Case Report

Clopidogrel-induced thrombotic thrombocytopenia after years of medication

Rateesh Sareen, Menka Kapil, Piyush Mathur[1], Madhulika Sharma[2]

Departments of Pathology and Transfusion Medicine, [1]Nephrology and [2]Medicine, Santokba Durlabhji Memorial Hospital and Research Centre, Jaipur, Rajasthan, India

Abstract

Thrombotic thrombocytopenic purpura (TTP) is a life threatening, fulminant disease characterized by fever, microangiopathy hemolytic anemia, thrombocytopenia, neurological signs and renal insufficiency. The real culprit is agglutinated platelets and fibrin which form micro thrombi, gets deposited in arterioles and capillaries without eliciting inflammatory response. The idiopathic cases of TTP are characterized by deficiency of ADAMTS-13 (a disintegrin and metalloprotease, with thrombospondin -1 like domains) metalloprotease activity. The use of antiplatelet drugs, the thienopyridine derivatives Clopidogrel & Ticlodipine, is associated with drug induced TTP. The literature studies indicate that most cases of thienopyridine associated TTP involve an antibody to ADAMTS-13 metalloprotease that cause thrombocytopenia and respond to therapeutic plasma exchange (TPE).We report a case of 59 year old male who was on Clopidogrel post coronary angioplasty since past five years. He presented to us with complaints of nose bleeding and renal insufficiency. The evaluation of this potentially fatal drug complication should be borne in mind by physicians for all patients receiving Clopidogrel treatment.

Keywords: ADAMTS-13, clopidogrel, thrombotic thrombocytopenic purpura

Address for correspondence: Dr. Rateesh Sareen, Department of Pathology and Transfusion Medicine, Santokba Durlabhji Memorial Hospital and Research Centre, Jaipur, Rajasthan, India.
E-mail: drrateeshsareen@yahoo.co.in

INTRODUCTION

Clopidogrel has largely replaced ticlopidine in clinical practice nowadays.[1] Ticlopidine and Clopidogrel are antiplatelet drugs that are thienopyridine derivatives both differing each other in terms of carboxymethyl group. In comparison to ticlopidine, clopidogrel has a lower rate of incidence of skin, hematological, gastrointestinal tract adverse effects, and a favorable dosing schedule.[2] These antiplatelet drugs have a short half-life. They act on adenosine diphosphate (ADP) binding sites on platelets which inhibit IIb/IIIa receptor expression responsible for binding of large vWF multimers.[3] Clopidogrel has a lower risk of thrombotic thrombocytopenic purpura (TTP) in comparison to ticlopidine (One case in 20,000 versus one case in 1600–5000).[4] In 1991 Page *et al*.[5] reported four cases of TTP with ticlopidine use; however, no TTP was reported in 19,185 patients in Phase III trials of clopidogrel.[6] The exact mechanism of clopidogrel-induced TTP is not unknown, but it is attributed to antibody formation.[1] The antibodies developing after 2 weeks of therapy and has high mortality rate if left untreated. Plasma exchange therapy results in 100% cure if the therapy is initiated within 3 days of diagnosis and if left untreated fatality is high. TTP is defined as pentad of fever, anemia,

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thrombocytopenia with renal impairment, and neurological symptoms.[7] The diagnosis of TTP can be made on the basis of the presence of microangiopathic anemia and thrombocytopenia without renal and neurological involvement as quite often the classical pentad is not seen in patients.[8]

