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Nonproliferative Forms of Lupus Nephritis: An Overview

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INTRODUCTION

Kidney involvement in systemic lupus erythematosus (SLE), generally termed lupus nephritis, is a major contributor to SLE-associated morbidity and mortality. Up to 50% of SLE patients will have clinically evident kidney disease at presentation, and, during follow-up, kidney involvement occurs in up to 75% of patients, with an even greater representation among children and young adults.[1] Lupus nephritis has been shown to impact clinical outcomes in SLE both directly via target organ damage and indirectly through complications of therapy. Most of the attention paid to lupus nephritis, in the medical literature as well as in past and ongoing clinical trials, has primarily focused on proliferative forms of lupus nephritis. This review highlights the importance of recognizing and treating nonproliferative forms of lupus nephritis.

DISEASE PRESENTATION

Most patients with SLE will have laboratory evidence of kidney involvement at some point in their disease. In about one-third of SLE patients, kidney involvement first manifests with proteinuria and/or microhematuria on urinalysis; this eventually progresses to reduction in kidney function. Whereas the proliferative forms of lupus nephritis can sometimes present with renal dysfunction at the time of diagnosis, the nonproliferative forms of disease will most commonly manifest in low-level hematuria and varying degrees of proteinuria with preserved kidney function. Indeed, if a patient with a nonproliferative form of lupus nephritis presents with significantly reduced glomerular filtration rate, the clinician should suspect either long-standing undiag-nosed disease or a second form of renal injury (eg, diabetic kidney disease, focal segmental glomerulosclerosis [FSGS]) alongside the lupus lesion.

Many urine and serologic tests have been studied as biomarkers for SLE and, specifically, lupus nephritis disease activity. These tests include standard laboratory values used to

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assess patients with lupus nephritis, such as measurement of kidney function (creatinine and/or cystatin C), urinary abnormalities (proteinuria and urinalysis with microscopic sediment), and immunologic markers of disease activity, including antinuclear antibodies, anti-double-stranded DNA antibody, antiphospholipid antibody, anti-Smith antibody, and serum complement levels (C3, C4, CH50). In addition, ongoing research has aimed to identify novel biomarkers of lupus nephritis using molecules specific to lupus (eg, anti-C1q antibodies), mediators of chronic inflammation (eg, tumor necrosis factor-like weak inducer of apoptosis), and generalized markers of kidney injury (urinary neutrophil gelatinase–associated lipocalin).[2,3] However, no serum or urine disease markers are able to provide as much information as a kidney biopsy. Hence, virtually all patients with SLE with suspected kidney involvement undergo one or more kidney biopsies at some point during their care.

KIDNEY BIOPSY FINDINGS: DISTINGUISHING PROLIFERATIVE FROM NONPROLIFERATIVE LUPUS NEPHRITIS

The 2012 American College of Rheumatology (ACR) Guidelines for Screening, Treatment, and Management of Lupus Nephritis recommended that all patients with clinical evidence of active lupus nephritis, previously untreated, undergo renal biopsy so that glomerular disease can be accurately classified according to the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) classification.[4] Neither the ACR guidelines nor the guidelines put out 1 year earlier by the ISN provided specific parameters for what constitutes “clinical evidence” of active lupus nephritis.[5] Most centers, however, will recommend kidney biopsy for patients with SLE who have microscopic hematuria and proteinuria greater than 500 mg/d if renal function is preserved. The threshold to biopsy will often be lowered (eg, at any degree of proteinuria) if serum complement levels (C3 and/or C4) are depressed or if there is any evidence of renal dysfunction.

The classic pattern of lupus nephritis is an immune complex–mediated glomerulonephritis that usually demonstrates the following features: (1) glomerular deposits that stain dominantly for immunoglobulin G (IgG) with codeposits of IgA, IgM, C3, and C1q, the so-called full-house immunofluorescence pattern; (2) extraglomerular immune–type deposits within tubular basement membranes, the interstitium, and blood vessels; (3) the ultrastructural finding of coexistent mesangial, subendothelial, and subepithelial electron-dense deposits; and (4) the ultrastructural finding of tubuloreticular inclusions, which represent “interferon footprints” in the glomerular endothelial cell cytoplasm.

