Thrombosis Research 183 (2019) 106–107

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

Severe persistent heparin-induced thrombocytopenia in a renal transplant patient

ARTICLE INFO

Keywords:
HIT
Heparin-induced thrombocytopenia
ATG
Persistent HIT

Heparin is commonly used in the renal transplant setting but heparin-induced thrombocytopenia (HIT) a serious adverse reaction to heparin appears to be infrequent in this patient population [1–3]. A subset of HIT antibodies considered "pathogenic" activate platelets in functional assays like the serotonin release assay (SRA) and can be distinguished from "benign" antibodies commonly seen in clinical practice that are positive in PF4/Polyanion ELISAs (PF4 ELISA) but are not platelet-activating [4]. While a clinical scoring system (4Ts score) can be helpful in making the diagnosis, calculating this score can be challenging in complex patients such as the one discussed in this report. Here, we describe a severe case of HIT in a renal transplant patient with non-classical HIT serologic results and initially unclear source of heparin exposure.

A 54-year-old Caucasian female with end stage renal disease due to polycystic kidney disease presented for deceased donor kidney transplantation. She had been maintained on peritoneal dialysis for approximately two years prior but was transitioned to hemodialysis via a tunneled catheter one week prior to transplantation due to peritoneal dialysis catheter malfunction. She underwent anti-lymphocyte induction therapy with rabbit antithymocyte globulin (ATG). Post-transplant, she was started on maintenance immunosuppression with mycophenolate mofetil, tacrolimus, and a steroid taper as well as infection prophylaxis with fluconazole, valganciclovir, and dapsone.

Preoperatively, the patient had a hemoglobin level of 10.1 mg/dL and a normal platelet count of 230,000/μL. Immediately post-transplant, hemoglobin was noted to be 9.6 mg/dL and platelets 139,000/μL (Fig. 1). Both parameters continued to decline throughout the hospital course, which was attributed to ATG (Fig. 1). On postoperative day 5 she was discharged with a hemoglobin of 8.0 mg/dL and platelet count of 26,000/μL. Repeat testing two days later demonstrated stable anemia and persistent marked thrombocytopenia with platelets now at 21,000/μL. The patient was readmitted for further evaluation, and workup was consistent with hemolysis (elevated lactate dehydrogenase of 900 units/L; Reference range: 135–214 units/L and low haptoglobin of < 10 mg/dL; Reference range: 30–200 mg/dL) and clinical suspicion was raised for dapsone-induced hemolytic anemia. With discontinuation of dapsone, her hemolytic markers and anemia promptly improved, but thrombocytopenia persisted. Despite the lack of a "smoking gun" heparin exposure that led to the precipitous decrease in platelet count, given the history of exposure to heparin prior to transplant (patient received a heparin flush at the time of peritoneal dialysis catheter malfunction 8 days prior to transplant and 2000 unit heparin boluses with hemodialysis treatments 7 and 5 days before transplant), testing for HIT was performed. PF4 ELISA was strongly positive at 1.3 OD (optical density) while the SRA was discordant and barely positive at 25% (positive cut-off, 20%). This led to the impression that the PF4 ELISA result was likely "false-positive", a common clinical finding [4].

Research testing was performed in a recently described HIT platelet activation assay, the PF4-dependent p-selectin expression assay (PEA), and PEA (Low PF4) [6,7]. The PEA (Low PF4), recently shown to be helpful in detecting HIT antibodies from severely affected HIT patients with autoimmune HIT [5] was positive at 52% (positive cut-off, 10%), and the PEA was also strongly positive at 109% (positive cut-off, 24%). A thorough re-review of the patient's medication records showed that she was exposed to 1000 units of heparin admixed in the ATG preparation on three occasions during the hospitalization (Fig. 1). Reactivity in the PEA (Low PF4) declined over the next 10 days and correlated well with a corresponding increase in platelet counts (Fig. 1). As reported recently in patients with severe HIT, the PEA remained strongly positive even after platelet recovery [5]. The patient was homozygous for Histidine at amino acid position 131 (HH131) of FcγRIIa, a genotype which may have protected the patient from macrovascular thrombosis despite the presence of strong, platelet-activating HIT antibodies [6]. The patient was started on treatment with the direct oral anticoagulant apixaban. Her thrombocytopenia and allograft function improved and at follow-up six weeks post-transplant, she had a platelet count of 298,000/μL and serum creatinine of 1.0 mg/dL with no recurrence of thrombocytopenia or new thrombosis.

