Identifying Atypical Hemolytic Uremic Syndrome in the Pregnancy-Postpartum Setting

A Guide To Differential Diagnosis

The information in this brochure is intended as educational information for healthcare professionals. It does not replace a healthcare professional’s judgment or clinical diagnosis.
Thrombocytopenia
Platelet count <150 × 10^9/L or
>25% decrease from baseline

AND

Microangiopathic hemolysis
Schistocytes and/or
Elevated LDH and/or
Decreased haptoglobin and/or
Decreased hemoglobin

Plus 1 or more of the following

Common Signs and Symptoms

Neurological symptoms
- Confusion and/or
- Seizures and/or
- Stroke 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 and/or
- Abdominal pain and/or
- Gastroenteritis/pancreatitis

Other Signs and Symptoms

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

Evaluate ADAMTS13 activity and Shiga toxin/EHEC test

While ADAMTS13 results are awaited, a platelet count >30 × 10^9/L and/or sCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

≤5%b ADAMTS13 activity

TTP

>5% ADAMTS13 activity

Atypical-HUS

Shiga toxin/EHEC positive

STEC-HUS

TMA can also manifest in the presence of clinical conditions such as the following

- Pregnancy-postpartum
- Malignant/severe hypertension
- Solid organ transplantation

- Autoimmune disease (eg, SLE, scleroderma)
- Hematopoietic stem cell transplantation

*Shiga toxin/EHEC test is warranted with history/presence of GI symptoms. *Range found in published literature is <5%-10%.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; HUS, hemolytic uremic syndrome; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EHEC, enterohemorrhagic Escherichia coli; GI, gastrointestinal; MI, myocardial infarction; sCr, serum creatinine; STEC-HUS, Shiga toxin–producing Escherichia coli–hemolytic uremic syndrome; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Differential Diagnosis of Atypical-HUS

1-4

Differential Diagnosis of Atypical-HUS

Microangiopathy; TTP, thrombotic thrombocytopenic purpura.
Differential Diagnosis: Identifying Atypical-HUS in the Pregnancy-Postpartum Setting

- Thrombotic microangiopathy (TMA) is a serious medical condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury.
- During pregnancy and the postpartum period, TMA can be caused by pregnancy-associated complications such as Hemolysis, Elevated Liver enzyme levels, and Low Platelet count (HELLP) syndrome or by other TMA disorders like atypical-HUS.
  - In patients with complement dysregulation, normal pregnancy and pregnancy complications that activate the complement system, such as HELLP, may precipitate atypical-HUS or cause additional manifestations, resulting in persistent TMA despite treatment.
  - Atypical-HUS is a disease associated with the chronic risk of a complement-mediated TMA that can be unmasked during or after pregnancy.
- A diagnosis of atypical-HUS may be missed when a woman presents with a TMA during pregnancy because it can present with similar clinical features to HELLP.
- Hemolysis is characteristic of both HELLP and atypical-HUS and hemolytic screening is essential to make a differential diagnosis.
- A high clinical suspicion for atypical-HUS should be raised if a woman presents with TMA during pregnancy along with the following characteristics:
  - Renal dysfunction.
  - Hemolysis with
    - Elevated LDH, specifically LDH >1000 U/L with serum creatinine (sCr) >1.1 mg/dL.
    - High LDH:AST ratio (>10:1) or low hemoglobin (<8 g/dL).
    - sCr >2.0 g/dL or persistently elevated sCr >1.1 g/dL for >72 hours postpartum.
- Elevated AST or ALT levels.
- >25% decrease in platelet count from baseline.
- Signs of persistent TMA more than 48 hours after delivery.
- Frequent presentation of TMA postpartum.
- History of previous TMA.
- Family history of renal impairment or atypical-HUS.
- History of previous pregnancy-related complications.

Timing of manifestation may identify patients with atypical-HUS:
- Atypical-HUS is a chronic disease, whereas symptoms of other pregnancy-associated conditions usually resolve within 24-48 hours of delivery.
- 79% of cases of atypical-HUS unmasked by pregnancy have been described in the postpartum period.