The ISN/RPS classification recognizes 6 different classes of immune complex–mediated lupus glomerulonephritis based on biopsy findings.[6] Class I represents the mildest possible glomerular lesion of immune deposits limited to the mesangium, without associated mesangial hypercellularity. In class II, the mesangial deposits detected by immunofluorescence and/or electron microscopy are accompanied by mesangial hypercellularity of any degree. In class III, there is focal and predominantly segmental endocapillary proliferation and/or sclerosis affecting less than 50% of glomeruli sampled. The active endocapillary lesions typically include infiltrating monocytes and neutrophils and may exhibit necrotizing features, including fibrinoid necrosis, rupture of glomerular

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basement membrane, and nuclear apoptosis. In class IV, the endocapillary lesions involve ≥50% of glomeruli sampled, typically in a diffuse and global distribution. Class V denotes membranous lupus nephritis. Subepithelial deposits are the defining feature, usually superimposed on a base of mesangial hypercellularity and/or mesangial immune deposits. In those patients with combined membranous and endocapillary lesions, a diagnosis of both class V and class III or IV is made. These mixed classes carry a worse prognosis than pure class V lupus nephritis. Class VI identifies advanced chronic disease exhibiting greater than 90% sclerotic glomeruli, without residual activity. Although there can be some degree of mesangial proliferation in class II cases, this review discusses the class I, II, and V lesions as examples of nonproliferative lupus nephritis.

CLASS I AND CLASS II LUPUS NEPHRITIS

Class I and class II lupus nephritis, which represent purely mesangial disease, carry a better prognosis than proliferative forms of lupus nephritis (ie, class III or IV) or the membranous form of lupus nephritis (ie, class V). In general, patients with class I and II lesions require no therapy directed at the kidney. Most patients will have good long-term renal outcomes, and the potential toxicity of any immunosuppressive regimen will negatively alter the risk-benefit ratio of treatment. An exception is the group of lupus patients with lupus podocytopathy (discussed later), who respond to a short course of high-dose corticosteroids in a fashion similar to patients with minimal change disease (MCD).

Optimal control of blood pressure through the renin angiotensin aldosterone system (RAAS) blockade is a cornerstone of conservative therapy in all forms of lupus nephritis and is the only required therapy for class I and class II lesions. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines recommend interruption of the RAAS with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers as first-line antihypertensive therapy in the management of proteinuric kidney diseases such as lupus nephritis.[7] These drugs decrease intraglomerular pressure, lower systemic arterial blood pressure, reduce urinary protein excretion, and delay the progression of chronic kidney disease to end-stage renal disease.[8–10] A report from the Lupus in Minorities: Nature versus Nurture cohort suggests that ACE inhibitor use delays the development of renal involvement in SLE.[11] Eighty of 378 patients (21%) in the cohort used ACE inhibitors. The probability of renal-involvement-free survival at 10 years was 88% for ACE inhibitor users and 75% for nonusers ($P = .01$), and by multivariable Cox proportional hazards regression analyses, ACE inhibitors use was associated with a longer time-to-renal involvement occurrence (hazard ratio 0.27; 95% confidence interval [CI] 0.09–0.78). ACE inhibitor use was also associated with a decreased risk of disease activity (hazard ratio 0.56; 95% CI 0.34–0.94).

The RAAS, and its pharmacologic blockade, may play a role in the pathogenesis and prognosis of SLE independent of its effects on systemic blood pressure and glomerular hemodynamics. Several animal studies have highlighted the inflammatory components of the RAAS and the potential benefits of RAAS blockade in reducing or eliminating this inflammation in lupus nephritis.[12] De Albuquerque and colleagues[13] treated lupus-prone mice with captopril and found that captopril treatment delayed the onset of proteinuria

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when administered to prenephritic mice and slowed disease progression in mice with early and advanced nephritis. These results were not seen in a control group treated with verapamil. The ACE inhibitor–induced improvement in renal disease correlated with reduced transforming growth factor (TGF)-β expression, particularly of the TGF-β1 and TGF-β2 isoforms, in the kidneys. Moreover, in vivo or in vitro exposure to captopril reduced splenic levels of interleukin-4 (IL-4) and IL-10, suggesting an effect of captopril on the immune system of treated animals. In an experiment on the effect of aldosterone blockade on the development and progression of glomerulonephritis in a murine model of lupus, spironolactone significantly reduced the incidence of nephrotic range proteinuria and, on histology, showed far less severe glomerular injuries (no crescents, diminished overall cellularity, and less prominent deposits in the capillary loops and mesangium) compared with controls.[14] The investigators found significant differences in anti–single-stranded DNA and anti–double-stranded DNA antibody levels between control mice and mice treated with spironolactone by 36 weeks of age, again highlighting a potential anti-inflammatory, immune-mediating component of RAAS blockade.

