
بسم الله الرحمن الرحيم

Classification and clinical presentation of MPGN

Dr Z. ROSTAMI

Professor of Nephrology

Baqiyatallah University of Medical Sciences

Membranoproliferative glomerulonephritis

MPGN is a pattern seen in LM in approximately 7–10% of all biopsy-confirmed GN

Typical hallmarks are endocapillary and mesangial hypercellularity, mesangial matrix expansion, and formation of capillary double contours resulting in a lobulated morphology.

However, these changes can vary from minimal to mesangial, endocapillary proliferative, exudative, crescentic, and sclerosing patterns, possibly portraying different time points of injury.

MPGN is a histologic lesion and not a specific disease entity.

The identification of an MPGN lesion in a kidney biopsy does not establish a specific diagnosis; rather, it should prompt the clinician to pursue a thorough evaluation to determine the underlying cause of the MPGN lesion

MPGN

MPGN can be primary/idiopathic disease (in which MPGN is used as a diagnostic term) or secondary to other known disease entities (Secondary to infections, autoimmune diseases and haematological disorders).

Primary MPGN is rare, with an estimated incidence of 1–3 cases/million/year , and the prognosis is unfavourable.

The secondary types are more common than the idiopathic types.

MPGN is classified into 2 broad categories based on IF staining pattern.

ARTICLE IN PRESS

KI REPORTS
KIReports.org

REVIEW

Challenges in the Diagnosis and Management of Immune Complex-Mediated Membranoproliferative Glomerulonephritis and Complement 3 Glomerulopathy

- Historically, MPGN was classified, based on the location of glomerular deposits (by electron microscopy [EM]), as type I (subendothelial), type II (intramembranous), or type III (subendothelial and subepithelial).
- The histopathologic finding of MPGN in this classification is one of the most challenging, since it does not refer to a specific disease entity but may instead be the result of different aetiologies (is not etiology/pathogenesis-based)
- In 2010, a new classification based on the pathologic composition of glomerular deposits by immunofluorescence (IF) of kidney biopsies was proposed, reclassifying the MPGN subtypes (1) to identify new entities or misdiagnosed (2) to highlight new diagnostic approaches (3) to differentiate the therapeutic approach.

classification on the basis of IF

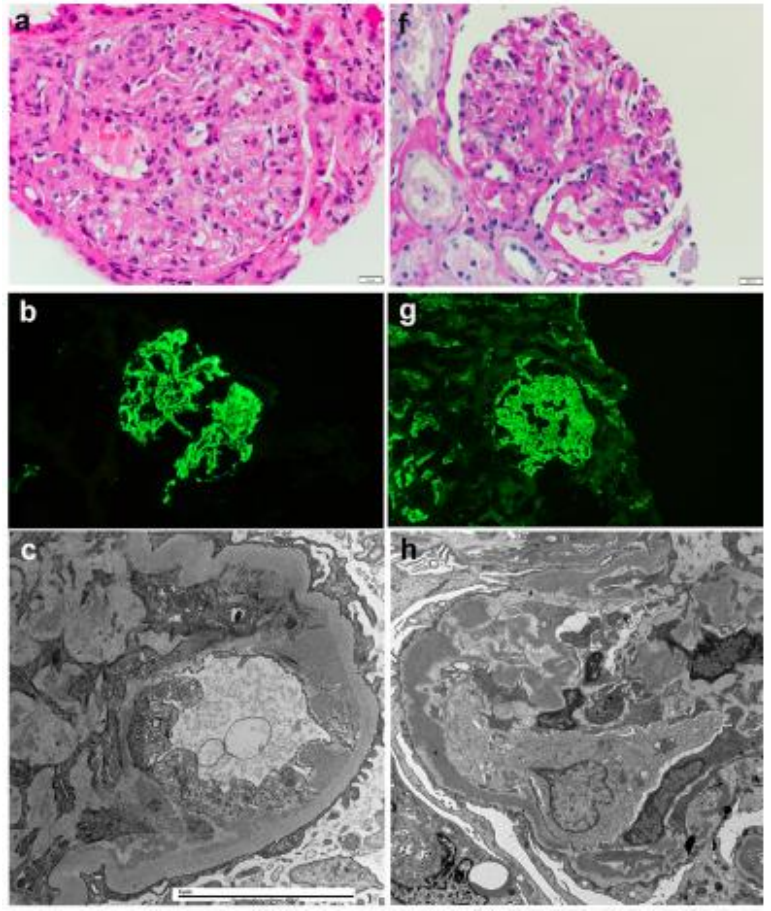
(i) Immune complex/monoclonal immunoglobulin-mediated MPGN (IC-MPGN) is characterized by the deposition of immunoglobulins and complement components.

