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Case Report

Chronic recurrent warfarin-induced skin necrosis in a patient with a mechanical mitral valve: a diagnostic mimic of pyoderma gangrenosum

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ABSTRACT

Warfarin-induced skin necrosis (WISN) is a rare but potentially life-threatening complication of warfarin therapy, often presenting within the first few days of initiation. It is more commonly seen in patients with underlying protein C or S deficiencies. We report the case of a 60-year-old female with a history of rheumatic heart disease who underwent mitral valve replacement (MVR) and was on Acitrom (acenocoumarol) as long-term anticoagulation prophylaxis. She presented with chronic, recurrent painful skin lesions involving the right lower limb, buttocks, and bilateral axillae. These lesions evolved from hyperpigmentation to ulcerative necrosis over a span of two years. Laboratory investigations revealed deranged coagulation parameters, and histopathological examination confirmed the diagnosis of WISN. Upon clinical suspicion, Acitrom was promptly discontinued, and the patient was switched to low molecular weight heparin. Aggressive wound care, including daily dressings and debridement, was initiated. The patient's condition gradually improved, and the necrotic lesions began to heal. This case highlights the importance of early recognition and prompt intervention in managing WISN. Timely discontinuation of warfarin and initiation of heparin therapy, along with supportive wound care, are crucial for favourable outcomes. This condition underscores the need for close monitoring of anticoagulation therapy and early diagnosis to prevent irreversible damage.

Keywords: Warfarin-induced skin necrosis, Anticoagulation, Chronic skin ulcer, Wound management, Mechanical heart valve, Cutaneous adverse drug reaction

INTRODUCTION

Warfarin is a widely prescribed oral anticoagulant, commonly used to prevent and treat thromboembolic disorders, such as deep vein thrombosis and pulmonary embolism, as well as in patients with prosthetic heart valves. WISN is a rare but potentially devastating complication, with an estimated incidence of 0.01% to 0.1% among patients receiving warfarin.[1] It typically presents within 3 to 10 days of initiating therapy, often beginning as painful, erythematous, purpuric lesions that evolve into hemorrhagic bullae and full-thickness necrosis, predominantly affecting adipose-rich areas such as the breasts, thighs, buttocks, and flanks.[1-3]

Pathogenesis is attributed to a paradoxical hypercoagulable state caused by early and rapid depletion of protein C, an anticoagulant with a short half-life relative to procoagulant vitamin K-dependent clotting factors.[1] This imbalance predisposes patients to microvascular thrombosis and subsequent skin necrosis. Risk factors include protein C/S deficiency, antithrombin III deficiency, female sex, obesity, and high initial warfarin doses.[2] While most cases are acute and resolve after prompt discontinuation of the anticoagulant, chronic or recurrent forms of WISN are exceedingly rare. These atypical presentations may be misdiagnosed as other dermatologic/vasculitic conditions such as pyoderma gangrenosum, necrotizing fasciitis or cutaneous vasculitis, potentially delaying appropriate treatment.[1]

We present a rare case of chronic, recurrent WISN in a 60-year-old woman with a mechanical mitral valve on long-term acenocoumarol therapy. Initially misdiagnosed as pyoderma gangrenosum, her condition was marked by recurrent necrotic ulcerations over two years, likely triggered by irregular anticoagulation and fluctuating international normalized ratio (INR) levels. This report underscores the importance of maintaining a high index of suspicion for WISN in patients with non-healing skin ulcers on vitamin K antagonists and highlights the diagnostic value of detailed anticoagulation history and early tissue biopsy.

CASE REPORT

A 60-year-old postmenopausal woman presented to the outpatient department with multiple painful, chronic skin lesions involving the right lower limb, right buttock, and bilateral axillae. She reported a gradually progressive course of skin involvement beginning two years prior, initially presenting as hyperpigmentation over the right leg that evolved into blistering lesions. These blisters eventually ruptured spontaneously, discharging serosanguineous fluid and leaving behind a chronic, non-healing ulcer on her right foot. Over time, she developed similar darkening and ulceration over her right knee, right and left axillae, and the right buttock, in that order.

Her medical history was significant for MVR performed 15 years ago for rheumatic heart disease. Since then, she had been prescribed variable doses of Acitrom (acenocoumarol) as long-term anticoagulation prophylaxis, but as per available medical records and family account, she had been taking it inconsistently and for a variable duration over the years. She also had T2DM for the past 3 years, controlled on oral hypoglycemics.

