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Case series of nonhealing wound and calciphylaxis in dialysis patients from Qatar (Treated with Multi-Interventional Strategy)

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ABSTRACT

Calciphylaxis is a rare and serious disorder that presents with skin ischemia and necrosis and is characterized histologically by calcification of dermal arterioles. It is also called “calcific uremic arteriolopathy” (CUA). It has a poor prognosis and often occurs in patients undergoing dialysis. We present six cases of calciphylaxis associated with a wide range of symptoms, including nonhealing thigh, abdominal wall, breast and penile ulcer. We report our experience of a multi-interventional strategy in treating patients with calciphylaxis and nonhealing ulcers.

Keywords: Calciphylaxis, Calcification, Hyperparathyroidism, Hemodialysis.

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Introduction

Calciophylaxis is a life-threatening complication in patients with kidney disease. The lesions are usually very painful and associated with ulcerations and necrosis [1]. Besides the involvement of skin, visceral and muscle arteries can be affected. Complications including septic episodes are common and explain the high mortality rate of about 45–80% [2]. Although previously considered rare, the incidence of calciophylaxis appears to be increasing, as suggested by an analysis of the United States Renal Data System [3]. The reasons for this apparent increase are unknown but may be due to risk factors like renal insufficiency, obesity, female gender, hyperparathyroidism and disturbed bone metabolism, therapy with vitamin

K antagonists, inflammatory states, and diabetes mellitus [2, 3]. A skin biopsy is used to confirm the diagnosis since there are other disorders that may mimic calciophylaxis. However, a skin biopsy is frequently not performed among patients who have active infection (bacteremia or sepsis), since a biopsy may invite further infection. Many clinicians reserve skin biopsy for ambiguous cases [4]. Imaging studies can strengthen the diagnosis of calciophylaxis and help to assess the extent of muscular and inner organ involvement [5]. Imaging modalities that have been used include plain radiographs, high-resolution computed tomography (CT) scans, mammography, and bone scans [6].

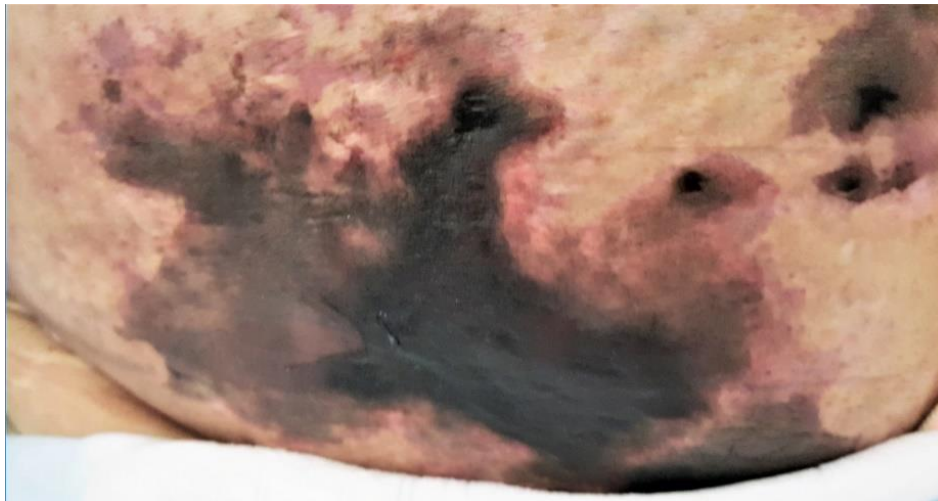


Figure 1: Necrotic Lesion of abdominal wall- of patient with peritoneal dialysis

Case (1) presentation:

A 59 years old female patient known to have long standing diabetes mellitus, hypertension, end stage renal failure secondary to hypertensive nephrosclerosis proved by kidney biopsy. She was maintained on automated peritoneal dialysis since April 2014. She presented to emergency department with severe lower abdominal and sacral pain, for which she required morphine injection. On physical examination there was tenderness, induration and blackish discoloration of lower abdominal wall and sacral area (Figure 1). Peritonitis was

ruled out by peritoneal fluid cell count and gram stain. Clinically the skin lesion was highly suspicious of calciophylaxis. So we recommended bone scan using triphasic technique to rule out calciophylaxis and CT scan to rule out other underlying pathology. Bone scan came suggestive of inflammatory process, but CT scan showed extensive calcification of abdominal wall blood vessels. Skin biopsy was taken to confirm the diagnosis. It showed panniculitis with necrosis and calcification of small vessels. Patient was admitted to intensive care unit due to septic shock because of E coli bacteremia and

was treated with IV antibiotic. To intensify her dialysis, we shift her to hemodialysis with infusion of sodium thiosulfate 25 gm 3 times/week post hemodialysis and she was started on hyperbaric oxygen therapy. Within a week of starting sodium thiosulfate infusion her pain was dramatically improved. Beside wound care and antibiotic used to treat wounds. We stopped calcium phosphate binder and active vitamin D. We dialyzed her with low calcium dialysate bath and used calcimimetic drug (cinacalcet) to treat her secondary hyperparathyroidism. We referred her to general surgeon for possible parathyroidectomy.

