Clots and Foamy Urine: Thrombotic Complications of Nephrotic Syndrome

Prayus Tailor, MD
October 5, 2013

Renal and Hypertension Symposium
Objectives

• Discuss the pathophysiology of thrombosis in nephrotic syndrome

• Identify risk factors for thrombotic/thromboembolic events in these patients

• Management of thromboembolic events in patient with nephrotic syndrome
Case Presentation

• HPI: 21 yo white male presents to hospital with 10 days of SOB, leg swelling and weight gain.

• 3 weeks prior, he injured his back while lifting weights and started ibuprofen 1,600mg daily.

• ROS: as above, sore throat.
Case (cont’d)

• Past Medical Hx: childhood asthma?
• Medications: ibuprofen
• Allergies: Ceclor
• Social Hx: university student, hockey player, no tobacco, ETOH or illicit drugs
• Fam Hx: no history of kidney disease
Case (cont’d)

- On exam:
- Pulse 80, BP 134/84, RR 16, SpO2 97% RA
- 3+ pedal edema bilaterally
- No rash
Case (cont’d)

• Labs:
  
  – Creat 1.2 mg/dL
  
  – Albumin 1.9 g/dL
  
  – UA – 600mg/dL protein, 6-10 WBC/hpf, 11-15 RBC/hpf, many granular casts
  
  – Urine protein to creatinine ratio 2043/242 = 8.4g/day.
  
  – Chol 205, LDL 121, Trig 159, HDL 52
Nephrotic Syndrome

• Proteinuria > 3.5g/day
• Edema
• Hypoalbuminemia
• Hypercholesterolemia
Hospital Course

• Prednisone initiated empirically
• ACE inhibitor
• Loop diuretic
• Bactrim for PCP prophylaxis
• Omeprazole for GI prophylaxis
• Calcium supplement
• KIDNEY BIOPSY
Light microscopy
Light microscopy
Immunofluorescence
Renal Biopsy - Diagnosis

• Membranous Nephropathy
Further course

• Pt returns to hospital 1 week after renal biopsy with complaints of:
  – Interscapular back pain
  – Shortness of breath

• SpO2 88% on RA.
Thromboembolism in nephrotic syndrome is due to multifaceted pathophysiology.

Kerlin B A et al. CJASN 2012;7:513-520
Nephrotic syndrome is a prothrombotic state of variable magnitude.

<table>
<thead>
<tr>
<th>Anti-Thrombotic</th>
<th>Pro-Thrombotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procoagulant</strong></td>
<td><strong>Pro-Thrombotic</strong></td>
</tr>
<tr>
<td>N or ↓ factor XI (160)⁸</td>
<td>N or ↓ factor XII (80)⁸,⁴⁹</td>
</tr>
<tr>
<td>↑, N, or ↓ factor II (69)⁸</td>
<td>↑, N, or ↓ factor V (330)⁸</td>
</tr>
<tr>
<td>↑, N, or ↓ factor VII (50)⁸</td>
<td>↑ fibrinogen (340)⁸</td>
</tr>
<tr>
<td>↑, N, or ↓ factor IX (56)⁸</td>
<td>↑, N, or ↓ factor VIII (330)⁸</td>
</tr>
<tr>
<td>↓ or ↑ Plt Function⁸,⁴⁸</td>
<td>↓ or ↓ AT (65)⁸,¹⁴,⁵⁴</td>
</tr>
<tr>
<td><strong>Anticoagulant</strong></td>
<td><strong>Pro-Thrombotic</strong></td>
</tr>
<tr>
<td>↑ protein C (62)⁸,¹⁴,⁵⁴,⁵⁵</td>
<td>↓ protein Z (62)⁴³,⁵⁴</td>
</tr>
<tr>
<td>↑, N, or ↓ protein S (69)⁸,¹⁴,⁵⁴</td>
<td>↓ or ↓ AT (65)⁸,¹⁴,⁵⁴</td>
</tr>
<tr>
<td><strong>Profibrinolytic</strong></td>
<td><strong>Pro-Thrombotic</strong></td>
</tr>
<tr>
<td>↑, N, or ↓ α₂-AP (70)⁸</td>
<td>↓ Plasminogen (92)⁸</td>
</tr>
<tr>
<td>↓, N, or ↓ tPA (72)⁶,⁵⁵</td>
<td>↑ fibrinogen (340)⁸</td>
</tr>
<tr>
<td><strong>Antifibrinolytic</strong></td>
<td><strong>Pro-Thrombotic</strong></td>
</tr>
<tr>
<td>↓ α₁-AT (54)⁸</td>
<td>↓ or ↑ PAI (52)⁸,⁴²</td>
</tr>
<tr>
<td>↑ Lp(a) (~500)⁸</td>
<td>↑ fibrinogen (340)⁸</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td><strong>Pro-Thrombotic</strong></td>
</tr>
<tr>
<td>*Thrombophilia</td>
<td>↑ RBC Aggregation⁸</td>
</tr>
<tr>
<td>#APL</td>
<td>Clot Structure⁸,⁶²</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia⁸</td>
</tr>
</tbody>
</table>