(ii) complement-mediated MPGN or C3G is characterized by glomerular deposits of complement components in the absence of significant immunoglobulin deposition. C3G arises from abnormalities in the control of the alternative complement pathway.

The term C3G **also** includes kidney lesions that do not show the typical alterations of MPGN but share C3-dominant staining.

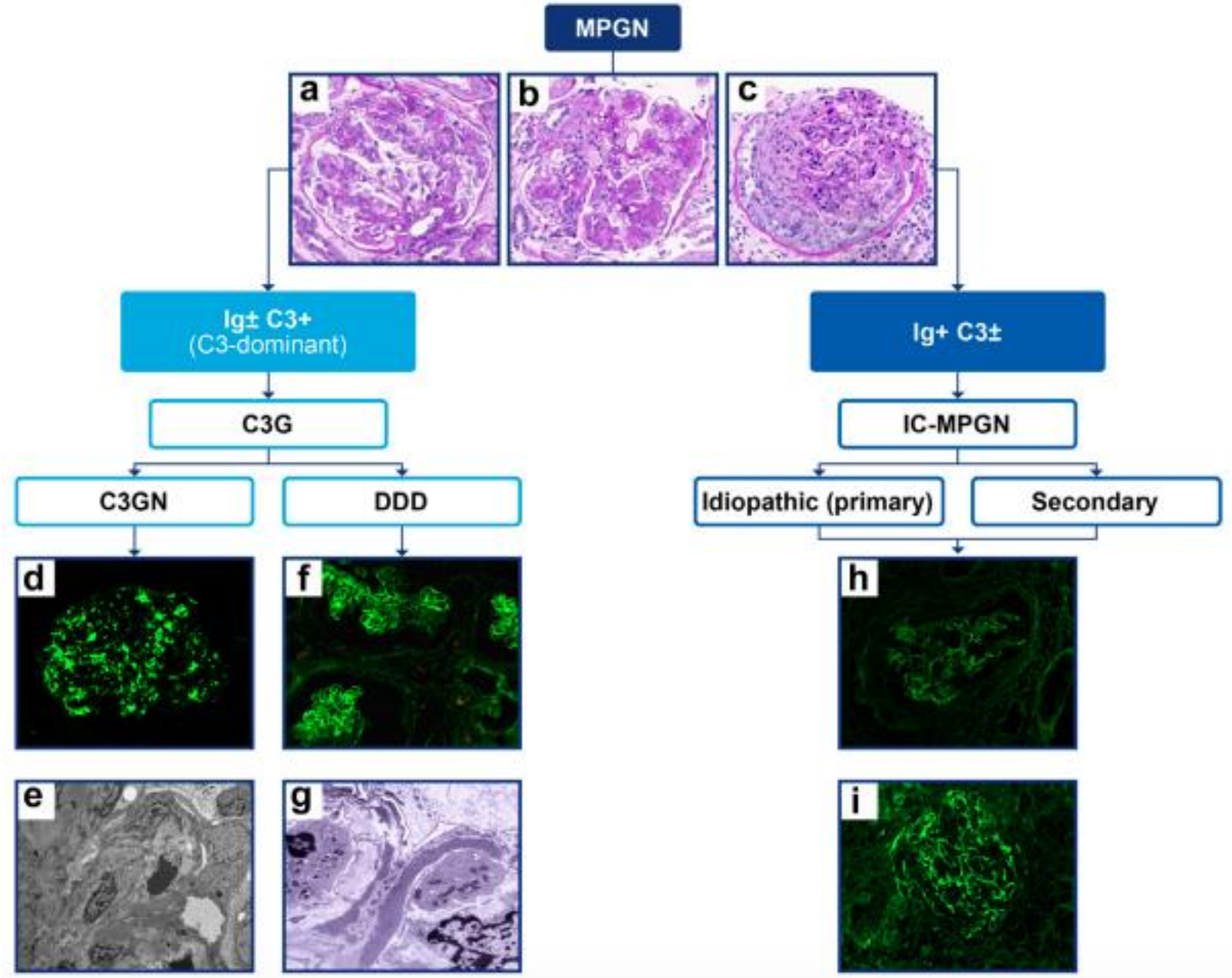
Using EM, C3G may be further classified as:

