

Ticagrelor-associated thrombotic thrombocytopenic purpura

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening, multisystem disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, renal dysfunction, and neurological disorders. Presence of microangiopathic hemolytic anemia, and thrombocytopenia are essential for diagnosis (1,2). In most cases, it is secondary to production of autoantibodies that reduce activity of a disintegrin and metalloproteinase with thrombospondin domain 13 (ADAMTS-13), which cleaves von Willebrand factor (vWF). Decrease in vWF degradation induces microvascular thrombosis, hemolytic anemia, and thrombocytopenia (3). Common laboratory findings include anemia and fragmented red blood cells (schistocytes), reduced platelet count, increased lactate dehydrogenase (LDH) level. Plasma exchange is life-saving treatment for TTP (4).

Three thienopyridines (ticlopidine, clopidogrel, and prasugrel) have been found to be related to TTP (5). Ticagrelor is a new agent now preferred to clopidogrel to treat acute coronary syndromes (6). In contrast to the thienopyridine family of drugs, ticagrelor has not previously been associated with TTP. Presently described is the first case of ticagrelor-linked TTP in literature.

Case Report

A 31-year-old male patient with no medical history or medication use presented at emergency department with chest pain that had been ongoing for 2 hours. Electrocardiography indicated ST elevation in V2-V6 derivations, indicating acute anterior myocardial infarction. He was immediately taken to catheterization laboratory. Coronary angiography revealed thrombosed stenosis of left anterior descending artery. Drug-eluting stent was implanted in culprit lesion. Results of tests done prior to procedure revealed normal hemogram values [hemoglobin (Hb): 15.7 g/dL, hematocrit (Hct): 43.8%, platelet count: 297.000 per mm³]. After loading dose of ticagrelor 180 mg, patient was prescribed ticagrelor 90 mg twice a day and discharged without complication. Five weeks later, however, he was admitted to outpatient clinic with fatigue, dyspnea, headache, and hemiparesis of left extremities. Patient was taking acetylsalicylic acid (ASA) 100 mg, nebivolol 5 mg once a day, and ticagrelor 90 mg twice a day at the time. Laboratory results showed anemia (Hb: 8.4 g/dL,

Hct: 25.0%), thrombocytopenia (platelet count: 20,000 per mm³), increase in LDH level (1074 U/L), and mild elevation of liver enzymes. Peripheral blood smear revealed schistocytes indicating fragmentation hemolysis. Patient had no fever, purpura, or renal failure. His prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, and fibrinogen levels were within normal limits. There was no sign of infection and HIV serology was negative. There was also no evidence of pathological findings on cranial magnetic resonance imaging. He was diagnosed with TTP and referred to tertiary hematology clinic for further treatment. Plasma exchange and steroid therapy were administered. Ticagrelor was discontinued. Clinical improvement was observed and TTP went into complete remission after total of 5 plasma exchange treatments. Afterwards, patient used only ASA as an antiplatelet drug and was followed for 6 months. No further intervention or treatment was needed.

Discussion

TTP is well known to be linked to thienopyridine derivatives. While estimated incidence of TTP caused by ticlopidine is 1 case per 1600 to 5000 patients, clopidogrel-related TTP is relatively rare with 197 cases reported as of 2011. Only 14 prasugrel-linked TTP cases were reported (4). Ticlopidin-related TTP is generally immune-mediated in contrast to clopidogrel-related TTP, which may be non-immunological. Clopidogrel-associated TTP mainly occurs within 2 weeks of therapy. Microvascular endothelial damage may be potential underlying mechanism in this drug. Unlike ticlopidin, clopidogrel, and prasugrel, ticagrelor does not belong to thienopyridine family. It works to inhibit same receptor as the thienopyridines, however, as reversible P2Y₁₂-ADP receptor antagonist (5). In contrast to clopidogrel-related TTP cases, present case of ticagrelor-related TTP occurred after first month of initiation of drug. Underlying mechanisms and optimal treatment methods need further investigation.

TTP is characterized by microangiopathic hemolytic anemia and thrombocytopenia. However, other causes, such as disseminated intravascular coagulation (DIC) should be kept in mind in differential diagnosis. PT, aPTT, fibrinogen, and D-dimer levels in TTP are generally normal, in contrast to DIC (4).

To the best of our knowledge, this is the first report of TTP-linked to ticagrelor. Management of ticagrelor-related TTP in this case was similar to previous thienopyridine-linked TTP cases. Cessation of ticagrelor therapy was the initial step, although stent thrombosis risk was elevated due to early discontinuation of dual anti-agregant regime. We believe that plasma exchange was also crucial treatment for ticagrelor-related TTP. Administration of steroid was concomitant therapy and continued for 2 months. Discontinuation of treatment was tapered gradually. Patient was advised about the possibility of relapse. During 6 months of follow-up, no relapse occurred with usage of ASA only as antiplatelet agent.

Conclusion

TTP could be a rare, yet possible, adverse effect of ticagrelor. Physicians should be aware of this uncommon side effect, given increased usage of ticagrelor in patients with acute coronary syndromes.

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