Importantly, lupus nephritis classes are not static entities and may transform from one class to another, both spontaneously and after therapy, and influence treatment decisions. In a review of more than 700 patients with lupus nephritis who underwent repeat biopsies during their disease courses, performed on average at 3.0 years after the initial biopsy, 52.6% of cases demonstrated some form of class switching.[15] This phenomenon of class switching is particularly important for patients whose biopsies show class I or class II lesions and have been maintained on conservative therapy alone. In 9 studies encompassing 519 lupus patients with repeat renal biopsies, the rate of class switching in patients with class I or class II lesions on their initial biopsies was 70% when a repeat biopsy was performed: 54% transforming into a proliferative (ie, class III or IV) lesion, 4% evolving into a pure class V membranous lesion, and 12% manifesting a mixed proliferative and membranous pattern.[15–23] This class switching is crucial to recognize because it may move a patient from a low-risk group that does not require immunosuppressive therapy to a high-risk group that does warrant renal-directed immunosuppression. Therefore, patients with class I or II lesions who manifest increased proteinuria and/or renal dysfunction despite effective use of RAAS blockade should be targeted for repeat biopsies.

LUPUS PODOCYTOPATHY

In 2002, Dube and colleagues[24] and Hertig and colleagues[25] described small series of patients with SLE, nephrotic syndrome, and biopsy findings of MCD or FSGS. Eight of 18 patients in these reports had mesangial deposits, including 7 of 11 with MCD and 1 of 7 with FSGS, consistent with concurrent mesangial lupus nephritis (ie, class I or II lesions). The patients with MCD universally showed rapid remission of nephrotic syndrome with steroid therapy; the response to steroids was inconsistent in patients with FSGS lesions. In 2005, Kraft and colleagues[26] reported 8 additional patients with SLE, nephrotic syndrome, and light microscopic findings of MCD, FSGS, or mesangial proliferative glomerulonephritis. These investigators argued that the development of nephrotic range proteinuria in patients with SLE without subendothelial or subepithelial immune deposits on biopsy is more likely a manifestation of SLE than the coexistence of idiopathic MCD/FSGS

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and SLE. The term lupus podocytopathy thus arose to describe these lesions as part of the lupus nephritis spectrum.

More recently, Hu and colleagues[27] presented 50 patients classified as having lupus podocytopathy, culled from a 14-year biopsy registry (2000–2013) and representing 1.3% of all lupus nephritis biopsies read at Nanjing University during this time period. Thirteen patients had normal light microscopy findings; 28 showed mesangial proliferative changes, and 9 had FSGS lesions. Forty-seven of the 50 patients had mesangial immune deposits as confirmed by immunofluorescence and electron microscopy. All of the patients had full nephrotic syndrome. This series, the largest cohort of lupus podocytopathy, provided representative data on clinical presentations, treatment responses, and relapse rates in patients with this entity. For example, the remission rate with immunosuppression of 94% was not altogether surprising on the basis of prior series, but the median time to remission of 4 weeks added a new layer of important, clinically relevant information. Response and relapse rates differed among the histologic subtypes: all of the patients with MCD and 27 of the 28 patients with mesangial proliferative changes responded, whereas nonresponders were disproportionately high in the FSGS subgroup. As with podocytopathies not associated with SLE, relapse rates were high (56%) and did not differ by histologic pattern. Therefore, many of these lupus podocytopathy patients will require multiple rounds of immunosuppression for relapses, and the use of steroid-sparing agents, such as mycophenolate mofetil (MMF), calcineurin inhibitors, cyclophosphamide, and rituximab, may need to be used in the same way these agents are used in frequently relapsing forms of steroid-sensitive MCD and FSGS.