Gestational age at presentation

A previous normal pregnancy does not exclude a diagnosis of atypical-HUS. If atypical-HUS or any TMA is suspected, involve a TMA expert in the diagnostic process.
**Case Study**

**Patient Overview**
- Female, aged 27 years, in the third trimester of pregnancy
- Presented to the emergency room with fatigue, nausea, vomiting, and upper right quadrant pain
- Lab results showed anemia, thrombocytopenia, and elevated AST, ALT, LDH and creatinine
- Family history of thrombotic thrombocytopenic purpura (TTP)

**Clinical Presentation and Management**

<table>
<thead>
<tr>
<th>Fatigue, nausea, vomiting, and upper right quadrant pain</th>
<th>Liver enzymes and platelets normalized</th>
<th>Premature delivery</th>
<th>Presented with thrombocytopenia, hemolysis, and kidney failure 6 months after HELLP diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP was excluded based on ADAMTS13 activity</td>
<td>5 days after PE/FFP</td>
<td>14 days after discharge</td>
<td>Second Hospital Admission</td>
</tr>
</tbody>
</table>
| Diagnosis: class 3 HELLP
  Treatment: PE and FFP                                 |                                      |                   | Diagnosis: atypical-HUS |

**Laboratory Values**

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Normal Values</th>
<th>At First Hospital Admission</th>
<th>5 Days After FFP/PE</th>
<th>At Second Hospital Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistocytes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Platelet count, × 10^9/L</td>
<td>150-450</td>
<td>121</td>
<td>218</td>
<td>118</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L</td>
<td>100-190</td>
<td>260</td>
<td>200</td>
<td>269</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.0-16.0</td>
<td>9.5</td>
<td>14.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Haptoglobin, mg/dL</td>
<td>36-195</td>
<td>7.8</td>
<td>40</td>
<td>6.4</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>0.5-1.5</td>
<td>2.4</td>
<td>1.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.6-1.3</td>
<td>1.5</td>
<td>0.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min/1.73 m²</td>
<td>90+</td>
<td>87</td>
<td>92.2</td>
<td>14.2</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>1+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.0-0.3</td>
<td>5.8</td>
<td>0.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>7-56</td>
<td>662</td>
<td>54</td>
<td>24</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>5-40</td>
<td>435</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td><strong>Differential diagnosis evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAMTS13 activity</td>
<td>≥5%</td>
<td>63%</td>
<td>63%</td>
<td>63%</td>
</tr>
</tbody>
</table>

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; FFP, fresh frozen plasma; HELLP, Hemolysis, Elevated Liver enzyme levels, and Low Platelet count syndrome; HUS, hemolytic uremic syndrome; PE, plasma exchange.

*Class 1 HELLP, platelet count <50 × 10^9/L (severe thrombocytopenia); class 2 HELLP, platelet count between 50-100 × 10^9/L (moderate thrombocytopenia); class 3 HELLP, platelet count between 100-150 × 10^9/L (mild thrombocytopenia).

**Differential Diagnosis**
- A diagnosis of atypical-HUS was made based on
  - The presence of TMA post-delivery and following discontinuaton of PE
  - ADAMTS13 activity level that was >5%, ruling out TTP as a cause of TMA

*The case described here is representative of physician experience and does not include actual patient data.*
Differentiation of atypical-HUS from other TMAs and pregnancy-associated conditions is essential for optimal management decisions. 

**Important Considerations for a Differential Diagnosis**

**Differentiation of atypical-HUS from other TMAs and pregnancy-associated conditions is essential for optimal management decisions.**

**HELLP Syndrome**

**Occurrence**
- Most commonly develops before delivery with a peak between 27 and 37 weeks.
- Can occur within 48 hours postpartum.

**Classic features**
- MAHA, platelets <100 × 10^9/L, AST/ALT >2× ULN, serum creatinine >1.1 mg/dL.

**Symptoms**
- Epigastric or right upper quadrant pain, nausea, vomiting, headache, visual disturbances.

**Treatment**
- Delivery.

**HELLP syndrome typically resolves within 48-72 hours post-delivery.**

If TMA persists, consider atypical-HUS.

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**Atypical-HUS**

**Occurrence**
- Most commonly occurs in the postpartum period.
- Less commonly unmasked during pregnancy.

**Classic features**
- MAHA, platelets <150 × 10^9/L, serum creatinine >2.0 mg/dL, negative STEC-HUS, ADAMTS13 >5%.

**Symptoms**
- Nausea, vomiting, abdominal pain, headache, altered mental status.

**Medical history**
- Clinical or family history of renal impairment or atypical-HUS, personal or family history of TMA, history of pregnancy-related complications, lack of response to PE.

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ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; aHUS, atypical hemolytic uremic syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; ESRD, end-stage renal disease; LDH, lactate dehydrogenase; HUS, hemolytic uremic syndrome; MAHA, microangiopathic hemolytic anemia; PE, plasma exchange; SBP, systolic blood pressure; STEC, Shiga toxin–producing *Escherichia coli*; TMA, thrombotic microangiopathy; ULN, upper limit of normal.
Atypical-HUS is a disease associated with the chronic risk of complement-mediated TMA that can be unmasked during or after pregnancy. A diagnosis of atypical-HUS may be missed during pregnancy because it can present with similar clinical features to HELLP.

If TMA is suspected it is important to include a multidisciplinary team of specialists in the diagnostic process.

References