Hepatitis C and the Kidney: More than Just MPGN

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Minnesota Viral Hepatitis ECHO
Disclosures

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Objectives

- Describe the types of kidney diseases that can be associated with hepatitis C (HCV) and appreciate that membranoproliferative glomerulonephritis (MPGN) is a histologic finding with several other causes.
- List the tests that can help identify patients who might have HCV related kidney disease.
- Be aware of the changes that direct acting antivirals have led to in the field of kidney transplantation.
First Description of HCV MPGN

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION

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Abstract Background and Methods. Hepatitis C virus (HCV) infection causes both acute and chronic liver disease and is also associated with mixed cryoglobulinemia. Whether HCV is also associated with renal disease, as is the hepatitis B virus, is not known. We describe the clinical, pathologic, virologic, and immunologic features of eight patients with HCV infection who were referred to nephrologists for glomerulonephritis. Four patients were treated with interferon alfa.

Results. All eight patients had proteinuria, and seven had decreased renal function. Renal biopsy in all patients revealed membranoproliferative glomerulonephritis, characterized by the deposition of IgG, IgM, and C3 in glomeruli. Electron microscopy of the biopsy specimens showed cryoglobulin-like structures in three of four patients. All eight patients had HCV RNA detected in their serum, elevated serum aminotransferase concentrations, and hypocomplementemia, and the majority had cryoglobulins and circulating immune complexes in their serum. Cryoprecipitates from the three patients who were tested contained HCV RNA and IgG anti-HCV antibodies to the nucleocapsid core antigen (HCVc or c22-3). IgM rheumatoid factors, present in all patients, bound anti-HCV IgG in all six patients tested. Four patients received interferon alfa for 2 to 12 months; all had evidence of decreased HCV replication and improvement of their renal and liver disease.

Conclusions. Chronic HCV infection is associated with cryoglobulinemia and membranoproliferative glomerulonephritis. The pathogenesis is unknown, but may relate to deposition within glomeruli of immune complexes containing HCV, anti-HCV IgG, and IgM rheumatoid factors. (N Engl J Med 1993;328:465-70.)
Pathogenesis of HCV MPGN

- Classic HCV associated glomerulonephritis is “type 1” MPGN.
- HCV infects CD5+ CD81+ B cells which stimulates production of polyclonal type 3 cryoglobulins. With sustained infection, monoclonal IgM kappa type 2 cryoglobulins develop.
- Cryoglobulin-immune complex deposits in the glomerular basement membrane (subendothelial)
- Takes time for MPGN to develop ~10-15 years of viremia
**What are Cryoglobulins?**

- Immunoglobulins that precipitate at 4°C
- Cryoglobulinemia rare in hepatitis A and hepatitis B infection

<table>
<thead>
<tr>
<th>Type</th>
<th>Composition</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Monoclonal Ig, mainly IgG, IgM, or IgA</td>
<td>Lymphoproliferative disorders</td>
</tr>
<tr>
<td>Type 2</td>
<td>Monoclonal IgM having RF activity and polyclonal Ig (mainly IgG)</td>
<td>Infections, autoimmune or heme disorders, idiopathic</td>
</tr>
<tr>
<td>Type 3</td>
<td>Polyclonal IgM having RF activity and polyclonal Ig (mainly IgG)</td>
<td>Infections, autoimmune or heme disorders, idiopathic</td>
</tr>
</tbody>
</table>

Renal Biopsy Findings

Figs A,B: Up to date, accessed 10/20/2022.
MPGN is not Pathognomonic for HCV

MPGN

**Ig positive**
- C3 positive
  - Infection
  - Autoimmune
  - Monoclonal gammopathy

**Ig negative**
- C3 positive
  - C3 glomerulopathy
  - DDD

Treatment of HCV MPGN

- DAAs have supplanted peg-interferon and are now recommended initial therapy.
- Corticosteroids ± plasmapheresis ± rituximab used in refractory cases.
Majority of Patients with Chronic HCV and Kidney Disease do not have MPGN

- 9,836 native kidney biopsies from 2007-2017

### The Kidney Diseases in HCV+ Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2007-2011, No. (%)</th>
<th>2012-2016, No. (%)</th>
<th>P Value</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HCV+ patients</td>
<td>101</td>
<td>172</td>
<td>.64</td>
<td>273</td>
</tr>
<tr>
<td>HCV-associated glomerulonephritis</td>
<td>41 (40.6)</td>
<td>74 (43.0)</td>
<td>.64</td>
<td>115 (42.1)</td>
</tr>
<tr>
<td>Other IC-mediated glomerular diseases</td>
<td>12 (11.9)</td>
<td>19 (11.0)</td>
<td>.98</td>
<td>31 (11.4)</td>
</tr>
<tr>
<td>Non-IC-mediated kidney diseases</td>
<td>48 (47.5)</td>
<td>79 (45.9)</td>
<td>.65</td>
<td>127 (46.5)</td>
</tr>
</tbody>
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HCV, hepatitis C virus; IC, immune complex.

