Collapsing glomerulopathy: a distinct pattern of glomerular injury

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Clinical features

- High prevalence in AA
- Severe proteinuria
- Rapid progression to renal failure
- Lack of response to standard therapies

Glomerular collapse but also sclerosis (late)
Pseudocrescent formation
History of Collapsing Glomerulopathy

  first description in 1978 as “malignant FSGS”

• Rao et al., N Engl J Med. 1984:
  “Focal segmental glomerulosclerosis in 10 pts with HIV infection”

• Wiess et al., Am J Kidney Dis. 1986:
  “Nephrotic syndrome, progressive irreversible renal failure, and glomerular "collapse": a new clinical-pathologic entity?” (6 pts)

• Detwiler et al., KI 1994:
  “Collapsing glomerulopathy: a clinically and pathologically distinct variant of focal segmental glomerulosclerosis.” (16 pts (13/16 AA)

• Valeri, Barisoni et al. KI 1996:
  “Idiopathic collapsing focal segmental glomerulosclerosis: a clinicopathologic study.” (43 pts)
Terminology
Collapsing or cellular lesion?

- Some authors use the term “cellular lesion” to indicate a lesion characterized by hypercellularity within the glomerular tuft or in the urinary space.

- Columbia classification scheme:
Collapsing FSGS
or
Collapsing Glomerulopathy?

Is collapse part of the FSGS spectrum
or
is part of the podocytopathy spectrum?

and

Is this distinction important?
Sclerosis versus collapse

FSGS

CG
Tubular microcysts
Conclusion I

Clinical presentation and morphology indicate that collapsing glomerulopathy is not a form of FSGS.
Is “collapsing” a disease or a pattern of glomerular injury?
Collapse is a pattern of glomerular injury

Incidence of collapsing pattern of injury at NYU (2003-2005)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic:</td>
<td>16 + 4 with severe AIN = 20</td>
</tr>
<tr>
<td>HIV-associated:</td>
<td>4 + 4 collapse and other GN = 8</td>
</tr>
<tr>
<td>PVB19:</td>
<td>= 1</td>
</tr>
<tr>
<td>Mesangial deposits:</td>
<td>4 unknown + 3 C1q + 2 lupus-like + 3 IgA + 2 Hep C associated MPGN = 16</td>
</tr>
<tr>
<td>MGN:</td>
<td>= 1</td>
</tr>
<tr>
<td>Diabetes:</td>
<td>= 3</td>
</tr>
<tr>
<td>TMA:</td>
<td>4 post Tx + 2 native kidney = 6</td>
</tr>
<tr>
<td>GBM abnormalities:</td>
<td>= 5</td>
</tr>
<tr>
<td>Familial:</td>
<td>2 families + 2 pts with fam. history = 5</td>
</tr>
<tr>
<td>Total</td>
<td>65 / 869 (7.3%)</td>
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</tbody>
</table>
CG: etiology and clinical associations

- **Idiopathic**
- **Genetic**
  - Syndromic - action myoclonus renal failure
  - Non-Syndromic - CoQ2 NP
- **Reactive**
  - Virus associated
    - HIV
    - parvovirus B19
    - CMV
  - Infections
    - filariasis
    - leishmania
    - TB
  - Autoimmune
    - Still’s disease
    - lupus like
    - RA
    - mixed connective tissue
  - Malignancy (myeloma, AML)
  - Medications
    - pamidronate
    - interferon
    - valproic acid
  - Vascular insult - TMA
  - Permeability factor
Why only some patients develop collapsing glomerulopathy?
Genetic susceptibility

- **Human:** [MYH9 is also a major-effect risk gene for CG.][1] MYH9 risk alleles are more frequent in AA. MYH9 protective alleles are more frequent in EA. *(Kopp et al. Nat Genet. 2008)*

- **Mice:** [Accelerated development of collapsing glomerulopathy in mice congenic for the HIVAN1 locus.][2] A gene on chromosome 3A1-A3 increases susceptibility to HIVAN, resulting in early onset and rapid progression of kidney disease. *(Chang et al KI 2009)*
Collapsing Glomerulopathy

- Specific genetic mutations
- Medications
- Activation of the immune system
- Dysregulation of mitochondrial activity
- Ischemic insult
- Infections
- Environmental factors
Collapsing glomerulopathy is a pattern of glomerular injury that can occur in association with various etiologic factors.
Which is the underlying mechanism of pseudocrescent formation and collapse of the basement membranes?
Pathogenesis of CG:
from podocyte injury to pseudocrescent formation

The dysregulated podocyte

Podocytes are injured

They dedifferentiate and dysregulate their phenotype

Dedifferentiated podocytes can re-enter the cell cycle and proliferate

Pseudocrescent formation

The exuberant renopoietic system

Podocytes are injured

They undergo apoptosis/death

CD24+CD133+ cells migrate from the Bowman’s capsule

Exuberant proliferation

Pseudocrescent formation
Hypothesis #1

The dysregulated podocyte phenotype
In collapsing glomerulopathy podocytes resemble immature precursors.