She gave a history of multiple prior hospital admissions over the past two years for similar complaints of skin ulceration, primarily involving the right lower limb. During these episodes, she had received multiple blood transfusions to manage persistent severe anemia, with hemoglobin levels consistently found to be low. Despite symptomatic treatment, the lesions would only partially improve and frequently recurred, prompting the current referral for comprehensive evaluation.

She denied any symptoms of fever, weight loss, systemic infection, or prior thrombotic events. There was no history of similar lesions in the family, no known connective tissue disorders, and no history of tobacco use or alcohol consumption.

Two months prior to her current presentation, she had undergone ayurvedic treatment for her skin ulcers without significant benefit.

On presentation to the medical intensive care unit (MICU), she complained of worsening pain and reduced range of motion in joints near the ulcerated skin regions. Physical examination revealed pallor, a blood pressure of 100/70 mmHg, pulse rate of 82 beats per minute, and an oxygen saturation of 98% on room air. Her random blood sugar was 214 mg/dL. The affected skin areas exhibited violaceous discolouration with ulceration, surrounding induration, and serous discharge. No crepitus or signs of systemic sepsis were present.

Initial laboratory investigations are shown in (Table 1). Her peripheral smear suggested dimorphic anemia. Coagulation studies showed a prolonged PT and aPTT on admission, which normalised over the next 12 days following cessation of Acitrom, as shown in (Table 2).

Table 1: Initial laboratory investigations.

Test	Result	Reference range	Unit
Hemoglobin	5.6	11.5-16.0	gm%
Total leucocyte count	10490	4000-11000	cumm
Platelet count	6.46	1.5-4.5	lakhs/cumm
ESR	35	0.0-20.0	mm/hr
Serum iron	8.36	37-158	µg/dL
Ferritin	14.6	30-400	ng/mL
Transferrin saturation	8.5	16-45	%
Albumin	2.0	3.5-5.2	g/dL
LDH	305	10-250	IU/L
HbA1c	5.8	4.8-5.6	%

Table 2: Coagulation profile.

Day	Partial thromboplastin time (aPTT)		Prothrombin time (PT)		INR
	Control (sec)	Test (sec)	Control (sec)	Test (sec)	
Day 1	32.7	52.0	14.0	28.4	2.32
Day 6	32.7	34.5	14.0	19.1	1.45
Day 9	32.7	29.8	14.0	15.0	1.09
Day 12	32.7	30.0	14.0	12.8	0.90

Microbiological cultures from wound swabs of the right foot grew *Klebsiella* spp., sensitive only to tigecycline and fosfomycin. Blood culture and sensitivity showed normal skin flora. Urine culture and sensitivity yielded no growth. Stool occult blood was negative.

Imaging studies included chest x-ray and an x-ray of the right foot (Figure 1).

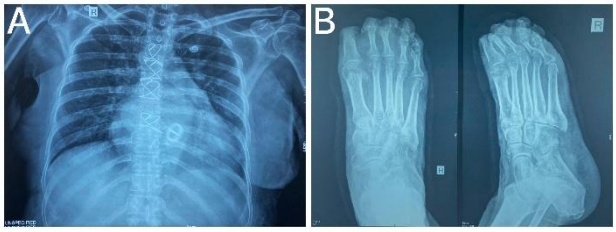

Figure 1 (A and B): Imaging studies.
(A) Chest X-ray: Cardiomegaly with ventricular configuration, sternotomy wiring *in situ*, and a radiopaque prosthetic valve. Lung fields appeared normal. (B) X-ray of the right foot: Osteopenia with destruction of distal phalanges of the great, second, and third toes; diffuse soft tissue swelling.

Skin punch biopsies were obtained from multiple sites to assess the nature of the cutaneous lesions.

Buttock biopsy

Two separate pathology reports were generated from 1 mm skin punch biopsies taken from the right buttock (Figure 2). A second report was requested due to diagnostic uncertainty and to obtain an additional opinion.

