Kidney biopsy in lupus nephritis: look before you leap

Geoffrey R. Bihl¹, Michelle Petri² and Derek M. Fine²

¹Nephrologist and Clinical Director, Winelands Kidney and Dialysis Center, Somerset West, South Africa and
²Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease primarily affecting women of reproductive age. There is a particular pre-disposition to develop SLE in those of African descent, including a growing incidence in sub-Saharan Africa [1,2]. When compared with white patients, a more aggressive course of disease and poorer outcomes are noted. Such effects are also seen with lupus kidney disease, which is also more common in black patients [3]. Indeed, during the course of their disease, the kidney is a major target organ in up to 60% of patients with SLE, with 25–50% presenting with kidney involvement already at the time of lupus diagnosis. The presentation of lupus nephritis is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis with haematuria and red cell casts. Features invariably include some degree of glomerular proteinuria—nephrotic in 45–65% of the cases.

Several studies have illustrated the lack of reliability of diagnoses rendered on the basis of clinical features alone [4,5]. Therefore, making a diagnosis on clinical grounds alone is problematic and risky, underscoring the need for kidney biopsy. With diverse renal histopathological findings possible in SLE-affected patients, biopsy determines not only the diagnosis and prognosis, but also substantially guides management of this complex disease. As the therapeutic armamentarium for lupus nephritis expands, it becomes even more imperative that the correct diagnosis be made prior to instituting therapy. In deciding whether to perform a biopsy, one must balance the risks of the biopsy procedure against the risks of limited diagnostic information, which may result in progression of potentially preventable renal disease or the unnecessary use of a possibly toxic therapy.

Questions to be answered by kidney biopsy

Does the patient indeed have lupus nephritis?

Renal involvement in SLE includes not only the various World Health Organization (WHO) classes of lupus nephritis, but also non-lupus kidney disease that may affect persons of similar age and gender. These diagnoses include, but are not limited to, renal thrombotic microangiopathy, drug-induced interstitial nephritis, focal segmental glomerulosclerosis and IgA nephropathy.

Due to its specific management by anti-coagulation, a thrombotic microangiopathy needs to be ruled out in all those with anti-phospholipid antibodies, which may be present in more than 15% of the SLE patients. In view of the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) in treating lupus arthritis and serositis, the possibility of interstitial nephritis and/or a minimal change lesion must be considered in those on such medication [6]. Focal segmental glomerulosclerosis, the most common cause of nephrotic syndrome in black patients, and IgA nephropathy, the most common glomerular disease worldwide, may mimic lupus nephritis with a very different prognosis and management; neither can be diagnosed on clinical grounds. Tissue diagnosis by kidney biopsy, therefore, takes on even greater importance when considering these diagnoses.

What type of glomerular histopathology is present?

The histopathological manifestations of lupus nephritis are classified into several categories, originally designated by the WHO in 1982. These have recently evolved under the auspices of both the International Society of Nephrology and the Renal Pathology Society [7]. The general structure includes six principal pathological patterns (classes I–VI), as shown in Table 1. This classification system, which also includes
### Classification and treatment of lupus nephritis

<table>
<thead>
<tr>
<th>WHO class*</th>
<th>Description</th>
<th>Treatment recommendations</th>
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<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial lupus nephritis</td>
<td>No specific therapy</td>
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<tr>
<td>Class II</td>
<td>Mesangial proliferative lupus nephritis</td>
<td>No specific therapy; renin-angiotensin blockade**</td>
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<tr>
<td>Class III</td>
<td>Focal (proliferative) lupus nephritis</td>
<td>Mild: as for class II or glucocorticoids</td>
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<td></td>
<td></td>
<td>Moderate: Glucocorticoids ± MMF</td>
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<tr>
<td>Class IV</td>
<td>Diffuse (proliferative) lupus nephritis</td>
<td>Severe: See treatment for class IV below</td>
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<tr>
<td></td>
<td></td>
<td>Induction (6 months): i.v. CYC or MMF</td>
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<td></td>
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<td>Maintenance: MMF or AZA or quarterly i.v. CYC</td>
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<tr>
<td></td>
<td></td>
<td>Glucocorticoids ± (ciclosporin, AZA, MMF, CYC)</td>
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<tr>
<td>Class V</td>
<td>Membranous lupus nephritis</td>
<td>No specific therapy</td>
</tr>
<tr>
<td>Class VI</td>
<td>Advanced sclerosing lupus nephritis</td>
<td></td>
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</tbody>
</table>

AZA, azathioprine; CYC, cyclophosphamide; i.v., intravenous; MMF, mycophenolate mofetil; WHO, World Health Organization.

