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Case Reports

Left Main Stent Thrombosis

Complicated by Eptifibatide-Induced Acute Thrombocytopenia

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A 57-year-old man with a history of coronary artery disease and placement of an implantable cardioverter-defibrillator presented at our emergency room with an anterior ST-elevation myocardial infarction. Cardiac catheterization revealed an acutely occluded left main coronary artery, which was revascularized successfully with a bare-metal stent. Periprocedurally, the patient received aspirin, clopidogrel, unfractionated heparin, and eptifibatide.

The patient was discharged a week later, but he returned to the emergency room the same day with recurrence of severe chest pain. Repeat cardiac catheterization revealed an acutely occluded stent, and the patient underwent repeat bare-metal stent placement and readministration of eptifibatide. On the next day, the patient's platelet count dropped acutely to less than 12,000/mm^3. A test for heparin-induced thrombocytopenia antibody was negative. After discontinuation of eptifibatide, the patient's platelet count gradually returned to normal, and he was later discharged from the hospital with no complications.

Eptifibatide-induced acute thrombocytopenia is a known but rare adverse effect. We review the handful of case reports in the medical literature, with emphasis on the prevalence, observed clinical course, and recently proposed physiologic mechanisms that probably are responsible for this phenomenon. ***(Tex Heart Inst J 2011;38(2):174-8)***

Key words: *Acute coronary syndrome; antibodies, monoclonal/adverse effects; coronary stenosis/blood; eptifibatide; GPIIb/IIIa inhibitor; megakaryocytes; peptides/adverse effects; platelet aggregation inhibitors/therapeutic use; platelet glycoprotein GPIIb-IIIa complex/antagonists & inhibitors; ST-elevation myocardial infarction; stents; thrombocytopenia/chemically induced/etiology*

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Eptifibatide, an anticoagulant that binds to glycoprotein (GP) IIb/IIIa receptor and thereby inhibits platelet aggregation, has a role in the treatment of acute coronary syndrome. However, there is a rare incidence of acute profound thrombocytopenia. We present the case of a patient who developed acute profound thrombocytopenia upon the readministration of eptifibatide, after he developed stent thrombosis.

Case Report

A 57-year-old man presented at our hospital's emergency room with new-onset severe chest pain that had occurred earlier that night. The pain was pressure-like, nonradiating, and 10/10 in severity; it had been intermittent but worsening in intensity throughout the night.

His medical history was significant for diabetes mellitus, hypertension, and the placement of an implantable cardioverter-defibrillator 16 years earlier for ventricular tachycardia. At that time, the patient had undergone coronary angiography, which had shown coronary artery disease, but no intervention had been performed. The patient was taking aspirin, metoprolol, lisinopril, glipizide, and atorvastatin. He had no known allergies. He was an active tobacco user but denied any history of alcohol or drug abuse.

On physical examination, the patient had a temperature of 98° F, heart rate of 67 beats/min, blood pressure of 105/67 mmHg, respiratory rate of 20 breaths/min, and oxygen saturation of 93% on room air. He was alert and oriented but in distress from his chest pain. His jugular venous pressure was elevated to the angle of the jaw. He had inspiratory bibasilar crackles on examination, no peripheral edema, and no cyanosis. Cardiac auscultation showed a regular rhythm and no murmurs, rubs, or gallops.

An electrocardiogram (ECG) showed ST-segment elevations in the anteroseptal leads with reciprocal changes in the inferior-limb leads (Fig. 1). An urgently performed transthoracic echocardiogram showed a left ventricular ejection fraction of 0.50, anteroapical and apical septal wall hypokinesis, mild-to-moderate mitral regurgitation, and moderate pulmonary hypertension. A portable chest radiograph showed

cardiomegaly, pulmonary edema, and the presence of a dual-chamber defibrillator. The initial laboratory results showed a troponin I level of 0.13 ng/mL. The patient had a white blood cell count of 15,900/mm^3, a hemoglobin level of 16.5 g/dL, and a platelet count of 220,000/mm^3. The electrolytes were significant for a blood urea nitrogen level of 23 mg/dL and a creatinine level of 1.44 mg/dL. Because of the patient's ischemic symptoms and ECG changes consistent with an anterior ST-elevation myocardial infarction (STEMI), he was taken urgently to the cardiac catheterization laboratory.

