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Case Report RADIOLOGY

Low-molecular-weight heparin-associated multiple digital necrosis in a patient as a result of heparin-induced thrombocytopenia syndrome

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ABSTRACT

Heparin-induced thrombocytopenia syndrome (HITS) is a rare complication of low-molecular-weight heparin (LMWH). It is an autoimmune-mediated side effect of LMWH which is caused by platelet-activating antibodies that recognize platelet factor-4/heparin complexes. Although HITS often leads to thrombosis in large veins and arteries, it can be presented as microvascular thrombosis. In this article, we report a case of HITS complicated with multiple digital necrosis after administration of LMWH.

Keywords: Heparin; heparin-induced thrombocytopenia; low-molecular weight heparin; thrombocytopenia.

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Heparin-induced thrombocytopenia syndrome (HITS) is a rare complication of low-molecular-weight heparin (LMWH) with a reported incidence of 0.2% [1]. It is an autoimmune-mediated side effect of LMWH which is caused by platelet-activating antibodies that recognize platelet factor-4 (PF4)/heparin complexes [2]. Although HITS often leads to thrombosis in large veins and arteries, it can be presented as microvascular thrombosis [2].

In this article, we report a case of HITS complicated with multiple digital necrosis after administration of LMWH. The objective of reporting this case is to highlight the clinical presentation and treatment of HITS as a complication in patients after administration of LMWH.

CASE REPORT

A 73-year-old man, with a weight of 105 kg, admitted to our hospital with chest pain symptom. After the diagnosis of myocardial infarction, he underwent coroner angiography emergently and he was treated by percutaneous transluminal coroner angioplasty. When he was admitted to the hospital, the platelet count was 391 × 10^9/L. The prothrombin time was 11 s (reference range: 11–13 s). LMWH (enoxaparin sodium 6000 Anti-XA IU/0.6 ml) twice a day was administered subcutaneously by the cardiologists as anticoagulation. On the 5th day of LMWH therapy, the patient complained of prolonged pain at the both upper and lower extremities and the control platelet count was 154 × 10^9/L. There were no

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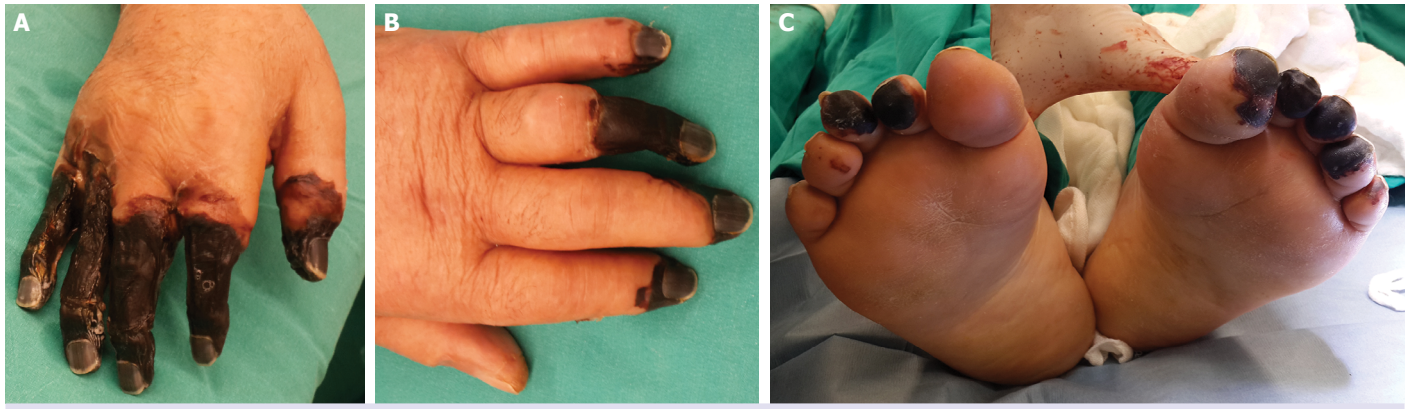

FIGURE 1. **(A)** Progressive ischemia was developed leading to necrosis of fingers. **(B)** The necrosis of fingers except the thumb of the left hand. **(C)** The necrosis of fingers in feet.

