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Renal disease in nail-patella syndrome: Clinical and morphologic studies

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Renal disease in nail-patella syndrome: Clinical and morphological studies. Clinical and morphological features of seven patients with the nail-patella syndrome are described. Progression to renal failure after a prolonged period of asymptomatic proteinuria is reported. Kidney tissue from these seven patients studied by light, immunofluorescent and electron microscopy demonstrated abnormalities characteristic of this disease. Focal glomerular basement membrane thickening was observed by light microscopy. Immunofluorescent microscopy showed focal glomerular basement membrane and arteriolar staining with serum proteins, predominantly IgM and β1C. Electron microscopy revealed markedly abnormal glomerular basement membranes containing bundles of cross-striated fibrils. These fibrils were more readily demonstrated in phosphotungstic acid-stained sections. The data presented suggest that the inborn error of connective tissue metabolism of the nail-patella syndrome is associated with renal disease as the result of deposition of collagen moieties in glomerular basement membranes with subsequent alterations of glomerular structure and function.

Atteinte rénale dans l'ostéo onycho dysplasie. Etude clinique et morphologique. Les aspects cliniques et morphologiques de sept malades atteints d'ostéo onycho dysplasie sont décrits. L'évolution vers l'insuffisance rénale après une période longue de protéinurie asymptomatique est décrite. L'étude du tissu rénal de ces sept malades par microscopie optique, immunofluorescence et électronique a montré des anomalies caractéristiques de l'affection. Des épaississements focaux de la basale glomérulaire ont été observés en microscopie optique. L'immunofluorescence a montré la fixation focale sur la basale glomérulaire et les artérioles de protéines sériques, essentiellement IgM et βIC. La microscopie électronique a révélé des anomalies majeures des membranes basales glomérulaires qui contenaient des faisceaux de fibrilles à striation transversale. Ces fibrilles étaient plus particulièrement mises en évidence dans les coupes traitées par l'acide phototungstique. Les résultats présentés ici suggèrent que l'affection congénitale du métabolisme du tissu de soutien dans l'ostéo onycho dysplasie est associée à une atteinte rénale qui traduit le dépôt de fractions de collagène dans la membrane basale glomérulaire et les altérations de structure et de fonction glomérulaire qui en découlent.

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Although renal dysfunction in the hereditary mesenchymal disease, the nail-patella syndrome, is most frequently manifested by asymptomatic proteinuria, progression to renal failure may occur. Initial morphologic descriptions of the kidney in this disease reported non-specific changes by light and electron microscopy [1, 2], but two recent case reports describe unusual changes in glomerular basement membranes [3, 4].

This report describes clinical features of seven patients with the nail-patella syndrome and morphologic observations on biopsy specimens from these patients studied by light, immunofluorescent and electron microscopy. These observations demonstrate an abnormality of glomerular basement membranes characteristic of this disease.

Clinical material

The family tree of cases 1–6 is shown in Fig. 1.

Case 1. This 33 year old man had several procedures during childhood for correction of a talipes equinovarus deformity and instability of the knees secondary to dislocation of hypoplastic patellae. His thumbnails were hypoplastic and iliac horns were present. Before four years of age he had 11 negative urinalyses, three with a trace of protein and three with 1+ protein, qualitatively. At four and one-half years of age quantitative urinary protein excretion was 2.85 g/24 h. Subsequently, all urines were 2+ or greater, qualitatively, for protein. At 19 years of age the blood urea nitrogen (BUN) was 18 mg/100 ml. He was found to have severe hypertension (240/110 mm Hg) and bilateral papilledema at 31 years of age. Serum creatinine was 3.0 mg/100 ml, albumin was 2.5 g/100 ml, and cholesterol was 275 mg/100 ml. An oral glucose tolerance test was within normal limits. The serum hemolytic complement was 73 units (normal, 48 to 70 units). Quantitative urinary protein excretion was 15.1 g/24 h. Intravenous pyelogram and audiogram were normal. During the next 18 months, renal

