Chapter 8: Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury

This chapter replaces the 2012 guideline chapter for idiopathic MPGN. Given the advances in our understanding of underlying etiology and the recognition that MPGN is not a disease but a pattern of glomerular injury, this updated chapter discusses the evaluation and management of the glomerular disease that often have a membranoproliferative pattern of injury, including C3G.[522]

The treatment of MPGN depends upon identification of an underlying cause. In most cases, the MPGN lesion derives from deposition of immunoglobulins and complement as either immune complexes (secondary to an underlying infection/autoimmune process), or monoclonal immunoglobulins, or is due to dysregulation of the alternative complement pathway.

In a few cases of immune complex–mediated MPGN, an identifiable underlying cause cannot be found despite extensive evaluation. This may be seen in children and young adults, but is rarely seen in adults. These patients are considered to have an "idiopathic" immune complex–mediated MPGN or immune complex–mediated MPGN of unknown etiology.

Because previous controlled trials included patients based on the old and now discarded electron-microscopic classification of MPGN, and not on the current classification that uses immunofluorescence microscopy in combination with presumptive disease pathobiology, there is insufficient high-quality evidence to form recommendations for the management of the various diseases that have MPGN histology. Therefore, practice points will be given to assist in clinical decision-making for these patients.

Nomenclature

The membranoproliferative pattern of GN is a light-microscopic pattern of kidney injury, characterized principally by an increased number of intraglomerular cells and diffuse thickening of the glomerular capillary walls. The clinical presentation is not specific, and patients commonly present with proteinuria (frequently associated with the NS), hypertension, glomerular hematuria, and abnormal kidney function. Hypocomplementemia (C3 and/or C4) is often, but not always, present. An MPGN pattern of injury may be found in many unrelated disorders (Figure 68). Identification of the pathogenic mechanisms specific for a disease is critical for appropriate management.

Membranoproliferative lesions were historically classified based on the location of deposits on electron microscopy examination as:

- *Type I MPGN* (MPGN I)—characterized by *subendothelial* and *mesangial* electron-dense deposits consisting of both immunoglobulin and C3
- *Type II MPGN* (MPGN II—Dense deposit disease [DDD])—characterized by electron-dense *intramembranous* deposits, predominantly consisting of complement
- *Type III MPGN* (characterized by *both subepithelial and subendothelial deposits*)

This historical classification was not based on disease pathogenesis, and as a result, different pathogenic processes fell under the collective designation of MPGN.

Advances in our understanding of underlying disease mechanisms leading to the development of a membranoproliferative pattern of kidney injury have resulted in a new pathobiology-based classification. The new classification relies on immunofluorescence examination; deposits are defined as primarily immunoglobulin (monoclonal), polyclonal immunoglobulin and complement, or predominantly complement (Figure 69).[523,524]

On the basis of the immunofluorescence findings, MPGN can be broadly divided into an immunofluorescence-negative subgroup, a complement-dominant subgroup, and an immunoglobulin subgroup, with or without complement. When MPGN is immunoglobulin-positive, regardless of the presence of complement, evaluation for infection, autoimmune disease, and monoclonal gammopathy should be done. Complement-dominant MPGN is further divided into C3/C4 glomerulopathy. A complement-dominant pattern requires evaluation of the alternative pathway of complement. Absence/trace Ig or C3 suggests a TMA.

It should be understood that the presence of an MPGN lesion implies that the pathogenic process has been present for some time and that other patterns of injury, including endocapillary proliferative GN, mesangioproliferative GN, and crescentic GN, may occur as a result of the same process. Thus, the type of lesion initially seen on light microscopy will depend, in part, on the timing of the kidney biopsy in relation to disease chronicity.[525]

Immune complex–mediated GN (ICGN) with an MPGN pattern

ICGN is characterized by the deposition of immune complexes containing both polyclonal immunoglobulins and