MPGN Secondary to Lyme Disease

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• **Lyme disease is a multisystem disorder with protean clinical manifestations that is caused by the tick-transmitted spirochete *Borrelia burgdorferi*. Infection caused by *B burgdorferi* is known to induce glomerulonephritis in animals. We report a patient with acute postinfection membranoproliferative glomerulonephritis after the clinical multisystem manifestation of Lyme disease, which was confirmed serologically. Although the patient was dialysis dependent for a protracted period of 5 months, the final outcome was excellent. *Am J Kidney Dis* 43:544-551.**

INDEX WORDS: Postinfection glomerulonephritis; membranoproliferative glomerulonephritis (MPGN); Lyme disease; *Borrelia burgdorferi*.

LYME DISEASE is a multisystem disorder caused by the tick-transmitted spirochete *Borrelia burgdorferi*. Its clinical manifestations are protean and include dermatologic, rheumatologic, neurological, and cardiac abnormalities. Its diagnosis requires high clinical suspicion and presents laboratory caveats. Although the spirochete is known to induce glomerulonephritis in animals, noticeably almost exclusively membranoproliferative glomerulonephritis (MPGN) with or without interstitial nephritis,[1,2] postinfection glomerulonephritis secondary to Lyme disease in humans has been reported only once in the literature to date.[3] We present a patient with acute renal failure caused by acute nephritic syndrome who became dialysis dependent for 5 months. Clinical suspicion was made after multiple clinical relapses of the disease with multisystem manifestations, and finally, Lyme disease was confirmed serologically and treated accordingly. The outcome is impressive and the patient finally regained normal urine volume and became dialysis independent.

CASE REPORT

A 76-year-old man was admitted to the hospital for acute renal failure. The patient had experienced oliguria and progressively intensifying leg edema during the past 2 weeks. At the same time, he had intermittent fever (up to 38.5°C), sore throat, fatigue, nausea, and migratory bone pain and arthralgias. A month before, he had migrated to Greece from the former Soviet Union State of Georgia. A few days before he migrated, the patient noticed a macular burning rash that started at his left leg as a single macular lesion and gradually expanded over both legs and arms. The rash lasted approximately 15 days, then subsided spontaneously and was followed by fever, fatigue, nausea, and oliguria. His medical history was free, and renal function was reported to be normal a year ago when last examined during a routine checkup.

On admission, the patient had low-grade fever (37.3°C), arterial hypertension (blood pressure, 180/100 mm Hg), sinus tachycardia (heart rate, 100 beats/min), and oliguria (urine volume, 400 mL/d). The rash manifested earlier had disappeared. Physical examination also showed spleen enlargement, leg edema, and pulmonary congestion. No signs of rheumatoid arthritis were noted. Basic laboratory examinations are listed in Table 1. Widal and Wright test results were negative. Serological test results for hepatitis viruses and human immunodeficiency virus were negative, as were results of blood, urine, and sputum cultures. A thorough immunologic workup and search for cryoglobulins were negative, and complement levels were near the lower normal values (C3a, 34 μg/mL [normal, 29 to 196 μg/mL]; C4d, 1.2 μg/mL [normal, 0.7 to 14 μg/mL]). Urine examination showed voiding of dense urine (special gravity $>$ 1.030) with normal acidity (pH 6), significant proteinuria (protein, 2 g/d), microscopic hematuria of glomerular origin (80 to 100 red blood cells/high-power field), pyuria (25 to 30 white blood cells/high-power field), and glucosuria (glucose, 100 mg/dL [5.6 mmol/L]). Ultrasound showed 2 near-normal sized kidneys (11 cm; cortex, 1.4 cm) with no signs of obstruction in either kidney. A heart ultrasound showed no signs of endocarditis or rheumatic fever.

