Clinical Case Report

Medicine®

OPEN

Rare heparin induced thrombocytopenia type I reaction in a hemodialysis patient

Case report

Wenxi Liu, PharmD[a], Chao Zhang, PhD[a,*], Qiong Bai, MD[b], Zhongliang Zhang, BS[a]

Abstract

Rationale: Heparin-induced thrombocytopenia (HIT) is a common antibody-mediated adverse reaction that occurs after heparin exposure. However, few case reports exist regarding nonantibody-mediated HIT.

Patient concerns and diagnoses: An 81-year-old female diagnosed with rapidly progressive glomerulonephritis (RPGN) presented with atypical presentation of non antibody-meditated HIT after using heparin during hemodialysis.

Interventions and outcomes: Patient was initiated on hemodialysis and presented with thrombocytopenia following administration of heparin during dialysis. After ruling out all other causes of thrombocytopenia, HIT was suspected to be the cause. Patient's 4Ts score was 6 points, and Naranjo adverse drug reaction probability scale was a score of 10. However, enzyme-linked immunoassay for platelet factor 4 (PF4)/heparin antibodies was negative, indicating non-antibody mediated HIT. Patient eventually continued hemodialysis without heparin.

Lessons: This patient case presented a rare presentation of HIT type I reaction due to heparin and demonstrated the importance of timely recognition of thrombocytopenia, appropriate diagnosis and management, and possible existence of a new atypical or subtype of HIT reaction.

Abbreviations: ANCA = anti-neutrophil cytoplasmic antoantibody, GBM = anti-glomerular basement membrane disease, HIT = heparin-induced thrombocytopenia, ITP = immune thrombocytopenic purpura, IV = intravenous, LMWH = low molecular weight heparin, PF4 = platelet factor 4, RPGN = rapidly progressive glomerulonephritis, TTP = thrombotic thrombocytopenic purpura, UFH = unfractionated heparin.

Keywords: adverse reaction, hemodialysis, heparin, thrombocytopenia

1. Introduction

Anticoagulation is often used during dialysis in order to reduce risk of extracorporeal circuit clot formation. Defined by its short-half life and improved safety profile, heparin is a common anti-coagulation agent used during dialysis sessions.[1,2] One of the main adverse reaction cause when heparin was given at outpatient dialysis clinics is heparin-induced thrombocytopenia (HIT) due to the formation of antibodies that activate platelet. Incidence of HIT is estimated at 1% to 5% of patients who received heparin products, with more cases associated with unfractionated heparin (UFH) when compared with low molecular weight heparin (LMWH), 5% and 0.5% respectively.[3,4]

There are 2 distinct types of HIT: type I and type II. Occurring up to 10% of HIT cases, HIT type I is a nonimmunologic reaction associated with heparin treatment, usually caused by direct interaction between heparin and platelet that induces platelet clumping or sequestration.[3] Typically occurs within 24 to 48 hours after heparin exposure, HIT type I is characterized by mild drop in platelet count (nadir platelet count of 100×10^9/L), which returns to normal with continued heparin administration. There is no laboratory test to diagnose HIT type I, which usually is not concerned for thrombosis. HIT type II is an immunologic reaction that is usually associated with thrombosis risk. Common pathological cause of HIT type II is due to the formation of antibodies to antigenic complexes of platelet factor 4 (PF4) and heparin, which leads to the production of HIT antibodies and platelet consumption. Occurring 5 to 10 days after initiation of heparin, type II HIT typically presents a platelet count drop of at least 50% of baseline (nadir platelet count of 20×10^9/L).[3,4] Due to risk of thrombosis in HIT type II, administration of nonheparin anticoagulant is crucial as stated in the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.[5]

Most of the HIT cases in clinical setting today fall into the category of antibodies-mediated type II HIT. In contrast, type I HIT cases are rarely reported since it is a mild, nonimmunologic reaction that recovers on its own. To our knowledge, no reports of type I HIT cases have been reported. We present here a type I HIT patient case.

Editor: N/A.

Disclosure: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

The authors have no conflicts of interest to disclose.

[a] Department of Pharmacy, [b] Department of Nephrology, Peking University Third Hospital, Beijing, China.

[*] Correspondence: Chao Zhang, Department of Pharmacy, Peking University Third Hospital, 49 North Garden Road, Haidian District, Beijing 100191, China (e-mail: laural.zhang@yahoo.com).