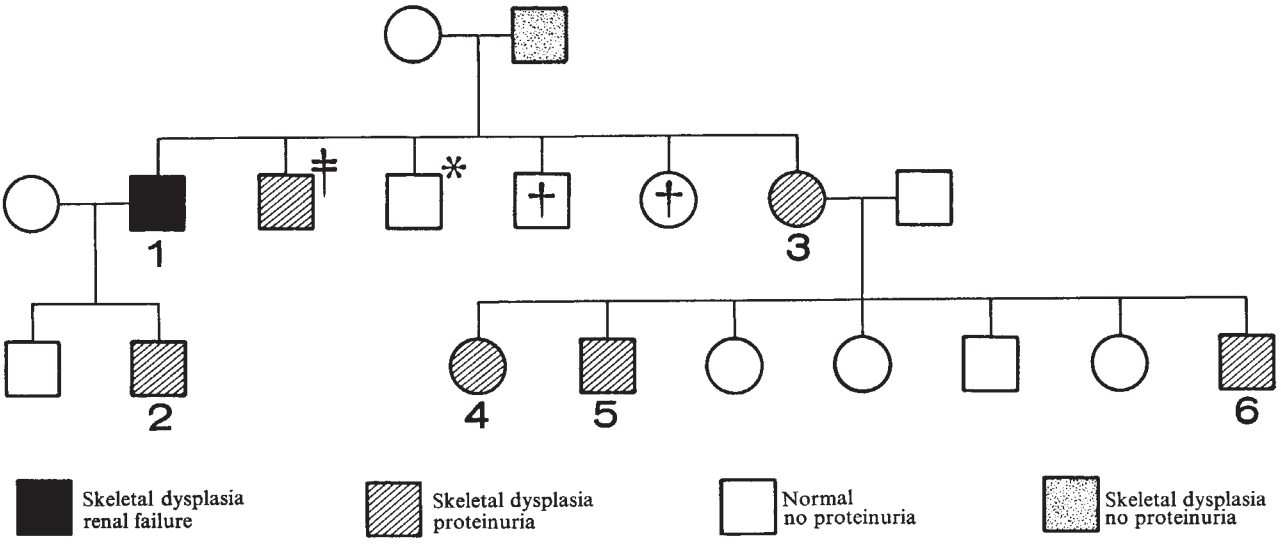

Fig. 1. *Diagram of family tree of Cases 1 through 6.* ∓ = accidental death; * = normal male with five children, all lacking proteinuria and skeletal dysplasia; + = death in newborn period.

failure was progressive and hemodialysis was required. Bilateral nephrectomy and splenectomy were performed prior to transplantation of a renal homograft from his mother. Five months after transplantation, osteonecrosis of the right femoral head was noted. One year after transplantation the BUN was 23 mg/100 ml and serum creatinine was 2.2 mg/100 ml. Urinary protein was less than 100 mg/24 h.

Case 2. This boy, a son of Case 1, had several orthopedic procedures performed for correction of right calcaneovalgus and knee deformities related to bilateral patellar aplasia. He has iliac horns and hypoplastic fingernails. Urinalysis prior to age five years was negative on 17 occasions. Between five and seven years of age, multiple urinalyses ranged from negative to 1+protein, qualitatively. After seven years of age, urine protein was 1+ or greater, qualitatively. At seven and one-half years of age, the BUN was 11 mg/100 ml, serum creatinine was 0.7 mg/100 ml, albumin was 3.2 g/100 ml, and cholesterol was 200 mg/100 ml. Serum β1C was 205 mg/100 ml (normal 164 ± 40 mg/100 ml). A sodium iothalamate clearance was 124 ml/min/1.73 m^2. Urinary protein excretion was 510 mg/24 h. An Addis count showed 1,000,000 red blood cells, 1,880,000 white blood cells and no casts per 12 h. An intravenous pyelogram and audiogram were normal. At eight years of age, the serum creatinine was 0.4 mg/100 ml and the urinary protein excretion was 0.5 g/24 h.

Case 3. This woman, a sister of Case 1, was noted to have fingernail deformities at birth. She had no joint or urinary symptoms. Asymptomatic proteinuria was noted before five years of age. During each of seven pregnancies between 18 and 26 years of age, 2 to 3+ proteinuria was observed. The diastolic blood pressure was 100 mm Hg or greater during three pregnancies. Physical examination at 29 years of age revealed bilateral patellar dislocation, 10° flexion contractures at both elbows and a blood pressure of 125/95 mm Hg. Thumb and index fingernails were hypoplastic and iliac horns were palpable. The BUN was 10 mg/100 ml, serum creatinine was 0.9 mg/100 ml, albumin was 2.9 g/100 ml, cholesterol was 296 mg/100 ml and β1C was 189 mg/100 ml. The fasting blood sugar was 69 mg/100 ml. A creatinine clearance was 114 ml/min. Quantitative urinary protein excretion was 2.53 g/24 h. An intravenous pyelogram was normal. Chlorothiazide and aldactone were given to control hypertension.

Case 4. This daughter of Case 3 was noted to have elbow deformities at birth. There were no symptoms referrable to renal disease. Urinalysis was negative at one year of age. At eight years of age the BUN was 15 mg/100 ml and urinary protein was 3+, qualitatively. Physical examination at 11 years of age revealed small, laterally placed patellae, hypoplasia and ridging of fingernails and a blood pressure of 100/60 mm Hg. Palpable iliac horns and webbed 90° flexion contractures of both elbows were present. An audiogram was normal. BUN was 18 mg/100 ml, serum creatinine was 0.7 mg/100 ml, albumin was 3.3 g/100 ml and β1C was 160 mg/100 ml. A sodium iothalmate clearance was 127 ml/min/1.73 m^2. Quantitative urinary protein excretion was 3.0 g/24 h. An Addis count showed 11,000,000 red blood cells, 3,000,000 white blood cells and 295,000 casts per 12 h. Urine culture showed no growth. An intravenous pyelogram was normal.