Case (2) presentation:

A 72 years old female patient known case of diabetes mellitus, hypertension, hypothyroidism, and end stage renal disease secondary to diabetic nephropathy on regular hemodialysis since 2015 three time per week via left arteriovenous graft. One year after initiation of dialysis the patient was admitted with severe pain and skin lesion on both upper thighs. Physical examination revealed indurated dermal plaques of the pannus with overlying ulceration and necrosis. CT scan of both thighs showed extensive vascular calcification. Her skin biopsy was highly suggestive of calciphylaxis. She was started on sodium thiosulfate infusion post hemodialysis and we increased her dialysis frequency to 4 times/week to intensify her dialysis. She was dialyzed with low calcium dialysate and treated with cinacalcet for her secondary hyperparathyroidism. She was referred for hyperbaric oxygen therapy, but she refused it due to difficult daily transportation. She was referred for parathyroidectomy as well, but she refused surgery due to high risk with general anesthesia. Her wound remained unhealed for almost 9 months due to infection and interruption of sodium thiosulfate treatment after 2 months of initiation due to unavailability of stock. It was resumed once again after one month and continued for almost 3 months. After nine months of supportive therapy including antibiotic therapy, opioid analgesics and

interdisciplinary wound care, her wound becomes completely healed.

Case (3) presentation:

80 years old female patient known to have end stage renal disease on four time per week hemodialysis secondary to diabetic nephropathy since 2011. Her other medical history included hypertension, diabetes since 2000, hypothyroidism and atrial fibrillation treated with warfarin. She had secondary hyperparathyroidism since 2013. She was referred to us from dialysis center in April 2013 with fever and pain in right breast associated with nonhealing wound around 8 cm at the nipple area for 6 months duration. Initially, she was diagnosed as warfarin induce skin lesion. As the clinical picture of the breast wound was highly suggestive of calciphylaxis. A punch skin biopsy from the wound came as necrotic and severely ulcerated epidermis, however, tissue biopsy from the wound showed medial dystrophic calcification of large vessels. CT imaging additionally showed severe calcifications of the blood vessels. We tried to treat her with multi-intervention strategy by stopping calcium-containing drugs, vitamin D compounds, and by using calcimimetic drug to achieve better control of calcium and phosphate levels, her dialysis sessions were extended, and low calcium dialysate was used. Infusion of sodium thiosulfate 25 gm three time per week was given during the last hour of hemodialysis session. Supportive therapy included antibiotic, opioid analgesics and interdisciplinary wound care. To enhance wound healing, hyperbaric oxygen therapy was used. There was a dramatic reduction in pain within 2 weeks of starting sodium thiosulfate and hyperbaric oxygen therapy. Within 3 months of this multi-interventional therapy wound was completely healed.

Case (4,) presentation

A 63 years old female patient known case of end stage renal failure on hemodialysis via right perm catheter since 2013, started after failing of renal transplant. She was transplanted in 1997,

and original disease was diabetic and hypertensive nephropathy. Four months after starting hemodialysis she presented with fever and a two weeks history of wound on right breast. She was admitted as case of line related infection. On clinical evaluation there was a 6cm x 5cm wound, indurated and with erythematous edges. Initially she was treated for breast abscess, but ultrasound showed no collection. CT scan showed subcutaneous edema, and no calcification. Despite treatment with broad spectrum antibiotic she remained febrile, wound biopsy was suggested to rule out calciphylaxis but unfortunately patient refused biopsy. She was discharge with follow up in wound care and breast clinic. Wound remained unhealed for almost 4 months and once again she was admitted with fever, this time CT scan showed calcification in both breast Vessels. Patient agreed for wound biopsy which showed skin necrosis with calcification. She was successfully treated with sodium thiosulfate and hyperbaric oxygen therapy.

Case (5) presentation:

A 57 years old male patient was admitted to our hospital with one-month history of pain and wound formation at glans and shaft of penis. He was on peritoneal dialysis since 2015. He initially presented to urology clinic with pain and wound at penile area. On physical examination, he had extensive necrotic gangrenous lesions on glans penis and shaft. The lesions were extremely painful, requiring high opioid doses for pain control. Wound biopsy showed necrotic tissue with dysmorphic calcification. He was diagnosed with calciphylaxis based on a clinical presentation combined with a medical history of diabetes, end-stage renal disease. Penile lesions were treated surgically, with debridement and partial penectomy. Unfortunately, the patient developed severe wound infection with Gram negative bacilli resistance to treatment and later on developed acute peritonitis with severe septic shock. The patient was transferred to intensive care unit, and then shifted to hemodialysis. Despite such

procedures the lesion progressed, the clinical condition worsened and eventually the patient died few days later due to septic shock.

