Thrombolytic therapy in acute pulmonary embolism due to heparin–induced thrombocytopenia type II

Azza A. Alafify, *MS, MD,* ***Tarig S. Al-Khuwaitir,*** *MRCP(UK), ABIM,*
Abdurahman M. Al-Mugheiri, *MBBS, MRCP(IR),* ***Djibril M. Ndao,*** *MD, CES.*

ABSTRACT

Hospitalized patients are in danger of deep venous thrombosis either due to a genetic tendency, immobilization or the underlying medical condition. Paradoxically heparin, the substance used to prevent this complication, can lead to thrombo-embolic phenomena, which can be life threatening. We report a case of heparin-induced thrombocytopenia, which caused a massive pulmonary embolism, and its management by administering a thrombolytic agent in a situation where bleeding seems inevitable.

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Heparin-induced thrombocytopenia (HIT) is important to consider in the differential diagnosis of thrombocytopenia (TCP) occurring in the hospital setting.[1] It consists of 2 types; HIT type I, being mild and resolving without treatment, and type II, being severe and causing devastating thromboembolic complications.[2] Fortunately, the incidence of the second type is below 3%.[2] In this report, we present a case of HIT type II in an orthopedic middle-aged male patient, on prophylactic unfractionated heparin, which lead to a massive pulmonary embolism, necessitating intervention with a thrombolytic agent, in the setting of low platelets.

Case Report. A 46-year-old male involved in a road traffic accident was admitted to our orthopedic service through the Accident and Emergency Department at Riyadh Medical Complex having sustained fractures to his left femur and patella. His systemic examination was normal and it was decided to operate. His complete blood count (CBC) before operation revealed a white cell count (WBC) of 13.4 x 10^3/ml, a hemoglobin (HGB) of 8.3 g/dl and a platelet count (PLT) of 263 x 10^3/ml. He was transfused with 2 units of packed red blood cells and the posttransfusion hemoglobin was 11.9 g/dl. Open reduction and internal fixation were performed. Postoperatively the patient remained stable, was asymptomatic, not ambulant and received unfractionated heparin 5000 units subcutaneously 3 times daily as antithrombotic prophylaxis. On the 10th postoperative day the medical team was consulted, as the patient developed symptoms of chest tightness, shortness of breathing, and dizziness. There was no loss of consciousness or hemoptysis. On examination he was restless, sweaty, centrally cyanosed, and in acute distress, hypotensive with a blood pressure of 80/50 mm Hg, tachycardic with a pulse of 120

From the Department of Cardiology (Alafify), Department of General Internal Medicine (Al-Khuwaitir, Al-Mugheiri) and the Hematology/Oncology (Ndao), Riyadh Medical Complex, Ministry of Health, Riyadh, *Kingdom of Saudi Arabia.*

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Address correspondence and reprint request to: Dr. Azza A. Alafify, Senior Registrar, Department of Cardiology, Riyadh Medical Complex, Ministry of Health, *Kingdom of Saudi Arabia*. Tel. +966 (1) 2864678/4355555. Ext. 1253. E-mail: alafifiazza@hotmail.com

beats/minute, temperature of 37.2ºC, and a respiratory rate of 30/minute. His jugular venous pulse was elevated to 10 cm from the sternal angle with a prominent v-wave. Auscultation revealed a loud P2. The chest and abdominal examinations were normal. The left lower limb was in a plaster of Paris, while the right lower limb showed no signs of a deep vein thrombosis. The patient was switched to intravenous unfractionated heparin with a loading dose of 7500 units followed by an infusion of 1000 units per hour. Intravenous fluids and inotropes were administered, and he was shifted to the intensive care unit (ICU). His arterial blood gases showed a pH of 7.5, pCO_2 of 30 mm Hg, pO_2 of 63 mm Hg with a saturation of 93%. The electrocardiogram revealed a sinus tachycardia of 120 beats/minute with an S1, Q3, T3 pattern and T-wave inversion in the right ventricular leads from V1-V3. The chest radiograph was unremarkable. Transthoracic echocardiogram revealed a dilated right atrium and ventricle, moderate pulmonary hypertension with normal left ventricular size and function. The ventilation perfusion scan showed multiple bilateral perfusion defects with a high probability of pulmonary embolism (PE) **(Figure 1)**.

