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Case report

An autopsy case of prolidase deficiency

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Summary. A 25-year-old female who suffered from longstanding incurable leg ulcers was found to have prolidase deficiency with iminodipeptiduria. On ultrastructural studies of autopsy specimens, the lamina densa of the epidermal basement membrane was found to show irregular splitting and the basement membranes of the dermal blood vessels were lamellated with interruptions. Lamellar changes and splitting of the basement membranes of the renal tubules, interstitial blood vessels and glomerular capillaries also occurred. These morphological abnormalities seem to be one of causes of the clinical symptomatology.

Key words: Prolidase deficiency – Basement membrane – Splitting

Introduction

Buist et al. (1972) described a probable case of prolidase deficiency, who had been previously reported as a syndrome resembling lathyrism with iminodipeptiduria by Goodman et al. (1968). Powell et al. (1974) described the first patient, in whose red and white blood cells prolidase activity was absent or markedly decreased. However, prolidase deficiency is still a rare disease and the genesis of its clinical manifestations remains to be made clear, in particular the correlations with histopathological abnormalities. The morphological abnormalities of this disease have been described only in the resected spleen (Goodman et al. 1968) and on the dermal capillaries around a leg ulcer (Ogata et al. 1981).

An autopsy case of prolidase deficiency has not been previously reported. The biochemical abnormalities during the lifetime of the patient described here have been previously reported by Isemura et al. (1979, 1981).

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Case report

A 25-year-old, mentally retarded female with characteristic facial features had suffered from incurable leg ulcers. She was born of a full term delivery through normal pregnancy, her parents were first cousins, and many of her brothers and sisters had died at young ages of unknown causes. At about 8 years of age, impetigo-like eruptions occurred on both lower legs. These eruptions turned into dermal ulcers which became confluent. At 11 years old after negative angiographic and biopsy findings a skin autograft failed.

The patient was admitted to the Niigata University Hospital at 23 years of age. The diagnoses of gangrenous pyoderma and hypoparathyroidism were made initially because of leg ulcers and tetanic convulsions with hypocalcaemia. Histological examination of a biopsy specimen from the leg ulcer revealed suppurative and non-specific inflammation, and no obvious changes were found on the renal biopsy.

At 24 years old, biochemical examination showed no prolidase activity in her erythrocytes, together with iminodipeptiduria. The values of prolidase activity in erythrocytes of her father and two elder brothers were also extremely low or moderate, although they had no clinical symptoms (Isemura et al. 1979).

Various skin lesions such as pigmentation and telangiectasia, erythematous exanthema and other skin lesions were observed during the hospital stay. Kienboeck's disease and chronic otitis media were also found. The leg ulcers tended to become more serious with time.

At 25 years of age, a skin graft was tried and failed in spite of normal angiography of the leg. Minute deposits of amyloid were observed in a right inguinal lymph node which was resected at angiography. Necrosis of the toes occurred and disarticulation at the metaphalangeal joints of all toes was necessary. After a while, the patient's temperature elevated and she developed watery diarrhoea and bloody stool. An emergency laparotomy with the diagnosis of ileus was performed and haemorrhagic enteritis was diagnosed. Amyloidosis was also observed in resected mesenteric lymph nodes and the appendix. At the same time jaundice appeared and high temperature, ranging from 39° C to 40° C, continued. Disseminated intravascular coagulation was suspected, and venous blood culture grew yeast-like fungi. A haematoma occurred in the left parietal lobe of the cerebrum soon afterwards and she died. Her clinical course was approximately eighteen years.

Laboratory findings at the early stage on admission to the Niigata University Hospital consisted of the following: RBC 465×10^4/cmm, Hb 11.3 g/dl, Ht 35.7%, reticulocyte 24‰, WBC 6000/cmm, platelet 18.2×10^4/cmm, TP 5.4 g/dl, Alb 57.4%, α_1-Gl 6.6%, α_2-Gl 10.5%, β-Gl 8.3%, γ-Gl 17.2%, IgG 1070 mg/dl, IgA 415 mg/dl, IgM 136 mg/dl, Na 144 mEq/l, K 2.3 mEq/l, Cl 94 mEq/l, Ca 2.7 mEq/l, Fe 33 γ/dl, IP 6.0 mg/dl, parathyroid hormone <0.3 μg/ml, calcitonin 376 pg/ml, CRP 4 (+), tuberculin reaction (−), ESR 70 mm/lhr–110 mm/2 hrs, IQ 52, normal karyotype.

