

# Catastrophic Complications of Intravenous Line Flushing with Unfractionated Heparin

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## ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a *clinicopathologic syndrome* because diagnosis is based on both clinical symptoms and laboratory data. We report a patient with multiple thromboembolic complications after daily flushing of intravenous line with small amounts of unfractionated heparin (UFH). At day 7 bilateral hemorrhagic infarction of the adrenal gland was misdiagnosed as adrenal adenoma. On day 10 thrombocytopenia was noted and the next day a myocardial infarction complicated by a left ventricular thrombus was diagnosed. On day 12, HIT was suspected. The pre-test probability for HIT according to the 4T-score was high (8/8 points) and detection of antibodies directed against the PF4/heparin-complex by particle gel immunoassay (Titer 1:1024) and ELISA (O.D. 2.784) was strongly positive. HIT can be induced by iv-line flushes with UFH. Arterial and venous thrombotic complications can be present before a clear platelet drop can be recognised.

**Keywords:** Heparin-Induced Thrombocytopenia; Adrenal Haemorrhagic Necrosis; 4T Score; PF4/Heparin-Antibodies

## 1. Introduction

Heparin-induced thrombocytopenia (HIT) is a severe antibody-mediated adverse effect of heparin. Affected patients are at risk for both arterial and venous thromboembolic complications [1]. Antibodies (usually IgG) directed against heparin-bound platelet factor 4 (PF4), together with heparin chains and PF4-tetramers, constitute macromolecular ternary complexes, which are able to activate platelets, endothelial cells and monocytes, leading to excessive in vivo thrombin generation [2,3].

HIT is a *clinicopathologic syndrome* because diagnosis is based on both clinical symptoms and laboratory data [4]. In the presence of venous and/or arterial thrombosis and concomitant administration of heparin, HIT should be always suspected. Potential thromboembolic complications are in particular deep venous thrombosis, pulmonary embolism, limb artery thrombosis, thrombotic stroke, myocardial infarction and adrenal hemorrhagic necrosis (indicating adrenal vein thrombosis) [4]. Whenever HIT is suspected, its pretest probability score should be determined by the 4T-score [5,6] and diagnostic procedures performed [7].

We describe an instructive case of HIT initially presenting with bilateral hemorrhagic infarction of the adrenal glands before a relevant drop of the platelet count

was noted and later on complicated by myocardial infarction, intracardial ventricular thrombus and limb artery thrombosis in the context of persistent high titer anti-PF4/heparin antibodies.

## 2. Methods

### 2.1. Determination of the 4T Score

The pre-test probability for HIT was calculated according to the 4T-score described by Warkentin [5,7]. Thrombocytopenia, timing of platelet count fall, presence or absence of thrombosis and other cause for thrombocytopenia were evaluated. Depending on the score, HIT probability can be clinically defined as high (6 - 8 points), intermediate (4 - 5 points) or low (0 - 3 points).

### 2.2. Detection of Anti-PF4/Heparin-Antibodies

Rapid detection of antibodies directed against the PF4/heparin-complex was achieved by a particle gel immunoassay (ID-H/PF4-PaGIA, DiaMed SA, Cressier sur Morat, Switzerland). Briefly, 10 µl of plasma were pipetted into the reaction chamber of the test IDcard followed by 50 µl of polymer particles (red high-density polystyrene beads coated with heparin/PF4 complexes). After incubation at room temperature for 5 min, the ID-card was centrifuged for 10 min in the dedicated

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ID-centrifuge (DiaMed SA). If there was not a significant level of anti-PF4/heparin-antibodies in the test sample, the particles sank to the bottom of the gel chamber. If anti-PF4/heparin-antibodies were present, the red polymer particles were cross-linked and remained on the top of the gel chamber. In case of a positive test with the undiluted sample, we repeated the assay with undiluted and serially diluted plasma or serum until the result was negative [8]. Thus, for a 1:2 dilution, 50 µl of plasma or serum were diluted with 50 µl of Diluent II (DiaMed SA), and subsequently dilutions were obtained by mixing 50 µl of the preceding one with 50 µl of Diluent II. The reported titre is the last positive detection followed by either indeterminate or negative results, as previously described [8].

