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REVIEW ARTICLE

Calciphylaxis: diagnosis and clinical features

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Abstract Calciphylaxis is a relatively rare disease, observed mainly in patients on dialysis, associated with high mortality rates, and characterized by painful skin ulceration. The pathogenesis of calciphylaxis is virtually unknown, although several risk factors, including warfarin therapy, hypoalbuminemia, and disturbances in calcium–phosphate metabolism, have been reported. The prevalence of calciphylaxis in Japan is likely to be less than 1:10,000 dialysis patients per year based on our nationwide survey in 2009. However, the results of the survey also showed that about 60 % of nephrologists in Japan are not familiar with the disease itself and it is highly likely that calciphylaxis is being overlooked. To facilitate recognition of calciphylaxis, we have proposed diagnostic criteria. At present, there is no specific therapy for calciphylaxis and general supportive measures, especially antibiotics for the accompanying infection and wound care, are important. Recently, sodium thiosulfate has been increasingly used to treat calciphylaxis and its efficacy should be evaluated by large clinical trials.

Keywords Calciphylaxis · Hemodialysis · Warfarin · Sodium thiosulfate

Introduction

Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare skin disease characterized by skin ulceration and necrosis with extreme pain, and mainly affects patients on chronic hemodialysis or peritoneal dialysis [1, 2]. The term, "calciphylaxis", was first described in 1961 as acute inflammation and ectopic calcification of skin and skeletal muscles in rats sensitized with "calcifying factors", such as parathyroid hormone and vitamin D followed by the administration of "challengers", such as metallic salts and ferrous–dextran [3]. This experimental model was originally thought to represent an animal model of dermatomyositis. In 1968, a case of hyperparathyroidism and skin lesions, which were characterized by calcifying panniculitis and fat and skin necrosis, was reported and the authors suggested that this case might represent a human example of calciphylaxis [4]. After this case report, similar patients with end-stage renal failure were reported and calciphylaxis has been increasingly recognized mainly in patients on chronic dialysis [5–7]. In these patients, however, skin lesions and pathological findings were clearly different from the rodent model. Therefore, the term calcific uremic arteriolopathy was proposed [2] and may be more appropriate, although calciphylaxis has often been reported in patients who were not uremic.

Epidemiology of calciphylaxis

In Western countries, the prevalence of calciphylaxis has been reported to range between 1 and 4 % in chronic hemodialysis patients [2], and this disease has also been reported in patients without uremia. The incidence of calciphylaxis was shown to be increasing in the previous study, although it is possible that increased awareness of this disease has resulted in this tendency. In Japan, the prevalence of calciphylaxis was completely unknown until our nationwide survey was performed in 2009 as part of a

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study of "Research on Intractable Disease of Health and Labour Sciences Research Grants". We sent questionnaires to all institutional members of the Japanese Society of Dialysis and Transplantation, and responses were obtained from 1,838 centers. Since the content and all the results of this survey have been reported elsewhere [8], only a brief summary is presented here. The responses showed that cases of calciphylaxis have been encountered at 151 of the centers in the past, involving a total of 249 cases. We also found reports of 72 sporadic cases in the Japanese literature over the past decade. Assuming that all the calciphylaxis cases in our survey and in the literature were seen within the past 10 years, the prevalence rate of calciphylaxis in Japan is calculated as less than three cases per 10,000 hemodialysis patients/year. On the other hand, only 6.4 % answered that they knew what calciphylaxis was, and about 60 % did not know about calciphylaxis. Therefore it is highly likely that calciphylaxis is being overlooked. Based on this surveillance, we have proposed diagnostic criteria of calciphylaxis in order to facilitate the recognition of this disease and have distributed a booklet about calciphylaxis to 3,760 hemodialysis centers and dermatology teaching hospitals [9]. If awareness of calciphylaxis is improved by these measures, the correct prevalence of this disease will be determined.

Clinical features of calciphylaxis

Presentation of a case

A 58-year-old Japanese man was admitted to hospital with multiple cutaneous ulcers on the right leg. The patient had a history of type 2 diabetes mellitus and had required percutaneous coronary intervention three times. Four years before admission, hemodialysis was begun for chronic renal failure. Eleven months before admission, warfarin therapy was started because of paroxysmal atrial fibrillation. Three months before admission, a small area of purple discoloration and tenderness appeared on the front of his lower right thigh. This area subsequently progressed to cutaneous ulcers with severe pain. Approximately 1 month before admission, skin culture yielded growth of Methicillin-resistant *Staphylococcus aureus*, and vancomycin was started. In spite of intensive local care of the skin lesion and therapy for infection, the skin ulcers did not improve and the patient was admitted to hospital. On examination, the skin of his leg had a large cutaneous ulcer with black eschars and surrounding erythematous lesions (Fig. 1a). There was no lymphadenopathy. The lungs were clear. The cardiac rhythm was regular, and grade 2 systolic murmur was heard. There was no sensory loss on either of the lower extremities. Pulsation of both popliteal arteries and the dorsal pedis was palpable. Debridement of the ulcers on the right thigh was performed and histological examination of the excised skin showed cutaneous necrosis and calcification of the tunica media and internal elastic membrane of small to medium-sized arterioles of the dermis and subcutaneous fat (Fig. 1c, d). These are characteristic findings of calciphylaxis. Twenty-five grams of sodium thiosulfate after each session of hemodialysis was started immediately. He experienced relief of pain after 1 week of sodium thiosulfate, and the skin ulcers improved very gradually. Eventually, the skin ulcers completely healed after 6 months of sodium thiosulfate therapy, leaving a skin scar.

