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COMPLEMENT-MEDIATED KIDNEY DISEASES TOOLKIT

A Basic Primer on Complement 3 Glomerulopathy (C3G)

Overview

What is C3 Glomerulopathy (C3G)

The kidney is susceptible to immune mediated injury by a variety of auto-immune insults. A rare subgroup is C3 Mediated glomerulonephritis (C3G) in which complements (particularly C3), which form the innate immune system, drive the disease process. C3G is driven by uncontrolled activation of the alternative complement pathway and encompasses both C3 glomerulonephritis (C3GN) and dense deposit disease (DDD).

This entity is being increasingly encountered in clinical practice in adults and children, and hence it is necessary to have a high degree of suspicion. In this primer, we will aim to cover the basic fundamentals of C3G.

How does C3G present?

There is no unique clinical feature typical of C3G. The clinical presentation can range from asymptomatic hematuria to proteinuria with gradual renal deterioration to rapidly progressive glomerulonephritis.

Extra-renal manifestations of C3G:

C3G may be associated with acquired partial lipodystrophy or retinal drusen.

Presentation and Diagnosis

How is C3G diagnosed?

Kidney biopsy is required for the diagnosis of C3G. Light microscopic findings can be diverse, and include membranoproliferative, mesangial proliferative, diffuse endocapillary proliferative, diffuse sclerosing and crescentic patterns. Immunofluorescence microscopy will show characteristic C3 deposition of *at least 2 orders of magnitude greater than any other immune reactant.* Electron microscopy (EM) will help to distinguish between C3GN and DDD.

C3GN Vs DDD

C3GN will demonstrate subendothelial $\pm$ subepithelial electron-dense deposits, whilst DDD is characterized by osmiophilic sausage-shaped intramembranous deposits on EM.

What is the differential diagnosis?

Post-infectious glomerulonephritis (PIGN) and monoclonal gammopathy of renal significance (MGRS) can both result in C3-dominant GN on kidney biopsies. A clinical history of a recent infection may point towards a diagnosis of PIGN, an entity which usually resolves within 8-12 weeks. Failure of resolution should prompt a repeat biopsy and work-up for C3G. Patients greater than 50 years of age at presentation should always be evaluated for dysproteinaemia.

What does the work-up for C3G include?

Evaluation of the complement cascade		
Functional Assays	CH50 (Classical) AP50 (Alternative)	Identification of affected complement pathway
Quantification Assays	C3, C4, Properdin	Upstream evidence of complement activation
	C3d, Bb, sMAC	Evidence of terminal complement cascade activation
	FI, FH, FB	
Delineation of the driving mechanism		
Autoantibody Assays	Anti-FH, Anti-FB, NeFs	Detect acquired drivers
Genetic Testing	C3, CFH, CFI, CFB, CFHR1-5	Detect variants associated with C3G
Others		
Hematological Assessment	SIEP, UIEP, SFLC, BME	Rule out MGRS

Key**:** AP50: Complement Alternative Pathway Activation 50%; Bb: Activated Factor B; BME: Bone Marrow Exam; C3d: Complement Component 3d; CFB: Complement Factor B; CFH: Complement Factor H; CFHR1-5: Complement Factor H Related Protein 1-5; CFI: Complement Factor I; CH50: Complement Hemolytic Activity 50%; FB: Factor B; FH: Factor H; FI: Factor I; NeF: Nephritic Factor; SIEP: Serum Immunoelectrophoresis; SFLC: Serum Free Light Chain; sMAC: Soluble Membrane Attack Complex; UIEP: Urine Immunoelectrophoresis.

It is recognized that the above-mentioned investigations, while comprehensive, may not be readily available.

Treatment and Prognosis

What is the treatment for C3 Glomerulopathy?*

All Patients	**All patients should have optimal blood pressure control with renin angiotensin aldosterone system inhibitors. Adequate lipid control should be achieved.**	
Moderate Disease	Proteinuria > 500mg / 24 hours despite supportive therapy *or* Moderate inflammation on kidney biopsy *or* Renal deterioration (increase in creatinine and/or proteinuria)	Prednisolone Mycophenolate Mofetil (MMF)
Severe Disease	Urine protein > 2000mg / 24 hours despite supportive therapy and immunosuppression (IS) *or* Severe inflammation on kidney biopsy (marked proliferative changes ± crescents) despite supportive therapy and IS *or* Renal deterioration (increase in creatinine and/or proteinuria) despite supportive therapy and IS Non-responders should be considered for a clinical trial where available	MMF and glucocorticoids If this fails, eculizumab / ravulizumab should be considered if indicated and available
Refractory Disease	Can consider eculizumab / ravulizumab	

*for all treatments, if indicated and available based on local context

Note: the suggested treatment is applicable only in the absence of MGRS.

What is the prognosis?

The available data to date estimates that 30-50% of adults reach end-stage kidney disease within 10 years of diagnosis.

What is the scope for kidney transplantation in C3 Glomerulopathy?

There is a significant dearth of transplant data for C3 Glomerulopathy. However, available literature suggests a high risk of recurrence with allograft failure within 10 years in 50%. There are no established preventive strategies but Eculizumab has been used.

References

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