Coronary angiography showed that the left main coronary artery (LMCA) was completely occluded with thrombus (Fig. 2), with a Thrombolysis in Myocardial Infarction (TIMI) flow of 0. After a failed attempt at intracoronary thrombectomy, we deployed a TAXUS® Liberté® 3.5 × 24-mm bare-metal stent (Boston Scientific Corporation; Natick, Mass), which yielded TIMI-3 flow (Fig. 3). The left anterior descending coronary artery also had 2 sequential lesions of circa 50% stenosis, and a 90% stenosis at the ostium of the 1st diagonal branch. The left circumflex coronary artery had a long 80% stenosis in the atriovenous groove, with residual proximal thrombus. The right coronary artery was dominant and aneurysmal, with a proximal 50% lesion that was ectatic with scattered plaques. The left ventricular end-diastolic pressure was 40 mmHg.

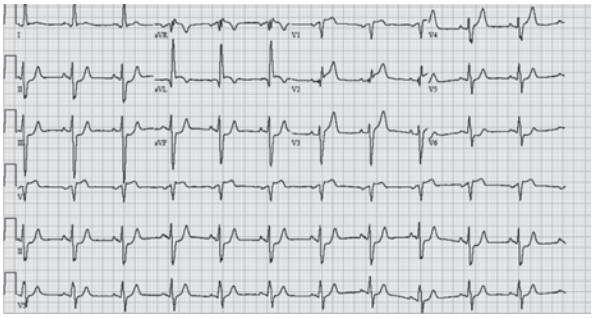

Fig. 1 *Electrocardiogram performed on admission shows sinus rhythm with evidence of left ventricular hypertrophy, left anterior fascicular block, and ST elevations in the anterior leads (with reciprocal changes in the inferolateral leads consistent with possible ST-elevation myocardial infarction).*

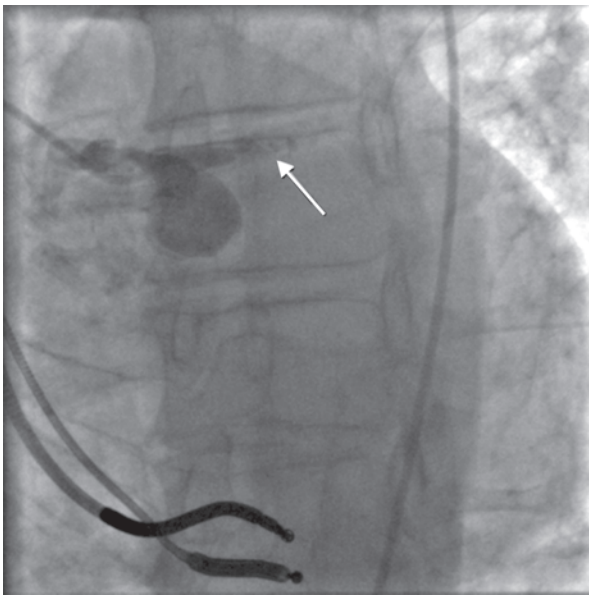

Fig. 2 *Coronary angiogram (left anterior oblique view) of the left coronary artery system shows a lesion with acute occlusion of the left main coronary artery, which has resulted in Thrombolysis in Myocardial Infarction (TIMI) 0 flow. The type C lesion is tubular, eccentric with moderate calcification, and completely occluded with thrombus (arrow).*

