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Parathyroidectomy as a Cure for Calciphylaxis in a Non-Dialysis Chronic Kidney Disease Patient?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 61
Final Diagnosis: Calciphylaxis
Symptoms: Finger pain
Medication: —
Clinical Procedure: Subtotal parathyroidectomy
Specialty: Nephrology

Objective: Unknown ethiology

Background: Calciphylaxis is a rare and fatal systemic disease which most commonly occurs in patients with end-stage renal disease. It is a poorly understood vascular calcification with unclear pathology that leads to vascular compromise due to vascular occlusion with endoluminal calcification.

Case Report: We report a case of a 61-year-old male with chronic kidney disease stage 5 who developed calciphylaxis. The patient was diagnosed with dry gangrene of the second and third digits of the right hand and second, third, and fourth phalanges of the left hand. Despite medical therapy and local wound care, the lesions progressively worsened with time. The patient was found to have secondary hyperparathyroidism (parathyroid hormone was 1028 pg/mL) and underwent subtotal parathyroidectomy. In our patient, the skin lesions due to calciphylaxis completely resolved over the course of 12 months.

Conclusions: Parathyroidectomy has been associated with clinical benefit in patients with calciphylaxis. Clinicians should consider parathyroidectomy in the setting of high parathyroid hormone and calciphylaxis. Although parathyroidectomy is an effective treatment option for calciphylaxis it is not a definitive treatment and calciphylaxis can occur, though rarely, even after parathyroidectomy. There is a need to do further studies in order to confirm the efficacy of parathyroidectomy.

MeSH Keywords: Calciphylaxis • Hyperparathyroidism, Secondary • Parathyroidectomy • Renal Insufficiency, Chronic • Vascular Calcification

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/917105

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Background

Calciphylaxis is a poorly understood vascular calcification with complex pathogenesis that leads to a severe form of vascular compromise due to vascular thrombotic occlusion with endoluminal calcification [1]. Possible factors involved in the pathogenesis of calciphylaxis are chronic kidney disease-mineral bone disease, chronic inflammation, and deficiencies in inhibitors of vascular calcifications (for example fetuin-A (2-Heremens-Schmid glycoprotein) and matrix Gla protein. Other factors that have been attributed to the pathogenesis of calciphylaxis include hyperparathyroidism, hyperphosphatemia, elevated plasma calcium x phosphate product, and active vitamin D supplementation.

It is also known as calcific uremia arteriolopathy [2] and is highly associated with end-stage renal disease [3]. According to the study conducted in the Fresenius Medical Care North America dialysis units, the incidence rate of calciphylaxis was 3.49 per 1000 patient-years among the end-stage renal disease patients who were on chronic hemodialysis [4].

Calciphylaxis is characterized by excruciating painful skin lesions such as livedo reticularis, reticulate purpura, indurated nodules, and violaceous plaques which are often complicated with blister formation, ulceration, necrosis and superimposed infection [5]. They most commonly develop in the areas with thick adipose tissue such as breast, abdomen, and gluteal region but it can also develop in other areas of the body. These findings result from the reduction in the arteriolar blood supply of the involved area.

We present a unique case, in a chronic kidney disease patient, of calciphylaxis which completely resolved after parathyroidectomy.

Case Report

The patient was a 61-year-old male with stage 5 chronic kidney disease who developed calciphylaxis with dry gangrene of his digits. His past medical history was also significant for colon cancer, type 2 diabetes mellitus (HbA1c was 9.1 recorded in July 2017), hypertension, liver cirrhosis, chronic pancreatitis, and gout. The patient's baseline creatinine was 4.2 mg/dL. The patient stated that he started noticing changes in the digits 3 months ago which had progressively worsened since then. It was associated with excruciating pain. Despite medical therapy with sodium thiosulfate and local wound care, the lesions progressively worsened with time. The patient was diagnosed with dry gangrene secondary to calciphylaxis in the second and third digits of the right hand and second, third, and fourth phalanges of the left hand (Figure 1). The patient underwent x-ray of both hands which showed extensive vascular calcifications (Figure 2).

Figure 1. Dry gangrene secondary to calciphylaxis in the second and third digits of the right hand and second, third, and fourth phalanges of the left hand.

