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Review article

# Lupus nephritis: When and how often to biopsy and what does it mean?

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ABSTRACT

Renal disease is a frequent complication of SLE which can lead to significant illness and even death. Today, a baseline renal biopsy is highly recommended for all subjects with evidence of lupus nephritis. Biopsy allows the clinician to recognize and classify different forms of autoimmune lupus glomerulonephritis, and to detect other glomerular diseases with variable pathogenesis which are not directly related to autoimmune reactivity, such as lupus podocytopathy. Moreover, not only glomerular diseases, but other severe forms of renal involvement, such as tubulo-interstitial nephritis or thrombotic microangiopathy may be detected by biopsy in lupus patients. Thus, an accurate definition of the nature and severity of renal involvement is mandatory to assess the possible risk of progression and to establish an appropriate treatment.

The indications to repeat biopsy are more controversial. Some physicians recommend protocol biopsies to recognize the possible transformation from one class to another one, or to identify silent progression of renal disease, others feel that good clinical monitoring is sufficient to assess prognosis and to make therapeutic decisions. At any rate, although any decision should always be taken by considering the clinical conditions of the patient, there are no doubts that repeat renal biopsy may represent a useful tool in difficult cases to evaluate the response to therapy, to modulate the intensity of treatment, and to predict the long-term renal outcome both in quiescent lupus and in flares of activity.

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## 1. Introduction to lupus nephritis

Renal involvement is common in SLE. Clinically, lupus nephritis may range, from an asymptomatic microscopic hematuria to a rapidly progressive renal disease associated with a constellation of signs and symptoms [1,2]. Histologically, lupus nephritis comprises a spectrum of glomerular, vascular, and tubulo-interstitial lesions. A first classification of lupus nephritis formulated by Pirani and Pollak in Buffalo, New York in 1974 [3] was updated a few years later [4] and was further reviewed by a common consensus of experts of the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) in 2004 [5,6]. This new classification reflects the need for improving categorization and terminology of lupus nephritis, based on the better knowledge of the pathogenesis of the various forms of SLE glomerulonephritis.

In the majority of cases, lupus glomerulonephritis is caused either by glomerular deposition of preformed circulating immune complexes or by autoantibodies directed against intrinsic or "planted" glomerular antigens [7]. In a few cases a direct damage of the kidney by soluble inflammatory mediators have been hypothesized [8]. Sources of immune complexes include circulating antinuclear, double-stranded anti-DNA, anti-C1q and crossreactive anti-glomerular autoantibodies, opsonized apoptotic particles, and neutrophil extracellular traps. Immune complex deposits can fix the complement fractions and initiate the complement cascade with recruitment of activated T cells and macrophages. The terminal activation of the membrane attack complex (C5b-C9) forms transmembrane channels which disrupt the cell membrane of target cells, leading to cell lysis and death [9]. Alternatively, the immune deposits can activate directly intrinsic glomerular cells with consequent release of inflammatory cytokines and chemokines [7]. Endothelial cells, podocytes or mesangial cells may be the target of these injuries. The pattern and severity of glomerular lesions depends on the location of the immune complexes and on their specificity, avidity, size and charge [10]. The classification of the ISN/RPS proposes to categorize the histomorphological glomerular lesions into six different classes [5,6]. The accuracy of the definition of each histological class requires that at least 10 glomeruli are present at light microscopy in the kidney specimen [11]. Although electron microscopy has a crucial role for the diagnosis and management of some cases [12], it is not available in all centers around the world. Thus, the new classification is mainly based on the evaluation of renal biopsy by light microscopy and immunofluorescence.

Class I includes glomeruli that appear normal at light microscopy but have mesangial immune complex deposits at immunofluorescence, sometimes with a "full house" pattern (Fig. 1a,b). Class I is very infrequently diagnosed and clinical manifestations are very mild or absent.

Class II is characterized by glomerular changes limited to the mesangial areas. There is an increase in mesangial cells and mesangial matrix with segmental or global patterns. (Fig. 1c,d). The presence of a few subepithelial or subendothelial deposits at immunofluorescence or at electron microscopy does not play against a diagnosis of class II, unless a thickening of the capillary walls is observed at light microscopy. The tubulo-interstitial area and vessels are generally normal. Most patients with class II present with normal renal function and asymptomatic urinary manifestations such as microscopic hematuria and/or non-nephrotic proteinuria.

Class III and Class IV, also called "focal" and "diffuse" lupus nephritis respectively, are characterized by proliferative glomerular lesions. The difference between the two forms is represented by the number of glomeruli affected by proliferative lesions, less than half in focal nephritis. Any active and chronic glomerular lesions may be present in different amounts, associations and severity. Signs of active glomerular lesions are endocapillary hypercellularity, leukocyte infiltration, fibrinoid necrosis, karyorrhexis, cellular or fibrocellular crescents, mesangial, subendothelial and/or subepithelial immune complex deposits, and intraluminal immune complex deposits, the so called hyaline thrombi. In association with active glomerular lesions, tubulointerstitial inflammation, tubular basement membrane immune deposits and vascular immune complex deposits are present. The main signs of chronic glomerular lesions are segmental or global glomerular sclerosis and fibrous crescents. Chronic extraglomerular lesions include chronic interstitial inflammation, interstitial fibrosis and arteriosclerosis. Based on the extension of active and chronic glomerular lesions, both class III and IV are subdivided in active (A), active and chronic (A/C), and chronic (C) forms.

Class III is defined by proliferative glomerular lesions in less than 50% of glomeruli (Fig. 2a,b). Both segmental and global glomerular involvement are typical of this class, being the segmental lesions more frequent. Few cases characterized by segmental necrotizing lesions with mild or absent hypercellularity and immune complex deposits have been reported. Some cases, but not all, are positive for antineutrophil-cytoplasmic antibodies, suggesting a different pathogenesis of these forms [13]. The clinical presentation of class III is extremely variable. It ranges from asymptomatic urinary abnormalities to nephrotic or nephritic syndrome with mild to moderate renal insufficiency and arterial hypertension.

Class IV or "diffuse lupus nephritis" is defined by the presence of proliferative lesions in more than 50% of glomeruli. Class IV is further subdivided into diffuse segmental lupus nephritis (class IV-S) when >50% of the involved glomeruli have segmental lesions, and diffuse global lupus nephritis (class IV-G) when >50% of the involved glomeruli have global lesions. Large subendothelial deposits determining the severe thickening of glomerular capillary walls are typically present in class IV together with all types of active lesions (Fig. 2c d). Even within different glomeruli, the type and severity of active lesions are variable. Focal or diffuse interstitial nephritis with edema and tubulitis is frequently associated to severe glomerular lesions. Vascular lesions are frequent. They can range from vascular immune deposits to thrombotic microangiopathy, necrotizing arteritis is uncommon. Generally, in class IV immunofluorescence reveals positively for IgG, IgA, IgM, C3, and C1q with mesangial subendothelial and subepithelial deposits. Occasionally, pauci-immune deposits are observed in class IV-S. When subepithelial deposits are present in more than 50% of the capillary walls the diagnosis of mixed class IV and V is formulated. The clinical presentation of class IVis usually characterized by active urinary sediment, severe proteinuria and/or renal dysfunction. However, in a number of cases, in spite of severe histological lesions the clinical presentation is mild. In comparison with class IV-S, class IV-G has generally more severe proteinuria, renal dysfunction, anemia, hypo-complementemia, anti dsDNA antibodies titers [14].

Class V includes membranous lupus nephritis with or without