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Thrombotic microangiopathy in patients with systemic vasculitis: a systematic literature review

Sistemik vaskülit hastalarında trombotik mikroanjiopati: bir sistematik literatür taraması

Ege Sinan Torun[1], **Selin Çelen**[2]

[1]*Demiroğlu Science University, İstanbul Florence Nightingale Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye*
[2]*Dörtyol State Hospital, Hatay, Türkiye*

Abstract

Features of thrombotic microangiopathy (TMA) rarely arise in patients with systemic vasculitis. We identified cases in which patients with systemic vasculitis developed clinical, laboratory, and/or histopathological features of TMA. A comprehensive, systematic literature review was conducted. It identified patients diagnosed with systemic vasculitis who showed clinical, laboratory, and/or histopathological features of TMA at or after vasculitis diagnosis. A total of 61 cases of TMA accompanied by systemic vasculitis were included. Antineutrophil cytoplasmic antibody-associated vasculitis was most commonly associated with TMA, accounting for 31 cases. Biopsy-proven renal TMA was present in 30 of the 61 patients. Systemic vasculitis was active in 46 cases and inactive in 11 (the remaining 4 cases could not be assessed for vasculitic activity). TMA attributed to secondary causes included drug- and vaccine-induced TMA (9 cases), thrombotic thrombocytopenic purpura (8 cases), hypertension including preeclampsia (8 cases), atypical hemolytic uremic syndrome (5 cases), and cytomegalovirus infection (2 patients). For TMA treatment, glucocorticoids were administered to 52 patients, plasma exchange to 35, cyclophosphamide to 26, and eculizumab to 6. TMA due to secondary causes can also occur in patients with systemic vasculitis. TMA features may develop with new-onset vasculitis or during relapses, and vasculitic activity may trigger TMA. Recognizing the underlying mechanisms is essential for targeted therapy. In cases associated with active systemic vasculitis, plasma exchange is often performed alongside immunosuppressives, and complement inhibition with eculizumab may offer benefits. These findings highlight the importance of timely diagnosis and individualized management to improve patient outcomes.

Keywords: Systematic literature review, thrombotic microangiopathy, vasculitis

Özet

Trombotik mikroanjiyopati (TMA) bulguları, sistemik vaskülitli hastalarda nadiren gelişebilmektedir. Bu çalışmada, TMA'nın klinik, laboratuvar ve/veya histopatolojik özelliklerinin geliştiği sistemik vaskülit olgularını derlemeyi amaçladık. Sistemik vaskülit tanısı konulmuş ve vaskülit tanısı anında veya sonrasında TMA'nın klinik, laboratuvar ve/veya histopatolojik özellikleri gelişen hastaların belirlenmesini sağlayacak kapsamlı bir sistematik literatür taraması yapılmıştır. Sistemik vaskülite eşlik eden TMA'lı 61 olgu çalışmaya dahil edilmiştir. Toplam 31 olgu ile TMA ile en sık ilişkili olan sistemik vaskülit grubu antinötrofil sitoplazmik antikor ilişkili vaskülitlerdi. Altmış bir hastanın otuzunda biyopsi ile kanıtlanmış renal TMA mevcuttu. Kırk altı olguda sistemik vaskülit aktifti, 11 hastada vaskülit inaktifti (kalan 4 olguda vasküliti aktivitesi değerlendirilememiştir). Bu olguların içinde ilaçlar ve aşılar (9 olgu), trombotik trombositopenik purpura (8 olgu), preeklampsi dahil olmak üzere hipertansiyon (8 olgu), atipik hemolitik üremik sendrom (5 olgu) ve sitomegalovirüs (2 hasta) gibi TMA'nın sekonder nedenleri de mevcuttu. TMA tedavisi için 52 hastaya glukokortikoidler, 35 hastaya plazma değişimi, 26 hastaya siklofosfamid ve 6 hastaya ekulizumab uygulanmıştır. Sistemik vaskülitli hastalarda sekonder nedenlere bağlı TMA da görülebilir. TMA özellikleri yeni başlayan vaskülit bulgularıyla beraber veya vaskülit nüksü sırasında gelişiyorsa, vaskülit aktivitesi TMA için potansiyel bir tetikleyici olabilir. Aktif vaskülitle ilişkili TMA olgularında immünsüpresiflere ek olarak, sıklıkla plazma değişimi yapılır ve bazı durumlarda ekulizumab ile kompleman inhibisyonu da faydalı olabilir. Bu bulgular, sistemik vaskülitle ilişkili TMA olgularında zamanında teşhisin ve bireyselleştirilmiş tedavinin daha iyi sonuçlar almak için ne kadar önemli olduğunu vurgulamaktadır.

