The Immunological Basis of Glomerular Disease in Leprosy—A Brief Review[1]

Amyloidosis and glomerulonephritis are the important glomerular lesions occurring in leprosy. Amyloidosis has only an indirect immune basis, but glomerulonephritis is a direct result of immunological mechanisms.

AMYLOIDOSIS

The prevalence of renal amyloidosis in biopsy and autopsy studies on unselected hospitalized patients with leprosy is shown in Table 1. A high prevalence of more than 30% has been reported from the U.S.A. and Argentina, but it is much less common in Panama, India, Japan, and Turkey. This geographical difference in prevalence is not merely due to observer variation, and may be related to diet or racial factors[2]. Even though the mean reported prevalence of amyloidosis in leprosy in tropical areas is only 5%, leprosy is still the most frequent cause of amyloidosis in areas endemic for leprosy[3,4].

Unlike the immunoglobulin derived amyloid of immunocyte dyscrasias[5], the amyloid deposits in leprosy are composed of a non-immunoglobulin protein designated AA and derived from a circulating serum precursor SAA[4]. There is, therefore, no direct link between immunoglobulins and amyloid in leprosy. However, an indirect immunological basis does exist in that it is frequently associated with recurrent erythema nodosum leprosum (ENL), which is an immune complex disease[6]. McAdam, *et al.*[4] have shown that SAA levels rise sharply during ENL reactions, and they suggest that this is secondary to the neutrophil leukocytosis which is also a feature of ENL. The SAA levels are also raised in leprosy patients with amyloidosis due to chronic trophic ulcers[4].

GLOMERULONEPHRITIS

Prevalence. The prevalence of glomerulonephritis in unselected renal biopsy and autopsy material from hospitalized patients with leprosy is given in Table 1. This table does not include the earlier postmortem studies summarized by Shwe[7] which contain references to "nephritis" without further specification of the type. The mean prevalence in biopsy studies is 37%. This is much higher than the 7% reported in autopsy studies, and the reasons for this difference undoubtedly include: a) the difficulty in identifying minor degrees of glomerular hypercellularity in autopsy material; b) an unconscious observer bias when examining biopsies, resulting in an over diagnosis of glomerular abnormalities, and accounting for the poor correlation with abnormal laboratory findings, and c) the fact that most biopsy studies were published after 1971 and reflect a greater awareness of this entity after the first renal biopsy study was presented[8]. The patients in these studies were not selected to match the prevalence of the different immunopathologic types of leprosy in the population from which they were taken. Most of the patients biopsied had lepromatous leprosy but non-lepromatous disease is much more common in these areas. Statistical analysis of such data to compare the prevalence of glomerulone-

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TABLE 1. *Prevalence of renal amyloidosis and glomerulonephritis in leprosy.*

Authors and year	Country	No. studied	Amyloidosis no. (%)	Glomerulonephritis no. (%)
Autopsies				
Kean and Childress, 1942[32]	Panama	103	4 (4%)	12 (12%)
Powell and Swan, 1955[33]	U.S.A.	50	19 (38%)	not given
Shuttleworth and Ross, 1956[34]	U.S.A.	18	10 (55%)	not given
Junnarkar, 1957[35]	India (Poona)	20	1 (5%)	not given
Desikan and Job, 1968[36,a]	India (Vellore)	37	3 (8%)	2 (5%)
Bernard and Vazquez, 1973[37]	Argentina	60	19 (32%)	2 (3%)
Ozaki and Furuta, 1975[38]	Japan	160	25 (15%)	not given
Renal biopsies on patients unselected for renal disease				
Shwe, 1972[7]	U.K.[b]	7	1 (14%)	2 (28%)
Mittal, *et al.* 1972[39]	India (Delhi)	30	0	8 (27%)[c]
Sainani and Rao, 1974[40]	India (Nagpur)	60	1 (2%)	8 (13%)
Johny, *et al.* 1975[41,d]	India (Vellore)	35	2 (6%)	13 (37%)
Gupta, *et al.* 1977[42]	India (Jabalpur)	50	0	3 (6%)
Cologlu, 1979[18]	Turkey	20	1 (5%)	10 (50%)
Peter, *et al.* 1981[43]	India (Calicut)	21	0	15 (71%)
Gupta, *et al.* 1981[44]	India (Allahabad)	21	3 (14%)	13 (62%)

[a] Includes the cases reported by Krishnamurthy and Job[45].
[b] Patients mainly of Asian origin.
[c] Glomerular hypercellularity described.
[d] A preliminary report on this study was presented in 1971[8].

phritis in different types of leprosy[9] is therefore not worthwhile. Glomerulonephritis has been reported in all types of leprosy except for the polar tuberculoid, pure neuritic, and indeterminate types.

