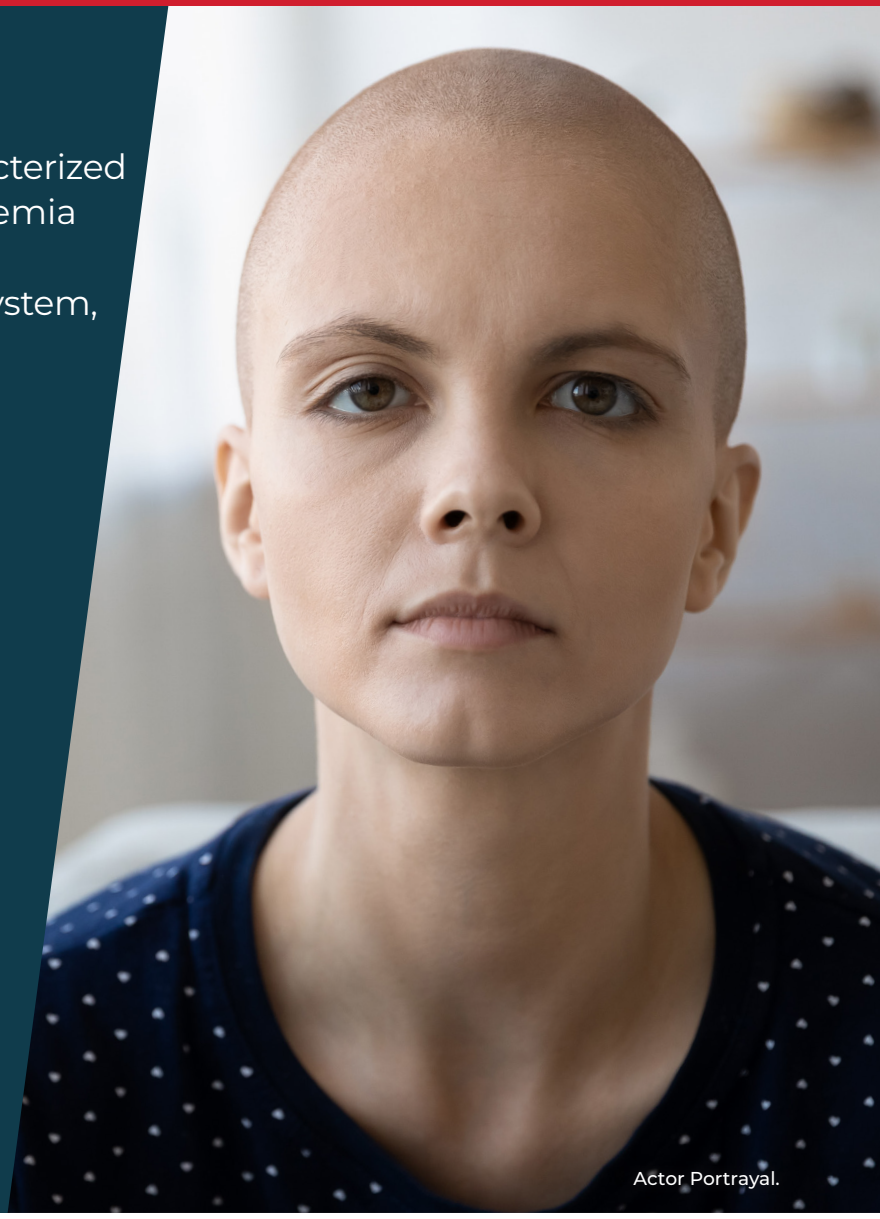
Identifying atypical-HUS in the presence of cancer or drug therapies

A guide to differential diagnosis of thrombotic microangiopathies (TMAs), specifically atypical-HUS

TMA is a medical emergency characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and involvement of at least one organ system, often including AKI.[1,2]

Atypical-HUS, a type of TMA, is primarily caused by complement dysregulation or conditions that trigger complement activation, resulting in endothelial injury, platelet activation, and microvascular thrombosis.[1]



Actor Portrayal.

