Identifying Atypical-HUS in the Presence of SLE

A guide to differential diagnosis of thrombotic microangiopathy (TMA) in the presence of SLE or other autoimmune diseases

Atypical-HUS, which can be triggered by SLE, is associated with continuous risk of complement-mediated TMA and life-threatening consequences1-4.

17.5% of patients with LN, a kidney disease caused by SLE, have been shown to develop TMA with progressive, life-threatening thrombocytopenia, MAHA, and progressive renal failure5,6+.

Prompt recognition, diagnosis, and management of TMA are all critical1,3,4,7.

>5x increased risk of in-hospital mortality in patients with SLE and TMA vs patients with SLE but without TMA7+.

*See † and ‡ on page 2 for study designs.

Atypical-HUS=atypical hemolytic uremic syndrome; LN=lupus nephritis; MAHA= microangiopathic hemolytic anemia; SLE=systemic lupus erythematosus.
Patients with SLE are at high risk for TMA

In autoimmune diseases such as SLE, autoantibodies that form immune complexes that activate the complement system are produced

SLE can cause TMA, a serious medical condition characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ injury

Could TMA in patients with SLE be more prevalent and more serious than realized?

TMA has been reported in up to 9% of patients affected by SLE

increased risk of in-hospital mortality in patients with SLE and TMA vs patients with SLE but without TMA

*Based on a cohort study of clinical and renal histopathological data of patients with biopsy-proven lupus nephritis (N=148) diagnosed from 2002 to 2008 at a hospital in China.

†Based on a retrospective cohort study of 35,745 hospitalized patients with a primary discharge diagnosis of SLE from 2003 to 2014 from the US National Inpatient Sample database. Data are presented as an odds ratio (OR) of in-hospital mortality of TMA SLE patients (12/188) vs non-TMA SLE patients (443/35,557; OR 5.54; P<0.001).

‡Based on a cohort study of clinical and renal histopathological data of patients with biopsy-proven lupus nephritis (N=341) diagnosed from 2000 to 2008 at a hospital in China.

AID=autoimmune disease; ESRD=end-stage renal disease.

SLE-associated TMA and atypical-HUS are difficult to distinguish. Consider atypical-HUS when the clinical course of SLE-associated TMA is unusually aggressive and unresponsive to conventional SLE treatment.
Along with a patient’s medical history, a high clinical suspicion for atypical-HUS should be raised if a patient treated for SLE continues to experience symptoms of TMA. Patients with TMA may:

- Have renal dysfunction
- Present with thrombocytopenia
- Be in their mid-40s or younger
- Present with MAHA

Atypical-HUS, a type of TMA caused by uncontrolled activation of terminal complement, is a life-threatening disease which may be triggered by SLE

- 17.5% of patients with LN, a subset of SLE, have been shown to develop TMA with progressive, life-threatening thrombocytopenia, MAHA, and progressive renal failure
- The onset of SLE can coexist with or precede a TMA; SLE can also trigger atypical-HUS

Diagnosing atypical-HUS requires excluding other conditions

- Atypical-HUS is characterized by pathologic terminal complement activation due to defects in regulation of the complement system, resulting in endothelial injury, TMA, and organ damage
- Atypical-HUS and TTP have different pathological causes and consequences
  - STEC-HUS, TTP, and other complement mediated TMAs should be ruled out through the assessment of ADAMTS13 and other key tests

SLE-associated TMA can be difficult to differentiate from atypical-HUS

The onset of SLE can coexist with or precede a TMA; SLE can also trigger atypical-HUS

STEC=Shiga toxin-producing Escherichia coli.

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; TTP=thrombotic thrombocytopenic purpura.

*Based on a cohort study of clinical and renal histopathological data of patients with biopsy-proven lupus nephritis (N=341) diagnosed from 2000 to 2008 at a hospital in China.

