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PAPER

Clinical presentation and monitoring of lupus nephritis

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The diversity of clinical presentations of lupus nephritis parallel the diversity of pathologic lesions seen in the kidneys of patients with SLE. Renal manifestations range from asymptomatic hematuria or proteinuria to overt nephritic and nephrotic syndromes, rapidly progressive glomerulonephritis, and chronic renal failure. Subclinical nephropathy both during presentation and during monitoring of disease activity is frequently missed because of the notorious unreliability of routine screening urinalyses performed in high-throughput clinical pathology laboratories. Requisitions for urine microscopy should be flagged for special attention in patients at risk for lupus nephritis. Depression of classic complement pathway components and high titers of anti-DNA, anti-nucleosome, or anti-C1q antibodies identify patients are increased risk of renal involvement or flares of nephritis. Several disease activity and damage indexes are available, but they are mostly used in clinical research setting and none has achieved wide use for standard clinical practice. *Lupus* (2005) **14,** 25–30.

Key words: lupus nephritis; lupus serologies; renal function; urine sediment

Introduction

It is well recognized that renal involvement contributes substantively to the morbidity of patients with systemic lupus erythematosus (SLE). While in modern times patients rarely die directly from uremia or lack of access to renal replacement therapies, early treatment of lupus nephritis and prevention of end stage renal disease are important objectives in management of patients with SLE. Major morbidity and premature death due particularly to cardiovascular complications are the results of the pathophysiology of several components of lupus nephritis, including protracted nephrotic syndrome, hypertension, renal failure and opportunistic infections.

The diligent clinician will be mindful that there are many variations in the clinical manifestations and pathologic appearances of lupus nephritis. It is imperative that clinicians who undertake the care of patients with SLE have an in-depth knowledge of the diverse clinical and pathologic manifestations of lupus renal disease. This is particularly important because the presenting features of lupus nephritis may be subtle and, if unattended, may result in the silent acquisition of irreversible renal damage. Effective treatment depends on recognition of early phases of renal disease, prior to the stages of nephron scarring, tubular atrophy and interstitial fibrosis.[1,2]

Criteria for diagnosis of lupus nephritis

Certain forms of renal involvement contribute to the diagnosis of SLE according to the widely accepted criteria of the American College of Rheumatology.[3] The criterion for diagnosis of a renal disorder includes the presence of: a) persistent proteinuria of greater than 0.5 g per day (or greater than 3+ urine dipstick reaction for albumin), or b) cellular casts, including red blood cell, hemoglobin, granular, renal tubular cell, or mixed. These elements are important in classification of SLE, particularly as inclusion criteria for patients in being considered for clinical research studies. It must be emphasized that, while these laboratory criteria define the minimal criteria for diagnosis of kidney disease, there are many other clinical features which are important in the management of lupus nephritis.[4,5]

Clinical syndromes and laboratory manifestations

To ascertain early renal involvement, patients with known or suspected diagnosis of SLE should undergo

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urinalysis screening at regular intervals because the onset of lupus nephritis is frequently asymptomatic. Patients should be queried about foamy urine or onset of nocturia both of which may be early signs of glomerular or tubular dysfunction. Foamy urine suggests substantial proteinuria. Both symptoms warrant further evaluation by urinalysis and renal function tests.[6] Microscopic hematuria is mostly discovered by screening urinalysis. Macroscopic hematuria is relatively rare; it usually indicates very severe renal involvement and warrants expedient assessment of renal function and quantification of proteinuria. Rapidly progressive glomerulonephritis (RPGN) is defined as doubling of serum creatinine within a three-month period, usually in the context of proliferative glomerulonephritis, fibrinoid necrosis and cellular crescents in the renal biopsy.

