

Case Report**Thrombotic Thrombocytopenic Purpura associated with Clopidogrel : a case report and review of the literature**Taleb Azarm^a, Ayatollah Sohrabi^{*b}, Hamid Mohajer^c, Arezou Azarm^d**Abstract**

Thrombotic Thrombocytopenic Purpura (TTP) is a life threatening, multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological changes, renal failure, and fever. These signs and symptoms are thought to be caused by microthrombi, composed of agglutinated platelets and fibrin, which deposit in the arterioles and capillaries without mediation by an inflammatory process. TTP can occur in the first two weeks of initiation of Clopidogrel therapy. Early signs of TTP may be a skin reaction, which may precede the onset of TTP or it may be other type of purpura or neurological changes. We report the clinical and laboratory findings in a 67 years old female patient in whom TTP developed soon after treatment with 40 mg/day oral Clopidogrel after 8 days. She developed thrombocytopenia (platelets count 12000 /mm³). Her clinical signs and symptoms were fever (39.6C), bleeding from the nose and gum, large skin bruises (purpura and ecchymoses), neurological changes including hallucinations, bizarre behavior, altered mental status (fluctuating), headache, and renal dysfunction. Physicians should be aware of the possibility early onset of this syndrome when initiate Clopidogrel treatment.

KEYWORDS: Thrombotic Thrombocytopenic Purpura (TTP), Clopidogrel, plasma exchange.

JRMS 2011; 16(3): 353-357

Thrombotic Thrombocytopenic Purpura (TTP) is a life threatening, multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological changes, renal failure and fever. These signs and symptoms are thought to be caused by microthrombi, composed of agglutinated platelets and fibrin, which deposits in the arterioles and capillaries in the tissues without an inflammatory process mediation.¹ Most idiopathic cases of TTP are characterized by ADAMTS13 (a disintegrin and metalloprotease, with thrombospondin-1-like domains) metalloprotease activity deficiency.^{1,2} Idiopathic cases occur at a rate of 3.7 per year per million people with a mortality rate of 10 to 20% for promptly treated cases. Its cause appears to be related to auto-antibodies against ADAMTS-13 that degrades von Willebrand factor.³⁻⁵

Acquired TTP is due to breast, gastrointestinal tract, and prostate cancer.⁶ Pregnancy can also trigger congenital and acquired TTP, especially in second trimester and postpartum after delivery.^{7,8,14} Some disease such as HIV, autoimmune diseases like systemic lupus erythematosus (SLE) may cause TTP by an acute immune-mediated response or dose-related toxicity.⁹ Heparin is the most common medication associated with thrombocytopenia (3-7% of patients with IV heparin use).

Other drugs which may be associated with TTP are Ticlopidine, Quinine, immune-mediated ingredient, cancer chemotherapeutic agents (Mitomycin C, Gemcitabine, Cisplatin, Tamoxifen, Bleomycin, Cytosine arabinoside, and Daunomycin), Cyclosporine A (CyA), oral contraceptives, Penicillin, Rifampin and anti platelet drugs like ticlopidine.¹⁰ Other factors

^a Professor in Hematology and Oncology Center, Isfahan University of Medical Sciences, Isfahan, Iran.

^b Insetructor, Department of Social Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

^c Resident of Internal Medicine, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

^d Cellular and Mulecular Biology, Isfahan, Iran.

* Corresponding Author

E-mail:

that can be associated with TTP are toxins (e.g. bee venoms), infectious process and sepsis, splenic sequestration, transplant-associated TTP, Vasculitis, vascular surgery (after 5-9 days), infections like Streptococcus pneumonia and cytomegalovirus.¹⁰⁻¹⁵

The antiplatelet drug Clopidogrel is a new thienopyridine derivative whose mechanism of action and chemical structure are similar to those of ticlopidine.¹⁶ The estimated incidence of ticlopidine-associated TTP is 1 per 1600 to 5000 treated patients, whereas no Clopidogrel-associated cases have been observed among 20,000 closely monitored patients treated in third phase of clinical trials and cohort studies.¹⁷ Because of the association between the usage of ticlopidine and TTP and other adverse effects, Clopidogrel has achieved widespread clinical acceptance because it has a more favorable safety profile in comparison with ticlopidine.²⁸ The two drugs are derivatives of thienopyridine, differing only in one carboxymethyl group.²⁰ They have short half-life in the circulation and different metabolites. These drugs act by blocking an adenosine diphosphate-binding site on platelets, which inhibits the expression of glycoprotein IIb/IIIa receptor in the high-affinity configuration that binds fibrinogen and large multimers of von Willebrand factor.²⁰

Case Report

We report the clinical and laboratory findings of a patient that developed TTP eight days after treatment with Clopidogrel. The patient was a 67 year old female who suffered from hypertension and Hyperlipidemia for seven years. She had chest pain and acute cardiac ischemia due to coronary artery disease 15 days before using Clopidogrel. She had received coronary artery stents (because the patient did not consent to surgery) and medicated with Clopidogrel 75 mg/day, Metoprolol 50 mg bd/day, Amlodipin 5 mg/day and Lovastatin 20 mg/day. The last three drugs had been administrated for seven years.

