Original Article

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Pathology Section

Clinicopathological Features of Thrombotic Microangiopathy in Renal Biopsies: A Retrospective Cross-sectional Study from Tertiary Care Centre in Kerala, India

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ABSTRACT

Introduction: Thrombotic Microangiopathy (TMA) is a clinico-pathological syndrome characterised by endothelial injury, microvascular thrombosis, and organ dysfunction. Renal involvement is common and may result from diverse primary and secondary aetiologies. The aetiological spectrum and histopathological manifestations of renal TMA vary considerably among different populations and clinical settings. Renal biopsy not only confirms the diagnosis but also provides valuable information regarding the pattern and chronicity of vascular and glomerular injury, which may have prognostic significance. Studies evaluating the spectrum of biopsy-proven renal TMA are limited, particularly from the Indian population, making such analyses important for improving diagnostic accuracy and patient management.

Aim: To evaluate the clinicopathological features and aetiological spectrum of TMA in renal biopsies.

Materials and Methods: This retrospective cross-sectional observational study was conducted in the Department of Pathology, Government Medical College, Kozhikode, Kerala, India and included all native and graft renal biopsies diagnosed with TMA between January 2020 and December 2024. Cases of Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and biopsies lacking definitive histological features of TMA were excluded. Clinical parameters (age, sex, blood pressure, proteinuria, haematuria, renal function), laboratory parameters (haemoglobin, platelet count, serum creatinine, serum albumin, complement levels), and histopathological features were evaluated. Acute and chronic TMA lesions were assessed, and cases were categorised according to underlying aetiology. Data were entered into Microsoft Excel and analysed using descriptive statistics. Continuous variables were expressed as mean±standard deviation, while categorical variables were presented as frequencies and percentages.

Results: Among 2,302 renal biopsies examined during the study period, 55 (2.4%) showed histological evidence of TMA. Forty-seven cases involved native kidneys and eight involved renal allografts. The mean age at presentation was 41.6±13.3 years, and 32.7% of patients were female. Hypertension-associated TMA was the most common aetiology, accounting for 30 (54.55%) of cases, followed by transplant-associated TMA 8 (14.55%), IgA Nephropathy 7 (12.73%) autoimmune diseases 5 (9.09%), infection-related TMA 3 (5.45%), atypical haemolytic uraemic syndrome 1 (1.82%) and snake bite 1 (1.82%). All infection-related cases were associated with Coronavirus Disease-2019 (COVID-19). Proteinuria (89%) and microscopic haematuria (61.8%) were common clinical findings. Histologically, vascular lesions predominated, with fibrointimal hyperplasia and arteriolar thrombi being the most frequent abnormalities. Chronic vascular changes were more common than acute thrombotic lesions. Only two (3.64%) patients had thrombocytopenia, including the single case of complement-mediated atypical Haemolytic Uraemic Syndrome (aHUS).

Conclusion: Secondary causes predominate in renal TMA, with hypertension-associated TMA being the leading aetiology. Chronic vascular lesions are common and may reflect delayed presentation and sustained endothelial injury. Renal biopsy remains essential for diagnosis, aetiological classification, and identification of uncommon causes of TMA.

Keywords: Hypertension, Kidney biopsy, Renal pathology Thrombotic Microangiopathy

INTRODUCTION

TMA is a pathological process, where endothelial damage, microvascular thrombi, and organ dysfunction are hallmarks with the kidneys as major organs affected [1]. TMA is caused by various pathological processes such as HUS, Thrombotic Thrombocytopenic Purpura, infection, autoimmunity, malignant hypertension, and drugs [1,2]. The pathogenesis of TMA involves the dysregulation in complement system, coagulation abnormalities, and damage to vascular endothelium causing substantial morbidity and mortality [3-5]. As TMA is a heterogeneous disease with high chances of irreversible kidney damage, prompt identification and intervention of TMA is crucial.

TMA can be classified into primary and secondary causes. aHUS in which there is dysregulation of the complement pathway due to mutations in genes that control the alternative pathway of complement system, is a primary form of TMA. Another primary cause is TTP, which results from severe deficiency of ADAMTS13, a von Willebrand factor-cleaving protease, leading to widespread platelet aggregation and thrombosis [4]. Recognition of these genetic forms of TMA is necessary since there is a chance that they will recur in transplants. Secondary TMA is caused by underlying processes such as infection, autoimmune conditions, malignancy, and medications.