At the late stage on admission, there were the additional abnormal data; TP 4.1 g/dl, Alb 47.9%, α_1-Gl 4.4%, α_2-Gl 3.3%, β&γ-Gl 44.4%, urine-sugar (+ + +) (7–15 g/day), protein (−), RBC (+ + +), WBC (+)–(+ + +), PSP 10%/15 min, 37% (total), creatinine clearance 47 ml/min, GOT 136 U/dl, GPT 41 U/dl, LDH 249 U/dl, Al-p 17.1 KAU, total bilirubin (direct) 10 mg/dl (5.7 mg/dl), TC 84 mg/dl, bleeding time 10 min, fibrinogen 90 mg/dl, platelet 2.6×10^4/cmm.

Gross anatomical findings. The nutritional state was highly emaciated (height: 162 cm, weight 34 kg). The whole skin was thin and showed moderate jaundice. Facial features with exophthalmus were characteristic. There were irregular extensive ulcers of both lower legs and all toes had been amputated at the metaphalangeal joints.

The heart weighed 175 g and spotty bleedings in the subepicardium were noted. A few verrucous thrombi, with granular surfaces, were situated on the atrial side of the mitral valve. There were haematomas in the parietal lobes (lt: $5 \times 5 \times 3.5$ cm, rt: $5 \times 4 \times 3$ cm in size) with rupture into the lateral ventricles and subarachnoid spaces and in the right parahippocampal region (0.5 cm in diameter) of the cerebrum.

Both kidneys weighed 100 g. Numerous, haemorrhagic foci were observed in the cortices and there was a dark reddish lesion of the left kidney, which was slightly retracted and $2 \times 5 \times 3$ cm in size. Sporadic haemorrhages were found in both lungs (lt. 240 g, rt. 200 g) and yellow-whitish nodular lesions were seen in the left lower lobe. There was irregular bleeding

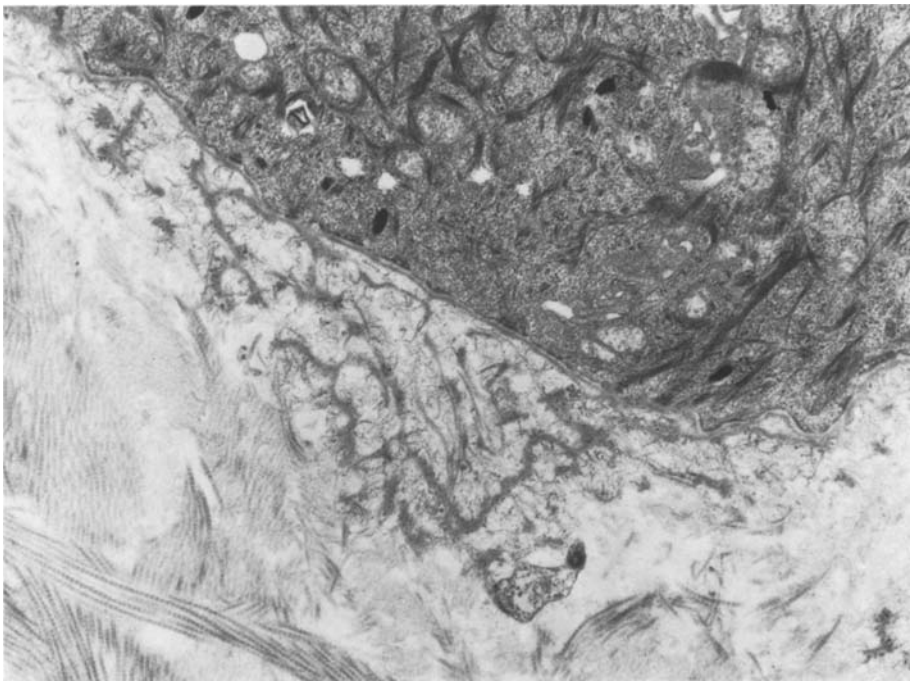

Fig. 1. Lamina densa of the epidermal basement membrane of the breast skin shows splitting and irregular net-like arrangement (× 11,600)

into the gastrointestinal mucosa, dark greenish turbid ascites (170 ml) and fibrous peritonitis. The spleen was swollen (420 g) and elastic-soft in consistency. On the cut surface, innumerable nodules were noticeable, dark reddish in color and half-miliary in size. There were two fresh infarctions (2.5 × 2.5 × 3 cm and 3 × 2.5 × 5 cm in size). The swollen liver was 2040 g in weight and soft in consistency with focal fibrous perihepatitis. It showed greenish discoloration and an emphasized lobular architecture without regenerated nodules on the cut surface.

