Discussion

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2nd year, General medicine

Introduction

- Warfarin-induced skin necrosis (WISN) is usually an unpredictable complication of warfarin therapy, occurring in 0.01 - 0.1% of warfarin treated patients.

History

- The first descriptions of this disorder came from the work of McLeanin 1916 and, later, Flood et al in 1943 described this condition in the form of ‘‘thrombophlebitis migrans disseminata’’ of the breast.

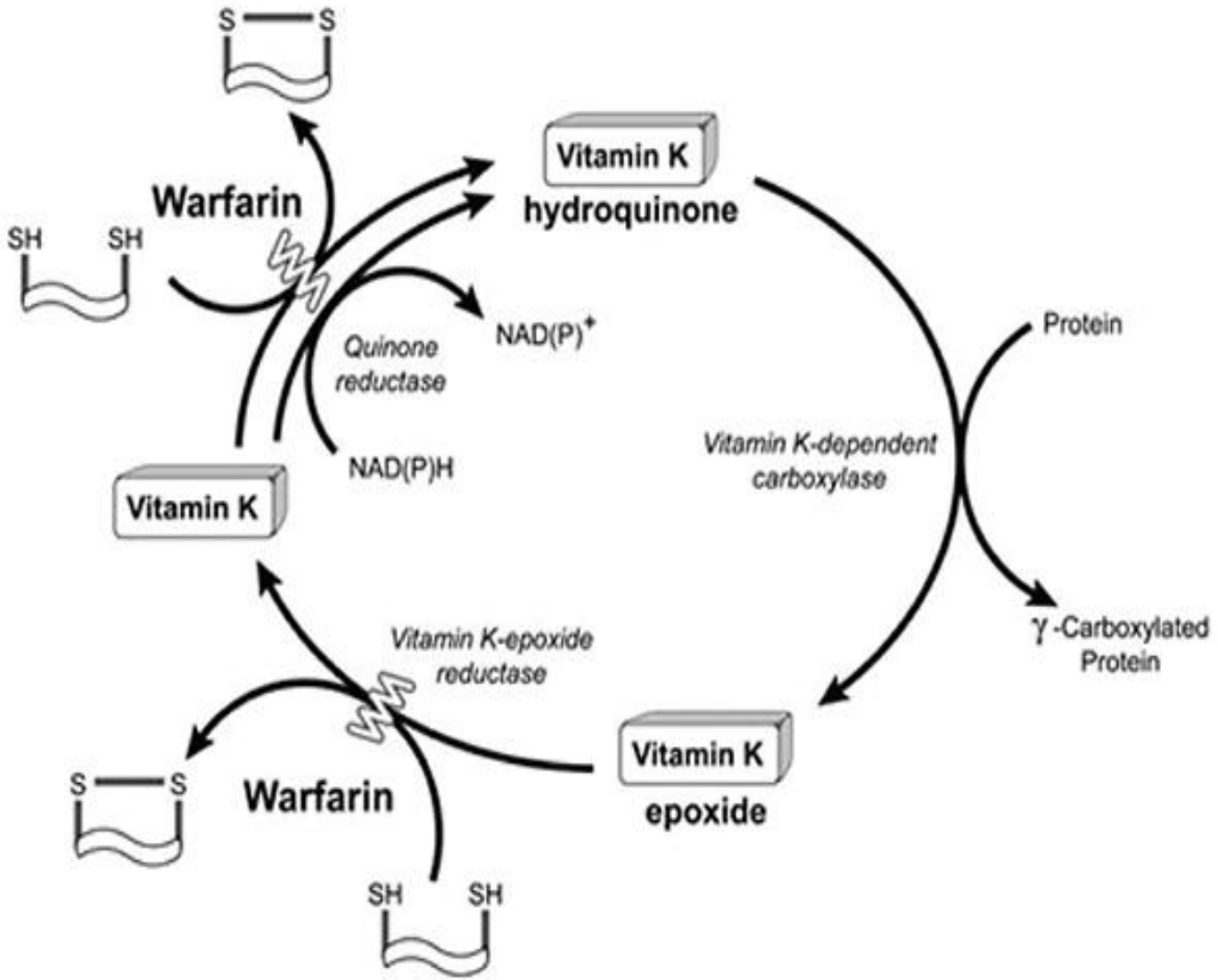
Risk factors

- Obesity
- Peri-menopausal age
- Viral infections
- Hepatic disease
- Drug interactions
- Deficiency of protein C, protein S or
- Factor V Leiden mutation
- Antithrombin III
- Hyperhomocysteinaemia
- Antiphospholipid antibodies

- Warfarinization with large loading doses or without initial concomitant heparinization, are common clues in the clinical history.

