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Thrombotic microangiopathy after kidney transplantion

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Abstract

Background and objectives: Thrombotic microangiopathy after kidney transplantation is rare but serious complication. The purpose of this study is to describe the cases of thrombotic microangiopathy after kidney transplantation.

Patients and Methods: This retrospective study used the reports of all kidney transplant biopsies that were done in Kurdistan region from January 2017 to April 2022. The biopsy reports with diagnosis of Thrombotic microangiopathy were extracted from this total number and the patients, and pathological data included in the reports were recorded.

Results: The total number of 1635 graft biopsies, of which 82 (5.01%) were found to have Thrombotic microangiopathy features. The mean age of studied patients with Thrombotic microangiopathy was (38.2 years) and male to female ratio as 2.3:1. We found 67.1% of cases of Thrombotic microangiopathy were associated with calcineurin inhibitor toxicity, 35.4% with rejection, 15.9% were recurrent thrombotic microangiopathy, and 40.2% were associated with other miscellaneous causes.

Conclusions: Thrombotic microangiopathy after kidney transplantation is rare but debilitating complication. The cause is multifactorial in most cases in the light of coexistence of multiple risk factors in the kidney transplant recipients. Further studies are required to disentangle these overlapping risk factors. And allow for better prevention and treatment of this condition.

Key words: CNI toxicity; Kidney transplantation; Thrombotic microangiopathy.

Introduction

Thrombotic microangiopathy (TMA) is a pathological lesion characterized by the presence of glomerular and or arteriolar thrombosis.[1] The pathological diagnosis is made by tissue biopsy.[2] Thrombotic microangiopathy (TMA) after kidney transplantation is a serious condition and is associated with poor outcomes.[3] The time of occurrence of TMA after kidney transplantation is variable ranging from days to year after transplantation. Which means there are different mechanisms involved in its occurrence[5] Thrombotic microangiopathy (TMA) after kidney transplantation is classified into de novo TMA i.e. (developed first time after transplantation without evidence of it before transplantation. Recurrent TMA (TMA was the cause of failure of the native kidney and it came back affecting the transplanted kidneys) Missing the diagnosis of TMA in the native kidneys before doing the transplantation is likely due to the unfortunate fact that most patients with End stage kidney disease don't undergo kidney biopsy of their native kidneys.[4] De novo TMA occurs in patients who have an acquired or genetic abnormality in alternative complement pathway when they get exposed to an additional triggering factor triggering event or factors, Including: Antibody mediated rejection, Immunosuppression associated TMA like CNI, Viral infections

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like CMV; BK, Genetic abnormalities in complement pathway, phenotypical shift of C3 glomerulopathy into a HUS after kidney transplantation, and missed diagnosis of TMA in the native kidneys.[4] Recurrent TMA can be due to a HUS, TTP and autoimmune diseases like scleroderma and SLE with or without antiphospholipid syndrome.[4] Pathological features of TMA are well defined, but the clinical features are different vary from systemic life threatening condition to pathological lesion restricted to the dysfunctional allograft. The etiological diagnosis can also be challenging in the light of various and overlapping triggers. Therapeutic options are also variable and include CNI withdrawal (temporarily or definitively), Plasma exchange, complement blockers, and treatment of underlying triggering factors. Given the significant negative impact of TMA on the patient and graft survival. It's very important to have a clearer understanding of clinical feature and etiology of this condition in order to be able to provide better and more effective preventive and therapeutic strategies. The aim of this study was to describe the clinical and pathological features of TMA after kidney transplantation.

Patients and methods

This is a retrospective observational study. We initially retrieved all reports of renal transplant biopsies that were done between January 2017 and April 2022 in 3 centers Erbil, Suleymaniah and Duhok kidney transplant centers. The indication of performing those biopsies was graft dysfunction; new onset proteinuria or delayed graft dysfunction. The total number of the transplant biopsies in our specified time frame was 1635, out of which 82 biopsy reports were found to describe features of TMA. All our data were fully anonymized before access and the study did not involve any human intervention and hence informed consent was not required. All data were coded and summarized using Microsoft Excel and analyzed by using Statistical Package for Social Sciences (SPSS). Suitable statistical tests (Chi square test and Fishers exact test) for data were implemented accordingly P value of less or equal to 0.05 were considered significant.

