Prognostic implications of complement factor H mutations in atypical HUS

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Patient Presentation

• 38F originally presented in 6/2001 with no other medical issues p/w generalized malaise and hematuria to ED. No fevers. No diarrheal prodrome. No mental status change.

  - Peripheral smear: schistocytes
  - Stool for Shiga-like toxin was negative
  - ADAMTS13 activity unknown
  - Started on plasmapheresis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>4.3</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt; 2000</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.9</td>
</tr>
<tr>
<td>Coomb’s</td>
<td>negative</td>
</tr>
</tbody>
</table>
Patient Presentation

• Rapid resolution of hematuria and fatigue
• Platelet count and bilirubin were normal after 6 days
• LDH had decreased to 700
• Renal function at time of discharge was unchanged
• Started on 2 agents for difficult to control blood pressure
• With discontinuation of plasmapheresis, there was increased hemolysis and plasmapheresis was restarted in 7/01
Patient Presentation

- Extensive workup for other etiologies of renal dysfunction were all negative
- Renal biopsy in 8/01 consistent with thrombotic microangiopathy
- Received vincristine x 3
- Plasmapheresis tapered
- Relapse 12/01:
  - Increased frequency of plasmapheresis
  - Cyclophosphamide
  - MMF
Patient Presentation

• Tapered plasmapheresis to q2w by 5/02
  - Cyclophosphamide discontinued
  - MMF tapered off
• Blood pressure still difficult to control, now on 4 medications
• Received rituximab without improvement
• Not able to completely taper off plasmapheresis, underwent splenectomy 12/03
• Was slowly weaned off plasmapheresis by 3/06
• Given stability of disease and borderline Stage V CKD was referred to UWMC Renal Transplant for evaluation
Atypical Hemolytic-Uremic Syndrome (aHUS)

- HUS is a thrombotic microangiopathy characterized by non-immune hemolytic anemia, thrombocytopenia, and renal impairment
- aHUS are cases not caused by production of Shiga-like toxin
- Inciting factors: infection, pregnancy, medications
- Develops due to the dysregulation of the alternative complement pathway
Pathophysiology of aHUS

- AP is constitutively active but tightly controlled by various regulatory proteins
- C3 hydrolysis initiates the AP eventually leading to deposition of C3b onto practically all plasma exposed surfaces
- Without tight regulation, will have unincumbered formation of MAC -> endothelial cell damage, platelet activation, and thrombus formation
- The fenestrated endothelium of the glomerular capillary bed continually exposes subendothelial matrix to circulating proteins. Thus, the lack of complement regulatory makes the kidney particularly vulnerable.
Patient Presentation

• Genetic mutation analysis showed she was heterozygous for a missense mutation in exon 22 (SCR20) of the gene CHF

• The specific variant was c.3643C>G, p.Arg1215Gly
Complement Factor H (CFH) mutations

- A plasma protein containing 20 homologous repeats (SCRs)
- Regulates the alternative pathway by competing with CFB for C3b recognition by acting as a cofactor for CFI and by enhancing dissociation of C3 convertase
- CFH binds to GAGs on basement membranes and endothelium through its C-terminal repeats.
- Contributes to endothelial protection when membrane regulators are present
- Majority of mutations are heterozygous and cluster at the C-terminal region (important for C3b binding and degradation)

Noris et al. NEJM 2009
Arg1215Gly

Impaired binding to heparin, C3d, and surface bound C3b

Jozsi et al JASN 2006
Treatment - Plasmapheresis

- 47/156 (30.1%) with non-Stx-HUS had CFH mutations

- CR: hematologic normalization and return to baseline renal function

- Of the 14 patients with MCP mutations treated, 12 achieved a CR, 1 PR, 1 ESRD (p<0.001)

<table>
<thead>
<tr>
<th>Outcome of the first episode</th>
<th>No mutation, no.</th>
<th>CFH mutation, no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>28 (81)</td>
<td>7 (40)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>30 (81)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>19 (81)</td>
<td>9 (40)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (81)</td>
<td>12 (40)</td>
</tr>
</tbody>
</table>

p = 0.05

Caprioli et al. Blood 2006
Outcomes in CFH mutations

- Worst long term outcome of all identifiable gene mutations in atypical HUS
- 50% survival rate at 10 years
  - CFI, C3, and anti-CFH autoantibodies have a 10 year survival of 80-90%
- Rate of ESRD or death is 70%
- Up to 10% have cardiac complications and increased CVS mortality
- Severe HTN frequent

Table 7: Long-term outcome of non-Stx–HUS patients

<table>
<thead>
<tr>
<th></th>
<th>No mutation, no.</th>
<th>CFH mutation, no.</th>
<th>MCP mutation, no.</th>
<th>IF mutation, no.</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with remission</td>
<td>36 (84)</td>
<td>9 (40)</td>
<td>12 (14)</td>
<td>2 (6)</td>
<td>.03</td>
<td>.007</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients with complete remission</td>
<td>22 (36)</td>
<td>3 (9)</td>
<td>4 (12)</td>
<td>2 (2)</td>
<td>.13</td>
<td>.08</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>Patients with complete remission, after recurrences</td>
<td>14 (36)</td>
<td>6 (9)</td>
<td>8 (12)</td>
<td>0 (2)</td>
<td>.13</td>
<td>.09</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>Patients with no remission</td>
<td>48 (84)</td>
<td>31 (40)</td>
<td>2 (14)</td>
<td>4 (6)</td>
<td>.03</td>
<td>.003</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>5 (48)</td>
<td>3 (31)</td>
<td>0 (2)</td>
<td>0 (4)</td>
<td>.91</td>
<td>.63</td>
<td>.64</td>
</tr>
<tr>
<td>ESRF</td>
<td>32 (48)</td>
<td>13 (31)</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>.03</td>
<td>.32</td>
<td>.29</td>
</tr>
<tr>
<td>Death</td>
<td>11 (48)</td>
<td>15 (31)</td>
<td>0 (2)</td>
<td>0 (4)</td>
<td>.019</td>
<td>.44</td>
<td>.18</td>
</tr>
</tbody>
</table>