Infection-related TMA is frequently seen in instances of HUS caused by Shiga Toxin-Producing *Escherichia coli* (STEC) [4]. Autoimmune diseases, particularly Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS), can lead to secondary TMA by inducing endothelial injury and hypercoagulability [2]. Malignancy-associated TMA is often linked to disseminated intravascular coagulation or direct vascular invasion by tumour cells [2,4]. Drug-

induced TMA is another significant secondary factor, with medications like Calcineurin Inhibitors (CNI), certain chemotherapeutic drugs, and certain antiplatelet drugs being identified as culprits [2,4]. With the increasing number of kidney transplants, it is important to recognise post-transplant TMA, which is predominantly de novo and most commonly associated with antibody-mediated rejection and CNI toxicity, although ischaemia-reperfusion injury and infections are also recognised causes [6].

While numerous research studies have explored the clinical and histological characteristics of TMA on a worldwide scale, limited data exist on its epidemiology and outcomes in Kerala [1,5,7-9]. The region has a high prevalence of Chronic Kidney Disease (CKD) and a substantial renal transplant population, making it important to understand the local aetiological spectrum and pathological patterns of TMA. Therefore, the present study was undertaken to evaluate the aetiological spectrum and histopathological patterns of TMA in native and transplant kidneys and to correlate the histopathological findings with the clinical characteristics of the affected patients.

MATERIALS AND METHODS

This retrospective cross-sectional study included all primary and secondary cases of TMA diagnosed on renal biopsies received in the Department of Pathology, Government Medical College, Kozhikode, Kerala, India between 1st January 2020 and 31st December 2024. The Institutional Ethics Committee approved the study (IEC No: GMCKKD/RP 2025/IEC/104) and since it was retrospective, consent waiver was obtained from the committee.

Inclusion criteria: All renal biopsies demonstrating histopathological features consistent with TMA were identified from the departmental records. Universal sampling (total enumeration) was adopted and all eligible biopsy-proven TMA cases identified during the study period were included in the study.

Exclusion criteria: Cases of ANCA-associated vasculitis and biopsies with clinical suspicion of TMA but lacking definitive histopathological evidence were excluded from the study.

Study Procedure

Renal biopsy specimens were routinely processed for light microscopy and stained with Haematoxylin and Eosin (H&E), Periodic Acid-Schiff (PAS), Jones Methenamine Silver (JMS), and Masson's trichrome stains. Histopathological evaluation was performed using light microscopy (Leica LX 500). The biopsy specimens were systematically assessed for glomerular, vascular, tubular and interstitial alterations. Histopathological evaluation included assessment of glomerular lesions (glomerular thrombi, endothelial swelling, mesangiolysis, glomerular ischaemic collapse, duplication/double contours of the glomerular basement membrane), vascular lesions (arteriolar and arterial thrombi, endothelial swelling or denudation, mucoid intimal oedema, fibrinoid necrosis, fibrous intimal thickening with onion-skin lamination, recanalised thrombi, hyalinosis), and tubulointerstitial changes (acute tubular injury, tubular atrophy, interstitial fibrosis, and interstitial inflammation). Immunofluorescence was performed on frozen sections using FITC-labelled antibodies against IgG, IgA, IgM, C3, C1q, kappa, and lambda. Immunofluorescence staining intensity was interpreted semi-quantitatively on a scale of 0 to 3+ with Olympus BX43F fluorescent microscope.

Demographic characteristics, clinical presentation, relevant laboratory investigations, and aetiological diagnosis were retrieved from patient's medical records and pathology request forms. Laboratory variables included haemoglobin, platelet count, serum creatinine, serum albumin, urine protein and serum C3 levels. Acute TMA was defined by the presence of fibrin thrombi within glomerular capillaries or arterioles, endothelial swelling or denudation, mesangiolysis in glomeruli, intramural fibrin deposition, and mucoid intimal oedema. Chronic TMA was defined by duplication (double contours) of glomerular capillary walls, glomerular ischaemic collapse, fibrous or mucoid intimal thickening with onion-skin lamination of arteries, recanalised thrombi, and arteriolar hyalinosis [1,3]. Based on the underlying aetiology, cases were categorised as hypertension-associated, infection-related, transplant-associated, autoimmune-associated, aHUS, or other causes.