The patient was treated with hemodialysis, and when stabilized, he underwent kidney biopsy. Light microscopic examination showed diffuse glomerular hypercellularity, pronounced lobulation, thickening of the capillary wall, and a double-contour pattern of capillary basement membrane, along with periglomerular lamellar fibrosis (Fig 1). Increased numbers of nuclei in the glomerular tuft were prominent, as was the presence of inflammatory cells (macrophages and neutrophils). In the tubulointerstitium, tubular

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Table 1. Blood Biochemical, Serological, and Cerebrospinal Fluid Examinations

Parameters	Values
At presentation	
Hematocrit (%)	35.3
Hemoglobin (g/dL)	12.1
White blood cell count ($\times 10^3/\mu L$)	12.6
Platelets ($\times 10^3/\mu L$)	721
Prothrombin time (s)	10.5
Partial thromboplastin time (s)	30
D-Dimers	1,000
Fibrinogen (mg/dL)	451
Serum creatinine (mg/dL)	6
Blood urea nitrogen (mg/dL)	126
Aspartate aminotransferase (U/L)	18
Alanine aminotransferase (U/L)	15
Erythrocyte sedimentation rate (mm/h)	54
C-Reactive protein (mg/L)	98
Antistreptolysin titer (IU/mL)	1,740
Rheumatoid factor (IU/mL)	206
On admission for GBS	
Serological tests	
Rheumatoid factor (IU/mL)	748
C-Reactive protein (mg/L)	50.6
Epstein-Barr virus	IgG^+/IgM^-
Herpes simplex virus	IgG^+/IgM^-
Adenoviruses	IgG^+/IgM^-
Parvovirus B19	IgG^+/IgM^-
Coxsackie B1-B5 viruses	IgG^+/IgM^-
CMV	IgG^+/IgM^+
HB_sAg	Positive
Venereal Diseases Research Laboratories test	Negative
Rickettsia typhi and *Rikettsia conorii*	IgG^+/IgM^-
B burgdorferi IgG	
Antibody-capture immunoassay (AU/mL)	14.6
ELISA (AU/mL)	22
Western blotting	OspC23 and 41 kda (Fla) positive
B burgdorferi IgM	
Antibody-capture immunoassay (AU/mL)	23
ELISA (AU/mL)	17
Western blotting	OspB, OspC23, p41, p20/18 positive
Cerebrospinal fluid	
Epstein-Barr virus	IgG^+/IgM^-
Herpes simplex virus	IgG^+/IgM^-
Coxsackie B1-B5 viruses	IgG^+/IgM^-
CMV	IgG^+/IgM^-
Parvovirus B19	IgG^+/IgM^+
Adenoviruses	IgG^+/IgM^+

NOTE. To convert hemoglobin in g/dL to g/L, multiply by 10; white blood cell count and platelets in $\times 10^3/\mu L$ to $\times 10^9/L$, multiply by 1; fibrinogen in mg/dL to μmol/L, multiply by 0.0294; serum creatinine in mg/dL to μmol/L, multiply by 88.4; blood urea nitrogen in mg/dL to mmol/L, multiply by 0.357.

Abbreviations: Osp, outer surface protein; 41 kda (Fla), 41-kdalton flagellar antigen; p41, recombinant antigen p41; p20/18, recombinant antigen p20/18.

dilatation with local tubular necrosis, tubulitis, and epithelial regenerative changes were evident, along with the presence of edema and inflammatory cells (mainly lymphocytes and macrophages) throughout the interstitium. Mild tubular atrophy and interstitial fibrosis were noted. Mild intimal thickening in some arteries also was found. Immunofluorescence microscopy was not performed because of an insufficient tissue sample; however, immunohistochemical stain in a paraffin section showed abundant C3 deposition in a coarse, broken, linear pattern and mild granular immunoglobulin G

(IgG) deposits along the capillary loops. A diagnosis of postinfection type I mesangiocapillary MPGN with accompanying mild acute interstitial nephritis was made.

