Warfarin Induced Skin Necrosis

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Abstract

Warfarin is a frequently used oral anticoagulant in the treatment and prevention of multiple medical conditions. Warfarin inhibits the vitamin-K dependent gamma-carboxylation of coagulation factors II, VII, IX, X and the anticoagulant proteins C and S. Rarely, skin necrosis occurs when the resultant initial procoagulant state in the first few days of starting warfarin leads to thrombosis in the dermal capillaries. Warfarin-induced skin necrosis (WISN) is usually an unpredictable complication of warfarin therapy, occurring in 0.01 - 0.1 % of warfarin treated patients, occasionally leading to death. This paper describes the clinical course of a patient who developed warfarin-induced skin necrosis and discusses the clinical manifestations, diagnosis, treatment, and prevention of this condition.
Introduction

Warfarin is the standard oral anticoagulant used in a variety of many major chronic illnesses. Warfarin inhibits the vitamin-K dependent gamma-carboxylation of coagulation factors II, VII, IX, X and the anticoagulant proteins C and S. One uncommon but a catastrophic adverse effect that can occur following the initiation of warfarin therapy is warfarin-induced skin necrosis [1].

Rarely (0.01 to 0.1 percent of warfarin-treated patients), skin necrosis occurs when the resultant initial procoagulant state in the first few days of starting warfarin leads to thrombosis in the dermal capillaries, leading to skin necrosis [2]. Skin necrosis affects areas of the body with a high fat content, such as breasts, thighs, buttocks, and abdomen. It is more common in females [3]. Onset of skin changes may begin from day one to day ten, with a peak incidence on day’s three to seven after initiating warfarin with development of frank necrosis 36 - 72 hours after onset of the initial skin lesion [4].

The condition is most often unilateral, but 30 percent of cases occur bilaterally with multiple lesions. Early recognition of this complication is very important because a delay in the diagnosis may lead to serious complications such as limb amputation [5].

Warfarin-induced skin necrosis was first described in 1943 [6]. It is also known as Coumadin-induced skin necrosis (CISN). A small number of cases occur in association with familial deficiency of protein C or protein S. An acquired deficiency of protein S secondary to development of anti-phospholipid antibodies has also been implicated [7].

This adverse drug reaction appears to be associated with larger doses of warfarin without the use of bridge therapy. A gradual approach, using heparin and low-dose warfarin and achieving a therapeutic INR in 7–10 days would lessen the risk without compromising the treatment [7].

Because it is a rare effect with an undetermined pathophysiology of disease, the treatment is not well established. Early recognition and treatment are important to avoid substantial morbidity and mortality.

I report a case of WISN, providing a complete review of the literature.

Case report

A 62-year-old Egyptian female with long standing type 2 diabetes and hypertension with a recent history of a cerebrovascular accident 2 months ago with residual aphasia and bulbar symptoms.

The patient presented to the emergency department with a few days history of left lower limb edema. Duplex ultrasound was done and revealed a left ilio-femoral DVT.

The patient was not admitted due to family refusal, so Tinzaparin 0.7 ml once daily s.c. and Warfarin 5 mg tab. once daily were prescribed with follow up at outpatient department to check her INR after 1 week.
The patient returned to the emergency department after 8 days by disturbed conscious level (GCS 10/15), chest infection and urinary tract infection.

The left lower limb was swollen but less than before with ecchymosis in the left thigh and left foot with blackish discoloration (Figure 1).

Figure 1: Warfarin-induced skin necrosis on thigh, leg and foot.

The patient was admitted in the medical ICU. CBC showed leukocytosis of 34000, severe anemia with hemoglobin of 6.6 mg/dL, and thrombocytopenia with a platelet count 111000. INR was 7.1 and Creat. was 1.2.

Warfarin-induced skin necrosis was suspected based on presentation, time since initiation of warfarin therapy and supratherapeutic INR.

Warfarin was stopped. The patient received vit. K 10 mg I.V. amp., 2 units PRBCs, 4 units FFP and broad spectrum antibiotic. Subsequent lab. Results were as follows, (Table 1)

<table>
<thead>
<tr>
<th></th>
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<th>3(^{rd}) day</th>
<th>4(^{th}) day</th>
<th>5(^{th}) day</th>
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<td>8.3</td>
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<td>Platelets</td>
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<td>182000</td>
<td>207000</td>
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<td>12.9</td>
<td>9.1</td>
<td>5</td>
<td>3.2</td>
</tr>
</tbody>
</table>
Other investigations

- Duplex ultrasound revealed sub-acute left ileo-femoral DVT.
- Abdominal ultrasound revealed fatty liver and grade II nephropathy.

Management

We put a plan of local wound care, waiting for improvement of the general condition of the patient for the definitive treatment.

After improvement of the INR in the 5th day of admission, Fondaparinux 2.5 mg once daily was started.

Unfortunately the patient died suddenly without any surgical intervention in the 6th day of admission.

Review of Literature

Warfarin-induced skin necrosis (WISN) is a complication of therapy with warfarin associated with a high morbidity and mortality [8]. In 1943, the necrotic changes were first time described on the skin of a patient taking warfarin, at that time it was called “disseminated thrombophlebitis migrans” [6] and were not related to the use of warfarin. Later in 1954, Verhagen reported 13 confirmed cases of warfarin-induced skin necrosis [9].

These lesions occur in approximately 0.01 to 0.1% of all patients receiving warfarin with a predilection for females in up to 90% of cases. The typical patient is a middle-aged, obese, female with history of deep vein thrombosis or pulmonary thromboembolism, with in most cases a reported protein C, S, Factor V Leiden, and antithrombin III deficiency [10].

