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CASE REPORT

Successful Treatment Using Apixaban in a Patient on Hemodialysis with Uremic Calciphylaxis

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Abstract: Calciphylaxis is a rare but serious condition in which microvessel occlusion occurs within the subcutaneous adipose tissue and dermis, leading to painful lesions. End-stage renal disease requiring hemodialysis and warfarin therapy can increase the risk of calciphylaxis. In this report, we describe the evaluation and treatment of a 75-year-old female patient with warfarin-induced calciphylaxis who presented unique symptoms. The patient required intensive care unit admission due to hemodynamic instability, which was treated with inotropes and broad-spectrum intravenous antibiotics. This description of the patient's unusual symptoms has the potential to provide insights needed to improve the diagnosis of future patients. Due to the unavailability of FDA-approved treatment for calciphylaxis, its management is based on data from observational studies and clinical experience.

Keywords: calciphylaxis, case report, ischemia, meropenem, warfarin

Introduction

Calciphylaxis is a rare but serious condition that is most frequently seen in female patients and those with recognized risk factors, such as end-stage renal disease (ESRD) requiring hemodialysis, electrolyte disturbance including hyperphosphatemia and hypercalcemia, hyperparathyroidism, hypoalbuminemia, obesity, and diabetes mellitus.[1] Medications including warfarin, calcium, vitamin D, and steroids have been shown to increase the risk of calciphylaxis.[2] In particular, this condition has been reported to occur in several patients who were receiving or had previously received warfarin therapy.[1,3–5] The majority of patients with warfarin therapy-associated calciphylaxis have presented with preexisting renal function impairment; however, this condition has also been reported in patients with normal renal function.[1,3–5] Calciphylaxis due to warfarin therapy is not commonly seen in practice with few cases reported in the literature. It is considered a serious, critical, and fatal condition as it leads to dermatological complications and systemic blood stream infection. Thus, proper diagnosis and effective therapy are crucial. In addition, there is limited literature on the use of DOACs as alternatives to warfarin in patients on dialysis with calciphylaxis.

Case Description

The study was approved by the Institutional Review Board of King Abdullah International Medical Research Centre, Jeddah, Saudi Arabia (protocol No. NRJ22J/032/02). Informed consent was obtained for study involvement. Further, written informed consent for the publication of this work was obtained from the patient.

Presentation

A 75-year-old female patient was brought to the emergency department by an ambulance. The patient had a history of hypoxia. On admission, she had an oxygen saturation level of 60% while receiving 4 liters nasal cannula oxygen for the first 24 hours of hospitalization, with no additional respiratory symptoms. Her daughter reported that during the 5 days prior to

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admission, the patient experienced decreased levels of consciousness, fatigue, and chills. The patient had a history of hospitalization at a different hospital 1 week prior to the time of admission for lower abdominal and inner thigh wounds that were severely tender, red, and had pruritic edges and ulceration with bus in the middle. During her admission at the previous hospital, wound irrigation and debridement were conducted and multiple cultures were taken. To treat the patient, a 5-day course of amoxicillin/clavulanic acid was initiated. Thereafter, the cultures were found to be positive for *Escherichia coli* resistant to the prescribed antibiotic. Accordingly, the patient was administered cefepime 1 g every 24 h for 10 days.

Medical History

The patient was bed bound with multiple bed sores and presented with the following preexisting conditions: diabetes mellitus with peripheral artery disease, atrial fibrillation, prior stroke, and ESRD requiring hemodialysis three times per week. The patient had a 20-year history of warfarin prescription for atrial fibrillation, with a therapeutic international normalized ratio (INR) of 2–3 for the majority of that time period. Within 2 months of the appearance of lesions, she was prescribed 2.5 mg apixaban twice daily in place of warfarin.

Physical and Laboratory Examinations

Laboratory results showed leukocytosis (17.6×10^9/L) consisting mainly of neutrophils (12.2×10^9/L), low albumin levels, and high calcium (2.9 mmol/L) and vitamin D 25-Hydroxy JD levels (130 nmol/L). Initially, septic shock secondary to hospital-acquired pneumonia was suspected over central line-associated bloodstream or wound infections. During the intensive care unit (ICU) admission, a wound culture testing for *Proteus mirabilis* showed resistance to piperacillin/tazobactam and sensitivity to meropenem.

