atypical-HUS

When a patient presents with TMA, identify the underlying cause for the appropriate diagnosis.[1-3]
Differential diagnosis for TMAs: atypical-HUS, TTP, and STEC-HUS[4-7]

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 ± blood and/or
Nausea/vomiting 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[a]

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	>5% ADAMTS13 activity	Shiga toxin/EHEC positive
TTP	Atypical-HUS	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

[a]Shiga-toxin/EHEC test is warranted in history/presence of GI. [b]Range found in published data is <5%-10%.

ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif member 13; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EHEC, enterohemorrhagic *Escherichia coli*; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; MI, myocardial infarction; SCr, serum creatinine; STEC, Shiga toxin-producing *E. coli*; TMAs, thrombotic microangiopathies; TTP, thrombotic thrombocytopenic purpura.

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Identifying atypical-HUS as the underlying cause of TMA is critical to making early optimal management decisions.[4,8]

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Though not required for diagnosis, the following may help determine if atypical-HUS is the underlying cause of TMA:

Complement-triggering conditions that unmask atypical-HUS[1-3,9]

Persisting TMA, despite standard management of the complement-triggering condition, may indicate an underlying genetic predisposition for atypical-HUS.[10-16]

70% of patients with atypical-HUS showed their first clinical manifestation while experiencing one of the following complement-triggering conditions (N=191)[17]:

- Diarrhea/gastroenteritis
- Upper respiratory tract infections
- Malignant hypertension
- Pregnancy-associated
- Transplant-associated
- Glomerulopathy
- Systemic disease (eg, systemic lupus erythematosus)
- Malignancy

A family history of atypical-HUS increases the risk for morbidities and premature mortality[18]

Patients with atypical-HUS should be assessed for the following[2,16,17,19]:

- Identification in the family of a genetic mutation associated with atypical-HUS
- Family history of TMA or blood clotting
- Family history of renal impairment, renal transplant, or dialysis

Failure to respond to initial plasma exchange/plasma infusion (PE/PI)[6,16]

Failure to respond is defined by any of the following[10,20]:

- After PEs daily for 5 days, platelet count and hemolysis are not improving
- After PEs daily, renal function is not improving
- Lack of impact on TMA outcome with PE/PI

Complement C3 levels[2,17]

Complement dysregulation is implicated in patients whose C3 levels are low, but normal C3 levels do not exclude a diagnosis of atypical-HUS.[16,17]

Genetic abnormalities

While not required for a diagnosis of atypical-HUS, identification of a complement-related genetic mutation can help confirm the clinical diagnosis.

Genetic mutations in atypical-HUS:

- Are still being discovered[17,20,21]
- Have not been identified in 30% to 50% of patients with atypical-HUS[17,18]
- Provide prognostic value when identified[1,2,17,18,22-25]

TMA, thrombotic microangiopathy.

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