

Integrilin Related Thrombocytopenia With Diffuse Alveolar Hemorrhage

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CASE:

A 66-year-old male presents to hospital with three days of progressive fatigue, bilateral leg swelling, and subjective fevers. He had worsening dyspnea on exertion severely affecting the activities of his daily living. The patient's past medical history is significant for coronary artery disease. He had a percutaneous coronary intervention three months prior with Xience drug-eluting stent placement to the right posterior descending artery. At the same time, due to severe aortic stenosis, a bioprosthetic Carpentier-Edwards mechanical aortic valve replacement was also done. His most recent transthoracic echocardiography demonstrated a left ventricular ejection fraction of 65% with stage one diastolic dysfunction. Other medical history includes chronic congestive heart failure- AHA Class C, hypertension, non-insulin dependent diabetes mellitus type 2, dyslipoproteinemia, benign prostatic hypertrophy, obstructive sleep apnea, and morbid obesity. No known drug allergies exist. Family history was negative for premature coronary disease but positive for hypertension. Past social history includes vocation as a farmer, active tobacco use with 30-pack year history, two glasses of wine weekly, and no illicit drug use. Medications include Glimepiride 2 mg daily, Metformin 1 gram daily, Gabapentin 100 mg t.i.d., Synthroid 40 mcg daily, Lasix 40 mg at night, Norvasc 10 mg daily, Lipitor 20 mg daily, aspirin 325 mg daily, Lyrica 50 mg t.i.d., Omeprazole 20 mg daily, Flomax 0.4 mg daily, Plavix 75 mg daily, Potassium 20 mEq daily, Quinapril 20 mg daily, Lopressor 50 mg b.i.d., Tramadol 30 mg t.i.d.

Review of systems on admission was notable for chills, subjective fever, dyspnea on exertion, orthopnea, and mild leg edema. Vital signs at presentation included a temperature of 102.5 degrees Fahrenheit, regular pulse at 110 bpm, brachial blood pressure of 91/70, respirations at 14 per minute, and oxygen saturation of 94% on bi-level positive pressure ventilation- 40%, 12/5 cm water. Physical exam demonstrates the patient in moderate distress with bilateral basilar rales at the bases, trace bilateral lower extremity edema. Heart was regular, with prominent A2 heart sound at the right sternal border. Osteopathic exam with T4-T7 RISr, AA rotated right.

The initial surface electrocardiogram showed sinus tachycardia, poor R wave progression, and lateral ischemia (see Figure 1). Portable Chest X-Ray demonstrated no active pulmonary disease, no cardiomegaly (see Figure 2). CK= 519; CKMB=10.1; Troponin I=5.33; BNP=543; Na: 142; K+: 3.8; Cl: 102; CO2: 24; BUN: 40; Cr: 1.83; Glucose: 254; Ca: 8.6; WBC: 11.5- 91% neutrophils; Hgb: 9.2; Hct: 27.6; Platelets: 191,000. Screening UA was positive for UTI.

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66 yr	Vent. rate	119	BPM
Male	PR interval	196	ms
	QRS duration	84	ms
Room:ER5	QT/QTc	292/410	ms
Loc:202	P-R-T axes	56 13 154	