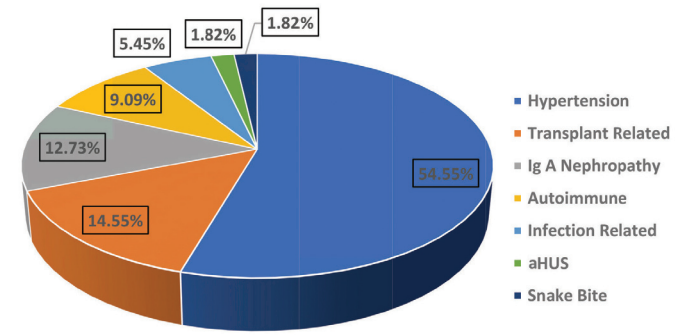
STATISTICAL ANALYSIS

Data were entered into Microsoft Excel and analysed descriptively. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarised using mean±standard deviation or median with range, wherever appropriate.

RESULTS

Over a period of five years, a total of 2,302 biopsies were examined, with 55 (2.39% of all biopsies) showing histological signs of TMA. Among these, 47 were from native kidneys and eight were from transplants. The mean±SD age of patients was 41.6±13.3 years with females making up 32.7 % of the participants. Various causes of TMA have been summarised in [Table/Fig-1]. The leading cause of TMA was hypertension (30 cases, 54.55%). At the time of clinical diagnosis, there was one pregnant patient and one post-partum patient. The pregnant patient was categorised as hypertension-associated TMA due to gestational hypertension, whereas the postpartum patient was classified under infection-associated TMA because of COVID-19 infection rather than as pregnancy-associated TMA. Notably, all infection-associated TMA cases were related to SARS-CoV-2 infection. All eight (14.55%) transplant recipients were receiving CNIs at the time of TMA diagnosis and were classified as having transplant-associated TMA. Among the transplant biopsies, rejection was the primary cause of TMA in five cases (63%), followed by CNI-induced toxicity in two cases (25%). The remaining transplant recipient developed TMA in the setting of an infection, with no evidence of rejection or CNI toxicity on biopsy. However, the precise aetiology could not be established, as the patient died before further investigations could be completed. Among the patients, 7 (12.73%) had IgA Nephropathy, 5 (9.09%) had autoimmune conditions, with Lupus Nephritis affecting four patients and scleroderma affecting remaining one. Single (1.82%) case of aHUS identified which was an eight-year-old girl presented as Microangiopathic Haemolytic Anaemia (MAHA) and thrombocytopenia. Genetic analysis showed deletion of CFHR3/CFHR1 gene, which results in abnormal complement activation and TMA. One (1.82%) case was associated with bite of Hump nosed pit viper. Clinical and laboratory features and histopathological findings are summarised in [Table/Fig-2,3], respectively. Only 2 (3.64%) patients had thrombocytopenia, one with atypical HUS and other postpartum COVID-19 patient.

Histopathological examination revealed that TMA lesions frequently exhibited a combination of acute and chronic changes within the same biopsy. Acute changes were seen in 31/55 (56.36%) cases, while chronic changes were present in 44/55 (80.0%) cases, with



[Table/Fig-1]: Causes of TMA.

Clinical presentation	Frequency (n=55)
Proteinuria	49
Accelerated hypertension	08
Rapidly progressive clinical failure	7
Microscopic haematuria	34
Altered RFT	5
Oliguria	3
Mean systolic BP (mm of Hg)	164.98
Mean diastolic BP (mm of Hg)	102.84
Lab parameters	**Values**
Mean Hb (g%)	9.2 (12-16 males, 11-13 females)
Mean platelet count (mm^3/lac)	2.63 (1.5-4)
Mean creatinine (mg/dL)	7.3 (0.7-1.2)
Serum albumin (g/dL)	4.58 (3.5-5)
Serum C3 (mg/dL) (Available in 44 patients)	
>90 (90-180)	29
<90	15

