# C3 Glomerulonephritis Associated with IgM Monoclonal Gammopathy and Low Grade B-Cell Lymphoma

**Dalya Al-Qaysi, M.D.**
**Yaseen Aleatany M.D.**
**Gahyun Gim, M.D.**
**Tala Eneizat Mahdawi, M.D.**
**Vaidyanathapuram Balakrishnan, M.D.**

St Elizabeth's Medical Center
Department of Internal Medicine
Brighton, MA, United States

Tufts University
School of Medicine
Boston, MA, United States

# Background

## Epidemiology:

- C3 glomerulopathies are rare diseases with an estimated incidence of 1-3 cases/ 1,000,000 annd point prevalence of 14 to 140 cases per 1,000,000. [1]
- The term C3 glomerulopathy was introduced recently to encompass all glomerular lesions with predominant C3 accumulation, which includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). [2,3].

## Pathogenesis:

- Mainly due to excessive activation or dysregulation of the complement alternate pathway, which is highly organized by the activity of C3 convertase. This dysregulation may occur as a result of mutations or functional inhibition of complement-regulatory proteins.

- The activity of C3 convertase can be increased by:

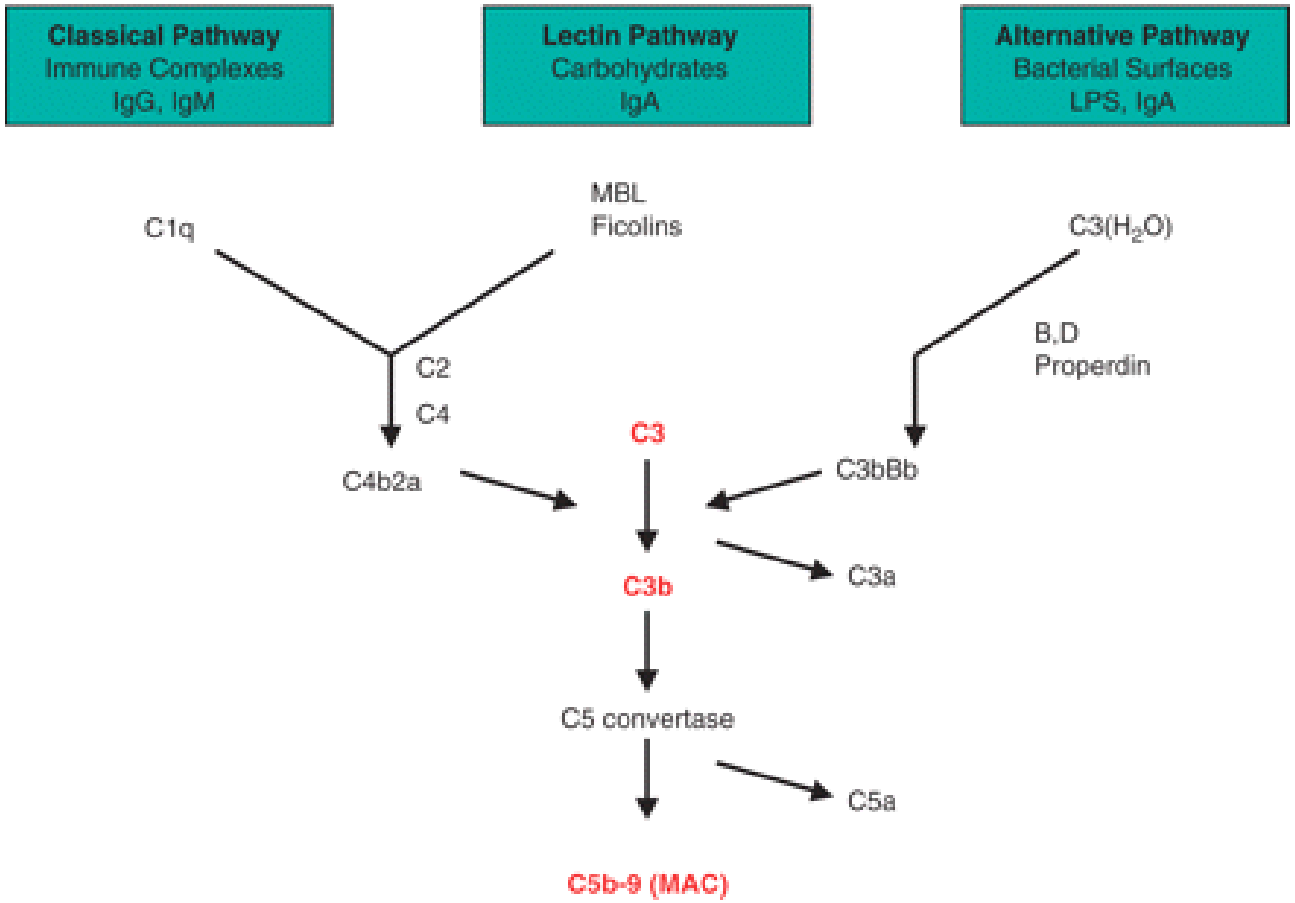
- Increased production of C3 nephritic factors (C3NeFs).
- Loss of functional factor H.
- Enzymatic cleavage of C3 by renin.

