Complement-Mediated Thrombotic Microangiopathy: An Update

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  • Alexion Pharmaceuticals
  • Octapharma Canada
  • Pfizer Canada
Objectives

• To define thrombotic microangiopathy (TMA) and present a contemporary classification based on our molecular understanding.

• To discuss the current understanding of the pathophysiology of atypical hemolytic uremic syndrome (aHUS), aka complement-mediated TMA.

• To review management of atypical HUS, with a focus on plasma therapy and eculizumab.

• To highlight a practical approach to diagnosing and managing TMA.
• 41yo male, congenital fused horseshoe kidney, no CKD, incarcerated hernia requiring surgical repair 2005, otherwise well.
• 1-week history of fever, anorexia, left sided abdominal pain, non-bloody diarrhea.
• No neurologic symptoms.
• Febrile 39.3°C, BP 190/101.
• CRP 172 mg/L, AST 17, ALT 34, ALP 92, GGT 81, amylase 174
• INR 1.1, aPTT 30s, fibrinogen 2.4, D-dimer >4000
• CT abdomen shows mildly enlarged pancreas & appendix, marked mural density c/w colitis, small amount intraperitoneal fluid.
Case

Hemoglobin | Platelets | Creatinine
---|---|---
309 | 236 | 261

Bone marrow biopsy “reactive”

Haptoglobin 2.30 “A few schistocytes”

Renal biopsy showing TMA

Stool C&S negative

Day of Admission

LDH 201

CARE
Question

• This patient’s presumptive diagnosis is:

A. Thrombotic thrombocytopenic purpura
B. Shiga toxin mediated hemolytic uremic syndrome
C. Malignant hypertension
D. Complement-mediated TMA (aHUS)
E. I have no idea but whatever it is, he needs plasma exchange.
• The next best test(s) is/are:

A. ADAMTS-13 activity/inhibitor
B. Stool for Shiga toxin ELISA or PCR
C. Complement-mediated disease genotyping
D. Anti-complement factor H antibody testing
E. All of the above
F. None of the above
What is TMA?

- A clinicopathological syndrome of microvascular stenosis causing shearing of red blood cells (and fragmentation) and thrombocytopenia.

- Multiple causes:
  - Fibrin clots (e.g. DIC)
  - VWF-platelet clots (e.g. TTP)
  - Endothelial injury
  - Vasculitis
  - Microvascular cancer

A Brief History of TMA

1924 - Moschcowitz first to describe TTP in 16yo patient.

1954 - First description of HUS (Gasser).

1975 - Familial form of HUS reported in 41 kindreds (Kaplan).

1966 - Amorosi and Ultmann describe the classic "pentad" of TMA.

1977 - Plasma infusions successfully used to treat TTP (Byrnes & Khurana).

1981 - Thompson reports low C3 in young boy with HUS.

1982 - Moake describes presence of ULVWF in TTP patients.

1981 - Thompson reports low C3 in young boy with HUS.

1991 - CAG demonstrates superiority of PE over PI to treat TTP.

1996-1997 - ADAMTS13 discovered and its deficiency in TTP patients reported.

1998 - Warwicker identifies Factor H mutation as cause of aHUS.

2000-Present - Increasing # mutations in complement system reported in aHUS.

2013 - Efficacy of eculizumab therapy in aHUS in phase II trials, leading to approval.

2016 - rADAMTS13 in clinical trials.
Classification of TMA by Molecular Mechanism

**Thrombotic Microangiopathy**
- Thrombocytopenia
- Microangiopathic hemolytic anemia
- End organ impairment

- Shiga toxin mediated TMA (Typical HUS)
- Complement-mediated TMA (aHUS)
- TTP (ADAMTS-13 deficient)
- Coagulation-mediated TMA (THBD)
- Cobalamin C deficiency
- DGKE deficient TMA

**Secondary TMA**
- Stem cell transplant
- Pregnancy/HELLP
- Drugs
- Malignant HTN
- Sepsis/DIC
- Autoimmune Dz
- Malignancy
- Streptococcal infxn
Atypical HUS

- Rare, potentially life-threatening form of TMA
- Annual incidence ~3-4/million
  - ~50% present in adulthood
  - Slight preponderance in females (adult onset)
- 20% have extrarenal involvement (GI, CNS, CV)
- 10-15% mortality during acute phase.

Cumulative survival without ESRD or death.