*Subclasses omitted (refer to Weening [7] for full classification).

**Renin-angiotensin blockade recommended as adjunct therapy for proteinuria in all classes.

assessment of disease activity and chronicity (not shown in the table), allows pathologists to standardize the reporting of renal pathological findings. Physicians are then able to tailor the treatment according to the glomerular involvement, being particularly aggressive with severe glomerular pathology.

Though a diagnosis of proliferative lesions may be suggested by a rapidly progressive glomerulonephritis, and membranous disease by an isolated nephrotic syndrome, a biopsy is still necessary to determine diagnosis in each instance, prior to instituting therapy. Determining diagnosis based on clinical judgement may be particularly difficult in patients presenting with low or moderate levels of proteinuria without acute renal failure. Such a presentation could be the result of mesangial lupus (class II), a mild membranous lupus (class V) or of greatest concern, a proliferative lesion, either with mild activity or in the early stages of a more active lesion (class III, IV); intervention could be significantly altered depending on which is present.

In addition to diagnosis, the prognosis of the lesion is predicted by the class, activity and chronicity of the glomerular pathology. Two recent articles on the role of biopsy have comprehensively reviewed the well-recognized relationship between the histological features on biopsy and the clinical course of lupus nephritis [8,9]. The WHO classification system is well-established in predicting outcomes, as are the National Institute of Health (NIH) histological activity and chronicity indices. Though clinical variables such as elevation of serum creatinine, nephrotic syndrome at presentation, persistent elevations of blood pressure, low haematocrit, hypocomplementaemia and presence of anti-dsDNA antibodies have prognostic value, the histological information obtained from biopsies, the most important of which are the presence of crescents and interstitial fibrosis, continues to be indispensable in enhancing outcome prediction.

It must also be highlighted that lupus nephritis is frequently focal. Therefore, larger tissue samples afford the clinician and pathologist a more accurate assessment of glomerular involvement. In order to adequately rule out a focal lesion, a biopsy should contain a minimum of 10 glomeruli for light microscopic analysis [10]. Given this, in the presence of a limited tissue sample, one must use some caution in interpreting results.

**What are the implications of the histopathology for differential therapy?**

Treatment strategies will differ based on biopsy findings. Table 1 delineates some of the accepted strategies, not as the definitive summary, but mainly to illustrate the complexity of the approach which could be appreciably altered based on these findings. For patients with classes I and II on biopsy, conservative management with renoprotective measures is warranted. These include strict blood pressure control, preferably with blockade of the renin–angiotensin system, avoiding nephrotoxins and the cessation of smoking. Such lesions are not usually treated with immunosuppression, unless needed for non-renal manifestations of the patient’s SLE.

The standard of care for WHO class IV disease, diffuse proliferative glomerulonephritis, the most sinister lesion, has been induction with intravenous cyclophosphamide and glucocorticoids, followed by cyclophosphamide maintenance. The ‘NIH protocol’ has typically been applied [11], though lower cyclophosphamide dosing based on the Euro-Lupus Nephritis Trial appears to be as effective [12]. More recently, mycophenolate mofetil (MMF) has demonstrated equal, if not better, efficacy vs cyclophosphamide in remission induction [13,14] and maintenance [15]. With its better toxicity and safety profile, MMF’s popularity as a primary therapy in combination with glucocorticoid therapy is growing.

Cyclophosphamide toxicity is especially relevant in women of childbearing age, where the risk of gonadal failure is not insignificant. Infectious complications are of particular concern, with high mortality rates seen in some clinical studies [16,17]. Though fewer infections have been seen with MMF, its suppression of the immune system is not inconsequential. For poor patients living in endemic areas, including those
from developing countries such as South Africa [2,18], there is a particularly high risk of acquiring serious infections such as tuberculosis [19,20], which is reaching epidemic levels, especially in the context of the increasing prevalence of HIV/AIDS. Outcome in such patients is especially poor when requiring hospitalization [21]. Prescribing the correct regimen for the defined histopathological picture, therefore, takes on even more importance. Patients may be spared these toxicities if obtained histopathology reveals a mild lesion (class II), a severely advanced chronic lesion (class VI) or the presence of non-lupus lesions, not requiring immunosuppressive therapy.

