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## Heparin-induced thrombocytopenia in a hemodialysis patient treated with fondaparinux: Nephrologists between two fires

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### Abstract

Heparin-induced thrombocytopenia (HIT) is caused by heparin exposure and presents with reduced platelet count. Patients undergoing hemodialysis (HD) treatment have increased risk of developing HIT due to prolonged exposure to unfractionated heparin or low-molecular weight heparin. We report a 79-year-old male patient with end-stage renal disease who developed type-II HIT during maintenance HD. Platelet count of the patient decreased gradually and antiplatelet factor IV antibody was found to be positive. The patient was treated with fondaparinux and continued heparin-free HD. Unfortunately, despite favorable initial response without any thrombotic episodes, the patient died due to severe sepsis complicated by gastrointestinal hemorrhage.

**Key words:** Heparin-induced thrombocytopenia, hemodialysis, fondaparinux, platelets

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### INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is defined as a decrease in platelet count during or shortly following

exposure to heparin.<sup>1</sup> In vivo heparin binds to platelet factor 4 (PF4), a heparin-neutralizing protein released from activated platelets.<sup>2</sup> In some patients, the heparin-PF4 complex triggers an immune response that results in the production of an antibody.<sup>3</sup> Two different types of HIT are recognized: type I is a benign form not associated with an increased risk of thrombosis. This form approximately affects 10% of patients treated with heparin and is

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characterized by a mild and transient thrombocytopenia (platelet count is rarely below  $100 \times 10^3/\text{mm}^3$ ).<sup>4</sup> HIT type II is immune mediated and associated with a risk of thrombosis.

Diagnosis of HIT requires consideration of both clinical likelihood and laboratory data. The patient with HIT has a recent history or current treatment with standard heparin or low-molecular weight heparin (LMWH). Other apparent causes of low platelet counts should be excluded. Finally, detection of the presence of antibodies that bind to heparin-PF4 complexes by immunoassays confirms the diagnosis. Prompt recognition and appropriate treatment are keys to prevent thrombosis associated with HIT.

Mainstay of treatment is withholding further doses of unfractionated heparin (UFH) or LMWH and prevention of thrombosis development. To this end, currently three nonheparin anticoagulants that do not cross-react with HIT antibodies, danaparoid, lepirudin, and argatroban, are available for alternative anticoagulation in HIT.<sup>5,6</sup>

A synthetic pentasaccharide, fondaparinux, does not cross-react with HIT antibodies, thus this drug has been used successfully to prevent HIT-related thrombosis.<sup>7,8</sup>

Hemodialysis (HD) patients are regularly administered with heparin to prevent catheter and dialysis tubing system thrombosis. Thus, patients on maintenance HD have a risk of developing HIT due to prolonged exposure to UFH or LMWH.<sup>9</sup> Treatment of HIT in HD patients is similar to those of patients not on HD. There are only three case reports describing use of fondaparinux in HD patients.<sup>10,11</sup>

Here, we report a HD patient who developed type-II HIT and successfully treated with fondaparinux.

