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Review Article

Treatment of membranous lupus nephritis

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ABSTRACT

Systemic lupus erythematosus is associated with renal involvement in almost 50–80% of cases. Although proliferative lupus nephritis is the most common form, isolated membranous lupus nephritis (MLN or class V lupus nephritis) accounts for 11–20% of cases while mixed proliferative and MLN (Class III + V/IV + V) can be seen in another 21–30%. MLN can present as either sub-nephrotic or nephrotic proteinuria with or without microscopic hematuria or renal dysfunction. These patients are at high risk of cardiovascular and cerebrovascular complications due to thrombotic tendency, dyslipidemia and hypertension. Uniform evidence regarding prognostic factors, outcome and therapy of MLN are still elusive. Systematic analysis of several studies have shown that sustained nephrotic proteinuria, failure to achieve complete remission and associated proliferative lesions denotes poor prognosis. In general, the long term renal survival rate is 50–90%, while end stage renal disease occurs in 12–22% cases. Transformation to proliferative nephritis is also well known, thus a close follow up is warranted in all pure MLN cases. Those with persistent nephrotic proteinuria, renal dysfunction and mixed histology should be treated aggressively with immunosuppressive agent while less severe cases can be managed with adjunctive therapies.

1. Introduction

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease with varied manifestations. The renal involvement in the form of lupus nephritis (LN) occurs in about 50–80% of cases[1,2] and is higher in Asians, Africans and Hispanics as compared to Caucasians.[3] The recent classification has proposed six classes of LN, of which Class V or pure membranous lupus nephritis (MLN) accounts for 11–20% of cases.[4,5] MLN used to be considered as a benign class of renal lupus, but over the years, it has been observed that untreated MLN is associated with various morbidities and mortality due to either nephrotic syndrome per se or complications associated with it. MLN can present as isolated "pure" MLN (Class V) or as mixed membranous with proliferative lesions (Class III + V/IV + V), the later accounts for about 22–31% cases of all LN.[6,7] As the incidence of pure MLN is less as compared to proliferative LN, studies dedicated to it have been few and data regarding population demographics and disease outcomes are meager. In this article, we will briefly review the

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available evidence on MLN with special emphasis on various treatment options and disease outcomes.

2. Clinical presentation

Both SLE and MLN affect predominantly young females. The female to male ratio is about 9:1.[1,2] MLN is more likely to present with renal disease before other systemic features of lupus are apparent. The presentation can be with nephrotic syndrome (50–70%), microscopic hematuria (25–50%) or renal dysfunction (10–30%) at the initial visit.[7,8] There can be associated hypoalbuminemia, dyslipidemia and vascular thrombosis. The cause of thrombosis in MLN is multifactorial including nephrotic state, antiphospholipid antibody and disease activity. Incidence of deep venous thrombosis and pulmonary thromboembolism range from 23 to 28% over 7–10 years and risk of arterial thrombosis is around 8.4% at 5 years and 16.7% at 10 years.[9–12] Antiphospholipid antibody has been reported in up to 40% of MLN and increases the risk of arterial thrombosis.[11] Unlike proliferative LN, there is less frequency of hypertension, positive serology or hypocomplementemia, and more incidence of nephrotic range proteinuria. Compared to idiopathic membranous nephropathy (IMN), MLN is seen predominantly in females of younger age group, has lesser degree of proteinuria and higher incidence of renal dysfunction.

3. Pathogenesis

The pathogenesis of SLE and MLN has not been clearly defined. Both auto antibodies and complement system are equally significant in the final pathway. Breaking of tolerance is triggered by increased apoptosis, decreased clearance of apoptotic debris with expression of auto-antigens on apoptotic blebs. The toll like receptors also plays a role in pathogenesis and activates the effector T cells and self reactive B cells.[2] These auto-reactive B cells produce antibodies to double stranded deoxyribonuclease (dsDNA)-histone complexes which are released from apoptotic debris.[13–15] Late stages of apoptosis release nucleosomes which contain high mobility group box-1 (HMGB1) which stabilizes nucleosomes and are also pro-inflammatory.[16]

In MLN, the pathogenesis is thought to be similar to that of IMN. There is either deposition of preformed antigen-antibody complexes in the basement membrane or the antibodies may get filtered through the filtration barrier and react with the antigens in glomerular basement membrane resulting in in-situ formation of antigen-antibody complexes.[2] These complexes lead to activation of the complement pathway, forming C5b-9 membrane attack complex which can then lead to podocyte injury and effacement of foot processes culminating into proteinuria.[17]

4. Pathology of MLN

The histological classification of LN and MLN has evolved since the first classification introduced by World Health Organization (WHO) in 1974. While the 1974 WHO classification divided LN into five classes with class V being MLN, the later modification done in 1982 further subdivided class V LN into 4 subclasses: Va, Vb, Vc, Vd, where Va was pure MLN, while Vb, Vc and Vd were MLN in combination with class II, III and IV LN respectively. In the further modification of this classification in 1995, the Vc and Vd subclasses were merged into class III and IV LN respectively.[18] The most recent classification was in 2003 by International Society of Nephrology/Renal Pathology Society (ISN/RPS), where LN has been classified into six classes with class V being MLN.[19] They have specified that Class V LN is characterized by diffuse thickening of glomerular basement membrane with global or segmental sub-epithelial immune deposits by immunofluroscence with or without mesangial deposits. Any combination with proliferative lesions should be considered only when the above pattern is seen in more than 50% tuft of more than 50% glomeruli and should be mentioned specifically as either class III + V or IV + V. Immunoflurosence classically shows full house pattern, with intense glomerular capillary wall and mesangial deposits of IgG1, IgG2, IgG3, C3 and C1q and negative expression of IgG4. This pattern is highly diagnostic of MLN.[20]

5. Management

Most of the evidence for treatment of MLN has been based on IMN trials and small uncontrolled studies. MLN was earlier considered as an indolent disease that can undergo spontaneous remission like IMN, however, long term follow up studies have shown that up to 25% patients with sustained proteinuria can culminate in end-stage renal disease (ESRD) due to either sclerosis or class transformation or they can develop various co-morbidities due to hyperlipidemia, atherosclerosis or hypercoagulable state.[21,22]

5.1. *Adjunctive therapies*

Blockade of renin-angiotensin-aldosterone system (RAAS), control of hypertension & lipid profile, and prophylactic anticoagulation forms important aspects of early management. Both the angiotensin converting enzyme inhibitors (ACE-I) or angiotensinogen receptor blockers (ARBs) can result in up to 50% reduction in proteinuria and can slow the progression of kidney disease.[23] In addition, hydroychloroquine (HCQ) should also be used in all patients. It has shown to reduce clinical flares, frequency of disease activity, frequency of transformation to class IV disease, progression to ESRD and prolong patient survival. Moreover, those on HCQ required only low doses of corticosteroids.[24–26] Prophylactic anticoagulation should be considered in high risk patients, like those who are immobilized, have massive proteinuria and serum albumin <2 g/dL.[12]

5.2. *Immunosuppressive therapy*

There is paucity of data to delineate an optimal immunosuppressive therapy in pure MLN. Those patients with subnephrotic proteinuria can be treated with above mentioned adjunctive therapies. However, persistent nephrotic range proteinuria along with severe hypoalbuminemia, renal