Case 5. This son of Case 3 had multiple orthopedic procedures for bilateral knee and foot deformities between one and eight years of age. There were no urinary symptoms. Urinalysis at two months and at one, two and four years of age were normal. Five urinalyses between six and eight years of age had a normal sediment. Qualitative tests for

urinary protein were negative on three occasions and 1+ twice. At seven years of age, quantitative urinary protein excretion was less than 100 mg/24 h. Physical examination at ten years of age showed a blood pressure of 100/70 mm Hg and hypoplastic thumbnails. BUN was 17 mg/100 ml, serum creatinine was 0.5 mg/100 ml and β1C was 138 mg/100 ml. A creatinine clearance was 118 ml/min/1.73 m^2. Quantitative urinary protein excretion was 260 and 180 mg/24 h on two separate occasions. An Addis count showed 2,000,000 red blood cells and no white blood cells or casts/12 h. Radiographic studies demonstrated iliac horns, subluxation of small proximal heads of radii and absence of patellae. An intravenous pyelogram was normal.

Case 6. This son of Case 3 has had multiple orthopedic procedures for correction of congenital bilateral talipes equinovarus deformities. At two and one-half years of age, physical examination showed small, easily displaced patellae, minimal flexion contracture deformities of both elbows and palpable iliac horns. Thumb and index fingernails were flattened. BUN was 11 mg/100 ml, serum creatinine was 0.7 mg/100 ml and β1C was 187 mg/100 ml. Creatinine clearance was 137 ml/min/1.73 m^2. Qualitative tests for urinary protein were negative on four occasions and trace and 1+ on single specimens. An intravenous pyelogram was normal.

Case 7. This boy had tendon transplants for stabilization of knee joints at eight years of age. At this time 1+ albuminuria was noted. There was no family history of orthopedic or renal disease. At ten years of age, physical examination revealed thin, flattened fingernails, very small patellae and 30° flexion contractures of both elbows. The blood pressure was 110/70 mm Hg. Urinary protein excretion was 2.5 g/24 h. Following treatment with prednisone, 60 mg/day for four weeks, urinary protein excretion was 1.3 g/24 h. Serum albumin was 2.5 g/100 ml, creatinine was 0.7 mg/100 ml, cholesterol was 414 mg/100 ml and β1C was 144 mg/100 ml. An Addis count showed 1,080,000 red blood cells, 720,000 white blood cells and 140,000 casts per 12 h. Creatinine clearance was 100 ml/min/1.73 m^2. An intravenous glucose tolerance test was normal. Iliac horns and dislocation of hypoplastic proximal radial heads were demonstrated radiographically. Audiogram and intravenous pyelogram were normal. At 15 years of age, he was asymptomatic. BUN was 16 mg/100 ml, creatinine clearance was 136 ml/min/1.73 m^2 and urinary protein excretion was 3.1 g/24 h.

Methods

Kidney biopsies from each of seven patients were fixed in formalin, embedded in paraffin, sectioned at four microns and stained with hematoxylin and eosin, periodic acid-Schiff (PAS), azocarmine and silver-methenamine. There were more than eight glomeruli/section in each biopsy specimen.

Portions of biopsy specimens for immunofluorescent microscopy were rapidly frozen in isopentane prechilled in liquid nitrogen, sectioned in a Lipshaw cryostat and stained with monospecific antisera to human IgG, IgM, IgA, β1C, Cl_q, properdin, fibrin and albumin by methods previously described [5].

Portions of kidney biopsy specimens from the seven patients were fixed in glutaraldehyde and osmic acid and embedded in Vestopal W®, Epon® and glycol methacrylate for electron microscopy. Thin sections of three to ten glomeruli and associated tubules from each case were stained with uranyl acetate and lead citrate. Other sections were stained with phosphotungstic acid (PTA) as described by Marinozzi [6]. Kidney biopsy specimens from living related transplantation donors and a variety of other kidney diseases were also stained with PTA for concurrent study.