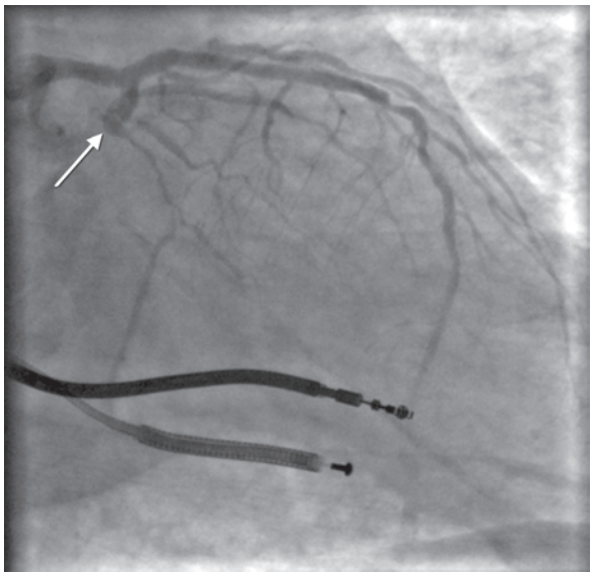

Fig. 3 *Coronary angiogram (right anterior oblique cranial view) of the left coronary artery system after stent placement shows 80% residual left circumflex disease and proximal residual thrombus (arrow).*

The patient's chest pain was relieved after percutaneous coronary intervention (PCI). He was given intravenous unfractionated heparin and a 180-µg/kg intravenous bolus of eptifibatide, followed by a 2-µg/kg/min infusion for 18 hours. He was started on infusions of amiodarone and lidocaine because of nonsustained ventricular tachycardia during the procedure. The patient also received a 600-mg loading dose of clopidogrel (subsequently 75 mg/d) and a continuation of aspirin (81 mg/d). His postprocedural hospital course was complicated by an elevated creatinine level and decompensated heart failure, with a peak troponin level of 755.51 ng/mL, but this gradually resolved and the patient was discharged on hospital day 7. He was to undergo outpatient stress testing and, if indicated, staged PCI.

Later on the day of discharge, the patient experienced acute onset of chest pain and returned to the emergency room, where a repeat ECG showed ST elevations in the

anterior leads (Fig. 4). Repeat cardiac catheterization showed proximal acute thrombosis of the bare-metal stent in the LMCA (Fig. 5). Intracoronary thrombectomy yielded thrombus, and a Liberté 3.5 × 12-mm bare-metal stent was redeployed in the area of the stent thrombosis (Fig. 6). The patient received another dose of intravenous heparin, and an intravenous bolus of 180 µg/kg of eptifibatide, followed by a 2-µg/kg/min infusion.

Routine laboratory testing the next morning—approximately 13 hours after the previous platelet count of 276,000/mm^3—showed an acute drop in the patient's platelet count, to less than 12,000/mm^3. Peripheral blood smears obtained during this time showed slight polychromatophilia, few ovalocytes, and rare platelets, with no evidence of microangiopathic hemolytic anemia. Because of the patient's increased risk

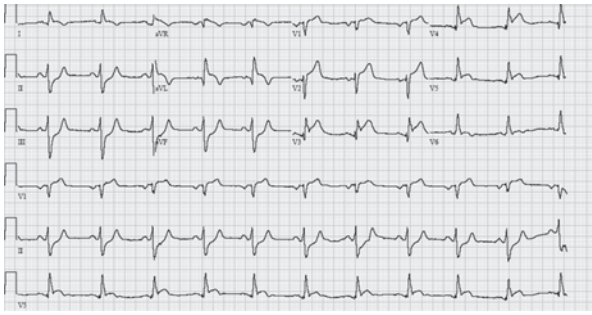

Fig. 4 *Electrocardiogram upon hospital readmission shows sinus rhythm, left ventricular hypertrophy, and left anterior fascicular block, with upward concave ST elevations in leads V_2 through V_4 and inferior reciprocal changes in the inferior leads that are possibly indicative of subacute stent thrombosis.*

