Case reports

Delayed profound thrombocytopenia after abciximab administration for coronary stenting in acute coronary syndrome. Case reports and review of the literature

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Profound thrombocytopenia occurring 1 week after drug administration is a seldom described, self-limiting and mostly uneventful immune reaction to abciximab. Quick differential diagnosis is essential, since other forms of thrombocytopenia associated with concomitant antithrombotic therapies may be much more severe and require prompt treatment. Awareness of this reaction may avoid unnecessary and risky discontinuation of other antiplatelet therapies in the critical phase after coronary stenting.

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Abciximab is a chimeric antibody fragment which inhibits platelet aggregation by blocking fibrinogen binding to the glycoprotein (GP) IIb/IIIa receptor. Its use in clinical practice has been approved to prevent ischemic complications during percutaneous coronary intervention, particularly in high-risk acute coronary syndromes[1]. Thrombocytopenia is the most severe side effect after abciximab administration, typically occurring within 96 hours, and should be specifically looked for by checking blood platelet counts 4 and 24 hours after the start of therapy. The incidence of this potentially severe complication among several thousands of patients enrolled in randomized clinical trials has been shown to be 2.4 to 4.2% if defined as platelet counts < 100 000/μl, or 1% if defined as < 50 000/μl[2-7]. A much less frequently described side effect is delayed profound abciximab-induced thrombocytopenia[8-13]. We describe two of such cases and discuss the potential implications for patient management.

Description of cases

Case 1. A 47-year-old man was admitted to our department due to an acute non-ST-elevation myocardial infarction with lateral negative T waves on the admission ECG. The echocardiogram revealed hypokinesia of the lateral and inferior segments of the left ventricle with normal ejection fraction. The patient's history included diabetes mellitus, obesity, hypertension, cigarette smoking, hypercholesterolemia, hyperhomocysteinemia, and mild renal failure. He had not received abciximab prior to the present episode. Initial antithrombotic therapy included aspirin, clopidogrel (300 mg loading dose, followed by 75 mg daily) and subcutaneous enoxaparin 8000 U bid. The baseline platelet count was 233 000/μl. Coronary angiography was performed 2 days after admission and showed multivessel disease with a thrombus image in the right coronary artery. Abciximab was administered after angiography as 0.25 mg/kg bolus followed by an infusion of 0.125 μg/kg/min for 12 hours. The lesion in the right coronary artery was treated by angioplasty with placement of a bare metal stent, and a critical lesion in the mid left anterior descending coronary artery was covered by a paclitaxel-eluting stent. Platelet counts at 6 and 24 hours after abciximab administration were 190 000/μl and 203 000/μl, respectively. Following angioplasty, the patient was treated with aspirin 100 mg/day, clopidogrel 75 mg/day, and enoxaparin 4000 U bid. Hospitalization was prolonged due to unstable glycemic control. Seven days after angioplasty, the patient developed acute thrombocytopenia (platelet

count 76 000/μl) with further decrease on day 8 (platelet count 24 000/μl). Pseudothrombocytopenia was excluded by the low platelet counts obtained in three separate tubes with different anticoagulants (EDTA, citrate, lithium heparin). A peripheral smear was performed and no schistocytes were seen. The patient tested negative for heparin-induced thrombocytopenia (HIT) by the heparin-induced platelet antibody enzyme-linked immunoabsorbent assay test. Aspirin and clopidogrel were discontinued. No bleeding occurred, so no platelet transfusion was administered. Platelet counts started to raise on day 9, were 119 000/μl on day 12, at which time clopidogrel was restored. On day 13 after abciximab treatment (platelet count 170 000/μl) aspirin was newly administered. The patient was discharged home on day 20. The platelet count was 243 000/μl. No drop in hemoglobin concentration was observed.

