

REVIEW

LEPROSY NEPHROPATHY: A REVIEW OF CLINICAL AND HISTOPATHOLOGICAL FEATURES

Geraldo Bezerra da SILVA JUNIOR(1), Elizabeth De Francesco DAHER(2), Roberto da Justa PIRES NETO(3), Eanes Delgado Barros PEREIRA(2), Gdayllon Cavalcante MENESES(4), Sônia Maria Holanda Almeida ARAÚJO(1) & Elvino José Guardão BARROS(5)

SUMMARY

Leprosy is a chronic disease caused by *Mycobacterium leprae*, highly incapacitating, and with systemic involvement in some cases. Renal involvement has been reported in all forms of the disease, and it is more frequent in multibacillary forms. The clinical presentation is variable and is determined by the host immunologic system reaction to the bacilli. During the course of the disease there are the so called reactional states, in which the immune system reacts against the bacilli, exacerbating the clinical manifestations. Different renal lesions have been described in leprosy, including acute and chronic glomerulonephritis, interstitial nephritis, secondary amyloidosis and pyelonephritis. The exact mechanism that leads to glomerulonephritis in leprosy is not completely understood. Leprosy treatment includes rifampicin, dapson and clofazimine. Prednisone and non-steroidal anti-inflammatory drugs may be used to control acute immunological episodes.

KEYWORDS: Leprosy; Hansen disease; Kidney dysfunction; Chronic kidney disease; Glomerulonephritis.

INTRODUCTION

Leprosy is a chronic disease caused by *Mycobacterium leprae*, an acid-fast bacilli, intracellular parasite, with predilection to Schwann cell and skin. The disease is highly incapacitating, and systemic involvement is reported in some cases⁴⁵. Renal involvement has been reported in all forms of the disease, and it is more frequent in multibacillary forms⁵¹. The present paper presents a review of the clinical and histopathological aspects of leprosy nephropathy.

EPIDEMIOLOGY: The number of leprosy patients is estimated to be between 10 and 15 million, distributed across more than 100 countries. In 2007, a total of 254,525 new cases were reported all over the world⁴⁵. Brazil is considered as having a high endemicity index and is the country with the second highest number of cases, with 37,610 new cases registered in 2009³⁸. Leprosy prevalence in Brazil was reduced by 85%, going from 17 to 3.8 cases/10,000 population in the period between 1985 and 2001³⁵.

LEPROSY PATHOPHYSIOLOGY: Infected persons with *M. leprae* are thought not to develop clinical disease. *M. leprae* is slow growing and the incubation period is long at 2-12 years. The *M. leprae* has a high infective power, but low pathogenic power³. Person-to-person spread via nasal droplets is believed to be the main route of leprosy transmission. Most people with leprosy are non-infectious. Patients with lepromatous leprosy excrete *M. leprae* from their nasal mucosa and skin and are infectious before starting treatment with multidrug

therapy. Contacts of these patients are, therefore, at increased risk of developing the disease. There may be a genetic predisposition to disease manifestation. Infection with *M. leprae* leads to chronic granulomatous inflammation in skin and peripheral nerves⁴⁶. Single-nucleotide polymorphism (SNP) association studies showed a low lymphotoxin- α (LTA)-producing allele as a major genetic risk factor for early onset leprosy. Other SNPs to be associated with disease and/or the development of reactions in several genes, such as vitamin D receptor (VDR), TNF- α , IL-10, IFN- γ , HLA genes, and TLR1 have also been suggested⁶. The type of leprosy that patients develop is determined by their cell-mediated immune response to infection. Patients with tuberculoid disease have a good cell-mediated immune response and few lesions with no detectable mycobacteria. Patients with lepromatous leprosy are anergic towards *M. leprae* and have multiple lesions with mycobacteria present⁴⁶. Schwann cells (SCs) are a major target for infection by *M. leprae* leading to nerve injury, demyelination, and consequent disability. Binding of *M. leprae* to SCs induces demyelination and loss of axonal conductance. Macrophages are one of the most abundant host cells to come in contact with mycobacteria. Phagocytosis of *M. leprae* by monocyte-derived macrophages can be mediated by complement receptors CR1 (CD35), CR3 (CD11b/CD18), and CR4 (CD11c/CD18) and is regulated by protein kinase⁶. The inflammation present in nerves is driven by mycobacterial antigens that activate a destructive inflammatory immune response mediated by CD4+ cells and macrophages, and with involvement of multiple pro-inflammatory cytokines, such as tumor necrosis factor α ⁴⁶. In the tuberculoid lesions there is a predominance of CD4+ auxiliary

