Eptifibatide-Induced Profound Thrombocytopenia After Percutaneous Intervention for Acute Coronary Syndrome: A Challenging Clinical Scenario

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ABSTRACT: Eptifibatide is a glycoprotein (GP) IIb/IIIa inhibitor used mostly in the treatment of acute coronary syndrome (ACS). The GP IIb/IIIa antagonists occupy the fibrinogen binding site at the GP IIb/IIIa and block thrombocyte aggregation independent of the initial activation pathway. Severe thrombocytopenia has been reported with eptifibatide use. Thrombocytopenia after ACS can have multiple etiologies. Human immunodeficiency virus (HIV) infection has also been implicated in immune-mediated thrombocytopenia. In this manuscript, we report a case of acute severe thrombocytopenia secondary to eptifibatide use in a patient with a history of HIV infection who presented with an ST elevation myocardial infarction. We also review the differential diagnosis and suggest management strategies in this challenging clinical scenario.

INTRODUCTION

Eptifibatide is a glycoprotein IIB/IIIA inhibitor used in the treatment of acute coronary syndrome (ACS). Acute profound thrombocytopenia has been reported as an adverse drug reaction to eptifibatide.[1] Although thrombocytopenia (platelets < 100,000) is estimated to occur in only 1% of patients irrespective of previous exposure to eptifibatide, acute severe thrombocytopenia (platelets < 20,000) can occur in 0.2% of those exposed to eptifibatide.[1] Differential diagnosis in these cases may also include pseudothrombocytopenia, heparin-induced thrombocytopenia (HIT), thienopyridine-induced thrombotic thrombocytopenic purpura (TTP), and immune-mediated thrombocytopenia associated with human immunodeficiency virus (HIV).[2] There is no known report of an association between eptifibatide-induced thrombocytopenia and HIV. The management of patients with concomitant HIV and thrombocytopenia is challenging as they often need concomitant therapy with anticoagulants and antiplatelet agents in the setting of recent ACS. We describe a case of eptifibatide-induced acute severe thrombocytopenia in a patient with both ACS and HIV.

CASE PRESENTATION

A 41-year-old African American female presented to the emergency room with 2 days of waxing and waning central chest pain that had become constant over the last 3 hours. She had a history of myocardial infarction 10 years ago, which was treated with bare metal stenting (BMS) to the proximal left anterior descending artery (LAD), as well as HIV (last CD4 count 250 cells/mm^3), hypertension, active cocaine use, and alcohol and tobacco abuse. Her current chest pain was associated with shortness of breath, nausea, vomiting, and diaphoresis. Vital signs at the time of presentation were blood pressure 210/120 mm Hg, heart rate 106 beats per minute, respiratory rate 20 per minute, and oxygen saturation 100% on 2 liters supplemental oxygen via nasal cannula. An initial electrocardiogram (EKG) demonstrated ST segment elevation in anterior leads (Figure 1). She was immediately given 325 mg of aspirin, 600 mg of clopidogrel, two doses of 0.4 mg sublingual nitroglycerine, and 2 mg morphine. A nitroglycerine drip was started at 40 mcg/min for incessant chest pain, and the cardiac catheterization laboratory was activated.

Upon arrival at the catheterization laboratory, she had a cardiac arrest with ventricular fibrillation. Cardiopulmonary resuscitation was initiated, and she converted to sinus rhythm after a 360-J shock. Coronary angiogram revealed 100% occlusion of the left anterior descending artery with in-stent thrombosis. Aspiration thrombectomy was performed to restore flow to the LAD. The patient received a heparin bolus of 70 U/kg and an eptifibatide bolus of 180 mg/kg followed by a 1 mcg/kg/min eptifibatide drip. She again went into ventricular fibrillation, suffered a cardiac arrest after restoration of flow, and was successfully defibrillated. At this point, she developed persistent hypotension with a systolic blood pressure of 70 mm Hg. This prompted the administration of multiple boluses of phenylephrine and a norepinephrine drip. A 2.75-mm x 23-mm drug eluting stent (DES) was placed in the proximal LAD covering the previous BMS. Her right coronary artery was small and nondominant,

