Atypical Hemolytic Uremic Syndrome (atypical-HUS): Identification and Management Considerations

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The objectives of this presentation are as follows

• Describe the clinical considerations in identifying atypical-HUS related thrombotic microangiopathy (TMA) and review the etiologies associated with it
• Increase confidence in diagnosing atypical-HUS associated with a complement-amplifying condition and recognize the importance of the ADAMTS13 assay and the timing of that assay
• Recognize the limitations of plasma therapy in atypical-HUS and understand factors that inform appropriate long-term management of patients with atypical-HUS

Following a review of this slide deck, we will give you the choice of 6 different patient cases to see how this information can be applied in different clinical scenarios
Defining TMA and its etiologies
**What is thrombotic microangiopathy (TMA)?**

**Clinical signs indicating a TMA**

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>Microangiopathic hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count &lt;150 × 10⁹/L or &gt;25% decrease from baseline</td>
<td>Schistocytes and/or Elevated LDH and/or Decreased haptoglobin and/or Decreased hemoglobin</td>
</tr>
</tbody>
</table>

AND

Plus 1 or more of the following:

**Common Signs and Symptoms**
- Neurological symptoms
  - Confusion and/or
  - Seizures and/or
  - Strokes and/or
  - Other cerebral abnormalities
- Renal impairment
  - Elevated creatinine level and/or
  - Decreased eGFR and/or
  - Elevated blood pressure and/or
  - Abnormal urinalysis results
- GI symptoms
  - Diarrhea and/or
  - Nausea/vomiting and/or
  - Abdominal pain and/or
  - Gastroenteritis/pancreatitis
- CV symptoms
  - MI and/or
  - Hypertension and/or
  - Arterial stenosis and/or
  - Peripheral gangrene
- Pulmonary symptoms
  - Dyspnea and/or
  - Pulmonary hemorrhage and/or
  - Pulmonary edema
- Visual symptoms
  - Pain and blurred vision and/or
  - Retinal vessel occlusion and/or
  - Ocular hemorrhage

**Other Signs and Symptoms**
- Confusion and/or
- Seizures and/or
- Stroke and/or
- Other cerebral abnormalities

CV=cardiovascular; eGFR=estimated glomerular filtration rate; GI=gastrointestinal; LDH=lactate dehydrogenase; MI=myocardial infarction.

At this point, it’s reasonable to ask, “what are the underlying causes of TMAs?” As it turns out, there are several underlying etiologies, as represented by this Venn diagram. They include: thrombotic thrombocytopenic purpura (TTP), Shiga toxin-producing *Escherichia coli* (STEC), and atypical-HUS. You can see that they are all unified by chronic uncontrolled complement activation; sometimes this is due to a complement-amplifying condition. The next slide will review these potential complement-amplifying conditions in detail.
TMAs can be associated with various complement-amplifying conditions\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Examples of complement-amplifying conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy\textsuperscript{a}/postpartum</td>
</tr>
<tr>
<td>Autoimmune diseases (eg, systemic lupus erythematosus)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Pregnancy-associated conditions such as HELLP (hemolysis, elevated liver enzymes, low platelet counts) syndrome.

Atypical-HUS: identification and impact on the patient
A diagnosis of TMA is based on the presence of thrombocytopenia and microangiopathic hemolysis plus 1 or more of the following: neurological symptoms, renal impairment, gastrointestinal symptoms, cardiovascular symptoms, pulmonary symptoms, or visual symptoms. Specific signs or symptoms associated with each of these are listed on the slide.
Identifying the etiology of a TMA requires a differential diagnosis (cont)^1-4

A diagnosis of TMA is based on the presence of thrombocytopenia and microangiopathic hemolysis plus 1 or more of the following: neurological symptoms, renal impairment, gastrointestinal symptoms, cardiovascular symptoms, pulmonary symptoms, or visual symptoms. Specific signs or symptoms associated with each of these are listed on the slide.

Where TTP and STEC-HUS have been ruled out, the TMA can be attributed to complement dysregulation. Atypical-HUS is a complement mediated TMA (CM-TMA) that has been more broadly or narrowly defined in different contexts, based on such factors as the presence and nature of a trigger and/or identification of an underlying genetic mutation.

References
TTP and atypical-HUS are driven by different pathophysiologic processes and require different management strategies.

