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Thrombotic microangiopathy in IgA nephropathy; new evidence and ideas

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ABSTRACT

The Oxford classification for IgA nephropathy (IgAN) does not currently include thrombotic microangiopathy (TMA) as a parameter, despite evidence that TMA can occur in IgAN patients and impact outcomes. Prior studies have found that a significant proportion of IgAN patients have histological evidence of TMA, either acute or organized, in their renal biopsies. Moreover, patients with TMA lesions in IgAN tend to have worse outcomes, including a greater percentage of sclerotic glomeruli, more tubulointerstitial fibrosis, and higher rates of doubling of serum creatinine or progression to end-stage renal disease compared to IgAN patients without TMA. Other researchers have suggested that TMA in IgAN is commonly located in the advanced steps of the disease and may be accompanying by severe hypertension and proteinuria. However, the Oxford system does not include TMA as a parameter. Therefore, further investigations are required to determine the clinical significance and optimal management of TMA in IgAN individuals. Renal arteriolar microangiopathic lesions can occur in immunoglobulin A nephropathy, but their role in disease progression has been unclear. Furthermore, the main limitation of the MEST-C classification is that it does not currently account for the presence and impact of TMA in IgAN, despite evidence that TMA is a common and clinically relevant histological finding in these patients.

Implication for health policy/practice/research/medical education:
Thrombotic microangiopathy appears to be a relevant histological finding in IgA nephropathy which may impact the outcome of this disease. The Oxford classification currently does not include it as a parameter, since its optimal integration remains an area of ongoing investigation.

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Introduction

IgA nephropathy (IgAN) is the main primary glomerulonephritis throughout world, leading to end-stage renal disease in 20–40% of patients (1). The Oxford classification for IgAN is a clinicopathological classification system that aims to identify specific histological features that can predict the prognosis of individuals with IgAN (1). This classification includes five histological features scored on kidney biopsies consisting of mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and finally crescents (C) (2). The five morphologic features (MEST-C scoring) were selected since they were reproducible, had the least sampling error, were easiest to score, and were independently associated with clinical outcomes (3). Previous authors found that, the morphologic lesion which is most consistently associated with poor clinical outcomes in multivariate analysis across multiple studies is T (tubular atrophy/interstitial fibrosis) score (4). The recent systematic review by Howie et al, by analysis of two large studies with independent observers to evaluate the reproducibility of the MEST-C scoring system in IgAN, showed moderate reproducibility for tubular atrophy/interstitial fibrosis (T variable). They also showed that reproducibility was moderate or poor for mesangial hypercellularity (M) and segmental glomerulosclerosis(S) components. Finally, they showed reproducibility was poor for endocapillary hypercellularity (E) and crescents(C) variables. Moreover, Howie et al detected that, The T component was related to

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58% of the observed outcomes (5). They concluded that IF/TA (tubular atrophy/interstitial fibrosis) appears to be the most predictive of outcomes, while the MEST-C components as a whole do not correlate with a significant proportion of outcomes, indicating varying degrees of prognostic value for individual components. Their results highlight the need for further refinement and validation of the MESTC scoring system in IgAN. They suggested continued efforts to improve the reliability and prognostic accuracy of histological scoring systems to enhance the management of IgAN (5). On the other hand, other histological features that have been investigated for potential inclusion; however, the focus have been on further validating the existing MEST-C scoring system across diverse patient populations. However, the working group behind the Oxford classification is reported to be actively investigating ways to potentially improve the prognostic accuracy of the system, by possibly combining the histological scores with clinical and biomarker data. Thrombotic microangiopathy (TMA) can occur in a subset of patients with IgAN, though the prevalence varies across different studies. This narrative review sought to understand the prevalence and characteristics of the microangiopathic lesions in immunoglobulin A nephropathy and their potential impact on disease progression.

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 like IgA nephropathy, end-stage renal disease, MEST-C score, Oxford classification, end-stage kidney failure, thrombotic microangiopathy and immunoglobulin A nephropathy.

