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DRUG-INDUCED THROMBOTIC MICROANGIOPATHY: A NARRATIVE REVIEW OF PATHOPHYSIOLOGY, CAUSATIVE DRUGS, DIAGNOSIS, AND TREATMENT

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1. ABSTRACT

Drug-induced thrombotic microangiopathy (DITMA) is a rare and potentially life-threatening condition that is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombi leading to variable degrees of dysfunction in organs, especially acute renal failure. DITMA represents a heterogeneous group of disorders, which can be caused by several medications through immune-mediated or dose-dependent toxic mechanisms that lead to endothelial injury and thrombus formation. In recent times, there has been an increase in the types of drugs involved, including targeted anti-cancer medications, immune checkpoint inhibitors, VEGF inhibitors, proteasome inhibitors, calcineurin inhibitors, and CAR-T cell therapy. Diagnosis of this condition is quite difficult due to overlapping clinical features with thrombotic microangiopathies such as thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome. Management involves stopping the causative agent immediately, as well as supportive care and management of the organ-related complications. Recent studies have shown that complement activation plays a role in the development of certain types of DITMA, thus justifying the use of complement pathway inhibition therapy with eculizumab and ravulizumab in certain patients. This narrative review comprehensively summarizes the history, epidemiology, pathophysiology, etiologic agents, symptoms, diagnostics, complications, and current treatment methods of DITMA.

Additionally, recent advances in the field of complement biology, biomarker discovery, precision medicine, and new treatments for DITMA have been addressed to help clinicians gain a better understanding of this complicated disease.

2. INTRODUCTION

Drug-induced thrombotic microangiopathy (DITMA) is a rare but potentially life-threatening disorder characterized by microvascular endothelial injury, which causes thrombocytopenia, microangiopathic hemolytic anemia, and variable degrees of organ dysfunction, most commonly involving the kidney and central nervous system.[1,2] With the increasing use of antineoplastic agents, immunotherapies, targeted therapies, and immunosuppressive drugs, DITMA has emerged as an increasingly recognized cause of secondary thrombotic microangiopathy (TMA).[1,3] Though a rare event, delayed diagnosis and continued exposure to the inciting drug can lead to irreversible renal injury, multi-organ failure, and increased mortality. This highlights the need for early detection and management.[2]

DITMA represents a heterogeneous group of disorders with different pathogenic origins.[1] They can be classified into two main categories: immune-mediated DITMA, whose origin is due to antibodies produced as a result of use of the drug, and results in damage to the vessel linings immediately after the use of the drug, and dose-dependent or toxicity-mediated DITMA, whose origin is chronic use of the drug and results in damage to the vessel linings.[1,3] Gemcitabine, quinine, calcineurin inhibitors, VEGF inhibitors, proteasome inhibitors, CAR-T therapy, and immune checkpoint inhibitors are some of the common drugs that cause DITMA.[1,3,5] Advances in molecular research have demonstrated that complement activation plays a role in this condition.[4]

DITMA can present with a broad spectrum of clinical manifestations, from kidney-only problems to severe disease affecting several organs, including the kidneys, brain, and blood pressure.[5] Its symptoms are similar to thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome, Shiga toxin-associated hemolytic uremic syndrome, and other secondary TMAs. This overlap complicates diagnosis, and clinicians should evaluate the patient's history, lab tests, ADAMTS13 activity, complement studies, sometimes a kidney biopsy, and carefully reconcile medications.[1,6]

Recent advances in understanding complement dysregulation have changed the way DITMA is managed. The main treatments are still to stop the causative drug quickly and provide

supportive care. Complement inhibitors such as eculizumab and ravulizumab have improved outcomes for some patients with complement-mediated diseases.[1,4,15] The emergence of new biomarkers, diagnostic modalities, and increased awareness of drug-induced TMAs have also played a role in improving early diagnosis and personalized therapy.[20,28] This narrative review will examine the epidemiology, pathophysiology, clinical presentation, diagnostic approach, renal involvement, current treatments, and emerging treatment modalities in drug-induced TMAs.[1,26]

3. KEYWORDS

Drug-induced thrombotic microangiopathy, Thrombotic microangiopathy, Endothelial injury, Complement activation, Acute kidney injury, Immune checkpoint inhibitors.

4. HISTORICAL PERSPECTIVE AND NOMENCLATURE

The concept of TMA as a distinct entity has evolved considerably since it was first described clinically in the early twentieth century. In 1924, Eli Moschcowitz described a life-threatening condition in a young woman that involved the presence of hyaline thrombi in the arterioles and capillaries, now known as thrombotic thrombocytopenic purpura (TTP).[8] Further research has established TMA as a pathological condition rather than a disease by itself; it is associated with endothelial injury, platelet-rich thrombus formation in microvasculature, microangiopathic hemolytic anemia, thrombocytopenia, and various stages of organ dysfunction. In the subsequent years, significant advances in hematology, nephrology, and pathology, several forms of TMA, namely TTP, ST-HUS, aHUS, transplantation-associated TMA, and secondary TMA.[5,6]

