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Histopathological features of thrombotic microangiopathies in renal biopsies

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ABSTRACT

Background: Thrombotic microangiopathy (TMA) is a morphologic lesion characterized by thrombi occluding microvasculature related to endothelial injury.
Objectives: This study aimed to assess the association between histopathological findings and etiology of TMA.
Patients and Methods: This cross-sectional study comprised a sample of 34 patients who underwent renal biopsy and received an initial TMA diagnoses resulting in 29 definitive TMA cases. We evaluated the TMA features and clinical histopathological correlation.
Results: The most frequent etiologies were atypical hemolytic uremic syndrome (aHUS) (n= 10; 34.5%), hemolytic uremic syndrome caused by Shiga toxin-producing Escherichia coli (STEC-HUS) (n=6; 24.1%) and secondary causes of TMA (n= 12; 41.4%). We found the following histological features; patients with aHUS had thrombi in 60% of biopsies, membranoproliferative glomerulonephritis (MPGN)-like pattern in 20% and ischemia in 20%; patients with STEC-HUS had thrombi (14.3%), MPGN-like pattern (14.3%), endothelial swelling (14.3%) and ischemia (57.1%); patients with secondary etiologies had thrombi (58.3%), endothelial swelling (16.7%), ischemia (16.7%) and MPGN-like pattern (8.3%).
Conclusions: The distribution of classic TMA findings was not related to etiology in spite of microthrombi having been found mostly in aHUS and secondary etiologies, whereas ischemia was found mainly in STEC-HUS. We did not find a histopathological pattern to each etiology of TMA.

Original Article

Implication for health policy/practice/research/medical education:
In a cross-sectional study on 34 patients with thrombotic microangiopathy (TMA) in renal biopsy, we found the distribution of classic TMA findings was not related to etiology in spite of microthrombi having been found mostly in atypical hemolytic uremic syndrome and secondary etiologies, whereas ischemia was found mainly in hemolytic uremic syndrome caused by Shiga toxin-producing *Escherichia coli.*
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1. Background

Thrombotic microangiopathy (TMA) is a histopathological entity characterized by thrombi occluding microvasculature related to endothelial injury. Clinical and laboratory features associated with TMA are thrombocytopenia, microangiopathic hemolytic anemia and organ damage, usually kidneys and brain (1).

Many causes of endothelial injury lead to TMA. Primary TMAs consist of diseases whose endothelial damage is involved in its own pathogenic mechanism. Atypical hemolytic uremic syndrome (aHUS) is a dysregulation of the complement system due to a lack of complement inhibitory factors leading to hyperactivity of alternative pathway. Thrombotic thrombocytopenic purpura is the result of a severe deficiency of ADAMTS13 (A disintegrin and metalloprotease with thrombospondin type 1 motif, member 13), a metalloprotease enzyme that cleaves von Willebrand factor (vWF) in multimers. In Hemolytic uremic syndrome caused by Shiga toxin-producing *Escherichia coli* (STEC-HUS) and hemolytic uremic

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syndrome associated with *Streptococcus pneumoniae* infection (pneumococcal HUS) the endothelial injury occurs by toxins (Shiga toxin made by enterobacteria and neuraminidase by invasive pneumococci infections, respectively) (2,3).

Among secondary etiologies are systemic lupus erythematosus (SLE), severe hypertension or malignant hypertension (MH), HIV-associated TMA, pregnancy-associated TMA (HELLP syndrome), disseminated intravascular coagulation (DIC), antibody-mediated rejection (AMR) in kidney transplant, malignancy-associated TMA and drug-mediated TMA, including antineoplastic agents (e.g. gemcitabine), immunosuppressive drugs (e.g. calcineurin inhibitors – CNIs) and antiplatelet therapy (e.g. clopidogrel and ticlopidine) (2,4).

