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Warfarin-induced major unilateral breast necrosis in a patient with antiphospholipid syndrome: A case report

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ABSTRACT

INTRODUCTION: Warfarin-induced necrosis is a rare complication associated with the use of warfarin in addition to antiphospholipid syndrome.

CASE PRESENTATION: A 50-year-old female patient with a known case of antiphospholipid syndrome started warfarin treatment for ischaemic changes in her toes and subsequently experienced warfarin-induced necrosis in her left breast. Then, warfarin treatment was suspended, and she was started on enoxaparin. Debridement was performed, and a skin graft was applied without complications.

DISCUSSION: Skin necrosis has many differential diagnoses, and physicians must take a proper history and perform a physical examination with proper investigations involving a multidisciplinary team, including plastic surgery, haematology, internal medicine, and wound care specialists. Plastic surgery offers many options for reconstruction depending on the patient's medical condition, the size of the wound and the location following the reconstructive ladder.

CONCLUSION: This case report presents a rare complication of warfarin in the context of antiphospholipid syndrome and describes the management of unilateral breast necrosis. Physicians should be highly suspicious of this condition in patients with skin necrosis who were administered warfarin or have antiphospholipid syndrome.

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1. Introduction

Warfarin is widely used as an anticoagulant either for treating or preventing clotting of the blood and is approved by the Food and Drug Administration (FDA) [1–3]. Full-thickness and subcutaneous tissue necrosis is rarely reported as a result of warfarin use with a prevalence of 0.1–0.01 percent [4]. In 1943, Flood et al. described the first case. Since then, there have been more than 300 reported cases, and approximately 40 of these cases involved the breast [5]. Widespread cutaneous necrosis secondary to thrombosis of the dermal microvasculature with full-thickness cutaneous necrosis is an exceedingly rare manifestation of antiphospholipid antibody syndrome and has been reported in only 24 cases worldwide to date to the best of our knowledge [6,7]. The exact mechanism of warfarin-induced skin necrosis is debated, but it is generally believed that the decrease in vitamin K-dependent coagulation factors causes a temporary hypercoagulable state along with other hypercoagulable conditions, such as protein C or S deficiency, antithrombin III deficiency, factor V Leiden mutation, antiphospho-

lipid antibody syndrome factor, V Leiden mutation, and infectious states [4,8–10].

We reported a rare case of a patient with antiphospholipid syndrome who experienced unilateral breast warfarin-induced necrosis after she started warfarin therapy. The patient was treated at Prince Sultan Military Medical City, Riyadh, Saudi Arabia. The work has been reported in line with the SCARE 2018 criteria [11].

2. Case report

A 50-year-old female patient with a Body Mass Index (BMI) of 39.1 kg/m² came to the emergency department of Prince Sultan Military Medical City, Riyadh, Saudi Arabia. Pain in the left breast started on the nipple and spread to the entire left breast.

The examination revealed swelling in the left breast with darkening skin colour that started from the nipple-areola complex and spread proximally as noted by the patient.

The patient was diagnosed with type II diabetes mellitus (DM) and hyperlipidaemia and was taking atorvastatin (20 mg/day) to control hyperlipidaemia as well as regular insulin, glargine and 750 mg metformin for DM control. The patient had a family history of type II diabetes mellitus via her parents, and no genetic or psychosocial history was noted.

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Fig. 1. Left breast showing necrotic tissue involving the nipple and the central area.

Three days ago, the patient complained of ischaemic changes in her toes. After a thorough investigation, the patient was diagnosed with anti-phospholipid syndrome. She was started on a prophylactic regimen of warfarin anticoagulation therapy with an initial dose of 10 mg/day with an INR of 1.0 (target was 2.5).

She was admitted with normal vital signs, and tests results, such as complete blood count, cardiac markers, ECG, and chest X-ray, were normal. The prothrombin time was 22.9 s (normal: 11 s) with an international normalized ratio (INR) of 2.0 and partial thromboplastin time of 48 s.

The diagnosis was bruising and ecchymosis after warfarin was started. She was given a pain killer with an appointment in the clinic after two days.

At the clinic, the pain worsened, and the skin ecchymosis became dark and larger with swelling. The condition had a necrotic basis involving the nipple and the central area (Fig. 1).

The diagnosis of warfarin-induced skin necrosis was highly suspected since it was a clinical diagnosis and other investigation results were normal. Hence, warfarin was stopped, and enoxaparin injections (80 mg/day) were started after haematology consultation. Ten days later, the patient was admitted. The case was discussed with the patient, and she agreed to the plan of the team and the producer. The demarcated necrotic area was debrided until the healthy tissue was reached. Haemostasis was secured, and vacuum-assisted closure (VAC) was applied until good granulation tissue was obtained. Heparin administration was reinitiated 8 h after the surgery. One week later, the wound was covered by split-thickness skin graft, which was harvested from the thigh and meshed. Then, VAC dressing was applied for 5 days and removed, and the split-thickness skin graft was taken. The patient did well postoperatively and was discharged, and the instruction for dressing was given to the patient with weekly visits to the clinic until completely healed. Then, the patient was followed up for one month, 3 months, and 6 months (Figs. 2 and 3). The procedure was performed by Dr. Abdulrahman AlSahabi, who is a consultant of plastic and reconstructive surgery. Adequate anticoagulant therapy with a warfarin dose of 5 mg/day was established without further complications.

