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Case Study

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IGA NEPHROPATHY WITH THROMBOTIC MICROANGIOPATHY - CASE SERIES FROM A TERTIARY CARE CENTRE IN SOUTH INDIA

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ABSTRACT

While Immunoglobulin A(IgA) nephropathy(IgAN) with Thrombotic microangiopathy (TMA) is often documented in biopsy reports, its impact in disease progression requires more research. Here we studied a case series of 10 patients of biopsy proven IgAN with TMA to analyse the clinical ,laboratory with serological data and their outcome. Mean age was 32± 5 years and no gender specific differences. All presented with uncontrolled blood pressures, renal failure and were dependent on dialysis and had high mortality. There were no evidence of TMA in blood investigations. Hence this study concludes that IgAN with TMA is associated with worse renal prognosis.

INTRODUCTION

Immunoglobulin A(IgA) nephropathy(IgAN) is the most prevalent primary glomerular disease, and is particularly common in the Asia pacific region.[1] Though intrarenal vascular lesions occur in IgAN, their role in disease progression is unclear.

Historically, it was thought that IgAN was only associated with Thrombotic microangiopathy(TMA) in cases of severe hypertension or advanced chronic kidney disease. But recent studies have shown TMA as a common histological feature of IgAN and can occur even in normotensive patients or with near normal renal histology. TMA is associated with worse renal prognosis, even after adjusting for the hypertension severity, as seen in few studies.[2]

Hence a retrospective examination of cases was done, inorder to analyse clinical features and impact of TMA in progression of IgAN, as Indian studies are sparse.

AIM: To analyse the clinical features and outcome of patients diagnosed with IgA nephropathy with Thrombotic microangiopathy.

PATIENTS AND METHODS

This study was done at a public sector hospital in one of the southern states of India. All patients with biopsy proven IgAN with TMA, admitted in Nephrology department from May 2022 – May 2024 were included. Casesheets were collected from medical records and analysed. Demographic details, comorbidities, laboratory parameters, biopsy reports and outcome and followup status noted.

RESULTS

This study included 10 patients of biopsy proven IgAN with TMA, with equal gender distribution and predominantly belonged to 3rd and 4th decade (Mean age 32 ± 5 years). All were hypertensive and presented with accelerated blood pressures and pulmonary edema. Details of cases, with clinical presentation, laboratory parameters, biopsy findings, outcome status mentioned in Table 1, 2, 3 and 4 respectively.

None of them had any laboratory findings of TMA. IgAN with TMA was diagnosed by renal biopsy. All were dependent on dialysis and were found to have access failures, with high rates of readmissions and high earlymortality.

Table 1: Case series.

	A	B	C	D	E	F	G	H	I	J
Age (years)	48	32	30	35	25	32	37	30	36	40
Gender (M or F)	F	M	M	F	F	M	F	F	M	M
Comorbidities	HTN	HTN	HTN	HTN	HTN	HTN	HTN	RVD, HTN	DM, HTN	HTN,DM
Symptoms at presentation	Acc HTN, pulmonary edema	Acc HTN, bipedal edema	Acc HTN	Acc HTN, anasarca	Acc HTN, pulmonary edema	Acc HTN, anasarca	Acc HTN, pulmonary edema	Acc htn Pulmonary edema	Acc htn	Acc HTN, pulmonary edema
Urine output	Nonoliguric	Anuric	Nonoliguric	Nonoliguric	Oliguric	Nonoliguric	Anuric	Oliguric	Oliguric	Oliguric
Fundus(HR)	Grade 3	Grade 2	Grade 4	Grade 1	Grade 4	Grade 3	Grade 4	Grade 2	Grade 2	Grade 4
Lab parameters										
CUE Protein/Rbc in Hpf	-2+ /0-1 /Hpf	1+/-8-10 /Hpf	2+ /15-20 /Hpf	1+/0-1/Hpf	Trace/4-5 /Hpf	ALB 2+, Rbc - 0-1	2+ /2-3 /Hpf	2+/1-2/Hpf	1+/4-5 /Hpf	Trace/4-5 /Hpf
24 hr urine protein(g)	0.9	1.2	2.2	0.8	0.5	2	0.4	2	0.7	0.5
Hb(g/dl) /Plt (Lakhs/L)	6 /1.5	7/98k	10/2	9.8/1.9	6.5/1.8	8/1.7	7/1.4	7.5/1.5	6.9/1.3	6.8/1.6
Creatinine (mg/dl)	6.6	8.5	11	8.3	7	5.6	12	10	11	7
Hemogram	← No schistocytes →									
Complements C3,C4	← Normal →									
Ana,Anca Hep B& C	← Negative →									
LDH(U/L)	110	168	179	150	142	159	122	155	132	142
Echo	Con LVH, moderate LVD (38%)	Con LVH	Con LVH	Con LVH	Con LVH grade 3 diastolic dysfunction	Con LVH	Con LVH, moderate LVD (35%)	Con LVH	Con LVH, moderate LVD (36%)	Con LVH grade 3 diastolic dysfunction

