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CASE REPORT

Lower Limb Paralysis as Initial Presentation of Arterial Embolism Secondary to Heparin-Induced Thrombocytopenia after Hip Fracture – a Case Report

Petros KAPSETAKIS[a], Georgios MAGARAKIS[a], Constantinos CHANIOTAKIS[a], Phaedon D ZAVRAS[b], Georgios KAVALARIS[c], Christos KOUTSERIMPAS[d], Kalliopi ALPANTAKI[a]

[a]Department of Orthopaedics and Trauma, Venizeleion General Hospital of Heraklion, Crete, Greece

[b]Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA

[c]Department of Radiology, Venizeleion General Hospital of Heraklion, Crete, Greece

[d]Department of Orthopaedics and Traumatology, "251" Hellenic Air Force General Hospital of Athens, 11525 Athens, Greece

ABSTRACT

Introduction: *Prophylactic anticoagulation (AC) with low molecular weight heparins (LMWHs) following hip fracture has reduced the incidence of severe thromboembolic events. However, heparin-induced thrombocytopenia (HIT) remains a serious complication in these patients.*

Clinical case: *We report an unusual case of thrombosis due to severe HIT in a 75-year-old female patient following intramedullary nailing for a hip fracture. The patient was taking Verapamine. On the fourth postoperative day she developed paralysis, paresthesia and mild pain over the right lower extremity; faint pulses were palpated. Computed tomography angiogram identified superficial artery occlusion leading to limb ischemia. Anti-platelet factor 4 (PF4) heparin antibody positivity confirmed the diagnosis of HIT. Urgent embolectomy was performed and the patient achieved full recovery.*

Discussion: *Arterial embolism presenting with severe neurological deficits is a rare complication of HIT.*

Conclusion: *A high index of suspicion and close platelet count monitoring is warranted for early diagnosis and treatment of this devastating condition that can be limb and life threatening.*

Keywords: HIT, arterial embolism, limb ischemia, hip fracture, neurological deficit.

Address for correspondence:
Dr. Kalliopi Alpantaki
Mailing address: 31 Menelaou Parlama str. Hearklion, Crete, Greece
Tel.: +30 6944519623, email: apopaki@yahoo.gr

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Abbreviations:
AC: anticoagulation
LMWHs: low molecular weight heparins
HIT: heparin induced thrombocytopenia
CT: computed tomography
PF4: platelet factor 4
VTE: venous thromboembolism
UFH: unfractionated heparin
ATE: acute arterial thromboembolism
IU: international unit
Labs: laboratory findings
Hb: hemoglobin
PLT: platelet count
WBC: white blood cell
SGOT: serum glutamyl oxaloacetic transaminase
SGPT: serum glutamic pyruvic transaminase
g-GT: gamma- glutamyl transpeptidase
ALP: alkaline phosphatase
Cr: creatinine
UR: urea
POD: postoperative day
HEP: HIT expert probability
aPTT: activated partial thromboplastin time
DTI: direct thrombin inhibitor

INTRODUCTION

Increased incidence of venous thromboembolism (VTE) commonly occurs after hip fractures and is associated with significant morbidity and mortality (1). Prophylaxis with low molecular weight heparins (LMWHs) has reduced the incidence of severe thromboembolic events in this patient population. Heparin induced thrombocytopenia HIT) is a rare immune-mediated adverse reaction following heparin exposure, which leads to a prothrombotic condition with life threatening complications if it goes unrecognized (2). Heparin induced thrombocytopenia was identified in approximately 5% of patients receiving unfractionated heparin (UFH) for VTE prophylaxis in an orthopedic surgery series (3). The risk of HIT is lower with LMWHs or fondaparinux (4).

The symptomatology can vary depending on the vessel(s) affected, though its most common manifestations include deep vein thrombosis, pulmonary embolism, embolic limb ischemia, cerebrovascular accidents and myocardial infarctions (5). Venous thrombotic events far more frequent than arterial ones, the latter of which account for only the 3%-10% of cases (6). Severe pain of sudden onset, cold, cyanotic extremities, pallor, paresthesia, paralysis and absent pulses distal to the site of the blockage is the cardinal manifestation of acute arterial thromboembolism (ATE). Neurological findings, including paresis, impaired sensation, or even paralysis, are related to ischemic damage of nerve fibers (7). We hereby report a rare case of a 75-year-old woman with acute limb ischemia caused by arterial embolism of the superficial femoral artery attributed to HIT subsequent to hip fracture surgery. Paralysis of the affected limb was the main presenting symptom. Clinical features, work-up and management are discussed.

