CASE REPORT

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Calciphylaxis: a literature review based in two case reports

Calcifilaxia: revisão da literatura a propósito de 2 casos clínicos

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ABSTRACT

Calciphylaxis is a rare and devastating obliterative vasculopathy, leading to ischemia and subcutaneous necrosis. In most cases it affects patients with renal disease and is associated with high morbidity and mortality. We present two case reports followed recently in our department, and a literature review on this topic. Case one refers to an 80-year-old Caucasian woman with chronic kidney disease stage 5 and primary hyperparathyroidism with secondary brown tumour and calciphylaxis. Case two refers to a 59-year-old Caucasian woman admitted with severe nephrotic syndrome associated with amyloidosis, that developed a catastrophic picture of calciphylaxis, ending in the patient's death. There is a critical need to understand the pathogenesis of calciphylaxis. Its comprehension is the only way to improve the survival of these patients, and may help to elucidate the pathophysiology of vascular calcification in general. Educating physicians in the prevention and early detection of calciphylaxis is crucial. Only by increasing the knowledge about risk factors, pathophysiology, response to treatment and outcome, will we be able to improve prophylaxis and therapy of patients with calciphylaxis, decreasing the high mortality of this entity.

Key-words: calciphylaxis; chronic kidney disease; primary hyperparathyroidism.

RESUMO

A calcifilaxia é uma vasculopatia obliterativa devastadora e rara que leva a isquémia e necrose subcutânea. Afeta principalmente doentes com doença renal crónica sendo responsável por elevada morbilidade e mortalidade. No presente trabalho apresentamos dois casos clínicos recentemente acompanhados no nosso serviço, fazendo uma revisão bibliográfica sobre este tópico. O primeiro caso refere-se a uma mulher de 80 anos com doença renal crónica estadio 5, calcifilaxia e tumor de brown associados a hiperparatiroidismo primário. O segundo caso refere-se a uma mulher de 59 anos admitida por síndrome nefrótica associada a amiloidose com um quadro de calcifilaxia súbito e catastrófico que terminou com o óbito da paciente. A compreensão da patogénese da calcifilaxia poderá melhorar a sobrevivência destes doentes e, eventualmente, ajudar a elucidar a fisiopatologia da calcificação

vascular em geral. Informar os médicos para a prevenção e deteção precoce da calcifilaxia é crucial. Apenas aumentando o conhecimento dos fatores de risco, fisiopatologia, resposta ao tratamento e prognóstico seremos capazes de otimizar a profilaxia bem como a terapia de doentes com calcifilaxia e diminuir a elevada mortalidade associada a esta entidade.

Palavras chave: calcifilaxia; doença renal crónica; hiperparatiroidismo primário.

INTRODUCTION

Calciphylaxis is a rare and serious disorder characterized by medial calcification of the arterioles, leading to ischaemia and subcutaneous necrosis. It most often affects patients with end-stage renal disease (ESRD), on chronic dialysis or following renal transplantation, and leads to high morbidity and mortality.

The term calciphylaxis emerged, in 1961, by Selye *et al.* during early animal experiments[1], as a systemic hypersensitivity reaction similar to allergic reaction (anaphylaxis), and the term was adapted to human medicine afterwards[2]. Despite the resemblance with the animal, the skin lesion described by Selye *et al.*, characterized by tissue calcification, in the human cases, vascular calcification predominates, and the term calcific uremic arteriolopathy (CUA) has been proposed as a more suitable name[3]. As this clinical disorder has been reported in patients without uraemia, CUA can also be misleading, and the term calciphylaxis is still widely applied.

The incidence and prevalence of calciphylaxis remains to be determined. It has been described that can reach up to 5% of dialysis-dependent patients[4], but recent data from Germany[5] and Japan[6] suggested incidence of 1%. Calciphylaxis is still overlooked by clinicians and improved clinical awareness, as well different environmental and ictogenic factors, may increase its incidence in the future.

Although the advances made in the comprehension of the disease, the heterogeneity of patients and disease manifestations, allied to its rarity, have been an obstacle to any large-scale randomized controlled trial, concerning understanding and treatment of this disease. To overcome the problem Hayashi *et al.* had conducted a systematic nationwide survey collecting data from all cases of calciphylaxis treated in the majority of Japanese dialysis centers. Afterwards the authors performed a case–control study to identify the characteristics of calciphylaxis in the Japanese dialysis population[6]. An Internet-based registry (http://www.calciphylaxie.de) was also started in Germany with about 160 cases prospectively collected since late 2006.

In this paper we present two case reports recently diagnosed in our department, and we will review the literature on this topic.