# Background

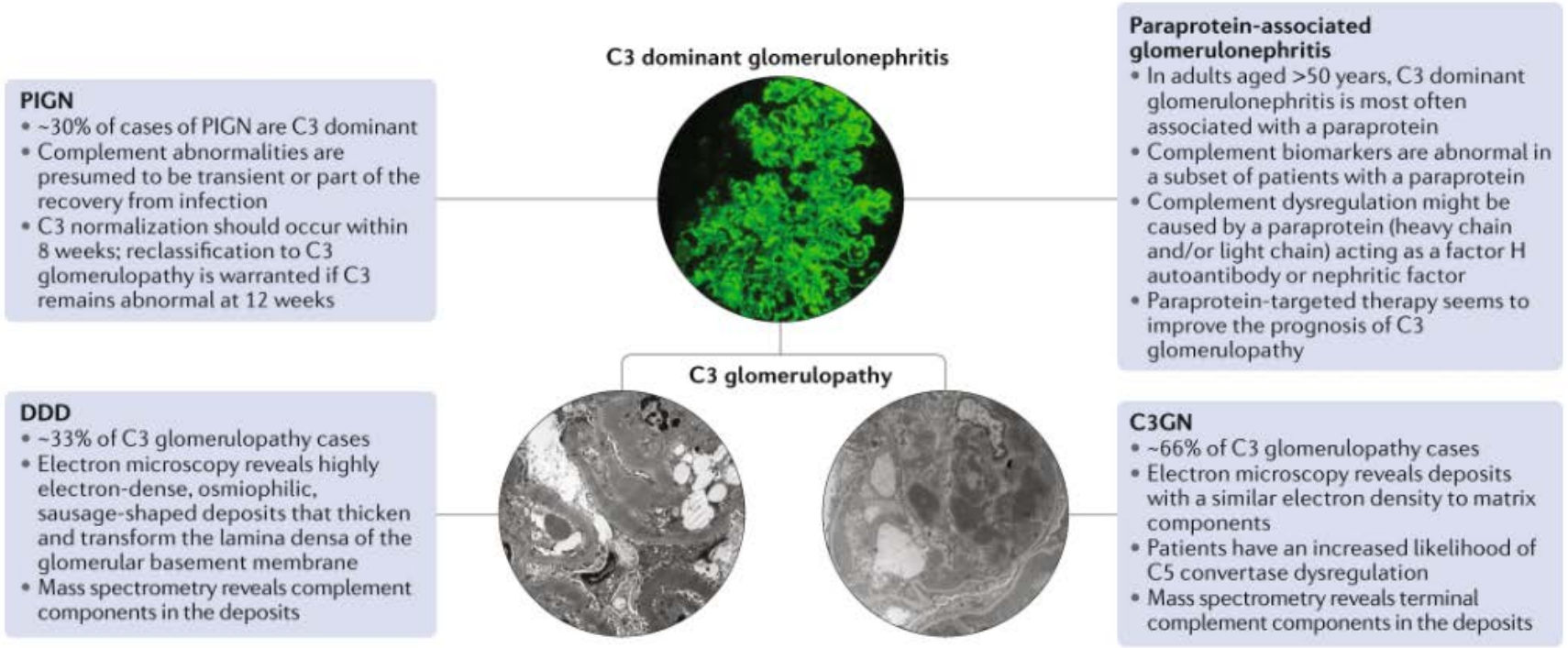
- The exact mechanism is still not well understood. But the disease process was found either inherited or acquired.
- The acquired mechanism is usually related to triggering factors including: Surgeries, infections, traumas, paraprotein and tumors.

