Warfarin–induced venous limb gangrene following heparin–induced thrombocytopenia during anticoagulation therapy for deep vein thrombosis and pulmonary thromboembolism

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Abstract
Heparin–induced thrombocytopenia (HIT) is a complication of anticoagulation therapy using heparin. We report a critical case of HIT during anticoagulation therapy with heparin and warfarin. A 67-year-old man was admitted to our hospital with deep vein thrombosis and pulmonary thromboembolism. Intravenous heparin and oral warfarin were initiated for anticoagulation. Eleven days after starting heparin therapy, the platelet count suddenly decreased to below 50,000/μl, indicative of type 2 HIT. Twelve days after starting heparin, an above-knee amputation was required for warfarin–induced venous limb gangrene. During anticoagulation therapy with heparin, attention must be paid to the risk of critical HIT. Furthermore, the risk of warfarin causing venous limb gangrene in patients with HIT must be considered.

Key words: heparin–induced thrombocytopenia, deep vein thrombosis, warfarin, venous limb gangrene

Introduction
Heparin–induced thrombocytopenia (HIT) is an adverse reaction during anticoagulation therapy using heparin, which is characterized by thrombocytopenia and a high risk of venous or arterial thrombosis5). HIT is classified into two types; type 1 is a non–immunologic response and type 2 is an immunologic response to heparin. Although the incidence of type 2 HIT (1% to 3%) is lower than that of type 1, type 2 HIT is more critical6). Type 2 HIT typically occurs 5–10 days after the start of heparin administration6). We report a critical case of type 2 HIT occurring 11 days after starting intravenous heparin for deep vein thrombosis (DVT) and pulmonary thromboembolism. Moreover, an above–knee amputation was required for venous limb gangrene due to the use of warfarin.

Case Report
A 67-year-old man was admitted to our hospital with swelling of the right leg (upper leg perimeter, 58 cm; lower, 39.5 cm). His past medical and surgical histories were unremarkable and he had not taken any medication before admission. He had no risk factors of DVT, such as antiphospholipid syndrome and prolonged bed rest. Vascular ultrasonography (Fig. 1A) and computed tomography (CT, Fig. 1B) demonstrated a mobile thrombus in the right external iliac vein and DVT was diagnosed. In addition, CT revealed multiple pulmonary thromboembolisms (Fig. 2). After implantation of an inferior vena cava filter (Günther Tulip® Vena Cava Filter, Cook Medical Inc., IN, USA), intra-venous urokinase (120,000 U, twice), and heparin sodium (10,000 U/day) were initiated. The dose of heparin was adjusted to maintain activated clotting time (ACT) between 160 and 180 sec. Anti–thrombin III (AT III)
level was normal (90%) on admission. Swelling of the right leg remained unchanged (upper, 58.5 cm; lower, 40 cm) 5 days after admission. A second CT revealed that extension of the thrombus to the right popliteal vein. Oral warfarin was co-administered. Eleven days after admission, severe cyanosis appeared in the right leg and the pain was intolerable with further increase in leg perimeter (upper, 63 cm; lower, 43 cm). Vascular ultrasonography demonstrated that the thrombus had extended to the right great saphenous vein. Furthermore, platelet count decreased from 319,000/μl at 5 days after admission to 48,000/μl. An emergency thrombectomy was performed via the right femoral vein using 3- and 5-Fr Forgarty embolectomy catheters (Edwards Lifesciences Corporation, CA, USA). After thrombectomy, a pulse spray catheter (Fountain® Infusion System, Merit Medical Systems, Inc., UT, USA) was inserted into the right external iliac vein for thrombolysis. Because type 2 HIT was suspected (4T’s score = 7), intravenous argatroban at a dose of 0.7μg/kg/min was started. Heparin and warfarin were discontinued immediately after the start of argatroban. The dose of argatroban (0.6 to 0.7μg/kg/min) was adjusted to maintain activated partial thromboplastin time (APTT) between 60 and 100 sec. Time courses of leg perimeter and laboratory data are shown in Table 1. Twelve days after admission, the right dorsal pedis and posterior tibial arteries became pulseless. With a strong suspicion of warfarin-induced venous limb gangrene, an
Table 1  Time courses of leg perimeter and laboratory data

