

Warfarin-Induced Skin Necrosis and Heparin-Induced Thrombocytopenia following Mitral Valve Replacement for Marantic Endocarditis

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Hemostatic physiology involves a complex interlinking of blood and endothelial factors. Its pharmacological manipulation invariably impacts at multiple molecular sites. Herein is reported an unusual case of coexistent warfarin-induced skin necrosis and heparin-induced thrombocytopenia following mitral valve replacement for thromboembolic phenomena

The multiplicity of biochemical factors involved in hemostasis lends itself to the occurrence of rare corruptions of this complex control system that are largely poorly understood. Warfarin-induced skin necrosis (WIN) occurs in approximately 0.01-0.1% of patients receiving warfarin therapy (1). The substantial necrosis incurred often requires extensive wound debridement, skin grafting, and sometimes amputation. Also a rarity, heparin-induced thrombocytopenia (HIT) infrequently produces skin lesions that mimic WIN. A case is reported of the coexistence of these hemostatic aberrations in a patient following mitral valve replacement for embolic cerebral insult secondary to non-bacterial thrombotic (marantic) endocarditis (NBTE).

Case report

A 58-year-old lawyer presented with left-sided weakness, paraesthesia and deteriorating vision, following an eight-week prodrome of malaise, dry cough, increasing dyspnea, and unsteady gait. He had hypertension, but no history of cerebrovascular disease. Examination revealed sinus rhythm with a heart rate of 76 beats per min, a blood pressure of 187/100 mmHg, and a soft pan-systolic murmur loudest at the apex, but no carotid bruits. The patient had multiple digital splinter hemorrhages and hepatomegaly, but no

associated with marantic endocarditis and bronchial adenocarcinoma. Thrombophilia in the face of endocarditis should be treated with a suspicion of underlying cancer.

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pyrexia. His left hemiparesis was accompanied by brisk reflexes, but no cerebellar signs.

Blood investigations showed a leukocyte count of $11.6 \times 10^9/l$, an erythrocyte sedimentation rate of 5 mm/h, and a C-reactive protein level of 37 mg/l. A full autoimmune screen was normal. Chest radiography, transthoracic echocardiography and carotid Doppler ultrasound scans were all normal. Cranial computed tomography (CT) showed multiple infarcts in the left frontoparietal region and right occipital cortex. Transesophageal echocardiography revealed the presence of a mobile mass on the posterior mitral valve leaflet. The blood cultures were sterile.

Despite two weeks of intravenous antibiotics (gentamicin 80 mg twice daily, benzylpenicillin 1.2 g four-hourly and flucloxacillin 2 g four-hourly, then vancomycin 500 mg daily) for presumed infective endocarditis, inflammatory markers remained elevated. Two further strokes causing dysphagia and expressive dysphasia were associated with CT brain scan-evidenced embolizations and reperfusion hemorrhages, causing delay to surgery. The patient then developed bilateral proximal deep vein thromboses, for which he was heparinized.

At surgery, both mitral leaflets showed ragged destruction, with a large vegetation on the posterior leaflet. The valve was replaced with a 23 mm CarboMedics (Sulzer Medical, Crawley, UK) mechanical prosthesis. After an uneventful initial postoperative recovery, the patient's International Normalized Ratio suddenly rose from 1.1 to 9.1 following a daily 10 mg warfarin loading dose for two days. Anticoagulation was reversed with fresh-frozen plasma. On the fifth

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postoperative day, he developed sudden painful discoloration of his nose and bilateral fingers and toes (Fig. 1A-C). Echocardiography showed a normally functioning prosthetic mitral valve and no vegetations, while hematology revealed thrombocytopenia, a neutrophil leucocytosis and deficiencies of antithrombin III and proteins C and S. A HIT screen was positive for antiplatelet-IgM. Both heparin and warfarin were stopped and anticoagulation continued with danaparoid (2500 units initially, then infused at 400 U/h for 2 h, 300 U/h for 2 h, then maintained at 200 U/h). Two days later the patient developed a cardiac tamponade which was percutaneously drained; he subsequently developed bilateral axillary vein thromboses.

Biopsy of the skin lesions confirmed WIN, but valve histology revealed marantic endocarditis only. Although polymerase chain reaction amplification was unavailable, both *Chlamydia* and *Coxiella* serology were negative. Tumor markers were elevated, with a carcinoembryonic antigen (CEA) of 230 µg/l and C19-9 of 42 kU/l. Bronchoscopy, CT and positron emission tomography localized a primary left bronchial carcinoma with mediastinal lymph node involvement.

The patient was treated palliatively in view of his general ill constitution, and eventually died from pneumonia.

Discussion

Although associated with a myriad of stress states, NBTE has been described as a subset of Trousseau's syndrome of malignancy and thrombosis (2). The condition is also strongly associated with mucin-secreting adenocarcinoma (3). The pathogenesis of NBTE remains unclear, but an abnormal valve surface may initiate microthrombus deposition. A hypercoagulable state, promoted by tumor mucin, antithrombin III deficiency and malignant cell procoagulant, is instrumental (2). Histology of both vegetations and emboli reveals agglutinated blood and platelet thrombi, with an absence of any inflammatory reaction (4). Because NBTE has no pathognomonic clinical features and is echocardiographically indistinct from bacterial endocarditis, diagnosis without histology is one of exclusion of infective cause. Systemic embolism occurs in the majority of cases, with the brain as the favored site (5).