Anti-PF4/heparin-antibodies were also detected by commercially available enzyme-linked immunosorbent assays (GTI-PF4 Enhanced, Genetic Testing Institute, Waukesha, WI, USA) and measured at 405 nm with a microtitre plate reader (Anthos ht III; Hemotec, Gelterkinden, Switzerland). Based on our and others' experience, we defined positive ELISA results as "potentially clinically relevant" when OD was  $\geq 1.000$  [3].

### 2.3. Heparin-Induced Platelet Aggregation Test

Heparin-induced platelet aggregation test (HiPAT) was performed according to Stricker *et al.* [9]. In a light transmission aggregometer (model PAP-4, Bio Data, Hatboro, PA, USA) four mixtures each containing 100 µl patient's platelet-poor plasma and 100 µl platelet-rich plasma from four different healthy donors are stirred for 4 min at 37°C in order to detect spontaneous heparin-independent aggregation. Thereafter, 10 µl of a solution of unfractionated heparin (Liquemin®, Drossapharm, Basel, Switzerland) and low molecular weight heparin (the preparation administered to the specific patient) are added to achieve a final concentration of 0.5 U/ml. Light transmission is recorded for up to 15 min. A positive test is defined by at least two out of four samples reaching  $\geq 50\%$  aggregation with abrogation of the reaction by a final heparin concentration of 100 U/ml.

### 2.4. Coagulation Assays

Coagulation assays were performed on a Behring Coagulation System automated analyser (Siemens Healthcare Diagnostics, Eschborn, Germany). aPTT was performed with Pathromptin SL (Siemens Healthcare Diagnostics) in duplicate and the average of measurements was calculated. Thrombin time was measured in duplicate with thrombin reagent (Siemens Healthcare Diagnostics), with final concentration of 1.5 U/ml (TT1) and 5 U/ml (TT2). Fibrinogen was measured according to Clauss [10]. D-dimers were measured according to the

manufacturer's instruction using an automated quantitative immunoassay (VIDAS D-dimer; bioMérieux, Marcy l'Etoile, France).

### 2.5. Case Presentation

A 70-year-old man was hospitalised because of local left foot infection after removal of one nail. He had a history of arterial hypertension, dyslipidemia and long-standing diabetes mellitus type 2. Current medication consisted of insulin, aspirin, ACE-inhibitor and beta-blocker. Laboratory data showed inflammation (CRP 75 mg/l, normal  $< 5$  mg/l) hyperglycaemia (glucose 15.39 mmol/l, normal 4.56 - 6.38 mmol/l) and renal insufficiency (creatinin 114 µmol/l, normal 62 - 106 µmol/l). Coagulation testing (Prothrombin time, Quick 100%, aPTT 29.6 sec, normal 25 - 40 sec) and haematological analysis (haemoglobin 156 g/l, leucocytes 10.5 G/l, platelets 212 G/l) were normal. Foot osteomyelitis was ruled out and a diagnosis of a pedal erysipelas was made. Antibiotic therapy with amoxicillin-clavulanate was installed. Thromboembolic prophylaxis with heparin was omitted, however the intravenous line was flushed daily with small amounts (300 U) of unfractionated heparin (UFH).

Despite antibiotic therapy no amelioration of local infection was noted and therapy was switched to cefepime. The clinical course was characterised by abdominal pain on day seven. A CT-scan showed bilateral hemorrhagic infarction of the adrenal glands initially misdiagnosed as adrenal adenoma. At this day the platelet count was within normal range (273 G/l, normal 140 - 380 G/l). No supplemental diagnostic or therapeutic procedures were performed. On day 10 laboratory tests revealed a thrombocytopenia (95 G/l) without signs of a disseminated intravascular coagulation (PT, Quick 95%, aPTT 29.6 sec, fibrinogen 4.4 g/l (normal 1.8 - 3.5 g/l)). The next day a myocardial infarction complicated by a left ventricular thrombus was diagnosed and treated conservatively. On day 12 heparin-induced thrombocytopenia (HIT) was suspected and the patient referred to our hospital.

