Heparin-induced thrombocytopenia and warfarin-induced skin necrosis: a case report

Trombocitopenia induzida por heparina e necrose cutânea por varfarina - Relato de caso

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Abstract: This paper describes a case of heparin-induced thrombocytopenia complicated by warfarin-induced skin necrosis in a 74-year old female patient hospitalized with diagnoses of a hip fracture, deep vein thrombosis and pulmonary thromboembolism. Warfarin-induced skin necrosis is a rare complication of anticoagulant therapy, with high morbidity and mortality that may be associated with heparin-induced thrombocytopenia.
Keywords: Heparin; Necrosis; Thrombocytopenia; Warfarin

Resumo: É relatado um caso de trombocitopenia induzida por heparina complicada, com necrose cutânea induzida por varfarina em paciente de 74 anos, sexo feminino, internada com diagnóstico de fratura do colo do fêmur, trombose venosa profunda e tromboembolismo pulmonar. A necrose cutânea induzida por varfarina é uma complicação rara da terapia anticoagulante, com alta morbidade e mortalidade, que pode estar associada à trombocitopenia induzida por heparina.
Palavras-chave: Heparina; Necrose; Trombocitopenia; Varfarina

INTRODUCTION

Anticoagulants are used in a variety of conditions that are commonplace in clinical practice, including deep vein thrombosis and pulmonary embolism. They are also indicated for the primary and secondary prevention of high-risk thromboembolic conditions such as chronic atrial fibrillation and thrombophilias. Nevertheless, their use may result in complications such as heparin-induced thrombocytopenia and warfarin-induced skin necrosis. The former is a frequent adverse event with the use of unfractionated heparin, while the latter is a less common complication that is not always easily recognized and is associated with high morbidity and mortality. [1]

CASE REPORT

A 74-year old white female patient (US) was admitted to the intensive care unit of the *Santa Casa de Misericórdia* in Ponta Grossa, Brazil on September 13, 2008 having been referred from another hospital emergency service. At the time of admission, she reported pain and swelling in her right leg, but had no respiratory complaints. She had had an episode of dyspnea and cyanosis of the extremities two days prior to admission. In addition, she had had a right hip fracture thirty days previously and was under conservative therapy at that moment. She also had a history of systemic arterial hypertension.

Physical examination at admission revealed

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obesity, good general condition, acyanotic, not pale, adequately hydrated, mentally alert and responsive to commands. Respiratory rate = 26 breaths/minute; heart rate = 90 beats per minute; arterial blood pressure = 120/70 mmHg; oxygen saturation = 97% in room air. Rhythmic heart rate and normal heart sounds, no murmur. Pleuropulmonary findings: presence of symmetrical vesicular murmur, with no adventitious sounds. Abdomen flaccid, not painful, no visceral enlargement. Bilateral edema of the lower limbs, worse on the right leg (3+/4). Computed axial tomography of the chest had been performed in another hospital and showed slight bilateral pleural effusions. Following Doppler ultrasonography of the lower limbs, the patient was diagnosed with deep vein thrombosis in addition to pulmonary embolism, which was confirmed by computed tomography angiography of the chest. Anticoagulation therapy with full-dose unfractionated heparin had been initiated in the institute of origin two days prior to admission at this unit. Anticoagulation therapy with unfractionated heparin was maintained and monitored with activated partial thromboplastin time (APTT). The dose was adjusted until the third day after admission; however, since the patient developed thrombocytopenia (platelet counts of 80,000, 52,000 and 76,000, respectively, in the first three days of hospitalization), the medication was then discontinued. Warfarin was initiated at a dose of 15 mg on the first day, 10 mg on the second day and 5 mg on the third day. On the sixth day of hospitalization, the patient developed diffuse skin eruptions, principally on pressure areas, with extremely hard edematous areas and erythematous, necrotic lesions in the perineal region and lower limbs (Figure 1). On the seventh day, clearly defined areas of necrosis appeared and the skin began to peel off, exposing exudative skin (Figure 2). This progressed to an extensive lesion with severe necrosis on the lateral surface of the right thigh (Figure 3). Warfarin was discontinued and vitamin K therapy was initiated. Anticoagulation therapy with unfractionated heparin was reinitiated and prednisone was introduced at a dose of 60 mg/day. On the eighth day of hospitalization, the appearance of the lesions improved. On the 11th day, the patient developed septic shock and acute kidney failure. Treatment was initiated with broad-spectrum antibiotics, mechanical ventilation and vasoactive drugs. On the 17th day, the patient developed multiple organ failure, progressing to cardiorespiratory failure, pulseless electric activity and death.

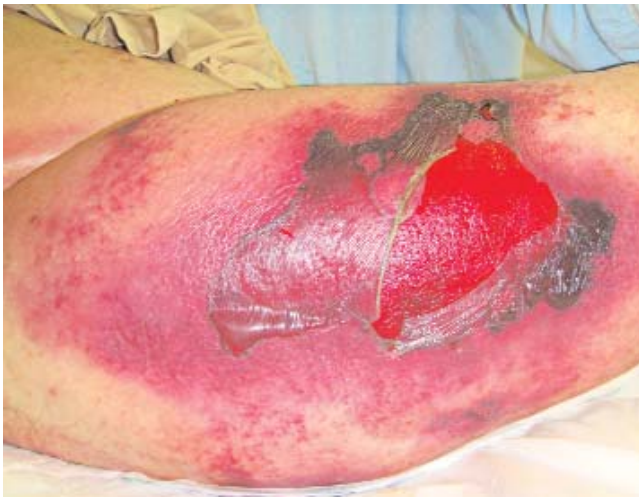

Figure 1: Perineal region and right leg with a hard edema and erythematous and necrotic lesions