Medicine (2018) 97:50(e13609)

Received: 22 August 2018 / Accepted: 19 November 2018

http://dx.doi.org/10.1097/MD.0000000000013609

2. Case presentation

An 81-year-old Asian female endorsed fatigue, weakness, and pitting edema at both extremities along with decrease in urine output for past 4 days. Past medical history included coronary heart disease for past 20 years. On presentation, patient presented with anemia and hematuria with foamy urine along with anemia. Laboratory results revealed hemoglobin 7.8 g/dL, platelet 162×10^9/L, blood urea nitrogen level of 35 mg/dL, and serum creatinine level of 8.98 mg/dL. Since both anti-neutrophil cytoplasmic autoantibody (ANCA) and antiglomerular basement membrane (GBM) disease antibody were positive, patient was diagnosed as Type I and Type III rapidly progressive glomerulonephritis (RPGN), and methylprednisolone 200 mg intravenous (IV) once daily was started along with hemodialysis. At the same time, patient's chest CT demonstrated progressive densities along with elevated procalcitonin of 0.601 ng/mL, and cefoperazone-sulbactam 1.5 g IV once daily was started due to concern for infection. Heparin (1000 U bolus followed by 500 U/h infusion) was administered as extracorporeal anticoagulation to prevent coagulation during hemodialysis sessions, which was scheduled on as needed basis. Patient had no prior exposure to heparin and did not receive heparin during this admission outside of hemodialysis. Platelet count decreased consistently following heparin administration with nadir count 48×10^9/L on day 12 (Fig. 1) with 4T score of 3 points (platelet decreased to 40×10^9/L, 2 points; possible other cause of thrombocytopenia, 1 point) after initiation of hemodialysis, and no signs of bleeding were observed.

Initially, thrombocytopenia was suspected to be caused by cefoperazone-sulbactam, which was switched to moxifloxacin. Hematology disorders such as immune thrombocytopenic purpura (ITP) or thrombotic thrombocytopenic purpura (TTP) were questioned. However, hematology disorders were ruled out with normal peripheral blood smear, laboratory tests, and *ADAM13* testing. Additionally, radiographic imaging also ruled out any evidence of thrombosis. Patient proceeded to continue hemodialysis session without heparin administration with platelet count increased back to 71×10^9/L (Fig. 1). Due to the need for long-term dialysis, arteriovenous fistula was placed, and heparin was given again during hemodialysis session afterward. Patient's platelet count decreased again following heparin exposure with nadir platelet count of 34×10^9/L on day 8 (Fig. 1) after heparin re-exposure, and 4T score of 6 points (platelet count decreased to 34×10^9/L, 2 points; platelet drop within 1 day with heparin exposure within past 30 days, 2 points; no other cause of thrombocytopenia, 2 point) after re-exposure to heparin. Due to recurrent thrombocytopenia, all heparin products were discontinued, and patient proceeded with hemodialysis session without any heparin, and platelet count recovered back to 115×10^9/L. Enzyme-linked immunoassay for platelet factor 4 (PF4)/heparin antibodies (Peking Union Medical

