Case Report

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Thrombocytopenia induced by both aspirin and clopidogrel in the same patient

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Key words
aspirin – clopidogrel – thrombocytopenia

Abstract. Aspirin and clopidogrel are used widely as antiplatelet agents due to their efficacy, safety, and tolerability. In rare cases, these agents can cause thrombotic thrombocytopenic purpura, but no report has documented severe thrombocytopenia in response to both drugs in the same patient. A 73-year-old female developed severe thrombocytopenia following treatment with clopidogrel. Platelet count recovered within 6 months of drug withdrawal without additional thrombopoietic therapies. Seven months after the last dose of clopidogrel, thrombocytopenia recurred on aspirin therapy. Again, platelet count rebounded gradually and independently. This case suggests that some patients who experience thrombocytopenia in response to one antiplatelet agent may react similarly to other antiplatelet agents.

Introduction

Antiplatelet medications are highly effective for the treatment and prevention of myocardial infarction, stent thrombosis, cerebrovascular accident, and other cardiovascular diseases [1]. Aspirin has been used as an anti-inflammatory drug for more than 100 years, and continues to be widely used in antiplatelet therapy because of easy administration and cost-effectiveness. Clopidogrel is a thienopyridine derivative with a mechanism of action similar to that of ticlopidine but with fewer hematological adverse effects. Like aspirin, clopidogrel has shown excellent safety, tolerability, and efficacy since its introduction. However, aspirin is well known for causing gastrointestinal upset and predisposing patients to gastrointestinal bleeding. Clopidogrel can cause diarrhea and rash, although it is less likely to cause gastrointestinal hemorrhage than aspirin. Both drugs may also cause thrombotic thrombocytopenic purpura (TTP) [2], but rarely lead to severe isolated thrombocytopenia. To the best of our knowledge, there are only four reports [3, 4, 5, 6] of clopidogrel-associated thrombocytopenia and three reports [7, 8, 9] of aspirin-associated thrombocytopenia. No case study has reported both aspirin- and clopidogrel-induced thrombocytopenia in the same patient.

Case description

A 73-year-old female with a history of hypertension (controlled with amlodipine, 5 mg/day) and Type 2 diabetes (controlled by insulin glargine, 8 U/day) presented with intermittent fever, dyspnea, and fatigue of 2 days' duration and was admitted to the respiratory department. Routine blood work at admission revealed a white blood cell (WBC) count of 30.1 × 10^9/l and a platelet (PLT) count of 53 × 10^9/l, while other values were within normal ranges or non-contributory. A chest CT scan revealed pathological changes in bronchia of both lungs, with the upper left and bilateral lower lungs showing signs of infection. Treatment included moxifloxacin (0.4 g q.d.) and ambroxol (30 mg b.i.d., i.v. drip). Routine blood work on Day 12 showed a WBC count of 4.0 × 10^9/l and a PLT count of 33 × 10^9/l. A physician in our hematology department recommended bone marrow examination to identify the cause of thrombocytopenia, but the patient's family refused such invasive examination considering her age. Hence, the hematologist suggested thrombocyte boost treatments. Recombinant

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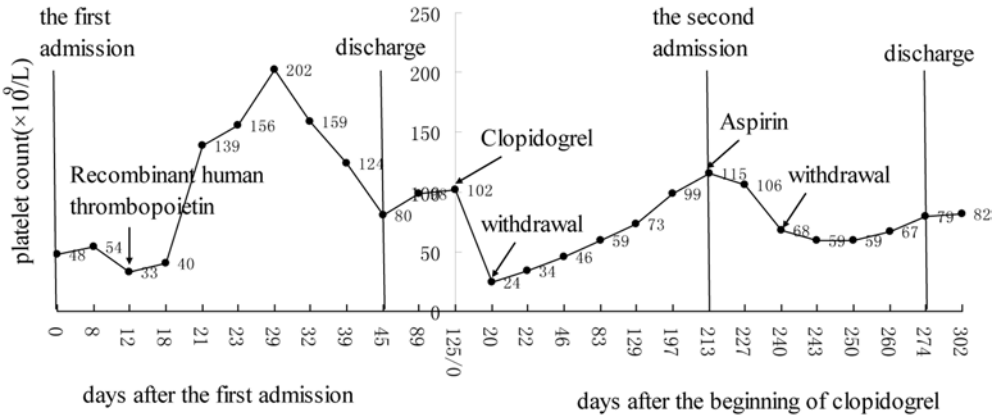

Figure 1. Platelet count over time in our case patient. The arrows mark the dates when recombinant human thrombopoietin, clopidogrel, and aspirin administration began.

human thrombopoietin was administered subcutaneously (15,000 units q.d.). On Day 13, however, the patient showed signs of cognitive dysfunction and a brain MRI scan indicated acute cerebral infarction. Given that platelet count was low, neurology staff discouraged use of antiplatelet agents. Citicoline (0.5 g q.d., i.v. drip), xueshuantong (0.5 g q.d., i.v. drip), and atorvastatin (20 mg q.n., oral) were prescribed. Platelet count increased significantly after seven consecutive days of thrombopoietic therapy. Routine blood work on Day 45 showed a WBC count of 4.2 × 10^9/l and a PLT count of 80 × 10^9/l. The patient had also regained pre-morbid mental faculties and was discharged with the advice to have her blood checked regularly. Platelet count on Day 45 after discharge was 100 × 10^9/l, and was still 102 × 10^9/l on Day 81. Clopidogrel (75 mg q.d.) was prescribed as a secondary prevention for stroke. Two weeks later, gum bleeding during tooth brushing was noted. Platelet count on Day 20 of clopidogrel therapy was 24 × 10^9/l, so use of clopidogrel was discontinued immediately. Platelet count rose slowly after drug withdrawal without thrombopoietic therapy and reached 99 × 10^9/l 6 months after clopidogrel discontinuation.

