



Thrombotic microangiopathy (TMA) in adult patients with solid tumors: a challenging complication in the era of emerging anticancer therapies

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Abstract

Thrombotic microangiopathy (TMA) is a syndrome that encompasses a group of disorders defined by the presence of endothelial damage leading to abnormal activation of coagulation, microangiopathic hemolytic anemia and thrombocytopenia, occlusive (micro)vascular dysfunction, and organ damage. TMA may occur in patients with malignancy as a manifestation of cancer-related coagulopathy itself or tumor-induced TMA (Ti-TMA) as a paraneoplastic uncommon manifestation of Trousseau syndrome. TMA can also be triggered by other overlapping conditions such as infections or more frequently as an adverse effect of anticancer drugs (drug-induced TMA or Di-TMA) due to direct dose-dependent toxicity or a drug-dependent antibody reaction. The clinical spectrum of TMA may vary widely from asymptomatic abnormal laboratory tests to acute severe potentially life-threatening forms due to massive microvascular occlusion. While TMA is a rare condition, its incidence may progressively increase within the context of the great development of anticancer drugs and the emerging scenarios in supportive care in cancer. The objective of the present narrative review is to provide a general perspective of the main causes, the key work-up clues that allow clinicians to diagnose and manage TMA in patients with solid tumors who develop anemia and thrombocytopenia due to frequent overlapping causes.

Keywords Thrombotic microangiopathy · Cancer-associated coagulopathy · Cancer-associated thrombocytopenia

Introduction

Thrombotic microangiopathy (TMA) is clinically defined as the presence of fragmentation hemolysis/microangiopathic hemolytic anemia (MAHA) and thrombocytopenia (MAHAT) leading to microvascular occlusion and different

levels of end-organ injury [1, 2]. The TMA syndromes include a complex group of clinical entities that share the same pathological features: microvascular endothelial damage involving arteriolar and capillary vessels with characteristic proliferation in the myocyte layer and the presence of fibrin or platelet aggregates or platelet/fibrin aggregates in the lumen and the vessel wall leading to the formation of microthrombi and microvascular occlusion. The adhesion of leukocytes to the damaged endothelial wall and abnormal von Willebrand factor (vWF) release can contribute to the progression of intravascular thrombosis, complement consumption, enhanced vascular shear stress, and decreased endothelial thromboresistance [1, 2].

The clinical spectrum of TMA is wide in relation to the etiology (hereditary and acquired causes), the target population primarily affected (children or adults) and the severity (mild to life-threatening forms). Significant advances have been achieved in recent years regarding the knowledge of the pathogenesis and the underlying conditions associated with the development of TMA since the first description by

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Moschcowitz in 1924 [3] and the historical description of thrombotic thrombocytopenic purpura (TTP) with predominant neurological involvement and the Shiga-toxic hemolytic uremic syndrome (HUS) for kidney dominant disease. The current clinical classification considers “primary TMA syndromes” as those described by evidence supporting a definite cause including four hereditary and five acquired disorders summarized in Table 1 [1, 2]. Of note, the underlying congenital cause may not be clinically expressed until a triggering condition, such as pregnancy, surgery, or an inflammatory disorder, precipitates an acute TMA episode. The treatment of patients with primary TMA syndromes is focused on the underlying condition.

On the other hand, the development of TMA may occur as a “secondary manifestation” of another underlying systemic condition such as infections, preeclampsia, autoimmune diseases, or cancer as shown in Table 2 [1]. In the context of patients with cancer, TMA can occur as an uncommon systemic manifestation of the complex cancer-associated coagulopathy itself [4–8] or as an adverse event of anticancer therapies or drug-induced TMA (Di-TMA) due

to non-dose-related idiosyncratic immunologic reactions or direct drug toxicity dependent on dose and timing [9]. Overall, overt TMA is a rare condition in daily oncological practice. However, the progressive increase of survival of patients with advanced cancer receiving successive lines of therapy [10] and the accelerated emergence of anticancer drugs in recent years has led to considering the diagnosis of TMA in a growing number of patients with cancer that present with hematological abnormalities.

The present narrative review focuses on the main causes associated with the development of TMA in patients with cancer, and practical work-up clues for clinicians to achieve correct differential diagnosis and management of TMA in the setting of patients with solid tumors.

