Archives of Hematology and Blood Diseases

Volume 1, Issue 1, 2018, PP: 13-16

Heparin-Induced Thrombocytopenia after Severe Injury in an Aged Woman: Using Clinical Scoring System

Yutaka Shimazu[1]*, Mamoru Toyofuku[2], Mitsuru Yamaguchi Masuda[3], Maiko Inada[4] Masaharu Nohgawa[5]

[1,5]Department of Hematology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan.
[2,4]Department of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan.
[3]Department of Surgery, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan.
yshimazu@kankyo.ne.jp

***Corresponding Author:** Yutaka Shimazu, M.D., Department of Hematology, Japanese Red Cross Wakayama Medical Center, 4-20, Komatsubara-dori, Wakayama 640-8558, Wakayama, Japan.*

Abstract:

A 75-year-old Japanese woman with severe injury suffered from immune-mediated heparin-induced thrombocytopenia (HIT) due to the use of unfractionated heparin for maintaining the arterial line. Testing for the HIT IgG antibody and a functional assay assessed by the platelet microparticle method confirmed the diagnosis of HIT. The 4Ts clinical scoring system was useful for predicting HITin this patient. Our case confirmed that severe injury may indeed be a risk factor for development of HIT, and demonstrated that only a small amount of heparin can induce HIT. We should be aware of the possibility of iatrogenic thrombocytopenia and thromboembolism (called HIT) in severely injured patients and should act accordingly without delay.

Keywords: *Heparin-induced thrombocytopenia, severe injury, clinical scoring system, direct oral anticoagulants*

Case Presentation

A 75-year-old Japanese woman was admitted to our clinic withsevere injury after being caught in a landslide. At the time of admission, she was in shock andwas treated with rapid fluid infusion. She was intubated and admitted to our intensive care unit. A central vein catheter and arterial line were inserted to support circulation. A small amount of unfractionated heparin (less than 20U/day) was used to maintainthe arterial line. At 4 days after admission, the circulatory dynamics were stable, so she was moved to the general ward unit without an arterial line and the heparin was stopped. At day 10, the central catheter into the internal jugular vein was occluded. Rivaroxaban administration was started at day 4. Next-day blood testing showed thrombocytopenia; the platelet count dropped from 161×10^9/L to 40×10^9/L within three days. Rivaroxaban was stopped for suspected drug-induced thrombocytopenia. At day 14, multiple arterial occlusions at the pulmonary, bilateral iliac and left popliteal artery were found. Heparin administration was started again. At day 15 after admission, she was referred to the Hematology Department for sustained thrombocytopenia and multiple arterial and venous thromboembolisms.

Vital signs at the time of our consultation were as follows: blood pressure 136/60 mmHg, heart rate 78/min, body temperature 37.4 °C, respiratory rate 18/min and SpO_2 99% in room air. Physical examination showed cyanosis of the left foot from ankle to the toe, and the left dorsal artery was not palpable. Using 4Ts clinical scoring system, which we describe latter, and her medical history suggested immune-mediated heparin-induced thrombocytopenia (HIT) for the etiology of thrombocytopenia with multiple thromboembolisms. A peripheral blood sample was taken to examine the HIT antibody. Heparin was discontinued immediately and the administration of argatroban was started. Results of other laboratory tests are listed in the Table 1. Besides thrombocytopenia, mild anemia, prolongation of activated partial thromboplastin time (APTT), and elevation of d-dimer, lactate dehydrogenase, c-reactive protein and brain natriuretic peptide were

demonstrated. The clinical course of the platelet count is depicted in the Figure 1. Testing of the HIT IgG antibody and functional testing assessed by the platelet microparticle method showed strong positivity by incubation with unfractionated heparin [1]. The diagnosis of immune-mediated HIT was confirmed. She was treated with argatroban for 2 weeks, and then switched to oral once daily rivaroxaban. Her platelet counts recovered to a normal level and no thromboembolism was detected.

Table 1. *Pertinent laboratory data of patient at the time of consultation to Hematology Department*

Complete blood count			Na	140	mEq/L
Leukocyte count	130,00	/μL	K	3.5	mEq/L
Erythrocyte count	368×10^4	/μL	Cl	105	mEq/L
Hemoglobin	10.8	g/dl	Ca	9	mg/dL
Hematocrit	32.4	%	C-reactive protein	10.22	mg/dL
Platelet count	3.4×10^4	/μL	Brain natriuretic peptide	1064.7	pg/mL
Blood chemical examination			Coagulation test		
Aspartate Aminotransferase	110	U/L	PT	76	%
Alanine Aminotransferase	35	U/L	PT-INR	1.18	
Alkaline Phosphatase	196	U/L	PT time	15.1	sec
Lactate dehydrogenase	694	U/L	APTT	81.4	sec
Total Bilirubin	0.8	mg/dL	D-dimer	15.68	μg/ml
Total Protein	6.2	g/dL			
Albumin	3.17	g/dL	Othere test		
Blood Urea Nitrogen	18	mg/dL	HIT antibody (IgG)	2.293	(normal range<0.400)
Creatinine	0.58	mg/dL			
Creatine Kinase	119	U/L			

