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Case report

Immunotactoid glomerulopathy with fingerprint immune deposits

A variant of lupus nephritis?

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Summary. Immunotactoid glomerulopathy is a distinct clinico-pathological entity which has recently been defined. The term immunotactoid refers to highly organized immune depositions appearing as rod-like microtubular structures in ultrastructural examination. We describe a patient with mixed connective tissue disease who demonstrates characteristic features of immunotactoid glomerulopathy. The diagnosis was made after excluding amyloidosis, cryoglobulinaemia and lupus nephritis. In addition to immunotactoid microtubules, ultrastructural examination also demonstrated presence of fingerprint depositions which were intimately mixed with immunotactoid structures. Fingerprint deposits have been described in lupus nephritis and cryoglobulin-related nephropathy, but rarely in other glomerulonephritis. These unique findings in our patient may suggest a previously unsuspected relationship between the syndrome of immunotactoid glomerulopathy and systemic lupus erythematosus.

Key words: Immunotactoid deposits – Congo Red-negative microfibrils – Amyloid-like microtubules – Fingerprint depositions

Introduction

In 1980, Schwartz described a patient with nephrotic syndrome and distinctive glomerular crystalline immune deposits and introduced the pathological entity of "immunotactoid glomerulopathy" (Schwartz 1980). The organised microtubular structures of his patient resembled those found in amyloidosis, cryoglobulinaemia, or systemic lupus erythematosus (SLE). More recently the same group reviewed 11 similar cases and defined this clinico-pathological entity by including a prognostic assessment through a mean follow-up period of over 4 years (Korbet 1985). The term "immunotactoid" refers to glomerular extracellular immune deposits which display a high degree of tubular organisation reminiscent of what are seen in crystalline structures. Similar microtubules can be seen in renal amyloidosis, nephropathy of cryoglobulinaemia and lupus nephritis from which immunotactoid glomerulopathy must be distinguished with because of different therapeutic and prognostic implications (Korbet 1985). Although immunotactoid glomerulopathy is relatively rare, new cases are recognized (Kobayashi 1988, Nakamura 1978, Rosenmann 1988). Some of the cases, previously described as Congo red-negative amyloid-like glomerulopathy possibly belong to this category (Alpers 1987; Duffy 1983; Panner 1980; Rosenmann 1977; Sturgill 1985).

Ultrastructural lamellated immune deposits, so-called "fingerprint" structures are reputed for its strong association with lupus nephritis and cryoglobulinaemia, but rarely with other forms of glomerulonephritis. Fingerprint structures, like immunotactoid deposits, are extracellular and identified within immune electron-dense deposits. However, fingerprint depositions have not been described in reported cases of immunotactoid glomerulopathy.

We describe here a patient with mixed connective tissue disease and pathological features diag-

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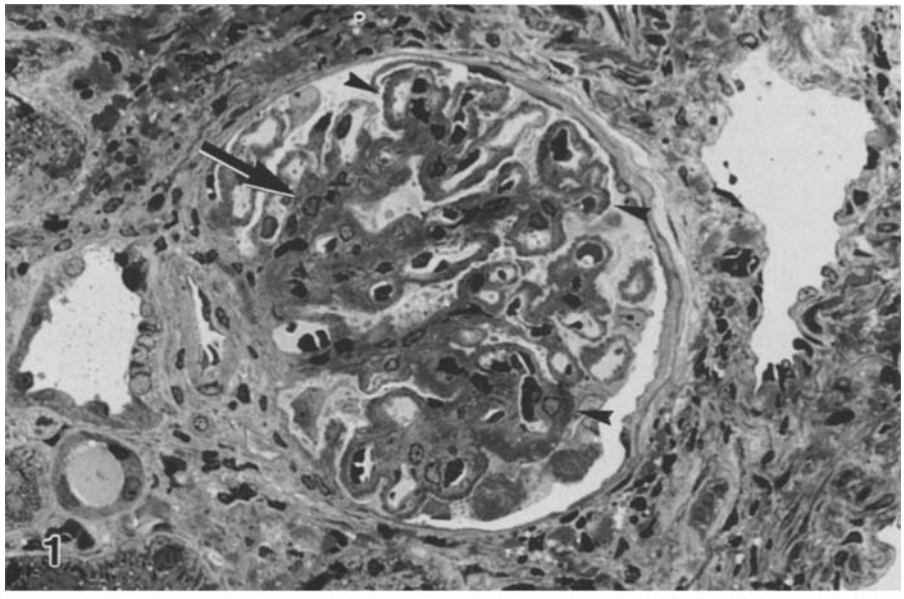

