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Case Report
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A Rare Case of Ticagrelor-Induced Profound Isolated Thrombocytopenia

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Ticagrelor is a new oral antiplatelet drug that has a strong proven benefit of reducing the rate of death from cardiovascular causes, myocardial infarction, and stroke compared with clopidogrel. Ticagrelor is widely used by patients with acute coronary syndrome. However, profound thrombocytopenia has never been previously reported in such patients. We herein present our experience with a case of profound thrombocytopenia after ticagrelor administration. No drug possibly associated with thrombocytopenia was concomitantly prescribed. The patient's platelet count recovered rapidly after ticagrelor and platelet transfusion were discontinued.

Key Words: Acute coronary syndrome • Adenosine diphosphate (ADP) antagonist • Thrombocytopenia

INTRODUCTION

Ticagrelor, is a direct-acting oral antagonist of the adenosine diphosphate (ADP) receptor P2Y12, and provides greater and faster P2Y12 inhibition than clopidogrel.[1] Ticagrelor differs from the thienopyridines in that it does not require metabolic activation, and produces reversible inhibition of the ADP receptor. The United States Food and Drug Administration approved ticagrelor in July 2011. Compared with clopidogrel, ticagrelor significantly reduces the rate of death from cardiovascular causes, myocardial infarction, and stroke.[2] The most common side effects caused by ticagrelor include major bleeding, dyspnea, and increased uric acid levels.[2,3] No profound thrombocytopenia related to ticagrelor has been previously reported. In contrast, thienopyridine ADP receptor-P2Y12 inhibitors such as ticlopidine, clopidogrel, and prasugrel are associated with profound thrombocytopenia.[4,5] We report a severe case of ticagrelor-associated, isolated thrombocytopenia with recovery of the platelet count upon discontinuation of ticagrelor and platelet transfusion.

CASE REPORT

A 77-year-old man had a history of hypertensive cardiovascular disease, dyslipidemia, and type 2 diabetes mellitus for more than 20 years. He had taken medication regularly including amlodipine (5 mg/day), pitavastatin (2 mg/day), metformin (1000 mg/day) and fludiazepam (0.5 mg/day) for many years. Additionally, the patient also had aspirin (100 mg/day) prescribed by clinicians in the outpatient clinics for years due to suspected ischemic heart disease. After manifesting increasingly frequent angina symptoms, a thallium scan showed a reversible perfusion defect in the apex, apical lateral wall, entire inferior wall, and the mid-basal inferoseptal/inferolateral wall, compatible with stress-induced ischemia in the territory of the right coronary artery. Subsequent coronary angiography revealed left

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main and triple vessel disease. Coronary artery bypass surgery was the first treatment choice, but the patient refused. We performed balloon angioplasty and deployed a drug-eluting stent into the right coronary artery culprit lesion on January 13, 2015. A single unfractionated heparin bolus of 5000 unit was given during the procedure. To treat unstable angina, a ticagrelor loading dose of 180 mg was given, followed by maintenance dosing of 90 mg twice per day. The patient was discharged 2 days later without complication.

The patient had a normal baseline platelet count of 174 × 10^9/L on January 13, 2015. Two weeks later, he suffered from diffuse purpura and ecchymosis on both arms and around the orbits. His body temperature was 36.4 °C at our emergency department. There was no fever episode detected recently, or after admission. The patient denied specific travel history. His consciousness was clear, and no neurologic abnormality was detected. Blood biochemistry revealed normal serum creatinine, aspartate aminotransferase, and alanine aminotransferase values. Profound isolated thrombocytopenia was observed (2 × 10^9/L) on January 31, 2015. His activated partial thromboplastin time (APTT) and prothrombin time (PT) were normal (APTT: 24.7 seconds; PT: 10.0 seconds; INR: 0.97). Schistocytes and other abnormalities suggestive of microangiopathic hemolysis were not observed on the patient's blood smears. Aspirin and ticagrelor were therefore immediately discontinued, and 12 units of concentrated platelets were administered, aspirin was added the next day. His platelet counts on day 9 and day 24 had increased substantially after platelet transfusion to 120 × 10^9/L and 150 × 10^9/L, respectively (Figure 1). The discrete purpura and ecchymosis improved significantly, and no additional blood transfusion was needed. Thereafter, clopidogrel was prescribed in combination with aspirin starting February 10, 2015.

The patient underwent balloon angioplasty and stent deployment to the left main and left anterior descending coronary artery stenotic lesion in May 2015 with intra-arterial heparin use. No thrombocytopenia was detected.

DISCUSSION

The most common causes of profound thrombocytopenia are medications, disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS). In DIC, profound thrombocytopenia is accompanied by coagulation factor depletion due to increased consumption; thus, the APTT and PT are prolonged. DIC was excluded in this case because the values for APTT and PT were normal. We also excluded TTP-HUS by both peripheral blood smear, which lacked evidence of microangiopathic hemolytic anemia, and no evidence of major organ involvement. Atypical infection will resulted in profound thrombocytopenia, such as dengue virus infection. In this case, the patient had no fever episode and there was also no specific travel history which included Southern Taiwan. Therefore, the likelihood for atypical infection was low.