According to the 4T-score the pre-test probability for HIT in this patient was high (8/8 points): the platelets decrease was  $> 50\%$  (2 points) and occurred between day eight and ten (2 points). No other evident causes of thrombocytopenia were present (2 points) and patient had thrombosis (2 points) [5].

Laboratory results at our institution confirmed thrombocytopenia (30 G/l) and showed a worsening renal function (creatinin 135 µmol/l, normal 59 - 104 µmol/l) as well as inflammation (CRP 326 mg/l, normal  $< 5$  mg/l). Coagulation tests were compatible with blood coagulation activation (PT, Quick 93%, aPTT 32.4 sec, fibrinogen 5.57 g/l, D-dimers 12,174 µg/l (normal  $< 500$  µg/l)). The titer of anti-PF4/heparin antibodies by ID-H/

PF4-PaGIA was very high (1:1024) and the ELISA for anti-PF4/heparin antibodies was strongly positive (O.D. 2.784). The HiPAT was clearly positive as well.

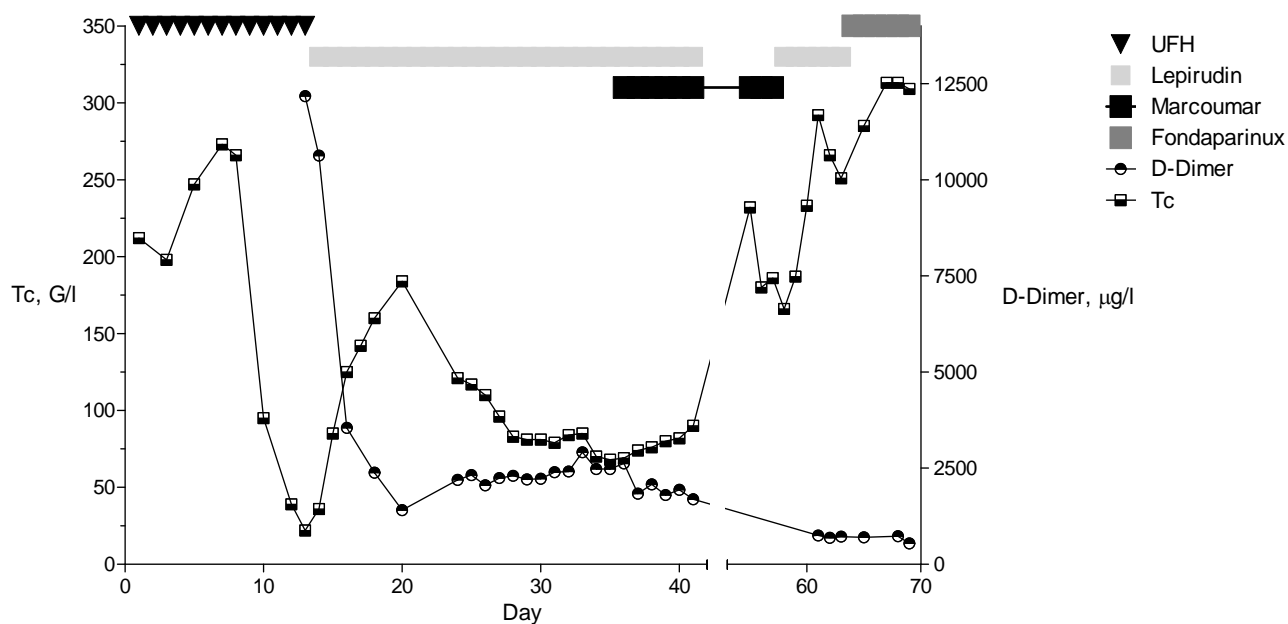
A diagnosis of HIT complicated by bilateral hemorrhagic infarction of the adrenal gland and myocardial infarction with intracavitary thrombus was made. Steroids and therapeutic anticoagulation with the direct thrombin-inhibitor lepirudin were started immediately.