Results

Out of 1635 biopsies done for patients after kidney transplant, 82 biopsies were detected with thrombotic microangiopathy after kidney transplantation (TMA) with prevalence of TMA in last 6 years (2017-2022) was (5.01%). Figure (1)

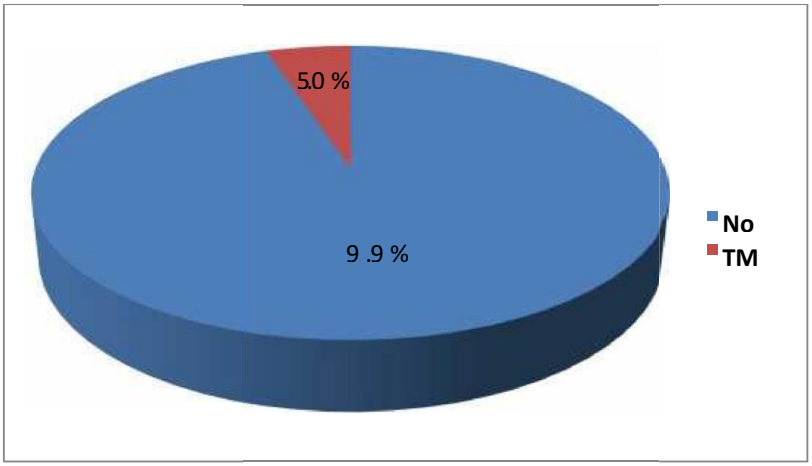

Figure (1): Prevalence of TMA in 6 years' duration (2017-2022)

The mean age of studied patients with TMA was (38.2 years) and range of 15-67 years; 20.7% of patients were at age group of less than 30 years, 31.8% of them were at age group 30-39 years, 28% of them were at age group 40-49 years and 19.5% of them were at age of 70 years and more. Male patients with TMA were more than females with male to female ratio as 2.3:1. Table (1)

Table (1): Demographic characteristics of patients with TMA

Variable	No.	%
Age mean±SD (38.2±12 years)		
<30 years	17	20.7
30-39 years	26	31.8
40-49 years	23	28.0
≥50 years	16	19.5
Gender		
Male	57	69.5
Female	25	30.5
Total	82	100.0

Mean time of doing biopsy of patients with TMA was (12.5 months); 25.6% of patients were done biopsy in less than one month duration, 53.7% of them were done biopsy in duration of 1-12 months and 20.7% of them were done biopsy in duration of more than 12 months. Mean serum creatinine of patients with TMA was (3.2 mg/dl); 6.1% of patients had serum creatinine level of 1.3 mg/dl and less, 79.3% of them had serum creatinine level of 1.4-5 mg/dl and 14.6% of them had serum creatinine level of more than 5 mg/dl. Induction method for patients with TMA was commonly ATG (96.3%) and rarely Basiliximab (3.7%). Table (2)

Table (2): Clinical characteristics of patients with TMA

Variable	No.	%
Time of biopsy (months post transplantation) mean±SD (12.5±26 months)		
<1 month	21	25.6
1-12 months	44	53.7
>12 months	17	20.7
Serum creatinine mean±SD (3.2±2.1 mg/dl)		
≤1.3 mg/dl	5	6.1
1.4-5 mg/dl	65	79.3
>5 mg/dl	12	14.6
Induction method		
ATG	79	96.3
Basiliximab	3	3.7
Total	82	100.0

The common type of TMA was both arteriolar and glomerular (47.6%), followed by; glomerular (30.4%) and arteriolar (22%). CNI toxicity was observed in 67.1% of patients with TMA and the rejection was detected in 35.4% of them. The recurrence of original TMA was obvious in 15.9% of patients and positive IFTA was observed in 26.8% of patients with TMA. Other pathological features were present in 40.2% of patients with TMA, Table (3) and Figures (2, 3), which include Antibody mediated rejection, Viral infections like CMV; BK, Genetic abnormalities in complement pathway, phenotypical shift of C3 glomerulopathy into a HUS after kidney transplantation, and missed diagnosis of TMA in the native kidneys [4]

Table (3): Biopsy features of patients with TMA

Variable	No.	%
TMA types Arteriolar	18	22.0
Glomerular	25	30.4
Both arteriolar and glomerular	39	47.6
CNI toxicity Yes	55	67.1
No	27	32.9
Rejection Yes	29	35.4
No	53	64.6
Recurrence of original disease TMA Yes	13	15.9
No	69	84.1
IFTA Yes	22	26.8
No	60	73.2
Other pathological features Yes	33	40.2
No	49	59.8
Total	82	100.0