Tumor-induced TMA

The pathogenesis of cancer-associated thrombosis is complex and multifactorial. On one hand, the cancer-associated thrombophilic state may be favored by several clinical risk

Table 1 Primary thrombotic microangiopathy (TMA) syndromes. Adapted from George JN [1]

Name	Cause	Clinical features
Hereditary disorders:		
ADAMTS13 deficiency-mediated TMA (also called TTP)	Homozygous or compound heterozygous ADAMTS13 mutations Mutations in CFH, CFI, CFB, C3, CD46, and other complement genes causing uncontrolled activation of the alternative pathway of complement	Initial presentation is typically in children. Acute kidney injury is uncommon. Patients with heterozygous mutations are asymptomatic
Complement-mediated TMA	Homozygous mutations in NMACHC (encoding methylmalonic aciduria and homocystinuria type C protein)	Initial presentation is often in children. Acute kidney injury is uncommon. Patients with heterozygous mutations may be asymptomatic
Metabolism-mediated TMA	Homozygous mutations in DGKE; mutations in plasminogen and thrombomodulin also implicated	Initial presentation is often in children < 1 year of age. Reported in one young adult with hypertension and acute kidney injury
Coagulation-mediated TMA		Initial presentation with acute kidney injury is typically in children < 1 year of age with DGKE mutations
Acquired disorders		
ADAMTS13 deficiency-mediated TMA (also called TTP)	Autoantibody inhibition of ADAMTS13 activity Enteric infection with a Shiga toxin-secreting strain of <i>Escherichia coli</i> or <i>Shigella dysenteriae</i>	Initial presentation is uncommon in children Acute kidney injury is uncommon Initial presentation is more common in young children, typically with acute kidney injury.
Shiga toxin-mediated TMA (also called ST-HUS)	Drug-induced antibodies, usually multiple cells affected Multiple potential mechanisms (e.g., VEGF inhibition)	Most cases are sporadic. Large outbreaks may occur Initial clinical presentation is acute kidney injury in children or adults
Complement-mediated TMA		Initial presentation is a sudden onset of severe systemic symptoms with anuric acute kidney injury
Drug-mediated TMA (immune reaction)		Gradual onset of renal failure occurs over weeks or months
Drug-mediated TMA (toxic dose-related reactions)		

ADAMTS13 a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13, DGKE diacylglycerol kinase, ST-HUS Shiga toxin-hemolytic uremic syndrome, TMA thrombotic microangiopathy, TTP thrombotic thrombocytopenic purpura, VEGF vascular endothelial growth factor

Table 2 Common disorders that may present with TMA as a secondary manifestation in the course of the disease. Adapted from George JN [1]

Disorder	Specific conditions
Solid tumors	Paraneoplastic or tumor-induced TMA (Ti-TMA): usually advanced cancer with systemic microvascular metastasis Drug-induced TMA (Di-TMA)
Hematologic	Aggressive non-Hodgkin lymphoma Chronic lymphocytic leukemia Myeloma Hematopoietic stem-cell transplantation
Severe arterial hypertension	Malignant hypertension Preeclampsia Eclampsia HELLP syndrome
Autoimmune	Systemic lupus erythematosus–lupus nephritis Systemic sclerosis Catastrophic antiphospholipid syndrome
Systemic infection	Viral: HIV, CMV, dengue, influenza, adenovirus, COVID-19 Fungal: aspergillus, mucormycosis Bacterial: tuberculosis Parasite: malaria
Other	Severe vitamin B12 deficiency (pseudo-thrombotic microangiopathy) Organ transplantation Surgery Any condition associated with DIC

CMV cytomegalovirus, COVID-19 coronavirus disease 2029, DIC disseminated intravascular coagulation, HELLP hemolysis, elevated liver-enzyme levels, and low platelets, HIV human immunodeficiency virus

factors including those related to vascular compression, surgery, immobility, or anticancer therapies, amongst the most common. Moreover, the malignant cells themselves and the neoplastic tissue as a whole are capable of interacting and activating the host hemostatic system and inducing hemostatic abnormalities most commonly favoring a prothrombotic balance in the host [11]. The clotting system may be directly activated by the malignant cells by the expression of tissue factor (TF), TF-bearing procoagulant microparticles and other molecules that interfere with the hemostatic system. Cancer cells may also promote the activation of blood coagulation by favoring the activation of host platelet, leukocyte and endothelial cell coagulation through direct cell–cell contact by specific surface adhesion receptors, and/or by the release of inflammatory cytokines and proangiogenic and growth-stimulating factors. The activation of platelets, leukocytes and endothelial cells favors the release of blood-cell procoagulant microparticles and neutrophil extracellular traps [6–8, 11]. Altogether, these pathological phenomena in the microcirculation contribute to the development of newly formed microvessels and local tumoral microthrombi that ultimately lead to the development of paraneoplastic or cancer-associated thrombosis broadly known as the Trousseau syndrome [4–6, 11, 12]. The most frequent clinical presentation of cancer-associated thrombosis is as venous thromboembolism including deep vein thrombosis and pulmonary embolism. Less frequently, cancer-associated coagulopathy may present as arterial thrombosis, characteristic

paraneoplastic migratory superficial thrombophlebitis, verrucous endocarditis, and systemic syndromes including disseminated intravascular coagulopathy (DIC) and TMA due to cancer itself or tumor-induced TMA (Ti-TMA) [7, 8]. The specific pathogenesis of Ti-TMA is not fully understood. MAHAT usually occurs in the context of advanced cancer with systemic microvascular metastases causing small vessel obstruction, blood cell damage, red cell fragmentation, and systemic thrombus formation with platelet consumption involving small or larger vessels. MAHAT may also occur in the context of extensive bone marrow infiltration by cancer cells or secondary necrosis [7, 13].

