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Case Presentation

Calciphylaxis in Hemodialysis

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Abstract

Calciphylaxis (CP) or uremic calcific arterial disease (CUA) is a rare, potentially fatal calcific vasculopathy characterized by calcific and thrombotic occlusion of the vessels of the subcutaneous and dermis leading to extremely painful necrotic lesions. It mainly affects patients with end-stage kidney disease (ESKD) and under long time dialysis. The only therapeutic option is represented by intravenous sodium thiosulfate. Currently, clear guidelines are lacking. We have had a good therapeutic response with doses of sodium thiosulfate in association with multidisciplinary management of the patient (vulnologist, dermatologist, nephrologist, dietitian, and cardiologist). There is limited literature on the use of DOAC therapy as a successful alternative to warfarin in patients on dialysis with calciphylaxis. The left atrial appendage closure could represent an important alternative to dicumarolics in patients with atrial fibrillation with calciphylaxis. A new perspective for the treatment of this disease is SNF472 a selective inhibitor of vascular calcification.

More Information

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Background

Calciphylaxis (CP) is a rare, life-threatening syndrome characterized by vascular calcification with occlusion of microvessels in the subcutaneous adipose tissue and dermis resulting in intensely painful, ischemic skin lesions [1]. Sepsis from infection of cutaneous wounds is the leading cause of death in patients with calciphylaxis. Calciphylaxis has a high risk of mortality; 1- year mortality rates are widely variable, ranging from 45% to 80% [2].

The incidence rate is 3.49 per 1,000 patient-years among patients receiving maintenance hemodialysis [3]. The diagnosis can be difficult, delaying potential life-saving treatments. Proper treatment requires a multi-specialty approach.

The diagnosis of certainty is obtained by biopsy of skin lesions. Histological aspects are suggestive but not pathognomonic [4]. Important risk factors are hyper parathyroidism, diabetes, obesity, repeated trauma at the sites of injury, and the use of drugs that antagonize vitamin K [5].

Elevations in phosphate and calcium levels increase the risk of calciphylaxis in patients undergoing dialysis. Patients with calciphylaxis have high parathyroid hormone (PTH) levels at the start of dialysis treatment [5], however, overuse of calcium and vitamin D supplements may lead to PTH suppression and low bone turnover, which may exacerbate extraskeletal calcium depositions [6]. Bisphosphonates may offer therapeutic benefits for patients with calciphylaxis in the setting of End Stage Kidney Disease (ESKD) [2].

Hypercalcemia and hyperphosphatemia should be corrected and the intake of vitamin D analogues and calcium-based binders should be eliminated; to reduce the risk of microvascular calcifications high levels of dialysate calcium should be avoided [7]. Increasing the length and frequency of dialysis sessions may accelerate wound healing [2,8] and help improve bone and mineral abnormalities. In patients on peritoneal dialysis, a transition to hemodialysis is recommended to improve the control of mineral metabolism [9].

Early surgical debridement in patients with CP is essential and hyperbaric oxygen represent an option. The use of sodium thiosulfate for CP given intravenously during hemodialysis at a dose of 12 g - 25 g three times a week at the end of the dialysis session represents the current therapeutic option [1,2].

Case report

We report the case of a 62-year-old obese, male patient

who after three months from the start of hemodialysis and in the two months following the introduction of warfarin for atrial fibrillation, developed ulcers with extremely painful necrotic eschars in the distal portion of the lower limbs.

After an initial suspicion of necrotizing livedoid vasculitis, an ultrasound ruled out macroscopic occlusions of the vascular circulation of the lower limbs. A biopsy of one of the necrotic lesions was performed by the dermatologist.

The analysis of the biopsy confirmed the diagnosis of calciphylaxis. Sodium thiosulfate was started at the dose of 12 g three times a week at the end of dialysis for 12 weeks. At the same time, warfarin was switched to subcutaneous calciparine although the repeated trauma resulting from the injections could favor the appearance of new lesions.

Vitamin D analogues were discontinued and dialysis time increased. The lesions have been treated by an expert vulnologist. The pain during the dialysis required the administration of morphine and fentanyl.

The patient underwent a left atrial appendage closure procedure and was sent back to the dietitian for food re-education. After 12 weeks we observed complete healing of the lesions.

Discussion

Calciphylaxis is a rare occurrence in dialysis and expresses a very severe microcirculation vasculopathy. The prognosis is poor and is burdened by a high infectious risk. The patient required multidisciplinary management that included the collaboration of the nephrologist, dermatologist and vulnologist allowing the complete healing of the lesions.

The patient was treated with sodium thiosulfate a known antioxidant agent that binds calcium deposited in the tissues, can change the local availability of calcification inhibitors, and allows a better control of the inflammation [1,2]. The treatment was well tolerated without hypotensive events, thirst, or metabolic acidosis. The drug was initially administered in saline, then to avoid the risk of fluid overload was administrated without.

Warfarin is one of the main risk factors for the onset of calciphylaxis due to the downregulation of the Gla-protein matrix (MPG), produced by the smooth muscle cell in the vascular wall, which prevents the transdifferentiation of the muscle cell into osteoblastic cell. Up to 50% of patients with CP took warfarin at the time of the diagnosis [10].

Given the need to suspend warfarin therapy and continue the anticoagulation, the patient left atrial appendage was closed. In hemodialysis patients, warfarin remains the therapy of choice in the prevention of cardio-embolism as direct oral anticoagulants (DOACS) are actually not recommended.

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 [11] although more studies are needed to prove its safety for this condition [12].

In the hemodialysis patient guidelines for CP are lacking, although the closure of the left appendage auricle is becoming more frequent as a procedure to prevent clots formation, in view of the multiple side effects of warfarin, also with pharmaco-economics advantages [13].

A selective inhibitor of vascular calcification associated with improved wound healing is SNF472 which has been shown to improve quality of life and better pain control on a phase three clinical trial and could represent an option in the future treatment of CP [14].

SNF472, the hexasodium salt of Myo-inositol hexaphosphate (IP6), is a first-in-class inhibitor of vascular calcification that has a novel mechanism of action: it physiochemically blocks the formation and progression of vascular hydroxyapatite crystals, selectively inhibiting vascular calcification. This drug may also inhibit the differentiation of vascular smooth muscle cells into osteoblast-like cells. It has been given 7 mg/kg intravenously three times weekly for 12 weeks [14].

Conclusion

Multidisciplinary management of the patient in combination with low doses of sodium thiosulfate allowed to successfully treat CP. Warfarin, the only drug available for cardio-embolism prevention in hemodialysis patients is a well-known risk factor for the development of CP. There is limited literature on the use of DOAC therapy as a successful alternative to warfarin in patients on dialysis with calciphylaxis. A valid treatment option for this condition is represented by the closure of the left atrial appendage. SNF472 a selective inhibitor of vascular calcification is opening new therapeutic perspectives for the treatment of CP.

Ethical considerations

The patient gave consent to the publication of the article and anonymity was maintained.

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