Clopidogrel Induced Thrombotic Microangiopathy Successfully Treated with Conservative Approach

Sir,

Thienopyridine derivatives are known to cause thrombotic microangiopathy (TMA). Ticlopidine induces antibodies to ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), also known as von Willebrand factor-cleaving protease leading to TTP and has largely been replaced by clopidogrel, a structurally similar compound with favorable side effect profile. Though extremely rare, clopidogrel is also known to cause TMA/TTP and only around 200 cases are reported globally.[1] To the best of our knowledge, this phenomenon has not been reported from India. We herein report a case of clopidogrel induced TMA (c-TMA) presented atypically as hemolytic-uremic syndrome (HUS) leading to rapidly progressive renal failure (RPRF).

A 44-year-old male presented with one-week history of anorexia, malaise, edema feet, and oliguria. One month prior to his illness, he was admitted at a local hospital for unstable angina, and was treated conservatively and prescribed clopidogrel, statin, nitrate, and beta blocker. His investigations at that time revealed hemoglobin of 12.0 g/dl and serum creatinine of 1.3 mg/dl. At presentation to us, he had pallor, pedal edema; pulse rate of 90/min and his blood pressure was 124/80 mm Hg. Rest of the examination was unremarkable.

The laboratory findings revealed hemoglobin of 7.2 g/dL, total leukocyte count of 10 × 10^3/μL, platelet count of 98 × 10^3/μL, blood urea of 80 mg/dl, serum creatinine of 5.2 mg/dl, total and direct bilirubin of 2.4 mg/dl and 0.5 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) of 76 IU/L and 40 IU/L, and lactate dehydrogenase (LDH) of 1600 IU/L. Coomb's test was negative. Peripheral blood smear showed significant number of schistocytes [up to 20 per 1000 red blood cells (RBC)]. Absolute reticulocyte count was 4.0%. His urine examination showed 3+ albumin, 8-10 RBC/hpf and 6-8 pus cells/hpf. Spot urine protein creatinine ratio was 4.5. Autoimmune workup, serum complement C3, and C4 levels were normal. Echocardiography showed normal cardiac function. In view of RPRF, renal biopsy was performed after stopping clopidogrel for 5 days. He was empirically treated with 3 daily doses of intravenous pulse methyl prednisolone, followed by oral steroids.

Renal biopsy revealed 16 glomeruli, majority of them showed ischemic thickening and wrinkling of basement membranes with evidence of mesangiolysis. Mild to moderate interstitial infiltration by lymphocytes along with few neutrophils was seen. Mild tubular atrophy along with interstitial fibrosis was seen involving 20% of the cortex studied. Few arterioles showed fibrin thrombi with luminal occlusion. Interlobular arteries revealed intimal fibrosis and myxoid change of the media [Figure 1]. Immunofluorescence (eight glomeruli) was negative for immunoglobulins and complement.

A diagnosis of TMA was made and he was continued on oral steroids. On further evaluation, we could not find any secondary predisposing causes of TMA. He had no preceding infections, evidence of connective tissue disease and exposure to other drugs. There was no history of malignant hypertension. Serology for antiphospholipid antibodies was also negative. Serology for ADAMTS13 activity, factor H level, anti-factor H antibody, and assessment of other components of complement pathway could not be done. It was presumed that TMA might be precipitated by clopidogrel use. As the patient could not afford plasma exchange (PLEX), he was continued on tapering doses of steroids with intermittent plasma infusions. His serum LDH level and hematological parameters were stabilized at end of 10 days. Urine output gradually improved. He responded to the treatment with a decline in serum creatinine to 2.1 mg/dl within 6 weeks of therapy and to 1.8 mg/dl at the end of 16 weeks.