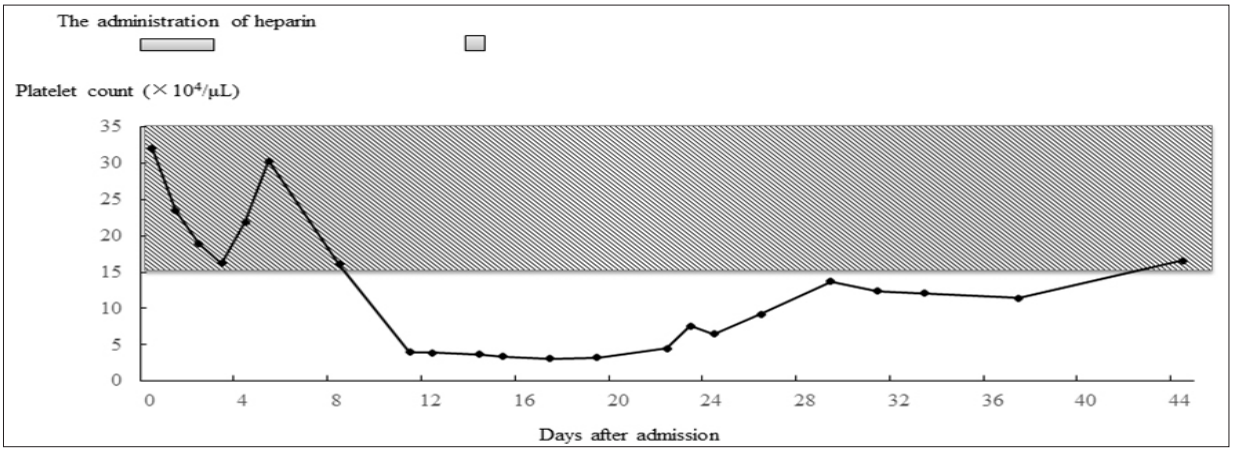

Fig 1. *The clinical course of platelet counts from the beginning to 44th days after admission. X axis indicates the days after admission (day) and Y axis indicates platelet counts (×10⁴/μL). The upper gradation square indicates the duration of heparin administration. The shaded square indicates the normal range of platelet counts.*

Discussion

HIT is caused by antibodies against platelet factor 4 (PF4) and heparin complex and is induced by heparin [2, 3]. Anti PF4/heparin antibodies lead to platelet activation and generate multiple thrombosis in high incidence [3, 4]. HIT is usually observed 5 to 14 days after heparin administration, because it takes at least 4 days for the generation of antibodies[5]. We retrospectively analyzed HIT antibodies from blood drawn from our patient on days 5, 14 and 29 and found that HIT antibodies were positive at day 14 and 29, but not day 5. We believe that HIT antibodies were present at around day 11 when thrombocytopenia was first detected (HIT type 2)[6]. However, the platelet count dropped transiently at day3. Interestingly, the platelet counts recovered rapidly within 2 days after stopping the administration of heparin at day 5 when we could not yet detect HIT antibodies (HIT type 1)[6]. In this case, the titer of HIT antibodies was quite high and the functional assay revealed that HIT antibody caused strong platelet activation in the presence of heparin. However, it is still difficult to diagnose HIT during the early time course (such as within 4 days). Besides measuring the existence of HIT antibodies, it is important to analyze the function of HIT antibodies. The platelet microparticle method is one of the platelet activation assays which could quantify the amount of platelet microparticleactivated by HIT antibody using flow cytometry[1].As the platelet microparticle method is strongly positive, the incidence of thromboembolic events may increase. The release of microparticle by HIT antibody activated platelet plays an important role in the pathology of HIT [1]. The close relationship between microparticles and thrombosis has also been reported [7, 8].

Although HIT antibody may develop later, HIT should be addressed as soon as it is suspected, even without confirmation of the presence of antibodies. In clinical practice, we can use the 4Ts clinical scoring system for predicting HIT: this system consists of four factors such as timing of heparin therapy, complications of thrombocytopenia and thrombosis, and exclusion of other causes[3,9]. In this case showed a score of 8 out of 8, highly indicative of HIT[9]. Other than 4Ts scoring system, HIT Expert Probability score had also been adapted[10]; using this system, this case scored 14 out of 17, also highly indicative of HIT. Besides clinical scoring systems, several risk factors for HIT have been reported; female sex, surgical patients, and major injuries[11, 12]. This case had two of these risk factors. Furthermore, this case makes it evident that HIT can be induced not only by the therapeutic administration of heparin but also by using a small amount of heparin for keeping arterial lines patentor by using heparin-coated catheters, as previously reported [13].