Anahtar Kelimeler: Sistematik literatür taraması, trombotik mikroanjiyopati, vaskülit

Correspondence / İletişim: Ege Sinan Torun MD,
Demiroğlu Science University, İstanbul Florence Nightingale Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
E-mail: egesinantorun@hotmail.com **ORCID ID:** orcid.org/0000-0002-4842-0683
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Introduction

Thrombotic microangiopathy (TMA) is defined clinically by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and ischemic organ injury.[1] The kidney is the most frequently injured organ. Other systems may also be affected, including the central nervous system, cardiovascular, respiratory, and gastrointestinal systems.[2] The definitive histological lesions and clinical findings of TMA result from several diseases. Therefore, the clinical term TMA refers to a group of conditions with these shared features.[3] TMA may develop in cases of reduced a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity, such as in thrombotic thrombocytopenic purpura (TTP). It may also occur in complement-mediated TMA (CM-TMA) due to dysregulation of the alternative pathway. This form is called atypical or CM-hemolytic uremic syndrome (aHUS). TMA can also occur secondary to infections, drugs, pregnancy-related disorders, such as preeclampsia, transplantation, malignancy, hypertension, and autoimmune disorders. These include systemic lupus erythematosus, antiphospholipid syndrome, scleroderma renal crisis, and vasculitides.[2]

Over the last decade, we observed TMA in two patients with systemic vasculitis. One patient had Takayasu arteritis. The other had granulomatosis with polyangiitis (GPA). Each case involved a different mechanism, which increased our interest in the topic.[4,5] In the case of Takayasu arteritis, malignant hypertension secondary to renal artery stenosis triggered TMA. Intensive antihypertensive treatment and renal artery stenting resolved the TMA. Immunosuppression was continued.[4] In the GPA case, disease activity caused TMA, which responded to rituximab.[5] Therefore, we inferred that TMA may develop in patients with vasculitis, either as a consequence of active disease or of secondary causes. Different causes require different treatment strategies, depending on the underlying mechanisms. A brief literature review found publications on TMA in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).[6,7] However, TMA in other vasculitides is not well-studied. Most reports are limited to case descriptions.[8-10] No comprehensive review has analyzed TMA features in different systemic vasculitides.

This systematic literature review aims to assemble all available cases of TMA in patients with systemic vasculitis, explore potential mechanisms of TMA, review therapeutic options, and analyze TMA outcomes, with an emphasis on histopathologically proven renal TMA.

Materials and Methods

We conducted this systematic literature review in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[11] The PRISMA Checklist is provided in the Supplementary Materials section. This review was not prospectively registered in International Prospective Register of Systematic Reviews (PROSPERO). This is acknowledged as a methodological limitation of this study.

Information Sources and Eligibility Criteria

We conducted a systematic literature review using the Cochrane Database, MEDLINE, Ovid, Scopus, and Web of Science. We considered studies published between January 1, 1950, and February 1, 2025, with no language restrictions. We included all patients with systemic vasculitides who showed clinical, laboratory, and/or histopathological features of TMA at or after diagnosis. TMA was diagnosed clinically based on either the classic triad—MAHA, thrombocytopenia, and ischemic organ injury—or histopathological features, as reviewed by Genest et al.[12] We also manually searched the reference lists of the collected literature for relevant articles. We excluded studies and case reports that did not provide details on clinical, laboratory, and histopathological features, treatment, and TMA outcome. Abstracts without full texts were omitted. We also excluded patients who developed features of vasculitis after an initial diagnosis of TMA. Grey literature was not included.