Eight days after receiving Clopidogrel she achieved thrombocytopenia (platelets count

12000 /mm³). Her clinical signs and symptoms were fever (39.6C), bleeding from the nose and gum, large skin bruises (purpura and ecchymoses), neurological changes including hallucinations, bizarre behavior, altered mental status (fluctuating), and headache.

Other findings such as laboratory tests were as the following: Renal dysfunction (serum Creatinine level 2.5 mg/dl); microangiopathic hemolytic anemia (schistocyte on peripheral blood film examination); hemoglobin 6.3 g/100; hematocrit values were less than 21 percent; reticulocyte count 18%; lactate dehydrogenase (LDH) 980 u/l; serum SGOT(AST) 118 u/l; SGPT(ALT) 39 u/l; Total Bilirubin 17.8 mg/100 and direct bilirubin 0.6 mg/100.

Clopidogrel treatment was discontinued and patient underwent plasma exchange for 40 cc/kg body weight every day. Her plasma was replaced with fresh frozen plasma (FFP). Daily plasmapheresis was started and the patient received an average exchange of 3000 ml of FFP each day. Eleven days after her admission and plasma exchange, signs, symptoms and laboratory abnormalities disappeared and the platelet count normalized. Plasmapheresis was stopped three days later. The patient was visited every two days for three weeks and then every week for four weeks in an outpatient clinic. Afterwards we followed her monthly for 6 month, meanwhile everything was alright, and all tests was within normal range.

Discussion

It seems that the characteristics of TTP in our case was different from other TTP cases who used Ticlopidine. In our case, TTP occurred 8 days after the initiation of treatment. Other studies suggest that Clopidogrel-associated TTP is 15 times more likely to occur within the first 2 weeks of drug use.^{17,18}

TTP is a fulminant disease characterized by platelet aggregation, thrombocytopenia, renal insufficiency, neurologic changes, and mechanical injury to erythrocytes. Most idiopathic cases of TTP are characterized by ADAMTS13 (a disintegrin and metalloprotease, with thrombospondin-1-like domains) and metallo-

protease activity deficiency. The use of anti-platelet agents such as the thienopyridine derivatives like Clopidogrel and ticlopidine, is known to be associated with drug induced TTP.¹⁷⁻¹⁹

TTP is a rare complication of thienopyridine treatment. Thienopyridine toxicity appears to occur by two different pathways, primarily characterized by the time of onset. If TTP occurs after 2 weeks of Ticlopidine or Clopidogrel therapy, therapeutic plasma exchange must be promptly performed to enhance likelihood of survival.²⁰

The mechanism by which Clopidogrel can cause TTP is not known.²¹ Patients with idiopathic and Ticlopidine-associated TTP have an immune-mediated deficiency of von Willebrand factor-cleaving protease activity in plasma.^{21,22} Since 1999, identification of Clopidogrel-associated TTP was started through independent active surveillance.²⁹ Subsequent cases have been identified by pharmaceutical suppliers of Clopidogrel and the Food and Drug Administration (FDA). The evaluation of quality and appropriateness of data for Clopidogrel-associated TTP cases reported during 1998 to 2002. Regarding Clopidogrel, it was through 3 reporting systems [independent active surveillance (n=13), pharmaceutical suppliers (n=24), and the FDA (n=13)] and identified prognostic factors associated with mortality.¹⁷

An article published in Prescriber Update in February 1997, advised that some studies have shown that in addition to some fatalities, Ticlopidine may cause life threatening hematological reactions that are usually reversible. Recent evidence indicates that its related mortality and adverse reactions may occur more frequently than what was expected previously.²²

The survival rate for patients suffering from

Clopidogrel-associated TTP was 71.2%. Receipt of therapeutic plasma exchange within 3 days of onset of TTP significantly increased the likelihood of survival (100% versus 27.3%). Clopidogrel-associated TTP often occurs within two weeks from drug initiation. If plasma exchange doesn't start soon, the rate of relapses and highly mortality will increase.²² TTP requires up to 30 plasma exchanges before clinical improvement occurred.

Our findings have important clinical implications. Clopidogrel has largely replaced Ticlopidine in clinical practice.²⁵ One of the reasons for this change was the association of TTP with the usage of Ticlopidine. Other reasons were the lower rates of skin, hematologic, and gastrointestinal adverse effects associated with Clopidogrel and its more convenient dosing schedule.^{23,24,26} The development of cardiac or neurologic changes after the initiation of Clopidogrel therapy may be mistakenly attributed to the underlying condition for which it was prescribed.^{18,19,24}

However, patients who take Clopidogrel should be warned about the risk of TTP and its symptoms. The likelihood of the death of patients on these medications can be reduced by up to 60% if cases with a high index of suspicion are referred to a hematologist for early intervention including plasmapheresis.^{19,23,27}

Conclusions

TTP can occur in the first two weeks of initiation of Clopidogrel therapy. Early signs of TTP may be a skin reaction, which may precede the onset of TTP or it may be an indication of purpura, and neurological changes. Complete blood count and creatinine level determination assist in the diagnosis. Physicians should be aware of the possible early onset of this syndrome when initiate Clopidogrel treatment.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

TA coordinated the study and prepared the manuscript. AS provided assistance in manuscript preparation. HM visited the patient and gathered the data. AA provided assistance in manuscript preparation. All authors have read and approved the content of the manuscript.

