

The Immunological Basis of Glomerular Disease in Leprosy—A Brief Review¹

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 factors². 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 dyscrasias⁵, the amyloid deposits in leprosy are composed of a non-immunoglobulin protein designated AA and derived from a circulating serum precursor SAA⁴. 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 no-

dosum leprosum (ENL), which is an immune complex disease⁶. 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 ulcers⁴.

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 Shwe⁷ 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 presented⁸. 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-

¹ Presented at the seminar on The Immunopathology of Leprosy, organized by the Indian Association of Pathologists and Microbiologists on 1 December 1981, at Trivandrum, Kerala, India.

² Williams, R. C., Cathcart, E. C., Calkins, E., Fite, G. L., Rubio, J. B. and Cohen, A. S. Secondary amyloidosis in lepromatous leprosy. Possible relationships of diet and environment. *Ann. Intern. Med.* **62** (1965) 1000-1007.

³ Date, A. and Job, C. K. The prevalence of amyloidosis in autopsy material. *J. Indian Med. Assoc.* **62** (1974) 287-288.

⁴ McAdam, K. P. W. J., Anders, R. F., Smith, S. R., Russel, D. A. and Price, M. A. Association of amyloidosis with erythema nodosum leprosum reactions and recurrent neutrophil leukocytosis in leprosy. *Lancet* **2** (1975) 572-576.

⁵ Glenner, G. C. Amyloid deposits and amyloidosis (the β -fibrilloses). *N. Engl. J. Med.* **302** (1980) 1283-1292 and 1333-1343.

⁶ Waters, M. F. R., Turk, J. L. and Wemambu, S. N. C. Mechanisms of reactions in leprosy. *Int. J. Lepr.* **39** (1971) 417-428.

⁷ Shwe, T. Immune complexes in glomeruli of patients with leprosy. *Lepr. Rev.* **42** (1972) 282-289.

⁸ Johny, K. V. and Karat, A. B. A. Renal biopsy studies in leprosy. *J. Assoc. Physicians India* **19** (1971) 117-118.

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, <i>et al.</i> 1972 ³⁹	India (Delhi)	30	0	8 (27%) ^c
Sainani and Rao, 1974 ⁴⁰	India (Nagpur)	60	1 (2%)	8 (13%)
Johny, <i>et al.</i> 1975 ^{41,d}	India (Vellore)	35	2 (6%)	13 (37%)
Gupta, <i>et al.</i> 1977 ⁴²	India (Jabalpur)	50	0	3 (6%)
Cologlu, 1979 ¹⁸	Turkey	20	1 (5%)	10 (50%)
Peter, <i>et al.</i> 1981 ⁴³	India (Calicut)	21	0	15 (71%)
Gupta, <i>et al.</i> 1981 ⁴⁴	India (Allahabad)	21	3 (14%)	13 (62%)

^a Includes the cases reported by Krishnamurthy and Job⁴⁵.

^b Patients mainly of Asian origin.

^c Glomerular hypercellularity described.

^d A preliminary report on this study was presented in 1971⁸.

phritis in different types of leprosy⁹ 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 terminology¹⁰, 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}.

⁹ Ng, W. L., Scollard, D. M. and Hua, A. Glomerulonephritis in leprosy. *Am. J. Clin. Pathol.* **76** (1981) 321-329.

¹⁰ Turner, D. R. *Glomerulonephritis*. Recent Advances in Histopathology, Number 10. Anthony, P. P. and Woolf, N., eds. London: Churchill Livingstone, 1978, pp. 235-257.

¹¹ Bedi, T. R., Kaur, S., Singhal, P. C., Kumar, B. and Banerjee, C. K. Fatal proliferative glomerulonephritis in lepromatous leprosy. *Lepr. India* **49** (1977) 500-503.

¹² Bullock, W. E., Callera, M. L. and Panner, B. J. Immunohistologic alteration of skin and ultrastructural changes of glomerular basement membranes in leprosy. *Am. J. Trop. Med. Hyg.* **23** (1974) 81-86.

¹³ Date, A., Neela, P. and Shastry, J. C. M. Membranoproliferative glomerulonephritis in a tropical environment. *Ann. Trop. Med. Parasitol.* **77** (1983) (in press).

¹⁴ Date, A., Thomas, A., Mathai, R. and Johny, K. V. Glomerular pathology in leprosy. An electron mi-

croscopic study. *Am. J. Trop. Med. Hyg.* **26** (1977) 266-272.

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 etiology¹⁰. This variety of morphological lesions suggests a heterogeneous 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 present¹⁸.

¹⁵ Drutz, D. J. and Gutman, R. A. Renal manifestations of leprosy. Glomerulonephritis—a complication of erythema nodosum leprosum. *Am. J. Trop. Med. Hyg.* **22** (1973) 496-502.

¹⁶ Iveson, J. M. I., McDougall, A. C., Leatham, A. J. and Harris, H. J. Lepromatous leprosy presenting with polyarthritis, myositis and immune-complex glomerulonephritis. *Br. Med. J.* **3** (1975) 619-621.

¹⁷ Singhal, P. C., Shugh, K. S., Kaur, S. and Malik, A. K. Acute renal failure in leprosy. *Int. J. Lepr.* **45** (1977) 171-174.

¹⁸ Germuth, F. G., Jr. and Rodriguez, E. *Immunopathology of the Renal Glomerulus. Immune Complex Deposit and Antibasement Membrane Disease*. Boston: Little, Brown and Company, 1973, pp. 209-210.

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 glomerulonephritis¹⁸.

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, respectively¹⁸. 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 leprosy²³.

