LUPUS NEPHRITIS (LN)

CHOWDHURY MNC

Systemic lupus erythematosus is a prototypical autoimmune disease that can potentially involve every organ. Its clinical spectrum is therefore extremely heterogeneous and varies from relatively mild cases involving only the skin or joints to life-threatening manifestations, with renal impairment, severe haematological or central nervous system disease. Kidney injury in SLE, lupus nephritis (LN) is a major cause of both morbidity and mortality, affecting over half of all SLE sufferers over the course of the disease.

The kidneys are diseased in 40 to 70% of cases of systemic lupus erythematosus (S.L.E.), and renal failure remains the commonest cause of death. In some series, kidney involvement (mainly haematuria, proteinuria) occurs in at least one third of patients with lupus and significantly affects survival. Where as in other series it shows LN affects up to 60% of adults and 80% of children with systemic lupus erythematosus (SLE). The initial clinical presentation of lupus nephritis ranges from asymptomatic proteinuria discovered on routine urinalysis to the nephrotic syndrome with or without renal impairment. Histologic examination of a renal-biopsy specimen is main step in confirming the diagnosis and guiding therapy. Those patients with predominantly focal or membranous changes alone tend to do well even in the absence of treatment, those with diffuse proliferative changes have a poor prognosis.

Despite vast improvements in the survival and well being of patients with this disease, our current understanding of its pathogenesis is incomplete and the risk of end stage renal disease is still unacceptably high.

Yung and Chan focus on the contribution of anti-double stranded DNA (dsDNA) antibodies to the pathology of lupus nephritis. Deposition of anti-dsDNA antibody-containing immune complexes in the kidney is an initiating factor in lupus nephritis. However, as this review discusses, direct and indirect binding of anti-dsDNA antibodies to cross-reactive antigens in the kidney also plays a major role. The downstream effects of this, including proliferation, apoptosis, inflammation, and fibrogenesis, are highlighted. In addition, recent data are discussed suggesting that mycophenolic acid (MPA), the active ingredient of the drug mycophenolate mofetil, has specific inhibitory effects on anti-dsDNA-induced processes, independent of its known immuno-suppressive actions.

The glomerular lesions of LN have been studied intensively over the last 5 decades, with the establishment and refinement of the International Society of Nephrology/Renal Pathology Society system for classifying the glomerular lesions as well as the development of composite indices of activity and chronicity. Classification of glomerular lesions in SLE was initially based on 5 year outcomes in patients who had not received treatment except for corticosteroids. Using patient survival as the outcome it was clear that patients with focal glomerular disease or membranous disease had slower progression and much better outcome at 5 years than those with diffuse disease, most of who died within 2 years of diagnosis. The validation of the current classification criteria and of activity and chronicity indices for determining treatment and predicting long term (>5 year) outcomes in the current era of optimized immunologic and medical interventions is still a work in progress. This is in part because outcome is linked to demographic factors including age, sex, and
ethnicity as well as to compliance, responsiveness to therapy, and number of relapses—which currently cannot be predicted from an initial renal biopsy.

Compared with the emphasis on glomerular lesions in lupus biopsies, less attention has historically been paid to lesions of the renal tubulointerstitial compartment, which include infiltrates with mononuclear cells, tubular atrophy, fibrosis, and tubular immune complex deposition. Several previous studies have shown that tubulointerstitial lesions correlate with glomerular injury\(^5,6\). A recent study by Hsieh et al, however, did not demonstrate a clear association between the magnitude of tubulointerstitial infiltrates and either the activity index or the glomerular histologic class; rather, the magnitude of tubulointerstitial infiltrates correlated with the tubular components of the chronicity score, which include tubular atrophy and fibrosis\(^7\). In addition, there is consensus that the presence of infiltrates does not correlate with the degree of interstitial immune complex deposition. It is currently not possible to predict clinically which patients will have tubulointerstitial infiltrates.