The incidence of Ti-TMA is unknown taking into account that subclinical cases with only abnormal laboratory abnormalities may occur, and that mild forms have probably been underreported in the medical literature. Overt cancer-associated MAHA-MAHAT is uncommon in daily practice with an estimated incidence of about 0.25 to 0.45 patients per million per year. The first description of TMA associated with stomach and lung cancers was published in 1962 by Brain et al. [14]. Since then, the clinical description of TMA as a rare paraneoplastic syndrome has been reported in several case reports and small case series comprehensively reviewed by several authors [15–19]. Ti-TMA has mainly been described as the initial presentation of solid organ malignancies usually associated with disseminated malignancy and adverse short-term outcomes and occasionally in the course of cancer progression or cancer recurrence. In a recent

systematic review by Lechner [18] including 168 cases of presumed Ti-TMA by excluding patients with cancer and potentially drug-induced and postoperative MAHA reported in the literature since 1979, the most frequent tumors were gastric, breast, prostate, lung, and cancer of unknown origin with 44, 36, 23, 16, and 12 cases, respectively. Of note, the median age of patients with gastric cancer with MAHA was 52 years (5 years younger than patients without MAHA). Cancer was metastatic in 91.8% of cases. Bone marrow infiltration by cancer cells was reported in 99/111 (81.1%) of the evaluable cases. Bone marrow infiltration was sometimes associated with bone marrow necrosis or fibrosis. Tumor emboli in the marrow have also been found in some cases at autopsy [20].

The clinical presentation of Ti-TMA may range from minimal abnormalities to a life-threatening condition. The clinical features may be as MAHA-MAHAT alone as a hematological finding or with clinical pictures mimicking other TMA conditions such as a TTP-like syndrome if fever or transient focal neurological abnormalities occur or as a HUS-like syndrome if there is kidney involvement. Pulmonary-TMA has also been described as the initial manifestation of metastatic solid tumors in adult patients presenting with MAHA, as well as respiratory symptoms and pulmonary infiltrates usually with short-term adverse outcomes [21, 22]. In the review by Lechner [18] pulmonary involvement was documented in 49 cases in whom the pathological histologic findings (most at autopsy) showed pulmonary carcinomatous lymphangitis, pulmonary microvascular tumor emboli and pulmonary microangiopathy abnormalities.

Drug-mediated TMA in patients with solid tumors

Pathophysiology

TMA has been associated with many drugs, although definitive causality has only been established in relatively few [23–25]. Drug-mediated TMA with endothelial damage leading to platelet aggregation and microthrombi predominantly in glomerular capillaries and arterioles occurs with cumulative renal damage by two main mechanisms:

(i) Direct dose- and time-dependent endothelial toxicity. Evidence supporting a causal role is limited. There may be multiple mechanisms for toxic drug-mediated kidney injury. Among the likely roles there is the potential inhibition of prostacyclin leading to endothelial dysfunction and increased platelet aggregation by calcineurin inhibitors (cyclosporine, tacrolimus), or inhibition of vascular endothelial growth factor (VEGF) in renal endothelial cells and podocytes causing gradual development of glomerular TMA. The typical presentation is related to slowly progressive kidney injury

frequently associated with arterial hypertension, although abrupt and severe TMA may also occur. The hematological abnormalities due to MAHAT often resolve while renal failure may persist.

(ii) Non-dose related idiosyncratic reactions or immune-mediated damage. The production of antibodies and immune complexes are able to react and activate multiple cell types including platelets, monocytes, and endothelial cells. The deposition of immune complexes often presents with abrupt onset of severe systemic symptoms, often with anuric acute kidney injury within hours after drug exposure that recur with drug administration. Chronic kidney disease with hypertension is common and end-stage renal disease may occur.

However, the specific mechanism of drug-induced TMA (Di-TMA) remains unclear for many drugs. Notably, the development of antibodies against a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13) have been reported leading to ADAMTS13 deficiency and drug-induced TTP. An aberrant uncontrolled activation of the alternative complement pathway leading to platelet aggregation and endothelial damage has also been suggested in some case reports.

Apart from the common drugs used in oncology, some medications used for other co-morbidities or as supportive treatment in cancer such as ticlopidine, clopidogrel and alendronate have been identified as probable causes of TMA.

