C3 Glomerulopathy – Update

Patrick D. Walker, M.D.
Arkana Laboratories
Little Rock, Arkansas
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
Membranoproliferative Glomerulonephritis

– We start with Pathology
Membranoproliferative Glomerulonephritis

- We start with Pathology

- Two of Richard Bright’s patients in the mid 1800’s were likely MPGN

- But MPGN begins with post-mortem analysis of glomerular changes (Volhard & Fahr early 1900’s)
Membranoproliferative Glomerulonephritis

- Allen in 1951 describes ‘Lobular Glomerulonephritis’

- Churg and Grishman - 1959 described ‘subacute glomerulonephritis’ with ‘mesangial cell interposition’

  - This at a time when the existence of the mesangial cell was still being debated by some including Allen
MPGN - History

– Dr. Renee Habib the first modern description of MPGN - 1961

– This became MPGN I
MPGN - History

- **Galle and Berger** describe **Dense Deposit Disease in 1962**
- Incorrectly, this became **MPGN II in 1974**
MPGN - History

– Clark West et al – 1965 Hypocomplementemia in MPGN

1918 – 2014
HISTORY – 1974 till 1993

– MPGN was sub-classified out from all other forms of glomerulonephritis and considered a DISEASE

– It had three patterns: MPGN I, II, III

– All three forms were thought to be related to Complement somehow

– Sure, there were a few other associations but mostly not important
HISTORY – 1993 an Earthquake

- Johnson et al report that 85% of patients with MPGN I have hepatitis C infection

HISTORY – 1993 an Earthquake

– Johnson et al report that 85% of patients with MPGN I have hepatitis C infection

HISTORY – 1993 until 2007

- Hepatitis C infection is just the beginning
- Secondary causes flood the landscape of MPGN
- But MPGN as a disease unto itself hangs on!
MPGN as a DISEASE Hangs on, but barely

– Primary: MPGN I, II, III (rare)

– Secondary
  – Associated with:
    – Autoimmune diseases
    – Dysproteinemias
    – Neoplasms
    – Renal allograft

– Secondary
  – Associated with:
    – Infections
    – Rheumatologic Diseases
    – Malignancy
    – Inherited Diseases
    – Other
MPGN as a *DISEASE* Hangs on, but barely

- 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
MPGN as a *DISEASE* Hangs on, but barely

— “…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
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?
  - Only ‘Complementarians’ saw this
    - Most Nephrologists and Renal Pathologists Missed It
      - I certainly did
- This will be final break point for MPGN

MPGN C3G Today

• A Collision between Glomerular Pathology (MPGN) and the Rapid Advancement in our Understanding of Complement-Related Renal Disease

• MPGN has become a clinico-pathologic Black Hole
MPGN – A Black Hole

– The use of the term **MPGN** does NOT lead to a clear clinical understanding!

– Everything has been pulled into its Maw!
How Do We Change This?

– Recognize that MPGN is a *PATTERN*, NOT a *disease*
Classification of Membranoproliferative Pattern

- 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 This is where we are
- But we have NOT arrived at the final destination
  - It is premature to think we have it figured out
Classification of Membranoproliferative Pattern

- Diagnostic Confusion
  - We still rely on the biopsy but must add more analysis
  - We have actually backed up a step in Naming
  - And gone forward a step in Mechanistic Understanding

- So, as always in Renal Pathology,
  - Detailed analysis of both the Pathologic Findings
  - Combined with Detailed Clinical Study provides the best Clinicopathologic Diagnosis
Membranoproliferative Pattern

What was: Primary MPGN I, II, III is Now:

– Membranoproliferative Pattern Associated with Abnormalities of the Complement System
  – MPGN I and MPGN III – Classical Pathway
  – MPGN II is now Dense Deposit Disease – Alternative Pathway
  – C3 Glomerulopathy with or without MP Pattern – Alternative Pathway
Membranoproliferative Pattern

What was: Primary MPGN I, II, III is Now:

- Membranoproliferative Pattern Associated with Abnormalities of the Complement System
- THIS DESTROYS THE CONCEPT OF PRIMARY (meaning we don’t have a clue)
- These patterns are associated with an etiology hence they are NOT Primary
Membranoproliferative Pattern

What was Secondary MPGN is Now:

- Membranoproliferative Pattern Associated with:
  - Autoimmune diseases
  - Dysproteinemias
  - Neoplasms
  - Renal allograft