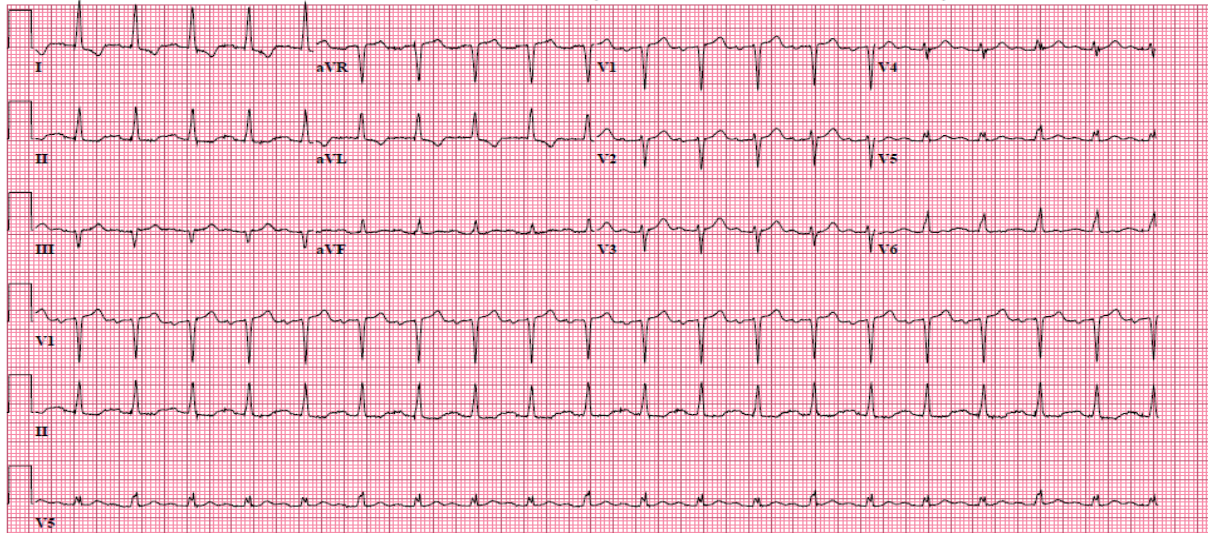


Figure 1: Initial EKG – Sinus Tachycardia. Poor R-wave progression. Lateral T-wave inversions.