Search Strategy

The search strategy is presented in detail in the Supplementary Materials.

Selection Process, Data Collection Process, Data Items

Initially, two reviewers (Ege Sinan Torun and Selin Çelen) independently reviewed only the abstracts of all results. Following this review, they independently identified studies that met the screening criteria. The full texts of the selected abstracts were independently examined, and duplicates were removed to identify eligible studies. After a final assessment and discussion of studies not selected by both reviewers, the reviewers reached a decision and confirmed the studies to be included. The following data were collected from each selected study and recorded in a table: patient sex and age at the time of TMA diagnosis; type of the systemic vasculitis and its clinical and laboratory features; vasculitis activity at the time of TMA diagnosis (determined from information in each case report); clinical, laboratory, and histopathological features of TMA; TMA treatment; TMA outcome; and general outcome of the patient (if present). The activity status of vasculitis at the time of TMA and the possible etiologies of TMA were determined by interpreting information in each case report. In cases where the two reviewers did not agree on the status of vasculitic activity at the time of TMA and/or its etiology, a consensus was reached after discussion among the authors.

Statistical Method

For continuous variables, mean±standard deviation, median (25-75%), and quartiles were used. Frequencies and percentages were used to describe categorical variables used. The IBM SPSS 25 statistical package was used.

Quality Assessment

The methodological quality of the included case reports was assessed by Ege Sinan Torun using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports. A single-assessor evaluation of this checklist is a methodological limitation of this systematic literature review.

Results

Our systematic literature review yielded 85 relevant manuscripts. Sixty-one cases of TMA in patients with systemic vasculitis were reported in 57 articles.[4,5,8-10,13-64] The flowchart of the systematic literature review is presented in Figure 1. Excluded cases and the reasons for their exclusion are presented in Supplementary Table 1.

Clinical Features of the TMA Cases Associated with Systemic Vasculitis

Descriptive features of TMA cases associated with systemic vasculitis are presented in Table 1. Forty patients were female and 21 were male. The mean age of the patients at the time of TMA diagnosis was 48.6±19.1 years (range, 10-84). Rheumatological diagnoses were as follows: microscopic polyangiitis in 12 patients, GPA in 11 patients, eosinophilic GPA in 7 patients, AAV in 1 patient, renal limited vasculitis in 1 patient, anti-glomerular basement membrane antibody disease in 3 patients, immunoglobulin A-associated vasculitis in 4 patients, cryoglobulinemic vasculitis associated with Sjögren syndrome in 1 patient, small vessel vasculitis in 2 patients, necrotizing vasculitis associated with monoclonal protein in 1 patient, polyarteritis nodosa in 3 patients, adenosine 2 deaminase deficiency in 1 patient, Takayasu arteritis in 1 patient, Behçet's disease in 3 patients, thromboangiitis obliterans in 1 patient, immune checkpoint inhibitor associated vasculitis in 1 patient, vasculitis associated with systemic lupus erythematosus in 5 patients, antiphospholipid syndrome in 1 patient and amyopathic dermatomyositis in 1 patient. Detailed information on the TMA cases associated with systemic vasculitis is presented in Supplementary Table 2.