Kidneys are commonly affected by TMA and their histopathological findings in light microscopy (LM) can be categorized as: 1– Glomerular changes: the microvasculature can be characterized by fibrinoid necrosis, fibrin and platelet thrombi, often with nuclear debris but no significant inflammation. Fragmented red blood cells (RBCs) are also commonly seen entrapped in thrombi, especially in acute phases. In addition, microscopic findings also include endothelial swelling, mesangiolysis and apparent thickening of capillary wall. Chronic changes such as glomerular basement membrane (GBM) remodeling with double contours and mesangial expansion may result in a membranoproliferative glomerulonephritis-like pattern (MPGN-like pattern); 2– Vascular changes: when involved, arterioles and arteries usually show thrombosis. They may also show necrosis of the vessel wall with intimal swelling, mucoid change and intimal proliferation. Those changes may lead to narrowed lumens and concentric lamination of intimal fibrosis causing "onion skin" appearance; 3–Tubule-interstitial changes: acute tubular necrosis is a frequent finding as a result of ischemic changes. Cortical necrosis may occur due to a severe acute ischemia after obstruction of microcirculation (2,5-8).

Regardless of the underlying etiology, all morphologic features are very similar. Therefore, renal biopsy rarely helps to establish etiological or prognostic information. Even so, the literature remains unclear although authors suggest pathological differences distinguishing causes of TMA. Some authors suggest some histopathological differences especially in secondary causes (2,5,7). A previous study suggests difference between histopathological TMA findings of STEC-HUS and aHUS (9).

2. Objectives

This study aimed to assess the association between histopathological findings and etiology after pathological analysis of kidney biopsy specimens.

3. Patients and Methods

3.1. Patients and study design

Data were collected from the medical records of all 3580 kidney biopsies performed (January 2000 to December 2017). This cross-sectional study included a sample of 34 (0.9%) patients who underwent renal biopsy and received a TMA report at the University Hospital of Botucatu Medical School, São Paulo, Brazil.

The clinical data systematically recorded were age, gender, TMA after kidney transplant and pregnancy-associated TMA. Two nephrologists conducted chart review in search of TMA etiological diagnoses and organized them in three groups: aHUS, STEC-HUS, secondary causes (SLE, AMR, MH, CNI and DIC).

We established as inclusion criteria the presence of histopathological TMA features and compatible clinical characteristics. Common clinical findings were thrombocytopenia, non-immune microangiopathic hemolytic anemia (decreased hemoglobin, elevated serum levels of lactate dehydrogenase, schistocytes in blood film and low serum haptoglobin, plus negative Coombs test) and organ injury (acute kidney injury) (3,6).

3.2. Renal histopathology

Two independent nephropathologists performed the analyses of all specimens. By LM, the following stains were used: hematoxylin and eosin, periodic acid-Schiff, Jones silver and Masson's trichrome. In immunofluorescence microscopy, stains used were IgG, IgA, IgM, C3, C1q and fibrinogen. None of those cases was evaluated by electron microscopy (EM).

The microscopic findings were divided into four groups: thrombi (arterial/arteriolar thrombi or within glomerular capillary), endothelial swelling, ischemia (cortical necrosis or acute tubular necrosis) and MPGN-like pattern (both criteria were considered: mesangial interposition and double contour appearance of GBM). Figure 1 shows some photographic examples of histopathological findings.

Each pathologist documented the absence or presence of each group of findings according to the histopathological criteria. We considered only TMA cases with the consensus between both pathologists.

3.3. Ethical approval

The study protocol was approved by the Ethics Committee of Botucatu Medical School, São Paulo, Brazil (Approval ID: 3.380.716). The current study was performed according to the tenets of the Declaration of Helsinki.