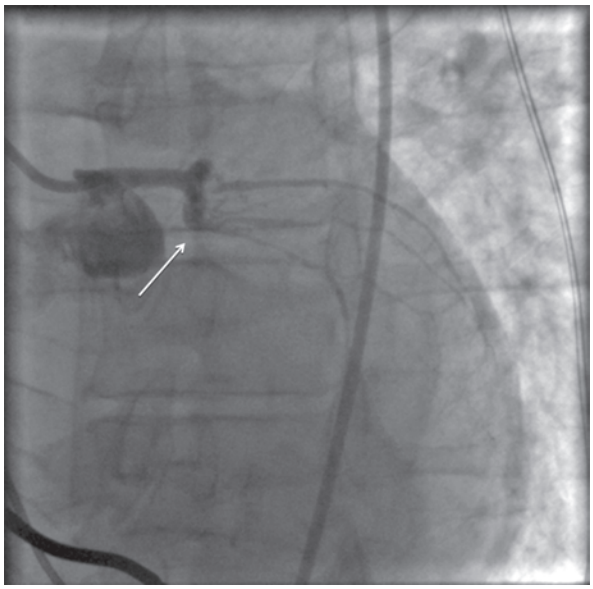

Fig. 5 *Coronary angiogram (left anterior oblique view) shows occlusion of the proximal stent (arrow) in the left main coronary artery.*

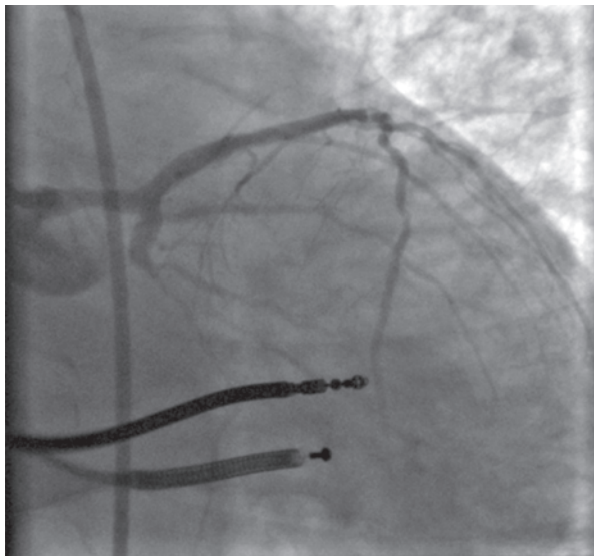

Fig. 6 *Coronary angiogram (right anterior oblique cranial view) after stent placement shows restoration of flow in the left main coronary artery.*

of hemorrhage, we discontinued all antiplatelet products, including aspirin, clopidogrel, heparin products, and eptifibatide, and we consulted our hematology department. A heparin-induced thrombocytopenia (HIT) platelet factor 4 antibody test was negative. On the basis of the acute drop in blood platelets and the negative HIT antibody test, we concluded that re-exposure to eptifibatide was the probable cause of the patient's acute thrombocytopenia. Aside from the aspirin administered in the emergency room, no other agent was administered before coronary angiography. The patient was closely observed for any bleeding events and for management of his ischemic heart failure. No major bleeding events occurred, and the patient's hemoglobin level remained stable. On hospital day 4 of readmission, the patient received a transfusion of 2 units of platelets to decrease the potential for bleeding complications while we removed an indwelling arterial sheath. The sheath had been retained postprocedurally to enable close hemodynamic monitoring, given the patient's hypotension and the possibility of his clinical deterioration due to severe heart failure. After the transfusion, the platelet count increased from 13,000 to 50,000/mm^3. Subsequently, the patient's platelet count continued to rise, which enabled us to restart both aspirin and clopidogrel (Fig. 7). The patient remained on carvedilol, angiotensin-converting enzyme inhibitor, statin, and diuretics, and was discharged on day 12 of his hospital readmission. However, he was readmitted to our county hospital with repeated exacerbations of heart failure. During these stays, the patient received low-molecular-weight heparin for prophylaxis of deep vein thrombosis and experienced no decrease in his platelet count, which