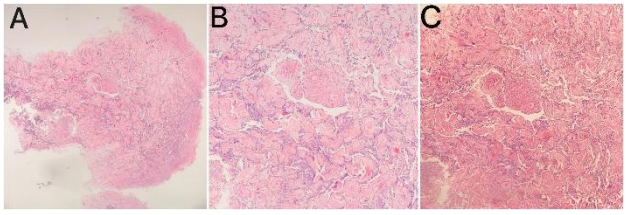

Figure 2 (A-C): Histological examination of a skin biopsy from the right buttock at increasing magnifications (H and E stain).
All panels demonstrate total epidermal ulceration with a dense neutrophilic exudate, and the dermis exhibits multiple pockets of neutrophilic aggregates with foci of fibrinoid necrosis involving blood vessels. (A) Low power: Provides a broad overview of the biopsy, highlighting the overall architecture and extent of epidermal ulceration (B) Intermediate power: Offers a closer look at the inflammatory infiltrate and details of vascular involvement. (C) High power: Reveals cellular morphology in detail, emphasizing areas of fibrinoid necrosis.

Report 1

The biopsy revealed complete ulceration of the epidermis with an overlying neutrophilic exudate. The dermis demonstrated pockets of fibrinoid necrosis and necrobiotic collagen surrounded by a neutrophil-rich inflammatory infiltrate. These features were suggestive of pyoderma gangrenosum.

Report 2

Sections showed total epidermal ulceration with dense neutrophilic exudate. The dermis contained multiple pockets of neutrophilic aggregates along with foci of fibrinoid necrosis involving blood vessels.

Impression

Features consistent with an acute inflammatory process with fibrinoid necrosis.

Right arm biopsy

A 1 mm skin punch biopsy from the right arm showed features of post-inflammatory fibrosis. The epidermis displayed acanthosis, while the dermis revealed densely packed parallel collagen fibres and a perivascular mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and a few eosinophils.

Autoimmune workup including anti-nuclear antibody (ANA) and anti-cardiolipin antibodies were unremarkable. Complement C4 was within normal range, but Complement C3 was mildly decreased at 77 mg/dL (reference range: 90-180 mg/dL). Protein C and protein S levels were also within normal range, ruling out hereditary deficiencies.

Given the clinical history of anticoagulation with warfarin, progression of skin necrosis over fat-rich areas, histological evidence of fibrinoid necrosis, and the absence of an alternative vasculitic or autoimmune etiology, a diagnosis of WISN was made.

Acitrom was discontinued. Based on cardiology consultation, the patient was initiated on low molecular weight heparin at a dose of 3000 IU three times daily (TID) on day 7, which was escalated to 5000 IU on day 10. Additional treatment included broad-spectrum antibiotics (piperacillin-tazobactam, metronidazole, tigecycline), 3 units of packed red blood cells, short-acting insulin, analgesics (paracetamol, aceclofenac, tramadol), proton pump inhibitors, lactulose, diuretics, and probiotics. Daily local wound care involved dressings with papain-urea debriding ointment, mupirocin and bromelain ointment, and 0.01% silver nitrate solution.

Gradual improvement in skin lesions and stabilization of lab parameters was noted over subsequent days. Serial gross clinical images were obtained from the right foot, leg, knee, buttock, right axilla, and left axilla over the period of several weeks (Figure 3-7).

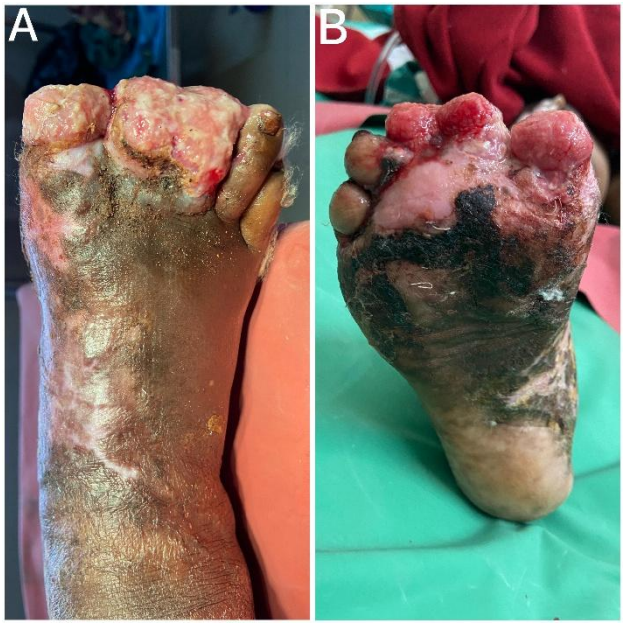

Figure 3 (A and B): Right foot-clinical progression at day 1 and 6.

