Nail-patella Syndrome with Renal Involvement and Antecubital Pterygia

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Abstract: Nail-patella syndrome (NPS) is a rare, autosomal-dominant hereditary disorder characterized by nail dysplasia and multiple osseous abnormalities. Some patients may develop renal function impairment and even end-stage renal disease. We treated a 42-year-old female patient with proteinuria who presented with a web-like structure over the antecubital fossa and hypoplastic patellae. In addition, she had other characteristic findings, including bilateral iliac horn, triangular nail lunulae and hypoplastic radial head. She had impaired renal function, and renal biopsy showed mesangial proliferative glomerulonephritis. Additional cases were found in her family. Her mother had most of the signs of NPS as well as advanced renal failure. Her elder sister had knee abnormalities without the web-like elbow condition. Both daughters also had the characteristic features of NPS. During follow-up 30 months after the initial examination, the patient had stable renal function and mild proteinuria.

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Key words:
nail-patella syndrome
antecubital pterygia
iliac horn
triangular lunulae
mesangial proliferative glomerulonephritis

Nail-patella syndrome (NPS) is a rare, autosomal-dominant hereditary disorder involving many organs of both ectodermal and mesodermal origin. This syndrome was first described by Chatelein in 1820, and more than 500 cases have been reported worldwide since Little's report in 1837. The estimated incidence of NPS is 22 cases per million [1]. Mutations in a transcription factor (LMX1B) gene in chromosome 9q34.1 have been identified with a high degree of penetrance but variable expressivities [2, 3].

The classic tetrads of NPS are hypoplastic or dysplastic patellae, nails, elbows and iliac horns. However, the most serious component of NPS is nephropathy. It is present in approximately one-third to one-half of all NPS patients, but the degree of involvement is inconsistent. Chronic benign proteinuria is the most common manifestation, but in approximately 15 to 30% of these cases, the syndrome may develop toward end-stage renal disease (ESRD). The "moth-eaten appearance" of irregular thickening of the glomerular basement membrane (GBM) with electron-lucent areas under electron microscopy is one pathognomonic feature of the syndrome, although the histologic changes do not correlate with the degree of impaired renal function [4].

We report the examinations of a patient who presented with proteinuria and was finally diagnosed as having NPS. She and her family members are the first reported cases of NPS in Taiwan. This has afforded us greater knowledge of the disease and may heighten awareness of this condition in clinical practice.

Case Report

A 42-year-old Taiwanese woman visited our outpatient clinic because of positive urine protein and high serum cholesterol during a regular check-up examination. Spot urinalysis using the dipstick test showed a protein concentration greater than 300 mg/dL. Under the impression of heavy proteinuria, she was admitted for renal biopsy. The patient was thin and small, at only 155 cm in height and 40 kg in weight. Physical examination at admission showed clear and alert consciousness and normal blood pressure (110/70 mmHg). The conjunctiva was not pale and sclera was not icteric. No neck mass or venous engorgement was noticed. Respiration and heart sounds were normal. The abdomen was soft and flat without palpable mass and the lower legs were free from edema. Laboratory tests revealed a serum creatinine concentration of

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0.96 mg/dL (84.9 μmol/L), 24-hour urine of 39.6 mL/minute, and daily protein loss of 1,880 mg/day. No hematuria, anemia or coagulopathy was noted, and all biochemistry examinations were within normal limits except for a total cholesterol of 247 mg/dL (6.39 mmol/L). Other findings, including viral markers for hepatitis B and C and immune profiles of C3, C4, antinuclear antibody, immunoglobulin G (IgG), IgA, IgM and IgE, were all within normal limits. Renal ultrasonography also showed no gross lesions.

Light microscopic examination of the renal biopsy specimen showed a mild increase in glomerular cells without significant tubular atrophy or interstitial fibrosis. Immunofluorescence study showed no immunoglobulin or complement deposition. Electron microscopy showed no thickening of the GBM, but foot processes were effaced without electrondense deposits (Fig. 1). The initial diagnosis was mesangial proliferative glomerulonephritis. After biopsy, trials of oral prednisolone 45 mg/day, along with other medications such as dipyridamole and enalapril, were conducted. The medication was discontinued 2 months later due to poor compliance and lack of significant clinical improvement. She was lost to follow-up for the next 6 months due to a lack of subjective complaints and some family problems.

