Tirofiban Induced Thrombocytopenia: A Rare but Severe Adverse Effect

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1. Introduction

Glycoprotein IIb/IIIa receptors present on platelet membranes are responsible for platelet aggregation by crosslinking von Willebrand factor and fibrinogen [1]. Glycoprotein IIb/IIIa receptors have been one of the major targets in the management of high risk acute coronary syndrome and in conjunction with angioplasty, especially for bailout during thrombotic complications [2].

Tirofiban, a small, non-peptide and a highly specific Glycoprotein IIb/IIIa (GPI), is a competitive inhibitor of the platelet fibrinogen receptor and when administered intravenously, tirofiban inhibits ex vivo platelet aggregation in a dose and concentration-dependent manner. It is a risk factor for severe thrombocytopenia [1,3]. The pathogenesis for this phenomenon is not completely clear but is believed to be due to drug-dependent antibodies that adhere to platelets only in the presence of the offending drug [1,3–6]. There is growing body of evidence to suggest that tirofiban alters the arrangement of glycoprotein receptors on the platelets, hence creating a new antigen which is then recognized and removed from the circulation due to immune-mediated reaction. This, in essence, is the disposal of thrombocytes which is the cause of the sudden and severe thrombocytopenia [7]. Severe thrombocytopenia can set in immediately after exposure to Tirofiban [6].

We hereby report a case of 69-year-old female with tirofiban-induced thrombocytopenia in which the platelet count dropped to within 12–24 h of administration with no other alternative explanation.

2. Case presentation

A 69-year-old female with past medical history significant for diabetes mellitus, coronary artery disease, and hypertension presented to the emergency department with complaints of chest pain that was substernal in nature, not associated with any radiation, diaphoresis, nausea, or vomiting. At the time of admission, patient physical examination was unremarkable. Her platelet levels were 224 k/mm$^3$ at baseline and troponins (<0.01). She was initially started on aspirin 81 mg. She had an invasive angiogram (Figure 1) due to high pre-test probability the next day and was administered tirofiban infusion during the heart catheterization, she had two drug eluting stents placed in mid and distal portion of left anterior descending artery that were found to have 85% stenosis and 80% stenosis, respectively.

The next day after percutaneous coronary intervention, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$. Her antiplatelets were held due to acute severe thrombocytopenia. Hematology service was consulted, patient had developed ecchymosis and mild epistaxis, on further evaluation it was determined that her platelets had decreased from 224 to 2 k/mm$^3$.
improved platelet count to 442 k/mm$^3$. The etiology of thrombocytopenia was concluded to be tirofiban induced as platelet count was not affected by antiplatelets when they were restarted and other alternative explanations for thrombocytopenia were ruled out.

3. Discussion

Thrombocytopenia is a prominent complication of GPIs with an incidence of severe thrombocytopenia (platelet count <50 k/mm$^3$) to be 0.2–0.5% \cite{1,3,5,8}.

Five different presentations of GPI-induced thrombocytopenia have been reported: (i) Acute Severe Thrombocytopenia (platelets <10 k/mm$^3$) within 12 h of first dose administration, (ii) Acute Thrombocytopenia within 12 h of second dose administration, (iii) Delayed Thrombocytopenia (5–7 days after exposure), (iv) Anaphylaxis after first or second exposure, and (v) Pseudo thrombocytopenia \cite{1,3}.

Drug-induced thrombocytopenia is a diagnosis of exclusion and other alternative diagnoses should be carefully evaluated. Heparin-induced thrombocytopenia is similar to tirofiban-induced thrombocytopenia, both occurring within 1–4 h or 7–14 days, but this can be ruled out if the patient has had no previous exposure \cite{1}. Aspirin and clopidogrel have not reported to result in cases of isolated acute severe thrombocytopenia \cite{3}. Studies have shown clopidogrel to occasionally be associated with TTP, which typically encompasses microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction \cite{3}. Pseudo thrombocytopenia, which is clumping of platelets, can be excluded on a peripheral smear \cite{4}. Dual anti-platelet drugs are another potential cause of thrombocytopenia, however, its onset occurs after days or weeks unlike our patient’s case \cite{5}.

To validate the hypothesis that tirofiban is, in fact, the offending agent, a case reported in 2007 employed ELISA and flow cytometry to confirm the drug-dependent antibodies were indeed formed only in the presence of tirofiban \cite{9}.

Studies explain how crucial it is to understand the life-threatening consequences associated with intracoronary use of tirofiban \cite{3}. A platelet count before and after use of tirofiban at 2–6-hour intervals is strongly encouraged \cite{3,4}. As the drug-dependent antibodies may persist for years, it is also essential for the patient to avoid the drug indefinitely in the future \cite{6}.

Just like any case of drug-induced thrombocytopenia, recovery begins as soon as tirofiban is discontinued, and continues to get resolved over the next few days with early supportive care using steroids, Ig-G immunoglobulins, and platelet transfusion if necessary \cite{1,3,6}. Patients with severe thrombocytopenia without significant bleeding must not have platelet transfused due to potential risk of stent thrombosis or reinfarction \cite{10}.

4. Conclusion

In conclusion, tirofiban-induced thrombocytopenia is a rare but serious complication. Tirofiban-induced
thrombocytopenia should be managed early and carefully due to the concomitant risk of bleeding and stent thrombosis or reinfarction.

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