathy	Nail-patella syndrome
Lipodystrophy	Nephrotic syndrome
GN in deficiencies of complement components	Lecithin-cholesterol-acyl-transferase deficiency

et al. 1973; Zimmermann and Burkholder 1975), even with giant subendothelial deposits (Okada et al. 1979). Ultrastructurally the deposits show a granular pattern (Okada et al. 1979). Our patients show unique filamentously structured deposits by electron microscopy, which are not comparable to the reported cases. In one of our cases immunohistology gave completely negative results. In the other IgA was indeed present in a slight granular parietal distribution, but C_3 was absent. In view of these findings we can exclude our patients from this entity.

Systemic lupus erythematodes also reported in a familial form (First 1973; Barsky et al. 1977), often occurs with diffuse irregular mesangial proliferation and transmembranous deposits. By electron microscopy these deposits are either granular or filamentous, and immunofluorescence usually shows IgG and classical complement components (Sinniah and Fengl 1976). Negative serological and inappropriate immunohistological findings in our patients are not compatible with familial lupus nephritis.

Glomerulonephritis associated with complement deficiency (Peters and Williams 1974; Agnello 1978) can be excluded by normal CH_{50} in the sera of three patients.

Immunological hereditary nephropathy is an entity characterized by a haemolytic uraemic syndrome associated with ischaemic glomerular changes and deposits of immuno-globulins and fibrin in glomeruli and renal vessels (Grottum et al. 1974). Our patients did not show any signs of haemolytic uremic syndrome nor of glomerular lesions related to ischaemia.

Negative staining by Kongored and Thioflavine as well as electron microscopic investigation exclude familial amyloidosis (Alexander and Atkins 1975).

We did not observe any clinical signs of lipodystrophy or low serum complement (Habib et al. 1977).

It is suggested that the localization of glomerular deposits is related to the molecular weight and size of circulating immune complexes. But other factors such as shape, electric charge and chemical composition may play an important role. It is assumed that complexes of high molecular weight are located in the mesangium or in a subendothelial position, whereas those of smaller size can penetrate the capillary basement membrane and produce subepithelial deposits (Mc Cluskey 1974; Albini et al. 1979). In spite of the giant subendothelial deposits in our cases we were unable to detect abnormal circulating substances.

Table 7. Ultrastructural characteristics of the deposits

Cryoglobulinemia		Familial glomerulopathy
mainly in bundles	*organisation*	irregular lay-out
annular and cylindrical	*shape of fibers*	straight and solid
300 Å in diameter up to 1 μ long		120 Å in diameter up to 0.12 μ long
fibrillar	*structure*	fine to medium granulated
rhombic cristals with periodic structure	*others*	——

According to the distribution of deposits and their filamentous structure we considered cryoglobulinaemia to be a possible cause even in the absence of reports of familial forms. Negative serological and different ultrastructural findings when compared with the literature (Porush et al. 1969; Feiner and Gallo 1977; Stoebner et al. 1979) let us to believe that no correlation exists (Table 7).

Another speculative explanation of deposition of an exclusively fibrillar material in glomeruli could be that mesangial or endothelial cells produce a pathological substance of unknown origin, as a consequence of an inborn error of metabolism.

We hope to receive more material which will permit further investigation of these unusual filamentous condensations. In a careful review of paraffin slides, from brain, lung, heart, liver and spleen, in the autopsy of Case 2, no other deposits were observed.

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