Warfarin-Induced Skin Necrosis in the Presence of Acute Hepatic Injury and May-Thurner Syndrome

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Abstract

Purpose: The purpose of the report is to describe a patient with warfarin-induced skin necrosis in the presence of acute hepatic injury and significant risk factors for venous thromboembolism, including protein C deficiency and May-Thurner syndrome. **Summary:** A 44-year-old female with multiple comorbidities presented to the emergency department with a significantly elevated international normalized ratio (INR > 15.9) rapidly reversed with vitamin K and fresh frozen plasma. Due to the findings of bilateral acute on chronic deep vein thromboses (DVTs) and suspected warfarin-induced skin necrosis, a heparin infusion was initiated but later discontinued due to endogenous partial thromboplastin times (PTT) elevations despite dose reductions. Although the necrosis encompassed large areas of the fatty tissue, the depth of necrosis remained mostly superficial. Supportive care and wound management were provided following warfarin reversal; no skin grafts or amputations were performed. **Conclusion:** A 44-year-old female developed a complicated probable warfarin-induced skin necrosis in the setting of acute liver failure, septic shock, May-Thurner syndrome, previously failed anticoagulation, and acute deep vein thrombosis.

Keywords

warfarin-induced skin necrosis, warfarin, skin necrosis, anticoagulation, May-Thurner syndrome, protein C deficiency, venous thromboembolism, cardiology

Introduction

Warfarin-induced skin necrosis (WISN) is a rare condition occurring in 1 in 10,000 to 100,000 patients taking warfarin.^{1–3} Females are at an increased risk of WISN as the female to male ratio of the disease is 4:1.³ Warfarin-induced skin necrosis is characterized by the formation of necrotic tissue developing most commonly in the microvasculature of fatty tissues in the breast, thighs, abdomen, and buttocks. The necrosis is proposed to be caused by decreased blood flow to adipose tissue.³ Although the condition is rare, it is reported to be most common in patients who are female, middle aged or perimenopausal, obese, or have a protein C or S deficiency.^{1,2,4} Symptoms of WISN often occur within 1 to 10 days of initiating warfarin, but have been reported after years of therapy.² Prior to formation of erythematous lesions or necrotic skin, patients may have pain, irritation, edema, or paresthesia at the affected site.² Differential diagnoses include heparin-induced thrombocytopenia and thrombosis (HITT), disseminated intravascular coagulation (DIC), purpura fulminans, necrotizing fasciitis, calciphylaxis, cholesterol microemboli, and cryoglobulinemia.²

The pathogenesis of WISN is not well understood. It has been proposed that WISN may be precipitated by an imbalance of the coagulable factors inhibited by warfarin through its antagonism of vitamin K.² It is described as a paradoxical prothrombotic state after an initial decrease in vitamin K-dependent clotting factors.^{3,5} This can lead to an interruption of blood flow from the formation of microthrombi that may cause necrosis.⁵ Protein C levels and activity seem to drop more rapidly than other factors following administration of warfarin.¹ For this reason, deficiencies in protein C and S have been proposed as major risk factors for the development of WISN.^{1,2,4,6} Becker proposed in 1987 that protein C deficiency was seen in multiple cases of WISN and may be an important factor in its development.⁷ Protein S is a cofactor that activates protein C and has also been described in the

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literature to cause WISN in the setting of warfarin therapy in some cases.^{1,2} Large loading doses of warfarin, failure to appropriately bridge with heparin products, infection, trauma, surgery, cancer, and thrombosis have also been proposed to increase the risk of WISN.^{1,2,6,7}

Consensus clinical guidelines do not exist for the management of WISN. Treatment includes discontinuation of warfarin, supportive care, surgical debridement of necrotic tissue, aggressive wound care, and topical bactericidal agents.^{1,2,5} Surgical debridement with or without skin grafting, mastectomy, or amputation have been reported in more than half of the cases.² Systemic antibiotics may be of benefit, but may further inhibit vitamin K–dependent clotting factors.² The primary mechanism for increased risk of bleeding with antibiotics is due to interference with intestinal flora involved in the formation of vitamin K and inhibition of cytochrome P450 enzymes involved in the metabolism of warfarin.⁸ Systemic corticosteroids or vasodilators have not been found to be effective.⁵ Heparin may be an option for patients with WISN to prevent additional venous thromboembolism (VTEs). Administration of fresh frozen plasma (FFP) or protein C concentrates have been attempted in the treatment of patients with a protein C deficiency to restore levels.^{1,2} A monoclonal antibody purified protein C concentrate has also been utilized for treatment of WISN.⁹ Restarting warfarin therapy for anticoagulation following recovery of WISN has been successful; however, it may precipitate reoccurrence of necrosis.^{1,2} Warfarin-induced skin necrosis may be prevented by avoiding loading doses of warfarin and bridging with injectable anticoagulants for a minimum of 5 days.²

Case Report

A 44-year-old obese female with a history of nonischemic cardiomyopathy, systolic congestive heart failure (HFrEF) with an ejection fraction of <25%, chronic deep vein thrombosis (DVT) requiring anticoagulation due to May-Thurner syndrome, and iron deficiency anemia presented to the emergency department.

