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SHORT REVIEW

Diagnosis of Lupus Nephritis – A Short Review

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Abstract

40-70% of patients with systemic lupus erythematous suffer lupus nephritis, knowing how to detect early clinical manifestations, biomarkers and the importance of kidney biopsy are essentials to offer an adequate treatment and improve prognosis.

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disorder which affect almost any organ or system (1). Some of the most common clinical features are mucocutaneous lesions, arthritis, renal involvement, hematological disorders, serositis and fever. 40-70% of SLE patients suffer from lupus nephritis (LN) whose dominant feature is proteinuria usually associated with urinary sediment abnormalities. (2) LN usually develops within the first 5 years of the onset of the disease. (3)

LN is typically treated with immunosuppressive drugs, such as glucocorticoids, and cyclophosphamide or mycophenolate mofetil (MMF). However, conventional immunosuppressive treatments are not uniformly effective, and even in patients who respond at first, 35% may relapse. (4)

Between 10% and 20% of patients with LN will develop chronic renal failure. (3) Early and accurate diagnosis of LN and early initiation of therapy are prior importance to prevent disease progression. (4)

2 | CLINICAL MANIFESTATIONS

SLE is usually diagnosed in young women in the third decade of life, represents the leading cause of systemic disease with secondary kidney involvement. (5)The clinical presentation ranging from “silent” LN (normal urinalysis results, normal function and no proteinuria in asymptomatic patients) to severe proteinuria and nephrotic syndrome (more than 3.5 g of protein per day) or acute nephritic syndrome, which can result in acute kidney failure. However, patients most commonly present with mild

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proteinuria and/or hematuria and, in some cases, leukocyturia. The urinary sediment is often "active"; that is, acanthocyturia and red blood cell casts are present. Occasionally, patients may present with advanced chronic kidney disease or hypertension as the initial manifestation of LN. (4) The prevalence of clinical manifestations in patients with lupus nephritis is proteinuria 100%, syndrome nephrotic 50%, microscopic hematuria 80%, macroscopic hematuria <5%, urinary red blood cell casts 30%, renal insufficiency 60%, rapid decline in kidney function 15%, hypertension 30% and tubular abnormalities 70%. (6)

3 | BIOMARKERS ON LUPUS NEPHRITIS

The traditional biomarkers include serum creatinine, hematuria, and proteinuria, with the latter being strongly associated with long-term kidney prognosis. The predictability of other immunological markers as anti-doble stranded DNA antibodies or complement C3 and C4 fraction is highly variable, with sensitivities ranging from 50-80% and specificities of around 75%. Potential biomarkers not yet incorporated into routine clinical practice include circulating levels of BAFF, APRIL, MBL, soluble IL-7 receptor, cystatin C, and IL-18 as well as urinary biomarkers that reflect the state of kidney damage in real time such as microRNAs and levels of MCP-1, TWEAK, NGAL, VCAM-1, and BAFF. An interesting approach in the future would be the combination of novel and traditional biomarkers in order to identify different activity patterns that allow an individual assessment of patients with LN. (5)

4 | KIDNEY BIOPSY IN LN

At present, kidney biopsy is used to establish a diagnosis of LN or other processes involving the kidneys in a patient with lupus; to correctly classify LN, which may have therapeutic and prognostic implications; and to determine the extent of acute and chronic kidney injury, which has therapeutic implications. (7)

Renal biopsy should be considered in SLE patients with new onset of proteinuria of more than 1 g/day with and without active urinary sediments, particularly in the presence of active lupus serology or impaired renal function. Some experts recommend renal biopsy at a lower threshold of proteinuria (eg, ≥500 mg/day). (8)

Although the decision to perform a kidney biopsy in SLE patients where there is clinical evidence of renal involvement seems straightforward, it has become somewhat controversial because of a prevailing view that all forms of NL can be adequately treated with corticosteroids plus mycophenolate mofetil (MMF). Nonetheless, the kidney biopsy is important to define the nature of renal involvement. Although immune-complex-mediated GN is the most cause of kidney disease in SLE, there are other mechanisms that result in renal injury which can only diagnosed with a biopsy, and require a different approach to management than immune-complex LN. (6) Besides LN, kidney injury in patients with lupus could be due to thrombotic microangiopathy (TMA)/ antiphospholipid nephropathy, non-immune complex podocytopathy, tubulointersticial nephritis, acute tubular necrosis, renovascular disease, or nephrotoxicity from medications. (7)

