# 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



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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]

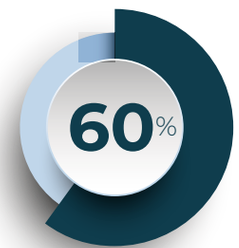
**Atypical-HUS is a result of either or both of these factors**[3,12]**:**

- 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)

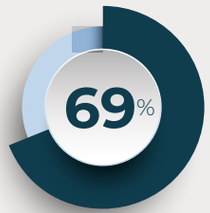
*Based on a 2021 cohort study of patients with TMA with severe kidney involvement (N=65) from the Limburg Renal Registry in the Netherlands and the Cliniques Universitaires Saint-Luc in Belgium.[11]
†Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in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

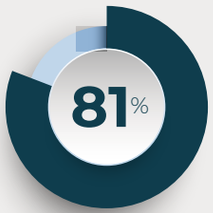
Other causes of TMA in patients with hypertensive emergency included drug-related mHTN, some systemic diseases, and IgA nephropathy.[8,10]

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

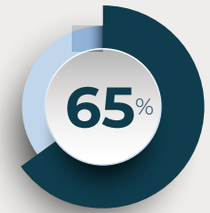
## Studies of patients with atypical-HUS have found that...



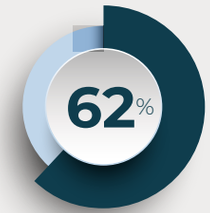

**had both atypical-HUS and mHTN appear around the same time** (n=49/71)[9]*




**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]

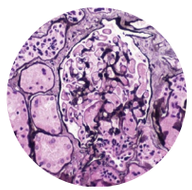
**PLASMIC score: a validated predictive tool**

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

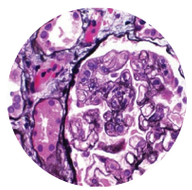
**Key predictive labs**

- 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]

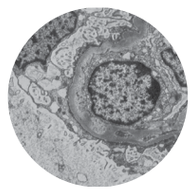
## IF APPROPRIATE,
a renal biopsy can reveal TMA[19,20]



**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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