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Renal Granuloma and Mesangial Proliferative Glomerulonephritis in Leprosy[1]

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In 1937 Mitsuda and Ogawa ([8]) described renal lesions in leprosy based on an analysis of 150 autopsy cases. After the introduction of percutaneous renal biopsy, a variety of renal lesions have been reported by some authors ([5, 6]). These include secondary amyloidosis, interstitial nephritis, pyelonephritis, and glomerulonephritis. The present report describes the histologic, immunofluorescence, and ultrastructural features of a renal biopsy specimen from a patient with borderline lepromatous leprosy and erythema nodosum leprosum.

CASE REPORT

A 17-year-old Yemeni man was admitted to the University Hospital with painful swelling of the fingers, hands, elbows, knees, and ankles, and fever and night sweats of 1 month's duration. He had experienced a similar attack 1 year previously and admitted a positive family history of leprosy.

Examination showed an ill-looking slim patient with a blood pressure of 110/60 mm Hg, a temperature of 39°C, and a pulse rate of 110/min. A swollen and erythematous face, injected conjunctivae, slight periorbital edema, and thick earlobes were noticed. The cardiovascular and respiratory systems were normal. Splenomegaly and hepatomegaly were present. Non-tender lymph nodes were felt in the cervical, axillary, and inguinal areas. Swelling of the hands reduced his grip strength considerably. All other joints were swollen and tender with limitations of motion. Non-tender macular rashes (hypopigmented in the center and hyperpigmented at the periphery) were present over the back and anterior chest. There was 1+ pitting edema of the lower extremities.

Laboratory investigations showed a hematocrit of 36%, white blood cell count of 7100/mm^3 with a normal differential, platelets 250,000/mm^3; the erythrocyte sedimentation rate was 63 mm in the first hr. Blood urea nitrogen, creatinine, glucose, serum electrolytes, calcium, phosphorous, and liver enzymes were all normal. Serum albumin was slightly reduced at 3.1 g/dl. Rheumatoid factor was positive at 1:20 dilution but antinuclear antibody was negative. C3, C4, and anti-streptolysin-O (ASO) titer were normal. Hepatitis B surface antigen was negative and the VDRL was nonreactive. A urinalysis showed 2+ protein, numerous pus cells, and 10 red blood cells per high-power field, but no red blood cell casts were seen. The 24-hr urinary protein excretion was 1.0 g, and the calculated creatinine clearance was 74 ml/min. The urine revealed growth of *Escherichia coli* but no tubercle bacilli after 6 weeks of culture. A chest X ray, intravenous pyleography, and ECG were normal, while radiographs of his hands, knees, and ankles showed soft-tissue swelling. A tuberculin skin test was negative after 72 hr. A skin biopsy showed the features of borderline lepromatous leprosy.

After treatment of his urinary tract infection, a kidney biopsy was performed and showed mesangial proliferative glomerulonephritis (Fig. 1). There was uniform hypercellularity of the glomeruli with no abnormalities of the glomerular basement membrane. Within the interstitium there were three well-defined granulomas which contained large, pale, epithelioid cells (Fig. 2). There was no caseation necrosis and no giant cells were present. Acid-fast bacilli

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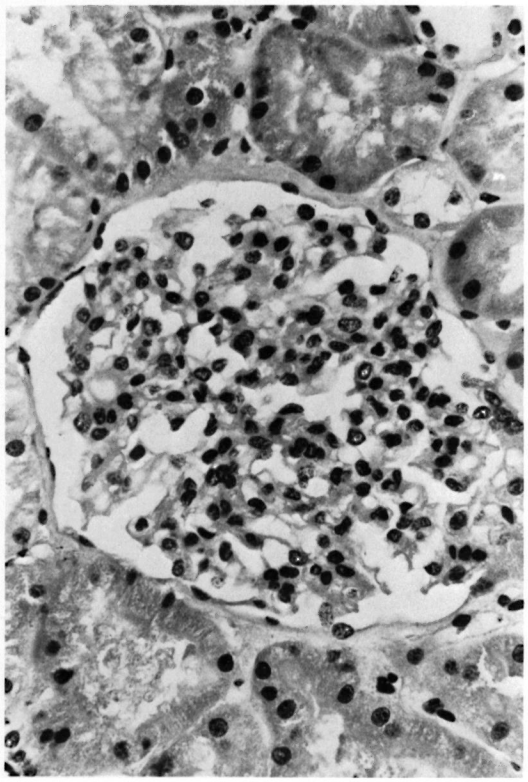

FIG. 1. Light microscopy appearance of a representative glomerulus from the biopsy. There is generalized glomerular hypercellularity, mainly involving mesangial cells (H&E ×750).

