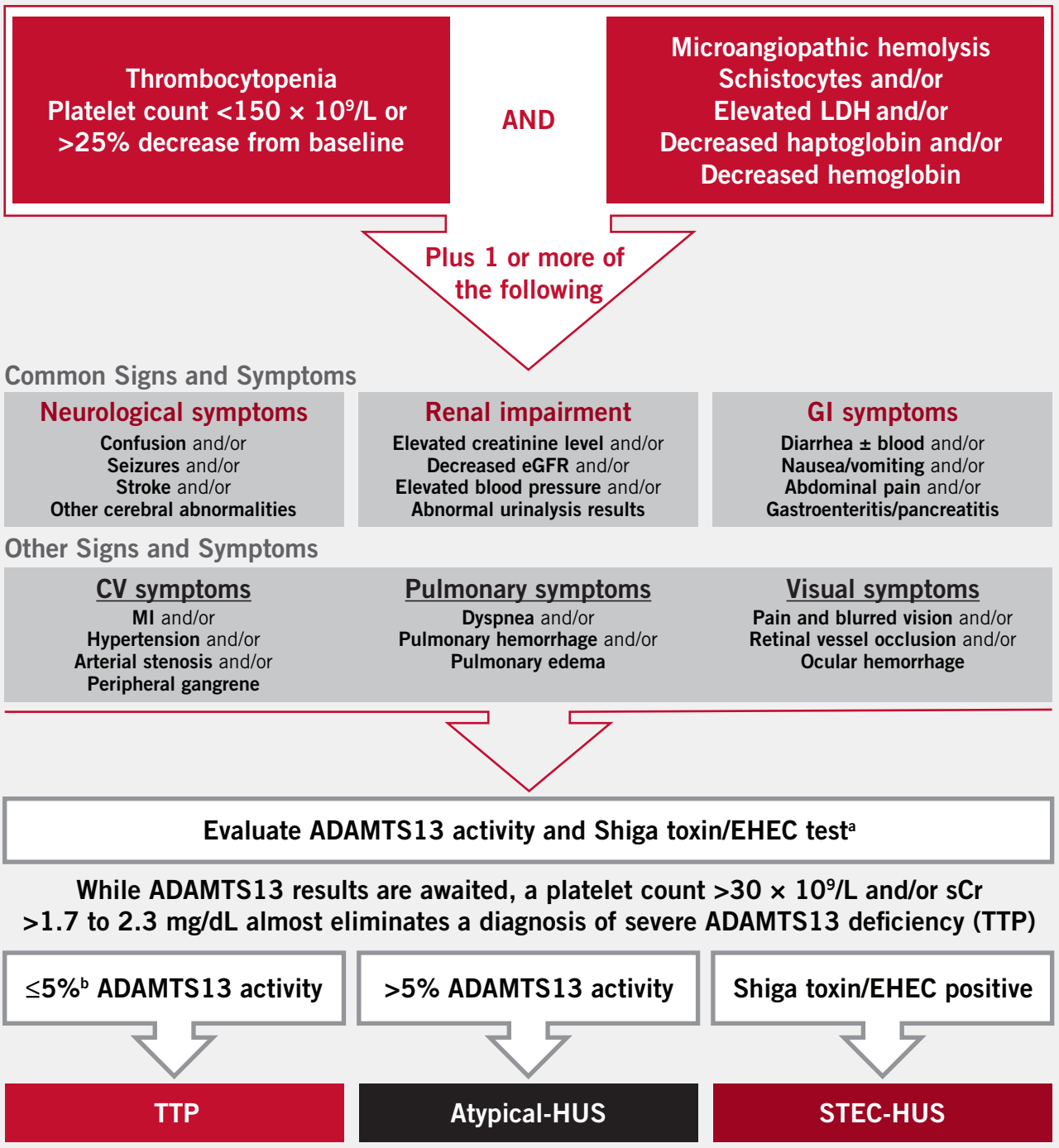
Identifying Atypical Hemolytic Uremic Syndrome in the Pregnancy-Postpartum Setting

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.