(A) Day 1: Dorsal view showing severe tissue necrosis and ulceration involving the toes. (B) Day 6: Plantar view illustrating extensive ulceration, black eschar, and underlying tissue exposure.

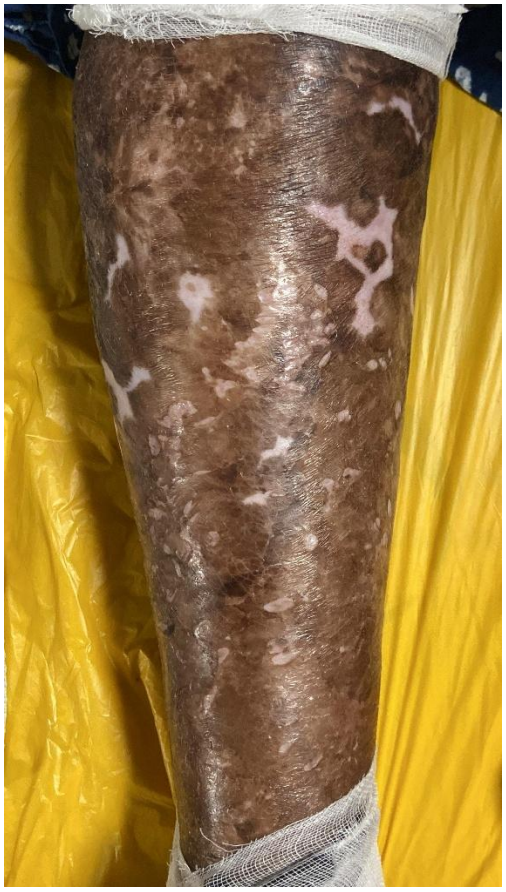

Figure 4: Right leg-presentation at day 1.

Clinical photograph of the right lower leg revealing patchy loss of pigment and irregular hyperpigmented areas.

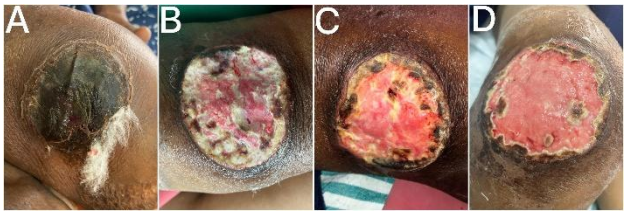

Figure 5 (A-D): Right knee-sequential follow-up images on day 1, day 6, day 11, and day 25.

Serial images demonstrating progressive debridement, with reduction in necrotic tissue and gradual emergence of healthy granulation tissue over time in the right knee ulcers.

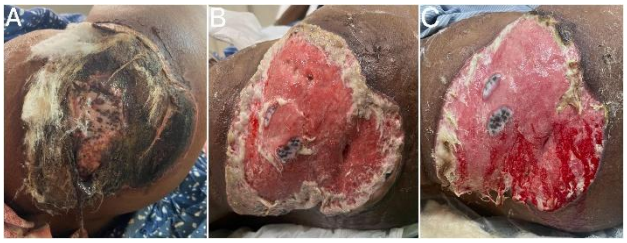

Figure 6 (A-C): Right buttock-sequential clinical progression on day 1, day 11, and day 25.

(A) Day 1: Extensive necrotic eschar with underlying induration and black discoloration of right gluteal region, suggestive of full-thickness tissue loss. (B) Day 11: Post-debridement wound bed on the right buttock showing granulation tissue with areas of slough and residual necrotic patches; evidence of early healing phase. (C) Day 25: Further wound progression with a clean granulating bed, reduced necrosis, and signs of epithelialization at the margins, indicating ongoing tissue repair.

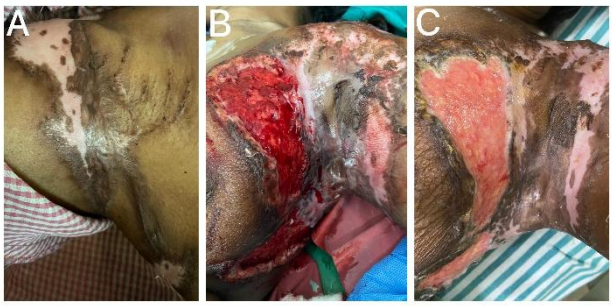

Figure 7 (A-D): Axilla.

