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Glomerulonephritis in Leprosy— A Percutaneous Renal Biopsy Study

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Thirty-five patients with lepromatous or borderline leprosy selected at random were investigated for evidence of renal disease. Renal functional impairment was detected in nearly two-thirds of the patients and histological lesions were present in 46%. Twenty-three per cent of the cases showed a proliferative type of glomerulonephritis, mesangial sclerosis without significant hypercellularity was seen in 11%, amyloidosis was present in 6%. One patient had interstitial nephritis.

Introduction

Renal involvement in leprosy has been recognized by Japanese workers since the beginning of the century. Mitsuda and Ogawa published their observations in English in 1937 and described "nephritis of all kinds" in leprosy in an autopsy analysis of 150 cases. Similar observations were also made by Kean and Childress (1942) from the Isthmus of Panama. Acute oedema of the hands and feet occasionally associated with proteinuria were later reported to complicate all clinical types of leprosy during reactive episodes and progressive reaction (Davison, 1961; Wheate, 1962; Cochrane, 1964). Impaired renal function and abnormal urinary sediment have also been observed in patients with leprosy in varying reactional states (Gokhale and Kurkure, 1958; Thomas *et al.*, 1970; Gutman, Lu and Durtz, 1973).

Amyloidosis of the kidney was the commonest histological abnormality observed by North American workers, occurring in nearly one-half of the patients with lepromatous leprosy (Powell and Swan, 1955; Shuttleworth and Ross, 1956; Williams, Cathcart and Calkins, 1965). Amyloidosis complicated leprosy in as many as 80% of cases in Spain (Granels, 1968). In contrast, renal amyloidosis was seen in only 6% of leprosy patients studied in Mexico (Williams, Cathcart and Calkins, 1965) and a similar low incidence was reported from Japan (Mitsuda and Ogawa, 1937) and India (Junnarkar, 1957; Desikan and Job, 1968; Sachdev, Puri and Bansal, 1969). Though amyloidosis complicated reactional leprosy much

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more frequently, it was seen in non-reactional types as well (Brusco and Masanti, 1963).

Renal failure secondary to amyloidosis was the leading cause of death in U.S. Sanatoria (Powell and Swan, 1955; Shuttleworth and Ross, 1956; Williams, Cathcart and Calkins, 1965) and even more so in Spain (Granels, 1968). In contrast, in only 4 out of 37 cases of leprosy (10.8%) studied at post mortem in South India was death attributable to renal failure (Desikan and Job, 1968). Junnarkar failed to demonstrate any remarkable renal lesion in 20 cases of lepromatous and tuberculoid leprosy at post mortem except for one instance of amyloidosis (Junnarkar, 1957).

There have been only a few renal biopsy studies in patients with leprosy. Durtz and Gutman reported 2 cases of proliferative glomerulonephritis in 8 biopsied cases of lepromatous leprosy with *erythema nodosum leprosum* from Taiwan (Durtz and Gutman, 1972, 1973). Another case with proliferative glomerulonephritis has been reported by Shwe (1972). The wide discrepancy in the nature of renal lesions seen in different countries prompted this enquiry into the nature of renal disease in leprosy in India.

Materials and Methods

Patients admitted to the Schieffelin Leprosy Research Sanatorium with different clinical types of leprosy with or without *erythema nodosum leprosum* and in varying stages of therapy were selected at random. The cases were divided into lepromatous and borderline groups according to the system of Ridley and Jopling, using clinical, histological and immunological criteria (Ridley and Jopling, 1966). The bacterial load was estimated after standard skin smears from 8 sites and was expressed as the bacterial index (BI) according to Ridley's scale (Ridley, 1964). Only patients with *erythema nodosum leprosum* were classified as having reaction. A 24 h urine sample was examined for acid fast bacilli.

Immunological studies included estimation of antistreptolysin O (ASO) titre (Rantz and Randall, 1945), antinuclear factor, rheumatoid factor and examination of lupus erythematosus (LE) phenomenon by the method of Magath and Winkle (1952).

