Pathology of Complement Mediated Renal Disease

Mariam Priya Alexander, MD
Associate Professor of Pathology

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The complement system: a double edged sword

- Primary role is to initiate and modulate immune responses to promote homeostasis and protection
- Maladaptive functions can lead to tissue injury
- A pathogenic role for complements has emerged for many types of glomerular disease

http://www.archedu.org/email/Jewellery/funcorner.html
Kidney injury mediated by serum complement in the absence of antibody

- C3 glomerulopathies
- Atypical post-infectious GN
- aHUS
C3 glomerulopathies

- Disease process related to abnormal control of the activation, degradation and deposition of complements.

- Characteristic feature includes:
  - predominant C3 fragment deposition
  - electron dense deposits on ultrastructural examination

- Subtypes
  - DDD
  - C3 glomerulonephritis
  - Atypical post infectious glomerulonephritis
  - Familial C3 glomerulopathy
  - CFHR5 nephropathy
Dense deposit disease

• A glomerular disease defined at the electron microscopic level by broad, linear, highly electron-dense ribbon-like material within the glomerular basement membrane, mesangium, Bowman capsule and TBM.

• Immunofluorescence stains predominantly for C3.
Natural history

- Rare
- Caucasian racial predominance (>80%)
- More commonly seen in children and adolescents
- Presentation includes:
  - Hematuria, Proteinuria, renal insufficiency
- Partial lipodystrophy and ocular drusens was noted with some.
Etiopathogenesis

• Persistent activation of alternate complement pathway
  • Autoantibodies:
    • C3Nef ( >100% children; 40% adults)
    • Autoantibodies to CFH, factor B

• Genetic abnormalities of complement component genes:
  • C3 mutation
  • Factor H mutation
  • Allelic variants of CFI, CFH, C3
Investigations

• Depressed C3 levels were universal in the pediatric group but detected significantly less in the adult group (100% versus 41.2%, $P < 0.001$).

• C4 was depressed in only a single patient (an adult).

• C3Nef >80%

• CFH mutations >17%
Prognosis

• Its natural history is variable, but approximately 50% of patients progress to ESRD within 8 to 10 yrs.

• Recurrence in the allograft
  • Inevitable
  • Late recurrence
  • Mild clinical manifestations
Differential diagnosis

- C3 glomerulonephritis
- Infection related/post-infectious glomerulonephritis
- MPGN with masked monoclonal deposits
- Monoclonal Immunoglobulin Deposition Disease
- C4DD
C3 glomerulonephritis

• a recently described entity that shows a glomerulonephritis on light microscopy

• bright dominant C3 staining on immunofluorescence microscopy

• Intermediately electron dense deposits on electron microscopy
Laser Dissection and Mass-Spectrometry

• Products of the AP:
  • C3 and C9 in large spectral numbers
  • C5, C6, C7, C8 in smaller amounts

• Vitronectin, clusterin and apolipoprotein E; regulators of complements in the fluid phase.

• Negligible amounts of C1, C2 and C4.

Natural history

- Age: 8 to 73 years (mean, 42.5 years)
- Male: female equal
- The mean serum creatinine at presentation 1.5 mg/dL
- All had hematuria and proteinuria
- Twenty-four hour urinary protein, mean was 5726 mg.

Natural history

• C3 levels were low in nine patients (40%)
• C4 levels were borderline low in only one patient, mostly normal
Etiopathogenesis

- Dysregulation of alternate complement pathway

Investigations

• Quantification of complement levels
  • depressed C3 levels in 40%
  • C4 was normal

• Specialized tests:
  • Functional assays
  • Levels of MAC, levels of FH, FI, FB

• Levels of C3Nef 45%

• Genetic analysis: CFH mutations >17%

• Monoclonal gammopathy and autoimmune panel
Prognosis

• Its natural history is variable, but approximately 50% of patients progress to ESRD within 8 to 10 yrs.

• Recurs in allograft
  • 70% recur
  • Clinically aggressive
  • Early post transplant
  • High risk of graft failure (~50%)
C3 glomerulonephritis associated with autoimmune diseases

- A cohort of 85 patients with confirmed C3GN
- Ten patients (3 male, 7 female; mean age 38.5 years) had an associated autoimmune disorder.
- The 7 female patients had autoimmune-related presentations. Of the 3 male patients, only 1 patient had autoimmune-related presentations.
- In 5 patients, the alternative pathway was evaluated. All had allele variants/polymorphisms associated with C3GN. One patient was also positive for C3Nef.

C3 glomerulonephritis associated with monoclonal gammopathy: a case series

• In this series 31% of those with C3 GN had evidence of a monoclonal immunoglobulin in serum

• Mean age: 54.5 years

• Abnormalities of the AC pathway in 7 of 9 patients tested.