Identifying Atypical-HUS in the Pregnancy/Postpartum Setting

Differential Diagnosis of Atypical-HUS[1-4]



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

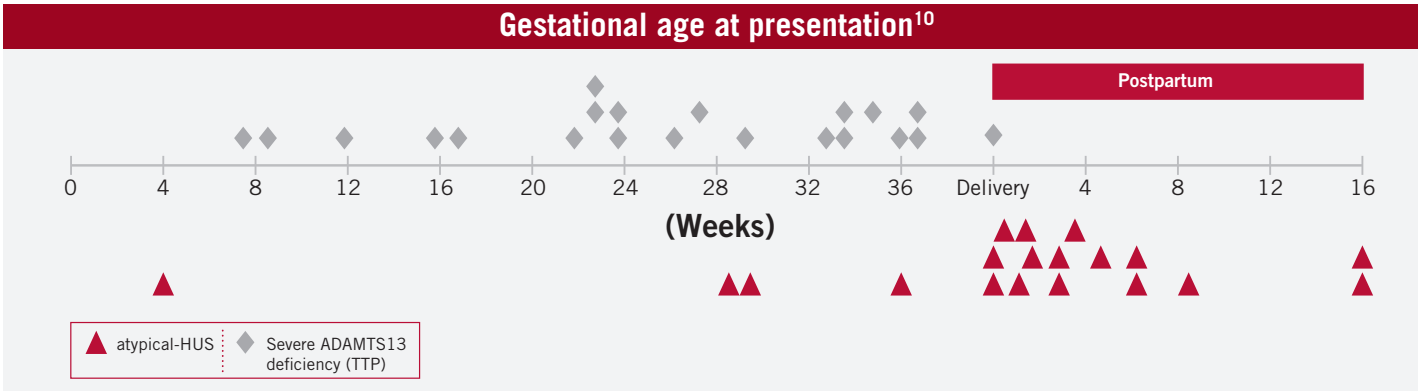
[a]Shiga toxin/EHEC test is warranted with history/presence of GI symptoms. [b]Range found in published literature is <5%-10%.

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: 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[1]
- 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[4,5]
  - In patients with complement dysregulation, normal pregnancy[6] 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[4]
  - Atypical-HUS is a disease associated with the chronic risk of a complement-mediated TMA that can be unmasked during or after pregnancy[4]
- A diagnosis of atypical-HUS may be missed when a women presents with a TMA during pregnancy because it can present with similar clinical features to HELLP[5]
  - Hemolysis is characteristic of both HELLP and atypical-HUS and hemolytic screening is essential to make a differential diagnosis[5]
- A high clinical suspicion for atypical-HUS should be raised if a woman presents with TMA during pregnancy along with the following charactertistics
  - Renal dysfunction[7]
  - Hemolysis with[5]
    - Elevated LDH, specifically LDH >1000 U/L with serum creatinine (sCr) >1.1 mg/dL[5]
    - High LDH:AST ratio (>10:1) or low hemoglobin (<8 g/dL)[5]
  - SCr >2.0 g/dL or persistently elevated sCr >1.1 g/dL for >72 hours postpartum[5]
  - Elevated AST or ALT levels[5]
  - >25% decrease in platelet count from baseline[5]
  - Signs of persistent TMA more than 48 hours after delivery[8,9]
  - Frequent presentation of TMA postpartum[10-14]
  - History of previous TMA[10,11,15,16]
  - Family history of renal impairment or atypical-HUS[11,16]
  - History of previous pregnancy-related complications[10]
- 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[7]
  - 79% of cases of atypical-HUS unmasked by pregnancy have been described in the postpartum period[10]

Gestational age at presentation[10]



A previous normal pregnancy does not exclude a diagnosis of atypical-HUS.[10] If atypical-HUS or any TMA is suspected, involve a TMA expert in the diagnostic process.[17]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HELLP, Hemolysis, Elevated Liver enzyme levels, and Low Platelet count syndrome; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; sCr, serum creatinine; TMA, thrombotic microangiopathy TTP, thrombotic thrombocytopenic purpura.

