



Book Supplement

Lupus Nephritis

The kidney is commonly affected in lupus. One third to one half of patients presenting with lupus have an abnormal urinalysis or some degree of renal dysfunction. Within the first 3 years of diagnosis of lupus, whether a patient will develop kidney disease becomes evident.

The pathogenesis of glomerular injury in this setting relates to the deposition of immune complexes, either as a consequence of *in situ* localization of an antigen followed by antibody binding or the deposition of preformed circulating immune complexes that launch a cascade of inflammatory events. These events include activation of the complement and coagulation cascades and leukocyte recruitment.

The site of immune complex deposition correlates with the clinical phenotype of the disease. Immune complexes deposited in the mesangium or subendothelium result in a focal or diffuse proliferative glomerulonephritis. Deposits that bind in the subepithelial region or within the GBM manifest as membranous nephropathy. Deposits that line the subepithelial space usually manifest as proteinuria that is often in the nephrotic range.

The classification of lupus nephritis into pathologic categories recently has been modified.

Classification of Lupus Nephritis	
Class	Description
I	Characterized by minimal mesangial immune deposits and glomeruli that still appear normal on light microscopy.
II	A mesangioproliferative glomerulonephritis with expansion of mesangial cells and matrix visible on light microscopy.
III	A focal nephritis with <50% of glomeruli actively involved with inflammation on light microscopy. These lesions can be proliferative or necrotizing.
IV	A diffuse glomerulonephritis with <50% glomerular involvement with a proliferative response or necrotizing lesions. These lesions are usually associated with subendothelial deposits.
V	Characterized by the presence of subepithelial immune deposits that result in membranous nephropathy.
VI	The chronic form of disease in which >90% of the glomeruli are globally sclerotic. Chances of long-term renal failure are high.

The clinical presentation of most patients with lupus nephritis mirrors the pattern of the histology. Patients with class I or II lupus nephritis typically have hematuria and/or proteinuria and usually do not have renal insufficiency. Those with class III or IV disease have acute nephritis with hematuria; proteinuria; typically erythrocyte casts; and, depending on the number of glomeruli involved, renal insufficiency. Patients with membranous nephropathy typically present with proteinuria, usually in the nephrotic range.

The following factors help to determine the outcome of patients with lupus nephritis: the presence of renal insufficiency at the time of biopsy, the severity of the renal histology, the presence of interstitial fibrosis indicating scarring, or the presence of crescents indicative of active and aggressive glomerulonephritis. Black race constitutes an independent predictor of end-stage kidney disease in patients with Class IV disease.

Disease severity determines the treatment in lupus nephritis. Studies supported by the National Institutes of Health indicate that treatment with intravenous cyclophosphamide once monthly for 6 consecutive months, with additional cyclophosphamide therapy administered every 3 months for up to 2 years, provides long-term improvement in renal function. Prednisone alone does not provide the same degree of renal protection over 10 years.

The advent of mycophenolate mofetil therapy has recently challenged the status of cyclophosphamide as the mainstay of immunomodulatory therapy. An alternative to cyclophosphamide therapy has been investigated because of the substantial side effects of this agent, which include major infection; mutagenesis; and premature ovarian failure in women. As induction therapy, mycophenolate mofetil appears equivalent to intravenous cyclophosphamide in patients with diffuse proliferative glomerulonephritis.

A U.S. study revealed that a higher number of patients achieved complete remission with mycophenolate mofetil compared with intravenous cyclophosphamide. Mycophenolate mofetil has been shown to be superior to intravenous cyclophosphamide in maintaining disease remission when intravenous cyclophosphamide was used for 6 months for induction, followed by mycophenolate mofetil, azathioprine, or intravenous cyclophosphamide for a period of up to 48 months. Mycophenolate mofetil and azathioprine also were superior to intravenous cyclophosphamide in maintaining remission with fewer side effects.

It is uncertain whether these less-toxic therapies will prevent end-stage renal disease over decades of use. When mycophenolate mofetil therapy is discontinued, recrudescence of disease is much more common than with intravenous cyclophosphamide therapy.

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