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

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**BACKGROUND**

**EPIDEMIOLOGY:**
- C3 glomerulopathies are rare diseases with an estimated incidence of 1-3 cases/1,000,000 and 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.
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
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 immunofluorescent 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


6. Renal pathology biopsy slides has been provided by Renal Pathology Services - Brigham and Women’s Hospital.