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INTEGRATED STUDY MASTER'S THESIS

" Thrombotic Microagiopathy and Kidney Injury "

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Abbrevations

TMA - Thrombotic microangiopathy

TTP - Thrombotic thrombocytopenic purpura

AHUS - Atypical hemolytic uremic syndrome

AKI – Acute Kidney injury

ADAMTS13 – A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13

CAPS – Catastrophic Antiphospholipid Syndrome

CM-TMA – Complement-mediated Thrombotic Microangiopathy

cTTP – Congenital Thrombotic Thrombocytopenic Purpura

HELLP – Hemolysis, Elevated Liver Enzymes, and Low Platelets

HSCT – Hematopoietic Stem Cell Transplantation

iTTP – Immune-mediated Thrombotic Thrombocytopenic Purpura

MASP-2 – Mannan-binding Lectin Serine Protease 2

PET – Preeclampsia Toxemia

STEC-HUS – Shiga Toxin–producing Escherichia coli Hemolytic Uremic Syndrome

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1. Summery

Thrombotic microangiopathy with its primery and secondary subtypes and their different pathogeneses, represents a very extensive picture of diseases. This literature review aims to provide a comprehensive picture of these diseases, as many of them can be potentially dangerous. Trombotic microangiopathy is characterized primarily by microvascular thrombosis and endothelial damage, as well as the resulting organ damage. Many organs can be affected, although the kidneys are primarily affected. With focus is on the latest findings of the last 5 years, immunological and molecular mechanisms, as well as therapeutic approaches and diagnostic methods, were investigated in order to gain a better understanding of this. One main focus is primarily on the ever-developing understanding of ADAMTS13 deficiency and complement dysregulation in the development of the diseases, but also on new diagnostic methods such as genetic testing and biomarkers. The effectiveness of targeted treatments with complement inhibitors, for example, was investigated, as were new therapeutic approaches. The results showed promising approaches that require further research. It was also shown that the prognosis and treatment depend above all on the correct diagnosis and adapted treatment.The integration of new knowledge has led to significant progress in research, but also shows the need of further research and development in some areas of thrombotic renal microangiopathies with the aim of improving diagnosis, personalizing treatment and guiding future nephrological research.

2. Keywords:

Thrombotic microangiopathy, kidney, complement system, atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, ADAMTS13, endothelial injury, renal histopathology, complement inhibition, eculizumab, ravulizumab, pregnancy-associated TMA, transplant-associated TMA, secondary TMA, microvascular thrombosis, acute kidney injury, autoimmune diseases, genetic mutations, biomarkers, differential diagnosis, plasma exchange, personalized therapy, cancer.

3. Methodology

When selecting the literature, particular care was taken to include recent scientific studies. The focus was on studies published in the last five years, as important developments in the field of thrombotic microangiopathies (TMA) with renal involvement have taken place during this period. These include advances in diagnostics and therapies such as eculizumab or ravulizumab. Both German-language and English-language articles were used. As most current research results are published in English, the majority of sources come from international journals. German texts were mainly used when they provided helpful overviews or clearly explained complex content. Older literature was only consulted if it was important for understanding basic mechanisms or for classifying current findings. This enabled a good balance to be struck between current knowledge and proven background knowledge. The research was mainly conducted via platforms such as PubMed and Google Scholar. Specific keywords were used that matched the respective subtopics of the paper. Medical guidelines and individual case reports were also included, especially if they described rare courses or special patient groups. The aim was to provide a well-founded and comprehensible overview of the current state of research.

4. Introduction

Thrombotic microangiopathies (TMAs) are a group of rare but clinically significant disorders characterized by microvascular endothelial injury, intravascular thrombosis, and a triad of microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction. Among the affected organs, the kidney plays a central role not only because of its dense and highly specialized microvasculature, but also due to its unique vulnerability to ischemic and thrombotic injury. In many cases, renal involvement is the first or most prominent manifestation of TMA and a key determinant of patient outcome.

The term TMA encompasses a broad range of syndromes that differ in etiology, pathophysiology, and therapeutic implications. Traditionally, a distinction is made between primary forms such as thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS), and secondary forms that occur in the context of infections, autoimmune diseases, malignancies, pregnancy, transplantation, hypertensive crises, or certain medications. Although these entities may share similar clinical and histopathological features, their underlying mechanisms are fundamentally different. Therefore, a precise and timely differential diagnosis is essential, not only

to initiate appropriate therapy, but also to avoid potentially harmful interventions such as unnecessary plasma exchange or immunosuppression.

In recent years, rapid advances in molecular medicine, immunology, and nephropathology have significantly enhanced our understanding of TMA. The identification of complement dysregulation, particularly of the alternative pathway, as a central driver in aHUS has led to the development and approval of targeted therapies such as eculizumab and ravulizumab, which have markedly improved patient outcomes. Similarly, the discovery of severe ADAMTS13 deficiency as the defining feature of TTP has enabled more accurate diagnostics and the establishment of individualized treatment regimens, including caplacizumab and recombinant ADAMTS13. Furthermore, new insights into genetic predispositions, such as mutations in complement regulatory proteins or coagulation-related genes, have reshaped our understanding of the interplay between inherited susceptibility and environmental triggers ("second hits"). Concurrently, histopathological diagnostics have evolved to include not only classical morphological criteria, but also immunohistochemical and ultrastructural findings, such as the detection of platelet-rich thrombi, endothelial swelling, and C4d deposition, which aid in subclassification and guide further diagnostics, including genetic and serological testing. Despite these advances, the clinical management of TMA remains challenging. The rarity and heterogeneity of the syndromes, their often fulminant clinical course, and the frequent overlap of features between different forms require a high degree of clinical suspicion and interdisciplinary collaboration. Moreover, the increasing availability of targeted therapies raises new questions regarding optimal treatment duration, long-term safety, cost-effectiveness, and the identification of patients most likely to benefit from such interventions.

The aim of this thesis is to provide an up-to-date review of thrombotic microangiopathies with renal involvement, with particular emphasis on the pathophysiological mechanisms, histological features, clinical presentations, and therapeutic options of the various subtypes. Special focus is given to complement-mediated TMA, TTP, and secondary forms such as pregnancy-, transplant-, or malignancy-associated TMAs. By analyzing recent literature from the past five years, this work intends to summarize current evidence and identify future research directions that may ultimately improve the care of patients affected by these complex and often devastating diseases.

5. Literature review

5.1 Pathogenesis of thrombotic microangiopathy

The pathogenesis of thrombotic microangiopathy is complex and involves a variety of molecular, cellular and immunological mechanisms that lead to endothelial damage, microthrombus formation and organ failure. Central to this is endothelial damage, which favors the release of von Willebrand factor (vWF), the activation of platelets and the initiation of the coagulation cascade.[13] A central pathomechanism of many forms of TMA is the dysregulation of the complement system. In particular, the uncontrolled activation of the alternative complement pathway play a decisive role. Under physiological conditions, a group of regulatory proteins - including factor H, factor I and MCP (CD46) - protect the body's own endothelium from excessive complement activation. However, mutations or autoantibodies against these regulators lead to a permanent activation of C3 and the formation of the membrane attack complex (MAC, C5b-9), which damages the endothelial cells and creates a prothrombotic microenvironment. [16,18]

