Abciximab for the treatment of an acute thrombotic coronary occlusion during stent implantation in a patient with severe hemophilia B

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Key words:
Antiaggregating agents; Coronary angioplasty; Stent.

Hemophilia B is a severe inherited coagulopathy caused by mutations in the gene that encodes factor IX. Surgical and invasive procedures in patients suffering from this congenital disease are to be considered as being at high risk of hemorrhage. We describe a case of a patient with unstable angina who suffered from severe hemophilia B, pre-treated with plasma purified factor IX concentrate and not on antithrombotic therapy, in whom the use of abciximab induced the complete lysis of an acute thrombus complicating the implantation of a stent on the left anterior descending coronary artery.

(Ital Heart J 2003; 4 (10): 728-730)

Received March 4, 2003; revision received May 28, 2003; accepted June 12, 2003.

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Introduction

Abciximab is a Fab fragment of a chimeric murine-human monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor and is therefore a powerful platelet aggregation inhibitor. It binds to the platelet glycoprotein IIb/IIIa receptor with a high affinity and a slow receptor off-rate, causing a long-lasting biological effect. Many controlled clinical trials[1] have demonstrated that the use of abciximab in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) procedures, significantly reduces the incidence of ischemic events in comparison with placebo or control therapy.

Hemophilia B is a sex-linked hemorrhagic coagulation disorder caused by a deficiency of factor IX associated with a certain high risk during invasive procedures.

To our knowledge, there are so far no reports regarding the use of abciximab during cardiac catheterization in hemophilic patients.

We describe a case of a patient with severe hemophilia B who underwent an elective stent implantation on the left anterior descending coronary artery complicated by an endoluminal acute thrombosis, in whom the use of abciximab induced the lysis of the thrombus achieving a complete vascular recanalization.

Case report

A 73-year-old male had a history of hypertension, type 2 diabetes mellitus and inherited severe (factor IX level < 1%) hemophilia B. He reported only one episode of major bleeding occurring during the extraction of a tooth when he was 54 years old. Starting from age 65, he complained of episodes of chest pain mainly during effort and, in more recent times, even at rest. The patient was not on any antianginal therapy. Due to the worsening of these symptoms, he was admitted to a regional hospital with a diagnosis of unstable angina and then referred to our Institution for an elective coronary angiography. At the time of admission, his blood pressure was 140/90 mmHg with a heart rate of 75 b/min. The ECG showed sinus rhythm with an ST-segment depression (2 mm) in leads DII, aVL and V_2-V_4. Transthoracic echocardiography revealed marked left ventricular wall hypertrophy and hypokinesis of the inferior wall with an ejection fraction of 55%.

Having obtained the advice of a hematologist, requested in view of the particular coagulopathy of the patient and of the relative risk of bleeding, the standard pre-treatment antithrombotic regimen with ticlopidine, acetylsalicylic acid and heparin[2] was avoided and 30 min before the interventional procedure, 30 IU/kg of high purity factor

IX product (AIMAFIX, Castelvecchio Pascoli-LU, Italy), reconstituted according to the manufacturer's instructions, were administered in intravenous infusion as replacement therapy. After 5000 IU of heparin we proceeded to the selective catheterization of the right and left coronary arteries that revealed a critical stenosis above the proximal part of the left anterior descending coronary artery and a subcritical stenosis at the origin of the first diagonal branch (Fig. 1A). The lesion was dilated using a 3.0 × 20 mm balloon (Ave X15, Medtronic, Minneapolis, MN, USA) at 8 atm for 35 s. Considering the characteristics of the lesion, a 3.0 × 12 mm Carbostent (Sorin Biomedica, Saluggia-VC, Italy) was implanted, with an apparently perfect deployment of the stent. After 1 min, an acute thrombus upstream from the stent and extending proximally towards the left main coronary stem was observed (Fig. 1B). The patient experienced angina and an ST-segment depression increase was noted on the recording leads of the ECG. The patient was immediately given an infusion of abciximab at the standard dosage of 0.25 mg/kg in intravenous bolus followed by 0.125 μg/kg/min in continuous intravenous infusion together with a further 2000 IU of heparin[3]. The clinical and electrocardiographic pictures stabilized within a few minutes. The following angiographic control (Fig. 1C) revealed that the thrombus had regressed with the persistence only of a focal *minus* image upstream from the stent and a good recanalization of the vascular lumen (TIMI 3 flow grade).

The patient had an uncomplicated post-procedure in-hospital course, without any elevation of the levels of the cardiac enzymes and with the normalization of the ECG. At the time of discharge, considering the high risk of intrastent restenosis and having again obtained the hematologist's advice and the patient's consent, clopidogrel was prescribed for 1 month. At 6 months of follow-up, the patient was in good clinical conditions and no hemorrhagic events had occurred.