Alternative pathway
Bacteria, spontaneous “tick over”

C3

Factor B

Factor D

C3b Bb

C3 convertase
C3bBb

C5 convertase
C3bBbC3b

C5b

C5

C5b-9 (MAC)

C6-C9

CFH

CFI

MCP

Gain of function of factor:
- C3
- Factor B

Loss of function of regulator:
- Factor H
- Factor I
- Membrane cofactor protein

Alternative pathway
Bacteria, spontaneous “tick over”
Thrombotic microangiopathy

Threshold for TMA

Trigger factors/conditions

Genetic predisposition

none

mild

severe

severe

(URTI, diarrhea, pregnancy are the most common)

Classification of TMA by Molecular Mechanism

Secondary TMA
- Stem cell transplant
- Pregnancy/HELLP
- Drugs
- Malignant HTN
- Sepsis/DIC
- Autoimmune Dz
- Malignancy
- Streptococcal infxn

Thrombotic Microangiopathy

Complement-mediated TMA

Shiga toxin mediated TMA (Typical HUS)

TTP (ADAMTS-13 deficient)

Coagulation-mediated TMA (THBD)

Cobalamin C deficiency

DGKE deficient TMA
The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy

Patients with TMA (n = 34)

Patients without TMA (n = 43)

## Secondary TMA: A Genetic Susceptibility?

<table>
<thead>
<tr>
<th>Cause</th>
<th>Presence of Complement Gene Variants</th>
<th>Type of Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>11/36 (34%)</td>
<td>CFH (7), CFI (2), combined (2)</td>
</tr>
<tr>
<td>Malignant HTN</td>
<td>6/34 (18%)</td>
<td>CFH (3), C3 (2), CFB (1)</td>
</tr>
<tr>
<td>Systemic disease (SLE, scleroderma)</td>
<td>12/49 (24%)</td>
<td>CFH (5), CFI (3), C3 (1), MCP (1), CFB (1), combined (1)</td>
</tr>
<tr>
<td>STEC-HUS</td>
<td>8/18 (44%)</td>
<td>CFH (2), CFI (1), C3 (3), MCP (1), combined (1)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>4/23 (17%)</td>
<td>CFH (3), CFI (1)</td>
</tr>
</tbody>
</table>

How do we diagnose aHUS?

- No consensus diagnostic criteria and no definitive diagnostic test.
How do we diagnose aHUS?

Red Cell Lysis

LDH → Urinary excretion → free Hb → Anemia → haptoglobin → bilirubin

Profile of hemolysis:
↓ Hb
↑ LDH
↑ bilirubin
↓ haptoglobin
± Urine hemoglobin/iron
How do we diagnose aHUS?

1) Confirm TMA
   • Mimics of RBC fragments = iron deficiency, hemoglobinopathies, hyposplenism, oxidative hemolysis, vitamin B12 deficiency
   • Have high index of suspicion for metastatic malignancy and infection (disseminated fungal, bacterial endocarditis).

2) Identify secondary causes of TMA
   • STEC-HUS – stool C&S, Shiga toxin ELISA or gene PCR if diarrhea

I do NOT perform PLEX for:
   a) STEC-HUS unless severe neurologic presentation
   b) Bone marrow transplant-associated TMA
   c) Gemcitabine-associated TMA
   d) Malignancy-associated TMA (metastatic)
3) “Rule in” TTP

- ADAMTS-13 activity/inhibitor (<10% suggestive of TTP)
  - Consider banking samples pre-PLEX

- Predictive scores ¹,²,³
  - Platelets <30,000-35,000 + Creatinine <177 μmol/L highly predictive of ADAMTS13 deficiency
  - Upfront steroids for suspected TTP

- Response to plasma exchange.

How do we diagnose aHUS?

4) aHUS “directed” investigations

- C3 and C4 levels – ~50% of patients with aHUS present with low C3 and normal C4

- Anti-CFH antibodies – 6-10% of aHUS patients

- Complement-mediated disorders genotyping - ~50-70% of aHUS patients

Enabling Diagnostic and Therapeutic Schedules in Developing Countries

As previously mentioned, the costs of diagnostic testing for a single case of aHUS ($\approx 10,000), for example, greatly exceeds annual incomes in developing countries. The costs for the recommended therapy (more than $27,000 for the first 4 weekly 300 mg doses) merely adds to exacerbate unaffordability in these regions. The current recommendations for diagnosis and therapy of aHUS are therefore simply not feasible for patients living in developing countries. This would account for nearly 80% of all human beings.