Case 2. A 53-year-old man with type 2 diabetes mellitus was admitted to our emergency room 1 hour after the beginning of chest pain, due to an acute coronary syndrome with transient ST-segment elevation in the inferior leads. Before transfer to the coronary care unit, he had a coronary angiography performed showing critical stenoses on the right (culprit) and circumflex coronary arteries. After heparin and abciximab boluses, both lesions were treated by angioplasty and bare metal stents, and abciximab infusion was continued for the next 12 hours. Ticlopidine and aspirin were administered throughout the hospital stay and at discharge, on day 5 after admission. No complications occurred after angioplasty, with peak creatine kinase-MB of 23 μg/l 11 hours after symptom onset, no drop in hemoglobin concentration (13.4 g/dl upon admission and 14.1 g/dl at discharge) and in platelet count (196 000/μl upon admission and 193 000/μl at discharge). On day 8 after the index episode, the patient was admitted to the Division of Allergology due to a presumably allergic erythema. His platelet count was 20 000/μl, with normal hemoglobin and white blood cell count. No ischemic or bleeding episodes occurred. The attending physician withdrew aspirin and ticlopidine and asked for hematologic consultancy which ruled out HIT or ticlopidine-related thrombocytopenia following the same methodology as in case 1, and advised to administer prednisone, restart aspirin and substitute clopidogrel for ticlopidine which was deemed responsible for the skin reaction. As shown in figure 1, the platelet count started to increase on day 9 and on the following days, up to a value of 140 000/μl at discharge on day 14 from the index episode, without any clinical complication.

Discussion

Thrombocytopenia (platelet counts < 100 000/μl) after abciximab administration has been reported in 2.4 to 4.2% of the cases, and severe thrombocytopenia (< 50 000/μl) in 1% of the cases[2-7]. The incidence and clinical severity of this complication has been reliably assessed in controlled clinical trials involving thousands of patients with acute coronary syndromes or undergoing coronary angioplasty. Factors favoring its detection in clinical practice were its recognition in the early clinical trials with abciximab[2,3] and the fact that it becomes manifest most often within 96 hours after the start of therapy, when patients are still under strict clin-

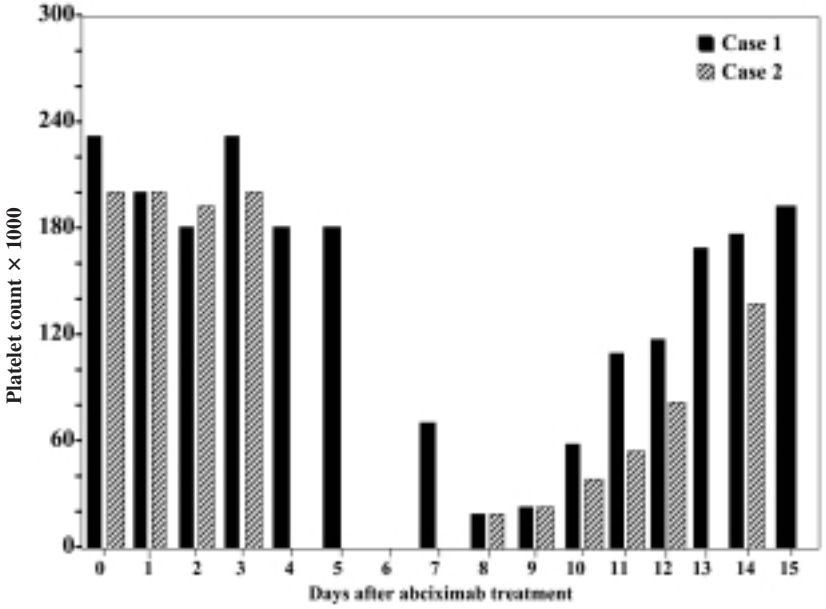

Figure 1. *Serial platelet counts after abciximab administration in the 2 patients. Day 0 is the day of abciximab administration. The first value reported is the pre-treatment value.*

ical and laboratory monitoring. In most cases, this early form of thrombcytopenia is benign, the nadir platelet count being typically about 75 000/μl, although occasional cases of acute profound thrombocytopenia (< 20 000/μl) requiring platelet transfusion have been reported. Case fatality has been reported to be 2% mainly due to ischemic events[7]. The underlying pathomechanism is poorly understood, though the most frequently discussed is an autoimmune cross-reaction of preexisting antiplatelet antibodies with cryptogenic epitopes on the platelet surface made available by conformational changes triggered by the binding of the GP IIb/IIIa blocker to its receptor (so called ligand-induced binding sites or LIBS)[14,15].

