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Case report

An Unusual Site of Calciphylaxis: A Case Report and Review of the Literature

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Abstract

Calciphylaxis is a rare and potentially fatal condition usually observed in patients with long-standing history of chronic kidney disease. It's a challenging disorder with a multifactorial etiology. Calciphylaxis occurs more often in fatty tissues of the abdomen, buttocks, genital and inner thigh regions. In these areas blood flow is lower, the potential for vascular kinking is higher and subsequently the risk for occurrence of thrombosis is increased compared to other areas of the body. Lesions of calciphylaxis typically need only days to a couple of weeks before the full picture is developed and it's difficult to establish a defined prognosis. The mortality rate is very high and the leading cause of death is sepsis from infected, necrotic ulcerated skin lesions. We report a patient on hemodialysis treatment suffering from calciphylaxis located at an unusual site. Because the mortality rate of patients with calciphylaxis is very high and depends especially on the presence of necrotic ulcerated lesion and possible bacterial contamination, which can lead to sepsis, early recognition and treatment is extremely important.

Key words: calciphylaxis, vascular calcification, thrombosis, skin necrosis

Introduction

Calciphylaxis or calcific uremic arteriolopathy (CUA) is a rare and potentially fatal condition usually observed in patients with long-standing history of chronic kidney disease. However, sporadic cases in patients with normal renal function have also been reported. The prevalence of calciphylaxis is assessed between 1 to 4% of dialysis patients [1,2]. It is characterized by calcification of tunica media of skin arteries, subcutaneous fat tissues and visceral organs with or without endovascular fibrosis, extravascular calcification and vascular thrombosis, leading to tissue ischemia and hence necrosis of tissues supplied by respective vessel. These histological features are associated with a clinical picture characterized by the presence of tender red areas developing into a livedoid pattern or violaceous nodular lesions of the skin that can evolve into tissue necrosis, eschar followed by frank ulceration, gangrene, or sepsis. In advanced stage lesions may be found in internal organs such as the heart and the lungs with consequent clinical symptoms. Lesions of calciphylaxis typically develop suddenly and progress rapidly. Calciphylaxis means a massive reduction in quality of life and is associated with a high mortality rate, ranging from 60 to 80% [3,4]. The leading cause of death is sepsis from infected, necrotic ulcerated skin lesions. Early diagnosis and treatment are vital for the patient. Herein, we report a patient newly on hemodialysis treatment suffering from calciphylaxis located at an unusual site. Calciphylaxis remains a condition under recognized by nephrologists and by other physicians including dermatologists and internists.

Case report

A 73-year-old woman with ESRD due to chronic calculous pyelonephritis presented at our outpatient clinic with black leathery eschar on the right breast. The lesion was

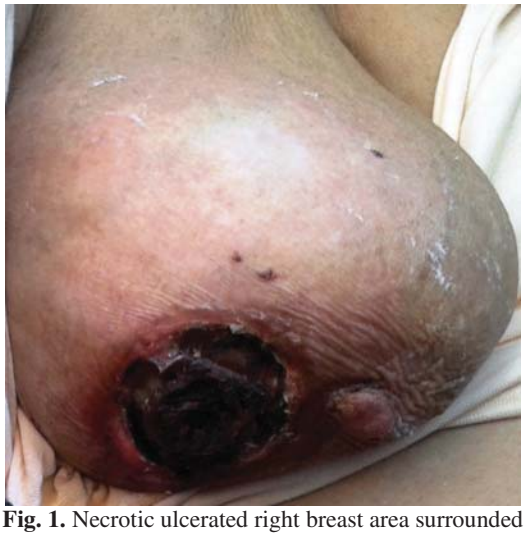

Fig. 1. Necrotic ulcerated right breast area surrounded by erythema.

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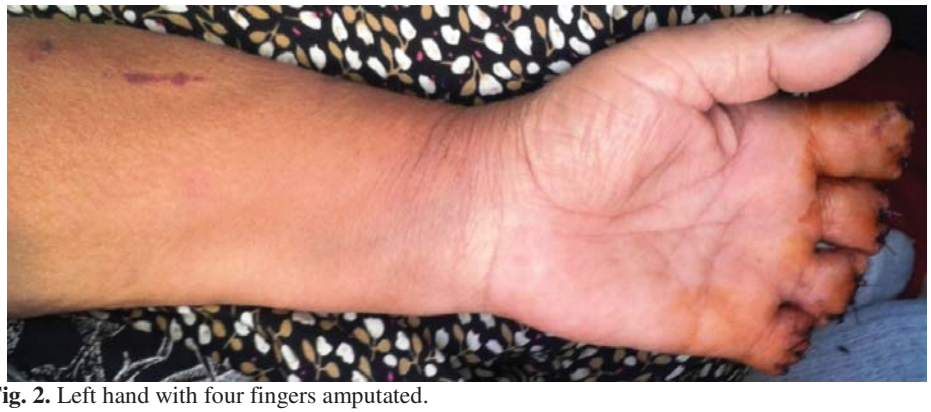

