Identifying atypical-HUS in the presence of hypertensive emergency

A guide to differential diagnosis of thrombotic microangiopathy (TMA) in the presence of hypertensive emergency

Hypertensive emergency is characterized by severely elevated blood pressure (>180/120 mmHg) associated with evidence of new or worsening end-organ damage[1]

- **Malignant hypertension (mHTN)**, a type of hypertensive emergency associated with poor prognosis, is a potential trigger for **atypical hemolytic uremic syndrome (atypical-HUS)**[1-4]
- As TMA is a known clinical feature of atypical-HUS, **detecting TMA among hypertensive emergency patients** should prompt urgent differential diagnosis, while treating the hypertensive emergency[5-7]
- **TMA** and **atypical-HUS** may be present and often overlooked in patients with mHTN. In a retrospective study of hospitalized patients with mHTN (N=199)[8]*:

20% (n=40/199) presented with TMA — **and of them** — **60%** (n=24/40) had atypical-HUS at baseline

EARLY DIAGNOSIS OF ATYPICAL-HUS CAN MINIMIZE THE RISK OF NEGATIVE OUTCOMES, INCLUDING KIDNEY TRANSPLANTS[3,9]

*Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[8]



Actor portrayal

aHUS Source

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.

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Recognize the critical role of hypertensive emergency as a trigger for atypical-HUS[2,3]

Hypertensive emergency may lead to TMA and unmask atypical-HUS[2,6,7,10]

Hypertensive emergency is severe hypertension with end-organ involvement[1]

- Overactivation of the complement system was found in 59% (n=17/29) of patients with hypertensive emergency and TMA[11]*
- Patients may present with key markers of TMA[8,9]

TMA is a medical emergency requiring immediate screening for an underlying cause[3,12]

TMA is characterized by[3,9]**:**

- **Microangiopathic hemolytic anemia:** Signs include decreased hemoglobin, elevated lactate dehydrogenase, decreased haptoglobin levels, and evidence of schistocytes in blood smears
- **Thrombocytopenia:** Low platelet count (<150 x 10^9/L or a >25% decrease in platelet count from baseline)
- One or more signs and symptoms of organ damage

Atypical-HUS is associated with continuous risk of complement-mediated TMA and life-threatening consequences[3,5,12]

Atypical-HUS is a result of either or both of these factors[3,12]**:**

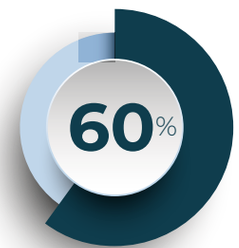
- A patient's genetic predisposition to complement dysregulation
- Exposure to factors or conditions that trigger complement activation such as hypertensive emergency

In patients with mHTN, could TMA and atypical-HUS be more common than you realize?

In a retrospective analysis of 199 patients with mHTN[8†]



of the patients presented with TMA (n=40/199)



of the patients with TMA had atypical-HUS (n=24/40)

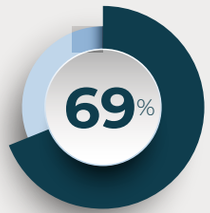
*Based on a 2021 cohort study of patients with TMA with severe kidney involvement (N=65) from the Limburg Renal Registry in the Netherlands and the Cliniques Universitaires Saint-Luc in Belgium.[11]
†Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[8]
IgA=immunoglobulin A.

While treating patients for hypertensive emergency, the presence of TMA should increase suspicion of atypical-HUS[8]

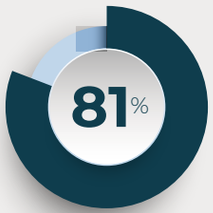
Other causes of TMA in patients with hypertensive emergency included drug-related mHTN, some systemic diseases, and IgA nephropathy.[8,10]

Early diagnosis and management for atypical-HUS in the presence of hypertensive emergency is critical[3,9,12]

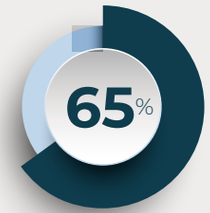
Studies of patients with atypical-HUS have found that...