Proteinuria is primarily a reflection of the extent of involvement of peripheral glomerular capillary loops. Thus, the degree of proteinuria tends to increase incrementally within the classes of mesangial to focal proliferative to diffuse proliferative lupus nephritis; membranous nephropathy, which by nature involves essentially all glomerular capillary loops, is characteristically accompanied by heavy proteinuria. Nephrotic range proteinuria is defined as proteinuria greater than 3.5 g per day; this degree of proteinuria usually causes the nephrotic syndrome which includes hypoalbuminemia, hyperlipidemia and, in the absence of diuretic therapy, peripheral edema.

Renal failure, by convention, refers to loss of glomerular filtration function. In SLE, renal failure is primarily caused by the hypercellularity and inflammation within the glomerulus, though nephrotoxic drugs and other prerenal and postrenal causes of azotemia should always be considered. Sudden, acute renal failure is exceptional; rapidly progressive renal failure (RPGN as defined above) occurs in a small fraction of lupus patients. Mostly, renal function fluctuates in parallel with remissions and exacerbations of lupus nephritis; chronic renal insufficiency results from cumulative damage and loss of nephrons, ultimately producing end-stage renal disease (ESRD). Renal tubular dysfunctions, such as impaired urine concentrating ability and renal tubular acidosis, are rarely clinically significant or demanding of therapy.

Urinalysis

Examination of urine is one of the most important and effective methods to detect and monitor the activity of lupus nephritis.[7] There are no universally accepted or easily applicable standards for urinalysis testing; patients present for urine testing under widely diverse circumstances, including differences in fluid intake, urine concentrating ability, urine pH, and level of renal function. Early morning, midstream, clean catch urine samples (preferably the second voiding of the day but obtained while the patient is still fasting) are recommended in order to ensure reasonably concentrated and acidic urine specimens. Dipstick tests generally give reliable results; however, vitamin C supplements may produce false-negative dipstick reaction for blood, which emphasizes the need for complementary microscopic analysis of the urine sediment. Given the fact that the prototypical lupus patient is both young and female, the clinician should resist the all too common mistake of discounting hematuria as being due to menstrual bleeding. It is recommended to perform urinalysis three or more days prior to or after cessation of menstrual periods.

The urine specimen must be processed expeditiously, lest the urine sediment deteriorates. Bacterial overgrowth in unattended urine specimens may render the urine alkaline, which in turn causes rapid deterioration of urinary casts. The urine specimen should not be refrigerated in order to avoid precipitation of crystals which greatly interferes with microscopic analysis.

Given the importance of finding cellular casts for diagnosis and monitoring lupus nephritis, we use 50 mL (which is larger than the conventional volume of 10 mL) of urine for preparation of urinary sediments. The decanted pellet of sediment is stained with one drop of Sedi-Stain© (Bectin–Dickinson, Franklin Lakes, New Jersey, USA). Using this large volume technique, we have set the threshold for clinically significant microscopic hematuria at >10 RBC per high power field (equivalent to ≥ 3 RBC per high power field if prepared from a 10 mL aliquot of urine). We consider that this method improves the chances of detecting cellular casts which are arguably among the most critical elements in defining the activity of lupus nephritis.

The morphology of urinary red blood cells helps to distinguish upper and lower urinary tract disorders. Dysmorphic (mis-shapen, fragmented) erythrocytes indicate inflammatory glomerular or tubulointerstitial disease, while monomorphic (normal) erythrocytes indicate bleeding in the lower tract (e.g., infection, urolithiasis, tumors). Erythrocytes, leukocytes, renal tubular epithelial cells are separately counted. Polarized light is used to detect free fat (doubly refractile fat bodies) and oval fat bodies (renal tubular epithelial cells containing fat droplets); lipiduria results from abnormal glomerular permeability to lipoproteins and possibly tubular epithelial cell injury caused by resorption of 'toxic' filtered proteins. Granular and fatty casts reflect proteinuric states; erythrocyte, leukocyte, and mixed cellular casts reflect inflammatory (nephritic) states; broad and waxy casts reflect chronic renal failure.

