C3G – An Update
What is C3 Glomerulopathy Anyway?

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C3 Glomerulopathy – Overview

• Discuss C3 Glomerulopathy (C3G)
  – How did we get to the current classification
  – What are the subsets of C3G
  – Demonstrate the pathologic features
  – What are the Pitfalls!
  – Algorithmic Approach
C3 Glomerululopathy – An Update

• But first, what we are leaving out
Complement in Glomerular Disease

- Post-Streptococcal GN
- Membranous Glomerulopathy
- Lupus Nephritis
- ANCA-Associated GN
- Humoral Transplant Rejection
- And on

These will NOT be discussed
C3 Glomerulopathy (C3G)

• This has become a very ‘hot’ diagnosis
• Source of some contention and a lot of confusion
  – C3G appears first in J Med Genet in 2007?
  – But lets move forward…

C3 Glomerulopathy

- The Problem is:
  - A Collision between Glomerular Pathology (MPGN) and the Rapid Advancement in our Understanding of Complement-Related Renal Disease
MPGN Today

- MPGN has become a *clinico-pathologic* waste basket
- The use of the term **MPGN** does NOT lead to a clear clinical understanding!
- MPGN is a **PATTERN, NOT a DISEASE**!
- One more time…
MPGN Today

• MPGN is a PATTERN, NOT a DISEASE!
MPGN is a *Pattern*, NOT a *Disease*

This is how it stood in 2010 when MPGN was STILL a *DISEASE*

- **Primary:** MPGN I, II, III
- **Secondary**
  - Associated with:
    - Autoimmune diseases
    - Dysproteinemias
    - Neoplasms
    - Renal allograft
- **Secondary**
  - Associated with:
    - Infections
    - Rheumatologic Diseases
    - Malignancy
    - Inherited Diseases
    - *Other*
MPGN is a **Pattern, NOT a Disease**

- MPGN Pathogenetic Mechanisms
  - Autoimmunity and Immune Complex Deposition
  - Chronic Infection
  - Complement Dysregulation
  - Monoclonal Ig Deposition Disease
  - Chronic Thrombotic Microangiopathy
  - Idiopathic

Glassock RJ, Nachman PH, MPGN NephSAP 9:138, 2010
Classification of MPGN 2010

• “…vigorous attempts to identify the underlying mechanisms must be undertaken whenever the MPGN pattern of injury is found on renal biopsy!”

• In other words, when the Dx is MPGN, you still don’t know what the patient has!

Glassock RJ, Nachman PH, MPGN NephSAP 9:138, 2010
Classification of MPGN

- We have progressed from post-mortem analysis of glomerular changes (Volhard & Fahr 1900’s)
- Through detailed histopathologic descriptions
  - MPGN and all its subtypes
- To various pathogenetic mechanisms all associated with a membranoproliferative pattern
- But we have NOT arrived at the final destination
  - It is premature to think we have it figured out
Classification of MPGN

- Diagnostic Confusion
  - We still rely on the biopsy but must add more analysis
Complement and MPGN

• A Sea-Change Begins in 2007
  – And a host of other publications
  – And that is what we will now discuss
Then and Now Pathology

• What was MPGN
  – Membranoproliferative Glomerulonephritis
    • Primary v Secondary
    • MPGN I, DDD or MPGN II, III
Membranoproliferative Glomerulonephritis is

Now – *Membranoproliferative Pattern*

- This pattern is associated with a variety of clinical syndromes and pathogenetic mechanisms.
Pathology and Complement

- *Membranoproliferative Pattern* may be associated with complement abnormalities.
- Abnormalities of the *Complement System* are associated with a variety of histopathologic patterns.
Changes in Primary MPGN - 2012

Changes in Primary MPGN - 2012

- Still Not Right! C3GN often has Ig deposits
C3 Glomerulopathy Consensus Conference 2013

• This is outstanding work! A Significant Advance

• Defined:
  – C3 Glomerulopathy
  – Outlined appropriate Complement work up
  – Explored treatment options

Consensus Conference Diagnostic Algorithm

Let’s break this down.
• Glomerulonephritis, not just MPGN
• C3 Dominant rather than C3 ONLY
• C3 Dominant is not a diagnosis, but leads down a path
Consensus Conference Diagnostic Algorithm

- C3G breaks out into two main patterns

- **DDD**
  - Specific genetic forms and/or autoantibodies
  - Not otherwise specified

- **C3 GN**
  - Specific genetic forms for example CFHR5 nephropathy and/or autoantibodies
  - Not otherwise specified

- Disease category: C3 glomerulopathy, Post-infectious GN, Other

- Morphological appearance: Glomerulonephritis with dominant C3
C3 Glomerulopathy
(C3G is the new abbreviation)

• Light Microscopy
  – Membranoproliferative Pattern – 65%-70%
  – Mild Glomerular abnormalities – 30%-35%

• Immunofluorescence Microscopy
  – C3 Dominant, not Only

• Electron Microscopy
  – Mesangial, Subendothelial and, Less Commonly Membranous Deposits
Dense Deposit Disease

- DDD has a distinctive pathologic appearance using the Electron Microscope

Unique Electron Dense Transformation of Glomerular Basement Membranes
Dense Deposit Disease

- The light microscopic appearance is variable
  - Membranoproliferative DDD (20-25%)
  - Mesangial Proliferative DDD (40-45%)
  - Crescentic DDD (15-20%)
  - Acute Proliferative and Exudative DDD (10-15%)

Moving to today

• C3G Focus Group was held in Upsalla, Sweden, June, 2015

  – Updated everything to current
  – Pathology to mechanisms to treatment
  – My job in the pathology section was to pose the ‘Most Pressing Question’
C3G Focus Group – 2015

• The Pressing Question?
  – How to Get the Diagnosis Right…
  – Without the right diagnosis
    • We are comparing apples to pears
  – We are better off than we were, but we still need to improve
The Pressing Question?