RENAL HISTOLOGY

Percutaneous renal biopsy was performed with a Franklin modified Vim-Silvermann needle following the method of Kark and Muechrcke (1954). Sections from all specimens were stained with hematoxylin eosin, periodic acid Schiff (PAS), congo red and Ziehl-Neelsen stains and examined with the light microscope. Sections were independently interpreted by two of us (KVJ and AD). The histological lesions were graded as follows:

(1) *Proliferative.* (PGN) Diffuse proliferative: showing diffuse hypercellularity of endothelial and mesangial cells with or without polymorphonuclear exudation in the glomerular tuft.

Mesangial proliferative: Hypercellularity of varying degree confined to the axial region.

(II) *Chronic sclerosing.* Showing glomerular hyalinization, focal tuft adhesions and interstitial scarring.

(III) *Mesangial sclerosis.* Glomeruli showing increase in PAS positive material in the axial region without significant hypercellularity.

(IV) *Amyloidosis.* Was confirmed by the presence of congo red positive material in the renal tissue.

(V) *Interstitial nephritis.* With predominant involvement of interstitium and tubules consisting of diffuse interstitial mononuclear cell infiltration, interstitial fibrosis and tubular atrophy.

RENAL FUNCTIONAL ASSESSMENT

Investigations included routine urine analysis for albumin and sediments, 24 h urine protein excretion (Thomas *et al.*, 1970), endogenous creatinine clearance (Bonsnes and Taussky, 1945) and blood urea estimation (Varley, 1967). Additional biochemical tests measured serum sodium, phosphorus, potassium, calcium, sugar, alkaline phosphatase and congo red retention (Varley, 1967). Serum protein was determined using cellulose acetate strips and Shandon universal electrophoretic apparatus (Kingsley, 1942; Smith, 1960).

Results

Adequate renal biopsies were obtained in the 35 patients analysed for this report. Thirty-four were males. The mean age of the group was 31.7 years and ranged from 18 to 57 years. Twenty-nine patients had lepromatous leprosy, 2 borderline lepromatous, 1 borderline borderline and 3 borderline tuberculoid. Mean duration of disease at the time of study based on the history was 9.8 years and ranged from 3 months to 25 years.

Those with lepromatous leprosy had a more prolonged illness (mean 10.3 years) than those with borderline leprosy (7.1 years). Twenty-four patients had past history of *erythema nodosum leprosum* of which 4 had ENL at the time of study. In the remaining 20 the last reaction had occurred within one week to 13 months prior to the study (mean 5 months). Five patients had received no form of anti-leprosy therapy at the time of study. Twenty-eight patients had been on therapy with single or multiple drugs for varying periods, the commonest drug employed being dapsone. The duration of treatment varied from a few months to over 10 years. The BI in the group ranged from 0 to 4.25 with a mean of 2.53. Acid fast bacilli were not present in the urine of any of the patients.

No definite statistical correlation could be established between any of the factors mentioned above and the presence of abnormal renal histology.

RENAL HISTOLOGY

Table 1 summarizes the histological findings in the 35 patients studied. Abnormal histology was seen in 16 cases (45%). Hypercellularity of the endothelial and mesangial cells was the most frequent histological abnormality.

In the most severe form seen in one case there was marked hypercellularity of the endothelial and mesangial cells and considerable polymorphonuclear exudation (15–25 per glomerulus) obliterating glomerular capillary lumena (Fig. 1). Diffuse endothelial hypercellularity without significant exudation was present in one case.

In the mesangial proliferative group, the hypercellularity was mainly confined to the axial region of the lobules (Fig. 2). The degree of hypercellularity varied.

In 1 patient, the glomeruli showed varying degrees of hyalinization, focal tuft adhesion, tubular atrophy, interstitial mononuclear cell infiltration and moderate arteriolar hyalinization. A few surviving glomeruli showed hypercellularity.