Histological findings. The skin of the breast and the abdomen were thin compared with control skin obtained from patients of the same age and sex. In some parts the epidermis was composed of only two or three layers of squamous cells. PAS reaction and silver impregnation showed irregularity and splitting of the basement membrane, though inflammation or other pathological lesions were not noticeable. Ultrastructural examination of the breast skin revealed irregular splitting and disruption of lamina densa of the epidermal basement membrane, where some collagen and elastic fibers were observed, but the lamina rara and hemi-desmosomes appeared to be normal (Fig. 1). The basement membrane of the small vessels in the dermis was lamellated and also interrupted in parts (Fig. 2). No morphological abnormalities of dermal collagen and elastic fibers were noticeable.

In the kidney, fibrin thrombi, occasionally with yeast-like fungi, were observed here and there in the glomerular capillaries and some Bowman's spaces. At slightly retracted lesion of the left cortex, a moderate amount of amyloid was deposited but in other areas of the kidneys, amyloid deposits were minute. The basal zones of the tubules were slightly thickened in parts as were the capillary walls of some glomeruli with a mild increase of mesangial matrix. Electron microscopically, the tubular basement membrane thickened irregularly and was highly lamellated (Fig. 3) and the vascular basement membranes of the interstitium also were lamellar. The basement membranes of glomerular capillaries were thickened and split

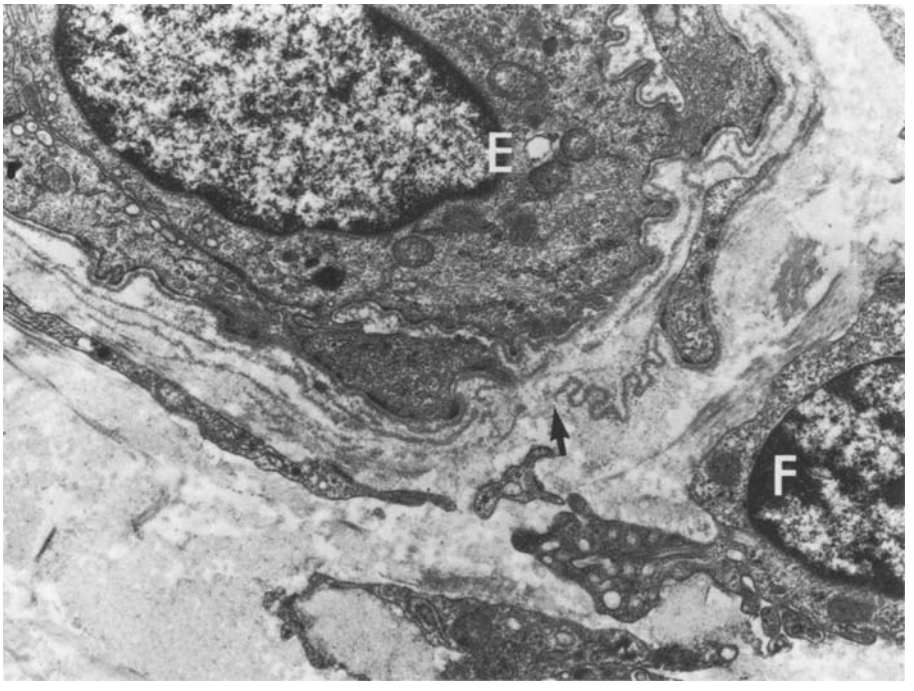

Fig. 2. The basement membrane of the dermal capillary is lamellated, with interruption in parts (*arrow*) (× 11,600). *E*; endothelium *F*; fibrocyte

(Fig. 4) and the processes of the podocyte cytoplasm appeared to cover and be interspersed with the split portion in parts. There were no electron-dense deposits in the thickened basement membrane of the glomerular capillary.

Amyloid deposition occurred in almost all organs except for the skin, lungs, liver, and brain. After potassium permanganate exposure (Wright et al. 1977) the amyloid lost affinity to alkaline congo red.

