CLINICAL CHARACTERISTICS, HISTOPATHOLOGICAL SPECTRUM, AND RENAL OUTCOMES OF BIOPSY-PROVEN THROMBOTIC MICROANGIOPATHY: A RETROSPECTIVE COHORT FROM NORTHEAST INDIA

Sharma Manjuri[1], Islam Moinul[2], Doley Prodip Kumar[3], Pegu Gayatri[4], Pegu Miranda[5]

Professor ,[1,3], Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam.
Associate Professor[4,5], Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam.
Consultant Nephrologist [2], Guwahati, Assam.

ABSTRACT

Introduction: Thrombotic microangiopathy (TMA) encompasses a heterogeneous group of disorders characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ injury, particularly affecting the kidneys. TMA is often initially detected on renal biopsy performed for evaluation of renal dysfunction. Aims of the study: To evaluate the clinical profile, etiological factors, and outcomes of patients with biopsy-proven TMA. Methods: This retrospective observational study was conducted in the Department of Nephrology at a tertiary care center. Records of patients presenting with rapidly progressive renal failure (RPRF) with evidence of TMA in native kidney biopsy from January 1, 2022, to December 30, 2023, were reviewed and analyzed. A total of 17 patients met the inclusion criteria. Results: The incidence of TMA was 14.7% among patients with RPRF. The median age was 32.5 years, and median serum creatinine was 8.7 mg/dl at presentation. Hypertension (52.9%) followed by headache (47.1%) were the most common presenting symptoms. Complement serology was predominantly normal. The most common etiology of TMA was malignant hypertension (41.2%), followed by IgA nephropathy (29.4%) and lupus nephritis (17.6%). Two patients with lupus nephritis-associated TMA received therapeutic plasma exchange (TPE) for 5 days, both showing significant improvement in renal function. Eleven patients (64.7%) required renal replacement therapy. At the 6-month follow-up, one patient had died due to acute left ventricular failure from accelerated hypertension, 8 patients remained dialysis-dependent, and 8 patients had achieved stable renal function. Conclusion : This study demonstrates that malignant hypertension, IgA nephropathy, and lupus nephritis are common etiologies for TMA. Hypertension and headache were the predominant presenting symptoms. Plasmapheresis appeared beneficial in patients with lupus nephritis-associated TMA, highlighting the importance of identifying underlying etiologies for appropriate management.

Keywords: Biopsy, Early Diagnosis, Anemia, Plasmapheresis, Thrombotic Microangiopathy.

INTRODUCTION

Thrombotic microangiopathy (TMA) represents a pathological process characterized by microvascular occlusion, thrombocytopenia, and microangiopathic hemolytic anemia (MAHA), leading to end-organ damage, particularly affecting the kidneys [1]. The hallmark histopathological feature is endothelial cell injury and platelet-rich thrombi in the microvasculature, resulting in mechanical hemolysis and multi-organ dysfunction [2]. The spectrum of TMA encompasses multiple clinical entities, including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), complement-mediated TMA, drug-induced TMA, pregnancy-associated TMA, malignancy-associated TMA, and secondary TMA associated with various systemic diseases such as malignant hypertension, systemic lupus erythematosus, and other autoimmune disorders [3]. The renal manifestations often dominate the clinical picture, resulting in acute kidney injury or rapidly progressive renal failure, necessitating renal biopsy for definitive diagnosis [4]. Despite advances in understanding the pathophysiology of TMA, its diverse etiologies and variable clinical presentations continue to pose significant diagnostic and therapeutic challenges for nephrologists. Early identification of the underlying cause is crucial for appropriate management and improving outcomes [5]. While plasma exchange therapy has revolutionized the management of certain TMA variants, particularly TTP, the optimal treatment approach for secondary forms of TMA remains less defined [6]. The present study aims to evaluate the clinical characteristics, etiological factors, and outcomes of patients with biopsy-proven TMA in a tertiary care center in Northeast India, where limited data exists regarding the spectrum of TMA.