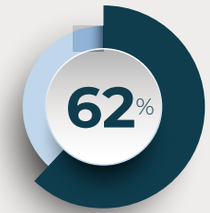
had both atypical-HUS and mHTN appear around the same time (n=49/71)[9]*



with both HE and atypical-HUS required dialysis at onset (n=57/70)[13]†



with atypical-HUS and mHTN who did not receive appropriate treatment required a kidney transplant (n=33/51)[9]*



with atypical-HUS progressed to kidney failure (n=16/26)[8]‡

In a study of 9 patients with hypertensive emergency who had atypical-HUS, hematological signs of TMA were uncommon, potentially reflecting smoldering cases of TMA. These cases of TMA can present as a persistent, progressive, and gradual disease course[7,14§]

*Retrospective analysis of patients with MHT and aHUS (N=1097) enrolled in the Global aHUS Registry and followed for ≥90 days from atypical-HUS diagnosis from 2012 to 2020.[9]
†Based on a French retrospective cohort analysis of patients with atypical-HUS, with or without concomitant hypertensive emergency (N=137), screened between 2000 and 2016.[13]
‡Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[8]
§A retrospective analysis of patients with severe hypertension with biopsy-proven renal TMA (N=9) from January 2005 onward at a medical center in the Netherlands.[7]

HE=hypertensive emergency; MHT=malignant hypertension.



In patients with atypical-HUS and mHTN (n=26),‡

Kidney survival at 5 years was 34%[8]

Without appropriate atypical-HUS management†

The renal survival rates of patients with hypertensive emergency and atypical-HUS were

36%[13] **At 1 year**

23%[13] **At 5 years**

Given the severity of atypical-HUS and hypertensive emergency, it's critical to diagnose patients quickly to minimize the risk of poor outcomes[3,9,12]

Recognize the patient with hypertensive emergency at risk for atypical-HUS and respond promptly

Studies show that characteristics of patients with atypical-HUS and hypertensive emergency may include:

- **Usually in their mid 40s or younger**[8,13*†]
- **Some have genetic complement abnormalities**[8,13‡]
- **Often have renal involvement and potentially severe kidney injury**[8,13*†]
- **May have extrarenal manifestations—including neurological**[8,13*†]



Actor portrayal.

Consider additional characteristics that may be present in patients with atypical-HUS and hypertensive emergency[8,12]

- Taking >2 antihypertensives to normalize blood pressure—while renal function continues to decline
- Requiring dialysis at presentation
- Having a family or medical history of TMA and/or kidney failure

*Based on a French retrospective cohort analysis of patients with atypical-HUS, with or without concomitant hypertensive emergency (N=137), screened between 2000 and 2016.[13]
†Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[8]
‡In 30%-40% of atypical-HUS patients, the cause is ill-defined, and the role of additional genetic or environmental factors remains debatable.[13,15]

Can you think of a patient with hypertensive emergency who wasn't responding to therapy the way you expected?

Rapid recognition of TMA is critical

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

STEP 1
Recognize TMA early[3]

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[12,16]

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[12,16]

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

Labs, or a PLASMIC score, can help predict a diagnosis[3,17,18]

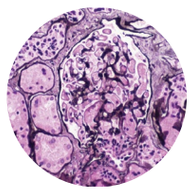
PLASMIC score: a validated predictive tool

- A score of 0 to 4 should trigger suspicion of atypical-HUS[17]

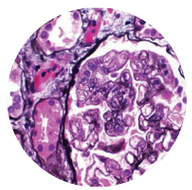
Key predictive labs

- A patient with TMA presenting a PU/CU of ≥1.5 g/g is less likely to have TTP[18]
- 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)[2]

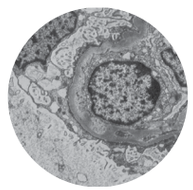
IF APPROPRIATE,
a renal biopsy can reveal TMA[19,20]



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[14,20]

*Range for ADAMTS13 deficiency found in published literature is <5%-10%.[16]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; aPTT=activated partial thromboplastin time; CU=creatininuria; DIC=disseminated intravascular coagulation; EHEC=enterohemorrhagic *E coli;* HUS=hemolytic uremic syndrome; INR=international normalized ratio; LDH=lactate dehydrogenase; PT=prothrombin time; PU=proteinuria; sCr=serum creatinine; STEC=Shiga toxin–producing *E coli*; TTP=thrombotic thrombocytopenic purpura.

Case study: hypertensive emergency and atypical-HUS

Angela

Overview: Presented to the ER with hypertensive emergency, headache, dyspnea, and sudden onset of blurred vision.


