

## Abciximab (ReoPro)-Induced Thrombocytopenia Diagnosed Through Measurement of Heparin-Dependent Antibody

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### ABSTRACT

Abciximab (ReoPro) is an extremely potent inhibitor of the glycoprotein IIb/IIIa receptor. Its main application is in the maintenance of coronary flow after suboptimal coronary intervention. Complications associated with this drug include bleeding and severe thrombocytopenia. We report a case of severe thrombocytopenia secondary to abciximab therapy for percutaneous coronary intervention in a 65-year-old woman suffering from an acute myocardial infarction. Her platelet count dropped to  $1,000/\text{mm}^3$  7 hours after abciximab administration and improved with transfusion of 12 units of platelet concentrate the following day. The patient was diagnosed through measurement of heparin-dependent antibodies and readministration of heparin. (*Korean Circ J* 2009;39:75-78)

**KEY WORDS:** Abciximab; Thrombocytopenia.

### Introduction

Abciximab is a potent inhibitor of the glycoprotein (GP) IIb/IIIa receptor. This agent binds to the platelet GP IIb/IIIa receptor and inhibits platelet aggregation by preventing binding of von Willebrand factor and fibrinogen to platelets.<sup>1)</sup> Abciximab has emerged as a key agent for improving clinical outcomes in high-risk patients undergoing percutaneous coronary interventions (PCI).<sup>2)</sup>

However, increased use of abciximab has led to increase incidence of hemorrhagic complications; specifically, acute profound thrombocytopenia (platelet count  $<20,000/\text{mm}^3$ ) can occur after abciximab administration.<sup>3,4)</sup> The development of this complication is not predictable, and caution should be exercised in every patient treated with abciximab.

We report a case of acute profound thrombocytopenia, confirmed by measurement of heparin-dependent antibody and heparin readministration. The patient's platelet count fell to  $<1,000/\text{mm}^3$  after abciximab administration.

### Case

A 65-year-old woman with a history of smoking and hypertension presented to our hospital with a 5-hour history of severe chest pain. Her blood pressure was 110/70 mmHg, and her pulse rate was 70 beats per minute. Her electrocardiogram revealed ST segment elevation in leads II, III, and aVF and reciprocal changes in leads I, aVL, and V1-V5 (Fig. 1). Twenty minutes after presentation, her systolic blood pressure dropped to 50 mmHg; electrocardiography revealed ventricular fibrillation. We defibrillated the patient with 300 J and performed cardiopulmonary cerebral resuscitation (CPCR). After her rhythm recovered to normal sinus rhythm, she underwent primary coronary angioplasty. Initial laboratory findings were as follows: white blood cell count  $6,840/\text{mm}^3$ , hemoglobin level 12.3 g/dL, platelet count  $154,000/\text{mm}^3$ , creatine kinase (CK) 64 U/L, troponin-I 0 ng/mL, and D-dimer 0.4  $\mu\text{g/mL}$ . The patient was given aspirin 100 mg, clopidogrel 300 mg, and heparin 5,000 IU bolus followed by 600 IU/hour. Cardiac catheterization demonstrated total occlusion of the mid-portion of the right coronary artery (RCA), 95% stenosis of the left anterior descending coronary artery, and 95% narrowing of the left circumflex coronary artery (Fig. 2A). The RCA lesion was treated with balloon angioplasty, and abciximab (10 mg) and heparin (2,000 IU) were given directly into the RCA (Fig. 2B). After PCI, the patient was transferred to the intensive