METHODS

This was a retrospective observational study conducted in the Department of Nephrology at Gauhati Medical College and Hospital, a tertiary care center in Guwahati, Assam, India. The study included patients who presented with rapidly progressive renal failure (RPRF) and had evidence of TMA on native kidney biopsy between January 1, 2022, and December 30, 2023. A total of 17 patients met the inclusion criteria. Inclusion Criteria includes 1) Age ≥ 18 years, 2) RPRF defined as a decline in renal function resulting in doubling of serum creatinine or requiring dialysis over a short period (weeks to months),3) Histopathological evidence of TMA on renal biopsy Exclusion Criteria includes 1) Patients with incomplete medical records, 2) Patients with renal transplant biopsies, 3) Patients with inadequate biopsy specimens. Patient medical records were reviewed for demographic information, clinical presentation, laboratory parameters, histopathological findings, treatment received, and outcomes. Laboratory data included complete blood count, renal function tests, liver function tests, coagulation profile, peripheral blood smear, urinalysis, complement levels (C3, C4), autoimmune markers (ANA, anti-dsDNA, ANCA), and viral serology.

TMA was diagnosed based on the histopathological findings on renal biopsy, including: - Endothelial cell swelling and detachment from the basement membrane - Fibrin thrombi in arterioles and glomerular capillaries - Mesangiolysis and double contours of glomerular basement membrane - Arterial and arteriolar fibrinoid necrosis and/or mucoid intimal thickening Primary outcomes included:1)Renal recovery (defined as independence from dialysis and stable renal function), 2) Persistent dialysis dependence,3) Mortality at 6-month follow-up. Statistical analysis was performed using SPSS version 25.0. Continuous variables were expressed as median with interquartile range (IQR) or mean ± standard

deviation (SD) based on the distribution of data. Categorical variables were expressed as frequencies and percentages.

RESULTS

Demographic and Clinical Characteristics:

During the study period, a total of 116 patients underwent renal biopsy for RPRF, of which 17 (14.7%) had histopathological evidence of TMA. The median age of patients with TMA was 32.5 years (IQR: 24-45 years), with a slight female predominance (52.9%). The median serum creatinine at presentation was 8.7 mg/dl (IQR: 5.3-11.2 mg/dl). The most common presenting symptoms were hypertension (52.9%), headache (47.1%), oliguria (41.2%), edema (35.3%), and fever (23.5%). Neurological manifestations, including altered sensorium and seizures, were observed in 17.6% of patients (Table 1).

Table1: Demographic and Clinical Characteristics of Patients with TMA (n=17)

Characteristic	**Value**
Demographicdata	
Medianage,years(IQR)	32.5(24-45)
Female gender,n(%)	9 (52.9%)
Clinicalpresentatation	
Hypertension,n(%)	9 (52.9%)
Headache,n(%)	8 (47.1%)
Oliguria,n (%)	7 (41.2%)
Edema,n(%)	6 (35.3%)
Fever,n(%)	4 (23.5%)
Neurological manifestations,n(%)	3 (17.6%)
Gastrointestinal symptoms,n(%)	3 (17.6%)
Visual disturbances,n(%)	2 (11.8%)
Vital signs atpresentation	
Median systolic BP,mmHg (IQR)	178(154-210)
Median diastolic BP,mmHg(IQR)	110(92-124)
Median pulse rate,beats/min (IQR)	88(76-100)

IQR:Interquartile Range, BP:Blood Pressure

Laboratory Findings:

Laboratory findings revealed anemia in 15 patients (88.2%), with evidence of hemolysis (elevated LDH, reduced haptoglobin, and schistocytes on peripheral blood smear) in 11 patients (64.7%). Thrombocytopenia (platelet count 3.5 g/day) in 5 patients (29.4%). Complement serology revealed low C3 levels in 4 patients (23.5%) and low C4 levels in 3 patients (17.6%), all of whom had lupus nephritis. Antinuclear antibody (ANA) was positive in 3 patients (17.6%), and anti-dsDNA antibody was positive in 2 patients (11.7%) (Table 2).