ENL is, however, not the sole cause of glomerulonephritis in leprosy, since glomerulonephritis often occurs in patients without ENL⁹. 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

²¹ Bajaj, A. K., Gupta, S. C., Sinha, S. N., Govil, D. C., Gaur, U. C. and Kumar, R. Renal functional status in lepromatous leprosy. *Int. J. Lepr.* **49** (1981) 37-41.

²² Thomas, G., Karat, A. B. A., Rao, P. S. S. and Prathapkumar, C. Changes in renal function during reactive phases of lepromatous leprosy. *Int. J. Lepr.* **38** (1970) 170-176.

²³ Reed, W. P. and Williams, R. C. Immune complexes in infectious diseases. *Adv. Intern. Med.* **22** (1977) 49-72.

²⁴ Bryceson, A. D. M. Immunology of leprosy. *Lepr. Rev.* **47** (1976) 235-244.

²⁵ Bullock, W. E. Anergy and infection. *Adv. Intern. Med.* **21** (1976) 149-173.

²⁶ Bhat, J. G., Gombos, E. A. and Baldwin, D. S. Depressed cellular immune response to streptococcal antigens in poststreptococcal glomerulonephritis. *Clin. Immunol. Immunopathol.* **7** (1977) 230-239.

²⁷ Hoffsten, P. E., Villalbos, R., Hill, C. and Klahr, S. T cell deficiency in immune complex glomerulonephritis. *Kidney Int.* **11** (1977) 318-326.

¹⁹ Cologlu, A. S. Immune complex glomerulonephritis in leprosy. *Lepr. Rev.* **50** (1979) 213-222.

²⁰ Date, A. and Johny, K. V. Glomerular subepithelial deposits in lepromatous leprosy. *Am. J. Trop. Med. Hyg.* **24** (1975) 853-856.

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 reported³⁰.

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 circulation²³ and which can cause glomerulonephritis in these patients¹⁶. 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 leprosy³¹.

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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²⁸ Eknayan, G. and Dillman, R. O. Renal complications of infectious diseases. *Med. Clin. North Am.* **62** (1978) 979–1003.

²⁹ Thyagarajan, S. P., Subramaniam, S., Solomon, S., Panchanadam, M. and Madanagopalan, N. Incidence of hepatitis B surface antigen and antibody in patients with liver diseases, blood donors and leprosy patients—a preliminary report. *Indian J. Med. Res.* **67** (1978) 528–534.

³⁰ Das, P. K., Klatser, P. R., Pondman, K. W., Huijshoven, H., Landheer, J. E., Leiker, D. L. and Rees, R. J. Dapsone and anti-dapsone antibody in circulating immune complexes in leprosy patients. *Lancet* **1** (1980) 1309–1311.

³¹ Nuti, M., D'Amelio, R., Seminara, R., Milano, C. F., Palmisano, L. and Aiuti, F. Circulating immune complexes detected by C1q solid phase assay in leprosy. *Int. J. Lepr.* **49** (1981) 27–30.

³² Kean, B. H. and Childress, M. E. A summary of 103 autopsies on leprosy patients on the Isthmus of Panama. *Int. J. Lepr.* **10** (1942) 51–59.

³³ Powell, C. S. and Swan, L. L. Leprosy: Pathological changes observed in fifty consecutive necropsies. *Am. J. Pathol.* **31** (1955) 1131–1147.

³⁴ Shuttleworth, J. S. and Ross, Sister Hilary. Secondary amyloidosis in leprosy. *Ann. Intern. Med.* **45** (1956) 23–28.

³⁵ Junnarkar, R. V. Late lesions in leprosy. *Lepr. India* **29** (1957) 148–154.

³⁶ Desikan, V. K. and Job, C. K. A review of post-mortem findings in 37 cases of leprosy. *Int. J. Lepr.* **36** (1968) 32–44.

³⁷ Bernard, J. C. and Vazquez, C. A. J. Visceral lesions in lepromatous leprosy. Study of sixty necropsies. *Int. J. Lepr.* **41** (1973) 94–101.

³⁸ Ozaki, M. and Furuta, M. Amyloidosis in leprosy. *Int. J. Lepr.* **43** (1975) 116–124.

³⁹ Mittal, M. M., Agarwal, S. C., Maheswari, H. B. and Kumar, S. Renal lesions in leprosy. *Arch. Pathol.* **93** (1972) 8–12.

⁴⁰ Sainani, G. S. and Rao, K. V. N. Renal changes in leprosy. *J. Assoc. Physicians India* **22** (1974) 659–664.

⁴¹ Johny, K. V., Karat, A. B. A., Rao, P. S. S. and Date, A. Glomerulonephritis in leprosy—a percutaneous renal biopsy study. *Lepr. Rev.* **46** (1975) 29–37.

⁴² Gupta, J. C., Diwakar, R., Singh, S., Gupta, D. K. and Panda, P. K. A histopathological study of renal biopsies in fifty cases of leprosy. *Int. J. Lepr.* **45** (1977) 167–170.

⁴³ Peter, K. S., Vijayakumar, T., Vasudevan, D. M., Leena Devi, K. R., Mathew, M. T. and Gopinath, T. Renal involvement in leprosy. *Lepr. India* **53** (1981) 163–178.

⁴⁴ Gupta, S. C., Bajaj, A. K., Govil, D. C., Sinha, S. N. and Kumar, R. A study of percutaneous renal biopsy in lepromatous leprosy. *Lepr. India* **53** (1981) 179–184.

⁴⁵ Krishnamurthy, S. and Job, C. K. Secondary amyloidosis in leprosy. *Int. J. Lepr.* **34** (1966) 155–158.