CASE 1

An 80-year-old woman was admitted for dialysis initiation. Relevant medical history includes chronic kidney disease (CKD) stage 5 due to secondary glomerulosclerosis (right nephrectomy for lithiasis at 54 years old) and tubulointerstitial nephritis. She was medicated with enalapril 20 mg/day and darbepoetin 20 µg/week, with no other associated drugs (like vitamin D analogues or calcium-based phosphate binders). At admission, she presented painful, indurated subcutaneous nodules in the lower limbs, and a deformation of the left clavicle, that the patient related with trauma 3 months earlier. Meanwhile, diffuse cranial heterogeneity with several infra-centrimetric lesions was found in a cranial CT performed to study syncopal episodes presented during haemodialysis. Of the following study we point: normal immunoelectrophoresis and serum free light chain; Calcium (Ca): 9.2 mg/dl; Phosphate (Pi): 4.5 mg/dl; intact parathyroid hormone (iPTH) › 2500 pg/ml. A parathyroid

Figure 1

Cutaneous lesions of calciphylaxis

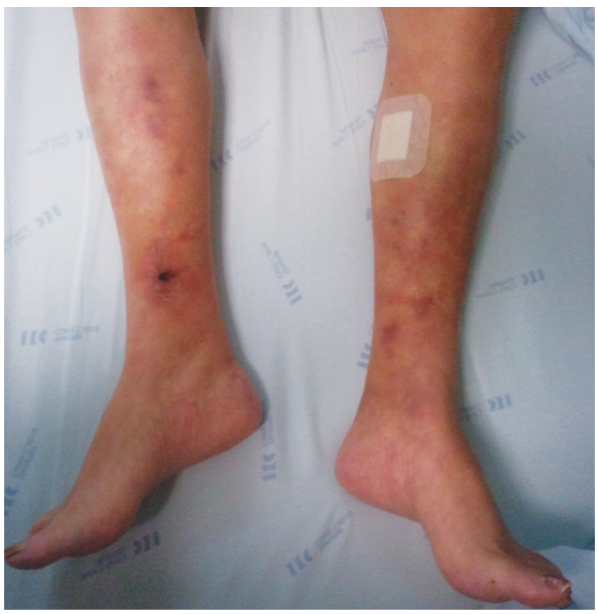
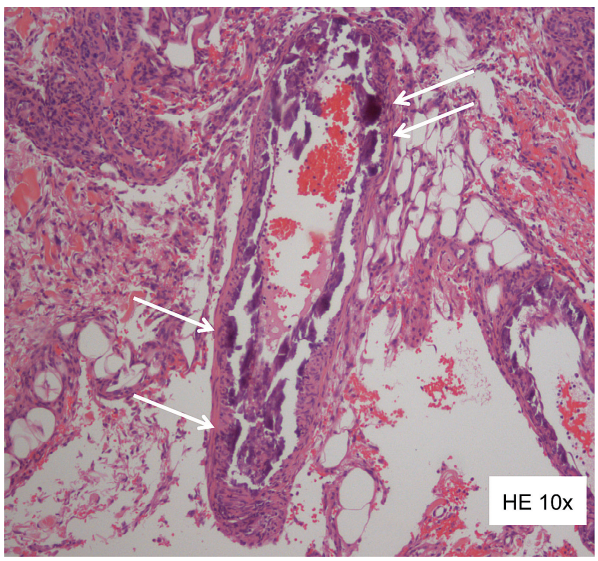


Figure 2

Medial calcification and intimal proliferation in small arteries.



ultrasound revealed nodules of solid hypoechoic characteristics (20×9 mm at right) and the scintigraphy, set with Sestamibi, revealed hyperfunctioning parathyroid tissue. At this time, an angio-CT was performed to the bone deformation, which revealed a bone lesion very likely to represent a Brown tumour. As the nodules in the lower limbs became more painful, with marmoreated skin and a dark ulcer (Fig. 1), a biopsy specimen of the skin was obtained and revealed calciphylaxis (Fig. 2). As a final diagnosis, primary hyperparathyroidism with secondary brown tumour and calciphylaxis were admitted. The lesions of calciphylaxis disappeared as haemodialysis, carbonate sevelamer and cinacalcet were initiated, with no further treatment required. The iPTH regressed to 1064 pg/ml and the patient is waiting for parathyroidectomy.