Because of the decreased renal function, the lepirudin starting-dose was 0.040 mg/kg/h, according to internal guidelines [11]. Laboratory monitoring was performed 4 hours after initiation of lepirudin infusion. Dose adjustments to achieve therapeutic ranges were performed according to internal guidelines as well [11]. Under this regimen the patient was within therapeutic range four hours after initiation of infusion of lepirudin (aPTT 74.2 sec, TT1 unclottable, TT2 21.3 sec) and persisted within therapeutic limits (results not shown). No bleeding complications occurred during therapy. Platelets recovered quickly (normalisation after four days) but dropped again without obvious cause although therapy with lepirudin was correctly performed. D-dimers persisted elevated and platelets remained long between 68 G/l and 85 G/l (**Figure 1**). An overlapping oral anticoagulation with vitamin K antagonists (VKA) was installed (target INR 2 - 3). However, during this time, the ELISA-OD were constantly high (OD  $\geq 2.000$ ). Despite therapeutic anticoagulation with VKA further thromboembolic complications occurred. Recently diagnosed peripheral arterial disease of the left foot worsened over the course of the following weeks dramatically. Antithrombotic therapy

with aspirin was switched to clopidogrel. One month after HIT-diagnosis the patient was discharged. Despite VKA and clopidogrel as well as a percutaneous thrombectomy, a forefoot amputation was inevitable. The patient was hospitalised again two weeks later. After amputation he was treated with lepirudin overlapping the selective factor-Xa inhibitor fondaparinux, leading to a normalization of D-dimers (**Figure 1**).

### 3. Discussion

HIT is a life-threatening, antibody-mediated, adverse effect of UFH or low-molecular-weight heparin. Surgery patients, especially undergoing orthopaedic surgery, are at high risk to develop HIT [12]. The risk decrease in general medical population and is low in pediatric and in patients undergoing chronic hemodialysis. HIT occurs more commonly in women than in men but is very rare in pregnant woman [13]. Our case shows that HIT can be induced by iv-line flushes with UFH and that severe thromboembolic complications (in this case bilateral hemorrhagic infarction of the adrenal glands) can occur before a clear platelet drop [14]. Venous thromboembolic complication may be severe but patients are at risk for arterial occlusion as well, in particular in peripheral limb, brain and coronary artery. Combination of inflammation and small amount of heparin promote development of antibodies directed against the PF4/heparin-complex. This case shows a classical but very rare initial manifestation of HIT in a non surgical patient which received only intermittent low quantity of heparin. This unusual



**Figure 1.** Platelet-count (Tc, foursquare) and D-dimers (ring-shaped) under administration of anticoagulants: unfractionated heparin (UFH, triangular), Lepirudin (square light), VKA (Marcoumar, square black) and Fondaparinux (square).

aspects render our case rare and interesting. Moreover, we show that despite initial anticoagulation with the direct thrombin inhibitor lepirudin and switch to VKA, after normalisation of platelet count activated coagulation can persist, particularly in patients with high titre antibodies directed against the PF4/heparin-complex.

At our institute we assess the titre of anti-PF4/heparin antibodies, on the one hand to overcome the low specificity of the test [8], on the other one to identify the patients that potentially need a prolonged therapeutic anticoagulation, as in this case. We propose to verify treatment efficacy not only by monitoring platelet count but also by serial D-dimers measurements and to monitor anti-PF4/heparin antibody titres. In case of persisting high antibody titres and high D-dimers values we suggest to extend anticoagulation over the recommended 3 months even if the platelet count has recovered.

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