The rheumatological diseases were active in 46 (75.4%) patients and inactive in 11 (18.0%). Information on disease activity was unavailable for 4 patients (6.6%). MAHA and thrombocytopenia were each present in 50 patients (82%), absent in 10 patients (16.4%), and unavailable in 1 patient (1.6%). Information on serum complement 3 and complement 4 levels was available for 16 and 13 patients, respectively. Serum complement 3 levels were low in 15 patients, and serum C4 levels were low in 9 patients. Thirty patients (49.2%) had biopsy-proven renal TMA. Sixteen patients (26.2%) did not have TMA on kidney biopsy. In 15 patients (24.6%), a kidney biopsy was not performed. Two patients had diffuse TMA observed in multiple organs. Two patients had TMA features on skin biopsy. TMA was observed on liver biopsy in 1 patient. One patient had TMA features in the cholecystectomy specimen. Twelve patients (19.7%) had neurological features associated with TMA. In 1 patient, details of neurological involvement were not specified. Alteration of consciousness was present in 3 patients; generalized tonic-clonic seizures were present in 2 patients; headache was present in 2 patients; mood changes were present in 2 patients; personality disorder, aphasia, and vision loss were each present in 1 patient. In one patient, the deterioration could also be associated with posterior reversible encephalopathy syndrome (PRES), which accompanied TMA. In one patient, grand mal seizure and coma were associated with hypertensive encephalopathy accompanying TMA, and in another patient, speech disturbance and disturbance of movement in the right upper extremity could also be associated with a small cerebral infarct accompanying TMA.

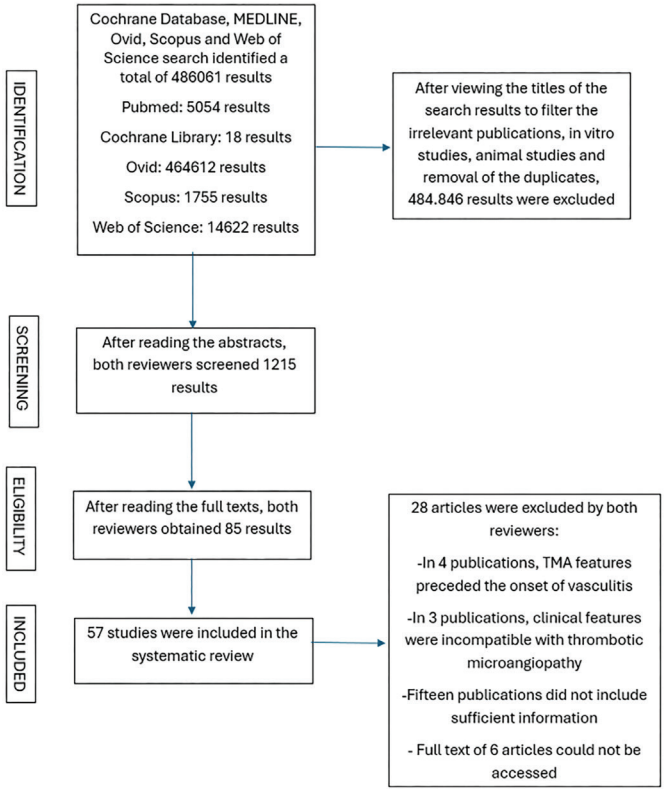

Figure 1. Flowchart
TMA: Thrombotic microangiopathy

Table 1. Descriptive features of cases of thrombotic microangiopathy associated with systemic vasculitis	
Sex	40 female, 21 male
Mean age	48.6±19.1 (minimum 10, maximum 84)
Vasculitis diagnoses of patients	- Microscopic polyangiitis (12 patients, 19.7%)-with accompanying systemic sclerosis in three patients, one of which is triggered by a silicone breast implant, - Granulomatous polyangiitis (11 patients, 18.0%), including one patient with a concurrent coronavirus-19 infection, - Eosinophilic granulomatous polyangiitis (7 patients, 11.5%), including one patient with concurrent systemic lupus erythematosus, - Antineutrophil cytoplasmic antibody-associated vasculitis (1 patient, 1.6%), - Renal-limited vasculitis (1 patient, 1.6%), - Anti-glomerular basement membrane antibody-associated disease (3 patients, 4.9%), including one patient with concomitant anti-proteinase 3 positivity and another with concomitant anti-myeloperoxidase positivity, - Immunoglobulin A-associated vasculitis (4 patients, 6.6%), - Cryoglobulinemic vasculitis associated with Sjögren syndrome (1 patient, 1.6%), - Small vessel vasculitis (2 patients, 3.3%), - Necrotizing vasculitis associated with monoclonal antibody (1 patient, 1.6%), - Polyarteritis nodosa (3 patients, 4.9%), - Adenosine deaminase 2 deficiency (1 patient, 1.6%), - Takayasu arteritis (1 patient, 1.6%), - Behçet's disease (3 patients, 4.9%), - Thromboangiitis obliterans (1 patient, 1.6%), - Immune checkpoint inhibitor-associated vasculitis (1 patient, 1.6%), - Systemic lupus erythematosus-associated vasculitis (5 patients, 8.2%)-with accompanying perinuclear antineutrophil cytoplasmic antibody positivity in one patient, accompanying antiphospholipid antibody positivity in one patient, and accompanying antiphospholipid syndrome in one patient, - Antiphospholipid syndrome (1 patient, 1.6%), - Amyopathic dermatomyositis (1 patient, 1.6%).
Vasculitis activity status	Active vasculitis in 46 patients (75.4%), inactive vasculitis in 11 patients (18.0%), insufficient data to assess disease activity in 4 patients (6.6%)