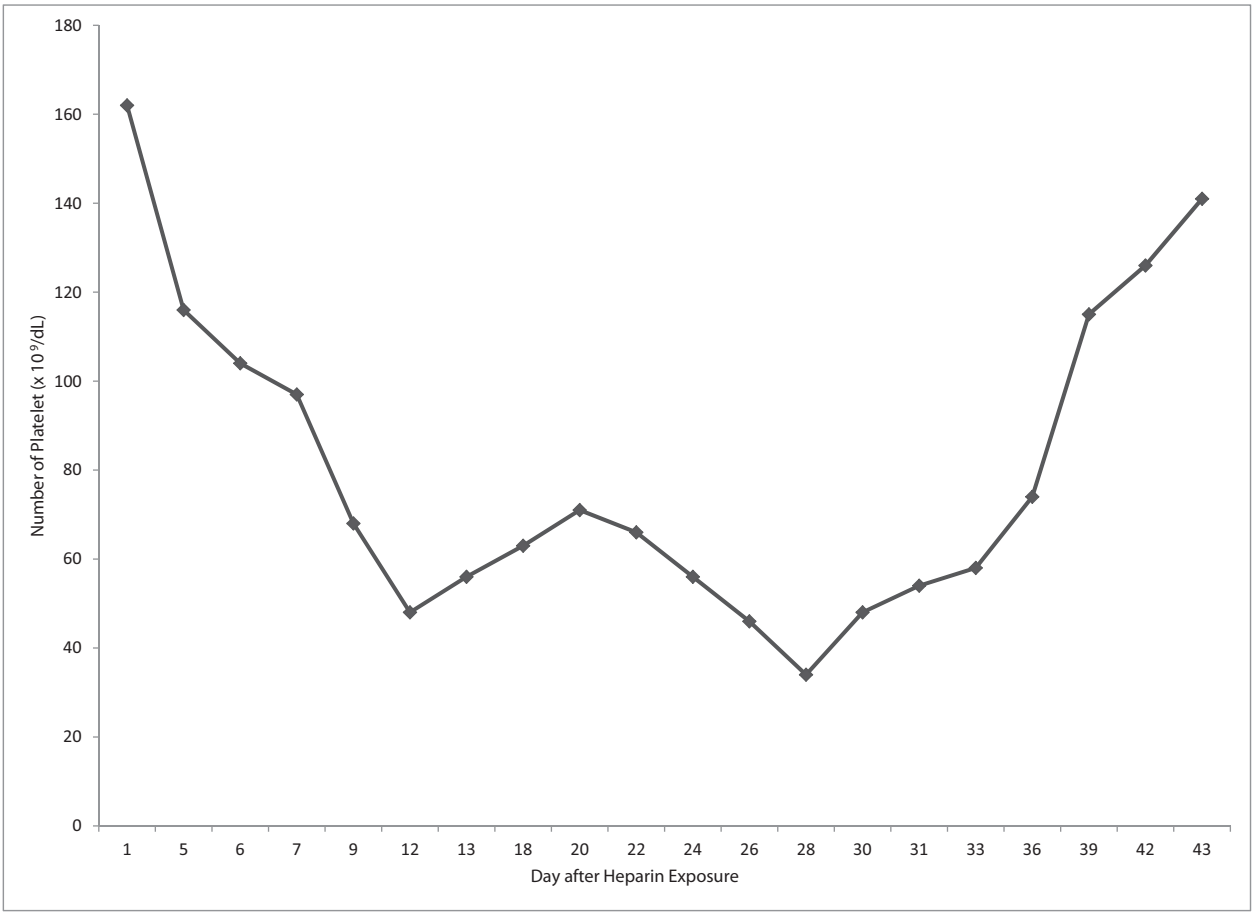

Figure 1. Platelet count change time course. Plate count change timeline during hospital admission with platelet count decrease occurred after receiving heparin during hemodialysis with nadir on day 12. Heparin was discontinued afterwards and re-introduced on day 20. Thrombocytopenia occurred again following heparin re-exposure with nadir on day 28.

College Hospital Medical Laboratory, Beijing, China) was negative.

Nonetheless, due her recurrent thrombocytopenia with heparin exposure, patient proceeded dialysis using argatroban, a direct thrombin inhibitor, at a 10 mg (250 mcg/kg bolus) followed by 5 mg/h (2 mcg/kg/min) infusion. Following dialysis on the same day, patient endorsed platelet count stable at 129×10^9/L. Patient eventually transitioned to using sodium citrate with hemodialysis.

3. Discussion

HIT is a serious adverse drug reaction that manifests as thrombocytopenia or thrombosis and require immediately assessment. Common HIT cases observed in clinical setting is categorized as HIT type II. For diagnosis of HIT, it is important to consider both clinical and laboratory findings. A clinical assessment tool, 4Ts score, can be utilized as assessment tool to evaluate likelihood of HIT and takes into account the severity of thrombocytopenia, timing of thrombocytopenia in relation to heparin exposure, the presence of thrombosis, and other causes of thrombocytopenia. If suspicion of HIT is high, an immunoassay can be done to examine the presence of HIT antibodies.[3] If the presence of HIT antibodies is detected, serotonin release assay can be done to measure platelet activation in the presence of heparin, a functional assay that serves to confirm HIT diagnosis. Due to various complications of HIT, it is important to accurately diagnose HIT and exclude other causes of thrombocytopenia in order to appropriately treat and manage patients.[2–4]

For our patient, heparin was used to prevent coagulation during dialysis sessions. Patient's platelet count decreased immediately following receiving heparin. To determine whether adverse drug reaction was drug related, the Naranjo adverse drug reaction probability scale resulted in score of 10, indicating there is a definite association between this patient's thrombocytopenia and heparin.[6] This score was calculated based on the following: there are previous report of this reaction (1 point), thrombocytopenia occurred after heparin administration (2 points), the thrombocytopenia improved after heparin was discontinued (1 point), thrombocytopenia reappeared when heparin was given again (2 points), there are no alternative causes other than drug that could cause the reaction (2 points), thrombocytopenia did not reappear when patient continued dialysis without any heparin (1 point), and thrombocytopenia (1 point). To evaluate possibility of HIT, patient's initial 4Ts score was 3 points. Thus, suspicion for HIT was low, and we attributed thrombocytopenia to other causes such as medications and hematology disorders. However, when heparin was used again during dialysis after eliminating other factors, patient's platelet count dropped again, corroborating an adverse drug reaction to heparin. The 4Ts score this time was 6 points. The high suspicion of HIT the second time prompted HIT antibodies examination and discontinuation of all heparin products. Nonetheless, negative result of HIT antibodies indicated that patient did not have HIT type II reaction. Naturally, patient was assumed to have experienced HIT type I reaction. In terms of management, HIT type I reaction did not normally require discontinuation of heparin products, but rather a mild decrease in platelet. However, in our case, patient's thrombocytopenia did not improve with continued heparin administration but instead decrease consistently. Therefore, we resorted to discontinue heparin and switch to other nonheparin anticoagulant such as argatroban during dialysis, a management strategy reserved for HIT type II reaction.[7]