Although during the course of the disease, antistreptolysin titers were intermittently negative, the diagnosis of poststreptococcal glomerulonephritis was considered likely, and the patient was treated accordingly; initially with a 20-day schema of cefotaxime (2 g/d). Additionally, when inflammatory indices had subsided, intravenous corticosteroid therapy (prednisolone, 50 mg/d) was administered because of intense inflammatory infiltrations in both glomeruli and tubules. The patient remained dialysis dependent and on oral therapy with 32 mg/d of methylprednisolone, gradually tapered during the next weeks. Outpatient follow-up was arranged for the ensuing time.

The course of the patient's disease was unusually protracted (Fig 2). Fifteen days later, during the course of an infection caused by *Pseudomonas aeruginosa*, the patient manifested acute hearing loss in both ears. The acoustogram showed severe neurosensorial deafness in both ears, and the diagnosis of acoustic mononeuritis was established. The respiratory infection was treated successfully with a 20-day schema of intravenous ceftriaxone, 1 g/d, and oral clarithromycin, 1 g/d, whereas the hearing deficit was promptly reversed with a new course of 3 g of corticosteroid pulse therapy, followed by oral methylprednisolone, 32 mg/d, with gradual tapering.

A month later, while the patient was still on hemodialysis treatment, he was readmitted for difficulty in standing and walking, as well as paresthesias in both upper and lower extremities, which progressed until the time of his admission. Neurological examination showed motor weakness in both lower extremities, absent deep-tendon reflexes, and peripheral-type hypoesthesia in both upper and lower extremities. Nerve conduction studies and needle electromyography showed an acute demyelinating peripheral neuropathy in both upper and lower extremities, more severe in the lower extremities, and acute denervation in the lower-extremity muscles. The diagnosis of Guillain-Barré syndrome (GBS) was established, and the patient was worked up for an infectious or systemic disease. From laboratory examinations, a characteristic high rheumatoid factor titer (748 IU/mL; normal range, 0 to 15 IU/mL) and C-reactive protein level (50.6 mg/L; normal range, 0 to 5 mg/L) were prominent. The rest of the results were normal, and a thorough immunologic profile was negative, except for circulating immune complexes detectable in serum. Results of tests for infections are listed in Table 1. Serological tests for cytomegalovirus (CMV) showed positive IgG and IgM, but a negative polymerase chain reaction (PCR) test for the virus. Hepatitis B surface antigen (HBsAg) was now positive, but PCR for hepatitis B virus DNA was negative. Several days later, positive results of the test for *B burgdorferi* became available (Table 1). However, the PCR test for the spirochete was negative. The patient had already been treated with a 3-day schema of intravenous immunoglobulin and started plasmapheresis (total, 11 sessions). Antibiotic treatment with intravenous ceftriaxone, 2 g/d, for 21 days and then imipenem, 500 mg/d, for the next 12 days was administered, as well. The patient responded impressively to the treatment with significant daily improvement in motility and subsidence of paresthesias.

On day 20 of treatment, the patient experienced acute chest pain, along with a low-grade fever and elevation of the ST segment on the electrocardiogram. The diagnosis of myopericarditis was made, which was confirmed by gallium myocardial scan. In the ensuing days, pericardial and pleuritic effusion erupted, which was found to be a transudate. A course of intravenous prednisolone treatment was started (25 mg/d), with a resulting rapid subsidence of serositis and the appearance of a typical transient pericardial and pleuritic friction sound. At that time, when the patient's condition had been stabilized, he underwent a second renal biopsy, indicated by the protracted acute renal failure. Histological examination confirmed the initial diagnosis, but showed an impressive abatement of glomerular and tubulointerstitial inflammation, mesangial hypercellularity, and double-contour pattern of capillary basement membranes (Fig 3). Immunofluorescence microscopy on frozen sections showed sparse IgG and mild granular C3 mesangial depositions, as well as along the capillary loops. In the subsequent 6 weeks, the patient experienced a gradual increase in urine volume, with a concomitant improvement in serum creatinine and urea levels. Finally, he regained normal urine volume and become dialysis independent 5 months after he first started hemodialysis therapy, with a serum creatinine level of 1.6 mg/dL (141 μmol/L). Repeated nerve conduction studies and needle electromyography 4 months later showed normal findings, and the patient has no sign of the preceding GBS. At that time, *B burgdorferi* IgG was positive, whereas IgM had become negative.