The first description of Di-TMA was reported in 1970 with quinine, and one year later the first anticancer drug Di-TMA was reported by Liu et al. [26] with mitomycin C (MMC), an antibiotic that works as a cell-cycle specific alkylating agent and is still used in bladder cancer. The pathogenesis of MMC-related Di-TMA is dose dependent [27]. The second anticancer drug described and having the strongest evidence as a cause of Di-TMA is gemcitabine, a pyrimidine analog currently used for several tumors. The mechanism associated with gemcitabine toxicity leading to TMA can be either dose-dependent or idiosyncratic [28].

Currently, there is a fast-growing list of potential TMA triggers within the setting of anticancer therapies. Several comprehensive reviews in recent years have examined case reports and series of patients [23–25, 29–32]. Table 3 summarizes the reported chemotherapy drugs associated with the development of Di-TMA and the mechanisms involved.

Great advances in the development in target anticancer drugs such as anti-angiogenic drugs and tyrosine kinase inhibitors (TKIs) have been achieved in the last decade. TKIs inhibit the intracellular signaling pathways of numerous tyrosine kinase receptors such as the VEGF receptor. VEGF is produced by podocytes and is critical in blood vessel growth as it regulates the integrity and function of the actin skeleton of endothelial cells [19, 33, 34]. Thus, the glomerular endothelium is particularly susceptible to

Table 3 Anticancer agents associated with the development of drug-induced TMA

Drug	Drug mechanism	Proposed TMA mechanism
Mitomycin C	Alkylating agent	Direct endothelial damage. Cumulative dose > 40–50 mg/m ² Immune-mediated damage Prostacyclin inhibition
Gemcitabine	Pyrimidine analog	Direct endothelial damage. Median cumulative dose > 20 gr/m ² Drug-dependent antibodies Alternative complement pathway dysregulation
Cisplatin Oxaliplatin Carboplatin	Platinum-based alkylating agents	Direct endothelial damage? (Cisplatin) Drug dependent antibodies? (Oxaliplatin) Unknown (Carboplatin)
Pegilated Doxorubicin	Anthracyclines alkylating agents	Unknown—coadministration with other potential triggers Direct endothelial and epithelial (podocyte) damage Cumulative dose > 880–1445 mg/m ²
Docetaxel Cabazitaxel Paclitaxel	Taxanes Microtubule inhibitors	Unknown—coadministration with other potential triggers inhibition of endothelial function and angiogenesis
Bleomycin	DNA strand breaks	Direct endothelial damage? Other potential triggers

VEGF inhibition. The inhibition of VEGF may occur by the development of antibody-mediated binding of the ligand (bevacizumab and aflibercept) or due to receptor inhibition (TKIs). The TMA induced by VEGF inhibitors is non-dose related and the usual clinical picture is a “preeclampsia-like” syndrome with arterial hypertension, proteinuria, TMA with severe renal damage, and similar histopathological findings. Several anti-TKIs have been related to the development of Di-TMA, mainly in case reports involving sunitinib, imatinib, or sorafenib. Both immune-mediated and direct endothelial toxicity mechanisms are probably involved in TKI-related TMA. Other targeted therapies commonly used in oncology have been associated with the development of Di-TMA, including palbociclib, cetuximab, trastuzumab, ramucirumab, and mTOR inhibitors (everolimus, sirolimus) [35].

The immune checkpoints are regulators of the immune system with a crucial role for self-tolerance and prevention of indiscriminate immune attack to self-proteins and healthy host cells. Immune checkpoint inhibitors (ICIs) are a new group of anticancer therapy formed by monoclonal antibodies that work by inhibiting self-tolerance pathways overexpressed on tumor cells or in the tumor microenvironment leading to an increase in endogenous immune response against tumors [36]. The currently approved ICIs include (i) atezolizumab that blocks the checkpoint proteins programmed death-ligand 1 (PD-L1) present on tumor cells or anti-PD-L1; (ii) pembrolizumab and nivolumab that block the checkpoint protein programmed death 1 (PD-1) or anti-PD1; and (iii) ipilimumab that blocks the cytotoxic T lymphocyte-associated protein 4 or anti-CTLA-4. ICIs allow the T cells to kill tumor cells and in recent years have become an emerging first line therapeutic strategy of immunotherapy for several solid organ and

hematologic malignancies. Unfortunately, ICIs have also been associated with the emergence of immune-related adverse events with clinical features such as autoimmune-like disorders with a wide range of clinical presentation. Regarding the development of potentially ICI-related TMA, some case reports have been published in the recent literature. In one out of 13 patients with ICI-induced acute kidney injury, Cortazar et al. [37] found TMA in the renal biopsy. A few other case reports have described patients with solid tumors who developed TMA with a temporal correlation with the use of ICIs [38–44]. The authors hypothesized on the potential causal role of ICIs for Di-TMA by the activation of cellular and humoral immune reactions, excessive inflammatory cytokine production or enhancement of complement-mediated inflammation. However, the data available from the reported cases including possible confounding factors (cancer itself, other concomitant drugs) does not allow clear causality to be established and the potential mechanisms involved remain uncertain. This is an area of great interest for further research given the great expansion in the use of ICIs in daily practice.