(A) Right axilla-presentation on day 1: Right axillary wound with irregular margins, necrotic tissue, and an erythematous base; early inflammatory phase with evidence of tissue destruction. (B) Left axilla on day 6: Left axillary wound showing exposed subcutaneous tissue with mixed necrotic and granulation tissue; surrounding skin exhibits erythema and desquamation. (C) Left axilla on day 15: Improvement in the left axillary wound with well-defined granulation tissue, decreased slough, and peripheral epithelialization; indicative of transition into the proliferative phase of healing.

DISCUSSION

Coumarin-based oral anticoagulants (COAs), including warfarin and acenocoumarol (Acitrom), remain widely used for long-term anticoagulation in conditions such as mechanical heart valves, atrial fibrillation, and venous

thromboembolism. While warfarin is the preferred agent in the Western world, Acitrom is more frequently used in India. These drugs have a narrow therapeutic index, and their metabolism is influenced by several genetic and environmental factors, resulting in significant inter-individual variability in response. Advances in pharmacogenetics have revealed that polymorphisms in genes such as CYP2C9 and VKORC1 affect the metabolism and sensitivity to COAs, potentially predisposing certain patients to complications like bleeding or thrombotic events during therapy initiation.[4]

WISN is one of the most feared complications of oral anticoagulation and typically manifests within the first few days of therapy. However, our patient presented with a chronic, recurrent form of WISN, developing painful, necrotic ulcerations over a two-year period. This delayed and relapsing presentation is rare and underlines the importance of considering WISN even in patients who have been on long-term anticoagulation, especially when INR fluctuations are frequent and therapy adherence is poor.

The pathophysiology of WISN is complex and primarily related to the paradoxical prothrombotic state that occurs at the onset of therapy. Warfarin rapidly reduces protein C and factor VII levels within 36-48 hours, while the decline in other procoagulant factors like IX, X, and II occurs more gradually. The imbalance between falling anticoagulant and persistent procoagulant activity results in microvascular thrombosis, particularly in subcutaneous venules, leading to ischemia and necrosis of the overlying skin.[5,6] This process predominantly affects areas with abundant subcutaneous fat such as the breasts, thighs, buttocks, and abdomen, where sluggish blood flow and low shear stress further exacerbate thrombus formation.[7,8] The pathology may be multifactorial as others have proposed not only thrombosis but hypersensitivity, capillary haemorrhage and direct toxicity from warfarin.[1,6]

The condition develops mainly in middle-aged women who are perimenopausal and obese.[3] Predisposing factors include protein C deficiency, protein S deficiency, Factor V Leiden mutation, Antithrombin III deficiency, Antiphospholipid antibody syndrome (Anticardiolipin antibody) and lupus anticoagulant.[1] Our patient did not exhibit any identifiable thrombophilic disorders. Nevertheless, intermittent INR monitoring, irregular dosing, and unrecognised pharmacogenetic variability may have contributed to transient hypercoagulable states.[1,4] This supports the idea that WISN may occur even in patients without hereditary thrombophilia, particularly if anticoagulation is not consistently monitored or managed.

Clinically, WISN typically begins with prodromal symptoms such as paraesthesia, localized burning, or erythema, which progress to purpura, petechiae, and eventually large ecchymotic plaques with central necrosis.[1] These changes can mimic a variety of other conditions, making early diagnosis challenging. Differential diagnoses include necrotising fasciitis, vasculitis, pyoderma gangrenosum, purpura fulminans, calciphylaxis, autoimmune skin diseases, acute arterial thrombosis, cellulitis, phlegmasia cerulea dolens, disseminated intravascular coagulopathy, hematoma, venous gangrene, septic and cholesterol emboli, snake venom-induced skin necrosis and even malignancies such as inflammatory breast cancer.[1,5,9] Our patient was initially misdiagnosed with pyoderma gangrenosum, leading to a delay in definitive management. This highlights the importance of maintaining a high index of suspicion for WISN in anticoagulated patients with atypical or non-healing skin lesions.