3.4. Statistical analysis

Results were expressed as numerical values and

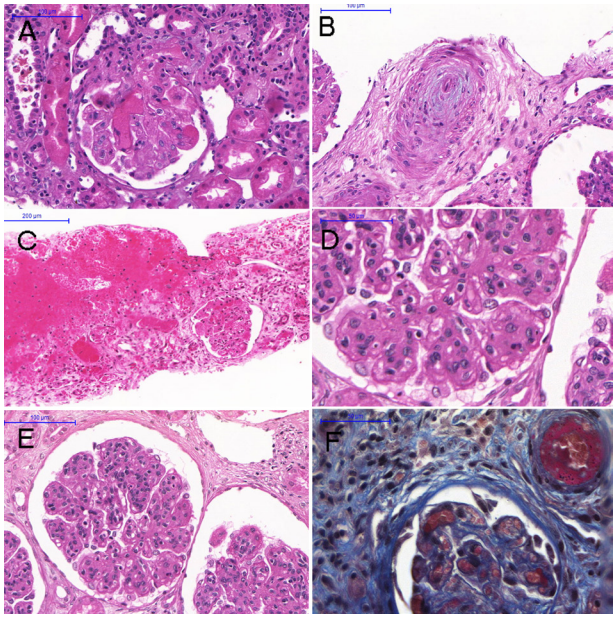

Figure 1. Histopathological features in light microscopy. (A) thrombi in afferent arteriole and within glomerular capillary (Hematoxylin and eosin, x200); (B) thrombi in arteriole and within glomerular capillary (Masson's trichrome, x400); (C) proliferative endarteritis (Hematoxylin and eosin, x200); (D) necrosis and bleeding of renal parenchyma and thrombi in adjacent glomeruli (Hematoxylin and eosin, x100); (E) Reduplication of glomerular basement membrane (Hematoxylin and eosin, x400); (F) MPGN-like pattern (Hematoxylin and eosin, x200).

percentages for categorical variables. Continuous variables were expressed as mean and standard deviations (SD). Comparisons were based on Pearson chi-square test for categorical data and Mann–Whitney U test for non-Gaussian-distributed continuous parameters. All tests were adjusted by Bonferroni correction. $P<0.05$ was regarded as statistically significant. All statistical analysis was performed with the use of software SPSS-25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp).

4. Results

4.1. Patients

We excluded 4 patients for not finding any clinical evidence of TMA or possible associated etiology after a chart review, even at a different time than that of biopsy. One patient was excluded for finding neither clinical nor histopathological evidence of TMA in biopsy. Hence, we considered those 5 cases as doubtful diagnosis.

Thus, this study included 29 biopsy-confirmed TMA patients (18 native kidney biopsies and 11 renal graft biopsies). Among them, 10 (34.5%) had aHUS as etiological cause, 6 (24.1%) STEC-HUS and 12 (41.4%) secondary causes of TMA. We found the following secondary causes: 5 (17.2%) patients with AMR, 3 (10.3%) MH, 2 (6.9%) SLE, 1 (3.4%) DIC and 1 (3.4%) CNI. Table 1 shows clinical and histopathological characteristics according to etiological diagnosis.

In relation to baseline characteristics, aHUS patients were predominantly female (60%) and had a mean current age of 33 years (SD=10). Half of them received aHUS diagnosis after kidney transplant. STEC-HUS patients were mostly male (85.7%) and on average 2 years old (SD= 1). Patients with secondary etiologies were mostly female (75%) and on average 38 years old (SD= 13). Half of them (50%) received diagnosis after kidney transplant (AMR and CNI).

4.2. Findings

When evaluating histological findings, aHUS patients had thrombi in 60% of biopsies, MPGN-like pattern in 20% and ischemia in 20%. STEC-HUS patients had thrombi (14.3%), MPGN-like pattern (14.3%), endothelial swelling (14.3%) and ischemia (57.1%). Among patients with secondary etiologies, we found thrombi (58.3%), endothelial swelling (16.7%), ischemia (16.7%) and MPGN-like pattern (8.3%). All features are shown in Figure 2.

A cluster of all histopathological features is shown in Table 2, organized by thrombi location (glomerular, arterial or both) and thrombi associated with MPGN-like pattern. There was not a clear distribution of findings according to etiology.

5. Discussion

In this paper, we evaluated 29 kidney biopsies in order

Table 1. Clinical and histopathological characteristics according to etiological diagnosis

	aHUS (n=10)	STEC-HUS (n=7)	Secondary etiology (n=12)	*P*
Clinical findings				
Female sex (%)	6 (60)	1 (14.3)	9 (75)	0.03
Age (y), mean (SD)	33 (10)	2 (1)	38 (13)	0.04
After kidney transplantation (%)	5 (50)	0 (0)	6 (50)	0.04
After pregnancy (%)	2 (20)	0 (0)	2 (16.7)	0.46