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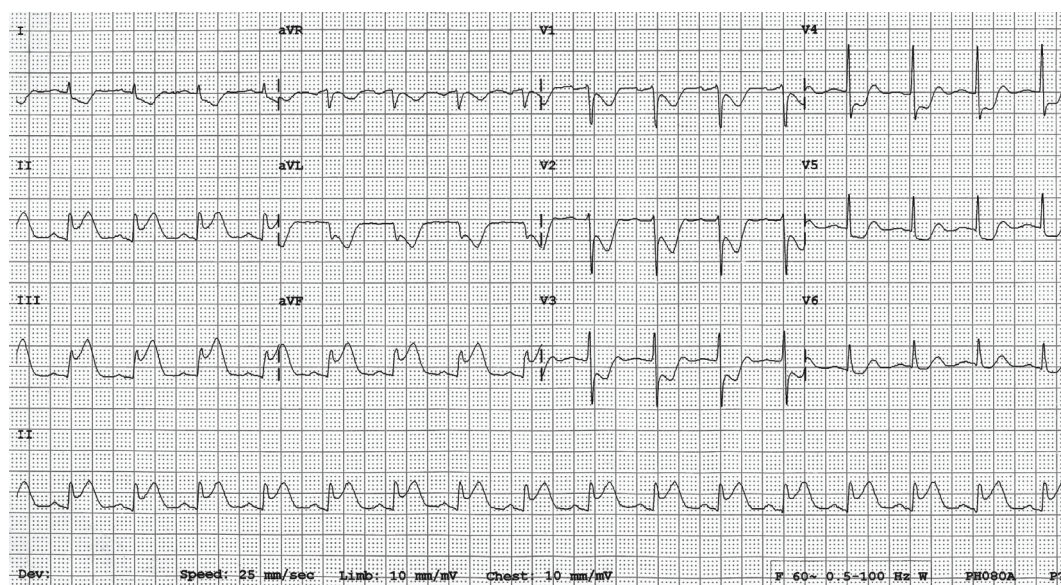


Fig. 1. Electrocardiogram showing acute inferior myocardial infarction.

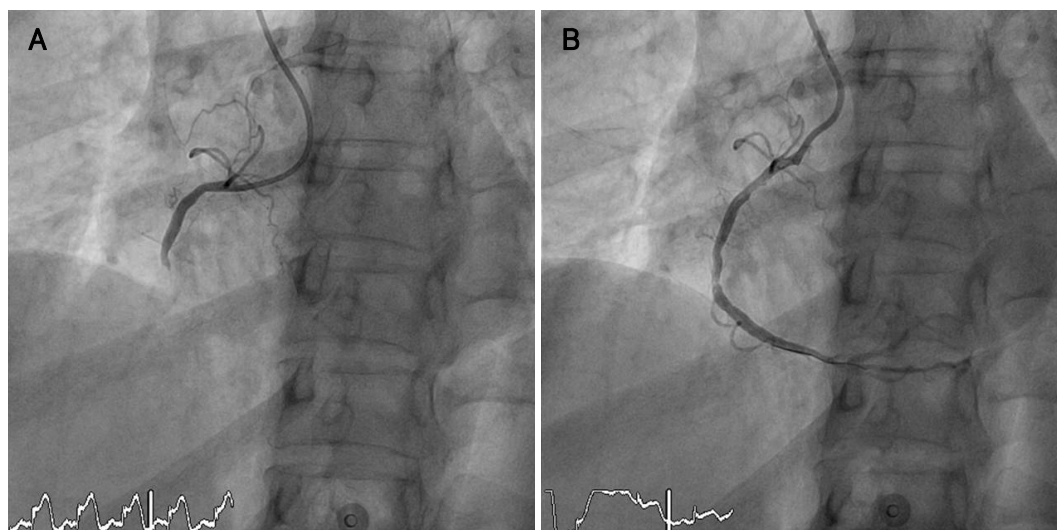


Fig. 2. Initial coronary angiogram (A) revealing total occlusion of right coronary artery (RCA). Coronary angiogram (B) after abciximab injection and balloon angioplasty demonstrates diffuse narrowing in the mid- and distal portions of the RCA.

care unit. Her platelet count was  $73,000/\text{mm}^3$  at 1 hour,  $6,000/\text{mm}^3$  at 3 hours, and  $1,000/\text{mm}^3$  at 6 hours after abciximab administration. Because she had gum bleeding and petechiae on both extremities, she was treated with platelet concentrate transfusion (6 units). We checked the platelet count in a sodium citrate tube sample, looked at a peripheral blood smear, and measured platelet-associated antibody, heparin-dependent antibody, fibrinogen, D-dimer, and prothrombin time (PT) before performing platelet transfusion; all parameters were within normal limits. We excluded pseudothrombocytopenia, heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP). The patient's platelet counts were  $57,000/\text{mm}^3$  and  $35,000/\text{mm}^3$  at six and ten hours after transfusion, respectively. She re-

ceived an additional six units of platelet concentrate, and her platelet count increased to  $75,000/\text{mm}^3$  on the second day and  $125,000/\text{mm}^3$  on the third day after abciximab administration.

By the seventh day after admission, the platelet count had fully rebounded, and the patient underwent a second PCI to treat the left circumflex and left anterior descending artery lesions. During the second procedure, heparin 5,000 IU/L was readministered; the follow-up platelet counts were  $137,000/\text{mm}^3$  and  $140,000/\text{mm}^3$  at 1 hour and 10 hours after heparin administration, respectively.

