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 consequences[1-4]

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 failure[5,6]*

Prompt recognition, diagnosis, and management of TMA are all critical[1,3,4,7]

>5x **increased risk** of in-hospital mortality in patients with SLE and TMA vs patients with SLE but without TMA[7]*

*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.


Actor Portrayal

Patients with SLE are at high risk for TMA[3]

In autoimmune diseases such as SLE, autoantibodies that form immune complexes that activate the complement system are produced[3,8]

SLE can cause TMA, a serious medical condition characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ injury[3,4]

- Autoimmune-associated TMA is associated with morbidity and mortality, including ESRD[3,9]*

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**[3]

increased risk of in-hospital mortality in patients with SLE and TMA vs patients with SLE but without TMA[7†]

*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.[9]

†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).[7]

‡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.[6]

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

Consequences observed in patients with LN and TMA

33%

of patients with TMA and LN experienced doubling of serum creatinine or progression to ESRD versus 3% with LN with no renal vascular lesions[6‡]

80%

of patients with LN and TMA **developed renal failure within 5 years of diagnosis**[9*]

~24%

of patients with LN had renal TMA despite treatment for the LN[9*]

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[1,3,4]

TMA in the presence of an SLE flare should prompt rapid, differential diagnosis to ensure appropriate disease management[3,10,11]

SLE-associated TMA can be difficult to differentiate from atypical-HUS[1,3,4]

Atypical-HUS, a type of TMA caused by uncontrolled activation of terminal complement, is a life-threatening disease which may be triggered by SLE[1,3]

- **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**[5*]
- The onset of SLE can coexist with or precede a TMA; SLE can also trigger atypical-HUS[3,12]

Diagnosing atypical-HUS requires excluding other conditions[1]

- 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[1,3]
- **Atypical-HUS and TTP have different pathological causes and consequences**[1,4]
  - STEC-HUS, TTP, and other complement mediated TMAs should be ruled out through the assessment of ADAMTS13 and other key tests[4]

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:

- **Be in their mid-40s or younger**[10†]
- **Present with MAHA**[1,5]
- **Have renal dysfunction**[10†]
- **Present with thrombocytopenia**[1,5]

*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.[6]

†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.[10]

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

Actor Portrayal

Can you think of a patient with TMA and an SLE flare who wasn't responding to therapy the way you expected?

Rapid recognition of TMA and atypical-HUS is critical[1,3,4]

TMAs present with similar signs and symptoms but can have distinct underlying causes[1]

STEP 1
Recognize TMA early[4]

TMA = **Thrombocytopenia**
Platelet count <150 x 10^9/L or >25% decrease from baseline
+ **Microangiopathic hemolysis**
Schistocytes *and/or* elevated LDH *and/or* decreased haptoglobin *and/or* decreased hemoglobin

AND 1 or more of the following:

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

STEP 2
Rapidly determine the cause of TMA[1,13]

Order an ADAMTS13 test immediately

≤10% ADAMTS13 activity*	Shiga toxin/EHEC positive	>10% ADAMTS13 activity*
✗	✗	✓
TTP	STEC-HUS	Strongly consider atypical-HUS

Clinical considerations while awaiting ADAMTS13 results

Rapidly rule out DIC in patients with TMA in the ICU[1,13]

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

Labs, or a PLASMIC score, can help predict a diagnosis[4,14,15]

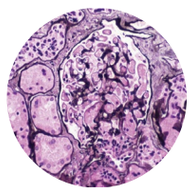
PLASMIC score: a validated predictive tool

- A score of 0 to 4 should trigger suspicion of atypical-HUS[14]

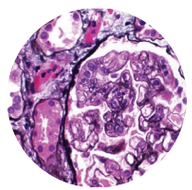
Key predictive labs

- A patient with TMA presenting a PU/CU of ≥1.5 g/g is less likely to have TTP[15]
- 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)[4]

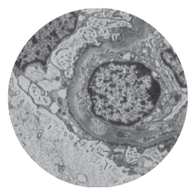
IF APPROPRIATE,
a renal biopsy can reveal TMA[16,17]



Glomerular/ arteriolar thrombi



Basement membrane splitting



Basement membrane formation and early cellular interposition

Adapted from Lusco MA, et al. *Am J Kidney Dis.* 2016;68(6):e33-e34.