Fig. 1. Glomerulus exhibiting a thickened capillary basement membrane with dense immune deposits (*arrowheads*) with segmental mesangial expansion (*arrows*). Toluidine blue (× 260)

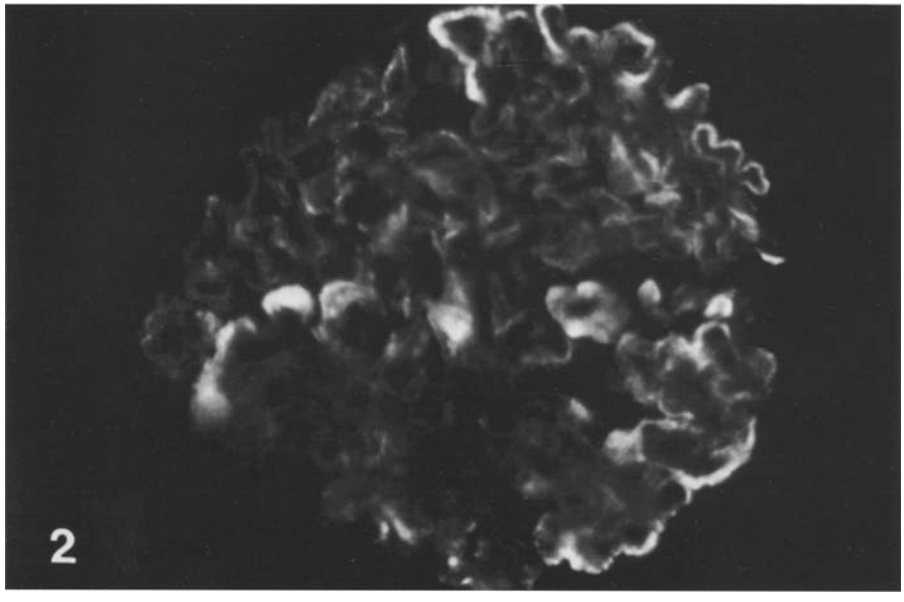

Fig. 2. Coarse granular staining of IgG in glomerular capillary wall, accentuated in some segments. FITC-anti-gamma (× 360)

nostic of immunotactoid glomerulopathy. The electron microscopy disclosed the presence of fingerprint structures in addition to immunotactoid microtubules. This ultrastructural relationship between immunotactoid glomerulopathy and lupus nephritis, complemented with similar clinical manifestations and pathogenetic mechanism, suggests that immunotactoid glomerulopathy shows overlapping features of SLE and mixed connective tissue disease, and may represent a variant of SLE.

Case report

A 36 year-old female was treated for SLE since 1984 at another institution. The diagnosis was based on malar rash, Raynaud's phenomenon, arthralgia and a positive ANA titer of 1:1280. The past record, however showed a consistently negative anti-DNA and a normal serum complement C3 and C4 levels. The patient was initially treated with high dose of prednisone and thereafter put on a maintenance dose with symptomatic control. Chloroquine treatment was given in 1985 for arthralgia and was discontinued because of lack of clinical response. Subsequently, she was referred to our institution in September 1986 because of the nephrotic syndrome.

The significant physical findings included a blood pressure of 130/80 mm Hg, a non-deforming arthropathy involving small joints and marked ankle oedema. Features of scleroderma such as calcinosis, sclerodactily, telangiectasia and skin tautness were not detected.

Laboratory data disclosed: normal blood cell count, ESR 93 mm/h, normal electrolytes, serum creatinine 75 μmol/l, creatinine clearance 79 ml/min, serum protein 47 gm/l, serum albumin 17 g/l, serum cholesterol 7.3 mmol/l, negative Coomb's and