The D-dimer was 6.4 u/l (normal ≤0.2 u/l), and lactate dehydrogenase was raised at 559 u/l. The CBC revealed WBC of 17.7 x 10^3/ml, HGB 10.3 g/dl and PLT of 85 x 10^3/ml. The PLT was repeated and found to be 65 x 10^3/ml with no PLT clumps reported on the peripheral film. The treating team was faced with the dilemma of a confirmed massive PE in a patient with hemodynamic instability in need of thrombolytic therapy yet with the presence of TCP. A hematological consult was made and the patient was ultimately given thrombolytic therapy with tissue plasminogen activator (tPA). Intravenous hirudin was used for anticoagulation to "bridge" the time interval, until warfarin therapy commenced 2 days later, would take effect. Our patient improved symptomatically and hemodynamically following thrombolytic therapy. The inotrops could be discontinued on the 2nd ICU day. No bleeding was observed and repeated Hemoccult tests were negative. The PLT count improved to 157 on the first to 270 x 10^3/ml on the second day post thrombolysis and reached 308 x 10^3/ml on the 7th day. Once the internationally normalized ratio reached 2 the patient was discharged on warfarin and was doing well 3 months later. A repeat transthoracic echocardiogram showed mild dilatation of the right atrium with mild tricuspid regurgitation and a systolic pulmonary artery pressure of 25 mm Hg.

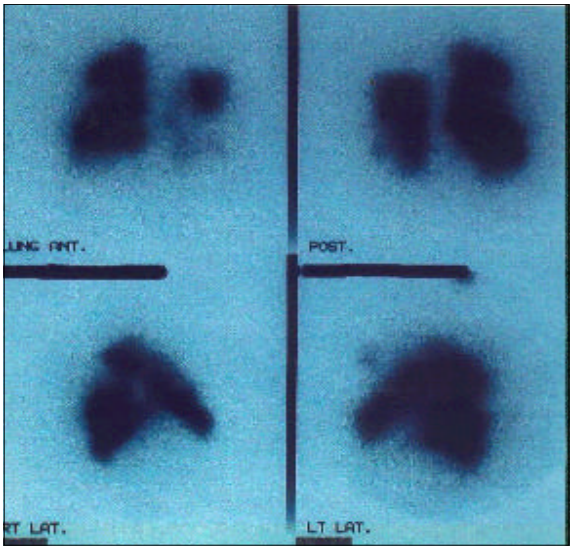

Figure 1 - Perfusion scan of the lungs revealing multiple perfusion defects.

Discussion. Heparin induced thrombocytopenia type II is a decrease in PLT count, which occurs between 5-10 days upon initiation of heparin therapy regardless of indication.[1,2] This is in contrast to non-immune heparin associated TCP, which can occur at any given time during the course of a patient's illness.[1] Numerous in vitro experiments have addressed the effects of heparin on platelets.[1] Although results are not always consistent it is agreed that in vitro heparin has a pro-aggregator effect on PLTs, which is related to the grade of sulfation and chain length of the former.[1,3] These direct heparin-PLT interactions are thought to cause the frequent phenomenon of early onset TCP in patients receiving unfractionated heparin typically in intravenously delivered therapeutic dosages.[1] The HIT type II is a prothrombotic drug reaction caused by PLT activating antibodies of the immunoglobulin G class 1 type that recognize complexes of PLT factor 4 (PF4) and heparin.[1,4] The resultant reduction in the PLT count seen in HIT usually is more than 50% or below 100 x 10/L.[1] The differential diagnosis includes HIT type 1 (mild TCP after 1-4 days of heparin therapy attributed to a direct interaction between heparin and circulating platelets with no intervention required), autoimmune TCP, drug dependent TCP, consumptive thrombo-hemorrhagic disorders, and other diseases associated with a substantial decrease in PLT count.[1,2] That HIT can lead to "paradoxical" thromboembolic complications was described as early as 1958.[1] We believe that the patient presented in our report is a classical example of HIT. He developed TCP in the appropriate time frame, following the initiation of heparin therapy, in association with massive PE. Deep vein thrombosis and PE are among the most common complications of HIT.[5,6] Although in severe pulmonary embolism, PLT activation by clot bound thrombin can result in a substantial decrease in PLT count (pseudo-HIT), this profound decrease did not