References

1. Sadler JE, Moake JL, Miyata T, George JN. Recent advances in thrombotic thrombocytopenic purpura. *Hematology Am Soc Hematol Educ Program*. 2004;407-23.
2. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002; 287(17): 2215-20.
3. Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN, McGee BM, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature* 2001; 413(6855): 488-94.
4. Tsai H-M, Rice L, Savode R, Chow TW, Moake JL. Antibody inhibitors to von Willebrand factor metalloproteinase and increased von Willebrand factor-platelet binding in ticlopidine-associated thrombotic thrombocytopenic purpura. *Ann Intern Med* 2000; 132(10): 794-9.
5. Furlan M, Robles R, Solenthaler M, Wassmer M, Sandoz P, Lämmle B. Deficient activity of von Willebrand-factor cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. *Blood* 1997; 89(9): 3097-103.
6. Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. *Blood* 2001; 98(6): 1662-6.
7. George JN. The association of pregnancy with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Curr Opin Hematol* 2003; 10(5): 339-44.
8. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med* 2006; 354(18): 1927-35.
9. Evens AM, Kwaan HC, Kaufman DB, Bennett CL. TTP/HUS occurring in a simultaneous pancreas/kidney transplant recipient after clopidogrel treatment: evidence of a nonimmunological etiology. *Transplantation* 2002; 74(6): 885-7.
10. Begue R, Dennehy PH, Peter G. Hemolytic uremic syndrome associated with *Streptococcus pneumoniae*. *N Engl J Med* 1991; 325(2): 133-4.
11. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; 347(8): 589-600.
12. Chang JC, Shipstone A, Llenado-Lee MA. Postoperative thrombotic thrombocytopenic purpura following cardiovascular surgeries. *Am J Hematol* 1996; 53(1): 11-7.
13. Au, WY, Lie, AK, Kwong, YL. Rituximab in thrombotic microangiopathy: response to Castagna et al. *Br J Haematol*. 2007; 139(1): 166.
14. Kincaid-Smith P, Fairley KF, Kloss M. Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. *Q J Med* 1988; 68(258): 795-815.
15. Wyllie BF, Garg AX, Macnab J, Rock GA, Clark WF; Members of the Canadian Apheresis Group. Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome: a new index predicting response to plasma exchange. *Br J Haematol* 2006; 132(2): 204-9.
16. Bennett CL. Two mechanistic pathways for thienopyridine-associated thrombotic thrombocytopenic purpura: a report from the SERF-TTP Research Group and the RADAR Project. *J Am Coll Cardiol* 2007; 50(12): 1138-43.
17. Zakarija A, Bandarenko N, Pandey DK, Auerbach A, Raisch DW, Kim B, et al. Clopidogrel-Associated TTP: An Update of Pharmacovigilance Efforts Conducted by Independent Researchers, Pharmaceutical Suppliers, and the Food and Drug Administration. *Stroke* 2004; 35(2): 533-7.
18. Rock GA. Management of thrombotic thrombocytopenic purpura. *Br J Haematol* 2000; 109(3): 496-507.
19. Palmisano J, Agraharkar M, Kaplan AA. Successful treatment of cisplatin-induced hemolytic uremic syndrome with therapeutic plasma exchange. *Am J Kidney Dis* 1998; 32(2): 314-7.
20. Patel TN, Kreindel M, Lincoff AM. Clopidogrel and Ticlopidine Mediation of TTP: A Case Report. *J Invasive Cardiol* 2006; 18(7): E211-3.
21. Majhail NS, Lichtin AE. Clopidogrel and thrombotic thrombocytopenic purpura: no clear case for causality. *Cleveland Clin J Med* 2003; 70(5): 466-70.
22. Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000; 342(24): 1773-7.
23. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, Yarnold PR, Kwaan HC, Green D. Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. *Ann Intern Med* 1998; 128(7): 541-4.
24. McCarthy LJ, Dlott JS, Orazi A, Waxman D, Miraglia CC, Danielson CF. Thrombotic thrombocytopenic purpura: yesterday, today, tomorrow. *Ther Apher Dial* 2004; 8(2): 80-6.

25. Wood AJ. Thrombotic thrombocytopenic purpura and clopidogrel: a need for new approaches to drug safety. *N Engl J Med* 2000; 342(24): 1824-6.
26. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; 364(9444): 1519-21.
27. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005; 45(12): 2088-92.
28. Mangalpally KK, Kleiman NS. The safety of clopidogrel. *Expert Opin Drug Saf* 2011; 10(1): 85-95.
29. Yoshii F. Clopidogrel-associated thrombotic thrombocytopenic purpura. *Rinsho Shinkeigaku* 2009; 49(6): 374-5.