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### DESCRIPTION OF THE TRAINING PROGRAM AT THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

The renal division at the University of Texas Southwestern Medical Center has enjoyed a long tradition of excellence in clinical training and basic science research. This division has trained many fellows who have subsequently become present-day leaders in the fields of nephrology and internal medicine. Initially under the directorship of Dr. Donald W. Seldin and now Dr. Robert J. Alpern, the program has continued to remain in the forefront of research and at the same time maintain excellence in clinical teaching.

The program offers both a clinical- and a basic science-oriented fellowship, depending on the interest of the potential trainee. There are 19 full-time faculty members who oversee fellows during clinical rotations and in the laboratory. The clinical tract involves 2 yr of training based primarily at Parkland Memorial Hospital and the Dallas V.A. Hospital. One to two months per year are spent at two private hospitals that have large nephrology and transplant programs. In addition to a busy consultative service, fellows gain experience in the management of both outpatient hemodialysis and peritoneal dialysis. The acute dialysis rotation at Parkland Hospital typically performs well over 200 procedures per month. During this rotation, the trainee becomes proficient in the techniques of CAVH, CAVHD, and CVVH. There is a large transplant program that is run by the nephrology division. The care of both kidney and kidney-pancreas transplant patients begins preoperatively and resumes in the recovery room directly under the supervision of members of the renal division. This supervision also extends to the outpatient management of transplant patients. The research tract consists of one clinical year followed by two or more years of research. There are currently 19 faculty members involved in research. Ongoing clinical projects include the study of cardiovascular hemodynamics during hemodialysis, lipid abnormalities in the nephrotic syndrome, immunosuppression in transplantation, and treatment of acute renal failure and hypertension. There are also research opportunities in the mineral metabolism division, headed by Dr. C.Y. Pak, which include the study of metabolic bone disease, nephrolithiasis, and osteoporosis. Ongoing basic science research projects include the study of molecular mechanisms of ion transport, G protein signaling, renal growth, and nitric oxide signaling. Other projects include studies directed at the regulation of renin synthesis and secretion and cellular mechanisms of allograft rejection and tolerance.

The educational activities of the division include a series of weekly lectures and journal clubs. The physiology lecture series covers in detail each section of the nephron and includes discussions of cellular and molecular biology. The series is concluded by a number of integrative lectures, some of which are given by Dr. D.W. Seldin. Renal grand rounds presented in coordination with the pathology and radiology departments covers virtually all aspects of clinical nephrology. Research conference includes visiting professors as well as local faculty members and provides a forum for the presentation of current research relating to the kidney. Both a clinical and a basic science journal club complete the weekly schedule.

## Leprosy-Associated Renal Disease: Case Report and Review of the Literature<sup>1</sup>

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### ABSTRACT

Leprosy is an infectious disease the principal clinical manifestations of which are anesthetic skin lesions and the development of peripheral neuropathy. The most common renal manifestation in leprosy patients is glomerulonephritis. Both immunofluorescent and electron microscopic studies suggest that the varied

glomerular lesions found in these patients are immune complex mediated. Other renal lesions that have been described include amyloidosis, tubulointerstitial disease, acute renal failure, and functional defects in the absence of identifiable histologic abnormalities. In this report, a patient is described who developed the clinical syndrome of rapidly progressive glomerulonephritis. The renal biopsy showed a diffuse endocapillary proliferative process with electron-dense deposits in the glomerular subendothelial and subepithelial spaces. Organisms consistent with *Mycobacterium leprae* were identified within several of the glomeruli.

**Key Words:** *Leprosy, glomerulonephritis, amyloidosis, interstitial nephritis, acute renal failure*

**L**eprosy is a chronic granulomatous disease caused by the acid-fast rod *Mycobacterium leprae*. Recent estimates place the total number of patients affected with leprosy at 10 million to 12 million (1). Most cases are found in Africa and Asia, with a lesser prevalence in South America and Mexico. In North America, a small focus of infection still remains in Texas and Louisiana, but over 90% of cases in this country can be traced to immigrants from leprosy-endemic countries.