DITMA was recognized as a clinical entity based on accumulating evidence that specific drugs were capable of causing TMA, independent of any underlying hereditary or primary complement deficiency.[2,7] Quinine, mitomycin C, cyclosporine, and tacrolimus were the common drugs mentioned in the early cases; however, further investigations expanded the list to include chemotherapy, vascular endothelial growth factor (VEGF) inhibitors, proteasome inhibitors, interferon, immune checkpoint inhibitors, and CAR-T therapies.[1,2,9] These findings established how drugs can be considered an important and even reversible cause of secondary TMA.[2,9]

In the past, DITMA was categorized into its two major types of pathological processes: the first being mediated through immunity, wherein immediate damage occurs to the endothelium

via drug-induced antibodies after the ingestion of the offending substance.[1,3] In contrast, the second type involves dose-related or toxicity-mediated reactions, wherein there is progressive damage to the endothelium after long-term use of the offending agent. Current evidence has considerably expanded the understanding of DITMA.[1,3,4] Available studies indicate that, in addition to the established pathogenic mechanisms, complement activation, endothelial injury, genetic susceptibility, and inflammatory pathways play important roles in the onset and progression of the disease. Consequently, DITMA is now recognized as a heterogeneous condition comprised of multiple pathogenic pathways.[4]

5. EPIDEMIOLOGY AND GLOBAL BURDEN

Drug-induced thrombotic microangiopathy (DITMA) is a rare yet increasingly recognized cause of secondary thrombotic microangiopathy, mainly due to the increasing utilization of chemotherapy drugs, immunosuppressive drugs, target-specific drugs, and immune checkpoint inhibitors.[1,3,9] While the true incidence of DITMA across the globe is unknown due to inadequate reporting, diagnostic challenges, and limited data available through case studies and systematic reviews, DITMA constitutes about 10–13% of all thrombotic microangiopathy cases that have been registered in large registries. This is mostly due to the misdiagnosis of cases as TTP, aHUS, and acute kidney injuries of other origins.[2,10,12]

DITMA's epidemiological trends have changed in the last twenty years due to the use of new drugs for the treatment of cancer and immune disorders.[1,5] Quinine, mitomycin C, and calcineurin inhibitors were the predominant causative agents of DITMA in the past.[2,9] Currently, gemcitabine, inhibitors of VEGF, inhibitors of proteasomes, immune checkpoint inhibitors, and CAR-T treatments have become the main causes.[1,9,13]

Most cases of DITMA occur among adults undergoing chemotherapy for cancer, immunomodulation for autoimmunity, transplant procedures, or chronic inflammation.[11,14] The most common form of damage is kidney involvement, which results in serious outcomes, including acute kidney injury, chronic kidney disease, and even dialysis.[4,11] Death is dependent upon the medication used and when the problem is detected and stopped, although there is a particularly bad outlook for those with chemically-induced disease.[11,13] In light of the rising trend in the usage of potentially dangerous drugs, there is a need to be more aware of the risk and early diagnosis of the condition.[4,12]

6. PATHOPHYSIOLOGY

Drug-induced thrombotic microangiopathy (DITMA) is a heterogeneous condition defined by endothelial cell damage, platelet-rich thrombus formation in the microvasculature, mechanical destruction of red blood cells, and organ ischemia.[1,7] In contrast to primary thrombotic microangiopathies, the pathophysiology of DITMA involves multiple distinct mechanisms, which depend on the specific drugs responsible for their development. There are four major mechanisms currently recognized: endothelial toxicity, immune-mediated damage, complement system activation, and altered regulation of coagulation and vascular physiology (figure: 1).[1,3,4]