The targeted therapies and ICIs potentially associated with the development of TMA and the hypothesized mechanisms involved are shown in Table 4. A systematic review on the published reports of Di-TMA associated with cancer drugs with updated information from the Oklahoma University is available online [45].

Table 4 Targeted and immunotherapies associated with the development of TMA in patients with solid tumors

Agent	Drug mechanism	TMA mechanism
Bevacizumab Aflibercept	Monoclonal antibody anti-VEGF. Inhibition of angiogenesis	Dose or non-dose-dependent Direct endothelial damage VEGF pathway inhibition
Sunitinib Sorafenib Imatinib Cabozantinib	TKI	Direct endothelial damage VEGF pathway inhibition (sunitinib) Dose or non-dose-dependent? (imatinib, sorafenib)
Everolimus Sirolimus	mTOR inhibitors	Dose dependent Renal endothelial damage Alternative complement pathway dysregulation
Palbociclib	CDK inhibitor	Non-dose-dependent VEGF pathway inhibition
Ipilimumab Pembrolizumab Nivolumab	Checkpoint inhibition of PDL1, PD1 or CTLA proteins	Non-dose-dependent Immune system dysregulation? Can induce anti-ADAMTS13 antibodies?

ADAMTS13 a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13, *AKI* acute kidney injury, *CDK* cyclin-dependent kinase, *CTLA* cytotoxic T-lymphocyte-associated protein 4, *mTOR* mechanistic target of rapamycin, *PDI* programmed death 1, *PDL1* programmed death-ligand 1, *TKI* tyrosine kinase inhibitors, *TTP* thrombotic thrombocytopenic purpura, *VEGF* vascular endothelial growth factor

Work-up for TMA diagnosis in patients with solid tumors

Clinical presentation

TMA is a rare condition in patients with solid tumors showing a trend towards an increasing incidence due to better awareness of this complication, the progressive survival of patients achieved in recent years leading to greater number of lines of anticancer drugs for longer periods of time, and emerging drug-induced toxicities.

The initial definition of a TMA is clinical and is based on the presence of the following:

- Non-immune (negative Coombs test) intravascular anemia: high levels of serum lactate dehydrogenase, indirect or unconjugated bilirubin, and reticulocyte count with undetectable or markedly decreased levels of haptoglobin.
- Fragmented red cells or schistocytes in the blood smear (although non-obligatory criteria for the diagnosis of TMA).
- Thrombocytopenia.
- Clinical features related to microthrombosis leading to organ dysfunction most commonly acute kidney injury, proteinuria, and arterial hypertension. Other clinical findings include purpura, digital gangrene, neurologic involvement, including seizures and altered consciousness, gastrointestinal symptoms, pancreatitis, hepatitis, and pulmonary involvement.