The principal clinical manifestations of the disease are anesthetic skin lesions, peripheral neuropathy, and palpable enlargement of peripheral nerves. Renal involvement in leprosy is a variable finding and most commonly takes the form of an immune complex-mediated glomerulonephritis. Direct involvement of the renal parenchyma with bacilli has only rarely been reported. In this report, we describe a patient with lepromatous leprosy who developed a proliferative form of glomerulonephritis. In addition, acid-fast bacilli consistent with *M. leprae* were identified in several glomeruli and in the interstitium. A review of the renal manifestations reported in leprosy is provided.

## CASE REPORT

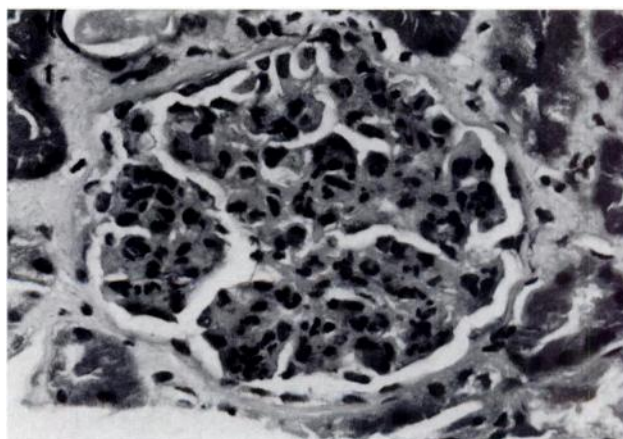
A 79-yr-old Latin-American man presented with a several-day history of hematuria, urinary frequency, and dysuria. The patient lived in Mexico and had no knowledge of prior kidney disease. The physical examination was significant for a malnourished man who was afebrile and normotensive. Numerous tender, violaceous, papulonodular lesions were found on the trunk and extremities. Facial erythema and thickened pinnae were present. Decreased cutaneous sensation was found over the neck, face, ankle, and feet. There were no palpable peripheral nerves. Laboratory examination showed a white blood cell count of 9.7, hematocrit of 33%, and a platelet count of 330K. Serum chemistries (in milliequivalents per liter) were: Na, 124; K, 5.2; Cl, 96. The blood urea nitrogen was 31 mg%, and the serum creatinine level was 1.9 mg%. Urinalysis showed 300 mg/dL protein. Microscopic

examination of the urine revealed more than 40 red blood cells per high-power field, three to five white blood cells per high-power field, and occasional hyaline casts. A urine culture was sterile. A cystoscopy was performed to evaluate the hematuria and was normal. A skin biopsy from a lesion on the upper extremity showed extensive mononuclear infiltrate in the superficial dermis. There were numerous vacuolated macrophages containing Fite stain-positive bacilli (leprae bacilli). No granulomas were seen, and the vessels were normal.

On the basis of the physical findings and the results of the skin biopsy, the patient was diagnosed with lepromatous leprosy. Antileprosy therapy consisting of dapsone and clofazimine was initiated. Three days after the initiation of therapy, clofazimine was discontinued and rifampin was started.

One week after the initiation of therapy, the serum creatinine increased to 2.1 mg%. A 24-h urine collection showed a creatinine clearance of 26.4 mL/min and 2.9 g of protein. Further laboratory studies showed an erythrocyte sedimentation rate of 90 mm/h; C<sub>3</sub>, 23 mg/dL (85 to 193 mg/dL); C<sub>4</sub>, 19.1 mg/dL (15 to 45 mg/dL); and negative serologies for hepatitis B surface antigen, human immunodeficiency virus, and syphilis. Antinuclear antibodies were positive at a titer of 1/80 (speckled pattern). Circulating cryoglobulins were not detected, and the rheumatoid factor was negative.

To evaluate the rapid decline in renal function, a percutaneous renal biopsy was performed. The specimen contained 35 glomeruli, most of which showed diffuse, endocapillary, proliferative glomerulonephritis (Figure 1). Three glomeruli contained cellular crescents. There was mild, patchy interstitial fibrosis with focal and mild tubular atrophy. No granuloma were identified. Small clusters of Fite stain-positive bacilli (leprae bacilli) in several glomeruli and in the interstitium were identified by light microscopy (Figure 2).



**Figure 1.** The glomerulus shows a diffuse, endocapillary, proliferative process with numerous neutrophils occluding the peripheral capillary loops (hematoxylin and eosin).





