



Thrombotic microangiopathy in IgA nephropathy:  
pathophysiology, histopathology, and treatment perspectives

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ARTICLE INFO	ABSTRACT
<p><b>Article type:</b> Review</p>	<p>The current narrative review study aims to provide an overview of thrombotic microangiopathy (TMA) in immunoglobulin A nephropathy (IgAN), with a particular emphasis on its pathophysiology, histopathology, and treatment options. The prevalence and clinical significance of TMA in IgAN may vary across different populations. Estimates suggest that TMA events occur in 2-50% of patients with IgAN. Endothelial injury is a key factor in TMA development in IgAN, triggered by immune complex deposition, complement activation, and potentially hypertension. TMA in IgAN correlates with vascular lesions, including arterial intimal sclerosis, arteriolar lumen reduction, and smooth muscle hypertrophy. Notably, patients with TMA show more intense deposition of C4, C3d, and C5b-9 complements. Treatment involves blood pressure management, immunosuppression, and targeted therapies such as eculizumab.</p>
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**Implication for health policy/practice/research/medical education:** Healthcare providers and educators should emphasize early detection and intervention targeting endothelial injury, complement activation, and genetic factors to optimize treatment outcomes and reduce the burden of TMA-related complications in IgAN.

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**Introduction**

Thrombotic microangiopathy (TMA) presents a multifaceted challenge in renal pathology, characterized by the formation of platelet thrombi within the renal microvasculature (1). While historically linked to conditions like thrombotic thrombocytopenic purpura and malignant hypertension, recent attention has turned to its presence in immunoglobulin A nephropathy (IgAN), the foremost primary glomerular disease worldwide (2,3). Epidemiological data reveals a wide range of its presence in IgAN cases. Additionally, TMA manifests with diverse renal patterns, ranging from arteriolar thrombi to glomerular capillary involvement (2,4-6).

While the primary characteristic of IgAN is mesangial IgA immune complex deposition, emerging evidence

suggests the involvement of intrarenal arterial and arteriolar lesions in disease progression (7,8). Recent studies have highlighted the complex interaction between complement activation, genetic factors, and vascular abnormalities in TMA, emphasizing TMA's role in driving IgAN pathogenesis (9,10).

The presence of TMA correlates with more severe disease phenotypes, leading to poorer prognoses and necessitating more aggressive therapeutic interventions (2,11). The heterogeneity of TMA in IgAN and its connection to various comorbidities could lead to underrecognition, which presents diagnostic and management difficulties for physicians (12). The present review focuses on the pathophysiology, histopathology, and treatment options for TMA in IgAN.

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### Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including; thrombotic microangiopathy, IgA Nephropathy, complement, histopathology, pathophysiology and treatment.

### Epidemiology of TMA in IgAN

The prevalence of TMA in IgAN may vary across different populations, estimates TMA occurs in 2-50% of patients with IgAN (4,6). Rodrigues et al reported, that 23% of IgAN patients in their group exhibited TMA (13). Another, a French study by Karoui et al on 128 IgAN patients showed 53% of their patients had TMA lesions in arterioles (2). Moreover, a Chinese cohort study involving 944 adult patients with IgAN found that 20.6% of patients had renal arteriolar microangiopathic lesions (14). Subsequent Dutch retrospective studies on 105 patients with IgAN showed that microangiopathic lesions were present in approximately 23% of IgAN biopsies, with a significant proportion of affected patients being normotensive (5). Furthermore, a study from Thailand among 267 patients reported TMA in 13% of IgAN patients (15).

### Clinical features and diagnosis

TMA presents as the formation of small thrombosis in the renal microvasculature, often observed in IgAN through renal biopsy (16). Renal biopsy is necessary for identifying TMA changes in IgAN (17). In a recent study by Neves et al, the diagnosis of TMA was conducted based on light microscopy and immunohistochemistry staining for CD61 (6). TMA is characterized by endothelial injury, platelet aggregation, and fibrin deposition. This cascade of events can lead to various clinical manifestations including higher serum creatinine levels, hematuria, proteinuria, and nephrotic syndrome (18-20). In the study by Rodrigues et al, the group with combined IgAN and TMA was characterized by more severe disease, including more frequent severe hypertension, nephrotic syndrome, lower glomerular filtration rate (GFR), and higher serum creatinine levels at the time of the biopsy (13). Previous studies also showed that, the presence of TMA worsens the prognosis of IgAN (21-23).