Results

Light microscopy. The biopsy specimens of the six patients with normal renal function (Cases 2–7) showed remarkably similar features. In each, focal glomerular basement membrane (GBM) thickening involving 1 to 5% of the GBM was observed (Fig. 2). There was minimal or no increase in the mesangial matrix. Hyaline droplets were seen at the junction of the afferent arteriolar wall and Bowman's capsule in five of six biopsies. In four patients the glomeruli showed no other abnormalities. One glomerulus of 15 in the specimen from Case 4 and two of 37 glomeruli in the specimen from Case 5 were hyalinized; one further glomerulus in the latter specimen had a fibroepithelial crescent. The arterioles, interstitium and tubules of four specimens were normal. The specimen from Case 3 showed minimal focal interstitial fibrosis and

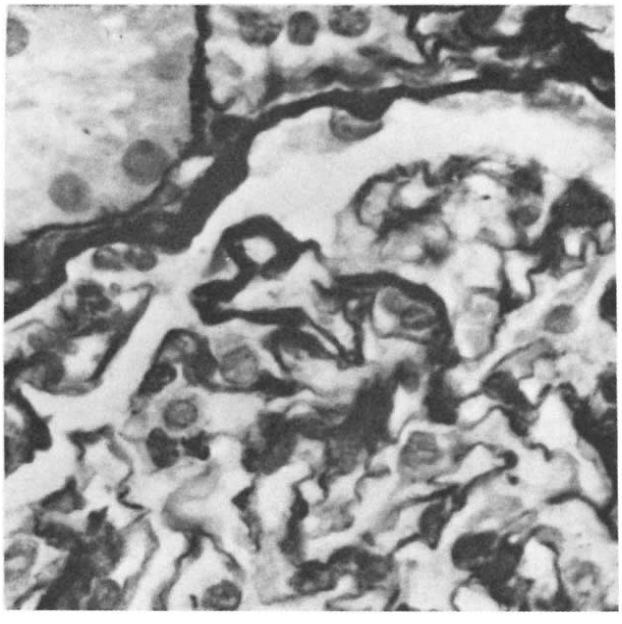

Fig. 2. *Portion of a glomerulus of Case 4 showing focal GBM thickening.* Silver methenamine stain (× 1,200).

Table 1. Clinical and glomerular morphologic features[a]

Case	Age *years*	Serum creatinine, *mg/100 ml*	Urinary protein *g/24 hr*	Light microscopy focal GBM thickening	Immunofluorescent[b] microscopy	Electron microscopy	
						Lucent areas in GBM	Collagen fibrils in GBM
1 biopsy	30	3.0	15.0	+[c]	−	−	−
nephrectomy	32	20	−	+[c]	++−+++ IgM, β1C[d], P[e]	+	+
2	$7^1/_2$	0.4	0.5	+	+−++ IgM[f], β1C	++	++
3	29	0.9	2.5	+	+ IgM[f], β1C	+	+
4	11	0.7	1.7	+	+−++ IgM, β1C	++	++
5	10	0.5	0.25	+	+ IgM, β1C	++	++
6	$2^1/_2$	0.7	trace	+	+ IgM, β1C	+	+
7	10	0.7	1.3	++	−, + β1C	+++	+++

[a] Morphologic abnormalities graded from + to +++ minimal to marked change or intensity of staining; − indicates not evaluated.
[b] interrupted linear GBM staining except where noted.
[c] many hyalinized glomeruli.
[d] nodular, granular staining.
[e] P=properdin.
[f] mesangial staining present.

specimens from Cases 3 and 4 showed focal tubular basement membrane thickening.

The open surgical biopsy specimen obtained from Case one, when the serum creatinine was 3.0 mg/100 ml showed a spectrum of glomerular changes in the 75 to 80 glomeruli per section. These ranged from near normal glomeruli with only minimal increase in mesangial matrix and local GBM thickening to complete hyalinization of more than one-third of the glomeruli. The remaining glomeruli appeared to show intermediate stages of the process including proliferation of mesangial cells and increased mesangial matrix, frequently evident in only one lobule of a glomerulus. Many PAS positive granular and nodular masses were present in mesangial areas and walls of afferent arterioles. Focal interstitial mononuclear cell infiltration, focal interstitial fibrosis and associated tubular atrophy and dilatation were present. Nephrectomy specimens removed two years after the open biopsy showed further progression of the earlier glomerular, interstitial and tubular changes. More than three-fourths of the glomeruli were completely hyalinized. A few of the remaining glomeruli showed minimal focal GBM thickening and occasional ballooning of glomerular cells by foamy material. Oil Red O staining of frozen sections demonstrated lipid droplets in some glomeruli in a distribution similar to that of the foamy cells. Arterial walls were markedly thickened with extensive subintimal proliferative change.

Immunofluorescent microscopy. Biopsy specimens from Cases 2 through 7 and the nephrectomy specimen from Case one were studied by immunofluorescence microscopy (Table 1). The specimen from Case 7 was stained for IgG and β1C only. Only non-obsolescent glomeruli of Case one showed positive staining. Glomeruli and arterioles in the majority of specimens (4/7) examined were negative for IgG. Cases 4 and 5 showed 1+ focal and local linear GBM staining and Case 7 showed 1+ focal and local mesangial staining. The glomeruli and arterioles in four specimens were negative for IgA. Cases 4 and 5 had 1+ focal and local staining in the mesangium and along the glomerular basement membrane.