Figure 2. By the use of a stain for acid-fast bacilli, organisms consistent with *M. leprae* can be demonstrated within several of the glomeruli (Fite).

Seven glomeruli were available for immunofluorescence studies. There was intense staining for immunoglobulin G (IgG) and coarsely granular C<sub>3</sub> along the peripheral capillary loops and mesangium. Stains for IgA and IgM were weakly positive. Electron microscopy showed dense deposits in the mesangium and subepithelial and subendothelial spaces (Figure 3).

Given the histologic evidence of a proliferative glomerulonephritis in the setting of a rapid loss in renal function, corticosteroids (prednisone, 60 mg p.o. daily) were added to the antileprosy regimen. Within 72 h, there was a fall in the serum creatinine concentration to 1.6 mg%. A complete resolution of his skin lesions was ultimately documented in follow-up in the Dallas city public health clinic. The patient subsequently returned to Mexico.

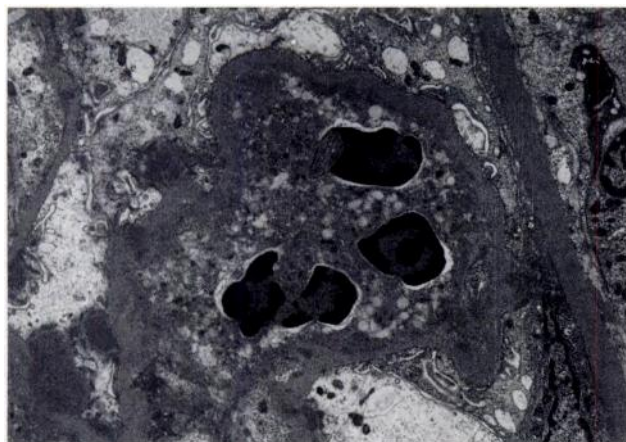


Figure 3. Electron photomicrograph showing a neutrophil occluding a peripheral capillary loop. Immune complex-type, electron-dense deposits can be seen subendothelially, whereas electron-dense "humps" are noted in the subepithelial space, consistent with a postinfectious glomerulonephritis.

## DISCUSSION

As originally conceived by Ridley and Jopling (2), the clinical manifestations of leprosy form a continuum largely dictated by the degree of cell-mediated immunity in a given patient (Table 1). Tuberculoid leprosy (paucibacillary) lies at one end of the spectrum and is characterized by vigorous cell-mediated immunity such that the replication of organisms is limited. Histology reveals well-organized epithelioid granulomas. Lepromatous leprosy (multibacillary) lies at the other end of the spectrum and is characterized by cellular anergy toward the organism. Bacilli are plentiful, and epithelioid cell formation is poorly developed. In contradistinction to cell-mediated immunity, antibody responses reach their highest level in lepromatous leprosy and are at the lowest in patients with tuberculoid leprosy (3). Between these two poles, the disease continuum is further subdivided into borderline tuberculoid, borderline, and borderline lepromatous, reflecting a declining degree of cell-mediated immunity and increasing degree of humoral responses.

The role played by different T cell subsets and cytokines in mediating this immunologic spectrum in patients with leprosy has recently been reviewed (4). In brief, tuberculoid granuloma are characterized by CD4<sup>+</sup> T lymphocytes responding to *M. leprae* antigens presented by macrophages in the context of HLA-DR. This interaction results in cytokine signaling between these cells, in which  $\gamma$ -interferon and interleukin-2 play a central role. The net result is the activation of macrophages and the induction of a vigorous cell-mediated response. By contrast, lepromatous granuloma are characterized by macrophages presenting the antigens of *M. leprae* in a different HLA class II-restricted context, namely, HLA-DQ. This type of presentation favors the activation of CD8<sup>+</sup> T lymphocytes, with the subsequent generation of a cytokine microenvironment in which interleukin-4 and interleukin-10 play a central role. The net result is the suppression of cell-mediated immunity with the facilitation of a humoral response.