The specimens from the leg ulcer showed non-specific chronic inflammation. The verrucous thrombi at the mitral valve consisted of yeast-like fungi. Fungal emboli were detected in the other areas of the heart, the brain and the kidneys. Diffuse fatty change of the liver was noticeable and the portal areas were fibrous with proliferation of bile ducts containing bile plugs and slight mononuclear cell infiltration. Marked bronchopneumonia was observed in the lower lobe of the left lung.

Discussion

Almost all patients with definite prolidase deficiency with iminodipeptiduria suffered from skin manifestations such as ulceration, fragility and teleangiectasia, and some showed mental retardation, unusual facial features, splenomegaly and so on. The family pedigrees of some patients suggested an autosomal recessive disorder (Powell et al. 1974; Jackson et al. 1975; Powell et al. 1977; Sheffield et al. 1977; Arata et al. 1979; Isemura et al. 1979; Ogata et al. 1981; Charpentier et al. 1981; Der Kaloustian et al. 1982; Pedersen et al. 1983).

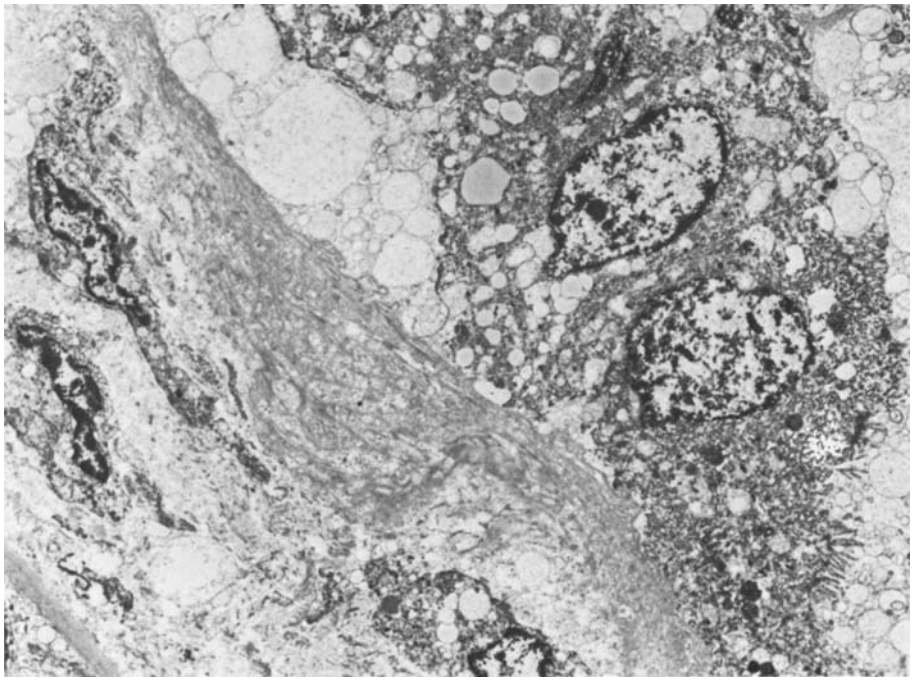

Fig. 3. The tubular basement membrane of the kidney reveals a thick and lamellar structure (× 3,200)