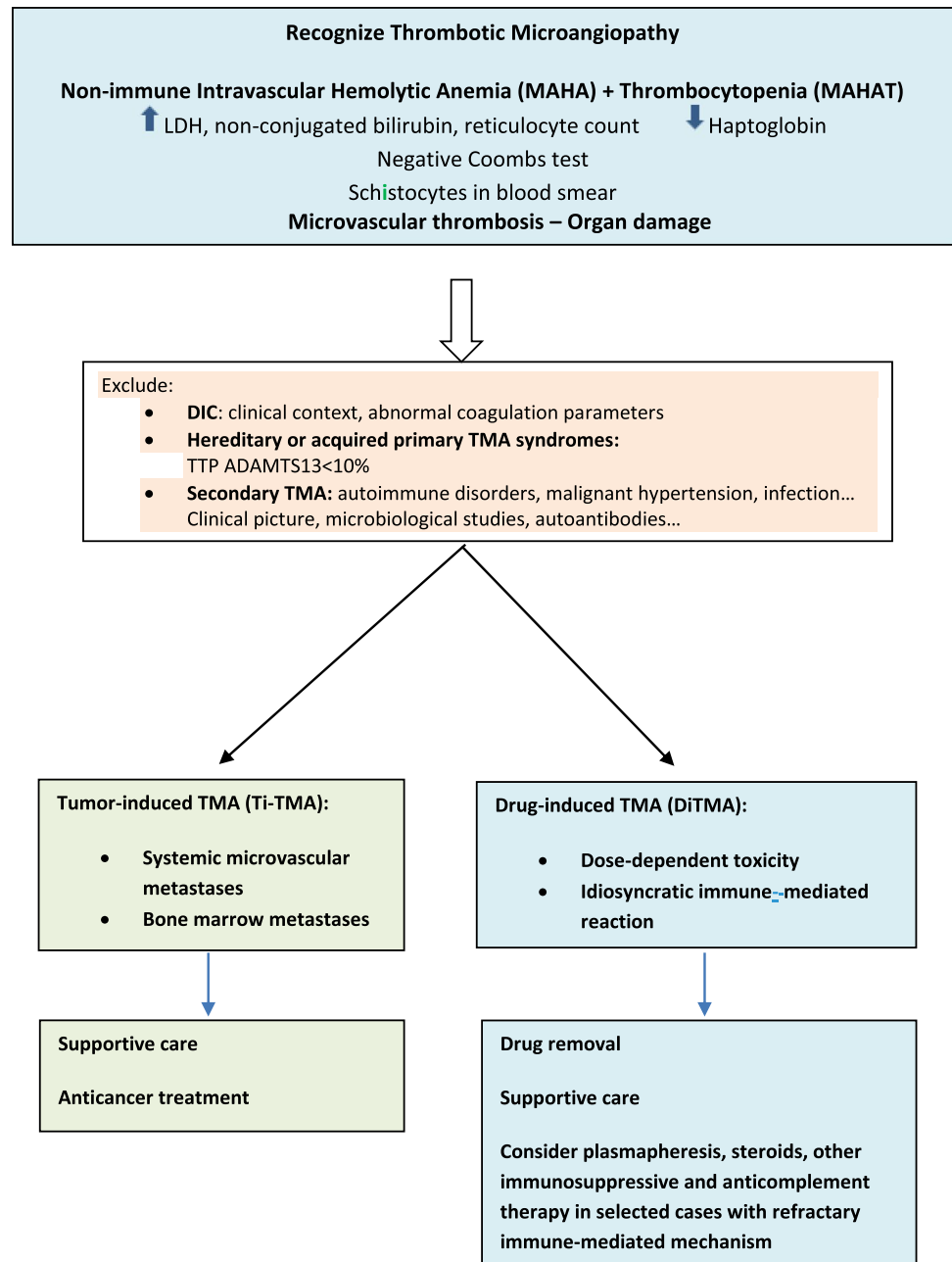
The clinical presentation of TMA may range from mild subacute clinical and laboratory abnormalities to a sudden

life-threatening condition. It is mandatory to recognize the clinical suspicion of TMA and distinguish the underlying mechanism of TMA rapidly as shown in Fig. 1. The clinical context of the patient and a detailed clinical history usually allow identification of one of the main mechanisms in patients with solid tumors. The context of TMA related to cancer itself or Ti-TMA is suspected in patients with overt disseminated cancer or in cancer progression. In cases with Di-TMA, a temporal relation of drug exposure is usually identifiable. The documentation of drug-dependent antibodies supports the clinical diagnosis (available for quinine) although a negative test does not exclude a drug association. The wide range of anticancer drugs associated with Di-TMA implies different clinical presentations, degree of kidney function impact, and reversibility.

Differential diagnosis

In critically ill patients with thrombocytopenia, DIC must be ruled out, since thrombocytopenia is the first and most sensitive sign of DIC [13, 46, 47]. DIC may occur in patients with solid tumors secondary to severe infection or sepsis or driven by cancer itself. It is crucial to identify the underlying disorder causing DIC for appropriate management. DIC is a syndrome which complicates a range of diseases. It is characterized by dysregulation of coagulation patterns leading to the generation of fibrin clots that may cause organ failure with concomitant consumption of platelets and coagulation factors that may result in excessive bleeding. In DIC, the coagulation parameters are usually abnormal including prolonged coagulation times (although they may be normal or indeed shortened), elevated levels of fibrin-related markers (D-dimer, fibrin degradation products) and elevation of

Fig. 1 Work-up for diagnosis and management of patients with solid tumors and thrombotic microangiopathy



fibrinogen levels (although they may be reduced but not commonly below the laboratory range except in cases with very severe DIC). The International Society of Thrombosis and Hemostasis has developed a calculator based on the scoring system for DIC available online [48]. This score can aid in the determination of possible overt DIC and non-overt DIC in patients with underlying conditions that may be associated with DIC. The sequential changes in the coagulation parameters over time usually allow the diagnosis of DIC to be established.

In contrast to patients with DIC, the coagulation parameters should be normal in patients with TMA.

Coronavirus disease 2019 (COVID-19) infection may be associated with blood cell count abnormalities. Coagulopathy that may lead to DIC in severe cases and also to TMA should be taken into account in the differential diagnosis and be excluded by early testing [49, 50]. In the context of the COVID-19 pandemic and massive vaccination, the vaccine-induced immune thrombocytopenia and thrombosis (VITT) syndrome associated with the ChAdOx1 nCoV-19 should be taken into account in patients with thrombosis and thrombocytopenia. The onset of VITT symptoms typically occurs 5–30 days after vaccination and usually shows positive anti-platelet factor 4.

