

# A Case of Heparin-Induced Thrombocytopenia with Repeated Episodes of Acute Lower Extremity Arterial Thromboembolism during a Short Time

Hidetoshi Masumoto, MD, Mitsuomi Shimamoto, MD, Fumio Yamazaki, MD,  
Masanao Nakai, MD, Shoji Fujita, MD, Tatsuya Itonaga, MD, and Ryota Nomura, MD

**The patient was a 55-year-old female. On the diagnosis of the right acoustic tumor, a subtotal extirpation was performed. Heparinized solution was administered, and on postoperative day 7, an occlusion of the left common femoral artery was confirmed. A continuous administration of heparin was initiated after a thrombectomy. On the following day, the platelet count decreased. Following confirmation of the recurrence of thromboembolism, we again performed a thrombectomy. Considering the possibility of heparin-induced thrombocytopenia (HIT), we terminated the administration of heparin, and treatment with danaparoid and argatroban was initiated. Two days later, she redeveloped thromboembolism. After the administration of danaparoid was terminated, the platelet count improved. (Ann Thorac Cardiovasc Surg 2007; 13: 365–367)**

**Key words:** heparin-induced thrombocytopenia, arterial thromboembolism, argatroban

## Introduction

Heparin has been widely used as an anticoagulant in clinical practice. A major adverse effect is heparin-induced thrombocytopenia (HIT). While various reports have been published regarding the incidence of HIT,<sup>1)</sup> the incidence of the disease has recently been estimated to be approximately 3%. Furthermore, the development of arterial and venous thromboses has been reported as complications in many cases.

## Case Report

The patient was a 55-year-old female who developed diplopia in April 2005, and left abducent nerve paralysis was suggested. Since the presence of a right acoustic tumor was confirmed, subtotal extirpation was performed

in May 2005. The platelet count at the time of hospitalization was 336,000/ $\mu$ L. During the operation, heparinized physiological sodium chloride solution (10 units/mL) was administered via the arterial line. On postoperative day 7, the patient experienced a cold sensation in her left lower limb. Since occlusion of the left common femoral artery had been confirmed by intravenous digital subtraction angiography, she was diagnosed with acute arterial thromboembolism. A thrombectomy was performed, during which a white-red thrombus was removed, and blood flow improved. To prevent postoperative thrombus formation, a continuous administration of heparin was initiated at a dose of 400 units/h. On the following day, the platelet count decreased to 23,000/ $\mu$ L. Since we confirmed the recurrence of acute arterial thromboembolism at the left lower extremity (occlusion of the superficial femoral artery), a thrombectomy was again performed. During the operation, a similar white-red thrombus was removed, and an improvement of blood flow was confirmed. The platelet count decreased to 16,000/ $\mu$ L, and therefore 10 units of platelets were transfused. The platelet count immediately increased to 86,000/ $\mu$ L, but decreased thereafter. Considering the possibility of HIT, the administration of heparin was suspended, and an intrave-

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*From Department of Cardiovascular Surgery, Shizuoka City Hospital, Shizuoka, Japan*

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Address reprint requests to Hidetoshi Masumoto, MD: Department of Cardiovascular Surgery, Shizuoka City Hospital, 10–93 Outemachi, Aoi-ku, Shizuoka 420–8630, Japan.

nous administration of 1,250 units of danaparoid (heparinoid) and an intravenous drip of 10 mg argatroban (antithrombin) were initiated twice daily. Two days later, the patient redeveloped left lower extremity arterial thromboembolism, and a thrombectomy was again performed. Considering the influence of danaparoid, the drug administration was suspended after the operation. Improvement was subsequently confirmed for the platelet counts, and arterial thromboembolism did not occur. Protein C activity was within the normal range (125%), and the protein S antigen level was slightly above normal (145%). It was confirmed clinically that the platelet count decreased after heparin administration and increased immediately after heparin administration was terminated. Based on a positive platelet aggregation test, the patient was diagnosed with HIT (type II). The administration of argatroban was continued for 12 days. On postoperative day 27, swelling was confirmed in the right lower limb and was diagnosed as deep vein thrombosis by echo-Doppler ultrasound. Therefore an oral administration of warfarin and cilostazol was initiated. Twenty days after the commencement, a filter was set at the inferior vena cava (Trapease®, Cordis, Miami, FL). It was confirmed that the lower extremity venous thrombus was attenuated and finally disappeared. Clinical data including changes in the platelet count are shown in Fig. 1.