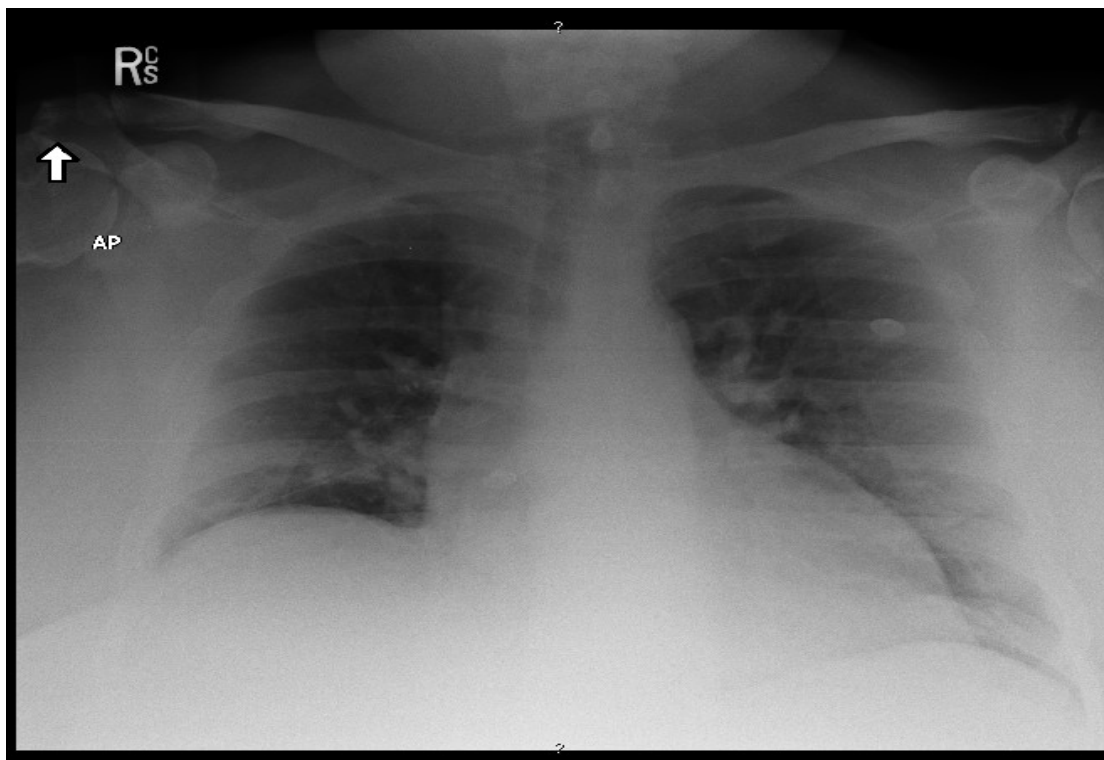


Figure 2: Initial AP CXR— The cardiac silhouette is within normal limits. The lungs are clear. . The costophrenic angles are clear. There is no active disease seen in the chest.

APPROACH:

Initial management was tailored towards treatment of Non-ST Elevation Myocardial Infarction (NSTEMI), urosepsis, and acute kidney injury. Specific therapy initiated for NSTEMI included lopressor, aspirin, Plavix, Lipitor, heparin infusion, and integrilin infusion. Vancomycin and Zosyn were given as part of his initial antibiotic regimen in the emergency department. However, only zosyn was continued for admission. The patient was admitted to the intensive care unit. Twelve hours after admission, a repeat complete blood count (CBC) revealed a drop in the hemoglobin from 9.2 to 7. Severe thrombocytopenia was noted, with the patient's platelets decreasing from 191,000 microL to 2,000 microL.

