CASE REPORT

Successful Treatment of Severe Heparin-induced Thrombocytopenia with Intravenous Immunoglobulin, Platelet Transfusion and Rivaroxaban: A Case Report

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Key words: heparin-induced thrombocytopenia; thrombosis; intravenous immunoglobulin; platelet transfusion; rivaroxaban

Abstract Heparin-induced thrombocytopenia (HIT) is a relatively infrequent complication of heparin administration. HIT can cause devastating thrombosis, making it one of the most serious adverse drug reactions encountered in clinical practice. We successfully treated a case of severe HIT presenting with thrombosis and life-threatening bleeding complications with intravenous immunoglobulin (IVIG), platelet transfusion and oral anticoagulant Rivaroxaban. In this case, we considered that IVIG played the most important role by preventing further thrombosis, increasing the platelet count, and ensuring the efficacy of Rivaroxaban. We therefore suggest that IVIG might be the optimal treatment for patients with this urgent condition.

HEPARIN-INDUCED thrombocytopenia (HIT) is an immune-mediated adverse reaction caused by antibodies that recognize platelet factor 4 (PF4) in complex with heparin or other linear polyanions. HIT is characterized by moderate thrombocytopenia and paradoxical arterial or venous thromboses.^[1] Although it is a relatively rare complication of heparin administration, HIT, which

usually occurs 5 to 14 days after starting heparin, may cause devastating thromboses, making it one of the most serious adverse drug reactions in clinical practice. In contrast to other drug-induced immune thrombocytopenia (DITP), HIT is characterized by a platelet count $<20 \times 10^9/L$ in only 10%–15% of cases,^[2] while thromboses rather than bleeding are the typical clinical manifestation. Treatment involves substituting heparin with an alternative (non-heparin) anticoagulant, and the antibodies then usually disappear 50–80 days after heparin withdrawal.^[3] The clinical and immunologic response to heparin discontinuation in patients with acute HIT follows a predictable pattern. Prophylactic

Received for publication May 22, 2018. Published online February 22, 2019.

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platelet transfusion is not recommended and four-limb screening compression ultrasonography is recommended in most cases. Here, we describe a patient with HIT and life-threatening hemorrhagic and thromboembolic complications who was treated successfully with intravenous immunoglobulin (IVIG), platelet transfusion and oral anticoagulation Rivaroxaban.

CASE DESCRIPTION

An 80-year-old woman was admitted to the Orthopedic Department due to traumatic hip fracture. She received low-molecular weight heparin calcium (Fraxiparine) (38 IU/kg) pre- and postoperatively as prophylaxis for thrombosis. On the 12th day (D12) of treatment, her platelet count fell from $245 \times 10^9/L$ (D9) to $2 \times 10^9/L$, with a left lower limb deep venous thrombosis (DVT). Her 4Ts score was 5 or 6, based on thrombocytopenia (platelet count $2 \times 10^9/L$) = 0 point; timing of onset = 1 or 2 points (platelet counts started to go down after day 9–12 of heparin exposure); thrombosis = 2 points (proven DVT); and no other cause = 2 points (no plausible alternate explanation for the thrombocytopenia). A polyspecific PF4 enzyme-linked immunosorbent assay was positive, with an optical density of 3.682. Unfortunately, despite no further coagulation disorders after heparin discontinuation on D12, she suffered severe gastrointestinal hemorrhage on D14 with platelet count of $2 \times 10^9/L$. The patient showed hematochezia (confirmed by feces routine test and occult blood test) with a fall in hemoglobin levels from 109 g/L to 74 g/L. The patient was fasted and treated with an acid inhibitor proton-pump inhibitor (Omeprazole) and red blood cell transfusion, together with nutrition support therapy. To balance the bleeding and anticoagulation complications, the patient was administered 0.4 g/(kg·d) IVIG to inhibit the ongoing platelet-activating effects of the circulating HIT antibodies and hasten platelet count recovery. Following the second dose of IVIG (D15 after the initiation of Fraxiparine) and a platelet transfusion (10 U), the platelet count rose from the nadir of $1 \times 10^9/L$ to $9 \times 10^9/L$ (both tested on D15), and then rose further to $30 \times 10^9/L$ on the next day. With continued use of IVIG, her platelet counts increased to $74 \times 10^9/L$ and $147 \times 10^9/L$ on the following 2 days, respectively (**Figure 1**). We also monitored coagulation test results over this period, including D-dimer (12.26–19.34 $\mu g/ml$), fibrinogen (3.48–4.47 g/L), activated partial throm-

boplastin time (APTT) (48.4–53.7 s) and prothrombin time (PT) (13.4–14.7 s), to exclude a diagnosis of HIT-associated disseminated intravascular coagulation (DIC). The patient was discharged and started to be treated with Rivaroxaban (10 mg once a day) on D18, with no further thromboembolic events. Her platelet count remained within the normal range after 3 months of follow-up ($231 \times 10^9/L$ at the last time), with no new thromboses.