Table2: Laboratory Findings at Presentation (n=17)

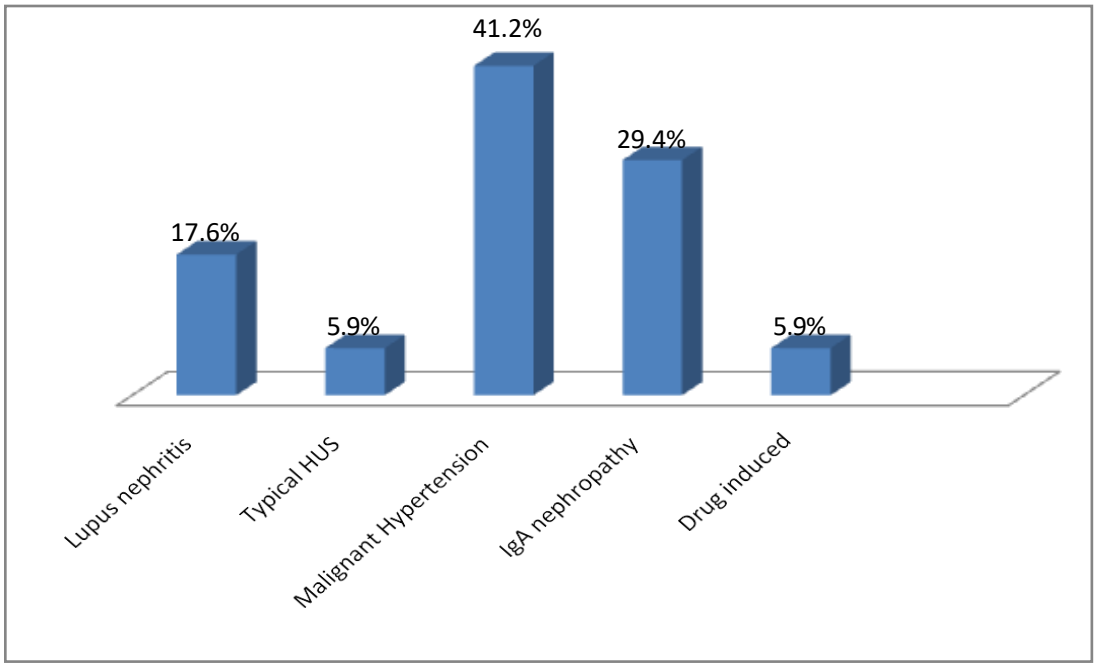
Parameter	Value
Hematological parameters	
Median hemoglobin,g/dL(IQR)	7.9(6.5-9.2)
Anemia (Hb<10 g/dl),n(%)	15 (88.2%)
Median platelet count,×10³/μL(IQR)	142(98-186)
Thrombocytopenia(<150,000/μL),n(%)	9 (52.9%)
Elevated LDH,n(%)	11 (64.7%)
Biochemicalparameters	
Median serum creatinine,mg/dL (IQR)	8.7(5.3-11.2)
Median blood urea nitrogen,mg/dL(IQR)	92(68-123)
Median lactate dehydrogenase,U/L(IQR)	642(452-897)
Median total bilirubin,mg/dL(IQR)	1.2(0.8-2.1)
Urinalysis	
Proteinuria,n(%)	17 (100%)
Median24-hour proteinuria, g/day(IQR)	2.8(1.4-4.6)
Nephrotic-range proteinuria, n(%)	5 (29.4%)
Hematuria,n(%)	14 (82.4%)
Immunologicalmarkers	
Low C3,n(%)	4 (23.5%)
Low C4,n(%)	3 (17.6%)
Positive ANA,n (%)	3 (17.6%)
Positive anti-dsDNA,n(%)	2 (11.7%)
Positive ANCA, n (%)	1 (5.9%)

IQR: Interquartile Range, Hb: Hemoglobin, ANA: Anti-nuclear Antibody, ANCA: Anti- neutrophil Cytoplasmic Antibody.

Etiological Factors:

The most common etiology of TMA was malignant hypertension (41.2%), followed by IgA nephropathy (29.4%) and lupus nephritis (17.6%). Other causes included ANCA-associated vasculitis (5.9%), drug-induced TMA (5.9%). (Figure 1).

Figure1:Etiological Distribution of TMA Cases (n=17)



Histopathological Findings:

All patients had histopathological features of TMA on renal biopsy. The most common findings were endothelial cell swelling (100%), fibrin thrombi in arterioles and glomerular capillaries (94.1%), mesangiolysis (88.2%), and arterial/arteriolar fibrinoid necrosis (76.5%). Double contours of the glomerular basement membrane were observed in 64.7% of cases (Table 3).