Table 2. Etiologies of thrombotic microangiopathy cases associated with systemic vasculitis	
Etiology	- Presumed vasculitic activity-31 patients (50.8%), - Thrombotic thrombocytopenic purpura-8 patients (13.1%): • Secondary to microscopic polyangiitis-2 patients, • Secondary to anti-glomerular basement membrane disease-2 patients, • Systemic lupus erythematosus (SLE)-1 patient, • SLE and eosinophilic granulomatous polyangiitis (EGPA)-1 patient, • Small-vessel vasculitis-1 patient, • Infection or clopidogrel-1 patient. - Atypical hemolytic uremic syndrome-5 patients (8.2%): • EGPA-3 patients, • Microscopic polyangiitis-1 patient, • Granulomatous polyangiitis-1 patient. - Presumed vasculitic activity and malignant hypertension-4 patients (6.6%), - Transplantation, tacrolimus use, and presumed vasculitic activity-2 patients (3.3%), - Malignant hypertension-1 patient (1.6%), - Preeclampsia-1 patient (1.6%), - Cyclosporine A and hypertension-1 patient (1.6%), - Vasculopathy (secondary to hypertension and possibly interferon signature)-1 patient (1.6%), - Micafungin use and cytomegalovirus (CMV) infection-1 patient (1.6%), - CMV infection-1 patient (1.6%), - Gemcitabine+carboplatin chemotherapy regimen-1 patient (1.6%), - Immune checkpoint inhibitors (combination of nivolumab and ipilimumab)-1 patient (1.6%), - Cyclosporine use-1 patient (1.6%), - Granulocyte colony-stimulating factor-1 patient (1.6%), - Early summer meningoencephalitis vaccine-1 patient (1.6%).

Among 30 biopsy-proven renal TMA cases, histopathological features were not specified for 10 patients. Thrombi and/or fibrin were detected in the lumen of glomerular capillaries or small arteries/arterioles in 13 patients. Thickening of capillary loops, double contouring of the basement membrane, thickened arterioles, and thickening and proliferation of the tunica intima were present in 8 patients; narrowing of the vessel lumen was noted in 8 patients; and intimal, endothelial, or subendothelial edema (swelling or expansion) was detected in 6 patients.

The etiology of TMA in each case is presented in Table 2. The most common etiologies were presumed vasculitic activity in 31 patients (50.8%), TTP in 8 patients (13.1%), and aHUS in 5 patients (8.2%). Other TMA etiologies included a combination of presumed vasculitic activity and malignant hypertension in 4 patients (6.6%) and a combination of transplantation, tacrolimus use, and presumed vasculitic activity in 2 patients (3.3%).

Treatment modalities for TMA are presented in Table 3. The main treatment modalities included glucocorticoids in 52 cases (85.2%), plasma exchange in 35 cases (57.4%), cyclophosphamide in 26 cases (42.6%), rituximab in 9 cases (14.8%), antihypertensive drugs in 9 cases (14.8%), eculizumab in 6 cases (9.8%), withdrawal of the offending drug in 6 cases (9.8%), and anticoagulation in 5 cases (8.2%).