CLINICAL CASE

A 75-year-old female patient presented to the emergency department of our hospital with an intertrochanteric fracture of the right hip after a low energy fall. Her past medical history was significant for hypertension and diabetes mellitus. The patient was admitted to the Orthopedics–Trauma wards for further management. She was given Verapamine 3500 International Units (IU) daily subcutaneously for VTE prophylaxis. Laboratory findings (labs) on admission were significant for: hemoglobin (Hb) 10.3 g/dL, white blood cell count (WBC) 7600 cells/mm^3 and platelet count (PLT) 147 K/μL; hepatic enzymes were within normal limits (serum glutamyl oxaloacetic transaminase (SCOT) = 20 IU/L, serum glutamic pyruvic transaminase (SGPT) = 11 IU/L, gamma-glutamyl transpeptidase (g-GT) = 11 IU/L and alkaline phosphatase (ALP) = 56 IU/L) as was renal function (Creatinine (Cr) = 0.98 mg/dL, and urea (UR) = 50 mg/dL).

On the third day of admission, the patient underwent a closed reduction and intramedullary nail fixation of the fracture (G-nail) under spinal anesthesia. Fixation was considered stable and the patient was mobilized and instructed to bear weight on the affected extremity as tolerated.

Postoperative labs revealed a mild drop in PLT to 138 K/μL and Hb to 8.8 g/dL. On the fourth postoperative day (POD; sixth day of admission), a significant fall in the PLT count to 57 K/μL (61.2% decrease from the admission value) was noticed. Positive antibodies against heparin – platelet factor 4 (PF4) confirmed the diagnosis of HIT (heparin-PF4 antibody value, 7 U; normal range less than 1 U) (2). Verapamine was

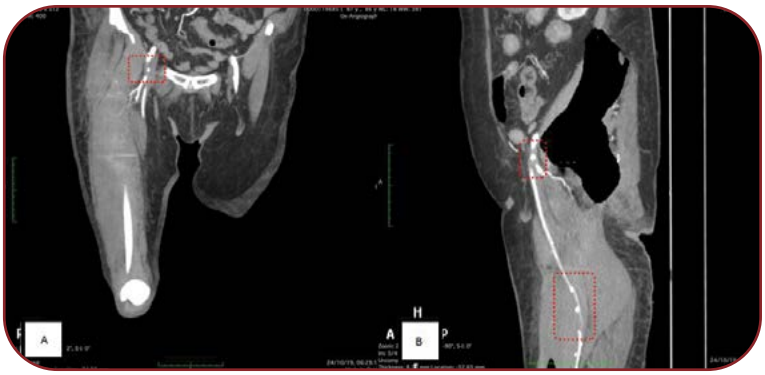

FIGURE 1. The extent of thrombus in CT angiogram coronal (A) and saggital (B) views

immediately stopped and treatment with fondaparinux 7500 IU daily subcutaneously was promptly started.

Over the following night, the patient complained of new onset weakness, numbness and mild pain of the right lower limb. On physical examination, peripheral pulses (both dorsalis pedis and posterior tibialis) were present, though weak. Motor exam revealed 0/5 strength over the right lower extremity. Light touch and pin prick sensation were impaired; patellar and Achilles reflexes were absent. The patient was sent for emergent CT scan of the lumbar spine to exclude any possible complications caused by spinal anesthesia. The result was negative for intracanal pathology. A subsequent CT angiogram (coronal and saggital views) of the right extremity was done, which revealed extensive thrombosis of the right superficial femoral artery (Figure 1). The vascular surgery team was consulted and early open embolectomy was performed. The patient recovered well postoperatively.

DISCUSSION

Heparin induced thrombocytopenia is an infrequent complication after exposure to heparin and less often to LWMHs. Two types of HIT have been described. Type I is a non-immunologic response to heparin treatment and is characterized by mild transient thrombocytopenia that has no thrombotic sequalae (2). Type II refers to a severe immunologic drug reaction, characterized by the presence of antibodies against the antigenic complex of heparin and PF4, which activate the coagulation cascade and can lead to extensive arterial and venous thrombosis (2). Heparin induced thrombocytopenia II usually occurs 5-14 days after thromboprophylaxis initiation with heparin products, but can also develop earlier if patients have been exposed to heparin within the previous three months (8). In the rare case of onset within the first 24 hours of exposure, a prior immune response is often the culprit. Heparin administration within the prior 3-12 months *vs* more than one year before did not seem to have any difference in the onset of HIT after re-exposure (9).

Unfractionated heparin imposes a greater risk as compared to LMWHs (4). Cardiovascular and interventions carry a high risk of HIT; the incidence of HIT following orthopedic surgeries has been reported to be approximately 0.5% after LMWHs and 5% after UFH use (6. 9). Women are more frequently affected (10).