Fig. 2. Left hand with four fingers amputated.

associated with intense local pain and the patient had a low grade fever of 38,1^{o} C. She referred the first symptoms were purpuric skin lesions that had appeared about 6 weeks earlier. Three weeks after the onset of the first symptoms, the patient noticed an ulcer, which was quickly covered by necrotic eschar. Relevant aspects of her medical history included nephrolithiasis, recurrent episodes of pyelonephritis, and arterial hypertension, but no other comorbidities and she was a non-smoker. She had been receiving hemodialysis for one month, using a central provisory catheter as vascular access. There is no information about the patient's chronic renal failure before starting hemodialysis because it was a late referral case. Physical examination revealed an obese lady (BMI 32,5).There was a painful necrotic ulcerated area surrounded by erythema on the right breast located at areola mamme near the nipple with a diameter of 4 cm (Figure 1).

The peripheral pulses were normally felt on the lower limbs. Four fingers of her left hand have been amputated several days before (Figure 2). She said that her fingers had had red to blue aspect (cyanosis) before amputation. The rest of her systemic examination was unremarkable. On presentation, her medication included: moxonidine 0,4 mg once daily, lercanidipine 10 mg once daily, calcitriol 0,25 mcg daily, calcium carbonate 3 g daily, erythropoietin ß adapted to haemoglobin levels, ferrum sucrose adapted to ferritin levels, omperazole 20 mg once daily, acetylsalicylic acid 100 mg once daily, furosemide 80 mg daily. Laboratory data showed the following abnormalities: BUN 89 mg/dl; creatinine 9,1 mg/dl; corrected plasma calcium 10.4 mg/dl; phosphorus 6,9 mg/dl; albumin 3,4 g/dl; alkaline phosphatase 428 IU/L; iPTH 869 pg/ml. Ht 29 %, Hb 9,8 g/dl, WBC 11300, platelets 255000, CRP 32 mg/l. Cryoglobulin, rheumatoid factor, antinuclear antibodies and antineutrophil cytoplasmic antibodies were all negative. Multiple blood cultures and wound swab cultures were also negative. The radiologic examination revealed an extensive vascular calcification. Lateral lumbar plan X-ray showed calcification of abdominal aorta and calcification of mesenteric artery (Figure 3a). Plain X-ray of pelvis demonstrated calcification of both femoral arteries and calcification of iliac vessels (Figure 3b). In radiography of hands calcification of an intermetacarpal artery and calcification of both radial arteries were readily visible (Figure 3c). Based on X-ray data of pelvis and hands, the vascular calcification score

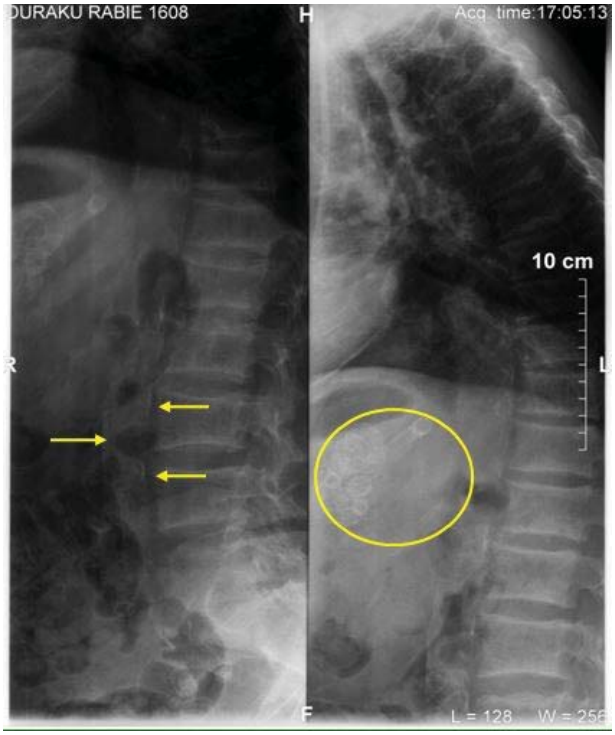

Fig. 3a. Lateral lumbar plan X-ray. Arrows indicate calcification of abdominal aort and circle shows calcification of the mesenteric artery.