DISCUSSION

Lyme disease is a multisystem disorder caused by the tick-transmitted spirochete *B burgdorferi*. It presents with protean clinical manifestations, including dermatologic, rheumatologic, neurological, and cardiac abnormalities. The vectors of Lyme borreliosis are several ixodid ticks that are part of the *Ixodes ricinus* complex. Lyme disease currently is the most common vector-borne infection in the United States and also presents endemic foci in Europe, Scandinavia, the former Soviet Union, China, Japan, and Australia.[4] As with other spirochetal infections, Lyme borreliosis generally occurs in stages, with remissions and exacerbations that include different clinical manifestations.[5]

Although there are interesting reports of MPGN with variable degrees of interstitial nephritis in animals with *B burgdorferi* infection,[1] and microscopic hematuria and/or mild proteinuria have been reported in association with *B burgdorferi*,[4] to the best of our knowledge, postinfection glomerulonephritis associated with Lyme disease in humans has been reported only once to

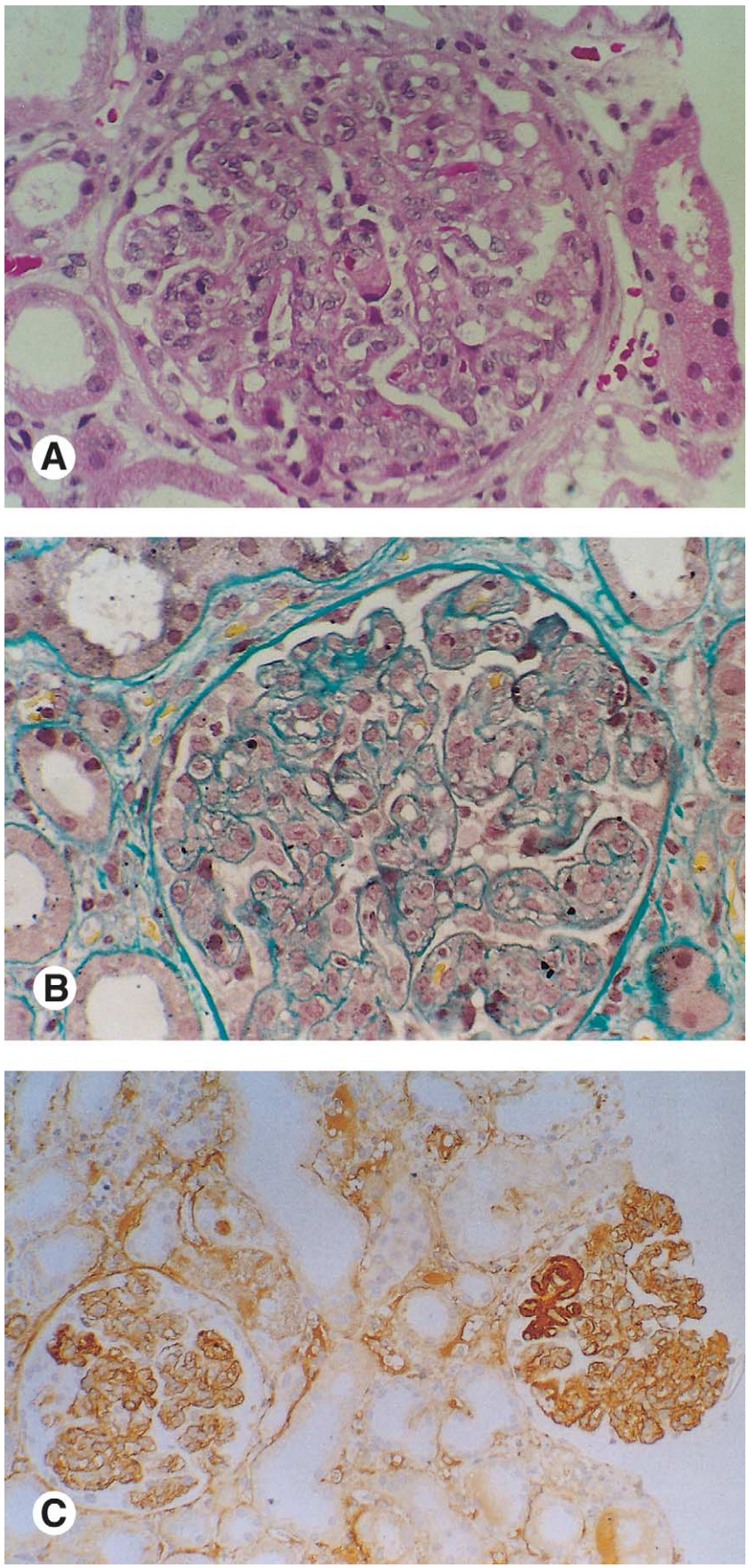

Fig 1. Histological examination of the first renal biopsy specimen shows (A) glomerular hypercellularity and thickening of the capillary wall (hematoxylin and eosin; original magnification ×400) and (B) hypercellularity in the mesangium, pronounced lobulation, and localized double contour of capillary basement membrane (Masson trichrome; original magnification ×400). (C) C3d immunohistochemical stain in paraffin section shows a coarse, broken, linear pattern with some areas of coarse deposition along capillary loops. (Original magnification ×200.)

