Acute profound thrombocytopenia secondary to local abciximab infusion

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Glycoprotein (GP) IIb/IIIa receptor antagonists are powerful antiplatelet agents that are typically used in percutaneous coronary intervention. All three GP IIb/IIIa agents currently approved for use in the United States cause thrombocytopenia as a rare side effect. Abciximab is unique to the class in that it is a modified monoclonal antibody to the GP IIb/IIIa receptor, a property that can lead to increased platelet destruction. Presented herein is a patient who received a local infusion of abciximab for a lower-extremity thrombus and within 2 hours developed an acute profound thrombocytopenia that likely caused a large retroperitoneal hematoma. This case demonstrates the importance of checking platelet count within 2 to 4 hours after local (in addition to systemic) abciximab administration. Additionally, this report outlines how other causes of acute precipitous platelet drops, such as heparin-induced thrombocytopenia and pseudothrombocytopenia, can be rapidly excluded and allow for the prompt initiation of optimal therapy to minimize bleeding.

CASE PRESENTATION

An 81-year-old man presented with a 4-hour history of sudden-onset, sharp pain in his left foot. The pain was associated with numbness in all five digits of his foot. He previously had heart failure, permanent atrial fibrillation, chronic kidney disease, and aortic stenosis. His aortic valve had been replaced by a bioprosthesis. Three weeks prior to admission, the patient had several episodes of hematuria, and warfarin was temporarily discontinued.

On arrival, he was in acute pain but afebrile. His blood pressure was 175/100 mm Hg; heart rate, 93 beats/minute; respiratory rate, 16 breaths/minute; and oxygen saturation, 99% on room air. His left foot was cold, and the great toe and distal tip of the second and third digits were blue. He had no sensation in any of his toes or in the dorsal and ventral aspects of his foot. His posterior tibial and dorsalis pedis arterial pulses were not palpable; his popliteal pulse was barely palpable. An electrocardiogram demonstrated right bundle branch block and atrial fibrillation. His hemoglobin was 10.4 g/dL; hematocrit, 31.5%; platelet count, 118,000/ μ L; and international normalized ratio, 0.9.

The patient was taken to the catheterization laboratory for percutaneous intervention for acute left lower limb ischemia. Fluoroscopy with contrast injection revealed an occlusive (99%)

thrombus at the bifurcation of the left superficial femoral and profunda femoris arteries with no collateral circulation. An AngioJet catheter was utilized with multiple passes to break up the thrombus. Repeat angiography showed mild improvement in flow but persistence of the thrombus. At this point, 10 mg of abciximab was injected directly into the remaining thrombus through a ClearWay infusion catheter. Angiography then revealed improved flow at the bifurcation of the superficial femoral and profunda femoris arteries but persistently poor flow below the knee. The ClearWay catheter was then advanced to the peroneal and anterior tibial arteries, and 5 mg of abciximab was injected locally at each site. Repeat angiography revealed a patent artery with complete resolution of the thrombus.

After the procedure, heparin was initiated with a goal partial thromboplastin time of 55 to 90 seconds. Six hours postoperatively, the patient's blood pressure acutely fell to 64/40 mm Hg, and his heart rate rose to 115 beats/minute. Repeat complete blood count revealed a hemoglobin of 7.8 g/dL, a hematocrit of 23%, and a platelet count of 10,000/ μ L. The heparin infusion was immediately stopped and the patient was given a 500-cc bolus of normal saline. Peripheral smear showed no platelet clumping. While there was concern for retroperitoneal bleeding, the patient was deemed to be too hemodynamically unstable to be taken for a computed tomography (CT) scan. A vasopressin infusion at a rate of 0.03 units/minute was initiated to maintain a mean arterial systolic pressure above 65 mm Hg. The patient was then transfused three "6-packs" of platelets followed by 2 units of packed red blood cells. When his blood pressure began to rise within 3 hours, the vasopressin was discontinued.

The following day, the patient complained of severe right flank pain and was urgently taken for a CT scan of the abdomen with contrast, which revealed a large right-sided retroperitoneal hematoma extending from the diaphragm to the pelvis. During the next 4 days, he required daily platelet infusions to maintain his platelet count above 50,000 cells/ μ L (*Figure*). On hospital day 5, a serotonin release assay was negative for heparin-induced thrombocytopenia (HIT). At discharge on hospital day 5, the

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Figure. Patient's platelet count following initial abciximab infusion and subsequent response to multiple infusions.

patient's platelet count had rebounded to 98,000 cells/μL, and his flank pain had resolved.

DISCUSSION

Platelet aggregation is known to play a major role in the pathogenesis of acute coronary syndromes and of ischemic complications following percutaneous coronary intervention (PCI). In recent years, multiple agents have been designed to modulate platelet aggregation. The most potent of these antiplatelet agents are the glycoprotein (GP) IIb/IIIa receptor inhibitors (1). Recently, the use of GP IIb/IIIa receptor inhibitors has been expanded to acute peripheral arterial occlusions, where their strongest effect is seen with intraarterial applications (2, 3). While this practice is currently off label, initial reports have shown this method to improve both short- and medium-term outcomes (3).