A 'telescopic' urine sediment contains the full range of cells and cast elements; it reflects elements of global nephron (glomerular and tubular) dysfunction with ongoing active disease superimposed on chronic renal - damage.

Accurate urinalysis requires careful and expeditious processing of the urine sample, good quality control procedures, and experienced personnel. It is important to remember that community-based clinical pathology laboratories for various reasons are frequently unable to identify pathologic casts in urinary sediment.[8] This undoubtedly stems in part from the high volume throughput of urine samples for general screening purposes. There are two recommended approaches to optimizing the accuracy of urinalysis. First, the clinician should 'flag' urine specimens from patients at substantial risk of lupus nephritis. Second, the clinician should, whenever feasible, personally review (and verify) the results of the findings from microscopic urinalysis.

Proteinuria

Proteinuria is a cardinal feature of renal parenchymal disease and may indicate glomerular or tubular pathology. Timed collection of urine protein (usually over 24 hours and in conjunction with measurement of creatinine clearance) represents the gold standard. However, test-to-test variability in proteinuria is common; this is mostly due to collection errors and differences in physical activity (bed rest tends to reduce and heavy exercise tends to increase proteinuria). Creatinine excretion, which should be nearly constant in a given patient, is an excellent method to judge the adequacy of timed urine collections. Replication of values of protein excretion rate is important before conclusions are drawn that clinically significant changes in proteinuria have occurred. We generally obtain three 24-hour urine collections to document average basal proteinuria and creatinine clearance before initiating treatment.

Spot urine protein/creatinine ratio has been increasingly widely adopted as a simpler method than 24-hour timed urine collections to estimate the degree of proteinuria. The numeric ratio of protein and creatinine concentrations approximates the number of grams per day of proteinuria. This method has steadily gained wider application due to its simplicity and convenience, for glomerular diseases in general[9] and lupus nephritis in particular.[10]

Urine protein electrophoresis is of limited importance and rarely performed as part of the standard evaluation of the patient with known lupus nephritis. Proteinuria is usually of glomerular origin and unselective (mirroring serum protein concentrations). Isolated tubular proteinuria (nonalbumin) is rare. Measurement of microalbuminuria (30–300 mg/day) has not been thoroughly investigated but is generally not considered as standard screening test in patients with suspected lupus nephritis.

Reduction in proteinuria is an important measure of favorable response to treatment in lupus nephritis.[11–13] Complete remission of abnormal proteinuria is defined as return to completely normal levels (i.e., <0.2 g per day, or urine protein/creatinine ratio <0.2). Partial remission of proteinuria is commonly defined by urine proteins of <0.5–1.0 g per day, or urine protein/creatinine ratio <0.5–1.0. Proteinuria may persist after remission of glomerular disease; this is referred to as 'fixed' proteinuria due to irreversible damage to glomerular capillaries.

Renal function tests

Glomerular dysfunction is usually more prominent and clinically important than tubular dysfunction in lupus nephritis. Serum creatinine is the most widely used screening test to detect abnormalities of glomerular filtration. It is important to recognize that the normal range of serum creatinine is rather wide and that the relationship between serum creatinine and creatinine clearance, as a surrogate for glomerular filtration rate (GFR), must be determined for individual patients. Serum creatinine is affected not only by GFR, but also by age and muscle mass. Several nomograms are available which quite reliably predict GFR from serum creatinine, age, race, gender and size of the patient.[6] Some clinical laboratories in the United States and Europe have adopted the practice of reporting calculated GFR as a supplement to the reporting of serum creatinine measurement. This growing practice should help identify patients with impaired renal function when serum creatinine falls within the reference range for this screening test.

Measures of true GFR (e.g., inulin, DTPA clearance), renal plasma/blood flow (e.g., para-aminohippurate, PAH, clearance) and filtration fraction (ratio of GFR to renal plasma flow) are sometimes used to enhance the accuracy and precision of measurement of changes in renal function. Because these tests are very labor intensive, expensive and may involve radionuclides, they are seldom used outside the research setting.