The clinical course of leprosy is generally indolent. Because of an inherent instability of the immune system, patients with borderline forms of the disease tend to drift toward one pole or the other, depending on whether treatment is initiated or not (5). A reversal reaction (type 1 lepra reaction) indicates a change toward the tuberculoid pole and is characterized by an increase in the degree of cell-mediated immunity. This type of reaction is typically seen during or after treatment. Without treatment, cell-mediated immunity tends to wane over time such that patients will downgrade toward the lepromatous pole. A second type of reaction, known as erythema nodosum leprae (ENL) (type 2 lepra reaction), typically occurs in lepromatous leprosy and less commonly in borderline lepromatous leprosy. This type of reaction is seen both spontaneously and after the initiation of treatment.

TABLE 1. Immunologic and histologic features that distinguish tuberculoid from lepromatous leprosy<sup>a</sup>

Feature	Tuberculoid	Lepromatous
Skin Lesions	Few, well-defined, anesthetic plaques and macules	Many, widely distributed, poorly margined plaques and macules
Histology	Organized granulomas with core of differentiated macrophages (epithelioid cells), surrounding mantle of lymphocytes	Disorganized granulomas with immature macrophages (histiocytes), few surrounding lymphocytes
Bacterial Number	Few	Abundant
Cell-Mediated Immunity	Vigorous	Poor, often anergic
Humoral Responses	Low	High
Erythema Nodosum Leprosom	Rare	Common

<sup>a</sup> Tuberculous and lepromatous leprosy form the polar ends of a disease continuum in which patients can be further classified as borderline tuberculoid, borderline, or borderline lepromatous.

ENL is manifested by tender cutaneous nodules, lymphadenopathy, iritis, orchitis, polyneuropathy, and urinary sediment abnormalities. Histologically, one finds evidence of vasculitis with neutrophilic infiltration into the granulomatous lesions. ENL is thought to be an immune complex disorder generated by a humoral response to the products of nonviable leprae bacilli (5). The clinical manifestations of ENL are thought to result from the widespread deposition of these immune complexes and, as such, resembles an arthus reaction.

The first report of renal involvement in leprosy was made by Hansen and Looft, who, in 1894, described a patient with "nephritis" (6). Mitsuda and Ogawa in 1937 and subsequently others (7–9) recognized that renal failure was an important cause of death in patients with leprosy. Since these early reports, a number of renal abnormalities have been described in patients with leprosy (Table 2). The lesions encountered include varying forms of glomerulonephritis, secondary amyloidosis, acute tubular necrosis, acute and chronic interstitial nephritis, pyelonephritis, and isolated functional renal tubular abnormalities in the absence of renal histologic changes. The identification of leprae bacilli in the renal parenchyma has only been reported in two prior renal biopsy cases (10,11).

TABLE 2. Renal manifestations of leprosy<sup>a</sup>

Glomerulonephritis
Endocapillary proliferative (11,12,14–16)
Mesangial proliferative (12,14)
Membranoproliferative (17)
Chronic sclerosing (16)
Crescentic (14,27,28)
Amyloidosis (9,31,32)
Acute tubular necrosis (27)
Acute tubulointerstitial nephritis (13,33,36)
Chronic tubulointerstitial nephritis (13,30,33)
Functional defects without histologic lesions (14,37)
Acidification defects
Impaired concentrating ability

<sup>a</sup> Numbers indicate references.

## Glomerulonephritis

The frequency with which glomerulonephritis occurs in patients with leprosy has been found to vary widely. By the use of renal biopsy material, glomerulonephritis has been found in 6 to 63% of patients (12–14). Much of this variability can be traced to differences in patient selection. For example, Date *et al.* obtained renal biopsy material in 19 patients who were selected for the presence of edema, proteinuria, and hematuria and found evidence of glomerulonephritis in 63% of patients (12). By contrast, Gupta *et al.* reported histopathologic changes in 50 cases of leprosy chosen at random and reported an incidence of glomerulonephritis of only 6% (13). Similarly, in 60 consecutive unselected patients, Chugh *et al.* found evidence of glomerulonephritis in 8.3% (14). Using findings on routine urinalysis as evidence of glomerulonephritis, Drutz and Gutman found urinary sediment abnormalities in only 11 of 636 patients screened at a leprasorium (15).