All three GP IIb/IIIa receptor inhibitors (abciximab, tirofiban, and eptifibatide) approved for use in the United States have been associated with an increased risk of thrombocytopenia, which can be attributed to a shared physiologic mechanism. GP IIb/IIIa receptor inhibitors bind to platelet surfaces and create ligand-induced binding sites. While ligand-induced binding sites are normal alterations occurring throughout a platelet's life cycle, the administration of GP IIb/IIIa inhibitors can cause formation of ligand-induced binding sites in such large amounts that they produce widespread platelet destruction (4).

Compared with the other two agents, abciximab has an additional characteristic that predisposes patients to a higher incidence of both mild (<100,000 cells/μL) and severe (<50,000 cells/μL) thrombocytopenia. Whereas tirofiban and eptifibatide are synthetic receptor antagonist molecules, abciximab is a modified chimeric monoclonal antibody. The same peptide sequence that gives abciximab its specificity for the GP IIb/IIIa receptor also predisposes it to naturally occur-

ring preformed immunoglobulin G (IgG) antibodies that attach to abciximab-coated platelets and result in splenic sequestration and destruction (5). In a 2002 study by Curtis et al, these preformed abciximab-coated platelet-reactive IgG antibodies were found to occur in 15 of 150 subjects with no previous exposure to abciximab and 15 of 16 patients with prior exposure (6). The increase in antibodies associated with reexposure explains the increase in thrombocytopenia from 2.5% to 6% to as high as 12% in patients with reexposure (7).

Identification of these preformed IgG antibodies would allow for identification of patients at high risk for thrombocytopenia. While several preemptive screening tests exist, the accuracy of these tests is

currently unknown (8). Without a proven screening modality for the prevention of abciximab-induced thrombocytopenia, focus is instead concentrated on prompt recognition.

Current recommendations call for obtaining a platelet count within 2 to 4 hours of initiation of GP IIb/IIIa inhibitors (8, 9). Additionally, abciximab is the only member of the class that requires platelet monitoring 24 hours following administration (due to its ability to induce antibodies at any point while remaining in the circulation) (8). It should be noted that while it is standard to obtain a complete blood count within a few hours of systemic GP IIb/IIIa administration, no current recommendations exist regarding local peripheral application, a caveat that has since been addressed by our institution. Once thrombocytopenia is identified in the setting of abciximab administration, attention should be focused on confirming the underlying etiology and initiating appropriate treatment to minimize bleeding complications.

Heparin is often concurrently administered with abciximab and can also cause thrombocytopenia. HIT can be identified by means of several functional assays. These assays are time consuming and may require up to a full week to complete, limiting their role as a confirmatory test. Fortunately, several characteristics allow HIT to be distinguished from abciximab-induced thrombocytopenia in the acute setting. HIT rarely causes platelet counts to drop below 30,000 cells/μL, and thus platelet counts below this number strongly suggest abciximab as the etiology (10). Etiologies can also be distinguished based upon time of onset. Abciximab-induced thrombocytopenia may occur from several hours to 10 days after administration. There are two types of HIT (HIT-I and HIT-II), which differ in both severity and time of onset. Thrombocytopenia associated with HIT-I usually occurs between 1 and 5 days and is usually mild, often resolving even with continued heparin treatment (10). HIT-II typically occurs between 4 and 20 days and causes a

more severe platelet drop that may result in thrombus formation (11). While there is some overlap between the onset of HIT and abciximab-induced thrombocytopenia, several general conclusions are helpful in differentiating between them. Thrombocytopenia developing within the first day or any severe thrombocytopenia developing within the first 3 to 4 days is likely due to abciximab. In contrast, HIT (specifically HIT-II) should be suspected in any thrombocytopenia that occurs after day 10. Separation of these two etiologies will allow for prevention of unnecessary discontinuation of both agents and minimize thrombotic complications secondary to PCI.

Once HIT is excluded, it is also important to exclude pseudothrombocytopenia, which is specific to abciximab. Pseudothrombocytopenia is caused by platelet clumping, causing a falsely decreased platelet level. It is likely caused by a similar mechanism as idiopathic thrombocytopenic purpura, which is due to precipitation of autoantibodies (12). This mechanism is reflected in the fact that while pseudothrombocytopenia occurs in over 2% of patients receiving abciximab, it has never been reported with the other two GP IIb/IIIa inhibitors (8). It can be rapidly identified by the presence of platelet clumping on peripheral blood smear (8, 13). Prompt separation of these two etiologies is critical, as the treatment of abciximab-induced thrombocytopenia is platelet transfusion, while this strategy in pseudothrombocytopenia may cause thrombosis (8).

Once abciximab-induced thrombocytopenia has been detected and the etiology has been confirmed, management is relatively simple and is guided by platelet count. Platelet counts below 50,000 cells/ μ L should prompt immediate cessation of abciximab (if actively being administered), and therapeutic platelet transfusions should be utilized in patients with significant bleeding or platelet counts below 20,000 cells/ μ L (14, 15). Platelet levels should continue to be closely monitored until signs of a transfusion-independent increase are observed. Platelet counts typically return to baseline over a period of 3 days to 2 weeks (8, 9).

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