AKI=acute kidney injury; atypical-HUS=atypical hemolytic uremic syndrome.

aHUS Source

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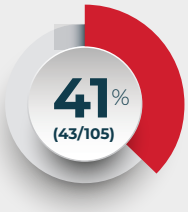
Don’t miss the signs: TMA may be overlooked in patients with cancer[3]

In a retrospective study of hospitalized patients in France with TMA (N=564)[4,a]:

had **cancer as an identifiable cause**[b]

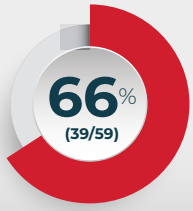


of those cases **were adenocarcinoma**[b]

In a retrospective study of adult French patients with cancer-associated TMA (N=59), cancer locations were as follows[5,c]:

- Breast cancer: 24% (n=14)
- Non-small cell lung cancer: 19% (n=11)
- Colorectal carcinoma: 10% (n=6)
- Gastric adenocarcinoma: 10% (n=6)
- Prostate adenocarcinoma: 10% (n=6)
- Unknown: 12% (n=7)

Screen for TMA in your patients with cancer



In 2/3 of cases, **cancer was diagnosed at the same time** as TMA[5,c]

TMA and DIC can be consequences of cancer, but the differential diagnosis is often difficult[6]

- Most patients with TMA **meet several diagnostic criteria** for DIC
- However, only **10%-15% of patients diagnosed with DIC also meet the criteria** for TMA

Patients with cancer and TMA are at risk of kidney injury and may require dialysis[5]

[a]Patients were separated into primary TMA (defined as TMA caused by atypical-HUS or TTP) and secondary TMA (defined as TMA caused by STEC-HUS, pregnancy, autoimmune, malignant HTN, malignancy, infection, transplantation, drugs, or other TMAs). The data presented here reflect those patients who did not have a diagnosis of atypical-HUS or TTP.[4]

[b]Range found in published literature is from 6%-19.8%.[4,7]

[c]This study included adult cancer patients with a confirmed TMA diagnosis. The study excluded patients with chemotherapy less than 4 months before TMA diagnosis, sepsis-induced TMA, and other causes of TMA, as determined based on extensive laboratory tests (virological and autoimmune tests, complement and ADAMTS13 activity assays).[5]

Vigilance required: TMA triggered by cancer therapies may be more common than realized[8]

Chemotherapy-associated TMA[8]:

- May be on the rise with increased multidrug use and is a potentially underrecognized cause of CKD in patients with cancer
  - —Can be mistaken for myelosuppression
- In some cases, hematologic recovery may be rapid following drug discontinuation
- Kidney recovery is often delayed and incomplete

Signs and symptoms of cancer therapy–induced TMA[8-10]:

- Acute kidney failure
- Worsening of proteinuria, often subnephrotic

- New onset or worsening headache

- Pulmonary edema
- Respiratory distress

- Worsening of hypertension
- Thrombocytopenia
- Anemia

Maintain a clinical suspicion of TMA in patients with cancer and/or on chemotherapy who present with thrombocytopenia, MAHA, and organ involvement.[3]

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; atypical-HUS=atypical hemolytic uremic syndrome; CKD=chronic kidney disease; DIC=disseminated intravascular coagulation; HTN=hypertension; MAHA=microangiopathic hemolytic anemia; STEC-HUS=Shiga toxin–producing *Escherichia coli*– associated hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

Exploring the links: Known therapies associated with TMAs

Type I Cancer Drug–Induced TMA[8,10]

Presentation:

- Delayed onset; usually 6-12 months after treatment initiation
- May be permanent and irreversible
- Presence of hematologic and respiratory manifestations, along with acute renal failure and hypertension

Examples:

- Mitomycin-C
- Carboplatin
- Cisplatin
- Bleomycin
- Gemcitabine
- Oxaliplatin

Type II Cancer Drug–Induced TMA[8,10]

Presentation:

- Onset may occur anytime after treatment initiation, including with prolonged treatment
- Potentially reversible and chance of recovery
- Presence of hematologic manifestations, hypertension, and proteinuria in some patients

Examples:

- VEGF inhibitors (eg, bevacizumab)
- Proteasome inhibitors
- Carfilzomib

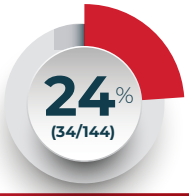
Other drugs with known association to TMA[9-12]

Cancer therapies	Antimicrobials	Illicit drugs/ toxic substances	In the posttransplant setting	Other prescription medications	
ICIs (pembrolizumab, nivolumab)	Levofloxacin	Cocaine	CNIs (cyclosporine A, tacrolimus)	Quinine	Oxymorphone ER
Docetaxel	Sulfisoxazole	Triclene	mTOR inhibitors (everolimus)	Valproic acid	Quetiapine
TKIs (eg, sunitinib)				Oxycodone hydrochloride ER	Onasemnogene abeparvovec

The medications shown are not meant to be an exhaustive or comprehensive list, but a selective representation for educational purposes.

In a retrospective study of 564 patients with TMA in France, those caused by drug therapies (n=144) are at risk for poor outcomes[4]:

Dialysis:



Death:

Drug-induced TMA and atypical-HUS can be difficult to differentiate.[8,10] Persistent TMA after stopping the offending agent may suggest underlying atypical-HUS.[13,14]

[a]Clinical outcomes during hospitalization in a retrospective study of 564 patients with TMA in France. Of the 144 patients whose TMA was drug associated, 98 patients were on anticalcineurin inhibitors, 11 patients were on gemcitabine, and 4 patients were taking a VEGF inhibitor.[4]

Atypical-HUS=atypical hemolytic uremic syndrome; CNI=calcineurin inhibitor; ER=extended-release; ICI=immune checkpoint inhibitor; mTOR=mechanistic target of rapamycin; TKI=tyrosine kinase inhibitor; TMA=thrombotic microangiopathy; VEGF=vascular endothelial growth factor.

The diagnostic challenge: Distinguishing between cancer-associated TMA and atypical-HUS can be difficult[7,15]

In an analysis of patients in the Global aHUS Registry, of the cases with a single identifiable cause (n=307)[16,a]:

Cancers were **one of the most common triggers** of atypical-HUS, affecting **18.9% (58/307) of patients**[16]

Median time from diagnosis of cancer to onset of atypical-HUS was **22.4 months**[16]

The median age at aHUS onset for patients with cancer and atypical-HUS was **~62 years**[17]

Atypical-HUS may present in patients with or without underlying pathogenic complement genetic variants[16]

- Only **4 of 37 tested patients (10.8%)** with cancer had a pathogenic complement genetic variant and/or anti-CFH antibodies
- Despite a negative test for genetic variant and/or anti-CFH antibodies, your patients **may still be at risk for onset of atypical-HUS**

[a]Patients with multiple associated triggers or clinical conditions were excluded from the primary analysis population.

aHUS=atypical hemolytic uremic syndrome; atypical-HUS=atypical hemolytic uremic syndrome; CFH=complement factor H; TMA=thrombotic microangiopathy.

A timely and accurate diagnosis of atypical-HUS is critical to inform management decisions and improve patient outcomes.[1,13]

Actor Portrayal.