A thorough examination of a kidney biopsy sample should include light microscopy, immunofluorescence analysis and electron microscopy. The histological information obtained from a kidney biopsy sample is considered adequate when ten or more glomeruli are imaged and analyzed. In terms of nomenclature, 'lupus nephritis' refers to immune complex-mediated kidney injury, with positive staining for deposits including IgG, IgA, IgM, C1q, C3 and C4. (4)

A recent study that compared pathological findings of 300 patients with SLE to a group of 560 patients with glomerular diseases secondary to immune complex deposition found that most cases of LN had at least 2 of the following 5 characteristics: {1} "full-house" deposits by immunofluorescence; {2} >2 + staining intensity for C1q; {3} extraglomerular deposits; {4} presence of subendothelial and subepithelial deposits; and {5} endothelial tubular-reticular inclusions. The presence of at least 2 of these features

had a sensitivity of 92% and a specificity of 89% for diagnosis of LN, while the presence of at least 3 of the 5 characteristics had a sensitivity of 80% and specificity of 95%. (5)

The ISN/RPS system classifies LN on the basis of where immune complexes accumulate in glomeruli, the presence or absence of mesangial or endocapillary proliferation, the overall extent of glomerular involvement (focal or diffuse) and glomerular injury (global or segmental), and whether glomerular injury is active (inflammatory) or chronic (sclerotic). In a general way, the ISN/RPS classes guide treatment decisions. (6)

The Renal Pathology Society/International Society of Nephrology (or RPS/ISN) classification include 6 classes: minimal mesangial lupus nephritis, mesangial proliferative lupus nephritis, focal lupus nephritis, diffuse lupus nephritis, membranous nephropathy, and advanced sclerosing lupus nephritis. (9)

Histologically, it is also important to distinguish between an active or chronic process as treatment modalities differ between the two. Evidence of an active process gives the physician substantial cause to pursue aggressive therapy in the patient, as opposed to a chronic process, which is more irreversible in nature and would not always justify aggressive therapy. Histological indices of an active process include endocapillary hypercellularity with or without leukocyte infiltration, karyorrhexis (fragmentation of the nucleus), fibrinoid necrosis, rupture of glomerular basement membrane, cellular or fibrocellular crescents, subendothelial deposits on light microscopy, and intraluminal immune aggregates. On the other hand, a chronic process would show glomerular sclerosis (either segmental or global), fibrous adhesion, and fibrous crescents. (10)

Patients with disease limited to the mesangium (class 2) generally do not need specific therapy for their kidney disease but may need immunosuppressive treatment for extrarenal SLE manifestations. Patients with mainly chronic injury (any class) or end stage damage (class 6) also do not need immuno suppression for LN, but may benefit from antiproteinuric, renoprotective measures. The proliferative classes (3 and 4) are often treated with potent immunosuppression, whereas nonproliferative, membranous LN (class 5) may be managed conservatively (antiproteinuric therapy) if patients have subnephrotic proteinuria, or with immunosuppression if patients have nephrotic range proteinuria. (6)

A repeat renal biopsy should be considered in patients with persistently active serological markers because it provides information on the following: (1) histological transformation of the classes of lupus nephritis; (2) the degree of residual activity in the kidneys; and {3} the extent of chronic irreversible changes and their progression since the initiation of immuno suppressive treatment. These data may help guide further treatment decisions. (8) However,protocol repeat biopsies are more controversial, but emerging data from observational cohort studies suggest that such biopsies may assist in making treatment decisions and help predict long-term renal outcomes. Protocol repeats biopsies have shown considerable discrepancies between clinical and histologic findings. For example, repeat biopsies done after 6 to 8 months of treatment in patients with a complete clinical response showed significant persistent histologic activity in 20% to 50% of cases. (7)

Although the role of a kidney biopsy at first presentation of kidney involvement in lupus is well established, the role for a repeat kidney biopsy is less clear. Generally, repeat kidney biopsies have been done on a “for cause” basis, for example, a flare of LN, treatment-resistant disease, or in cases in which it is unclear whether persistent proteinuria is due to active disease or chronic nephrosclerosis. (7)

5 | CONCLUSION

The importance of early detection and treatment are paramount since lupus nephritis is a major cause of morbidity and mortality in SLE and delayed diagnosis is a risk factor for end-stage renal disease.

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