(M-male, F- female, HTN- hypertension, DM- diabetes mellitus, RVD- Retroviral disease, Acc- Accelerated, HR- Hypertensive retinopathy, Hpf-high power field, Hb-Hemoglobulin, Plt- Platelet, Hep- Hepatitis, LDH- lactate dehydrogenase, Con LVH- concentric left ventricular hypertrophy, LVD – LV dysfunction)

Table 2: Renal Biopsy Findings:- CHRONIC IGA NEPHROPATHY WITH THROMBOTIC MICROANGIOPATHY(Figure A-D).

Light microscopy	A	B	C	D	E	F	G	H	I	J
Glomerular Sclerosis		Global (5/7)	Global (13/18)		Global (8/11)	Focal (4/10)	Global(4/14)	Focal global (8/15)	Global (11/12)	
Mesangial/ Endocapillary Cellularity	Focal global (5/14)	Present, mild	Present, mild	Global (12/12)	Present, mild	Present Mild	Present	Present	Present Mild	Global (12/12)
Crescents		1 fibrocellular	2 cellular 2 fibrocellular		3 fibrous, 2 fibrocellular	3 fibrous, 1 fibrocellular	1 fibrocellular	2 cellular, 3 fibrocellular, 2 fibrous		
Interstitial Fibrosis & Tubular Atrophy	20%	30%	40%	70%	55%	60%	40%	45%	50%	70%
Vessels Arterioles-	Fibrinoid deposits+ Intimal myxoid change Partial lumen occlusion+	Intimal myxoid change Partial lumen occlusion+	Fibrinoid deposits+ myointimal hyperplasia Intimal myxoid change	Fibrinoid deposits+ lumen occlusion+	Mild intimal fibrosis Myointimal hyperplasia Fibrin thrombus+	Myointimal hyperplasia, fragmented Rbc's Partial luminal occusion	Fibrinoid deposits Intimal myxoid changes, myointimal hyperplasia, partial luminal occlusion	Fibrin fragmented Rbcs Luminal occlusion	Mild intimal fibrosis Myointimal hyperplasia Fibrin thrombus+	Fibrinoid deposits+ lumen occlusion+
Arteries	Not involved	Mild intimal fibrosis	Intimal fibrosis	Intimal hyperplasia, narrowed lumen		Hyalinosis		Onion skinning		Intimal hyperplasia, narrowed lumen
Immunofluorescence	Mesangial deposits-coarse granular IgA and C3c	Mesangial deposits-coarse granular IgA	Mesangial deposits-coarse granular IgA and C3c	Mesangial deposits-coarse granular IgA and C3c	Mesangial deposits-coarse granular IgA	Mesangial deposits-coarse granular IgA and C3c	Mesangial deposits-coarse granular IgA	Mesangial deposits-coarse granular IgA and C3c	Mesangial deposits-coarse granular IgA and C3c	Mesangial deposits-coarse granular IgA and C3c

Table 3: Evaluation of TMA.

	A	B	C	D	E	F	G	H	I	J
Thrombophilia profile Antiphospholipid Antibody Anti Scl-70 (scleroderma)	← Negative →									
Genetic testing for complement mutation	Positive **C3 1855 G>T EXON 15 pVal 615Leu** Autosomal dominant, Heterozygous, uncertain significance	← Not done →								

Table 4: Outcome and Follow up.

	A	B	C	D	E	F	G	H	I	J
Dialysis dependent	← Yes →									
Dialysis vintage	3 months	6 months	2months	25days	30 days	3 months	1.5 months	1 month	2 months	3months
Readmission	2 Pulmonary edema	1 Acc HTN	1 Acc HTN, Seizures, Encephalopathy		1 Pulmonary edema		2 Seizures, encephalopathy	1 Acc htn	1 Pulmonary edema	1 Acc HTN
Access	Multiple access failure. AVF – primary failure	AVF – functioned good	Central Luminal thrombus+	B/l central luminal thrombus+		AVF primary failure. Right Tunnelled catheter-functioned	Multiple access failures Placed on CAPD	(noncompliant)	Primary AVF failure B/L jugular thrombus	Right tunnelled catheter+ AVF primary failure
Transplant	-	-	-	Underwent LRRT (Mother donor) Stable graft function for 1 year Acute rejection- at 15th month (C4d negative) Persistent renal dysfunction Chronic allograft nephropathy- 18th month	-	-	-	-	-	-
Mortality	4th month	6th month	3rd month	18th month	1st month	3rd month	2nd month	1st month	3rd month	3rd month