### Etiology of TMA in IgAN

The pathophysiology underlying TMA in IgAN is complex and multifactorial (24). TMA in IgAN involves endothelial injury triggered by dysregulation of the complement system, exacerbating thrombosis (12,25). Endothelial damage promotes platelet aggregation and activates the coagulation cascade, contributing to TMA (26). This condition leads to organ ischemia and systemic

symptoms, including hypertension (27). Genetic factors also play a role, with certain polymorphisms increasing susceptibility to TMA in IgAN, possibly leading to hypertension as a consequence (12,28). Moreover, poorly galactosylated IgA itself can directly cause endothelial damage (29). Studies show that IgAN patients with TMA lesions exhibit higher levels of galactose-deficient IgA compared to those without these vascular lesions (29, 30).

### Genetics of TMA in IgAN

Genetic mutations linked to TMA in patients with IgAN underscore the significance of genes associated with the complement system (31). Specifically, mutations in genes regulating the alternative complement pathway, such as those encoding complement factor H and complement factor I (32), have been implicated in the development of atypical hemolytic uremic syndrome which shares clinical characteristics with TMA (33,34). However, the study by Edey et al found no mutations of complement factor H in a substantial cohort of IgAN patients (35). Besides, previous studies shown the association of IgAN with genetic variations in the HLA gene family, as well as other genes like TAP1/PSMB and DEFA across diverse populations. These genetic factors may contribute to the pathogenesis of IgAN and its complications, including TMA (36-38). Still, endothelial damage induced by C5b-9 leads to increased expression of the von Willebrand factor gene, promoting platelet activation and the formation of thrombi (26).

### The role of complement

Complement deposits, particularly C4d, were preferentially observed in arterioles in IgAN with TMA (39). C4d deposition is generally attributed to lectin pathway activation, which has been linked to disease severity and histologic features (40,41). Glomerular C3 deposition has been shown to correlate with disease progression (26,42). The study by Li J et al demonstrated over 90% of IgAN patients with TMA lesions had arteriolar deposits of C3d, C5b9, and C4d (31).

### Histopathological aspect of TMA in IgAN

TMA predominantly manifests in arterial and arteriolar locations, with a notable absence of glomerular involvement (43,44). Histologically, TMA in IgAN is characterized by fresh fibrinous vascular thrombi, distinguished by the presence of bright reddish staining fibrinous material and marked dilation with smoothing of the internal elastic lamina (45,46). Chronic lesions exhibit organized thrombi with recanalized vascular channels, often displaying an "onion-skin" appearance (47,48). Correspondingly focal myocyte necrosis may be present, often in association with thrombi (2,42). IgAN-associated TMA is correlated with

more severe vascular lesions, including arterial intimal sclerosis, arteriolar lumen reduction, and smooth muscle hypertrophy, suggesting a complex interplay of vascular pathologies in the context of IgAN (12,14). A more intense deposition of C4d, C3d, and C5b-9 has been described in IgAN patients with TMA as compared with patients with other types of vascular lesions or patients without histological vascular damage (5,25,31).

### Comorbidities of TMA in IgAN

Several studies have linked TMA in IgAN with poor prognosis (6,46). Recent studies showed that individuals with combined IgAN and TMA including frequent severe hypertension, acute kidney injury, nephrotic syndrome, lower GFR, and severe tubular atrophy/interstitial fibrosis at the time of biopsy (13,15).

### Treatment

The treatment approach has two main aspects: general management and targeted therapies. General strategies include controlling blood pressure with ACE inhibitors or ARBs, immunosuppressive therapy with corticosteroids, and supportive care for fluid balance and anemia (20, 49). Targeted therapies focus on complement inhibitors like eculizumab (50, 51). Emerging therapies include factor B inhibitors (iptacopan), C3 inhibitors (pegcetacoplan), factor D inhibitors (vemircopan, pelecopan), C5 inhibitors (ravulizumab, cemdisiran), and C5a receptor 1 inhibitors (avacopan) showing helpful results (52-54). These novel treatments have the potential to revolutionize outcomes for patients with TMA in IgAN (55).

### Conclusion

The primary cause of TMA in IgAN is endothelial injury triggered by factors such as immune complex deposition, complement activation, and potentially hypertension. This process leads to platelet aggregation, thrombus formation, and activation of the coagulation pathway, ultimately resulting in TMA symptoms. IgAN-associated TMA is correlated with more severe vascular lesions, including arterial intimal sclerosis, arteriolar lumen reduction, and smooth muscle hypertrophy. The treatment plan involves managing blood pressure with ACE inhibitors or ARBs, using corticosteroids to suppress the immune system, and providing supportive care alongside targeted therapies focused on inhibiting complement activation, such as eculizumab. Emerging drugs targeting complement components offer promising prospects for improving outcomes in IgAN-associated TMA.

### Authors' contribution

**Conceptualization:** Ali Rastegar-Kashkouli.

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### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

### Declaration of generative AI and AI-assisted tools in the writing process

During the preparation of this work, the authors utilized ChatGPT—a chatbot developed by OpenAI—to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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