TABLE 1

Summary of renal histology in 35 cases

	Histology	Number of patients			Percentage incidence
		Lepromatous	Borderline	Total	
(I)	Proliferative	7	1	8	22.8
	Diffuse	2	—	2	5.7
	Mesangial	5	1	6	17.1
(II)	Chronic sclerosing	1	—	1	2.9
(III)	Mesangial sclerosis	3	1	4	11.4
(IV)	Amyloidosis	2	—	2	5.7
(V)	Interstitial nephritis	1		1	2.9
	Normal	15	4	19	54.3
	Total	29	6	35	

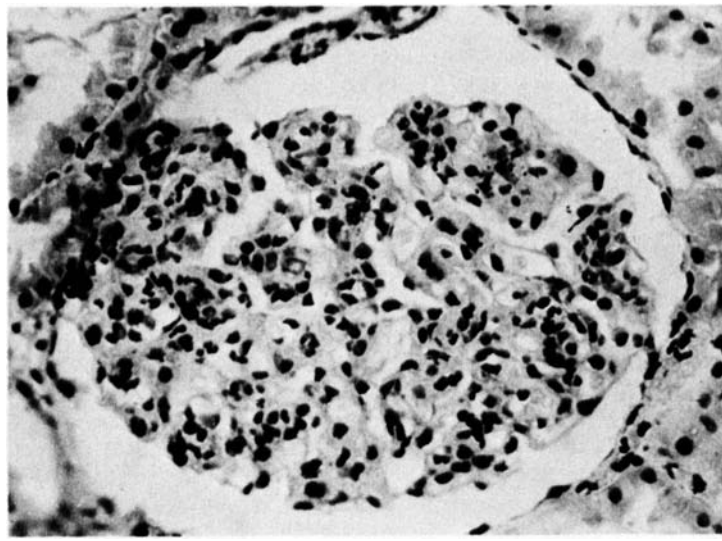

Fig. 1. Shows marked hypercellularity of endothelial and mesangial cells and polymorphonuclear exudation in the glomerulus—case from Group I (HE x 400).

Increase in PAS positive material in the axial region with no increase in cells was the only abnormality in 4 patients grouped under mesangial sclerosis (Fig. 3).

Amyloid deposition in the kidney was present in 2 cases, both of whom presented the features of nephrotic syndrome. One of these had extensive involvement of the glomeruli and vessels with associated renal failure. In the other the involvement was less extensive.

Interstitial fibrosis, mononuclear cell infiltration and tubular atrophy were the histological abnormalities in 1 case. The glomeruli appeared relatively unaffected. Two other patients showed occasional small collections of mononuclear cells along with proliferative glomerular disease. Granulomata and acid fast bacilli were not seen in any of the sections examined. Nineteen patients (54.3%) showed normal renal histology.

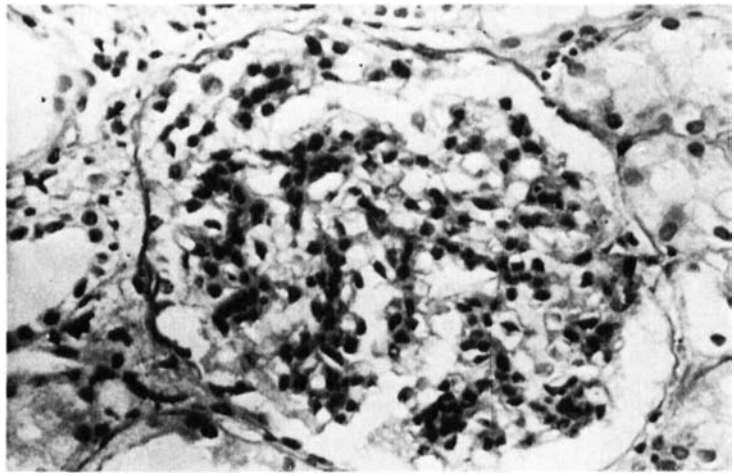

Fig. 2. Shows marked, mesangial hypercellularity grouped under "mesangial proliferative"–case from Group I (PAS x 400).