Treatment and Outcomes/Follow-Up

At the time of admission to the emergency department of our hospital, the ICU team was consulted. Thereafter, the following treatments were initiated: 5 mcg/min norepinephrine continuous infusion, with a target mean arterial pressure MAP > 65; 2.25 g piperacillin/tazobactam every 6 hours; a single 1 g dose of intravenous vancomycin; and 20 grams of intravenous human albumin 20%.

Multiple teams, including dermatology, general and plastic surgery, and nephrology, were consulted. Hemodialysis was urgently initiated, as recommended by the nephrology team. Their impression was warfarin-induced calciphylaxis, in agreement with dermatology team members, who conducted a skin biopsy that revealed neutrophilic dermatitis involving blood vessels. As a result, the dermatology team recommended clinical and serological correlations to confirm the diagnosis of calciphylaxis and exclude other bacterial or viral infections.

In the ICU, the clinicians shifted the patient to 1 g meropenem every 24 hours, as recommended by the infectious diseases team based on culture results and sensitivity. After 5 days of ICU admission, the patient was transferred to the medical ward under the care of the internal medicine team. Calciphylaxis was their top differential diagnosis, based on the clinical picture and the patient's risk factors for the illness. The patient completed 14 days of meropenem therapy in addition to undergoing daily wound care, hemodialysis, and close monitoring of calcium and phosphate levels to avoid any further complication and clinical worsening.

Discussion

Our patient was an older female with atrial fibrillation with prior stroke and ESRD on hemodialysis. She had been on warfarin therapy for the past 20 years for prevention of stroke due to atrial fibrillation. She presented with infected abdominal and thigh wounds. Based on laboratory and imaging findings, warfarin-induced calciphylaxis was the primary differential diagnosis. The patient was shifted to apixaban and was started on broad-spectrum antibiotics based on the culture results. Apixaban was well tolerated with no new calcific lesion occurring after switching. The management of our patient was based on data from observational studies and clinical experience. More studies are needed to establish management guidelines for this serious adverse drug event.

Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare, life-threatening disorder characterized by chronic arteriole and capillary calcification in both the dermis and subcutaneous adipose tissue, leading to cutaneous

ischemic necrosis.[6] The disorder is associated with high morbidity and mortality rates of 60–80%, mainly due to wound infection and subsequent sepsis.[6] Multiple risk factors for calciphylaxis have been identified including ESRD requiring hemodialysis, electrolyte disturbance including hyperphosphatemia and hypercalcemia, hyperparathyroidism, hypoalbuminemia, obesity, diabetes mellitus, female sex, and medications including warfarin, calcium, vitamin D, and steroids.[1]

Warfarin is an oral anticoagulant that antagonizes vitamin K activity, which leads to the inhibition of hepatic clotting factors (II, VII, IX, and X) synthesis. Warfarin is indicated for the treatment and prophylaxis of thromboembolic disorder and atrial fibrillation- or cardiac valve replacement-derived emboli complications. Fatal and serious calciphylaxis has been reported in patients with and without a diagnosis of ESRD. A retrospective cohort study published in 2015 that included 2234 hemodialysis patients reported five cases of calciphylaxis.[7] All five cases involved female patients and of those, four had undergone warfarin therapy.[7] A case-control study of Japanese ESRD patients diagnosed with calciphylaxis published in 2012 concluded that warfarin therapy and reduced serum albumin levels are significant and strong risk factors for calciphylaxis development among hemodialysis patients in Japan.[8]

The precise pathogenesis of calciphylaxis is not completely understood. The following two subtypes of vitamin K are present: vitamin K1, which is crucial for activating hepatic clotting factors, and vitamin K2, which is essential in preventing vascular calcium deposition.[9] Warfarin is considered to promote calciphylaxis via the matrix protein Gla, which is a vitamin K2-dependent inhibitor of calcium deposition in the arteries. Inhibition of the Gla protein by warfarin promotes calcium deposition, leading to calciphylaxis.[9] In particular, small blood vessels become clogged as a result of thrombosis and calcification. Skin lesions that developed consequently were frequently purpuric, indurated plaques with necrosis.[9]