Positive (1 to 3+) staining for IgM was present in all six specimens studied. Interrupted linear staining along the glomerular basement membrane (Fig. 3a) was the predom-

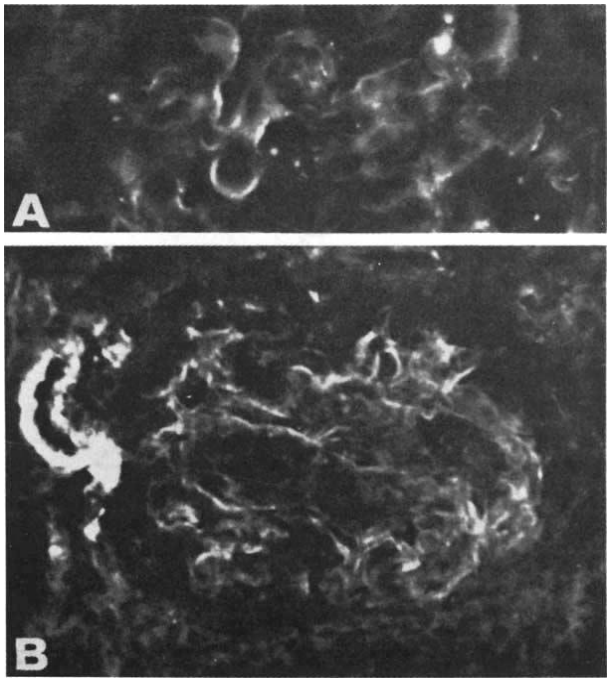

Fig. 3. *Immunofluorescence micrographs.* a) portion of glomerulus of Case four showing focal linear GBM staining (anti-IgM); b) glomerulus and afferent arteriole of Case two showing focal GBM and intense arteriolar staining (anti-β_1C).