- The vast majority of cases of anticoagulant induced skin necrosis have been attributed to coumarin congeners (bishydroxycoumarin, phenprocoumon, acenocoumarol, and sodium warfarin)

Figure 2. The Vitamin K Cycle



Pathogenesis

- Protein C is a VIT K dependent natural antithrombotic glycoprotein circulating as an inactive zymogen that is activated by thrombin.

- Activated protein C is augmented by binding of the protein S cofactor leading to inhibition of factors Va and VIIIa, which, in turn, activate factors II (prothrombin) and X, respectively down regulating thrombin formation.

- 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

  (proteinC, 6 - 8 hours vs. factor VII- 6hrs

  factor IX- 24hrs

  factor X- 40hrs

  factor II- 60hrs)

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- This would paradoxically render a temporary hypercoagulable state

- In those patients already deficient in the natural anticoagulants, i.e., protein C, protein S and anti-thrombin III, this hypercoagulable state is further amplified resulting in the development of thrombi in the microvasculature of the skin

- Notably, the prothrombin time (or international normalised ratio, INR) used to test the effect of warfarin is highly dependent on factor VII

- This is the reason why patients can have a therapeutic INR (indicating good anticoagulant effect) but still be in hypercoagulable state.

- Although protein C deficiency has been implicated in less than 50% of cases, the association of protein S and antithrombin III deficiency has been reported

- Lupus anticoagulant has also been associated with skin necrosis.

- Warfarin had a direct toxic effect (toxic vasculitis) at the junction of the precapillary and arterial capillary of the dermovascular loop.

- The drug-damaged capillaries dilate and rupture, and petechiae develop quickly.

- Veins distal to the injured capillaries thrombose, creating stasis of blood and tissue necrosis. Consequently, arteries in the skin and subcutaneous tissue are spared, whereas capillaries, venules, and, occasionally, subcutaneous veins are occluded selectively

- Another proposed theory is hypersensitivity to warfarin.

Clinical features

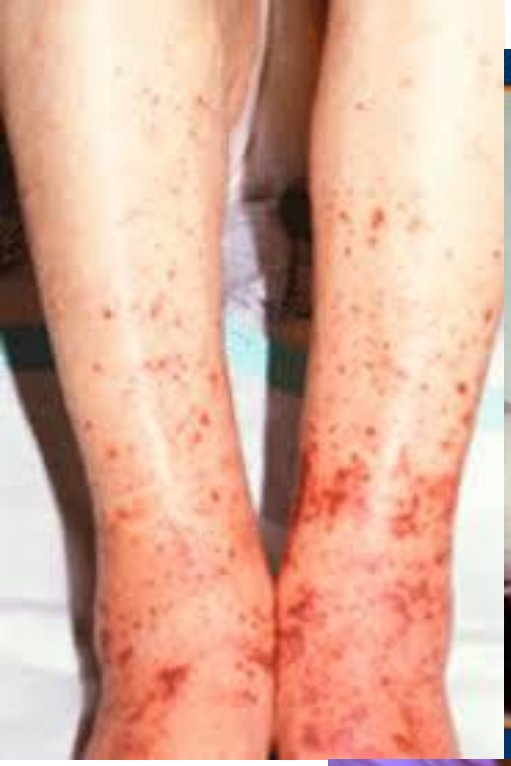
- Onset is usually between the 3rd-8th day of warfarin therapy, with development of frank necrosis 36 -72 hours after onset of the initial skin lesion.