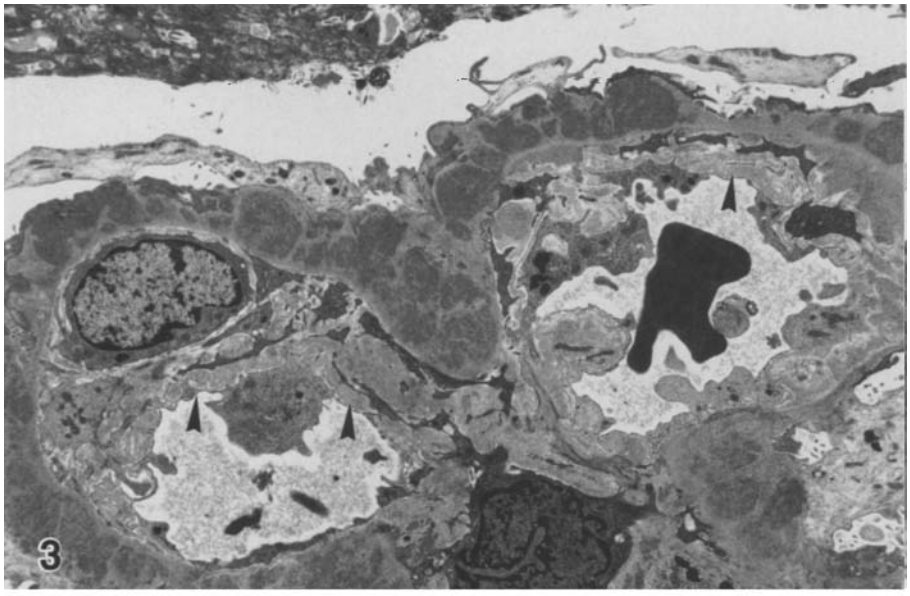

Fig. 3. Glomerular basement membrane with heavy subepithelial electron-dense deposits. Duplication of capillary basement membrane is focally seen (*arrowheads*). The epithelial foot processes are extensively fused. Lead citrate and Uranyl acetate (× 3900)

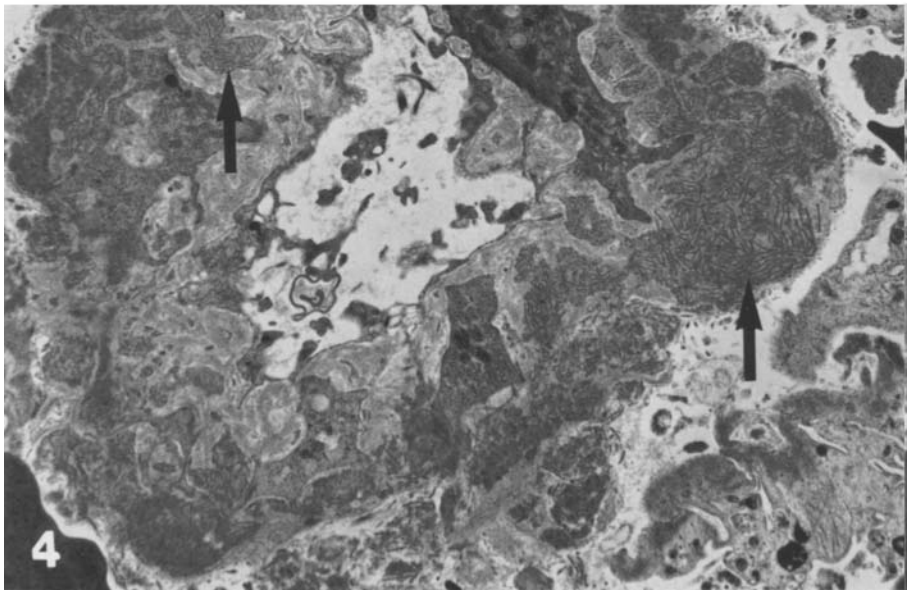

Fig. 4. A markedly thickened capillary basement membrane demonstrating immunotactoid microtubules within electron-dense deposits (*arrows*). Lead citrate and Uranyl acetate (× 5200)

VDRL tests, undetectable rheumatoid factor, cryoglobulins and normal serum CH50, C3 and C4 levels. Cryoglobulins were excluded in 2 occasions by absence of precipitate in serum samples stored at 4° C, 20° C and 37° C, after 24 h (Whicher 1987). Antinuclear factor was detected with with a titer of 1:1280 and a speckled pattern detected by an anti-human IgG subclass. The anti-RnP titer was 1:1280. Anti-DNA, anti-Sm, anti-Ro and anti-La antibodies were not demonstrated. Antibodies to Scl-70 were not performed. Serum immunoelectrophoresis showed no abnormality. Serum for hepatitis B surface antigen was negative by reversed passive haemagglutination. Cytomegalovirus and herpes simplex infections were excluded by negative complement fixation test. Epstein Barr virus titers were all normal. Urine protein amounted to 4.3 g/24 h, and Bence Jones protein was not detected. Bence Jones protein was excluded by absence of abnormal band/bands in electrophoresis of concentrated urine (Whicher 1987). Microscopic glomerular haematuria was present and urine cultures were negative. Skin biopsy was not performed as there was no clinical indication.

