DIAGNOSIS AND MANAGEMENT OF HCV-RELATED GN

CC Szeto
Department of Medicine & Therapeutics
The Chinese University of Hong Kong
DISCLOSURES

• Gilead Sciences Inc: consultancy

• AstraZeneca: conference support

• Pfizer: speaker and conference support

• Baxter Healthcare: speaker, research grant and consultancy

• Fresenius Medical Care: research grant
HCV INFECTION IS A SYSTEMIC DISEASE

HCV AND RENAL DISEASE

• glomerulonephritis and renal failure are important extrahepatic complications of HCV infection

• liver disease may be mild or clinically absent

• autopsy studies
  • in patients with HCV cirrhosis, 60% had evidence of GN
  • in patients without cirrhosis, 33% had renal involvement
HISTOLOGICAL PATTERNS

• membranoproliferative glomerulonephritis
  • also called mesangiocapillary GN
  • most common form

less common
• membranous nephropathy
• IgA nephropathy
• focal segmental glomerulosclerosis
• polyarteritis nodosa
• fibrillar glomerulonephritis
• immunotactoid glomerulopathy

Diagnosis: renal biopsy is necessary!
MECHANISM OF KIDNEY INJURY

Pathogenesis of HCV-related GN

- type II mixed essential cryoglobulinaemia
  - systemic vasculitic syndrome
  - most common cause is chronic HCV (>80% cases)
  - happen in ~10% of HCV infected patients
    - GN in 60% of these patients
    - MCGN is the most common form
      - glomerular deposition of HCV proteins

- MCGN without cryoglobulinaemia also possible

- all patients with HCV-associated GN have detectable HCV RNA in serum

VS. CRYOGLOBULINEMIC GLOMERULOPATHY

**Brouet’s classification**

- **Type I:** Isolated monoclonal immunoglobulin (IgG, IgM) - Multiple myeloma; Waldenstrom macroglobulinemia
- **Type II:** Polyclonal immunoglobulin (IgG) in association with monoclonal immunoglobulin (usu. IgM κ chain) with RF activity - Hepatitis C virus; HIV
- **Type III:** Polyclonal antiglobulin bind to polyclonal IgG - Rheumatic diseases, hepatitis C virus

**NB.**

- type II and III are “mixed” cryoglobulinemia; rheumatoid factor positive
- cryoglobulinemic glomerulopathy most common in type II
CRYOGLOBULINEMIC GN: PATHOLOGY

<table>
<thead>
<tr>
<th></th>
<th>LM</th>
<th>IF</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV with cryoglobulinemic GN</td>
<td>MPGN pattern with “wire loop” lesions or hyaline thrombi</td>
<td>IgM and IgG with both κ and λ light chain</td>
<td>mesangial and subendothelial ED deposits; type II may have microtubular structure (20-30 nm)</td>
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<tr>
<td>HCV with MPGN</td>
<td>MPGN pattern without “wire loop” lesions or hyaline thrombi</td>
<td>polyclonal IgG and IgM</td>
<td>mesangial and subendothelial ED deposits; duplication of GBM</td>
</tr>
<tr>
<td>type 1 cryoglobulinemic GN</td>
<td>MPGN pattern with “wire loop” lesions or hyaline thrombi</td>
<td>monoclonal IgG or IgM</td>
<td>mesangial and subendothelial crystalline / paracrystalline deposits</td>
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<tr>
<td>lupus nephritis</td>
<td>endocapillary proliferation or “wire loop” lesions or hyaline thrombi</td>
<td>polyclonal IgG; full house pattern</td>
<td>mesangial, subendothelial, or subepithelial ED deposits</td>
</tr>
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# Assessment of Histological Activity

<table>
<thead>
<tr>
<th>Activity Index (maximum, 22)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>Grading</td>
<td></td>
</tr>
<tr>
<td>Endocapillary proliferation</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Mesangial proliferation</td>
<td>0-2</td>
<td></td>
</tr>
<tr>
<td>Extracapillary proliferation</td>
<td>&gt;0 to &lt;10 = 1</td>
<td>≥10 to &lt;20 = 2</td>
</tr>
<tr>
<td>(% glomeruli)</td>
<td>≥20 = 3</td>
<td></td>
</tr>
<tr>
<td>Double contours/basement</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>membrane thickening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial infiltrate (%</td>
<td>&gt;0 to &lt;30% = 1</td>
<td>&gt;30 to &lt;60% = 2</td>
</tr>
<tr>
<td>cortex)</td>
<td></td>
<td>&gt;60% = 3</td>
</tr>
<tr>
<td>Endoluminal thrombi (%</td>
<td>&gt;0 to &lt;30% = 1</td>
<td>&gt;30 to &lt;60% = 2</td>
</tr>
<tr>
<td>glomeruli)</td>
<td></td>
<td>&gt;60% = 3</td>
</tr>
<tr>
<td>Arteritis</td>
<td>2 (if present)</td>
<td></td>
</tr>
<tr>
<td>Thrombi/microangiopathy</td>
<td>2 (if present)</td>
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</table>
# Assessment of Histological Chronicity