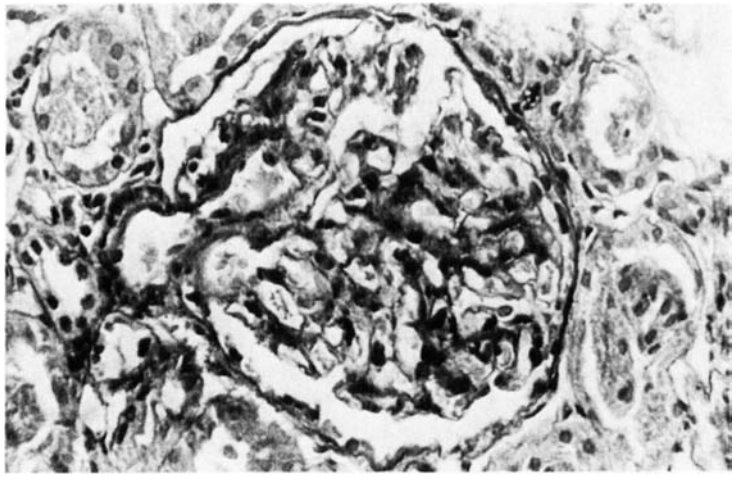

Fig. 3. Increase in PAS +ve material in the mesangium with no hypercellularity, grouped under mesangial sclerosis–case from Group III (PAS x 400).

CLINICAL FINDINGS AND INVESTIGATIONS

Table 2 summarizes the clinical features and investigations in the cases with abnormal renal histology.

The 2 patients with amyloidosis presented with nephrotic syndrome. Another patient who presented with nephrotic syndrome had no significant lesion on light microscopy. Marked mesangial proliferation was the histological appearance of the 1 patient with an acute nephritic picture with oedema, oliguria, haematuria and hypertension of sudden onset (Cameron, 1970). Massive proteinuria (>4 g/24 h) was seen in 3 patients. Eight other patients had minimal proteinuria

TABLE 2

Summary of findings in 16 patients with abnormal renal histology

No.	Histology	Leprosy			Symptom	B.P.	Proteinuria	Sediments		Creatinine clearance	ASO Titre
		Clinical	Reactional status	B.I.				RBC/HPF	WBC/HPF		
1.	Diffuse proliferative	LL	PR	1	Oedema	Normal	320 mg	8–10	–	83	166
2.	Diffuse proliferative	LL	PR	3.75	Nil	Normal			–	71	250
3.	Mesangial proliferative	LL	Nil		Acute nephritic	150/120	190 mg	35–40	–	71	–
4.	Mesangial proliferative	LL	PR	3	Oedema	Normal			–	–	125
5.	Mesangial proliferative	LL	PR	3.25		Normal			–	90	333
6.	Mesangial proliferative	LL	PR	2.62		Normal			–	80	100
7.	Mesangial proliferative	BT	Nil	0		Normal			–	58	333
8.	Mesangial proliferative	LL	PR	3.12	Oedema	Normal	380 mg	8–10	–	52	625
9.	Chronic sclerosing	LL	PR	1.12		Normal			6–10	74	333
10.	Mesangial sclerosis	LL	PR	2.62		Normal	420 mg		–	80	–
11.	Mesangial sclerosis	LL	PR	3.0	Oedema	Normal			–	62	333
12.	Mesangial sclerosis	LL	Nil	4.25		Normal			–	73	125
13.	Mesangial sclerosis	BT	Nil	0		Normal			–	71	166
14.	Amyloidosis	LL	PR	3.25	Nephrotic	Normal	6.6 g		–	104	50
15.	Amyloidosis	LL	Nil		Nephrotic	Normal	10.4 g		–	18	250
16.	Interstitial nephritis	LL	PR	3.62	Oedema	Normal	360 mg		8–12	38	125

LL – Lepromatous Leprosy. BI – Bacterial Index. BT – Borderline tuberculoid. PR – Past reactions.

