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RESEARCH ARTICLE

WARFARIN INDUCED SKIN NECROSIS

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ABSTRACT

Warfarin induced skin necrosis (WISN) is a rare, unusual, unpredictable dermatological complication of anticoagulant therapy. As anticoagulation is a component of major therapy in many chronic illnesses, the recognition of this condition is crucial for prompt management of morbidity and mortality associated with this condition. We report a case of 25 year old woman who received warfarin for cerebrovenous thrombosis without proper overlap of Heparin resulting in WISN.

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INTRODUCTION

Warfarin induced skin necrosis is a rare toxicity of warfarin with a prevalence of .01%-.1%. It is associated with high morbidity, often necessitating aggressive surgical intervention and may be fatal in the absence of early accurate diagnosis and treatment. Originally described in 1943, WISN was first associated with oral anticoagulants in 1954. It was first described by Flood and colleagues (Flood *et al.,* 1943) who reported a case of a gangrenous breast but erroneously believed it was due to an underlying coagulopathy and not because of the drug therapy (Kipen, 1961) first correctly ascribed the gangrenous skin changes to anticoagulant therapy. By 2000, only 300 cases had been reported internationally. Most cases occur in patients receiving treatment for cereberovenous thrombosis (VTE), 25% of WISN occurs in patients with cardiac indications for therapy (e.g. atrial fibrillation, valve replacement) or cerebrovascular insufficiency. To our best of knowledge there are only few case reports of WISN from India (Berkompas, 1991; Mahapatra *et al.,* 2006).

CASE REPORT

A 25 year old female was admitted in a hospital with generalized tonic and clonic convulsions after intrauterine death of fetus.

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The diagnosis of venous-thromboembolism was made in that hospital after detailed evaluation. She was given Low molecular weight heparin (LMWH) 0.6 ml twice daily for three days. It was discontinued and warfarin 5 mg/day was started. The patient was discharged on warfarin on the sixth day. She presented to us with three days history of bluish discoloration of both buttocks and both wrists 10 days after the discharge (Fig 1, 2). The ecchymosed lesions rapidly progressed to hemorrhagic bullae turning into skin necrosis. Hemogram, blood biochemistry was within normal limits and I.N.R was 1.18. Her thrombophilia work up could not be done due to financial constraints. Diagnosis of WISN was made and warfarin was stopped. Vitamin K, fresh frozen plasma was administered along with parental anticoagulant. The skin necrosis was dealt with debridement and proper dressings with topical antibiotics. The patient improved clinically and was discharged with a follow up advice of undergoing skin grafting.

DISCUSSION

Warfarin, the common anticoagulant is used by millions daily but warfarin induced skin necrosis is a rare complication. Typically the condition is reported in middle-aged obese, perimenopausal women receiving warfarin treatment for pulmonary embolism, deep venous thrombosis, myocardial infarction, or valvular heart surgery (Chan *et al.,* 2000). In 90% cases, the painful necrotizing lesions appear within 3 to 6 days of initiation of warfarin therapy.