HIT has been reported in 0.2–5% of patients exposed to heparin; however its incidence is less well established in the renal transplant population. Based on the "4Ts" scoring system, our patient had a low probability of HIT (4Ts score = 3) due to unclear heparin exposure. This, combined with the low-positive SRA result of 25% led her caregivers to conclude that the patient did not have HIT. Despite this SRA result, the patient's sample strongly activated PF4-treated platelets in the PEA a phenomenon that has

Abbreviations: HIT, heparin-induced thrombocytopenia; PF4, platelet factor 4; ATG, rabbit antithymocyte globulin; PF4 ELISA, PF4/polyvinylsulfonate enzyme-linked immunosorbent assay; PEA, PF4-dependent P-selectin expression assay; SRA, serotonin release assay

https://doi.org/10.1016/j.thromres.2019.10.014
Received 17 September 2019; Received in revised form 27 September 2019; Accepted 16 October 2019
Available online 21 October 2019
0049-3848/

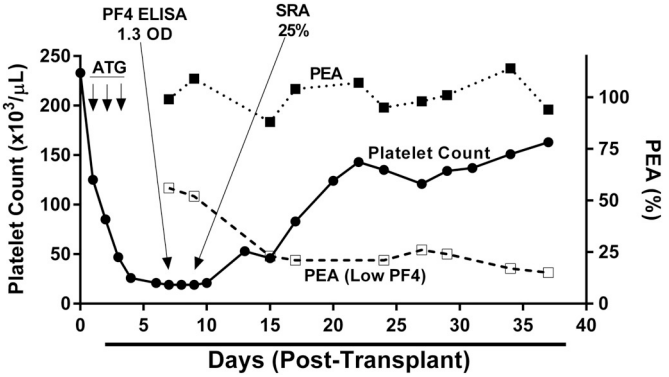

Fig. 1. Severe protracted thrombocytopenia due to HIT. Left ordinate denotes platelet count (solid circles). Right ordinate depicts PEA (solid squares) and PEA, Low PF4 (open squares). PEA and PEA, Low PF4 results shown are the average of duplicate measurements, while SRA, PF4 ELISA and platelet counts shown are single determinations. Solid arrows denote ATG treatment.

been recently reported [6,7]. Evolving understanding of HIT pathogenesis suggests that normal plasma immunoglobulin G can compete with HIT antibodies for binding to the platelet IgG receptor, FcγRIIa and limit antibody-mediated platelet activation [5]. Platelets with the HH131 genotype can bind both IgG_1 and IgG_2 immunoglobulins present in normal plasma thereby making these platelets more resistant to activation by HIT antibodies than platelets expressing the RR131 Fc receptor genotype which bind IgG_1 alone [5]. Thus, it is likely that the HH131 genotype present in this patient afforded some degree of protection from thrombosis.

Addition of heparin (and hydrocortisone) to antithymocyte globulin is not uncommon as a means to prevent thrombophlebitis and deep vein thrombosis with infusion [8] but this is not always appreciated by healthcare providers. Preoperative heparin exposure likely triggered HIT immunization but did not appear to cause HIT as evidenced by normal platelet counts at the time of surgery. While the decrease in platelet count from 233,000/μL to 139,000/μL was rapid and occurred within ~3 h of ATG exposure, the possibility of HIT evolving solely due to pre-operative heparin exposure cannot be completely ruled out. In addition, low or negative serotonin release can be seen in HIT patients, as recently reported [9,10]. This case, in addition to highlighting the challenges associated with clinical variability in HIT presentation and limitations with currently available HIT diagnostic testing also suggests the need for a careful review of medication history and formulations so that heparin exposure can be clearly documented in patients suspected of this potentially serious disorder.

Author contribution

DC, ES and TK were involved in the clinical care of the patient. AP oversaw research testing. DC wrote the first draft and all authors edited the manuscript and approved its final version.