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(1) School of Medicine, Master in Collective Health, Health Sciences Center, University of Fortaleza. Fortaleza, Ceará, Brazil.

(2) Post-Graduation Program in Medical Sciences, Department of Internal Medicine, Federal University of Ceará. Fortaleza, Ceará, Brazil.

(3) Department of Community Health, School of Medicine, Federal University of Ceará. Fortaleza, Ceará, Brazil.

(4) School of Pharmacy, Federal University of Ceará. Fortaleza, Ceará, Brazil.

(5) Department of Internal Medicine, School of Medicine, Federal University of Rio Grande do Sul. Porto Alegre, Rio Grande do Sul, Brazil.

Correspondence to: Elizabeth De Francesco Daher. R. Vicente Linhares 1198, 60135-270 Fortaleza, Ceará, Brasil. Phone/Fax: +55 85 32249725, +55 85 32613777. E-mails: ef.daher@uol.com.br, geraldobezerrajr@yahoo.com.br, elvino.barros@gmail.com, robertojusta@secrel.com.br, eanes@fortalnet.com.br, gdayllon@yahoo.com.br, soniaholanda.unifor@gmail.com

T cells and Th1 cytokines such as IL-2 and IFN-gamma, while in lepromatous (Virchowian) lesions suppressant T cells, CD8+, and Th2 cytokines such as IL-4, IL-5 and IL-10³ predominate. In the tuberculoid type, the exacerbation of cellular immunity and the production of pro-inflammatory cytokines (IL-1 and TNF-alpha) prevents the bacilli proliferation, but can cause injury to the host due to the lack of regulator factors. In the Virchowian type, the production of PGL-1 (*phenolic glycolipid antigen-1*) and LAM (*lipoarabinomannan*) antigens by the bacilli, inside macrophages, favors the escapade of the bacilli from the intramacrophage oxidation, because these antigens have a suppressant effect over macrophage activity, and then favors bacilli proliferation³.

CLINICAL MANIFESTATIONS: Leprosy is characterized by tegumentary lesions and nervous system injury. The clinical presentation is variable and is determined by the host immunologic system reaction to the bacilli. During the course of the disease there are the so called reactional states, in which the immune system reacts against the bacilli, exacerbating the clinical manifestations. There are two types of reactional states: reversal reaction (type I), which is more common in the paucibacillary forms, and erythema nodosum (type II), more common in multibacillary forms⁴⁵. The disease is divided into four forms, according to the criteria established by the World Health Organization: indeterminate, tuberculoid, dimorphous and virchowian. The diagnosis and classification are based on clinical findings and complementary tests, such as bacilloscopy, which allow the classification in multibacillary and paucibacillary.

EFFECTS OF IMMUNOSUPPRESSION, HIV AND TRANSPLANT IN LEPROSY: At the beginning of the HIV epidemic there was a fear that HIV infection could increase the risk of leprosy development or that the co-infection (HIV-leprosy) would cause a more severe disease⁴⁶. This hypothesis was not confirmed, since some studies have shown that patients receiving highly active antiretroviral therapy are more likely to develop borderline tuberculoid leprosy than other types of leprosy⁴⁶. HIV infection has not been reported to increase susceptibility to leprosy, impact on immune response to *M. leprae*, or to have a significant effect on the pathogenesis of neural or skin lesions to date. The initiation of antiretroviral treatment has been reported to be associated with activation of subclinical *M. leprae* infection and exacerbation of existing leprosy lesions (type I reaction) likely as part of immune reconstitution inflammatory syndrome⁶. Leprosy has also been reported to occur after organ transplantations, but this is not frequent and immunosuppressant therapy did not seem to affect the course of leprosy manifestations^{4,55}. The course of leprosy seems not to be affected by immunosuppression⁵⁵.

