Case report

Vasculitis and renal disease in nail-patella syndrome: case report and literature review

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SUMMARY A 57 year old man with nail-patella syndrome (NPS) and associated renal disease is described who developed an inflammatory polyarthropathy and polyarteritis-like vasculitis. Vasculitis and serum complement abnormalities have not previously been reported in NPS. NPS is a rare autosomal dominant connective tissue disorder affecting both mesenchymal and ectodermal tissue. The condition is reviewed with particular reference to its renal pathology, including the distinctive electron microscopic (EM) finding of collagen deposition in the glomerular basement membrane (GBM). The possibility of the underlying collagen abnormality acting as a trigger for immune-inflammatory changes is discussed.

Key words: collagen, basement membrane, polyarteritis.

Case report

A 57 year old white man was hospitalised in November 1985 for investigation of symmetrical polyarthritis and recent onset paraesthesia and petechial skin rash of the legs (two weeks). We noted typical clinical features of NPS: positive family history, hypoplastic thumbnails and patellae, and severe knee and elbow arthropathy bilaterally (15 years). There was a six month history of significant morning stiffness (four hours) in association with bilateral symmetrical pain and swelling of elbows, wrists, and metacarpophalangeal (MCP) joints, occasionally relieved by non-steroidal drug therapy. The past history was also notable for chronic renal failure, hypertensive heart disease, and atrial fibrillation (10 years). A right nephrectomy in 1982, at which time the creatinine clearance was 70 ml/min, showed a small end stage kidney with an embolised right renal artery. Routine histology showed generalised glomerulosclerosis and cortical atrophy.

Examination showed a pale, anicteric, hypertensive man with hypoplastic thumbnails and a petechial skin rash on the legs and ankles. Joint examinations showed moderately swollen and tender wrists and MCP joints bilaterally, 10 degree flexion deformities of both elbows without synovial thickening, effusions, or subcutaneous nodules, and gross knee malalignments with bilateral 30 degree flexion deformities, marked crepitus, and boggy synovial tissue. The patellae were small and laterally displaced. A symmetrical, mixed sensory motor, stocking type peripheral neuropathy of the lower limbs was found.

Blood results included a normochromic, normocytic anaemia (haemoglobin 100 g/l), white blood cells $17.7 \times 10^9/l$ (89% polymorphonuclear, 6% lymphocytes), platelet count $395 \times 10^9/l$, reticulocytes 0.5%, Westergren sedimentation rate 108 mm/1st h, urea nitrogen 14 mmol/l, creatinine 309 $\mu\text{mol/l}$, sodium 137 mmol/l, potassium 5.0 mmol/l, normal serum calcium, alkaline phosphatase, liver function tests, and muscle enzymes, negative rheumatoid factor, hepatitis B surface antigen, antinuclear antibodies (HEP₂ substrate), direct Coombs test and cryoglobulin search, normal IgG and IgM levels, IgA 4.33 g/l (normal 0.7–3.12),

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CH₅₀ 55 U/ml (normal 64–192), normal C2, C3, C4, and C5, and C1q binding assay of 40% (normal <13%). Urine analysis showed ++ proteinuria, a 24 hour protein excretion of 2200 mg, and creatinine clearance of 60 ml/min.

Am x ray examination showed hypoplastic patellae with severe medial compartment osteoarthritis of both knees, hypoplastic radial heads with osteophyte formation of both elbows, iliac bony spurs (horns), pathognomonic of NPS, and soft tissue swelling around the MCP joints of the hands. Abdominal ultrasound showed a normal sized left kidney (11.5 cm), electromyography showed normal proximal muscles, and nerve conduction studies disclosed a severe generalised lower limb peripheral neuropathy. Calf muscle biopsy showed chronic round cell infiltration of medium sized arteries with varying degrees of involvement. Special elastic stains confirmed a necrotising vasculitis (Fig. 1). Immunofluorescent studies were negative. Abnormal collagen deposition could not be recorded by EM study.

Fig. 1 A small artery of skeletal muscle is thrombosed (T) and chronically inflamed. The area of most intense vasculitis (arrows) shows destruction of elastica (El) and muscularis. (Verhoeff-Van Gieson stain.)

Fig. 2 This glomerular loop contains a group of collagen fibrils (arrows) between the endothelial cell (En) and basement membrane (BM). The podocyte (P) and luminal contents (L) are unremarkable. (Uranyl acetate-lead citrate stain.)

Synovial fluid was not obtainable. Knee synovial biopsy showed a mild chronic synovitis, predominantly plasma cell in type. Synovial immunofluorescent studies and EM screening for abnormal collagen were negative. EM study of the nephrectomised kidney disclosed irregular thickening of the GBM with collagen deposition in the lamina densa and interna, subepithelial and subendothelial areas (Fig. 2). The periodicity of the collagen was 46 nm, similar to measurements made in other subjects with NPS.

MANAGEMENT

The upper limb polyarthritides were successfully treated with indomethacin (25 mg three times a day) over a three week period. In the setting of necrotising vasculitis and chronic renal disease, prednisone (60 mg/day) and cyclophosphamide (100 mg/day) were started. The former was tapered to 15 mg daily and the latter discontinued after six months at the time of successful bilateral knee arthroplasties. Blood

results at this time included a normal white cell count and sedimentation rate, creatinine 336 $\mu\text{mol/l}$, CH_{50} 64 U/ml, and C1q binding assay of 40%, indicating the continued presence of circulating immune complexes. The nature of these complexes was not determined. Maintenance therapy included prednisone 15 mg daily and sulindac 150 mg twice daily.