When treating HIT, the first step is to stop heparin and start an alternative anticoagulant therapy without delay. If we do not start anticoagulation, the risk for thromboembolism remains high (about 6% per day) for about one month after stopping heparin[3,14]. Also, prolongation of APTT in some HIT cases has been reported recently [15]. Prolongation of APTT was also observed in this case. If we reduce the dose of argatroban due to bleeding risk according to the results of APTT, the thrombosis could become worse, as previously reported. We used a regular dose of argatroban for 2 weeks, then switched to rivaroxaban for another 2 weeks without any adverse events. The efficacy and safety of using direct oral anticoagulants (DOAC, such as rivaroxaban) has been confirmed for the treatment of HIT [16]. Because monitoring of APTT is not necessary for DOAC, the use of DOAC is particularly useful when prolongation of APTT is observed.

Conclusion

In conclusion, this case confirms that severe injury may indeed be a risk factor for HIT and demonstrates that only a small amount of heparin can induce HIT. We should beware of the possibility of iatrogenic thrombocytopenia and thromboembolism (called HIT) and act accordingly, without delay.

Abbreviations

APTT, activated partial thromboplastin time; DOAC, direct oral anticoagulants; HIT, heparin-induced throm bocytopenia; PF4, platelet factor 4, PT, prothrombin time.

Acknowledgments

We thank Dr. Miyata S and Dr. Maeda T, Division of Transfusion Medicine, National Cerebral and Cardiovascular Center for analyzing HIT antibodies and performing the functional assay.

References

[1] Maeda T, Nakagawa K, Murata K, Kanaumi Y, Seguchi S, Kawamura S, et al. Identifying patients at high risk of heparin-induced

thrombocytopenia - associated thrombosis with a platelet activation assay using flow cytometry. Thromb Haemost 2017;117:127–38. doi:10.1160/TH16-06-0482.

[2] Amiral J, Bridey F, Dreyfus M, Vissoc AM, Fressinaud E, Wolf M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thromb Haemost 1992; 68: 95–6.

[3] Arepally GM. Heparin-induced thrombocytopenia. Blood 2017;129:2864–72. doi:10.1182/blood-2016-11-709873.

[4] Warkentin TE. Drug induced immune mediated thrombocytopenia — From purpura to throm bosis. N Engl J Med 2007; 356: 891–3. doi: 10. 1056/NEJMp068309.

[5] Greinacher A, Kohlmann T, Strobel U, Sheppard J-AI, Warkentin TE. The temporal profile of the anti- PF4/heparin immune response. Blood 2009; 113:4970–6. doi:10.1182/blood-2008-08-173062.

[6] Brieger DB, Mak KH, Kottke-Marchant K, Topol EJ. Heparin-induced thrombocytopenia. J Am Coll Cardiol 1998;31:1449–59.

[7] Piccin A, Sartori MT, Bisogno G, Van Schilfgaarde M, Saggiorato G, Pierro AMD, et al. New insights into sinusoidal obstruction syndrome. Intern Med J 2017;47:1173–83. doi:10.1111/imj.13550.

[8] Piccin A, Murphy C, Eakins E, Kunde J, Corvetta D, Di Pierro A, et al. Circulating microparticles, protein C, free protein S and endothelial vascular markers in children with sickle cell anaemia. J Extracell Vesicles 2015;4:28414.

[9] Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. Blood 2012;120:4160–7. doi:10.1182/blood-2012-07-443051.

[10] Joseph L, Gomes MP V, Al Solaiman F, St John J, Ozaki A, Raju M, et al. External validation of the HIT Expert Probability (HEP) score. Thromb Haemost 2015;113:633–40. doi:10.1160/TH14-05-0472.

[11] Warkentin TE, Sheppard J-AI, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 2006; 108:2937–41. doi:10.1182/blood-2005-11-012450.

[12] Lubenow N, Hinz P, Thomaschewski S, Lietz T, Vogler M, Ladwig A, et al. The severity of trauma determines the immune response to PF4/heparin and the frequency of heparin-induced thrombocytopenia. Blood 2010;115:1797–803. doi:10.1182/blood-2009-07-231506.

[13] Linkins L-A, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin induced thrombocytopenia. Chest 2012;141:e495S–e530S. doi:10.1378/chest.11-2303.

[14] Greinacher A, Eichler P, Lubenow N, Kwasny H, Luz M. Heparin-induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic aPTT range. Blood 2000;96:846–51.

[15] Greinacher A, Warkentin TE. The direct thrombin inhibitor hirudin. Thromb Haemost 2008;99: 819–29. doi:10.1160/TH07-11-0693.

[16] Warkentin TE, Pai M, Linkins L-A. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. Blood 2017;130:1104–13. doi:10.1182/blood-2017-04-778993.

Citation: **Yutaka Shimazu, Mamoru Toyofuku, Mitsuru Yamaguchi Masuda, Maiko Inada, Masaharu Nohgawa**. *Heparin-Induced Thrombocytopenia after Severe Injury in an Aged Woman: Using Clinical Scoring System. Archives of Hematology and Blood Diseases. 2018; 1(1): 13-16.*