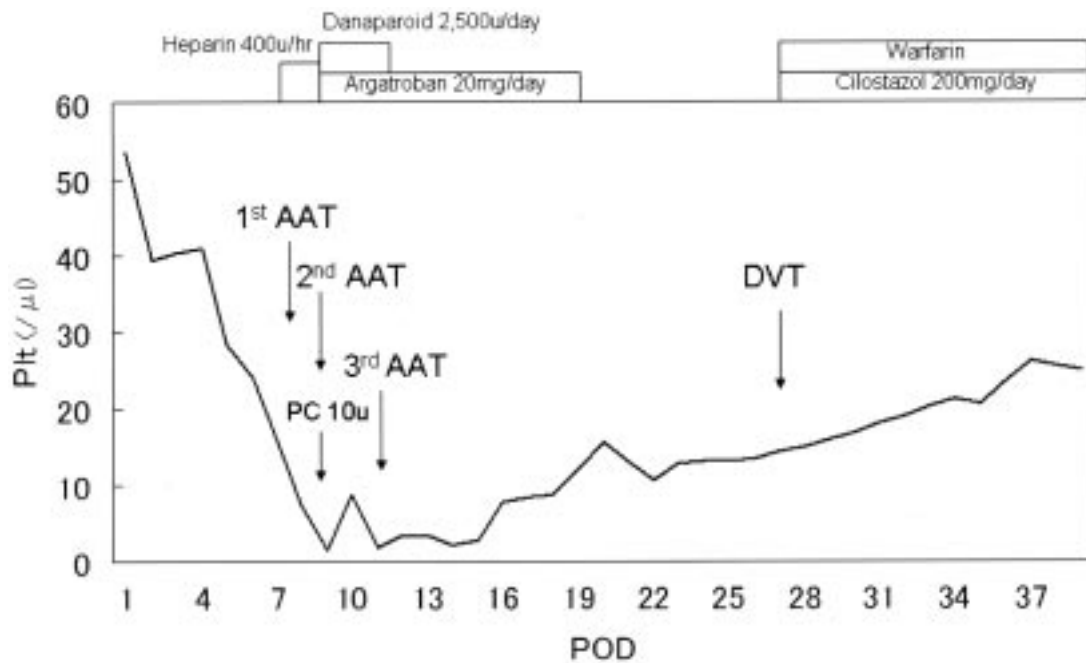
## Discussion

HIT occurs in two types.<sup>2)</sup> Type I HIT is caused by nonimmune mechanisms as a result of the physical and biological features of heparin. On the other hand, Type II HIT is caused by an immune mechanism in which a heparin-specific autoantibody is involved. When heparin is administered in the presence of platelet factor 4 (PF4), which is released from activated platelets, an immune complex can form and result in the production of an anti-PF4/heparin antibody (HIT antibody). This complex initially causes platelet aggregation, which is followed by a decrease in platelet counts and the development of thrombosis. PF4 released in this process is considered to further aggravate HIT, thrombosis, and the decrease in platelet counts.<sup>3)</sup> Moreover, thrombin released from activated platelets causes vascular endothelial disorder and the appearance of tissue factor in a vicious circle.<sup>1)</sup> Based on these facts, it is anticipated that thrombin inhibitors will play a leading role in the treatment of HIT. When the clinical diagnosis is established, a decrease in the platelet count greater than 50% in patients treated with heparin, no decrease in

the platelet count as a result of other diseases, and immediate improvement of the platelet count after the cessation of heparin administration should be confirmed. For such diagnosis, the platelet aggregation test<sup>4)</sup> and the enzyme-linked immunosorbent assay (ELISA) test to confirm HIT antibody are available.<sup>5)</sup> A correct diagnosis can be ensured by performing both of these tests. When HIT is suspected from a clinical perspective, even if a negative result is obtained in any of the tests, the administration of heparin should be terminated and alternative drugs should be used instead. This case was diagnosed as Type II HIT based on her clinical course and the results of a platelet aggregation test. Furthermore, the thrombus removed during the first operation was visually confirmed to be a red-white thrombus. Therefore it was considered to include a platelet aggregation clot, a so-called white clot syndrome that is specific to HIT.

For the treatment of HIT, the administration of heparin, which acts as an antigen, is terminated, and thrombin is deactivated through the use of a thrombin inhibitor. When thrombosis develops as a complication, an anti-thrombin agent is applicable.<sup>6)</sup> In this case, danaparoid and argatroban were initially used as anticoagulants instead of heparin. However, since acute arterial thrombosis occurred, the administration of danaparoid was suspended and clinical improvement was observed subsequently. Danaparoid is low molecular weight heparinoid, which is recommended for anticoagulant therapy of HIT patients in the U.S. and Europe. Warkentin et al. reported that the *in vitro* and *in vivo* cross-reactivity of danaparoid would be 10% and 5%, respectively,<sup>1)</sup> and therefore careful consideration is required in the use of this agent. Since the chemical structure of argatroban differs completely from that of heparin, it exhibits no cross-reactivity with HIT antibodies and thus exhibits significant effects as a specific antithrombin agent.<sup>7)</sup> However, no clear guidelines are available regarding the administration methods, dosage, and dosing duration of argatroban. Lewis et al. suggested that a continuous administration of the agent would be effective for the treatment of arterial thrombosis and venous gangrene in HIT patients. They administered the agent at  $2.0 \pm 0.1$   $\mu\text{g}/\text{kg}/\text{min}$  for  $5.3 \pm 0.3$  days on average, and 10% of the patients underwent amputation of a limb.<sup>8)</sup> In the present case, 20 mg of argatroban was divided into two doses so that the agent could be administered twice each day, and this was considered to be effective for the acute-phase treatment.

When deep vein thrombosis occurred, an oral administration of warfarin was initiated. The use of warfarin



**Fig. 1.** Clinical course.

AAT, acute arterial thrombosis; DVT, deep vein thrombosis; Plt, platelet; PC, platelet concentrate; POD, postoperative day.

for acute phase HIT is contraindicated in principle because it may induce a decrease of protein C activity. In the present case, thrombin/antithrombin 3 complex (TAT) activity decreased to 23.8  $\mu\text{g/L}$  at the onset of warfarin treatment, and no decrease in the platelet count was observed. Thus it was considered that the clinical level of the disease had reached the chronic phase, and thus warfarin administration was initiated. The subsequent resolution of the venous thrombus was confirmed, and no other thrombi developed.

## Conclusion

We performed thrombectomy and anticoagulant therapy for an HIT patient who repeatedly developed acute arterial embolism during a short time, and we obtained good results. It is considered important to prevent severe thrombotic complications by establishing a diagnosis at the early stage and providing treatment after correctly assessing the conditions of HIT.

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