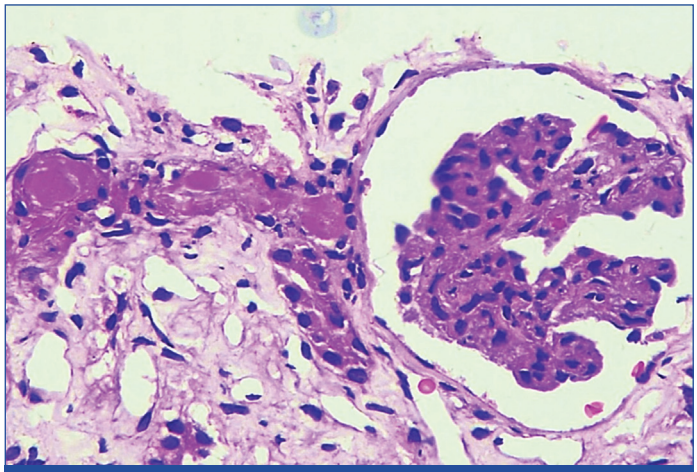
[Table/Fig-2]: Clinical and laboratory parameters.

nephritis, six of the eight renal allograft biopsies, and 19 of the 30 hypertension-associated cases. Chronic TMA changes were observed in the case of aHUS, all three COVID-19-associated cases, the case of scleroderma, three of the four lupus nephritis cases, all seven cases of IgA nephropathy, two of the eight renal allograft biopsies, and 27 of the 30 hypertension-associated cases. Overall, chronic TMA changes predominated in the study cohort, while acute lesions were frequently superimposed on chronic vascular injury, particularly in hypertension-associated TMA, lupus nephritis, and COVID-19-associated TMA. Representative histopathological features of acute and chronic TMA are illustrated in [Table/Fig-4-7].

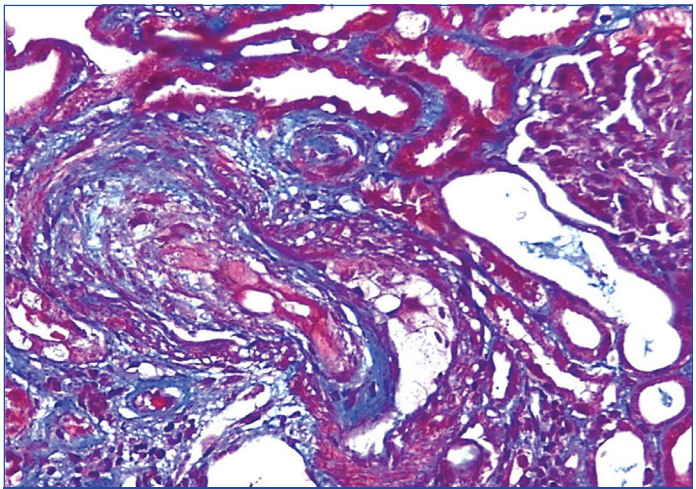
Only one patient with aHUS fulfilled the criteria for systemic TMA, presenting with both MAHA and thrombocytopenia. Another patient, a postpartum woman with COVID-19 infection, also had thrombocytopenia; however, the absence of peripheral blood smear findings and other laboratory investigations precluded confirmation of systemic TMA. The remaining cases could not be reliably classified as isolated renal TMA or systemic TMA because other investigations required to assess systemic microangiopathic haemolysis were unavailable.