Discussion

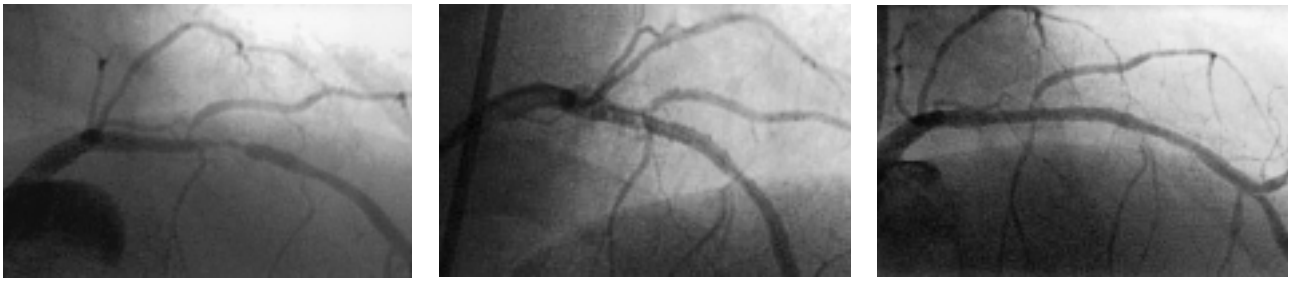
Hemophilia B or Christmas' disease is a severe hemorrhagic disorder due to mutations in the gene that encodes factor IX. Depending on the circulating factor IX blood levels, it is commonly classified as mild, moderate or severe. In severe hemophilia, spontaneous bleeding into the joints, soft tissues and vital organs is frequent, whereas in mild hemophilia, bleeding usually occurs only after major trauma or surgery. For these reasons, surgical and interventional treatments have always been considered as being at high risk of hemorrhage[4,5].

The reduced levels of factor IX, whilst conferring some protection[6], do not preclude the presence of coronary artery disease in patients with hemophilia B[7]. In fact, the prevalence of coronary artery disease in the hemophilic population, although lower than that observed in the normal age-matched population, is likely to increase owing to the advances in therapeutic management in recent decades with a consequent increase in life expectancy.

From many years, in case of surgical procedures in hemophilic patients, substitution treatment that consists of the replacement of the defective coagulation factor, is mandatory. Replacement therapy has proven to be the only tool able to protect from the risk of major bleeding during invasive procedures in this category of patients[8]. Nevertheless, while there is considerable experience in the use of factor concentrates for the prophylaxis of elective orthopedic and general surgery, there are very few reports concerning cardiac catheterization procedures in hemophilic patients[9]. A recent study, even though enrolling a very small number of cases, has shown the safety of coronary angiographic procedures in patients with hemophilia A or B pre-treated with factor VIII or IX concentrates respectively[10].

Nevertheless, although replacement therapy protects from major hemorrhagic events and permits the completion of interventional procedures even in these high-risk patients, it is however considered thrombogenic[8,10,11] and a potential source of serious thrombotic complications during PTCA.

To date, only a few cases of acute coronary occlusion during replacement therapy with intravenously administered factor VIII or IX in hemophilic patients, have been described in the literature[12]. In particular,



A B C

Figure 1. A: *coronary angiogram. Critical stenosis above the proximal segment of the left anterior descending coronary artery.* B: *coronary angiogram after stent implantation. Acute thrombus formation upstream from the stent.* C: *coronary angiogram after abciximab treatment. Complete resolution of the thrombotic occlusion.*

concentrates of factor IX are considered to be more thrombogenic than factor VIII[13].

With regard to the present case report, it is therefore reasonable to postulate that factor IX substitution treatment could have promoted the intraluminal formation of a thrombus following the implantation of the stent.

It is therefore our opinion that coronary angioplasty in hemophilic B patients should be considered as a dangerous trickery between the risk of bleeding on the one hand, and the unforeseeable thrombotic events due to the pro-coagulation effect of replacement therapy on the other.

It has been widely demonstrated that a significant reduction in the acute complication rate for PTCA was obtained by resorting to glycoprotein receptor IIb/IIIa blockers. Nowadays, these drugs are indicated in patients who are candidates for PTCA.

In this clinical setting, the use of glycoprotein receptor IIb/IIIa blocker drugs reduces the need of emergency procedures or surgical bypass, also reducing the short- and long-term mortality[3,14-16]. On the other hand, multivariate analysis revealed that the use of adjunctive abciximab during percutaneous coronary interventions was independently associated with the occurrence of major and minor bleeding[17]. For these reasons, glycoprotein IIb/IIIa blocker drugs are not indicated in several clinical conditions with a high hemorrhagic risk. However, no data exist up today about their effective and safe administration in patients submitted to percutaneous coronary intervention with congenital coagulopathies, e.g. hemophilia, in whom the use of substitutive factors can restore a normal coagulative pattern.

So far, this is the first case report that suggests the efficacy and safety of the use of abciximab for the treatment of acute coronary thrombosis complicating a stent implantation in a patient with severe hemophilia B. Of course, larger and controlled studies are warranted to better evaluate the safety and efficacy profiles of cardiac interventional procedures in patients with congenital clotting disorders so as not to delay or avoid cardiac investigations and interventions even in these high-risk patients.

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