- 1) dense deposit disease (DDD, type II MPGN in the previous classification), with highly electron-dense deposits sausage-shaped in the GBM,
- 2) C3 glomerulonephritis (C3GN), with mesangial, subendothelial, subepithelial and intramembranous deposits, but without the typical electron-dense deposits of DDD.



C3GN DDD

Under the new designation, the previous subtypes termed MPGN type 1 and 3
may be classified as either C3GN or IC-MPGN, and DDD replaces MPGN type 2.
The term MPGN remains suboptimal for classification because a large proportion (up to 66%) of IC-MPGN and C3G cases do not display an MPGN pattern by LM



MPGN without immunoglobulin or complement deposition

- A histologic pattern that may resemble MPGN on LM can be seen in:
- the healing phase of thrombotic microangiopathies (eg, TTP-HUS),
- antiphospholipid antibody syndrome,
- nephropathy associated with bone marrow transplantation,
- chronic kidney allograft nephropathy,
- radiation nephritis,
- malignant hypertension.

- The common underlying cause of the MPGN pattern in such patients is endothelial injury followed by reparative changes.
- IF does not show significant immunoglobulin or complement deposition
- EM does not show electron-dense deposits along the capillary walls.

Monoclonal gammopathies: MPGN with masked deposits

The term ‘masked deposits’ refers to Ig deposits that show false negative staining by IF on frozen tissue, but which can be detected when IF is performed on paraffin-embedded tissue.

Failure to identify these "masked" monoclonal immunoglobulins can result in missing the diagnosis of monoclonal gammopathy-associated MPGN and incorrectly diagnosing these patients as having only C3GN.

It is important that these cases are not misdiagnosed as C3 glomerulopathy, as most are associated with a low-grade lymphoma or plasma cell dyscrasia

Differential diagnosis of C3GN and DDD

DDD is characterized by highly electron-dense osmiophilic deposits with a “ribbon-like” or “sausage-shaped” appearance in the GBM

in comparison, C3GN exhibits less-dense deposits, which are usually amorphous or cloudy in appearance within the mesangium and can appear as ill-defined subendothelial inclusions.