The clinical course of a typical case of calciphylaxis has been presented here. Calciphylaxis can probably be defined as tissue injury due to local ischemia caused by metastatic calcification of small to medium-size vessels. Organ damage by calciphylaxis has been reported, not only in cutaneous tissue (calciphylaxis cutis) but also in internal organs (visceral calciphylaxis), including lung, pancreas, heart, and various other organs [10, 11]. However, the most common damage is to skin and subcutaneous tissues. The skin lesions in this disease usually begin with the appearance of extremely painful violaceous mottling, resembling livedo reticularis. This skin lesion gradually progresses to ulcers and eschars can develop (Fig. 1a, b). Lesions increase in size over weeks or months and become deeply ulcerated. The skin ulcer sometimes extends down to the fascia and becomes very vulnerable to secondary infection, which can develop into fatal systemic infection, such as sepsis.

Calciphylaxis is often classified as proximal (above the knee or elbow) and distal (below the knee or elbow) types, and the proximal type seems to occur more frequently than the distal type [2]. Indeed, in our study, a proximal lesion was involved in 21 cases out of the 28 definite cases selected because of the characteristic skin lesion and/or the pathological findings on skin biopsy from the cases collected by our nationwide surveillance. The proximal type is reported to have a higher mortality rate than the distal type, although, in our survey, the mortality rates of both types were similar (distal type 70 %, proximal type 76 %). Penile calciphylaxis is classified as a proximal type and is known to have a very poor prognosis [12]. In the literature, the mortality rate was 64 % and the mean time to death was 4 months, although no specific risk factors compared with the usual proximal type were found. In our study, two cases of penile calciphylaxis were reported and both patients died within 1 year.

No specific laboratory findings were reported although several risk factors have been reported [13–16]. Secondary hyperparathyroidism and disturbances in calcium–phosphate metabolism were often found to be risk factors for the development of calciphylaxis, and it has been suggested

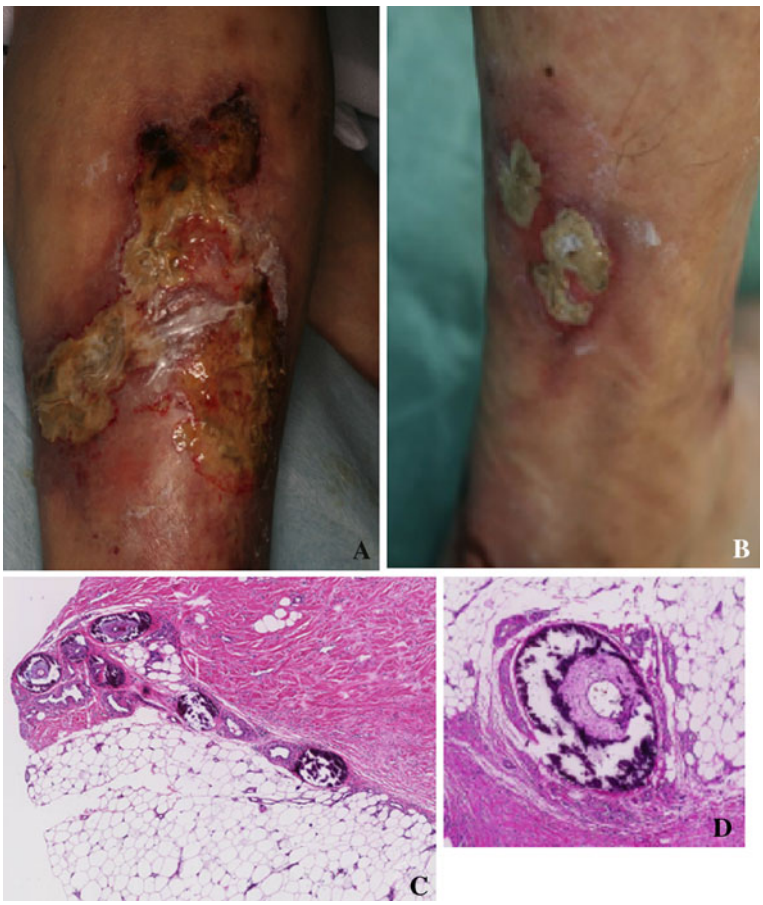

Fig. 1 **a**, **b** Typical skin lesions in calciphylaxis with ulcers and eschars. **c**, **d** Typical histopathological findings in arterioles including calcification of the tunica media and internal elastic membrane of the small arteriole of dermis and concentric stenosis due to edematous intimal thickening

