Warfarin-Induced Skin Necrosis in Patients With Low Protein C Levels

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Abstract- Warfarin-induced skin necrosis (WISN) is a rare complication of anticoagulant therapy associated with a high incidence of morbidity and mortality requiring immediate drug cessation. At particular risk are those with various thrombophilic abnormalities, especially when warfarinisation is undertaken rapidly with large loading doses of warfarin. Cutaneous findings include petechiae that progress to ecchymosis and hemorrhagic bullae. With the increasing number of patients anticoagulated as out-patients for thromboprophylaxis, we are concerned that the incidence of skin necrosis may increase. We present a case of WISN with low protein C level. He was a 50-year-old male who came to our department because of acute infarction in irrigation area of the superior cerebellar artery. He had intermittent atrial fibrillation and was started on anticoagulant therapy. After few day of therapy, he developed skin necrosis, and his level of protein C was low. Warfarin-induced skin necrosis is a rare but serious complication that can be prevented by routine screening for protein C, protein S or antithrombin deficiencies or for the presence of antiphospholipid antibodies before beginning warfarin therapy.

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Introduction

Stroke is one of the most significant risks associated with atrial fibrillation. Non-valvular atrial fibrillation (AF) is the most common cause of cardioembolic stroke and a powerful risk factor for strokes with overall risk ranges from 2.5% to 4% per year (1). Oral anticoagulants (OAC) reduce this risk, but also increase the risk of hemorrhagic stroke and major bleeding. Among all other side-effects of warfarin therapy, skin necrosis is a rare but serious (2). Warfarin-induced skin necrosis (WISN) occurs in only 0.01%-0.1% of patients taking the drug (3). WISN develops mainly in middle-aged women who are usually perimenopausal, obese and have been treated for deep vein thrombosis or pulmonary embolism (4). The site of the lesion is random and unpredictable, but the breast is the most common site in women, followed by the buttocks and thighs. In men with WISN involvement of penile skin may is common (5). The skin lesions of WISN begin as erythematous macules and, if appropriate therapy is not initiated promptly, evolve to become purpuric and necrotic (6). Dermal biopsy demonstrates ischemic necrosis of the cutaneous tissue with cutaneous vessel thrombosis and surrounding interstitial hemorrhage (7,8). Protein C is a 62-kD, vitamin K-dependent glycoprotein synthesized in the liver. It circulates in the blood as an inactive zymogen at a concentration of 4 μg/mL (9). Its activation into the serine-protease-like enzyme, activated protein C (aPC), is catalyzed by thrombin when it is bound to the endothelial proteoglycan thrombomodulin (10,11). Activated protein C (aPC) exerts its anticoagulant activity primarily through inactivation of coagulation factors Va and VIIIa, which are required for factor X activation and thrombin generation. The catalytic activity of activated protein C (aPC) is greatly enhanced by the vitamin K-dependent cofactor protein S (12). A deficiency of activated protein C (aPC) disturbs the delicate balance between procoagulant and anticoagulant proteins and engenders a prothrombotic environment. The role of activated protein C (aPC) and other anticoagulant proteins in this balance appear to be especially important in the slow-flowing venous circulation, in which there is

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prolonged exposure of procoagulant proteins and platelet phospholipids to the vessel wall. This may explain, in part, why protein C deficiency appears to be associated primarily with venous thrombosis. There is a lot of causes of acquired protein C deficiency: acute thrombosis, warfarin therapy, liver disease, vitamin K deficiency, sepsis, disseminated intravascular coagulation (DIC) and hematopoietic stem cell transplantation (13,14). With the increasing number of patients' anticoagulated as out-patients for thromboprophylaxis, incidence of skin necrosis may increase.

Case Report

A 50-year-old male, came to our department with ataxia, speech problems, nausea, and vomitus. He had irregular heart rhythm because of intermittent atrial fibrillation. During the examination, he was eupneic, afebrile, with irregular heart rhythm. In the neurologic examination, we noticed truncal ataxia, left-hand dysmetria, and he was dysarthric. The platelet count was 220×103/μL. CT scan showed acute ischemic lesion in irrigation territory of the superior cerebellar artery which was confirmed by MR two days after. During hospitalization newly diabetes mellitus was discovered, and peroral therapy was started. 24 hour ECG recording, showed intermittent atrial fibrillation. The cause of his stroke was intermittent atrial fibrillation, and his CHADS-VASC score was 5.