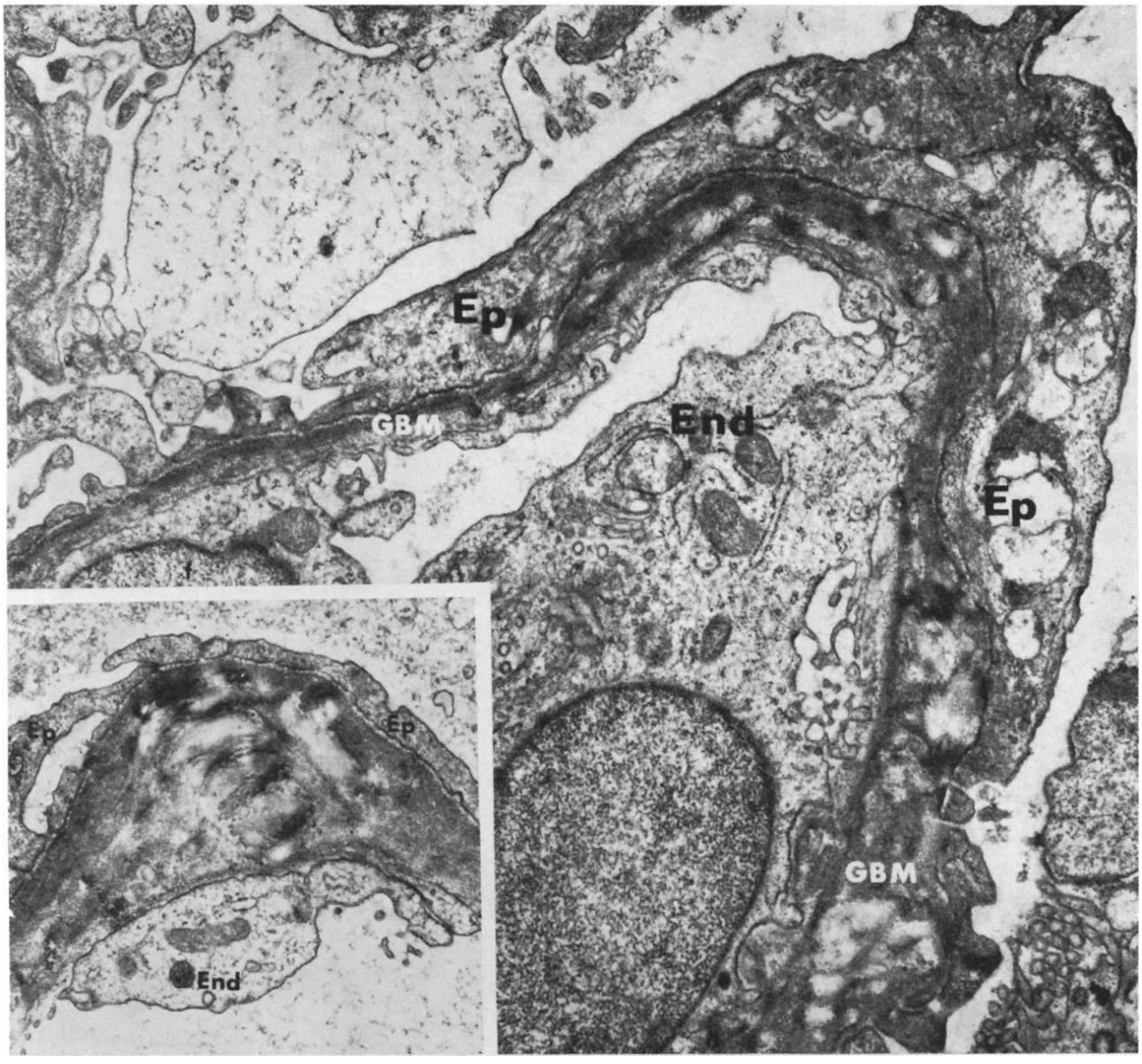

Fig. 4. *Electron micrographs of glomerular capillary loops of Case two.* Portions of the glomerular basement membrane (GBM) appear normal while other areas are increased in width and demonstrate numerous characteristic lucent and dense areas (× 24,000). The insert shows at higher magnification a segment of glomerular capillary wall containing many curvilinear fibrils. End, endothelial cell; Ep, epithelial cell; lead citrate and uranyl acetate stain (× 29,000).

inant pattern in all specimens except Cases 2 and 3 where a major portion of the staining was mesangial. Specimens from Cases 1, 4, 5 and 6 showed 2+ nodular and diffuse staining of the stalk region and afferent arteriolar walls.

Positive staining for β1C was found along the GBM in all seven cases. This varied from approximately 10% of the GBM in Cases 3 and 5 to diffuse staining of the entire GBM of Case one. The staining was predominantly linear and interrupted linear, although Case one had intense (2 to 3+) nodular staining along the GBM. In each of the specimens studied, there was intense nodular staining of afferent arteriolar walls frequently extending into the glomerular stalk (Fig. 3b).

Positive (1+) focal mesangial and GBM staining for Cl_q was observed in glomeruli of Cases 2 and 3.

The glomeruli were negative for properdin in the five biopsy specimens studied; however, strong (2 to 3+) nodular staining was present along the entire GBM in the nephrectomy specimen of Case one. Afferent arteriolar walls in the five biopsies showed 1+ granular and nodular staining.

The glomeruli of Cases 3 and 4 showed negative or trace staining for fibrinogen. Cases 2, 5 and 6 showed