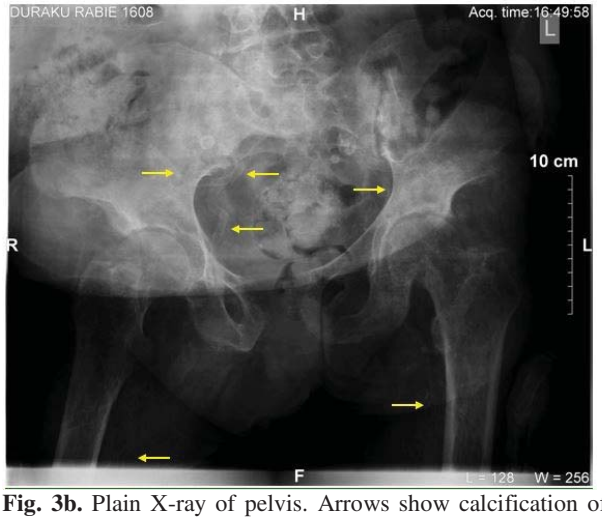

Fig. 3b. Plain X-ray of pelvis. Arrows show calcification of both femoral arteries and iliac vessels.

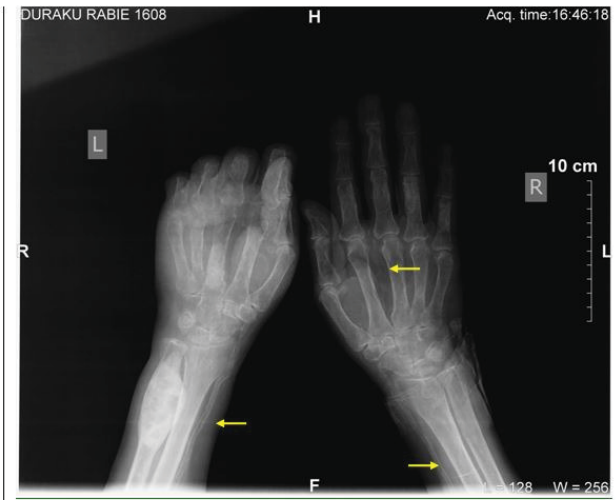

Fig. 3c. Radiography of hands. Arrows demonstrate calcification of an intermetacarpal artery and calcification of both radial arteries.

as prescribed by Adragao was seven (39). What was our dilemma? The history of chronic renal disease, presence of markedly raised PTH levels along with the clinical picture of widespread necrosis with erythema made calciphylaxis a possibility. But, the location and picture of the lesion was suggestive not only of calciphylaxis but of breast cancer also (i.e. Paget's disease of the nipple). On the other side, the prevalence of malignancy is growing up in end-stage renal disease patients. Thirteen percent of patients evaluated for a transplant and 10% of patients on waiting list carry the diagnosis of a malignancy [5].At this point the confirmation of diagnosis was a crucial issue in order not to initiate a cascade of unjustified therapeutic measures. The patient was reviewed by the oncologists and a deep incisional skin biopsy was performed. The specimens showed intimal hyperplasia and intramural calcification in an arteriole of the subcutaneous tissue which is characteristic for calciphylaxis (Figure 4).

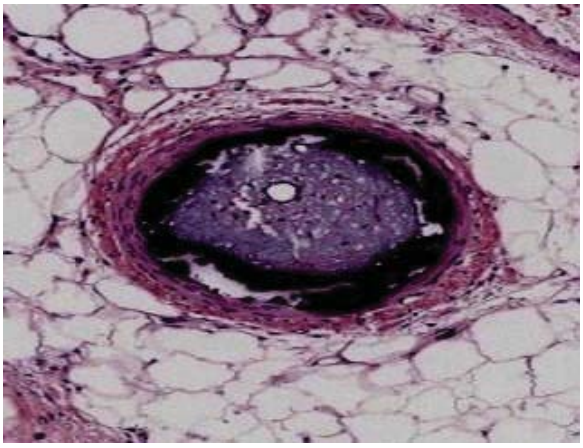

Fig. 4. Intramural calcification and intimal hyperplasia in an arteriole of the subcutaneous tissue (hematoxylin-eosin, original magnification ×400).