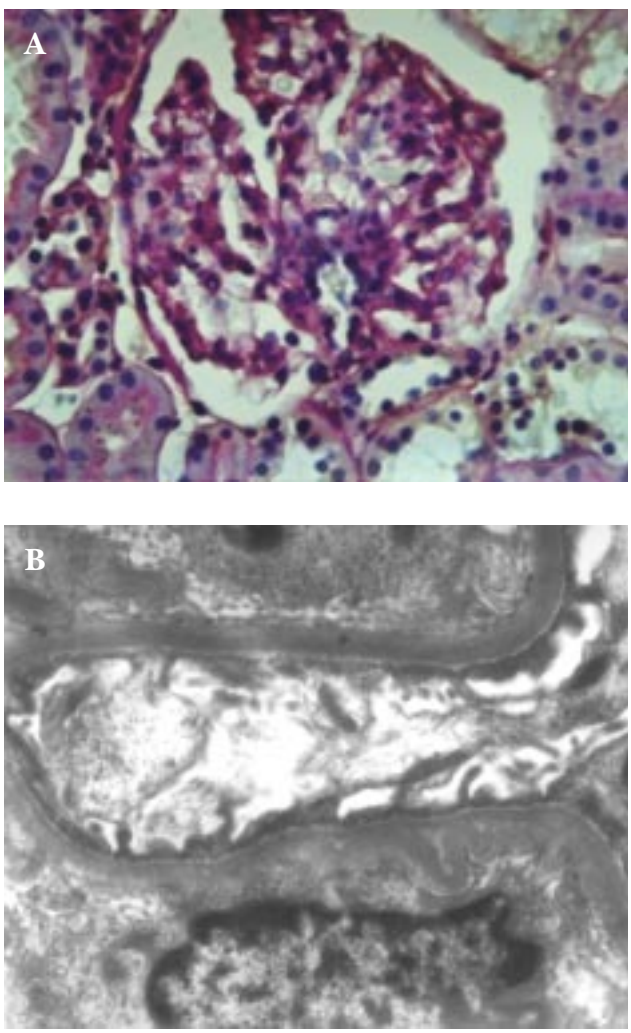

Fig. 1. *Kidney biopsy. A) Light microscopy showing some segmental mesangial hypercellularity (PAS stain, x 400). B) Transmission electron microscopy showing glomerular basement membrane thinning, with an estimated thickness of about 250–350 nm, and foot process effacement.*

Upon her first visit after returning to our hospital, the doctor discovered that the patient was unable to fully extend her elbow while her blood pressure was being checked. Closer examination revealed that she had a web-like structure in the bilateral anterior elbow fossa, antecubital pterygia (Fig. 2), and small bilateral patellae. A detailed family history was taken and the defects in the patella and elbow were also noted in her mother and two daughters (Fig. 3). The presentations of proteinuria and small patellae led to consideration of a diagnosis of NPS.

Kidney, ureter and bladder roentgenography showed the existence of bilateral iliac horns, which is a pathognomic finding in NPS (Fig. 4). Roentgenography of the knee joints showed bilateral patellar hypoplasia and lateral subluxation, and hypoplasia of the femoral lateral condyles. Other findings included bilateral radial head hypoplasia and posterior subluxation, and hypoplasia of humeral lateral condyles. The range of motion in both elbows was limited. No significant scoliosis, ankle, or foot abnormality was identified.

The patient's nails were mostly normal, but triangular lunulae were detected in the second to fourth fingers on both hands (Fig. 5). The renal biopsy specimen was retreated with a double stain of uranyl acetate and phosphotungstic acid (PTAH) and reviewed under electron microscopy, but there were no new specific findings. Eye examination showed no abnormal findings such as irregular hyperpigmentation in the inner margin of the iris (Lester sign) or open-angle glaucoma. During follow-up 30 months after the initial examination, the patient had fluctuating but asymptomatic proteinuria. Renal function was stable with no evidence of deterioration.

