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Case Report

Effectiveness and safety of therapeutic plasma exchange to modify the functionality of heparin-induced thrombocytopenia antibodies and correct profound thrombocytopenia: A case report and literature review

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Introduction

Heparin-induced thrombocytopenia (HIT) is a rare but life-threatening complication of heparin therapy. Specific IgG antibodies recognize heparin-modified platelet factor 4 (PF4/H IgG) and activate the platelets, increasing the risk of thrombosis. The thrombocytopenia is typically moderate, with a median platelet count nadir of approximately 50× 10^9/L,[1] but more severe thrombocytopenia in patients with HIT has been described. In these patients, severe clinical outcomes and high PF4/H IgG optical density (OD) values have been reported.[2] Guidelines recommend that heparin treatment is ceased upon HIT diagnosis and therapeutic dosing of non-heparin coagulants (e.g., argatroban, bivalirudin, danaparoid, fondaparinux, or direct oral anticoagulants) is initiated to counterbalance the hypercoagulability state observed in the acute phase of HIT.[3] The treatment with non-heparin anticoagulants likely increases major bleeds (8–35% risk of major bleeding).[4] Critically ill patients and patients with comorbidities may have even greater risks of bleeding.[5]

We report a case of a patient with HIT and a very low platelet count (1×10^9/L). Repeated therapeutic plasma exchange (TPE) was conducted to remove HIT antibodies and increase platelet count so that non-heparin anticoagulation therapy could be introduced. An IgG-specific anti-PF4/H enzyme immunoassay (EIA) (PF4 IgG, Immucor GTI Diagnostics) and a platelet function test for antibody reactivity (^{14}C-serotonin release assay [SRA]) were both positive when the patient was diagnosed with HIT. However, we observed that SRA values rapidly decreased after treatment, leading to a platelet count increase despite the persistence of high PF4/H IgG titers measured with EIA.

Case Report

A 57-year-old man with a history of mitral valve prolapse was admitted in September 2021 to the cardiology department for mitral valve endocarditis caused by *Streptococcus oralis*. He was treated with amoxicillin and a dental exam revealed an infected tooth that was then treated accordingly. In November 2021, reconstructive surgery of the patient's mitral valve was required. He received postoperative curative anticoagulation with unfractionated heparin (UFH) for paroxysmal atrial fibrillation followed by low molecular weight heparin (LMWH). Eight days after the first dose of UFH, platelet count decreased to 60 × 10^9/L (from 89 × 10^9/L 2 days before) and HIT was suspected (the intermediate 4Ts score was 4 points). Accordingly, LMWH was discontinued and danaparoid was started. Despite the change in anticoagulation treatment, platelet count declined to 1 × 10^9/L on day 9, leading to the decision to end treatment with danaparoid. The patient presented spontaneous bilateral epistaxis, petechiae, and pericardial effusion on echocardiography. He received intravenous immunoglobulin (IVIG) (1 g/kg × 1 day) and subcutaneous thrombopoietin-like fusion protein (750 μg) for the treatment of suspected immune thrombocytopenia. The patient also received a platelet transfu-

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sion (1 unit × 2 days) for persistent epistaxis and suspicion of hemopericardium. No biological or clinical improvement was observed. Steroid therapy was not given because *Enterococcus faecalis* was isolated from blood cultures. The SRA and PF4/H IgG EIA (OD: 3.4; cut-off: 0.4) were positive, confirming the diagnosis of HIT. The patient had no clinical signs of arterial or venous thrombosis. The hemoglobin was stable at 8 g/dL without hemolysis. Renal function and liver function were normal. The patient was negative for antiphospholipid antibodies, including anti-cardiolipin and anti-β2 glycoprotein.

The patient was transferred to the ICU on day 11. TPE was initiated for major thrombocytopenia and the risk of hemodynamic failure secondary to pericardial effusion. TPE was performed on three consecutive days (1.5 × volume plasma exchange was performed without heparin anticoagulation and fresh frozen plasma [FFP] was the fluid replacement). Improvement of platelet count after each TPE was observed (from 1×10^9/L to 25, 87, and 102×10^9/L, after the first, second, and third TPE, respectively). The SRA was negative soon after the first and second TPE; however, it returned to positive immediately before the second and third sessions. It remained negative after the third TPE. Figure 1 shows the increase in serial platelet counts and the decrease in antibody reactivity (determined by SRA) despite the EIA-IgG remaining strongly positive (OD: 2.0 after the third TPE).

Argatroban anticoagulation was initiated 4 days after the third TPE. The patient was discharged home after his platelet count recovered and argatroban was switched to apixaban 5 mg twice daily. One month later, he underwent percutaneous pericardial drainage and atrial flutter catheter ablation in the cardiology department.