Table3:Histopathological Findings on Renal Biopsy (n=17)

Histopathological Feature	**Number of Patients (%)**
Endothelial cell swelling	17 (100%)
Fibrin thrombi in arterioles/capillaries	16 (94.1%)
Mesangiolysis	15 (88.2%)
Arterial/arteriolar fibrinoid necrosis	13 (76.5%)
Double contours of glomerular basement membrane	11 (64.7%)
Glomerular ischemic changes	9 (52.9%)
Mucoidintimal thickening	7 (41.2%)
Corticalnecrosis	3 (17.6%)

In patients with IgA nephropathy, mesangial proliferation with IgA deposits was observed in addition to TMA features. In lupus nephritis cases, immune complex deposits and endocapillary proliferation were seen along with TMA. The case of ANCA-associated vasculitis showed fibrinoid necrosis and crescents formation in addition to TMA features.

Treatment and Outcomes:

All patients received supportive care, including blood pressure control, correction of fluid and electrolyte imbalances, and treatment of the underlying cause. Eleven patients (64.7%) required renal replacement therapy at presentation. Two patients with lupus nephritis-associated TMA received therapeutic plasma exchange (TPE) for 5 days in addition to immunosuppressive therapy, both showing significant improvement in renal function. At the 6-month follow-up, one patient (5.9%) had died due to acute left ventricular failure from accelerated hypertension, 8 patients (47%) remained dialysis-dependent, and 8 patients (47%) had achieved stable renal function (Table 4).

Table4: Treatment and Outcomes(n=17)

Treatment/Outcome	**NumberofPatients (%)**
Treatmentmodalities	
Anti-hypertensive therapy	15 (88.2%)
Renal replacement therapy	11 (64.7%)
Hemodialysis	10 (58.8%)
Peritoneal dialysis	1 (5.9%)
Therapeutic plasma exchange	2 (11.7%)
Immunosuppressive therapy	3 (17.6%)
Outcomesat6 months	
Death	1 (5.9%)
Dialysis dependence	8 (47%)
Stable renal function	8 (47%)

A comparison of baseline characteristics between patients who achieved stable renal function and those who remained dialysis-dependent or died showed significant differences in median systolic blood pressure (p=0.032), presence of neurological manifestations (p=0.043), and median serum creatinine at presentation (p=0.021) (Table 5).

Table5: Comparison of Baseline Characteristics Between Patients with Favorable and Unfavorable Outcomes