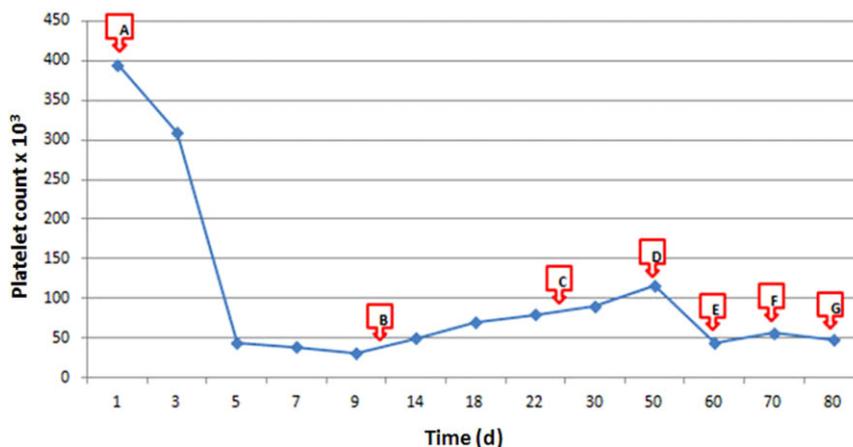
## CASE REPORT

We admitted a 79-year-old male patient with increasing uremic symptoms and hypervolemia. The patient had had metastatic prostate cancer, for which he had undergone transurethral resection operation. He also had chronic kidney disease due to obstructive uropathy. At admission he had bilateral 3+ pedal edema, presacral edema, and bilateral crackles at lung bases. His blood pressure was 130/80. Heart auscultation revealed an S3 and tachycardia without any murmurs. Other aspects of physical examination were unremarkable. Laboratory data at presentation were as follows: urea: 176 mg/dL, creatinine: 5.8 mg/dL, sodium: 136.7 mEq/L, potassium: 4.70 mEq/L, calcium: 8.1 mg/dL, phosphorus: 5.4 mg/dL, ESR: 45 mm/h, CRP: 119 mg/L, AST: 53 u/L, ALT: 20 u/L, albumin: 3.4 g/dL, total protein: 6.4 g/dL, hemoglobin: 9.4 g/dL, platelet count:  $394 \times 10^3/\text{mm}^3$ , WBC count:  $8.8 \times 10^3/$

$\text{mm}^3$ . Coagulation parameters were as follows: INR: 1.5, PT: 17.9 seconds, aPPT: 27.2 seconds. We placed an internal jugular vein central catheter and initiated intermittent HD with UFH. The symptoms of the patient lessened; however, he developed fever at the 10th day of his hospitalization, for which he was administered cefoperazone + sulbactam. The platelet count of the patient decreased gradually up to  $34 \times 10^3/\text{mm}^3$ . Peripheral smear confirmed thrombocytopenia excluding other causes. There were no fragmented erythrocytes. Coagulation parameters were within normal values during the course of thrombocytopenia. Antiplatelet factor IV antibody was found to be positive. With diagnosis of HIT type II, we changed HD anticoagulation order to saline rinse without any UFH or LMWH use. We also used heparin-free catheter lock solution. We monitored platelet counts of the patient and administered fondaparinux since other preparations, namely danaparoid, lepirudin, and argatroban, were not available in our country at that time. We used fondaparinux at a dose of 1.5 mg/day because of diminished renal function of the patient. We could not identify any origin for the high fevers even after multiple blood and urine cultures and change of the central venous catheter. There was no vegetation in the heart valves on transthoracic echocardiogram. Platelet counts gradually increased under this treatment up to  $116 \times 10^3/\text{mm}^3$  without any thrombotic episodes (Figure 1). But on the 70th day of hospitalization the patient developed sepsis. He was administered imipenem and vancomycin. Platelet counts decreased after sepsis. During the course of the hospitalization, he developed upper gastrointestinal bleeding presented with melena and hypotension. Because of hemodynamic instability, he was transferred to medical intensive care unit (ICU) where he was resuscitated with packed red blood cell suspensions and crystalloids. Fondaparinux was discontinued. The platelet count was between  $40$  and  $60 \times 10^3/\text{mm}^3$  during the course of ICU stay. Coagulation parameters were INR: 1.4, PT: 17.1 seconds, aPPT: 38.0 seconds. The patient died on the 80th day of hospitalization due to septic shock complicated by upper gastrointestinal bleeding.

## DISCUSSION

Owing to protracted exposure to heparin via both during intermittent HD sessions and catheter lock solutions, HD patients are at risk of developing HIT. A UK survey on HIT reported an incidence of 1.6%.<sup>12</sup> Interestingly, the intensity of antibodies with enzyme-linked immunosorbent assay is greater after starting dialysis therapy and then decreases with time on dialysis.



