Heparin-induced thrombocytopenia complicated by warfarin-induced skin necrosis

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Warfarin is an integral component of heparin-induced thrombocytopenia (HIT) treatment. It is also known to have serious adverse effects associated with its use, such as skin necrosis and venous limb gangrene. Skin necrosis occurs in approximately 0.01–0.1% of patients receiving warfarin therapy. The likelihood of someone having both HIT and warfarin-induced skin necrosis (WISN) is unusual and represents a complicated scenario for clinicians. We report the case of a patient who was admitted for shortness of breath and chest pain with subsequent coronary artery bypass grafting (CABG) and mitral valve replacement (MVR). She was later diagnosed with HIT and received warfarin therapy only to be readmitted with signs and symptoms of WISN three days later.

Case report

A 64-year-old, 80-kg African-American woman was admitted to the hospital after complaining of a two-day history of shortness of breath, diaphoresis, and chest pain. Her medical history included hypertension, heart failure (ejection fraction of 15%), and myocardial infarction. Admission medications included triamterene–hydrochlorothiazide 37.5 mg–25 mg p.o. daily and lisinopril 10 mg p.o. daily. Aspirin 325 mg p.o. daily, clopidogrel 75 mg p.o. daily, atenolol 50 mg p.o. twice daily, furosemide 40 mg p.o. twice daily, and digoxin 0.25 mg p.o. alternating with digoxin 0.125 mg p.o. every other day were started immediately. The next day—hospital treatment was discontinued. Warfarin was also initiated after surgery and the patient’s platelets rapidly increased after heparin was discontinued. She was discharged one week later. Three days after discharge, she was readmitted after complaining of severe pain and swelling of the fatty tissue of her right flank that began the day after she was discharged. Some blistering and necrosis were noted on the lesion. Histological sections showed focal thrombosis of vessels in the deep reticular dermis consistent with WISN. Local wound care was given to manage the WISN, lepirudin was initiated, and warfarin was discontinued and reinstated one week later at a low dosage.

Conclusion. A patient with HIT developed severe skin necrosis after initiation of warfarin therapy.

Index terms: Anticoagulants; Dosage; Heparin; Necrosis; Skin diseases; Thrombocytopenia; Toxicity; Warfarin

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day 1—she underwent cardiac catheterization, which revealed moderate pulmonary hypertension, a reduced ejection fraction, severe mitral regurgitation, and severe coronary artery disease (80% left main coronary artery, 90% left anterior descending, and 100% circumflex and obtuse marginal). After cardiac catheterization, clopidogrel was discontinued and treatment with subcutaneous enoxaparin 80 mg twice daily was initiated. Platelets ranged from 318,000 to 335,000/mm³ during the first five days of hospitalization. On hospital day 6, the patient underwent CABG and MVR, and her platelets decreased to 263,000/mm³.

Postoperatively, the patient remained on an intraaortic balloon pump with unfractionated heparin (UFH) in the intensive care unit. On day 9, she developed tachypnea and a left groin hematoma and pseudoaneurysm on day 22. No aneurysm of the left lower lobe pulmonary embolism. The CT scan revealed a pulmonary embolism. She had a computed tomography (CT) scan on day 25. Her platelets continued to rise and consistently remained >200,000/mm³ throughout the remainder of her hospitalization. By day 29, the INR was 4.9 and her platelets were 203,000/mm³. She was discharged home on warfarin 2.5 mg p.o. daily with a follow-up appointment scheduled for four days later. Including her admission diagnoses, she was discharged with two additional diagnoses: urinary tract infection and post-CABG atrial fibrillation. Her other discharge medications included digoxin 0.125 mg p.o. alternating with 0.25 mg p.o. every other day, atorvastatin 40 mg p.o. daily, amiodarone 200 mg p.o. daily, ramipril 5 mg p.o. daily, nitrofurantoin 100 mg p.o. twice daily, atenolol 50 mg p.o. twice daily, aspirin 81 mg p.o. daily, furosemide 40 mg p.o. twice daily, spironolactone 25 mg p.o. daily, and potassium chloride 20 meq p.o. twice daily.

Three days after discharge, she was readmitted after complaining of severe pain and swelling of the fatty tissue of her right flank that measured 10 cm in diameter (Figure 1). Some blistering and necrosis were noted. A clinical pharmacist was consulted to evaluate the patient for drug-induced skin necrosis. It was noted that her readmission platelet count was 214,000/mm³ and INR was 3.8.