RENAL INVOLVEMENT: Renal involvement in leprosy was first described in the beginning of the XX century, through necropsy studies, in which glomerulonephritis and tubulointerstitial lesions were described^{28,36}. Different renal lesions have been described in leprosy, including acute and chronic glomerulonephritis, interstitial nephritis, secondary amyloidosis and pyelonephritis^{19,41,48}. There are several reports of renal involvement in leprosy, as summarized in Table 1.

The exact mechanism that leads to glomerulonephritis in leprosy is not completely understood. The *M. leprae* may be directly involved in renal injury and it has already been detected in glomeruli of infected patients. The glomerular lesion is probably caused by immunologic mechanism, with complement decrease and immune complexes

deposition in glomerular basement membrane, subendothelial and subepithelial space, detected by electronic microscopy^{19,41,48}. Some studies have also detected mesangial proliferation and the presence of IgA in the mesangial area⁵³. The pathophysiology of renal involvement in leprosy is illustrated in Fig. 1.

A consistent relation between the lepromatous form, erythema nodosum and kidney disease has been described in some studies¹⁸. Although leprosy nephropathy is more frequent in the multibacillary form, it can also occur in other forms and in the absence of the reactional state¹⁹.

A large retrospective study with 923 leprosy patients followed in a tertiary hospital in Brazil found acute kidney injury in 3.8% of cases, and 65% of them had the multibacillary form. Risk factors for kidney injury were reactional state, multibacillary classification and advanced age¹⁰.

RENAL LESION MECHANISM: Erythema nodosum leprosum is a reactional state characterized by immune complexes formation in circulation and subsequent deposition in vessels and tissues. Sometimes they are determined by Hansen's bacilli antigens which are released into circulation after the beginning of antibiotic therapy⁹. The antigens are recognized by host antibodies, and then immune complexes are formed. After this, immune complexes can deposit in the glomerulus or can occur by the formation of immune complexes *in situ*. However, not all glomerulonephritis in leprosy are associated with erythema nodosum, which raises the hypothesis of multifactorial influence in the development of leprosy nephropathy. In the virchowian form there is a cellular immunity decrease and a hyperactivation of humoral immunity, which makes the patient susceptible to the formation of immune complexes³⁰.

The antigen that can induce the formation of immune complexes can originate from Hansen's bacilli or even from therapeutic agents. Anti-dapsone antibodies have been detected in the circulation of leprosy patients. Auto-antibodies have also been described in leprosy, mainly cryoglobulins with IgG and IgM¹³.

Some patients with lower limb ulcers and secondary infections by *Streptococcus* presented a higher frequency of glomerulonephritis⁷.

URINARY FINDINGS: Hematuria has been described in leprosy, mainly in the virchowian form and during erythema nodosum state, even in the absence of evident glomerulonephritis¹⁸. Microscopic hematuria is found in 12-16% of cases, which is higher than what is found in the general population (0.5-2%)^{7,17,57}. This complication can disappear after a few months of specific treatment⁹.

Proteinuria has been described in several studies and its prevalence varies from 2.1 to 68%, and it is also more frequent in the multibacillary forms^{7,27,29,39,50}. Proteinuria varies from 0.4 to 8.9g/day. Nephrotic syndrome is not frequent in leprosy. RAMANUJAM *et al.*⁴⁴ reported five cases in the virchowian form, four were in reactional state and only two had amyloid deposits detected.

Other urinary abnormalities, such as cylindruria and leukocyturia, are more frequently found in the virchowian form with reactional state. In the milder forms these abnormalities are uncommon⁴⁴.