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### The Kidney Diseases in HCV+ Patients

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<th>P Value</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases of HCV-associated glomerulonephritis</td>
<td>41</td>
<td>74</td>
<td>.32</td>
<td>115</td>
</tr>
<tr>
<td>Focal proliferative glomerulonephritis pattern</td>
<td>1 (2.4)</td>
<td>5 (6.8)</td>
<td>.32</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Diffuse mesangial proliferative pattern</td>
<td>15 (36.6)</td>
<td>43 (58.1)</td>
<td>.03</td>
<td>58 (50.4)</td>
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<tr>
<td>Diffuse membranoproliferative pattern</td>
<td>19 (46.3)</td>
<td>14 (18.9)</td>
<td>.01</td>
<td>33 (28.7)</td>
</tr>
<tr>
<td>Proliferative glomerulonephritis with crescentic lesions</td>
<td>3 (7.3)</td>
<td>6 (8.1)</td>
<td>.88</td>
<td>9 (7.8)</td>
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<tr>
<td>Membranous pattern</td>
<td>3 (7.3)</td>
<td>6 (8.1)</td>
<td>.88</td>
<td>9 (7.8)</td>
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HCV, hepatitis C virus.
Non-GN Kidney Diseases Found in Patients with Chronic HCV Infection

<table>
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<tr>
<th>Characteristic</th>
<th>2007-2011, No. (%)</th>
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<tr>
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<td>101</td>
<td>172</td>
<td>273</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>18 (17.8)</td>
<td>36 (20.9)</td>
<td>54 (19.8)</td>
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<tr>
<td>Arterionephrosclerosis</td>
<td>12 (11.9)</td>
<td>22 (12.8)</td>
<td>34 (12.5)</td>
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<tr>
<td>Obstruction/reflux</td>
<td>3 (3.0)</td>
<td>3 (1.7)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>5 (5.0)</td>
<td>2 (1.2)</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td>1 (1.0)</td>
<td>1 (0.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>3 (3.0)</td>
<td>1 (0.6)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Acute tubular injury</td>
<td>2 (2.0)</td>
<td>4 (2.3)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>0 (0.0)</td>
<td>2 (1.2)</td>
<td>2 (0.7)</td>
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<tr>
<td>LCDD/LCCN</td>
<td>0 (0.0)</td>
<td>2 (1.2)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4 (4.0)</td>
<td>6 (3.5)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Total non-IC-mediated glomerular disease</td>
<td>48 (47.5)</td>
<td>79 (45.9)</td>
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HCV, hepatitis C virus; HIV, human immunodeficiency virus; IC, immune complex; LCDD, light chain deposition disease; LCCN, light chain cast nephropathy.
How to Evaluate for MPGN

Test

PCP/Hepatologist
• Urinalysis
• Spot urine protein to creatinine ratio (microalbumin/Cr OK)
• BMP
• C3 and C4
• Cryoglobulins
• Renal US

Nephrologist
• Urine sediment exam
• Native renal biopsy

Hepatitis C and Renal Transplant
Timeline of FDA Approval of Direct Acting Antivirals

- Telaprevir (Incivek)
- Boceprevir (Victrelis)
- Sofosbuvir (Sovaldi)
- Simeprevir (Olysio)
- Ledipasvir/Sofosbuvir (Harvoni)
- Velpatasvir/sofosbuvir (Epclusa)
- Ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak, Viekira XR)
- Daclatasvir (Dalclinza)
- Ombitasvir/paritaprevir/ritonavir (Technivie)
- Elbasvir/grazoprevir (Zepatier)
- Glecaprevir/pibrentasvir (Mavyret)
- Velpatasvir/sofosbuvir/Voxilaprevir (Vosevi)
UNOS Waiting List

- ~89,888 patients waiting for a kidney transplant
  - Severe shortage of organ donors
  - Difficult to find a living donor
- Average waiting time for a deceased donor kidney transplant in Minnesota is 5 years
Advantages of HCV NAT Positive Donor to HCV Negative Recipient Transplant

**Patient**
- Reduced wait time
- Decreased mortality
- Potentially higher quality kidney
- High likelihood of HCV cure with DAA treatment post-transplant

**Society**
- Reduce organ discard rate
- Lower ESRD costs
Transplanted 10 HCV NAT+ kidneys into 10 HCV-recipient recipients
Grazoprevir/elbasvir x 12 wks; started empirically pre-operatively
Primary outcome: SVR12

Results

- 100% achieved SVR12
- Median Cr at 24 weeks post-txp was 1.05 mg/dL (0.9-2.0 mg/dL)
- No acute rejections
Transplanted 20 HCV NAT+ kidneys into 10 HCV- recipients

Same DAA as EXPANDER

All patients had detectable viremia by day 5
  – All 20 patients had undetectable viral loads within 4 weeks of DAA initiation

All 20 patients had SVR12

NEW OPTION FOR KIDNEY TRANSPLANTS

In a Minnesota first, a patient received a donor kidney that was infected with now-curable hepatitis C.