Case definition criteria has recently been developed by an expert hematology panel [51, 52].

The exclusion of primary TMA syndromes is vital and often difficult requiring the expertise of multidisciplinary teams as these conditions require rapid and specific treatment in particular atypical HUS and TTP [7, 11, 53, 54]. Rapid evaluation is needed in order to rule out TTP in acutely ill patients with TMA as prompt initiation of adequate treatment has a critical impact on the outcome. TTP is a rare life-threatening condition with a 10–20% mortality upon proper treatment. The reported incidence of TTP is two to six cases per million per year and predominantly occurs in young females (median age 40 years; female 77%) with a sevenfold increase in incidence among blacks. In contrast, cancer-associated TMA more often occurs in older age patients with no sex or race disparities. The onset of TTP is typically acute (several days) with commonly preserved renal function parameters, whereas the onset of cancer-related TMA is typically gradual (weeks to months) with renal involvement being occasional in Ti-TMA and common in Di-TMA. Respiratory symptoms (which are rare in TTP) have frequently been reported in patients with Ti-TMA [17–22]. Coagulation tests are normal in TTP. Nowadays, the determination of the ADAMTS13 activity with an urgent ADAMTS13 assay is of special value in this setting. ADAMTS13 is a zinc metalloprotease responsible for cleaving vWF multimers that are secreted by vascular endothelial cells in order to prevent inappropriate platelet aggregation and thrombosis in the microvasculature. ADAMTS13 deficiency results in unusually large vWF multimers and the risk of platelet thrombi in small vessels with high shear rates. There is an increasing availability of commercial ADAMTS13 essays that can confirm/exclude TTP in real time. The presence of anti-ADAMTS 13 antibodies or severely decreased ADAMTS13 activity (< 10%) supports the clinical diagnosis of hereditary or acquired TTP (also called ADAMTS13 deficiency-mediated TMA). In contrast, normal or mildly decreased (> 20%) ADAMTS13 activity is observed in patients with cancer-associated TMA. However, ADAMTS13 is synthesized in the liver, and therefore, any degree of liver failure may also lead to low ADAMTS13 activity. Indeed, a severe reduction in ADAMTS13 can be documented in severe sepsis-associated DIC and has also been found to be very low or absent at presentation in cases of Ti-TMA and normalized after successful treatment of MAHA and cancer [17]. Moreover, some drugs such as ticlopidine can induce anti-ADAMTS13 antibodies resulting in TTP.

Distinguishing between Ti-TMA, Di-TMA, and atypical HUS or aberrant uncontrolled activation of alternative complement as a suggested causal mechanism leading to TMA by some drugs can be challenging, as all are diagnosed by exclusion and none are associated with severe

ADAMTS13 deficiency. Complement-mediated TMA that may be acquired is not distinguished from hereditary complement-mediated TMA. The now commercially available complement genetic studies, aimed at assessing mutations in complement proteins and anti-H factor autoantibodies, should be investigated in selected patients in order to provide a more specific diagnosis. Normal plasma levels of C3, C4, and complement factors H, B do not exclude the diagnosis of complement-mediated TMA.

A kidney biopsy can provide diagnostic and prognostic information, although it is an invasive procedure that is difficult to perform because of high bleeding risk in most patients and is usually not necessary in the routine work-up of patients with TMA.

Several additional overlapping disorders can cause anemia, thrombocytopenia and DIC in patients with solid tumors that may coexist with TMA and hinder the interpretation of laboratory testing. The most common disorders to consider for a comprehensive clinical evaluation including the clues for the differential diagnosis are shown in Table 5 [55].

Management of TMA in patients with solid tumors

Evidence-based medical guidance on the management of cancer-related TMA is scarce. Given the wide spectrum of potential causes for TMA in cancer patients, it is essential to establish the diagnosis of the underlying condition leading to TMA. It is recommended to start plasmapheresis or plasma exchange (PEX) until ADAMTS13 activity is known unless an alternative diagnosis is clear. PEX replaces patient plasma with donor plasma, allowing the removal of potential endothelial damaging agents or autoantibodies, and the replacement of certain molecules essential for endothelial function, such as ADAMTS13 [56]. PEX plays a central role in the management of patients with TTP and the high mortality rate without treatment creates urgency to begin PEX. As soon as a severe reduction in ADAMTS13 activity confirms TTP, PEX should be continued until remission. Further immunosuppressive therapy with steroids and other immunosuppressive agents may be appropriate. Some authors recommend the use of steroids in the initial phase of TTP as immunomodulators, but the value of corticosteroids is still uncertain and there are no prospective trials. In refractory cases, the use of other immunosuppressants such as rituximab and complement pathway inhibitors can be considered.

