AJKD
In Practice

Membranous Lupus Nephritis: The Same, But Different

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Membranous lupus nephritis (MLN) has a favorable prognosis compared to proliferative lupus nephritis (PLN) or combined MLN/PLN, although a significant proportion of cases will progress to end-stage kidney disease. There is considerable morbidity associated with thrombotic complications and treatment. Nondirected care includes renin-angiotensin-aldosterone system blockade, cardiovascular risk management, and antimalarial agents. There may be a role for corticosteroid monotherapy in some patients, but this requires further investigation. Clinical trials and observational reports have led to different immunosuppression regimens for MLN, although high-grade evidence favoring a particular agent remains elusive. Established medications used in the treatment of PLN, such as mycophenolate, cyclophosphamide, and azathioprine, may also be efficacious in MLN, or at least steroid sparing. The calcineurin inhibitors appear promising as an alternative treatment in MLN, particularly with emerging experimental data supporting their nonimmunologic antiproteinuric effects. There is also emerging evidence for "multitargeted therapy" in combined MLN/PLN, although the long-term efficacy is still unproved.
Am J Kidney Dis. 68(6):954-966.

INDEX WORDS: Membranous lupus nephritis (MLN); class V lupus nephritis; systemic lupus erythematosus; immunosuppression; calcineurin inhibition; renal prognosis; end-stage kidney disease; pathophysiology; rituximab; review.

Joanne M. Bargman, MD, FRCPC, was an International Distinguished Medal recipient at the 2016 National Kidney Foundation Spring Clinical Meetings. The International Distinguished Medals are awarded to honor individuals who have made significant contributions to the field of kidney disease and furthered the goals of the National Kidney Foundation.

CASE PRESENTATION

A 25-year-old Haitian woman presented for follow-up with new-onset leg edema for 2 weeks. Systemic lupus erythematosus (SLE) and class IIIa lupus nephritis had been diagnosed 1 year earlier following a presentation with microscopic hematuria, subnephrotic proteinuria (protein excretion of 1.3 g/d), hypoalbuminemia (albumin of 30 g/L), and normal estimated glomerular filtration rate (GFR; >90 mL/min/1.73 m^2). Extrarenal manifestations at that time included photosensitivity, alopecia, oral ulcers, polyarthritis, leukopenia, Coombs positive hemolytic anemia, and thrombocytopenia. Positive serologic markers included antinuclear antibodies, anti−double-stranded DNA (anti-dsDNA) antibodies, anti-Sm, and antiribonucleoprotein antibodies, with low levels of detectable C3 and C4. Subsequent treatment with high-dose oral prednisone, mycophenolate mofetil (MMF; later azathioprine [AZA] due to an intolerance), and hydroxychloroquine had resulted in an excellent clinical and serologic response after 3 months, with resolution of skin lesions, normalization of cell counts and complement and serum albumin levels, and a reduction in proteinuria to protein excretion < 0.5 g/d. The patient had remained well on maintenance therapy (AZA and low-dose prednisone) until 2 weeks preceding the current presentation. There were no extrarenal signs or symptoms of active lupus. Serum albumin level was low (20 g/L) and proteinuria had protein excretion of 9.4 g/d. Serum complement levels and GFR remained normal. There was stable low-level positivity for anti-dsDNA antibodies. A repeat kidney biopsy showed pure membranous lupus nephritis (MLN). The prednisone dose was increased, and cyclosporine (CsA) and an angiotensin-converting enzyme inhibitor were added to the patient's ongoing treatment regimen. The patient improved gradually and achieved complete remission of proteinuria after 32 months. There have been no subsequent relapses in the intervening 24-month period since the time of complete remission, with CsA having been gradually weaned and discontinued in the interim.

INTRODUCTION

Lupus nephritis is a manifestation of SLE in up to 75% of patients during the course of their disease, often presenting earlier in those of African or Hispanic ethnicity.[1] MLN, or International Society of Nephrology/Renal Pathology Society class V lupus nephritis, is less frequently encountered than class III or IV proliferative lupus nephritis (PLN), accounting for 10% to 20% of cases.[2] Proliferative and membranous forms may coexist as combined disease or appear independently in the same patient as distinct presentations. Histologically, MLN is characterized by findings of podocyte foot-process effacement with global or segmental continuous granular subepithelial immune deposits, often with concomitant mesangial immune deposits. Scattered subendothelial deposits by immunofluorescence or electron microscopy are considered acceptable and part of the pathogenic

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Received April 15, 2016. Accepted in revised form July 6, 2016. Originally published online September 24, 2016.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.07.026

process if there are no accompanying light microscopy changes consistent with PLN.[3] If light microscopy changes of PLN are present in this setting, a diagnosis of combined MLN/PLN is made.