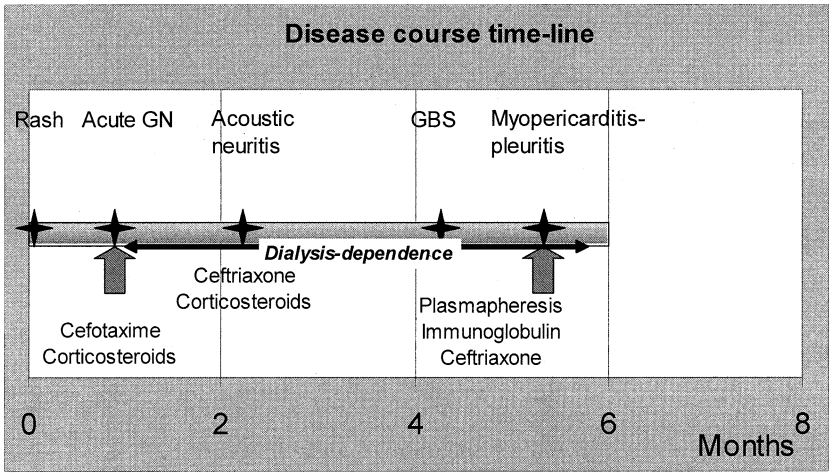

Fig 2. Time line of the disease course and treatment; arrows show when renal biopsies were performed.

date.[3] However, the prominent neurological syndrome in that case made the diagnosis of Lyme disease evident early in the course of the disease. Postinfection MPGN is a typically immune-complex–mediated glomerulonephritis, and among the numerous identified causes in humans are other spirochetal infections. It is of interest that in dogs with *B burgdorferi* infection, as well as in the sole case reported in humans, MPGN is the characteristic histological lesion. The precise histological lesions found in dogs were periglomerular lamellar fibrosis and inflammatory infiltration of the glomeruli with macrophages and neutrophils and glomerular basement membrane (GBM) splitting, with variable degree of interstitial nephritis.[1,2] Renal histological examination showed much the same pattern in our patient, with glomerular inflammatory infiltration with polymononuclear cells, GBM double contour, and tubulitis, along with mild interstitial edema and interstitial inflammatory infiltration with lymphocytes and polymorphonuclear cells. Immunohistochemical findings in our patient (pronounced irregular deposits of C3 along the GBM, restricted IgM and IgG deposits along GBM) also paralleled those of the dogs.