Variables	HTN (n=30)	Graft (n=8)	IgA (n=7)	Lupus (n=4)	Scleroderma (n=1)	COVID-19 (n=3)	aHUS (n=1)	Snake bite (n=1)
Glomerular changes								
Fibrin thrombi	9	1	Nil	4	Nil	1	Nil	1
Fibrillary appearance	3	Nil	Nil	Nil	Nil	1	Nil	Nil
Mebrano proliferative pattern	7	Nil	Nil	3	1	3	1	Nil
GBM splitting	6	1	Nil	3	1	3	1	Nil
Ischaemic wrinkling	12	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Diffuse global glomerulosclerosis	3	Nil	Nil	1	Nil	Nil	Nil	Nil
Crescents	2	Nil	Nil	Nil	Nil	2	Nil	Nil
Mesangiolysis	1	Nil	Nil	Nil	Nil	Nil	Nil	1
Tuft necrosis	Nil	Nil	Nil	Nil	Nil	1	Nil	1
Arterial and arteriolar changes								
Fibrinoid necrosis	1	Nil	Nil	Nil	Nil	1	Nil	Nil
Thrombi in artery	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Thrombi in arteriole	19	6	7	Nil	1	Nil	Nil	Nil
Fibro intimal hyperplasia	27	2	7	Nil	1	1	Nil	Nil
Mucoid intimal thickening	11	Nil	1	Nil	1	1	Nil	Nil

[Table/Fig-3]: Histopathological features.



[Table/Fig-4]: Acute Thrombotic Microangiopathy (TMA) showing a bloodless glomerulus with arteriolar fibrin thrombus (H&E stain, 400x).

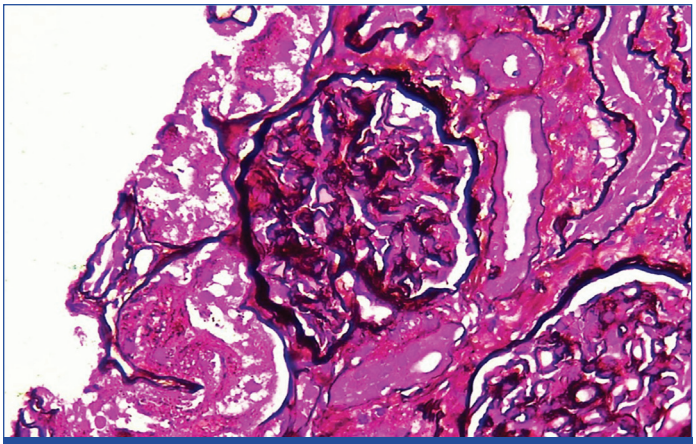


[Table/Fig-5]: Acute Thrombotic Microangiopathy (TMA) showing a fuchsinophilic fibrin thrombus within an arteriole (Masson Trichrome stain, 400x).

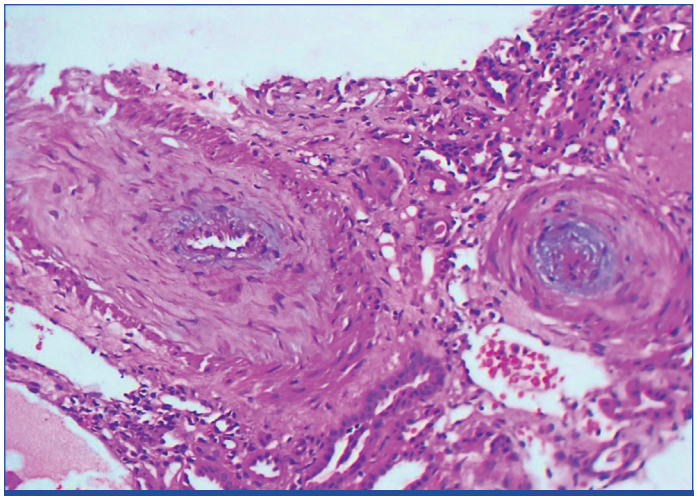
considerable overlap between the two groups. As both acute and chronic lesions could coexist in the same biopsy, these categories were not mutually exclusive. Acute TMA changes were identified in the single case of hump-nosed pit viper envenomation, one of the three COVID-19-associated cases, all four cases of lupus

DISCUSSION

The TMA represents a clinicopathological syndrome characterised by endothelial injury, microvascular thrombosis, and variable degrees of ischaemic damage affecting many organs. Renal



[Table/Fig-6]: Chronic Thrombotic Microangiopathy (TMA) showing glomerular basement membrane reduplication (double contour formation) {Jones Methenamine Silver (JMS)} stain (400x).