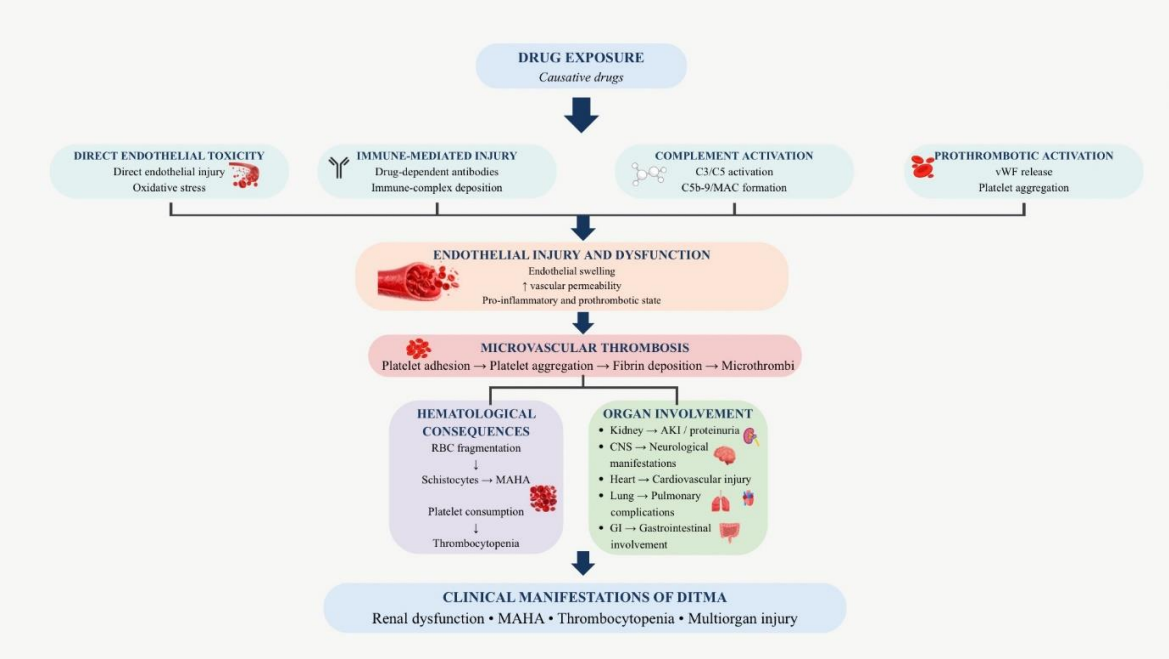

Figure 1: Pathophysiological mechanisms of drug-induced thrombotic microangiopathy.

6.1 Direct endothelial toxicity

The direct toxicity to the endothelium is the most prevalent cause of DITMA, which is mostly related to dose-dependent exposure to anti-cancer or immunosuppressive medications.[1] The cytotoxic agents, such as gemcitabine, mitomycin C, calcineurin inhibitors, and proteasome inhibitors, are known for producing gradual damage to endothelial cells by inducing oxidative stress, mitochondrial dysfunction, and apoptosis of vascular endothelium cells.[9,22,23,25] The damage to the endothelial layer causes loss of its antithrombotic property, revealing subendothelial collagen and tissue factor and leading to platelet adhesion, activation, and aggregation in microcirculation.[7] Narrowing of arterioles and capillaries

leads to erythrocyte destruction and thrombocytopenia, causing ischemic injury primarily to the kidneys because of their dense microvascular network.[1,9]

6.2 Immune-mediated drug-induced thrombotic microangiopathy

Immune-mediated DITMA is an idiosyncratic condition characterized by drug-dependent antibody-mediated attack on platelets, endothelial cells, or circulating plasma proteins after administration of a certain drug.[2,10] As compared to the toxicity-mediated disease, immune-mediated DITMA can take place suddenly even at low exposure or upon re-exposure to the drug.[3] Classic examples of causative agents are quinine, while ticlopidine and other newly developed drugs have been reported. Antibody-dependent binding stimulates endothelial cells and platelets, causing microvascular thrombosis and hemolysis. Symptoms appear within a few hours to days after taking the drug and disappear soon after withdrawal of the drug.[2,10,24]

6.3 Complement activation and microvascular injury

Several recent studies have established complement activation as an important mediator in the pathophysiology of several cases of DITMA. Activation of the alternative complement pathway caused by vascular injury from drugs leads to overproduction of C3a, C5a, and membrane attack complex (C5b-9). This results in amplification of the inflammation of endothelial cells, increased vascular permeability, and recruitment of leukocytes and platelets, leading to thrombosis of microvessels.[4] A dysregulated complement system seems to be an important factor in patients under treatment with immune checkpoint inhibitors, VEGF inhibitors, and some chemotherapeutic drugs, explaining why some patients suffer from the development of severe and persistent symptoms even when the drug is discontinued. Recognition of complement-related damage has made it possible to treat certain cases of DITMA with complement inhibitors like eculizumab and ravulizumab.[12,15,16,17]

6.4 Drug-specific mechanisms and organ susceptibility

Various drug classes cause TMA via diverse, but often converging, pathways.[1] VEGF blockers cause endothelial cell death through interference with the vascular endothelial growth factor signalling pathway, resulting in glomerular endothelial cell dysfunction and TMA of the kidney only.[12] Proteasome inhibitors increase oxidative stress and apoptosis of endothelial cells, whereas calcineurin inhibitors induce vasoconstriction, dysfunction of the endothelium, and enhanced platelet aggregation.[22,25] Immune checkpoint blockers may cause complement-dependent endothelial cell damage due to immune dysregulation, and CAR-T cells cause cytokine-mediated endothelial cell activation and complement

amplification.[16,18,21] While any organ is vulnerable, kidneys are more predisposed to developing TMA because of the large extent of microcirculation and large endothelial surface area in the kidneys.[9] Endothelial cell injury will eventually result in ischemia, fibrosis, and permanent loss of renal function in the absence of timely intervention.[20]

7. DRUG CLASSIFICATION AND CAUSATIVE AGENTS

DITMA can be generally categorized into immune-mediated and toxicity-mediated forms based on the mechanism of its pathogenesis.[1,3] Immune-mediated DITMA develops in response to the production of drug-dependent antibodies against platelets, neutrophils, endothelial cells, or other blood elements when exposed to the causative drug, causing sudden endothelial injury and DITMA.[2,10] The development of immune-mediated DITMA usually happens within a few hours of re-administration of the causative drug and can be reversed rapidly after withdrawal. Quinine continues to be the most established cause of immune-mediated DITMA; however, some other drugs like oxaliplatin and vancomycin have been identified.[1,2,7]

On the contrary, toxicity-mediated DITMA develops due to progressive endothelial injury caused by continuous administration of the offending drug. It is frequently reported with antineoplastic drugs, immunosuppressive drugs, and targeted therapies.[1] Endothelial injury causes platelet activation, dysregulation of the complement system, microvascular thrombi formation, and ultimately organ dysfunction with renal involvement. Recent literature has also identified complement activation as a contributory factor in certain cases of toxicity-mediated DITMA, and hence complement-based therapy could be considered in cases of DITMA refractory to treatment.[1,4,15]

The advent of specific anticancer drugs, immune checkpoint inhibitors, CAR-T cell therapy, and other biologic drugs is continuously changing the spectrum of DITMA.[12,17,18,21] The early identification of potentially harmful drugs and the cessation of the causative agent are the most efficient methods for preventing irreversible organ damage in patients.[1,20]

The major categories of DITMA, commonly implicated drugs, associated mechanisms, clinical features, and key management approaches are summarized in Table 1.