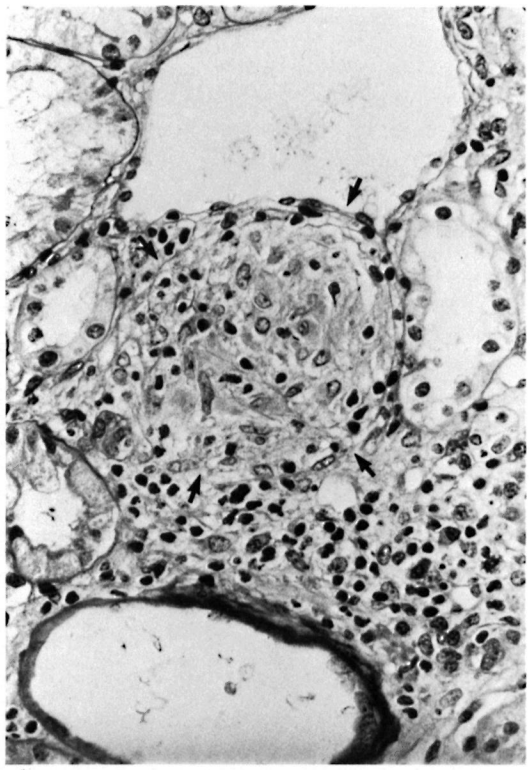

FIG. 2. A discrete granuloma (outlined by arrows), only about twice the cross-sectional area of a convoluted tubule, situated in the interstitium (H&E ×750).

(AFB) were not demonstrable by Wade-Fite or Ziehl-Neelsen staining. The tubules and blood vessels were unremarkable. Immunofluorescence showed granular deposits of C3 along the glomerular basement membrane and in the mesangium. IgM, IgG, and IgA were not demonstrable. Electron microscopy revealed swelling of glomerular epithelial cells and proliferation of mesangial cells, with a mildly increased amount of mesangial matrix. There were numerous dense deposits in the mesangial areas, mainly subjacent to the glomerular basement membrane (Fig. 3).

The patient was given prednisolone 40 mg daily and showed a dramatic response of the joint symptoms, the erythematous skin rash, and the periorbital edema. One week later daily treatment with dapsone 100 mg, rifampin 450 mg, and clofazimine 100 mg was started. He was discharged in good condition and when last seen, 2 months after initiation of therapy, showed clinical improvement. The urinalysis did not show proteinuria, pyuria, or microscopic hematuria. The calculated creatinine clearance was 85 ml/min.

DISCUSSION

Glomerulonephritis is one of several renal lesions that have been described in leprosy. Moreover, all of the morphological types of glomerulonephritis, except focal sclerosis, have been reported in this chronic mycobacterial infection ([2]).

The glomeruli in this patient exhibited features of mesangial proliferative glomerulonephritis and electron-dense deposits in the mesangium. Immunofluorescence staining revealed granular deposits of complement (C3) in the mesangium and in the glomerular basement membrane. Although immunoglobulins were not demonstrable, a positive C3 along with the presence of electron-dense deposits was indicative of immune complex glomerulonephritis. Isolated

C3 positivity may also occur in membranoproliferative glomerulonephritis type 2, but both light- and electron-microscopic studies did not reveal capillary wall involvement by dense deposits. During resorption of immune complexes, immunoglobulins may be resolved early but complement persists longer and stains positively by immunofluorescence.

The most interesting finding in this case was the presence of three epithelioid granulomas in the renal interstitium in which no AFB could be demonstrated. A review of the literature did not reveal any report of AFB-positive granulomas in the kidney. However, one case of a leproma without AFB was described by Sainani and Rao [11] and occasional ones by other authors in autopsy studies [8, 9]. The reason for such an uncommon occurrence is not known, but it has been postulated that the renal tissue is more resistant to *Mycobacterium leprae* than other organs [5]. The absence of caseation necrosis in these well-defined epithelioid granulomas would favor a leprous origin. They might have resulted as a reaction to lodgment of *M. leprae* in the interstitium.

