Identifying Atypical Hemolytic Uremic Syndrome in the Transplantation 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.
**Differential Diagnosis of Atypical-HUS**

**Thrombocytopenia**
- Platelet count <150 × 10⁹/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**

- Neurological symptoms
- Renal impairment
- GI symptoms

**Common Signs and Symptoms**

<table>
<thead>
<tr>
<th>Neurological symptoms</th>
<th>Renal impairment</th>
<th>GI symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion and/or Seizures and/or Stroke and/or Other cerebral abnormalities</td>
<td>Elevated creatinine level and/or Decreased eGFR and/or Elevated blood pressure and/or Abnormal urinalysis results</td>
<td>Diarrhea ± blood and/or Nausea/vomiting and/or Abdominal pain and/or Gastroenteritis/pancreatitis</td>
</tr>
</tbody>
</table>

**Other Signs and Symptoms**

<table>
<thead>
<tr>
<th>CV symptoms</th>
<th>Pulmonary symptoms</th>
<th>Visual symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI and/or Hypertension and/or Arterial stenosis and/or Peripheral gangrene</td>
<td>Dyspnea and/or Pulmonary hemorrhage and/or Pulmonary edema</td>
<td>Pain and blurred vision and/or Retinal vessel occlusion and/or Ocular hemorrhage</td>
</tr>
</tbody>
</table>

**Evaluate ADAMTS13 activity and Shiga toxin/EHEC test**

While ADAMTS13 results are awaited, a platelet count >30 × 10⁹/L and/or sCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

<table>
<thead>
<tr>
<th>≤5% ADAMTS13 activity</th>
<th>&gt;5% ADAMTS13 activity</th>
<th>Shiga toxin/EHEC positive</th>
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<tbody>
<tr>
<td>TTP</td>
<td>Atypical-HUS</td>
<td>STEC-HUS</td>
</tr>
</tbody>
</table>

**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

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*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.*
Thrombotic microangiopathy (TMA) is a serious medical condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury. TMA has been associated with solid organ transplantation and is found in >40% of renal biopsy specimens during episodes of antibody-mediated rejection. Although antibody-mediated rejection is a common cause of TMA, many other factors can contribute to the development of posttransplantation TMA, including ischemia-reperfusion injury, drug toxicity related to calcineurin inhibitors, viral infections, underlying atypical hemolytic uremic syndrome (atypical-HUS).

Atypical-HUS is a disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA. Solid organ transplantation is a complement-amplifying condition that can cause manifestations of TMA in patients with atypical-HUS. The risk of TMA manifestations in patients with atypical-HUS following renal transplantation has been reported to range from 20% to more than 80%, depending on the presence of a specific genetic mutation. Risk for TMA is also deemed high in patients without a genetic mutation who have received a renal transplant.

It is important to diagnose atypical-HUS promptly in patients who have received a renal transplant. In patients with atypical-HUS, posttransplantation TMA manifestations can significantly increase the risk for graft loss.

Atypical-HUS should be considered if a patient presents with posttransplantation TMA and the following characteristics:

- Microangiopathic hemolysis
  - Schistocytes or fragmented RBCs
  - Low haptoglobin level
  - Low hemoglobin level
  - Elevated lactate dehydrogenase level
  - Elevated bilirubin level
- Thrombocytopenia
- Clinical involvement of ≥1 organ system (eg, kidney, GI tract, CNS)
- ADAMTS13 activity >5% and negative STEC test result
- Mutations or polymorphisms in genes such as C3, CFB, CFH, CFHR1, CFI, MCP, and THBD
- Persistent TMA despite having addressed the potential cause (eg, management of antibody-mediated rejection, adjustment of immunosuppressant therapy, management of infection)
- Family or individual history of TMA
- Neurological symptoms (eg, irritability, confusion, stroke)

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; CNS, central nervous system; GI, gastrointestinal; HUS, hemolytic uremic syndrome; RBC, red blood cell; STEC, Shiga toxin–producing Escherichia coli; TMA, thrombotic microangiopathy.
Case Study

Patient Overview

- Female, aged 41 years, presented to emergency department with diarrhea, abdominal pain, and vomiting 13 days after renal transplantation
- Received a renal transplant from a deceased donor
  - Number of human leukocyte antigen incompatibilities was 1 for each locus (A, B, DR); cross-match was negative
  - Histology of allograft 1 day after transplantation was normal
- No family history of renal failure; developed ESRD following pregnancy complications