A finding that emerged in virtually every case series of lupus podocytopathy is that morphologic findings of FSGS are associated with a distinctly worse prognosis. In the series from Hu and colleagues,[27] patients with FSGS compared with those with MCD or mesangial proliferative changes had higher rates of hypertension and acute kidney injury on clinical presentation and more severe tubulointerstitial involvement on biopsy. In follow-up, not only were the patients with FSGS less likely to respond to therapy, but also, when responses did occur, the remissions happened later, at a median of 8 weeks compared with 4 weeks for the MCD and mesangial proliferative subgroups. These observations raise the question of whether it is appropriate to use the same umbrella term of lupus podocytopathy for all 3 of these patterns of glomerular injury.

The ISN/RPS classification of lupus does not include lupus podocytopathy. A 2016 paper[28] proposed fairly simple criteria to diagnose lupus podocytopathy: (1) clinical presentation of full nephrotic syndrome in a patient with SLE, (2) diffuse and severe foot process effacement, and (3) the absence of subendothelial or subepithelial immune deposits. Mesangial deposits and mesangial proliferation were not part of the criteria. If these findings are present, then the additional diagnosis of mesangial proliferative lupus nephritis (ie, class II) is merited. If mesangial deposits are not accompanied by mesangial proliferation, the diagnosis of minimal mesangial lupus nephritis (class I) is given. In this manner, the classic forms of immune complex–mediated lupus nephritis are separated from lupus podocytopathy, with a willingness to diagnose both in the appropriate situation, and the need for a mesangial proliferative category of lupus podocytopathy is avoided. Lupus podocytopathy was also subdivided into patients who would otherwise meet criteria for

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MCD or FSGS, including the morphologic subtypes of FSGS (collapsing, tip lesion, and so forth).

CLASS V LUPUS NEPHRITIS

Class V, or membranous, lupus nephritis is defined by subepithelial immune deposits. The membranous alterations may be present alone or on a background of mesangial hypercellularity and mesangial immune deposits. In the past, reports have varied regarding renal survival rates for different populations with membranous LN. These differences were, in part, due to problems with the World Health Organization (WHO) classification of lupus nephritis, which included proliferative lesions superimposed on pure lupus membranous nephropathy (WHO class Vc and Vd) along with those with only predominantly pure membranous features (Va and Vb).[6] With the updated ISN/RPS classification, a distinction was clearly made between pure class V lesions and mixed proliferative and membranous cases (III + V or IV + V lesions). The latter follows a much more aggressive course, and treatment generally should focus on the proliferative component (discussed later). In contrast, patients with pure membranous lupus nephropathy, especially when proteinuria remains in the subnephrotic range, often do extremely well regardless of treatment options and may not require any specific therapy beyond RAAS blockade.

Most treatment regimens studied for pure class V lupus nephritis with nephrotic range proteinuria have been based on successful therapies used for primary membranous nephropathy. For example, Austin and colleagues[29] randomized 42 patients with membranous lupus nephritis to 3 groups: cyclosporine for 11 months (on top of steroids), alternate-month intravenous pulse cyclophosphamide for 6 doses (also on top of steroids), and alternate-day prednisone alone. At 1 year, the cumulative probability of remission was 27% with prednisone, 60% with cyclophosphamide, and 83% with cyclosporine. Remissions occurred more quickly in the cyclosporine group, but there were fewer relapses in the cyclophosphamide group.[30] Similar data are available from small numbers of patients treated with tacrolimus monotherapy.[31–34] Two large trials of MMF versus intravenous cyclophosphamide induction in lupus nephritis,[35,36] conducted primarily in patients with proliferative lesions, included 84 (of total 510) patients with pure membranous lesions. In a pooled analysis of these participants, remissions, relapses, and overall clinical course were similar in the membranous patients treated with oral MMF and intravenous cyclophosphamide induction therapy.[37] Therefore, the 2012 ACR guidelines for Screening, Treatment, and Management of Lupus Nephritis allowed for MMF as first-line immunosuppression for patients with class V lupus nephritis requiring immunosuppression due to nephrotic range proteinuria and/or declining renal function.