From that perspective, international cooperations facilitating a proper diagnostic work-up in a stringent and cost-efficient manner are indispensable for diagnosis, and more so with regard to therapy, of many individuals suffering from these serious and life-threatening diseases. This should be embedded in scientifically encouraged cooperations between developing and so called developed countries.

The first and deciding step in the diagnostic work-up of a patient with HUS is to exclude Stx-induced HUS. Even this critical diagnostic step is not possible for most patients in developing countries. Together with the exclusion of secondary HUS forms (including cobalamin deficiency and diacylglycerol kinase ε [DGKE] HUS which can be suspected clinically), the next essential diagnostic tests are those for ADAMTS13 activity and testing for CFH-Ab.

Thus, as a first step of cooperation, the HUS study group, Innsbruck, provided Stx stool ELISA test kits for the Center for Pediatric Nephrology and Transplantation, Cairo University, for a project we began in 2011. From all patients presenting with suspected HUS, serum, ethylenediaminetetraacetic acid (EDTA) plasma and citrate plasma samples were collected before initiating therapy and stored at 80°C. All patients with a positive stool in the Stx ELISA were excluded from further diagnostic work-up unless they presented as recurrent cases. From all other patients, the stored samples were sent to the German–Austrian HUS study group center at Innsbruck Medical University for further work-up. As the rapid diagnosis of CFH-Ab HUS has a direct impact on further treatment strategies, screening for CFH-Ab, and ADAMTS13 activity was performed for all included patients as the first step of complement diagnostics. CFH-Ab patients were not included for a further genetic work-up; nevertheless, DNA was extracted and stored. Altogether, samples from 10 patients with acute HUS patients (two males, eight females) seen at the Center for Pediatric Nephrology and Transplantation, Cairo University during the years 2011 to 2012, were sent to Innsbruck Medical University, Austria. In two patients, CFH-Ab was detected. Although 50% of patients showed signs of decreased ADAMTS13 activity, no ADAMTS13 levels below 10%, indicating TTP, were detected. In addition, ADAMTS13 inhibitors were not detected. The decrease in ADAMTS13 activity might be a secondary phenomenon of the thrombotic microangiopathy.

The complement genetic analysis of these patients are ongoing and yet not completed. Although treatment recommendations for patients with CFH-Ab–associated aHUS had been received from Innsbruck Medical University, the delay in sending samples (up to 6 months) and receiving results (for CFH-Ab testing 2 weeks, genetics still pending), represented an obstacle toward their application. Thus, all patients received a similar protocol of PE, and symptomatic therapy as required (e.g., antihypertensives).

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**How do we diagnose aHUS?**

[Diagram showing diagnostic approach]

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Case

Hemoglobin

Platelets

Creatinine

Day of Admission

LDH 201

Stool C&S negative

Bone marrow biopsy “reactive”

Haptoglobin 2.30 “A few schistocytes”

Renal biopsy showing TMA
Question

• I would treat this patient with:

A. Plasma infusion
B. Plasma exchange
C. Anti-hypertensive medications
D. Eculizumab
E. Steroids
F. B and E
Complement-Mediated TMA: Treatment

- Plasma
- Eculizumab
- Renal ± Liver Transplant
- Immunosuppression
Plasma Exchange
• Overall response ~70%. No difference between PI vs PE.
• Significant heterogeneity in PE volume, frequency, duration, delayed initiation.

Plasma Therapy

<table>
<thead>
<tr>
<th>Mutation</th>
<th>CFH</th>
<th>CFI</th>
<th>C3</th>
<th>THBD</th>
<th>MCP</th>
<th>CFH Ab</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>63%</td>
<td>25%</td>
<td>57%</td>
<td>88%</td>
<td>97%</td>
<td>75%</td>
<td>69%</td>
</tr>
<tr>
<td>ESRD-death</td>
<td>37%</td>
<td>75%</td>
<td>43%</td>
<td>13%</td>
<td>3%</td>
<td>25%</td>
<td>31%</td>
</tr>
</tbody>
</table>


• How to prescribe plasma therapy? **NOBODY KNOWS!**
  1) Start as soon as possible.
  2) Use plasma exchange over plasma infusion.
  3) Continue daily until hematologic parameters are normal and renal function stabilizes.
  4) Taper depending on response.
Eculizumab

Alternative pathway
Bacteria, spontaneous “tick over”

Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies

<table>
<thead>
<tr>
<th>Trial 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis of aHUS with:^a:</td>
</tr>
<tr>
<td>- Progressing TMA:^b</td>
</tr>
<tr>
<td>- ≥4 PE/PI sessions in the week before screening</td>
</tr>
<tr>
<td>17 Were treated with eculizumab</td>
</tr>
<tr>
<td>15 Completed 26 weeks of treatment</td>
</tr>
<tr>
<td>13 Entered extension phase</td>
</tr>
<tr>
<td>5 Continued extension phase to data cutoff for 2-year analysis (median duration, 100 weeks):^a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis of aHUS with:^a:</td>
</tr>
<tr>
<td>- No platelet count decrease &gt;25% during the 8-week observation period</td>
</tr>
<tr>
<td>- ≥1 PE/PI session every 2 weeks, but ≤3 times per week for ≥8 weeks</td>
</tr>
<tr>
<td>20 Were treated with eculizumab</td>
</tr>
<tr>
<td>20 Completed 26 weeks of treatment</td>
</tr>
<tr>
<td>19 Entered extension phase</td>
</tr>
<tr>
<td>16 Continued extension phase to data cutoff for 2-year analysis (median duration, 114 weeks):^a</td>
</tr>
</tbody>
</table>

Hematologic Improvement

- Mean platelet count change from baseline (x10⁹/L)
- 26-Week treatment period
- Extension treatment period
- 73x10⁹/L (Mean ↑ platelets) 75x10⁹/L
- Hematologic Normalization 90%
Renal Improvement

Mean ↑ eGFR: 37 mL/min/1.73m² (trial 1)
8 mL/min/1.73m² (trial 2)

4/5 pts stopped dialysis, 2 new dialysis
TMA and Adverse Events

• TMA event-free status
  o Trial 1 - 88% (15/17)
  o Trial 2 – 95% (19/20)

• Adverse Events
  o Well tolerated
  o 1 death – intestinal hemorrhage (?)
  o No cases of meningococcal infection
  o No cases of neutralizing antibodies

Does eculizumab work?

SEEMS SAFE AND EFFECTIVE

• Improves TMA.
• Improves or stabilizes renal function.
• Enables patients to stop plasma therapy.
• May or may not prevent ESRD, need for transplant, or death.
• Without major toxicity.
World's most expensive drug - which costs up to $700,000 per year - too expensive, Canada says

By Tom Blackwell

Canada's drug-price regulator has taken the rare step of calling a hearing into what is considered the world's most expensive prescription medicine, accusing its manufacturer of exceeding the permissible price cap.

The yearly cost per patient of as much as $700,000 is even more than the manufacturer, Alexion Pharmaceutical, charges in the United States, which typically has the steepest prices globally, says the Patented Medicines Price Review Board (PMPRB).

Soliris is a breakthrough, potentially lifesaving treatment for two rare blood diseases, affecting about 180 patients in Canada.

The board, which has not held an excessive-price hearing since 2012, said it had demanded the U.S.-based firm lower the price and pay back revenue it made above the cap. It refused both requests, according to formal allegations issued by board staff.

"Alexion continues to sell Soliris to Canadians at the highest international price among the comparator countries," says the staff document.

If a board adjudication panel finds the price is excessive at a hearing to be held no later than March 6, it could order a cost reduction and the repaying of surplus income.

Soliris has caused waves throughout the world in recent years with its eyebrow-raising price tag, but this may be the first attempt by a regulator anywhere to force a rollback.
Case

**ADAMTS13 39%**
• Anti-CFH antibody negative.
• 5 months after – Sickkids genotyping shows heterozygosity for C3 mutation (intron 18, c.2246-2A>G).

• 6 months after - Eculizumab approved by third party insurer
• Patient vaccinated against meningococcus.
• Switched to eculizumab (900mg IV weekly x 4 week induction, 1200mg IV q2weeks ongoing).
Conclusions

• Complement-mediated TMA (aHUS) is a rare, potentially life-threatening condition, often resulting from a genetic predisposition combined with a triggering event.
  o Patients with secondary TMA may also harbour predisposing genetic variants, which is an emerging area of interest.

• Complement-mediated TMA is a clinical diagnosis.
  o ADAMTS-13, Shiga toxin ELISA or gene PCR and anti-CFH Ab testing have the most value in directing therapy.
  o Platelets <30 and serum creatinine <177 argues strongly for TTP.

• The current “standard of care” is eculizumab therapy but access remains a significant issue.
  o Plasma exchange remains the mainstay of therapy in many Canadian centres.
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Thank You

Enjoy CHC-WEST 2016!