KIDNEY BIOPSY IN LUPUS NEPHRITIS: SEIZE THE OPPORTUNITY

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ABSTRACT

Lupus nephritis is common in systemic lupus erythematosus (SLE), occurring in up to 60% of affected adults during the course of their disease. The histopathologic manifestations of lupus nephritis are diverse and determine not only the diagnosis and prognosis, but also substantially guide management of this complex disease. As the armamentarium available to treat lupus nephritis expands it becomes even more imperative that the correct diagnosis be made prior to instituting therapy. When deciding whether to pursue kidney biopsy we need to balance the risks of limited diagnostic information, which may include potentially preventable progression of renal disease or the avoidable use of a possibly toxic therapy, with the risk of a kidney biopsy. With the advances in imaging technology and biopsy needle mechanics kidney, biopsies have become safer and generally well tolerated. The combination of safer biopsies with a greater need than ever for correct diagnosis has made the risk/benefit for performing renal biopsies even more favorable in most cases of new kidney involvement in systemic lupus erythematosus.

Key words: Systemic Lupus Erythematosus; Kidney Biopsy; Therapy.

RESUMO

A nefrite lúpica é comum no Lúpus Eritematoso Sistémico (LES), ocorrendo em cerca de 60% dos adultos afectados por esta doença. As manifestações histopatológicas de nefrite lúpica são diversificadas e determinam não só o diagnóstico e prognóstico, mas também a orientação terapêutica desta doença complexa. À medida que o arsenal terapêutico disponível para tratar a nefrite lúpica expande, torna-se cada vez mais imperativo estabelecer um diagnóstico correcto antes de instituir a terapêutica. Quando se decide se se efectua uma biópsia renal é necessário balançar os riscos de uma informação diagnóstica limitada (informação que potencialmente pode permitir a prevenção da doença renal ou, pelo contrário, evitar o uso de terapêuticas tóxicas) com o risco de uma biópsia renal. Com os avanços na tecnologia de imagem e na mecânica das agulhas de biópsia as biópsias renais tornaram-se mais seguras e melhor toleradas. A combinação de biópsias mais seguras com uma maior necessidade de obter um diagnóstico correcto fez com que a relação risco/benefício da biópsia renal ficasse mais favorável na maioria dos casos de envolvimento renal no LES.

Palavras-Chave: Biópsia Renal; Lúpus Eritematoso Sistémico; Terapêutica

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Introduction

The role of kidney biopsy in the evaluation of kidney disease in patients with systemic lupus erythematosus (SLE) has been the subject of much debate over the years. Though some early studies[1] concluded that biopsy added little relevant clinical information, most clinicians now accept the benefits of performing renal biopsies in lupus nephritis.[2-4] The timing of such biopsies remains the source of some controversy. Some have recommended the use of renal biopsy in all patients newly diagnosed with SLE,[5] while others have suggested that biopsy be performed only selectively in those whose renal involvement has failed to respond to therapy.[6] In this review I hope to show that biopsy can provide critical information in the diagnosis and management of lupus nephritis and should be considered in any SLE patient with clinical evidence of kidney involvement.

Kidney Involvement in SLE

The kidney is a major target organ of SLE. Up to 60% of patients with SLE will develop renal manifestations at some point in their course, with 25-50% presenting with kidney involvement early.[7] The clinical presentation of kidney involvement is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis. Features generally include varying degrees of glomerular involvement with proteinuria – nephrotic in 45-65% of cases[7]– as well as hematuria with red cell casts and/or acute renal failure.

Diagnostic utility and rationale of kidney biopsy in SLE

The histopathologic manifestations of lupus nephritis are classified into several categories originally designated by the World Health Organization (WHO) classification in 1982.[8] These criteria have undergone a subsequent revisions,[9] the most recent of which evolved under the auspices of both the International Society of Nephrology and the Renal Pathology Society.[10] The general structure includes 6 principal pathologic patterns (classes I--VI), shown in Table I. The system has allowed physicians and pathologists taking care of those with lupus nephritis to reliably compare renal pathologic findings in a disease with complex histopathologic manifestations.

The focal and diffuse forms of lupus nephritis (classes III and IV, respectively) are distinguished from each other only by the percentage of glomeruli involved. These renal lesions generally present with nephritic urine sediments and progressive renal failure. In contrast, the membranous lesion (class V) typically presents with nephrotic-range proteinuria. Several studies, however, have illustrated the unreliability of diagnoses rendered on the basis of clinical features alone.[11-14] The kidney biopsy therefore becomes an essential tool in the differentiation of the histopathologic classes.