Treatment modalities for TMA resulted in a complete response in 29 patients (47.5%), a partial response in 19 patients (31.1%), a poor response in 12 patients (19.7%), and in one patient, TMA was detected postmortem; therefore, that patient did not receive any treatment for TMA. Among thirty patients with TMA proven by kidney biopsy, creatinine returned to normal (with residual hematuria and/or proteinuria remaining in some cases) in 8 patients (26.7%), 5 patients (16.7%) had chronic and stable kidney disease; and 17 patients (56.6%) remained dialysis dependent. Eleven patients (18.0%) died ; 1 patient was diagnosed with TMA postmortem. Four patients passed away after deterioration of their general condition, 2 patients died suddenly, 2 patients experienced acute bowel perforation, 1 patient suffered myocardial infarction, and 1 patient died a few months after TMA onset due to urothelial malignancy.

Quality Assessment

Quality assessment of the included articles, according to the JBI Critical Appraisal Checklist for case reports, is presented in the Supplementary Materials section.

Table 3. Treatment modalities for thrombotic microangiopathy cases associated with systemic vasculitis

Treatment modalities	- Glucocorticoids-52 patients (85.2%), - Plasma exchange-35 patients (57.2%), - Cyclophosphamide-26 patients (42.6%), - Rituximab-9 patients (14.8%), - Antihypertensive drugs-9 patients (14.8%), - Eculizumab-6 patients (9.8%), - Withdrawal of the offending drug-6 patients (9.8%), - Anticoagulation-5 patients (8.2%), - Azathioprine-4 patients (6.6%), - Fresh frozen plasma transfusion-4 patients (6.6%), - Transfusion of other blood products-3 patients (4.9%), - Intravenous immunoglobulin-3 patients (4.9%), - Mycophenolate mofetil-3 patients (4.9%), - Acetylsalicylic acid-3 patients (4.9%), - Ganciclovir-2 patients (3.3%), - Delivery (birth)-2 patients (3.3%), - Renal artery stenting-1 patient (1.6%), - Cholecystectomy-1 patient (1.6%), - Infliximab-1 patient (1.6%), - Tocilizumab-1 patient (1.6%), - Dipyridamole-1 patient (1.6%), - Prostacyclin analogue-1 patient (1.6%).

Discussion

To our knowledge, no other systematic review has assembled TMA cases among multiple vasculitis subtypes. The relatively small number of cases indicates that the clinical and histopathological features of TMA are rarely observed in patients with systemic vasculitis. However, clinicians should remain vigilant for these TMA features, as they may also occur in patients with active vasculitis or history of vasculitis, albeit rarely. Currently, there are no specific treatment recommendations for patients with vasculitis and accompanying TMA.

TMA features secondary to TTP, aHUS, infections, medications, malignancy, transplantation, hypertensive emergencies, and pregnancy pathologies can also be observed in any patient, including patients with newly diagnosed active vasculitis or patients with a history of vasculitis. In this regard, the clinical approach and treatment modalities for these secondary TMA etiologies (such as plasma exchange for TTP, complement inhibition for aHUS, treatment of the underlying infection, malignancy, or hypertension, withdrawal of the causative medication, delivery, among others) do not seem to differ from those used in patients without clinical features or a history of vasculitis.[65,66]