After diagnosis of this index case, another doctor found a second case with typical NPS characteristics and advanced

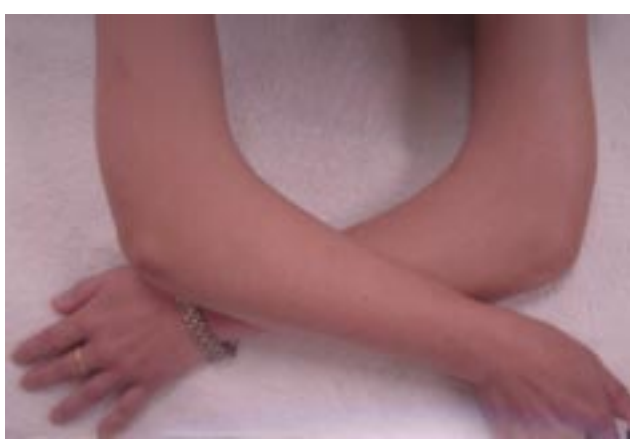

Fig. 2. *Web-like structure in the bilateral anterior elbow fossa of the index case, which has presented in all affected cases in this family.*

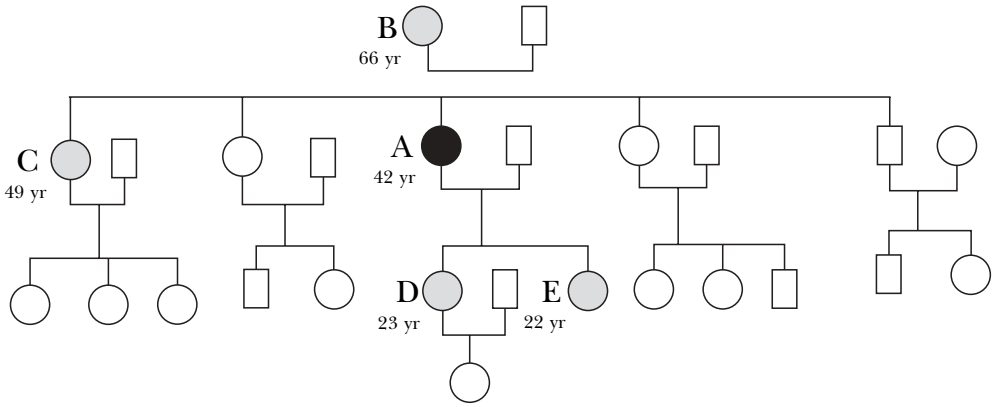

Fig. 3. *A) Family pedigree of the index case patient: (●) index case, (◯) affected members, and (○) unaffected members.*

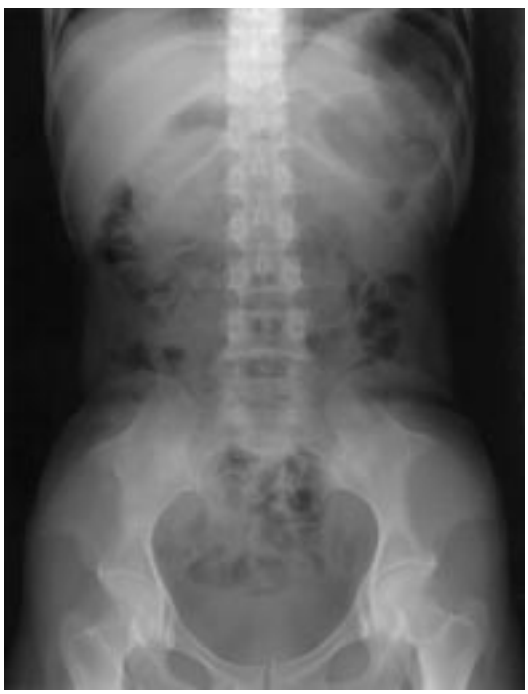

Fig. 4. *Kidney, ureter and bladder roentgenogram showing prominent protrusion of iliac crests, indicating bilateral iliac horns, which is a pathognomonic sign of nail-patella syndrome.*

renal failure (serum creatinine, 4.3 mg/dL/380.3 μmol/L). After taking a detailed family history, she was found to be the mother of the index case. Renal size measured by sonography revealed small kidneys (left kidney, 8.10 cm; right kidney, 7.39 cm in longitudinal axis). No kidney biopsy was performed because of the clinical risk and the patient's nonconsent. Both daughters of the index case also had hypoplastic patella and antecubital pterygia. The elder daughter had recently delivered a baby girl, and according to their description, the baby does not display gross elbow or knee anomalies found in other family members. The clinical presentations of all affected cases in this family are shown in the Table.

