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A case on escitalopram induced thrombotic microangiopathy

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ABSTRACT

Incidence rate of thrombotic microangiopathy (TMA) with Escitalopram, an anti-depressant drug has been estimated at 0.0059%. The case illustrates the observation in a 42-year-old female patient of South Indian descent, who presented with a 6-week history of progressive increase in breathlessness with evident signs of pallor and oedema. On examination the patient was found to have hypoxia and orthopnoea. The diagnosis of TMA was arrived at on the basis of lab values of elevated serum creatinine, blood urea, lactose dehydrogenase and reduced platelet count. Although ultrasound sonography revealed normal kidney size, the renal biopsy indicated towards TMA. The drug-induced TMA was speculated on grounds of chronic history of Escitalopram consumption and absence of other causal factors such as family history. The patient was provided therapy comprising of plasmapheresis, diuretics, anti-hypertensives and antibiotics. On subsidence of the condition after nine sessions of plasmapheresis, the patient was discharged. However, on follow-up after ten days revealed re-emergence of TMA as evident from the renal markers, LDH and platelet counts. Although the subject was advised to undergo further sessions of plasmapheresis, the patient stated financial impediments and therefore referred to government medical college for further follow-up.

INTRODUCTION

Thrombotic microangiopathy (TMA) is defined as a histopathological lesion characterized by vessel wall thickening (mainly arterioles or capillaries) intraluminal platelet thrombosis and partial or complete obstruction of the vessel lumina. Consumption of platelets and red blood corpuscles occur in the microvasculature of brain, kidney and other organs and is reflected in the laboratorial evidences of thrombocytopenia and haemolytic anaemia. Such thrombus can obstruct the microvasculature and culminate in ischemia and infarction of end-organs comprising of brain and kidney. Based on the predominance of lesion in microvasculature of either kidney or the brain, the condition is clinically stratified into haemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) respectively [1]. Although variety of drugs have been implicated to have a causative role in the development of TMA;the mechanism of causation remains obscure and only 15% of the overall incidence has been attributed to the condition.

Escitalopram is an antidepressant drug (selective serotonin reuptake inhibitors) indicated by US-FDA for the treatment of major depressive disorder and generalized anxiety disorder. The incidence of TMA in patients treated with Escitalopram is an infrequent and under-represented complication with the incidence rate being as low as 0.0059%. Although the condition is rare, it is associated with significant morbidity and mortality unless early diagnosis with rigid follow-up using renal and haematological monitoring is initiated in such patients. Timely identification of such incidents is vital from another perspective that re-exposure to the drug can culminate in fatal outcomes. The following case report, the first one from South India, explicates a case of escitalopram induced TMA.

CASE REPORT

A 42-year-old female patient who presented with complaints of acute onset of breathlessness was referred from a local primary care hospital. The patient was characterized by average build and nutrition with clinical signs and symptoms of pallor, oedema, orthopnoea and hypoxia (spO_2 80% on room air). The patient had presented to the local hospital 6-8 week weeks hitherto with similar complaints and although relieved, developed progressive into the current state with presentation of orthopnoea. Although the patient denied history suggestive of any chronic illness in the past, she admitted to have been consuming Escitalopram prescribed for therapy of depressive illness for the past 1 ½ years.

The patient had stage III hypertension (210/120 mmHg), tachycardia (110beats/min), elevation of jugular venous pressure (JVP) and bilateral basal crepitation and fever (temperature - 100°F). A progressive decline in the haemoglobin (Hb) level was observed with 7.8 gm/dL on the initial day that fell to 5.6 gm/dL by the fifth day with concurrent haematocrit value of 16%. Even after an attempt was made to elevate the Hb to 9.5 gm/dL by the infusion of 2 units of packed cells and haemoglobin, the value dropped to 8.1 gm/dL after 2 days. The total leucocyte count (TLC) on the initial day of hospitalization was estimated to be 22.67×10^3 cell/mm^3 and the differential count on the same day provided polymorph and lymphocyte values of 92% and 6% respectively. The blood urea level was at an elevated value of 177 mg/dL analogous to blood sugar elevation to 248 mg/dL. There was indication of proteinuria as evident from urine protein level of 68 mg/dL. Elevation was also conspicuous with serum phosphate and serum creatinine with values of 8.7 mg/dL and 8.6 mg/dL respectively. Liver function test (LFT) was not altered much as apparent from normal bilirubin levels, SGOT (44 IU/L) and SGPT (48 IU/L) values.