The most common histologic findings in patients with glomerulonephritis are endocapillary proliferative glomerulonephritis, mesangial proliferative glomerulonephritis, and membranoproliferative glomerulonephritis (16,17). Less commonly reported are lesions of chronic sclerosing and crescentic glomerulonephritis (16). Electron microscopy frequently shows evidence of immune deposits (12). Most commonly, these deposits have been identified in the mesangium and subendothelial space. Less frequently, intramembranous or subepithelial dense deposits are found (18,19). Immunofluorescence studies have typically shown granular deposits of IgG and C<sub>3</sub> along the capillary wall and mesangium (16). Less commonly, IgM, IgA, and fibrin are seen. These findings suggest that the varied glomerular lesions described in patients with leprosy are probably different manifestations of immune complex-induced glomerulonephritis.

The nature of the antigen in the immune complex is as yet unknown but is suspected to be a product of *M. leprae*. ENL is also felt to be an immune complex

disorder involving mycobacterial antigens released during the breakdown of *M. leprae*. In this regard, deterioration in renal function, urinary abnormalities suggestive of glomerulonephritis, and biopsy-proven glomerulonephritis have been reported to occur more frequently in patients with lepromatous leprosy complicated by ENL (15,20). Moran *et al.* found detectable circulating immune complexes in 76% of patients with lepromatous leprosy and active ENL as compared with only 33% with lepromatous disease without ENL (21). Hypocomplementemia is also found during such reactions (16,22). The underlying immunologic response favoring humoral immunity to the exclusion of cell-mediated processes is likely responsible for the increased incidence of immune complex-induced glomerulonephritis in patients with lepromatous leprosy.

Despite the fact that circulating immune complexes are mostly found in lepromatous leprosy, glomerulonephritis has also been reported to occur in nonlepromatous forms of the disease. In fact, in an analysis of 187 renal biopsy specimens collected from a literature review, Ng *et al.* found the incidence of glomerulonephritis in the two groups to be similar (16). This observation raises the possibility that nonmycobacterial antigens may also be involved in the generation of glomerulonephritis (Table 3). Patients with leprosy are known to be commonly coinfecting with microorganisms that could conceivably contribute to the generation of an immune complex disorder. Examples of such infections include bacteria such as streptococci and staphylococci, parasites, and viruses such as hepatitis B and C (12,23). An additional factor that could contribute to the development of glomerulonephritis is the formation of dapsones:antidapsones antibodies, which are known to develop during the course of treatment in some patients (24). Autoantibody production primarily due to cryoglobulins has also been reported in patients with leprosy (11,25). In a number of cases, glomerular deposits consisting of cryoglobulins have been identified (17). Finally, cell-mediated immune injury is a possible, but not yet proven, cause of glomerular damage.

The clinical features of glomerulonephritis in patients with leprosy most commonly consist of asymptomatic hematuria and/or proteinuria (26). On occasion, the proteinuria can become substantial and result in the nephrotic syndrome. Less frequently,

patients can present with a nephritic clinical picture. In some of these cases, the clinical course is one of rapidly progressive glomerulonephritis manifesting as oligoanuric renal failure (27,28).

The principal antimicrobial agents used to treat patients with leprosy are dapsones, rifampin, and clofazimine. In those patients who develop ENL, corticosteroids and thalidomide have both been found effective in controlling the systemic manifestations of the reaction. With regard to glomerular disease occurring in this setting, Weiner and Northcutt described a beneficial effect of steroids on renal function in a patient with membranoproliferative glomerulonephritis and cryoglobulinemia whose renal failure had deteriorated in the setting of an episode of ENL (17). That case, as well as our own case, provides at least anecdotal evidence of a beneficial effect of corticosteroids in the treatment of glomerulonephritis. Whether corticosteroids play a role in the treatment of glomerular disease not associated with ENL is unknown. Also unknown is whether the clinical course of leprosy-associated renal disease is altered during the chronic treatment of the underlying infection with antimicrobial agents alone.

### Amyloidosis

Progression to chronic renal failure has been well documented in patients with renal amyloidosis. The incidence of renal amyloidosis in leprosy ranges from 2 to 55% (8,17,29–32). Much of this variability can be traced to geographic differences in the reported incidence of the disease. In both autopsy and biopsy studies from the United States, amyloidosis has been reported in up to 55% of patients (9,31,32). By contrast, similar studies in Mexico, Africa, and India have found the incidence of amyloidosis to be less than 10% (29,30,33,34). The reason for this geographic variability is not clear but may be related to genetic differences, number of leprae reactions, nutritional status, or differences in management (31).