Light microscopy. Using standard terminology[10], Table 2 lists the different histological types of glomerulonephritis reported in the studies given in Table 1 and in other studies of leprosy patients biopsied for clinical renal disease[9, 11, 12, 13, 14, 15, 16, 17]. It is seen that all morphological types of glomerulonephritis, except focal sclerosis, have been reported in leprosy. Most of these types of glomerulonephritis are known or suspected to have an immune complex etiology[10]. This variety of morphological lesions suggests a heterogenous pathogenesis, but not necessarily different etiologies, since it is well known that a single disease like systemic lupus erythematosus can involve the glomeruli to produce either diffuse or focal, membranous or proliferative, glomerulonephritis. This variety presumably reflects differences in the amount and type of immune complexes present[18].

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TABLE 2. *Morphological types of glomerulonephritis in leprosy.*

Diffuse endocapillary proliferative[7,9,13,14,15,32,37,39,40,41,43,44]
Diffuse mesangial proliferative[14,15,16,18,41,43,44]
Diffuse crescentic[11,17,18]
Diffuse membranous[43]
Diffuse mesangiocapillary[13]
Focal proliferative[12,14]
Diffuse sclerosing[7,32,41,42,43]
Minimal change disease[41,43,a]

[a] Normal histology on light microscopy, but unsampled focal proliferative lesions may have been present.

Immunohistochemistry. Immunohistochemical studies of kidney tissue in leprosy have shown granular deposits of IgG and C3, and less frequently IgM, IgA and fibrin, located in the glomerular mesangium and/or, along the capillary walls[7, 9, 11, 16, 19]. This pattern of staining is typical of an immune complex glomerulonephritis[18].

Ultrastructure. Electron microscopic studies also confirm the immune complex origin of this disease. Glomerular dense deposits have been reported in the mesangial-subendothelial region[12, 13, 14, 19] or subepithelially[9, 14, 20], corresponding to the experimental localization of small, relatively soluble, and large, poorly soluble complexes, respectively[18]. This again indicates that different types of immune complexes are involved in the production of this condition. Other ultrastructural findings, such as neutrophil leukocyte infiltration, foot process fusion, mesangial proliferation, expansion and interposition, and basement membrane duplication and thickening[9, 12, 14, 19], are secondary effects of immune complex deposition.

Etiological considerations. The morphological evidence summarized above shows that the glomerulonephritis occurring in leprosy is of the immune complex type. The source of these immune complexes is, as yet, unknown since the antigens responsible have not been demonstrated in the glomerular deposits. However, indirect evidence is available indicating certain possible etiological relationships.

ENL is an immune complex disease involving mycobacterial antigens released by breakdown of *Mycobacterium leprae*[6]. ENL reactions are also accompanied by abnormalities of renal function[15, 21, 22]. It would thus seem likely that glomerulonephritis in some patients could be a manifestation of ENL caused by deposition of mycobacterial antigen-antibody complexes. Such circulating mycobacterial antigen-antibody complexes have been demonstrated in many patients with leprosy[23].

ENL is, however, not the sole cause of glomerulonephritis in leprosy, since glomerulonephritis often occurs in patients without ENL[9]. In addition to ENL, patients in the lepromatous half of the disease spectrum have depressed cell-mediated immunity (anergy) with exaggerated and uncontrolled humoral immune responses[24, 25], resulting from loss of T cell control. Such a situation is known to promote the development of immune complex glomerulonephritis[26, 27]. Given this predisposing situation, a variety of antigens may trigger immune complex formation. Anergy would

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also delay elimination of bacteria such as streptococci and staphylococci and viral agents, such as hepatitis B virus, which are commonly present and also well known causes of glomerulonephritis[14,28,29]. The list of potential antigens extends even to therapeutic agents since dapsone-antidapsone antibodies in circulating immune complexes have been reported[30].

Also significant are the many autoantibodies found in leprosy[23, 24]. Of these the best documented are the IgG-IgM cryoglobulins which are frequently present in the circulation[23] and which can cause glomerulonephritis in these patients[16]. While the above factors are more commonly recognized in patients with disease in the lepromatous half of the immunopathologic spectrum, circulating immune complexes and a variety of autoantibodies are also frequent in patients with tuberculoid leprosy[31].

Immune complex glomerulonephritis in leprosy may therefore have a multifactorial origin. The antigens involved could either be mycobacterial and specific to leprosy, or non-mycobacterial, exogenous antigens and autoantigens which also cause glomerulonephritis in patients without leprosy. Depressed T cell function with exaggerated B cell activity present in some patients would also favor development of immune complex glomerulonephritis. This multifactorial origin is reflected in the variety of morphological expressions of this condition.

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