(<0.5 g in 24 h), of which 5 patients had abnormal renal histology. Five patients had microscopic hematuria of which 3 had a proliferative glomerular lesion. Blood urea was within the normal range in all except 2 patients, 1 with nephrotic syndrome and amyloidosis and the one with acute nephritic disease (130 and 54 mg% respectively). The endogenous creatinine clearance was less than 75 ml/min in 21 out of 33 patients (63.6%) of which 10 had abnormal histology.

The tissue retention of congo red was 64 and 44% in 2 patients who had renal amyloidosis. In all the other patients the retention was less than 20%. The L.E. phenomenon could not be demonstrated in any of the 31 patients, each tested on 3 occasions. Antinuclear and rheumatoid factors were also negative in all 28 patients examined. ASO titre was raised above 333 Todd units in 35.5% of patients studied (Koshi, *et al.*, 1967). To examine the influence of a possible coincidental streptococcal infection in PGN of leprosy, those with normal ASO, raised ASO and the whole group were compared. No difference was found in the frequency of PGN in the various groups.

Discussion

Renal amyloidosis is the commonest renal complication and the major cause of death in lepromatous leprosy in U.S. and Spain (Powell and Swan, 1955; Shuttleworth and Ross, 1956; Granels, 1968; Brusco and Masanti, 1963). In India, renal failure is a rare cause of death in leprosy (Desikan and Job, 1968), possibly due to the low incidence of amyloidosis. However, both ante mortem and post mortem studies in India have revealed non-amyloid renal disease in more than 50% of patients (Desikan and Job, 1968; Mittal *et al.*, 1972). Renal functional impairment during reactive episodes followed by improvement in the quiescent phase has also been observed (Gokhale and Kurkure, 1958; Thomas *et al.*, 1970). These observations and also the present study suggest that renal disease in leprosy, though common in India, is resolving and self limiting and does not contribute significantly to the mortality.

The present study has revealed a high incidence of proliferative glomerulonephritis in leprosy. The presence of cases in this series showing diffuse proliferation and exudation, varying degrees of mesangial proliferation and pure mesangial sclerosis without proliferation could be interpreted as showing stages of resolution of an originally diffuse proliferative glomerulonephritis. If this is true the time taken for this process of resolution is not clear from the available data. It would seem, however, that the exudative reaction and diffuse hypercellularity resolve faster than the later stages of mesangial proliferation and sclerosis as evidenced by the larger number of cases seen with histological changes suggesting resolution in a cross-section study of this type. The one case showing changes of chronic glomerular disease may suggest that occasionally proliferative glomerulonephritis of leprosy does not resolve completely but progresses to irreversible damage.

The pathogenesis of the proliferative lesion is not clear, but the alterations in serum complement suggestive of complement consumption reported by Durtz and Gutman (1972, 1973) as well as the demonstration of immunoglobulins and BIC in the glomeruli in 3 cases of lepromatous leprosy by Shwe (1972) suggest that an immune complex mechanism is involved.

In this study, no definite relationship could be observed between the occurence

of PGN and the duration of illness, bacterial load, presence of ENL, or the ASO titre. None of these patients had a positive L.E. cell test.

The other renal lesions in leprosy such as interstitial nephritis and pyelonephritis are mostly seen at autopsy (Desikan and Job, 1968). Interstitial nephritis appears to be more often associated with advanced stages of the disease of very long standing. The one patient in the present series who showed diffuse interstitial disease had lepromatous leprosy for over 25 years, the longest duration of illness in the whole group, but only one episode of reaction. The prolonged disease state itself unrelated to reactive episodes has been held responsible for the lesion (Brusco and Masanti, 1963). Possibly, prolonged chemotherapy may also be contributory to the development of interstitial nephritis.

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