**TTP**

- Insufficient ADAMTS13 activity (≤5%) leaves vWF intact
  - ADAMTS13 deficiency
  - Progressively smaller, inactive multimers
  - Fully unfolded vWF aggregates with platelets

Suppress/remove inhibitor autoantibody/replace ADAMTS13

**Atypical-HUS**

- Genetic defects lead to chronic uncontrolled activation of the complement system

- Gain of function
- Loss of function
- Autoantibodies

Endothelial damage
Platelet activation
Inflammation

Suppress/remove inhibitor autoantibody/replace ADAMTS13

Atypical-HUS results from genetic defects of complement proteins, leading to uncontrolled complement activation.

- The alternative pathway of the complement system is upregulated by either gain-of-function mutations in activators, loss-of-function mutations in inhibitors, or autoantibodies to inhibitors.
- This leads to endothelial damage, platelet activation, and inflammation.

**References**

Complement dysregulation leads to atypical-HUS1-7

As noted on the last slide, the alternative pathway of the complement system is upregulated by either gain-of-function mutations in activators, loss-of-function mutations in inhibitors, or autoantibodies to inhibitors. The culmination of these defects leads to endothelial damage. In addition, however, anaphylaxis, inflammation, platelet activation, and thrombosis can also occur.
Next, let’s discuss the likelihood of atypical-HUS presenting with complement-amplifying conditions. An analysis based on the screening of 273 consecutive patients with atypical-HUS for complement abnormalities registered in the International Registry of Recurrent and Familial HUS/TTP from 1996-2007 showed that atypical-HUS is unmasked by a complement-amplifying condition in 69% of patients. Among patients in whom atypical-HUS was unmasked by a complement-amplifying condition, 24% had diarrhea or gastroenteritis, 18% had upper respiratory tract infection, 8% had malignant hypertension, and 7% had pregnancy-associated complications.
Atypical-HUS can cause symptoms, and sometimes damage, to a variety of different organ systems, including the central nervous system, cardiovascular system, and the gastrointestinal system. In fact, CV complications can occur at presentation or following hematological normalization and are potentially fatal1,2.

References
The risk of TMA is ongoing, unpredictable, and life-threatening in patients with atypical-HUS\textsuperscript{1-4}

- It is imperative that patients be diagnosed and managed appropriately as early as possible\textsuperscript{5}

Pediatric patients have a lower risk of developing ESRD compared with adult patients
(adjusted hazard ratio 0.55 [95% CI, 0.41-0.73])\textsuperscript{1,\textasciitilde}

\textsuperscript{1}Global, observational study of atypical-HUS, including both retrospective and prospective enrollment. At time of data cutoff (November 30, 2015), 851 patients were enrolled.


**Figure:**
- **ESRD-free survival, %**
  - Pediatric (n=387): 79% (1-year) and 73% (5-years)
  - Adults (n=464): 69% (1-year) and 51% (5-years)

It is imperative that patients be diagnosed and managed appropriately as early as possible. These data here emphasize this point. As we can see with this observational study, pediatric patients have a lower risk of developing end-stage renal disease compared with adult patients (adjusted hazard ratio 0.55 [95% CI, 0.41-0.73]); sex, race, family history of atypical-HUS, time from initial presentation to diagnosis, and potential complement-activating conditions were not associated with ESRD risk.\textsuperscript{1}

**Reference**

Family history and/or medical history can increase the suspicion of atypical-HUS

While waiting for ADAMTS13 activity results, any information that may substantiate the suspicion of atypical-HUS would be helpful in the diagnosis.

Family history and medical history may help substantiate the suspicion of atypical-HUS. If a physician suspects atypical-HUS, it may be informative to ask the patient if (s)he has relatives that have experienced signs or symptoms consistent with TMAs, such as unexplained renal failure or cardiovascular disease due to unknown causes. Also, any previous signs or symptoms consistent with TMA, such as hypertension, unexplained stroke, myocardial infarction, preeclampsia, or hemolysis, elevated liver enzymes, low platelet counts (HELLP) syndrome persisting after pregnancy may substantiate the suspicion of atypical-HUS.

Next, we consider other findings that may also substantiate the suspicion of atypical-HUS.
We have previously reviewed that atypical-HUS is a disease of complement dysregulation involving the alternative pathway. A low C3/normal C4 level suggests alternative pathway activation. So, measuring C3 and C4 levels may substantiate the atypical-HUS diagnosis in some patients. However, 80% of patients with atypical-HUS have normal serum C3 levels. Therefore, C3 may be too inconsistent for diagnostic purposes.
Atypical-HUS: management considerations
Next, we will review the effect of therapeutic plasma exchange on patients with an ADAMTS13 activity of >5% or <5%.