GLOMERULONEPHRITIS: Glomerulonephritis represents the

Table 1
Studies and case reports on kidney involvement in leprosy

Reference	Number of cases	Age (years)	Gender	Clinical picture	Kidney biopsy
Iveson (1975) ²³	1	19	M	Poliarthritis AKI	Diffuse proliferative lesion
Date (1977) ¹²	19			Proteinuria Hematuria	Diffuse proliferative lesion Amyloidosis
Singhal (1977) ⁵³	3			AKI	Acute tubular necrosis Crescentic nephropathy
Gupta (1981) ²⁰	21				Diffuse proliferative lesion Amyloidosis
Phadnis (1982) ⁴²	50				Membranoproliferative nephropathy Membranous nephropathy Amyloidosis
Chugh (1983) ⁷	60			Proteinuria Hematuria AKI	Mesangial proliferative lesion (8.3%) Diffuse proliferative lesion (8.3%) Amyloidosis (5%)
Jayalakshmi (1987) ²⁵	35	74		AKI	Interstitial nephritis Amyloidosis
Al-Mohaya (1988) ²	1	17	M	Proteinuria	Membranoproliferative nephropathy
Madiwale (1994) ³⁴	2	30-45	M	Proteinuria Hematuria	Crescentic nephropathy
Ahsan (1995) ¹	1	79	M	Hematuria AKI	Diffuse proliferative lesion
Lau (1995) ³¹	1	71	M	AKI Drug hepatitis	Interstitial nephritis
Nakayama (2001) ³⁸	199	47-74	M (79.3%)		Amyloidosis (31%) Diffuse proliferative lesion (5%); Focal proliferative (4%); Membranoproliferative (2%); Membranous (1%); Mesangial proliferative lesion (0.5%) Glomerular sclerosis (11%) Tubulo-interstitial nephritis (9%) Granulomata (1%)
Oliveira (2008) ⁴⁰	59	43 ± 15	M (51%)	Concentration defect (84%) Acidification defect (30%) Function loss (50%)	No
Sharma (2010) ⁴⁹	1	25	F	AKI Proteinuria	Crescentic nephropathy
Silva Junior (2010) ⁵²	1	58	M	CKD	AA Amyloidosis
Daher (2011) ¹⁰	923	41 ± 19	M (53.3%)	Proteinuria (4.8%) Hematuria (6.8%) Function loss (3.8%)	No

M: Male; AKI: Acute kidney injury; CKD: Chronic kidney disease.

most frequent type of kidney disease in leprosy. In renal biopsy studies glomerulonephritis was found in more than 30% of patients³⁰, which is higher than what is found in necropsy studies (7%)¹³. In the multibacillary form, the prevalence of glomerulonephritis is higher⁸. Erythema nodosum has a strong correlation with the occurrence of glomerulonephritis, although there are some reports of its occurrence in reactional state type I^{7,9}. Almost all kinds of glomerulonephritis have been described in

leprosy^{7,13}, and there is no specific histopathological pattern in leprosy nephropathy. There is a discrete predominance of membranoproliferative glomerulonephritis, which are in general associated with infectious disease-associated nephropathies^{20,24,42,49}.

HISTOPATHOLOGICAL FINDINGS: The diversity of histopathological lesions found in leprosy suggests a heterogeneous

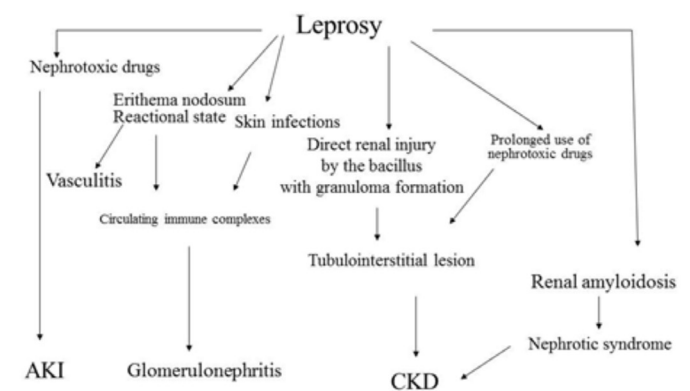


Fig. 1 - Pathophysiology of renal involvement in leprosy. AKI = acute kidney injury; CKD = chronic kidney disease.

disease but not necessarily with different etiologies¹³. Immunohistochemical studies with renal tissue have identified the presence of granular deposits of IgG and C3, and less frequently IgA, IgM and fibrin in the mesangium and in the glomerular capillaries, which is characterized by immune complex deposits or *in situ* formation. Electronic microscopy confirms the presence of dense granular deposits in mesangial-subendothelial and subepithelial regions^{14,26}. Complement consumption in some cases reinforces the hypothesis of an immune complex-mediated disease³⁰.