Circulating immune complexes were detected in serum of our patient, and the rest of the clinical syndrome that our patient developed over time also was suggestive of an immune-complex mechanism. Immune-complex mechanism is engaged in the pathogenesis of GBS, and this also provides the rationale for treatment with plasmapheresis and immunoglobulins. It is interesting that a case of GBS complicating a child with serological evidence of infection caused by *B burgdorferi* has been reported,[6] and GBS is reported as a possible cause of MPGN (through a supposed "Guillain-Barré infectious agent").[7] The acoustic mononeuritis and serositis that appeared during the course of the *B burgdorferi* infection in our patient and their rapid remission with corticosteroid treatment also speak for an immunologic disorder. The prominent high rheumatoid factor levels also are suggestive of immunostimulation caused by the infection and compatible with the immune-complex pattern of the clinical syndrome (MPGN, GBS, acoustic mononeuritis). Rheumatoid factors are anti-IgG autoantibodies, usually of IgM type, which is the characteristic finding of seropositive arthritides, most commonly rheumatoid arthritis. However, they sometimes also are encountered in the absence of rheumatoid arthritis, as in our patient, and, in these cases, most often repeated or chronic infections, it signifies stimulation of the immune system versus self-antigens.[8]

Initially, the immune response in Lyme disease seems to be suppressed, which may be an important mechanism in allowing the spirochete to disseminate. However, within several weeks, peripheral-blood mononuclear cells of patients begin to have heightened responsiveness to *B burgdorferi* antigens or mitogens. The specific IgM response peaks between the third and sixth week of infection and often is associated with polyclonal activation of B cells, including elevated total serum IgM levels, circulating immune complexes, and cryoglobulins. The specific IgG response develops gradually over

