

Case Report

Case report: Late onset warfarin-induced skin necrosis

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Warfarin induced skin necrosis (WISN) represents a rare complication of warfarin therapy that is associated with high incidence of morbidity and mortality. It usually presents in susceptible patients within 10 days of initiation of therapy. The study report a case of 24 years old gentleman who is known to have a unique rare inborn error of metabolism (primary hyperoxaluria), and was diagnosed with late onset WISN after being on warfarin for 28 months for recurrent pulmonary embolisms. The skin lesions in the study patient were not associated with underlying protein C or S deficiency.

Key words: Warfarin induced skin necrosis, primary hyperoxaluria (PH), calciphylaxis, end stage renal disease (ESRD).

INTRODUCTION

Warfarin-induced skin necrosis (WISN) is a rare complication with a high incidence of morbidity and mortality associated with usage of warfarin that requires immediate drug cessation (Nazarian et al., 2009). It occurs in only 0.01 to 0.1% of patients taking warfarin, and usually appears during the early 10 days of treatment (Amato et al., 2003). Early dermatological findings include petechiae that progress to ecchymoses and hemorrhagic bullae. Diffuse dermal microthrombi with endothelial cell damage and red cell extravasation with progression to full-thickness coagulative necrosis are the usual pathological findings encountered in microscopic assessments. WISN can be falsely diagnosed with various conditions, such as vascular ischemic lesions, calcinosis cutis and calciphylaxis. High index of clinical suspicion with the histopathological finding is usually the key to diagnosis (Nazarian et al., 2009).

OBJECTIVES

1. Describe the condition of warfarin induced skin

necrosis (WISN).

2. Alert the physicians for the rare possibility of late onset WISN.

3. Describe the differential diagnosis of WISN and its possible predisposing factors.

CASE REPORT

The study, present a 24 years old gentleman who is known to have type 1 hyperoxaluria that was diagnosed at the age of 9. He developed end stage renal disease (ESRD) as a consequence of his primary illness, and he has been receiving hemodialysis since 2011.

Patient was admitted with 2 attacks of pulmonary embolism (PE) on August, 2012 and December, 2013, subsequently requiring lifelong anticoagulation therapy with warfarin at a dose of 2.5 to 3.5 mg once daily adjusted to maintain a therapeutic international normalized ratio (INR) of 2 to 3. The patient was presented to the emergency department in December,

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Figure 1. Skin necrosis of the right foot.



Figure 2. Skin necrosis of the right knee. Lesion was located on the right knee, with an open deep wound, clear edges and regular borders. Blackish discoloration in the base is noted.

2014, complaining of nagging right foot pain that developed 1 week prior to his presentation. He noticed a skin lesion overlying the site of the pain.

On examination, his vitals were within normal limits, the lesion was located on the dorsal aspect of the right foot, with blackish discoloration of the overlying skin. The lesion was round, with irregular borders, measuring 3x3 cm² (Figure 1) without any surrounding erythema. On palpation the lesion was tender.

Distal pulses were intact including the dorsalis pedis arteries in both feet. Vascular surgeons were consulted to rule out underlying ischemia, who recommended that a computed tomography (CT) angiogram to be performed. CT revealed patent arterial flow up to the dorsalis pedis arteries.

The study main differential diagnosis was cutaneous calciphylaxis, due to the fact of prolonged period of ESRD and hemodialysis. During the course of his admission, a similar lesion appeared on his right knee (Figure 2). Dermatology consult was obtained, and a punch skin biopsy of 4 mm depth was done. Biopsy pathology reported features consistent with warfarin induced skin necrosis (Figure 3). Other options of novel anticoagulants were not possible as he had ESRD. The patient was then switched to low molecular weight heparin (LMWH) enoxaparin injections instead of warfarin as a long term anticoagulation therapy.