Patient has been stable for 2 years on low dose corticosteroids, normotensive, free of ankle oedema. Recent investigations showed a creatinine clearance of 80 ml/min, serum albumin 36 g/l, urine protein of 1 g/24 h. Anti-DNA and cryoglobulins remained negative. Antinuclear factor was positive at 1:640.

Results

The tissue was prepared by standard techniques for light, immunofluorescent and electron microscopies as previously described (Lai 1986).

For light microscopy, sections were stained with haematoxylin and eosin, periodic acid-Schiff,

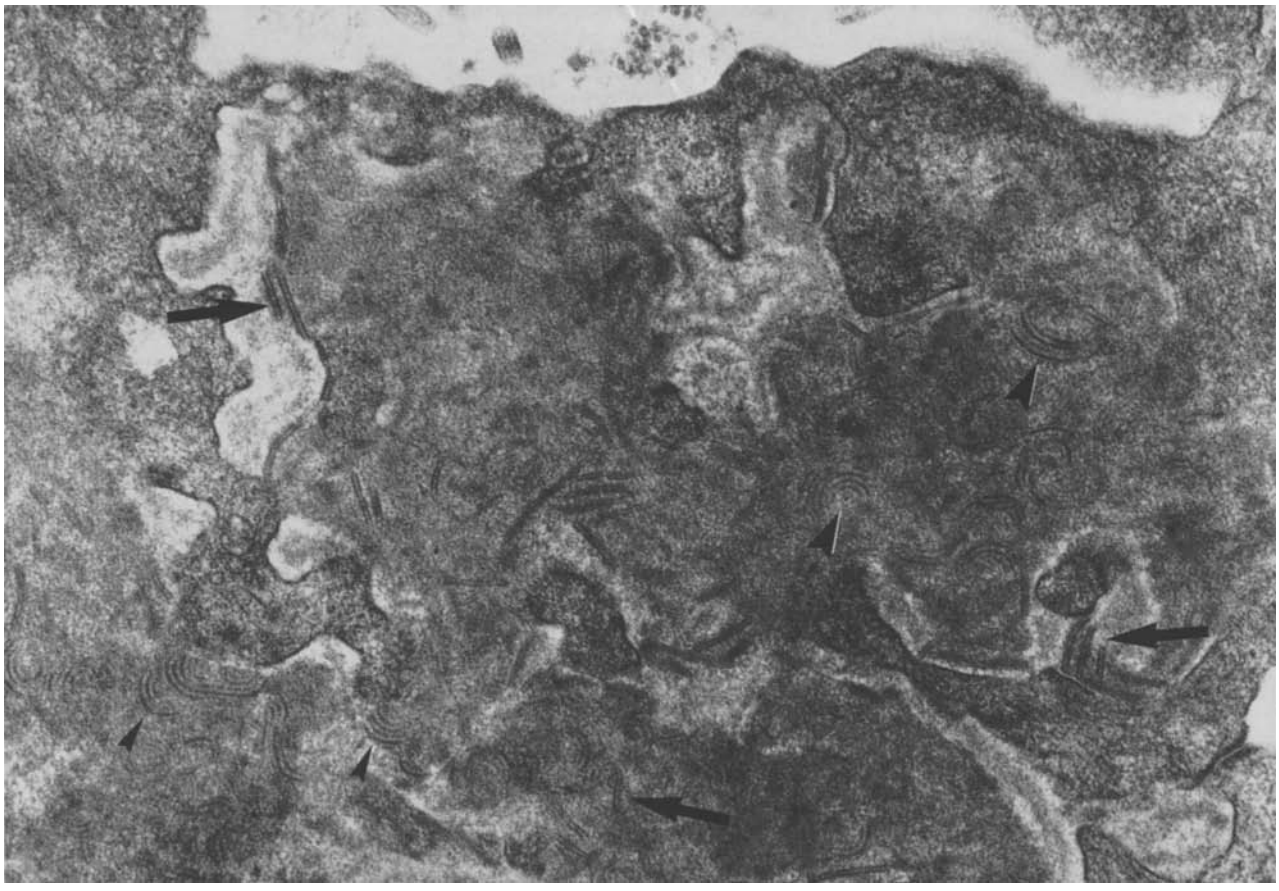

Fig. 5. Coexistence of microtubular structures (*arrows*) and fingerprints deposits (*arrowheads*) within glomerular immune deposits. Lead citrate and Uranyl acetate (× 32800)