Table 1: Classification of drug-induced thrombotic microangiopathy.

Category	Common drugs	Mechanism	Typical Clinical Features	Key Management
Immune-mediated DITMA	Quinine, Oxaliplatin, Vancomycin	Drug-dependent antibodies causing acute endothelial injury	Sudden onset MAHA, thrombocytopenia, AKI after drug exposure	Immediate drug withdrawal; supportive care; selected cases may benefit from plasma exchange or complement inhibition
Toxicity-mediated DITMA	Gemcitabine, Mitomycin C	Direct cumulative endothelial injury	Progressive renal dysfunction, hypertension, MAHA	Drug discontinuation, supportive care, consider eculizumab in refractory cases
Calcineurin inhibitors-associated DITMA	Tacrolimus, Cyclosporine	Endothelial injury and complement activation	AKI, hypertension, post-transplant TMA	Dose reduction or withdrawal; alternative immunosuppression
VEGF inhibitors-associated DITMA	Bevacizumab, Aflibercept, Ranibizumab	VEGF inhibitors causing glomerular endothelial injury	Proteinuria, hypertension, renal-limited TMA	Discontinue VEGF inhibitor; blood pressure control
Proteasome inhibitors-associated DITMA	Bortezomib, Carfilzomib	Endothelial injury and complement activation	AKI, MAHA, thrombocytopenia	Drug withdrawal; supportive care; consider complement inhibition
ICI-associated DITMA	Nivolumab, Pembrolizumab, Ipilimumab	Immune-mediated endothelial injury with complement activation	AKI with systemic or renal-limited TMA	Stop immunotherapy; corticosteroids; selected patients may receive eculizumab.
CAR-T cell therapy-associated TMA	CAR-T cell therapies	Cytokine-mediated endothelial injury and complement activation	Multiorgan dysfunction, AKI, thrombocytopenia	Supportive care; treat cytokine release syndrome; consider complement inhibition

8. CLINICAL FEATURES AND PRESENTATION

The clinical picture of drug-induced thrombotic microangiopathy (DITMA) is highly variable and depends on the etiological drug, the underlying disease, and the degree of damage to microvascular endothelium.[1,3] The presence of the classical triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ dysfunction is usually noted in DITMA; however, there is considerable heterogeneity in the severity and character of involvement of various organs.[5,7] The onset may be rapid in immune-mediated DITMA,

occurring within hours to days of taking the drug, or insidious in toxicity-mediated DITMA associated with prolonged use of the etiological drug.[2,10]

Renal function impairment is the most frequent organ manifestation, with patients presenting with acute renal failure, decreased urine output, proteinuria, hematuria, and newly developed or deteriorated hypertension.[9,11] The development of dialysis-dependent renal impairment may result from extensive renal injury if timely diagnosis and treatment are not done.[11] Central nervous system involvement characterized by headaches, confusion, seizures, visual changes, and impaired consciousness can occur because of cerebral microvascular ischemia; however, its presence is usually less pronounced than in thrombotic thrombocytopenic purpura (TTP).[5] Symptoms involving the gastrointestinal tract (abdominal pain, nausea, vomiting, and diarrhoea) and constitution (fatigue and malaise) may also be present.[1,9]

The laboratory results commonly show schistocytes on peripheral blood smear, high levels of lactate dehydrogenase (LDH), low haptoglobin, indirect hyperbilirubinemia, thrombocytopenia, and different levels of renal dysfunction indicated by increased serum creatinine.[6] Based on the underlying pathophysiology, the complement system activation tests are high in some cases.[4] Severe deficiencies of ADAMTS13 are not present in the vast majority of DITMA cases, thus allowing one to distinguish between DITMA and TTP of an autoimmune origin.[9,19,23-25] The detailed drug history should be taken into account, especially in the case of treatment with chemotherapy drugs, calcineurin inhibitors, VEGF inhibitors, proteasome inhibitors, immune checkpoint inhibitors, or quinine.[1,15]

9. DIAGNOSIS

9.1 Diagnostic principle

The diagnosis of drug-induced thrombotic microangiopathy (DITMA) is made with a high index of suspicion due to the clinical presentation being similar to other types of thrombotic microangiopathies such as TTP, Shiga toxin-associated hemolytic uremic syndrome (ST-HUS), atypical hemolytic uremic syndrome (aHUS), transplant-associated TMA, and secondary TMAs secondary to autoimmune disorders, infections, and malignancies.[5,6] The diagnosis is made by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ damage, and a temporal relationship should be established with exposure to the offending agent. A thorough history of medication use is critical in making the diagnosis.[1,2,3,6,10]

