

Calciophylaxis: fatal complication of cardio-metabolic syndrome in patients with end stage kidney disease

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Nefrología 2008; 28 (1) 32-36

SUMMARY

Calciophylaxis characterized by spheric skin ulceration due to subcutaneous small arterioles calcification, is a rare disease but usually fatal. Disorders of calcium metabolism and vascular calcifications are common in dialysis patients but calciophylaxis prevalence is low in patients with end stage renal disease. So we proposed other emergent factors implicated in calciophylaxis development. Methods: We studied retrospective 8 patients who developed calciophylaxis in our service from January 2001 to December 2006. Results: All patients were female with mean age at diagnosis 68.5 ± 6.7 years. All patients were receiving hemodialysis therapy and 6 patients had been receiving hemodialysis less than four months. Six patients had diabetes mellitus type II and all patients were obese ($BMI > 25 \text{ kg/m}^2$). All patients had metabolic syndrome (APTIII) with bad control hypertension and 6 (75%) were receiving anticoagulation therapy with warfarin. Patients didn't have severe alterations of calcium metabolism, all had product calcium-phosphorus < 55 . All patients developed low blood pressure at the beginning of dialysis treatment ($98.3 \pm 22.7/60 \pm 18,29 \text{ mmHg}$). 7 patients present proximal lesions in fatty regions like abdomen and thighs. Histopathologic examination reveals calcium deposits in arteriole-sized and small vessels with vascular thrombosis. Prognosis was poor, seven patients died secondary to a sepsis originated in infected cutaneous ulcers. Conclusions: calciophylaxis is a disease with poor prognosis and high mortality, without specific treatment actually. Female gender, obesity associated with diabetes mellitus and cardiometabolic syndrome, anticoagulant therapy with warfarin and low blood pressure associated with hemodialysis therapy, are risk factors to develop calciophylaxis, in absence of severe disorders of calcium metabolism. In these patients is important to avoid hypotension episodes during dialysis, dialysis hypotension appears to be an important risk factor who promotes ischemia of subcutaneous adipose tissue.

Key words: Calciophylaxis. Obesity. Metabolic syndrome. End chronic kidney disease.

RESUMEN

La calciofilaxia, caracterizada por la ulceración isquémica de la piel secundaria a la calcificación de las pequeñas arteriolas subcutáneas, es una enfermedad poco frecuente pero con mal pronóstico. Los pacientes con ERCT tienen

un riesgo alto de calcificaciones patológicas debido a las alteraciones del metabolismo calcio-fósforo, pero solo un pequeño número desarrollan esta enfermedad. Por ello es lógico pensar que hay otros factores que condicionan el desarrollo de la calciofilaxia. **Métodos:** Con el fin de identificar estos posibles factores implicados en su génesis, hemos analizado de forma retrospectiva las características de los 8 pacientes con ERCT que presentaron calciofilaxia en nuestro hospital entre de enero 2001 a diciembre 2006. **Resultados:** Los 8 pacientes eran mujeres con edad media de $68,5 \pm 6,7$ años. Todas presentaban ERCT en hemodiálisis periódica (HD) y en 6 casos la calciofilaxia apareció en los primeros 4 meses del inicio del tratamiento con HD. Seis de las pacientes eran diabéticas tipo 2 y todas eran obesas ($IMC > 25 \text{ kg/m}^2$), 3 con obesidad grado 4 o mórbida. Todas cumplían criterios de síndrome metabólico (APT III), habían sido hipertensas mal controladas y en un 75% de los casos recibían tratamiento con anticoagulantes cumarínicos por distintas causas. No presentaban alteraciones severas del metabolismo calcio-fósforo: todas tenían un producto $CaxP < 55$. En todos los casos se controló estrictamente la Presión arterial (PA) con el tratamiento con HD manteniendo cifras medias de PA de $98,3 \pm 22,7/60 \pm 18,29 \text{ mmHg}$ en el momento de la aparición de los síntomas. La mayoría de las pacientes (7/8), presentaron las lesiones a nivel proximal en las zonas con mayor depósito de grasa como muslos y abdomen. El estudio histológico de las lesiones en todos los casos demostró calcificación de pequeñas arteriolas subcutáneas asociada a paniculitis y trombosis de pequeños vasos. La evolución clínica fue mala ya que siete de las ocho pacientes murieron como consecuencia de una sepsis de origen cutáneo. La exéresis quirúrgica de los nódulos no modificó la mala evolución. **En conclusión:** La paniculitis calcificante en pacientes con ERCT es una enfermedad rara pero de mal pronóstico y elevada mortalidad. El sexo mujer, la obesidad asociada a Diabetes y Síndrome metabólico, el tratamiento anticoagulante y el excesivo control de la presión arterial al inicio del tratamiento con HD pueden favorecer su aparición incluso en ausencia de alteraciones relevantes del metabolismo Ca-P-PTH. Debido a la epidemia actual de DM, obesidad y síndrome metabólico es de esperar que el número de pacientes con estas características que desarrollen ERCT y calciofilaxia vaya en aumento.