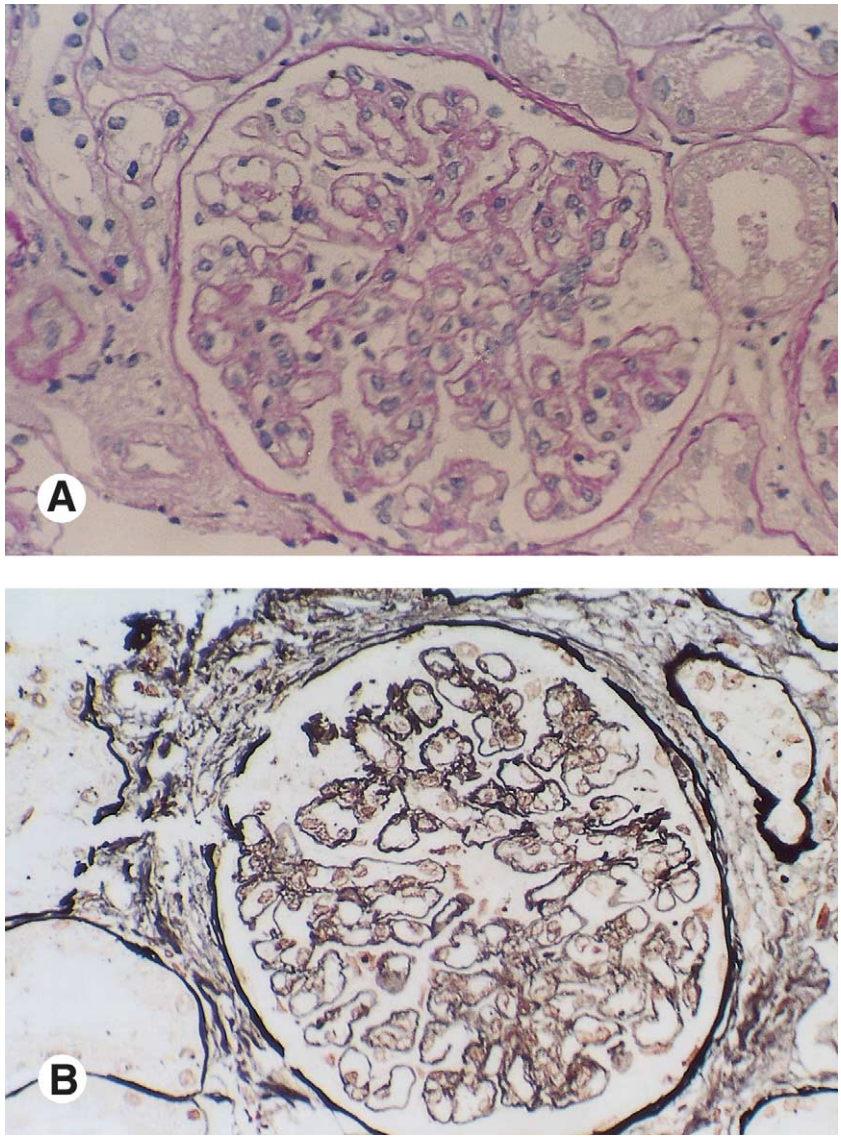

Fig 3. Histological examination of a specimen from the second renal biopsy shows (A) MPGN in remission: mild mesangial hypercellularity and localized capillary wall thickening with focal double contour pattern. (Periodic acid–Schiff; original magnification ×400.) (B) Silver stain shows double contour of capillary basement membranes and mild periglomerular fibrosis. (Silver methenamine; original magnification ×400.)

months to an increasing array of spirochetal polypeptides and nonprotein antigens. Immune antibodies are required for the immune-mediated killing of spirochetes by the classical complement pathway.[4] However, serum immunoglobulin levels were not high in our patient, and this could be attributed to their intense consumption in immune complexes in active renal inflammation, as well as to corticosteroid treatment that the patient already had been administered. This finding, along with the finding that in *B burgdorferi* infections, complement levels are normal or increased, also could explain that C3 and C4 levels were near the lower normal values and not really low. Furthermore, immunostimulation is evidenced by false-positive results for CMV IgM, HBsAg, and antistreptolysin titers at some time during the course of the disease. These results intrigued serious diagnostic dilemmas initially, but in the end, the history, clinical presentation, and more specific examinations allowed us to discriminate the false positivity of these tests (CMV DNA PCR, negative; hepatitis B virus DNA PCR, negative; blood and sputum cultures, negative; antistreptolysin titers, intermittently negative), which also has been reported in other cases of immunologically mediated diseases.[9]

The protracted course of acute renal failure,

which is exceedingly rare in postinfection glomerulonephritis, was impressive and urged us to perform the second renal biopsy. Acute tubulointerstitial nephritis on the grounds of the sclerotic tubulointerstitial and glomerular lesions of the senile kidneys obviously was implicated in the protracted renal dysfunction. Moreover, hemodialysis treatment itself in the setting of acute renal failure might have been a hemodynamic burden on renal function. However, we believe the impressively fruitful results of combined therapy against the infection and immunostimulation advocate the hypothesis that continuous immunostimulation and immune-complex formation by the persistent infection might have acted in concert with other strenuous factors toward the prolonged course of renal dysfunction. Similarly, the 2 full courses of antibiotic therapy that the patient had received earlier failed to detain additional clinical exacerbations of the disease, which probably suggests the involvement of immunologic mechanisms in the progression of the multisystem syndrome, rather than an intractable infection.