However, PEX is of no benefit in most cases of cancer-associated TMA. In patients with secondary TMA, it is mandatory to treat the underlying condition. In patients with cancer-associated TMA there is no beneficial role for

Table 5 Common causes of anemia and thrombocytopenia in patients with solid tumors

Condition	Causes	Diagnostic tools
Anemia	Hemorrhage Iron, folate, and/or vitamin B12, vitamin B6, copper deficiency Chronic inflammation (cytokine-mediated anemia) Hypoendocrine state (thyroid, adrenal, pituitary) Uremia Chemotherapy/radiotherapy-induced toxicity Aplastic anemia Myelophthitic anemia (primary myelofibrosis and bone marrow infiltration by metastatic solid tumors) Systemic vasculitis Intrinsic/inherited hemolysis: <ul style="list-style-type: none"> • RBC Membrane: PNH, hereditary spherocytosis, hereditary elliptocytosis • Hemoglobinopathies: sickle cell anemia, thalassemia • Enzymes: G6PD deficiency, pyruvate kinase deficiency Extrinsic/acquired hemolysis: <ul style="list-style-type: none"> -Immune-mediated: <ul style="list-style-type: none"> • Warm and cold primary or secondary to malignancies: lymphoma, monoclonal gammopathies, solid tumors • Drugs • Autoimmune disorders: SLE, APS, sclerodermia • ABO-incompatibility transfusion reaction -Infections: malaria -Mechanical hemolysis: cardiac valves, HUS, TTP, DIC, splenomegaly, MAHA, MAHAT, TMA 	High reticulocyte count Search for acute bleeding origin Ferritin, total iron-binding capacity, vitamin B12, folate measurement Vitamin B6 and copper levels in selected cases Bone marrow iron stain in selected cases Hormonal tests Renal function Bone marrow examination Parvovirus B19 in selected cases Peripheral blood smear Genetic studies Haptoglobin, indirect bilirubin, LDH, Coombs test Cold agglutinins Autoantibodies: aPL, ANA, Aanti-Sc170, anti-ds DNA, ACA, RNA polymerase III Microbiological studies Blood smear (schistocytes, plasmodium) ADMTS13 activity
Thrombocytopenia	Chemotherapy, radiation therapy Drugs (decreased bone marrow production or increased peripheral destruction) DIC Immune-mediated thrombocytopenia purpura (primary or secondary to neoplasia) Splenomegaly Heparin-induced thrombocytopenia (HIT) COVID-19 infection–VITT	Coagulation times, fibrinogen, D-dimer and fibrin degradation products measurement Bone marrow examination Antiplatelet factor 4 Microbiological studies

ACA anticentromer antibodies, ANA antinuclear antibodies, aPL antiphospholipid antibodies, APS antiphospholipid syndrome, COVID-19 coronavirus disease 2019, DIC disseminated intravascular coagulation, HUS hemolytic uremic syndrome, MAHA microangiopathic hemolytic anemia, MAHAT microangiopathic hemolytic anemia with thrombocytopenia, RBC red blood cells, PNH paroxysmal nocturnal hemoglobinuria, SLE systemic lupus erythematosus, TMA thrombotic microangiopathic anemia, TTP thrombotic thrombocytopenic purpura, VITT vaccine-induced immune thrombocytopenia thrombosis

PEX, steroids or other immunosuppressive agents used in TTP. The prognosis of patients with cancer TMA is usually extremely poor due to disseminated cancer but specific anticancer therapies should be indicated whenever possible. The use of platelet transfusions for severe thrombocytopenia (usually withheld in TTP because of the risk of worsening microthrombotic complications) would be appropriate in cancer-associated TMA.

Regarding the management of Di-TMA, there are no trials to guide its management. Treatment relies on prompt drug cessation of the suspected causative agent, blood pressure control and supportive care therapy including red cell and platelet transfusion. In cases due to a dose-dependent mechanism, the prognosis is usually favorable with drug discontinuation. The role of PEX is very limited in the management

of Di-TMA as only a small proportion of cases (associated with ticlopidine) are associated with ADAMTS13 antibodies. However, if antibody-mediated TMA is suspected, a trial with plasmapheresis could be useful. There are emerging case reports and small retrospective cohorts of successful outcomes with complement inhibition with eculizumab, a monoclonal antibody against complement factor C5 [57, 58] and rituximab [59] for the management of gemcitabine-induced TMA. However, none of these latter therapies can be formally recommended, since there are no prospective randomized trials evaluating their efficacy and safety in this setting.

In summary, TMA is a potentially life-threatening condition that requires prompt recognition and precise diagnosis. In patients with solid tumors, TMA is usually a

paraneoplastic manifestation of cancer itself or secondary to direct or immune-mediated drug toxicity, with the treatment of cancer and drug removal being the main interventions for patients in this setting. Rapid and precise differential diagnosis is required to exclude TTP, atypical HUS, and DIC in order to optimize the proper treatment of these potentially life-threatening conditions as soon as possible.

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Declarations

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