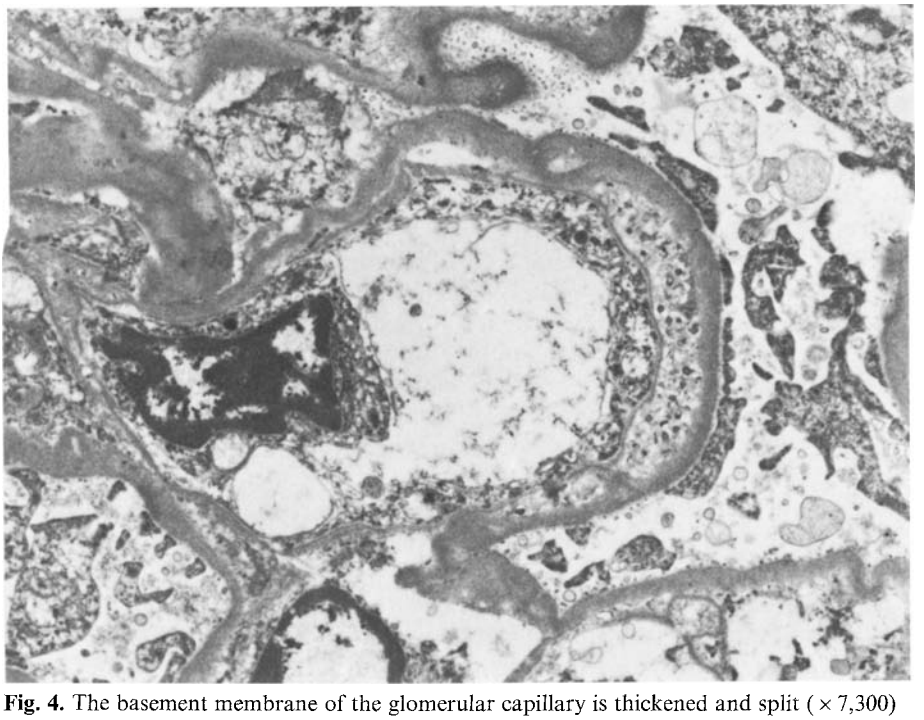

Fig. 4. The basement membrane of the glomerular capillary is thickened and split (× 7,300)

The role of prolidase as a dipeptidase is to cleave dipeptides with C-terminal proline or hydroxyproline. Biochemical studies have been done but have failed to provide a uniform view of the role of prolidase deficiency in clinical symptoms. At first, it was suggested that collagen metabolism was disturbed (Powell et al. 1974; Jackson et al. 1975). A few analyses of the dermal collagen indicated that intermolecular cross linking of collagen was not normal while the amino acid composition was not significantly different from normal samples (Goodman et al. 1968; Isemura et al. 1979, 1981). On the contrary, it was suggested that the urinary proline-containing dipeptides derived from additional sources other than collagen (Powell et al. 1977; Sheffield et al. 1977) and the hydroxylation of proline in collagen secreted by the skin fibroblasts from the patient of Sheffield et al. (1977) was normal (Royce and Danks, 1982). Moreover, the role of prolidase deficiency in the production of clinical symptoms remains to be defined, as was pointed out by the fact that the prolidase deficient siblings of patients showed no clinical manifestations (Arata et al. 1979; Isemura et al. 1979).

A few descriptions of morphological abnormalities in prolidase deficiency have been reported: ultrastructurally, the collagen fibers in the wall of the trabecular artery of a resected spleen lacked a well ordered arrangement with disruption of associated elastin (Goodman et al. 1968) and the accumulation of fibrils consistent with amyloid fibrils was observed around the capillaries in the dermis around the leg ulcer (Ogata et al. 1981). The breast skin of the present case was thin compared with controls but no morphological abnormalities of the collagen fibers in the dermis could been detected, as described for abdomial skin by Arata et al. (1979). In our patient, the lamina densa of the epidermal basement membrane split irregularly while the lamina rara and hemi-desmosomes appeared to be normal. The basement membranes of the dermal blood vessels lamellated with interruption in parts. Moreover, the same changes occurred in the basement membranes of glomerular capillaries, tubules and interstitial vessels. However, where these abnormalities of basement membranes were observed, amyloid substance was not detected. Therefore, it is suggested that the abnormalities of basement membranes may have some role in causing clinical symptoms, such as the skin manifestations.

Components of the basal lamina including type IV collagen are synthesized and secreted by both epithelial and non-epithelial cells which have basement membranes (Cohen and Hay 1971; Martinez-Hernandez et al. 1974; Jaffe et al. 1976). However, basal lamina and hemi-desmosomes are grown only when human epidermal cells are cultured on plastic dishes coated with collagen gel, but they do not form when on untreated dishes (Hirone and Taniguchi, 1980). This seems to suggest that elements of connective tissue may have an important role in building up a complete basal lamina. The dermis of our patient was thin, and the analysis of her dermal collagen suggested that the dermal collagen had the higher type III collagen content than in normal skin and therefore failed to ensure a normal maturation process and change of collagen cross-links (Isemura et al. 1981). It may be reasonable to assume that deficiency of prolidase would interfere with

the formation of the normal structure of basal lamina and biochemical analysis of basement membranes is necessary in future.

The amyloidosis in this case is likely to be secondary and related to the longstanding leg ulcers. Further, the results with potassium permanganate suggest that the amyloid fibril protein is protein AA.

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