A short look at the MEST-C system

The MEST-C score provides a comprehensive assessment of the severity of IgAN and is associated with renal prognosis; since a higher total MEST-C score (0-7 points) is associated with a worse renal outcome (4). Patients can be classified into three groups based on the total MEST-C score: O-grade I (0-1 points), O-grade II (2-4 points), and O-grade III (5-7 points). The hazard ratios for renal progression are significantly higher for O-grade II (HR 2.8) and O-grade III (HR 6.3) compared to O-grade I (4,6). Additionally, combining the MEST-C score with clinical factors like eGFR, proteinuria, and treatment further improves the ability to predict renal prognosis in IgAN patients (4). The main limitations of the MEST-C classification system for IgAN include an inconsistent predictive value of individual components (5). While the segmental glomerulosclerosis and IF/TA (tubular atrophy/interstitial fibrosis) components have been consistently shown to have high prognostic relevance, the predictive value of mesangial hypercellularity, endocapillary hypercellularity, and crescents parameters has been more variable across different studies (7,8). There is limited ability to predict short-term prognosis since the MEST-C score appears to be better at predicting long-term renal outcomes rather than short-term prognosis in IgAN (9,10).

Thrombotic microangiopathy in IgAN

Thrombotic microangiopathy is a histological finding which occurs in IgAN; however, its clinical significance is not well detected. The previous study by El Karoui et al on 128 IgAN individuals found that 53% had lesions of TMA, either acute or organized, in arteries and/or arterioles. Patients with TMA had a significantly greater percentage of sclerotic glomeruli and worse tubulointerstitial fibrosis compared to those without TMA (11). This investigation also detected that patients with TMA lesions in IgAN tend to have worse outcomes, including a larger percentage of sclerotic glomeruli, more tubulointerstitial fibrosis, and higher rates of doubling of serum creatinine or progression to end-stage kidney failure compared to IgAN patients without TMA. The study by El Karoui et al also demonstrated that a doubling of serum creatinine or end-stage renal disease occurred in all individuals with laboratory evidence of TMA, 42% with morphologic aspects but no laboratory evidence, and 11% without TMA (11). Another by study Neves et al on 21 IgAN cases showed that 9.5% had glomerular thrombi and 14.3% had endothelial edema or denudation, which are acute findings of microangiopathic lesions (12). Likewise, the morphologic findings of 102 IgAN, displayed lesions of TMA in 2% of patients in our previous study in 2012 (13).

Histopathological lesions of TMA in IgAN

Renal biopsy studies have shown that histological evidence of TMA is associated with vascular changes such as arteriolar wall thickening and hyaline deposits (12). The specific histological findings of TMA in IgAN, categorize them as acute or chronic (11,12). Acute findings included glomerular thrombi, edema or endothelial denudation, mesangiolysis, arteriolar thrombi, edema, intramural fibrin, and myocyte necrosis (11,12,14). Chronic findings were double contours of capillaries with mesangial interposition, arteriolar hyaline deposits, and arterial fibrous intimal thickening with concentric lamination (11,12,14).

Mechanisms of TMA in IgAN

Activation of the complement system appears pivotal in IgAN, with past researches indicating that histological signs of TMA stem from alternative complement activation across with reduced serum C3 levels (15). Rossi et al sought to evaluate the link between low-serum C3 levels and end-stage kidney disease, investigating whether this connection indicates the presence of ongoing TMA