significant changes in the other parameters of the complete blood count at the time of admission to the hospital and at the 5th day of LMWH treatment. The control prothrombin time was 13 s. There was no history of thrombophilia, protein C and S deficiency. The fingers were swollen with tenderness and warmness. Doppler ultrasonography assessment of both upper and lower extremities showed arterial and venous thrombosis at the radial and ulnar arteries and veins of both upper extremities, and tibialis posterior and dorsalis pedis arteries and veins of both lower extremities. HITS was diagnosed by significant decrease in platelet count, physical examination, enzyme-linked immunoassay (ELISA) test against the PF4/heparin complex, and Doppler ultrasonography. The optical density of the ELISA test was >1.0. No confirmation test was performed as it indeed requires a specialized laboratory for platelet aggregation tests. As a result, the diagnosis of HITS was only based on high clinical probability and the positive screening ELISA test. The 4-T test which scores four parameters such as platelet fall, timing of platelet fall, thrombosis, and other causes for the thrombocytopenia is high correlation with HITS with the scores between 6 and 8 [3]. In our patient, this score was 6. After the hematology clinic consultation, the LMWH administration was stopped and fondaparinux 7.5 mg/0.6 ml subcutaneous treatment was started in the 6th day of LMWH treatment. In the 7th and 8th days of LMWH treatment, platelet count increased to 308 × 10^9/L and 412 × 10^9/L, respectively. The increase in platelet count supported our diagnosis. On the day 12, progressive ischemia was developed leading to necrosis of fingers, the demarcation line started to become clear, in both hands except the thumb of the left hand, in the second and third fingers of the right foot, and in the fingers of the left foot except the little finger (Fig. 1). On the day 16, after the informed consent form is taken, the necrotic fingers were amputated. The fondaparinux treatment was continued till the post-operative 4th month. Warfarin or direct oral anticoagulants were not used in the treatment of myocardial infarction or HITS of this patient.

DISCUSSION

There are two types of HITS [4]. Type 1 is associated with direct heparin-induced platelet activation that causes a transient thrombocytopenia and usually normalizes within 2 days after the LMWH administration [4]. Type 2 is an immune-mediated systemic condition characterized by platelet activation resulted with thrombocytopenia and is seen at the 4–10 days of LMWH administration [4]. Late-onset HITS with thrombocytopenia is an another form presented up to 100 days after the drug administration [4]. The significant decrease of platelet count in our patient was determined in the 5th day of the administration of LMWH and it was revealed as type 2 HITS. Although platelet count rose very rapidly, the use of fondaparinux did not lead to clinical improvement as ischemia progressed to gangrene, indicating fondaparinux failure. This may imply that fondaparinux may not be effective in case of arterial thrombosis and microvascular thrombosis.

The clinical presentation of HITS includes fever, chills, flushing, hypertension, tachycardia, dyspnea, diarrhea, and local skin reactions at the heparin injection region [4]. Furthermore, the 4-T test is a clinical scoring test which scores four parameters such as platelet fall, timing of platelet fall, thrombosis, and other causes for

the thrombocytopenia which is high correlation with HITS with the scores between 6 and 8 [3]. In our patient, 4-T clinical score was 6 which was correlated with high risk of HITS.

HITS could be associated with or without thrombosis. These patients can present with thrombosis up to 3 weeks after the heparin is started [5]. When HITS is strongly suspected or confirmed, Doppler ultrasonography can rule out thrombosis [5]. Thrombosis could affect the duration of treatment in these patients [5]. Moreover, abdominal pain, hypertension, or bilateral adrenal hemorrhage could be associated with adrenal vein thrombosis or severe headache could be associated with cavernous sinus thrombosis in the patients with HITS [5]. At the time that HITS-related thrombosis became evident, comparison of the actual platelet count peak at days 6 and 7 shows the fall in the platelet count for more than 50% which indicates HITS [5]. Patients who have HITS with thrombosis require therapeutic dose anticoagulation for at least 3 months [5]. In our patient, the fall in the platelet count was more than 50% in the 5th day and the thrombosis was associated with HITS. In our patient, we used the fondaparinux treatment for 4 months.

In the management of a patient with HITS, unfractionated heparin and LMWH should be discontinued, including heparin-coated intravascular catheters [6]. Except the evidence of clinical bleeding, in the treatment of acute HITS, the platelet transfusions are contraindicated because platelet transfusions can increase the risk of thrombosis [5, 6]. The risk of bleeding in these patients is low [5]. There are three classes of alternative non-heparin anticoagulant therapy agents which are required in the treatment of HITS [6, 7]. Lepirudin, argatroban, dabigatran, and bivalirudin are the direct thrombin inhibitors [6]. Danaparoid is a heparinoid recommended for the treatment or prevention of thrombosis in HITS [6]. Fondaparinux is an antithrombin III-dependent selective inhibitor of activated factor-Xa which is recommended in the treatment of thrombosis in HITS [6]. In our patient, we used fondaparinux only because direct thrombin inhibitors such as lepirudin and heparinoids are not currently available in our country. The manufacturer ceased the production of lepirudin in May 2012. However, an option could have been direct oral anticoagulants, although they may fail in case of arterial thrombosis. Moreover, drugs could be imported from other countries in rare diseases.

LMWH is a rather frequently used agent for treatment and prophylaxis in anticoagulation in many cases. Although we attempt to solve the microvascular and macrovascular circulation problem of the patients with LMWH, it could set a bar against success of our operations with this side effect. We wanted to attract attention about the side effects of the administration of LMWH that can lead up to irreversible effects.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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