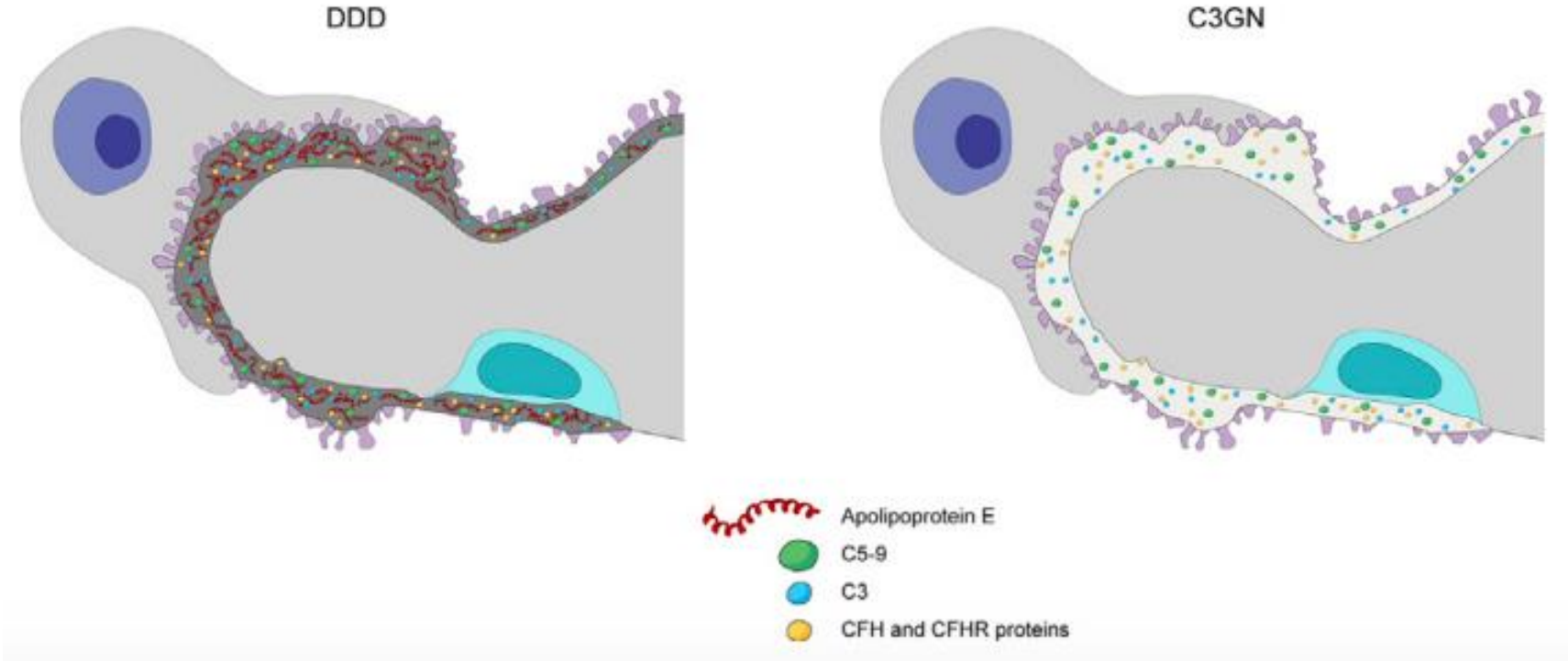
Recent study (March 2024) suggests that dense deposits in DDD are enriched in apolipoprotein E compared with C3GN, and that apolipoprotein E staining may augment the differentiation of C3GN and DDD.

Apolipoprotein E is enriched in dense deposits and is a marker for dense deposit disease in C3 glomerulopathy