sum hemostatic potential is variably increased

Kerlin B A et al. CJASN 2012;7:513-520

©2012 by American Society of Nephrology
Epidemiology

• Incidence
  – Adults: 25%
    • Upto 37% in Membranous GN
    • 24% cumulative incidence in MPGN, MCD, FSGS
  – Children: 3%
    • Upto 25% Membranous GN or SLE Class V.
    • 17% in secondary NS due to vasculitis
    • 10% in congenital NS occurring w/i 3 mos of life

Kerlin BA, Ayoob R, Smoyer WE. CJASN 2012;7:513-520
Distribution of venous thromboembolic event (VTE) during the observation time.

Lionaki S et al. CJASN 2012;7:43-51
Incidence of RVT by type of nephrotic syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>MN</th>
<th>MPGN</th>
<th>MCD</th>
<th>FSGS</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Llach et al.</td>
<td>230.0 (20/69)</td>
<td>22.2 (6/27)</td>
<td>20.0 (2/10)</td>
<td>25.0 (1/4)</td>
<td>9.8 (11/41)</td>
</tr>
<tr>
<td>Chugh et al.</td>
<td>42.9 (3/7)</td>
<td>20.0 (1/5)</td>
<td>26.3 (5/19)</td>
<td>0 (0/5)</td>
<td>25 (2/8)</td>
</tr>
<tr>
<td>Wagoner et al.</td>
<td>51.9 (14/27)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Velasquez et al.</td>
<td>60.0 (3/5)</td>
<td>40.0 (4/10)</td>
<td>NS</td>
<td>28.6 (2/7)</td>
<td>50 (2/4)</td>
</tr>
<tr>
<td>TOTAL</td>
<td><strong>37.0 (40/108)</strong></td>
<td>26.2 (11/42)</td>
<td>24.1 (7/29)</td>
<td>18.8 (3/16)</td>
<td>28.3 (15/53)</td>
</tr>
<tr>
<td>TOTAL for combined</td>
<td>—</td>
<td>—</td>
<td>24.1 (21/87)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MPGN, MCD, and FSGS</td>
<td>—</td>
<td>—</td>
<td>24.1 (21/87)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Kerlin BA, Ayoob R, Smoyer WE. CJASN 2012;7:513-520
Multivariate analysis to identify predictors of VTE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th><strong>P Value</strong>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnostic biopsy (yr)</td>
<td>0.99</td>
<td>0.97, 1.01</td>
<td>0.39</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2.13</td>
<td>1.02, 4.44</td>
<td>0.04</td>
</tr>
<tr>
<td>24-hour proteinuria (g/d)</td>
<td>0.98</td>
<td>0.93, 1.04</td>
<td>0.59</td>
</tr>
<tr>
<td>Immunosuppressive therapy, any</td>
<td>1.72</td>
<td>0.85, 3.47</td>
<td>0.13</td>
</tr>
<tr>
<td>Site of registry (GDCN/TGRN)</td>
<td>0.67</td>
<td>0.36, 1.24</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum albumin (g/dl)b</td>
<td>2.13</td>
<td>1.32, 3.46</td>
<td>0.002</td>
</tr>
</tbody>
</table>

```
Lionaki S et al. CJASN 2012;7:43-51
```
Adjusted risk of VTE by the level of serum albumin