†Based on an analysis of adult patients with SAID-TMA (n=41) and aHUS (n=78) from 2000 to 2019, from a French TMA registry.
Rapid recognition of TMA and atypical-HUS is critical. TMAs present with similar signs and symptoms but can have distinct underlying causes.

**STEP 1**
Recognize TMA early

- Neurological symptoms
- Pulmonary symptoms
- Visual symptoms
- Cardiovascular symptoms
- Renal impairment
- Gastrointestinal symptoms

Order an ADAMTS13 test immediately

<table>
<thead>
<tr>
<th>≤10% ADAMTS13 activity*</th>
<th>Shiga toxin/EHEC positive</th>
<th>&gt;10% ADAMTS13 activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP</td>
<td>STEC-HUS</td>
<td>Strongly consider atypical-HUS</td>
</tr>
</tbody>
</table>

Clinical considerations while awaiting ADAMTS13 results

Rapidly rule out DIC in patients with TMA in the ICU

- A normal coagulation profile (PT, aPTT, INR, D-dimers) indicates TMA

Labs, or a PLASMIC score, can help predict a diagnosis

- PLASMIC score: a validated predictive tool
  - A score of 0 to 4 should trigger suspicion of atypical-HUS

Key predictive labs

- A patient with TMA presenting a PU/CU of ≥1.5 g/g is less likely to have TTP
- A platelet count >30 x 10^9/L and/or sCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

**STEP 2**
Rapidly determine the cause of TMA


Although renal biopsy is not required for diagnosis of atypical-HUS, it may reveal smoldering cases of TMA in atypical-HUS.

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*Range for ADAMTS13 deficiency found in published literature is <5%–10%.

aPTT=activated partial thromboplastin time; CU=creatininuria; DIC=disseminated intravascular coagulation; EHEC=enterohemorrhagic Escherichia coli; INR=international normalized ratio; LDH=lactate dehydrogenase; PT=prothrombin time; PU=proteinuria; sCr=serum creatinine.
Timely diagnosis of atypical-HUS and clinical intervention are imperative to improving outcomes\(^1,4\)

Comorbid conditions and diseases can trigger terminal complement activation\(^4,17\)

Atypical-HUS develops as a result of

- A patient’s predisposition for complement dysregulation\(^1,4,19\) and/or
- Exposure to factors or conditions that trigger complement activation\(^1,4,19\)

Autoimmune diseases that may unmask atypical-HUS\(^4\)

- APS/CAPS\(^3\) (catastrophic antiphospholipid syndrome)
- SLE/LN\(^3,20,21\) (systemic lupus erythematosus/lupus nephritis)
- Scleroderma and SRC\(^2,3\) (scleroderma renal crisis)

High morbidity and mortality, regardless of the presence, absence, or type of complement dysregulation\(^22^*\)

- 56% of adults progress to ESRD or die within 1 year\(^22^*\)
- 77% with CFH mutation have ESRD or die within 3 years\(^23^†\)

*Based on a nationwide study of pediatric and adult French patients with atypical-HUS between 2000 and 2008 (N=214).\(^22\)
†A registry study of patients with atypical-HUS enrolled in the International Registry of Recurrent and Familial HUS/TTP from 1996 to 2007 (N=273).\(^23\)
CFH=complement factor H.

Act fast—early clinical intervention is crucial to achieving optimal management of atypical-HUS\(^1\)
### Baseline
- **Age:** 19 years old
- **Height:** 157.5 cm (5ft 2in)
- **Weight:** 63.5 kg (140 lb)
- **BMI:** 26
- **Not pregnant**

### Medical history
- **SLE diagnosed at age 18**
- **Biopsy proven LN Class II**
- **No history of surgery or recent transplant**

### Blood pressure: 130/80 mmHG
### Heart rate: 110 bpm
### Oxygen saturation: 99%
### Temperature: ~38.3°C (101°F)

### Family history
- **Mother is on dialysis for ESRD of unknown etiology**
- **Father died of a heart attack at age 51 without history of any comorbid conditions**
- **Cousin has LN Class II**
  - LN has not improved
  - Now on dialysis
  - Low platelets and clotting events