Only a few cases of delayed profound thrombocytopenia have been reported[8-13], with only two case series also studying the development of specific drug-induced antibodies and published in hematology journals[12,13]. Delayed thrombocytopenia is not even reported in the ReoPro package leaflet, so that most clinical cardiologists are unaware of its existence. The actual incidence of this form is unknown, since this event is more likely to occur after hospital discharge, and even the cases described here were discovered since the patients had an intercurrent illness requiring prolongation of hospital stay (case 1) or an early rehospitalization due to an allergic reaction to ticlopidine (case 2). In both our cases, as in previous reports, the nadir platelet count was 20 000/μl between day 8 and 9 with a spontaneous and uneventful recovery within a few days. The mechanism behind delayed thrombocytopenia is unclear, although the most likely explanation is the development of drug-induced antibodies against the abciximab-platelet complex[12,13]. Abciximab binds to GP IIb/IIIa with high affinity and can be detected on circulating platelets for up to 2 weeks after its administration. Persistence of the drug would offer the opportunity to develop a humoral immune response against sensitized platelets. Two studies report the presence of this kind of IgG and IgM antibodies in patients who develop thrombocytopenia[12,13]. The binding of immune complexes to platelets will enhance clearance by the reticuloendothelial system and the spleen. Another possibility is that immunoglobulins could recognize neoepitopes expressed on the platelet surface after the drug has bound (once again, a LIBS mechanism as in the case of early thrombocytopenia).

Despite the profound degree of thrombocytopenia described in most reported cases[8-13] as well as in the present two, the course of delayed thrombocytopenia is self-limiting, with full recovery of platelet counts within 1 week. Most cases, as ours, were uneventful, although gastrointestinal or nose bleeding, petechial ecchymoses and oozing from venipuncture sites have been reported. Nevertheless, its recognition may be important due to potential clinical implications. Although the majority of the cases are probably unrecognized or found by chance, as it was in our cases, the clinical suspicion must arise when, a few days after abciximab administration, a patient develops petechial ecchymoses or even mild gastrointestinal or nose bleeding. If the platelet count is < 100 000/μl, further platelet counts should be performed in three tubes (EDTA, citrate, heparin) in order to rule out pseudothrombocytopenia. The failure to differentiate this form, which has been shown to be the cause of 36% of all low platelet counts in abciximab-treated patients and is not associated with any clinical event[15], could lead to the interruption of concomitant antiplatelet therapies, to unnecessary platelet transfusion, and expose to the risk of thrombotic events. If true thrombocytopenia is confirmed, further differential diagnosis includes disseminated intravascular coagulation and thrombotic thrombocytopenic purpura (TTP). Normal coagulation tests, absence of schistocytes on the peripheral smear and a normal baseline platelet count before abciximab administration can exclude these diagnoses. Acute thrombocytopenia may also be caused by other antithrombotic drugs commonly associated with abciximab[16]. HIT occurs in 2-3% of the cases and typically 1 to 5 days (HIT type 1) or after 5 days (HIT type 2) following heparin administration. HIT-1 is caused by a direct platelet-aggregating effect of heparin and is relatively benign, whereas HIT-2 is a rare disorder which is related to the presence of autoantibodies against the platelet factor 4-heparin complex, with platelet counts falling to < 50 000/μl. Antiplatelet factor 4 antibodies should be measured to exclude this potentially fatal form often associated with venous and arterial thrombosis. Ticlopidine and clopidogrel may rarely cause TTP too. About 100 cases have been reported with ticlopidine[17]. Ten to 20% of the cases develop within 2 weeks of drug exposure, an additional 20% between weeks 3 and 4, and approximately 80% by 12 weeks. Importantly, the onset may be delayed for several days after discontinuation of ticlopidine. Also, 11 cases of TTP have been reported after only 2 weeks of clopidogrel administration (one case after 3 days)[18]. Thienopyridine-induced TTP is not associated with drug-induced platelet-reactive antibodies, but it involves microangiopathic hemolytic anemia, renal failure, and mental status abnormalities so it can be easily distinguished[19].

