A Case of Heparin-Induced Thrombocytopenia Type 2 after Repair of Juxtarenal Abdominal Aortic Aneurysm

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Abstract

Heparin-induced thrombocytopenia (HIT) is still a relatively uncommon condition and it is not well known how to administer argatroban during continuous hemodiafiltration (CHDF). A 72-year-old man required CHDF with heparin because of the oliguria and hyperpotassemia directly after the open repair of a juxtarenal abdominal aortic aneurysm. As the postoperative blood platelet count dropped and there was a thrombus in the CHDF circuit, HIT was suspected and nafamostat mesilate, but not heparin, was immediately administered for CHDF. As heparin-platelet factor 4 complex was positive, we diagnosed him with HIT and started argatroban while monitoring the activated clotting time (ACT), resulting in no further obstruction of the CHDF and an increase in the platelets. There was no disadvantage for administering nafamostat mesilate which we have commonly used instead of heparin, we should have used argatroban once we suspected HIT. It may be important to consider the history of heparin especially in administering heparin and it may be useful to monitor the ACT when initially starting argatroban for patients with HIT.

Keywords

- heparin-induced thrombocytopenia
- nafamostat mesilate
- argatroban

Heparin-induced thrombocytopenia (HIT) is a rare condition but it is serious.¹ Although in Japan only argatroban has been approved for anticoagulation in HIT type 2, it is still relatively uncommon and it is not well known how to administer argatroban during continuous hemodiafiltration (CHDF). We report a rare case of HIT type 2 with acute renal dysfunction after the open repair of a juxtarenal abdominal aortic aneurysm (AAA).

Case Report

A 72-year-old man with a history of percutaneous coronary intervention (PCI) due to myocardial infarction was referred

to our hospital with a pulsatile abdominal mass. He was administered heparin for the coronary angiography of the follow-up 11 months ago. The patient's height was 167 cm and body weight was 69 kg (body mass index, 24.8). Physical examination was unremarkable except for the abdominal mass. Laboratory examination showed blood urea nitrogen of 22.0 mg/dL and serum creatinine of 1.43 mg/dL. Echocardiography showed severe hypokinesis at the inferior and posterior wall and left ventricular dysfunction (ejection fraction, 38.2%). Enhanced chest and abdominal computed tomography (CT) revealed a juxtarenal AAA measuring 58 × 48 mm (–Fig. 1). Open repair was selected in spite of his poor heart function. A standard midline approach was

Fig. 1 Preoperative enhanced chest and abdominal computed tomography revealed a juxtarenal abdominal aortic aneurysm (AAA) measuring 58 × 48 mm. (a) The level of the right renal artery, (b) the level of the middle abdominal aorta, (c) the level of the maximum AAA.

employed to expose the juxtarenal AAA. After proximal clamping was performed above the left renal artery (RA) but below the right RA, distal clamping was performed of both common iliac arteries (CIAs), as well as clamping of the inferior mesenteric artery (IMA), and then open repair was performed between the infrarenal aorta and CIAs with IMA reconstruction using a 20 × 11 mm knitted bifurcated graft under a total of 9,000 units of unfractionated heparin (UFH). The proximal clamp time was 65 minutes.

The patient required CHDF with heparin for anticoagulation because of the oliguria and hyperkalemia directly after the operation. As the preoperative blood platelet count was 195,000/ μ L but dropped to 76,000/ μ L and there was a thrombus in the CHDF circuit on the 4th postoperative day, HIT was suspected and nafamostat mesilate, but not heparin, was immediately administered for CHDF. As heparin platelet factor 4 complex (heparin PF4 complex) was positive, HIT was diagnosed, and argatroban was started on the 10th postoperative day. Because laboratory examination showed increases of aspartate aminotransferase and alanine aminotransferase and the anticoagulation was monitored with an activated clotting time (ACT) of around 180 seconds, the starting dose of argatroban was a bolus of 0.23 μ g/kg/min. After changing to argatroban, no further circuit obstruction of the CHDF was observed and the blood platelets slowly recovered. The patient required hemodialysis (HD) on the 14th postoperative day (**Fig. 2**). As anticoagulation was adjusted based on the presence or absence of a thrombus in the HD circuit, the starting dose of argatroban was 5 mg, with its maintenance

dose ranging from 5 mg per hour to 7 mg per hour. Because the patient had a history of PCI, the administration of clopidogrel (75 mg/d) was restarted.

On the contrary, the patient presented with mild abdominal distention, and abdominal X-ray showed an increase of small intestinal gas on the 2nd postoperative day. Postoperative CT revealed a thick wall of the ascending colon on the 11th postoperative day. Moreover, as the tops of the patient's left first and fourth toes were necrotic after the operation, we suspected ischemic colitis because of an embolism during the operative clamping. The patient's abdomen recovered gradually after continuous intravenous perfusion of total parenteral nutrition, while the necrotic toes were resected and the open wounds were lapped with gauze with antimicrobial after cleaning by fresh water until they were covered with granulation tissues. The patient was discharged on foot on the 73th postoperative day. The heparin PF4 complex was positive at about the 3rd month after surgery, whereas it was negative at the 6th month after surgery. When the patient underwent HD using nafamostat mesilate at about the 4th month of surgery at a neighboring hospital, there was no problem and the patient finally need not HD at approximately 8th month.