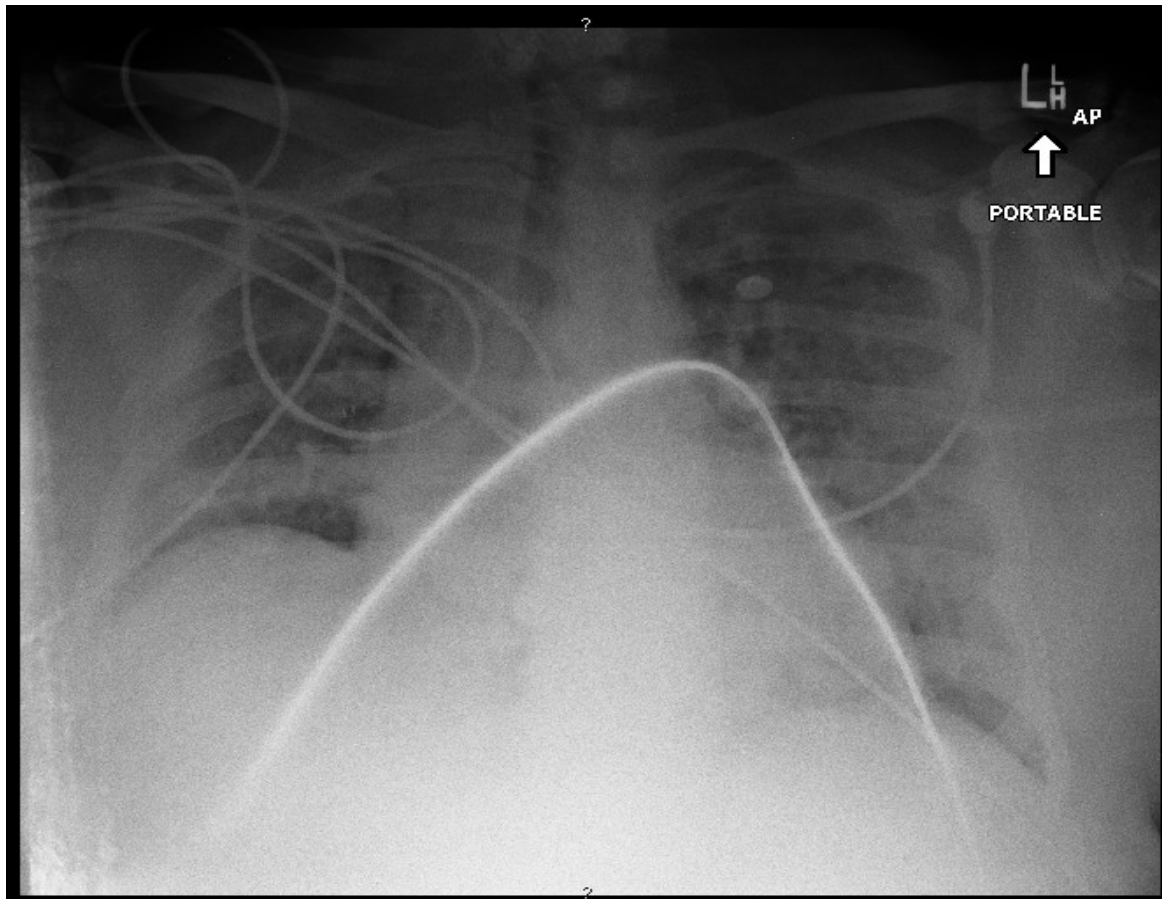


Figure 3: AP PCXR 12 hours after admission— There is moderate bilateral airspace disease not visualized on the previous examination. The cardiac silhouette is top normal and unchanged. There is stable elevation of the right hemidiaphragm.

At the same time, the patient developed hemoptysis and severe respiratory distress. A stat portable chest X-ray showed bilateral airspace disease (see figure 3). Alveolar hemorrhage was suspected and immediate intubation and mechanical ventilation was performed. The

bronchoscopy done at the bedside confirmed bleeding in the lungs (see figure 4 for the pulmonologist's report). Pseudothrombocytopenia was ruled out with a repeat CBC drawn in a citrate tube demonstrating a platelet count of 3,000/ microL. Peripheral smear was completed but with too few platelets present for histological comment. The International Normalized Ratio (INR) was noted to be 1.8. Decreased platelet production, dilution, and splenic sequestration were not compatible with the clinical picture due to its rapidity. Thrombocytopenia due to disseminated intravascular coagulation was also ruled out. A careful inventory of the patient's medications was undertaken. Given the rapidity of onset, heparin, plavix, aspirin, and zosyn were discontinued but deemed highly unlikely as causative agents. A serologic test for heparin induced antibody (HIT) panel was sent and was later on confirmed to be negative for HIT. Intergrilin was the only remaining agent suspected capable of causing this sudden-onset severe thrombocytopenia. As such, it was discontinued immediately. The case was discussed in detail with the hematologist who agreed with the diagnosis of integrilin-induced thrombocytopenia based on clinical grounds. A number of blood products including platelets (6 packs), several units of packed red blood cells and fresh frozen plasma were transfused, eventually stabilizing the patient's clinical status and blood profile. No evidence of recurrent bleeding was noted during the next several days. The patient was extubated without complications after a week of being in a mechanical ventilator. His antiplatelet therapy in the form of aspirin 162 mg and plavix 75 mg was reinstated. The patient was transferred out of the ICU on hospital day 8. He was discharged to a sub-acute rehabilitation facility on day 11.

REASON FOR PRESENTATION

The use of IIb/IIIa inhibitors, such as Integrilin, has seen a tremendous rise as part of the treatment for acute coronary syndromes. It is important for clinicians to realize however, that the potential serious side effects of integrilin include severe, sudden-onset, life threatening thrombocytopenia. Therefore, close clinical monitoring of the platelet count is warranted within at least four hours after initiation of treatment. Clinicians should be cognizant of the signs and symptoms of bleeding such as purpura, hemoptysis, mucosal bleeding, etc. Judicious use of this potent medication demands understanding of this possible adverse reaction.

DISCUSSION:

Platelet glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors block fibrinogen binding to the activated GP IIb/IIIa, and have been used for treatment of high-risk patients with NSTEMI. GP IIb/IIIa is a member of the integrin family of cell adhesion receptors and is essential for normal hemostasis. Following platelet activation, the IIb/IIIa complex undergoes a dramatic conformational change that allows the adhesive protein, fibrinogen, to bind, forming a bridge between platelets that mediates platelet-platelet interactions and thrombus formation.