Palabras clave: Calciofilaxia. Obesidad. Síndrome metabólico. Enfermedad renal crónica terminal.

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INTRODUCTION

Calciphylaxis, also known as «uremic gangrene syndrome», «uremic calcifying arteriopathy», or «calcifying panniculitis», is a rare disease associated to end-stage chronic renal disease (ESCRD). The prognosis is poor due to its high mortality. It is characterized by ischemia and skin necrosis secondary to calcification, fibrodysplasia of the intimal layer, and thrombosis of the small dermo-epidermic arterioles. Its prevalence ranges 1%-4% of dialysis patients.¹ In spite of having been described for the first time by Seyle in 1962,² the etiopathogenesis of this syndrome is still unclear. ESCRD patients have increased risk for pathological vascular calcifications associated to calcium-phosphorus metabolism impairments, although only a small number of them develop this dramatic disease. Thus, it is reasonable to think that there are other factors involved in the development of calciphylaxis. Aiming at identifying these factors, we undertook this study in which we analyzed the characteristics of those patients developing the disease at out hospital for the last six years.

PATIENTS AND METHODS

We present 8 female patients on hemodialysis (HD) with calciphylaxis that were diagnosed by means of biopsy at the Gregorio Marañón General University Hospital from January 2001 to December 2006. The biopsies were reviewed by an experienced dermatopathologist on this field, who verified in every case the characteristics of this disease such as calcium deposits within the arterioles and small vessels associated to endovascular fibrosis and thrombosis. The histological samples were studied by means of light microscopy and hematoxylin-eosin and silver stains.

Data from each patient were gathered regarding anthropometrical parameters, etiology of ESCRD, time on dialysis, cardiovascular risk factors, parameters of calcium-phosphorus metabolism and PTH, markers of inflammation, location and type of lesions, medications used during the progression of the disease, and therapies used for calciphylaxis, survival, and death cause.

RESULTS: CHARACTERISTICS OF THE PATIENTS

The characteristics of the study patients are described in table I.

All patients studied were females on HD, with an age range comprised 60-79 years. In 5 patients, calciphylaxis occurred within the first four months from starting on hemodialysis therapy. None of the patients had received previous renal transplant. All had varying obesity levels, 4 had grade 2 obesity, 1 grade 3, and 3 grade 4 or morbid obesity. All the patients met the criteria for metabolic syndrome according the ATPIII³ (defined as simultaneous presence of 3 or more of the following criteria: hypertension (AHT), triglycerides > 150 mg/dL, HDL-cholesterol < 50 mg/dL, baseline glycemia > 110 mg/dL, and waist perimeter > 88 cm in women). We may underline that in spite of a personal history of poorly controlled AHT in all patients, the blood pressure (BP) was strictly controlled with HD therapy and the average BP

Table I.

AGE	68.5 ± 6.7 años
ETIOLOGY OF ESCRD	
Diabetes Mellitus n (%)	6 (75%)
Vascular n (%)	1 (12.5%)
Unknown n (%)	1 (12.5%)
BMI (kg/m ² n)	37.6 ± 5.3
MEAN TIME ON HEMODIALYSIS BEFORE THE DIAGNOSIS	32.5 ± 44 months
Time on dialysis < 4 months n (%)	5 (62%)
MEDICATIONS USED BEFORE THE DIAGNOSIS n (%)	
Warfarin	6 (75%)
Calcitriol p.o.	6 (75%)
Calcium carbonate supplements	3 (37.5%)
Phosphorus chelating agents	3 (37.5%)
Systemic corticosteroids	1 (12.5%)
METABOLIC SYNDROME (≥ 3 ATPIII criteria) n (%)	8 (100%)
AHT	7 (87.5%)
Triglycerides >150 mg/dl	7 (87.5%)
HDL-Cholesterol < 50 mg/dl	5 (62.5%)
Baseline fasting glycemia basal >110 mg/dl	6 (75%)
Waist perimeter > 88 cm	8 (100%)
MEAN LABORATORY VALUES	
Calcium mg/dl	8.7 ± 0.76
Phosphorus mg/dl	4.5 ± 0.79
Calcium x Phosphorus product mg ² /dl ²	39.6 ± 6.9
< 55 mg ² /dl ² n (%)	8 (100%)
PTH n (pg/ml)	644 ± 535
- < 300 pg/ml (%)	3 (37.5%)
- > 300 pg/ml (%)	5 (62.5%)
Albumin mg/dl	2.1 ± 0.34
CRP	5.5 ± 1.7
MEAN BP (during two months prior to the development of the lesions)	
SBP mmHg	98.3 ± 22.7
DPB mmHg	60 ± 18.29