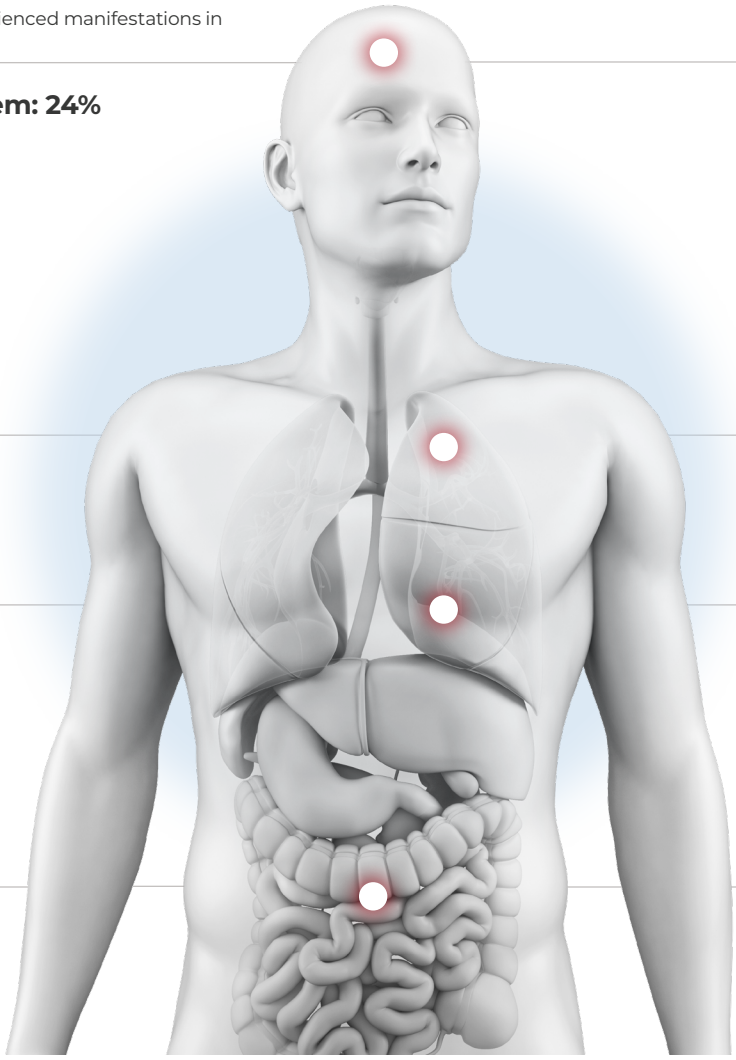
Recognizing the signs and symptoms of atypical-HUS in your patients with cancer

Many patients with cancer **had eGFR <40 mL/min/1.73 m²** closest to onset of atypical-HUS, **indicating kidney injury**[16]

Normal eGFR: ≥90 mL/min/1.73 m².[18]

Extrarenal manifestations in patients with cancer and atypical-HUS[16,a]:

Some patients may have experienced manifestations in >1 organ class.



Central nervous system: 24%

(n=14/58)

- Seizures
- Altered consciousness
- Headaches
- Visual disturbances

Pulmonary: 26%

(n=15/58)

- Pulmonary edema
- Pulmonary embolism
- Pulmonary hemorrhage

Cardiovascular: 48%

(n=28/58)

- Hypertension
- Heart failure
- Myocardial infarction

Gastrointestinal: 45%

(n=26/58)

- Abdominal pain
- Diarrhea
- Vomiting

In general, these symptoms can present in atypical-HUS as[19,b]:

[a]From an analysis of patients in the Global aHUS Registry (N=307), of whom 58 patients had cancer as an identifiable trigger of atypical-HUS. Patients with multiple associated triggers or clinical conditions were excluded from the primary analysis population.[16]

[b]From a review integrating findings from national registries, multicenter cohorts, and published case series to describe the spectrum, prevalence, and clinical outcomes of extra-renal manifestations in atypical-HUS.[19]

The signs and symptoms shown are not meant to be an exhaustive or comprehensive list, but a selective representation for educational purposes.

aHUS=atypical hemolytic uremic syndrome; atypical-HUS=atypical hemolytic uremic syndrome; eGFR=estimated glomerular filtration rate; TMA=thrombotic microangiopathy.