CASE 2

A 59-year-old Caucasian woman with past medical history relevant for uterine cancer treated with radiotherapy, complicated by radiation cystitis, radic colitis with colostomy. She developed severe nephrotic syndrome associated with amyloidosis in renal and skin biopsies, not able to be characterized by immunohistochemistry, was admitted due to acute on chronic renal failure [plasmatic urea (Pu) 115mg/dl, plasmatic creatinine (Pcr) 2.6 mg/dl] secondary to dehydration, *Escherichia Coli* urinary infection and bilateral hydronephrosis. Renal function improved after initiation of antibiotics and ureter catheterization. At the 26th day, following a nosocomial infection, a further deterioration of the renal function was observed. Laboratory findings revealed Pu: 138 mg/dl; Pcr 4.1mg/dl; Pi 14.9mg/dl; serum calcium 6.6 mg/dl; iPTH 265 pg/dl; Albumin: 1.2 mg/dl. A *livedo reticularis* in the lower limbs (thighs and legs) changed rapidly to extensive necrosis plaques. A biopsy specimen of the skin confirmed the suspicion of calciphylaxis. The patient started an intensive dialysis programme along with sevelamer and local wound care with surgical debridement, which improved her condition. One month later, a general clinical worsening was observed associated to bleeding dyscrasia (INR: 14.4; apTT: 82.1 s), most likely associated to factor X deficit, resultant of its connection to amyloid fibrils. The patient continued to deteriorate and died on the 75th day.

HOW TO RECOGNIZE AND DIAGNOSE CALCIPHYLAXIS

Confirmation of calciphylaxis is a crucial issue as late intervention is associated with unjustified therapeutic measures and poorer prognosis.

Diagnosis requires a high degree of clinical suspicion and is made clinically based in a triad:

a) Painful skin lesions, often refractory to standard analgesics[4].

b) Cutaneous lesions with characteristic progressive appearance. Initial lesions appear as red sub-cutaneous nodules or violaceous plaques, often in a *livedo reticularis* pattern. Lesions may increase in size and form ecchymosis or single indurated plaque formation, finally ending in characteristic black skin, deeply ulcerated scars and necrosis[7].

c) Medial calcification and intimal proliferation in small arteries are characteristic histological features[4], along with thrombotic vaso-occlusion, without vasculitic pattern.

Tissue biopsy remains the gold standard for diagnosis, but should not be routinely performed because of the risk of sampling error, inoculating or spreading infection and tissue trauma leading to ulcer progression[7-9].

The progressive lesions may reflect two processes of disease: initially calcific arteriolopathy, and lately ischaemic necrosis, related to reduced perfusion or vascular thrombosis[10,11]. This suggests that these skin lesions may be the equivalent of the lesions found in myocardial infarction[12]. Lesions frequently occur over areas with high adipose tissue content as it has less blood supply than other tissues[8, 9]. These lesions can be classified as distal (extremities), often in slim and malnourished patients, or proximal (trunk, thighs and/or buttocks), often in obese patients. Proximal pattern is more associated with deep ulcerations and fat tissue necrosis[8]. The distal pattern appears to have a better survival rate[13].

Many dermatologic disorders resemble the superficial lesions of calciphylaxis, but a careful patient history and histopathology can distinguish them[7]. Clotting disorders, such as protein C, protein S and antithrombin III deficiency and autoimmune diseases, may present with similar skin lesions and should be excluded[4]. A detailed list of differential diagnoses, as peripheral vascular disease, vasculitis, atheroembolism, warfarin therapy, has been published[10].

Currently, imaging plays a limited role in diagnosing calciphylaxis. Mammography has been proposed but can be a painful procedure[14], but bone scintigraphy with Tc99m methylene diphosphate has shown promise as a diagnostic tool for calciphylaxis in the detection of subcutaneous calcium deposits[9,15].

SEARCHING THE RECIPE FOR CALCIPHYLAXIS

The pathophysiology of calciphylaxis is complex and poorly understood. Many factors have been appointed as potential risk factors for the development of calciphylaxis but they faced significant limitations in the distinction between causality and pure association.

The most mentioned risk factor is CKD, particularly end-stage renal disease, metabolic abnormalities, and therapies associated as chronic kidney disease–mineral bone disorders[5,9,16,17], (CKD-MBD) definition according to the KDIGO nomenclature[18].

Hyperphosphataemia, hypercalcaemia and hyperparathyroidism play a well documented pathologic role in vascular calcification but its effect on the genesis of calciphylaxis is not as well established[4,8,13,17]. The vast majority of dialysis patients with comparable degrees of CKD-MBD never develop calciphylaxis and often calciphylaxis patients do not show uncontrolled values of mineral metabolism at the time of diagnosis. The discrepancy found in biochemical parameters may be partly explained by methodological variations in assays and by different intervals between the exposition to calcification promoting factors and clinical manifestations of calciphylaxis[19]. For the development of calcyphilaxis, the total calcium load and hyperphosphataemia period seems much more relevant than the isolated

measurement of high calcium or high phosphate serum levels.