that parathyroidectomy might be beneficial in cases with extremely high levels of parathyroid hormone [17]. In addition to these factors, female gender, BMI, steroid use, liver disease, serum aluminum concentration, and hypoalbuminemia were determined as risk factors in previous studies. In our study [8], using logistic analysis, hypoalbuminemia and warfarin use were significant, although other previously reported factors, such as calcium–phosphate products, gender, and parathyroid hormone levels, were not significant.

Histopathological findings of calciphylaxis include medial calcification of small arteries and arterioles, intimal proliferation, small vessel thrombosis and endovascular fibrosis, tissue ischemia, subcutaneous fat necrosis, and panniculitis. The diameter of calcified small arteries was characteristically around 100 μm. Among these findings, medial calcification and intimal proliferation were diagnostic findings of skin biopsy (Fig. 1c, d). Skin biopsy and characteristic histopathological findings are the gold standard for a diagnosis of calciphylaxis [18], although skin biopsy per se can worsen the skin lesions and should be not performed routinely. In most cases, however, debridement of the skin ulcer is performed and a specimen for pathological study can be obtained.

Differential diagnosis of calciphylaxis

Based on our survey and the clinical data obtained, we have proposed diagnostic criteria in a previous paper [9] (Table 1). In our study, 28 cases were diagnosed as definite calciphylaxis. From analysis of the clinical data from these 28 cases, we conclude that characteristic skin lesions are sufficiently diagnostic for calciphylaxis if end-stage renal failure is present. Since skin biopsy can worsen the skin lesions, it is recommended only if the clinical features do not meet the criteria for a definite diagnosis. The differential diagnosis for calciphylaxis is shown in Table 2. Among the various diseases which can show similar skin lesions, warfarin skin necrosis [19] and diabetic gangrene are the most important to differentiate. A medical record of recent warfarin administration may favor a diagnosis of warfarin skin ulcer, although warfarin is also a risk factor for calciphylaxis. Careful observation of the skin lesion is essential for differentiation of warfarin skin ulcer from calciphylaxis. It is very difficult to differentiate a solitary skin ulcer of calciphylaxis from diabetic gangrene. In these circumstances, histopathological observation of the skin is required to make a final diagnosis. Skin biopsy also distinguishes warfarin necrosis from calciphylaxis. Biopsy specimens of warfarin

Table 1 Proposed diagnostic criteria for calciphylaxis

The diagnosis of calciphylaxis can be made when:
1. The following clinical features are all present, or
2. Two of the following clinical features and typical histopathological findings are present.
Clinical features
1. A patient on chronic hemodialysis for chronic kidney disease or with a GFR of less than 15/ml/min/1.73 m^2
2. More than 2 painful and non-treatable skin ulcers with concomitant painful purpura
3. Painful and non-treatable skin ulcers on the trunk, extremities, or penis with concomitant painful purpura
Histopathological findings
Skin biopsy is recommended only if the three clinical findings presented above are not present. Typical histopathological findings of the skin are as follows:
Necrosis and ulceration of the skin with calcification of the tunica media and internal elastic membrane of small to medium-sized arterioles of dermis and subcutaneous fat are essential for the diagnosis
Concentric stenosis due to edematous intimal thickening is also seen in the small to medium-sized arterioles of dermis and subcutaneous fat

Table 2 Differential diagnosis of calciphylaxis

History and laboratory test
To rule out the following diseases, a history of gadolinium administration should be checked, and cryoglobulin, antinuclear antibody, and anti-phospholipid antibody should be determined
There is no specific laboratory test for calciphylaxis
Differential diagnosis
The following diseases should be ruled out:
Diabetic gangrene, skin necrosis due to heparin-induced thrombocytopenia, warfarin skin necrosis, scleroderma, nephrogenic systemic fibrosis, cholesterol embolization, cellulitis, cryoglobulinemia, therapy with hydroxyurea, antiphospholipid antibody syndrome, thermal injury, necrotizing fasciitis, venous disease with stasis, skin lesions due to ectopic calcification

necrosis usually demonstrate fibrin thrombi within cutaneous vessels with interstitial hemorrhage.