Treatment of delayed thrombocytopenia is often unnecessary, particularly if the patient is not bleeding. Platelet counts respond promptly to platelet transfusion, which is recommended if platelet counts fall < 20 000/μl, or < 50 000/μl in presence of active bleeding. Except in the case of gastrointestinal bleeding, aspirin and clopidogrel, which are crucial in preventing stent thrombosis, should not be discontinued. It should be remembered that, contrary to common sense, the most severe risk of drug-induced thrombocytopenia is not bleeding but thrombosis: this is well known for HIT[19], but it probably applies also to the early[7] and delayed[8,13] abciximab-induced forms. The mechanism of prothrombosis associated with abciximab-induced thrombocy-

Table I. Differential characteristics of thrombocytopenia associated with antithrombotic drugs following percutaneous coronary intervention/stenting.

	Thienopyridine (ticlopidine, clopidogrel)	GP IIb/IIIa blocker (abciximab)	Heparin (mostly UFH)
Onset	2-12 weeks	Early: within 12 hours Delayed: 8 days	5 to 14 days. Rapid onset may occur (within hours)
Extent (platelet count)	Severe (< 20 000)	Early: mostly moderate (50-75 000), occasionally < 20 000 Delayed: severe (< 20 000)	Moderate (40-70 000)
Bleeding	Possible	Possible (gastrointestinal, gingival, nose)	No
Thrombosis	Thrombotic thrombocytopenic purpura	Thrombosis less likely, possibly related to discontinuation of ASA and thienopyridine	Severe/fatal thrombosis more likely
Diagnosis	Fever, renal failure, neurological changes Associated low RBC-WBC count Blood smear	Petechiae Normal RBC-WBC count Normal blood smear. No anti-PF4 antibodies	Venous or arterial thrombosis Anti-PF4 antibodies (very sensitive, non-specific, excellent for rule out)
Outcome if untreated	50-60% mortality 15-20% mortality if treated by plasmapheresis	Mostly benign and self-limiting	Death 20% Thrombosis 20-50% Amputation 20%
Treatment	Corticosteroids and plasmapheresis	Only in case of bleeding: platelet transfusion Continue thienopyridine	Direct thrombin inhibitors (argatroban, bivalirudin, lepirudin) Fondaparinux *Combine* with coumadin

ASA = acetylsalicylic acid; GP = glycoprotein; PF4 = platelet factor 4; RBC = red blood cells; UFH = unfractionated heparin; WBC = white blood cells.

topenia is still unclear[13], but in the case of the early form it has been postulated that discontinuation of other antithrombotic therapy may be responsible, at least in part, for the subsequent ischemic events. Since patients with delayed thrombocytopenia will have almost invariably received a coronary stent 1 week earlier, we think that knowledge of the generally benign course of this drug reaction is essential in order to avoid the mistake of withdrawing aspirin and ticlopidine or clopidogrel.

Abciximab should not be readministered to patients who have developed thrombocytopenia after the first exposure; a good alternative therapy could be another GP IIb/IIIa inhibitor, which has been successfully administered without any platelet decrease in patients with history of abciximab-induced thrombocytopenia[20,21].

In summary, profound thrombocytopenia occurring 1 week after drug administration is a seldom described, self-limiting and mostly uneventful immune reaction to abciximab. Quick differential diagnosis, as reported in table I, is essential since other forms of thrombocytopenia associated with concomitant antithrombotic therapies may be much more severe and require prompt treatment. Awareness of this reaction may avoid unnecessary and risky discontinuation of other antiplatelet therapies in the critical phase after coronary stenting.

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