<table>
<thead>
<tr>
<th>Serum Albumin (g/dl)</th>
<th>N</th>
<th>Patients with VTE</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range ≥3.0</td>
<td>219</td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8 to &lt;3.0</td>
<td>66</td>
<td>3</td>
<td>1.41</td>
<td>0.34, 5.87</td>
<td>0.64</td>
</tr>
<tr>
<td>2.6 to &lt;2.8</td>
<td>74</td>
<td>2</td>
<td>2.17</td>
<td>0.63, 7.46</td>
<td>0.22</td>
</tr>
<tr>
<td>2.4 to &lt;2.6</td>
<td>72</td>
<td>4</td>
<td>2.05</td>
<td>0.59, 7.12</td>
<td>0.26</td>
</tr>
<tr>
<td>2.2 to &lt;2.4</td>
<td>77</td>
<td>1</td>
<td>1.31</td>
<td>0.31, 5.62</td>
<td>0.72</td>
</tr>
<tr>
<td>2.0 to &lt;2.2</td>
<td>82</td>
<td>8</td>
<td>4.32</td>
<td>1.46, 12.77</td>
<td>0.01</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>142</td>
<td>15</td>
<td>3.56</td>
<td>1.28, 9.88</td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;2.8 vs. ≥2.8</td>
<td>447/285</td>
<td></td>
<td>2.53</td>
<td>1.17, 5.47</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Renal survival probability among MN patients with and without VTE.

Lionaki S et al. CJASN 2012;7:43-51
Who Should be Anticoagulated?

Prophylactic anticoagulants in Idiopathic Membranous Nephropathy (IMN)

• “We suggest that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin 2.5 g/dL and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using oral warfarin. (2C)”

KDIGO Clinical Practice Guidelines for Glomerulonephritis June 2012.
Management

• Unfractionated Heparin
• LMW Heparins
  – Enoxaparin can be used
    • Creatinine Clearance 10-29 mL/min: decr dose 30% or give q24h
    • Creatinine Clearance < 10 mL/min: decr dose 50%, give q24h. Monitor factor Xa levels.
    • Not FDA approved for use in dialysis patients
Management (cont’d)

• Warfarin
  – How does nephrotic syndrome cause warfarin resistance?
    • Hypoalbuminemia – may increase the free fraction of warfarin leading to increased clearance & decr t½
    • Hyperlipidemia – observational increase in warfarin sensitivity with lipid lowering rx (esp TG’s) and decrease in sensitivity with IV lipids (TPN).
    • Diuretics - may decrease the response to warfarin by reducing the plasma volume, with a subsequent increase in clotting factor activity.

Management (cont’d)

• Rivaroxaban
  – FDA approved to treat DVT and PE
  – NOT STUDIED IN NEPHROTIC PATIENTS.
  – Creatinine Clearance ≥ 30mL/min – no dose adjustment
  – Creatinine Clearance < 30mL/min – AVOID USE.
Management (cont’d)

- Thrombolytic therapy
  - Severe bilateral RVT’s
  - Severe pulmonary embolism
Duration of Anticoagulation

• 6 months and:
  – improvement in albumin to greater than 2.8 (opinion)
  – resolution of nephrotic syndrome (opinion)
Questions?

Thank You

ptailor@delawarekidney.com