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### Susanna

#### Overview:
Presented to ER with headache, fever, and Grade 2+ edema of bilateral lower extremities.

### Lab values

<table>
<thead>
<tr>
<th></th>
<th>Prior labs (8 months ago)</th>
<th>Lab values at presentation</th>
<th>Reference values24-36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Blood Count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count (x 10^9/L)</td>
<td>5.3</td>
<td>7.5</td>
<td>4.5-11</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.5</td>
<td>8</td>
<td>12-16</td>
</tr>
<tr>
<td>Haptoglobin (mg/dL)</td>
<td>29</td>
<td>30-200</td>
<td></td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>155</td>
<td>70</td>
<td>150-350</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>1350</td>
<td>60-160</td>
<td></td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>8.4</td>
<td>0.5-1.5</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral Smear</strong></td>
<td></td>
<td>Present (1+)</td>
<td>Absent</td>
</tr>
<tr>
<td>Schistocytes present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation Panel</strong></td>
<td></td>
<td>12/26/1.1</td>
<td>11-13.5/25-35/0.8-1.1</td>
</tr>
<tr>
<td>PT/aPTT/INR (seconds)</td>
<td></td>
<td>450</td>
<td>≤500</td>
</tr>
<tr>
<td>D-dimers (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coombs test</td>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.8</td>
<td>1.3</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m^2)*</td>
<td>108.8</td>
<td>60.7</td>
<td>≥90</td>
</tr>
</tbody>
</table>

*As measured by the CKD-EPI creatinine equation (2021). BMI=bmi mass index; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; ER=emergency room.
Case Study: Identifying atypical-HUS in the setting of SLE

On Day 2, Susanna started to decompensate, noting:
- Shortness of breath
- Worsening edema
- Drop in urine output
- Change in urine color with foam present
- Lupus serological tests—ANA, C3, C4, and CH50—were ordered by Susanna’s healthcare team to further assess her condition

<table>
<thead>
<tr>
<th>Lab Values at Day 3: Despite initial treatment, Susanna’s condition has not improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory values at admission</td>
</tr>
<tr>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>White blood cell count (x 10^9/L)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
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<td>Coombs test</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m^2)^*</td>
</tr>
<tr>
<td>CMV PCR</td>
</tr>
<tr>
<td>ANA (units)</td>
</tr>
<tr>
<td>C3 (mg/dL)</td>
</tr>
<tr>
<td>C4 (mg/dL)</td>
</tr>
</tbody>
</table>

Day 3, hematology and nephrology ordered tests to rule out a spectrum of potential causes of TMA:
- Differential diagnosis included DIC, TTP, infectious diseases, including STEC-HUS, and complement-mediated TMA due to other triggers

Susanna’s ADAMTS13 activity level came back at 85%

^{*As measured by the CKD-EPI creatinine equation (2021).
ANA=antinuclear antibody; C=complement component; CH50=complement total blood test; CMV=cytomegalovirus; PCR=polymerase chain reaction.}

Given Susanna’s clinical scenario and ADAMTS13 results, her team concluded that she had atypical-HUS
Don’t wait—when TMA is suspected in patients with SLE, conduct rapid differential diagnosis to ensure appropriate disease management

SLE-associated TMA can be difficult to differentiate from atypical-HUS1,3,4

- **Atypical-HUS**, which may be triggered by SLE, is associated with **continuous risk of complement-mediated TMA and life-threatening consequences**1-4

- SLE-associated TMA and atypical-HUS have similar signs and symptoms and are difficult to distinguish from one another, underscoring the critical need for a differential diagnosis4,8,10,27

- In atypical-HUS, rapid identification, diagnosis, and clinical intervention are crucial to helping patients improve their outcomes1,4

References:


Advance your knowledge of the atypical-HUS diagnosis at aHUSSource.com/physician

bit.ly/3PweEiE