Although pure MLN has a better renal prognosis than PLN, it is still associated with significant morbidity, including the risk for thrombosis associated with severe hypoalbuminemia, a transition to PLN in approximately one-third of patients, and risk for progression to end-stage kidney disease in ~10% of patients after 10 years.[4,5] The optimal treatment strategy for MLN remains unknown, but typically involves immunosuppression for patients with nephrotic-range proteinuria, declining GFR, or combined MLN/PLN. As is often the case with glomerular disease, there is a paucity of high-quality trial evidence to guide practitioners. This is reflected in the low level of evidence accompanying the recommendations of the recent KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for glomerulonephritis in relation to the treatment of MLN.[6] This review focuses on the various pathophysiologic, clinical, and therapeutic considerations involved in treating patients with MLN.

PATHOPHYSIOLOGY

Murine models have demonstrated that the development of PLN or MLN appears to be dependent on T helper cell type 1 (T_H1) or T_H2 cytokine production, respectively.[7] Hence, the imbalance of T_H1:T_H2 ratio in a patient may be a critical determinant of the histologic class of lupus nephritis that ensues. MLN has been described in the absence of other extrarenal manifestations or serologic markers of active SLE and even in the face of ongoing immunotherapy for PLN.[8,9] This observation also supports a different pathogenesis to that of PLN. In SLE, autoantibodies form immune complexes within the vascular compartment or, through antigenic mimicry, autoantibodies may cross-react with glomerular basement membrane (GBM) antigens to form in situ immune complexes. The latter mechanism has been demonstrated in animal studies in the case of α-actinin, a GBM protein that cross-binds actin for cytoskeletal integrity. The introduction of anti-DNA antibodies with cross-reactivity to α-actinin leads to proteinuria and ultrastructural changes in the GBM, including podocyte foot-process effacement and subendothelial and subepithelial immune complex deposits.[10] Known lupus-associated autoantibodies to both DNA and non-DNA antigens, including Ro, La, and C1q, have been demonstrated as constituents of these immune deposits in patients with lupus nephritis.[11,12] In MLN, GBM immune complex deposition occurs primarily in the subepithelial location, the reasons for which are unclear, and dictates a nonproliferative disease course.

Noninvasive diagnostic testing in MLN has had limited advances. Screening for anti–phospholipase A_2 receptor (PLA_2R) antibodies, since their discovery in primary membranous nephropathy, is becoming more common in nephrotic syndrome. These antibodies are expected to be negative in patients with secondary causes of membranous nephropathy owing to the different antigenic targets of autoimmunity, as demonstrated by Beck et al[13] and others[14] in cohorts with primary membranous nephropathy. Antibodies to ribosomal P protein are a potentially useful noninvasive marker to discriminate MLN from PLN in patients with SLE, particularly when detected in the absence of anti-dsDNA antibodies, although this may not be applicable to all ethnicities.[15,16] A recent study compared urinary biomarker excretion and histologic features of lupus nephritis. Elevated urinary levels of monocyte chemoattractant protein 1, transferrin, and α-1-acid glycoprotein, combined with the creatinine clearance and serum C4 level, demonstrated good diagnostic potential to selectively identify cases of pure MLN from a mixed lupus nephritis cohort.[17]

A diagnosis of MLN versus primary membranous nephropathy may become evident only following kidney biopsy, particularly if serology and complement levels are noncontributory (Table 1). Histologic features more consistent with a diagnosis of MLN include mesangial (Fig 1) and occasional subendothelial immune complex deposition. Immunoglobulin G (IgG) deposits in primary MN are predominantly of the IgG4 isotype, whereas IgG1 and IgG3 isotypes are predominant in MLN (see granular deposition of IgG in Fig 2). There may also be glomerular staining for IgA, IgM, and C1q, which is not a typical feature of primary membranous nephropathy. Tubular basement membrane immunoglobulin staining is rare in primary membranous nephropathy, but is frequently seen in MLN. Also, endothelial cell tubuloreticular inclusion bodies seen on ultrastructural examination are highly suggestive of a secondary cause of membranous nephropathy, such as lupus nephritis or viral infection.[18]

CLINICAL PRESENTATION

Patients are typically young women. Although clinical manifestations of lupus nephritis are similar in all ages and both sexes, men may be prone to a more severe disease course.[19] Commonly, MLN presents with features of nephrotic syndrome, although proteinuria may be subnephrotic. Microhematuria, and possibly red blood cell casts, may be evident on urine microscopy. Hence, the presence of red blood cell casts does not necessarily imply class III or IV involvement, although combined MLN/PLN must be considered. Results of antinuclear antibody testing are