see commentary on page 929

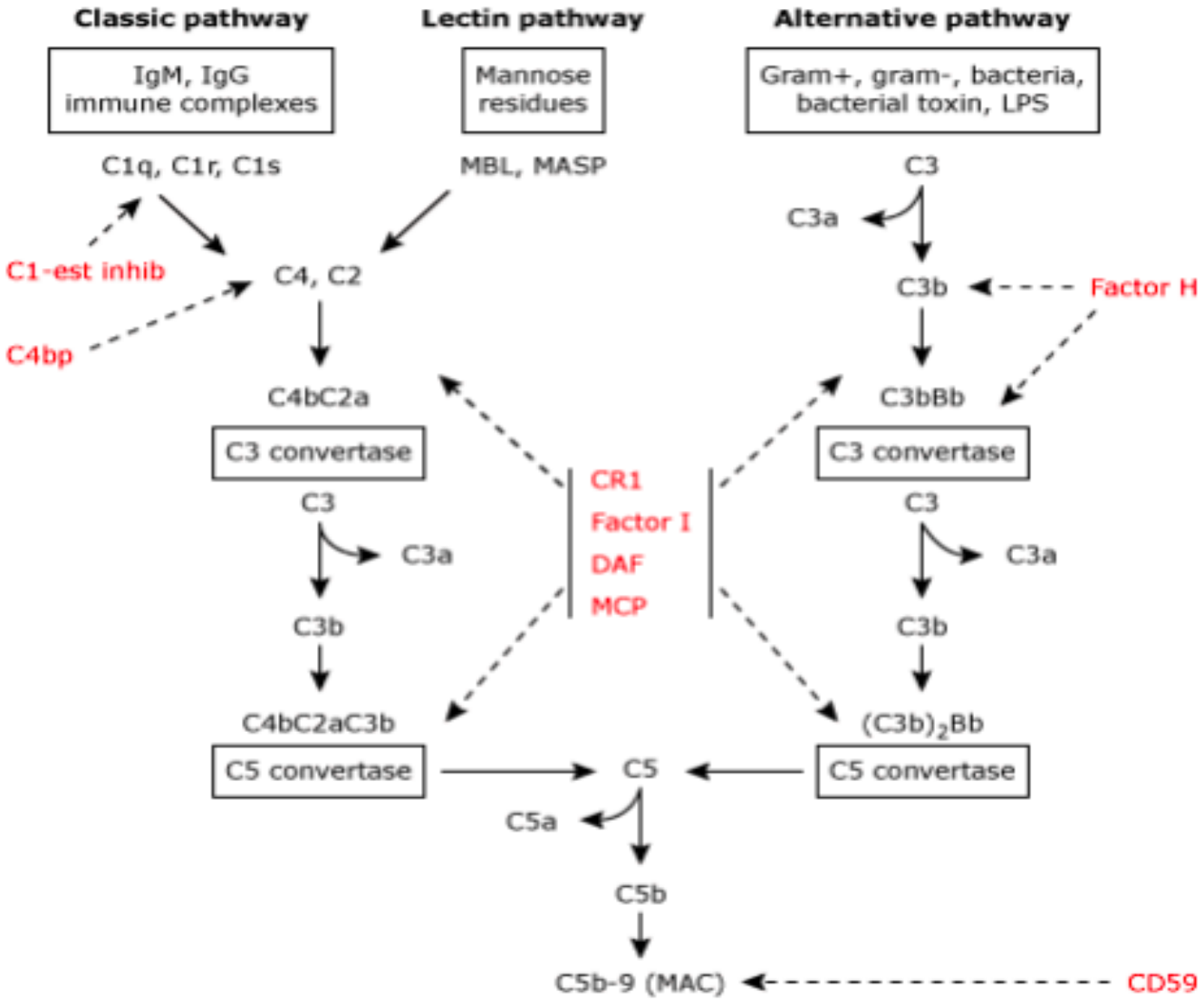
OPEN

- ApoE staining may be used as an adjunct to EM for the diagnosis of DDD and might be valuable when EM is not available.



There are two main pathways:

- the classic pathway, which is activated when IgG or IgM antibodies bind to antigens,
- the alternative pathway, which does not require the presence of antibodies and can be autoactivated by spontaneous cleavage of C3 to C3b, leading to the formation of C3 convertase.



The Role of the Complement System in C3G Pathophysiology

IC-MPGN and C3G share overlapping pathologic features, with dysregulation of the complement system playing a key role in the pathogenesis of both diseases.

Overactivation of the alternative complement pathway (AP) is the primary driver of C3G pathophysiology, which leads to accumulation of C3 in the glomerulus, resulting in kidney inflammation and damage.

In many patients, uncontrolled activation of the AP in C3G is driven by genetic abnormalities in key AP genes and/or acquired autoantibodies against complement proteins such as the C3 and C5 nephritic factors, that stabilize the AP C3 and C5 convertases, respectively, thereby prolonging their half-life

The Role of the Complement System in IC-MPGN Pathophysiology

The role of the complement system in the pathogenesis of IC-MPGN is less well-understood, and mechanisms leading to the deposition of immune complexes remain unknown.

Immune complexes in both idiopathic and secondary IC-MPGN activate the classical complement pathway, whereas several studies have reported similar levels of genes and/or acquired autoantibodies against complement proteins in patients with **idiopathic IC-MPGN and C3G** .

In addition, the prevalence of low serum C3 with normal serum C4, indicative of AP activation, is considerable in patients with idiopathic IC-MPGN and C3G. This highlights a role for overactivation of the AP in idiopathic IC-MPGN.