• Rx of two patients for the malignancy (1 with CLL and 1 with MGUS) resulted in improved renal function.

Differential diagnosis

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- Monoclonal Immunoglobulin Deposition Disease
- C4DD
Infection related glomerulonephritis
IgA
### Endocarditis related glomerulonephritis

<table>
<thead>
<tr>
<th>Immunoreactant</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>13 (27%)</td>
<td>18 (37%)</td>
<td>14 (29%)</td>
<td>46 (94%)</td>
</tr>
</tbody>
</table>

- **C3 only or C3 + single Ig**
  - n (%)
  - C3 + IgG 2 (4%) 8 (16%)
  - C3 + IgM 3 (6%)
  - C3 Only 18 (37%)

- **Combined Igs**
  - n (%)
  - IgG IgM 3 (6%) 6 (12%)
  - IgG IgA 3 (6%)
  - IgM IgA 2 (4%)

- **Negative for all**
  - n (%)
  - Negative 3 (6%)

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Differentiating between C3 dominant immune complex and complement mediated glomeruonephritis—is it possible?
C4d as a Diagnostic Tool in Proliferative GN

Sanjeev Sethi,* Samih H Nasr,* An S. De Vriese,† and Fernando C. Fervenza‡

*Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology and †Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; and ‡Division of Nephrology, AZ Sint-Jan Brugge, Brugge, Belgium

Differential diagnosis

• C3 glomerulonephritis
• Infection related/post-infectious glomerulonephritis
• MPGN with masked monoclonal deposits
• Monoclonal Immunoglobulin Deposition Disease
• C4DD
Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits

Christopher P. Larsen¹, Nidia C. Messias¹, Patrick D. Walker¹, Mary E. Fidler², Lynn D. Cornell², Loren H. Hernandez², Mariam P. Alexander², Sanjeev Sethi² and Samih H. Nasr²

• MPGN pattern that show false negative staining for monoclonal immunoglobulins by routine immunofluorescence.

• Monoclonal immunoglobulin deposits were unmasked by performing immunofluorescence on formalin-fixed paraffin embedded tissue after protease digestion.

Kidney International (2015) 88, 867–873; published online 8 July 2015
Routine IF was negative for immunoglobulins
IgG by IF-P

kappa by IF-P

lambda by IF-P

Slides and case kind courtesy of Dr. Samih Nasr
Clinicopathological details

- 16 cases
- A mean serum creatinine of 2.7 mg/dl and mean 24 h proteinuria of 7.1 g.
- Hypocomplementemia was present in two-thirds of patients.
- Fourteen patients had a paraprotein on serum immunofixation, all of which matched the IF.
- Bone marrow biopsy showed plasma cell dyscrasia or B-cell lymphoproliferative disorder in 13 patients.
Ten of these patients had findings on biopsy most consistent with C3 glomerulonephritis prior to performing paraffin immunofluorescence.

A high index of suspicion is necessary to avoid misdiagnosis in these cases, as many would have been mistakenly diagnosed as C3 glomerulopathy or unclassified MPGN if paraffin immunofluorescence was not performed.
Differential diagnosis

- C3 glomerulonephritis
- Infection related/post-infectious glomerulonephritis
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- Monoclonal Immunoglobulin Deposition Disease
- C4DD
C4 glomerululopathy

• In 2014, a new type of complement-mediated GN.

• **C4 Dense-Deposit Disease**

C4 Glomerulopathy: A Disease Entity Associated With C4d Deposition

Sanjeev Sethi, MD, PhD, Patrick S. Quint, PhD, Conall M. O'Seaghdha, MD,
Fernando C. Fervenza, MD, PhD, Vanesa Bijol, MD, Anthony Dorman, MD,
Surendra Dasari, PhD, Richard J.H. Smith, MD, Paul J. Kurtin, MD, and
Helmut G. Rennke, MD
**C4 glomerulopathy**

- Characterized by deposition of C4 in the absence of C3, C1q, and immunoglobulin.
- This disorder was called:
  - C4 dense deposit disease if there were dense C4 deposits along the glomerular basement membrane (by EM)
Clinical presentation

- A short series of 3 patients.
- All presented with proteinuria, and 2 patients also had hematuria.
- Kidney function was preserved in 2 patients.
- Evaluation for autoimmune disease, infection, and paraprotein yielded negative results in all patients.
- Complement levels were normal, although 1 patient had borderline low C4 levels.
Pathological features

- Kidney biopsy showed mesangial proliferative or membranoproliferative glomerulonephritis with bright C4d staining and absent or minimal C1q, C3, and immunoglobulin.