9.2 Diagnostic workup

The initial laboratory workup consists of complete blood count, peripheral smear with evaluation for schistocytes, serum lactate dehydrogenase (LDH), haptoglobin, indirect bilirubin, reticulocyte count, serum creatinine, urinalysis, coagulation panel, and direct antiglobulin (Coombs) test.[5,6] Measurement of ADAMTS13 activity is required in all patients to exclude immune-mediated TTP, whereas testing of stools for Shiga toxin is recommended when there is diarrhea.[5,6] Studies for complement factors such as C3, C4, and soluble C5b-9 as well as genetic analysis in selected patients may help diagnose complement-mediated disorders, especially if there is persistent TMA after drug cessation.[4,15]

Renal biopsy is useful in cases with predominant renal involvement or for diagnostic uncertainty and shows endothelial swelling, mesangiolysis, fibrin thrombi, double contour of the glomerular basement membranes, and arteriolar intimal edema. Other histopathological findings can be used in differentiation between DITMA and other causes of acute renal injury and chronic glomerulopathy.[22,26] The clinical examination should consider the involvement of the nervous system, cardiovascular problems, and the extent of renal failure to select an appropriate therapy.[1,12,20] A contemporary diagnostic approach considers the combination of clinical picture, laboratory findings, pathological evaluation, and causality analysis of the suspicious drug.[5,12]

10. Complications and Prognosis

Drug-induced thrombotic microangiopathy (DITMA) leads to considerable morbidity and mortality in patients who have delayed diagnosis or removal of the causal drug.[1,5,11] The kidneys are the organ that is often involved, where microvascular thrombosis can lead to AKI, CKD, hypertension, and, in worst cases end-stage renal disease that requires chronic dialysis.[9,11] Toxicity-induced DITMA by gemcitabine, calcineurin inhibitors, and vascular endothelial growth factor (VEGF) inhibitors leads to renal impairment due to continuous damage to the endothelium of the renal microvasculature.[19,23,25]

The extra-renal complications of DITMA include the development of neurologic events like seizures, alteration in mental state, encephalopathy, and stroke due to microvascular ischemia of the brain.[5,9] Cardiovascular complications arise due to microvascular thrombotic obstruction and include myocardial ischemia, heart failure, and severe hypertension due to widespread endothelial dysfunction.[5,11] Additionally, persistent thrombocytopenia, anemia due to transfusions, multiple organ dysfunction, and infection due to prolonged

hospitalization and immunosuppressive drugs can complicate the course of DITMA in patients.[1,5] In patients with oncologic conditions, cessation of the necessary chemotherapy due to DITMA can adversely affect outcomes and prognosis.[9,13,17]

The prognosis of DITMA depends on the underlying cause of DITMA, the degree of organ involvement, the underlying condition, and early detection of DITMA.[1,11] The prognosis of immune-mediated DITMA is good when the offending drug is promptly withdrawn from the treatment regimen, while toxicity-mediated DITMA tends to be a slowly progressing condition with incomplete recovery of renal function.[1,23,24] Recent findings indicate that the activation of complement is a significant factor in the pathogenesis of severe cases of DITMA, while there have been patients who have shown improvement of renal and blood function after the administration of complement inhibitors like eculizumab or ravulizumab.[4,15,16] However, late detection continues to result in irreversible damage to the kidney and increased mortality rates.[11,23]

11. MANAGEMENT

11.1 Immediate drug withdrawal and supportive care

Management is primarily based on early recognition and prompt discontinuation of the offending drug. Drug withdrawal limits ongoing endothelial injury and improves the chances for hematologic improvement.[1,2,7] Re-administration of the drug must be prevented, especially in immune-mediated DITMA cases, as re-exposure to the culprit drug can cause quick relapse of the condition.[2,3,24] Detailed drug history, which includes prescribed medications, over-the-counter drugs, herbal supplements, and recent use of cytotoxic or biologic drugs, is an important step in evaluating the patient.[1,5]

Therapy aimed at supporting the patient should be personalized depending on the severity and organs involved.[5,11] Hospitalization and continuous monitoring of hematologic profile, renal function, electrolytes, blood pressure, and neurologic status are common steps in treating DITMA patients.[5,6,11] Transfusion of red blood cells can be required for the treatment of anemia, but platelets should be used only in case of life-threatening hemorrhage or invasive procedures, as they may theoretically exacerbate microthrombi formation.[5,6] Careful fluid management, correction of electrolyte imbalance, blood pressure reduction, and prevention of the administration of nephrotoxic drugs are basic supportive actions. Renal replacement therapy might be necessary in patients with severe acute kidney injury.[9,11]

11.2 Plasma exchange and immunomodulatory therapy

In contrast to immune-mediated TTP, therapeutic plasma exchange (TPE) is rarely used in DITMA. This procedure is highly effective in treating TTP since it eliminates anti-ADAMTS13 antibodies and supplies normal ADAMTS13 enzyme; yet most patients with DITMA develop the disease due to direct endothelial toxicity or complement-mediated injury, rather than severe deficiency of ADAMTS13.[2,5,7] Thus, routine use of plasma exchange is not advised once DITMA has been diagnosed. However, if TTP is suspected, plasma exchange should not be delayed while waiting for ADAMTS13 results because late administration significantly increases the mortality rate.[5,6]