In recent reports, warfarin therapy[8], low serum albumin level and high plasma glucose level were significantly associated with calciphylaxis[6,8].

Albumin level has already been related to the risk of thrombotic complications in nephrotic syndrome and as a marker for calcification. Even so, its role is confounded as it is regulated as negative acute-phase reactant, and can reflect malnutrition and increased dialysis-related mortality[13,14,20].

Other risk factors frequently mentioned include female gender[9,16], probably related to increased fat mass, diabetes[4,5,8,9,16], obesity[14,16] and hypercoagulable states, resulting from protein C and S deficiency[17,21,22], or antiphospholipid syndrome[23]. The pathologic changes of calciphylaxis promote by themselves thrombus formation that can be exacerbating by hypercoagulable states[16].

A systematic review of conditions associated with non-uraemic calciphylaxis has been published[19]. Most cases are due to primary hyperparathyroidism, malignancies[24,25], connective tissue diseases[26,27] and alcoholic liver disease[16,19,22]. Hyperparathyroidism is the most commonly reported condition but still has not been consistently recognized as an independent risk factor for the development of calciphylaxis[4,19].

Research in cardiovascular and bone diseases has identified a link between bone and vascular calcification. Factors such as receptor activator of nuclear factor-kB [RANK], RANK ligand and osteoprotegerin (OPG), which plays important roles in mineral deposition and bone resorption, also seems to regulate extra-skeletal mineralization. Derangement of this system has been tied to certain bone diseases and may underlie the pathogenesis of calciphylaxis[12,16,28]. Also, polymorphisms or deficiencies of OPG result in increased arterial calcification[29].

Some of the factors that can predispose to calciphylaxis (iPTH, corticosteroids, aluminum, liver disease, autoimmune states and various forms of inflammation) are known to increase the expression of RANK ligand, decreasing the expression of OPG, thus activating RANK and prompting calciphylaxis[16,19]. Furthermore, histological examinations suggest that calcification is associated with increased expression of osteopontin by smooth muscle cells[20].

In the first patient, we find that primary hyperparathyroidism, supported by the osteolitic lesions and Brown tumour, was the sensitizing factor (despite the normal calcium and phosphorus serum levels at presentation) and that renal failure was the trigger to calciphylaxis. For the development of calciphylaxis, the total calcium load and hyperphosphataemia period seems much more relevant than the isolated measurement of high calcium or high phosphate serum levels. In the second patient we can assume that factor X deficit, associated to amyloidosis, CKD and severe hypoalbuminaemia (Alb: 1.2 g/dl) were the predisposing factors. While acute exacerbation of chronic kidney failure, associated with acute hyperphosphataemia (Pi: 14.9 mg/dl), was the main trigger to calciphylaxis. In both cases CKD, as well as CKD-MBD, were present.

ROLE OF CALCIFICATION INHIBITORS

Deficiencies in vascular calcification inhibitors, such as fetuin-A and matrix Gla protein (MGP), have been postulated to play a key role in calciphylaxis[12,28,30]. Fetuin-A levels are reduced in patients with renal failure and in patients with inflammation[31]. Serum levels of both calcification inhibitors are especially low in patients with calciphylaxis, and the ability to inhibit basic calcium phosphate precipitation is much lower than in healthy controls[30,31]. Warfarin suppresses MGP function, which may explain the increased risk of calciphylaxis associated with this therapy[4-6,32].

The fact that only a small minority of patients develop calciphylaxis makes a multifactorial pathogenesis most likely. Selye's induced calcification in a two-step model, suggesting a sequential course of pathophysiological events, which closely approximates the description of vascular calcification that might occur in human calciphylaxis[1]. In a modern definition of Selye's calciphylaxis we may admit that probably the disease is a result of multiple factors that can sensitize and predispose patients to calciphylaxis development. These factors directly or indirectly activate NFkB, resulting in bone pathology and vascular calcification[12].

HOW TO TREAT CALCIPHYLAXIS?

There is no evidence-based medicine treatment option available for patients with calciphylaxis and a standard protocol has not been formally developed, due to late diagnosis and dismal prognosis. The heterogeneity of treatment amplifies the difficulties in establishing a correct evaluation of the success of different therapeutic approaches. Moreover, with the advances in our understanding new treatment options have emerged.

Calciphylaxis involves a multidisciplinary approach. Dermatologists, surgeons and nephrologists need to work hand-in-hand.