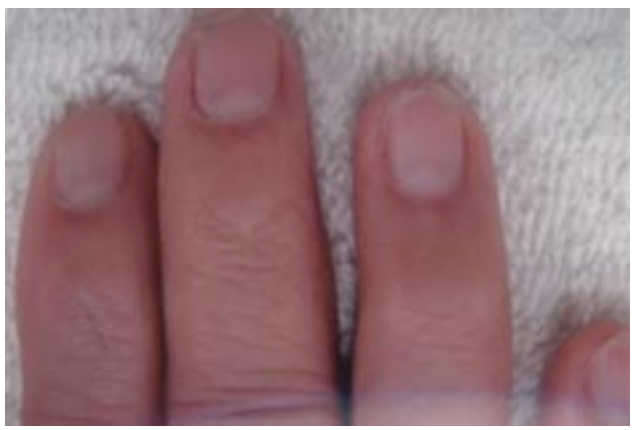

Fig. 5. *Triangular lunulae over the nails of the second to fourth fingers on both hands of the index case.*

Discussion

NPS has been described worldwide in up to 500 cases since 1837. It has also been called iliac horn syndrome, onycho-osteodysplasia, osteo-onychodysplasia, and hereditary osteo-onychodysplasia (HOOD) syndrome. Our review of the literature found only one reported case of a female of Chinese ethnicity in Singapore [5] and three cases of unknown racial origin reported in Hong Kong and Singapore [6, 7], but none in Taiwan.

In 1964, Carbonara and Alpert reviewed 60 affected patients belonging to 25 previously identified families, and concluded that most cases (84%) were diagnosed with NPS only after having sought medical assistance for conditions unrelated to NPS [8]. Most of these patients' physical activities were not hampered, and the disease was usually diagnosed in the patients' second or third decades of life. Diagnosis of the index case in this report was made incidentally after several

Table. Clinical and roentgenographic characteristics of the index case and family members

Family cases, age	Clinical presentation/characteristic findings					Roentgenographic findings		
	Proteinuria	Renal function impairment	Knee deformity	Antecubital pterygium of elbow	Triangular lunulae of nail	Iliac horn	Hypoplastic patellae	Hypoplastic radial head
Index case, 42 yr	+	+	+	+	+	+	+	+
Mother, 66 yr	+	+	+	+	+	–	+	+
Elder sister, 49 yr			+	–				
Elder daughter, 23 yr	–	–	+	+	–	–	+	–
Younger daughter, 22 yr			+	+	–			

clinical visits when the patient was 42 years old. Her mother was 66 years old at the time of diagnosis. Careful physical examination and clinical suspicion are the keys to correct diagnosis.

NPS-associated nephropathy was first reported by Hawkins and Smith in 1950 [9]. The most common clinical manifestation is persistent and moderate proteinuria. However, some cases may be associated with microscopic hematuria, hypertension, and impaired urine concentration. Nephrotic syndrome has also been observed in some patients. Progression to ESRD occurs in about 30% of patients with renal symptoms, but usually many years after discovery of proteinuria [4]. Light microscopy and immunofluorescence study are generally unhelpful, showing normal or near-normal glomeruli, with negative or nonspecific segmental deposits of IgM and C3 in sclerotic areas. Electron microscopy reveals definite lesions in the GBM, including irregular thickening and lucent rarefactions within the lamina densa, the moth-eaten appearance, and dark fibrillar material with the periodicity of collagen within the electron-lucent areas and in the mesangial matrix.

Our patient presented with asymptomatic non-nephrotic-range proteinuria, which was consistent with the most common manifestation of nephropathy. Immunofluorescence and electron miscroscopy of the renal biopsy specimen were near normal, with only a mild increase in glomerular cells, giving the impression of membranoproliferative glomerulonephritis. Double-staining the renal biopsy specimen with uranyl acetate and PTAH failed to show the characteristic features of irregular thickening and lucent rarefactions within the lamina densa and dark fibrillar material with the periodicity of collagen. One possible explanation is that, according to many previous studies, there is no correlation between renal histologic findings and clinical presentation. Marked pathologic findings without clinical symptoms and signs in long periods of follow-up have also been reported. Thus, this case suggests that the histologic findings might not be the cause of the functional nephropathy, and nephropathy might merely coexist or be a coincidental finding. Thus, the previously proposed pathognomonic finding of renal pathology might require further evaluation.