Actor portrayal

Baseline

- **Age:** 34 years old
- **Height:** 155 cm (5 ft 1 in)
- **Weight:** 62 kg (137 lb)
- **BMI:** 25.9
- **Not pregnant**

Hypothetical patient case.

Medical history

- History of hypertension since age 25
- Unremarkable first pregnancy
- Preeclampsia in 3rd trimester of second pregnancy (G2P2)
- Managed with diuretic

Family history

- Father: history of renal failure and ESRD at age 59 of unknown causes

Vital signs

- **Blood pressure:** 235/125 mmHg
- **Heart rate:** 100 bpm
- **Oxygen saturation:** 100%
- **Temperature:** 37.0°C (98.6°F)

Lab values

		Prior labs (8 months ago)	**Lab values at presentation**	Reference values[21-23]
Complete Blood Count	White blood cell count (x 10^9/L)	5.3	**11**	4.5-11
	Hemoglobin (g/dL)	12.5	**8.9**	12-16
	Haptoglobin (mg/dL)		**20**	30-200
	Platelet count (x 10^9/L)	250	**130**	150-350
	LDH (U/L)		**500**	60-160
	Reticulocytes (%)		**2.5**	0.5-1.5
Peripheral Smear	Schistocytes present	No	**2+**	Absent
Comprehensive Metabolic Panel	BUN (mg/dL)	14	**30**	8-20
	eGFR (mL/min/1.73 m^2)*	108	**33**	≥90
	Serum creatinine (mg/dL)	0.7	**1.9**	0.5-1.0
	Bilirubin (mg/dL)	0.4	**3.4**	0.0-0.3
Other Tests	Blood pressure (mmHg)	141/85 (Stage 2 Hypertension†)	**235/125**	<120/<80
	Pregnancy test		**Negative**	
	Urine toxicology		**Negative**	

*Calculated using https://reference.medscape.com/calculator/251/egfr-using-ckd-epi-2021-update.
†As per the AHA/ACC 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[1]
bpm=beats per minute; BMI=body mass index; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; ER=emergency room; ESRD=end-stage renal disease; G2P2=gravida 2 para 2.

Case study: hypertensive emergency and atypical-HUS

Treatment initiation: Angela was treated with IV vasodilators and eventually put on an IV calcium channel blocker. Blood pressure came down slowly (by about 25% each day). However, on **Day 3**, repeat lab measurements did not improve. On **Day 4**, nephrology and hematology consults were requested given a lack of improvement of hematologic and renal parameters.

Lab values at Day 5: Angela's blood pressure had improved with initial treatment, but her labs deteriorated

		Prior labs (8 months ago)	Lab values at presentation	**Day 5 values**	Reference values[21-23]
Complete Blood Count	White blood cell count (x 10^9/L)	5.3	11	**10**	4.5-11
	Hemoglobin (g/dL)	12.5	8.9	**7.5**	12-16
	Haptoglobin (mg/dL)		20	**15**	30-200
	Platelet count (x 10^9/L)	250	130	**78**	150-350
	LDH (U/L)		500	**700**	60-160
	Reticulocytes (%)		2.5	**3**	0.5-1.5
Peripheral Smear	Schistocytes present	No	2+	**3+**	Absent
Comprehensive Metabolic Panel	BUN (mg/dL)	14	30	**42**	8-20
	eGFR (mL/min/1.73 m^2)*	108	33	**23**	≥90
	Serum creatinine (mg/dL)	0.7	1.9	**2.5**	0.5-1.0
	Bilirubin (mg/dL)	0.4	3.4	**0.2**	0.0-0.3
	Indirect bilirubin (mg/dL)		3.4	**3.5 (elevated)**	0.3-1.2
Other Tests	Blood pressure (mmHg)	141/85 (Stage 2 hypertension†)	235/125	**125/82**	<120/<80
	ADAMTS13			**Pending**	
	Shiga-toxin			**Negative**	
	Vitamin B levels (pg/mL)			**305**	200-800

86% of patients with hypertensive emergency and atypical-HUS did not recover normal renal function despite receiving antihypertensive treatment[24‡]

Angela's worsening creatinine, hemolysis, and renal failure led the treatment team to suspect TMA

- Her differential diagnosis included DIC, TTP, infectious diseases including STEC-HUS, and CM-TMA due to other triggers

48% ADAMTS13 activity level: consider a diagnosis of atypical-HUS[3]

The information in this presentation is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis. Tests listed may not be available at all institutions.