Making a diagnosis on clinical grounds is particularly difficult, for example, when patients present with low or moderate levels of proteinuria without acute renal failure. Such a presentation could be the result of mesangial lupus, a mild membranous lupus or of greatest concern, a proliferative lesion, either with mild activity or in early stages of a more active lesion. Without a biopsy these cannot be distinguished. Though it can be argued that in these cases the more severe forms of disease will progress to a point where a biopsy will be prompted,[6] at that point there may already be significant damage to the kidney if an active proliferative lupus nephritis were present. With early intervention shown to result in better outcomes, it would be imperative that a kidney biopsy be performed so that an early diagnosis can be made.[15-17] Biopsy is therefore indicated even in the presence

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Table I. Classification and Treatment of the Different Forms of Lupus Nephritis

WHO Class*	Description	Immunosuppression recommendations†
Class I	Minimal mesangial lupus nephritis	No specific therapy
Class II	Mesangial proliferative lupus nephritis	No specific therapy
Class III	Focal (proliferative) lupus nephritis	Mild: none or glucocorticoids Severe: See treatment for class IV below
Class IV	Diffuse (proliferative) lupus nephritis	Induction (6 mo): Cyclophosphamide or MMF Maintenance: MMF or AZA
Class V	Membranous lupus nephritis	Glucocorticoid +/- cyclosporine
Class VI	Advanced sclerosing lupus nephritis	No specific therapy

* Subclasses omitted (refer to Weening et al.[10] for full classification)
†Recommendations derived from Rose et al.[53]

of apparent mild clinical involvement (Table II). Because the optimal treatment of lupus nephritis varies with the type of glomerular disease (see below and Table 1), the provision of definitive diagnosis by kidney biopsy becomes even more essential.[3, 4, 18]

It must also be taken into account that the differential diagnosis of kidney involvement in SLE extends beyond the WHO or ISN classification to include renal thrombotic microangiopathy, usually related to the presence of antiphospholipid antibodies, which may be present in 15-90% of SLE patients.[19] Other non-lupus causes of kidney disease that may affect a person of similar age or gender (for example, IgA nephropathy, focal segmental glomerulosclerosis or non-steroidal anti-inflammatory drug induced acute interstitial nephritis) must also be considered.[20, 21] The differentiation of these disorders is once again enhanced by performance of kidney biopsy.

The need for performance of a second biopsy in follow-up and assessment of treatment efficacy remains controversial. Failure to respond adequately to therapy, suggested by persistent proteinuria or worsening renal function, should prompt a repeat biopsy. By revealing a transition from one histopathologic class to another[22] (most commonly class IV to V while under treatment[7]), a change in activity or chronicity of the previous lesion[23], or the presence of non-lupus disease, repeat biopsy may result in a substantial change in treatment.

Since histopathologic patterns in lupus frequently transform spontaneously,[7] even in the presence of an established diagnosis with a mild histopathologic lesion (class I or II) one should remain vigilant for clinical and laboratory evidence of change in disease activity. Such changes should be assessed with a kidney biopsy.

Histopathology as a Predictor of Outcome

In addition to making a definitive diagnosis, the prediction of outcomes is significantly enhanced

Table II. Indications for Performance of Kidney Biopsy in Lupus Nephritis

Increasing creatinine
Urine protein > 500 mg per 24 hours OR Urine protein-to-creatinine ratio > 0.5 g protein/g creatinine
Hematuria and/or Red Blood Cell Casts
Presence of cellular casts

Table III. Key Points: Advantages of Performing Kidney Biopsy

Early diagnosis = Better outcome
Correct diagnosis means appropriate therapy for severity of disease Insufficient therapy results in loss of kidney function Inappropriate therapy may result in exposure to unnecessary toxicity
Histopathologic features allow prognosis determination
Allows for comparison at future time point if second biopsy becomes necessary

by information obtained by renal biopsy.[24, 25] Two recent commentaries on the role of kidney biopsy in lupus nephritis have thoroughly and effectively reviewed the well recognized relationship between the histological features on biopsy and the clinical course of lupus nephritis.[4, 18] The WHO classification system is well established in predicting outcomes,[26-28] as are the NIH histologic activity and chronicity indices.[23, 29-31]

The availability of this information is helpful in ensuring that the type, duration and intensity of treatment match the severity of the disease.