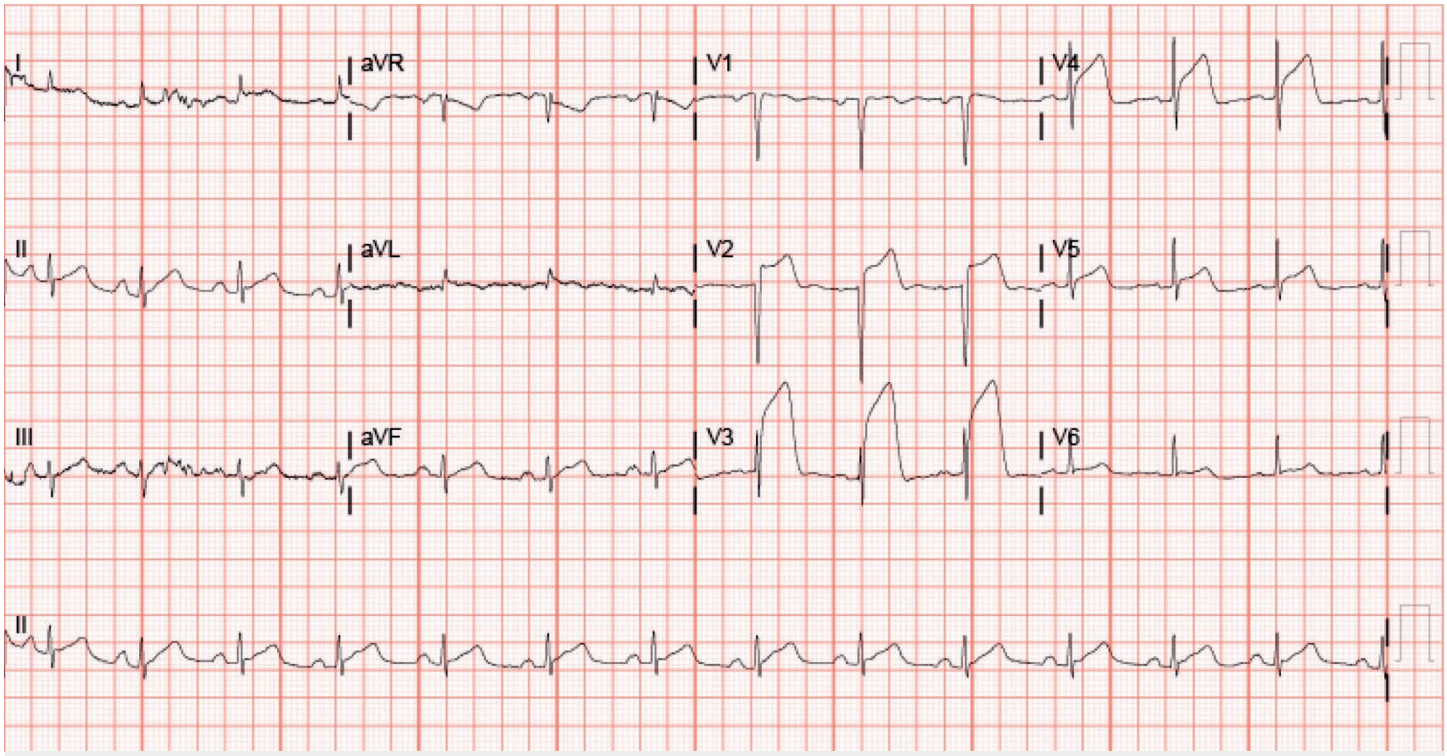

Figure 1.
Electrocardiogram at presentation showing ST elevations in V2-V4 consistent with anterior ST elevation myocardial infarction.

and her left circumflex was large and nonstenotic. She was transferred to the cardiac intensive care unit (CCU) after the procedure. Three hours later, the CCU nurse notified the house staff about a hematoma in the patient's left groin where the arterial sheath was placed.

The patient had a 4-cm x 6-cm hematoma just medial and distal to the left common femoral artery (CFA) sheath. At this point, direct pressure was held on the CFA just proximal to the sheath hub. Blood work revealed a hemoglobin level of 10 mg/dL (11 mg/dL on admission) and a platelet count of 7,000/mm^3 (180,000/mm^3 on admission). Repeat blood work revealed a platelet count of 10,000/mm^3 (Figure 2); there was no clumping on smear and no change when the sample was placed in a non-ethylenediaminetetraacetic acid tube. Eptifibatide was stopped. Activated clotting time (ACT) was 245 seconds. Protamine sulfate 20 mg IV was administered to reverse the effect of heparin. After 10 minutes, the ACT was 155 seconds, the arterial sheath was pulled, and manual pressure was held for 20 minutes, after which the FemoStop® external compression device (St. Jude Medical) was applied. Two units of 6-pack platelets were transfused. An urgent computed tomography (CT) scan of the abdomen and pelvis did not reveal any retroperitoneal hematoma. Aspirin and clopidogrel were continued. The patient's platelet count increased rapidly over the next day and was 123,000/mm^3 at discharge. She was discharged without any further events.