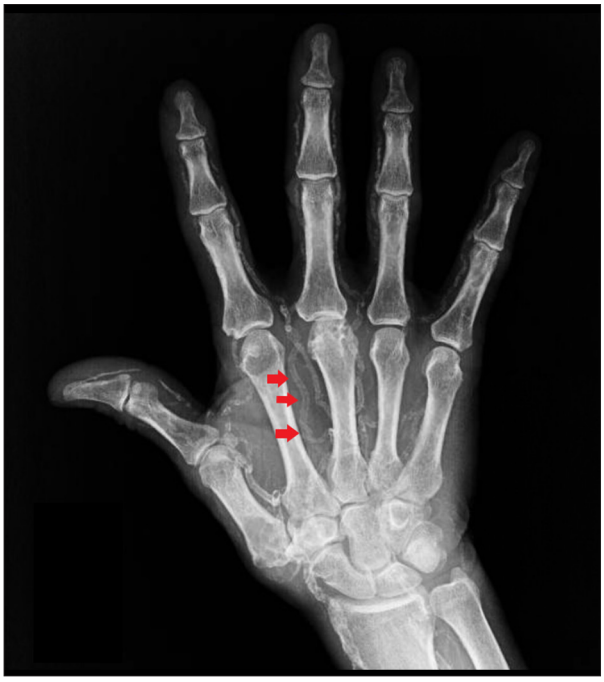

Figure 2. X-ray of the hand showing vascular calcification.

The patient underwent bilateral upper extremity arterial duplex evaluation which showed calcification of the arterial system and decreased velocities with biphasic Doppler waveforms were observed in the extremities on the right upper extremity,

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Table 1. Trend of calcium, phosphorus and parathyroid hormone.

	Before MT	After MT	After ST POD: 1	After ST POD: 12	After ST POD: 18	After ST POD: 322
Calcium	7.8 mg/dL	8.3 mg/dL	7.1 mg/dL	6.3 mg/dL	8.3 mg/dL	7.3 mg/dL
Phosphorus	6.6 mg/dL	6.6 mg/dL	6.6 mg/dL	2.6 mg/dL	3.1 mg/dL	2.7 mg/dL
PTH	1028 pg/mL		117.5 pg/mL	8.98 pg/mL	7.23 pg/mL	17.88 pg/mL

MT – medical therapy; ST – surgical therapy; POD – post-operative day; PTH – parathyroid hormone.

and calcification of the arterial system and normal arterial hemodynamics in the left upper extremity.

The patient was found to have secondary hyperparathyroidism (parathyroid hormone was 1028 pg/mL). He had low calcium, high phosphate, high alkaline phosphatase, and low vitamin D deficiency. The patient's hyperparathyroidism was unresponsive to medical therapy. Both medical and surgical treatment options were discussed with the patient and the patient decide to opt for the surgical option. The patient underwent subtotal parathyroidectomy on July 13, 2017. Parathyroid glands were excised and only half of the right superior parathyroid gland was preserved. Parathyroid pathology showed parathyroid hyperplasia in all of the resected parathyroid glands. The patient had no intra-operative or post-operative complications. The patient was admitted to the intensive care unit (ICU) for monitoring. The patient's parathyroid hormone level after surgery was 117 pg/mL which trended down to 7.23 pg/mL 18 days post-surgery. The patient had hypocalcemia post-operatively and was given multiple doses of calcium and calcitriol. Due to worsening of fluid overload and pulmonary edema refractory to medical management the patient was started on hemodialysis on July 21, 2017 via left forearm arteriovenous fistula. The patient's clinical condition improved, and the patient was discharged. The patient had an amputation of the right middle finger at the metacarpophalangeal joint at another hospital in 2018 due to infection.

The patient's parathyroid hormone and calcium levels were monitored. The trend is shown in Table 1. The patient was advised to be compliant with his diabetic diet and his medication. The patient's electrolytes where monitored and the patient received regular hemodialysis as per his schedule. The patient had significant improvement in the skin changes in the remaining fingers after 12 months of parathyroidectomy (Figure 3).

Figure 3. Skin findings after 12 months of parathyroidectomy.

Discussion

Risk factors for calciphylaxis include diabetes mellitus, hyperphosphatemia, secondary hyperparathyroidism, female sex, medications (including calcium-based binders, vitamin D analogs, nutritional vitamin D, systemic glucocorticoids, and warfarin) hypoalbuminemia, hypercoagulable states, obesity, and inflammatory and autoimmune medication [6]. Although calciphylaxis is found in patients with advanced chronic kidney disease on dialysis [7], it can also occur in patients with chronic kidney disease not on dialysis [8]. Our patient had several of the aforementioned risk factors. The patient had uncontrolled diabetes mellitus (HbA1c was 9.1) and secondary hyperparathyroidism. Keeping good blood glucose levels and monitoring calcium-phosphate levels in high-risk patients can decrease the risk of developing calciphylaxis in high-risk patients.