Two punch biopsies were taken of the lesion measuring 0.4 and 0.5 cm. Histological sections showed focal thrombosis of vessels in the deep reticular dermis consistent with WISN. This led the admitting physician to incorrectly label the patient as allergic to warfarin. An alternative diagnosis of venous limb gangrene was excluded. The punch biopsies were consistent with WISN, and the patient did not have a deep venous thrombosis or distal ischemic necrosis of the limbs consistent with venous limb gangrene.

Since the patient was on warfarin therapy, a hypercoagulability workup was not performed. Per the recommendations of the hematology department, phytonadione 10 mg i.v. was administered every six hours for one day and warfarin was discontinued the next day. After the biopsies were performed, the surgery department managed the necrotic lesion with local wound care. Lepirudin was initiated at 0.075 mg/kg/hr and continued for the duration of her hospitalization based on the hospital-approved protocol. Warfarin 1 mg p.o. daily was resumed approximately one week later and the dosage was gradually increased over several weeks and the patient was discharged with a stable, therapeutic INR.

Discussion

Reliable data on the incidence of WISN are not available, but it is estimated to occur in between 1:100 and 1:1,000 of patients receiving anticoagulants.1,4 Although rare, WISN is a serious adverse effect with significant morbidity that requires early diagnosis and supportive care. The first...
case report describing WISN was published in 1943, with more than 200 cases published in the medical literature. This effect is mostly seen in obese, middle-age women with a dominant underlying diagnosis of an acute venous thromboembolic event. Men and women appear to be at equal risk for WISN; however, women are four times more likely to have complications from WISN. The lesions usually occur in areas of subcutaneous fatty tissue such as the breasts, thighs, and buttocks; however, skin damage can occur on the trunk, extremities, face, and male genitalia. The first symptoms of skin injury typically occur within three to seven days of warfarin initiation and are described as being extremely painful. Early reports suggested that skin lesions were more likely to occur when excessive loading doses were used. Pain is usually the first symptom, followed by a petechial rash that progresses to a red to bluish-black ecchymosis with a sharply demarcated border and erythematous rim. The development of hemorrhagic bullae and full-thickness skin necrosis represents irreversible injury. Eighty percent of lesions appear on the lower half of the body. Although lesions typically involve only one area, 35% of patients are affected at multiple sites, with more than half of these patients requiring surgery. The patient reported here exemplifies the above description.

Treatment of patients with isolated WISN involves discontinuing warfarin therapy and resuming anticoagulation with UFH until the necrotic lesions heal. More than 50% of patients with WISN will require surgical intervention. Warfarin should be reinitiated with low dosages of 1–2 mg for 3–4 days, with dosage increases at increments of 1–2 mg until the desired INR is achieved over a period of 10–12 days. This should be done with concurrent UFH administration. However, in the setting of HIT, UFH or low-molecular-weight heparin (LMWH) cannot be used for anticoagulation in these patients. A direct thrombin inhibitor (DTI) or alternative anticoagulant must be used in place of UFH or LMWH. If signs and symptoms of WISN occur in someone who has achieved a therapeutic INR with warfarin therapy, warfarin should be discontinued and the patient should receive vitamin K 10–20 mg i.v. with or without fresh frozen plasma to restore endogenous anticoagulants and proteins C and S.

To date, there have been a total of 11 patient cases reported in the PubMed database describing HIT in conjunction with WISN. Six of these patients were not treated per guidelines established by the American College of Chest Physicians. However, DTIs had not received marketing approval by the Food and Drug Administration at that time. Treatments described in these cases included discontinuing warfarin and UFH, converting UFH to LMWH, restarting warfarin prior to platelet count recovery, and rechallenging the patient with UFH or LMWH. Several of these patients also received warfarin loading doses of >10 mg.

The patient reported here did not have an appropriate transition with a DTI to warfarin therapy during her first admission because warfarin was started two days prior to her DTI therapy. Her platelet counts recovered before warfarin initiation, but it is likely that WISN occurred in this patient because of a hypercoagulable state induced by warfarin monotherapy, as well as HIT. This patient received a two-day course of lepirudin therapy. She did not receive a loading dose of warfarin; however, because of concomitant amiodarone therapy and the inhibition of cytochrome P-450 isoenzymes 2C9, 3A4, and 1A2 may have intensified the anticoagulant response to warfarin. An objective causality assessment using the Naranjo et al. probability scale revealed a probable adverse drug event (score = 7).

Conclusion
A patient with HIT developed severe skin necrosis after initiation of warfarin therapy.

Figure 1. Warfarin-induced skin necrosis.
References