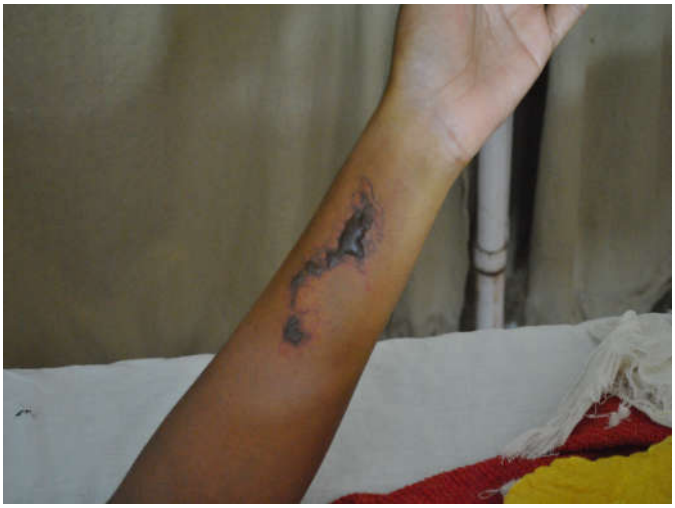

Figure 1. Skin necrosis in hand region

Figure 2. Skin necrosis in gluteal region

Classically, the lesions appear in the breast, buttock, abdomen, or thigh where significant underlying subcutaneous fat tissue is present. Onset of skin changes may begin from day one to day ten, with a peak incidence on day three to six after initiating warfarin. Although the condition also occurs in men, the female: male ratio is described as 9:1. The initial manifestation is a well localized indurated erythematous area of skin which may develop a *peau d'orange* appearance. Within 24 to 48 hours, petechiae develop that progress to hemorrhagic bullae and change quickly to full-blown necrotic eschar. The eschar may eventually slough or require extensive surgical debridement. The exact aetio-pathogenesis of this condition and the reason for its predilection for adipose tissue remain obscure but may be multifactorial (Chan *et al.,* 2000; AD-El DD *et al.,* 2000). Several theories have been suggested related to the pathogenesis of WISN. Nalbadian and colleagues (Nalbadian *et al.,* 1965) proposed that warfarin had a direct toxic effect (toxic vasculitis) at the junction of the precapillary and arterial capillary of the derma-vascular loop. Local factors, like variation in local temperature, trauma and inadequate local perfusion, have been suggested. Warfarin acts by inactivating vitamin K dependent clotting factors II, VII, IX, X. Protein C and S which are natural anticoagulants are also inhibited by warfarin. Protein C has a shorter half life of 6 hours as compared to factor II and X which have half lives of 2-5 days. Therefore protein C and S are depleted first resulting in procoagulant actions in the first days of use of warfarin. This helps explain the early emergence of warfarin-induced skin necrosis, a micro thrombotic lesion tropic to central fatty areas of the body. Patients with congenital protein C deficiency are particularly susceptible.

It is thus thought to occur from a transient imbalance in the procoagulant and anticoagulant pathways leading to small vessel thrombosis and subsequent dermal necrosis. An inherited or functional deficiency of proteins C and S has been reported by various authors (Chan *et al.,* 2000; AD-El DD *et al.,* 2000). Despite these proposed etiologies, the majority of patients with WISN do not have an identifiable inherited hypercoagulable state, and whether a causal relationship exists in those who do is uncertain. Warfarin-necrosis has been reported in patients with normal levels of protein C and S (DeFranzo *et al.,* 1995). The necrosis may be prevented by identifying high-risk patients and avoiding large loading doses of warfarin (Flood *et al.,* 1943). The initial treatment remains supportive and conservative. The necrosis may be prevented firstly by identifying high-risk patients. Acutely ill women started on warfarin for prophylaxis or treatment of thrombo-embolic disease and those with plasma protein C and S and Antithrombin III deficiencies are at the highest risk. Second, large loading doses of warfarin (>15mg) are not recommended; a daily dose of 7.5mg to 10mg is often prescribed, with adjustments as necessary. Full heparinization should be achieved before starting warfarin.

The initial treatment remains supportive and conservative as no consensus exists regarding the best treatment. It is generally recommended to discontinue warfarin although it has not been shown to alter the outcome. Heparin should be started in high doses and vitamin K and FFP should be administered to restore protein C and S levels. Good care of wound and sometimes skin grafting may be required (Pourdeyhimi and Bullard, 2014). If allowed to run its natural course, the condition is associated with significant morbidity and deaths have been reported in severe cases. The diagnosis of WISN is clinical though biopsy may help in diagnosis. Skin biopsy shows clotting within blood vessels in the skin without inflammation.

Conclusion

Clinicians also should be aware of the syndrome and especially attuned to patient's early complaints of localized skin discomfort especially in the breast, buttocks, and thighs even in the absence of overt signs. A high level of suspicion may allow rapid reversal of warfarin with therapeutic heparinization before the syndrome processes begin.

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