Calciphylaxis is a clinical diagnosis, and biopsy of the lesion is not needed to confirm the disease. Biopsy of the lesion can be done if there is a need to rule out other disorders that might mimic calciphylaxis. Imaging modalities that have been used to evaluate calciphylaxis are radiograph, computed tomography scan, ultrasonography, nuclear bone scintigraphy, and mammogram.

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Calciphylaxis is associated with poor prognosis and the mortality rate can be high as 60% to 80% [1]. Advanced disease at the time of diagnosis, presence of cardiovascular disease, ischemic and necrotic changes in the proximal skin and soft tissues, and use of warfarin are risk factors for worse prognosis [3]. Development of cutaneous ulcers increases the risk of mortality by 2-fold. One of the highest causes of mortality in patients with calciphylaxis is infection. Patients on hemodialysis have a higher mortality rate as compared to non-dialysis patients.

The optimal treatment of calciphylaxis is preventing it from developing by controlling phosphate and calcium balance. For patients at risk of developing calciphylaxis, medications that contribute to calciphylaxis should be stopped if possible. Treatment options for calciphylaxis include sodium thiosulfate, tissue-plasminogen activator, bisphosphonates, cinacalcet, surgical debridement, and subtotal parathyroidectomy [9].

Once calciphylaxis sets in, it is very important to take good care of the wound as these wounds are prone to superimposed infection. The wound care team should be consulted regarding the selection of dressings, use of enzymatic and chemic debridement agents; negative pressure wound therapy, and use of topical or systemic antibiotics. Surgical debridement is reserved for infected wounds because of increased risk of sepsis and non-surgical management is reserved for non-infected wounds.

One of the proposed mechanisms of action of sodium thiosulfate is that it dissolves the insoluble calcium salts embedded in the involved tissue [10]. Oral sodium thiosulfate has been associated with secondary prevention of calciphylaxis [11]. Inhibition of macrophages and proinflammatory cytokines has been proposed as the mechanism of action for bisphosphonates in calciphylaxis. According to a study done at Fresenius Medical Care North America; the majority of the patients who received sodium thiosulfate showed clinical improvement during the study [4]. The role of cinacalcet in the management of calciphylaxis is assumed to be related to its action in decreasing serum parathyroid hormone and thus stabilizing the calcium and phosphate balance.

Parathyroidectomy has been associated with clinical benefit in patients with calciphylaxis and one of the proposed mechanisms of action is by transient uptake of calcium and phosphate by the bone which leads to lower calcium and phosphate product. Hungry bone syndrome is one of the most common complications after parathyroidectomy and patient calcium levels need to be monitored after the procedure. According to a retrospective analysis, patients who received parathyroidectomy had a longer median overall survival of 80 months as compared to patients who were treated non-surgically (35 months) ($P<0.001$) [12]. According to another study, patients with stage 5 chronic kidney disease who underwent subtotal parathyroidectomy had better 6 months ($P=0.04$) and overall survival ($P=0.02$) compared to the patients who were treated non-surgically [9].

Parathyroidectomy is particularly effective in the management of calciphylaxis in patients with hyperparathyroidism. There was a remarkable improvement in calciphylaxis after parathyroidectomy in our patient. The initiation of dialysis in our patient might have also contributed to the remarkable improvement in calciphylaxis.

Although parathyroidectomy is an effective treatment option for calciphylaxis it is not a definitive treatment and calciphylaxis can happen, though rarely, even after parathyroidectomy. According to a case report a 60-year African American male patient developed calciphylaxis after subtotal parathyroidectomy [13]. Parathyroid hormone suppression by itself is a risk factor for calciphylaxis [14]. One of the proposed mechanisms for the development of calciphylaxis after parathyroidectomy is that low level of parathyroid hormone and decrease bone turnover might led to a higher level of calcium in the circulation resulting in soft tissue calcification. The role of parathyroidectomy in calciphylaxis is controversial. There is limited research done on this topic, and most of the literature is derived from small retrospective studies [15]. The optimal treatment for calciphylaxis is unknown. There is a need to do a large scale randomized controlled trial to confirm the efficacy of parathyroidectomy in the treatment of calciphylaxis.

Conclusions

Calciphylaxis is a poorly understood rare disease which is associated with significantly high morbidity and mortality. We report a case of calciphylaxis which was successfully treated with subtotal parathyroidectomy. There is a dire need to conduct studies to assess the effectiveness of various treatment options of calciphylaxis.

Conflict of interest

None.

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