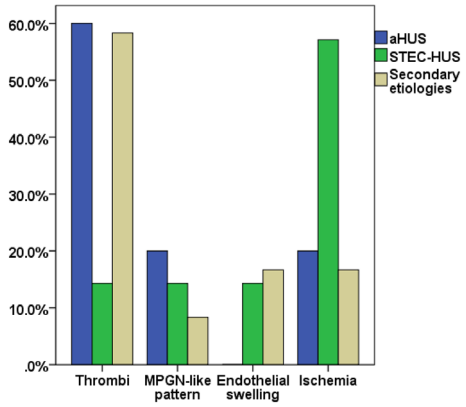

Figure 2. Histopathological features distributed by etiology.

to achieve a histological pattern of TMA. Although the TMA was characterized by thrombi in microvasculature due to endothelial injury, other findings may be found in TMA biopsies. A spectrum of histological features allows us to sort in acute or chronic, even so it is not possible to define an etiology exclusively by the histology. Another challenge in TMA is the discordance between timing of clinical and pathological manifestations (5,8).

To date, the pathological mechanism in TMA that leads to preferably endothelial cell damage in kidneys is still unknown. It is known that the glomerular endothelium cell health depends on vascular endothelial growth factor (VEGF), without which intense angiogenesis occurs. In TMA, regardless the cause, there is an endothelial damage with dysregulation of coagulation, inflammation and vascular tone control (10,11).

In an acute phase of TMA progression, active glomerular lesions may be seen as glomerular thrombi, endothelial swelling or denudation, fragmented red blood cells, subendothelial flocculent material by EM, mesangiolysis and microaneurysm. In arterioles, active lesions may be thrombi, endothelial swelling or denudation, intramural fibrin, fragmented red blood cells, intimal swelling and/or myocyte necrosis. Finally in arteries, they may be thrombi, myxoid intimal swelling, intramural fibrin and fragmented red blood cells (8).

Both LM and EM may show chronic lesions. Double contours of peripheral capillary walls and variable mesangial interposition are seen by LM, whereas new subendothelial basement membrane and widening of the subendothelial zone are seen by EM. Those glomerular changes may also be called MPGN-like pattern. In arterioles, we may find hyaline deposits while, in arteries, fibrous intimal thickening with concentric lamination ("onion skin" appearance) (8).

Probably, chronic TMA patients present mild clinical manifestations which make it difficult to identify clinical correlation with all MPGN-like pattern biopsies. Our study showed MPGN-like pattern in 20% of aHUS patients, being even less in other etiologies. A temporal mismatch between clinical and morphologic manifestations makes etiology definition difficult in patients with MPGN-like pattern, especially in secondary TMA. STEC-HUS is more easily diagnosed, mainly related to diarrhea, accordingly chronic lesions were less common (14.3% of STEC-HUS patients).

Regarding etiologies, we found 34.5% of aHUS although it is an ultra-rare disease (12) (the annual incidence is about 0.5 to 2 per million adults and 3.3 per million children or adolescents) (13). A possible explanation for this finding is that this study was conducted in a transplant center located in a high complexity hospital, where there is also a maternity unit. aHUS can be revealed in both situations (14,15). Moreover, the presence of micro-thrombi in 60% of aHUS patients suggests that we performed early biopsy in this diagnostic suspicion.

According to the literature, severe STEC-HUS cases are related to ischemic lesions(13). An experimental study demonstrated different glomerular features between type of Shiga toxin (stx). Stx type 1 was related to endothelial lesion, while stx type 2 to mesangiolysis (16). Besides suggesting biopsy indication occurs more often in longstanding acute kidney injury, the type of toxin might be responsible for ischemia in 57.1% of STEC-HUS biopsies.

In a renal transplant scenario, many TMA etiologies may represent a diagnosis challenge. There are three

Table 2. Histopathological features of thrombotic microangiopathy in renal biopsies

	aHUS (n=10)	STEC-HUS (n=7)	Secondary etiology (n=12)	*P*
Histopathological findings				
Only glomerular thrombi (%)	3 (30)	0 (0)	1 (8.3)	
Only arterial thrombi (%)	1 (10)	1 (14.3)	2 (16.7)	
Glomerular and arterial thrombi (%)	2 (20)	0 (0)	4 (33.3)	0.42
Membranoproliferative-like pattern (%)	1 (10)	1 (14.3)	1 (8.3)	
MPGN-like pattern + thrombi (%)	1 (10)	0 (0)	0 (0)	
Endothelial swelling (%)	0 (0)	1 (14.3)	2 (16.7)	
Ischemia (%)	2 (20)	4 (57.1)	2 (16.7)	

