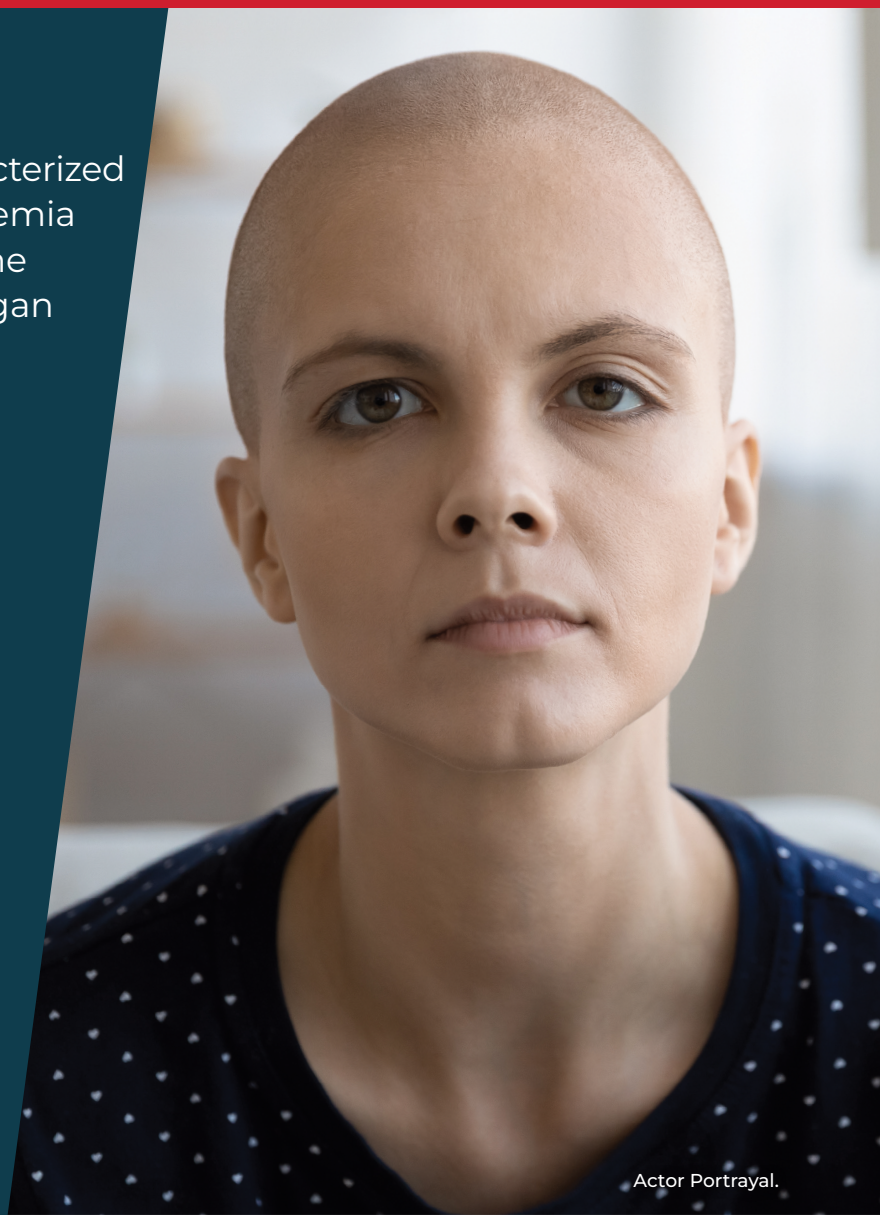
Identifying atypical-HUS in the presence of cancer or drug therapies

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 one or more signs and symptoms of organ damage, 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]

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



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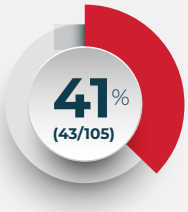
Don’t miss the signs: TMA may be overlooked in patients with cancer[3]

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

had **cancer as an identifiable cause**

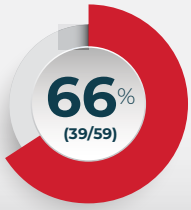


of those cases **were adenocarcinoma**

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

- 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 cases, **cancer was diagnosed at the same time** as TMA[5,b]

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 hypertension, 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]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]

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

Vigilance required: TMA triggered by cancer therapies may be more common than realized[7]

Chemotherapy-associated TMA[7]:

- 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[7-9]:

- 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 1 or more signs and symptoms of organ damage.[3]

CKD=chronic kidney disease; MAHA=microangiopathic hemolytic anemia; TMA=thrombotic microangiopathy.