value for the two months before developing the disease was SBP 98.3 ± 22.7 and DPB 60 ± 18.2 mmHg. This marked decrease in mean BP values occurred after dry weight adjusting with HD and was sustained in spite of discontinuing antihypertensive medications in all the patients. Six patients were on coumarinic anti-coagulant therapy, in four of them due to chronic atrial fibrillation, one for prosthetic valve, and another one for thrombosis of the superior vena cava. One out of 8 patients was on steroid therapy (Prednisone 10 mg/day) for rheumatoid arthritis therapy. In all cases, the calcium x phosphorus product was < 55 mg²/dL², and three patients had PTH < 300 pg/mL. Six patients received treatment with oral calcitriol (dose 0.25-0.50 mcg three times in a week), 3 with calcium carbonate supplements (1.5-3 g/day), and 3 with non-calcium based phosphorus chelating agents (2 patients with aluminum hydroxide and 1 patient with Sevelamer). Three patients had been submitted to parathyroidectomy due to severe secondary hyperparathyroidism before developing the disease. In all cases, the parameters of inflammation were altered at the time of diagnosis; all the patients had low serum albumin levels and high CRP levels.

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CHARACTERISTICS OF THE SKIN LESIONS AND CLINICAL PRESENTATION OF THE DISEASE

In all the patients the lesions started as nodules and extremely painful indurated and erythematoviolaceous plaques (fig. 1). Within the next days, these lesions got enlarged and ulcerated, producing necrotic lesions (fig. 2). In 7 out of 8 patients, these lesions presented a characteristic central distribution predominating in areas with higher fat deposition such as the thighs and the abdomen. In one patient, the lesions occurred distally, involving the left lower limb.

All patients had a skin biopsy taken. The biopsies showed changes characteristic of calciphylaxis, such as calcium deposition within the arterioles and small vessels associated to endovascular fibrosis (figs. 3 and 4). The lesions showed skin necrosis at different levels (epidermal, dermal, and hypodermal), and in most of the patients (6/8) panniculitis and thrombosis of the small vessels and arterioles was observed, as well as of the small vessels and arterioles of the dermal-epidermal junction.

The patients course was very poor: 7 (87.5%) died within a mean time of 51 ± 21 days from the onset of the lesions, as a result of sepsis of skin origin. In 5 patients, surgical exeresis or debridement of the lesions was done with no change in their poor prognosis. Calcium carbonate supplements and calcitriol were also discontinued at the time of diagnosis, warfarin was replaced by low molecular weight heparins (LMWH), and the dialysis rate was increased to 6 sessions/week, and from 3 h to 3.5 h/session). In one patient, therapy with biphosphonates was started (sodium etidronate 200 mg/day), which was discontinued since there was no clinical improvement after 10 days on treatment.

In only one patient the lesions regressed until disappearance after switching the therapy to LMWH, daily HD, and discontinuation of vitamin D analogues. This patient presented obesity, with a BMI of 33 kg/m^2 and type 2 DM, and was being treated with warfarin and had altered inflammatory parameters such as CRP of 6.4 and albumin of 2.5 mg/dL.



Figure 1. Erythematoviolaceous plaque at the external side of the thigh.



Figure 2. Necrotic lesions at the internal side of the right thigh.