Approximately 6 months after clopidogrel withdrawal, the patient presented with a swallowing disorder, slurred speech, and left-side movement dysfunction of one day's duration and was admitted to the neurological department. A brain MRI scan indicated acute cerebral infarction in addition to pre-existing cerebral lesions. Magnetic resonance angiography showed arteriosclerotic stenosis of the carotid artery while routine blood analysis indicated a platelet count of 115 × 10^9/l. After the first discharge 7 months earlier, the patient's blood pressure was well controlled but not her blood glucose. Thus, insulin i.h. (Novolin 30R, 8 U/6 U b.i.d., glargine insulin 12 U qn) was administered in addition to citicoline (0.5 g q.d., i.v. drip), aspirin (0.1 g q.d., oral), atorvastatin (20 mg q.n., oral), and amlodipine (5 mg q.d., oral). After 2 weeks on aspirin, PLT count was 106 × 10^9/l, but fell to 68 × 10^9/l 27 days later, so aspirin was discontinued. Ten days after aspirin withdrawal, platelet count was still low (59 × 10^9/l). From then on, however, platelet count rebounded gradually and independently. Figure 1 shows changes in platelet count before and after the administration of these two antiplatelet agents. Given the slow rebound of PLT count, bone marrow examination was again recommended in order to investigate the possibility of a blood disorder. Of the 36 megakaryocytes examined by bone marrow cytology, 3 were promegakaryocytes, 30 were granular megakaryocytes, and only 3 were platelet-producing megakaryocytes, indicating that our patient suffered from a platelet production defect.

Discussion

There are at least three mechanisms for drug-induced thrombocytopenia (DITP): marrow suppression, immunological reactions, and nonimmunological thrombocytopenia [10]; but the exact mechanisms of clopidogrel- and aspirin-induced thrombocytopenia

remain unclear. The most widely accepted model for DITP postulates that pre-existing antibodies with low affinity to platelet epitopes are converted to high-affinity antibodies in the presence of an inducing drug [11]. Demonstration of drug-dependent anti-platelet antibodies is required to confirm this particular DITP etiology. However, because such testing is not widely available and requires substantial time, it is not feasible to wait for test results before deciding whether to discontinue a potential causative drug. Moreover, tests for drug-dependent antibodies can be negative in patients with probable DITP. George et al. [12] established several criteria for evaluation of DITP: (1) drug administration precedes thrombocytopenia, while recovery from thrombocytopenia is complete and sustained after drug withdrawal; (2) other drugs administered prior to thrombocytopenia are continued or reintroduced after discontinuation of the suspected drug; (3) other etiologies of thrombocytopenia are excluded; (4) re-exposure to the suspected drug results in recurrent thrombocytopenia.

In our patient, the platelet count measured during the first hospitalization for lung infection was lower than normal and rose after 1 week of thrombopoietic therapy. Regular blood tests over the 6 months after discharge revealed a maintained platelet count of around 100×10^9/l. Clopidogrel was administered after confirmation of normal platelet count, but 2 weeks later, bleeding was noted and platelet count was found to be lower than 30×10^9/l. Platelet count rose gradually after clopidogrel withdrawal. More than half a year after drug withdrawal, the patient was admitted again for cerebral infarction. On presentation, platelet count was normal and remained so for the first 2 weeks of aspirin therapy. Platelet count fell after 4 weeks, however, and remained low for the first 10 days after withdrawal of aspirin before rising again. Insulin, antihypertensive drugs, and lipid-decreasing drugs were also taken during aspirin and clopidogrel therapy and were not stopped after thrombocytopenia was diagnosed.

These clinical features fulfill the four conditions proposed to establish a causal link between DITP and the use of antiplatelet agents [12]. While it remains uncertain if thrombocytopenia after administration of antiplatelet agents was related to previous thrombocytopenia events, we believe the thrombocytopenia observed prior to antiplatelet drug administration (on first admission) was probably related to serious pulmonary infection. Indeed, Okoli et al. [13] reported a similar case in which a patient suffered immune thrombocytopenia caused by mycoplasma pneumonia infection.

In general, thrombocytopenia recovery usually begins within 1 – 2 days after the antiplatelet drug is discontinued, and recovery is usually complete within a week [11]. Our patient exhibited severe thrombocytopenia after 2 weeks of drug therapy and recovery was slow (taking months) after discontinuation. This slow recovery may stem from the persistence of drug-dependent antibodies as occurs in quinine-induced thrombocytopenia. In such cases, patients are advised to avoid the drug that caused thrombocytopenia. Alternatively, platelet production may be compromised, as was likely the case in our patient based on bone marrow cytology.

Patients taking an antiplatelet agent should be monitored carefully for hematological adverse effects, especially in the first 3 months of therapy. Early recognition and prompt initiation of treatment can be lifesaving in patients exhibiting hematological adverse effects of antiplatelet agents [14]. However, Nannucci et al. [7] reported a case of stroke recurrence following aspirin discontinuation due to severe auto-immune thrombocytopenia. Their case raises the question of whether discontinuation of the antiplatelet agent contributed to stroke recurrence in our patient. How to best manage antiplatelet therapy in patients at risk of both stroke and DITP is a clinical question that warrants further study.

Conclusion

This case suggests that patients afflicted by thrombocytopenia after taking an antiplatelet agent may react similarly to other antiplatelet agents. Such patients should be closely monitored both during treatment and for a significant period after drug withdrawal.

Conflicts of interest

None.

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