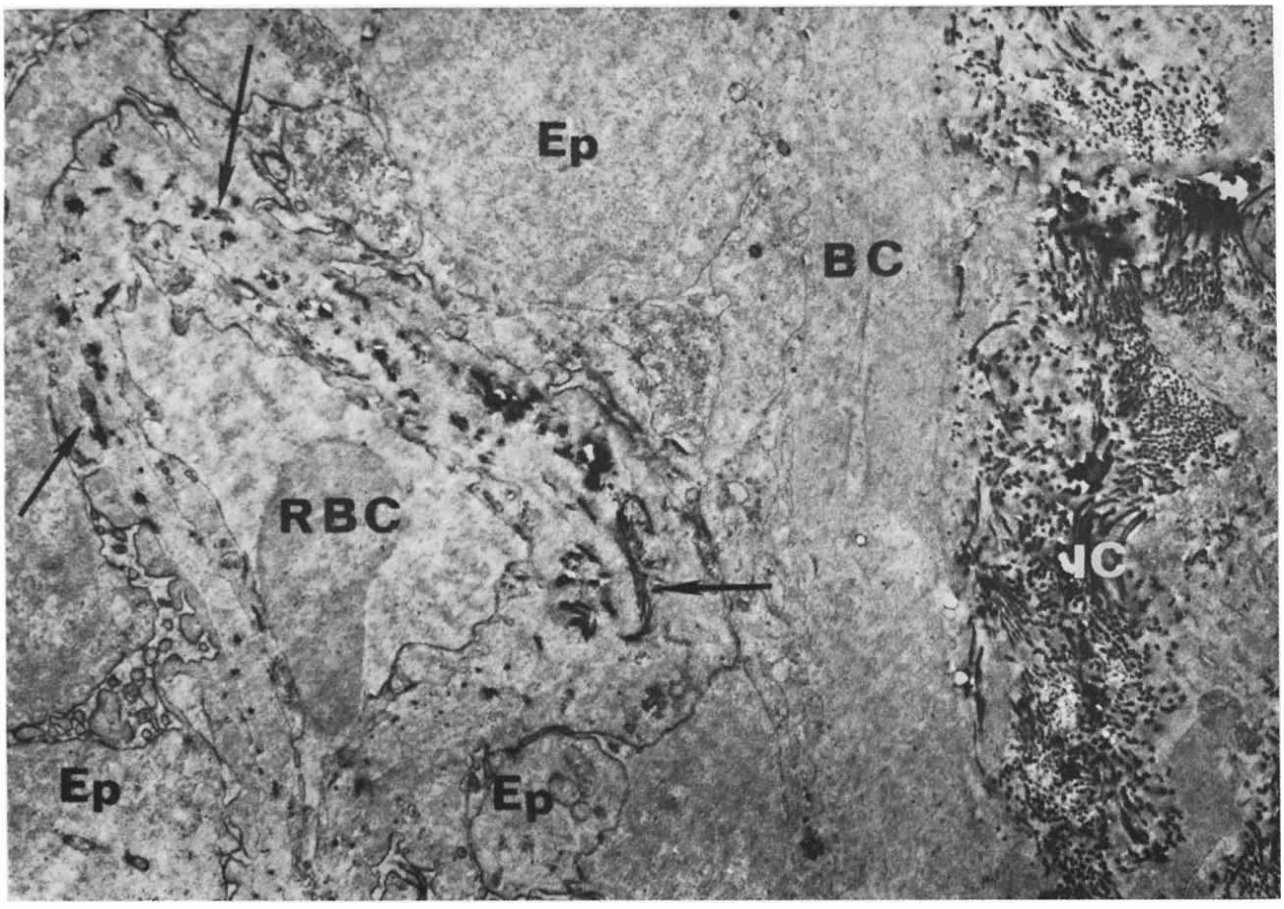

Fig. 5. *Electron micrograph of PTA-stained kidney of Case seven.* Numerous intensely stained fibrils (arrows) are present within the otherwise negatively stained glomerular basement membrane. Staining of interstitial collagen (IC) is strongly positive while that of Bowman's capsule (BC) membrane is negative. Ep, epithelial cell; RBC, red blood cell; PTA stain (× 29,000).

1+ local interrupted linear, mesangial and stalk staining. Glomeruli in the nephrectomy specimen from case one showed 1 to 2+ linear GBM staining.

Staining of glomeruli in specimens from four patients was negative for albumin. Cases 4 and 5 showed very focal 1+ thick linear staining of the GBM. There was strong (2 to 3+) granular and nodular staining for albumin in several tubules in each specimen.

Electron microscopy. Abnormalities of glomerular basement membranes (GBM) were observed in glomeruli of each of the seven patients with the nail-patella syndrome. The extent and type of abnormality varied within glomeruli of each case and abnormalities were always focal within glomeruli. Typical lesions consisted of broadened areas of mottled GBM containing irregular lucent zones adjacent to curvilinear densities containing periodic fibrils (Fig. 4). The lucent areas usually contained low density material but apparent holes in the GBM were also noted. Increased density was observed along a portion of borders of many apparent holes within the GBM suggesting that some holes were cutting artifacts in areas of tissue of markedly variable density similar to that observed in areas of interstitial collagen (Fig. 5).

PTA staining demonstrated variable numbers of dense periodic fibrils within the GBM of each patient (Figs. 5 and 6 and Table 1). The extent of GBM abnormalities did not correlate well with the age of the patients, the clinical presentation, or the level of renal function. For example, Cases 2, 4, and 7, children with proteinuria, showed the most diffuse and severe abnormalities, while changes were minimal and focal in the few remaining open glomerular capillaries in the nephrectomy specimen of Case one.

Periodicity of the fibrillar bundles within the abnormal GBM was more readily appreciated in PTA stained sections. PTA-negative GBM was always present in adjacent capillaries of the same glomerulus. Fibrils with periodicity were not demonstrated within the GBM in any of the control specimens or other diseases studied.

Abundant PTA-positive collagen fibrils were regularly observed in the interstitial spaces adjacent to tubular basement membranes. Tubular basement membranes were

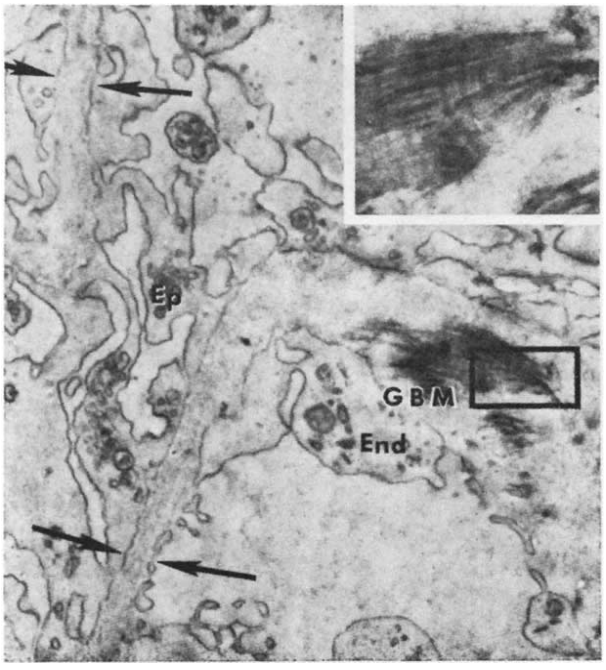

Fig. 6. *Ultrastructural features of glomerular capillary loops of Case 2 stained with PTA.* Portions of the GBM appear normal (arrows) while other portions are widened and contain PTA positive fibrils (× 22,000). The insert, a higher magnification of the enclosed area, demonstrates periodicity within these cross-striated fibrils. Ep, epithelial cell; End, endothelial cell; PTA stain (× 58,000).

occasionally irregularly laminated and thickened, but PTA staining did not demonstrate dense periodic fibrils within these membranes or those of Bowman's capsule.