Discussion

We report using TPE to successfully manage HIT associated with a very low platelet count and hemorrhage in a 57-year-old male. Standards of care recommend cessation of heparin treatment and initiation of non-heparin anticoagulant at a therapeutic intensity to overcome HIT-associated hypercoagulability. For our patient, the priority was to reduce the risk of bleeding before introducing non-heparin anticoagulation. Two alternative therapeutic strategies have been proposed to address this situation: TPE and IVIG. A recent systematic review reported 113 cases of HIT treated with TPE or IVIG, with 10 of those cases being refractory HIT successfully treated with TPE.[6] The average number of TPE procedures was four, with the plasma volume exchanged varying from 3 L to 1.5 × plasma volume in five cases. In eight cases, TPE replacement fluid was reportedly a combination of albumin and FFP (n=4), FFP and/or pooled plasma (n=2), albumin alone (n=1), or normal saline and FFP (n=1). The authors reported a post-treatment platelet count > 150×10^9/L over an average of 6 days in the group of patients with refractory HIT treated with IVIG or TPE. In four TPE-treated cases, the antibody level decreased; in two others, the rate increased. The authors concluded that both IVIG and TPE should be considered as initial therapy or for patients with refractory HIT. However, this review was limited by a lack of randomized clinical trials and prospective data, primarily based on single case reports. The plasma volume exchanged in our patient reached 5 L per session, and only FFP was used as replacement fluid because of the high hemorrhagic risk associated with the very low platelet count (1×10^9/L) and the resulting risk of hemodynamic failure. The three TPE sessions were associated with a rapid rise in platelet count. Interestingly, PF4/H IgG titers decreased very moderately after each TPE session, with OD remaining over 2.0. Similarly, SRA results fluctuated after the initial TPE sessions before remaining negative, as previously described by Warkentin et al.[7] *In vitro* data suggested that IgG-containing plasma might be more effective than albumin in inhibiting HIT antibody-mediated platelet activation, likely by competing for binding to Fcγ receptors on target cells.[8] A recent population-based study compared the use of TPE with IVIG in HIT[9] and showed that compared to non-treated cases, IVIG- and TPE-treated cases were associated with increased mortality rates, major bleeding, infection, longer hospital stays, and higher total costs. This study of a population of patients with very severe HIT whose outcomes worsened after TPE or IVIG has unclear significance and found no significant differences in outcomes, highlighting that both IVIG and TPE may still be useful. Our patient had already received IVIG 24 h before he was admitted to the ICU, but because of the high risk of hemodynamic failure and the desire to avoid waiting for the efficacy of IVIG, TPE was started. Guidelines on using TPE for refractory HIT or as initial therapy are limited.[4] Guidelines from the American Society for Apheresis on using TPE in clinical practice suggest individualized decision-making in patients with HIT and thrombosis and those undergoing cardiopulmonary bypass.[10]

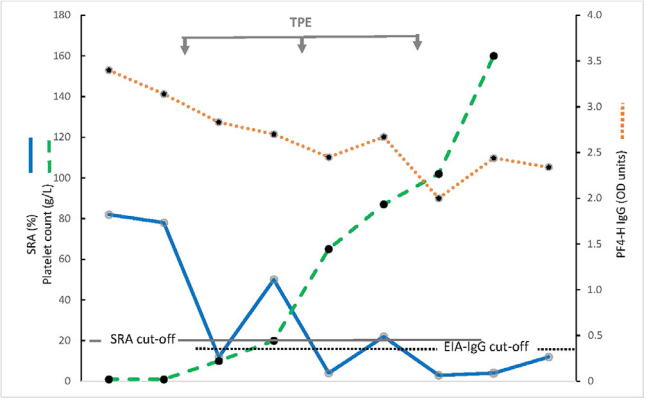

Figure 1. Time course of platelet count, SRA, and PF4/H IgG EIA results in relation to the TPE performed on three consecutive days. Platelet count increased and antibody reactivity decreased despite the persistence of strong EIA-IgG positivity.
EIA: Enzyme immunoassay; OD: Optical density; PF4/H IgG: Heparin-modified platelet factor 4; SRA: Serotonin release assay; TPE: Therapeutic plasma exchange.

Conclusions

In this case report, we demonstrate the effectiveness and safety of TPE via plasma-containing immunoglobulins in the treatment of HIT. TPE can be a therapeutic approach enabling therapeutic anticoagulation, even in cases of significant bleeding. However, no clear, practical guidelines are available, and further studies are needed to fully validate this approach.

Author Contributions

Audrey Graser: Conceptualization, Writing original draft, Writing Review and Editing, Visualization, Supervision. Anne Bauters: Conceptualization, Writing original draft, Writing Review and Editing, Visualization. Jean-Luc Auffray: Writing original draft, Writing Review and Editing. Caroline Vayne: Writing original draft, Writing Review and Editing. François Provot: Writing original draft, Writing Review and Editing. Merce Jourdain: Conceptualization, Writing original draft, Writing Review and Editing. Laurent Robriquet: Conceptualization, Writing original draft, Writing Review and Editing, Visualization, Supervision.

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Ethics Statement

We used the principle of non-opposition of the use of data, and the patient gave oral consent.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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