Histopathological examination remains a valuable diagnostic tool. In early lesions, fibrin thrombi within dermal venules and small-calibre vessels are characteristic, along with subepidermal hemorrhage, necrosis, and a neutrophilic infiltrate.[1] These features were consistently observed in our patient's multiple skin biopsies and played a critical role in redirecting the diagnosis toward warfarin-induced necrosis.

Management of WISN centres on the immediate discontinuation of the offending COA. In patients with a continued indication for anticoagulation, intravenous unfractionated heparin or low molecular weight heparin (LMWH) is the preferred alternative.[5] Our patient showed marked clinical improvement following the discontinuation of Acitrom and initiation of LMWH, supporting the reversibility of WISN when identified early. The approach to warfarin reversal based on INR levels is summarised in (Table 3). Reintroduction of COAs, if required, must be done cautiously, starting at low doses without a loading dose and overlapping with heparin until the INR is in the therapeutic range.[9]

Table 3: Warfarin reversal strategies based on INR levels.

INR	Bleeding status	Recommendation
4.5-10.0	No bleeding	Omit 1-2 doses of warfarin; routine use of vitamin K not recommended. Monitor INR closely.
>10.0	No bleeding	Hold warfarin; give oral vitamin K (2.5-5 mg). Resume warfarin when INR is therapeutic.
Any INR	Serious or life-threatening bleeding	Hold warfarin; give IV vitamin K (5-10 mg) + prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP). Repeat vitamin K every 12 hours if needed.

Table constructed based on recommendations from Holbrook et al, CHEST 2012, and not directly reproduced from the source.[10]

Direct oral anticoagulants (DOACs), such as rivaroxaban (a factor Xa inhibitor) and dabigatran (a direct thrombin inhibitor), offer advantages over warfarin in many clinical scenarios. DOACs have more predictable pharmacokinetics, fewer dietary interactions, and do not require regular INR monitoring. Importantly, they do not impact protein C or S levels, making them potentially safer in patients predisposed to WISN.[11] However, in patients with mechanical heart valves, such as in our case, DOACs are contraindicated due to insufficient evidence of efficacy and safety in this subgroup.[12]

Occasionally, vitamin K is used to reverse untoward warfarin effects. Protein C concentrates can be used for life-threatening coagulation. Prostacyclin has also been found to be effective. Large areas of skin necrosis may require skin grafting.[5]

Supportive wound care is crucial in managing the cutaneous manifestations of WISN. While our patient responded to conservative debridement and local care, nearly half of all WISN cases eventually require surgical intervention. Negative pressure wound therapy (NPWT) has emerged as an effective adjunct for complex wounds, promoting granulation tissue formation, reducing local edema, and enhancing vascular perfusion.[13] In refractory cases, other modalities such as maggot debridement therapy (MDT) have shown some promise in selective debridement of necrotic tissue.[14]

In conclusion, this case underscores the need for heightened clinical vigilance for WISN even in patients with long-term exposure to oral anticoagulants, particularly in the context of irregular dosing or fluctuating INR levels. Given the potential for delayed or recurrent presentations, especially in individuals without classical risk factors, early biopsy, thorough history, and consideration of WISN in the differential diagnosis of chronic ulcerative dermatoses are essential. Comprehensive management, including appropriate anticoagulation transition, wound care, and avoidance of unnecessary immunosuppression, is vital for optimal outcomes.

CONCLUSION

This case highlights a rare presentation of chronic, recurrent WISN in a patient with a mechanical mitral valve and poor adherence to long-term anticoagulation. Unlike the typical acute onset seen within days of warfarin initiation, our patient developed insidious, relapsing skin lesions over a period of two years, initially misdiagnosed as pyoderma gangrenosum. The chronicity, diagnostic delay, and involvement of multiple fat-rich areas make this case distinct and add to the limited body of literature on atypical WISN presentations. It underscores the need for heightened clinical suspicion of WISN in patients with a history of variable INR control, even outside the conventional time window. This case also reinforces the importance of proper warfarin initiation protocols, continuous INR monitoring, and interdisciplinary management. Early recognition, timely discontinuation of the offending agent, and appropriate wound care are critical to improving outcomes. Our report serves as a reminder that vigilance toward rare adverse drug reactions can significantly influence patient prognosis and may prevent long-term morbidity.

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