

Heparin-Induced Thrombosis without Thrombocytopenia Causing Fulminant Pulmonary Embolism after Off-pump Coronary Artery Bypass Grafting

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ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a rare immune-mediated complication of heparin administration. A potentially life-threatening complication, HIT is difficult to diagnose in patients in the intensive care unit after cardiac surgery because there can be multiple reasons for thrombocytopenia. Moreover, immune-mediated platelet consumption may be masked by reactive thrombocytosis, which is common in the typical postoperative course after cardiac surgery. We report the case of a 57-year-old male patient who developed fulminant pulmonary embolism following heparin-induced thrombosis without thrombocytopenia after off-pump coronary artery bypass surgery.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a rare but severe complication of heparin therapy. HIT is attributed to an immune response characterized by complexes of heparin and platelet factor 4 (PF4) [Warkentin 2004]. HIT type I presents the more benign form and is associated with mild thrombocytopenia (100,000-130,000/ μ L). It usually occurs 1 to 4 days after the initiation of heparin therapy. Usually, HIT type I has no clinical impact and resolves when heparin administration is stopped. It is caused by direct interaction between heparin and platelets rather than via an antibody-mediated effect [Chong 1992]. The more serious but less common manifestation is HIT type II. Occurring approximately 7 to 10 days after administration of heparin, it is associated with more severe thrombocytopenia (<100,000/ μ L). HIT type II is caused by an antibody-mediated effect on platelets and shows an increased propensity for venous and arterial thromboembolic events, such as venous thrombosis, venous gangrene, pulmonary embolism (PE), myocardial infarction, stroke,

visceral infarction, and limb gangrene [Chong 1992]; however, platelet consumption may be masked by reactive thrombocytopenia and/or thrombocytosis, which are common in the typical postoperative course after cardiac surgery [Selleng 2008]. HIT with thrombosis (HITT), also known as the white clot syndrome (WCS) is a subcategory of HIT. Patients with HITT develop platelet clots (white clots), which lead to arterial and venous thrombotic events [Ananthasubramaniam 2000]. In a previous study, Warkentin et al [1996] found PE to be the most common life-threatening thrombotic event and the most common cause of death in patients with HITT. We describe the rare case of a 57-year-old male patient who underwent a 1-vessel off-pump coronary artery bypass (OPCAB) surgery. Three days later, he developed fulminant PE following heparin-induced thrombosis without a significant decrease in the platelet count.

CASE REPORT

A 57-year-old male patient was admitted to the hospital because of exertional dyspnea and angina pectoris. Cardiovascular risk factors included smoking and hypertonia. Furthermore, the patient had chronic obstructive pulmonary disease and pulmonary emphysema. The patient was not routinely evaluated for deep vein thrombosis (DVT) and PE before OPCAB operation because there were no supporting clinical symptoms and signs. Furthermore, the patient had no pre-existing conditions for thrombosis, and we noted neither a personal nor a familial history of DVT or PE. A coronary angiogram revealed chronic occlusion of the proximal left anterior descending coronary artery (LAD). The patient was placed on a heparin drip (unfractionated porcine heparin), and bypass surgery was planned. The following day, he underwent OPCAB surgery with the left internal mammary artery used for the distal LAD. We administered 15,000 units of unfractionated porcine heparin intravenously. Postoperatively, weaning the patient from the respirator was prolonged because of restricted gas exchange. Considering the patient's preexisting lung disease, a suspicion of pneumonia arose, and we started antibiotic treatment immediately. On postoperative day 3, the patient's condition suddenly deteriorated, and cardiopulmonary resuscitation became necessary. The patient was brought immediately to the operating room, where the

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Figure 1. Massive recent thrombi showing multiple “white clots” (platelet rich).

suspicion of graft failure could not be confirmed. The patient had a depressed right ventricular function, however, so we performed an intraoperative transesophageal echocardiographic evaluation, which demonstrated turbulences in the vicinity of both pulmonary arteries. In this context, we suspected acute PE. Inspection of the main pulmonary trunk after longitudinal incision revealed massive recent thrombi of both pulmonary arteries that reached to the lobar and segmental arteries. Using cardiopulmonary bypass, we were able to remove the thrombotic material under direct vision. The thrombotic material showed multiple “white clots” (platelet rich) typical of the WCS (Figure 1). The results of postoperative testing for HIT by means of a commercial enzyme-linked immunosorbent assay (PF4 Enhanced[®]; GTI, Waukesha, WI, USA) for detecting antibodies against the heparin/PF4 complex were positive, although the platelet count was in the normal range with a postoperative nadir of 178,000/ μL (Figure 2). Despite treatment with an intra-aortic balloon pump, catecholamine therapy had to be increased. Because of the patient's depressed right ventricular function and hemodynamic instability, we decided to use venoarterial extracorporeal membrane oxygenation (ECMO). The patient was stabilized hemodynamically and then transferred to the intensive care unit. Unfortunately, the cardiac and pulmonary function did not recover, and the patient died from multi-organ failure on postoperative day 12 (9 days after ECMO implementation).