Clinical presentation and diagnosis

Patients with these disorders may exhibit similar clinical characteristics at disease onset, such as proteinuria, hematuria, decreased kidney function, nephrotic syndrome, and hypertension; definitive diagnosis therefore requires a kidney biopsy.

However, distinguishing IC-MPGN and C3G by kidney biopsy remains a challenge, due to overlap in the composition of glomerular deposits and the subjective grading of IF staining intensity.

In addition, consecutive biopsies in the same patient may reveal a change in IF pattern from IC-MPGN to C3G, or vice versa, depending on the time course of the disease.

genetic abnormalities

Up to 40% of patients with C3GN and up to 33% of patients with DDD have detectable genetic abnormalities (such as CHFR5) in AP genes.

Nevertheless, the presence of AP factor gene variants in C3G illustrates the role of AP overactivation in disease pathogenesis, and highlights the importance of complement genetic testing in all patients after a pathologic diagnosis of C3G.

role of autoimmunity in the development of both C3G and IC-MPGN.

The detection of autoantibodies in patients with C3G (up to 46% of C3GN and up to 86% of DDD) is more likely than the detection of pathogenic gene variants.

C3NeF is the most common autoantibody detected, but autoantibodies that stabilize the C3 convertase of the lectin pathway and classical complement pathway (C4 nephritic factors), or those that recognize other complement proteins including C1q, C3, factor H, and factor B, have also been documented.

Fluctuation of C3 nephritic factors has been reported but has not been correlated with disease activity in patients with C3G.

HLA

a significant increase in the prevalence of HLA serotypes DQ2, B8, and DR17 was identified in patients with idiopathic IC-MPGN and C3G, suggesting that autoimmune processes may play a role in disease development.

In a subsequent study, HLA-DR17 was associated with kidney failure in C3GN and IC-MPGN, but not in DDD.

Switching has been reported

Whether idiopathic IC-MPGN and C3G are distinct entities or two aspects of the same disease remains a debated question,

because C3G and idiopathic IC-MPGN exhibit similar clinical presentations and patient outcomes, including similar risk of progression to kidney failure and prevalence of nephrotic syndrome.

Kidney pathologic features on LM and IF may vary from one biopsy to another in the same patient throughout the disease course.

This suggests that some cases of idiopathic IC-MPGN may fall in the same disease continuum as C3G.

This may be caused by an infectious trigger at onset that activates the lectin pathway, classical complement pathway, and AP, with the classical complement pathway becoming less active as the infection resolves and/or due to immunosuppression

workup for known secondary causes of IC-MPGN

Infection
Hepatitis B and hepatitis C virus (HCV) should be excluded by serology,

while chronic bacterial infections should be excluded by culture, including blood cultures

Patients with a history of recent sore throat or skin infection should undergo serologic testing for factor B.

We do not test for fungal and parasitic infections in absence of evidence

Autoimmune diseases
SLE, Sjögren's disease and systemic sclerosis

other than serologic testing for lupus, we would not evaluate for Sjögren's disease and systemic sclerosis in the absence of suggestive manifestations.

Monoclonal gammopathy
serum protein electrophoresis and immunofixation, serum free light chains, and urine protein electrophoresis and immunofixation.

Bone marrow examination may be required to identify the clone (B cell or plasma cell) producing the pathogenic monoclonal immunoglobulin, in order to delivery appropriate chemotherapy.

Subsequent evaluation for the cause of Complement-mediated MPGN

measuring C3, C4, CH50 (classic pathway), and AH50 (alternative pathway).

All patients with a complement-mediated MPGN should undergo genetic analysis for mutations and allele variants of complement factors and assays for autoantibodies to complement regulating proteins (eg, factors H and I), including testing for C3 nephritic factor (C3NeF),

if available, serum levels of the membrane attack complex.

summary

The diagnosis and management of IC-MPGN and C3G requires a comprehensive approach utilizing kidney biopsy, IF microscopy, complement workup, genetic testing, and evaluation of noncomplement etiologies, particularly in the context of IC-MPGN.

Whereas overactivation of the AP is the underlying cause of C3G, the role of the complement system in the pathogenesis of IC-MPGN is less clear, particularly with respect to the idiopathic form.