- Infections
- Rheumatologic Diseases
- Malignancy
- Inherited Diseases
- Other

- ABNORMALITIES OF COMPLEMENT
- Ignoring the Classical Pathway because this discussion is focused on C3G
- Recall the first clear description of C3 Glomerulopathy was published in 2007 by Servais et al
- This was followed by more and more recognition and publications
- MPGN was already in trouble, but this blew it apart!
MPGN was in Trouble, C3G blew it up - BECAUSE

- **Membranoproliferative Pattern** may be associated with complement abnormalities

- **BUT**

- Abnormalities of the **Complement System** are associated with a variety of histopathologic patterns
Changes in Primary MPGN - 2012

OOPS, Still NOT CORRECT!

C3GN Often Has Immunoglobulin Deposits
C3 Glomerulopathy Consensus Conference 2012

– Just as the Columbia Concept of C3GN was in Press, Pickering et al arranged a meeting of leading lights in Complement and Renal Disease

– The meeting was held in Cambridge and attended by Nephrologists, Pathologists and Complement Scientists of all sorts
C3 Glomerulopathy Consensus Conference 2012

– The meeting was held in Cambridge and attended by Nephrologists, Pathologists and Complement Scientists of all sorts

– They discussed

– Definitions

– Diagnostic Work Up

– Treatment Options
C3 Glomerulopathy Consensus Conference 2012

- After a hard-working conference and a great deal of post-conference discussion
- They produced an outstanding paper where
  - They defined C3 Glomerulopathy as it is known today
  - Outlined the appropriate work up of Complement
  - Explored treatment options
  - Developed a diagnostic algorithm
Definition of C3 Glomerulopathy (C3G)

- Glomerular disease caused by abnormalities in the alternative pathway of complement

- AGAIN

- C3G is defined as a glomerular disease caused by abnormalities in the alternative pathway of complement
C3 Glomerulopathy – Diagnostic Algorithm

Let’s break this down

Morphological appearance

Glomerulonephritis with dominant C3

Disease category

C3 glomerulopathy

Post-infectious GN

Other

DDD

C3 GN

Specific genetic forms and/or autoantibodies

Not otherwise specified

Specific genetic forms for example CFHR5 nephropathy and/or autoantibodies

No otherwise specified
C3 Glomerulopathy — Diagnostic Algorithm

- Glomerulonephritis, not just MPGN
- C3 Dominant rather than C3 ONLY
C3 Glomerulopathy – Diagnostic Algorithm

Morphological appearance

- Glomerulonephritis with dominant C3

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

C3 Dominant is not a diagnosis, but leads down a path
C3 Glomerulopathy - Diagnostic Algorithm

- C3G breaks out into two main patterns

Diagram:
- Disease category: C3 glomerulopathy, Post-infectious GN, Other
- Morphological appearance: Glomerulonephritis with dominant C3
- DDD:
- C3 GN:

[Diagram showing the flow and relationships between categories and appearances]
Definition of C3 Glomerulopathy (C3G)

- Glomerular disease caused by abnormalities in the alternative pathway of complement
- There are currently three main syndromes
  - Dense Deposit Disease (no longer referred to as MPGN II)
  - C3 Glomerulonephritis (C3GN, a subset of C3G)
  - Complement Factor H Related Protein (CFHR) Glomerulonephritis
- These three subsets are, by definition, caused by abnormalities in the alternative pathway of complement
C3 Glomerulopathy

- 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 V C3 Glomerulopathy

- C3G has a charcoal ‘smudge’ appearance but Gray not Black
- DDD is a calligraphy line drawn on the GBM
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%)

CFHR protein induced glomerulopathy

- The light microscopic appearance is variable
  - Membranoproliferative pattern
  - Mesangial Proliferative pattern

Zipfel PF et al Molec Imunol 67: 21-30, 2015 Review
Moving to today

- C3G Focus Group was held in Uppsala, 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

– Most Pressing Pathology 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
How to Get the Diagnosis Right…

– C3G is way over-diagnosed BUT,

  on the other hand

– C3G cases are being missed
Getting the Diagnosis Right

NEXT

– Review some of the known pitfalls
– And add a new one
C3G is **Not** always C3 only