The most remarkable clinical feature of this patient and her family members was the web-like structure over the antecubital area since birth. This rare feature of NPS, antecubital pterygia, has been reported in only 4% of NPS cases, and an association with renal involvement has been suggested [10]. Kieser first reported a case of NPS with antecubital pterygium in 1939 in Germany, with a true web extending along the antecubital fossa from the distal third of the upper arm to the proximal third of the forearm associated with impaired elbow flexion, pronation, supination, and extension. Our patient had limitation of elbow joint range of motion, and had typical roentgenogram findings of a hypoplastic posterior dislocated radial head with a hypoplastic lateral condyle of the humerus. Multiple pterygium syndrome (or familial pterygium syndrome) is easily differentiated from antecubital pterygia of NPS due to differing involved areas and none of the changes in the patella, radial head, iliac horn, or nails that are typical of NPS.

Patella involvement was another marked feature in this family. From birth, the patella was laterally displaced when the knee joint flexed, and the degree of displacement worsened progressively with age. Roentgenograms revealed hypoplastic and lateral subluxation of the patella and hypoplastic femoral lateral condyle. This was consistent with the typical knee joint findings of previous reports. Diseases that should be differentiated from NPS include small patella syndrome [12] and RAPADILINO syndrome [13].

Pathognomonic iliac horns appear in about 70% of NPS cases, and involvement is mostly bilateral. The iliac horn is asymptomatic, but palpable on physical

examination. The nails of our patient, upon closer examination, revealed typical triangular lunulae [14] over the second to fourth fingers on both hands. That is, there was a triangular shape rather than the normal half-moon crescent of the nail bed, with the peak pointing to the fingertip in the midline, which has been proposed as one pathognomonic feature. More common and well-known pathologic features of the nails, such as hypoplastic or dysplastic nails, small nails, thickened or depressed nails, discoloration, and longitudinal splitting or ridging, are absent. Nail changes are usually bilateral and symmetric and affect the thumbs and index finger more often than other digits. However, in this case, the patient and her mother had no thumb involvement.

NPS is a rare autosomal-dominant hereditary disease. It is linked to ABO typing and adenylate kinase [15]. Fine mapping by McIntosh et al identified the locus at 1-2cM to 9q34.1 [16]. Dreyer et al showed that NPS was caused by mutations in the LMX1B gene [2]. Sixty-five mutations in Lmx1b have been identified in NPS cases [3]. LMX1B belongs to a family of highly related LIM-homeodomain transcription factors that are involved in pattern formation during development. In *Lmx1b*(-) mice, there are nail dysplasia and skeletal defects similar to those observed in NPS patients. The expression of both alpha (3) and alpha (4) type IV collagen is strongly diminished in the GBM [17, 18]. Further pathogenesis and genetic studies are now being carried out worldwide to solve the mystery of body patterning and the less well-known renal involvement of NPS.

The prognosis of NPS depends on the presence and severity of renal involvement, which seems to affect 30 to 50% of NPS patients, 14 to 30% of whom may progress to ESRD [4]. The course of renal disease is extremely variable and inconsistent, suggesting that nongenetic factors may be involved in the rapid deterioration of renal function observed in some patients. For example, superimposed nephritis such as membranous glomerulonephritis, IgA nephropathy, Goodpasture's syndrome and necrotizing angitis have been observed in patients with NPS [19–22]. Although there is no specific therapy available for NPS, it can be successfully treated with renal transplantation without recurrence and with no development of anti-GBM antibodies. This case presented fluctuating proteinuria unresponsive to prednisolone treatment but stable renal function. A benign course is anticipated, but further follow-up was indicated. The patient's mother had advanced renal failure and decreased bilateral kidney size, and was receiving conservative treatment with an angiotensin-converting enzyme inhibitor, a calcium channel blocker, antiplatelet medication and regular follow up.

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