The patient was previously treated for cholecystitis and community-acquired pneumonia. Warfarin therapy was initiated at the time for treatment of chronic DVT with an enoxaparin bridge. Antibiotics were administered concomitantly with warfarin during hospitalization with daily monitoring and pharmacist-managed adjustments. Warfarin was chosen as a result of previously reported failure of rivaroxaban therapy and noncompliance to enoxaparin over the last 2 years due to medication cost. The patient was discharged after 10 days with a therapeutic international normalized ratio (INR) and instructed to take 4 mg of warfarin by mouth daily. Concomitant home medications were evaluated for drug-drug interactions with outpatient follow-up for warfarin management. The patient presented to her primary care provider for her follow-up after discharge and complained of tingling and pain located in her thighs. The patient's INR was

Figure 1. Hospital day 1, mottled bilateral lower extremities.

drawn at the visit and she was instructed to continue her warfarin dose that evening, as her labs had not resulted prior to her leaving the office. When the INR of 4.9 resulted the following day, the provider contacted the patient and instructed her to stop warfarin. Based on the discussion with the patient's family, the patient was compliant at home with warfarin therapy. The patient presented later that same day to our emergency department with increased swelling and leg pain.

On admission, the physical exam revealed purple discoloration of her bilateral lower extremities (Figure 1), a large ulcer to the left lateral thigh with darkening and mottling of the skin to the bilateral proximal thighs, and clear fluid-filled bullae to the proximal left leg wrapping around to the patient's back. Prior to admission, the patient's family did not note any signs of rash. The patient presented with an elevated INR (>15.9) and was treated with vitamin K 10 mg intramuscular once and 6 units of FFP. Elevated liver function tests (aspartate aminotransferase [AST]: 5188 IU/L, alanine aminotransferase [ALT]: 1373 IU/L, ALP) were also present on admission. The patient's initial liver dysfunction was presumably caused by cholelithiasis, as identified on computed tomography (CT). She quickly decompensated and required intubation and vasopressor therapy. The skin became denuded, affecting the breasts, abdomen, upper thighs, and legs. There was a hard-necrotic area noted on the lateral aspect of the left thigh and peeling of the other affected areas. Necrotizing fasciitis was initially suspected, but was subsequently ruled out, due to lack of abscess or soft tissue air seen on CT. Necrotic areas of the bilateral lower extremities (Figure 2) continued to extend to the upper aspects of the medial, posterior thighs, buttocks, abdomen, and bilateral breasts. Warfarin-induced skin necrosis was suspected due to the patient's presentation and recent warfarin initiation. Debridement was considered but not completed due to the superficial nature of the wounds. The necrosed areas were covered with vaseline gauze. On hospital day 6, the patient experienced asystole requiring cardiopulmonary resuscitation (CPR) and was resuscitated. A Doppler ultrasound of the legs revealed bilateral acute on chronic DVTs, and a pulmonary embolism was suspected as a possible cause of the arrest. The patient was

Figure 2. Hospital day 7, necrotic areas of the bilateral lower extremities.

placed on continuous infusion heparin for the treatment of the bilateral DVTs, possible pulmonary embolism (PE). Unfractionated heparin therapy was complicated by her bilirubin level of 28.15 as it interfered with anti-Xa assays. In addition, her baseline partial thromboplastin times (PTT) were elevated. The patient intermittently received continuous renal replacement therapy (CRRT) throughout admission due to acute renal failure and severe acidosis. The protein C activity level was 42%, representing a deficiency, despite receiving FFP. Protein S activity was 88% in 2015 in the setting of low protein C deficiency (67%) and, therefore, was not repeated during this admission. Surgical intervention of the necrotic tissues was not indicated. Wound healing did not improve throughout admission despite attempts at aggressive wound care, likely due to underlying comorbidities of May-Thurner syndrome and systolic heart failure (left ventricular ejection fraction <25%), both compounded by her acute illness. An acute heart failure exacerbation was not noted in the presentation of the patient. The patient was not a candidate for further vascular intervention for May-Thurner syndrome due to occluded iliac vein stents, cardiomyopathy, and previous mechanical intervention attempts. Unsuccessful attempts to transfer the patient to a burn center were made for optimal wound care. Over the course of her hospital stay, she suffered additional complications, such as septic shock due to pneumonia, increasing clot burden, and acute renal failure. The patient briefly recovered, was able to be extubated, and was weaned from vasopressor support. However, she later decompensated and expired due to septic shock and severe cardiomyopathy, despite multiple courses of broad-spectrum antibiotics. Her hospital stay totaled 19 days. Lab values throughout admission can be found in Table 1.