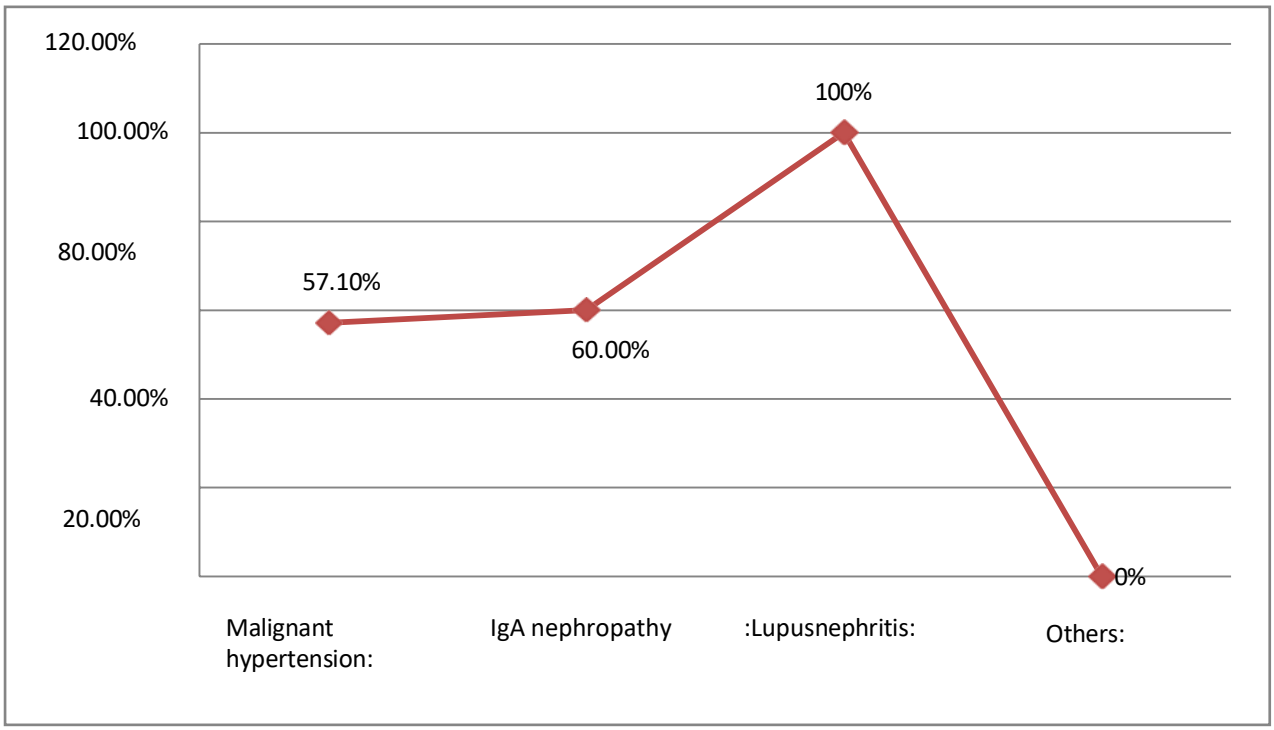
Characteristic	StableRenalFunction (n=8)	Dialysis Dependence orDeath(n=9)	p-value
Median age, years(IQR)	30.5(22-40)	35(26-48)	0.362
Female gender, n (%)	5 (62.5%)	4 (44.4%)	0.464
Median systolic BP, mmHg (IQR)	160(142-176)	196(170-224)	0.032
Median diastolic BP, mmHg (IQR)	98(85-110)	118(100-130)	0.045
Neurological manifestations,n(%)	0 (0%)	3 (33.3%)	0.043
Median hemoglobin, g/dL(IQR)	8.3(7.0-9.5)	7.4(6.0-8.9)	0.285
Median platelet count, $\times 10^3/\mu L$ (IQR)	158(112-210)	132(85-165)	0.176
Median serum creatinine, mg/dL (IQR)	6.4(4.2-8.1)	10.8(7.9-13.2)	0.021
Median LDH,U/L (IQR)	520(386-720)	768(562-995)	0.038

Etiology of TMA, n(%)			0.282
Malignant hypertension	3 (37.5%)	4 (44.4%)	
IgA nephropathy	3 (37.5%)	2 (22.2%)	
Lupus nephritis	2 (25.0%)	0 (0%)	
Others	0 (0%)	3 (33.3%)	

IQR:Interquartile Range, BP:Blood Pressure, LDH:Lactate Dehydrogenase
Statistically significant ($p<0.05$)

Renal survival (defined as independence from dialysis) showed that patients with malignant hypertension and lupus nephritis had better renal survival compared to other etiologies, although the difference did not reach statistical significance (p=0.062) (Figure 2).

Figure2: Survival Curve for Renal Survival Based on Etiology



Among the patients who achieved stable renal function, 3 had malignant hypertension, 3 had IgA nephropathy, and 2 had lupus nephritis (both of whom received TPE). The patient who died had malignant hypertension with severe left ventricular hypertrophy and developed acute left ventricular failure.

DISCUSSION

This retrospective study provides insights into the clinical profile, etiological factors, and outcomes of patients with biopsy-proven TMA in a tertiary care center in Northeast India. The incidence of TMA in our cohort of patients with RPRF was 14.7%, consistent with previous studies reporting TMA in 4-15% of patients undergoing renal biopsy for acute kidney injury [3,7].The median age of patients in our study