Cancer-associated TMA and atypical-HUS are difficult to distinguish. Consider atypical-HUS when the clinical course of cancer-associated TMA is unusually aggressive and unresponsive to conventional treatment.[1,7,15]

Diagnostic algorithm

Connecting the dots: Screen for and diagnose atypical-HUS in the presence of cancer and certain drugs with persistent TMA

Identify the TMA and review patient's family and medical history[1]

Thrombocytopenia
Platelet count <150 x 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 SYMPTOMS

- **Neurological symptoms**
- **Kidney impairment**
- **Gastrointestinal symptoms**

OTHER SYMPTOMS

- **Cardiovascular symptoms**
- **Pulmonary symptoms**
- **Visual symptoms**

Determine the cause of TMA with confirmatory testing[a]

TTP[b]
- ADAMTS13 activity ≤5%-10%

Atypical-HUS
ADAMTS13 activity >5%

STEC-HUS
- Shiga toxin/EHEC positive

Adapted from Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11)(suppl 11):2-15.

[a]Consider a coagulation panel to confirm or rule out DIC.[13]
[b]PLASMIC score ≥5.[20]

If atypical-HUS is identified, rapid management is critical to patient outcomes.[1,13]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; atypical-HUS=atypical hemolytic uremic syndrome; APS=antiphospholipid syndrome; DIC=disseminated intravascular coagulation; EHEC=enterohemorrhagic *Escherichia coli*; INR=international normalized ratio; LDH=lactate dehydrogenase; PLASMIC=platelets, hemolysis, anemia, schistocytes, mean corpuscular volume increased, and INR <1.5, and creatinine <2; PCR=polymerase chain reaction; SLE=systemic lupus erythematosus; STEC-HUS=Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

Case study: Management of atypical-HUS in a patient with cancer[21]

Mary

Overview:

- 39-year-old woman with recently diagnosed left breast invasive ductal carcinoma reported to outpatient clinic for cycle 1 of dose-dense doxorubicin and cyclophosphamide
- Pre-labs drawn prior to chemotherapy indicated anemia, thrombocytopenia, and kidney impairment

Hypothetical case based on a real patient.

Actor Portrayal.

Medications prior to hospital admission:

- Antihypertensive
- Calcium acetate
- Prednisone

Initial presentation:

- **Vitals:** BP (mmHg): 138/94; HR (bpm): 74
- **Physical examination:** Unremarkable with the exception of mild lower extremity edema
- **Initial labs:**
  Hb (g/dL): 8.0; Plts (x 10^3 mcL): 65; LDH (U/L): 631; SCr (mg/dL): 4.59

Day 0 (Community Hospital)

- TTP was initially suspected
- ADAMTS13 testing was performed, followed by the initiation of plasma exchange
- Started on an antihypertensive medication, diuretics, and prednisone

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; AKI=acute kidney injury; atypical-HUS=atypical hemolytic uremic syndrome; BP=blood pressure; Hb=hemoglobin; HR=heart rate; LDH=lactate dehydrogenase; Plts=platelets; SCr=serum creatinine; TTP=thrombotic thrombocytopenic purpura.

Days 1-12 (Community Hospital)

Day 10

- ADAMTS13 results came back at 62%
- PLEX was discontinued

Day 11

- Kidney biopsy was performed and showed thrombotic microangiopathy
- Presence of schistocytes, elevated LDH, thrombocytopenia, and kidney biopsy confirmed diagnosis of atypical-HUS

Days 13-42 (Academic Center)

Day 13:

- Mary was transferred to an academic center
- Mary received required meningococcal vaccinations and was started on antibiotic prophylaxis

Day 14:

- C5 inhibition was initiated

Day 42

- Platelets had doubled by Day 42
- Mary was discharged
- Became dialysis dependent and will continue dialysis as an outpatient

Laboratory values[21,22]