At the same time, the endothelial damage triggers an inflammatory cascade, which is amplified by cytokines, growth factors (such as VEGF) and interactions with immune cells. VEGF in particular plays a dual role here: on the one hand it protects the vascular endothelium, on the other hand its inhibition (e.g. by oncological therapies) can trigger TMA-like damage, which is observed in particular in glomerulus function.[11,12] The various initiation pathways of complement activation - classical, lectin-mediated and alternative - all lead to the activation of C3, the central switching point in the complement system. Recent studies have also shown that extrinsic proteases such as thrombin and plasmin can also directly cleave C3 and C5 and thus induce complement activation independently of traditional pathways. [16,18] In addition to complement dysregulation, a deficiency of ADAMTS13 plays a central role in TTP (thrombotic thrombocytopenic purpura). This enzyme cleaves ultra-long vWF multimers. If it is deficient (genetically or due to autoantibodies), uncontrolled platelet aggregation at vWF occurs, particularly in the CNS. [13] Bacterial toxins, such as the Shiga toxin in STEC-HUS, also binds to specific receptors (e.g. Gb3) on glomerular endothelial cells. They block protein biosynthesis and lead to apoptosis of the endothelial cells. This leads to the release of prothrombotic microparticles and complement activation. [13] Histopathologically, TMA appears as a combination of endothelial swelling, mesangiolytic changes, subendothelial fibrin deposition, double layers of the glomerular basement membrane and microthrombi in

arterioles and capillaries.[11] However, these changes are not pathognomonic for a specific form of TMA and must always be interpreted in the context of clinical and laboratory findings. In addition to systemic complement activation, studies have shown that local (tissue-resident or intracellular) complement activity - for example through the so-called "complosome" - also plays a role in pathogenesis. Intracellular C3a/C5a generation in immune cells influences metabolic and immunological programs of the cells and enhances the inflammatory response.[18] TMA is a multifactorial syndrome in which immunological, hematological, toxic and genetic mechanisms interact to produce a disturbed vascular homeostasis with thrombus formation in the microcirculation. The molcular pathogenesis is crucial for the therapeutic decision - especially for the targeted use of complement inhibitors such as eculizumab.

Mechanism	Description	Relevant Subtypes
Endothelial Cell Damage	Plays a central role; leads to vWF release, platelet activation, and coagulation	All TMA forms
Complement Dysregulation	Uncontrolled activation of the alternative pathway; leads to MAC (C5b-9) formation and endothelial cell injury	aHUS, CM-TMA, p-aHUS, TA-TMA
ADAMTS13 Deficiency	Leads to uncontrolled platelet aggregation on UL-vWF multimers	TTP (iTTP, cTTP)
Shiga Toxin Effect (STEC-HUS)	Binds to Gb3 receptors, blocks protein synthesis → endothelial apoptosis	STEC-HUS
VEGF Inhibition	VEGF deficiency (e.g., due to cancer therapy) causes endothelial dysfunction	Drug-induced TMA
Cytokines/Immune Cells	Amplify inflammation and complement activation	Secondary TMAs (e.g., autoimmune, transplant)
Complement via Extrinsic Proteases	Thrombin/plasmin cleave C3/C5 independently of classical pathways	aHUS, systemic inflammation
Complosome (intracellular complement activity)	Local complement activation in immune cells; enhances inflammation	Emerging research field, aHUS
Histological Features	Endothelial swelling, mesangiolysis, subendothelial edema, glomerular double contours, microthrombi	Diagnostic for all TMA forms

Table 1

The table summarizes central pathogenetic mechanisms of thrombotic microangiopathies and assigns them to the respective subtypes.

5.2 Histological features of thrombotic microangiopathy

The histological features of thrombotic microangiopathy can be seen in various tissue compartments of the kidney in both acute and chronic stages. Histologically, TMA can be characterized by changes in the glomeruli, arterioles and interstitial areas. These changes can be visualized by light microscopic, electron microscopic and immunohistochemical methods and make a decisive contribution to the differentiation of TMA types and diagnostic classification.

Acute histological features

In the acute phase of TMA, thrombi in glomerular capillaries and arterioles are the central feature. These consist of fibrin, platelet agregates and fragmented erythrocytes. Under the light microscope, they appear as eosinophilic masses in the capillary lumens (Fig. 1A). CD61 immunohistochemistry is used for the specific detection of platelets in thrombi and allows a differentiated visualization of even the smallest platelet aggregates (Fig. 1B).[79] In addition, pronounced endothelial swelling, occasionally with detachment of the cells from the basement membrane, is typical. Mesangiolysis, i.e. the dissolution of the mesangial matrix, occurs frequently and can lead to glomerular microaneurysms. Subendothelial edema, intramural fibrin and myxoid intimal swelling are observed in arterioles (Fig. 2A, 2B).[79]

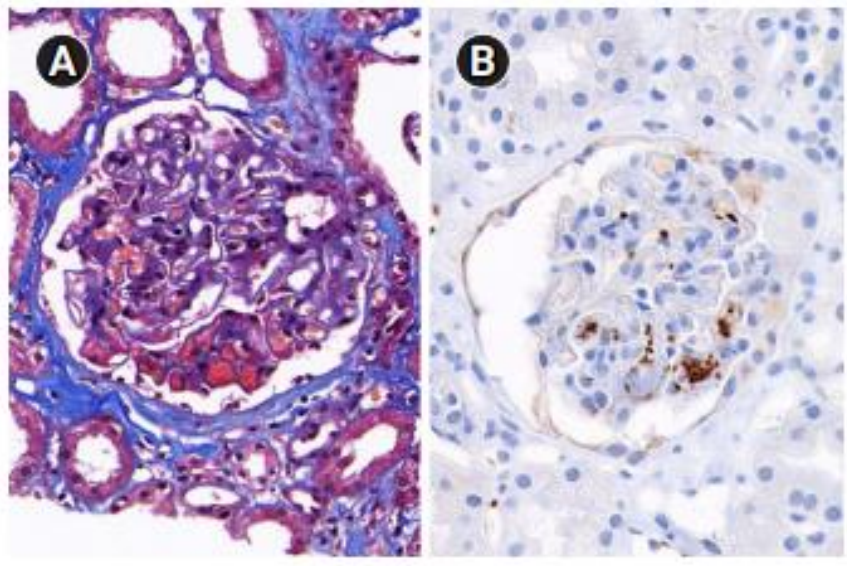

Figure 1

Masson trichrome staining shows thrombi in the capillary lumen (A), CD61 staining identifies platelet aggregates (B) Source: Kim et al, 2022, Renal research and clinical practice

Accompanying endothelial swelling and detachment of the endothelial cells from the glomerular basement membrane can be seen. Subendothelial edema often leads to the formation of a “fluffy”, electron-lucent material between the endothelium and basement membrane, which is visible in electron microscopy. (Fig. 3A)[79]

Chronic histological features

Chronic TMA is characterized by remodeling processes in the vessel walls. Particularly striking is the double contour of the glomerular basement membrane - also known as the “tram-track” pattern - which is caused by subendothelial matrix deposition (Fig. 3B). In arteries, fibrotic intimal thickening, partly with onion-skin-like lamination (“onion-skin” lesions, Fig. 2D) and hyaline arteriolosclerosis can be seen.[78.79]