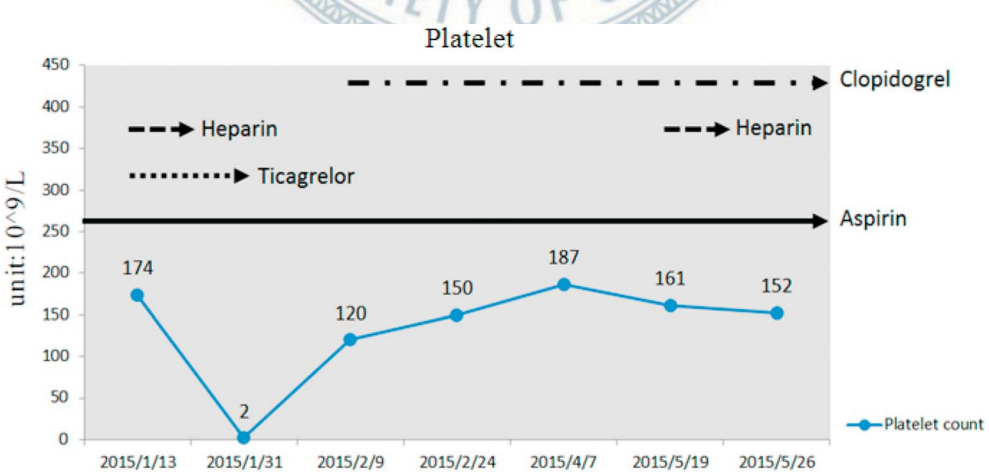

Figure 1. *The time sequence of platelet counts. Note the patient had normal baseline platelet count. Eighteen days after ticagrelor administration, the platelet count decreased to 2 × 10^9/L. The drug was discontinued, and 12 units of platelets were given immediately. The platelet count completely normalized nine days after discontinuation of ticagrelor. There was no thrombocytopenia detected after administration of heparin again four months later.*

Profound thrombocytopenia can also occur with administration of anti-platelet agents or anticoagulant medicines during acute coronary syndrome, and unfractionated heparin and glycoprotein IIb/IIIa receptor antagonists.[6] Heparin-induced thrombocytopenia is characterized by a decrease in the platelet count by greater than 50% from the highest platelet count value, with onset 5 to 10 days after heparin therapy begins.[7] The "4Ts" scoring system, included thrombocytopenia, timing of platelet count fall, thrombosis or other sequelae and other causes for thrombocytopenia, has been validated in numerous studies for excluding heparin-induced thrombocytopenia.[8] Use of a scoring system that takes into account the timing and magnitude of the platelet count fall, new thrombosis, and the likelihood of other reasons for thrombocytopenia is helpful in assessing the pretest probability of heparin-induced thrombocytopenia. In our case, the timing of the platelet count drop after exposure to heparin was more than 2 weeks, and minimum platelet count was 2×10^9/L. There was no clinical symptom or sign indicating a thrombotic event had occurred. Our patient gained two points in the 4Ts score, which had a high negative predictive value (97%-99%), and re-exposure to heparin four months later did not induce thrombocytopenia again, making heparin-induced thrombocytopenia impossible. The other possible medication that can cause thrombocytopenia is aspirin. However, the patient had taken aspirin for more than one year without a problem, which made a diagnosis of aspirin-induced thrombocytopenia less likely. There was no explicit food intake that will interfere with Cytochrome P450 3A system. Finally, after discontinuing administration of ticagrelor, the platelet count quickly recovered. Thus, the diagnosis of ticagrelor-associated severe isolated thrombocytopenia was confirmed.

Antiplatelet drugs are widely used in the primary and secondary prevention of thrombotic cardiovascular disease, including thienopyridine derivatives such as ticlopidine, clopidogrel, and prasugrel, and non-thienopyridine such as ticagrelor. Some cases of thrombotic thrombocytopenic purpura and isolated thrombocytopenia associated with ticlopidine and clopidogrel have been published.[5] Since ticagrelor-associated thrombocytopenia was not yet well characterized, its clinical picture and mechanism of action were unclear. Our patient underwent percutaneous coronary intervention and stenting due to left main and triple vessel disease, and subsequent dual antiplatelet use, including aspirin and ticagrelor. Diffuse ecchymosis related to profound thrombocytopenia was observed after 2 weeks of exposure of ticagrelor, without the detection of gastrointestinal bleeding or intracranial bleeding. The patient's thrombocytopenia was successfully corrected by discontinuing ticagrelor and receiving a platelet transfusion. We added aspirin back to the regimen, and clopidogrel was added 10 days after the aspirin. No thromboembolic event occurred after discontinuing antiplatelet therapy. This experience showed that not only thienopyridine derivatives can induce severe thrombocytopenia, but also ticagrelor can result in profound and reversible isolated thrombocytopenia; it is possible that P2Y12 inhibitors share the same risk. Profound thrombocytopenia will resume after discontinue ticagrelor without additional treatment.

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