Monitoring patients with lupus nephritis

Selected serologic tests may be useful for monitoring activity of lupus nephritis and in guiding treatment. While antinuclear antibodies (ANA) are cardinal markers for diagnosis of SLE, titers of these antibodies are not useful in gauging either the severity or the activity of lupus nephritis. Anti-DNA antibodies correlate better with both type and activity of lupus

nephritis.[14] Anti-DNA antibodies occur more frequently and in higher titers in proliferative (Class III or IV) than in membranous (Class V) nephropathy. However, there are many exceptions to this rule. High titers of anti-DNA can occur in patients with little nephritis and severe nephritis can occur in patients with no or low-titers of anti-DNA antibodies.

In general, changes in anti-DNA titers are more valuable clinically than are the absolute levels of these autoantibodies. Rising anti-DNA titers are true harbingers of exacerbation of lupus nephritis.[15] However, we do not consider the correlation to be strong enough to recommend pre-emptive treatment for isolated changes in anti-DNA titers. Patients with only rising titers of anti-DNA warrant intensified monitoring for evidence of clinical signs of lupus flares. Other autoantibodies, such as anti-nucleosome and anti-C1q, are under study for assessment of their use in monitoring activity of lupus nephritis.[16]

Monitoring serum complement components has been considered to be useful in management of lupus nephritis. However, there are ongoing controversies about whether levels of complement components correlate reliably with disease activity or are useful predictors of renal flares.[17] While falling levels of C3 and/or C4 complement components usually predict impending flares of lupus nephritis, the historical practice of using serum complement levels to guide the level of ongoing treatment has been largely abandoned. At the present time, patients with either rising anti-DNA antibodies and/or falling complement levels should be compulsively monitored for other early clinical signs of activity at which point pre-emptive treatment should be promptly instituted.

Other laboratory parameters for monitoring lupus nephritis have been examined in the research setting. Measurement of circulating immune complexes (by a wide range of tests) has generally been abandoned as an ineffective method of monitoring patients with SLE or lupus nephritis. Measurements of the complement activation fragments, complement receptors and late complement membrane attack complex, C5b-9, have been suggested as methods for monitoring disease activity. Experimental studies have also suggested that plasma and urinary cytokines (e.g., interleukin-6) or their receptors (e.g., interleukin-2 receptors) may predict lupus activity, but these tests are not generally available in the clinic at the present time.

Remission

There are no universal criteria for remission of lupus nephritis. Whether it would be useful to distinguish partial and complete remissions has not been thoroughly studied. However, it is evident in reading the literature that there is great ambiguity about the concepts of remission. Until consensus is formed on clinically validated definitions of remission, there will be wide variations in descriptions of the natural history of lupus nephritis.

Currently, the notion of partial remission of lupus nephritis is important in deciding the transition from induction therapy to maintenance therapy. In severe lupus nephritis, we think there is reasonable justification to move from induction therapy to maintenance therapies if there is partial remission (i.e., objective improvement in urine sediment and renal function). However, we do not believe that partial remission should be accepted as a criterion to discontinue cytotoxic drug therapy unless there are attendant contraindications. Our studies found a very high rate of relapse with early discontinuance of cytotoxic drug therapy and we would continue therapy for several months after complete remission of lupus nephritis.

In proliferative lupus nephritis, we define complete remission as clearing of cells and casts from the urine sediment, reduction of proteinuria to <1 g per/day, inactive extrarenal disease and, ideally, normalization of lupus serologic tests (complement components and anti-DNA). One should be aware that a substantial minority of patients may not achieve a complete remission after even many months of immunosuppressive drug therapy. We generally continue maintenance therapy for one year beyond complete remission as the best method of reducing risk of relapse of lupus nephritis. It is noteworthy that antinuclear antibodies (ANA) become negative in a tiny fraction of patients, including those in sustained clinical remission. Hence, we would not use the ANA in defining remission or making decisions about discontinuing treatment.