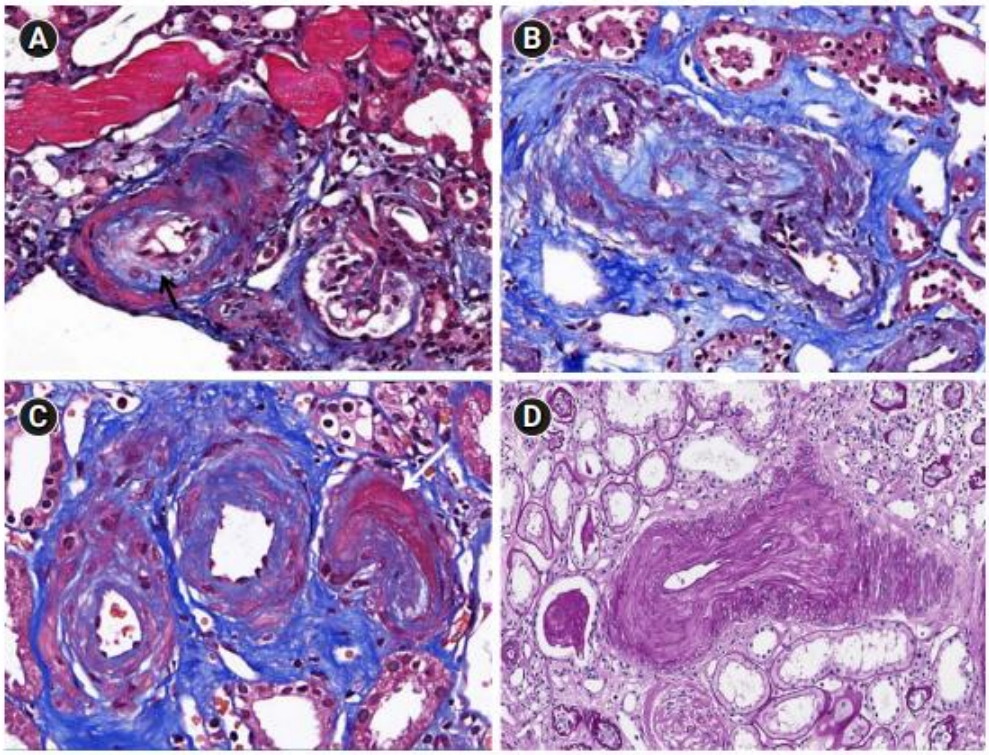

Figure 2

Myxoid changes and fibrosis in arteries, onion skin-like lamellae (D) Source: Kim et al, 2022, Renal research and clinical practice

Electron microscopic findings

Electron microscopy provides particularly impressive images of the ultrastructural changes in TMA. Even in the early stages, the endothelium detaches from the glomerular basement membrane with the formation of subendothelial clear zones (so-called "subendothelial edema"). These spaces contain amorphous material and cell debris and are considered pathognomonic for endothelial damage. In the further course, duplications of the basement membrane can be observed. These result from repeated endothelial cell damage and repair processes and can be clearly delineated under the electron microscope as double lamellae. In addition, an intraluminal organization of thrombi can be detected.[78,79] (Fig. 3A-B)

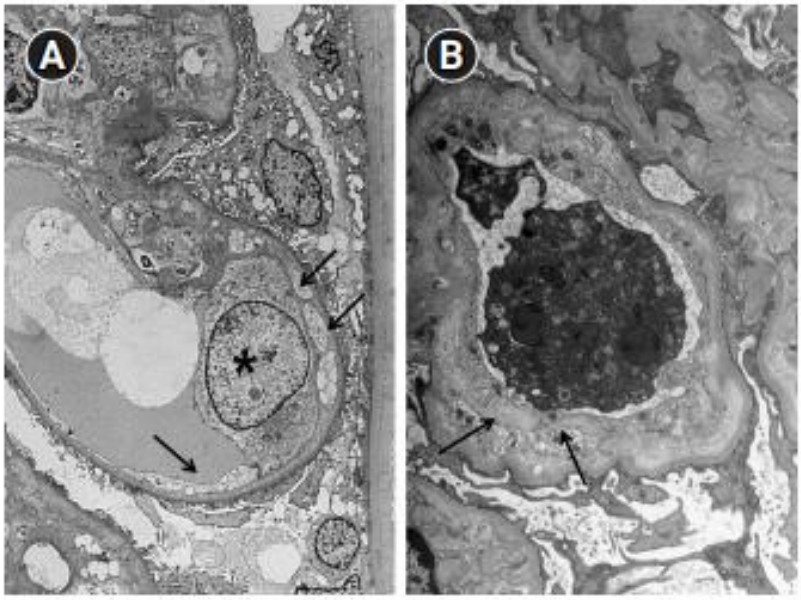

Figure 3 Figure 3 Electron microscopy - Glomerular changes

Endothelial cell detachment and subendothelial deposits (A), doubling of the basement membrane (B) Source: Kim et al, 2022, Renal research and clinical practice

Immunohistochemical markers

CD61 (a marker for thrombocytes) and C4d are of particular importance for immunohistochemical diagnostics. CD61 specifically marks thrombotic areas, although interpretation can be complicated by non-specific granular appearances. C4d is increasingly used to differentiate TMA in the context of complement activation, e.g. in atypical HUS or transplant-associated TMA. Positive C4d staining

along the arterioles or glomerular capillary walls supports the diagnosis of complement-mediated damage.[78,79]

The histological features of TMA are essential for the diagnosis and differential diagnosis. While acute forms are dominated by thrombi and endothelial damage, chronic forms are characterized by remodeling processes of the vessel wall. A differentiated assessment using light and electron microscopy as well as additional immunohistochemical staining (e.g. CD61, C4d) is essential for a reliable diagnosis and treatment decision. In combination with clinical parameters, histological TMA patterns can indicate the need for genetic testing or specific therapies such as complement inhibition at an early stage.

5.3 Classification of thrombotic microangiopathies

The modern classification of TMA is increasingly based on the underlying molecular pathomechanisms (e.g. complement activation, ADAMTS13 deficiency), as classic clinical classifications do not adequately reflect the heterogeneous etiology. Nevertheless, the distinction between primary (idiopathic/genetic) and secondary (acquired/trigger-induced) forms remains clinically relevant.

1. Primary forms of TMA

These forms arise due to genetic or autoimmunological disorders without an external cause, but can be triggered by "second hits" (e.g. infections, birth, medication).

a) Thrombotic thrombocytopenic purpura

- Cause: ADAMTS13 activity <10 %
- Etiology: Autoantibodies against ADAMTS13 (acquired TTP) or genetic defects (Upshaw-Schulman syndrome)
- Clinic: mainly CNS symptoms, less renal failure
- Therapy: plasmapheresis, caplacizumab, rituximab

b) Complement-mediated thrombotic microangiopathy or Atypical haemolytic uraemic syndrome (aHUS)

- Cause: dysregulation of the alternative complement pathway
- Etiology: Mutations in CFH, CFI, CD46, THBD, C3, CFB or autoantibodies against CFH
- Clinic: Renal failure, hypertension, thrombotic microangiopathy in other organs
- Therapy: Complement inhibition (eculizumab, ravulizumab)

c) Hereditary TMAs (complement-independent)

- DGKE mutation: Early childhood TMA, no complement dysregulation
- MMACHC (cblC defect): Methylmalonic acidemia + homocystinuria with neurological and renal manifestations
- Clinic: Frequently recurrent, therapy-refractory courses
- Therapy: specific depending on the mutation (e.g. hydroxycobalamin for cblC)

2. Secondary TMAs (trigger-dependent, often mixed patterns) These forms are induced by external triggers, but may involve a genetic predisposition. They often show histologically similar features to primary forms.

a) Drug-induced TMA Classic triggers:

- VEGF inhibitors (e.g. bevacizumab, aflibercept)
- Calcineurin inhibitors (e.g. cyclosporine, tacrolimus)
- Mitomycin C, gemcitabine
- Pathogenesis: Endothelial dysfunction, complement activation
- Localization: Frequently renal-limited TMA
- Therapy: Discontinuation of the drug, eculizumab if necessary

b) Pregnancy-associated TMA Entities: Pre-eclampsia, HELLP syndrome, pregnancy aHUS