Though clinical variables such as elevation of serum creatinine and nephrotic syndrome at presentation, persistent elevations of blood pressure, low hematocrit, hypocomplementemia and presence of anti-DNA antibodies have prognostic value,[5,25,29,31-36] the histologic information obtained from biopsies enhances outcomes prediction significantly.[24, 25, 37]

Current Treatment Options in Lupus Nephritis

With a growing armamentarium of drugs available to treat lupus nephritis, the need for biopsy prior to initiating therapy has become even more pressing. The optimal treatment regimen in lupus nephritis varies according to WHO class (Table I).[7, 38] Patients with the mildest forms of lupus nephritis (WHO class I or II) generally do well without specific intervention, such as blockade of the renin--angiotensin system. In the absence of appropriate immunosuppressive therapy, however, the proliferative forms (Class III and IV) of lupus nephritis typically progress to chronic renal failure.[39] The benefits of early treatment are well documented.[16] Since late and inadequate therapy allows active lesions to evolve into chronic irreversible ones, there is a tendency to treat all patients with proliferative lesions regardless of severity. In patients with the most aggressive forms of lupus nephritis, aggressive therapy is warranted.

What becomes important then is having an accurate diagnosis with appropriate determination of severity, as the blind use of these drugs may result in significant toxicity to the patient who otherwise might not have been exposed to a particular drug. The side effects of glucocorticoids are well known and are particularly disliked by patients. The physiologic effects include accelerated atherosclerosis, infections, osteoporosis, avascular necrosis of bone and induction of diabetes mellitus. Cyclophosphamide, which is usually given in monthly boluses by the "NIH protocol", has immediate toxicity including nausea, vomiting, hair loss, and fatigue. Major toxicities include cytopenias, serious infections, hemorrhagic cystitis, malignancy and, of enormous importance to most young female patients, gonadal failure.[40] Serious infections are common in SLE and death from infection correlates with the recent use of glucocorticoids and cyclophosphamide.[40, 41]

The more recent use of mycophenolate mofetil (MMF) has provided a drug that has equal if not better efficacy compared with cyclophosphamide, with much less toxicity.[42-44] In addition to risk of infections, particularly viral ones, the toxicities of MMF are more limited and include predominantly reversible abdominal pain, diarrhea and leukopenia.[45-48] It is this improved toxicity compared with most of the other agents that has resulted in the growing use of MMF in the treatment of lupus nephritis and further reinforces the need for accurate histopathologic diagnosis.

Patients may be spared all these toxicities if histopathology obtained by biopsy reveals a mild lesion (class I or II), a severely advanced chronic lesion (class VI), or the presence of non-lupus lesions.

Safety of Kidney Biopsy

Kidney biopsy is most frequently performed by percutaneous approach with either ultrasound or CT guidance. These techniques have been established as safe and effective in obtaining renal parenchyma. With improved imaging and the use of semi-automated biopsy guns, complications are uncommon and those of most concern are related to bleeding. Major complications, those requiring need for blood transfusion or invasive intervention, have been reported in 0[49] to 6.4 %[50] of biopsies. Predictors of complications have included high creatinine and low starting hematocrit.[51] Patients with SLE may be at risk of bleeding due to concurrent corticosteroid use and platelet dysfunction, though this has not been studied. In high-risk patients such as those with ongoing anticoagulation needs in the context of antiphospholipid antibody syndrome, or those with low platelet counts, alternative biopsy methods have been used such as transjugular kidney biopsy and

surgical laporoscopic biopsy.[52]

The only absolute contraindication to percutaneous kidney biopsy is the inability of the patient to cooperate with the procedure. Relative contraindications include the presence of a bleeding diatheses, such as those mentioned above, solitary kidney and advanced kidney disease with bilaterally small kidneys[52]. In bleeding diatheses, if the bleeding risk can be minimized before and for a few days after the biopsy, then a percutaneous approach can be used. However, there is still an increased bleeding risk for at least 6 weeks after the procedure.[52]

Conclusion

The goals of management of patients with lupus nephritis are early treatment of disease and prevention of end-stage renal disease. In order to achieve these objectives is becomes clear that kidney biopsy is essential in the establishment of early and definitive diagnosis, allowing appropriate type, duration and intensity of treatment that will match the class and severity of the disease defined by both clinical and histopathologic parameters. To be effective, the clinician must be aware of the diverse clinical and pathologic manifestations of lupus nephritis. It is especially important that the clinician recognize early stages of renal involvement at which point kidney biopsy should be performed without delay. This will allow effective treatment prior to the development of irreversible damage.

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