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CLINICAL PROFILE AND OUTCOME OF THROMBOTIC MICROANGIOPATHY WITH RENAL FAILURE – A CASE SERIES

Nephrology

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ABSTRACT

Introduction - Endothelial cell damage and/or malfunction can cause thrombotic microangiopathy (TMA), a pathological lesion seen in a wide range of diseases. Although microangiopathic haemolytic anaemia, thrombocytopenia, and ischemic end-organ injury are frequently observed in conjunction with TMA lesions, renal-limited forms of TMA are frequently observed in clinical practice. Severe condition known as an atypical haemolytic uremic syndrome (aHUS) is caused by an overactive alternative complement system and frequently has a hereditary component. **Methodology-** This was a cross-sectional observational study carried out for 24 months at a tertiary care centre. All the data collected were tabulated and analysed. **Results-** 18 patients with thrombotic microangiopathy with renal failure were selected and their demographical, clinical, laboratory findings, radiological and disease manifestations (outcomes) were tabulated and analysed. The cause of TMA in patients due to CHF mutation was 5 (27.7%) and pregnancy-related was 3 (16.6%). The Mean creatinine at presentation was 4.7 mg/dL. The mean Blood urea nitrogen (BUN) at presentation was 49.28 mg/dl. **Conclusion-** Major causes of TMA in the current observational case series were CHF mutation-related, pregnancy-related and HIV related. The most common kidney biopsy features were GBM thickening, endotheliosis, fibrin thrombosis and arterial thrombosis.

KEYWORDS

Thrombotic microangiopathy (TMA), Renal failure, (Case series, Infection, Transplantation), Acute Kidney injury, renal limited TMA

INTRODUCTION

The most typical clinical features of thrombotic microangiopathy (TMA) include thrombocytopenia, ischemic organ damage, and microangiopathic haemolytic anaemia (MAHA). [1] The kidney is the organ that is most commonly damaged, although other internal systems such as the central nervous system, cardiovascular and respiratory systems, and gastrointestinal tract may also experience harm. [2] Taxonomy and nomenclature used to define TMA continue to evolve with research unveiling the molecular mechanisms causing the distinctive endothelial damage and development of microvascular thrombi.[3] Systemic signs of TMA, like MAHA and thrombocytopenia, are not always necessary for diagnosis. Pregnancy-associated TMA can be associated with HUS (predominantly renal involvement) or TTP (predominantly hematological and neurological involvement) in the context of solid organ transplantation or glomerulonephritis. Endothelial damage is essential in TMA formation, but specific vascular beds may be affected due to underlying genetic factors. [2] Thus, we present a case series evaluating the clinical course, treatment response, and patient and graft outcomes in patients affected by thrombotic microangiopathy (TMA).

METHODOLOGY

A crossectional observational case study carried out between 1-01-21 to 1-01-23 [24 months] at *Topiwala National Medical College* [TNMC] and *BYL Nair Charitable Hospital, Mumbai 400008*.

SCREENING OF DATA

Data collection was done by screening all the patients with renal dysfunction enrolled in TNMC. Patient's hospitalization history, treatment, and follow-up data were recorded from the Medical Records section [MRO] and tabulated for analysis. Diagnosis of TMA was confirmed with *Macroangiopathic haemolytic anaemia* (*MAHA*) and/or histopathology. Patients were divided into three groups based on age group, Group 1 [18-40 Years], Group 2 [41-65 years] and Group 3 [>66 years].

RESULTS

A total of 1734 patients were screened from the available internal documents. Out of these, 18 patients met the criteria and were included in this observational study. The baseline features of patients are shown in Table 1.

Table 1: Baseline Characteristics Of Patients

Variable	Result
Age (Mean±SD)	34.9±6.5
Gender (Male: Female)	10:8
Creatinine (Mean±SD) at presentation (mg/dl)	4.7±1.9 mg/dL
Mean blood urea nitrogen (BUN) at presentation (mg/dl)	49.28 mg/dl
Fever at presentation	Present – 9 (50%)
Puffiness of face/pedal edema	Present – 15 (83.3%)
Oliguria/anuria	Present – 14 (77.7%)
Nausea/vomiting	Present – 13 (72.7%)
Headache	Present – 9 (50%)

Common clinical presentations: vomiting (72%), headache (50%), fever (50%), and rash (7%). Pallor was frequent, while cyanosis and clubbing were rare. Most triggering events in females were pregnancy-related (33.3%). All patients had unstable kidney function (creatinine <1 mg/dL).