The most important message of this review is that, in many of these vasculitis cases, underlying secondary causes of TMA were absent and clinical, laboratory, and histopathological features of TMA occurred in the context of presumed vasculitic activity. Among our 61 cases of vasculitis with associated TMA, the possible mechanism was presumed to be vasculitic activity in 31 cases (50.8%). It should be noted that in several of the cases in which we interpreted the possible mechanism of TMA as "presumed vasculitic activity", a necessary workup for the detection of TTP and aHUS was not performed. Therefore, we may have overestimated the percentage of TMA cases due to "presumed vasculitic activity". However, among 61 cases, 7 of the 8 TTP cases were presumed to be secondary to vasculitis, and all 5 of the aHUS cases were presumed to be associated with vasculitis. Endothelial damage is a core component of TMA.[3] In the clinical course of many vasculitic diseases, endothelial dysfunction and injury are key drivers in disease pathogenesis.[67-71] Therefore, endothelial damage induced by vasculitic activity may lead to features of TMA in genetically predisposed individuals. In cases where TMA was presumed to be due to vasculitic activity, including TTP and aHUS cases secondary to accompanying vasculitis, potent immunosuppressive treatments administered to appropriately control vasculitic activity also helped resolve the underlying TMA in most cases. As our preliminary literature review suggested, TMA was most often observed in AAV cases. Among the 61 cases, 31 (50.8%) had concomitant AAV. In the study by Dellal et al.[72], among 8 vasculitis patients, 4 were diagnosed with AAV. In addition, a series by Chen et al.[6] reported 30 histopathologically confirmed renal TMA cases among 220 AAV patients, and Manenti et al.[7] reported 8 histopathologically confirmed TMA cases among 46 AAV patients. Therefore, we hypothesize that complement activation and endothelial injury, both of which are important for AAV pathogenesis[73], can also lead to TMA in some genetically predisposed patients. However, TMA can also be observed in other vasculitides, albeit less frequently. Identifying the factors that predispose some vasculitis patients to develop TMA features during active disease episodes will be a promising area for future research, and, given the rarity of TMA in vasculitis patients, global collaboration among multiple vasculitis centers may be necessary.

MAHA, thrombocytopenia, and ischemic organ injury are key features of TMA.[1] Hematological features of TMA are widely recognized by clinicians. However, these features may not accompany histopathological TMA in some cases, and the kidney is the most frequently injured organ in TMA.[2] A case series of AAV demonstrated histopathologically proven renal TMA to be associated with poor renal survival and high risk of progression to end-stage renal disease.[6,7] Among the 61 cases of TMA associated with vasculitis that we have assembled, 30 patients (49.1%) had renal biopsy findings compatible with TMA. Creatinine levels normalized in only 8 cases, and 17 patients became dialysis dependent. As in the case series reported by Chen et al.[6] and Manenti et al.[7], the renal prognosis was poor among these patients. Data from Chen et al.'s[6] study demonstrated that renal TMA was associated with all-cause mortality, whereas the data from Manenti et al.'s[7] study found no association between TMA and hazard of death. The creation of global databases for reporting TMA cases associated with vasculitis, specifically ANCA-associated vasculitis, and the long-term clinical follow-up of these patients may provide further information on this potentially significant subject. However, histopathological TMA is not confined to the kidneys. Among 61 cases, TMA features were observed in multiple organs in 2 patients, on skin biopsy in 2 patients, in liver biopsy in 1 patient, and in cholecystectomy material in 1 patient. Therefore, pathologists should also be vigilant for TMA features in other organs in appropriate settings, including patients with active systemic vasculitis and/or a history of vasculitis. Neurological involvement related to TMA was present in approximately 20% of cases, although it was not histopathologically confirmed. In three patients, concomitant etiologies of the neurological symptoms were identified: PRES, cerebral infarct, and hypertensive encephalopathy. In an observational cohort of 49 patients with a first TMA event between 1995 and 2016, neurological manifestations were observed in 42 patients (85.7%) Most of them were considered severe, including confusion, personality changes, sensorimotor loss, seizures, stupor or coma, and ischemic or hemorrhagic stroke. Authors highlighted that, while the effect of neurological