*Calculated using https://reference.medscape.com/calculator/251/egfr-using-ckd-epi-2021-update.
†As per the AHA/ACC 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[1]
‡A retrospective analysis of patients from 2003 to 2006 in China with severe or malignant hypertension accompanied by biopsy-proven renal TMA lesions (N=21).[24]
CM-TMA=complement-mediated TMA; IV=intravenous.

Given Angela's clinical scenario and ADAMTS13 results, team concluded that she had atypical-HUS

Suspect TMA in patients with hypertensive emergency and conduct rapid differential diagnosis for atypical-HUS



Given that hypertensive emergency is a known trigger of atypical-HUS, early diagnosis and management are critical[2,3,9]

- **TMA** and **atypical-HUS** may be present and often overlooked in patients with mHTN. In a retrospective study of hospitalized patients with mHTN (N=199)[8]*:

  20% **of patients with mHTN had TMA** — **and of them** — **60%** **had atypical-HUS at baseline**

- **Controlled hypertension** without resolution of associated renal failure **may indicate atypical-HUS**[6,7,25]

- While treating patients for hypertensive emergency, the **presence of TMA** should **increase suspicion of atypical-HUS**[8]

- **If TMA is suspected**, it is important to include a multidisciplinary team of specialists in the diagnostic process[26]

PROMPT DIAGNOSIS AND INTERVENTION IN ATYPICAL-HUS CAN LEAD TO IMPROVED OUTCOMES[3,9,12]

*Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[8]

References: 1. Whelton P, et al. *Hypertension.* 2018;71:e13-e115. **2.** Boulestreau R, et al. *J Am Heart Assoc.* 2022;11:e023397. doi:10.1161/JAHA.121.023397 **3.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11)(suppl 11):2-15. **4.** Amraoui F, et al. *J Clin Hypertens (Greenwich).* 2014;16(2):122-126. **5.** Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418. **6.** Asif A, et al. *J Nephrol.* 2017;30(3):347-362. **7.** Timmermans SAMEG, et al. *Kidney Int.* 2017;91(6):1420-1425. **8.** Cavero T, et al. *Nephrol Dial Transplant.* 2023;38:1217-1226. **9.** Halimi JM, et al. *J Nephrol.* 2023;36:817-828. **10.** Halimi JM, et al. *BMC Nephrol.* 2022;23:39:1-10. **11.** Timmermans SAMEG, et al. *Kidney Int Rep.* 2021;6(4):1099-1109. **12.** Azoulay E, et al. *Chest.* 2017;152(2):424-434. **13.** El Karoui K, et al. *Haematologica.* 2019;104(12):2501-2511. **14.** Kim YJ. *Kidney Res Clin Pract.* 2022;41(5):524-532. **15.** Fakhouri F, et al. [published correction appears in *Lancet.* 2017;390(10095):648]. *Lancet.* 2017;390(10095):681-696. **16.** Vincent JL, et al. *Crit Care.* 2018;22(1):158. **17.** Wynick C, et al. *Thromb Res.* 2020;196:335-339. **18.** Burguet L, et al. *J Clin Med.* 2022;11(3):648. **19.** Lusco MA, et al. *Am J Kidney Dis.* 2016;68(6):e33-e34. **20.** Campistol JM, et al. *Nefrologia.* 2015;35:421-447. **21.** Padilla O, Abadie J. Blood tests: normal values. Merck Manuals Professional Version. Updated September 2022. Accessed May 3, 2023. https://www.merckmanuals.com/professional/resources/normal-laboratory-values/blood-tests-normal-values **22.** Estimated glomerular filtration rate (eGFR). 2022. National Kidney Foundation. Accessed May 3, 2023. https://www.kidney.org/atoz/content/gfr **23.** The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. US Department of Health and Human Services. Published August 2004. https://www.nhlbi.nih.gov/files/docs/guidelines/jnc7full.pdf **24.** Zhang B, et al. *Hypertens Res.* 2008;31(3):471-483. **25.** Langman C. *Haematologica.* 2012;97(suppl 1):195-196. **26.** Uriol Rivera MG, et al. *PLoS ONE.* 13(11):e0206558. doi:10.1371/journal.pone.0206558

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