periodic acid-silver methenamine, Masson trichrome, Congo red and crystal violet. All 6 glomeruli examined showed segmental mesangial expansion with slight hypercellularity (Fig. 1). The glomerular capillary basement membrane was markedly thickened and showed widespread fushinophilic deposits. Silver impregnation demonstrated "spikes" projections of the basement membrane, sometimes the silver stain circumscribed deposits to reveal a "honeycomb" appearance. Necrotizing lesion and haematoxyphil bodies were not identified. Congo red or crystal violet stains were negative. The tubules showed mild focal atrophy and interstitial fibrosis. No vasculitis or hypertensive changes were seen.

Direct immunofluorescence microscopy was performed using FITC-conjugated anti-human alpha, gamma and mu heavy chains, kappa and lambda light chains, Clq, C3, C4 and fibrinogen (Behringwerke AG, FRG). All six glomeruli examined demonstrated a heavy granular staining for IgG (3+), kappa (2+), lambda (2+), C3 (2+), C4 (1+), Clq (trace), and IgA (trace) mainly distributed in the glomerular capillary wall while the staining in the mesangium was less conspicious (Fig. 2). IgM and fibrinogen were not detected. The nuclei of tubular epithelial cells were positive for IgG (2+) indicating the presence of antinuclear factors. Staining with Thioflavin T was negative.

Electron microscopy revealed three glomeruli with preserved tufts architecture and segmental mesangial hypercellularity. Massive electron-dense deposits were present in the capillary basement membrane, mainly distributed in subepithelial sites (Fig. 3). Mesangial and subendothelial distributions of electron-dense deposits were modest. Distinct immunotactoid microtubules were identified within electron-dense deposits, in both intramembranous and mesangial sites, and appeared massive in some areas but inconspicuous in others (Fig. 4). These microtubules were non-branching, usually straight, at times slightly bent, but are different from reticular "microtubules", myxovirus-like structures described in SLE. At higher magnifications, they displayed an electrolucent core giving an "hollow" appearance (Fig. 5). Their calculated

diameter were constant and ranged between 25 to 40 nm while their length varied markedly. In addition, characteristic "fingerprint" lamellated structures were seen within the electron-dense deposits, coexisting with immunotactoid microtubules described above. Transitional form of organized structures between fingerprint and immunotactoid microtubules were not identified. Although immunotactoid microtubules and fingerprints were intimately associated (Fig. 5), they were not connected or attached, but appeared as independent structures.

The epithelial cell foot processes were extensively fused with intracytoplasmic fibrillary osmiophilic staining in areas adjacent to the basement membrane. Both mesangial and endothelial cells were relatively intact. Duplication of basement membrane and mesangial cell interposition are occasionaly seen (Fig. 3), but absent in the majority of capillary loops so that the diagnosis of mesangiocapillary glomerulonephritis is not justified. The glomerular pathology remains predominantly membranous nephropathy. Intracellular reticular bodies or microtubules sometimes observed in lupus nephritis were not detected. Electron-dense deposits and microtubular structures were not identified in tubular basement membrane.

Discussion

Our patient was managed with the initial diagnosis of SLE, but the clinical and serological criteria were insufficient and precluded the diagnosis (Tan 1982). In the absence of detectable antibodies to double-stranded DNA, further characterization of the serum antinuclear antibodies became necessary. Although serum for anti-Scl-70 was not performed, the clinical features and the negative anti-Ro and anti-La were against the diagnosis of systemic sclerosis. An elevated titer of antibodies to ribonucleoprotein (RnP) alone and lack of serological markers for SLE helped to establish the diagnosis of mixed connective tissue disease (MCTD) in light of the clinical presentation (Bennett 1977; Nakamura 1978). It is of interest that our patient did not initially show clinical evidence of renal involvement. This "latent" period may partly explain the earlier notion that renal involvement is rare in MCTD (Fuller 1977; Nakamura). But recently, renal involvement was found to be more common in patient with MCTD (Bennett 1977). The glomerular pathology was often membranous nephropathy as in our case and in many instances, the pathogenesis was related to the formation of immune complexes (Bennet 1977; Fuller 1977).