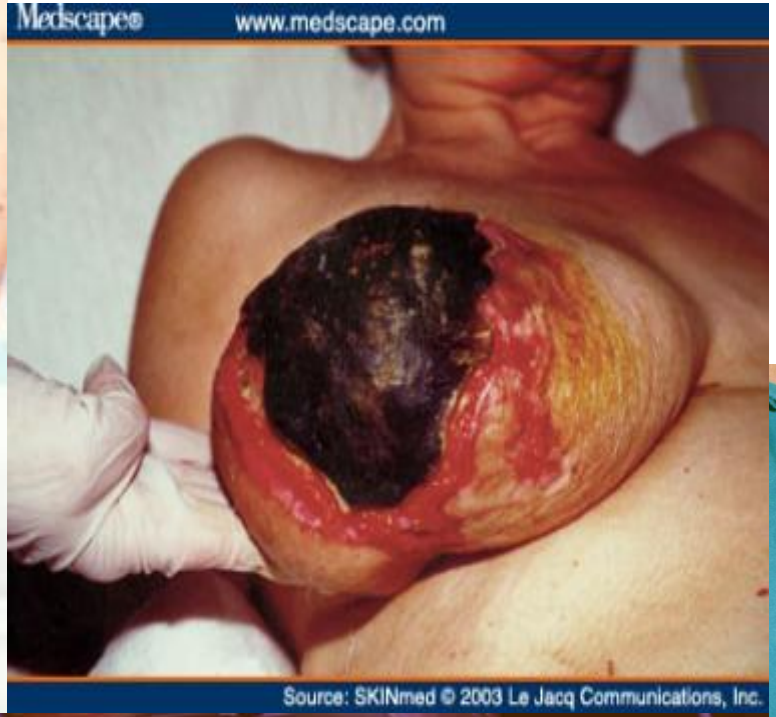
- Paresthesia is present initially and is followed by a painful, well- circumscribed, edematous, and erythematous plaque resembling peau d'orange with purpura.

- Large blood-filled blisters that rapidly break down, accompanied by progressive necrosis of the underlying dermis and subcutaneous fat, are later sequelae.

- Tissue destruction is often considerable and the resultant scarring is very disfiguring.

- Occasionally, the onset of this condition is delayed for weeks or months although in most instances this reflects an interrupted therapeutic regimen.

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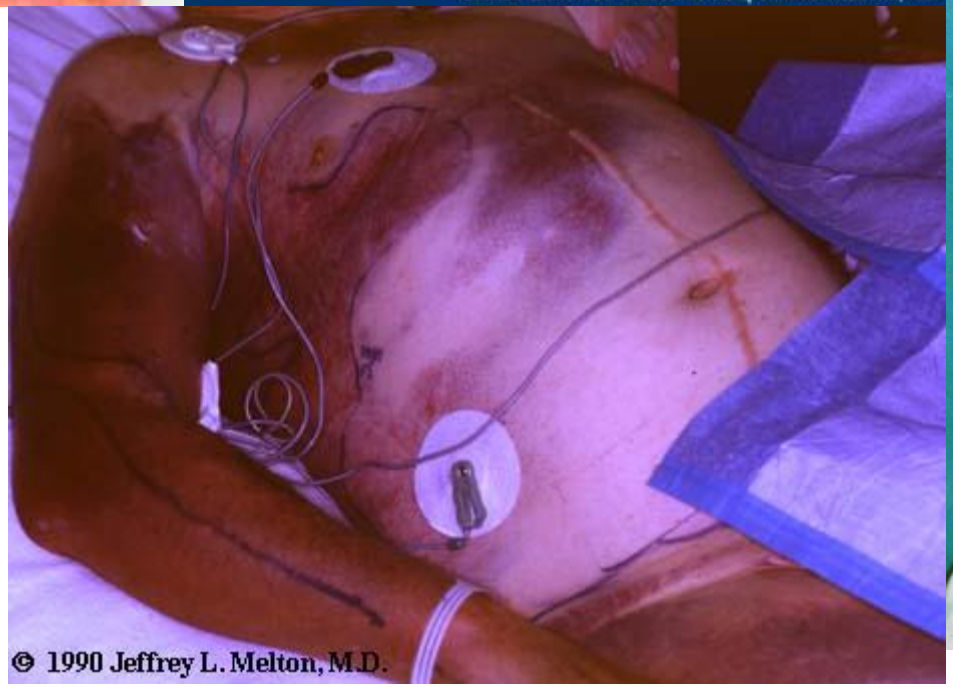
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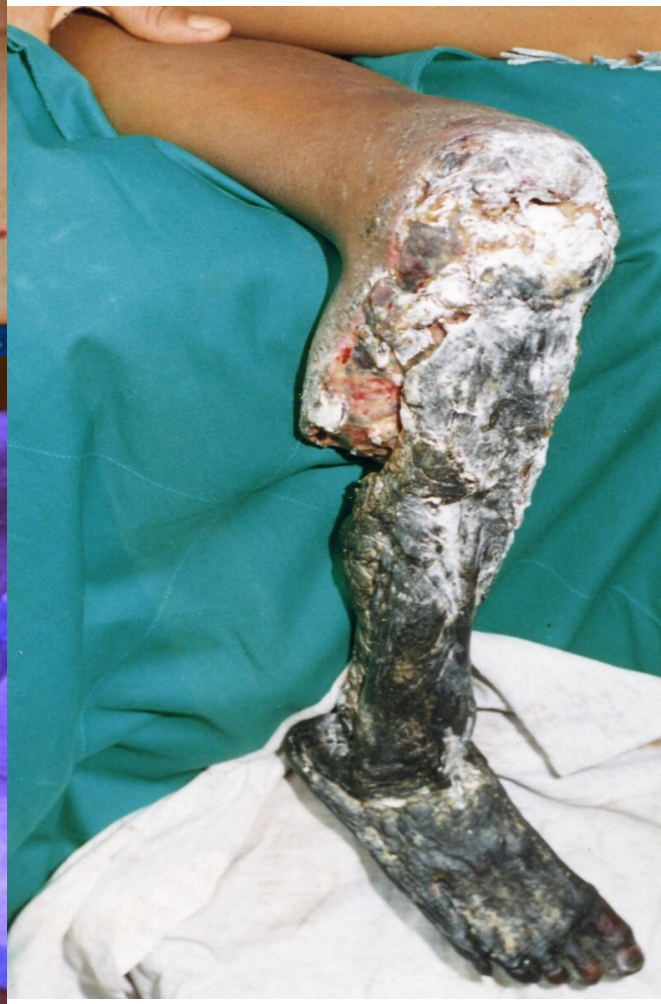

