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CASE REPORT

Skin Necrosis induced by warfarin and associated protein C deficiency

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Abstract :

Protein C deficiency is a common cause for hypercoagulable state and can be inherited or acquired. Early in warfarin treatment, serum levels of vitamin K dependent antithrombotic protein C falls, even before other clotting factors. This causes a temporary prothrombic state, leading to venous thrombosis in subcutaneous and dermal vessels causing haemorrhagic infarction and skin necrosis. We report here a post aortic valve replacement patient who presented with a painful necrotic skin lesion of 2 weeks duration on the medial aspect of his right thigh .Patient was on anticoagulant treatment (T.Acitrom-5mg od) and his protein C level was well below normal limits, which helped in the diagnosis of warfarin induced skin necrosis in this case. Reversal of warfarin therapy was adopted, followed by surgical debridement and skin grafting.

Key words **:**

Skin necrosis, Warfarin, Hypercoagulable state, Protein C deficiency.

Introduction :

Warfarin skin necrosis develops 3-8 days of starting the drug in absence of heparin, especially if loading doses are used. This complication is rare and occurs in 1 in 10,000 persons treated with warfarin. It coincides with early drop in vitamin K sensitive factor-Protein C, which exerts anticlotting effect by inactivating factors Va & VIIIa of blood clotting cascade. The acquired state of protein C deficiency leads to non-inflammatory thrombosis in the subcutaneous and dermal vessels causing painful well dermarcated erythematous plaques which become necrotic, especially in areas with abundant subcutaneous fat .[1]This syndrome can be reversed by stopping warfarin and administering injection vitamin K, low molecular weight heparin, purified protein C or fresh frozen plasma.

Case report

A 48 years old man, got admitted with H/o fever and a painful necrotic lesion over the medial aspect of right thigh of 3 weeks duration (Figure 1).

Not a diabetic but a known case of hypertension on medication. Patient gave H/o Aortic valve replacement surgery, done 2 years ago. No H/o trauma, insect bite, nor previous thrombotic episodes. Patient was on T. Acitrom 5mg daily, during admission. His protein C level was checked and found to be low (Plasma Protein C level-39%; Normal value in adults 70-130%). A provisional diagnosis of Warfarin induced skin necrosis with cellulitis and necrotizing fasciitis was made. International Normalised Ratio (INR) on admission was 2.56 and Inj.Heparin 5000

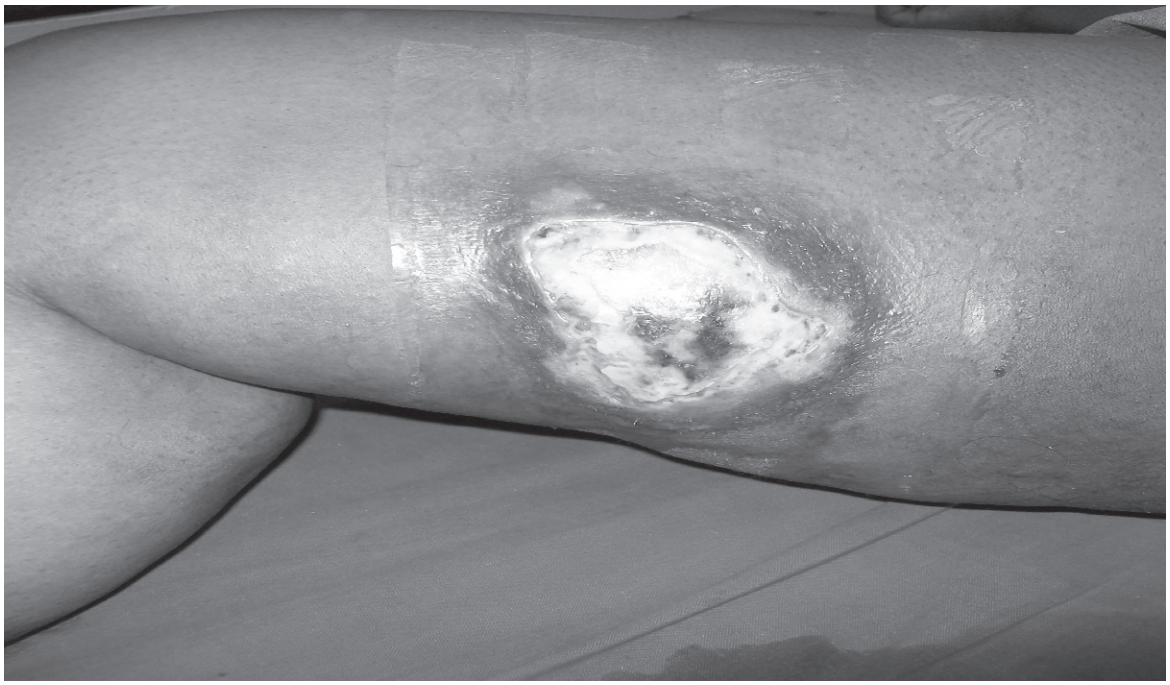

Figure 1. Necrotic Skin lesion on patient's right thigh.