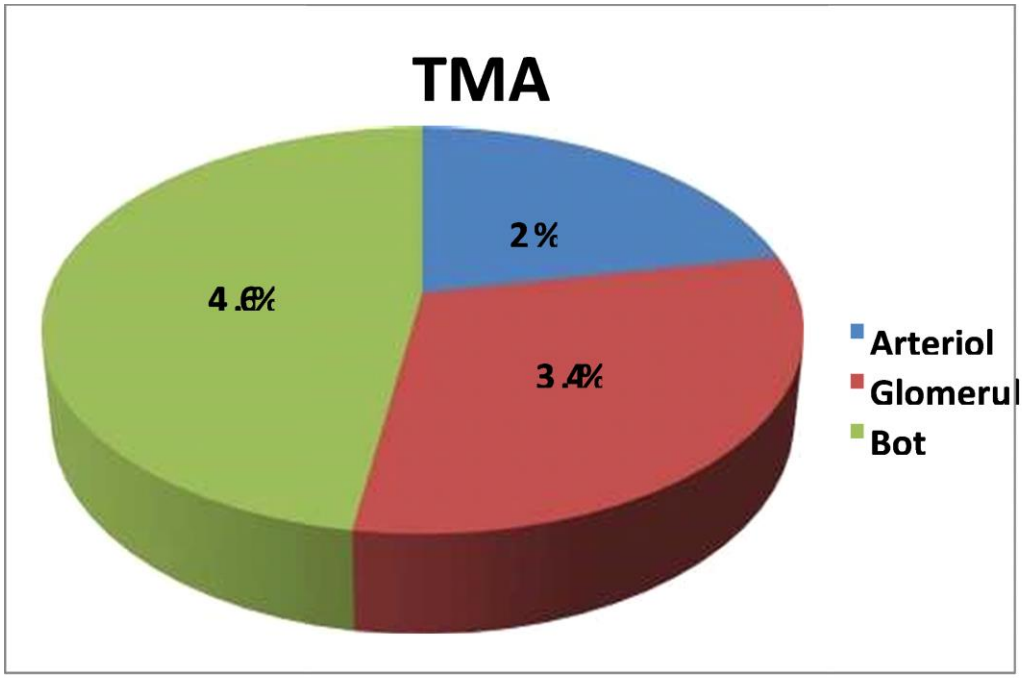

Figure (2): Types of patients with TMA

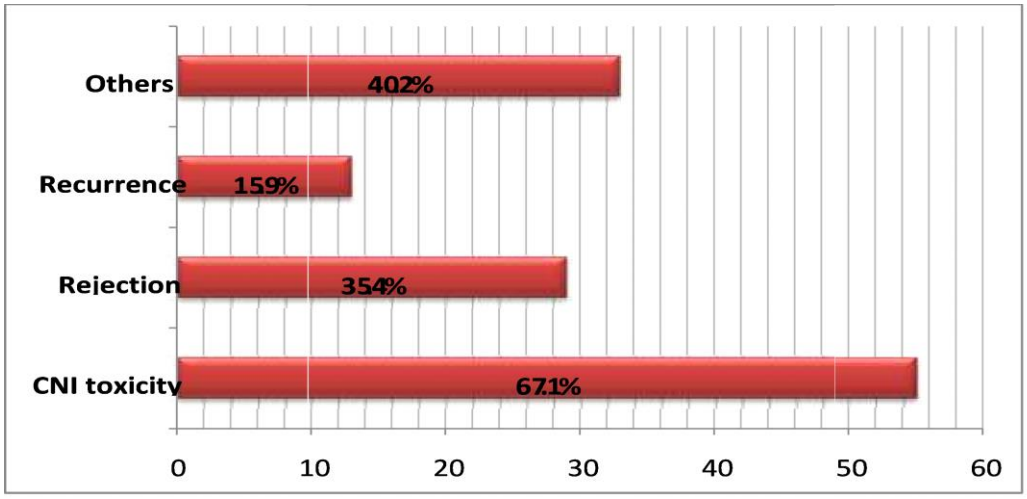

Figure (3): Etiological factors for TMA

No significant differences were observed between patients with positive recurrence and patients with negative recurrence regarding age (p=0.59) and gender (p=0.49).

Table (4): Distribution of patients' demographic characteristics according to recurrence of TMA

Variable	Recurrence of original disease TMA Yes		No		p value
	No.	%	No.	%	
Age					0.59
<30 years	4	30.8	13	18.8	
30-39 years	4	30.8	22	31.9	
40-49 years	4	30.8	19	27.5	
≥50 years	1	7.7	15	21.7	
Gender					0.49
Male	8	61.5	49	71.0	
Female	5	38.5	20	29.0	

Table (5): Distribution of patients' clinical characteristics according to TMA recurrence

Variable	Recurrence of original disease TMA Yes		No		p value
	No.		No.	%	
Time of biopsy (months post transplantation)					0.5
<1 month	2	15.4	19	27.5	
1-12 months	7	53.8	37	53.6	
>12 months	4	30.8	13	18.8	
Serum creatinine					0.002
≤1.3	0	-	5	7.2	
1.4-5	7	53.8	58	84.1	
>5	6	46.2	6	8.7	
Induction method					0.44
ATG	13	100.0	66	95.7	
Basiliximab	0	-	3	4.3	

S=Significant, NS=Not significant.