Caprioli et al. Blood 2006
Noris et al. NEJM 2009
# Complement Pathway Mutations

**Table 2** Summary of clinical outcome in patients with aHUS

<table>
<thead>
<tr>
<th>Genetic defect</th>
<th>Frequency</th>
<th>Response to short-term plasma therapy</th>
<th>Long-term outcome</th>
<th>Outcome after kidney transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>20–30%</td>
<td>Rate of remission: 60% (dose- and timing-dependent)</td>
<td>Rate of death or ESRD: 70–80%</td>
<td>Rate of recurrence: 80–90%</td>
</tr>
<tr>
<td>CFI</td>
<td>4–10%</td>
<td>Rate of remission: 30–40%</td>
<td>Rate of death or ESRD: 60–80%</td>
<td>Rate of recurrence: 80–90%</td>
</tr>
<tr>
<td>CFHR1 &amp; 3 with CFH autoantibodies</td>
<td>6%</td>
<td>Rate of remission: 70–80%</td>
<td>Rate of death or ESRD: 30–40%</td>
<td>Rate of recurrence: 20%</td>
</tr>
<tr>
<td>MCP</td>
<td>10–15%</td>
<td>No indication for therapy</td>
<td>Rate of ESRD or death: &lt;20%</td>
<td>Rate of recurrence: 15–20%</td>
</tr>
<tr>
<td>CFB</td>
<td>1–2%</td>
<td>Rate of remission: 30%</td>
<td>Rate of death or ESRD: 70%</td>
<td>Recurrence in one case</td>
</tr>
<tr>
<td>C3</td>
<td>5–10%</td>
<td>Rate of remission: 40–50%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Rate of recurrence: 40–50%</td>
</tr>
<tr>
<td>THBD</td>
<td>5%</td>
<td>Rate of remission: 60%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Recurrence in one case</td>
</tr>
</tbody>
</table>

Waters et al. Pediatr Nephrol 2011
Treatment - Eculizumab

- Trial 1: 17 patients with low platelets and renal damage progressing on plasma exchange or infusion
- 53% had normalization of platelet count by Day 7
- 87% of patients treated through extension treatment period had normal platelet counts
- 76% of patients had decrease in serum creatinine by ≥ 25%
- Dialysis discontinued in 4 of 5 patients
Treatment - Eculizumab

- Trial 2: 20 patients stable platelet counts and renal insufficiency on chronic plasma exchange or infusion with persistent evidence of hemolysis

- Median time from diagnosis to screening was 48m

- Primary endpoint: TMA event free survival for at least 12 weeks
  - 25% decrease in platelets
  - Require plasma exchange/infusion
  - Initiation of dialysis

- 80% (16/20) at 26 weeks met endpoint.

- Both trials showed improvement in HC-QOL
Kidney Transplantation

- Variable prognosis after transplantation depending on the genetic mutation
- Graft failure occurs in 90% of those with recurrent disease after transplantation
- Pts with MCP mutations or autoantibodies to CFH have low recurrence rates
- In patients with CFH mutations rate of recurrence is 80-90% (71% after 1 year)
- All patients should undergo genotyping prior to transplantation

Table 9. Outcome of kidney transplantations in patients with non-Stx-HUS

<table>
<thead>
<tr>
<th></th>
<th>No mutation, no.</th>
<th>CFH mutation, no.</th>
<th>MCP mutation, no.</th>
<th>IF mutation, no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney transplant recipients</td>
<td>14</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Transplanted kidneys</td>
<td>17</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Kidney outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good renal function at 1 y</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Disease recurrence on the graft</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Caprioli et al. Blood 2006
Zuber et al. Nat Rev Nephrol 2011
Kidney Transplantation

- Preventative therapy a must in patients with mutations at high risk of recurrence
- 5 carried CFH mutation, 4 in SCR20
- Median follow-up was 14.5 months
- ? Increased risk of complications from immunosuppression
Kidney Transplantation

- Plasmapheresis has failed to improve graft survival in setting of aHUS recurrence.

- Interestingly, 15/37 patients in Legendre study had history of kidney transplant.

- Case series and reports suggest eculizumab delays recurrence, however recurrences after cessation of treatment are common.

Nurnberger et al. NEJM 2010
Zuber et al. Transplant Reviews 2013
Combined Liver-Kidney Transplant

- Complement regulatory plasma proteins are synthesized in liver

- Poor outcomes in initial case reports with development of hepatic failure and massive thrombosis (liver complement mediated injury due to dominant negative effect)

- With addition of intensive plasma therapy since 2004 prior to surgery, outcomes have improved. Most recent attempts have used eculizumab

- Given improved outcomes recently with eculizumab, combined liver-kidney transplant risk of morbidity and mortality too high to be recommended
Conclusions

- Atypical HUS is associated with complement dysregulation with high morbidity and mortality
- It can be refractory to plasma exchange. Low threshold to utilize eculizumab.
- Prognosis is dependent on type of complement mutation
- All patients being evaluated for kidney transplantation should undergo mutational testing
- Data suggests significant benefit to eculizumab around the time of kidney transplant in patients with high risk mutations