Renal biopsy of our patient revealed massive deposition of extracellular, microtubular structures in ultrastructural examination. These amyloid-like microtubules were distributed within glomerular electron-dense deposits, both within capillary basement membrane and mesangium. Microfibrils related to subunits of connective tissue component of the glomerular basement membrane were excluded, as they are usually small in size (3 to 13 nm in diameter) and are associated with electrolucent deposits (Hsu 1979). Microfibrils of amyloidosis are of small diameter (7–10 nm) and were excluded by the absence of specific histochemical stainings of the beta pleated-sheet protein conformation (Bourgeois 1987; Korbet 1985). Large microtubules of size similar to immunotactoid structures have been described in glomerular deposits in light chains disease, cryoglobulinaemia and lupus nephritis (Bengtsson 1975; Gallo 1980; Grishman 1967; Linder 1983). In our patient, monoclonal light chain gammopathy was clinically excluded. Serum cryoglobulin was not detected in several occasions and the serum immunoglobulin levels were normal.

The relationship between immunotactoid glomerulopathy and MCTD remains to be clarified. In the group of eleven patients with immunotactoid glomerulopathy described by Korbet, one patient had the concomitant diagnosis of MCTD, similar to our present case. Another patient in this group had elevated antinuclear factors, but characterization of these antinuclear antibodies were not available and the diagnosis of MCTD was neither confirmed or excluded (Korbet 1985). Furthermore, in nephropathy associated with MCTD, intracytoplasmic microtubular structures were described in the glomerular endothelial cells, but immunotactoid microtubules have not been identified or reported previously, with the exception of Korbet's one single case and of the patient we describe here (Korbet 1985; Fuller 1977). From these observations, it is apparent that a small subset of patients with the syndrome of immunotactoid glomerulopathy also has diagnostic features of MCTD.

Association of immunotactoid structures with electron-dense immunoglobulins and complement components leaves little doubt on their composition. The physico-chemical conditions which are critical for the formation of crystalline structures remain poorly understood (Shifferli 1987), except perhaps in cryoglobulinaemia, where temperature appears to be a putative physical factor. Although these immunotactoid structures mimic viral particles, the identification of a viral aetiology in these

cases has been unsuccessful (Duffy 1983; Fresco 1970).

The ultrastructural association of microtubular structures and fingerprint deposits have been described in lupus nephritis and cryoglobulin-related nephropathy, rarely in membranoproliferative glomerulonephritis (Bengtsson 1975; Davis 1976; Grishman 1967; Kim 1981). These organized immune deposits are regarded as highly characteristic, although not diagnostic in lupus nephritis (Grishman 1967; Kim 1981; Schwartz 1982). The patient we describe here with the diagnosis of MCTD is unique in demonstrating this ultrastructural combination of immunotactoid glomerulopathy and fingerprint depositions. This observation supports Schwartz's suggestion that immunotactoid glomerulopathy may represent more than one disease entity with common morphological expression (Korbet 1985). Similar microfibrils have recently been described in membranous nephropathy associated with lymphoma (Rosenmann 1988).

Our patient with immunotactoid glomerulopathy and MCTD, not only shares some of the highly characteristic pathological findings with lupus nephritis patients, but also demonstrates a immune complex pathogenesis and clinico-serological manifestations similar to SLE patients. From these observations, an alternate view may be held: the syndrome of immunotactoid glomerulopathy is an overlapping manifestation of systemic lupus erythematosus and mixed connective tissue disease, and may represent a variant of lupus nephritis.