Table 2: Details Of Kidney Biopsy Features, Radiological Investigation, And Cause Of TMA.

Patient no	Kidney biopsy features	Radiological investigation	TMA - Cause
1	Acute cortical necrosis post-transplant, C4D-neg, CD4-neg	CT-B/L Small kidneys, REVERSE RIM SIGN-S/O ACN (prior to transplant)	Pregnancy-related
2	GBM Thickening, Endotheliosis, Fibrin Thrombosis	Normal sized kidney	Pregnancy-related
3	GBM Thickening, Endotheliosis, Fibrin Thrombosis, Arteriolar Thrombosis, ATN	Normal sized kidney	Pregnancy-related
4	GBM Thickening, Endotheliosis, Fibrin Thrombosis, Arteriolar Thrombosis, ATN	Normal sized kidney	CFH Mutation
5	GBM Thickening, Endotheliosis, Fibrin Thrombosis, Arteriolar Thrombosis, ATN	Normal sized kidney	MCP Mutation
6	GBM Thickening, Endotheliosis, Fibrin Thrombosis, Arteriolar Thrombosis, ATN	Normal sized kidney	CFH Mutation
7	GBM Thickening, Endotheliosis, Fibrin Thrombosis, Arteriolar Thrombosis, ATN, Chronicity	Normal sized kidney	Anti-factor H Antibody
8	GBM Thickening, Endotheliosis, Fibrin Thrombosis, Arterial Thrombosis, Chronicity, ATN	Normal sized kidney	Anti-factor H Antibody
9	Patchy Acute Cortical Necrosis	Borderline	Pregnancy-related
10	GBM Thickening, Endotheliosis, Fibrin Thrombosis, IFTA-50-55%, Chronicity	Normal sized kidney	CFH Mutation
11	Diffuse Acute cortical necrosis with ATN	Normal sized kidney	Pregnancy-related
12	Ischaemic Wrinkling Of GBM, Endotheliosis, Hyperplastic Arteriopathy	Normal sized kidney	CFHR Mutation
13	GBM Thickening, Endotheliosis, Hyaline Thrombosis In Capillary Tuft	Normal sized kidney	Pregnancy-related
14	Ischaemic Wrinkling of Capillary Endotheliosis, With Subendothelial Widening.	Normal sized kidney	Pregnancy-related
15	Cortical Scaring Involving 26-30 % Renal Tissue, Diffuse ATN In Non-Scared Cortex	Normal sized kidney	HIV related
16	Not Done (Unwilling)	B/L Bulky kidneys	CFH Mutation
17	Ischaemic Wrinkling of Capillary Endotheliosis, With Subendothelial Widening.	B/L Bulky kidneys	Anti-factor H antibody
18	Basement Membrane Thickening, Glomerular Sclerosis &Hyaline Change In Arteriole	B/L Bulky kidneys	Not Known

Abbreviations: GBM, Glomerular basement membrane; CFHR, complement factor H–related; MCP, *membrane cofactor protein; ATN, Acute tubular necrosis; HIV, human immunodeficiency virus; IFTA, Interstitial fibrosis and tubular atrophy.*

Kidney biopsy in seventeen patients revealed glomerular basement membrane thickening, endotheliosis, fibrin thrombosis, and arteriolar thrombosis. Leading TMA causes were pregnancy-related (38.9%), anti-factor H antibody-related (16.6%), and CHF mutation-related (16.6%). (Table-2)

Table 3: Details Of Immunosuppression Drug Used, Plasmapheresis, Complications Of HD/Plex, Recovery (Outcome).