(16). They included all patients diagnosed with IgAN through biopsy and the development of end-stage kidney failure, or death. Out of 56 patients, 21% had low-levels of serum C3 at the time of their renal biopsy. TMA was notably more prevalent in the low-serum C3 group. In addition, low serum C3 level was strongly linked to a higher risk of developing end-stage kidney disease (16). Recently, Puapatanakul et al retrospectively studied renal biopsies of 267 patients with primary IgAN (1995 to 2015). This investigation detected TMA in 13% of cases. This morphologic lesion was accompanied by a history of malignant hypertension, lower estimated glomerular filtration rate higher proteinuria, and higher mean arterial pressure at diagnosis compared to cases without TMA. They also showed According to the Oxford MEST-C classification had a substantial relationship with the T2 variable (severe tubular atrophy/interstitial fibrosis). However, they could not show this association with mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, or the presence of crescents. After a median follow-up of 50 months, their patients with TMA had a significantly higher risk of progression to end-stage kidney disease and all-cause mortality, they concluded that TMA is an independent predictor of end-stage kidney disease (17). More recently Yang et al studied a group of immunoglobulin A nephropathy patients who were divided into two groups of renal TMA group (23 individuals) versus non-renal TMA group (46 individuals). Their study found children with IgAN and renal TMA exhibited more severe clinical and pathological features. The results of this study also suggested that endocapillary hypercellularity and C3 staining were accompanying by an increased risk of renal TMA in children with IgAN. Additionally, the kidney survival rate was smaller in the group with renal TMA compared to the group without it. Yang et al also demonstrated that C3 deposition and renal TMA were identified as separate risk factors for the progression to end-stage kidney failure (18). Yang et al also concluded that renal TMA has been recognized as an independent parameter for the occurrence of kidney failure in children diagnosed with this disease (18). Accordingly, immunohistochemical studies have shown a relationship between TMA lesions in IgAN and deposits of complement proteins C4d and C5b-9 (12,19,20). Likewise, the presence of TMA was correlated with a greater number of chronic lesions and hypertension, suggesting that local complement activation may play a role in the development of TMA in IgAN (21-23). Meanwhile, genetic studies have detected mutations in complement genes to hypertension-associated TMA, implying that complement dysregulation may be involved in the pathogenesis of TMA in IgAN (23-25). In a retrospective study, Yang et al sought to clarify the significance of intra-renal vascular lesions in patients with IgAN by comparing clinical data between those with and without such lesions. Among the 138 patients evaluated, 88 were found to have at least one intra-renal vascular lesion (26). Notably, individuals exhibiting arteriolar wall thickening also displayed an elevated serum creatinine level, across with a reduced glomerular filtration rate, and a higher urine protein-to-creatinine ratio. Additionally, these patients had an increased proportion of global glomerulosclerosis and a greater histologic grade of interstitial fibrosis and tubular atrophy at the time of biopsy. The findings indicate that arteriolar wall thickening in IgAN is associated with decreased glomerular filtration rate and increased global glomerulosclerosis (26). Furthermore, this study showed reduced glomerular filtration rate and global glomerulosclerosis correlate with the progression toward end-stage kidney failure. Though the direct association amid vascular lesions and end-stage kidney failure remains somewhat ambiguous, a marginally significant association was identified in connection with arterial wall thickening (26). The study across with a meta-analysis by Dong et al examined 450 patients diagnosed with IgAN (27). This study revealed that individuals exhibiting microangiopathy presented significant differences in clinical characteristics when compared to those without microangiopathy. Specifically, individuals in microangiopathy group were significantly older and demonstrated higher blood pressure, increased proteinuria, deteriorating kidney function, and elevated uric acid levels. Moreover, pathological comparisons further illustrated disparities; since individuals with microangiopathy exhibited greater amounts of global glomerulosclerosis and interstitial fibrosis/tubular atrophy versus non-microangiopathy group. Also, the presence of microangiopathic lesions was found to be independently associated with composite kidney outcomes (defined as a combined event, incorporating a decrease in glomerular filtration rate ≥50%, end-stage kidney failure and renal transplantation or death) among IgAN patients, signifying its importance in disease progression. Further, this correlation was substantiated through a meta-analysis that included 2098 individuals from five independent cohorts. The aggregated data indicated a considerably concerning adjusted risk—specifically, a 187% increased likelihood of poor renal outcomes in patients with microangiopathy versus those without. Finally, they concluded that microangiopathic lesions could serve as a valuable prognostic tool for predicting disease progression in IgAN, providing insights that extend beyond the well-established Oxford MEST-C score (27).

Treatment considerations for IgAN with TMA

As mentioned above, having TMA on biopsy is an independent risk factor for progression to chronic renal failure requiring kidney replacement therapy, beyond other histologic predictors in the Oxford classification (12). Therefore, effective treatment of hypertension is important, however TMA can occur even in normotensive patients (12,14). Immunosuppressive therapy with steroids has been administered in crescentic IgAN with TMA, but

recovery of kidney function is often poor. Plasmapheresis has been tried in some cases, but its efficacy is unclear (2,12,14,28,29).

Conclusion

Histological evidence of TMA is common in IgAN, with both acute and chronic vascular lesions observed. These lesions have been associated with worse renal outcomes and a faster progression to end-stage renal disease. However, the Oxford classification of IgAN, which is widely used to predict prognosis, does not currently include TMA as a prognostic factor. Whether renal TMA should be incorporated into the Oxford classification (MEST-C) to better predict prognosis, should be envisage in the future.

Authors' contribution

Conceptualization: Hamid Nasri.
Validation: Paniz Pourpashang.
Investigation: Hamid Nasri.
Resources: Paniz Pourpashang.
Data curation: Paniz Pourpashang.
Visualization: Hamid Nasri.
Supervision: Hamid Nasri.
Writing–original draft: Paniz Pourpashang, Hamid Nasri.
Writing-review and editing: Hamid Nasri.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity 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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