A study by GROVER *et al.*¹⁹, with 72 leprosy patients undergoing renal biopsy found the following histopathological patterns: membranous nephropathy (31.5%) and mesangioproliferative glomerulonephritis (11.1%). VALLÉS *et al.*⁵⁶ reported one case of IgA nephropathy in a patient with the virchowian form, with reduction in glomerular filtration rate.

Several renal biopsy studies have been performed in leprosy. JOHNY *et al.*²⁶ performed renal biopsies in 35 patients with leprosy and identified histological abnormalities in 45% of them, and the most frequent was proliferative glomerulonephritis. GUPTA *et al.*²⁰ performed renal biopsies in 21 patients with virchowian leprosy, and found proliferative glomerulonephritis in 13 of them. GROVER *et al.*¹⁹, in a study with 54 renal biopsies found 12 cases (22.2%) of diffuse proliferative glomerulonephritis (11 virchowian and one tuberculoid). They also found two cases of rapidly progressive glomerulonephritis, with acute kidney injury. Membranous nephropathy was found in 17 cases (31.5%). PHADNIS *et al.*⁴² performed 50 renal biopsies and identified membranous nephropathy in two cases and membranoproliferative glomerulonephritis in six cases, of whom 45 had the lepromatous form and had reactional state. Interstitial nephritis was observed in 10 patients and amyloidosis in one case. Chronic kidney disease caused by secondary amyloidosis has also been described in leprosy⁵² (Fig. 2).

TUBULOINTERSTITIAL LESION: Interstitial nephritis is one of the most common histological findings in leprosy^{12,20,37}. This has been described in patients with lepromatous leprosy, and is present in more than 20% of cases¹⁹. It seems to be related to disease duration and the long-term treatment with nephrotoxic drugs²⁶.

The identification of specific lesions in leprosy is described as the presence of granulomas in renal interstitium, with evidence of

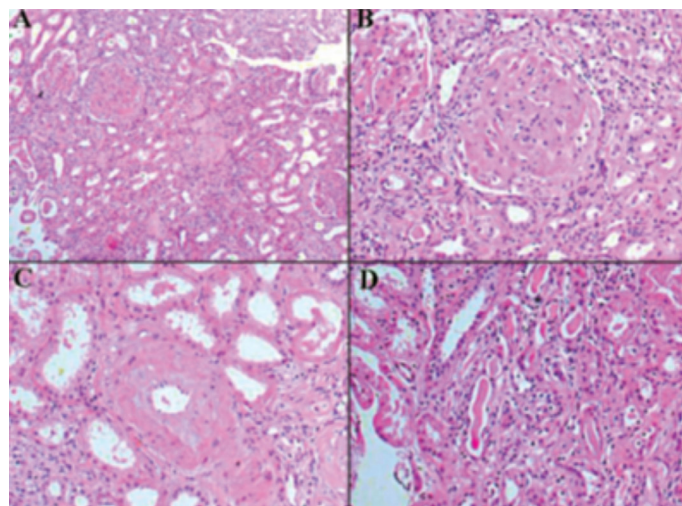


Fig. 2 - Kidney biopsy from a patient with leprosy and chronic kidney disease showing amyloid deposits (A), H&E, x200; glomeruli without mesangial proliferation, with amyloid deposit in mesangium, H&E, x400; amyloid deposit, H&E x200; tubules without abnormalities, H&E x200. Reprinted from Silva Junior *et al.* *Rev Soc Bras Med Trop.* 2010;43:474-6.⁵²

mononuclear cells with vacuolized cytoplasm, without the presence of Hansen's bacilli^{43,47}. Epithelioid granuloma and the Hansen's bacilli have already been detected in renal parenchyma³⁸. The low incidence of granulomas in renal tissue is due to the fact that renal tissue presents a resistance to *M. leprae* or the fact that the bacteria has a low affinity to renal tissue⁴².