BRONCHOSCOPY REPORT

Date 3/11/09
 Precop. Diagnosis Alveolar Hemorrhage
 Premedications _____
 Anesthesia _____
 Allergies _____
 Medicinal History _____
 Fluoroscopy _____ Photography _____
 Lab Data: pH _____ PaO₂ _____ PaCO₂ _____
 Hb _____ Hct _____ TWBC _____ PT _____ PTT _____
 Platelets _____ EKG _____ PPD _____

SPECIMENS LOCATION

HISTOLOGY
 Bronchial
 Transbronch.
 Carina
 EM

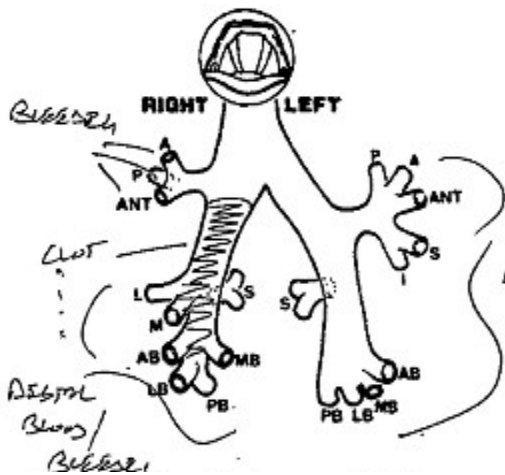
BRUSHING

Cytology
 AFB
 Gram's
 Fungal
 Special

WASHING

Routine
 AFB
 Fungal
 Cytology
 Immunology

BRONCHOSCOPIC FINDINGS



Distal Blood Bleeding
 Distal Blood Return
 IMPRESSION:

Pools (R)

IMPRESSION:

1. Clot formation in the right mainstem bronchus intermedius into the right middle and right lower lobe segments.
2. Distal bleeding noted from the right upper lobe, right middle lobe and right lower lobe, consistent with alveolar hemorrhage.
3. Distal blood return from the left upper lobe lingula and left lower lobe segments, without evidence of active bleeding.

Figure 4: Bronchoscopy report subsequent to development of acute bilateral alveolar airspace disease and hemoptysis.

Inappropriate activation of IIb/IIIa contributes substantially to cardiovascular disease. The development of effective fibrinogen receptor antagonists, therefore, has been a major breakthrough in the management of coronary artery diseases.

Eptifibatide is a small protein which interacts with the IIb/IIIa receptor on the platelet surface [2,6]. Eptifibatide has been associated with profound thrombocytopenia, although this is exceedingly rare. More common reactions have been noted with a related medication, abciximab [3].

Profound thrombocytopenia, classified as a decrease in platelet count to <20,000/ microl within 24 hours, is an associated class effect of GP IIb/IIIa inhibitors. Current literature suggests thrombocytopenia associated with eptifibatide occurs in less than one percent [3].

Retrospective data analysis is as follows: The ESPRIT trial included 1,040 patients receiving eptifibatide, with occurrence of thrombocytopenia <20,000/ microL of 0.2% [1,9]. The PURSUIT trial included 4,614 patients treated with eptifibatide, with incidence of thrombocytopenia <20,000/ microL of 0.1% [1,5]. It is recommended that once eptifibatide is initiated, surveillance of the platelet count should be done 2-6 hours after the drug is started [11].

The exact pathophysiology of eptifibatide associated thrombocytopenia remains unknown [2]. One theory posits an immunologic mechanism. Drug dependent antibodies to platelet membranes in certain patients may induce a change in the conformation in the GP IIb/IIIa receptors on the platelet surface [2,6]. This may lead to lead to auto-destruction of platelets by existing serum antibodies.