[Table/Fig-7]: Chronic Thrombotic Microangiopathy (TMA) showing fibrointimal hyperplasia and mucoid intimal oedema of arteries (H&E stain, 400x).

involvement is common and often requiring kidney biopsy for diagnosis and assessment of disease severity. Recent studies have emphasised the heterogeneity of renal TMA and the importance of clinicopathological correlation in identifying underlying aetiologies and predicting outcomes [1-5]. In this study, different causes of renal biopsy confirmed TMA, considering clinical, laboratory, and pathological correlations were studied. A comparative analysis of the clinicopathological characteristics of the present study and other major published studies is presented in [Table/Fig-8] [7-9]. A total of 55 cases of biopsy-proven renal TMA were identified over a five-year period, constituting about 2.39% of all renal biopsies. This frequency was slightly higher than that reported by Yu XJ et al., (1.4%) and substantially higher than that observed in some Indian series [9,10] reflecting differences in biopsy practices, and underlying disease prevalence. The mean age of presentation in the present cohort was 41.6 years, indicating that TMA predominantly affects young and middle-aged adults, consistent with previous studies [8-10].

A notable finding of the present study was the predominance of secondary causes of TMA in our region, emphasising the importance of identifying underlying aetiologies rather than considering TMA as a primary disorder alone. Hypertension-associated TMA constituted the largest subgroup, accounting for more than half of all cases. Similar observations have been reported by Yu XJ et al., and Manickam N et al., where malignant hypertension emerged as the leading cause of biopsy-proven renal TMA [7,8]. In contrast, Johny J et al., identified autoimmune conditions as the main cause,

Parameter	Nair GG et al., Kerala (2026)	Yu XJ et al., China, 2014 [7]	Manickam N et al., Uttar Pradesh, 2022 [8]	Johny J et al., Vellore, 2026 [9]
Study period	2020-2024	2000-2012	2012-2017	2011-2022
Study design	Retrospective	Retrospective	Retrospective	Retrospective
Total TMA cases	55	109	40 biopsies (39 patients)	87
Percentage of TMA	2.39%	1.4%	Not stated	0.5%
Mean age (years)	41.6±13.3	34.0±11.1	31±12	31.7±9.9
Female sex (%)	32.7%	35.8%	59%	57.5%
Native kidney biopsies	47 (85.45%)	109 (100%)	33 (82.5%)	76 (87.4%)
Graft biopsies	8 (14.55%)	Excluded	7 (17.5%)	11 (12.6%)
Most common aetiology	Hypertension-associated TMA	Malignant hypertension	Malignant hypertension	Autoimmune disease
HTN associated TMA	54.55%	56%	39%	14.9%
Autoimmune-associated TMA	9.09%	15.6%	18% (LN)	25.2%
Transplant-associated TMA	14.55%	1.8% HSCT	17.5%	12.6% (Renal) and 9.1% (BMT)
aHUS	1.82%	7.3%	21%	18.4%
Infection-associated TMA	5.45% (all COVID-19)	Rare	Not reported	Included under other causes
Mean serum creatinine (mg/dL)	7.3	~5.4	5.6 ± 2.5	4.85
Mean haemoglobin (g/dL)	9.2	9.5	8.1 ± 2.5	8.1 ± 1.9
Microscopic haematuria	61.8%	64.2%	55%	70.1%
Proteinuria	89%	64.2%	92.5%	1144 mg/day
Predominant pathology	Vascular lesions (fibrointimal hyperplasia, arteriolar thrombi)	Chronic vascular TMA	Arterial and arteriolar changes predominates in malignant hypertension; mixed lesions in aHUS/LN	Mesangiolysis (74.7%) and other glomerular changes
Dialysis dependence/ ESRD	Not available	ESRD in 56%	20-57% depending on aetiology	46% dialysis-dependent
Mortality	Not available	7.3%	Not reported	10.3%
Major conclusion	Secondary TMA, particularly hypertension-related TMA, predominates.	Malignant hypertension is the leading cause followed aHUS and pregnancy related.	Malignant hypertension (commenest cause) and lupus nephritis showed 'isolated renal TMA'; postpartum TMA and aHUS have systemic manifestations.	Autoimmune diseases and aHUS predominate; TMA associated with significant renal morbidity.

