Bilateral Lower Extremity Gangrene Requiring Amputation Associated with Heparin-Induced Thrombocytopenia

A Case Report

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Heparin use, both prophylactically and therapeutically, is prevalent among hospitalized patients. Patients on heparin may develop a thrombocytopenia that is self-limited. Fewer patients develop a heparin-induced thrombocytopenia that can cause severe bleeding and thrombosis owing to intravascular platelet aggregation. The authors present a case report of heparin-induced thrombocytopenia in a patient who underwent aortic arch and aortic valve replacement that resulted in bilateral above-knee amputations. The patient developed limb ischemia related to heparin-associated thrombosis, but had a delay in antibody seroconversion. Early and accurate diagnosis of heparin-induced thrombocytopenia requires a high clinical suspicion and may be present despite the absence of serum antibodies.

Introduction

Heparin is a common cause of thrombocytopenia in hospitalized patients. Between 10% and 15% of patients receiving therapeutic doses of heparin develop thrombocytopenia. Heparin-induced thrombocytopenia (HIT) can cause severe bleeding and thrombosis owing to intravascular platelet aggregation. Heparin-induced thrombosis, sometimes called the "white clot syndrome," can be fatal unless recognized promptly. Most cases of HIT are mediated by a complex formed between heparin and the platelet-derived heparin neutralizing protein, platelet factor 4.[1-4]

The diagnosis of HIT is based on 3 criteria: (1) Recent or ongoing exposure to heparin, (2) the presence of at least 1 clinical feature of the syndrome (usually thrombocytopenia), and (3) laboratory evidence of heparin-dependent antibodies. HIT must be distinguished from other causes of thrombocytopenia.[1-4] Importantly, heparin use is often associated with an early fall in the platelet count that usually occurs within the first 4 days of initiation and recovers

Vasc Endovasc Surg 40:161–164, 2006

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without cessation of heparin treatment. This nonimmune heparin-associated thrombocytopenia has not been found to be associated with thrombosis and does not necessitate discontinuation of heparin. We present here a case report of a patient who received heparin therapy following aortic tissue valve replacement and aortic root repair with graft and developed bilateral lower extremity arterial clots 6 days postoperatively in the setting of positive heparin antibody titers. Ultimately the patient required bilateral above-knee amputations.

Case Report

The patient was a 70-year-old Filipino male with a history of systemic hypertension who presented with a 2-week history of severe back and chest discomfort. A computed tomography (CT) scan of the chest revealed a dissection of the ascending aorta. The patient was admitted and treated with antihypertensive medications. The patient underwent repair of the ascending aorta and transverse arch with a prosthetic graft as well as aortic valve replacement with a 25 mm bovine pericardial paramount valve. On postoperative day 1, the patient required reoperation for bleeding and required evacuation of extensive mediastinal and pleural clots and suture ligation of mediastinal fat and chest wall bleeders. Postoperatively a heparin drip was used for anticoagulation of the aortic graft and valve replacement.

The patient was ambulating and recovering well until postoperative day 6, when he developed pain and weakness in the lower extremities. Physical examination revealed cool lower legs with motor and sensory loss below the knees and mottling extending to the midthigh bilaterally. The patient had palpable femoral and popliteal pulses bilaterally, although no pulses or Doppler signals were present in the dorsalis pedis or posterior tibial arteries. In addition, the patient was noted to have patchy areas of cyanosis in the nose and left upper limb. Laboratory analysis revealed a white blood cell count of 24, a hematocrit of 35, platelet count of 66 (decreased from a baseline of 150), creatinine of 3.6, partial thromboplastin time (PTT) of 47, and international normalized ratio (INR) of 2.0. Creatine kinase level was 12,591 U/L. Two heparin-associated platelet antibodies were negative. CT scan was urgently performed but revealed no acute dissection, and an echocardiogram revealed no proximal source of embolization.

The patient was suspected of having heparin-induced thrombocytopenia, and the thrombin inhibitor argatobran was initiated at 2 micrograms/kg/minute. The patient was taken urgently to the operating room, where he underwent left popliteal artery exploration. A bounding pulse was noted in the popliteal artery with absence of diastolic flow suggestive of distal occlusion. The gastrocnemius did not bleed and appeared nonviable. Bilateral posterior tibial and dorsalis pedal artery exploration and thrombectomy was performed with removal of long arterial clots. Bilateral 4-compartment fasciotomy was also performed. At the termination of the procedure, pulses were palpable in bilateral posterior tibial and dorsalis pedis vessels. However, Doppler signals were highly suggestive of distal thrombosis.