Interstitial fibrosis is a component of the chronicity score and is recognized as a poor prognostic indicator in LN. There is also strong agreement in the literature that the presence of tubulointerstitial infiltrates independently correlates with worse long term outcome\(^5,6,8\). Early studies indicated that tubulointerstitial infiltrates were associated with poorer glomerular function at presentation and poorer long term outcome, and that glomerular function at followup correlated with the numbers of monocyte/macrophages found on initial biopsy. These findings were confirmed recently by Hsieh et al, who demonstrated that tubulointerstitial inflammation was associated with decreased glomerular filtration rate and higher serum creatinine level at the time of biopsy but that a predominance of B or T cells per se did not correlate with either of these variables\(^5\). Strikingly, 37% of patients with severe tubulointerstitial inflammation at biopsy progressed to having renal failure within 24 months. Histologic involvement of the tubulointerstitial compartment has been observed on repeat biopsy even in patients whose disease is clinically in remission. Poor long term outcomes were particularly noted when interstitial infiltrates of mononuclear cells were still present on the second biopsy\(^9\).

Immunosuppressive therapy consists of glucocorticoids combined with a cytotoxic drug (which for decades has been high-dose intravenous cyclophosphamide) to achieve a prompt response. The high rate of renal relapse (35%) justifies long-term maintenance immunosuppression. Between 10 and 20% of patients with lupus nephritis ultimately require renal-replacement therapy. Within the past decade, clinical researchers — thanks to the outstanding collaboration of patients with lupus nephritis — have carried out well-conducted, controlled trials aimed at improving the efficacy and safety of the immunosuppressive regimen. Advances have been achieved, such as the use of a more patient-friendly, shortcourse induction regimen, in which low-dose intravenous cyclophosphamide is followed by long-term azathioprine maintenance therapy (as described in the Euro-Lupus Nephritis Trial\(^10\), and the introduction of mycophenolate mofetil, an immunosuppressive drug used successfully in transplantation. Mycophenolate mofetil was shown to be at least equivalent to cyclophosphamide in inducing an initial renal response\(^11-13\). In the last decade, mycophenolate mofetil (MMF) has emerged as a regimen that is not inferior to intravenous or oral cyclophosphamide for induction therapy of LN\(^14\). In clinical practice, MMF is now the preferred induction regimen for patients with LN who wish to preserve fertility, in childbearing women. MMF is also preferred in patients seeking to avoid toxicity like hemorrhagic cystitis, bladder cancer, hair loss, nausea and anorexia. However due to lacking of data favoring use of MMF in two situations there is preference of use of cyclophosphamide like long term preservation of renal function with the use of MMF as an induction agent and in case of rapidly progressively glomerulonephritis due to lupus\(^15,16\).

The therapeutic options for proliferative and membranous lupus nephritis that is resistant
to conventional treatment. There is no universal definition of treatment resistance in lupus nephritis. Controlled trials in refractory lupus nephritis are largely unavailable. Open-labeled studies have reported success of newer immunosuppressive drugs, immunomodulatory therapies, and the biological agents such as mycophenolate mofetil (MMF), calcineurin inhibitors, leflunomide, intravenous immunoglobulin, immunoadsorption, and rituximab in the treatment of cyclophosphamide (CYC) resistant proliferative lupus nephritis. More aggressive CYC regimens have been used in lupus nephritis, but at the expense of more toxicity. For membranous lupus nephritis (MLN), a combination of corticosteroids with azathioprine, chlorambucil, cyclosporin A, MMF, or CYC is initially effective in two-thirds of patients. More aggressive and costly regimens should be reserved for truly refractory disease with persistent nephrotic syndrome or declining renal function. Evidence regarding the efficacy of MMF in refractory MLN is conflicting and controlled trials are necessary to resolve the controversy. The treatment of refractory lupus nephritis remains anecdotal. An international consensus in the renal response criteria should be developed and validated so that controlled trials can be performed to compare the efficacy of various treatment modalities.

References