(Acc- Accelerated, HTN- hypertension)

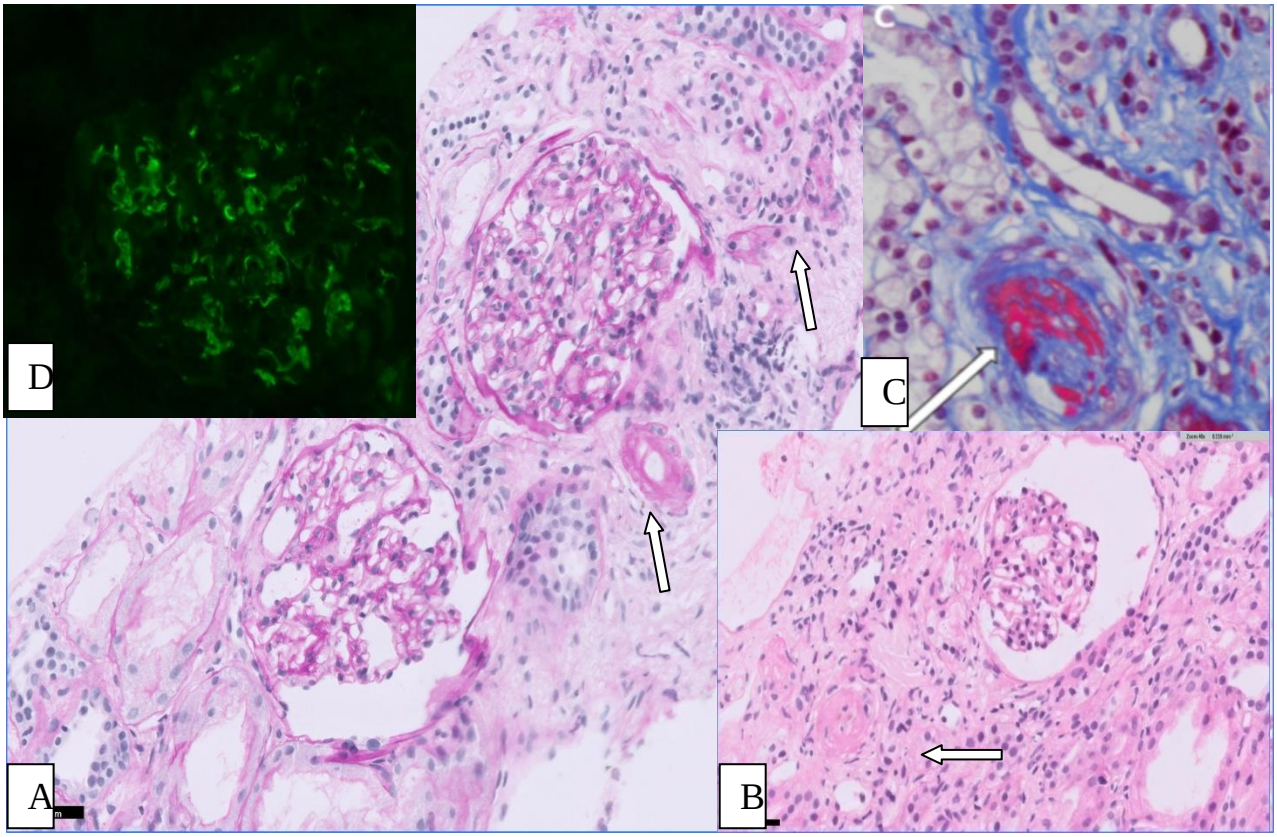

Figure A: (PAS) and B(H&E): obsolescent glomerulus+, ischemic changes+, no increase in cellularity, segmental sclerosis or crescent. Tubules dilated, with mild tubular injury, interstitial infiltration+. Small vessel changes included Fibrin deposits, initial myxoid changes with partial luminal occlusion. Figure C(MT): Fibrin deposits+ Figure D: IF- coarse granular mesangial IgA deposits.

DISCUSSION

Vascular lesions on kidney biopsy including arterial wall thickening, arteriolar hyaline changes and microangiopathic lesions are common in IgAN. However the role of these lesions in disease progression remains controversial and pathological scoring systems for IgAN such as those by Haas[8] and Oxford[12] classification do not consider such lesions.

