Understanding MPGN In the Native and Transplanted Kidney

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Membranoproliferative glomerulonephritis (MPGN), also termed mesangiocapillary glomerulonephritis, is a diagnosis based on a glomerular injury pattern common to a heterogeneous group of diseases (1). MPGN is characterized by both an inflammatory (proliferative) and resolving (membrane) phase. Histologically, the proliferative phase is characterized by an increase in mesangial and endocapillary cellularity, and the resolving phase is characterized by an increase in mesangial matrix and capillary wall remodeling with basement membrane material forming a wall, resulting in double contour formation.

Previously, MPGN was classified into MPGN types I, II, and III, based on the ultrastructural location of the electron-dense deposits along the capillary walls. This classification did not take into account the underlying pathophysiology and was based purely on electron microscopic findings. However, a new Mayo classification of MPGN has recently been proposed that is based on the pathophysiology of MPGN (1,2). Immunofluorescence (IF) studies are the key to this classification, which now classifies MPGN into immune complex–mediated MPGN or complement-mediated MPGN (Figure 1). The basis of immune complex–mediated MPGN is the IF finding of mesangial and capillary wall Ig deposits with or without C3. Deposition of Ig activates the classic pathway of complement. As a result, C3 is often noted on IF studies along with the immune deposits. Furthermore, the type of immune deposits indicates the underlying cause. For example, deposition of monotypic Ig such as IgG-κ or IgM-λ indicates an underlying monoclonal gammopathy/dysproteinemia (3). By contrast, IgM deposits are often noted in chronic viral infections such as hepatitis C, whereas IgM-predominant deposits with smaller amounts of IgG are often noted in autoimmune diseases (4). Thus, immune complex–mediated MPGN typically results from one of three underlying disease mechanisms: monoclonal gammopathy/dysproteinemias, infections, or autoimmune diseases.

By contrast, complement-mediated MPGN results from glomerular deposition of C3 and other complement factors and degradation products (5). Deposition of C3 and complement factors results from dysregulation and overactivation of the alternative pathway of complement. The alternative pathway of complement is usually tightly regulated; however, dysregulation of the alternative pathway of complement can occur as a result of mutations/polymorphism (inherited) or autoantibodies (acquired) to complement regulating proteins, such as factor H, B, or I. In complement-mediated MPGN, the IF findings are characterized by dominant C3 staining with absent or scant Ig. The term C3 glomerulopathy is also used to define complement-mediated MPGN, inasmuch as other patterns in addition to the MPGN pattern, such as mesangial or diffuse proliferative glomerulonephritis, may be present. Electron microscopy further subdivides C3 glomerulopathy into C3 glomerulonephritis and dense deposit disease (DDD). In C3 glomerulonephritis, the deposits are discrete and are present in the mesangium and subendothelial region of the capillary walls and occasionally the intramembranous and subepithelial regions of the capillary walls as well. By contrast, in DDD the deposits are large, extremely dense (osmiophilic), and intramembranous, often resulting in marked thickening of the glomerular basement membranes.

It can be appreciated that the new Mayo classification attempts to elucidate the underlying causes of MPGN by dividing it into immune complex–mediated and complement-mediated disease. The classification facilitates appropriate evaluation, leading to identification of the correct cause. Treatment should then be based on the underlying pathogenesis of MPGN. Recent retrospective studies have tried to compare the course and prognosis between the two groups of MPGN. However, in fairness, one cannot adequately compare the two groups in retrospective studies because the underlying causes were poorly understood at the time, and none of the groups received specific treatment aimed at the cause.

The new Mayo classification of MPGN bears on the understanding of recurrence of MPGN after kidney transplantation. MPGN recurs in up to 50 to 70 percent of transplant recipients. Among the immune-complex MPGNs, recurrence rates are very high for MPGN resulting from monotypic Ig deposition from an underlying monoclonal gammopathy. Current recommendations include treatment of the monoclonal gammopathy before transplantation. By contrast, the recurrence rates of MPGN from infections and autoimmune disease are relatively low. With regard to complement-mediated MPGN, C3 glomerulonephritis recurs in almost two thirds of patients, with graft failure resulting in half of the patients within 6 to 7 years of recurrence (6). DDD also has a high rate of recurrence after kidney transplantation and results in graft failure in up to 50 percent of patients, with graft loss occurring within 2.5 years of transplantation.

To summarize, the new Mayo classification of MPGN is easy to understand, is based on the underlying pathophysiology, and divides MPGN into immune complex–mediated MPGN and complement-mediated MPGN for further pathologic subheadings. The classification facilitates appropriate laboratory evaluation, leading to identification of the underlying cause of MPGN and the hope of better guidance for management.

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Figure 1. **Proposed classification scheme for MPGN into immune complex–mediated and complement-mediated MPGN, based on immunofluorescence microscopy (IF) findings. Immune complex–mediated MPGN is characterized by the presence of immunoglobulins (Ig) and/or C3, while complement-mediated MPGN is characterized by the presence of bright C3 and absent/scant Ig. Evaluation of immune complex–mediated MPGN should include work-up for monoclonal gammopathy, autoimmune diseases, and infections. On the other hand, evaluation of complement-mediated MPGN should include work-up for functional, acquired, and inherited abnormalities of the alternative pathway of complement.**