The patient was followed in the clinic until six months postoperation without complications and with good wound healing and no other skin necrosis in other areas. The patient was happy with the result. The patient was offered bilateral breast reduction to remove the left scar from the skin graft and nipple reconstruction, and she agreed. The work has been reported in line with the SCARE 2018 criteria [11]. Additionally, this work was submitted with a Research Registry unique identifying number (UIN) of research registry 6258 [26].

3. Discussion

Warfarin-induced necrosis is rare but serious. The condition is noted in approximately 1:10,000 patients who receive warfarin



Fig. 2. Post debridement and VAC dressing.



Fig. 3. Post skin graft and completely healed.

with predisposing factors, including perimenopausal age, obesity, viral infection, hepatic disease, and drug interactions [12].

Additionally, blood diseases, including deficiency of protein C, protein S or factor V Leiden, hyperhomocysteinaemia, antithrombin III, and antiphospholipid antibodies, represent underlying risk factors [12–16].

Warfarin inactivates vitamin K-dependent clotting factors, including II, VII, IX, and X and proteins C and S, which may cause an imbalance that leads to paradoxical activation of coagulation, resulting in a hypercoagulable state and thrombosis. This condition is especially noted for protein C given that its concentration is more rapidly reduced compared with the other clotting factors given its shorter half-life [12–14].

The most commonly affected patients are obese, middle-aged women, and the most affected areas contain subcutaneous fat, such as breasts, buttocks, thighs, and abdomen [17].

The condition typically occurs during the first days of starting warfarin; however, there are reported cases in which necrosis was described later [4,18,19].

It is an uncommon condition but causes calamitous complications with exceedingly rare association with a familial deficiency of protein C or protein S, and acquired protein S deficiency secondary

to the development of antiphospholipid antibodies has also been reported [14,15].

Antiphospholipid antibody syndrome is an autoimmune disease that causes an increased risk of blood clots, thrombocytopenia, and small vessel thrombosis [7].

With recurrent skin necrosis, antiphospholipid antibody syndrome should be suspected, and warfarin should be stopped. The condition is diagnosed with an elevation of titers of systemic lupus erythematosus or lupus anticoagulant. Although its mechanism is not clear, it is hypothesized that antibodies have a direct effect on coagulation by direct endothelial injury, activation of platelets, modulation of protein C and S, interference with antithrombin III, and inhibition of phospholipid placental anticoagulant protein-1 [6,20,21].

The manifestation of warfarin-induced skin necrosis typically starts with pain and erythema followed by petechial haemorrhages, black discoloration, bullae and ultimately necrosis.

Warfarin-induced skin necrosis should be suspected in all patients administered large doses of warfarin or without heparinization even with a normal clotting profile and typically occurs 3–5 days after initiating the treatment. However, there are reported cases that occur months to years after the treatment is initiated. The diagnosis is based on the skin, location of the wound, noncompliance, histopathology analysis, and timing of the presentation with consideration of the differential diagnosis, such as microembolization, disseminated intravascular coagulation, necrotizing fasciitis, inflammatory breast cancer, ulcers, cellulitis, and haematoma [22].

The literature reports methods of management, including immediate cessation of warfarin to prevent further necrosis. Plasmapheresis also facilitated the successful removal of antiphospholipid antibodies, and vitamin K administration, fresh frozen plasma, and protein C were replaced. The use of rivaroxaban was reported, yielding a response. High-dose steroids are recommended to reduce vasculitis. Wound care treatment should be provided until the final demarcation. Thereafter, debridement and reconstruction options include primary repair if the wound is small or a skin graft or flap [4,18,19,23–25].

4. Conclusion

Skin necrosis has a very wide differential diagnoses, which may occasionally be missed in some cases. Performing a proper history, physical examination, and investigation with other specialties is a perfect method to reach the correct diagnosis. The presence of a good reconstruction service will provide the patient more options depending on the patient's condition, the size, and the location of the defect.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

The study is exempt from ethical approval in our institution as it is a "Case report" and not a research study.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy

of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Abdullah AlQhtani, wrote the manuscript and review it.

Abdulrahman Alsaahbi, the surgeon, supervision the whole process.

Ahmad Ashammery, Collecting the data, pictures, and following the patient.

Registration of research studies

1. Name of the registry: researchregistry.
2. Unique identifying number or registration ID: researchregistry6258.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5fb11a45c3c8170015f45f24/>.

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