In this retrospective study of 10 IgAN cases, microangiopathic lesions constituted 10% of total IgAN over the study period. They were significant risk factors for the development of kidney progression events. All TMA lesions were strongly associated with glomerulosclerosis and T2(Tubular atrophy/Interstitial fibrosis) lesions, indicating chronicity.

All were hypertensive, among which 7 were already on ACE inhibitors or ARBs. Majority were admitted in critical care with Hypertensive emergencies, and were anuric to oliguric. None had gross hematuria. Hypertensive retinopathy and LVH was observed in all and four had Grade 4 retinopathy changes. Few had subnephrotic proteinuria and 3 had active urine sediments. There were no laboratory evidence of TMA and serum complements were normal and immunological workup were negative. Only one, underwent genetic testing for complement and was found to have heterozygous C3 mutation.

All were dependent on dialysis, however had short vintage with frequent readmissions with uncontrolled pressures, pulmonary edema and seizures. Multiaccess failure owing to thrombosis were another major hurdle, with primary fistula failures and central vein occlusion. Mean survival was only 3month±20days. Only 1 patient underwent live transplant, however had graft dysfunction and subsequently failed and expired after 18 months.

Until now, few studies have evaluated TMA in IgAN. Study by El Karoui et al[2] on French cohort of 128 IgAN individuals, found that 53% had TMA lesions, either acute or organised, in arteries and/or arterioles and had larger percentage of sclerotic glomeruli, worse tubulointerstitial fibrosis and worse outcome. Only 11 % had laboratory evidence of TMA, however genetic testing was negative. Likewise, study by Neves et al[3] on 21 IgAN cases, observed laboratory evidence of TMA in 50 % and 9.5% had glomerular thrombi and 14% had endothelial denudation, suggestive of acute TMA. Recently Puapatanakul et al[4] retrospectively studied renal biopsies of 267 IgAN patients and detected TMA in 13%.This morphological lesion was accompanied by history of malignant hypertension, lower estimated glomerular filtration rate, higher proteinuria and higher mean arterial pressures at diagnosis and had a high risk

of ESKD progression and all cause mortality.

Activation of the complement system appears pivotal in IgAN, with past researches indicating that histological signs of TMA arise from alternative complement activation, however serum complements remain normal. There are small case reports which showed genetic studies detecting mutation in complement gene.[5] However Indian studies on IgAN with TMA are sparse.

Table 5: On comparison with available literature.

	Our study 2024	Neves et al (Brazil)(2020	Karoui et al (France)(2012)	Puapatanakul et al(Thailand) (2023)
N o of patients	10	21	128 IgAN 68 - TMA	267 patients - IgAN 21 –TMA
Duration of Study	2 years	8 years	6 years	20 years
Mean Age±SD	32 ± 5 years	32± 6 years	38 ± 7years	35 ± 5years
Comorbidities	HTN	HTN	HTN-48	HTN -21
Presentation-(common)	Accelerated HTN, Pulmonary edema	Accelerated HTN, Hematuria	Accelerated HTN	Accelerated HTN
RRT requirement	All cases	15	30	19
Lab evidence of TMA	No	Yes High LDH-13 Schistocytes- 4 Low platelet- 3 Low C3-6	8	-
Genetic testing	1	No	Negative	
Outcome status	9– expired 1-Lrrt, but had Chronic graft dysfunction and expired in 18th month	15- RRT (followup -7 months)	34-RRT	Followed up -50 months All TMA cases – ESKD risk(HR-5.8, 95% CI-3.1-10.9) and Mortality-(HR-2.4, 95% CI-1.1-5.4)

As mentioned by Neves et al[3], having TMA on biopsy is an independent risk factor for progression to chronic renal failure requiring dialysis, beyond other histologic predictors in the Oxford classification. Therefore effective treatment of hypertension is important, however TMA can occur even in normotensive patients. Immunosuppressive therapy with steroids and cyclophosphamide have been administered in crescentic IgAN with TMA, but recovery of renal function is often poor. Plasmapheresis has been tried in some cases, but efficacy unclear. Complement inhibitors for cases with positive complement mutations are tried in few cases.[5]

Hence renal microangiopathic lesions are frequent in IgAN and their presence is independently associated poor outcome. If confirmed in other larger population, such lesions could be considered for inclusion in formal classification schemes of IgAN and also to develop proper management strategies.

CONCLUSION

- Thrombotic microangiopathy(TMA) lesions are severe in IgAN, and constitute 10% of total IgAN cases.
- High suspicion of TMA is needed when young population present with accelerated HTN and retinopathy, despite absence of clinical and biochemical features.
- Biopsy is the definitive modality for diagnosis.
- Need for Renal Replacement Therapy is 100%.

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