WIN affects mainly middle-aged, perimenopausal obese women. Lesions usually appear over fatty areas at between three and six days after commencing warfarin for thromboembolic disease, rather than for antithrombotic prophylaxis for prosthetic heart valves or dysrhythmias. Early histology of WIN lesions reveals postcapillary venular fibrin deposition and widespread dermal and subcutaneous fatty hemor-

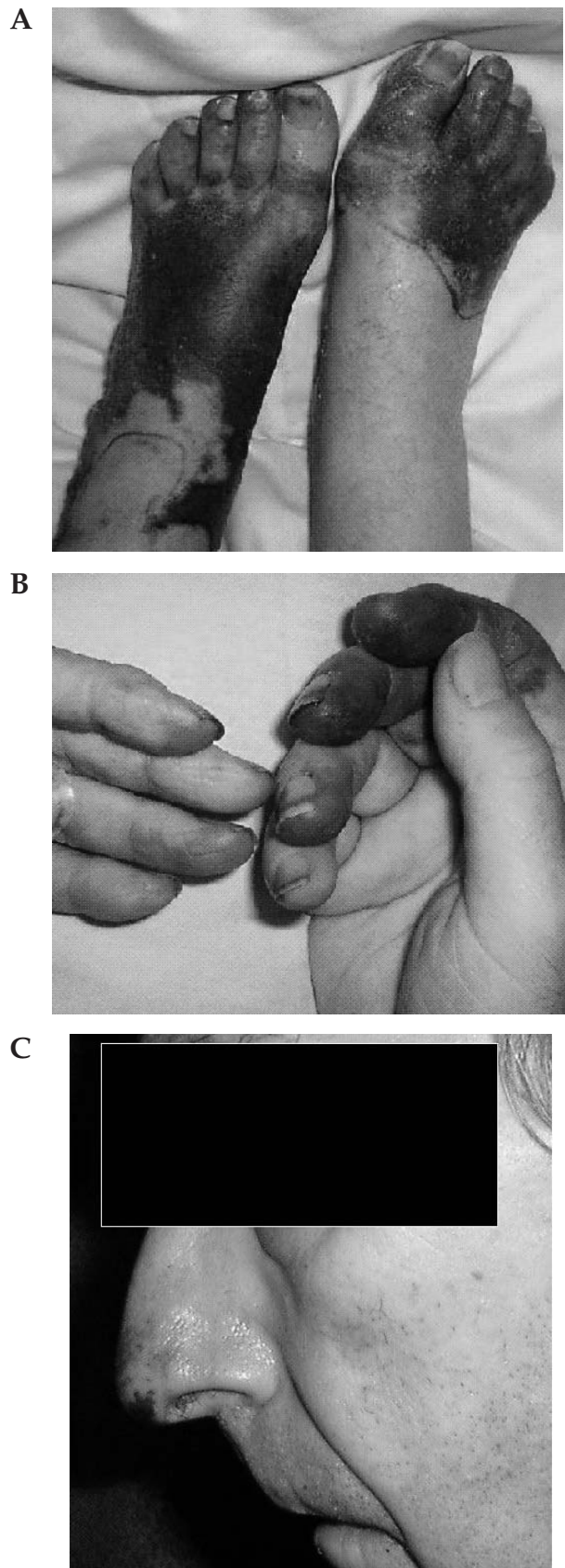


Figure 1: Warfarin-induced skin necrosis affecting (A) the feet, (B) the right hand and (C) the nose.

rhage and necrosis (6).

Aberrations of the vitamin K-dependent factors of the coagulation system - particularly protein C - are the favored etiological base for WIN. A deficiency of protein C, which inhibits activated factors V and VIII, predisposes to a thromboembolic phenomenon. Warfarin therapy causes a fall in protein C in these patients at a rate faster than that of other vitamin K-dependent factors, thereby producing a transient prothrombotic state. Cases of skin necrosis associated with protein C cofactor, protein S, deficiency are far less frequent.

Screening for deficiency of protein C or S is neither cost-effective nor practical with regard to withholding anticoagulant treatment. Large loading doses, however, should be avoided. Treatment of the skin lesions is as for full-thickness burns, with a combination of silver sulfadiazine dressings and/or skin grafting. Healing has reportedly been facilitated by a reversal of the warfarin effect with vitamin K, by prostacyclin (7), and by reconstitution of protein C levels with purified protein C concentrate (8). For those patients with an absolute requirement for oral anticoagulation, warfarin can be reintroduced incrementally at low dosage.

Interim anticoagulant therapy in this patient was complicated by HIT, which itself was atypical in that the antiplatelet antibodies were of the IgM isotype rather than IgG. HIT has itself been implicated as a risk factor for the development of WIN (9). Paradoxical thrombosis occurs in 25% of cases of HIT, attributed to platelet activation by heparin antibody binding (10), and can itself cause cutaneous lesions.

In conclusion, vigilance for underlying malignancy should be exercised in the presence of endocarditis and prothrombotic tendency. In addition, the possibility of WIN and HIT should be considered when anticoagulating for thrombophilia.

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