Discussion

NPS, or hereditary onycho-osteodysplasia, was first described in 1820 by Chatelain who reported a patient with congenital anomalies of the nails, elbows, and knees.¹ Little in 1897 and Wrede in 1909 further described families with the triad of anomalies.^{2,3} Turner in 1933 described iliac crest flaring with prominent anterior superior spines,⁴ and Fong applied the term iliac horns to the list of abnormalities,⁵ so completing the tetrad of diagnostic features of the syndrome: (a) hypoplastic or absent patellae, (b) dysplastic, hypoplastic, or absent thumbnails, (c) iliac horns, and (d) elbow abnormalities, including hypoplastic or subluxed radial heads. Any combination of these anomalies may arise in an affected individual.

This rare disorder is inherited as an autosomal dominant, which in 10% of cases is on the same chromosome carrying the ABO system.⁶⁻⁸ In the USA the incidence is reported to be 4.5 cases per million and in England 22 cases per million.⁹ Renal changes occurring in this disorder were first described by Hawkins and Smith in 1950.¹⁰ In a detailed family study they noted clinical features of chronic glomerulonephritis in four of 21 affected individuals, without particular age or sex distribution. In another study clinical renal involvement was reported in 42% of 29 subjects.¹¹ The usual clinical indicator of renal involvement is proteinuria with only occasional microscopic haematuria or frank clinical features of glomerulonephritis.

A number of reports of patients with nephritis, some progressing to renal failure, have appeared, however, recording non-specific GBM thickening on light microscopy.¹²⁻¹⁴ Curtis *et al* found that end stage renal failure developed in at least 21 patients with NPS,¹⁵ suggesting the aggressive nature of renal involvement in some subjects with NPS. Pozo and Lapp and Ben-Bassat *et al* were the first investigators to report the presence of electron lucent areas in the thickened GBM.^{16,17} The latter group also described deposition of collagen fibers in the GBM, a finding apparently unique to NPS, and in the mesangium, but this latter finding is known to occur in many forms of glomerulonephritis, including diabetes mellitus and amyloidosis. The

GBM collagen could not be properly characterised. Morita *et al* reported similar changes in a man aged 34 in renal failure, and in his son aged 6 with asymptomatic proteinuria.¹⁸ Sabnis *et al* reported on three patients with clinical and ultrastructural renal involvement but no evidence of skeletal abnormalities.¹⁹ The authors felt these cases represented partial or incomplete gene penetration of NPS. Dombros and Katz similarly reported NPS-like renal lesions in the absence of skeletal abnormalities in a 34 year old woman who presented incidentally with asymptomatic haematuria.²⁰

In searching for reports of vasculitis or autoimmune disease occurring in NPS subjects, we found only one case report of Goodpasture syndrome, occurring in a 17 year old man.¹⁵ The characteristic clinical, renal, histological, EM, and immunofluorescent features of both syndromes were present in this patient. Complement levels were not reported. The authors postulate that the occurrence of two rare syndromes in the same patient was either coincidental or in some way immunologically related.

Immunofluorescent studies of renal tissue from subjects with NPS have been reported by Hoyer *et al*¹⁴ and Bennett *et al*.²¹ Although there was evidence of immunofluorescent staining, usually trace-positive focal $\beta_2\text{C}$ in varying locations and patterns, these investigators did not feel immunological mediation of the disease was likely. Hoyer *et al* investigated seven patients with NPS, six of whom were family members. One subject (aged 33) had developed renal failure after a prolonged period of asymptomatic proteinuria. Serum complement levels (either $\beta_2\text{C}$ or haemolytic complement activity) were not reduced in any patients. Positive staining for $\beta_2\text{C}$ was present in all seven renal biopsy specimens. IgM staining was positive (six of seven) and typical EM findings of NPS were found in all seven. The authors suggest that the GBM abnormality may reflect a disturbance in synthesis of GBMs as a manifestation of a diffuse connective tissue disorder or, alternatively, may reflect entrapment within the GBM of circulating collagen precursors and assembly of these moieties into fibrils with the appearance of mature interstitial collagen.¹⁴

Bennett *et al*, in a study of 72 patients with NPS, found 36 subjects with skeletal manifestations. EM studies on 12 subjects and two unaffected relatives showed typical GBM abnormalities of NPS in the former group. There were no consistent immunofluorescent findings, with negative deposits in three subjects, trace deposits in another three, and IgG or IgM-C3 complexes in varying locations in three others. Serum complement and immunoglobulin levels measured in 10 patients were normal.

Urinary screening was negative for abnormal acid mucopolysaccharides (11 of 12) and negative for amino acids (all 12).²¹

Necrotising vasculitis with serum complement or IgA abnormalities, or both, have not previously been reported in NPS. The aetiological significance of these changes in the absence of antinuclear antibodies or immune complex deposition is unclear. A diagnosis of polyarteritis nodosa or polyangiitis overlap syndrome is suggested in our patient by the clinical and histological findings.²² An inflammatory polyarthropathy as in our subject has been reported in two patients with NPS in whom no other cause for arthritis could be found.²³ The renal pathology in our patient was characterised by long standing hypertension and renal failure, with the NPS glomerular lesion recorded on EM study. Renal vasculitis could not be proved in the absence of angiography or biopsy of the remaining kidney. Studies have not shown any correlation between the presence of the NPS renal lesion and extent of clinical renal disease.^{18, 20} Investigators have suggested the association of renal and skeletal lesions in NPS may be due to a metabolic disorder causing aggregation of collagen and a disturbance in synthesis or degradation, or both, of collagen.^{14, 18} The finding by Schleutermann *et al* in 1969 that the locus for the syndrome is closely linked to that of adenylate kinase on chromosome 9 may prove highly significant in the eventual complete characterisation of the collagen disorder in this distinctive syndrome.²⁴

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