DISCUSSION

Warfarin exerts its anticoagulation effect through its

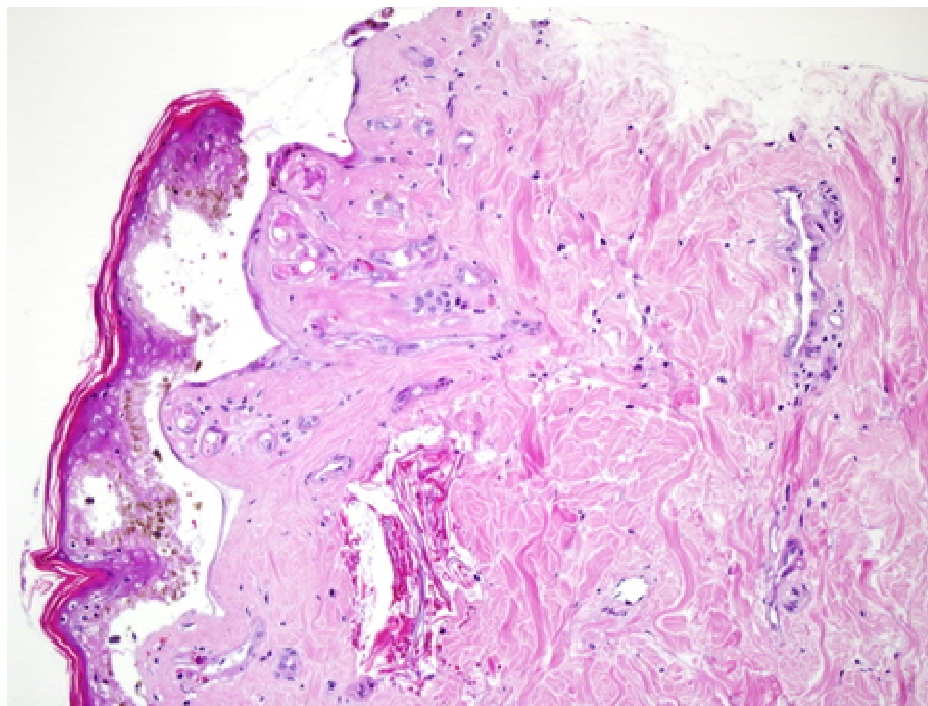


Figure 3. Histopathological finding of WISN: This section showing features of almost complete Epidermal necrosis in addition to Dermal fibrosis. Thrombosed blood vessels can be seen in the papillary dermis. No calcifications can be seen in this section.

inhibitory action on Vitamin K dependent clotting factors (x, ix, vii, ii) which usually takes around 72 to 96 h till reaching the peak anticoagulatory effect. It also inhibits the naturally occurring endogenous anticoagulants (Protein C and Protein S) in the initial phase of its pharmacological action, before reaching the steady peak level of anticoagulation. Thus, producing a paradoxical effect that manifest in susceptible patients who have underlying protein C or S deficiency as skin necrosis (Essex et al., 1998; Horton and Bushwick, 1999).

There are around 300 cases in the literature report of web solution international network (WSIN) worldwide (Chan et al., 2000), most of the cases reporting the skin lesions to appear within the first 10 days of initiating warfarin therapy (Amato et al., 2003). The study found 4 cases only describing the lesions to appear after 1 year of therapy (17 months, 3 years, 4 years and 7 years) (Essex et al., 1998; Muniesa et al., 2004; Xin et al., 2014). The study patient was on warfarin for 28 months. He received 2.5 to 3.5 mg of warfarin once daily during this period of time; his dose was adjusted to maintain an INR of 2 to 3. There were no episodes of subtherapeutic or supratherapeutic INR readings.

Interestingly, he was not found to have any underlying protein C or S deficiency. Both levels of protein C and S were measured, and they were 94 and 96 U/dl, respectively (Reference range was between 70 to 130 IU/dl for Protein C and 70 to 148 U/dl for Protein S).

Potential causes of late onset WSIN include: unintended discontinuation and then resuming warfarin, acute liver dysfunction and drug-drug interactions (Essex et al., 1998).

In regards to the study patient, he received warfarin for 6 months when he was diagnosed with the first PE, and then was off warfarin for 10 months till he was diagnosed with the second PE that necessitated lifelong therapy with warfarin. This “no warfarin” period can be accounted as a possible cause of the skin necrosis observed later, but the fact that he maintained a therapeutic range of INR (between 2 to 3) throughout his therapy period makes this possibility unlikely. Furthermore, he did not suffer from any reason that would compromise his liver function, and alter the clotting factors metabolism nor did he had a drug-drug interaction that is known to alter warfarin metabolism and deviate the INR from the therapeutic range.

The study patient’s skin lesion diagnosis exhibited a diagnostic difficulty due to the multiple differential diagnosis considered. The most probable diagnosis giving the fact he is a long term hemodialysis patient (for 5 years), is the possibility of calciphylaxis, which is also called calcific uremic arteriolopathy. It is a rare complication (estimated to occur in 1 to 4% of patients on hemodialysis) of ESRD that presents with similar skin necrosis findings, associated with high morbidity and mortality rates of 60 to 80%, most often due to sepsis

(Hayashi et al., 2012; Brandenburg et al., 2012; Jean et al., 2010; Chacon et al., 2010).

The difficulty in diagnosing the study patient was also in part due to his unique rare primary illness. Primary hyperoxaluria (PH) is an inborn error of glyoxylate metabolism, with a rare prevalence of one to three per million (Levy and Feingold, 2000; Cochat et al., 1995; Kopp and Leumann, 1995), characterized by the overproduction of oxalate, which is deposited as calcium oxalate in several organs. In specific, the kidney is a major target for oxalate deposition, which in some cases may lead to ESRD. It is sub-classified into three types; type 1 being the most common, accounting for about 80% of patients with PH (Hoppe and Langman 2003). Calcium oxalate deposition occurs as well in the heart, blood vessels, joints, bone, and retina manifested as systemic oxalosis (Watts, 1994; Hoppe et al., 2009; Tang et al., 2015).

One of potential sites of deposition is in the skin, causing calcinosis cutis, which is a syndrome characterized by the deposition of calcium salts in the skin and subcutaneous tissue. This chronic condition is sub-classified into five subtypes: dystrophic, metastatic, idiopathic, iatrogenic and calciphylaxis (Reiter et al., 2011).

The one method in which the study could differentiate between various causes with the highest possible degree of accuracy was through a skin biopsy, and performing a histopathological assessment, which the study did, and to the study surprise, the results came back with features consistent with warfarin induced skin necrosis (Figure 3).

Conclusion

Late onset warfarin induced skin necrosis occurring after 2 years of consistent warfarin usage is a possibility that can be diagnosed with skin biopsy in correlation with clinical suspicion^[1]. The treatment is a complete cessation of warfarin therapy, and the use of other means of anticoagulation is also needed.

Conflict of interest

Authors have none to declare.

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