A significant association was observed between both arteriolar and glomerular TMA type and patients with positive recurrent TMA (p=0.001). No significant differences were observed between patients with positive recurrence and patients with negative recurrence regarding CNI toxicity (p=0.64), rejection (p=0.79), IFTA (p=0.73) and other pathological features (p=0.63).

Table (6): Distribution of patients' biopsy features according to TMA recurrence.

Variable	Recurrence of original disease TMA					
		Yes			No	p value
	No.		%	No.	%	
TMA types						0.001[S]
Arteriolar	1		7.7	17	24.7	
Glomerular	0		-	25	36.2	
Both arteriolar and glomerular	12		92.3	27	39.1	
CNI toxicity						0.64
Yes	8		61.5	47	68.1	
No	5		38.5	22	31.9	
Rejection						0.79
Yes	5		38.5	24	34.8	
No	8		61.5	45	65.2	
IFTA						0.73
Yes	3		23.1	19	27.5	
No	10		76.9	50	72.5	
Other pathological features						0.63
Yes	6		46.2	27	39.1	
No	7		53.8	42	60.9	

S=Significant, NS=Not significant

Discussion

Our study shows that the prevalence of TMA in graft biopsy throughout 6 years was 5.01%. This low incidence is similar to other studies like Reynolds et al[6] and Txiera et al.[7] Regarding demographic features of our patients they were mainly young with mean age. 38.2 years, which was similar to the results of studies by Reynolds et al,[6] Zariffan et al, [8] Karthikeyan V et al[9] and Teixeira et. Al.[7] In our study TMA incidence was higher 'among Males with male female ratio 2.3: 1 which is similar to the results of Ganesh et al[2] but different from the results if previous studies like Reynolds et al,[6] Zariffan et al,[8] Karthikeya V et al[9] and Teixeira et. Al.[7] The time of incidence of TMA was greatly variable similar to the results of Reynolds et al,[6] and Teixeira et al.[7] In our study the incidence rejection associated TMA was 35.4% which lower than other studies like Satoskar et al[10] 55% and Wu et al[11] 52% but it 'was higher than the results of Teixeira et al[7] 13%. The incidence of recurrent TMA in our study was 15.9% which was higher than that of Ganesh et al[2] 8.3%. The incidence of CNI associated TMA in our study was 67.1% which was higher than seen in other studies like Ganesh et al[2] 16.6%, Teixeira et al[7] 13%, but was nearly similar to results of the study by Nava et al[13] 47.2%. Recent advances in understanding etiology of TMA have doubted the significant connection of CNI to the incidence of TMA after kidney transplantation especially after understanding the role of complement dysregulation in TMA occurrence. It has been predisposed that there must be some additional trigger or predisposing factor for TMA in those patients who develop TMA while taking

CNI given the fact that it does not happen in ALL patients taking those drugs.[14] Regarding the location of the thrombi, the results of our study was different from Teixeira et al.[7] The highest proportion of our patients had both arteriolar and glomerular thrombi 47.6%, 30.4% had only glomerular thrombi, 22% had arteriolar thrombi. Whereas in the study by Teixeira et al[7] the highest proportion had glomerular thrombi 50% followed by 29% arteriolar thrombi, and the lowest proportion had both arteriolar and glomerular thrombi 21%. IFTA was found in 26.8% of biopsies which is lower that found in the study by Teixeira et al [2] 97%. The risk of recurrence is genetically determined. [1, 16-18] Regarding recurrent TMA the only significant association was with serum creatinine and TMA types. Whereas in the study conducted by Reynolds et al, [6] no factor was significantly associated with TMA apart from young age of recipient. Limitations of our study are in being retrospective studies, [20, 21] lack of detailed diagnostic workup including complement genetic analysis and no information about ADAMTS13 like other previous studies. [22, 23] We had no information about the living donors after donation of their kidneys[24] nor had we information about recipient nephrectomy which may lower recurrence risk.[25]And like other retrospective studies we had no information about whether the TMA was systemic or localized [6, 26] which has implication in determining the short term survival, but long term survival is similar in both forms[27, 28] Another limitation regarding the recurrent TMA cases, performing genetic testing at time of diagnosis of TMA would be fundamental for assessing the possible outcome.[29] Genetic testing also has therapeutic benefit because unlike de novo TMA which has limited treatment options, recurrent TMA has an effective therapy by blockade of c5-9 through Eculizumab.[30] Still this study is considered the first study in Kurdistan region to shed the light on the topic of TMA after kidney transplantation and describe clinical and pathological features of biopsy proven TMA

Conclusions

Thrombotic microangiopathy is a rare but serious complication after kidney transplantation. The main contributors were CNI toxicity and rejection. But the etiology is multifactorial in most cases. The incidence cannot be attributed to a single factor. Larger prospective studies are required to clarify etiological factors, therapeutic options and patient and graft outcome.

Conflicts of interest

The author reports no conflicts of interest.

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