We report a case of heparin-induced thrombocytopenia thrombosis (HITT) syndrome in a patient prophylactically treated with low molecular weight heparin. A 66-year-old man underwent radiofrequency-assisted partial liver resection for colorectal carcinoma liver metastases a year-and-a-half after he had been operated for rectal cancer. In the postoperative period, patient was prophylactically treated with reviparin sodium. On the 8th postoperative day, the platelet count decreased by more than 50% without clinical signs of thrombosis. HITT syndrome was suspected on the 19th postoperative day, after iliacofemoropopliteal thrombosis had developed, and related diagnosis was supported by the strongly positive particle gel agglutination technique immunodiagnosis. Heparin was withdrawn and alternative anticoagulant, danaparoid sodium, was introduced in therapeutic doses. Despite delayed recognition, favorable clinical outcome was achieved. HITT syndrome should be considered with priority among the possible causes of thrombocytopenia in a surgical patient on heparin.

Keywords: heparin-induced thrombocytopenia, thrombosis, low-molecular-weight heparin, liver metastasis

INTRODUCTION

Immune heparin-induced thrombocytopenia (HIT) is an important adverse drug reaction caused by heparin-dependent antibodies, typically of the immunoglobulin G (HIT-IgG), that induce platelet activation and marked thrombin generation ("hypercoagulability state") characterized by increased risk of both venous and arterial thrombosis and coumarin-induced necrosis. Thus, HIT is a unique form of a drug-induced thrombocytopenia paradoxically associated with thrombosis - heparin-induced thrombocytopenia/thrombosis syndrome (HITT or HITTS). All patients on heparin therapy, irrespective of their age, or heparin type, dose or route of administration, are at risk of developing HIT antibodies, with an incidence of up to 8%. HIT occurs in approximately 0.5 - 5% of patients treated with heparin for at least 5 days. Subsequently, approximately 38-76% of patients with HIT develop thrombosis; about 10% with HITTS require limb amputation; and approximately 20-30% die within a month.

Based on the literature data, patients at the highest risk of HIT include postoperative orthopedic, cardiac and vascular surgery patients. Data are not available for general surgery patients, but it is suggested that the patients undergoing major abdominal surgery might be at a risk similar to the one present with other major surgical procedures.

When HIT/HITTS is suspected on the basis of the platelet count fall of 50% or more from baseline, and/or development of a new thrombosis or skin manifestations between days 4 and 14 after the initiation of heparin, heparin therapy should be discontinued and an alternative anticoagulant therapy started in therapeutic dose, even before laboratory confirmation. In hospitalized patients in whom thrombocytopenia is a common occurrence associated with various etiologies, HIT/HITTS often remains unrecognized and misdiagnosed.

CASE REPORT

A 66-year-old man, with a BMI of 23, was admitted at the HPB and Liver Transplant Unit, Clinic for Digestive Surgery of the Clinical Centre of Serbia, with medical history of weight loss, increased level of tumor markers, and CT scan demonstrating liver metastasis. His medical history was negative for thrombotic events and adverse events associated with heparin treatment. Previously, he had been operated for rectal cancer and postoperatively received 6 cycles of chemotherapy (5 Fluorouracil/Leucovorin). Liver metastases were demonstrated in segments I,
VI and VIII. After the preoperative assessment, radiofrequency-assisted partial liver resection was performed. Postoperative course was complicated with pleural effusion requiring pleural drainage. Postoperative anticoagulant therapy included prophylactic subcutaneous injections of low-molecular-weight heparin (LMWH) - reviparin sodium, administered in two daily doses of 1750 IU, started on the 1st postoperative day. The concomitant therapy included antibiotics, infusion, prokinetics and H2-receptor antagonists. Infusion and prokinetics therapy was discontinued on postoperative day 3, and antibiotic and H2-receptor antagonist therapy was discontinued on postoperative day 15.

The platelet count was 186x10⁹/L preoperatively. On the 7th postoperative day, the platelet count was 136x10⁹/L. On the 8th postoperative day, the platelet count decreased to 70x10⁹/L without clinically apparent thrombosis. On the 18th postoperative day, left lower limb was swollen and painful and deep venous thrombosis was clinically suspected. Left iliacofemoropopliteal thrombosis was confirmed by Doppler ultrasound, and vascular surgeon administered unfractionated heparin in continuous infusion. The following day, transfusion medicine department was consulted.

The patient was suspected of having highly probable HITTS, based on a new thrombotic event, magnitude of thrombocytopenia (platelet count was 33x10⁹/L, Figure 1), timing of thrombocytopenia in relation to heparin exposure and absence of other plausible causes for the decrease in platelet count. Coagulation status examination revealed extremely high increase in D-dimer level (5853µg/L), which was in keeping with increased in vivo thrombin generation.

According to "4 T's" scoring system proposed by Warkentin, the likelihood of HIT was scored with maximum 8 points that indicated a high pretest probability. Diagnosis of HIT was supported by a strongly positive serology for HIT antibodies using the gel agglutination technique assay (ID PF4/heparin antibody test, Diamed AG, Cressier, Switzerland). In addition, alternative explanations for the decrease in platelet count were ruled out by diagnostic means. LMWH was replaced immediately with indirect Xa/IIa inhibitor - danaparoid sodium. Danaparoid sodium treatment was monitored by quantifying antifactor Xa activity in an assay using danaparoid sodium as a standard. Danaparoid sodium was administered as i.v. bolus 2,500 U, then as a step-down i.v. infusion: 400U/h x 4h followed by 300U/h x 4h, and finally the maintenance infusion rate of 200 U/h. Therapeutic range of 0,7 U antifactor Xa U/mL in plasma was achieved.

There was a rapid improvement in clinical signs and platelet count. After five days the platelet count normalized, D-dimer was significantly reduced, and patient was cautiously transitioned to a vitamin K antagonist treatment, started when the platelet count reached a stable normal value.

The patient was discharged from the hospital while receiving oral anticoagulant therapy (INR 2.51), and did well on periodical follow-up visits. After a 3-month follow-up, treatment with oral anticoagulant therapy was stopped.

FIGURE 1
DYNAMIC OF PLATELET COUNT DURING HOSPITAL STAY
DISCUSSION

HIT starts as an immune-mediated mechanism primarily involving platelets, but then switches to a mainly thrombin driven coagulation problem. Despite the improvement in laboratory testing and the introduction of new anticoagulants, the diagnosis and treatment of HIT/HITTS still remain a challenge to physicians.

In this report, we emphasized the problem of late recognition and misdiagnosis of HIT, even when thrombosis had developed, illustrating the lack of awareness about the most threatening complication of heparin treatment.

Namely, the possibility of HIT has not been suspected on 8th postoperative day when blood work revealed an abrupt fall in platelets from 136x10^9/L to 70x10^9/L, on 8th postoperative day when blood work revealed the most threatening complication of heparin treatment. With respect to possible adverse and devastating clinical outcome, HITTS should be considered with priority among the possible causes of thrombocytopenia in a surgical patient on heparin. Danaparoid sodium seems to be an appropriate anticoagulant in liver disease thanks to its pharmacokinetic characteristics and mode of excretion.

SUMMARY


Ključne reči: heparinom indukovana trombocitopenija, tromboza, nisko molekularni heparin, metastaze u jetri

REFERENCES