- In this study by Pishko et al, patients had either severe ADAMTS13 deficiency (less than 5%) or non-severe ADAMTS13 deficiency (greater than 5%).
- Daily hematological laboratory values and time to hematological recovery were collected and compared between the two groups.
- More deaths were observed in patients without severe ADAMTS13 deficiency.
- Hematological recovery was observed in both groups, but plasma exchange did not prevent premature mortality and resulted in limited renal recovery in patients without severe ADAMTS13 deficiency.
- Therefore, patients with an ADAMTS13 activity of >5% or <5% are treated with PE and have hematological remission that may appear normal based on laboratory values but are still at risk of organ damage and death.

References
Patients without severe ADAMTS13 deficiency do not have a significant clinical benefit from TPE

Let’s now review data on the survival of patients without severe ADAMTS13 deficiency who are treated with therapeutic plasma exchange.

- All patients in this study had ADAMTS13 levels greater than 10% and TMA
- Outcomes were compared between patients who did and did not receive plasma exchange therapy
  - Patients were matched based on clinical criteria including age; sex; ethnicity; Charlson Comorbidity Index score; history of prior solid organ or bone marrow transplant; presence of neurological symptoms, sepsis, shock, and/or multiorgan failure; platelet count; creatinine level; LDH level; and international normalized ratio.
- Patients who received plasma exchange therapy did not have improved rates of survival, suggesting that there were no additional clinical benefits with plasma exchange in patients with ADAMTS13 levels greater than 10%
- Clinically relevant variables such as serum creatinine, alanine aminotransferase, the platelet count on Day 4, the presence of sepsis, shock or multiorgan failure at presentation, and Charlson comorbidity index independently predicted 90-day mortality

This data shows that PE is not an adequate management strategy for patients with ADAMTS13 levels greater than 10%. Also based on these data, we can see that timely diagnosis is crucial to allow patients to receive appropriate management.

Reference
Potential exposure to any complement-amplifying condition may lead to TMA manifestations in patients with atypical-HUS.

Examples of factors that may increase risk for TMA manifestations in patients with atypical-HUS include:


20 Examples of factors that may increase risk for TMA manifestations in patients with atypical-HUS are shown on this slide, and include renal transplant, patient age, identified genetic mutation, postpartum, and history of TMA.

This is not a comprehensive list, but is intended to provide examples of factors that may increase risk for TMA. Anything that amplifies complement is a risk factor for TMA.
The number of new genetic abnormalities discovered in patients with atypical-HUS continues to increase over time\(^1-4\)

**High morbidity and mortality regardless of mutation identification\(^1,5\)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No mutation identified</th>
<th>Mutation identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or end-stage renal disease</td>
<td>28%</td>
<td>40%</td>
</tr>
<tr>
<td>Death, ESRD, or permanent renal damage: At first clinical manifestation(^a)</td>
<td>65%</td>
<td>63%</td>
</tr>
<tr>
<td>Death, ESRD, or permanent renal damage: In the first year after diagnosis(^b)</td>
<td>82%</td>
<td>76%</td>
</tr>
</tbody>
</table>

**Identification of genetic complement mutations is not required for atypical-HUS diagnosis or management decisions\(^6\)**

ESRD=end-stage renal disease; HUS=hemolytic uremic syndrome.

\(^a\)Mutations consisted of membrane cofactor protein (MCP), complement factor H (CFH), and factor I (CFI). No mutation identified: n=81. Mutation identified: n=60.

\(^b\)Mutations consisted of MCP, CFH, CFI, complement component 3 (C3), and thrombomodulin (THBD). No mutation identified: n=119. Mutation identified: n=116.


Identification of genetic complement mutations is not required for atypical-HUS diagnosis or management decisions.

**REFERENCE**

Summary

• Atypical-HUS is characterized by thrombotic microangiopathy that can involve multiple organ systems\(^1\)

• Atypical-HUS is a complement-mediated disease, which can be unmasked by complement-amplifying conditions such as malignant hypertension and pregnancy/postpartum complications\(^{1,2}\)

• Atypical-HUS is a life-threatening disease
  • Promptly differentiate from TTP and STEC-HUS using ADAMTS13 activity and Shiga toxin testing and initiate appropriate management plan early for atypical-HUS\(^ {1,3}\)

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; HUS=hemolytic uremic syndrome; STEC-HUS=Shiga toxin-producing Escherichia coli hemolytic uremic syndrome; TTP=thrombotic thrombocytopenic purpura.