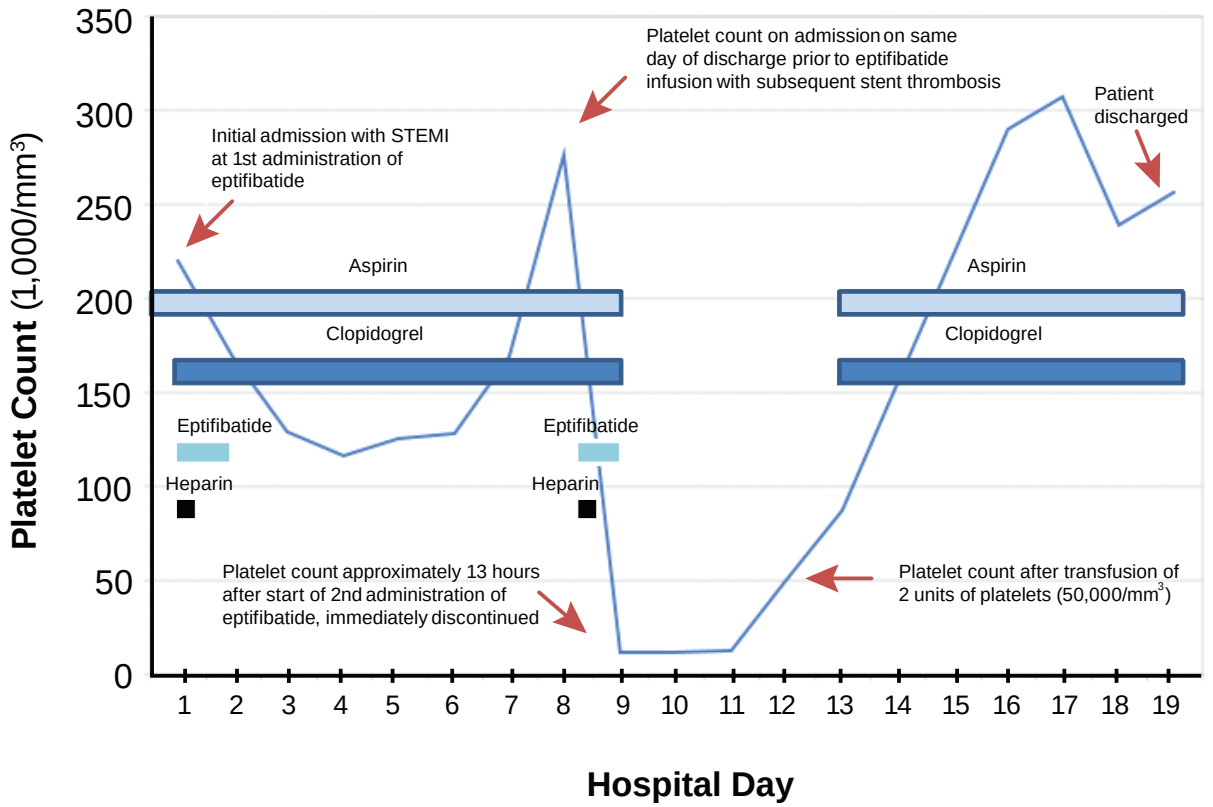

Fig. 7 *Diagram shows platelet trend along with significant hospital events. Relevant antiplatelet and anticoagulant therapies and their time of initiation and discontinuation are shown.*

STEMI = ST-segment-elevation myocardial infarction

strengthens the likelihood that eptifibatide was the cause of the acute thrombocytopenia.

Discussion

In the pathophysiology of acute coronary syndrome, platelet aggregation and thrombus formation play a key role in the genesis of an ischemic cascade that results in thrombotic occlusion. Platelet aggregation is initiated by activation of platelet GPIIb/IIIa receptors, and the inhibition of this process has been the subject of multiple studies on reducing morbidity and death in patients who present with stent implantation, acute coronary syndrome, or both.[1,2] Eptifibatide, tirofiban, and abciximab bind to recognition sites on the activated GPIIb/IIIa receptor, which inhibits binding to fibrinogen. Intravenous GPIIb/IIIa receptor antagonists, along with dual oral antiplatelet therapy, currently have a Class IIa indication for their usage at the time of primary PCI in certain patients who present with a STEMI, including those with a large thrombus burden and those who have not received adequate thienopyridine loading.[3]