Although renal biopsy is not required for diagnosis of atypical-HUS, it may reveal smoldering cases of TMA in atypical-HUS[17,18]

*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]

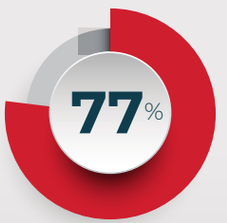
APS/CAPS[3]
(catastrophic antiphospholipid syndrome)

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*]

of adults **progress to ESRD or die within 1 year**[22*]



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]

Case Study: Identifying atypical-HUS in the setting of SLE

Susanna

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

Baseline

- **Age:** 19 years old
- **Height:** 157.5 cm (5ft 2in)
- **Weight:** 63.5 kg (140 lb)
- **BMI:** 26
- **Not pregnant**

Hypothetical patient case.

Medical history

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

Medical history

- **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

Lab values

		Prior labs (8 months ago)	**Lab values at presentation**	Reference values[24-26]
Complete Blood Count	White blood cell count (x 10^9/L)	5.3	**7.5**	4.5-11
	Hemoglobin (g/dL)	11.5	**8**	12-16
	Haptoglobin (mg/dL)		**29**	30-200
	Platelet count (x 10^9/L)	155	**70**	150-350
	LDH (U/L)		**1350**	60-160
	Reticulocytes (%)		**8.4**	0.5-1.5
Peripheral Smear	Schistocytes present		**Present (1+)**	Absent
Coagulation Panel	PT/aPTT/INR (seconds)		**12/26/1.1**	11-13.5/25-35/0.8-1.1
	D-dimers (ng/mL)		**450**	≤500
Other Tests	Coombs test		**Negative**	Negative
	Serum creatinine (mg/dL)	0.8	**1.3**	0.5-1.0
	eGFR (mL/min/1.73 m^2)*	108.8	**60.7**	≥90

*As measured by the CKD-EPI creatinine equation (2021).
BMI=body 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

Lab Values at Day 3: Despite initial treatment, Susanna's condition has not improved

		Laboratory values at admission	**Day 3 Labs**	Reference values[24-26]
Complete Blood Count	White blood cell count (x 10^9/L)	7.5	**10**	4.5-11
	Hemoglobin (g/dL)	8	**5**	12-16
	Haptoglobin (mg/dL)	29	**Undetectable**	30-200
	Platelet count (x 10^9/L)	70	**75**	150-350
	LDH (U/L)	1350	**2000**	60-160
	Reticulocytes (%)	8.4	**9**	0.5-1.5
Peripheral Smear	Schistocytes present	Present (1+)	**Present (3+)**	Absent
Coagulation Panel	PT/aPTT/INR (seconds)	12/26/1.1	**15/30/1.2**	11-13.5/25-35/0.8-1.1
	D-dimers (ng/mL)	450	**600**	≤500
Other Tests	Coombs test	Negative	**Negative**	Negative
	Serum creatinine (mg/dL)	1.3	**2.5**	0.5-1.0
	eGFR (mL/min/1.73 m^2)*	60.7	**27.7**	≥90
	CMV PCR		**Negative**	Negative
	ANA (units)		**90**	<1.0
	C3 (mg/dL)		**60**	90-180
	C4 (mg/dL)		**5**	10-40

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-HUS[1,3,4]

- **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 diagnosis[4,8,10,27]
- **In atypical-HUS, rapid identification, diagnosis, and clinical intervention** are crucial to helping patients improve their outcomes[1,4]

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

bit.ly/3PweEiE

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