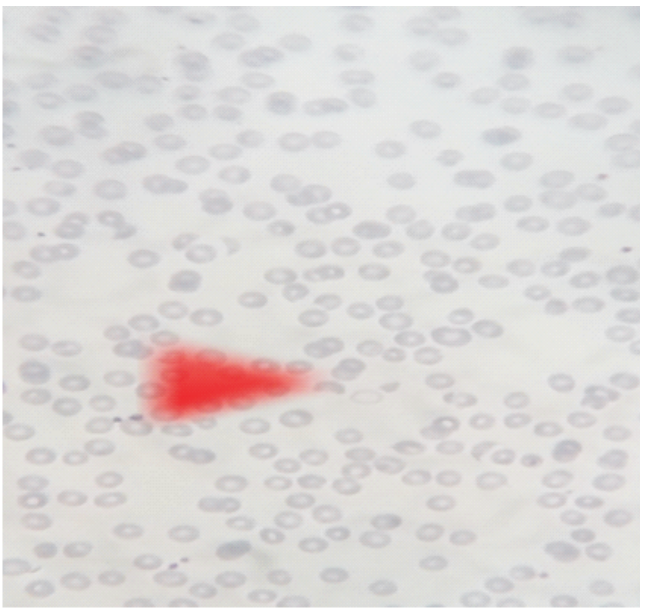

Figure 1

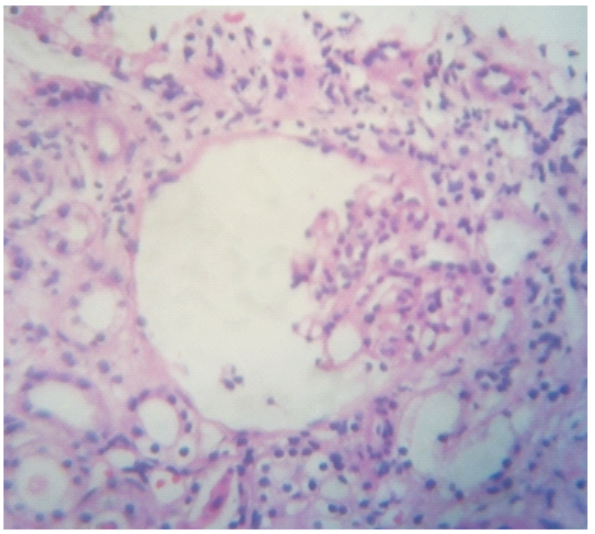

Figure 2

Speculation on possibility of the current condition of the patient being attributed to TMA was substantiated by further work-up which showed further rise in blood urea level to 227 mg/dL, serum creatinine level to 9.7 mg/dL and LDH level to 1168 U/L. Noticeable reduction was also observed in the platelet count as well as C-3 component (60mg/dL). The possibility if drug induced TMA was further strengthened by the fact that the patient did not have any other predisposing causes such as family history for development of the condition. Ultrasound sonography test (USG) of the kidney revealed normal size and Antinuclear antibody (ANA) profile was tested as negative. Among the

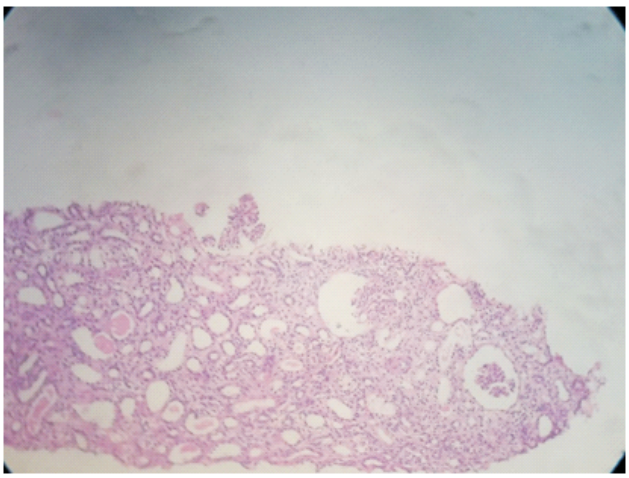

Figure 3

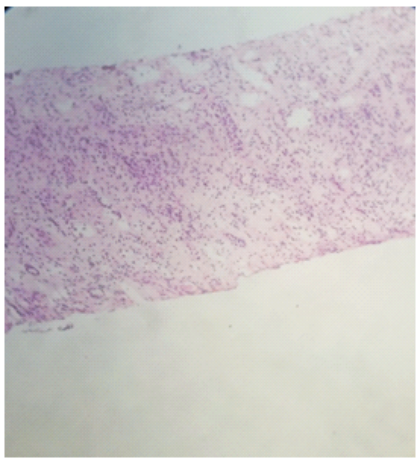

Figure 4

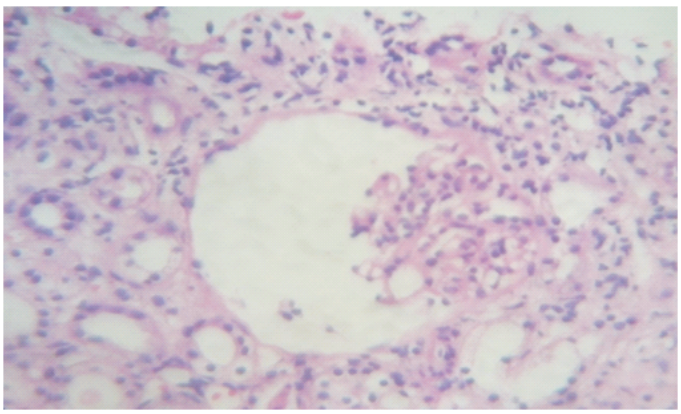

Figure 5

diagnostic tests, peripheral blood smear test revealed normochromic normocytic anaemia which further revealed erythroid regeneration, possibly associated with haemolysis mild thrombocytopenia, and scistocytes. Other investigations revealed leucocytosis, thrombocytopenia, hypoalbuminemia and advanced renal failure with renal biopsy prompting towards TMA.

