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Late-Onset Warfarin-Induced Skin Hemorrhagic Bullae and Spontaneous Intramural Hematomas of The Gastrointestinal Tract

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ABSTRACT

This case report describes a 62-year-old female with a history of ischemic heart disease and atrial fibrillation on long-term warfarin therapy who presented with gastrointestinal bleeding and unusual skin manifestations. This report highlights the potential for late-onset warfarin-induced skin hemorrhagic bullae and spontaneous intramural hematoma of the gastrointestinal tract (SIHGT), underscoring the need for vigilance in patients on anticoagulation therapy.
Keywords: *Warfarin, Skin Necrosis, Hemorrhagic Bullae, Intramural Hematoma, Gastrointestinal Tract, Anticoagulation Therapy*

Introduction

Warfarin is a commonly prescribed anticoagulant used to prevent thromboembolic events, particularly in individuals diagnosed with atrial fibrillation. Although effective, the administration of warfarin can lead to various complications, with bleeding being the most prevalent (Verhagen, 1954). A rare yet significant complication associated with warfarin is skin necrosis, which generally manifests within the initial days of treatment. Nonetheless, instances of late-onset skin necrosis have been documented, occurring anywhere from 15 days to 15 years following the commencement of therapy (Essex *et al*., 1998). Additionally, spontaneous intramural hematomas of the gastrointestinal tract (SIHGT) represent another uncommon complication linked to anticoagulation treatment (Carkman *et al*., 2010). This report presents a case of late-onset warfarin-induced skin necrosis and spontaneous intramural hematomas in a 62-year-old woman occurring three years post-therapy initiation. The objective of this case

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report is to explore these complications within the framework of a patient undergoing long-term warfarin treatment.

Case Presentation

A 62-year-old woman with a notable medical history of ischemic heart disease and atrial fibrillation treated with anti-remodeling medications (enalapril, metoprolol, and atorvastatin), along with warfarin for the past three years, presented with a two-day history of abdominal cramps, hematemesis, and melena. She had no family history of bleeding or thromboembolic events and had been adherent to her medication regimen without any changes to her routine diet or introduction of new medications.

Physical examination revealed dark bullae on the right tibia and urticaria-like skin eruptions. Laboratory tests indicated a decrease in hemoglobin levels from 12 g/dL to 10 g/dL, alongside an International Normalized Ratio (INR) of 2.8, with normal platelet count and aPTT. An upper gastrointestinal (GI) endoscopy revealed significant thickening and subepithelial hemorrhage throughout the distal second duodenum, with certain areas exhibiting a bluish discoloration indicative of an intramural hematoma.

Warfarin was discontinued, and the patient was started on unfractionated heparin (UFH), vitamin K, and two units of fresh frozen plasma (FFP). During a one-week course of therapeutic unfractionated heparin (UFH), the patient's lesions stabilized and began to regress. Within two weeks, her skin lesions healed. Given her history of ischemic heart disease and atrial fibrillation, she was restarted on 2.5 mg of warfarin, with unfractionated heparin (UFH) continued for five days before warfarin was gradually increased to a final dose of 5 mg. UFH was then discontinued. INR levels were regularly monitored during her stay at the hospital and were found to be within the therapeutic range. The patient was discharged three weeks after her initial presentation.

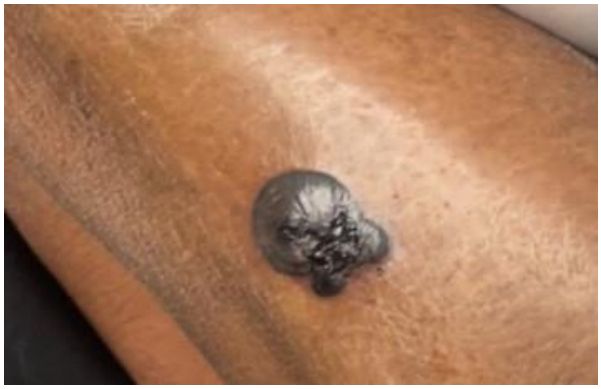

Figure 1: Dark bullae on the right tibia.

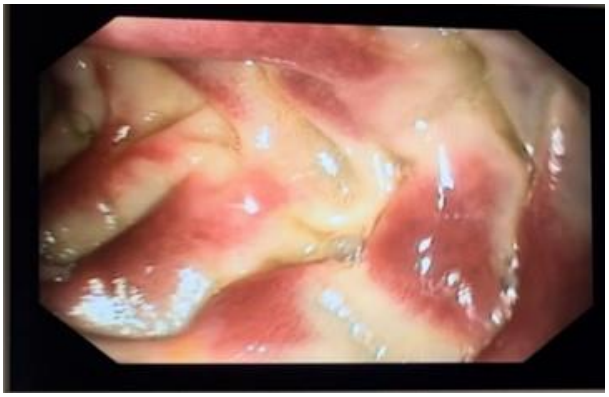

Figure 2: Endoscopic finding spontaneous Intramural hematoma of duodenum.