- Pathomechanism: endothelial damage, complement activation, coagulopathy
- Differential diagnosis: Overlap with TTP or aHUS
- Therapy: Induction of labor, eculizumab if necessary for persistent TMA

c) Autoimmune disease-associated TMA Lupus erythematosus (SLE), antiphospholipid syndrome (APS)

- Mechanisms: autoantibodies, complement activation, vasculitic component
- Typical: Combined with other lupus manifestations
- Therapy: Immunosuppression, possibly complement inhibition

d) Malignant hypertension-associated TMA

- Pathogenesis: Mechanical stress → endothelial damage → microthrombi
- Clinic: Renal TMA without systemic haemolysis possible
- Therapy: Rapid blood pressure reduction, ACE inhibitors if necessary

e) Transplant-associated TMA

- Especially after kidney transplantation (de novo or recurrent)
- Trigger: Immunosuppressants, AK-mediated rejection, infections
- Clinic: proteinuria, increase in creatinine, often gradual
- Therapy: change in immunosuppression, eculizumab in individual cases

3. Infection-associated TMAs a) STEC-HUS (Shiga toxin-associated) Trigger: E. coli, produces Shiga toxin

- Pathogenesis: Toxin binding to Gb3 receptors in glomerular endothelium → cell apoptosis + thrombosis
- Clinic: Diarrhea (often bloody), kidney failure in children
- Therapy: Supportive (fluid, dialysis), no antibiotics!

b) Pneumococcal HUS Often occurs in small children

- Pathogenesis: Release of neuraminidase → change in the cell surface → complement activation
- Diagnosis: Coombs test positive (rare in TMA)
- Therapy: Supportive, exchange transfusion if necessary

c) Viral TMA

- HIV, CMV, SARS-CoV-2 as triggers

- Mechanisms: Immune-mediated, endothelotoxic

Additional classification approaches (therapy-oriented)

- Complement-dependent vs. complement-independent
- ADAMTS13-deficient vs. ADAMTS13-intact
- Systemic vs. glomerular limited
- Eculizumab-responsive vs. non-responsive

Treatment Option	Indication	Comment
Plasmapheresis (Plasma Exchange)	iTTP, unclear TMA diagnoses	Removes autoantibodies against ADAMTS13 and replaces the missing enzyme; standard therapy for TTP
Eculizumab	aHUS, p-aHUS, TA-TMA, severe COVID-TMA	C5 inhibitor; blocks complement cascade and protects endothelium; meningococcal vaccination required
Ravulizumab	aHUS, p-aHUS	Long-acting C5 inhibitor with longer infusion intervals than Eculizumab
Caplacizumab	iTTP	Prevents vWF-platelet interaction; reduces thrombosis risk and accelerates recovery
Rituximab	iTTP, autoimmune TMA	Anti-CD20 antibody for B-cell depletion and suppression of autoantibody production
Immunosuppressants (e.g., steroids, cyclophosphamide)	Autoimmune TMA (SLE, APS), secondary forms	Controls underlying disease and inflammation; often combined with plasmapheresis
Antihypertensive therapy	HTN-TMA, SSc-TMA	Rapid blood pressure reduction is essential; RAAS inhibition often helpful
Supportive therapy (e.g., dialysis, fluids, transfusion)	STEC-HUS, viral TMA, severe renal insufficiency	Basic measure in all TMAs to support organ function
Discontinuation of causative drugs	Drug-induced TMA (e.g., gemcitabine, VEGF inhibitors)	Essential to prevent further endothelial damage
Cancer therapy (chemo, surgery)	Cancer-associated TMA	Treating the underlying malignancy can improve TMA

Table 2

This table provides a structured overview of the most important treatment methods for various forms of thrombotic microangiopathy (TMA). The typical areas of application and key clinical indications are summarized for each treatment option. It includes both targeted therapies - such as complement inhibitors (e.g. eculizumab, ravulizumab) and anti-vWF antibodies (e.g.caplacizumab), as well as supportive measures and treatment strategies for secondary causes such as autoimmune diseases, hypertension, infections or tumor diseases.

5.4 Clinical presentation of thrombotic microangiopathy

Main hematologic features

At the center of the hematological picture is MAHA a form of hemolytic anemia in which erythrocytes fragment due to mechanical stress in the constricted capillaries. Typically, schistocytes, i.e. fragmented erythrocytes, are found in the blood smear. In addition, there is an increased reticulocyte count, reduced haptoglobin (due to binding to free hemoglobin), increased indirect bilirubin level and a greatly increased LDH value, which reflects both hemolysis and tissue ischemia.[17] Thrombocytopenia is caused by the increased consumption of platelets in the context of intravascular aggregation and thrombosis formation. The direct antiglobulin test (Coombs test) is usually negative, which rules out immune-mediated hemolysis, an important differentiation from autoimmune hemolytic anemia.[17]

Organ involvement

The clinical symptoms of TMA result from ischemic damage to the affected organs. The most commonly affected organs are the kidneys, central nervous system (CNS), heart and gastrointestinal tract. Renal manifestations include acute renal insufficiency, proteinuria, hematuria and often arterial hypertension. Renal symptoms are particularly pronounced in HUS and aHUS and can worsen within a very short time.[17,92]

CNS symptoms are particularly common in TTP and include headaches, confusion, epileptic seizures, cognitive deficits and even coma or ischemic stroke. [92]

Thrombotic thrombocytopenic purpura : Caused by a pronounced lack of ADAMTS13 activity, usually as a result of autoantibodies (iTTP). Clinically dominated by neurological symptoms, petechial hemorrhages, and only mild renal involvement. The disease is a medical emergency with high mortality without immediate plasmapheresis.[85,87]

Shigatoxin-associated HUS: Often occurs in children after infection with EHEC and is usually accompanied by prodromal bloody diarrhea. Renal insufficiency is in the foreground. Neurological involvement is rarer, but possible.[94]

Atypical HUS: Based on a dysregulated activation of the alternative complement pathway. The presentation is clinically similar to STEC-HUS, but without previous diarrhea. There are often severe and rapidly progressive renal dysfunctions, frequently also extrarenal manifestations such as skin lesions, myocardial infarction or pancreatitis. [17,92]

Secondary TMAs: They develop in the context of other underlying diseases such as systemic lupus erythematosus, malignant hypertension, medication (e.g. calcineurin inhibitors, chemotherapeutic agents), transplants or pregnancy. The clinical features are often subtle and overlap with the underlying disease, making diagnosis difficult.[92]

The neurological manifestations of TMA range from mild headaches to severe cognitive disorders and epileptic seizures. Reversible lesions such as Posterior Reversible Encephalopathy Syndrome (PRES) or ischemic strokes are frequently found in imaging procedures (MRI).[92] Patients with neurological symptoms often require intensive medical care and show a higher comorbidity at diagnosis, although mortality is not necessarily higher. The kidney is one of the most frequently affected organs, as renal tissue is particularly sensitive to endothelial dysfunction. Histopathology shows endothelial cell swelling, fibrinoid necrosis of small vessels, mesangiolytic changes and thrombotic microangiopathy in the glomerulus and arterioles.[17]