	Day 0	Day 1	Day 5	Day 7	Day 10	Day 13	Day 14	Day 15	Day 30	Day 42
	PLEX started at community hospital	Chemotherapy given at community hospital			**ADAMTS13** results came back and PLEX discontinued	Transfer to academic center	**C5 therapy** started			Started on dialysis and will continue as an outpatient
Hb (g/dL) Ref values: 12-16	8.0	7.2	6.6	6.7	7.5			7.1	7.0	8.0
Plts (x 10^3 mcL) Ref values: 150-350	65	67	109	101	74			100	94	177
LDH (U/L) Ref values: 60-160	631	675	858	891	1297			870	778	550
SCr (mg/dL) Ref values: 0.5-1.0	4.59	4.97	6.32	7.23	9.15			11.32	8.48	4.99

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; atypical-HUS=atypical hemolytic uremic syndrome; C5=complement component 5; Hb=hemoglobin; LDH=lactate dehydrogenase; PLEX=plasma exchange; Plts=platelets; SCr=serum creatinine; TTP=thrombotic thrombocytopenic purpura.

Summary

Early recognition and management of TMA and the rapid diagnosis of atypical-HUS are critical to patient outcomes[1,13]

According to one analysis of the Global aHUS Registry, **cancer is a common identifiable trigger of atypical-HUS**, occurring in 18.9% (58/307) of patients[16,a]

If TMA persists despite removal of the offending agent, this may indicate underlying atypical-HUS[1,13,14]

Rapid identification of TMA, diagnosis of atypical-HUS, and early disease management are crucial in improving clinical outcomes[1,13]

Actor Portrayal.

[a]In an analysis of patients in the Global aHUS Registry with a single associated trigger or clinical condition (N=307). Patients with multiple associated triggers or clinical conditions were excluded from the primary analysis population.[16]

aHUS=atypical hemolytic uremic syndrome; atypical-HUS=atypical hemolytic uremic syndrome; CFH=complement factor H; TMA=thrombotic microangiopathy.

References: 1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11)(suppl 11):2-15. **2.** Dong G, et al. *Medicine (Baltimore).* 2024;103(35):e39431. **3.** Font C, et al. *Support Care Cancer.* 2022;30(10):8599-8609. **4.** Bayer G, et al. *Clin J Am Soc Nephrol.* 2019;14(4):557-566. **5.** Decaestecker A, et al. *Nephrol Dial Transplant.* 2023;38(4):913-921. **6.** Wada H, et al. *Thromb J.* 2018:16:14. **7.** Vorobev A, et al. *Int J Mol Sci.* 2024;25(16):9055. **8.** Aklilu AM, Shirali AC. *Kidney360.* 2023;4(3):409-422. **9.** Mazzierli T, et al. *Front Pharmacol.* 2023;13:1088031. **10.** Izzedine H, Perazella MA. *Am J Kidney Dis.* 2015;66(5):857-868. **11.** Gudsoorkar P, et al. *Semin Nephrol.* 2022;42(6):151345. **12.** Ávila A, et al. *Front Med (Lausanne).* 2021;8:642864. **13.** Azoulay E, et al. *Chest.* 2017;152(2):424-434. **14.** Asif A, et al. *J Nephrol.* 2017;30(3):347-362. **15.** Java A, Kim AHJ. *J Rheumatol.* 2023;50(6):730-740. **16.** Licht C, et al. *Nephrology (Carlton).* 2024;29(8):519-527. **17.** Licht C, et al. *Nephrology (Carlton).* 2024;29(suppl 8):519-527. **18.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int.* 2024;105(4S):S117-S314. **19.** Formeck C, Swiatecka-Urban A. *Pediatr Nephrol.* 2019;34(8):1337-1348. **20.** Wynick C, et al. *Thromb Res.* 2020:196:335-339. **21.** Data on file. Alexion Pharmaceuticals, Inc.; 2025. **22.** Merck Manual. Merck & Co. Inc.; Rahway, NJ; 2022.

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