Exploring the links: Known therapies associated with TMAs[7,9]

Type I Cancer Drug–induced TMA[7,9]

Dose/duration-related toxicity

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
- Bleomycin
- Carboplatin
- Gemcitabine
- Cisplatin
- Oxaliplatin

Type II Cancer Drug–induced TMA[7,9]

Immune-mediated reactions

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 (eg, bortezomib)
- Carfilzomib

Other drugs reported to be associated with TMA[8-13]

Cancer therapies	Antimicrobials		Illicit drugs/ toxic substances	In the posttransplant setting	Other prescription medications	
ICIs (nivolumab, atezolizumab)	Levofloxacin	Foscarnet[a]	Cocaine	CNIs (cyclosporine A, tacrolimus)	Quinine	Oxymorphone ER
Docetaxel	Sulfisoxazole	Micafungin[a]	Triclene	mTOR inhibitors (everolimus)	Valproic acid	Quetiapine
TKIs (eg, sunitinib)	Atovaquone[a]	–	–	–	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,b]:

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.[14,15]

[a]The package insert did not suggest a risk for TMA.[13]

[b]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 was diagnosed by the treating physician with no standardized criteria for atypical-HUS diagnosis and no central confirmation of diagnosis conducted.

CNI=calcineurin inhibitor; ER=extended release; HUS=hemolytic uremic syndrome; 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[16,17]

In an analysis of patients in the Global aHUS Registry, of the cases with a single identifiable cause (N=307)[18,a]:

Cancers were **one of the most common triggers** of atypical-HUS, affecting **18.9% (58/307) of patients**[18]

The median time from diagnosis of cancer to onset of atypical-HUS was **22.4 months**[18]

The median age at atypical-HUS onset for patients with cancer and atypical-HUS was **~62 years**[19]

Atypical-HUS may present in patients with or without underlying pathogenic complement genetic variants[18]

- 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. Atypical-HUS was diagnosed by the treating physician with no standardized criteria for atypical-HUS diagnosis and no central confirmation of diagnosis conducted.[18]

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

A timely and accurate diagnosis of atypical-HUS is critical to inform management decisions and improve patient outcomes.[1,14]

Actor Portrayal.

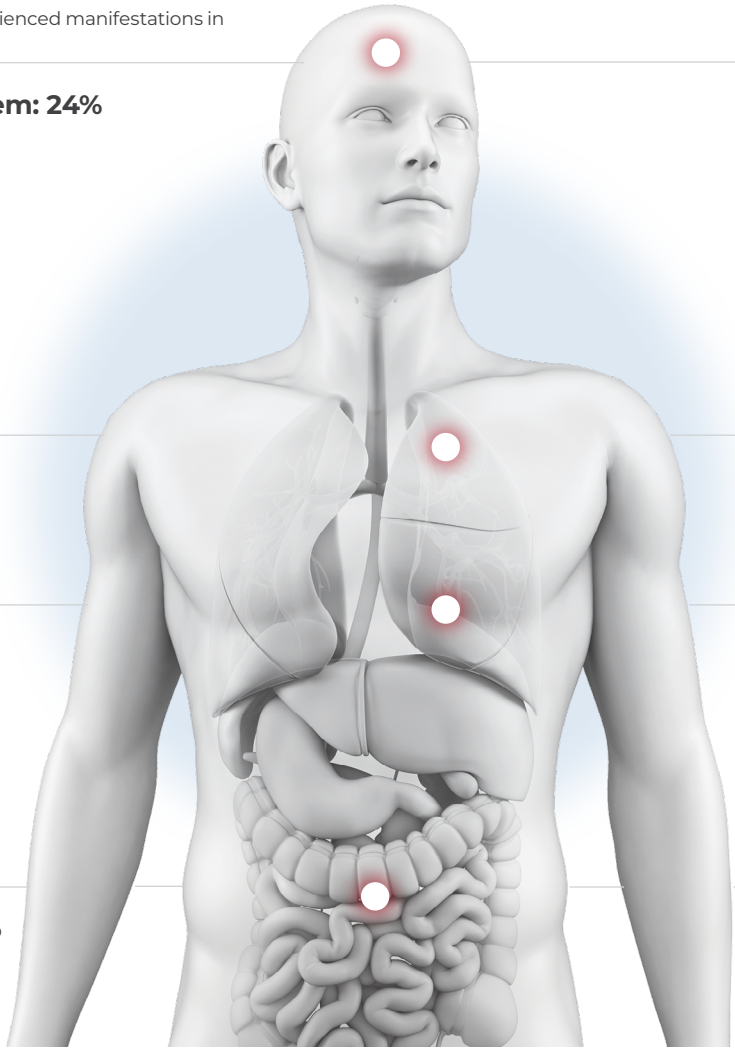
Recognizing the signs and symptoms of atypical-HUS in your patients with cancer