A small portion of patients develop 'fixed proteinuria' as a result of severe, irreparable injury to glomerular basement membranes. Proteinuria of this cause is usually <2 g/day, but occasionally may be in the nephrotic range. In a patient with otherwise quiescent SLE and lupus nephritis (by clinical, serological and urine sediment criteria), it may be difficult to define fixed proteinuria of a nonimmunologic cause without a renal biopsy. The typical biopsy shows marked thickening and lucency of glomerular basement membranes without substantial immune complex deposits. Failure to recognize persistent proteinuria in this context can lead to over treatment of patients and needless exposure to serious toxicities.

Relapse

One of the most perplexing aspects of the natural history of lupus is its remitting and relapsing course.

Modern treatment neither cures lupus, nor completely prevents exacerbations. Furthermore, each major exacerbation of lupus nephritis is expected to leave residual and cumulative irreversible (often subclinical) renal damage. The more episodes of relapse, the greater is the likelihood of irreversible damage and progression to permanent renal failure.

Exacerbations of lupus nephritis can emerge from a state of partial remission (improvement from initial baseline disease activity) or from a state of complete and sustained remission. Approximately one-third to one-half of patients have a relapse of nephritis after achieving partial or complete remission of proliferative lupus nephritis. The relative risk of renal functional deterioration was much greater for nephritic flares than for proteinuric flares. Thus, nephritic exacerbations clearly have adverse effects on renal prognosis, while proteinuric exacerbations have much less prognostic importance. These observations argue in support of strategies to minimize probabilities of flares of nephritis.

Nephritic flares with modest increases in proteinuria (e.g., <2 g/day) and without concomitant rise in serum creatinine are usually managed without a renal biopsy and with an empiric trial of moderate dose prednisone (e.g., 0.5 mg/kg) for 4–6 weeks followed by gradual tapering. Failure to completely resolve within two months should prompt re-evaluation, possibly with information from repeat renal biopsy (particularly if activity of the urinary sediment is ambiguous), and consideration of cytotoxic drug therapy. With steroid-resistant nephritic flares, we usually re-cycle therapy using the same guidelines as proposed for initial immunosuppressive drug therapy.

Management of incipient flares of lupus nephritis is controversial. Some reports claim that rises of anti-DNA activity predict impending flares which could be averted by pre-emptive boosts in corticosteroid therapy,[19] but this approach is not widely accepted. While many agree with the general value of monitoring anti-DNA (or other serologic) activity, most clinicians would use this information as motivation to intensify clinical screening for supportive signs of lupus activity prior to boosting therapy.

Lupus disease activity and damage instruments

Several disease activity and end-organ damage assessment tools have been developed for use in SLE. Among those most commonly used for categorizing disease activity are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the Systemic Lupus Activity Measure (SLAM) and the British Isles Lupus Assessment Group (BILAG). The Systemic Lupus International Collaborating Clinics: American College of Rheumatology (SLICC/ACR) damage index is used to denote cumulative and mostly irreversible end organ damage. Generally, these instruments are used to facilitate selection and monitoring of patients for clinical research studies more often than for clinical practice, though the latter remains a desirable objective.[20,21]

A substantive shortcoming of these instruments arises from the fact that they attempt to capture the activity of all the system components of SLE. The instruments vary in style and purpose between those that attempt to capture disease activity based on the presence of absence of a clinical or laboratory abnormality (SLAM), to another which uses weighted scores of component activity at a particular point in time (SLEDAI), to one that focuses on changes in disease activity over time and their implications for therapeutic interventions (BILAG).

The BILAG is based on the principle of the clinician's intention to treat. Estimates of degrees of abnormalities are scored separately and are based on a checklist of defined abnormalities of blood pressure, urine sediment, proteinuria, renal function and pathology are used to indicate the urgency of indications for therapeutic intervention (described as: A, Disease that requires urgent action with disease modifying agents; B, Disease that demands close attention and/or minor therapeutic changes; and C, Disease that is static or inactive warranting little change). While none of these instruments is widely used in clinical practice, the BILAG (and its variations under development) has perhaps the most potential for practical utility in monitoring and treating patients with lupus nephritis.

