Thrombocytopenia and purpura-like lesions associated with clopidogrel

Carlo Briguori, Fiore Manganelli, Marco Picardi*, Bruno Villari, Bruno Ricciardelli

*Laboratory of Interventional Cardiology and Department of Cardiology, Clinica Mediterranea, *Department of Hematology, "Federico II" University of Naples, Naples, Italy*

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We report a case of moderate thrombocytopenia associated with purpura-like phenomenon (four ecchymoses) that occurred within 72 hours of clopidogrel initiation and resolved promptly with drug withdrawal. This 61-year-old patient previously experienced an adverse skin reaction to ticlopidine without changes in the platelet count and without any other laboratory abnormalities. Since the introduction of clopidogrel instead of ticlopidine for the prevention or treatment of several cardiovascular diseases, only 11 cases of thrombotic thrombocytopenic purpura among more than 3 million individuals treated with clopidogrel have been reported. Recently, a case of severe thrombocytopenia, without concomitant purpura-like lesions, during therapy with clopidogrel has been described. To our knowledge, this is the first case of thrombocytopenia associated with purpura-like lesions with no evidence of thrombotic thrombocytopenic purpura during clopidogrel treatment.

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Address:

Dr. Carlo Briguori

Laboratorio di Cardiologia Interventistica
Clinica Mediterranea
Via Orazio, 2
80121 Napoli
E-mail:
cabrig@hotmail.com

Ticlopidine and clopidogrel, two antiplatelet drugs, are structurally related derivatives of thienopyridine. They inhibit the activation of the glycoprotein IIb/IIIa complex by blocking an adenosine diphosphate receptor. Besides the more common skin and gastrointestinal adverse effects, agranulocytosis and thrombotic thrombocytopenic purpura (TTP) are serious adverse reactions to ticlopidine. The ticlopidine-associated TTP has been reported with an estimated incidence of at least 1 case per 5000 patients treated and with a mortality rate of 33%[1,2]. Clopidogrel has been approved recently and has rapidly replaced ticlopidine for the prevention of ischemic events (stroke, myocardial infarction, vascular death) because it has a more favorable safety profile and a better overall tolerability. More than 3.7 million people have received clopidogrel during the 2 years since it has become available and only 11 cases of TTP were identified during worldwide post-marketing surveillance of the drug[3]. Furthermore, to our knowledge, there is only one report of a severe thrombocytopenia associated with clopidogrel administration[4]. We report a case of moderate thrombocytopenia associated with purpura-like phenomenon that occurred within 72 hours of clopidogrel initiation and resolved promptly with drug withdrawal. Interestingly, this patient previously experienced an adverse skin reaction to ticlopidine without a change in platelet count or any other laboratory abnormalities.

Case report

On February 26, 2000, a 61-year-old patient with a sustained ventricular tachycardia that occurred during a stress ECG performed according to the Bruce protocol was admitted to our coronary care unit. The patient had a long-standing history of hypertension, dyslipidemia and a previous (May 1998) inferior myocardial infarction. In June 1998, he underwent coronary angiography for recurrent ischemia and then coronary artery bypass graft surgery (left and right internal mammary arteries anastomosed to the left anterior descending artery and right coronary artery respectively).

At the time of admission, the patient had a normal blood count and a platelet count of $211*10^9$/l. Two days later, he underwent coronary angiography showing patency of the left internal mammary artery, total occlusion in the proximal segment of the right internal mammary artery, and a critical (90% in diameter), type B2 lesion in the proximal right coronary artery (deemed as the culprit lesion). Three days before the planned percutaneous transluminal coronary angioplasty on the culprit lesion, the blood count was still normal and antiplatelet therapy with ticlopidine (250 mg twice daily) was started.

After 2 days, an itchy skin rash appeared on the patient's arms and thorax and a repeat blood count revealed normal white cell ($8.3*10^9$/l) and platelet ($209*10^9$/l) counts. Three days later, in view of the fact that the skin rash persisted, ticlopidine was stopped and the allergic reaction progressively resolved; the platelet count was still normal ($198*10^9$/l). On March 7, a balloon angioplasty was successfully performed on the lesion in the proximal right coronary artery and the patient was discharged home on aspirin (325 mg daily). Before starting the procedure, unfractionated heparin (70 IU/kg i.v.) was administered. Three months later, he was again admitted to our hospital because of the recurrence of angina (unstable angina class IIB according to Braunwald's classification). Urgent coronary angiography showed a critical (90% in diameter) restenosis in the proximal right coronary artery that was treated with stent implantation (S670 Medtronic Ave, Santa Rosa, CA, USA; 3.5 mm in diameter, 16 mm in length). The final result was satisfactory (residual stenosis < 10%, and TIMI flow 3). The day before the procedure, aspirin alone (325 mg) was administered. Before starting the procedure, the patient was given unfractionated heparin (70 IU/kg i.v.) and abciximab (bolus, 0.25 γ/kg i.v.). After the procedure, abciximab infusion (0.150 γ/kg/min i.v. for 12 hours) and clopidogrel (loading dose 300 mg *per os*) were administered. The patient had a normal baseline platelet count at the time of admission ($220*10^9$/l) and 48 hours after the procedure ($190*10^9$/l) when he was discharged on aspirin (160 mg daily) and clopidogrel (75 mg daily). Three days later, the patient presented with four ecchymoses, the largest on the medial surface of his left thigh ("purpura-like" lesions) (Fig. 1A). A blood count revealed moderate thrombocytopenia (71 000/mm^3). In order to exclude pseudothrombocytopenia, this result was confirmed by a repeat platelet count in another anticoagulant (citrate). Furthermore, platelet clumping was not evident on a blood smear of anticoagulated blood[5]. Laboratory findings showed a normal hemoglobin level, normal white blood cell counts and normal liver and renal function tests. The fibrinogen level, prothrombin time, and partial thromboplastin time were within normal limits. Clinical evaluation was not suggestive of splenomegaly. Moreover, the patient had no fever or neurological symptoms. Clopidogrel was promptly discontinued and blood counts performed 48 and 96 hours later revealed a rise in the platelet count (103 $000*10^9$/l) and a normalization (142 $000*10^9$/l), respectively (Fig. 1B). During the following days, the purpura-like lesions progressively disappeared and regular monitoring of the platelet count ruled out recurrence of thrombocytopenia.