- DDD is the prototypic C3G

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>C3</th>
<th>C1q</th>
</tr>
</thead>
<tbody>
<tr>
<td>pdw</td>
<td>20%</td>
<td>34%</td>
<td>13%</td>
<td>100%</td>
<td>19%</td>
</tr>
<tr>
<td>nasr</td>
<td>27%</td>
<td>37%</td>
<td>13%</td>
<td>100%</td>
<td>10%</td>
</tr>
<tr>
<td>n=94</td>
<td>22%</td>
<td>35%</td>
<td>13%</td>
<td>100%</td>
<td>16%</td>
</tr>
</tbody>
</table>

- 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 THEN
  - **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
  - 17 year old male with hematuria/proteinuria and elevated creatinine
C3 ‘only’ is not really C3G

– Paraffin IF unmasks these pretenders

– 17 year old male with hematuria/proteinuria and elevated creatinine

– Preliminary Diagnosis

– Membranoproliferative Pattern with IF Features c/w C3

Glomerulopathy
C3 ‘only’ is not really C3G
– Paraffin IF unmasks these pretenders

Routine IgG

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

- Paraffin IF unmasks these pretenders

Kappa on Paraffin IF after Protease

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

– Paraffin IF unmasks these pretenders
  – 17 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 (Alternative Pathway)
  - The Wrong Treatment while awaiting complement work up
  - Eculizumab at > $500,000/year

2016 © 17th Congress of the International Pediatric Nephrology Association. All rights reserved - Any reproduction even in part is prohibited.
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 GLOMERULONEPHRITIS**
  - Co-infectious or Post-infectious
Summary

– C3G is **Not** always C3 only

– DDD is the prototypic C3G and frequently has Ig’s

– On the other hand…

  Abnormalities of the alternative pathway of complement often do not show a membranoproliferative pattern
Summary

- Membranoproliferative Pattern with C3 only may Not actually be C3 only
  - Paraffin IF with protease digestion
- GN and C3 ONLY 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
- Rule out Infection-Related Glomerulonephritis
- Very rarely, unmask light chain related problem
  - B-cell lymphoma
  - Cryoglobulinemia (usually associated with infection)
Thanks to All of You

– And to all the patients we serve, but who actually are our best teachers
Questions?
Appendix
MPGN Collides with Complement
Membranoproliferative Glomerulonephritis
Accretes all the various etiologies to
Become Membranoproliferative Pattern
Membranoproliferative Glomerulonephritis

Becomes: Membranoproliferative Pattern
NOW

Classification of Membranoproliferative Pattern

– 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 all in flux
Pathologists and Nephrologists Pondered

– What shall we do???????
In 2012, Columbia took up the Challenge

- STAMPEDE!
- Actually, not all of Columbia
- Only Bomback and D’Agati

Bomback

D’Agati
I know, let’s go to Cambridge!
Aside – why do I mock Consensus?

– Query: What was the biggest problem faced by Christopher Columbus as he tried to convince various sponsors to fund his attempt to find India by sailing west?
Aside – why do I mock Consensus?

– Query: What was the biggest problem faced by Christopher Columbus as he tried to convince various sponsors to fund his attempt to find India by sailing west?

1. The world is too big, you cannot pack enough supplies!
2. You are Incompetent and will never succeed!
3. The Earth is Flat! You will sail off the edge and die, Fool!
4. The expenses will bankrupt us!
5. The return on investment is too small!
Aside – why do I mock Consensus?

Query: What was the biggest problem faced by Christopher Columbus as he tried to convince various sponsors to fund his attempt to find India by sailing west?

1. *The world is too big, you cannot pack enough supplies!*
2. **You are Incompetent and will never succeed!**
3. **The Earth is Flat! You will sail off the edge and die, Fool!**
4. *The expenses will bankrupt us!*
5. *The return on investment is too small!*

* = True   ** = NOT True
Aside – why do I mock Consensus?

— Christopher Columbus and the Flat Earth

— In about 1870, a myth was propagated that, after the fall of the Roman Empire to around 1300 AD, everyone thought the Earth was flat
— Even today, there are people who believe that this was how people living during those times viewed the world

— Consensus either way is wrong!
Consensus is NOT Science

- Science is NOT a democracy
- Science seeks Truth, not a majority vote
- However, a conference focused on a specific topic provides an environment for debate
  - Evidence is presented and argument ensues
  - The result is more clarity, not necessarily final clarity, but more clarity
The Algorithm from the Consensus Conference is Excellent

I propose a slight modification
Proposal

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

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