These typical pathological findings and characteristic skin lesions established the diagnosis of calciphylaxis. The first steps of therapy were toward lowering of serum phosphorus, calcium and PTH levels. For this reason calcitriol was discontinued, cinacalcet 30 mg daily was initiated, the dose of calcium carbonate was reduced from 3g to 1g daily (further dose was titrated), sevelamer hydrochloride was started 3200 mg daily and low calcium dialysate (calcium concentration 1,25 mEq/L) was instituted. We started to treat the patient with antibiotic, cefuroxime at a dose of 2 g daily. 25 grams of sodium thiosulphate (100mL of a solution at 25% STS) were infused three times per week. The thiosulphate was administered immediately after dialysis. The dry necrotic lesions were gently hydrated to promote a moist wound environment, encouraging autolytic debridement and cell migration. Tramadol was used for pain relief. Two weeks later the serum parathyroid hormone, calcium, and phosphorus levels improved; 623 pg/ml, 9,6 mg/dl and 6,2 mg/dl, respectively, but clinical status worsened. Multiple blood cultures and wound swab cultures were repeated and pseudomonas aeruginosa was isolated. Based on germ sensitivity imipenem-cilastatin and ciprofloxacine were instituted. After 3 days gentamicin was added. The patient died eight days later from sepsis.

Discussion

Calciphylaxis is a challenging disorder with a multifactorial etiology. The term calciphylaxis was originally coined by Hans Selye based on his early animal experiments in the 1960s [6]. He induced systemic and local inflammation and soft-tissue calcification in rodents with a combination of local trauma and an inducer (such as parathormone, active vitamin D, hypercalcemia). Thus, it was thought that this disorder involved "anaphylactic" inflammation and calcification, hence the name: calciphylaxis. But, calciphylaxis has very little to do with true anaphylaxis.
The pathogenesis of calciphylaxis is not fully understood. There are local and systemic risk factors and underlying causes that finally lead to development of calciphylaxis. Reported mineral abnormalities do not explain the process of thrombosis leading to ischemia [7]. Vascular calcification is an active process and is not sufficient to produce skin necrosis. However, calcific narrowing of small vessels provides the background for additional processes that may ultimately culminate in the development of CUA. Vascular calcification and thrombosis are both required to produce lesions of calciphylaxis [8]. Significantly low functional levels of protein C and S, which are known for their role in the anticoagulation pathway, have been reported in patients with CUA. But, low persisting levels have been shown even when lesions were healing [9]. Calciphylaxis is more common in whites and females are affected three times more frequent than males [10]. It occurs more often in fatty tissues of the abdomen, buttocks, genital and inner thigh regions. In these areas blood flow is lower, the potential for vascular kinking is higher and subsequently the risk for occurrence of thrombosis is increased in comparison with other areas of the body [11].

There is a long list of presumed risk factors. Uremia seems to be a very important pathogenetic factor besides other predisposing condition such as: use of vitamin D, use of calcium-based and aluminum-based phosphate binders, obesity, rapid weight loss, elevated calcium, phosphate and PTH levels, use of vitamin K antagonists (warfarin), hypotensive dialysis episodes, local trauma, injection of medications such as iron dextran, remote and/or recent use of corticosteroids, coagulation abnormalities, diabetes mellitus and insulin injections, concomitant vascular disease, fetuin A deficiency and liver disease [4,12-14]. Cases of calciphylaxis are also reported to be associated with primary hyperparathyroidism, cirrhosis, multiple myeloma, leukemia, rheumatoid arthritis and the milk-alkali syndrome [10,12]. But all these risk factors suffer from the inability to establish the cause-effective relationship between marker and clinical event-a condition for defining a parameter as risk factor. Although these abnormalities are frequently seen in patients with kidney failure, calciphylaxis is relatively rare. The previous factors are more trigger factors than real risk factors. Lesions of calciphylaxis typically need only days to a couple of weeks before the full picture is developed. In majority of cases it is difficult to formulate a defined prognosis. We should be carefully and highly suspicious in patients with risk factors for calciphylaxis complaining of dermal pain and associated skin changes such as subcutaneous nodules, plaques or livedo reticularis in order to prevent future events. Development of skin ulceration places the patients at high risk for sepsis and increased mortality. We should intensively treat the underlying metabolic abnormalities and not allowing the development of non-healing skin ulceration.