<table>
<thead>
<tr>
<th>Days after admission</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<tbody>
<tr>
<td>Upper leg perimeter (cm)</td>
<td>58</td>
<td>58</td>
<td>58</td>
<td>58</td>
<td>58.5</td>
<td>58</td>
<td>58</td>
<td>58</td>
<td>58</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Lower leg perimeter (cm)</td>
<td>39.5</td>
<td>39</td>
<td>39</td>
<td>39</td>
<td>40</td>
<td>39.9</td>
<td>39.7</td>
<td>39.8</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT (×10^4/μl)</td>
<td>37.3</td>
<td>33.9</td>
<td></td>
<td>31.9</td>
<td></td>
<td>13.8</td>
<td></td>
<td>4.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT (sec)</td>
<td>163</td>
<td>175</td>
<td>174</td>
<td>144</td>
<td>153</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>37.7</td>
<td>41.4</td>
<td>43.1</td>
<td>41.8</td>
<td>46.3</td>
<td>91.6</td>
<td>62.8</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PT-INR</td>
<td>1.21</td>
<td>1.23</td>
<td>1.19</td>
<td>1.35</td>
<td>1.76</td>
<td>2.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AT III (%)</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88</td>
<td>85</td>
</tr>
</tbody>
</table>

PLT, platelet count; ACT, activated clotting time; APTT, activated partial thromboplastin time; PT-INR, prothrombin time–international normalized ratio; AT III, anti–thrombin III.

above-knee amputation of the right leg was performed under general anesthesia. AT III decreased from 85% before onset of gangrene to 50% before amputation. However, since AT III recovered to 79% on the day after amputation, AT III supplementation was not given. The HIT antibody by enzyme–linked immunosorbent assay (ELISA) was strongly positive (2.435 OD). Pulse spray catheter–directed thrombolysis (urokinase 120,000 U, twice per day) was continued for 3 weeks after surgery. Because HIT antibody remained strongly positive for 2 months (2.569 OD at 2 months after admission), it took over 2 months for the platelet count to recover to above 100,000/μl. Warfarin was restarted 5 months after amputation and prothrombin time–international normalized ratio (PT-INR) was maintained around 2.0. The patient was discharged after rehabilitation with an artificial leg.

Discussion

Type 2 HIT is an immune–mediated disorder typically occurring 5–10 days after the start of heparin therapy5, and is caused by binding of platelet–activating IgG antibodies (HIT antibodies) to multi–molecular complexes of platelet factor 4 and heparin on platelet surfaces41.

In the present case, the patient became critically ill with a sudden decrease in platelet count (<50,000/μl) 11 days after starting heparin therapy. Because HIT was strongly suspected, heparin and warfarin were immediately discontinued and intravenous argatroban was started before the result of HIT antibody testing using ELISA was available. When HIT is suspected, early conversion to argatroban therapy without waiting for the result of ELISA may be important because the condition of the patient deteriorates while waiting.

Despite early conversion to argatroban therapy, an above-knee amputation of the right lower extremity could not be avoided in the present case. The United States Food and Drug Administration recommends an initial dose of argatroban of 2.0 μg/kg/min for HIT, whereas the initial dose recommended in Japan is 0.7 μg/kg/min. The difference in the initial dose of argatroban may affect the outcome in the present case.

Furthermore, this unfavorable outcome may be partially due to the use of warfarin. Warfarin therapy is a standard therapy for DVT and/or pulmonary thromboembolism. However, in patients with HIT, warfarin may cause severe complications such as skin necrosis and venous limb gangrene5. Srinivasan et al.6 reported six cases of warfarin–induced skin necrosis and leg limb gangrene in patients with HIT, with one patient requiring breast and leg amputations. They reported that these complications emerged 2–7 days after warfarin initiation. Warkentin et al.7 also reported venous limb gangrene associated with the use of warfarin in patients with HIT. They reported that patients with venous limb gangrene had higher PT-INR, lower protein C activities, and persistently elevated thrombin–antithrombin complex levels. In their report, the median peak PT-INR was 5.8 in patients who had venous limb gangrene and 3.1 in those who did not develop venous limb gangrene. Furthermore, Wallis et al.8 analyzed 51 HIT patients receiving warfarin for non–HIT indications and concluded that modest doses of warfarin did not increase the incidence of venous limb gangrene. In their report, 47% of the patients received warfarin 2.4 ± 0.4 days prior to the onset of HIT8. In the present case, warfarin therapy was initiated 6 days before the onset of HIT and PT-INR was 2.59 at the onset of HIT. The dose of warfarin used in the present case was lower than those described in
previous reports\textsuperscript{7,8}. However, once venous limb gangrene develops, a limb amputation may be unavoidable. Although the patient underwent a thrombectomy the day before amputation, critical limb ischemia could not be prevented because of venous limb gangrene. Therefore, we should bear in mind the risk of warfarin causing venous limb gangrene in patients with HIT, even when the warfarin dose is modest.

We reported a case of type 2 HIT during anticoagulation therapy using heparin and warfarin for DVT complicated by pulmonary thromboembolism. During anticoagulation therapy using heparin, attention must be paid to the possible risk of critical HIT. Furthermore, the risk of warfarin causing critical complications such as venous limb gangrene in patients with HIT must be considered.

**Disclosure Statement**

All authors have no conflict of interest.

**References**