5.5 Complement-mediated thrombotic microangiopathy

Complement-mediated thrombotic microangiopathy, formerly known as atypical hemolytic uremic syndrome, is a life-threatening form of TMA caused by dysregulated activation of the alternative complement pathway. The pathophysiology is based on a chronic or excessive activation of the alternative complement pathway, in which proteins such as C3, factor B (CFB), factor H (CFH), factor I (CFI) or the membrane co-factor protein (MCP/CD46) are affected. This activation leads to increased formation of the C5b-9 complex (membrane attack complex), which directly damages the endothelium and leads to thrombus formation in the microcirculation.[72,76,77](Fig. 4) Around 60 % of patients with aHUS show genetic mutations in complement regulator genes or pathological autoantibodies, such as anti-FH antibodies.[76] Mutations in the CFH gene account for around a quarter of cases, MCP around 10%, CFI 6%, C3 and CFB around 2-6% each.[76] In many patients, there is also a trigger situation such as infection, pregnancy, pancreatitis or vaccination that causes

the disease to manifest.[12,71,73] More recent data also show correlations with inflammatory bowel diseases such as ulcerative colitis or malignant haematological diseases such as CLL, in which complement activation occurs through monoclonal IgM immunoglobulins.[72,73] Rarer variants such as gain-of-function mutations in the CFB gene have also been described, which lead to excessive C3b deposition on cell surfaces.[76]

Treatment is aimed at interrupting the complement cascade. The monoclonal antibody eculizumab, is the first-line therapy and prevents the formation of the membrane attack complex. This can maintain or improve kidney function and prevent progression to terminal renal failure.[73,74,77] In genetically confirmed cases with a high tendency to relapse, e.g. CFH or MCP mutations, long-term eculizumab therapy is recommended.[68] In cases without mutations, a gradual reduction or even discontinuation can be considered.[68] Plasmapheresis is particularly useful in the initial phase if no genetic or serological diagnosis is available or eculizumab is not available. It can eliminate pathogenic autoantibodies and supply missing complement regulators.[12,71] In infectiously triggered episodes (e.g. due to influenza H1N1 or acute pancreatitis), disease progression could also be prevented with eculizumab.[12,71] Early diagnosis, ideally with complementary biochemical and genetic diagnostics, is essential for targeted therapy. The identification of genetic variants allows the prognosis to be assessed and improves patient management, both with regard to therapy and the risk of transplantation.[76,77]

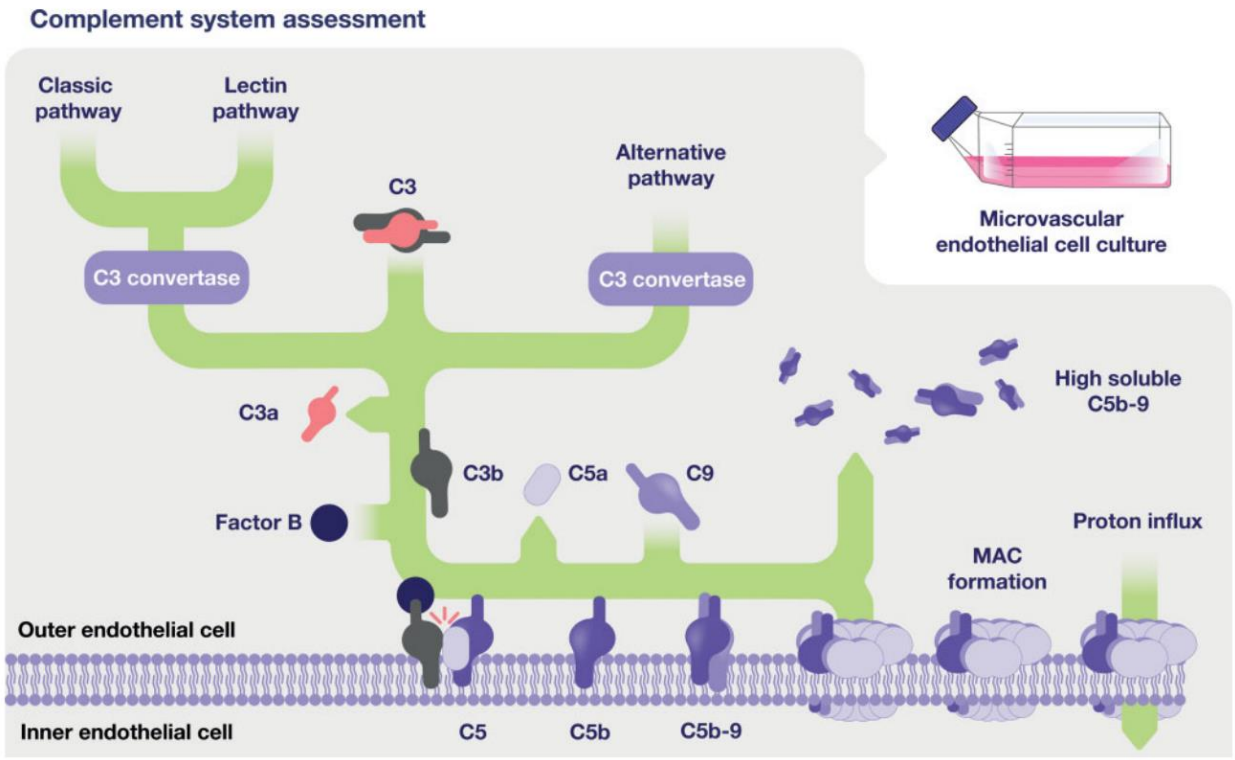

Figure 4 The complement system

The complement system is part of the innate immune defense and protects the body from pathogens and altered cells. It is activated via three pathways - the classical, the lectin and the alternative pathway - and leads to the cleavage of the protein C3 into C3a and C3b. C3b intensifies the defense reaction, which ultimately leads to the cleavage of C5. Among other things, this produces the membrane attack complex (MAC), which is deposited in cell membranes and destroys them. Disorders in the complement system can be caused by genetic defects, faulty regulation or acquired causes. To check the function, for example, soluble C5b-9 or its deposition on vascular cells is measured. Source: (From Thrombotic microangiopathies assessment: mind the complement by M. Blasco et al., 2021)

5.6 Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is a rare but potentially life-threatening form of thrombotic microangiopathy . The disease is characterized by pronounced thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and variable organ damage, particularly to the central nervous system and kidneys. In a renal-limited form, TTP can manifest itself primarily through acute renal failure and is diagnosed histologically by vascular TMA patterns without pronounced thrombosis.[79]

Pathophysiologically, classic immune-mediated TTP (iTTP) is characterized by a severe reduction in the activity of the enzyme ADAMTS13 (<10%), which is usually caused by autoantibodies. This protease cleaves ultra-long von Willebrand factor (ULVWF) multimers, which otherwise lead to pathological thrombus formation in the microcirculation.[81] In hereditary forms (cTTP), there is a genetic defect. In addition to ADAMTS13 deficiency, complement activation processes may contribute to pathogenesis, particularly via C3a and SC5b-9 activation, indicating involvement of the alternative complement pathway.[81] A special feature of the renal-limited form is the frequently discrete thrombocytopenia with simultaneous severe renal failure. This has also been described in clopidogrel-induced TTP in which there is no ADAMTS13 deficiency. In this case, direct endothelial damage and release of ULVWF appear to be in the foreground.[82] These atypical forms pose a diagnostic challenge, especially as classic criteria such as fever or neurological symptoms may be absent.[82]

Diagnosis is primarily based on the determination of ADAMTS13 activity and inhibitors. Due to logistical and time restrictions, empirical treatment can also be used in cases of clinical suspicion. Treatment is based on therapeutic plasma exchange (TPE), which removes the autoantibody and replaces ADAMTS13. This is supplemented by glucocorticoids, rituximab for B-cell depletion and caplacizumab, which blocks the binding of ULVWF to platelets.[81] In pregnancies with TTP, a distinction must be made between iTTP and cTTP. While immunosuppression and TPE are indicated for iTTP, cTTP patients benefit from prophylactic plasma infusions to prevent relapses.[83] TTP can also occur in systemic autoimmune diseases such as SLE. Here, studies show that SLE-

TTP tends to have a milder renal course than primary iTTP.[84] TTP is a heterogeneous disease with potential renal manifestations. Timely diagnosis, including by renal biopsy if the aetiology is unclear, and targeted, multimodal therapy are crucial for the prognosis. Future research should further clarify the role of the complement system, as new therapeutic targets such as eculizumab could be considered here.