The two most common syndromes of TMA include HUS and TTP. TMA with significant neurological dysfunction, severe thrombocytopenia, fever and relative renal sparing was designated as TTP, while the term HUS was applied to cases with predominant renal involvement without neurological features.[2] HUS associated renal lesions are more severe and contain fibrin-rich thrombi, as opposed to the platelet-rich thrombi seen in TTP.[3] The thienopyridine mediated TMA resembles TTP rather than HUS. Ticlopidine has largely been replaced by clopidogrel, due to its frequent adverse effects like TMA and neutropenia. The incidences of

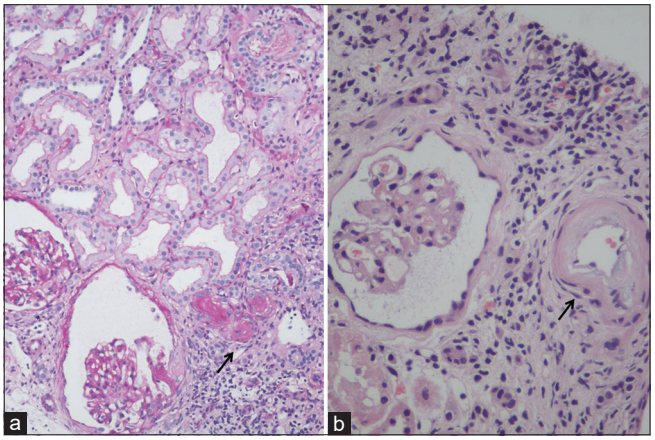

Figure 1: (a) Arrow pointing the arterioles show fibrinoid deposits in their walls and fibrin thrombi occluding their lumina. (b) Arrow showing intimal myxoid change affecting a small artery. Glomeruli in both fields show ischemic changes with collapse and wrinkling of basement membranes (periodic acid-Schiff, ×200)

Table 1: Comparison between t-TMA and c-TMA

TMA	t-TMA	c-TMA
Time to onset	2-12 weeks	Within 2 weeks
Mechanism	ADAMTS-13 mediated	Not known
Thrombocytopenia	Severe	Moderate
Renal function	Normal	Renal insufficiency
ADAMTS-13 levels	<5%	>15%
Antibodies to ADAMTS-13	100%	Not known
PLEX	PLEX is useful	Doubtful benefit
Response to PLEX	90%	50%
Relapses	None	None

microangiopathy, c-TMA: Clopidogrel induced thrombotic microangiopathy, ADAMTS-13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, PLEX: Plasma exchange

t-TMA and c-TMA are about 1 in 1600 ticlopidine and 1 in 80,000 clopidogrel-treated patients, respectively.[1] T-TMA occurs due to development of antibodies to ADAMTS-13 leading to TTP within 2–12 weeks of drug initiation, and clinical and laboratory findings resemble those of idiopathic TTP with respect to neutralizing autoantibodies, severe ADAMTS-13 deficiency and rapid response to PLEX.[4] C-TMA occurs generally within 2 weeks of drug initiation, but can occur later also. The mechanism of c-TMA is not fully understood. Important differences between t-TMA and c-TMA are mentioned in Table 1.[1] Combined therapy with statins could be a risk-factor as these have an inhibitory effect on cytochrome P450 (CYP3A4), responsible for the conversion of clopidogrel to its active metabolite.[5] Supportive care and drug avoidance may be the only beneficial management in most of the cases. The role of immunosuppressive agents is not clear. PLEX is helpful in severe cases presenting especially as TTP.

Our patient presented with RPRF about one month after initiation of clopidogrel. His clinical diagnosis was HUS due to prominent renal involvement, mild thrombocytopenia, and absence of neurological changes. It was confirmed on renal biopsy showing features of TMA. The patient did not have any other predisposing factors, therefore we assumed that clopidogrel was the culprit drug as it was recently started. Combined therapy with statin could also be a contributing factor. Clopidogrel was withheld and he was continued on steroids with plasma infusions and showed improvement in 10 days. This is an unusual presentation, as c-TMA generally presents as TTP rather than HUS. Unfortunately, we could not evaluate gene mutations, antibodies for complement regulators and ADAMTS-13 in our patient. Because clopidogrel is widely prescribed, clinicians should be vigilant and aware of this rare possible complication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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