Calciphylaxis may be diagnosed based on a variety of factors. These include a clinical description of necrotic and painful skin ulcerations, occurring most frequently in the lower extremities (90% of calciphylaxis cases); however, lesions can also occur on the hands, fingers, tongue, trunk, abdomen, and buttocks. Histopathological findings indicative of calciphylaxis include diffuse dermal micro-thrombi with endothelial cell damage and red cell extravasation with progression to full-thickness coagulative necrosis.[10] The mean duration of warfarin therapy before calciphylaxis development is $\geq$ 32 months.[10] The exclusion of differential diagnoses including vasculitis, pyoderma gangrenosum, and infection is essential for a prompt diagnosis of calciphylaxis and initiation of timely treatment.[10]

Currently, no FDA-approved treatment for calciphylaxis is available. The management strategy for calciphylaxis is based on data from observational studies and clinical experience. Principally, calciphylaxis management involves the discontinuation of offending agents, optimal pain management, dialysis, daily wound care, correction of hypercalcemia and hyperphosphatemia, and avoidance of hyperparathyroidism. Intravenous sodium thiosulfate (STS) in combination with sodium nitrite have been approved for treating cyanide poisoning. Multiple studies have recommended STS as a calciphylaxis skin lesion treatment because it has both vasodilator and antioxidant properties, which facilitate wound healing.[11] STS neutralizes reactive mechlorethamine species, which in turn diminishes levels of tissue injury-causing hydroxyl radicals. No optimal dose for STS in the treatment of calciphylaxis has been established; however, use of 25 g three times per week has been reported in the literature. In patients undergoing dialysis, the same dosage as that of non-dialysis patients is recommended. Further, treatment should be provided during the last hour of a hemodialysis session or an hour after the session.[11] The duration of therapy has been reported to range from 3 to 4 weeks, or until complete symptom resolution is observed.[11] Hyperbaric oxygen therapy for 90 min per day for 25 sessions has been used in the treatment of calciphylaxis as a secondary option to STS; however, the evidence regarding the effectiveness of hyperbaric oxygen therapy for calciphylaxis cases remains insufficient.[12] The EVOLVE trial examined the effects of cinacalcet on calciphylaxis events in hemodialysis patients.[13] A total of 3861 participants were considered; of those, 24 developed calciphylaxis during follow-up. Calciphylaxis risk was lower among those who received cinacalcet than in those receiving placebo (6 versus 18, respectively; unadjusted relative hazard ratio [HR]: 0.31; 95% confidence interval: 0.13–0.79).[13]

Empirical antibiotic therapy is recommended for treating calciphylaxis-induced wound infections.[14] Broad-spectrum antibiotics are indicated for septic shock treatment, similar to the 14-day meropenem therapy regimen prescribed in the present case. Surgical debridement of calciphylaxis-associated wounds is recommended if antibiotic therapy fails to improve the wound infection.

There is limited literature on the use of DOAC therapy as a successful alternative to warfarin in patients on dialysis with calciphylaxis. A retrospective analysis determined that apixaban is a safe and effective alternative to warfarin in patients experiencing calciphylaxis.[14] Twenty ESRD patients who developed calciphylaxis were included. These patients were on hemodialysis and received apixaban therapy to treat venous thromboembolism and atrial fibrillation. The study revealed that apixaban therapy may be safely used in patients requiring anti-coagulation therapy.[14] In our patient, the shift to apixaban therapy was well tolerated, with no new calcific lesion development occurring after the transition.

Conclusion

Apixaban is a safe alternative to warfarin in calciphylaxis as shown in our case. More studies are needed to prove its safety for this condition. It is crucial to establish a guideline to improve the understanding of this serious adverse drug event and pharmacological treatment options available.

Data Sharing Statement

All data for this study are provided within the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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