Many patients with cancer **had eGFR <40 mL/min/1.73 m²** closest to onset of atypical-HUS, **indicating kidney injury**[18]

Normal eGFR: ≥90 mL/min/1.73 m².[20]

Extrarenal manifestations in patients with cancer and atypical-HUS[18,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[21,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.[18]

[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.[21]

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

Cancer-associated TMA and atypical-HUS are difficult to distinguish. There are no specific clinical guidelines for differentiating between cancer-induced TMA and cancer-triggered atypical-HUS.[1,16]

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 the 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]
- ≤10% ADAMTS13 activity[c]

Atypical-HUS
>10% ADAMTS13 activity[d]

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.[14]
[b]PLASMIC score >5.[22]
[c]Values in literature range from <5%-10%.[1]
[d]Values in literature range from >5%-10%.[1]

If atypical-HUS is identified, rapid management is critical to patient outcomes.[1,14]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; DIC=disseminated intravascular coagulation; EHEC=enterohemorrhagic *Escherichia coli*; HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; PLASMIC=platelets, hemolysis, anemia, schistocytes, mean corpuscular volume increased, and international normalized ratio <1.5, and creatinine <2; 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[23]

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 (mm Hg): 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; BP=blood pressure; Hb=hemoglobin; HR=heart rate; HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; Plts=platelets; SCr=serum creatinine; TTP=thrombotic thrombocytopenic purpura.

Days 1-11 (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

Laboratory values[23,24]

	Day 0	Day 1	Day 5	Day 7	Day 10
	PLEX started at community hospital	Chemotherapy given at community hospital			**ADAMTS13** results came back and PLEX discontinued
Hb (g/dL) Ref values: 12-16	8.0	7.2	6.6	6.7	7.5
Plts (x 10^3 mcL) Ref values: 150-350	65	67	109	101	74
LDH (U/L) Ref values: 60-160	631	675	858	891	1297
SCr (mg/dL) Ref values: 0.5-1.0	4.59	4.97	6.32	7.23	9.15

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; Hb=hemoglobin; HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; PLEX=plasma exchange; Plts=platelets; SCr=serum creatinine.

Summary

Early recognition and management of TMA and the rapid diagnosis of atypical-HUS are critical to patient outcomes[1,14]

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[18,a]

If TMA persists despite removal of the offending agent, this may indicate underlying atypical-HUS[1,14,15]

Rapid identification of TMA, diagnosis of atypical-HUS, and early disease management are crucial in improving clinical outcomes[1,14]

ONESOURCE®
Personalized Patient Support from Alexion

Complimentary, personalized patient support program

We can help with:

- Providing educational materials about atypical-HUS along the journey
- Connecting patients for peer-to-peer discussions through Peer Connects
- Sharing information about live and virtual community events, advocacy groups, and other resources
- Offering support for patients and their healthcare providers in navigating insurance coverage and access

[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. Atypical-HUS was diagnosed by the treating physician with no standardized criteria for atypical-HUS diagnosis and no central confirmation of diagnosis conducted.[18]

aHUS=atypical hemolytic uremic syndrome; HUS=hemolytic uremic syndrome; 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.** Aklilu AM, Shirali AC. *Kidney360*. 2023;4(3):409-422. **8.** Mazzierli T, et al. *Front Pharmacol*. 2023;13:1088031. **9.** Izzedine H, Perazella MA. *Am J Kidney Dis*. 2015;66(5):857-868. **10.** Gudsoorkar P, et al. *Semin Nephrol*. 2022;42(6):151345. **11.** Ávila A, et al. *Front Med (Lausanne)*. 2021;8:642864. **12.** Klomjit N, et al. *Am J Hematol*. 2023;98(12):E369-E372. **13.** Yin Y, et al. *Front Pharmacol*. 2025;16:1658963. **14.** Azoulay E, et al. *Chest*. 2017;152(2):424-434. **15.** Asif A, et al. *J Nephrol*. 2017;30(3):347-362. **16.** Vorobev A, et al. *Int J Mol Sci*. 2024;25(16):9055. **17.** Java A, Kim AHJ. *J Rheumatol*. 2023;50(6):730-740. **18.** Licht C, et al. *Nephrology (Carlton)*. 2024;29(8):519-527. **19.** Licht C, et al. Supplementary material. *Nephrology (Carlton)*. 2024;29(8):519-527. **20.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int*. 2024;105(4S):S117-S314. **21.** Formeck C, Swiatecka-Urban A. *Pediatr Nephrol*. 2019;34(8):1337-1348. **22.** Wynick C, et al. *Thromb Res*. 2020:196:335-339. **23.** Data on file. Alexion Pharmaceuticals, Inc.; 2025. **24.** Merck Manual. Merck & Co. Inc.; Rahway, NJ; 2022.

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