[Table/Fig-8]: Comparison of major clinicopathological characteristics of renal biopsy-proven TMA across published studies [7-9].

indicating variations in disease distribution based on location and institution [9]. Unlike earlier studies that largely emphasised malignant hypertension, only eight of the 30 hypertensive patients in the present cohort fulfilled the criteria for accelerated hypertension, while the remaining patients had a prior diagnosis of hypertension and were on treatment. This observation might indicate a lack of awareness of previous instances of accelerated hypertension prior to diagnosis, as blood pressure might have been somewhat managed by the time of assessment. Another interpretation was that TMA could arise in specific hypertensive individuals even without typical accelerated or malignant hypertension, suggesting a more complex pathogenesis than previously recognised.

Histologically, these cases demonstrated prominent vascular changes, including fibrointimal hyperplasia, mucoid intimal oedema, arteriolar thrombosis, and ischaemic glomerular alterations similar to previous literature [8]. Severe hypertension causes endothelial injury through mechanical stress, resulting in platelet activation and microvascular thrombosis [1]. In the present cohort, vascular lesions were considerably more frequent than glomerular thrombi, supporting the concept that arterial and arteriolar injury represent the dominant pathological process in hypertension-related TMA. The high burden of hypertension in our population may reflect delayed diagnosis, suboptimal blood pressure control, and late presentation to tertiary care centre.

Nevertheless, emerging evidence suggests that hypertension-associated TMA might not always be solely a secondary disorder. Timmermans SAMEG et al., demonstrated that in some cases of severe hypertension with TMA confirmed by renal biopsy, patients may have underlying complement abnormalities, categorising them as part of complement-mediated TMA and leading to a worse renal outcome [10]. Importantly, these patients may not exhibit the classical features of complement-mediated TMA, such as overt MAHA or thrombocytopenia. Therefore, identifying TMA through renal biopsy in hypertensive patients should trigger consideration of assessing the complement pathway, regardless of the blood-related symptoms, as early detection of a complement-mediated process could have significant implications for treatment, prognosis, and prevention.

Transplant-associated TMA was the second most common cause identified in the present study. Among the eight graft biopsies, five cases were associated with rejection and two were attributed to CNI toxicity. One additional patient developed TMA following infection without evidence of rejection or drug toxicity. Post-transplant TMA is increasingly recognised as a severe complication associated with poor graft outcomes [11,12]. The pathogenesis is multifactorial and includes ischaemia-reperfusion injury, antibody-mediated rejection, CNI toxicity, mTOR inhibitors, infections, complement activation, and recurrent complement-mediated disease [5,11,12]. Recent evidence suggests that endothelial injury serves as the final common pathway irrespective of the initiating trigger [11]. The predominance of rejection-associated TMA in the present study was consistent with observations reported by Harshan N et al., from Kerala, who similarly identified rejection as the most frequent cause of transplant-associated TMA [5]. Early recognition of these lesions is critical because prompt treatment of rejection or modification of immunosuppressive therapy may prevent irreversible graft damage.

Seven patients in the present study demonstrated TMA in association with IgA nephropathy. Notably, all patients had concomitant hypertension. El Karoui K et al., reported that TMA lesions are more common in IgA nephropathy than previously recognised and are strongly associated with severe hypertension, advanced renal dysfunction, and poor renal prognosis [13]. The coexistence of TMA and IgA nephropathy may reflect endothelial injury induced by uncontrolled hypertension, although complement activation and inflammatory mediators may also contribute [13]. The predominance of vascular lesions observed in the present study patients supports the important role of hypertension in the pathogenesis of TMA in this setting.

Autoimmune disorders accounted for a minor proportion of cases in the present cohort, with lupus nephritis being the most common. Histologically, these biopsies demonstrated involvement of glomerular capillaries predominantly. Previous studies have reported a prevalence of renal TMA in lupus nephritis ranging from 0.5% to 24.3%, depending on patient selection and diagnostic criteria [1,14]. The pathogenesis of TMA in lupus nephritis is multifactorial and may involve immune complex-mediated endothelial injury, complement activation, antiphospholipid antibodies, severe hypertension, and thrombotic events [1,14]. Song D et al., demonstrated that the presence of TMA in lupus nephritis is associated with more severe renal disease and poorer outcomes [14]. The present study results indicate the importance of a thorough assessment for TMA abnormalities in lupus nephritis biopsies, as their identification could impact both prognosis and treatment. One patient in the present series had scleroderma renal crisis. Renal biopsy showed chronic TMA with prominent vascular involvement, a finding characteristic of systemic sclerosis-associated vasculopathy. Similar observations have been reported by Tonsawan P et al., who described obliterative vascular lesions as the hallmark pathological feature of scleroderma renal crisis [15]. It is suggested that immune complexes containing scleroderma-specific autoantibodies might be responsible for endothelial activation in these instances [1].