Discussion

Warfarin-induced skin necrosis is the most likely diagnosis based on the clinical findings including skin presentation with necrosis in fatty tissue, supratherapeutic INR on

admission, and recent initiation of warfarin therapy. The patient had WISN risk factors described in the literature, including female gender, middle age, obesity, and protein C deficiency. The patient reported pain and paresthesias in her thighs prior to the onset of necrosis, which is a common symptom preceding the onset of WISN.² The location of the necrosis on the breasts, abdomen, upper thighs, and legs are consistent with WISN. A Naranjo score was calculated to be 7, which indicates probable cause that the suspected drug led to the clinical adverse event.¹⁰ The absence of mottling in her toes and fingers effectively rules out global ischemia and hypotension as the etiology. Although most WISN cases present 1 to 10 days after initiation of therapy, there have been case reports presenting longer than 10 days after warfarin initiation.² A skin biopsy was not performed in this patient. The cause of the patient's liver dysfunction is unknown; however, contributing factors included cholelithiasis, recent acute cholecystitis, or ischemic hepatitis. Liver dysfunction and consumption of clotting factors due to formation of microemboli within the vasculature likely contributed to the patient's supratherapeutic INR of >15.9. Although vitamin K was given intramuscularly due to this supratherapeutic INR, intramuscular administration of vitamin K is not the preferred route of administration due to increased risk of muscle hematoma.¹¹ Acute hepatic dysfunction is known to disrupt synthesis of clotting factors, specifically protein C, which decreases more rapidly than other vitamin K-dependent factors.⁹ Because WISN is suggested to be caused by an imbalance of clotting factors including protein C, the patient's acute hepatic dysfunction may have contributed to the development of WISN.^{3,5} In a previous case report, a patient with cholecystitis presented with 3 episodes of skin necrosis. The last episode occurred without warfarin administration and was proposed to be due to decreased vitamin K clotting factors related to cholestasis.¹² In addition to our patient's liver dysfunction and current warfarin therapy, recent cholecystitis may have increased her risk of WISN.

Our patient had marginal protein C deficiency approximately 2 years prior to presentation (protein C activity 67%), and was lower during the current admission at 42%. Other factors contributing to protein C deficiency included infection, liver failure, sepsis, and trauma.^{4,13} The diagnosis of protein C deficiency may be supported by low levels, in spite of administration of FFP. The presence of May-Thurner syndrome could have increased the risk of WISN in our patient due to abnormal compression of the iliac vein, further impairing blood flow to her thighs.¹⁴ The venous compression results in an increased risk of DVTs, pelvic congestion syndrome, and varicose veins.¹⁴

The patient in our case report received a substantial amount of clotting factors, including protein C, within the 6 units of FFP administered on admission. The FFP may have helped decrease the extent of the necrosis.¹⁵ Activated protein C was not considered or given due to repletion with FFP. A monoclonal antibody purified protein C concentrate

Table 1. Lab Results During Hospital Admission.

Hospital day	Admission	1	2	3	4	5	6	7	14	19
AST (IU/L)	5188	3907	3186	1860	917	483	273	184	100	353
ALT (IU/L)	1373	1112	1201	917	650	550	421	375	94	87
ALP (IU/L)	279	198	221	223	221	233	230	221	200	284
Bilirubin (mg/dL)	6.00	4.95	10.02	15.74	22.78	26.95	28.15	26.21	16.71	6.56
CK (IU/L)	2225	—	—	—	—	—	—	184	—	—
CK-MB (ng/mL)	50.34	—	—	—	—	—	—	2.07	—	—
BNP (pg/mL)	35754	—	—	—	—	—	—	—	—	—
WBC (thous/ μ L)	25.8	21.6	21.2	20.6	25.7	22.3	19.2	15.3	31.4	26.6
Platelets (thous/ μ L)	222	155	133	119	126	119	—	—	104	33
INR	>15.9	2.7	4.3	2.3	2.1	1.8	2.1	2.7	1.5	3.7
Protein C activity reflex (%)	—	—	—	—	—	—	—	—	—	—
PCT (ng/mL)	31.00	—	12.34	—	9.61	—	—	—	15.54	10.97