In the case of immune-mediated DITMA, especially quinine-associated disease or immune-mediated reaction with drug-dependent antibodies, plasma exchange is sometimes combined with corticosteroid therapy; however, available evidence remains limited regarding the effectiveness of this approach.[2,24] While corticosteroids can be considered in some immune-mediated cases, especially those where autoimmune mechanisms are suspected, they do not play any role in toxicity-induced DITMA. Other immunosuppressants, such as rituximab, are usually used only in refractory immune TTP but not in DITMA.[3,5,6,7]

11.3 Complement inhibition: Eculizumab and ravulizumab

It is becoming increasingly clear that complement activation plays an important role in the development of various forms of DITMA, especially those related to chemotherapy, immune checkpoint inhibitors, calcineurin inhibitors, and serious endothelial injuries.[4,16] These findings have prompted a growing interest in complement inhibition at the level of C5 with monoclonal antibodies.[1,15] Eculizumab, an inhibitor of the formation of membrane attack complex (C5b-9), reduces endothelial injury, platelet activation, and microthrombosis.[4] Case series and observational studies have shown clinical benefit in terms of hemoglobin levels, renal function, and independence from dialysis in patients with complement-dependent DITMA who were resistant to conventional treatments.[16,24]

Ravulizumab, the prolonged-acting C5 inhibitor based on eculizumab, provides sustained complement inhibition through a much less frequent dosing regimen and equivalent therapeutic efficacy.[15] Although there is limited evidence on ravulizumab application in DITMA at the moment, the results of therapy in cases of atypical hemolytic uremic syndrome (aHUS) predict analogous efficacy and convenience. Some recent systematic reviews prove the potential usefulness of complement inhibition in selected severe or persistent DITMA

cases, especially with proven or suspected complement involvement.[15] Before administration of eculizumab or ravulizumab, it is necessary that the patient receives the meningococcal vaccination and undergoes antibiotic prophylaxis since the suppression of terminal components of complement greatly increases susceptibility to invasive infection due to Neisseria meningitidis.[4,15]

In general, complement inhibitors are not recommended as the primary treatment for DITMA, but are rather a useful treatment alternative for selected patients.[1,4,15]

11.4 Drug-specific management

DITMA management should be tailored depending on the offending agent and the pathological process involved.[1,11] Management of gemcitabine-induced TMA involves stopping the drug, aggressive supportive measures, control of blood pressure, and use of renal replacement therapy where applicable.[23] While plasma exchange has shown mixed results, emerging data indicate that complement inhibition by eculizumab might improve hematological recovery and renal outcomes in selected patients with severe or refractory disease.[1,4,23]

Regarding TMA related to CNI use, commonly observed following solid organ or hematopoietic stem cell transplant, management entails dose reduction and discontinuation of the tacrolimus and/or cyclosporine drugs, with possible conversion to an alternate immunosuppression therapy. Close monitoring of organ function and drug levels is critical in preventing recurrence of TMA.[25,27]

For patients with TMA due to VEGF inhibitors, withdrawal of the offending VEGF agent, careful control of blood pressure, and close monitoring of renal function and proteinuria is recommended. The majority of these patients will have resolution with discontinuation of the therapy, though renal damage persists in severe cases.[19]

For proteasome inhibitor-associated TMA, early withdrawal of bortezomib or carfilzomib is recommended, with supportive care being the mainstay of management, while complement inhibition shows promising results in refractory cases as reported in individual cases.[1,4,23,29] Similarly, ICI-associated TMA mandates immediate cessation of therapy along with a high corticosteroid dose for immune-related toxicity.[16,17,18] Complement inhibition has shown promising results in some patients, and evidence is available in the form of case reports.[16,18]

CAR-T cell therapy-associated TMA is a relatively recently emerging clinical entity and is defined by endothelial damage, systemic inflammation, and complement system activation.[21] The treatment includes mainly supportive care, cytokine release syndrome if present, optimization of renal dysfunction, and consideration of complement inhibitors in refractory disease.[4,21] In case of quinine-induced immune DITMA, lifelong abstinence from quinine-containing medications is imperative because the recurrence of disease after taking quinine again can be life-threatening. Most of the cases recover with medication cessation and supportive management, whereas complement inhibition has also been successfully employed in some cases.[24]

11.5 Renal replacement therapy and long-term follow-up

Acute kidney injury is one of the most severe complications of DITMA and can lead to the necessity of temporary hemodialysis or kidney replacement therapy in critically ill patients.[6,10] While some patients recover partially or completely from DITMA after discontinuing the toxic agent, some other patients progress to chronic kidney disease or end-stage kidney disease, which would need lifelong dialysis treatment.[1,6,25] Therefore, patients must be followed up for signs of persistent or recurring disease by assessing their renal function, blood pressure, urine analysis, complete blood count, and hemolysis.[10,24]

11.6 Emerging therapeutic strategies

Further developments in knowledge about endothelial injury and complement dysregulation have allowed for the design of new treatment strategies for DITMA.[11] Among such drugs are long-acting complement inhibitors like ravulizumab that allow for extended terminal complement inhibition while reducing the number of treatments compared to eculizumab and improving compliance in selected patients.[16] Novel complement-targeted agents under investigation act at various levels of the complement activation pathway and aim to prevent irreparable damage to endothelium and infections.[11]