Clinical Presentation and Management

### Before Transplantation

- Unspecific angiosclerotic lesions on renal biopsy
- Therapy: dialysis

### Renal Transplantation

- Induction therapy: thymoglobulin, tacrolimus, mycophenolate, and methylprednisolone
- Progress appeared normal

### 7 Days Posttransplantation

- Discharged from hospital

### 13 Days Posttransplantation

- Diagnosis: antibody-mediated rejection
- Therapy: high-dose steroids, PE, monthly IVIg

### 6 Months After Starting Treatment for Rejection

- Recurrent TMA (anemia, thrombocytopenia)

### Laboratory Values

- At presentation:
  - An underlying dysregulation of the complement system was considered, but evaluations were negative
  - Low factor H activity was determined to be insufficient to consider a diagnosis of atypical-HUS at that time

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Values</th>
<th>7 Days Posttransplantation</th>
<th>At Presentation (13 Days posttransplantation)</th>
<th>6 Months After Starting Treatment for Antibody-Mediated Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, × 10⁹/mm³</td>
<td>4.2-11.4</td>
<td>4.2</td>
<td>7.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>35.3-46.1</td>
<td>27.2</td>
<td>18.7</td>
<td>26</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.0-16.0</td>
<td>9.0</td>
<td>6.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Platelet count, × 10⁹/L</td>
<td>150-450</td>
<td>187</td>
<td>120</td>
<td>119</td>
</tr>
<tr>
<td>Haptoglobin, mg/dL</td>
<td>36-195</td>
<td>ND</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.6-1.3</td>
<td>1.2</td>
<td>3.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L</td>
<td>100-190</td>
<td>185</td>
<td>685</td>
<td>700</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>&lt;1.2</td>
<td>0.2</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Schistocytes per 1000 RBCs</td>
<td>0</td>
<td>ND</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Differential diagnosis evaluations</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complement function tests</th>
<th>Normal Values</th>
<th>7 Days Posttransplantation</th>
<th>At Presentation (13 Days posttransplantation)</th>
<th>6 Months After Starting Treatment for Antibody-Mediated Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH50 activity</td>
<td>—</td>
<td>ND</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum levels of C3, C4, FI, MCP (CD46)</td>
<td>—</td>
<td>ND</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Factor H activity, %</td>
<td>86-103</td>
<td>ND</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Anti-factor H antibodies</td>
<td>—</td>
<td>ND</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>C3d/C3</td>
<td>&lt;1.4</td>
<td>ND</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td>ADAMTS13 activity, %</td>
<td>&gt;5</td>
<td>ND</td>
<td>&gt;5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Stool test for Shiga toxin <em>Escherichia coli</em></td>
<td>—</td>
<td>ND</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; HUS, hemolytic uremic syndrome; ND, not determined; RBC, red blood cell; TMA, thrombotic microangiopathy.

Differential Diagnosis

- A diagnosis of atypical-HUS was made 6 months after the start of treatment for antibody-mediated rejection, based on
  - TMA recurrence in the absence of antibody-mediated rejection
  - Shiga toxin–negative stool test result
  - ADAMTS13 activity >5%, ruling out thrombotic thrombocytopenic purpura
- Genetic testing confirmed a heterozygous single nucleotide polymorphism in short consensus repeat 15 of complement factor H
Differentiation of atypical-HUS from other causes of posttransplantation TMA is essential for optimal management decisions.\cite{4,6-8,12-14,18}

**Possible Causes**
- CNI/mTORi toxicity
- Infection
- Antibody-mediated rejection

**Management**
- Treatment modification
- Anti-infective agents
- Steroids, PE, IVIg

**Atypical-HUS**
- Underlying dysfunction (TTP or atypical-HUS), particularly with family or personal history
- ADAMTS13 >5%
- Shiga toxic/EHEC negative

**Differential Tests**

**TMA persists despite management**

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ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; CNI, calcineurin inhibitor; EHEC, enterohemorrhagic *Escherichia coli*; HUS, hemolytic uremic syndrome; IVIg, intravenous immunoglobulin; mTORi, mammalian target of rapamycin inhibitor; PE, plasma exchange; STEC, Shiga toxin–producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.
Atypical-HUS is a serious disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA\textsuperscript{4,8}

Solid organ transplantation is a complement-amplifying condition that can cause manifestations of TMA in patients with atypical-HUS\textsuperscript{2,4}

It is important to diagnose atypical-HUS promptly in patients who have received a transplant because posttransplantation TMA significantly increases the risk for graft loss\textsuperscript{12}

If TMA is suspected, it is important to include a multidisciplinary team of specialists in the diagnostic process\textsuperscript{19}

HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

References