Discussion

Warfarin-induced skin necrosis commonly occurs 3 to 5 days after initiating treatment, but late-onset cases can present from 15 days to 15 years after therapy initiation (Essex *et al*., 1998). In this patient, the skin necrosis developed after several years of continuous warfarin use, underscoring the importance of ongoing vigilance. Warfarin's anticoagulant effect results from its inhibition of vitamin K-dependent gamma-carboxylation of clotting factors II, VII, IX, and X. However, natural anticoagulants like protein C and protein S are also affected by this process (Verhagen, 1954). The rapid decline in protein C concentration compared to other vitamin K-dependent procoagulant factors with longer half-lives can lead to a paradoxical hypercoagulable environment, resulting in the formation of microthrombi in cutaneous and subcutaneous venules.

Hypersensitivity reactions, protein C deficiency, and the direct toxic effects of warfarin are potential etiological mechanisms (Cabane *et al*., 1994). Although a clinical diagnosis and consultation with the testing laboratory are often necessary, it was not feasible to determine protein C or S levels in this patient due to financial constraints. Diagnostic tests for protein C and S concentrations are neither sensitive nor specific, and no available assays are accurate during warfarin therapy, with some clotting-based assays also being affected by other anticoagulants.

Cutaneous toxicities linked to warfarin, including dermatitis and urticaria, are infrequently observed. The most concerning complication, skin necrosis, occurs in approximately 0.01% to 0.1% of individuals (VERHAGEN, 1954). Similar to heparin-induced thrombocytopenia, warfarin-induced skin necrosis represents a paradoxical hypercoagulable response, leading to the formation of occlusive thrombi in cutaneous and subcutaneous venules. It presents abruptly as painful erythematous plaques, predominantly affecting adipose-rich regions such as the buttocks, hips, and breasts, although it can also manifest on the

extremities (Bircher *et al*., 2006). These plaques may evolve into bullae, which subsequently blister and progress to full-thickness skin necrosis. Our patient presented with an abrupt onset of dark bullae on the right tibia and urticaria-like skin eruptions.

Intramural duodenal hematoma was initially described in 1838 by McLauchlan as a "false aneurysmal tumor occupying nearly the whole of the duodenum" during an autopsy of a 49-year-old who died of duodenal obstruction (Jones *et al*., 1971). Duodenal hematoma is a very rare condition, with few cases reported in patients undergoing anticoagulant treatment (Carrilero Zaragoza *et al*., 2016; Wong and Thomas, 2014). Other conditions usually associated with duodenal hematoma include upper endoscopy procedures, non-traumatic conditions, and various coagulation disorders (Chang *et al*., 2015; Eichele *et al*., 2013; Frostick *et al*., 1984; Tseng *et al*., 2010). In our case, the patient's hematoma appeared in the context of warfarin toxicity. Symptoms of duodenal hematomas are non-specific, including abdominal pain and small bowel obstruction; hematemesis is a rare occurrence (Veldt *et al*., 2011). This is consistent with our patient's clinical presentation. The diagnosis usually requires an abdominal CT, revealing a large homogenous mass in the duodenum, although MRI may be used for better evaluation of potential underlying causes or secondary complications (Niehues *et al*., 2019), unfortunately we couldn't able to send CT or MRI imaging because of financial reason. However, upper GI endoscopy revealed significant thickening and subepithelial hemorrhage throughout the distal second duodenum, with bluish discoloration indicative of an intramural hematoma. Therapeutic management of duodenal hematomas is mainly conservative if patients are in stable condition. Patients who have undergone WISN and require long-term anticoagulation currently lack definitive guidelines for the reintroduction of warfarin. It has been suggested that a gradual approach to reaching the therapeutic dose of warfarin may serve as an effective method for mitigating this condition and significantly lowering the likelihood of WISN recurrence. The temporary procoagulant effect associated with warfarin can be managed through the administration of heparin, thus it is recommended to incrementally increase the dosages of both medications until the desired INR is achieved (DeFranzo *et al*., 1995). Our patient was treated conservatively with FFP and UFH, leading to clinical improvement.

Conclusion

This case highlights the potential for late-onset complications of warfarin therapy, including skin necrosis and spontaneous intramural hematomas of the gastrointestinal tract. Clinicians should maintain a high index of suspicion for these complications in patients on long-term anticoagulation, even when INR values are within the therapeutic range. Further research and awareness are needed to optimize the management and monitoring of patients on warfarin.

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Consent for Publication

Written informed consent was obtained from to patient to publish his medical information in this report. A copy of the written consent was available for review by the Editor-in-Chief of this journal.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this case report.

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