The occurrence of tubular dysfunction is frequent, varying from 25 to 85% of cases, in both multibacillary and paucibacillary forms^{7,40}. Urinary acidification defect has been described in 20 to 32% of patients, and urinary concentration defect in 85% of cases^{16,40}. Renal tubular acidosis has also been described^{16,21,40}.

CHRONIC KIDNEY DISEASE: Chronic kidney disease (CKD) has been reported as one of the causes of death in leprosy, mainly in the first studies of leprosy nephropathy^{5,28,36,43}. CKD is mainly caused by amyloidosis and is also more frequent in the virchowian form^{26,33,52}. It has also been reported in patients with the tuberculoid form³³. A correlation between the duration of the disease and the development of amyloidosis has not been observed²⁶. A positive correlation was detected between the occurrence of erythema nodosum and secondary amyloidosis in leprosy^{15,32,33}. Serum levels of amyloid protein A increases in erythema nodosum episodes and remains high for several months. LOMONTE *et al.*³² described the evolution of eight patients with leprosy who developed CKD and required renal replacement therapy.

DRUGS TOXICITY: Despite not being common, renal abnormalities due to leprosy specific treatment have been described. There are reports on acute tubular necrosis, interstitial nephritis and papillary necrosis causing acute kidney injury in leprosy^{7,15}.

Acute kidney injury can occur due to interstitial nephritis secondary to rifampicin use, which is more common with higher doses (900-1200mg) than the usual (450-600mg)²². Dapsone can induce hemolysis and intravascular coagulation, which can lead to acute tubular necrosis⁵⁴.

TREATMENT: Leprosy treatment encompasses specific therapy to overturn *M. leprae*, avoid immunological complications and prevent physical deformities, simultaneously promoting physical and psychosocial rehabilitation. Additionally, health authority notification is mandatory³⁵. WHO-standardized leprosy therapy includes rifampicin, dapsone and clofazimine. Prednisone (1 to 2 mg/kg/day) and non-steroidal anti-inflammatory drugs (NSAI) may be used to control acute immunological episodes. Erythema nodosum leprosum may sometimes have a protracted course (months, or years) and is usually treated with NSAI, steroids, thalidomide, clofazimine and pentoxifylline. It must be kept in mind that all are potentially nephrotoxic. Hemodialysis or kidney transplant are alternatives in treating leprosy ESRD. Post-transplant immunosuppression apparently does not modify leprosy response to drugs. However, acute transitory deterioration of its course has been reported⁴.

CONCLUSION

Renal involvement is an important complication in leprosy, which should be investigated in every patient. Multibacillary status seems to be the main risk factor for kidney dysfunction in this disease. Different kinds of glomerulopathy have been described in association with leprosy. Specific treatment seems to impact on renal function improvement.

RESUMO

Nefropatia da hanseníase: revisão dos aspectos clínicos e histopatológicos

A hanseníase é doença crônica causada pelo *Mycobacterium leprae*, altamente incapacitante e com envolvimento sistêmico em alguns casos. O envolvimento renal tem sido relatado em todas as formas da doença, sendo mais frequente nas formas multibacilares. A apresentação clínica é variável e determinada pela reação do sistema imunológico do hospedeiro ao bacilo. Durante o curso da doença podem ocorrer os chamados estados reacionais, nos quais o sistema imune reage contra o bacilo, exacerbando as manifestações clínicas. Diferentes lesões renais tem sido descritas na hanseníase, incluindo glomerulonefrites, nefrite intersticial, amiloidose secundária e pielonefrite. O mecanismo exato que leva à glomerulonefrite na hanseníase ainda não está completamente esclarecido. O tratamento da hanseníase inclui o uso de rifampicina, dapsona e clofazimina. Prednisona e anti-inflamatórios não-hormonais podem ser usados no controle dos episódios imunológicos agudos.

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