occur in our patient.[7,8] Posttransfusion TCP can also lead to a decrease in PLT count to levels not observed in this case and follow a different time course.[8] In addition to the exclusion of PE and post transfusion induced TCP, he had not been on any PLT lowering agent. Ideally a positive in vitro assay for antibodies is required to diagnose HIT.[9] This was not available on a timely basis to our team. Yet we believe that the circumstantial evidence, time frame and PLT count identify this case as HIT. Despite the production of anti-platelet antibodies not all patients develop the clinical syndrome of HIT, the asymptomatic cases being in the majority.[1] However, patients with previous exposure to heparin can have a more rapid onset of TCP.[1] In symptomatic HIT patients, the antibodies involved are of the IgG class in more than 80% of cases with IgM and IgA involved in the remaining.[1]

What are the therapeutic options then when faced with a patient with HIT type II and massive PE? Firstly, massive PE is an indication for immediate thrombolysis.[10] Secondly, the presence of HIT requires the immediate cessation of heparin therapy.[1] The next step would be to continue anticoagulation with warfarin, this however would be detrimental since it impairs the ability of the protein C natural anticoagulant pathway to down-regulate thrombin generation leading to micro-vascular thrombosis and tissue necrosis.[5] The appreciation of the coagulation system activation in HIT provides a rationale for treatments that reduce thrombin generation.[5] This can be achieved by inhibiting factor Xa with danaparoid or by inhibiting thrombin directly with lepirudin, argatroban and hirudin.[1,5,7] We choose in our patient to thrombolyse him with tissue plasminogen activator, stopped unfractionated heparin and used hirudin as a "bridge" to warfarin. Hirudin not only inhibits free, but also clot bound thrombin.[1] Monitoring hirudin therapy is somewhat problematic, since the activated prothrombin time (APTT) shows considerable variability, especially at higher hirudin plasma levels (APTT more than 70 seconds), were the correlation becomes poor.[1] No problems were encountered in our patient. Recently, a group from Saudi Arabia proposed the use of plasmapheresis to create a state of "artificial" anticoagulation prior to the introduction of warfarin, which is a feasible yet expensive approach, which we would have considered if hirudin was not available.[11] An important observation from our case is the absence of bleeding, however, it has been stated that thrombolysis is never a problem when low platelets are due to HIT (Goldhaber SZ, 2005). The seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic therapy has given guidelines as to the prevention of HIT.[12] In patients on postoperative antithrombotic prophylaxis and HIT risk >1%, the recommendation is every other day PLT count monitoring between postoperative day 4 and 14 or until unfractionated heparin is stopped or whichever occurs first.[12] The subsequent duration of oral anticoagulation following an episode of thromboembolism depends on the risk of recurrence if the treatment is stopped and the risk of bleeding if treatment is continued.[13] Since our patient's risk of recurrence after surgery is low, 3 months of anticoagulation was indicated, however, the optimal duration of anticoagulation following acute PE remains mired in controversy with a meta-analysis in 2001 suggesting a longer course of oral anti-coagulant therapy to be superior to a short course.[14,15] We therefore opted for a total duration of oral anticoagulation for 6 months.

In conclusion, we can say that a rational approach to the common clinical condition of HIT can lead to appropriate management even in life threatening situations.

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