An association with hematological cancers is largely based on the observation that functional inhibition of complement-regulating proteins may result from a monoclonal gammopathy. [4]

# Complement Pathway in Glomerulonephritis




- System of circulating proteins that form an important component of innate immunity
- 3 pathways of activation that converge at C3
- Classical pathway activated by immune complexes
- Activation of C3 leads to the formation of the membrane attack complex




Adapted from : Smith RJH, Appel GB, Blom AM, et al. C3 glomerulopathy - understanding a rare complement-driven renal disease. Nat Rev Nephrol 2019; 15:129 [1]

# Case Presentation

78-year-old man with hypertension, who underwent left total hip arthroplasty, that was complicated by wound infection requiring incision and drainage with a wound culture growth of MRSA and Proteus mirabilis. He was appropriately treated then discharged. Readmitted with persistent left hip pain, worsening dependent edema, and profound oligoanuric acute kidney injury with a serum creatinine (S.Cr) of >9 mg/dL.

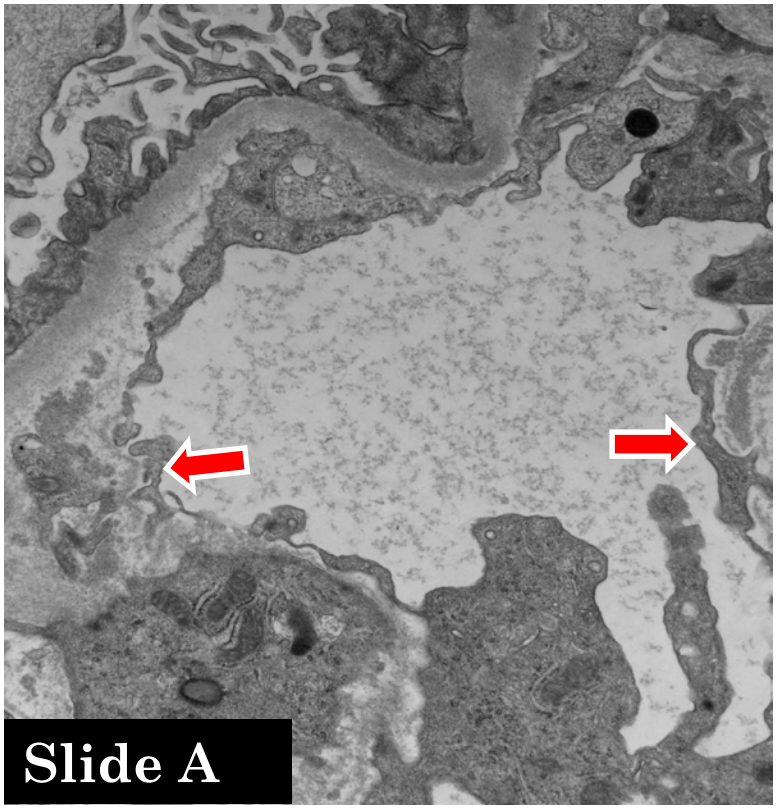
Urine studies:

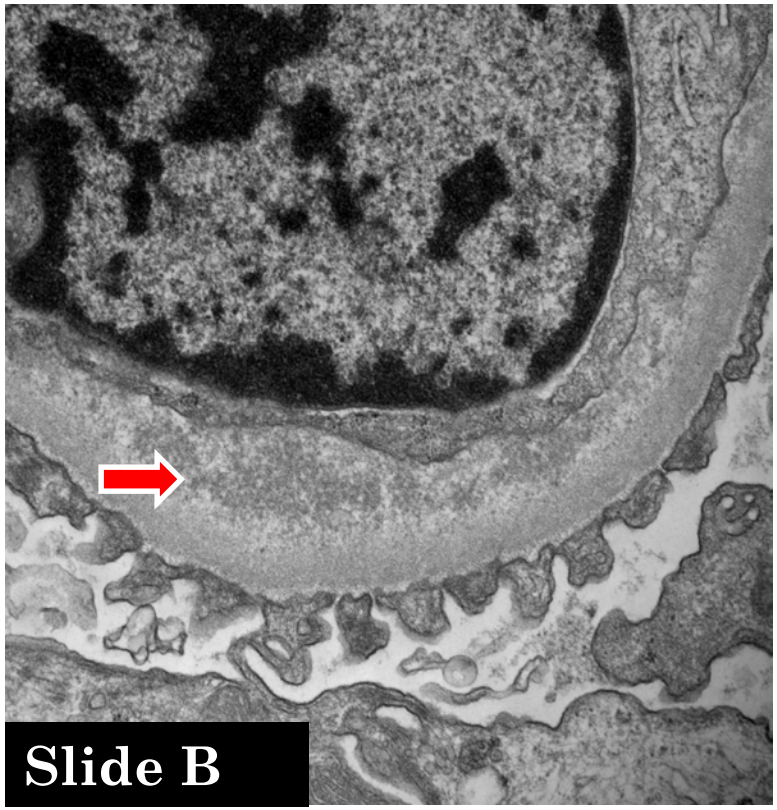
- Proteinuria
- Microscopic hematuria
- Urine sediment showed numerous erythrocytes, leukocytes but no cellular casts.
- Random urine protein:creatinine ratio was >2.5 g/g.

# Case Presentation

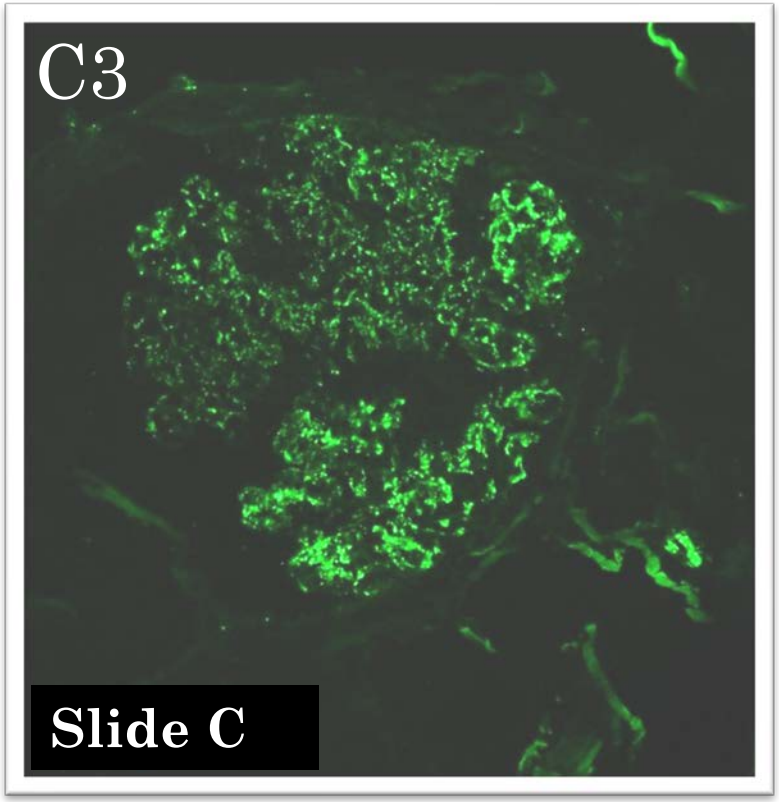
Serological work-up:

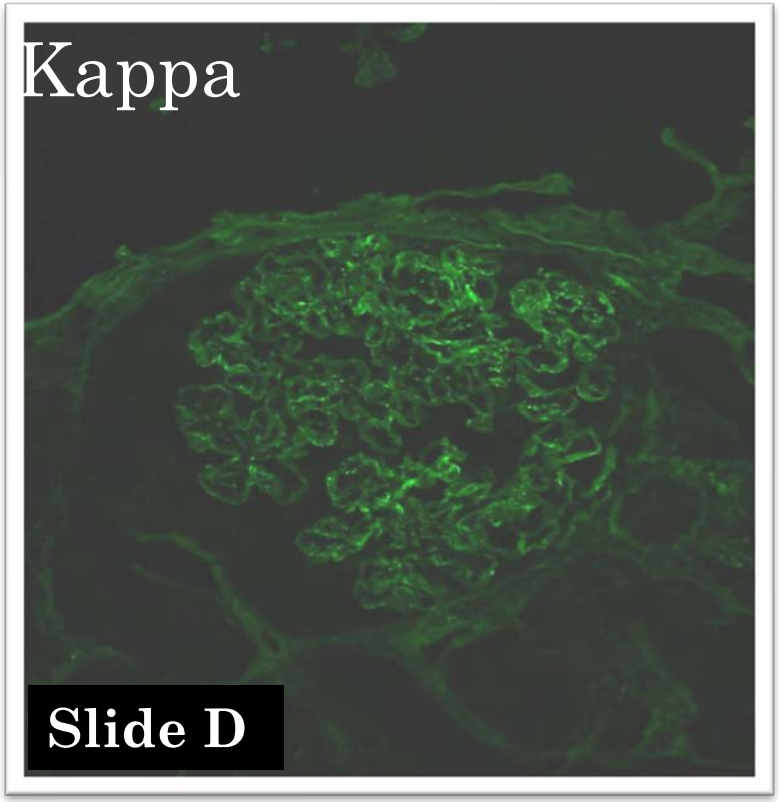
- Low C3 and normal C4 level.
- Positive perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) with undetectable anti-myeloperoxidase antibodies.
- Serum and urine protein electrophoresis with immunofixation was positive for an IgM-kappa monoclonal paraprotein.




Slide A and B: Renal biopsy tissue electron microscopy shows subendothelial, intramembranous, and hump-like subepithelial and mesangial electron dense deposit.




Slide C and D: Renal biopsy , immunofluorescence (IF) staining microscopy studies shows C) C3 immunnofluoresent staining and D) IgM/Kappa restricted cellular infiltrate in the interstitium.

# Bone marrow biopsy

Negative for multiple myeloma or lymphoma but flow cytometry demonstrated a mild clonal excess of B lymphocytes of uncertain significance (kappa:lambda ratio=8) raising the possibility of a **low grade B-cell lymphoma.**

# Treatment Course

He was initiated on high dose intravenous methylprednisolone followed by high dose oral prednisone. 72-hrs later, his urine output improved and hemodialysis was discontinued. At discharge, his S.Cr was 2.8 mg/dL. Corticosteroids were slowly tapered during three months and he received four doses of weekly rituximab infusion. Subsequently, proteinuria resolved and S.Cr stabilized.

# Conclusion

- C3GN is a rare disease that usually occurs after a triggering event in predisposed/vulnerable patients. A previous study showed that a history of infection, positive autoimmune findings, and monoclonal gammopathy (IgM) were present in 33 of 114 (28.9%), 28 of 114 (24.6%), and 36 of 95 (37.9%) patients, respectively [4].
- In the present study, we present the case of a patient with multiple triggering factors that resulted in C3GN which was responsive to management with glucocorticoids and immunomodulatory therapy.

# References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4. Ravindran A, Fervenza FC, Smith RJH, De Vriese AS, Sethi S., C3 Glomerulopathy: Ten Years' Experience at Mayo Clinic. Mayo Clin Proc. 2018 Aug
5. Zand L, Kattah A, Fervenza FC, Sethi S., C3 glomerulonephritis associated with monoclonal gammopathy: a case series. Am J Kidney Dis. 2013 Sep.
6. Renal pathology biopsy slides has been provided by Renal Pathology Services - Brigham and Women's Hospital.