Case Study[a]

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

First Hospital Admission	5 days after PE/FFP	14 days after discharge	Second Hospital Admission
Fatigue, nausea, vomiting, and upper right quadrant pain TTP was excluded based on ADAMTS13 activity	Liver enzymes and platelets normalized	Premature delivery	Presented with thrombocytopenia, hemolysis, and kidney failure 6 months after HELLP diagnosis
Diagnosis: class 3 HELLP[14,a] Treatment: PE and FFP	Discharged from hospital		Diagnosis: atypical-HUS

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.

[a]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).[14]

Laboratory Values

Laboratory Tests	Normal Values	At First Hospital Admission	5 Days After FFP/PE	At Second Hospital Admission
Schistocytes	No	Yes	Yes	Yes
Platelet count, × 10^9/L	150-450	121	218	118
Lactate dehydrogenase, U/L	100-190	260	200	269
Hemoglobin, g/dL	12.0-16.0	9.5	14.3	4.2
Haptoglobin, mg/dL	36-195	7.8	40	6.4
Reticulocytes, %	0.5-1.5	2.4	1.6	3.9
Creatinine, mg/dL	0.6-1.3	1.5	0.8	5.2
Estimated glomerular filtration rate, mL/min/1.73 m^2	90+	87	92.2	14.2
Proteinuria	0	1+	0	0
Bilirubin, mg/dL	0.0-0.3	5.8	0.1	6.2
Alanine aminotransferase, IU/L	7-56	662	54	24
Aspartate aminotransferase, IU/L	5-40	435	33	26
Differential diagnosis evaluation				
ADAMTS13 activity	≥5%	63%	63%	63%

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; FFP, fresh frozen plasma; IU, international unit; PE, plasma exchange.

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

[a]The case described here is representative of physician experience and does not include actual patient data.

Important Considerations for a Differential Diagnosis

Differentiation of atypical-HUS from other TMAs and pregnancy-associated conditions is essential for optimal management decisions[10,18]

HELLP Syndrome

Occurrence[14]
- Most commonly develops before delivery with a peak between 27 and 37 weeks
- Can occur within 48 hours postpartum

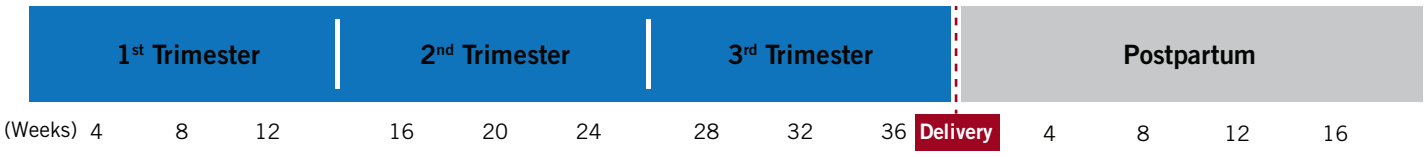
Classic features[5]
- MAHA, platelets <100 × 10^9/L, AST/ALT >2× ULN, serum creatinine >1.1 mg/dL

Symptoms[5]
- Epigastric or right upper quadrant pain, nausea, vomiting, headache, visual disturbances

Treatment[5]
- Delivery

HELLP syndrome typically resolves within 48-72 hours post-delivery[5]

If TMA persists, consider atypical-HUS[8,9]



Atypical-HUS

Occurrence[10,19]
- Most commonly occurs in the postpartum period
- Less commonly unmasked during pregnancy

Classic features[1,2,4,5]
- MAHA, platelets <150 × 10^9/L, serum creatinine >2.0 mg/dL negative STEC-HUS, ADAMTS13 >5%

Symptoms[5]
- Nausea, vomiting, abdominal pain, headache, altered mental status

Medical history[9,10,14,15,20]
- 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

Atypical-HUS

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[4]

A diagnosis of atypical-HUS may be missed during pregnancy because it can present with similar clinical features to HELLP[5]

If TMA is suspected it is important to include a multidisciplinary team of specialists in the diagnostic process[17]

HELLP, Hemolysis, Elevated Liver enzyme levels, and Low Platelet count syndrome; HUS, hemolytic uremic syndrome; TMA, thrombotic microangiography.

References

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ALEXION