DISCUSSION

This case represents a challenging clinical situation involving the management of a patient with acute profound thrombocytopenia after coronary intervention and stent placement. An immediate dilemma in this type of scenario is whether or not to discontinue all antiplatelet and anticoagulant medications. In the setting of recent stent placement, especially a DES, discontinuing aspirin and P2Y12 inhibitors (such as clopidogrel) may be fatal due to the high risk of stent thrombosis. However, bleeding complications from low platelets can be devastating as well. Bleeding can be further exacerbated by heparin, which is often utilized in the management of ACS. Since heparin-induced thrombocytopenia (HIT) is a potential cause of thrombocytopenia in this setting, it is of upmost importance that heparin be discontinued until the etiology of thrombocytopenia is identified. In our patient, we reversed heparin with protamine sulfate due to active bleeding in the groin but continued dual antiplatelet therapy with aspirin and clopidogrel to minimize the risk of stent thrombosis.

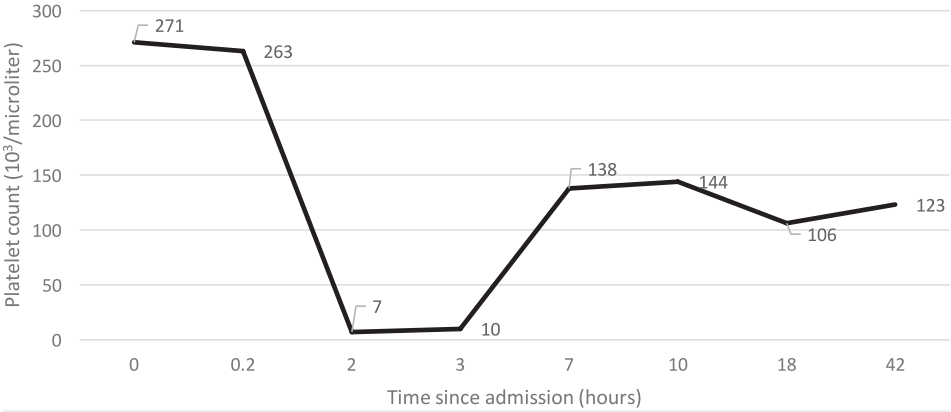

Figure 2.
Platelet count trend during hospitalization.

Thrombocytopenia is defined as a platelet count < 100,000/mm^3, with severe thrombocytopenia < 50,000/mm^3 and profound thrombocytopenia < 20,000/mm^3.[3] GP IIb/IIIa inhibitors are known to cause thrombocytopenia in 0.7% to 2% of patients after initial exposure and up to 4.6% in patients after re-exposure.[4,5] Thrombocytopenia occurring in this scenario can be attributed to multiple etiologies. In our patient, the possible causes of thrombocytopenia included drug induced (i.e., eptifibatide and clopidogrel), HIT, HIV, and pseudothrombocytopenia (Table 1). A review of the peripheral smear excluded pseudothrombocytopenia. Clopidogrel-induced thrombocytopenia is known to present as thrombotic thrombocytopenic purpura (TTP-HUS). Our patient did not have any clinical manifestations of TTP-HUS, and recovery of the platelet count after stopping eptifibatide further ruled out clopidogrel-induced thrombocytopenia. Although we reversed heparin with protamine sulfate, HIT type II was unlikely as it is not known to present acutely within a few hours of the first exposure; HIT type I was also excluded as our patient had not been exposed to heparin products in the previous 100 days. Another possible etiology could have been HIV-induced immune mediated thrombocytopenia. However, while it has been reported in literature, HIV-induced thrombocytopenia is usually indolent in its course, and severe bleeding manifestations are rare despite low platelet counts.[6] Moreover, the rapid onset and rapid recovery of platelet count following discontinuation of eptifibatide supports eptifibatide-induced thrombocytopenia as the likely etiology.