Histopathology

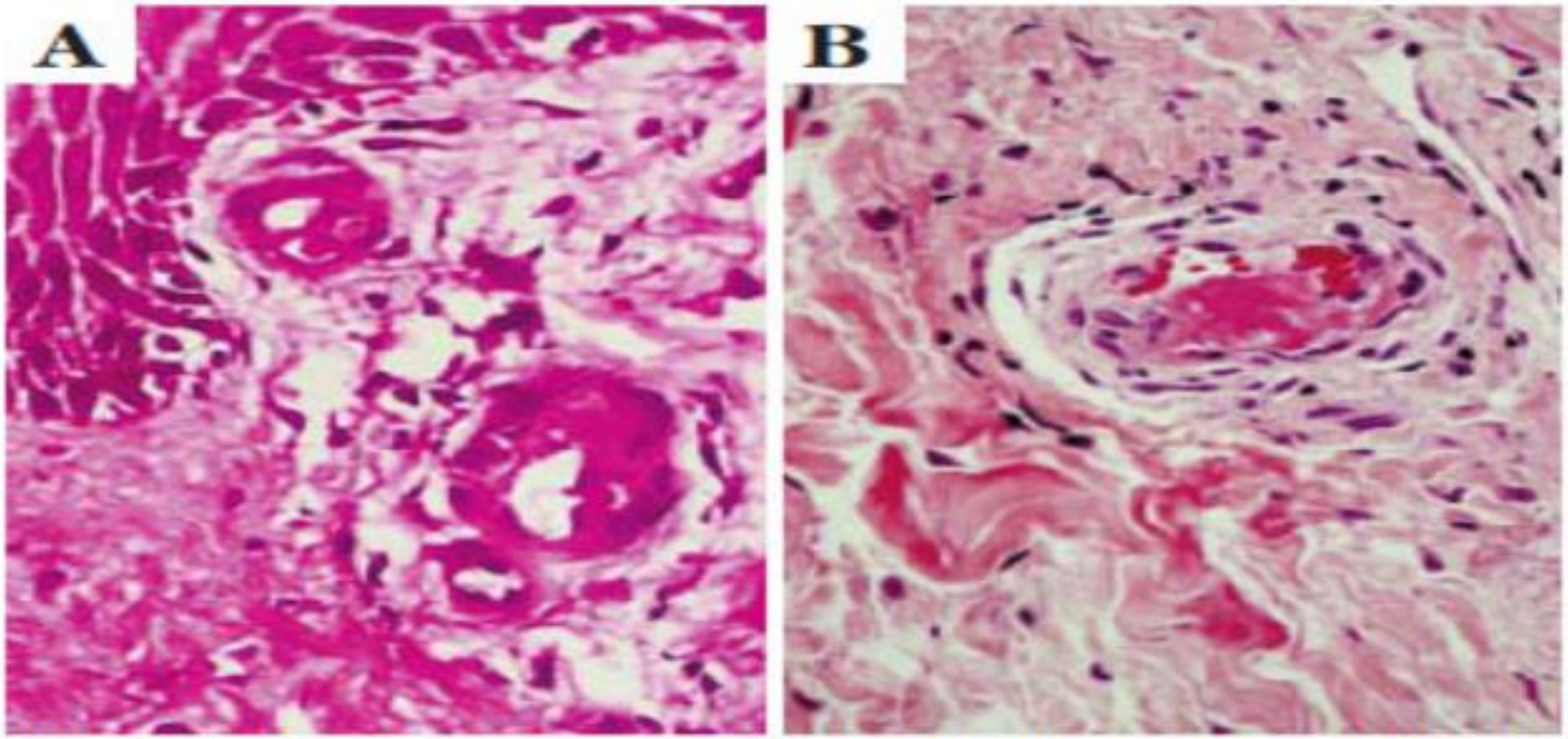

FIGURE 6: In (A), we observe papillary dermis vessels occluded by thrombi and hyalinized wall, in addition to perivascular edema (HE, 400x). In image (B), the occluded vessel shows fibrin and red blood cells in the thrombus, with slight perivascular lymphomononuclear infiltration (HE, 400x)

Table I. Clinical mimics of warfarin-induced skin necrosis

	Features of mimics	Features of WISN
Purpura fulminans	Children, shock, fever, gangrene	Middle-aged women, afebrile, aseptic
Necrotizing fasciitis	Purulent culture-positive wound, rapidly progressive	Nonpurulent wound, nonconfluent, often multiple sites of cutaneous involvement
Calciphylaxis	Calcium deposits in dermis and subcutaneous vessels highlighted by von Kossa stain, patients with end-stage renal disease on hemodialysis	No perivascular or dermal calcification, no association with underlying kidney disease
Cryoglobulinemia (types II and III)	Leukocytoclastic vasculitis, history of lymphoproliferative, autoimmune, or infectious disorder, elevated cryocrit, positive ANA	No primary vasculitis, no association with underlying disorder
Cholesterol microemboli	Intravascular cholesterol clefts, usually involves toe	No cholesterol deposits, usually involves thighs, buttocks, breasts
Decubitus ulcer	Chronic lesion overlying bony protuberance, history of inactivity	Acute onset, involvement of areas of increased subcutaneous fat, history of thrombus
Inflammatory breast carcinoma	Carcinoma on tissue biopsy specimen	Diffuse thrombotic vasculopathy

Treatment