Emerging new biomarkers like soluble C5b-9, endothelial injury, and inflammation biomarkers can contribute to earlier diagnosis and risk stratification and serve as guidance in personalizing the therapy.[11,22] Discovered biomarkers in transplantation-related TMA cases may be useful in the future for DITMA as well; however, further studies are needed.[22] Furthermore, DITMA occurring in children and transplant patients highlights the need for collaboration of hematology, nephrology, oncology, transplant medicine, and clinical pharmacy specialists for optimal management of patients.[6,11,14]

12. FUTURE DIRECTIONS

The future directions in the study of DITMA include the development of earlier diagnostic strategies and targeted treatment of the disease as well as refinement of its classification. Knowledge about complement activation has led to the emergence of novel therapies that can inhibit complement activity, such as eculizumab and ravulizumab, as potential treatments for DITMA; however, there is a need to conduct prospective clinical trials for the optimal use of these drugs in DITMA.[4,15,16] The discovery of novel biomarkers, including soluble C5b-9 and markers of endothelial dysfunction, may help in the earlier detection of DITMA and its risk factors and monitoring of the treatment response.[28] In addition, there is a need for multicentre registries and international cooperation to clarify the incidence, spectrum, and outcome of DITMA caused by novel antitumor agents, immune checkpoint inhibitors, and CAR-T cell therapy.[17,18,21] The developments in pharmacogenomics, personalized medicine, and pharmacovigilance using artificial intelligence will help identify high-risk patients and implement treatment strategies.[1,3]

13. CONCLUSION

Drug-induced thrombotic microangiopathy (DITMA) represents a rare but potentially fatal condition, characterized by endothelial dysfunction, microvascular thrombosis, microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction of varying degree with particular renal involvement. The disease is heterogeneous and can involve immune-related or dose-dependent toxicity. Increasing evidence suggests that complement activation contributes to the pathogenesis of a subset of DITMA cases, although its clinical significance varies according to the causative drug and underlying mechanism. Early recognition, drug cessation, thorough diagnostic assessment, and appropriate therapy are crucial to optimize clinical outcomes and prevent irreversible organ damage. Advances in complement modulating therapies, advances in knowledge regarding endothelial biology, and development of new biomarkers offer promising opportunities in terms of therapy and diagnostics. However, evidence remains limited for many emerging drugs, and further research in the form of prospective studies and international registries, along with standardization of treatment approach, is needed. In view of the growing use of targeted anticancer, immunomodulatory, and biological treatments, it is increasingly important that DITMA be recognized by hematologists, nephrologists, oncologists, and clinical pharmacists at the earliest to prevent severe complications and improve quality of life.

14. ABBREVIATIONS

DITMA: Drug-Induced Thrombotic Microangiopathy

TMA: Thrombotic Microangiopathy

MAHA: Microangiopathic Hemolytic Anemia

TTP: Thrombotic Thrombocytopenic Purpura

aHUS: Atypical Hemolytic Uremic Syndrome

VEGF: Vascular Endothelial Growth Factor

CAR-T: Chimeric Antigen Receptor T-cell

ICI: Immune Checkpoint Inhibitor

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18. REFERENCES

1. Tommaso Mazzierli, Allegretta F, Enrico Maffini, Allinovi M. Drug-induced thrombotic microangiopathy: An updated review of causative drugs, pathophysiology, and management, 2023 Jan 9; 13.
2. Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN. Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood, 2015 Jan 22; 125(4): 616–8.
3. Chatzikonstantinou T, Gavriilaki M, Anagnostopoulos A, Gavriilaki E. An Update in Drug-Induced Thrombotic Microangiopathy, 2020 May 22; 7.
4. Johann M, Caravaca-Fontan F, Fakhouri F, Frangou E, Bruchfeld A, Floege J, et al. Complement activation in secondary thrombotic microangiopathies. Nephrology Dialysis Transplantation [Internet], 2025 May 15; 40(11): 2193–206.
5. Leisring J, Brodsky SV, Parikh SV. Clinical Evaluation and Management of Thrombotic Microangiopathy. Arthritis & Rheumatology, 2023 Nov 30; 76(2): 153–65.
6. Thompson GL, Kavanagh DJ. Diagnosis and treatment of thrombotic microangiopathy. International Journal of Laboratory Hematology, 2022 Sept 1; 44(S1): 101–13.
7. Pisoni R, Ruggenenti P, Remuzzi G. Drug-Induced Thrombotic Microangiopathy. Drug Safety, 2001; 24(7): 491–501.
8. Zakarija A. Thrombotic Microangiopathy Syndromes. Cancer Treatment and Research, 2009; 115–36.