References

Alpers CE, Rennke HG, Hopper J, Biava CG (1987) Fibrillary glomerulonephritis: An entity with unusual imunofluorescence features. Kidney Int 31:781–789

Bengtsson U, Larsson O, Lindstedt G, Svalander C (1975) Monoclonal IgG cryoglobulinemia with secondary development of glomerulonephritis and nephrotic syndrome. Q J Med 175:491–503

Bennett RM, Spargo BH (1977) Immune complex nephropathy in mixed connective tissue disease. Am J Med 63:534–541

Bourgeois N, Buyssens N, Goovaerts G (1987) Case for the Panel: Ultrastructural appearance of amyloid. Ultrastruct Pathol 11:67–77

Davis BK, Cavallo T (1976) Membranoproliferative glomerulonephritis. Localization of early components of complement in glomerular deposits. Am J Pathol 84:283–298

Duffy JL, Khurana E, Susin M, Gomez-Leon G, Churg J (1983) Fibrillary renal deposits and nephritis. Am J Pathol 113:279–290

Fresco R (1970) Virus-like particles in systemic lupus erythematosus. N Engl J Med 283:1231–1233

Fuller TJ, Richman AV, Auerbach D, Alexander RW, Lottenberg R, Longley S (1977) Immune-complex glomerulonephritis in a patient with mixed connective tissue disease. Am J Med 62:761–764

Gallo GR, Feiner HD, Katz LA, Feldman GM, Correa EB, Chuba JV, Buxbaum JN (1980) Nodular glomerulopathy associated with nonamyloidotic kappa light chain deposits and excessive immunoglobulin light chain synthesis. Am J Pathol 99:621–643

Grishman E, Porush JC, Rosen SM, Churg J (1967) Lupus nephritis with organized deposits in the kidneys. Lab Invest 16(5):717–725

Hsu HC, Churg J (1979) Glomerular microfibrils in renal disease: a comparative electron microscopic study. Kidney Int 1979; 16:497–504

Kim YH, Choi YJ, Reiner L (1981) Ultrastructural "fingerprint" in cryoprecipitate and glomerular deposits: a case report of systemic lupus erythematosus. Hum Pathol 12:86–89

Korbet SM, Schwartz MM, Rosenberg BF, Sibley RK, Lewis EJ (1985) Immunotactoid glomerulopathy. Medicine 64(4):228–243

Kobayashi Y, Fujii K, Kurokawa A, Kamiyama M, Miyazawa H (1988) Glomerulopathy with amyloid-stain-negative microfibrillar glomerular deposits. Nephron 48:33–39

Lai KN, Mac-Moune Lai F, Chan KW, Ho CP, Leung ACT, Vallance-Owen J (1986) An overlapping syndrome of IgA nephropathy and lipoid nephrosis. Am J Clin Pathol 86:716–723

Linder J, Vollmer RT, Croker BP, Shelburne J (1983) Systemic kappa light-chain deposition. An ultrastructural and immunohistochemical study. Am J Surg Pathol 7:85–93

Nakamura RM, Tan EM (1978) Recent progress in the study of autoantibodies to nuclear antigens. Hum Pathol 9:85–91

Panner BJ (1980) Rapidly progressive glomerulonephritis and possible amyloidosis. Arch Pathol Lab Med 104:603–609

Rosenmann E, Eliajim M (1977) Nephrotic syndrome associated with amyloid-like glomerular deposits. Nephron 18:301–308

Rosenmann E, Brisson ML, Bercovitch DD, Rosenberg A (1988) Atypical membranous glomerulonephritis with fibrillar subepithelial deposits in a patient with malignant lymphoma. Nephron 48:226–230

Sadjadi SA, Sobel HJ (1987) Congo red-negative amyloid-like glomerulopathy: report of a case. Am J Kidney Dis 9:231–234

Schwartz MM, Lewis EJ (1980) The quaterly case: Nephrotic syndrome in a middle-aged man. Ultrastruct Pathol 1:575–582

Schwartz MM, Roberts JL, Lewis EJ (1982) Subepithelial electrondense deposits in proliferative glomerulonephritis of systemic lupus erythematosus. Ultrastruct Pathol 3:105–118

Shifferli JA, Merot Y, Cruchaud A, Chatelanat F (1987) Immunotactoid glomerulopathy with leucocytoclastic skin vasculitis and hypocomplementemia: a case report. Clin Nephrol 27(3):151–155

Sturgill BC, Bolton WK, Griffith KM (1985) Congo Red-negative amyloidosis-like glomerulopathy. Hum Pathol 16:220–224

Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Green Shaller J, Talal N, Winchester RJ (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277

Whicher JT, Calvin J, Riches P, Warren C (1987) The laboratory investigation of paraproteinaemia. Ann Clin Biochem 24:119–132

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