As part of the therapy, the patient underwent renal replacement therapy with dialysis and plasmapheresis and was administered Inj. Frusemide 140 mg stat with further doses to be administered at 100 mg q8h. Attempt was made at establishing serum electrolyte balance through administration of sodium bicarbonate 500 mg q6h and antibiotic therapy was initiated with parenteral Cefoperazone/Sulbactam bid. Blood pressure management was initiated with Cilnidipine 10 mg stat with follow up using same dose using twice daily dosing.

To achieve the required control, α and β blocker carvedilol 3.125 mg was prescribed as bid dosing. Subsequently Clonidine 100mg and alpha blocker Prazosin hydrochloride 2.5mg tablet were also included to reduce the uncontrolled blood pressure.After 9 sessions of plasmapheresis, the clinical features of TMA ameliorated with stabilization of B.P, platelet count and lowering of LDH. The platelet level increased to 123×1000 cells/mm^3 with near normalization ofblood urea reading to 48mg/dLand serum creatinine to 4 mg/dL.

The patient was discharged from the in-patient setting and advised to follow-up after 10 days as out-patient. However, there was evidences of gradual worsening of TMA indicating parameters with LDH elevating from discharge value of 226 U/L to 464 U/L, blood urea elevation to 114 mg/dL and serum creatinine elevation to 114 mg/dL. Derangements were once again apparent in haematological values with Hb level dropping to 7.1g/dL and platelet count dropping to 130×10^3cells/mm^3. The patient was instructed to undergo further sessions of plasmapheresis till achievement of complete remission. However, the patient cited financial impediments and was therefore referred to government medical college for continuation of therapy.

DISCUSSION

The term thrombotic microangiopathy was initially used in 1952 to delineate the observation of disseminated thrombosis observed post-mortem in smallest caliber vasculature [2].It was later identified that TMA could be recognized ante-mortem through microangiopathic hemolyticanemia (MAHA) which indicated directcontact amidst the red cell corpuscles and the affected blood vessels. The abnormally high shear stress catapulted by endothelial damage and thrombosis within microvasculature lead to aggregation of thrombocyte and RBC destruction. Although the non-immune mediated hemolysis produces a negative Coomb's test, a positive reaction is obtained as a result of the autoimmune conditions such as systemic lupus erythematosus (SLE) or alloimmunity (due to transfer of blood products). Another reason for the positivity of the test may be attributed to the neuraminidase mediated p-HUS. Elevation in serum LDH has diagnostic capability since their levels reflect hemolysis and/or tissue ischemia and can be used to monitor disease progression. Disseminated intravascular coagulation is distinct from TMA on the basis of lesser delineated thrombocytopenia and abnormal clotting factors [3].

Renal histopathological features of TMA are apparent on light microscopy and can be visualized as arteriolar and/or glomerular intracapillary thrombosis, frequently accompanied by accumulation of fragmented erythrocyteswithin capillary lumens, and focally ischemic or congestedglomerular tufts. In the background of malignant HT, the severe arterial and arteriolar injury may be visualized with or without generalized thrombosis. Renal biopsy is seldom ordered in patients with renal manifestations of TMA since scarce etiological or prognostic details is added to the already obtained laboratory tests. However, biopsy may be used to differentiate between antibody-mediated rejection from other probable source of TMA in post-renal transplant subjects. Nativerenal biopsy may also be of value where an alternative (orcoexistent) lesion is suspected such as in glomerulopathy. Patients with chronic TMA may develop membrane-proliferative pattern composed of 'double contours' of the basement membrane of glomerulus, which lacks the immune deposit features of glomerulonephritis.

Urgent and empirical therapeutic plasma exchange and fresh frozen plasma administration is recommended in children as per 2009 guidelines developed by European Pediatric Study Group for HUS. But this has to be performed only after ruling out the presence of Shigella toxin producing *E. coli*[1].Another effective strategy is the administration of Eculizumab which is a humanized monoclonal antibody inhibiting activation of C5 component of complementary pathway and has demonstrated promising murine model of HUS [4].

Since most TTP is autoimmune in origin,patients who respond inferiorly or relapse generally receive adjunctive immunosuppressive therapy with TPE.Some groups endorse use of steroids in all subjects suspected of having contracted TTP [5].

CONCLUSION

Escitalopram induced thrombotic microangiopathy is a rare subtype of histopathological lesion of capillaries and arterioles.Plasma exchange is a proven therapy and there is a growing evidence that it facilitates resolution of organ dysfunction and improve outcomes of secondary Thrombotic Microangiopathy.

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