situations: recurrence, *de novo* TMA and associated to antibody mediated rejection (AMR) (11,17). One Brazilian cohort study with 1549 patients found 1.1% of *de novo* TMA after kidney transplantation, excluded AMR and recurrent HUS. CNIs withdrawal was the first step in 59% of patients, followed by plasma exchange or plasma infusion (35%). Graft survival after *de novo* TMA was 43% in 4 years, significantly less than those who did not have TMA after kidney transplant (85.6%)(18). The early CNI withdrawal in *de novo* TMA patients probably decreased biopsies indications after kidney transplant in our hospital, which performs on average 120 kidney transplants a year (19).

In acute phase of AMR, circulating donor-specific antibodies (DSA) can lead to a lytic endothelial cells injury in kidney graft microvasculature associated to complement activation, which is characterized by endothelial swelling, cell necrosis, classic TMA and neutrophilic infiltration. Chronically, AMR can be expressed by sub-lytic endothelial cells injury whose histological findings can be MPGN-like pattern (proliferative-reparative changes named transplant glomerulopathy), pro-coagulant changes as micro-thrombi or inflammatory infiltration manifested as glomerulitis and capillaritis. Peritubular capillary C4d staining helps us to diagnose AMR and it was positive in 55% of *de novo* TMA biopsies (20,21). In C4d-negative AMR cases, increased expression of validated gene transcripts in the biopsy tissue could be an indicative of antibody interaction with vascular endothelium (22). The involvement of the entire vascular tree and endarteritis are features of AMR(17). The group of secondary TMA had 5 patients (41.6%) with AMR, all of them C4d-positive. The small number of cases precluded a separate analysis.

Pregnancy is responsible for unmasking 20% of aHUS among women, mostly in postpartum (14). A differential diagnosis of TMA related to pregnancy is known as HELLP syndrome, in which renal microvasculature and hepatic sinusoids damage occur due to preeclampsia. Preeclampsia provides an unbalance between proangiogenic factors (VEGF) and antiangiogenics factors (sFlt1 – tyrosine kinase Fms-like soluble type 1) (23). In HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome, ordinary renal lesions (glomerular endotheliosis and ATN) resolve after delivery (24,25).

Out of all possible secondary TMA causes, we found MH, DIC and SLE. A dysregulation of complement and coagulation systems can give rise to DIC after an endothelial damage, which is a cause of TMA due to sepsis (26).

According to the literature, TMA is related to 15% of MH biopsies since there is a predominant involvement of arterioles and interlobular artery with intimal proliferation leading to narrowed lumens ("onion skin" lesions) (5,27).

TMA in SLE patients may be associated with several possibilities; overlapping Scleroderma, aHUS, MH, antiphospholipid syndrome and TTP, in addition to endothelial involvement of SLE activation. TMA was found in 24% of biopsies with lupus nephritis, mostly in class IV. Endocapillary hypercellularity was more prevalent in lupus patients with TMA than those without TMA. A previous study found that TMA in lupus nephritis biopsies was an independent risk factor for renal outcome (28).

6. Conclusions

Although the distribution of classic TMA findings was not related to etiology, however, micro-thrombi were found mostly in aHUS and secondary etiologies. Furthermore, ischemia was found mainly in STEC-HUS. Evaluation of combined features did not help us demonstrating a histopathological pattern in kidney biopsy-proven TMA patients.

Limitations of the study

We acknowledge that this study has limitations. It has a small sample of biopsies and many possible etiologies. Probably just severe TMA cases or those who did not respond to the initial treatment had kidney biopsy indication. We needed to believe in different medical evaluations by doing chart review. Furthermore, the grouping of secondary TMA causes precludes the understanding of each single entity details.

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Authors' contribution

MEN was responsible for writing this manuscript and literature review. LMS and HVGV were responsible for chart review. DCS and RMV were responsible for histopathological analysis. LGMA was responsible for study conception and data analysis. All authors provided intellectual content for this study.

Conflicts of interests

MEN and LGMA, reported having provided teaching assistance to Alexion Pharmaceuticals. Other authors have no conflicts of interest to declare. This manuscript did not receive grants.

Ethical considerations

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

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