DISCUSSION

A very low platelet count is very unusual in patients with HIT, and a platelet count $< 10 \times 10^9/L$ accordingly scores zero point in the 4Ts pretest scoring system.^[2, 4] Based on its immunopathogenesis involving PF4/heparin antibodies, HIT is one of the leading causes of drug-induced reactions among hospitalized patients.^[5] A previous retrospective analysis identified the extent of platelet count decrease as one of the most important risk factors for thrombosis.^[6] The current patient had an abrupt decrease in her platelet count to $1 \times 10^9/L$ after the initiation of Fraxiparine, with no preceding slow decrease, suggesting the magnitude of platelet count decrease was likely to reflect the titer of platelet activating anti-PF4/heparin antibodies. Naturally occurring anti-PF4/heparin antibodies are rare in healthy individuals, and there have been only 12 reported cases of “spontaneous HIT” associated with high-titres of platelet-activating anti-PF4/heparin antibodies without prior heparin exposure, presenting with clinical complications of thrombocytopenia and/or thrombosis.^[7–12] Of these 12 cases, 7 patients had undergone recent orthopaedic surgery, suggesting

Figure 1. Correlation between thrombocyte count, clinical course, and treatment. The letters indicate the platelet counts: a. $2 \times 10^9/L$; b. $1 \times 10^9/L$; c. $2 \times 10^9/L$; d. $1 \times 10^9/L$; e. $9 \times 10^9/L$; f. $30 \times 10^9/L$; g. $74 \times 10^9/L$; h. $147 \times 10^9/L$.

that mechanical compression^[13] may have facilitated antigen exposure through heightened platelet and/or endothelial activation.^[14] It is therefore possible the severe thrombocytopenia in the current patient, without pre-immunization or re-exposure to heparin before, was caused by mechanical compression, causing her blood platelets level to drop dramatically after exposure to heparin. Severe HIT may thus be precipitated by double-hits (both mechanical extrusion and heparin exposure).

Wester *et al.*^[15] concluded the incidences of thromboembolic and hemorrhagic complications were remarkably high in critically ill patients with HIT. However, our patient developed thromboembolic and life-threatening hemorrhagic complications without multiple organ dysfunction syndrome. HIT is the most common form of DITP, and IVIG (1 g/kg body weight for 2 consecutive days) is recommended in patients with DITP who develop major bleeding symptoms.^[16] Based on the successful response to IVIG in cases of HIT,^[17-18] we considered 0.4 g/kg IVIG for 5 consecutive days as suitable treatment for this severe condition. Platelet transfusions are not recommended due to thrombotic potential concerns.^[19-20] This limitation is particularly relevant, given that lower platelet counts not only prompt platelet transfusion, but also increase thrombotic risk in HIT patients.^[6] Transfusion of platelet concentrates might be considered in the event of life-threatening bleeding,^[3, 21] while IVIG has been shown to augment platelet count recovery in mouse models of DITP.^[22] We administered platelet transfusion treatment based on IVIG for 2 consecutive days, with continuous increases in platelet count to $9 \times 10^9/L$ at 1 h and $30 \times 10^9/L$ at 12 h after transfusion, with no further thromboembolic events. This suggests that IVIG can promote platelet count recovery by inhibiting activation of platelet by HIT-IgG, thus ensuring the efficacy of platelet transfusion whilst inhibiting the increased thrombotic risk in these patients.

HIT is a pro-thrombotic disorder. Recognizing the clinical and laboratory features of HIT allows immediate discontinuation of heparin, and the administration of alternative anticoagulants to avoid serious thrombotic complications. The choice of anticoagulant should be based on patients' hepatic and renal functions, clinical stability, drug availability, and physician preference.^[21] In the current case, we chose factor Xa (Rivaroxaban) instead of the recommended agents (e.g. Argatroban, Bivalirudin, Desiru-

din, Danaparoid, Fondaparinux) because of a drug shortage. Rivaroxaban does not cross-react with HIT antibodies.^[23] However, published reports on the use of this agent in patients of acute HIT are limited, and low trough levels may not provide adequate protection for highly pro-thrombotic states such as HIT.^[24-25] A single-arm study of Rivaroxaban for HIT was closed early due to slow accrual.^[26] However, Rivaroxaban may be an ideal candidate treatment for HIT because it is administered orally by fixed dosing, requires no laboratory monitoring and is effective in the treatment of venous and arterial thromboembolism in other settings. The present patient had no recurrent thrombosis at 3 months of follow-up. We suggest that the administration of IVIG in this case not only ensured that the platelet transfusion was effective, but also provided time for Rivaroxaban to work. Three months of anticoagulation treatment is generally considered sufficient for patients with HIT complicated by thrombosis, and the current patient remained well over this time period.

In conclusion, severe HIT complicated with both thrombosis and bleeding is rare, and IVIG provides a fast, safe and effective therapeutic option for reversing aggressive thrombocytopenia in patients with immune-mediated HIT. The current case suggests that IVIG, platelet transfusion and oral anticoagulant Rivaroxaban may be a suitable treatment strategy for such patients. We hypothesized that IVIG was the most important element of the treatment, by preventing further thrombosis, allowing safe and efficient platelet transfusion, and ensuring the effective use of Rivaroxaban.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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