DISCUSSION

HIT is an immune-mediated prothrombotic disorder that occurs after exposure to heparin. Thromboembolic events (arterial and venous thrombosis) and thrombocytopenia, which is commonly defined as an absolute platelet count of $<100,000/\mu\text{L}$ or a 50% decrease in the count from baseline, are the clinical manifestations of HIT [Warkentin 2004]. In

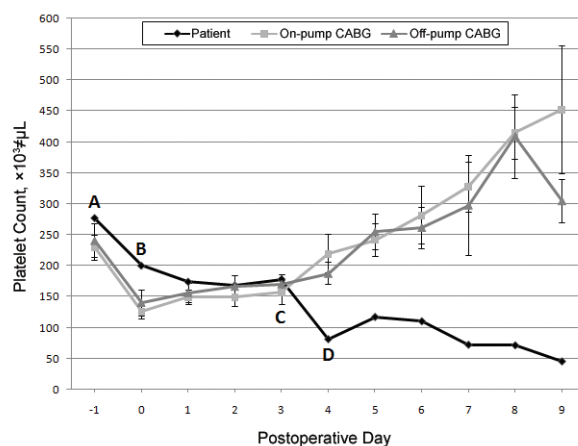


Figure 2. Course of platelet counts for the patient compared with courses of the mean platelet count (\pm SE) for 10 patients who underwent off-pump coronary artery bypass grafting (CABG) (mean age, 59.2 ± 8.7 years) and for 10 patients after on-pump CABG (mean age, 58.3 ± 7.09 years). Indicated are the patient's platelet counts on admission (A), immediately after off-pump CABG (B), at the platelet nadir of 178,000/ μL (C), and immediately after emergency operation with implementation of venoarterial extracorporeal membrane oxygenation (D).

contrast to the platelet count profile after on-pump coronary surgery, changes in the platelet count that occur after off-pump coronary surgery are currently less well understood [Pouplard 2005]. In a retrospective study, Cartier and Robitaille reviewed their experience with on-pump and off-pump coronary surgery with respect to thromboembolic complications. Thromboembolic complications occurred in 1% of 500 off-pump cases, compared with 0.5% in a cohort of 1476 on-pump cases; however, the difference did not reach statistical significance [Cartier 2001]. Tibayan et al [2008] reported a case in which HIT developed without thrombocytopenia after OPCAB surgery. In this case, a computed tomography evaluation, which was obtained to evaluate unknown fever, a decrease in oxygen saturation to 93%, and a mild increase in the heart rate, revealed a saddle pulmonary embolus. After positive results were obtained in HIT testing, the oral anti-coagulation treatment was changed to warfarin. The patient was discharged on postoperative day 28, and he remained well at the 3-month follow-up. The patient in our case presented with HIT without thrombocytopenia, which caused fulminant PE after OPCAB surgery. The case seemed straightforward, with the only noteworthy observation being the patient's restricted gas exchange in the intensive care unit after the operation. Prolonged respiratory weaning is not uncommon after cardiac surgery and is often caused by infections or a preexisting lung disease. Considering the patient's preexisting lung disease, however, a suspicion of pneumonia arose, and antibiotic treatment was started immediately. We did not suspect PE in this context. The incidence of DVT and PE after coronary artery bypass grafting varies, depending on postoperative thromboprophylaxis, the presence of indwelling central venous catheters in the lower extremities, and early ambulation. Lastly, the diagnosis of DVT remains

challenging because DVT is typically silent and lacks reliable and reproducible clinical symptoms and signs, with <5% of patients with DVT having obvious clinical findings [Reis 1991] and PE often being the first clinical event prior to the diagnosis of DVT [DeLaria 1991; Josa 1993]. HIT, which is generally associated with a high incidence of DVT and PE, occurs in approximately 3.8% of patients who have undergone cardiac surgery and have been placed on high-dose intravenous unfractionated heparin postoperatively [Shammas 2000]. In our case, the patient was exposed to heparin pre-, intra-, and postoperatively. There were no clinical signs of DVT or PE before the operation; however, DVT, as well as PE, could not be fully excluded, because we did not evaluate DVT or PE in terms of failing clinical signs. Furthermore, there were no preexisting conditions for thrombosis, and neither a personal nor a familial history of DVT or PE was noted. Unfortunately, the patients' condition suddenly deteriorated, necessitating cardiopulmonary resuscitation. The subsequent emergency operation revealed surprisingly large pulmonary emboli. Although there were no clinical signs of type II HIT, the heparin-induced platelet-activation assay returned positive results after a huge thrombus was removed from the pulmonary arteries. Classically, the clinical manifestation of HIT type II is associated with a significant drop in the platelet count and any thromboembolic complications. In our case, there was no significant decrease in the platelet count and only a prolonged respiratory weaning, which is not rare after cardiac surgery and is often caused by infections or a preexisting lung disease. Despite the use of ECMO and maximum pharmacotherapy, the patient died from multiorgan failure on postoperative day 12.

CONCLUSIONS

The consequence of this case to be kept in mind is that HIT may develop in any patient after cardiac surgery and may cause severe postoperative complications with a high incidence of morbidity and mortality. Therefore, knowledge

of HIT, as well as consideration of preoperative testing in all cardiac surgery patients, may help prevent potentially disastrous consequences to such patients.

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