Discussion

To our knowledge, this is the first case of thrombocytopenia associated with purpura-like phenomenon and with no evidence of TTP during clopidogrel treatment[3,4]. An interesting feature is that our patient had previously experienced an adverse skin reaction to ticlopidine without a change in platelet count or any other laboratory abnormalities. Since clopidogrel and ticlopidine are similar molecules, it is possible that the pathogenetic mechanism of TTP was similar in both cases. In fact, immunoglobulin inhibitors of the von Willebrand factor-cleaving protease activity were detectable in 2 patients with TTP following the use of clopidogrel, a finding that resolved in one individual[3].

Our patient had a normal baseline platelet count before heparin, abciximab, and clopidogrel treatment. Splenomegaly was not detected, nor was any abnormality noted in a peripheral blood smear (e.g. clumping of platelets, schistocytes), in serum creatinine, lactic dehydrogenase and fibrinogen levels or in red and white blood cell counts to suggest TTP.

Except for heparin and abciximab, the patient did not receive any other drug likely to induce thrombocytopenia. Thrombocytopenia is a well-recognized complication of heparin therapy[6,7]. In our patient, no drop in the normal baseline platelet count was noted during heparin therapy. In fact, he developed thrombocytopenia after cessation of heparin and, therefore, he was not

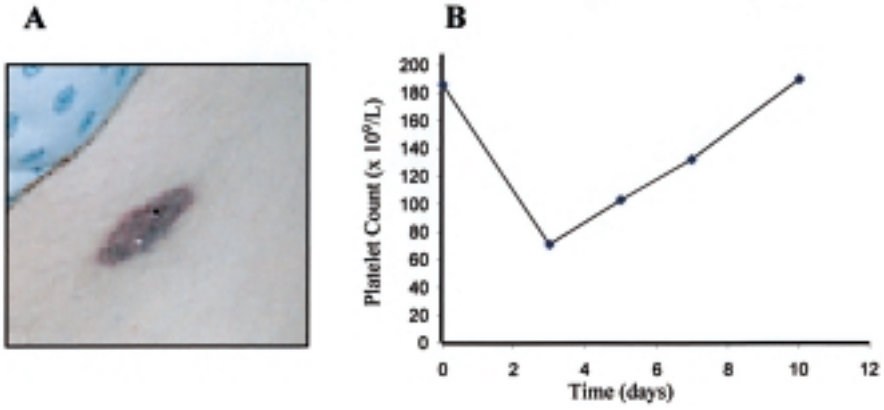

Figure 1. A: *ecchymoses on the medial surface of the left thigh.* B: *time sequence of platelet count in our patient. Day 0 refers to when he was discharged on clopidogrel (75 mg daily) and aspirin (160 mg daily) 48 hours after the percutaneous intervention and the loading dose of clopidogrel (300 mg).*

tested for heparin-dependent antibodies. Our patient had a normal platelet count at baseline and for at least 72 hours following abciximab administration. The lack of a temporal correlation between thrombocytopenia and abciximab administration and the rapid recovery in the platelet count rendered abciximab an unlikely cause of delayed thrombocytopenia in our patient.

Clopidogrel and thrombocytopenia. Few data exist about the occurrence of thrombocytopenia associated with clopidogrel[8-10]. In the CLASSICS trial, moderate thrombocytopenia (between 50 and $70*10^9$/l) occurred in 0.6% of cases[9]. In the CAPRIE trial[8] the rate of severe thrombocytopenia (< $50*10^9$/l) was 0.19% for clopidogrel vs 0.10% for aspirin. Rare cases of aplastic anemia have been reported[11]. Elmi et al.[4] have recently reported a case of severe (< $20*10^9$/l) thrombocytopenia associated with clopidogrel and treated with suspension of the drug and immunoglobulin G administration. Recently, Bennett et al.[3] reported 11 cases of TTP among more than 3 million individuals treated with clopidogrel. Ten of the 11 patients responded to plasma exchange, but 2 required 20 or more exchanges before resolution of the adverse reaction.

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