- WISN is a rare but serious complication of warfarin therapy, associated with high morbidity and mortality rates, and often requires surgical intervention.

- Early recognition has important implications for treatment and reduction in severity of complications.

- Withhold the drug
- Prothrombin concentrates
- FFPs
- Vitamin K injection
- Protein C and S concentrates
- Surgical intervention

- It is suggested that a 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 electively anticoagulated

- Patients known to be at risk of WISN (those with a previous episode, protein C or S deficiency and antiphospholipid antibodies) should also be warfarinised in this gradual way

- Conventional heparin and low molecular weight heparin act by a different mechanism than warfarin, so these drugs can also be used to prevent clotting during the first few days of warfarin therapy and thus prevent warfarin necrosis (this is called ‘bridging’).

- Since the clot-promoting effects of warfarin are transitory, patients with protein C deficiency or previous warfarin necrosis can still be re-started on these drugs if appropriate measures are taken.

- These include gradual increase in dosage of warfarin starting from low dose, and supplemental administration of protein C (pure or from fresh frozen plasma), if required

- Direct thrombin inhibitors such as rivaroxaban, apixaban, dabigatran have been found to be equally potent as warfarin with decreased incidences of intracranial bleed, reduced need of monitoring and no risk of CISN.

Conclusion

- Increased awareness and timely action about this complication may prevent devastating necrotising dermatological complication

THANK YOU