DISCUSSION

Heparin-induced thrombocytopenia (HIT) is a common and often catastrophic consequence of the use of unfractionated heparin, which leads to a state of hypercoagulability with thrombotic complications in 30-75% of patients. Its incidence ranges from 0.2 – 5% of patients exposed to heparin for more than four days and is associated with the use of unfractionated heparin, female patients and surgeries. [1] There are two types of HIT. Type I is milder, with less severe thrombocytopenia, whereas type II is more severe and involves the formation of antibodies to heparin-platelet factor 4 complex. Diagnosis is suggested by the onset of thrombocytopenia with no other apparent cause, thrombosis associated with thrombocytopenia, a reduction in platelet count ≥ 50% even in the absence of absolute thrombocytopenia and necrotic skin lesions at the site of the heparin injection. [1] Warfarin therapy in patients with heparin-induced thrombocytopenia may cause deep vein thrombosis to progress to gangrene of the limbs and warfarin-induced skin necrosis. [2]

Warfarin-induced skin necrosis is a rare but severe complication of oral anticoagulant therapy, ranging in prevalence from 0.01% to 0.1%. It typically occurs in obese, perimenopausal women of around 50 years of age in treatment with warfarin for thromboembolic disease. It is often associated with the administration of high doses of the medication and develops 1-10 days after initiation of therapy, usually between the third and sixth days. The patients most susceptible to this complication are those with lupus anticoagulant, hypersensitivity to heparin, protein C or S deficiency or antithrombin or factor VII deficiency. [3,4]

The pathogenesis is explained by the procoagulant effects that warfarin may exert during the first days of its use. This phenomenon occurs because

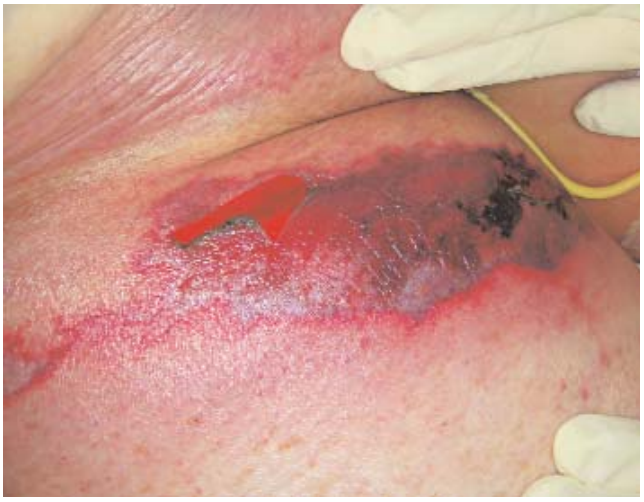

Figure 2: Clearly defined areas of necrosis and the presence of skin detachment, exposing exudative skin in the proximal region of the thigh

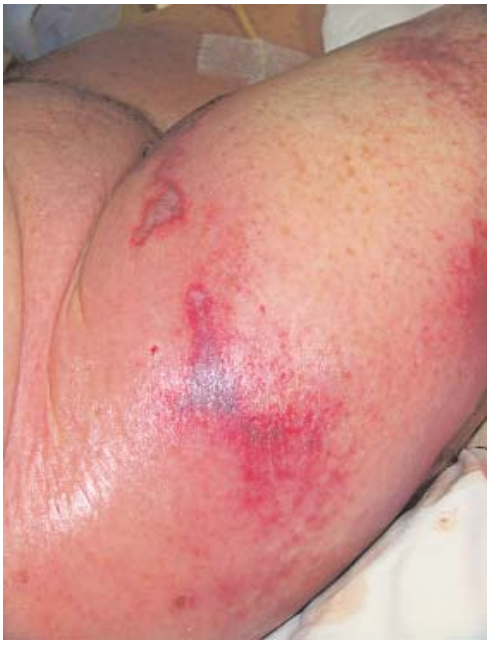

Figure 3: Extensive lesion with severe necrosis on the lateral surface of the thigh

protein C, a natural anticoagulant that is dependent on vitamin K, has a shorter half-life (5 hours) compared to most of the procoagulant factors (factors II, IX and X), levels dropping rapidly after initiation of warfarin. This transitory procoagulant/anticoagulant imbalance is exacerbated when there is a deficiency of protein C, leading to a state of hypercoagulability with thrombotic occlusion of the microvasculature. Clinically, the patient's first complaints are of paresthesia, erythematous eruption or discomfort at the site of the lesion. The lesions are well-defined, painful, initially erythematous or hemorrhagic, and include the formation of hemorrhagic blisters, skin necrosis and pressure ulcers. [5,6] The use of lower doses of warfarin is believed to reduce the risk of the patient developing a state of hypercoagulability caused by the fall in protein C levels in the first 36 hours of anticoagulant therapy. [7] Therapeutic regimens are suggested to maintain protein C levels stable during the critical period following initiation of warfarin use, with a low initial dose (1-2 mg/day) and daily increases of 1-2 mg/day until reaching the desired international normalized ratio (INR) in around 10 days. [8] Reports also suggest that interruption or continuation of warfarin treatment does not alter the cure or progression of the pressure ulcer. [8]

The patient described in the present report presented risk factors for HIT and warfarin-induced skin necrosis: being female, elderly and obese. The use of high doses of coumarins was another predisposing factor for warfarin-induced skin necrosis. Tests were not performed to investigate for antiphospholipid antibodies or for protein C or S deficiency. In view of the widespread use of anticoagulant therapy in patients with thrombotic events, the importance of recognizing and preventing these complications in a timely manner should be emphasized, as well as the need to investigate hereditary or acquired thrombophilias in these patients. ❑

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