<table>
<thead>
<tr>
<th>Sclerosis Index (maximum, 16)</th>
<th>Lesion</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global sclerosis (% glomeruli)</td>
<td>&gt;0 to &lt;10 = 1</td>
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<tr>
<td></td>
<td></td>
<td>≥10 to &lt;20 = 2</td>
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<tr>
<td></td>
<td></td>
<td>≥20 = 3</td>
</tr>
<tr>
<td></td>
<td>Segmental sclerosis (% glomeruli)</td>
<td>&gt;0 to &lt;10 = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥10 to &lt;20 = 2</td>
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<tr>
<td></td>
<td></td>
<td>≥20 = 3</td>
</tr>
<tr>
<td></td>
<td>Fibrotic crescents (% glomeruli)</td>
<td>&gt;0 to &lt;10 = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥10 to &lt;20 = 2</td>
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<tr>
<td></td>
<td></td>
<td>≥20 = 3</td>
</tr>
<tr>
<td></td>
<td>Mesangial sclerosis</td>
<td>0-3</td>
</tr>
<tr>
<td></td>
<td>Tubular atrophy and interstitial fibrosis (% cortex)</td>
<td>&gt;0 to &lt;30% = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;30 to &lt;60% = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;60% = 3</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis</td>
<td>1 (if present)</td>
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PROGNOSIS

• 1/3 remission, often spontaneous
• 1/3 gradual progression to end stage
• 1/5 intermittent exacerbation
• overall 10-year survival ~80%
• age, baseline serum creatinine, and proteinuria are independent predictors of dialysis-dependent renal failure

EXPERIENCE IN THE PAST

• patients with moderate proteinuria and progressive renal function worsening (but not RPGN)
  • sustained viral response with IFN-α ± ribavirin: 15% to 55%
  • but has no effect on renal function deterioration

• renal function is better preserved with steroid therapy traditional regimen:
  • pulse methylprednisolone 0.5-1.0 g/day for 3 days
  • then prednisolone 0.5 mg/kg/day
  • gradually tail to 10 mg/day
  • total treatment for 6 months
**Anti-viral Therapy for HCV-related GN: Rationale**

i.e. patients with mild proteinuria and stable renal function

- possibility of spontaneous remission
- substantial observational data showing that remission of hematuria, proteinuria, and improvement of GFR in patients with HCV-associated GN who obtained sustained HCV RNA clearance by DAAs

Other supportive measures
- ACE inhibitor / ARB
- blood pressure control
- diuretics for symptom relief

DAA: THE EVIDENCE

- 44 consecutive patients with HCV-associated mixed cryoglobulinemia
- sofosbuvir-based direct-acting antiviral therapy
- SVR12 and SVR24: 100%

- Birmingham Vasculitis Activity Score
  - 5.41 ±3.53 at baseline
  - 2.35 ±2.25 at week 4
  - 1.39 ±1.48 at week 12
  - 1.27 ±1.68 at week 24

- mean cryocrit value
  - 7.2 ±15.4% at baseline
  - 2.9 ±7.4% at week 12
  - 1.8 ±5.1% at week 24

CONCERN WITH ANTI-VIRAL THERAPY

• limited published data
• in all patients with proteinuria reduction, HCV RNA clearance was observed at the end of antiviral therapy

concern
• uncertain effect on long-term renal outcome
• clinical benefit in patients with SVR may be transient
• dissociation between viral and renal response could happen later i.e. relapse of vasculitis possible despite SVR

SEVERE CASES: TRADITIONAL APPROACH

• steroid therapy as previous, plus:

• cyclophosphamide: 2 mg/kg/day for 8 to 16 weeks

• plasma exchange: 3L plasma three times / week for 2 to 3 weeks

• rituximab: 375 mg/m²/week for 4 weeks
IS THIS APPROACH EFFECTIVE

• retrospective study of 105 patients with essential mixed cryoglobulinemia vasculitis and renal involvement, followed for 72 months (85% HCV positive)

• 80% had oral or pulse steroids and/or cytotoxic agents
• 67% had plasma exchange

• patient survival at 10 years was 49%
• long term renal remission in 14%

RITUXIMAB IS BETTER

• 59 patients with cryoglobulinemic vasculitis and related skin ulcers, active glomerulonephritis, or refractory peripheral neuropathy
• randomized to
  • rituximab (2 infusions of 1 gm each, with a second course at relapse)
  • conventional treatment plus steroid; AZA or CP; or plasmapheresis

• survival at 12 months: 64.3% versus 3.5%
• Birmingham Vasculitis Activity Score decreased only after rituximab
  11.9 ± 5.4 at baseline
  → 7.1 ± 5.7 at month 2
  → 4.4 ± 4.6 at month 24

Another RCT on rituximab

- 24 patients with cryoglobulinemic vasculitis in whom antiviral therapy had failed to induce remission

- randomized to
  - rituximab (375 mg/m²/week for 4 weeks)
  - best available therapy (maintenance or increase in immunosuppressive therapy)

- remission at 6 months: 83% versus 8%

## Summary of Current Recommendations

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>stable renal function; non-nephrotic proteinuria</td>
<td>direct acting antiviral therapy</td>
</tr>
<tr>
<td>cryoglobulinemia flare, nephrotic syndrome, or RPGN</td>
<td>direct acting antiviral therapy + immunosuppressive treatment ± plasma exchange</td>
</tr>
<tr>
<td>active HCV-associated GN not responding to direct acting antiviral therapy</td>
<td>rituximab</td>
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</tbody>
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