**Figure 1** Diagram showing changes in platelet counts and major clinical events during the course of the hospitalization. (A) Patient hospitalized with uremia and hypervolemia. (B) Cefoperazone + sulbactam discontinued. (C) Heparin-induced thrombocytopenia type II diagnosed and fondaparinux 1.5 mg/d started. (D) Fondaparinux and heparin-free hemodialysis continued. (E) Imipenem and vancomycin started due to sepsis. (F) Gastrointestinal bleeding developed and fondaparinux stopped. (G) Patient died due to sepsis and gastrointestinal bleeding.

Clinical trials have repeatedly demonstrated superior efficacy of fondaparinux over other anticoagulants as venous thromboembolism prophylaxis.<sup>13</sup> However, experience is limited regarding use of fondaparinux as a means of HD anticoagulation.<sup>14</sup> Sombolos et al.<sup>14</sup> showed that fondaparinux sodium at an intravenous dose of 2.5 mg can be used successfully as an anticoagulant during a 4-hour conventional HD session in patients dialyzed with low-flux polysulfone dialyzers.

Fondaparinux has also been used to treat and prevent thrombosis in case of HIT. Several case reports and series have described successful use of fondaparinux in HIT.<sup>7</sup> Fondaparinux was thought until recently not to cross-react with heparin-PF4 complexes. However, recent case reports showed the contrary.<sup>8,15,16</sup> Patients who were treated with fondaparinux developed type-II HIT.

Use of fondaparinux both as an HD anticoagulant and thromboprophylactic agent in HD patients has been reported only in three patients to date.<sup>10,11,17</sup> The half-life is markedly increased in patients with end-stage renal disease (ESRD). Thus, dose reduction either as 2.5 mg on alternate days or 0.2–0.5 mg/day is recommended. We used 1.5 mg/day both as a means of HD anticoagulation and thromboprophylaxis. We could not use lower doses because of repeated clot formations during HD sessions. Our patient did not experience a venous or arterial thrombotic event during the course of the treatment with fondaparinux. However, on the 70th day of hospitalization, he experienced an upper gastrointestinal hemorrhage manifesting with melena and hypotension. Initially increased platelet counts started to decrease this time possibly due

to severe sepsis. Although we lost our patient because of septic shock, fondaparinux effectively prevented development of any arterial and/or venous thrombosis. HD patients, especially in settings of acute dialysis, are at increased risk of hemorrhage. On the other hand, despite thrombocytopenia, patients with HIT are prone to paradoxical thromboembolic events.

In conclusion, we found fondaparinux effective in type-II HIT in our HD patient. Type-II HIT poses thrombotic threats to inflicted patients. Thus, anticoagulation with direct thrombin inhibitors must be used to prevent these untoward effects. Because we lacked direct thrombin inhibitors in our country, we used fondaparinux as the alternative anticoagulant agent in this patient. In contrast to patients without ESRD, HD patients have greater risk for hemorrhagic complications of anticoagulant agents. Caring physicians are under the heavy burden of balancing prevention of thrombosis with prevention of iatrogenic hemorrhage.

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## Testicular angina during hemodialysis: An unusual complication of ultrafiltration

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### Abstract

During hemodialysis, the development of hypotension or symptoms suggestive of ischemia is used as a surrogate marker for the establishment of dry weight. These symptoms manifest commonly as muscle cramps, chest pain or abdominal pain. Hemodialysis patients are also prone to vascular calcification which may be medial or intimal. We report the case of a 68-year-old male who developed testicular pain while attempting to establish dry weight. Computerized tomography scan of his abdomen showed extensive vascular calcification. The end result in this case was bilateral orchiectomy. Histopathology revealed hyperplastic arteriosclerosis with intimal calcification contributing to ischemia.

**Key words:** Vascular, calcification, testicular, angina