units bd started along with injection Vit K. He was taken up for stage I surgery after INR value reached 1.16.Excision of necrotic skin, subcutaneous fat and fascia was done. Two units of FFP were given per-operatively. Culture of necrosed tissue showed no growth. HPE report: suppurative inflammation with abscess formation and necrotic tissue. Split skin grafting of the raw area was done after 72 hrs (Figure 2.) Injection Heparin stopped on the 3rd post-op day and T.Acitrom 3mg once a day, restarted. Patient discharged and advised to repeat PT/INR after 1 week.

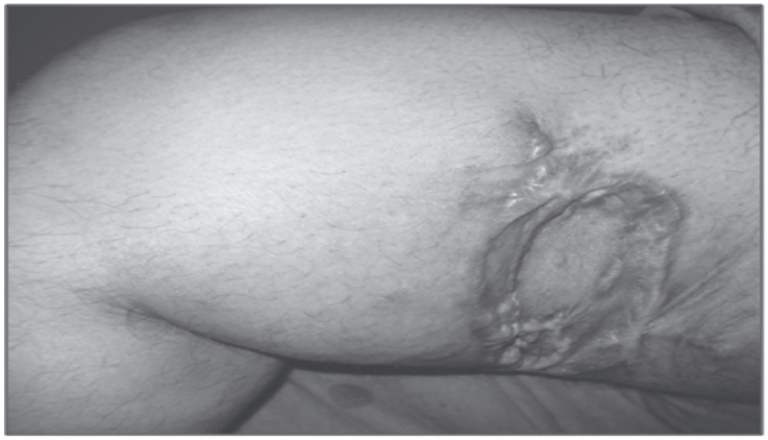

Figure 2. Healed area after skin grafting

Discussion :

Protein C (synthesized in liver) is activated to protein Ca, when thrombin binds to thrombomodulin.Its activity is enhanced by its cofactors Protein S. Activated Protein C is a serine protease which inactivates factors Va & VIIIa in blood. Protein C deficiency is congenital or acquired. Congenital deficiency of protein C is an inherited autosomal genetic disorder and can be heterozygous (1 in 300 adults) or homozygous (1 in 160-360,000 births).Type I deficiency has decreased protein C level, while Type II has normal protein C level but decreased functional activity. Deficiency can cause increased risk of thrombosis with recurrent clots in veins leading to primary deep vein thrombosis, pulmonary embolism and childhood strokes.[1] Acquired protein C deficiency is commonly seen in patients with deep vein thrombosis, acute disseminated intravascular coagulation, infections, post-op state, malignancy severe liver disease, Acute respiratory Distress syndrome, Hemolytic uremic syndrome, Vitamin K deficiency/Warfarin treatment etc. Warfarin/Coumadin induced skin necrosis, is a rare but severe complication of treatment with loading doses of warfarin or related anti-vitamin K anticoagulants. Male to female ratio of occurrence is 1:3.Drug eruption normally occurs between 3rd to 5th day of therapy, the first symptom being pain and redness in affected area which become petechial and later purpuric. They resolve or progress to form irregular bloody bullae with eventual necrosis and slow healing eschar. Favoured sites are breasts, thighs, buttocks, penis and anus where excess subcutaneous fat is present. Rarely, facia & muscles are involved[2-4]. In initial stages of warfarin treatment, the inhibition on protein C & factor VII is more than of other vit K dependant coagulation factor II,IX& X,as each of these protein have different half lives. This imbalance leads to hypercoagulable state and thrombosis, causing skin necrosis and in severe cases even gangrene of limbs[5,6]. Purpura fulminans ,occurs in children who are homozygous for certain proteinC mutations[7].

For reversal of Warfarin therapy, stop warfarin & start Injection vitamin K, Heparin or other Low molecular weight Heparin. Prothrombin Complex Concentrates, Fresh Frozen Plasma or Recombinant activated factor VII can also be given.Less severe cases of necrosis may heal spontaneously with or without scarring, while some may need surgical debridement and skin grafting.

Conclusion :

Clot promoting effects of coumarin drugs are transitory, so patient with protein C deficiency or previous warfarin necrosis can still be restarted on these drugs at low doses. The risk of direct drug toxicity of warfarin can be considered less severe, when related to risk of underlying clotting disorder for which warfarin was prescribed.(eg) Pulmonary embolism. Using Warfarin to thin the blood and prevent clots rarely can cause brief increased clotting and severe skin wounds. Patients are at risk if they are not treated with the blood thinning drug heparin before taking Warfarin.[8]Evaluating Protein C levels before

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starting on warfarin therapy will benefit the patients in identifying pre-existing deficiency state, which can precipitate such necrotic skin lesions.

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