Eptifibatide is a synthetic cyclic heptapeptide that contains a modified lysine-glycine-aspartic acid, a sequence that recognizes the binding site of platelet GPIIb/IIIa. Other GPIIb/IIIa inhibitors, such as abciximab, are classified as humanized monoclonal antibodies that reduce immunogenicity, and tirofiban is a nonpeptide mimetic.[4]

The incidence of eptifibatide-associated acute profound thrombocytopenia is rare. In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, the rate of acute profound thrombocytopenia among eptifibatide recipients was reported as 0.2% (9 patients), versus less than 0.1% (2 patients) in the placebo group.[1] Also, in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial,[2] there was an incidence of acute profound thrombocytopenia of 0.2% (2 patients) among eptifibatide recipients, versus no cases in the placebo group. When Russell and colleagues[5] reviewed the medical literature in 2009, 16 cases of eptifibatide-associated acute profound thrombocytopenia had been reported. Seven of the 16 cases were associated with previous exposure to eptifibatide or another GPIIb/IIIa inhibitor. This phenomenon has also been documented in other GPIIb/IIIa antagonists: for example, the ReoPro Readministration Registry, which followed the effects of readministration of abciximab in 500 patients, saw an incidence

of 2.4% of profound thrombocytopenia (<20 × 10^9/L).[6] Tirofiban, in clinical trials,[7] has shown a thrombocytopenia (<50 × 10^9/L) incidence of 0.2% to 0.5%.

Although Lorenz and colleagues[8] found no evidence of antibody response in 28 healthy volunteers who underwent repeated exposure to eptifibatide, Bougie and coworkers[9] found that 9 patients who experienced acute profound thrombocytopenia after exposure to tirofiban (n=4) and eptifibatide (n=5) had high titers of immunoglobulin G antibody, which reacted with the GPIIb/IIIa complex. Two of the patients who were exposed to eptifibatide had a history of exposure to GPIIb/IIIa inhibitors. The authors theorized that these antibodies were monoclonal antibodies that recognized ligand-induced binding sites induced in the GPIIb/IIIa heterodimer when the heterodimer reacted with a ligand-mimetic drug; this reaction would cause immune-mediated platelet destruction.

Upon bone marrow examination in 1 patient who had acute thrombocytopenia thought to be due to eptifibatide readministration, Greinacher and associates[10] noted impaired megakaryocytopoiesis together with a predominance of early megakaryocyte stages in the presence of eptifibatide-dependent GPIIb/IIIa-specific antibodies. The patient had a prolonged course of thrombocytopenia.

There has also been a reported instance of eptifibatide-induced thrombocytopenia and thrombosis.[11] Gao and co-authors[12] surmised that the subunits of both the integrin β_3 cytoplasmic domain and the platelet receptor FcγRIIa must be present to trigger the signaling cascade that induces the phenomenon of antibody-mediated thrombocytopenia and thrombosis.

The usual therapy for eptifibatide-induced thrombocytopenia has consisted of discontinuing eptifibatide, close monitoring of platelet counts, and treating bleeding complications with platelet transfusions. No pharmacologic antidote has been reported to reverse acute thrombocytopenia. In their review of the reported cases of eptifibatide-induced acute thrombocytopenia, Russell and colleagues[5] noted that the average platelet nadir was 4,000 to 5,000/mm^3 (range, 1,000–19,000/mm^3) and that the average time to platelet recovery was 5 days (range, 2–18 d). The average time to onset was 7 to 8 hours (range, 1–24 hr), excluding 1 case of delayed-onset thrombocytopenia. One of the 16 patients died. This abnormal response, although uncommon, highlights the need for close platelet monitoring after the administration of GPIIb/IIIa antagonists.

In conclusion, we present a rare case in which acute profound thrombocytopenia was provoked by the readministration of eptifibatide and was resolved by the discontinuation of that agent. In addition, the patient experienced no bleeding complications and had no subsequent episodes of thrombocytopenia upon re-exposure to heparin-based and antiplatelet medications.

Acknowledgment

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