Multiple mechanisms of thrombocytopenia have been proposed in HIV patients, including immune-mediated peripheral destruction, bone marrow suppression from infected megakaryocytes, and secondary causes such as hypersplenism, bone marrow infiltration from infections and lymphomas, and myelosuppressive effects of HIV medications.[7] The prevalence of antiplatelet antibodies increases as disease progresses, however their exact role in thrombocytopenia is unclear. Some of the antibody has been shown to be bound to epitopes with homology to HIV proteins, suggesting molecular mimicry. The presence of this antibody was associated with thrombocytopenia, and infusion of this antibody in mice led to thrombocytopenia.[8]

The proposed mechanisms of GP IIb/IIIa inhibitor-mediated thrombocytopenia include direct platelet activation by the drug or immune-mediated platelet destruction due to antiplatelet antibodies, which are active only in the presence of GP IIb/IIIa inhibitors.[9] Another possible mechanism is the induction of conformational change in GP IIb/IIIa receptors by these drugs; this, in turn, may lead to expression of neoepitopes or ligand-induced binding sites, which are recognized by naturally occurring antibodies.[10] It is unknown whether antiplatelet antibodies caused by HIV would mediate platelet destruction in the presence of GP IIb/IIIa inhibitors, akin to naturally occurring antiplatelet antibodies or those formed due to prior exposure to these drugs.[9] The expression of neoepitopes on the platelet surface due to conformational change of receptors from GP IIb/IIIa inhibitors may also provide binding sites for HIV-induced antibodies. This would be an interesting line of investigation and, if proved, would likely diminish the use of these drugs in HIV-positive patients.

Therapies such as steroids and immunoglobulins that are used in thrombocytopenic purpura have not been investigated for GP IIb/IIIa inhibitor-induced thrombocytopenia. Platelet transfusion is needed to tide over the acute crisis in the event of active bleeding. In many similar cases reported in the literature, all antiplatelet agents were discontinued in patients suspected of having eptifibatide-induced thrombocytopenia.[11,12] We followed a different approach since we had placed a DES in the proximal LAD a few hours earlier, continued aspirin and clopidogrel, and reversed heparin and platelet transfusion.

In conclusion, this case demonstrates that uninterrupted dual antiplatelet therapy for eptifibatide-induced thrombocytopenia in patients who have had recent stent placement is feasible. Alternative etiologies of thrombocytopenia should be considered in these patients.

DIFFERENTIAL DIAGNOSIS	CONFIRMATION	ONSET AND NADIR OF PLATELET COUNT	MANAGEMENT
Pseudothrombocytopenia	Review of peripheral smear and recollection of blood in non-EDTA coated vials	Acute, variable	None
Heparin-induced thrombocytopenia type 1	14C-serotonin release assay, heparin-induced platelet aggregation	2 days, 100-120,000/mm^3	Discontinue all heparin-containing products
Heparin-induced thrombocytopenia type 2	14C-serotonin release assay, heparin-induced platelet aggregation	4-10 days or earlier, 20,000 – 100,000/mm^3 (Drop in platelet count > 50% of baseline)	Discontinue all heparin-containing products
Thienopyridine-induced thrombotic thrombocytopenic purpura	Schistocytes in peripheral smear, elevated creatinine, anemia, clinically identical to TTP (confusion, headache, renal failure, nausea, vomiting, diarrhea), severely reduced ADAMTS13 activity (< 10%)	Days-months, < 20,000/mm^3	Supportive; discontinue P2Y12 inhibitor
Human immunodeficiency virus-induced thrombocytopenia	Exclusion of other causes in the appropriate clinical setting	Years, slow indolent decline in platelet count in severe cases, < 20,000/mm^3	Exclude secondary causes, discontinue marrow-suppressing medications, and control HIV infection
Glycoprotein IIb/IIIa-induced thrombocytopenia	Exclusion of other causes in the appropriate clinical setting	Hours, < 20,000/mm^3	Discontinue GP IIb/IIIa with platelet transfusion

Table 1.
Summary of the etiologies of thrombocytopenia in the current case. EDTA: ethylenediaminetetraacetic acid; TTP: thrombotic thrombocytopenic purpura; ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HIV: human immunodeficiency virus; GP: glycoprotein

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords
eptifibatide, thrombocytopenia, acute coronary syndrome

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