Barisoni and Kopp 2002
Differently from other podocytopathies, in CG podocytes are de-differentiated

Barisoni, Mundel et al. JASN 1999
In idiopathic and HIV-associated CG dedifferentiated podocytes have a dysregulated phenotype.
In CG de-differentiated podocytes re-enter the cell cycle and proliferate

Barisoni et al. KI 2000
Loss of synaptopodin expression precedes glomerular damage in HIV-CG

Barisoni et al. JASN 1999, 10: 51-61
Inheritable CoQ2 NP:
In CoQ2-associated CG podocyte phenotype is dedifferentiated but not dysregulated
Hypothesis #2

The renopoietic system
Hierarchical distribution of CD133⁺CD24⁺PDX⁻ and CD133⁺CD24⁺PDX⁺ cells within human glomeruli
Exuberant proliferation of CD24+CD133+ resident progenitor cells is the cause of pseudocrescent formation

Smeets et al, JASN 2009
Conclusion III

Collapsing glomerulopathy is a proliferative podocytopathy
Amelioration of nephropathy in mice expressing HIV-1 genes by the cyclin-dependent kinase inhibitor flavopiridol
Conclusions

• CG is a proliferative disease, different from other podocytopathies, histologically defined by glomerular collapse and pseudocrescent formation.

• Both intrinsic cell damage and reactive mechanism of injury may play a role in podocyte injury, provided a predisposing genetic background.

• Pseudocrescents may be the result of exuberant proliferation of dedifferentiated podocytes or of renopoietic resident cells, or both.

• Recognition of the unique etiologies and pathogenetic mechanism for CG should guide therapeutic intervention.
## Classification of CG

<table>
<thead>
<tr>
<th>Idiopathic forms</th>
<th>Genetic forms</th>
<th>Reactive forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Idiopathic CG</td>
<td>• Non-Syndromic COQ2</td>
<td>• Infection</td>
</tr>
<tr>
<td></td>
<td>• Syndromic Action myoclonus-renal failure (SCARB2)</td>
<td>Viruses (HIV-1, parvovirus B19, CMV) Others (Loa loa filariasis, visceral leishmaniasis, Mycobacterium tuberculosis*)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Disease associations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult Still’s disease, thrombotic microangiopathy, multiple myeloma</td>
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<tr>
<td></td>
<td></td>
<td>• Medication</td>
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<td></td>
<td></td>
<td>Interferon-alpha, pamidronate</td>
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</table>
In “reactive” forms of CG podocyte phenotype is preserved in non-affected glomeruli.

Barisoni, Thomas et al. ASN 2004
The *kd/kd* mouse is a model of spontaneous CG

*Barisoni, Madaio, Eraso, Gasser, and Nelson. JASN 2005*

The susceptibility gene has been mapped on chromosome 10 and encodes a prenyltransferase-like mitochondrial protein (PLMP)

*(Dell et al. Mamm Genome 2000)*
Collapsing glomerulopathy: Three pathogenetic variant

IDIOPATHIC
INHERITED
REACTIVE
Expression of podocyte maturity markers in podocytopathies

MCNS  FSGS  CG
Podocyte de-differentiation and dysregulation lead to proliferation

**Proliferative index (PI) expressed as Ki-67 positive podocytes per total number of podocytes**

- **HIV-AN**: 8
- **Coll. Idiop.**: 5

The graph shows the proliferative index for different conditions:
- CG
- I-FSGS
- S-FSGS
- MCD
- Normal adult kidney
Viruses and podocyte injury
HIV-1 expression in renal epithelial cells or selectively in podocytes alone leads to CG

Bruggeman JCI 1999

Barisoni, KI 2000

Zhong et al. KI 2005
Human renal glomerular and tubular epithelial cells contain HIV-1 mRNA and DNA

Bruggeman et al. JASN 2000
Association of parvovirus B19 infection with collapsing glomerulopathy

Moudgil et al. Ki 2001

PVB19 DNA was detected in renal biopsies of 78.3% of patients with idiopathic CG by PCR, and localized to the epithelial cells and podocytes by in situ hybridization.
Genetic forms of CG
Mitochondrial activity is reduced in renal parenchyma