In our case, the patient denied any recent exposure to heparin products over the past several months. On the third day of admission, she acutely developed new-onset thrombocytopenia with nadir PLT count to 57 K/μL, accompanied by new neurologic symptoms in the setting of acute arterial thrombosis. Thrombocytopenia can occur independently of HIT in the first 1-2 days postoperatively, especially in patients undergoing major operations such as hip replacement or cardiovascular surgery (9). In the present case, the patient developed thrombocytopenia four days after LMWH initiation and the diagnosis was confirmed with the presence of positive anti heparin-PF4 antibodies. Importantly, heparin-PF4 antibody positivity is frequently observed in patients treated with LMWHs and UFH, without overt HIT (11).

For the above reasons, prognostic tests and clinical scores have been proposed to distinguish patients with HIT from those with threatening thrombocytopenia due to other reasons. The "4Ts" pre-test clinical score is a tool used to predict the probability of HIT. The test has demonstrated good negative predictive value in patients with low probability outcome, though intermediate and high values are not predictive and further evaluation is needed (12, 13). The HIT Expert Probability (HEP) score has a similar diagnostic value and it is often the preferred tool among clinicians with limited experience and in critically ill patients, though further studies are needed to establish its suitability in every-day clinical practice (14, 15).

Venous thrombosis is the most common complication of HIT; 17% to 55% of untreated pa-

tients who develop HIT present with DVT and/or PE. Arterial thrombotic events, including ischemic limb artery occlusion, thrombotic stroke, and myocardial infarction, occur less often in approximately 3%-10% of cases (6). To our knowledge, we hereby describe the first case of HIT presenting with new neurologic deficits in the setting of arterial embolism following hip fracture nailing.

Acute arterial embolism usually presents with acute sudden onset pain, cold, pallor, cyanosis, paresthesia, paralysis, and absent pulses distal to the site of the embolism. Ischemic damage to nerve fibers may result to paresis, hypoesthesia, or even paralysis of the affected limb. In such cases, neurological symptoms may prevail (7). In most cases of acute arterial embolism, pulses peripheral to the occlusion are absent, but if collateral circulation has been established, they may be maintained or reduced. In such patients, pain onset may be more subtle and its severity less intense (7, 16). Therefore, sudden occlusion of a proximal artery without existing collateral network results to an acutely ischemic leg, whereas occlusion of the superficial femoral artery in the presence of well-established collateral circulation may be asymptomatic or atypically present (7, 17). In our case, CT angiogram revealed some evidence of collateral circulation, likely enough to preserve some degree of blood supply to the limb (Figure 1). Sufficient collateral circulation is a significant prognostic factor for a favorable outcome, since it ensures limb blood supply, reduces ischemic damage and prevents irretrievable tissue necrosis until the culprit is repaired (17).

Cessation of heparin or LMWH administration is of utmost importance for HIT management and alternative anticoagulants must be started immediately (9). In our case, fondaparinux was administrated subcutaneously when thrombocytopenia was identified and HIT suspected. Fondaparinux has been shown to reduce the risk of thrombocytopenia in patients following major orthopedic surgery (18). Cross-reactivity with HIT antibodies has been noted and there have been literature reports regarding possible fondaparinux-induced HIT (19, 20).

Argatroban is a direct thrombin inhibitor (DTI) recommended for HIT management regardless of the presence of thrombosis. It is safe for patients with renal impairment but activated partial thromboplastin time (aPTT) monitoring is required (17). Bivalirubin is another DTI approved for HIT management. After the acute stage of HIT, vitamin K antagonists can be used, but not before platelets have substantially recovered (usually at least above 150 K/μL) (5). Finally, direct oral anticoagulants have gained ground towards HIT treatment and represent an attractive option, as they do not require aPTT monitoring and achieve peak blood levels rapidly.

Low molecular weight heparins are commonly used in orthopedic patients; however, the frequency of regular PLT monitoring for HIT monitoring has not been established so far. For patients with an intermediate risk for HIT, the American College of Chest Physician guidelines suggest monitoring the PLT count every 2-3 days from day 4 until day 14 or until LMWHs are stopped (6). However, implementation of such instructions in every-day life becomes hard to incorporate, as patients are commonly discharged home on LMWHs after surgery. PLT count monitoring during this critical period is a logistical challenge and imposes significant demands on health care system resource expenses (5). ❑

CONCLUSION

Severe neurologic complications are an unusual presentation of vascular events in the setting of HIT. Increased index of suspicion is warranted to establish early diagnosis and treatment of this variably presenting disease which can lead to devastating complications.

Conflicts of interest: none declared.
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