• How to Get the Diagnosis Right…
  – Too much overcalling and, the other way
  – C3G cases are being missed
The Pressing Question?

• Get the diagnosis right…
  – Review some of the known pitfalls
  – And add a new one
C3G is *Not* always C3 only

- DDD is the prototypic C3G

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– Ig’s are present in a significant percentage of cases of DDD
Misdiagnosis the other way

• Are we missing cases of C3G **BECAUSE** they have Ig’s? Servais et al looked at it *the other way*

• Started with patients with **An abnormality of the Alternative Pathway of Complement**

• **8 of 26 had a membranoproliferative pattern and all had C3 and one or more Ig’s**
C3 ‘only’ is not really C3G

- These are the Major Entities miscalled C3G
  - Autoimmune Diseases (e.g. SLE)
  - Infection-Related GN (e.g. Infective Endocarditis)
  - Paraprotein-related disease
C3 ‘*only*’ is not really C3G

- These are the Major Entities miscalled C3G
  - Autoimmune Diseases (e.g. SLE)
  - Infection-Related GN (e.g. Infective Endocarditis)
  - Paraprotein-related disease

- Why? Because they are NOT C3 ONLY

- If it is Called C3G and it is NOT C3G – 

  *Wrong* Work Up and *Wrong* Treatment
C3 ‘only’ is not really C3G

- Paraffin IF can unmask these pretenders
C3 ‘only’ is not really C3G

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine
C3 ‘only’ is not really C3G

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine
- Preliminary Diagnosis: Membranoproliferative Pattern with IF features consistent with C3 Glomerulopathy
C3 ‘only’ is not really C3G

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine

**Routine IgG**

**IgG on Paraffin IF after Protease**
C3 ‘only’ is not really C3G

- Paraffin IF unMASKS these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine

Kappa on Paraffin IF after Protease

Lambda on Paraffin IF after Protease
C3 ‘only’ is not really C3 ONLY

- Paraffin IF unmasks these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine
C3 ‘only’ is not really C3G

- Paraffin IF unmask these pretenders
- 67 year old male with hematuria/proteinuria and elevated creatinine

Final Diagnosis: Membranoproliferative Pattern with IgG/Kappa deposits

- Comment: rule out paraprotein-related disease

Patient found to have a B-cell lymphoma
C3 ‘only’ is not really C3G

• Patient found to have a B-cell lymphoma

• C3G is WRONG
  – Would have led to delayed diagnosis at best
  – Incorrect and Expensive Work Up
  – Possibly the Wrong Treatment
GN and only C3 are **NOT** all C3G

- Worldwide, the most common cause of a glomerulonephritis with C3 deposits in the absence of immunoglobulins is?
GN and only C3 are **NOT** all C3G

- Worldwide, the most common cause of a glomerulonephritis with C3 deposits in the absence of immunoglobulins is?

- **INFECTION-ASSOCIATED GLOMERULOPATHY**
  - Co-infectious or Post-infectious
Patients with true C3G are negative for C4d
C4d as a Diagnostic Tool in Proliferative GN

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

J Am Soc Nephrol 26: 10.1681/ASN.2014040406

C4d Positive in different forms of ICGN
So, in Summary

• C3G is *Not* always C3 only
  – DDD is the prototypic C3G and frequently has Ig’s

• On the other hand…
  – MPGN with Ig’s may be due to an abnormality of the alternative pathway of complement, in effect a C3G

• Consensus conference addresses this – but must be used
Summary

• MPGN with C3 only may Not be C3G
  – Paraffin IF with protease digestion
  – C4d

• GN and only C3 are NOT all C3G
  – The most common cause is Infection-Associated Glomerulonephritis
Proposal

• The goal is to identify patients with abnormalities of the Alternative Pathway of Complement
The Algorithm from the Consensus Conference is Excellent

Morphological appearance

- Glomerulonephritis with dominant C3

Disease category

- C3 glomerulopathy
- Post-infectious GN
- Other

C3 glomerulopathy

- DDD
  - Specific genetic forms and/or autoantibodies
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C3 GN

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I propose a slight modification
C3 Dominant (not ‘Only’) Proliferative GN with or without Membranoproliferative Features

R/O Infection-Related GN
R/O Autoimmune Related GN

Negative

Paraffin IF & C4d

Both Negative
Paraffin IF Positive
C4d Positive

W/U Abnormalities of the Alternative Pathway of Complement

Positive
C3 Glomerulopathy

Negative
Other

Other

So far only paraprotein-related diseases have been unmasked. Still, Clinico-pathologic correlation is required. May still be a C3GP or due to an ‘Other’
Thank you

• Organizers
• Sponsors
• To You
• And to all the patients we serve, but who actually are our best teachers