Bilateral Arm Gangrene Associated With Heparin-Induced Thrombocytopenia After Extracorporeal Cardiopulmonary Resuscitation

Kansuke Ito, MD; Toshiaki Isogai, MD; Makiko Takada, MD; Tetsushi Tatsumi, MD; Kazuaki Enatsu, MD; Hiroyuki Tanaka, MD, PhD; Tamotsu Tejima, MD, PhD

Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication triggered by the production of antibodies to platelet factor 4 (PF4)-heparin complexes. HIT reportedly occurs in up to 5% of patients exposed to heparin regardless of the dose, timing, or treatment route. HIT can cause arterial and venous thromboses with a mortality rate as high as 20%, and can occur in patients with no history of heparin exposure. A recent study demonstrated that anti-PF4 antibodies induced by PF4/polyanion complexes on bacterial surfaces were similar to HIT antibodies. We herein report a case of HIT involving no history of exposure to heparin or any recent recognized event such as infection. The present patient developed HIT-related gangrene in the bilateral arms. Heparin indication was driven by the need for extracorporeal cardiopulmonary resuscitation in the critical care unit. The condition eventually required amputation of both arms.

A 62-year-old woman without a remarkable past medical history presented to a tertiary care center with cardiopulmonary arrest due to refractory ventricular fibrillation. She immediately underwent veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in combination with intra-aortic balloon pumping via the femoral arteries and veins. The patient had severe left ventricular dysfunction. She was given the first 3,000 units of unfractionated heparin (UFH) from a catheter inserted into the right femoral artery immediately before coronary angiography, which showed no significant stenosis. She received UFH 10,000 units/day via the right internal jugular vein for the...
maintenance of extracorporeal circulation and the prevention of thromboembolic complications. Meanwhile, the platelet count had fallen from 142×10^9/L on admission to 15×10^9/L on hospitalization day 3. All heparin products were discontinued due to the rapid progression of thrombocytopenia and bleeding at the VA-ECMO femoral access sites. Shortly thereafter she developed swelling in the bilateral arms, and cyanosis. HIT was suspected on the basis of a 4Ts score of 6, which includes 4 feature of HIT: (1) degree of thrombocytopenia; (2) timing of thrombocytopenia; (3) presence of thrombosis; and (4) likelihood of other causes of thrombocytopenia. Genetic thrombophilia was ruled out on laboratory parameters. Two different anti-PF4/heparin enzyme immunoassays (EIA) were positive, with optical density units of 2.362 (EIA-IgG/A/M, Diagnostica Stago, Asinère-sur-Seine, France [cut-off, 0.443]) and 2.389 (EIA-IgG/A/M, Genetic Testing Institute, Waukesha, WI, USA [cut-off, 0.400]). Functional assay was positive for platelet activation. Argatroban was initiated for the treatment of HIT, but on hospitalization day 10 the patient developed gangrene of the bilateral upper extremities (Figure 1). In addition, the condition of the upper extremities was complicated by a local infection refractory to antibiotics, which eventually required bilateral humeral amputation. On pathology of the upper limbs, occlusive thrombi were identified in the veins and arteries (Figure 2). Warfarin was started when the platelet count exceeded 150×10^9/L, and argatroban was stopped after a 1-week overlap with warfarin. At 3-month follow-up, platelet count was 160×10^9/L, and both the antigen and functional assays were negative. Given that left ventricular function had slightly improved after intensive care, VA-ECMO and intra-aortic balloon pumping were removed on hospitalization day 4 and 7, respectively. Follow-up echocardiography showed diffuse hypokinesis without hypertrophy.

Endomyocardial biopsy showed no specific finding. Thus ventricular fibrillation due to idiopathic cardiomyopathy was suspected, and an implantable cardioverter defibrillator was implanted. The remaining hospitalization period was eventless, and she was transferred to a rehabilitation facility on hospitalization day 112.

This patient lacked a history of heparin exposure and had a normal platelet count on admission. She later developed thrombocytopenia and thrombosis after heparin administration for extracorporeal circulation. Laboratory findings showed strong positive PF4-dependent EIA and strong positive platelet activation assay. Rapid-onset HIT without prior heparin exposure was thus diagnosed on both clinical and serological bases.

The incidence of heparin-induced skin lesions is reportedly 0.2% among patients exposed to the drug. Most skin lesions occur at the local injection site, but a few cases of necrotizing lesions distant from the heparin injection site have also been reported. In the present case, UFH was injected via the catheter inserted into the right femoral artery before a coronary angiography on hospitalization day 1, and was given continuously via the central venous catheter inserted into the right internal jugular vein until hospitalization day 3. No other UFH treatment route was used. HIT thrombosis occurred distant from the heparin injection site, probably due to the arterial and venous thrombi caused by HIT-associated systemic hypercoagulability.

In the present case, a devastating thromboembolic complication of HIT occurred, and upper limb amputation was required to save the patient’s life. A diagnosis of HIT requires high clinical suspicion. We present this report to familiarize the reader with the clinical presentation of an unusual complication of HIT in order to facilitate rapid diagnosis and initiation of appropriate treatment.

References