5.7 Pregnancy-associated thrombotic microangiopathy

Pregnancy-associated atypical hemolytic uremic syndrome is a rare but serious form of thrombotic microangiopathy that occurs in connection with pregnancy or the puerperium. The pathophysiology of p-aHUS is primarily based on dysregulated activation of the alternative complement pathway, which leads to endothelial damage, microthrombus formation and ultimately the classic triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury.[3,4,7]

Although pregnancy complications such as preeclampsia and HELLP syndrome may have similar clinical features, p-aHUS differs in that renal function typically does not spontaneously improve after delivery. While pre-eclampsia and HELLP syndrome usually resolve within 72 hours of delivery, in p-aHUS the hemolysis and kidney damage persist.[3,5] Typical trigger mechanisms for complement activation are inflammatory processes in the puerperium, migration of fetal cells into the maternal circulation as well as blood loss and infections.[3] Risk factors for the development of p-aHUS include preeclampsia, postpartum haemorrhage, nulliparity and genetic predispositions for complement regulation defects, even if no mutations can be detected in many affected women.[4,5]

The treatment of p-aHUS is based on the targeted blockade of the terminal complement pathway, whereby the therapy options today primarily include the monoclonal antibodies eculizumab and ravulizumab. Eculizumab, was the first agent to be approved for aHUS and interrupts the complement cascade, thereby stopping endothelial damage.[3] Early initiation of therapy with eculizumab often leads to a rapid recovery of platelet count, stabilization of hemolysis parameters and improvement of renal function, as several case reports have shown.[5] Recent experience shows that ravulizumab, can also be used effectively in p-aHUS. Ravulizumab has a longer half-life compared to eculizumab and therefore allows less frequent infusions, which improves the patients' quality of life.[4] In recent case reports, ravulizumab was able to quickly end dialysis dependency and led to a sustained normalization of laboratory parameters. While plasmapheresis used to be a standard therapy, today it is primarily a temporary solution if specific complement inhibition is not yet available or the diagnosis remains uncertain.[3,7] Vaccination against meningococci is essential before starting C5 inhibition due to the increased risk of infection. Alternatively, prophylactic

antibiotic therapy can be given until vaccine immunity is established.[3] In the long term, it is recommended that treatment with eculizumab or ravulizumab be individually controlled. Discontinuation of treatment is possible if the haematological and renal course is stable, especially if the triggering cause is clearly identifiable and there is no genetic risk profile.[3,4] P-aHUS is a rare but serious complication of pregnancy whose prognosis can be significantly improved by early diagnosis and targeted therapy with complement inhibitors.

5.8 Transplant-associated thrombotic microangiopathy

Transplant-associated thrombotic microangiopathy is a severe complication after hematopoietic cell transplantation (HCT) that typically occurs within the first 30 to 60 days after transplantation.[8] Clinically, TA-TMA manifests with microangiopathic hemolytic anemia (MAHA), persistent schistocytosis, thrombocytopenia and microthrombosis leading to ischemic organ damage, particularly of the kidneys, but also of the lungs and central nervous system.[8,9]

The pathophysiology of TA-TMA is based on endothelial damage triggered by various pre- and post-transplant insults. Risk factors include myeloablative conditioning, acute graft-versus-host disease (GVHD), infections and the use of calcineurin inhibitors.[8] The uncontrolled activation of the complement system, in particular the terminal complement pathway, plays an important role here, leading to the formation of the membrane attack complex C5b-9. This complement activation is not always genetically determined, but genetic variants in complement regulatory genes such as CFH, CFI and CD46 have been detected in some patients.[8] Diagnostically, the detection of TA-TMA relies on clinical criteria such as new or persistent schistocytosis, thrombocytopenia, anemia and signs of hemolysis, complemented by biomarkers such as soluble C5b-9 (sC5b9). Although sC5b9 is a promising biomarker, it has limitations in terms of sensitivity and specificity.[8]

The treatment of TA-TMA remains a challenge, as no standardized therapy is currently established. Earlier approaches such as plasmapheresis showed only limited success in TA-TMA.[8,9] Today, complement inhibition with eculizumab is considered one of the most effective therapeutic options. Eculizumab, blocks the formation of C5b-9 and thus prevents endothelial damage.[9] In a documented case of an adolescent who developed TA-TMA after autologous bone marrow transplantation, early administration of eculizumab led to a rapid improvement in pulmonary hemorrhage, anemia, thrombocytopenia and renal function. The patient required no further treatment after three doses of eculizumab and showed stable renal function values over several years.[9] Further therapeutic options are currently being investigated, including ravulizumab, a long-acting C5 inhibitor, and new complement blockers such as narsoplimab and pegcetacoplan.[8] Despite these advances, treatment remains complex and depends on the severity of the disease and organ

involvement. It is particularly important to emphasize that early diagnosis and initiation of therapy are crucial for successful treatment and organ preservation.[8,9] TA-TMA is a serious endothelial disease caused by a combination of transplant-related risk factors and complement activation. Complement inhibition, particularly through early administration of eculizumab, has been shown to be effective in reducing morbidity and mortality in these patients.

5.9 Infection-associated thrombotic microangiopathy

Infection-associated thrombotic microangiopathy (TMA) is an important secondary form of TMA caused by various infectious agents, including Shiga toxin-producing Escherichia coli (STEC), Pneumococcal, influenza viruses, CMV, HIV, Sars-Cov 2 and hepatitis B viruses. The pathophysiology differs depending on the pathogen: In the case of infection with STEC, such as E. coli, Shiga toxins lead to binding to the globotriaosylceramide (Gb3) receptor on endothelial cells. After binding, the toxins are retrogradely transported into the Golgi apparatus and subsequently into the endoplasmic reticulum, where the active A1 subunit damages the 28S rRNA of the ribosomes and inhibits protein biosynthesis. This leads to apoptosis of the endothelial cells, activation of the coagulation cascade and ultimately to the formation of microthrombi.[22,24] In addition to direct cell toxicity, complement activation appears to play a role, which further increases endothelial damage.[24] Stx2-producing strains are particularly dangerous and are more likely to cause severe courses including hemolytic uremic syndrome (HUS). In the context of viral infections such as influenza or COVID-19, TMA is primarily mediated by an excessive immune response. In COVID-19-associated TMA, the uncontrolled activation of the complement system via all three pathways (classical, lectin, alternative) plays a decisive role. The resulting endothelial damage syndrome leads to microthrombus formation, vascular inflammation and multi-organ failure.[19] Infection has also been documented as a trigger for complement mediated TMA in H1N1 influenza, often in combination with genetic predispositions such as mutations in the CD46 gene.[21] Another example of infectiously triggered TMA is a hepatitis B virus infection. In transplanted patients, HBV can trigger glomerulonephritis with concomitant TMA via the formation of immune complexes, as described in a patient with a new HBV infection after kidney transplantation.[20]

The treatment of infectious-associated TMA depends largely on the aetiology. In STEC-HUS, the most important approach is supportive therapy, in particular volume management, electrolyte correction and renal replacement therapy if necessary. The use of antibiotics is usually avoided due to the risk of toxin release.[22,24] Anti-complement therapies such as eculizumab are currently only used for severe refractory courses or atypical presentations. Complement inhibition with eculizumab has been successfully used in influenza-associated TMA, particularly when genetic

complement dysregulation (e.g. CD46 mutation) has been detected.[21] In this case, initial treatment often involved plasmapheresis to remove immune complexes and circulating toxic factors before the targeted use of complement inhibitors. In hepatitis B-associated TMA, the focus is on antiviral therapy. In one documented case, treatment with entecavir led to an improvement in both viral load and renal function. Complement blockade was not used in this case.[20] It is clear that early detection of the causative infection and a pathogen-specific therapeutic approach are crucial for the prognosis of infectious-associated TMA.