The development of amyloidosis is much more frequent in lepromatous leprosy. There has been a striking association between the development of amyloidosis and a history of recurrent bouts of ENL (35). During such reactions, there is a marked elevation in the serum protein AA concentration that can be persistent over several weeks (35). This finding has potential relevance to the pathogenesis of amyloid in these patients because the chemical analysis of deposits has demonstrated the fibrils to be primarily composed of the AA protein. Because ENL is not a feature of tuberculoid leprosy, amyloidosis is not typically seen in these patients. Those patients in whom it has been described have typically had chronic neurotrophic ulcers (35). There is no specific treatment for amyloidosis, but early and aggressive treatment of leprosy with particular attention to preventing recurrent episodes of ENL may prove effective in eliminating this complication.

TABLE 3. Possible mechanisms of glomerular injury in leprosy

Deposition of Circulating Immune Deposits
<i>M. leprae</i> antigen-antibody complexes
Non-leprae-containing immune complexes
(streptococci, staphylococci, parasites, viruses)
Dapsones-antidapsones immune complexes
In Situ Immune Complex Formation
Cryoglobulinemia
?Cell-Mediated Immune Mechanisms

## Acute Renal Failure

Although most of the renal lesions associated with leprosy clinically present with chronic renal failure, the development of acute renal failure has occasionally been reported. Singhal *et al.* described three such patients with lepromatous leprosy (27). In two, oliguric renal failure developed during treatment with dapsone and was complicated by the development of hemolytic anemia. Biopsy specimens in both cases demonstrated acute tubular necrosis. The third patient presented with anuric renal failure with biopsy findings consistent with crescentic glomerulonephritis. More recently, Madiwale *et al.* described two additional patients with crescentic glomerulonephritis presenting in this manner (28). Finally, drug-induced interstitial nephritis needs to be considered in leprosy patients who develop acute renal failure (36).

## Tubulointerstitial Abnormalities

Tubulointerstitial renal disease has been a commonly described finding in both autopsy and renal biopsy studies of leprosy patients (30,33). Abnormalities have included pyelonephritis as well as acute and chronic interstitial nephritis. The pathogenesis of these inflammatory cell infiltrates remains unexplained. It is unlikely that these lesions are due solely to the underlying mycobacterial infection; however, clinical data are unavailable in most studies that would allow one to identify other factors potentially involved in the pathogenesis of these lesions.

Interestingly, urinary concentrating defects and impaired distal tubular acidification have been found in patients with leprosy in the absence of histologic abnormalities. Gutman *et al.* found that 9 of 47 adult leprosy patients (5 with lepromatous, 3 with borderline, and 1 with tuberculoid leprosy) failed to decrease the urine pH appropriately in response to an ammonium load (37). Two of these nine patients and five others without acidification defects demonstrated a diminished ability to maximally concentrate the urine in response to fluid deprivation. Renal biopsy specimens obtained in six of these patients were normal. Similarly, Chugh *et al.* described 9 of 36 patients with acidification and/or concentrating defects who also had normal renal histology (14). All of those patients had either lepromatous or borderline lepromatous forms of the disease. The mechanism underlying these defects is currently unknown.

## SUMMARY

Of the various renal lesions discussed previously, the clinicopathologic features of our patient best fits an immune complex-mediated glomerulonephritis. Although not measured, it is likely that our patient had circulating immune complexes, given his diagnosis of lepromatous leprosy and clinical features of active ENL. Interestingly, within several days of the initiation of therapy, the patient's renal function deteriorated, with evidence of ongoing complement con-

sumption. It is interesting to speculate that the presence of bacilli within the renal parenchyma may have contributed to the rapid deterioration in renal function. The release of a large quantity of leprae antigens induced by the bactericidal actions of the chemotherapy would provide the substrate for *in situ* immune complex formation in close proximity to the glomeruli. The rapid improvement in renal function in response to the administration of corticosteroids is similar to that in the patient described by Weiner and Northcutt (17).

In summary, leprosy is a multisystem infectious disease that can involve the kidney in a variable number of ways. An immune complex-mediated glomerulonephritis is the most common form of renal involvement. Anecdotally, steroids may be effective in treating glomerulonephritis, particularly when associated with ENL. The natural history of glomerular disease in the absence of ENL is unknown.

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