Other abnormalities of glomerular capillary walls included focal irregular broadening of the subendothelial space and occasional PTA-positive fibrils within this space. Epithelial cell foot processes frequently showed fusion and broadening of their attachment to the GBM. These epithelial cell changes often occured adjacent to areas of abnormal structure within the GBM but were also found associated with otherwise normal appearing GBM.

Glomerular mesangial areas in several patients showed a slight increase in the number of cells and a moderate increase of matrix.

Study of arterioles of five patients showed the internal elastic membrane to be abnormal in seven of eight vessels. Abnormalities included marked irregularity of width, interruption of continuity and variably decreased density within the branching membranes. One arteriole contained a large homogeneous granular mass.

Discussion

This report provides evidence that the skeletal manifestations and renal dysfunction in the nail-patella syndrome may be pathogenetically related. Patellar hypoplasia or aplasia, elbow deformities secondary to proximal radial head hypoplasia and iliac horns are associated with fingernail dysplasia in this autosomal dominant disease [7, 8]. Hawkins and Smith first called attention to renal involvement in this disease [9]. Light microscopy of the kidney has shown nonspecific changes such as focal glomerular basement membrane thickening. The initial electron microscopic report described changes including GBM thickening and wrinkling with focal fusion of visceral epithelial cell foot processes [1].

Electron lucent areas in thickened glomerular basement membranes were recently described by del Poso and Lapp [3] and also observed by Ben-Bassat, Cohen and Rosenfield [4]. In the latter case, abundant collagen fibrils were described within glomerular basement membranes (4). In the present report, such abnormalities were demonstrated in the GBM of each of seven patients with the nail-patella syndrome. These findings confirm the observation of Ben-Bassat et al [4] that bundles with the appearance of interstitial collagen are present within the glomerular basement membranes and thus help to establish this unique abnormality as the characteristic ultrastructural feature of this disease. Such collagen bundles, to our knowledge, have not been demonstrated within glomerular basement membranes in any other disease. This abnormality was present even when proteinuria was very minimal (less than 300 mg/day) and thus may precede increased urinary protein excretion and represent the earliest manifestation of renal disease.

The only consistent glomerular abnormality noted by light microscopy, was focal GBM thickening. Hyaline droplets were also frequently seen at the junction Bowman's capsule with the afferent arteriole. Such droplets have also been seen in hypertension and diabetes mellitus [10] and less frequently in individuals without manifest renal disease [11].

Immunofluorescent studies of the kidney in this disease have not been previously described. Focal deposition of serum proteins, most frequently IgM and β1C along the GBM and within arteriolar walls of each biopsy, was observed in the present study. However, the pattern and extent of deposition did not suggest that the renal lesions in this disease are primarily the result of immunologic injury. Presence of these proteins may reflect their entrapment within the abnormal membranous structure demonstrated by electron microscopy. Similar observations have been made in diabetes mellitus [12].

Factors responsible for progression to renal insufficiency [13] in this disease have not yet been established. Prolonged periods of asymptomatic proteinuria were observed in the family studied. Case 3 had asymptomatic proteinuria from childhood but renal function remained normal at 29 years of age. Cases 2, 4, and 7 have also had proteinuria for several years. Case one had proteinuria for 25 years before renal insufficiency was observed. Thus, progression to renal failure may occur even after prolonged periods of asymptomatic proteinuria.

Although the link between the ultrastructural GBM abnormalities observed and skeletal dysplasia in this disease has not yet been defined, they may be pathogenetically related. The GBM abnormality may reflect a disturbance in synthesis of glomerular basement membranes as a manifestation of a diffuse connective tissue disorder. Alternatively, the abnormality may reflect entrapment within the glomerular basement membrane of circulating collagen precursors and assembly of these moieties within the GBM into fibrils with the appearance of mature interstitial collagen. An appealing hypothesis is that synthesis and/or degradation of skeletal collagen is enzymatically deranged, whereby increased quantities of collagen precursors or fragments might be released into the general circulation. Due to the filtration function of the glomerulus, entrapment of such precursors or fragments in the GBM might be followed by assembly to morphologically mature collagen within the glomerular basement membranes. The absence of changes in tubular basement membranes or the membranes of Bowman's capsule may support this concept, since these membranes have a composition that is similar to that of the GBM but have different functional roles.

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