Because of the lack of specific laboratory tests we should carefully consider other possible diagnosis as erythema nodosum, leukocytoclastic vasculitis, pyoderma gangrenosum, cellulitis, venous ulcers, bullous pemphigoids, and vibrio vulnificus infection. Radiological examinations are helpful but do not confirm the diagnosis. Plain X-ray of involved parts of the body may reveal area of calcification representative of small vessel calcification. Calcification is common in persons with ESRD, and not specific for calciphylaxis. However, a recent study including patients with calciphylaxis have presented with more vascular calcifications, and a net-like pattern of calcifications [15]. Ultrasound is a noninvasive and less painful alternative. It can show diffuse parenchymal edema, skin thickening and more importantly echogenic foci with posterior acoustic shadow that are suggestive of calcification [16]. Bone scintigraphy may be used as a noninvasive diagnostic tool with tracer accumulation in the calcified subcutaneous areas [17]. Nuclear bone scans have been reported as promising diagnostic tool for calciphylaxis. Serial bone scanning can also possibly be used to monitor progression or regression of the disease [18]. Histologic examination is considered the gold standard in diagnosis of calciphylaxis. The role of skin biopsy in the diagnosis of calciphylaxis is controversial. A punch or deep incisional biopsy is usually performed. Punch biopsies may not be adequate because the quantity of tissue obtained may not be enough for diagnosis. A deep incisional cutaneous biopsy is usually diagnostic. But, a deep incisional biopsy may invite further infection in the presence of an active infection and performed on a non-ulcerated lesion it could result in a non-healing wound or could exacerbate the pain [19]. However, only a biopsy allows a reliable diagnosis. Formulating appropriate therapy has been limited by a lack of clear understanding of the disease pathophysiology. No drug has official approval for treatment of calciphylaxis and no randomized controlled trial is available to guide management of affected patients. Treatment approaches to CUA are widely variable and derived from case reports or case series, or from pathophysiological considerations. A multidisciplinary therapeutic approach is recommended. The potential harmful trigger factors should be eliminated, including the discontinuation of therapy with calcitriol, calcium based phosphate binders, vitamin K antagonists and parenteral iron treatment.

The basis of therapy in patients with CUA is normalization of calcium, phosphorus and parathyroid hormone metabolism. Restriction of calcium and phosphorus intake should be considered. Use of noncalcium, nonaluminum phosphate binders and low-calcium bath dialysis is advocated [20]. In calciphylaxis cases associated with hyperparathyroidism successful use of calcimimetics has been reported [21,22]. Parathyroidectomy in patients with high levels of serum PTH appears to improve clinical condition, but evidence regarding improved survival is lacking [23,24]. Beneficial effect of bisphosphonates has been reported in some cases of calciphylaxis. These drugs can increase osteoprotegerin production and inhibit vascular calcification [25,26]. Wounds that are very painful require analgesia. Non-steroidal anti-inflammatory drugs or opioid pain medications should be used instead of morphine as byproducts of morphine can cause hypotension and slow the flow in the pannicular arterioles and consequently increase the risk of thrombosis [27]. The use of hyperbaric oxygen therapy may be an option in treatment of cutaneous ulcers of calciphylaxis. The aim is to restore tissue oxygen to normal or above-normal levels and thus enhance angiogenesis, fibroblast proliferation, and collagen production [28,29]. Sodium thiosulphate (STS) is the most used and studied drug in cases of calciphylaxis. Although the mechanism of action of STS is not completely elucidated, it is proposed to increase solubility of the calcium deposits and thereby be efficacious whether in uremic or nonuremic cases [30-32]. STS is an antioxidant agent and a chelator of cations (e.g., calcium) and initially was used as an antidote for cyanide and cisplatin toxicity. The antioxidant properties may help repair endothelial cell dysfunction and promote vasodilation. The mechanism for pain relief has been hypothesized to be due to the antioxidant properties of STS. Pain relief has been prescribed as the most remarkable change in cases of use of STS. This relief has been noted in majority of patients within the first days after initiation of treatment. Furthermore, the enhanced aqueous solubility of calcium thiosulphate allows successful mobilization and clearance of the vascular and soft tissue calcium deposits [33,34]. STS can be given orally [35], intravenously [36] or intraperitoneally [37]. The most commonly reported dose has been 25 g after or during each dia-

lysis session (5-75 g). Infusion times vary from 30 to 60 minutes. Generally it is well tolerated. But, some adverse effects such as nausea with emesis and development of an anion gap metabolic acidosis have been reported.
Low-dose tissue plasminogen activator has been successfully used in some cases of calciphylaxis (38). The role of anticoagulation in all cases of calciphylaxis is controversial, because most patients with ESRD have a prolonged bleeding time due to the uremic condition.

Conclusions

To the best of our knowledge there are very few cases reported in the literature with lesion of calciphylaxis located on the breast and moreover the lesion appeared during the first month of hemodialysis treatment. On the other hand, the majority of cases of calciphylaxis due to uremic condition need a long-standing history of renal replacement therapy. Because the mortality rate of patients with calciphylaxis is very high and depends especially on the presence of necrotic ulcerated lesion and possible bacterial contamination, which can lead to sepsis, early recognition and treatment is extremely important.

Conflict of interest statement. None declared.

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