To our knowledge, there are no patient case reports of HIT type I reaction. There have been few cases of dialysis patients who developed HIT, with most cases categorized as HIT type II reaction. Lim et al[9] presented a case report of recurrent HIT due to heparin rinsing in a hemodialysis patient. The case described an 80-year-old woman with chronic renal failure requiring hemodialysis who developed HIT type II on day 7 after first heparin administration, and immunoassay indicated presence of HIT antibodies. Heparin was then discontinued and argatroban was started. Additionally, Chan et al[10] presented a case of 58-year-old woman with acute kidney injury was initiated on heparin-free hemodialysis. Subsequent thrombocytopenia development and positive HIT antibodies led to HIT type II diagnosis, and patient was eventually put on plasmapheresis. In contrast, our patient case presented a unique patient case of HIT type I along with clinical presentation and management. Upon closely examining patient's presentation, there were couple clinical features that do not exactly correlate with HIT type I. Unlike typical HIT type I clinical presentation, our patient's platelet count dropped below normal nadir count of 100×10^9/L along with thrombocytopenia that required discontinuation of heparin. Patient presented with low baseline platelet count; however, no hematology disorders were found to explain low baseline count. Therefore, it would be hard to conclusively categorize the reaction as HIT type I. In fact, the unique features of this patient case might elude to a possible third type of HIT reaction or an atypical HIT type I reaction.

Furthermore, other causes could have complicated occurrence of thrombocytopenia in the patient. Hemodialysis could have affected platelet count and resulted in hemodialysis-associated thrombocytopenia. Daugirdas et al[8] delineated that platelets are activated during hemodialysis due to exposure of blood to the roller pump segment and circuit, which can cause subsequent thrombocytopenia. Platelet count normally decreased slight during the first hour of hemodialysis but returned to normal near the end of hemodialysis session. In chronic hemodialysis patients, significant platelet drop can be observed, resulting in mild predialysis thrombocytopenia. However, in the presenting case, our patient is a new hemodialysis patient, not a chronic hemodialysis patient. Additionally, patient's thrombocytopenia did not resolve by the end of hemodialysis session, which indicated that thrombocytopenia is unlikely to hemodialysis.

This patient case presented an atypical presentation of HIT type I reaction due to heparin, which adds to the lack of current report of HIT type I reaction along with management strategies. In contrast to the benign nature of HIT type I reaction as stated in literature, this patient required discontinuation of heparin and initiation of nonheparin anticoagulant, a treatment strategy similar to that of HIT type II reaction. This patient case contributed to the importance of timely and accurate diagnosis of types of HIT reaction along with appropriate management strategies. Despite negative HIT antibodies detected in this patient, she nonetheless demonstrated a reaction to heparin manifested in thrombocytopenia. Additional immunological testing could be developed in the future in order to better characterize various atypical HIT reactions. It is important for clinicians to be aware of clinical presentation of different HIT types along and manage symptoms accordingly.

Author contributions

Conceptualization: Wenxi Liu, Chao Zhang.
Investigation: Zhongliang Zhang.

Methodology: Wenxi Liu.
Supervision: Qiong Bai.
Writing – original draft: Wenxi Liu.
Writing – review & editing: Wenxi Liu, Chao Zhang.

References

[1] Murea M, Russell GB, Daeihagh P, et al. Efficacy and safety of low-dose heparin in hemodialysis. Hemodial Int 2017;22:74–81.
[2] Vlachopanos G, Ghalli FG. Antithrombotic medications in dialysis patients: a double-edged sword. J Evid Based Med 2017;10:53–60.
[3] Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. Postgrad Med J 2007;83:575–82.
[4] Lee GM, Arepally GM. Diagnosis and management of heparin-induced thrombocytopenia. Hematol Oncol Clin N Am 2013;126: 541–63.
[5] Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia. CHEST 2012;141:e495S–530S. Suppl.
[6] Naranjo CA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.
[7] Davenport A. What are the options for anticoagulation needs in dialysis for patients with heparin-induced thrombocytopenia? Semin Dial 2011;24:382–5.
[8] Daugirdas JT, Bernardo AA. Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia. Kidney Int 2012;82:147–57.
[9] Lim JH, Kang KP, Lee S, et al. Recurrent heparin-induced thrombocytopenia due to heparin rinsing before priming the machine in a hemodialysis patient: a case report. Hemodial Int 2017;21:E30–3.
[10] Chan KM, Cheung CY, Chau KF. Heparin-induced thrombocytopenia due to heparin lock in a hemodialysis patient: a case report. Hemodial Int 2014;18:555–8.