manifestations on the acute clinical course of TMA appears modest, these manifestations may have an important impact on the development of chronic cognitive impairment.[74] In their retrospective cohort study of adult patients hospitalized at a tertiary center between January 2004 and October 2016 who were diagnosed with TTP, HUS, and aHUS, Weil and Rabinstein[75] analyzed a total of 42 TTP, 16 HUS, and 20 aHUS episodes in 37 TTP, 16 HUS, and 15 aHUS patients. They reported that at least one neurologic symptom was observed in 83% of TTP episodes and 88% of HUS episodes, but in aHUS patients in only 35% of episodes; neurologic symptoms were less likely to be present in aHUS than in TTP ($p<0.001$) or classic HUS ($p=0.002$). The most common neuroimaging finding was PRES (observed in 8 episodes of TTP, 4 episodes of HUS, and in both episodes of aHUS). Most patients had favorable long-term outcomes. Among the TMA features in the vasculitis patients we assembled, the percentage with neurological symptoms was somewhat lower. This may be due to the low percentage of TTP and aHUS cases among the patients with systemic vasculitis we have assembled.

No studies have evaluated the treatment of AAV cases presenting with clinical and/or histopathological features of TMA. However, most AAV cases can cause rapidly progressive glomerulonephritis, and therapeutic plasma exchange is recommended in this scenario.[76] Plasma exchange is the cornerstone of TTP treatment and can be used for many TMA etiologies.[2] Thus, plasmapheresis could be considered in AAV cases with TMA, even if they do not present with clinical features of rapidly progressive glomerulonephritis.

Among the 61 cases of vasculitis with accompanying TMA, 15 patients had low complement 3 levels and 9 patients had low complement 4 levels. Therefore, one can hypothesize that complement activation occurs during the development of TMA in some patients with systemic vasculitis, leading to consumption of serum complement 3 and/or complement 4. It is well established that complement inhibition with eculizumab is the treatment of choice for CM-TMA observed in aHUS. There is also rationale to use this treatment modality in other types of secondary TMA, including TMA secondary to autoimmune diseases.[67] Therefore, complement inhibition with eculizumab may also have a role in the treatment of TMA cases secondary to active vasculitis. Both therapeutic plasma exchange and complement inhibition can also help control vasculitic activity and mitigate TMA features. However, data demonstrating the efficacy and safety of therapeutic plasma exchange and/or eculizumab, when used in addition to immunosuppressive treatment, for TMA cases secondary to presumed vasculitic activity are needed before further recommendations can be made.

Study Limitations

A limitation of this review is our arbitrary determination of possible mechanisms of TMA in some cases. The low number of cases, the lack of assessment of ADAMTS13 activity and complement regulatory factors in many cases, the nature of the included publications (all case reports), and the relatively low prevalence of TMA among patients with systemic vasculitis are additional limitations of this review. Since this review is based exclusively on published case reports, publication bias is an additional limitation: cases with favorable, dramatic, or unusual outcomes are likely overrepresented, while unremarkable or fatal cases may remain unpublished. The absence of registration of this systematic literature review in PROSPERO and the single-assessor evaluation using the JBI Critical Appraisal Checklist are additional methodological limitations.

Conclusion

Physicians should be vigilant for the clinical, laboratory, and histopathological features of TMA in patients with active or prior systemic vasculitis. Once TMA features are detected, careful history-taking and appropriate laboratory tests are necessary to determine the etiology and detect secondary causes, such as TTP, aHUS, drug-induced TMA, infection-associated TMA, hypertensive emergencies, pregnancy-related pathologies, malignancy, and transplantation-associated TMA. If TMA features develop in the context of new-onset systemic vasculitis or during a vasculitis relapse, disease activity may be a trigger and an etiologic factor for TMA, especially in AAV patients. Although there are no guidelines for the management of concomitant TMA during the treatment of systemic vasculitides, plasma exchange is frequently performed in addition to immunosuppressive therapies, and in some cases, complement inhibition may be beneficial. Biopsy-proven renal TMA may be associated with a poor renal outcome and possibly with increased mortality.

Footnotes

Author Contributions

Concept: E.S.T., S.Ç., Design: E.S.T., S.Ç., Data Collection or Processing: E.S.T., S.Ç., Analysis or Interpretation: E.S.T., S.Ç., Literature Search: E.S.T., S.Ç., Writing: E.S.T., S.Ç.

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