Discussion

There are two clinical forms of HIT. HIT type 1 has a benign course, with platelet counts recovering without heparin withdrawal and no clinical consequences, while HIT type 2 constitutes a clinical-pathological syndrome with a strong

Fig. 2 A summary of the postoperative course. The solid line indicates creatinine (Cr: mg/dL), while the dotted line indicates blood platelets (Plt: $\times 10^4/\mu\text{L}$). CHDF, continuous hemodiafiltration; Cr, serum creatinine; HD, hemodialysis; HIT, Heparin-induced thrombocytopenia; UFH, unfractionated heparin; Plt, blood platelets.

association with thrombotic events.² Clinically, HIT type 2 is very important and it occurs in 1 to 3% of patients treated for 1 to 2 weeks with UFH, compared with approximately 0.1% for patients receiving low-molecular-weight heparin.³ As regards, the timing of HIT, Girolami and Girolami reported onset of HIT type 1 is between 1 and 4 days, while that of HIT type 2 is between 5 and 14 days.² In this case, although we initially suspected HIT when the blood platelet count dropped as well as the thrombus in the CHDF circuit on the 4th postoperative day, we thought the timing of HIT was a little bit early, and, thus, we could not diagnose him with HIT and administered nafamostat mesilate, which we have commonly used instead of heparin. However, Warkentin et al had previously reported that in patients without previous exposure to heparin, a fall in the platelet count occurs at approximately 5 to 10 days after the initial treatment (delayed onset), while in patients who have not received heparin for 3 months, thrombocytopenia may occur within the first 24 hours after reexposure (acute onset).⁴ Moreover, once sensitized heparin, patients may develop HIT a short time after repeat exposure and may manifest symptoms during or soon after the procedure.⁵ In this case, as he did not be taken heparin for 11 months, we thought the reexposure of heparin promoted the thrombocytopenia. Although there was no disadvantage for administering nafamostat mesilate, we should have used argatroban once we suspected HIT. We think that it may be important to consider the history of heparin especially in administering heparin.

Japanese guideline for HIT was based on the American and European guidelines.⁶ Although in Japan only argatroban has

been approved for anticoagulation in HIT type 2 and there are many reports about HIT, it is not still common how we administer it for CHDF. As Japanese is smaller than people in Europeans and Americans, it has suggested that argatroban at 0.7 $\mu\text{g/kg/min}$ should be the initial dose for HIT patients without liver dysfunction, and 0.2 $\mu\text{g/kg/min}$ for patients with liver dysfunction.⁷ Moreover, anticoagulation was monitored with an ACT of between 150 and 200 seconds.⁷ As we diagnosed him with HIT type 2 and we started argatroban on the 10th postoperative day after confirming that the heparin PF4 complex was positive, we started argatroban while monitoring an ACT of around 180 seconds. In this case, the initial dose was 0.23 $\mu\text{g/kg/min}$ because of his mild liver dysfunction, which is consistent with the suggestion. Finally, as the anticoagulation was adjusted based on the presence or absence of a thrombus in the HD circuit or not, the starting dose of argatroban was 5 mg, and its maintenance dose ranged from 5 to 7 mg/h.

Miyata and Yamamoto⁷ have reported that heparin PF4 complex is generally negative within between 50 and 85 days after withdrawal of heparin. However, in this case, it was positive at about the 3rd month after surgery, while it was negative at the 6th month after surgery.

Kelton and Warkentin⁸ have reported that there are some immune reactions against heparin- and patient-dependent risk factors, such as platelet Fc γ receptor numbers or increased platelet-associated PF4 levels may also play a role, while Pötzsch et al⁹ have reported the study of the use of heparin during cardiopulmonary bypass in patients with a history of HIT. Even though after heparin PF4 complex was

negative, we had not better use heparin during HD in case the patients have some immune reaction against heparin without special cases.

We conclude that it may be important to consider the history of heparin especially in administering heparin and it may be useful to monitor the ACT when initially starting argatroban for patients with HIT.

Conflict of Interest

All authors have no conflict of interest.

References

- 1 Warkentin TE, Greinacher A, Koster A, Lincoff AM; American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6, Suppl):340S–380S
- 2 Girolami B, Girolami A. Heparin-induced thrombocytopenia: a review. *Semin Thromb Hemost* 2006;32(8):803–809
- 3 Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332(20):1330–1335
- 4 Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001;344(17):1286–1292
- 5 van Sambeek MR, Segeren CM, van Dijk LC, van Essen JA, Dippel DW, van Urk H. Endovascular repair of an extracranial internal carotid artery aneurysm complicated by heparin-induced thrombocytopenia and thrombosis. *J Endovasc Ther* 2000;7(5):353–358
- 6 Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3, Suppl):311S–337S
- 7 Miyata S, Yamamoto H. The treatment of heparin-induced thrombocytopenia (HIT) [in Japanese]. *Jpn J Thromb Hemost* 2008;19(2):195–198
- 8 Kelton JG, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. *Blood* 2008;112(7):2607–2616
- 9 Pötzsch B, Klövekorn WP, Madlener K. Use of heparin during cardiopulmonary bypass in patients with a history of heparin-induced thrombocytopenia. *N Engl J Med* 2000;343(7):515