The patient's feet never regained warmth or capillary refill in spite of palpable pulses. Thrombolysis was not attempted and argatroban was continued postoperatively at therapeutic levels. Bicarbonate was administered to alkalinize the urine. Within 12 hours, the dorsal pedis and posterior tibial arteries pulses were attenuated and eventually disappeared. Heparin-associated platelet antibodies were initially borderline but seroconverted to positive 2 days later. A decision was made not to reattempt thrombectomy given the appearance of nonviable muscle, refractory heparin-induced thrombosis, and assumed small-vessel thrombosis. The creatine kinase levels decreased to 1,200 U/L. He was observed closely in the intensive care unit and did not develop any hyperkalemia, acidosis, or loss of renal function. He did not regain muscle viability or function. The lower extremities progressed to be nonviable with mummification of the skin below the knee despite palpable pulses. Bilateral above-knee amputation was performed after a pyrophosphate scan revealed no perfusion below the knee (Figure 1). The amputations sites are healing well and the patient is undergoing physical therapy. Coumadin was initiated for long-term anticoagulation.

Discussion

Heparin is widely used for prevention and treatment of thrombotic disorders and is often effective; however, it can cause serious adverse effects.

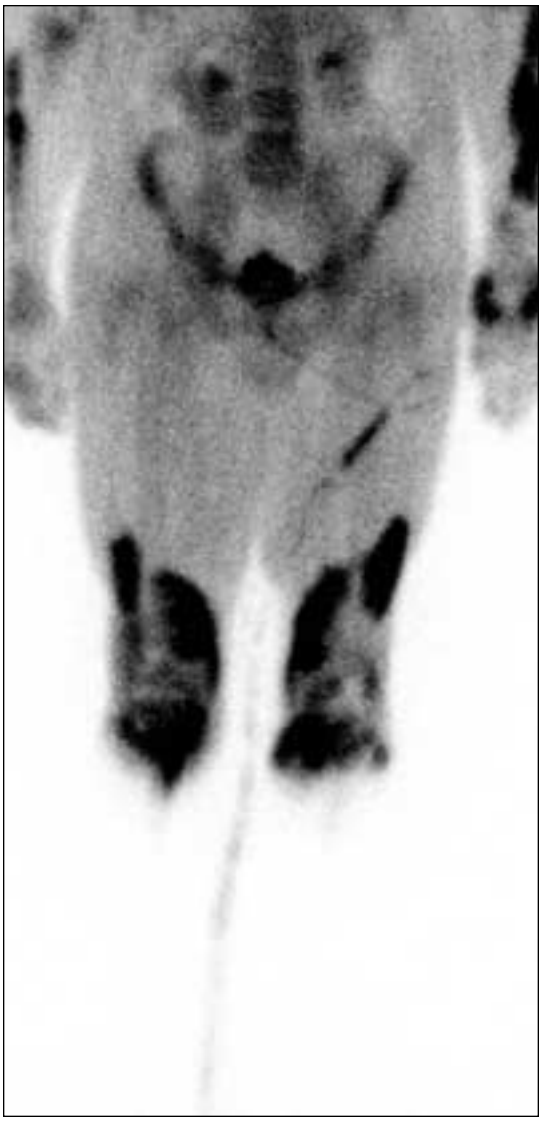

Figure 1. Pyrophosphate scan showing no muscle uptake below the knees in the lower extremities. Increased uptake is noted in the injured muscle of the distal thigh. Seen between the lower extremities is the Foley catheter.

One of these is heparin-induced thrombocytopenia (HIT), a common, serious, and potentially life-threatening condition, and one for which diagnosis can be difficult.[1-3] Clinically there are 2 types of HIT, type I and type II.[1] The mechanism of type I is still unknown but it is likely to be nonimmune and is probably related to its platelet proaggregating effect. Heparin causes mild platelet aggregation in vitro, and possibly also causes mild platelet aggregation in vivo, particularly in the patients with activated platelets.[1-4] This results in increased platelet sequestration in the spleen and thrombocytopenia. HIT type II is immune mediated and is caused by an antibody to the heparin-platelet factor 4 (PF4) complex. Antibody binding causes platelet activation, generating procoagulant platelet-derived microparticles, and activating endothelial cells and monocytes. These diverse effects likely explain the thrombocytopenia and thrombotic events observed in HIT. Cases of both arterial and venous thrombus causing limb threat and ischemia have been reported.[5-7]