Treatment of calciphylaxis

The first line of therapy consists of wound care and appropriate antibiotics for infection [16, 20]. The barrier to infection provided by the skin is severely damaged by ulcers: local and generalized infections, such as sepsis, are inevitable. Since infection is a leading cause of death in calciphylaxis, appropriate and rigorous antibiotic therapy is essential for this disease. Because of severe pain and the accompanying condition, malnutrition is often seen. Therefore, nutritional support is also very important. To facilitate wound healing, debridement of skin ulcers is another part of essential care for calciphylaxis. From retrospective analysis, it has been shown that appropriate surgical debridement is a statistically significant treatment for calciphylaxis [20]. Peritoneal dialysis was shown to be a risk factor in the previous report; therefore, patients on continuous ambulatory peritoneal analysis (CAPD) should be changed to hemodialysis.

Most authors in the previous case reports recommend rigorous control of calcium–phosphate metabolism and secondary hyperparathyroidism. In patients in whom parathyroid gland hypertrophy is seen, parathyroidectomy has been recommended. A retrospective analysis of 13 cases documented the superiority of parathyroidectomy over medical management of hyperparathyroidism [17]. Recently, cinacalcet therapy has also been reported to be a useful therapeutic option for patients with calciphylaxis and hyperparathyroidism [21]. To reduce serum phosphate levels, non-calcium phosphate binders are recommended to avoid an increase in serum calcium levels, which has been reported to be a risk factor for the development of calciphylaxis.

Hyperbaric oxygen is usually used for the treatment of decompression sickness, carbon monoxide or cyanide poisoning, and arterial gas embolism. It is also known that hyperbaric oxygen is effective to facilitate wound healing. The addition of hyperbaric oxygen to other general measures seems to be beneficial in improving wound healing and reducing mortality [22]. Hyperbaric therapy is generally safe and most side effects, including myopia and symptomatic otic barotrauma, are mild and reversible in most cases, while severe side effects, such as seizures, are only seen in exceptional cases. Since hyperbaric oxygen is relatively safe, this therapy can be given to patients with calciphylaxis, although not many facilities possess the

equipment for hyperbaric oxygen. In addition, this therapy is rather expensive and medical insurance may not reimburse for calciphylaxis. For these reasons, hyperbaric oxygen has been used only on very few occasions.

Corticosteroids, used locally or systemically, are not warranted for the treatment of calciphylaxis. One previous report identified corticosteroid use as an independent risk factor for the development of calciphylaxis [16]. Furthermore, the high risk of wound infection and sepsis means that systemic use of corticosteroids should be avoided.

Sodium thiosulfate, which was originally used as an antidote to cyanide poisoning, has gained attention in the treatment of calciphylaxis recently [21, 23–26]. Sodium thiosulfate is a reducing agent, forms water-soluble complexes with many kinds of metals, and is thought to exert beneficial therapeutic effects on calciphylaxis in two ways: formation of calcium thiosulfate complexes and antioxidant activity. The benefits of intravenous injection of this compound were first reported in patients with tumoral calcification [27], which is a complication of end-stage renal failure and resembles calciphylaxis. The first case of calciphylaxis successfully treated with sodium thiosulfate was reported by Cicone et al. [23], and the patient showed dramatic improve in her pain and skin lesion. With this treatment, pain was relieved 2 weeks after the first injection, and, thereafter the skin lesions gradually improved. Sodium thiosulfate was given for 8 months without serious side effects and skin lesions were completely resolved. After this case report, sodium thiosulfate was used for many patients and several case studies were reported. In most of the patients, rapid relief of ischemic pain was experienced within days to weeks, and wound healing took 8 weeks or longer. Minor side effects, which include nausea, vomiting, and headache, were frequently reported, and high anion gap metabolic acidosis due to accumulation of thiosulfuric acid was also reported as the most likely side effect. Metabolic acidosis may induce impairment of bone metabolism and hypocalcemia. Indeed, in experimental animals, it was shown that bone strength was reduced with chronic sodium thiosulfate administration. Given the high mortality of calciphylaxis and the intolerable pain of skin ulcers, sodium thiosulfate should be tried for definite cases of calciphylaxis, even though clinical evidence from randomized controlled trials is lacking. Since an organized clinical trial has never been performed, there is no standard dose or duration of sodium thiosulfate administration. In most cases, 25 g of sodium thiosulfate (100 ml of 25 % solution) was administered intravenously as an infusion over 30–60 min three times a week after hemodialysis. In its pentahydrate form, sodium thiosulfate has a molecular weight of 248 Da and is easily dialyzed. When administered during hemodialysis, about 50 % of the dose is eliminated by dialysis. Therefore, sodium thiosulfate should be administered after the session of hemodialysis.

In conclusion, calciphylaxis is a rare but often fatal disorder in patients on chronic hemodialysis, and clinical suspicion is the single most important feature of the diagnosis. I hope that the diagnostic criteria proposed by our study group will facilitate the recognition of this disease.

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