5.10 Emergency-Associated Thrombotic Microangiopathy

Hypertensive Emergency-Associated Thrombotic Microangiopathy is a secondary form of thrombotic microangiopathy that can occur in severe hypertensive crisis. The pathophysiological mechanism is based on severe damage to the endothelium, triggered by extremely high blood pressure levels, which lead to mechanical stress on the vessel wall. This leads to microthrombus formation, microangiopathic hemolytic anemia and thrombocytopenia.[26,27] In hypertensive emergencies, the characteristic organ damage is mainly found in the kidney, heart and retina. Renin-angiotensin-aldosterone system (RAAS) activation plays an important role in pathogenesis: elevated aldosterone levels increase endothelial damage, which in turn contributes to the development of TMA.[27,28] Studies show that there is an increased risk of multiple organ damage and TMA, particularly in patients with highly elevated plasma aldosterone concentrations.[28] Renal biopsies in HTN-TMA show typical findings such as malignant nephrosclerosis with fibrinoid necrosis of small arteries, “onion-skin” changes and thrombotic occlusion of the glomerular capillaries.[25,26] The microvascular damage not only affects the kidneys, but can also lead to pulmonary alveolar hemorrhage, as has been described in individual cases.[25,27]

The treatment of HTN-TMA is primarily based on rapid and controlled blood pressure reduction. Effective antihypertensive therapy can limit microvascular damage and reverse hemolysis and thrombocytopenia.[26] In many patients, haematological parameters (platelet count and haemoglobin) normalize with adequate blood pressure control alone, as has been repeatedly documented.[26,27] Antihypertensive strategies typically include intravenous blood pressure lowering using drugs such as nicardipine or hydralazine, followed by a switch to oral antihypertensives, including calcium channel blockers, ACE inhibitors or angiotensin II receptor blockers.[27,28] In particular, inhibition of the RAAS using ACE inhibitors or angiotensin II receptor blockers showed favorable effects on vascular healing.[27] In particularly severe cases with severe hypervolemia, acute renal insufficiency

or lack of blood pressure control, ultrafiltrative procedures or renal replacement therapy may be necessary.[29] In individual cases, an interventional procedure, such as stent implantation for renal artery stenosis, was also required to treat the source of hypertension directly.[29] The prognosis of HTN-TMA is closely linked to early detection and effective blood pressure control. While renal function may improve with treatment in some cases, it is not uncommon for severe initial renal damage to result in the need for dialysis.[25,26]

5.11 Cancer-Associated Thrombotic Microangiopathy

Cancer-Associated Thrombotic Microangiopathy is a serious complication of malignant diseases and their therapy. The pathophysiology of CA-TMA is based on two main mechanisms: on the one hand, the direct infiltration of tumor cells into the microvasculature can lead to mechanical endothelial damage; on the other hand, cancer therapy itself can cause damage to the endothelium through toxic or immune-mediated mechanisms.[30,45] Primary tumor-associated TMAs often occur in patients with metastatic adenocarcinomas, such as breast, prostate, gastric or lung carcinomas. These tumors cause microvascular embolization, which leads to red blood cell fragmentation and platelet consumption.[44,45] Adrenocortical carcinomas have also been associated with the development of persistent TMAs, with complete remission of TMA not always achieved even after tumor resection.[30] In addition to tumor-related mechanisms, numerous cancer therapies can trigger TMA. Particularly relevant here are anti-VEGF inhibitors such as bevacizumab and ramucirumab, which cause pronounced glomerular endothelial damage by inhibiting the endothelial VEGF signaling cascade.[31] Tyrosine kinase inhibitors (TKIs) such as pazopanib or sorafenib can also lead to TMA by disrupting vascular integrity.[31] Immune checkpoint inhibitors such as pembrolizumab also induce TMAs through excessive immune activation and secondary complement activation.[37] Another key trigger is the chemotherapeutic agent gemcitabine, which can cause TMA through both direct endothelial damage and complement activation.[36] Similar mechanisms have been described for pegylated liposomal doxorubicin preparations (PLD).[32] Clinically, CA-TMA often presents with microangiopathic hemolytic anemia (MAHA), thrombocytopenia, increased LDH, decreased haptoglobin and signs of acute renal failure.[31,42] Differentiation from classic TTP is challenging, but crucial, as the therapeutic approaches differ. While a severe ADAMTS13 reduction (<10 %) is present in TTP, this is generally not present in CA-TMA.[83] Histopathologically, renal biopsies show endothelial swelling, thrombus formation in the glomerular capillaries and fibrinoid necrosis.[31,32]

Treatment depends on the etiology, in tumor-associated TMA, the focus is on targeted therapy of the underlying disease. Effective tumor control, for example through chemotherapy or surgical resection, can significantly improve TMA.[30,45] In the case of therapy-associated TMA, immediate discontinuation of the triggering substance is necessary to prevent further endothelial damage.[31,39] Therapeutic plasma exchange (TPE) is primarily used when the differentiation between TTP and CA-TMA is unclear or when severe hematologic symptoms are present.[39,43] Recent case reports also discuss the use of complement inhibitors such as eculizumab in refractory CA-TMA, particularly in gemcitabine- or bevacizumab-associated TMA.[36,37] The prognosis for CA-TMA is generally unfavorable, especially if the TMA is due to advanced tumor disease or the renal insufficiency has become irreversible.[30,45] Another exciting therapeutic concept in the future could be the use of recombinant ADAMTS13, which has already shown promising results in terms of safety and efficacy in studies in patients with congenital TTP.[95]

5.12 Autoimmune-associated thrombotic microangiopathy

Autoimmune-associated thrombotic microangiopathy comprises a group of diseases characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ dysfunction, particularly of the kidneys. These manifestations often occur in patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc) or antiphospholipid syndrome (APS).The pathophysiology of this form of TMA is complex and includes, in particular, activation of the complement system and direct endothelial damage. In SLE-associated TMA, activation of both the classical and alternative complement pathways is observed, leading to endothelial dysfunction and microthrombus formation.[49] Of particular relevance here is the presence of anti-factor H autoantibodies, which promote excessive complement activation and can cause complement-mediated TMA.[47] Extracellular vesicles (EV) also play a central role in pathogenesis. These vesicles carry prothrombotic molecules and can enhance the immune response and the thrombosis cascade, which in turn promotes endothelial damage.[51] In patients with systemic sclerosis, particularly in the context of a scleroderma renal crisis (SRC), SSc-associated TMA often occurs. This is characterized histologically by arteriolar thrombosis, endothelial swelling and minimal immune deposits. In normotensive cases, diagnosis can be more difficult, which underlines the importance of early biopsy diagnosis.[46,57] Antiphospholipid syndrome is also a significant cause of TMA in an autoimmune context. Triple-positive patients with high aGAPSS in particular are at high risk of thrombotic microangiopathies and renal vascular lesions.[53] Multi-organ TMA can occur in the context of catastrophic antiphospholipid syndrome (CAPS), which is associated with a particularly high mortality rate.[58] A particular form of TMA occurs under anti-TNF-α therapy, especially in

patients with rheumatoid arthritis or Crohn's disease. Lupus-like nephritis, ANCA-associated vasculitis and primary TMA have been observed here, although diagnosis is complicated by the large number of possible renal pathologies.[52]