Case (6) Presentation:

63 years old female patient known case of end stage renal failure on peritoneal dialysis since 2013, secondary to analgesic nephropathy and hypertensive nephrosclerosis. She has morbid obesity and hypothyroidism. Patient was seen in peritoneal dialysis clinic with complaint of mild skin redness of abdominal wall near to PD catheter site. After one month she presented with increase in size of lesion on abdominal wall. On examination the wound was small (2 x 2 cm) open but dry with induration. She was treated as a case of infected wound vs cellulitis with iv antibiotic and referred to wound care clinic. Patient was reassessed after one month for abdomen wall skin lesion, which increased in size and became superficially ulcerated with no discharge.

Discussion:

Over the last five years we diagnosed six patients with severe calciphylaxis. Our patient came from both dialysis modality, three patients from peritoneal dialysis and three patients from hemodialysis. All patients developed calciphylaxis despite cinacalcet therapy and achieving calcium, phosphate, and intact PTH serum levels within the recommended ranges. Our patients had several predisposing factors for calciphylaxis including hyperparathyroidism, obesity, and diabetes, use of warfarin therapy, and being a female gender. Interestingly we have only one male patient with calciphylaxis, and all of our patients had been dialyzing for less than four years. Moreover, one of our patient was diagnosed with calciphylaxis four months after initiation of dialysis.

Elevated plasma calcium concentration, hyperparathyroidism, hyperphosphatemia, or abnormalities in the coagulation may be found, but none of them is responsible for the pathogenesis of calciphylaxis^[8]. Predominantly, calciphylaxis involve the lower extremities but two of our patients had breast involvement, one

with penile and one came with abdominal wall calciphylaxis. Isolated cases of vascular calcifications with normal renal function are described [9]. For most patients with suspected calciphylaxis, a skin biopsy is recommended to confirm the diagnosis since there are other disorders that may mimic it. Imaging modalities that have been used include plain X ray, high-resolution CT scans, mammography, and bone scans [10]. We used bone scan and mammogram in two of our patients and it came negative for soft tissue calcification. Skin biopsy was performed in five patients.

A multi-interventional strategy is likely to be more effective than any single therapy [11]. We used sodium thiosulfate infusion in five patients and the pain dramatically improved within 1 week with good result, indicating this drug is a very good candidate for the treatment of this condition. There are no randomized controlled trials that have proven a benefit of sodium thiosulfate infusion in this setting. Perhaps the best data that support its efficacy are from a retrospective review of 53 hemodialysis patients who had received sodium thiosulfate for calciphylaxis [12]. One of our patients developed metabolic acidosis as side effect of sodium thiosulfate corrected with high bicarbonate dialysate bath... We used hyperbaric oxygen therapy in all of our patients except two. We did not treat any patient with Vitamin K.

We optimize the dialysis prescription to achieve the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) goals of dialysis adequacy [13]. We used non-calcium-containing phosphate binders, such as sevelamer carbonate and prefer to use cinacalcet to treat hyperparathyroidism as well we referred all of our patients for parathyroidectomy.

Conclusion:

We think that calciphylaxis is not rare, but it is rarely diagnosed in renal patients. It can be devastating if not diagnosed early and treated properly. The diagnosis can be difficult and may not recommend biopsy. There are very few

cases reported in the literature with lesion of calciphylaxis located in unusual area of body, like breast, penis, and abdomen. as the patients we presented. Majority of cases of calciphylaxis occurred in patient with long standing dialysis, 6-7 years. All our patients were dialyzed for less than four years. One of our patients had calciphylaxis during first four months of hemodialysis. Our patient had several predisposing factors for calciphylaxis, such as hyperparathyroidism, obesity, and diabetes that had been present for a long time, and two of our patients were taking warfarin anticoagulation. We treated all our patients using multi-interventional strategy. Starting with stopping of medications that can precipitate hypercalcemia, normalization of high serum calcium and phosphate levels, administration of sodium thiosulfate, we used hyperbaric oxygen therapy in all our patients except two.. In all our treated patients we observed the effectiveness of treatment with sodium thiosulfate combined with hyperbaric oxygenation therapy. After observing the positive results and improved quality of life in patients, it appears that this multi-intervention strategy in treating calciphylaxis are likely to play important roles in calciphylaxis management.

Conflict of interest: None

The manuscript has been seen and approved by all authors and that it is not under consideration for publication elsewhere in any language.

The patients had given their consent for the case report to be published.

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