Leprosy patients have depressed immunity and are prone to an increased incidence of urinary tract infections, interstitial nephritis, and urinary tuberculosis [3]. In this case, the urine culture was negative for AFB, and an intravenous pyelographic study did not show the radiologic features of tuberculosis. A reduction in creatinine clearance to less than 75 ml per min has been reported in leprosy subjects, and this is suggestive of defective glomerular function [12]. This patient's creatinine clearance has improved considerably upon initiation of therapy.

Erythema nodosum leprosum (ENL) is an immune complex disease and its reactions are accompanied by abnormalities of renal function [4, 12]. Some authors believe that glomerulonephritis is more common in patients with ENL [4, 10], while others have reservations of such an association [1]. Several workers have noted a striking association between episodes of ENL and the subsequent development of amyloidosis [7].

In conclusion, mesangial proliferative glomerulonephritis in leprosy is of immune complex origin, and epithelioid granulomas may result from deposition of bacilli in the interstitium. When lepra reactions develop they should be controlled as quickly as possible. This may help in reducing the risk of renal involvement in this chronic disease.

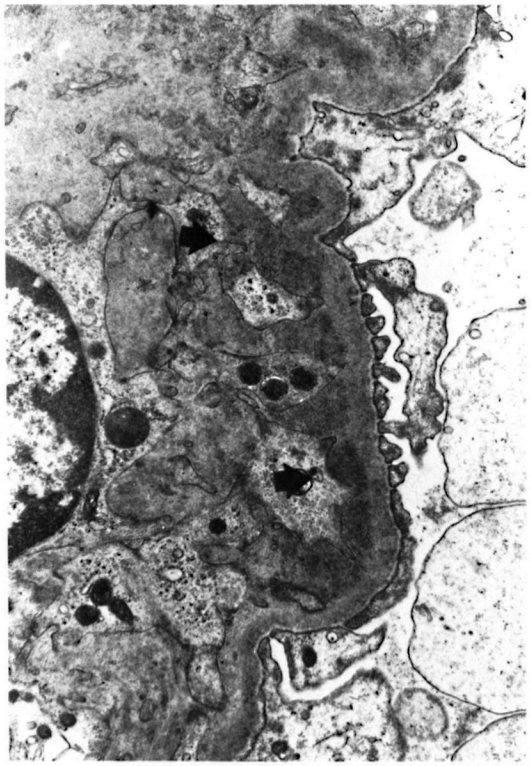

FIG. 3. Electron micrograph showing edge of a mesangial area with dense deposits subjacent to the glomerular basement membrane (arrowheads) (×8000).

SUMMARY

A 17-year-old, Yemeni male patient with borderline lepromatous leprosy and erythema nodosum leprosum (ENL) developed a nephritic range proteinuria. A renal biopsy revealed mesangial proliferative glomerulonephritis and epithelioid granulomas in the interstitium. The presence of granular immunofluorescence for C3 and electron-dense deposits in the glomeruli indicated an immune complex glomerulonephritis. Clinical signs of ENL subsided rapidly under steroid treatment. The unusual combination of proliferative glomerulonephritis and epithelioid granulomas in leprosy is presented and discussed.

RESUMEN

Un paciente masculino Yemenita de 17 años, con lepra lepromatosa y eritema nodoso leproso (ENL),

desarrolló un cuadro nefrítico con proteinuria. Una biopsia renal reveló la existencia de glomerulonefritis mesangial proliferativa y granulomas epitelioides en el intersticio. La presencia de inmunofluorescencia granular por C3 y de depósitos electrodensos en los glomérulos indicaron que la glomerulonefritis estuvo causada por complejos inmunes. La sintomatología clínica del ENL cedió rapidamente durante el tratamiento con esteroides. Se presenta y se discute la rara combinación de glomerulonefritis proliferativa y de granulomas epitelioides en la lepra.

RÉSUMÉ

Un malade yéménite de sexe masculin, agé de 17 ans, et atteint de lèpre lépromateuse et d'érythème noueux lépreux (ENL) a développé une protéine compatible avec une néphrite. Une biopsie rénale a révélé une glomérulonéphrite mésangiale proliférative, ainsi que des granulomes épithélioïdes au niveau de l'interstitium. La présence d'une immunofluorescence granulaire pour C3, ainsi que des dépôts opaques aux électrons dans les glomérules, constitue les signes d'une glomérulonéphrite à des complexes immuns. Les signes cliniques de l'ENL ont rapidement disparu à la suite d'un traitement par les stéroïdes. La combinaison inhabituelle d'une glomérulonéphrite proliférative et de granulomes épithélioïdes dans la lèpre est présentée et discutée.

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