- Laser microdissection and mass spectrometry of glomeruli in all 3 patients showed large to moderate numbers of spectra matching C4.

- Furthermore, analysis of amino acid sequences showed that they were localized to the C4d portion of C4.
Kidney injury mediated by serum complement in the absence of antibody

- C3 nephropathies
- Atypical post-infectious GN
- aHUS
Atypical postinfectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement

Sanjeev Sethi\textsuperscript{1}, Fernando C. Fervenza\textsuperscript{2}, Yuzhou Zhang\textsuperscript{3}, Ladan Zand\textsuperscript{2}, Nicole C. Meyer\textsuperscript{3}, Nicolò Borsa\textsuperscript{3}, Samih H. Nasr\textsuperscript{1} and Richard J.H. Smith\textsuperscript{3,4,5}

The diagnostic criteria of ‘atypical’ post-infectious glomerulonephritis:

Persistent hematuria and proteinuria, with or without a history of preceding infection.

Renal biopsy showing features of post infectious glomerulonephritis—

(a) proliferative glomerulonephritis on LM,
(b) mesangial and/or capillary wall C3 with or without immunoglobulin staining on IF microscopy and
(c) subepithelial ‘hump-like’ deposits

Abnormalities of the AP of complement.
AP complement pathway abnormalities

- Functional and genetic studies of the alternative pathway identified autoantibodies or mutations in complement genes.
- Seven patients were positive for C3Nefs, which were associated with other functional abnormalities of the AP in six patients.
- Four patients had mutations of complement genes, including three patients with mutations in CFH and one patient with a mutation in CFHR5.
Kidney injury mediated by serum complement in the absence of antibody

- C3 nephropathies
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Definition

• Atypical HUS is characterized by a thrombotic microangiopathy that results in a hemolytic anemia, thrombocytopenia, and multiorgan dysfunction

• results from abnormalities in the alternative pathway of complement
Pathology

• Acute thrombotic microangiopathy
  • Blood vessels
  • Tubules and interstitium
  • Glomeruli

• Chronic thrombotic microangiopathy
  • Blood vessels
  • Tubules and interstitium
  • Glomeruli
Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities

Sjoerd A.M.E.G. Timmermans¹, Myrurgia A. Abdul-Hamid², Joris Vanderlocht³, Jan G.M.C. Damoiseaux⁴, Chris P. Reutelingsperger⁵ and Pieter van Paassen¹; for the Limburg Renal Registry

¹Department of Nephrology and Clinical Immunology, Maastricht University Medical Centre, Maastricht, the Netherlands; ²Department of Pathology, Maastricht University Medical Centre, Maastricht, the Netherlands; ³Department of Transplantation Immunology, Maastricht University Medical Centre, Maastricht, the Netherlands; ⁴Central Diagnostic Laboratory, Maastricht University Medical Centre, Maastricht, the Netherlands; and ⁵Department of Biochemistry, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands


Pregnancy-Associated Hemolytic Uremic Syndrome Revisited in the Era of Complement Gene Mutations

Fadi Fakhouri,* Lubka Roumenina,† François Provot,‡ Marion Sallée,§ Sophie Caillard,‖ Lionel Couzi,§ Marie Essig,** David Ribes,†† Marie-Agnès Dragon-Durey,††† Frank Bridoux, §§ Eric Rondeau,|| and Veronique Frémeaux-Bacchi†††

*Department of Nephrology and UMR 643, CHU de Nantes; †Cordeliers Research Center, INSERM UMR 872, Paris, France; ‡Department of Nephrology, CHU Lille, Lille, France; §Department of Nephrology, CHU de Marseille, Marseille, France; ‖Department of Nephrology, CHU de Strasbourg, Strasbourg, France; ¶Department of Nephrology, CHU Pellegrin, Bordeaux, France; **Department of Nephrology, CHU de Limoges, Limoges, France; ††Department of Nephrology, CHU de Toulouse, Toulouse, France; †††Assistance Publique-Hopitaux de Paris, Hôpital Européen Georges-Pompidou, Service d’Immunologie Biologique, Paris, France; §§Department of Nephrology, CHU de Poitiers, Poitiers, France; and || Assistance Publique-Hopitaux de Paris, Department of Nephrology, CHU de Tenon, Paris, France

“Renal pathology is an art rather than an exact science and those of us who practice it have to weigh up evidence from morphology, immunohistochemistry and clinical features in order to make a diagnosis that will allow the nephrologist to judge the best way to investigate and manage the patient”

-Terence Cook
THANK YOU
alexander.mariam@mayo.edu