Our case demonstrates heparin-induced thrombocytopenia causing arterial thrombosis in a patient whose platelets declined after the initiation of heparin therapy, although seropositivity to heparin was not evident until after the thrombosis had occurred. It is thus of paramount importance to have a strong clinical suspicion for the diagnosis of HIT-associated thrombosis, for seropositivity may lag and the window for appropriate treatment may be missed with dire consequences to the patient and operative outcome. This principle is important given the ubiquity of heparin usage in cardiothoracic, vascular, orthopedic, and neurosurgical procedures.

This case also demonstrates the difficulty in determining amputation level in spite of limb physical appearance. In this case, a pyrophosphate scan was useful in helping the patient's family understand the need for above-the-knee amputation. The pyrophosphate scan evaluates the uptake of technetium-99m pyrophosphate and reflects muscle viablility and activity. Absence of uptake indicates nonviability; increased uptake suggests necrosis, inflammation, or hyperperfusion. Pyrophosphate scans have also been a useful adjunct in predicting the need for amputation in extremities damaged by electrical injury and burns.[8]

Once HIT is suspected, it is important to withhold heparin. Despite cessation of heparin, 25% to 32% of patients will develop new thromboembolic complications, 23% will experience death, and 4% to 8% will require amputation.[9] Thrombin inhibitors such as argatroban can be used for anticoagulation in patients with heparin-associated antibodies. Argatrobran has a half-life of 45 minutes and is excreted by the kidney. Intravenous administration is started at 2 micrograms/kg/minute, and adjusted for a goal PTT of 1.5 to 3 times normal. Argatrobran has the disadvantage that it also elevates the INR and can thus make concomitant coumadin dosing a challenge. Early reports in patients with HIT who undergo

treatment with argatroban demonstrate a death rate of 16.9%, amputation rate of 1.9%, and a new thromboembolic event rate of 8.1%.[10,11] In this case, his lower extremity vessels rethrombosed despite therapeutic levels of argatroban, owing to residual thrombosis in the microvascular and medium-sized arteries. Ultimately, additional investigation will be required to generate and evaluate novel anticoagulants in the treatment of heparin-induced thrombocytopenia. Furthermore, the development of new assays to improve early detection of heparin-induced thrombocytopenia might help to prevent serious complications and reduce patient morbidity and mortality rates.

Acknowledgments

The authors acknowledge the help of Johannes Czernin, MD and Cecilia Yap of the Division of Nuclear Medicine, Department of Molecular and Medical Pharmacology at UCLA, in obtaining the pyrophosphate scan images.

REFERENCES

1. Warkentin TE, Levine MN, Hirsh J, et al: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332:1330-1335, 1995.
2. Chong BH: Heparin induced thrombocytopenia. Br J Haematol 89:431-439, 1995.
3. Chong BH: Heparin-induced thrombocytopenia. Blood Rev 2:108-114, 1988.
4. Warketin TE, Chong BH, Greinacher A: Heparin-induced thrombocytopenia: Towards consensus. Thromb Haemostas 79:1-7, 1998.
5. Diamant DS: Lower extremity amputation secondary to heparin-associated thrombocytopenia with thrombosis. Arch Phys Med Rehabil 77:1090-1092, 1996.
6. Vignon P, Gueret P, Francois B, et al: Acute limb ischemia and heparin-induced thrombocytopenia: The value of echocardiography in eliminating a cardiac source of arterial emboli. J Am Soc Echocardiogr 9:344-347, 1996.
7. Harris KA: Venous gangrene—further understanding. Can J Surg 37:368-369, 1994.
8. Affleck DG, Edelman L, Morris SE, et al: Assessment of tissue viability in complex extremity injuries: Utility of the pyrophosphate scan. Trauma 50:263-269, 2001.
9. Hirsh J, Heddle N, Kelton JG: Treatment of heparin-induced thrombocytopenia. Arch Intern Med 164: 361-369, 2004.
10. Lewis BE, Wallis DE, Leya F, et al: Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 163:1849-1856, 2003.
11. Lewis BE, Wallis DE, Berkowitz SD, et al: Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 103:1838-1843, 2001.