All infection-related cases in the present study were associated with SARS-CoV-2 infection which constituted a distinct subgroup not reported in earlier pre-pandemic series. Histological examination predominantly revealed chronic glomerulopathy. The imbalance in complement and coagulation system, along with a widespread cytokine storm, leads to damage to endothelium in such patients [1]. Akilesh S et al., demonstrated that TMA-like lesions can be a cause of acute kidney injury and proteinuria in COVID-19 patients [16]. Although the number of cases in the present study was limited, these findings further support the association between COVID-19 and renal microvascular injury.

In the present study, only one case of primary TMA was identified. This child patient was diagnosed with atypical HUS caused by complement issues, identified through the presence of a CFHR3/CFHR1 deletion. Detecting such genetic irregularities is crucial because individuals with complement-related aHUS might respond well to specific treatment using eculizumab [1,2]. Noteworthy points from our research include that thrombocytopenia was observed in only two patients: one with atypical HUS and the other with TMA associated with postpartum COVID-19. The low prevalence of thrombocytopenia highlights the predominance of renal-limited TMA in the present cohort and may explain why many cases required kidney biopsy for diagnosis. Primary TMAs are typically diagnosed based on thrombocytopenia, MAHA, and specific lab results, often making renal biopsy unnecessary. Therefore, studies relying on biopsies may show secondary TMAs more prominently while downplaying the real frequency of primary TMA.

A single case of TMA associated with hump-nosed pit viper envenomation was identified in the present study. Snakebite-associated TMA is an increasingly recognised cause of acute kidney injury in tropical countries. A systematic review by Noutsos T et al., demonstrated that hump-nosed vipers (Hypnale species) were among the most frequently reported snake species associated with TMA worldwide [17]. This particular case was unique in displaying necrosis of the glomerular tuft on kidney biopsy, likely indicating severe damage to the endothelial cells and small blood vessels caused by the venom's toxin.

The prognosis of renal TMA varies according to the underlying aetiology and the severity of renal injury. Complement-mediated TMA and transplant-associated TMA generally have poorer renal outcomes,

while infection- drug- and snakebite-associated TMA may show recovery following treatment of the precipitating cause. Although hypertension-associated TMA is often considered a secondary form, research indicates that some patients have complement irregularities and experience adverse renal outcomes [10]. Furthermore, chronic histological changes such as vascular intimal fibrosis, tubular atrophy, and interstitial fibrosis are linked to a poorer prognosis regardless of the cause [7]. Therefore, accurate aetiological classification and assessment of chronic renal damage are essential for prognostication and management.

Limitation(s)

This study had several limitations. First, its retrospective design resulted in incomplete clinical and laboratory information in some cases limiting comprehensive clinicopathological correlation. Second, being a single-centre study, the findings may not be fully generalisable to other populations. Third, advanced complement studies and genetic evaluation were not available in all cases, preventing comprehensive aetiological classification. Finally clinical follow-up data were unavailable for all patients, limiting assessment of long-term renal outcomes.

CONCLUSION(S)

Renal TMA is an uncommon but important cause of renal dysfunction with a diverse aetiological spectrum. Hypertension-associated TMA was the predominant form in the present cohort, followed by transplant-associated disease. Chronic vascular lesions were more frequent than acute thrombotic changes, suggesting delayed presentation and sustained endothelial injury in many patients. Renal biopsy remains indispensable for confirming the diagnosis, identifying the underlying aetiology, and assessing the extent of acute and chronic vascular injury, particularly in patients with atypical clinical presentations. Greater awareness of common and emerging causes of TMA may facilitate earlier diagnosis and improve renal outcomes.

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