Story by JEREMY OLSON • Photo by JEFF WHEELER • Star Tribune

When the estimated wait for a donor kidney stretched from four years to five, and then from five to eight, C.J. Dabney started to fear that he would die before getting a transplant. So he didn’t need convincing earlier this year when doctors offered a radical new alternative — a kidney infected with hepatitis C.

“I’m in,” he said.

On Friday Dabney, 54, became the first patient in Minnesota to receive a kidney from a donor who was carrying the virus.

“Five years ago, this would have been impossible to do,” said Dr. Jeffrey Wang, the nephrologist who recommended the procedure. The difference is new drug therapies that are curing what was previously a chronic infection, making the organs safe for transplant by healing the kidney’s recipient.

Wang and transplant specialists at HCMC in Minneapolis said they hope the development can reduce waiting times that have sometimes amounted to a death sentence for patients.

See KIDNEY on A10

“Five years ago, this would have been impossible to do.”
Nephrologist Dr. Jeffrey Wang, about the donor kidney received by C.J. Dabney, above, at HCMC in Minneapolis.
Acknowledgements

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Adley Lemke, PharmD

Molecular Lab/Pathology
Aaron Lambert, MB (ASCP)
Glen Hansen, PhD

Pre-transplant Coordinators
Bobbie, Jenny, Lori, Patty
# Proportion of US Deceased Donor Kidney Transplants by Donor/Recipient HCV Status

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</thead>
<tbody>
<tr>
<td>D Ab−, NAT−/R Ab−</td>
<td>10,258 (92.6)</td>
<td>13,253 (92.7)</td>
<td>13,762 (92.3)</td>
<td>14,120 (90.4)</td>
<td>15,062 (87.0)</td>
<td>15,713 (86.3)</td>
<td>16,795 (87.1)</td>
<td>71,117 (87.1)</td>
<td>106,080 (89.2)</td>
</tr>
<tr>
<td>D Ab−, NAT+/R Ab−</td>
<td>8 (0.1)</td>
<td>16 (0.1)</td>
<td>187 (1.3)</td>
<td>367 (2.4)</td>
<td>571 (3.3)</td>
<td>718 (3.9)</td>
<td>743 (3.9)</td>
<td>321 (3.9)</td>
<td>2,931 (2.5)</td>
</tr>
<tr>
<td>D Ab−, NAT+/R Ab−</td>
<td>14 (0.1)</td>
<td>40 (0.3)</td>
<td>56 (0.4)</td>
<td>329 (2.1)</td>
<td>896 (5.2)</td>
<td>1,062 (5.8)</td>
<td>1,049 (5.4)</td>
<td>423 (5.2)</td>
<td>3,869 (3.3)</td>
</tr>
<tr>
<td>D Ab+, NAT+/R Ab+</td>
<td>246 (2.2)</td>
<td>342 (2.4)</td>
<td>299 (2.0)</td>
<td>225 (1.4)</td>
<td>182 (1.1)</td>
<td>124 (0.7)</td>
<td>83 (0.4)</td>
<td>33 (0.4)</td>
<td>1,534 (1.3)</td>
</tr>
<tr>
<td>D Ab+, NAT+/R Ab+</td>
<td>548 (4.9)</td>
<td>653 (4.6)</td>
<td>599 (4.0)</td>
<td>576 (3.7)</td>
<td>602 (3.5)</td>
<td>595 (3.3)</td>
<td>620 (3.2)</td>
<td>274 (3.4)</td>
<td>4,467 (3.8)</td>
</tr>
<tr>
<td>Total</td>
<td>11,074 (100)</td>
<td>14,304 (100)</td>
<td>14,903 (100)</td>
<td>15,617 (100)</td>
<td>17,313 (100)</td>
<td>18,212 (100)</td>
<td>19,290 (100)</td>
<td>8,168 (100)</td>
<td>118,881 (100)</td>
</tr>
</tbody>
</table>

Ab, antibody; D, donor; DDKT, deceased donor kidney transplant; HCV, hepatitis C virus; NAT, nucleic acid amplification testing; R, recipient.

Data from UNOS STAR deceased donor files.

Shetty A. Curr Opin Organ Transplant. 2022;epub ahead of print.
Take Home Points

- HCV induced MPGN presents with subacute to acute onset of acute kidney injury, microscopic hematuria with active sediment, and proteinuria usually with other extrarenal symptoms.
- HCV induced MPGN is less commonly found in the DAA era.
- DAAs have revolutionized the field of kidney transplantation by allowing HCV NAT positive donor to negative recipient transplants to be possible.