References

1 Houssiau FA. Management of lupus nephritis: an update. *J Am Soc Nephrol* 2004; **15**: 2694–2704.
2 Balow JE, Boumpas DT, Austin HA III. Lupus Nephritis. In Brady HR, Wilcox CS eds. *Therapy in Nephrology and Hypertension.* 2nd edition. London: WB Saunders, 2003: 153–164.
3 Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271–1277. Updated criteria: Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997; **40**: 1725.
4 Balow JE, Boumpas DT, Austin HA III. Systemic lupus erythematosus and the kidney. In Lahita RG ed. *Systemic Lupus Erythematosus*. 4th edition. Elsevier: Amsterdam, 2004; 877–912.
5 Lewis EJ, Schwartz MM, Korbet SM eds. *Lupus nephritis*. Oxford: Oxford University Press, 1999: 1–315.
6 Levey AS, Coresh J, Balk E *et al*. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137–147.
7 Fogazzi GB, Ponticelli C, Ritz E. *The Urinary Sediment*, 2nd edition. Oxford: Oxford University Press, 1999; 1–188.

8 Rasoulpour M, Banco L, Laut JM, Burke GS. Inability of community-based laboratories to identify pathological cast in urine samples. *Arch Pediatr Adolesc Med* 1996; **150**: 1201–1204.
9 Chitalia VC, Kothari J, Wells EJ *et al.* Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. *Clin Nephrol* 2001; **55**: 436–447.
10 Christopher-Stine L, Petri M, Astor BC, Fine D. Urine protein-to-creatinine ratio is a reliable measure of proteinuria in lupus nephritis. *J Rheumatol* 2004; **31**: 1557–1559.
11 Chan TM, Li FK, Tang CS *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; **343**: 1156–1162.
12 Korbet SM, Lewis EJ, Schwartz MM *et al.* Factors predictive of outcome in severe lupus nephritis. *Am J Kidney Dis* 2000; **35**: 904–914.
13 Illei GG, Takada K, Parkin D *et al.* Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy. *Arthritis Rheum* 2002; **46**: 995–1002.
14 Hahn BH. Antibodies to DNA. *N Engl J Med* 1998; **338**: 1359–1368.
15 Berden JH. Lupus nephritis (Nephrology Forum). *Kidney Int* 1997; **52**: 538–558.
16 Trouw LA, Groeneveld TW, Seelen MA *et al.* Anti-C1q autoantibodies deposit in glomeruli but are only pathogenic in combination with glomerular C1q-containing immune deposits. *J Clin Invest* 2004; **114**: 679–688.
17 Marto N, Bertolaccini ML, Calabuig E *et al.* Anti-C1q antibodies in nephritis: correlation between titres and renal disease activity and positive predictive value in systemic lupus erythematosus. *Ann Rheum Dis*; published ahead online 29 July 2004 at http://wd.bmjjournals.com/cgi/reprint/and.2004.0249453v1
18 Manzi S, Ahearn JM, Salmon J. New insights into complement: a mediator of injury and marker of disease activity in systemic lupus erythematosus. *Lupus* 2004; **13**: 298–303.
19 Bootsma H, Spronk P, Derksen R *et al.* Prevention of relapses in systemic lupus erythematosus. *Lancet* 1995; **345**: 1595–1599.
20 Urowitz MB, Gladman DD. Clinical monitoring. In *The clinical management of systemic lupus erythematosus*, 2nd edition. Schur PH ed. Lippincott-Raven: Philadelphia, 1996: 225–233.
21 Strand V, Gladman D, Isenberg D *et al.* Endpoints: consensus recommendations from OMERACT IV. Outcome measures in rheumatology. *Lupus* 2000; **9**: 322–327.