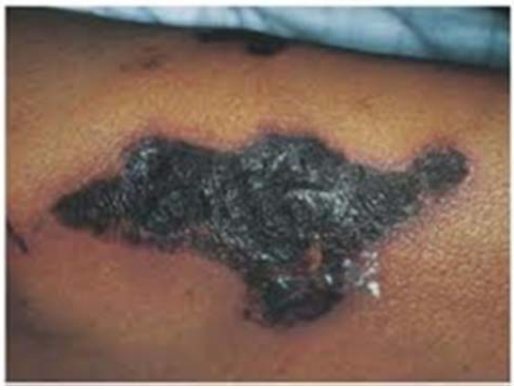

Figure 1. Skin necrosis induced by warfarin

We introduced anticoagulant therapy with warfarin in a total dosage of 5 mg/D. He had low levels of protein C (0.39, referent interval is 0.7-1.4). On the second day of anticoagulant therapy, his INR was 1.8, and he developed an area of extremely tender erythema on her left calf, surrounded by bruising. This was recognized as early skin necrosis, and he was immediately treated with intravenous unfractionated heparin, vitamin K, and fresh frozen plasma. Therapeutic heparinization, initially with unfractionated, then with low molecular weight heparin was continued for two weeks, during which time her calf began to heal. Because of the strong risk for another stroke, we introduced in therapy novel anticoagulant therapy (dabigatran, in daily doses of 300 mg). His calf healed with no permanent skin damage. After 6 months, he did not have any new neurological complications.

Discussion

Warfarin-induced skin necrosis is rare, but serious side effect of anticoagulant therapy. This side effect typically appears during the early 10 days of therapy. At particular risk are those with various thrombophilic abnormalities, especially when warfarinisation is undertaken rapidly with large loading doses of warfarin. The pathogenesis of WISN is still obscure. Thrombosis, hypersensitivity, hemorrhage, factor VII deficiency, protein C and S deficiency, and direct toxic effects of warfarin have been suggested as potential mechanisms, but other hypercoagulable conditions such as lupus anticoagulant, factor V Leiden or antithrombin III deficiency have also been associated with skin necrosis. Some cases occur in association with a familial deficiency of protein C or protein S, and hereditary protein C deficiency is considered a major risk factor. Heterozygous protein C deficiency is inherited in an autosomal dominant fashion. In type I deficiency, there is a quantitative deficiency in the plasma protein C concentration, and type II protein C deficiency is associated with decreased functional activity and normal immunologic levels of protein C We represented a patient with an embolic stroke which is a candidate for anticoagulant therapy. Because of high risk for the new embolic incident; initially, we gave him a warfarin in a total dosage of 5 mg, inspite of low levels of protein C. He developed skin necrosis the second day of therapy, so we discontinued warfarin. When warfarin therapy is started, there is a more rapid fall in the concentration of protein C than of the other vitamin-K-dependent procoagulant factors. The temporary hypercoagulable state which results is believed to lead to the development of WISN in susceptible individuals (16). The use of large loading doses of warfarin may exacerbate this effect and particularly at risk are those with an inherited deficiency of protein C or other impairment of the protein C pathway. Patients known to be at risk of WISN (those with a previous episode, protein C or S deficiency and, our data suggest, antiphospholipid

antibodies) should also be warfarinised in this gradual way or treated with novel anticoagulant therapy, as what have been done with our patients (17). A consequence of the growth in the number of indications for warfarin therapy is that many patients are now started on warfarin and rapid warfarinisation in the out-patient setting without concomitant heparinization may put some patients, such as those with undetected thrombophilic abnormalities, at risk of WISN (18). The more gradual approach, using low-dose warfarin and aiming to achieve a therapeutic INR in 10–12 days would lessen this risk without compromising the treatment of patients who are being selectively anticoagulated. In patients with high risk for new embolic stroke and with known risk of WISN (those with a previous episode, protein C or S deficiency and, our data suggest, antiphospholipid antibodies) should be treated with novel anticoagulant therapy (19). Once the signs of irreversible skin injury are apparent (hemorrhagic bullae) there is no convincing evidence that the various therapeutic approaches affect the eventual outcome (21). Nevertheless, if patients are carefully monitored in the initial phases of treatment (localized erythematous-edematous lesions with hemorrhagic component) so that excessive doses of warfarin are avoided and vitamin K is administered, it is possible to prevent progression of skin necrosis (22).

Patients should be screened for protein C or S or antithrombin deficiencies, or for the presence of antiphospholipid antibodies before beginning warfarin therapy (23). Large swings in international normalized ratio should be avoided during initiation of warfarin (especially in patients at risk of WISN and in those not receiving heparin). Finally, early diagnosis (for the occurrence of painful, sudden, well-localized erythematous-edematous lesions with a hemorrhagic component) may lessen the amount of permanent tissue damage (24).

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