The treatment of autoimmune-associated TMA depends on the underlying autoimmune disease and the severity of the TMA. High-dose immunosuppression with glucocorticoids forms the basis. In addition, plasmapheresis, cyclophosphamide or rituximab are used, especially in refractory courses or suspected concomitant thrombotic thrombocytopenic purpura.[55] If complement activation is detected or anti-factor H antibodies are present, treatment with eculizumab, can be considered.[49] In cases of APS-associated TMA, long-term anticoagulation is also required. The current data show that autoimmune-associated TMA has a complex pathophysiology involving both immune-mediated and thrombotic mechanisms. Early and differentiated diagnosis as well as an individualized therapeutic approach are crucial for the prognosis of patients.

6. Discussion

Diseases from the group of thrombotic microangiopathies with renal involvement are characterized by an extremely complex interplay of different pathophysiological processes. Immunological, genetic, hematological and vascular factors interact closely. Even if they have a common final pathway in the form of microvascular thrombus formation and organ damage, the triggering causes, clinical features and treatment options vary considerably.The kidneys in particular are quickly affected as their microvessels are particularly sensitive to endothelial dysfunction. In many cases, renal abnormalities such as acute renal failure, proteinuria or hematuria are the first signs of systemic TMA, which underlines the central role of nephrology in the diagnosis. Whereas in the past, clinical symptoms were primarily used to classify the various forms of TMA, today the underlying molecular mechanisms are increasingly being taken into account. This reorientation has direct therapeutic consequences: Instead of general plasmapheresis in cases where the cause is unclear, targeted intervention is now possible, for example through complement blockade in cases of genetic complement activation or through immunosuppression in cases of autoantibody-mediated pathogenesis.Many patients do not develop TMA solely on the basis of a genetic predisposition, but only in combination with an additional trigger such as infection, birth, transplantation or drug therapy. This so-called “second-hit” model illustrates the relevance of a comprehensive medical historry and interdisciplinary consideration of each individual case.

One of the most significant developments in recent years has been the realization that dysregulation of the complement system plays a key role in many forms of TMA above all in atypical haemolytic uremic syndrome (aHUS). The targeted blockade of this system by agents such as eculizumab or ravulizumab has proven to be groundbreaking and has openned up a causal therapy for many patients for the first time.It has also ben shown that a pronounced deficiency of ADAMTS13 whether genetic or caused by autoantibodies - is characteristic of thrombotic thrombocytopenic purpura (TTP). The possibility of detecting this enzyme deficiency by means of targeted diagnostics now allows differentiated and often life-saving treatment with plasmapheresis, caplacizumab and, if necessary, rituximab. The fact that complement mechanisms could also be involved here is currently the subject of intensive research.

Secondary forms of TMA in particular, for example in connection with pregnancy, tumor diseases, infections or organ transplants, pose a major diagnostic challenge. Differentiation from other causes of acute kidney damage is offten only possible through a combination of clinical, laboratory and histological findings. Here, histological examination is of central importance. Light and electron microscopy as well as specific marker such as C4d or CD61 help to classify typical changes - although the findings must always be considered in the overall picture.

Not only the diagnosis, but also the therapy still raises questions: How long should complement inhibition be carried out? When is it possible to discontinue treatment without risking a relapse? How can the benefits of these expensive and immunomodulating therapies be weighed up against possible long-term consequences? New substances such as recombinant ADAMTS13 or alternative complement inhibitors offer potential additions to the therapeutic arsenal. In addition, many exciting fields of research are currently opening up. For example, the development of sensitive biomarkers such as cell-free DNA, soluble C5b-9 or endothelial microparticles could enable more precise diagnostics and progression monitoring in the future. The use of artificial intelligence (AI) in medical image analysis is also becoming increasingly important. Deep learning models could, for example, help to identify subtle microvascular patterns that human examiners miss and thus contribute to a more objective classification. Genetic risk profiles could also be evaluated more quickly with the help of AI and integrated into treatment decisions. Another key objective of future research is to conduct controlled studies on new active substances such as narsoplimab or pegcetacoplan and on the efficacy of recombinant therapies in previously refractory cases. There is also a lack of knowledge on the optimal duration of treatment, discontinuation strategies and late effects. There is a great need for research in this area, particularly for patients with a genetic predisposition and a high risk of relapse. Finally, the psychosocial aspect must not be overlooked:

For many patients, a chronic disease such as TMA, especially if dialysis or long-term immunosuppression is necessary, means a massive reduction in quality of life. Studies that systematically investigate this reality of life could contribute to the development of better care concepts. It is clear that research into TMA is not only medically challenging, but also highly relevant in terms of research strategy and offers a wide range of starting points for future interdisciplinary studies and innovations.

7. Conclusion

Diseases that are summarized under the term thrombotic microangiopathies of the kidney form a diverse and complex group. Despite different causes, symptoms and therapeutic approaches, what they have in common is damge to the endothelial cells, the formation of microthrombi in small vessels and functional disorders of affected organs. In recent years, the understanding of these clinical pictures has increased significantly - particularly due to advances in molecular genetics, immunology and histopathological diagnostics. A particular focus is on the role of complement activation, especially in atypical hemolytic uremic syndrome (aHUS). These findings have enabled targeted treatments such as the inhibition of the complement system with eculizumab or ravulizumab.

At the same time, a key mechanism has also been identified in thrombotic thrombocytopenic purpura, namely a deficiency in ADAMTS13. This has led to the development of new diagnostic procedures and therapies, including recombinant ADAMTS13 and the drug caplacizumab. For successful treatment, it is now crucial to differentiate between primary and secondary forms of TMA. Secondary forms can be trigggered by pregnancy, medication, transplants, infections or autoimmune diseases, for example. Individual treatment planning therefore requires precise differentiation. Histopathological examination of the kidneys, supported by immunohistochemical methods and electron microscopy remains a key diagnostic tool. Nevertheless, it is importtant to always interpret these findings in the context of the clinical picture. Genetic examinations and the analysis of specific biomarkers now allow a more precise classification and better prognosis assessment. Despite all the progress made, there are still many unanswered questions. Diagnosis is often difficult, as different forms of TMA are clinically similar and specialized tests are not always available. In addition, aspects such as the optimal duration of treatment, the risk of relapses and long-term progression - especially when using complement inhibitors - have not yet been

conclusively clarified. In addition, new forms of TMA are emerging, for example in connection with cancer, COVID-19 or modern immunotherapies. These developments necessitate ongoing scientific research.

TMA diseases are exemplary for the close connection between immunology, nephrology and haematology. The growing knowledge about their development has already led to important therapeutic advances. Nevertheless, further research is still needed to improve diagnostics, further develop treatment strategies and sustainably improve the quality of life of affected patients.

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