9. Izzedine H, Perazella MA. Thrombotic Microangiopathy, Cancer, and Cancer Drugs. American Journal of Kidney Diseases [Internet], 2015 May 2; 66(5): 857–68.
10. Saleem R, Reese JA, George JN. Drug-induced thrombotic microangiopathy: An updated systematic review, 2014-2018. American Journal of Hematology, 2018 Aug 6; 93(9).
11. Bayer G, von Tokarski F, Thoreau B, Bauvois A, Christelle Barbet, Cloarec S, et al. Etiology and Outcomes of Thrombotic Microangiopathies. Clinical Journal of the American Society of Nephrology, 2019 Mar 12; 14(4): 557–66.
12. Hanna R, Gibney R, Boysen-Osborn M. Thrombotic Microangiopathies. Emergency Medicine Clinics of North America [Internet], 2025 Aug; 43(3): 407–20.
13. Ayari L, Elliott M, Go R, Godby R, Hook C, Rouse R, et al. HTRS2025.P1.30 Chemotherapy-induced thrombotic microangiopathy – clinical presentation, treatment, and outcomes: the Mayo Clinic experience. Research and Practice in Thrombosis and Haemostasis [Internet], 2025 Nov; 9: 103050.
14. Monteiro L, Maria Helena Vaisbich-Guimarães, Sridharan M, Tran CL, Sethi S. Thrombotic microangiopathy in children. Pediatric Nephrology, 2022 Jan 18; 37(9): 1967–80.
15. Shahid K, Qayyum S. Eculizumab Versus Ravulizumab for the Treatment of Atypical Hemolytic Uremic Syndrome: A Systematic Review. Cureus [Internet], 2023 Sept 29; 15(9): e46185–5.
16. Muniz TP, Patriquin CJ, Saibil S D. Presumed complement-mediated, checkpoint inhibitor-induced thrombotic microangiopathy in a patient with metastatic melanoma. BMJ Case Reports [Internet], 2021 July; 14(7): e242075.
17. Cruz MT, Landrón FG, López N, Alcántara LP, Markides DM, Burk KJ, et al. Hematologic immune-related adverse effects of immune checkpoint inhibitors: a review. Supportive Care in Cancer, 2025 Oct 1; 33(10): 912–2.
18. Kwak SH, Shah CV. A brief review of renal-limited thrombotic microangiopathy associated with immune checkpoint inhibitors. Journal of Onco-Nephrology, 2023 Jan 4; 7(2): 105–10.
19. Hanna RM, Tran NT, Patel SS, Hou J, Jhaveri K D, Parikh R, et al. Thrombotic Microangiopathy and Acute Kidney Injury Induced After Intravitreal Injection of Vascular Endothelial Growth Factor Inhibitors VEGF Blockade-Related TMA After Intravitreal Use. Frontiers in Medicine, 2020 Oct 7; 7: 579603–3.
20. Rubio-Haro R, Quesada-Carrascosa M, Hernández-Laforet J, Ferrer Gómez C, De Andrés J. Diagnostic-therapeutic algorithm for thrombotic microangiopathy. A report of two

cases. Revista Española de Anestesiología y Reanimación (English Edition) [Internet], 2022 Mar 10; 69(3): 179–82.

21. Wu MS, Abbal Koirala. Thrombotic microangiopathy following chimeric antigen receptor T-cell therapy. Clinical Nephrology - Case Studies, 2023 Jan 1; 11(1): 17–21.
22. Nagaoka K, Katagiri D, Matsunami M, Chinen M, Seki K, Fukuda J, et al. Kidney Biopsy Proven Thrombotic Microangiopathy Induced by Methamphetamine. Internal Medicine [Internet], 2023 Oct 19; 63(11): 1603–8.
23. Daviet F, Franck Rouby, Pascale Poullin, Moussi-Francès J, Sallée M, Stéphane Burtey, et al. Thrombotic microangiopathy associated with gemcitabine use: Presentation and outcome in a national French retrospective cohort. British Journal of Clinical Pharmacology, 2018 Dec 18; 85(2): 403–12.
24. Ng JY, Lenton D, Kerridge I, Wong C. A Case Report of Quinine-Induced Thrombotic Microangiopathy Successfully Treated with Eculizumab. Journal of Investigative Medicine High Impact Case Reports, 2024 Jan 1; 12: 23247096241235617–7.
25. Alfredo Gutiérrez-Govea, Basilio Jalomo-Martínez, Luis Alberto Evangelista-Carrillo, José Ignacio Cerrillos-Gutiérrez, Miguel Medina-Pérez. Thrombotic microangiopathy associated with calcineurin inhibitor induction doses in patients with a kidney transplant. Clinical Case Reports, 2024 June 28; 12(7): e9125–5.
26. Kim YJ. A new pathological perspective on thrombotic microangiopathy. Kidney Research and Clinical Practice, 2022 June 21.
27. Moake JL, Byrnes JJ. Thrombotic Microangiopathies Associated with Drugs and Bone Marrow Transplantation. Hematology/Oncology Clinics of North America [Internet], 2005 June 19 [cited 2026 July 21]; 10(2): 485–97.
28. Li A, Bhatraju PK, Chen J, Chung DW, Hilton T, Houck K, et al. Prognostic Biomarkers for Thrombotic Microangiopathy after Acute Graft-versus-Host Disease: A Nested Case-Control Study. Transplantation and Cellular Therapy, 2021 Apr; 27(4): 308.e1-308.e8.
29. Yui JC, Keer J Van, Weiss BM, Waxman AJ, Palmer MB, D'Agati V D, et al. Proteasome inhibitor-associated thrombotic microangiopathy. American Journal of Hematology, 2016 June 11; 91(9).