Pathogenesis

The pathophysiological mechanisms for warfarin-induced skin necrosis, despite several theories, remain uncertain, although, it has been informed to be related with micro vascular thrombosis, hypersensitivity to warfarin and a direct toxic effect of the drug. However, the most likely mechanism seems to be a temporary imbalance between the anticoagulant-procoagulant system, more specifically associated with a rapid decrease in C and S protein levels during initial therapy with warfarin [11], so warfarin can induce a paradoxical hypercoagulable state in the early stages of treatment, usually within 3 to 10 days of therapy initiation, associated with inadequate overlap with heparin [12].

The pathogenesis is believed to be secondary to a more rapid initial reduction in blood levels of vitamin K-dependent anticoagulants (proteins C and S) than the procoagulants (factors II, IX, X) during the warfarin anticoagulation, although other factors may also be involved. The lowering of protein C level occurs much earlier, as the half-life of protein C is much shorter compared with most of the procoagulant factors (protein C, 6 - 8 hours vs. factor VII, 6 hours; factor IX, 24 hours; factor X, 40 hours; factor II 60 hours). This would paradoxically render a temporary hypercoagulable state in the
patient. In those patients already deficient in the natural anticoagulants, i.e., protein C, protein S and antithrombin III, this hypercoagulable state is further amplified resulting in the development of thrombi in the microvasculature of the skin [7].

The risk of WISN may be increased in the setting of HIT [13]. Numerous case reports have described an association between the two conditions [14-18].

The generation of procoagulant, platelet derived micro particles observed in HIT is postulated to accelerate the rate of protein C consumption, thus contributing to the early warfarin-induced protein C deficiency and an increased state of hypercoagulability [14, 19, 20]. These micro particles, along with the procoagulant HIT antibodies, may also contribute to an increase in thrombin, which predisposes the patient to the development of micro vascular thrombosis during warfarin treatment [14,21]. The combination of these factors can lead to catastrophic hypercoagulable consequences, so warfarin should be avoided until complete platelet recovery is achieved [22].

Clinical Picture

Warfarin induced skin necrosis typically develops in middle-aged, obese females treated with warfarin for deep venous thrombosis or pulmonary embolism. WISN usually appears 3 - 8 days after initiating warfarin treatment in susceptible individuals, although it may appear later. The patient first presents an erythematous rash poorly demarcated and often associated with tissue soft edema and paresthesias, subsequently might appear petechiae progressing within hours to ecchymosis and large hemorrhagic blisters that turn into a frank necrosis [23].

The spectrum of tissue damage ranges from self-limited, superficial tissue loss capable of healing by spontaneous granulation, to injury requiring surgical débridement with skin grafting, to extreme tissue sloughing and loss with extensive deficits occasionally leading to amputation [5]. It frequently affects areas with abundant subcutaneous fatty tissue such as breasts, thighs, and buttocks. In males, the penis is affected while the breasts are spared [7].

WISN is usually diagnosed clinically, based on patient criteria, patient symptoms, lesion appearance, and history of recent warfarin therapy. Approximately 83 % to 90 % of patients develop symptoms between days 3 and 8 of warfarin treatment.

The differential diagnosis of warfarin induced skin necrosis is pyoderma gangrenosum, necrotizing fasciitis, cellulitis, ecthyma, calciphylaxis, hematoma and Fournier’s gangrene (when lesions occur in the penis).

Although not required for diagnosis, skin biopsy will often reveal subepidermal hemorrhages with adjacent epidermal necrosis and congestion and thrombosis of superficial dermal capillaries [24].

Prophylaxis

Anticoagulation should be started with heparin or LMW heparin and full heparinization should be achieved before starting warfarin. Oral anticoagulation with warfarin should be introduced with small or moderate doses and large loading doses should be avoided [25].
The American College of Chest Physicians guidelines recommend bridge therapy for at least 5 days and until the INR is stable and therapeutic (more than 2) for at least 24 hours in patients receiving warfarin for treatment of a DVT [26]. A high index of suspicion is required for early diagnosis and intervention by rapid reversal of warfarin.

**Treatment**

No current consensus exists regarding how to best treat WISN. Current treatment options are based on previously published case reports. Warfarin should be immediately discontinued once WISN is suspected. Rapid reversal of warfarin effects with intravenous vitamin K and FFP or 4-factor PCC [26, 27]. After reversing warfarin to a therapeutic or subtherapeutic INR unfractionated or low molecular weight heparin should be started to prevent further clotting and necrosis. Regression of skin necrosis has been described using a protein C concentrate in patients with protein C deficiency [28].

Proper local wound care with topical antibiotics and frequent dressing is important. Some wounds can heal without surgical intervention, but many patients need surgery for debridement and skin grafting and in some cases, amputation may be necessary.

Some clinicians have reported the recurrence of WISN in patients reintroduced to warfarin [29]. Successful reintroductions of oral anticoagulation have been reported. To minimize the risk of recurrent skin necrosis, oral anticoagulation therapy with warfarin was started at 1 mg/day with a very slow increase in the dose [30]. Although recurrence is rare, the cautious reuse of warfarin is recommended for patients with significant need for long term anticoagulant therapy and long-term subcutaneous therapy with unfractionated or low-molecular-weight heparin is appropriate. Also novel oral anticoagulants (NOACs) can be safely used in WISN for long term anticoagulant therapy [31].

After the acute event is resolved, the patient and family members may need to consider testing for Protein C and S or Antithrombin III deficiencies.

**Conclusions**

Warfarin Induced Skin Necrosis is a rare but serious complication of warfarin therapy, associated with high morbidity and mortality rates. Early recognition and treatment are essential to prevent further complications. Once it is suspected, warfarin should be stopped and the patient should be given Vitamin K and FFP to reverse the effects of warfarin.

**Consent**

Written informed consent was obtained from the relatives of the patient for publication of this case report and any accompanying images.
References