CASE REPORT

We report a case of a 59-year-old male admitted with complaints of body ache and nosebleed in the emergency department of tertiary care hospital in western India. There was a history of vague fever for few days. The patient was a known case of ischemic heart disease and had undergone percutaneous transluminal coronary angioplasty in 2009, in an outside center. He was on regular medications which included clopidogrel as antiplatelet drug. The initial laboratory examination at the time of admission revealed - hemoglobin 14.0 g/dL, red blood cell (RBC) count 4.76 × 109/mm^3, white blood cell count 9.88 × 103/mm^3, and platelet count 20 × 109/mm^3. The differential showed polymorphs - 80%, lymphocytes - 16%, eosinophils - 1%, and monocytes - 3%. Reticulocyte count was 1.2% and osmotic fragility test was normal. A peripheral blood smear showed schistocytes, fragmented RBCs, and occasional crenated RBCs [Figure 1]. The serum biochemistry showed blood urea - 54 mg/dl and creatinine - 2.6 mg/dl. Liver function tests were near normal - serum glutamic-oxaloacetic transaminase - 108/IU, serum glutamate-pyruvate transaminase - 30 IU/L, total bilirubin - 5.1 mg/dl, direct bilirubin - 1.1 mg/dl, total protein - 5.9 mg/dl, albumin - 3.3 mg/dl, globulin - 2.6 mg/dl, A/G ratio - 1.27, and gamma GT - 24 mg/dl. Serum electrolytes were within normal limits and HIV, HBsAg test was nonreactive. Erythrocyte sedimentation rate was 20/mm hr, prothrombin time - 15.2, INR - 1.18 activated partial thromboplastin time - 42.2 s, and serum lactate dehydrogenase (LDH) was 6031 IU/L. Test for dengue antigen was negative. The direct and indirect comb's test was negative along with ANA and rheumatoid factor which was negative. Urine examination showed the presence of hematuria – 14–16 RBC/hpf and grade + 3 proteinuria. Blood and urine culture were unremarkable. Thyroid profile was normal and serum Vitamin B12 was <159 pg/ml. Thrombocytopenia raised LDH, deranged renal function, and presence of schistocytes in peripheral blood raised suspicion of TTP. However, there was absence of any neurological signs or symptoms. Literature search revealed that clopidogrel may cause TTP on rare occasions. To confirm our diagnosis, an ADAMTS-13 assay was done which was found to be deficient, supporting the possibility of clopidogrel-induced TTP. The ADAMTS 13 activity was below <3 L (normal – 68%–163% activity) and ADAMTS 13 inhibitor was high 3.2 BEU (normal range <0.4 BEU).

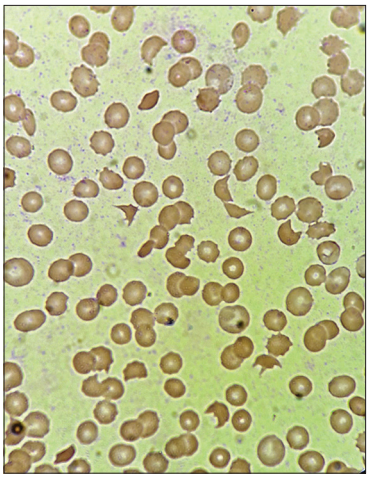

Figure 1: Peripheral blood film Leishman stain (×100) showing schistocytes

DISCUSSION

TTP can be caused by acquired or hereditary etiology. The acquired form as seen in this patient is caused by autoantibodies that are formed against ADAMTS-13. ADAMTS-13 a protease functions by cleavage of large multimers.[9] The autoantibody binding to ADAMTS-13 decreases the activity of the protease enzyme which in turn allows large multimers binding to platelets forming microthrombi resulting in thrombocytopenia and microvascular occlusion.[10] The microangiopathic hemolytic anemia component in TTP was noticed in the form of schistocytes in peripheral blood of the patient.

In our case, TTP was attributed secondary to medication. The other causative agents of TTP are drugs such as cancer chemotherapeutic agents (mitomycin C, gemcitabine, cisplatin, tamoxifen, bleomycin, cytosine arabinoside, and daunomycin), cyclosporine A, oral contraceptives, penicillin, and rifampin.[11-15] Infectious agents such as streptococcus pneumonia and cytomegalovirus, vascular surgery, vasculitis, organ transplant, splenic sequestration, and sepsis.[11-15]

Clopidogrel the new thienopyridine derivative is similar to ticlopidine.[3] It has a favorable safety profile in comparison to ticlopidine particularly as causative agent for TTP.[1] It works by irreversibly blocking the P2Y12 component of ADP receptor on the platelet surface preventing aggregation of platelets.[16] The incidence of TTP in clopidogrel recipients is 12/1 million.[17] There are studies in literature suggest that there is early <2 weeks occurrence of

clopidogrel-induced TTP[2,4,5] and few studies where TTP was observed year after discontinuation of medication.[16,17]

TTP in our case occurred after 5 years of initiation of therapy[18] whereas most of the cases of clopidogrel-associated TTP in literature are suggestive of early occurrence.[3,6-16] The exact mechanism of clopidogrel-induced TTP remains unknown. The long latent period in our case makes it a significant finding. The clinical recognition of the syndrome that characterizes clopidogrel-associated TTP is extremely crucial for the quick initiation of therapy. Our case is perhaps the only case where TTP developed after years of clopidogrel use. The case is important as it hints toward possible etiological link and it conveys information to the medical community regarding serious adverse effect of clopidogrel.

CONCLUSION

It is prudent that all clopidogrel recipients should be warned about the risk of TTP and its symptoms and in cases of high index of suspicion urgent hematologist intervention like plasma pharesis should be initiated.[19,20]

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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