Through previous clinical data of the abciximab-induced thrombocytopenia, eptifibatide related thrombocytopenia might be better understood. In many case reports, abciximab has been associated with precipitous thrombocytopenia within hours of administration in GP IIb/IIIa-inhibitor naïve patients [3]. This reaction differs from other drug-dependent anti-platelet antibodies that have much longer exposure times prior to immune memory. Literature review suggests that a minimum of 2-3 weeks may be needed for the development of potential immune-mediated antibody responses [3].

A hypothesis to explain the rapid thrombocytopenia following initial exposure to GP IIb/IIIa inhibitors centers on immune response. Certain individuals may have pre-existing antibodies which interact with the medication-altered GP IIb/IIIa molecule [3]. The relative rare response to eptifibatide may be due to a relative paucity of such pre-existing antibodies [3,4]. Changes within the GP IIb/IIIa molecule itself due to platelet aging may predispose the patient to this reaction[3]. Although antibodies may appear to be involved in integrilin-induced thrombocytopenia, the relative rare response to eptifibatide may be due to a relative paucity of such pre-existing antibodies to this drug [3,4].

It is important to account for alternative sources of thrombocytopenia however. Sepsis, disseminated intravascular coagulation, pseudothrombocytopenia, infection, and other medications should be investigated. If eptifibatide or other GP IIb/IIIa inhibitor reaction is suspected, these agents should be quickly discontinued. The plasma half-life of eptifibatide is approximately 2 hours, and bleeding times return to baseline within 1 hour after eptifibatide is discontinued [1].

Management of acute bleeding from integrilin-induced thrombocytopenia includes discontinuation of the drug, platelet transfusion, and supportive care. Our patient's profound symptoms were probably confounded by the presence of other agents that promote bleeding like heparin, aspirin, and plavix. These agents are often used together for the treatment of acute coronary syndromes. However, heparin rarely causes profound thrombocytopenia, and if thought to complicate the scenario, should be reversed with protamine. This was considered in

our case but was not implemented. It was thought that since the half-life of integrilin is short, platelet recovery should be attained by integrilin cessation and by transfusion of platelets and other blood products to correct other coagulation defects. Regardless of platelet transfusion, the platelet counts usually return to baseline in 4-5 days [11].

Our patient was also being treated for a systemic infection. Although DIC as a cause of thrombocytopenia was entertained, the rapidity of onset and lack of thrombosis made this scenario unlikely.

Cases of vancomycin-induced thrombocytopenia have also been described in the literature. Proposed mechanisms include hapten-complex formation with platelets, and antibody formation leading to lysis. This phenomenon occurs less frequently than HIT and is usually seen 8 days after vancomycin initiation. Some published data however, also describe cases of thrombocytopenia after the first day of administration. Platelet counts range from 1,000 to 60,000 [11]. Studies show that this entity is not usually responsive to platelet transfusions. Our patient did receive a dose of Vancomycin in the emergency department. It may still be that his thrombocytopenia was from Vancomycin. However, the probability that Vancomycin is the cause of our patient's thrombocytopenia was greatly diminished by his response to platelet transfusions.

Clinicians may sometimes face a decision whether to continue aspirin and plavix especially in patients who recently had coronary stents placed. Literature suggests that antiplatelet therapy should only be held in patients with high risk for bleeding and whose platelet counts are below 20,000 [10]. Needless to say, our patient's respiratory decline and alveolar hemorrhage dictated the need to stop all anticoagulant and antiplatelet therapy. Fortunately, his recently placed coronary stents did not show evidence of occlusion.

CONCLUSION

Integrilin (eptifibatide) is a potent adjunct medication in the treatment of acute coronary syndromes. It is important to understand the possible adverse events relating to eptifibatide administration. Adequate literature documents the class risks of thrombocytopenia associated with glycoprotein IIb/IIIa inhibitor administration— specifically abciximab, but growing case reports such as this, document similar risk with eptifibatide. Prompt recognition and treatment of eptifibatide-associated thrombocytopenia can serve to minimize patient morbidity and mortality.

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