The data supporting the use of other immunosuppressive agents are less robust. Rituximab and abatacept have been used off-label for pure class V lesions based on post hoc analyses of studies that included both proliferative and nonproliferative cases of lupus nephritis with higher response rates in patients with nephrotic range proteinuria.[38,39] There has also been renewed interest in calcineurin inhibitor use in patients with class V lupus nephritis based on the early results with the novel calcineurin inhibitor, voclosporin. In a phase 2 study, whose results were presented in abstract form, voclosporin (at low and high doses added on top

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of background steroids and MMF) yielded complete remission rates at 48 weeks between 40% and 49% compared with a 24% complete remission rate in control group patients treated with steroids and MMF alone. This drug is now being evaluated in a larger phase 3 study with planned enrollment exceeding 300 patients (clinicaltrials.gov identifier NCT 03021499).

MIXED PROLIFERATIVE AND NONPROLIFERATIVE LUPUS NEPHRITIS

Some patients with lupus nephritis will have evidence of endocapillary proliferative disease, fulfilling criteria for either class III or class IV lesions, as well as a membranous nephropathy pattern of glomerular basement membrane thickening due to subepithelial deposits, fulfilling criteria for class V disease. These mixed cases should be classified as III + V or IV + V, and the treatment is usually dictated by the proliferative lesion. Therefore, first-line therapy will generally be a combination of steroids with cyclophosphamide or MMF for induction therapy, followed by MMF for maintenance therapy.

Another induction treatment strategy studied in small settings is to combine a calcineurin inhibitor with MMF plus corticosteroids. This multitargeted immunosuppressant regimen is akin to those used in protecting kidney transplants. For example, Bao and colleagues[40] randomized 40 patients with diffuse proliferative LN superimposed on membranous LN (ISN class IV + V) to induction therapy with MMF, tacrolimus, and steroids (multitarget therapy) or intravenous cyclophosphamide plus steroids. Intention-to-treat analysis revealed a higher rate of complete remission with multitarget therapy at both 6 and 9 months (50% and 65%, respectively) than with cyclophosphamide (5% and 15%, respectively). Adverse events were lower in the multitarget group, too. In a subsequent report using a much larger patient population drawn from 26 nephrology centers across China, this multitarget therapy at 24 weeks, compared with cyclophosphamide-based induction, showed higher rates of complete (46% vs 26%) and complete plus partial (84% vs 63%) remission. The median time to overall response was shorter in the multitarget group as well.[41]

Recently, these investigators have reported an open-label, multicenter study for 18 months to assess the efficacy and safety of multitarget maintenance therapy in patients who had responded at 24 weeks during the induction phase.[42] Those induced on multitarget therapy (N = 116) remained on low-dose MMF, tacrolimus, and prednisone, whereas those induced with cyclophosphamide (N = 90) were given azathioprine plus prednisone. The multitarget and azathioprine groups had similar cumulative renal relapse rates (6% vs 8%, respectively), and serum creatinine levels remained stable in both groups. The azathioprine group had more adverse events (44% vs 16% for multitarget therapy). The caveats for both the induction and the maintenance phase of these multitarget therapy studies include (a) whether they will be generalizable beyond Asian populations of lupus nephritis and (b) whether the remission rates achieved will be sustained once calcineurin inhibitors are weaned off, given the high rate of proteinuria relapse when calcineurin inhibitors have been stopped in other glomerular diseases.

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SUMMARY

The approach to patients with class I, II, and V lesions of lupus nephritis requires an understanding of the unique nature of each of these lesions as well as the possibility that, over the course of disease, class switching may occur. Conservative, nonimmunomodulatory therapy is sufficient for all patients with class I and II lesions and for patients with class V lesions, preserved renal function, and nonnephrotic range proteinuria. For patients who require kidney-targeted immunosuppression, MMF is the current mainstay of therapy, but a variety of other treatment options, ranging from multitargeted therapy to novel agents under investigation, are available for patients whose disease courses stray outside the conventional parameters.

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KEY POINTS

- Class I and class II lupus nephritis do not require immunosuppressive therapy but are prone to class switching to more aggressive lesions. A low threshold for repeat biopsy should be used in these patients.
- Class V lupus nephritis with preserved renal function and subnephrotic proteinuria usually has a good prognosis and can be treated conservatively with blockade of the renin angiotensin aldosterone system.
- If immunosuppressive therapy is warranted for class V lupus nephritis, as with proliferative lupus nephritis, mycophenolate mofetil has emerged as the most commonly used first-line therapy.