Declaration of competing interest

A.P. discloses the following conflicts: A patent application has been filed related to diagnostic testing in HIT (Method of Detecting Platelet-Activating Antibodies That Cause Heparin-Induced Thrombocytopenia/Thrombosis; PCT/US14/62591). AP has equity ownership in Retham Technologies LLC. The other authors have no relevant conflicts of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Acknowledgments

We would like to thank Curtis Jones, BS and Shannon Pechauer, BS from Versiti Wisconsin for performance of the PEA and for FcγRIIa genotyping. This study was supported in part by funds from National Institutes of Health grant HL133479 (A.P.).

References

[1] B.A. Anderegg, G.M. Baillie, A. Lin, J. Lazarchick, Heparin-induced thrombocytopenia in a renal transplant recipient, Am. J. Transplant. 5 (6) (2005) 1537–1540.
[2] M. Muzaffar, X. Li, S. Ratnam, Successful preemptive renal retransplantation in a patient with previous acute graft loss secondary to HIT type II: a case report and review of literature, Int. Urol. Nephrol. 44 (3) (2012) 991–994.
[3] S. Dracopoulos, V. Vougas, T.I. Kassimatis, T. Theodoridis, M.E. Ali, T. Apostolou, Heparin-induced thrombocytopenia type II: a serious hazard in preemptive renal transplantation: a case report, Transplant. Proc. 39 (10) (2007) 3481–3484.
[4] C. Pouplard, M.A. May, S. Iochmann, J. Amiral, A.M. Vissac, M. Marchand, Y. Gruel, Antibodies to platelet factor 4-heparin after cardiopulmonary bypass in patients anticoagulated with unfractionated heparin or a low-molecular-weight heparin: clinical implications for heparin-induced thrombocytopenia, Circulation 99 (19) (1999) 2530–2536.
[5] A. Padmanabhan, C.G. Jones, S.M. Pechauer, B.R. Curtis, D.W. Bougie, M.S. Irani, B.J. Bryant, J.B. Alperin, T.G. Deloughery, K.P. Mulvey, B. Dhakal, R. Wen, D. Wang, R.H. Aster, IVIg for treatment of severe refractory heparin-induced thrombocytopenia, Chest 152 (3) (2017) 478–485.
[6] A. Padmanabhan, C.G. Jones, B.R. Curtis, D.W. Bougie, M.J. Sullivan, N. Peswani, J.G. McFarland, D. Eastwood, D. Wang, R.H. Aster, A novel PF4-dependent platelet activation assay identifies patients likely to have heparin-induced thrombocytopenia/thrombosis, Chest 150 (3) (2016) 506–515.
[7] C. Vayne, E.A. Guery, C. Kizlik-Masson, J. Rollin, A. Bauters, Y. Gruel, C. Pouplard, Beneficial effect of exogenous platelet factor 4 for detecting pathogenic heparin-induced thrombocytopenia antibodies, Br. J. Haematol. 179 (5) (2017) 811–819.
[8] M. Wolf, J.L. Descourouez, D.R. Hager, A. Djamali, Peripheral administration of antithymocyte globulins: a review of current literature, Transplant. Rev. (Orlando) 27 (1) (2013) 17–20.
[9] K.A. Pandya, E.G. Johnson, G.A. Davis, A. Padmanabhan, Serotonin release assay (SRA)-negative HIT, a newly recognized entity: implications for diagnosis and management, Thromb. Res. 172 (2018) 169–171.
[10] T.E. Warkentin, J.I. Sheppard, J.W. Smith, D.M. Arnold, I. Nazy, Timeline of heparin-induced thrombocytopenia seroconversion in serial plasma samples tested using an automated latex immunoturbidimetric assay, Int. J. Lab. Hematol. 41 (4) (2019) 493–502.

Divya Chawla[a], Ehab Saad[a], Talal Khairi[a], Anand Padmanabhan[b,c,*,**]
[a] *Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA*
[b] *Blood Research Institute, Versiti Wisconsin, Milwaukee, WI, USA*
[c] *Department of Pathology, Medical College of Wisconsin, Milwaukee, WI, USA*
E-mail address: anand.padmanabhan@bcw.edu (A. Padmanabhan).

* Corresponding author at: Versiti Blood Research Institute, Milwaukee, WI, USA.
** Corresponding author at: Medical College of Wisconsin, Milwaukee, WI, USA.