Note. AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; CK = creatine kinase; CK-MB = creatine kinase–muscle/brain; BNP = brain natriuretic peptide; WBC = white blood cell count; INR = international normalized ratio; PCT = procalcitonin.

was not utilized in the treatment of this patient. Heparin therapy was not started initially in this patient due to anemia, elevated INR, and high risk of bleeding on admission. Heparin therapy was attempted but PTTs continued to increase despite dose reductions and therapy was ultimately discontinued. After discontinuation, PTTs remained elevated.

Chronic treatment options for our patient would be limited due to failed anticoagulation with rivaroxaban, proposed WISN with warfarin, and previous compliance issues with enoxaparin due to cost. The patient's organ dysfunction would further limit optimal agents. In the setting of improved renal function and measures to ensure medication accessibility, low molecular weight heparin may be the preferred therapy option. The patient eventually expired due to septic and cardiogenic shock. Her extensive leg wounds and pneumonia were likely sources of infection, in spite of broad-spectrum antimicrobial coverage.

Conclusion

Although WISN has been reported in the literature, it has not been reported in the presence of acute liver failure and septic shock. Both of these conditions are known to cause imbalances in clotting factor production and may have played a role in the formation and recovery process of WISN in the patient case presented.¹⁶ This case can assist clinicians with helpful insight to various treatment approaches to WISN in the setting of a decompensated patient with multiple comorbidities and imbalances.

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References

1. Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin-induced skin necrosis. *Br J Surg*. 2000;87(3):266-272.
2. Nazarian RM, Van Cott EM, Zembowicz A, Duncan LM. Warfarin-induced skin necrosis. *J Am Acad Dermatol*. 2009;61(2):325-332.
3. Kakagia DD, Papanas N, Karadimas E, Polychronidis A. Warfarin-induced skin necrosis. *Ann Dermatol*. 2014;26(1):96-97.
4. Teepe RG, Broekmans AW, Vermeer BJ, Nienhuis AM, Loeliger EA. Recurrent coumarin-induced skin necrosis in a patient with an acquired functional protein C deficiency. *Arch Dermatol*. 1986;122(12):1408-1412.
5. Biscoe AL, Bedlow A. Warfarin-induced skin necrosis diagnosed on clinical grounds and treated with maggot debridement therapy. *BMJ Case Rep*. 2013;1-5.
6. Coumadin® (warfarin sodium) oral tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
7. Becker CG. Oral anticoagulant therapy and skin necrosis: speculations on pathogenesis. *Adv Exp Med Biol*. 1987;214:217-222.
8. Baillargeon J, Holmes HM, Lin Y, Raji MA, Sharma G, Kuo Y-F. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med*. 2012;125(2):183-189.
9. Schramm W, Spannagl M, Bauer KA, Rosenberg RD, Birkner B, Linnau Y, Schwarz HP. Treatment of coumarin-induced skin necrosis with a monoclonal antibody purified protein C concentrate. *Arch Dermatol*. 1993;129(6):753-756.

10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239-245.
11. Sankar MJ, Chandrasekaran A, Kumar P, Thukral A, Agarwal R, Paul VK. Vitamin K prophylaxis for prevention of vitamin K deficiency bleeding: a systematic review. *J Perinatol.* 2016;36 (suppl 1):S29-S35. doi:10.1038/jp.2016.30.
12. Hofmann V, Frick PG. Repeated occurrence of skin necrosis twice following coumarin intake and subsequently during decrease of vitamin k dependent coagulation factors associated with cholestasis. *Thromb Haemost.* 1982;48(3):245-246.
13. Walker FJ. Protein C deficiency in liver disease. *Ann Clin Lab Sci.* 1990;20(2):106-112.
14. Lugo-Fagundo C, Nance JW, Johnson PT, Fishman EK. May-Thurner syndrome: MDCT findings and clinical correlates. *Abdom Radiol (NY).* 2016;41(10):2026-2030.
15. Pourdeyhimi N, Bullard Z. Warfarin-induced skin necrosis. *Hosp Pharm.* 2014;49(11):1044-1048.
16. Dhainaut JF, Marin N, Mignon A, Vinsonneau C. Hepatic response to sepsis: interaction between coagulation and inflammatory processes. *Crit Care Med.* 2001;29(suppl 7):S42-S47.