According to the Centers for Disease Control and Prevention in the United States, the diagnosis of Lyme disease is based primarily on the presence of a characteristic clinical picture, exposure in an endemic area, and an elevated antibody response to *B burgdorferi*.[10] Although a tick bite is not a prerequisite for the diagnosis, exposure history is key in guiding appropriate serological testing. Culture of the spirochete from patient specimens permits a definitive diagnosis, but in most instances, this procedure has yielded positive results only in patients with erythema migrans skin lesions. Similarly, it often is difficult to find spirochetes in histological sections. Although serological testing in Lyme disease can be performed with a high degree of sensitivity and specificity, testing is not standardized. Thus, false-negative and false-positive results, as well as interlaboratory differences in results, have been a considerable problem. False-positive test results have been associated with infectious endocarditis, infectious mononucleosis, CMV infection, rheumatoid arthritis, systemic lupus erythematosus, and other spirochetal disease, such as syphilis and periodontal disease, which were all excluded in our patient.

Serological tests currently available for use in this disorder include indirect enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay, antibody-capture immunoassay, and Western blotting or immunoblotting. Because antibody testing is associated with a high rate of false positivity and the symptoms under evaluation need not be related to active Lyme disease, careful clinical evaluation is the only means of determining whether clinical manifestations are related to the disease.[11,12] It is proposed that the combination of an ELISA for the detection of IgM and IgG anti–*B burgdorferi* antibodies and a Western blot to confirm the questionable ELISA results offers the greatest sensitivity and specificity for the laboratory diagnosis of Lyme disease at present. Moreover, serodiagnosis early in the infection is insensitive because the specific immune response in Lyme disease develops slowly. After antibiotic treatment, antibody titers decrease slowly, but most patients who had later manifestations of the illness remained seropositive for years. The production of new class-specific ELISAs with purified recombinant antigens of *B burgdorferi* seems promising.[13]

PCR for the detection of spirochetal DNA in patient tissue and fluid is promising, but not clinically validated. PCR has been used to amplify and detect *B burgdorferi* DNA in cultured spirochetes, *Ixodes dammini* ticks, infected animals, or patients with Lyme disease. However, the sensitivity of PCR determinations has not been as good in cerebrospinal fluid, blood, or urine samples. Thus, the value of PCR as a reliable diagnostic test is still being researched.[4] In the patient we present, we documented the clinical diagnosis of Lyme disease, which we made on clinical grounds (lower-extremity rash, general symptoms, arthralgias, postinfection MPGN, acoustic mononeuritis, GBS, myopericarditis pleuritis, the time sequence of clinical manifestation, and endemic area of origin) with the combined use ELISA for the detection of IgM and IgG anti–*B burgdorferi* antibodies and Western blot to confirm ELISA results, which is reported to be the approach that offers the greatest sensitivity and specificity for the laboratory diagnosis of Lyme disease. We stepped forward diagnostically with the search in blood for spiro-

chetal DNA with nested PCR after the results of the antibodies became available, at a time when the patient had already started antibiotic treatment, whereas previously he also had been administered courses of corticosteroids. We consider these factors important for the negativity of PCR, which is a method not yet clinically validated. Furthermore, we considered that serological test results for IgM became negative during follow-up at a time when all clinical manifestations of the disease were in remission.

The outcome of treatment in our patient has been excellent. After being dialysis dependent for 5 months, the patient regained most of his baseline renal function. Renal function improvement followed the treatment of *B burgdorferi* infection with intravenous ceftriaxone, which is the treatment of choice for *B burgdorferi* infections. Furthermore, we consider that plasmapheresis and immunoglobulin and corticosteroid therapy had a key role in renal function improvement, as well as in the impressive subsidence of GBS, acoustic mononeuritis, and myopericarditis, manifestations attributed to immune-complex formation secondary to the infection.

In conclusion, *B burgdorferi* is a possible cause of postinfection MPGN in humans, as well as in animals, presumably of immune-complex cause. Because of the protean and variable clinical manifestations of the disease and laboratory difficulties, the disease can evade diagnosis. It takes high clinical suspicion and very delicate laboratory investigation to avoid diagnostic problems. The clinical course of glomerulonephritis can be exceedingly protracted unless specific treatment is administered. The final outcome in the patient we present has been excellent.

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