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CASE REPORT

Profound thrombocytopenia induced by clopidogrel with a prior history of long-term safe administration

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Abstract

Clopidogrel has shown an excellent safety, tolerability and efficacy ever since its marketing. However, here we report a rare case with profound thrombocytopenia following clopidogrel administration previously safely exposed to this same drug. This reminds us that thrombocytopenia might be induced by clopidogrel even with a prior, safe history of long-term administration.

Key words: Clopidogrel; Thrombocytopenia; Coronary artery disease; Stent

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INTRODUCTION

Clopidogrel, in combination with aspirin, is commonly used for the prevention of thrombosis in patients who have received coronary artery stents[1]. Moreover, it has shown an excellent safety, tolerability and efficacy since its marketing[2]. However, there have been cases of clopidogrel-associated serious adverse effects, including cases of thrombocytopenia and severe allergic reaction (including cutaneous reactions and angioedema)[3,4]. Here we report a rare case of thrombocytopenia induced by clopidogrel in a patient with a prior history of safe, long-term administration.

CASE REPORT

A 58-year-old male had a super-lateral wall myocardial infarction without revascularization on February 20, 2000. On November 26, 2002, he presented with an exertional angina pectoris, and coronary angiography showed a 95% stenosis of the left anterior descending artery (LAD), which was treated with a 3.5 mm × 24 mm of sirolimus-eluting Cypher coronary stent (Cordis Corporation, Warren, New Jersey) after an oral loading dose of 300 mg of clopidogrel (Co. sanofei Winthrop Industrie, France). After stenting, he received a daily dose of 75 mg of clopidogrel until November 30, 2003, with persistently normal laboratory tests, including platelet count, and without any other side effects.

He was referred to our department due to an acute super-lateral wall myocardial reinfarction on December

17, 2008. Emergent coronary angiography showed a total occlusion of the intermediate branch (IB), a 90% stenosis of the right coronary artery (RCA) and a patent LAD, with the Cypher stent. Thus, the lesion in the IB was treated with a balloon angioplasty, and, subsequently, a 2.5 mm × 18 mm Vision coronary stent (Guidant Corporation, USA) was implanted. At the time of stenting, coagulation function assays and the complete blood count were normal, with a platelet count of 207 × 10^9/L, a leukocyte count of 8.08 × 10^9/L and a neutrophil percentage of 59%. To prevent the thrombosis of the stent, an oral loading dose of 300 mg of aspirin and 300 mg of clopidogrel (Co. Sanofi Winthrop Industrie, France) were administered before the procedure, followed by a daily dose of 300 mg aspirin and 75 mg of clopidogrel. In addition, heparin and tirofiban were administered during and after the procedure, respectively. Additional drugs included atenolol, atorvastatin and nitrates. About 8 h after the intervention, the patient presented with a mid-high fever and the platelet count sharply dropped to 4 × 10^9/L without obvious bleeding and/or thrombosis. The platelet count was immediately repeated taking blood samples with citrate as the anticoagulant, in order to rule out EDTA-dependent pseudothrombocytopenia. However, values were confirmed at 4-6 × 10^9/L, accompanied by an increasing leukocyte count (14.31-15.81 × 10^9/L) and a neutrophil percentage of 95.7%-96.4%. Tirofiban was discontinued, while clopidogrel was maintained, due to its safe history of administration. Intravenous dexamethasone and promethazine, followed by platelet transfusion and high doses of human immunoglobulin, were started. The platelet count persisted very low, with a nadir count of 2 × 10^9/L and minor bleedings in the urinary and alimentary tract. Blood bilirubin and coagulation function assays remained normal and a bone marrow biopsy showed an actively proliferating marrow with increased megakaryocytes but no platelet-generated megakaryocytes. Thus, on the 4th d, clopidogrel was discontinued and replaced by cilostazol, 200 mg per day, orally. Then, the platelet count stably increased to > 50 × 10^9/L, without using platelet transfusions and/or human immunoglobulins. The highest platelet count, i.e. 319 × 10^9/L, was reached on the 12th d, together with a leukocyte count of 8.63 × 10^9/L and neutrophil percentage of 68.5%. Occult blood tests, carried out on urine and stool samples, were both negative again. The diagnosis of clopidogrel-associated thrombocytopenia was highly suspected and aspirin was subsequently resumed. The patient was discharged with a normal complete blood count, and placed on oral aspirin, 100 mg daily, and cilostazol, 200 mg daily, combined with atenolol, atorvastatin and nitrates.

The patient received another stenting procedure in his RCA and aspirin, 300 mg, plus cilostazol, 200 mg, per day, orally, on February 16, 2009. Four months later, the patient again complained of chest pain induced by strenuous exertion, and x-ray computerized tomography of the coronary arteries showed a 50% in-stent restenosis of both the IB and the RCA. In view of further, possible coronary intervention, and based on the previous safe history of clopidogrel administration, and after careful consideration, the patient took half a tablet of clopidogrel (37.5 mg). Just an hour later, he reported chills, followed by fever and, several hours later, he developed gingival bleeding, hemorrhagic spots and petechial purpura of both upper extremities. The platelet count dropped from 213 × 10^9/L to 6 × 10^9/L, while the leukocyte count increased from 6.45 × 10^9/L to 9.06 × 10^9/L and the neutrophil percentage from 57.9% to 93% within 6 h. The platelet count recovered promptly in 3 d upon clopidogrel withdrawal. No major adverse event occurred.

DISCUSSION

Thrombocytopenia is a rare but dangerous adverse effect of clopidogrel, encompassing thrombotic thrombocytopenic purpura (TTP), isolated thrombocytopenia and autoimmune thrombocytopenia[5-7]. The features of the present case included: (1) a 1-year safe history of clopidogrel administration; (2) two events of clopidogrel-associated thrombocytopenia without evidence of TTP; and (3) rapid drops of the platelet count accompanied by typical chills and fever. As of today, there have been reported only five cases of clopidogrel-induced thrombocytopenia without evidence of TTP. However, none of them had a safe history of clopidogrel administration and none had allergic manifestations at the time the platelet count dropped. The clinical manifestations reported in our case could not be completely explained by the clopidogrel-associated thrombocytopenia reported before[8]. Certainly, both episodes of thrombocytopenia were induced by clopidogrel, and the mechanism may be due to a rare but severe allergic reaction upon repeated exposure to clopidogrel. This suggests that clopidogrel may induce some sensitizing antibodies at the time of the first treatment. When clopidogrel was administrated for the second time, these antibodies led to thrombocytopenia. This problem may be solved by desensitization, should the allergic mechanism be demonstrated to be dependent on an IgE type of allergic reaction[9]. In this rare situation, clopidogrel can be effectively replaced, such as in our case, with cilostazol, an anti-platelet drug which is not of common use in the Western countries. Furthermore, the new generation anti-platelet drugs, such as ticagrelor and prasugrel, might also play a role[10-12].

To the best of our knowledge, this is the first case of potential sensitization-associated thrombocytopenia brought about by clopidogrel. Thrombocytopenia always poses a dilemma in the management of patients, especially those in whom stents were recently placed. Additionally, nearly every antiplatelet agent might induce thrombocytopenia, and this makes more complicated to decide which drug one should discontinue first[13]. The case we reported above reminds us that a rare, allergic thrombocytopenia might be induced by clopidogrel, even in patients with a prior history of safe, long-term administration.

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