P-No	Immunosuppression drug used	Plasmapheresis (Frequency)	Duration of HD	Current serum creatinine level (mg/dl)	Recovery (outcome)
1	Tab Prednisolone, Tab Tacrolimus, Tab Mycofenolate mofitil	Yes (10)	6 months	Patient died	Not Recovered
2	No	Yes (7)	8 sessions	0.9	Completely recovered
3	Tab Prednisolone, Tab Mycofenolate mofitil	Yes (10)	No	0.8	Completely recovered
4	Tab Prednisolone	Yes (7)	2 Years (still on HD)	4.5	Not Recovered
5	No	Yes (7)	1 Year	Patient died	Not Recovered
6	Tab Prednisolone, Tab Mycofenolate mofitil	Yes (7)	6 Moths	Patient died	Not Recovered
7	Tab Prednisolone, Tab Mycofenolate mofitil	Yes (7)	3 months	1.9	Partially recovered
8	No	Yes (7)	Still on HDs	5.2	Not Recovered
9	No	Yes (7)	Still on HD	4.2	Not Recovered
10	Tab Prednisolone, Tab Mycofenolate mofitil	No	No	2.1	Partially recovered
11	Tab Prednisolone	Yes (17)	1 month/15 HD sessions	0.9	Completely recovered
12	No	No	Still on HD	5.9	Not Recovered
13	No	Yes (7)	No	0.9	Completely recovered
14	No	Yes (7)	NO	0.8	Completely recovered
15	-	No	8 months	5.1	-
16	No	Yes (5)	Since 2 months	3.9	Not Recovered
17	No	No	4 months	5.8	Not Recovered
18	-	No	-	1.5	Not Recovered

Abbreviation - P No – Patient number.

Prednisolone and Mycophenolate mofetil (MMF) were commonly used for immunosuppression. Plasmapheresis (PLEX) was given to 72.2% of patients. Around 40% achieved full recovery (serum creatinine < 1 mg/dl), while three patients succumbed to TMA complications. Over 45% did not fully recover. (Table-3)

DISCUSSION

TMA demands urgent examination and treatment. Many TMA-related

disorders involve complement dysregulation, and research explores complement-coagulation pathway interactions. [5]

Plasmapheresis is a simple extracorporeal procedure to remove specific components from plasma. It can be performed as an emergency or planned procedure. Early in the management process, it can effectively reduce serum triglycerides. [6] CM-TMA (complement-mediated or atypical HUS) is caused by complement dysregulation, involving classical and lectin pathways. [7,8]

Pregnancy and the peripartum period exhibit three TMA etiologies: CM-TMA, HELLP syndrome, and TTP, with pregnancy-associated renal cortical necrosis potentially mimicking TMA. [9] Tight control of complement activation is necessary throughout pregnancy to ensure maternofoetal tolerance.[10] Women who are genetically predisposed to complement dysregulation may develop overt CM-TMA during pregnancy as a result of inflammation, infection, or haemorrhagic problems.[11,12] In the current study seven patients were diagnosed with TMA caused due pregnancy which is supported by the study conducted by Lattuada A et.al. [13]

TMA can develop as a result of a solid organ transplant or hematopoietic stem cell transplantation (HSCT). Some researchers suggest that HSCT-TMA is an endothelial version of graft-versus-host disease.[14] Specific TMA causes in solid organ transplant recipients (particularly kidney transplant recipients) include recurring or de novo CM-TMA in the allograft, antibody-mediated rejection, drug-induced TMA, and infections.[15] TMA in antibody-mediated rejection has been hypothesised to be mediated by classical pathway activation in the presence of donor-specific antibodies.[16] Direct contributions to endothelial damage and complement dysregulation are among the processes implicated in drug-induced TMA in transplant. [17,18]

CONCLUSION

Thrombotic microangiopathy (TMA) is a serious condition found in various life-threatening diseases. Endothelial injury is a central feature in TMA patients involving the kidney. In this study, Primary TMA (55.4%) (caused by autoantibodies to ADAMTS13 or complement factor H) and secondary TMA (38.9%) (pregnancy-associated or post-transplantation) were most common. Early investigation and prompt treatment, such as plasmapheresis and immunosuppression, are essential to reduce TMA-related morbidity and mortality.

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