Case report

Profound drug-induced thrombocytopenia before urgent cardiopulmonary bypass

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Abstract

A patient with acute coronary syndrome scheduled for urgent coronary artery bypass grafting developed a profound thrombocytopenia during therapy with intravenous heparin and the glycoprotein IIb/IIIa inhibitor tirofiban. Heparin-induced thrombocytopenia and all other possible aetiologies were unlikely and the low platelet count had to be attributed to tirofiban. Anticoagulation during cardiopulmonary bypass was successfully managed with standard heparin. Implications for the diagnosis of coagulation disorders and the management of perioperative anticoagulation are discussed. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The incidence of glycoprotein IIb/IIIa inhibitor-related thrombocytopenia is low compared to heparin-induced thrombocytopenia (HIT) [1,2]. However, treatment of acute coronary syndrome includes currently both heparin and a glycoprotein IIb/IIIa inhibitor in many cases. Emergency cardiopulmonary bypass grafting is often required in these patients. A low platelet count in this situation particularly challenges the perioperative management of anticoagulation.

2. Case report

A 52-year-old patient presented with acute coronary syndrome (antero-lateral ST-segment depressions in the electrocardiogram, negative laboratory tests for myocardial necrosis). Initial platelet count was $191 \times 10^3 \text{\mu L}^{-1}$. Subsequent therapy included intravenous nitroglycerin 2 mg h$^{-1}$, oral metoprolol 100 mg day$^{-1}$, subcutaneous low molecular weight heparin 0.6 ml day$^{-1}$, subcutaneous low molecular weight heparin 0.6 ml day$^{-1}$, intravenous tirofiban 0.4 mg h$^{-1}$ and oral acetylsalicylic acid 100 mg day$^{-1}$. Cardiac catheterization revealed a severe multi-vessel disease. The patient was scheduled for coronary artery bypass grafting (CABG) and an intra-aortic balloon pump (IABP) was inserted. An infusion with heparin 1000 units h$^{-1}$ was started and tirofiban therapy continued. Three hours later, platelet count was $16 \times 10^3 \text{\mu L}^{-1}$. Microscopic examination of an EDTA-blood sample did not reveal platelet aggregation. In exchange for heparin and tirofiban therapy, hirudin 0.2 mg h$^{-1}$ was started suspecting heparin-induced thrombocytopenia (HIT II). The nadir of $9 \times 10^3 \text{\mu L}^{-1}$ platelets was reached 6 h later. Twelve units of platelets were transfused, and the platelet count increased to $40 \times 10^3 \text{\mu L}^{-1}$ immediately and to $112 \times 10^3 \text{\mu L}^{-1}$ in the next 36 h (Fig. 1). Bleeding or thrombo-embolic complications did not occur. Heparin-platelet factor 4 antibodies could not be found and empiric heparin exposition (5000 units i.v.) did not reveal a platelet decrease. Cardiopulmonary bypass (CPB) in moderate hypothermia (32°C) was thus performed under conventional anticoagulation with heparin. Anaesthesia and CABG were uneventful, IABP therapy was stopped 6 h after CPB. Intraoperative blood loss was 1800 ml. Two units of fresh frozen plasma and 12 units of platelets were given. Postoperative platelet count was $80 \times 10^3 \text{\mu L}^{-1} 6$ h after CPB and recovered to normal values during the following 2 days. Oral acetylsalicylic acid 200 mg day$^{-1}$ was initiated again. The patient recovered well and was dismissed from the intensive care unit on the second postoperative day.
3. Discussion

Suspecting a glycoprotein IIb/IIIa-related profound thrombocytopenia during intravenous heparin therapy the more common and potentially harmful diagnoses and causes for thrombocytopenia, primarily pseudo-thrombocytopenia and HIT, have to be ruled out at first [2]. In our patient, pseudo-thrombocytopenia was excluded by a normal microscopic examination of the EDTA blood sample. Assuming a HIT the anticoagulation regime was changed to hirudin. HIT Type I usually causes only a mild asymptomatic thrombocytopenia early in the course of heparin therapy. HIT Type II, on the other hand, has a delayed onset and a severe thrombocytopenia is typical. Based on its immunologic aetiology, anti-PF4 antibodies are predominantly expressed [1]. However, in 5–10% of patients other platelet antigens may be responsible for the development of thrombocytopenia and anti-PF4 antibodies cannot be found. Specific antigenic or functional tests (fluorescence-linked immunofiltration assay, heparin-induced platelet-aggregation assay) are necessary for diagnosis [3]. These tests are not suitable in an emergency situation, because they require time-consuming pre-analytical procedures and are available at specialized institutions only, but may confirm the diagnosis later on.

In our patient however, thrombocytopenia developed 48 h after the first administration of heparin. Anti-PF4 antibodies could not be found. A heparin re-exposition during the application of hirudin for ruling out the remaining probability of HIT showed a negative result. However, if performed during direct thrombin inhibitor therapy, this test has its limitations. Furthermore, acetylsalicylic acid could induce thrombocytopenia, but platelet count normalized during continued application.

Also, IABP therapy may cause thrombocytopenia, yet platelets increased during pump support. Other causes for thrombocytopenia were very unlikely in our previously healthy patient.

Therefore, finally, we assumed the profound platelet decrease in our patient to be tirofiban-associated. Acute idiosyncratic or delayed immune-mediated reactions to tirofiban are possible mechanisms of induction of platelet destruction. Differences in incidence and aetiology may be attributed to the different properties of glycoprotein IIb/IIIa inhibitors [4]. The differentiation between glycoprotein IIb/IIIa inhibitor and HIT II is most important regarding anti-
coagulation for cardiopulmonary bypass. Anticoagulation procedures other than clinical routine are prone to errors and complications, predominantly if applied on an emergency basis. In case of HIT II, anticoagulation may be performed applying the thrombin inhibitor recombinant hirudin [1,5]. However, severe perioperative bleeding associated with hirudin has been described [5]. No antidote is available [3] and a specific anticoagulation monitoring system (whole blood ecarin clotting time) is required [6]. Alternative methods would be the application of the thrombin inhibitor lepirudin or the factor Xa-inhibitor danaproid sodium. However, the incidence of bleeding is increased during the use of these two drugs [7]. Recently, tirofiban pre-treatment for anticoagulation with heparin has been successfully used in a considerable number of patients with HIT II without increased incidence of bleeding [3]. The concept is based on the inhibition of the glycoprotein IIb/IIIa receptor by tirofiban during application of the antigenic heparin [3,8]. It offers the advantages of conventional anticoagulation monitoring by activated clotting time and of reversal of anticoagulation by protamine. In our patient, however, this management might have been fatal since thrombocytopenia was very likely to be tirofiban- rather than heparin-associated.

In summary, perioperative management of a potential glycoprotein IIb/IIIa inhibitor-related thrombocytopenia is complex and should be based on confirmation or exclusion of the most common aetiologies, mainly HIT.

References