The initial management of the disease consists of supportive management, such as diligent wound care. Patients undergoing wound debridement appear to have improved survival[16]. Aggressive infection therapy is needed, as sepsis is the chief cause of death. Pain control is of great importance and nutritional support of patients affected by malnutrition is vital.

Reduce or, if possible, discontinue medications that have been implied in calchiphylaxis[8]. Probably the role of the iatrogenic intervention has been fundamental in the final step of the disease leading sensitized patients to calciphylaxis[33]. Indeed, calciphylaxis does not appear to be part of natural progressive CKD (as renal anaemia), since most patients do not develop it. Surprisingly, most patients with calciphylaxis benefited of medical surveillance and, therefore, the development of calciphylaxis might actually have iatrogenic components[8,33].

In fact, various pharmacologic or biological agents have been implicated in causing calciphylaxis, the most well-known being high-dose vitamin D and its analogues[9,16], calcium supplementation[9], warfarin[16], chemotherapy agents[21], iron dextran[9,38] and erythropoietin[13]. Steroids are controversial and have been implicated as a cause[16], as well as a therapeutic option[9,16,17,19].

Control of metabolic disturbances (hyperparathyroidism, hypercalcaemia, hyperphosphataemia) makes good clinical sense, although better outcomes have not been demonstrated[16,34]. Calcium loads can be decreased by reducing dialysate calcium to levels of ≤ 1.25 mmol/L and administering calcium-free phosphate binders. It has been showed that reducing the amount of calcium salts administered can drop the incidence of calciphylaxis[33]. Intensifying dialysis sessions in affected patients to increase calcium and phosphate removal[8] or changing from peritoneal to haemodialysis may help[33].

The most significant progress in treatment has been the use of sodium thiosulphate(STS)[35,36]. STS sequesters calcium ions to form highly soluble calcium thiosulfate complexes and can prevent calcium phosphate precipitation[36-38]. It is also an effective antioxidant and may, thus, limit tissue damage[39]. The benefits of STS in calciphylaxis patients include rapid pain relief and successful wound healing within weeks to months of initiating therapy[37, 39]. Side-effects, as metabolic acidosis, are low. One interesting new development may be the topical use of a 25% STS ointment[40].

Hyperbaric oxygen therapy (HBO) has been shown to improve wound healing counteracting tissue hypoxia by supplying high concentrations of oxygen; however, positive effects were largely limited to patients with distal forms of calciphylaxis[4,36].

Parathyroidectomy can improve calciphylaxis, but it should be limited to cases of refractory hyperparathyroidism with calcium receptor antagonists[3,41]. Cinacalcet has the unique ability to lower parathyroid hormone, calcium, and phosphate levels[7,42]. Application of bisphosphonates[42] and vitamin K supplementation is controversial[32].

All treatment alternatives available should be used for the treatment of calciphylaxis to promote synergistical actions that maximize the potential for wound healing and subsequent patient recovery[7].

As the pathogenesis of calciphylaxis is being better understood, targeted molecular therapies may become the way for therapeutic prevention.

PROGNOSIS

Calciphylaxis is a severe and life-threatening condition, with a mortality rate ranging from 46% to 80%[16]. It has been noted that the highest mortality is associated with secondary infection of the cutaneous lesions, leading to sepsis[7].

Factors associated with poorer overall prognosis include skin lesions involving the trunk, ulceration of skin lesions, female gender, increased weight, and the need for vascular surgical intervention[9,17,43].

CONCLUSION

Calciphylaxis is a rare, life-threatening complication of ESRD, although not exclusive to these patients.

There is a critical need to understand pathogenesis of calciphylaxis. Its comprehension is the only way to improve the survival of these patients and it may help to elucidate the pathophysiology of vascular calcification in general.

As seen in our case reports, it is fundamental to recognize the risk factors and keep great awareness to make the diagnosis as soon as possible in order to start the treatment and try to prevent the drastic consequences of the disease.

As we further expand our understanding of the complexity of vascular calcification, new therapeutic agents with the potential for preventing vascular calcification will arise. The effect of the introduction of non calcium--containing phosphate binders on the incidence and prevalence of calciphylaxis remains to be seen.

The participation in national and international registers of calchiphylaxis is an excellent tool to get an idea of the epidemiology of the disease[5].

Educating physicians to prevention and detection of calciphylaxis is crucial. Only by increasing the knowledge of risk factors, pathophysiology, response to treatment and outcome, will we be able to improve prophylaxis as well as the therapy of patients, and to decrease the high mortality of this entity.

Conflict of interest statement:None declared.

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