was 32.5 years, which is lower than reported in Western studies but similar to data from other Indian studies [8,9]. This may reflect the different demographic profile and etiological factors in the Indian population. The female predominance (52.9%) observed in our study has been reported in several other studies and may be related to the higher prevalence of autoimmune disorders in females [2]. Hypertension was the most common presenting symptom (52.9%), followed by headache (47.1%). This is consistent with previous studies highlighting the high prevalence of hypertension in patients with TMA, particularly those with malignant hypertension and renal involvement [10]. The neurological manifestations observed in 17.6% of our patients underscore the multi-system nature of TMA and the importance of comprehensive clinical evaluation. Our statistical analysis revealed significant differences in baseline characteristics between patients who achieved stable renal function and those who remained dialysis-dependent or died. Higher systolic and diastolic blood pressure ($p=0.032$ and $p=0.045$, respectively), presence of neurological manifestations ($p=0.043$), higher serum creatinine ($p=0.021$), and higher LDH levels ($p=0.038$) at presentation were associated with poor outcomes. These findings are consistent with previous studies identifying severe hypertension, neurological involvement, and markedly elevated serum creatinine as predictors of poor prognosis in TMA [11]. Laboratory findings in our study revealed a high prevalence of anemia (88.2%) and evidence of hemolysis (64.7%), but thrombocytopenia was present in only 52.9% of patients. This highlights that the classical triad of TMA (microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury) may not be present in all cases, particularly those with secondary forms of TMA [12]. The absence of the complete triad should not delay the diagnosis if other features suggest TMA. The etiological spectrum of TMA in our study revealed malignant hypertension as the most common cause (41.2%), followed by IgA nephropathy (29.4%) and lupus nephritis (17.6%). This distribution differs from Western studies, where complement-mediated TMA and drug induced TMA are more commonly reported [3]. The high prevalence of malignant hypertension in our cohort may reflect delayed presentation and poor blood pressure control in our patient population. The association between IgA nephropathy and TMA has been increasingly recognized, with studies reporting TMA in 2-8% of IgA nephropathy cases [13]. El Karoui et al. demonstrated that the presence of TMA lesions in IgA nephropathy is associated with worse renal outcomes, emphasizing the need for careful histopathological evaluation and aggressive management [13]. Lupus nephritis-associated TMA, observed in 17.6.% of our patients, has been reported in 8-15% of lupus nephritis cases and is considered a poor prognostic factor [14]. Interestingly, both patients with lupus nephritis-associated TMA in our study showed significant improvement with plasma exchange therapy, consistent with recent studies suggesting the benefit of TPE in these patients [15]. Regarding treatment and outcomes, 64.7% of our patients required dialysis at presentation, highlighting the severity of renal involvement. The mortality rate of 5.9% at 6-month follow-up is lower than reported in some studies [16] but may increase with longer follow-up. The high rate of persistent dialysis dependence (47%) underscores the poor renal prognosis associated with TMA, particularly when diagnosis and treatment are delayed. The favorable response to plasma exchange in lupus nephritis-associated TMA observed in our study is noteworthy. While the efficacy of TPE in TTP is well established, its role in secondary forms of TMA, particularly those associated with autoimmune diseases, remains debated [6]. Our findings, albeit in a small number of patients, support the consideration of TPE in selected cases of secondary TMA. This study has several limitations. First, the retrospective design and small sample size limit the generalizability of our findings. Second, specialized tests for ADAMTS13 activity, complement genetics, and antibodies against complement regulatory proteins were not available, which might have provided further insights into the pathogenesis. Third, the follow up period was relatively short (6 months), and longer follow-up would be

valuable to assess long-term outcomes.Despite these limitations, our study provides valuable information on the spectrum of TMA in patients with RPRF in a tertiary care center in Northeast India, where data on this condition are limited.

CONCLUSION

This study demonstrates that malignant hypertension, IgA nephropathy, and lupus nephritis are common etiologies for biopsy-proven TMA in our setting. Hypertension and headache were the predominant presenting symptoms, while the classical triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury was not always present. Statistical analysis identified higher blood pressure, neurological manifestations, higher serum creatinine, and higher LDH levels at presentation as significant predictors of poor outcomes. Plasma exchange may be beneficial in carefully selected patients with lupus nephritis-associated TMA, although larger prospective studies are required, highlighting the importance of identifying underlying etiologies for appropriate management. Early diagnosis and aggressive treatment of the underlying cause are essential to improve outcomes in patients with TMA. Further prospective studies with larger sample sizes and longer follow-up periods are needed to better understand the natural history and optimal management strategies for different forms of TMA.

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