Therefore, we confirmed that her thrombocytopenia was caused by abciximab, not by heparin. She was discharged on the twelfth day after admission without major complications.

## Discussion

Abciximab is a Fab fragment of the chimeric antibody 7E3. It prevents platelet aggregation by inhibiting the binding of adhesion molecules to the glycoprotein IIb/IIIa receptor,<sup>5)</sup> and it is used to reduce the ischemic complications of balloon angioplasty and stent implantation.<sup>6-10)</sup> However, its associated complications include bleeding and acute profound thrombocytopenia. Acute profound thrombocytopenia (platelet count  $<20,000/\text{mm}^3$ ) is very rare; it has been reported in less than 1% of patients treated with abciximab.<sup>11)12)</sup> Risk factors for thrombocytopenia after abciximab treatment include older age ( $>65$  years), lighter body weight ( $<80$  kg), and lower baseline platelet count ( $<200,000/\text{mm}^3$ ).<sup>13)</sup> The mechanism of abciximab-induced thrombocytopenia is presumably immune-mediated. One specific projected mechanism involves the critical presence of preexisting serum antibody to the platelet surface antigen. Gp IIb/IIIa antagonists may induce a conformational change in Gp IIb/IIIa receptors on the platelet surface, thus leading to the expression of new epitopes that are recognized by the antibodies already present in the plasma.<sup>14)</sup>

In most PCI cases, abciximab is concomitantly used with heparin. Therefore, the diagnosis of abciximab-induced thrombocytopenia is possible after HIT is excluded. HIT is the most common form of drug-induced thrombocytopenia, with an incidence ranging from 1% to 2%.<sup>15)</sup> There are at least two discrete forms of HIT, and the most clinically important is type II.<sup>4)</sup> Type II HIT is more severe than type I HIT, and it is mediated by an immune mechanism; it begins 4 to 10 days after exposure to heparin. Abciximab-induced thrombocytopenia can be identified within a few hours after abciximab infusion, and it resolves within 2-5 days. Thus, this time interval can help in discriminating this diagnosis from HIT.<sup>16)</sup> HIT antibodies in the serum of patients with HIT are potentially diagnostic. The HIT antibody test has 80% sensitivity and 90% specificity in patients with no previous heparin exposure.<sup>17)</sup> Pseudothrombocytopenia is the source of about 30% of all cases of low platelet counts.<sup>18)</sup> Pseudothrombocytopenia is distinguished from true thrombocytopenia through examination of peripheral blood smears (PBS) and platelet counts in sodium citrate samples. Pseudothrombocytopenia is characterized by platelet clumping in PBS and no thrombocytopenia in sodium citrate, although thrombocytopenia is apparent in ethylenediaminetetraacetic acid (EDTA) tube samples. TTP and DIC can be distinguished based on D-dimer, fibrinogen, prothrombin time, and PBS examination.

The management of thrombocytopenia is not well established. Ferguson et al.<sup>19)</sup> recommended that platelet counts be checked at 4 and 24 hours after first-time

abciximab treatment so that any thrombocytopenia could be detected. Prophylactic platelet transfusion should be strongly considered if the platelet count is  $<20,000/\text{mm}^3$ . Platelet transfusion can also be considered for thrombocytopenia in the range of  $20,000$ - $50,000/\text{mm}^3$  in patients with abnormal hemostasis. In the absence of hemorrhage, platelet counts  $>20,000/\text{mm}^3$  can be followed every 6 hours until levels reach  $>50,000/\text{mm}^3$ .

In this case, thrombocytopenia occurred within a few hours after abciximab treatment. We were able to exclude other causes of thrombocytopenia (HIT, pseudothrombocytopenia, and TTP) based on laboratory findings. Finally, we confirmed abciximab-induced thrombocytopenia based on measurement of heparin-dependent antibody and readministration of heparin; this confirmation was not available in a previously reported case.<sup>20)</sup>

Abciximab is commonly used in conjunction with heparin during PCI. However, if thrombocytopenia occurs within a few hours, abciximab-induced thrombocytopenia should be considered over HIT. Serial platelet counts and coagulation indices should be evaluated thereafter to more accurately diagnose or confirm the cause of thrombocytopenia. Platelet transfusions should also be considered in the treatment of severe thrombocytopenia.

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