Management of class III and V lesions is less well-established. While milder class III lesions may respond well to corticosteroids, more aggressive lesions frequently require the addition of MMF or cyclophosphamide, with treatment recommendations following those of class IV disease.

Membranous (class V) lupus is not a benign disease. Long-term consequences include impaired renal function, increased risk of hypercoagulability and hyperlipidaemia. The addition of immunosuppressive drugs may affect long-term renal survival, reduce the risk of complications from nephrotic syndrome and increase remission [22,23]. Due to the lack of large randomized controlled studies, there is no strong evidence-based regimen for the treatment of this entity [24]. Similar remission rates seen at 12 months after treatment with concurrent glucocorticoid therapy have been seen with the use of cyclophosphamide, cyclosporine, azathioprine and MMF [24,25]. However, due to its toxicity, cyclophosphamide is not generally used as a first line agent. The use of cyclosporin is limited by hypertension and nephrotoxicity, and the lack of sustained remission with this therapy. Angiotensin antagonists should be used whenever possible, in conjunction with immunosuppressive therapy to limit proteinuria [24].

With the advent of potentially effective new therapies focused on the treatment of specific lesions, the need for biopsy may become even more important.

Safety of kidney biopsy

Any consideration of the benefits of kidney biopsy must include knowledge of the risks of the procedure. With improved imaging and the use of semi-automated biopsy guns, complications are uncommon. However, bleeding remains of foremost concern. Major complications, those requiring blood transfusion or invasive intervention, have been reported in 0–6.4% of biopsies. Predictors of complications have included low haematocrit and high creatinine. Patients with SLE may have an additional risk of bleeding due to concurrent corticosteroid use or platelet dysfunction, though this has not been studied.

For patients on anti-coagulants, it is essential to correct any clotting abnormality prior to biopsy. This may require a switch from warfarin to short-acting heparin, which is then reversed prior to biopsy. Aspirin and other NSAIDs must also be discontinued prior to the procedure. Restarting anti-coagulation or anti-platelet agents following a percutaneous procedure, although often necessary, is also of concern as there may be a risk of bleeding for up to 6 weeks.

Relative contraindications to biopsy include the presence of a bleeding diathesis, solitary kidney and advanced kidney disease with bilaterally small kidneys. In such high-risk patients, alternative procedures have been used, such as transjugal biopsy and surgical laparoscopic biopsy. As with the clinical presentation of lupus nephritis, each patient should be assessed on his or her own merits, to judiciously weigh the risks and benefits of renal biopsy (Table 2).

Conclusion

Management goals in patients with lupus nephritis include the early diagnosis and appropriate therapy whilst preserving overall kidney function without undue side-effects. In order to realise such goals, it is clear that a kidney biopsy is essential in establishing diagnosis and prognosis, and guiding treatment. In order to offer an effective level of care, the clinician must be aware of the diverse clinical and pathological manifestations of lupus nephritis especially in the early stages of the disease, when optimal and prompt therapy may well prevent irreversible damage.

Conflict of interest statement. Dr Bihl has received honoraria from Roche Pharmaceuticals.

Table 2. Suggested indications for performance of a kidney biopsy in lupus nephritis

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<th>Indication</th>
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<tr>
<td>Acute renal failure indicated by a rising creatinine</td>
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<td>Urine protein &gt;500 mg per 24h or urine protein:creatinine ratio &gt;0.5 g protein/g creatinine</td>
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<td>Haematuria in the presence of any level of proteinuria</td>
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<tr>
<td>Presence of red and/or white cell casts (cellular casts)</td>
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<td>Failure to respond adequately to therapy or relapse after therapy</td>
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</table>

*Reference [26].
Therapeutic approaches in autosomal dominant polycystic kidney disease (ADPKD): is there light at the end of the tunnel?

Gerd Walz

Renal Division, Freiburg, Germany

Keywords: mTOR inhibitors; polycystic kidney disease; tacrolimus; vasopressin-2 receptor antagonist

The new kids on the block

For more than three decades, autosomal dominant polycystic kidney disease (ADPKD) researchers around the globe, spurned by millions of affected patients, have tried to elucidate the mechanisms that lead to cyst formation and progression of renal failure in this heterogenous disease. It was not until recently that realistic therapeutic interventions have come within reach. This editorial will briefly summarize the key findings that led the researchers to test vasopressin-2-receptor antagonists (V2RA) and mammalian targets of rapamycin (mTOR) inhibitors in animal models of polycystic kidney disease, and will highlight why these therapeutic avenues might be more promising and fortunate than their predecessors (Table 1).