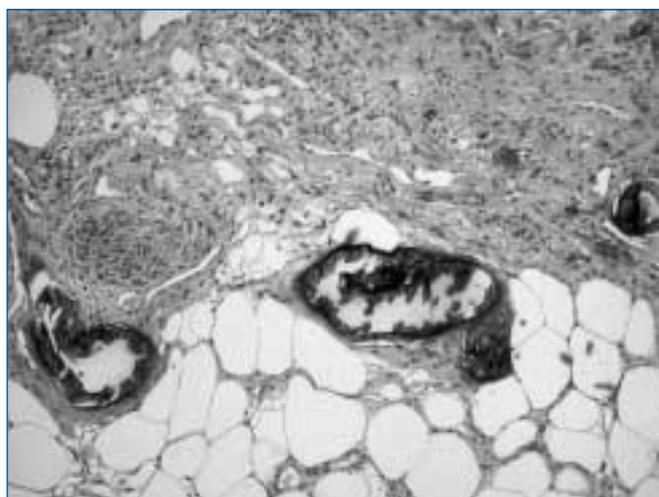


Figure 3. Histological image. Calcification of the walls of the arteries in the dermal-epidermal junction together with irregular lymphohistiocytic infiltrates at the hypodermis (Hematoxylin/Eosin, X40).

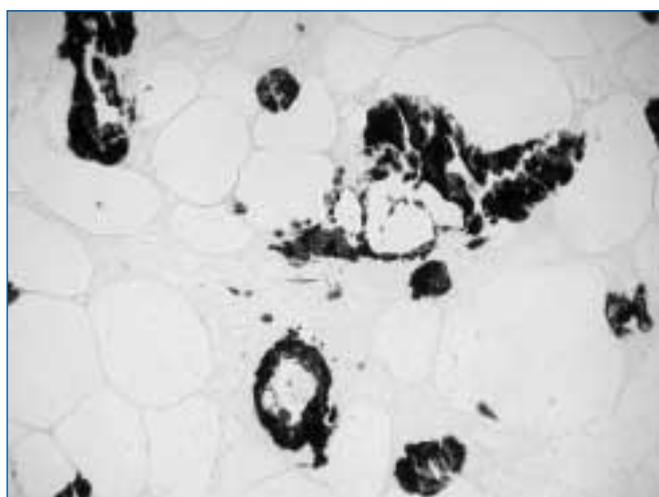


Figure 4. Histological image with silver staining (Von Kossa) in which calcium deposition is observed within the small-sized arteries at the hypodermis (X40).

DISCUSSION

Calcium-phosphorus metabolism impairments are the basis for the development of pathological vascular calcifications and calciphylaxis. However, even though almost every ESKRD patient presents these changes, the development of calcifying panniculitis is exceptional. The aim of this study was to characterize the group of patients developing calciphylaxis and identifying possible risk factors for developing this disease.

All the patients studied shared common characteristics, all were women, Caucasian, obese, and met the criteria for metabolic syndrome, and after hemodialysis therapy they presented low BP values. The preponderance of this disease among the female gender of Caucasian origin has already been described in other studies.⁴

The relationship between obesity, which is associated to the presence of diabetes mellitus and metabolic syndrome,⁵ and calciphylaxis is unclear, although it seems to be favored by the increase in the subcutaneous fat tissue and its circulation compromise. The subcutaneous compartment is increased in obesity due to fat tissue increase at that level. The expansion of this compartment induces tension increase to the fibroelastic septa penetrating it and containing the blood vessels irrigating the skin and subcutaneous tissue. This skin vascular system is a low-pressure one. The tension increase promotes traction of the fibroelastic septa and vessels promoting, on the one hand, vascular calcification and, on the other hand, this increase in vascular resistance decreases the regional flow.⁶ If BP decline is added to the effects of obesity on skin circulation compromise, as it happened in the patients studied after hemodialysis therapy onset, there is hypoperfusion of the subcutaneous tissue favoring skin ischemia. This effect is even more pronounced when there is vascular calcification (as it happens in many ESKRD patients) since calcified vessels cannot get dilated to increase the blood flow in response to hypotension-induced hypoperfusion. This mechanism may be the triggering factor of calciphylaxis in the patients in our study, who all were obese and poorly controlled hypertensive patients until starting on hemodialysis therapy. With this technique, when volume overload causing AHT is corrected, there is a depletion of the intravascular volume compromising perfusion, essentially in low-pressure systems or with vascular calcification.⁷ Most of the patients presented proximal lesions, at sites of increased fat deposition such as the abdomen and thighs, supporting this theory.⁸

The disease presentation was similar in all the patients, with occurrence of extremely painful nodules and erythematoviolaceous plaques on the thighs and the abdomen, rapidly progressing to ulceration and necrosis. This central presentation form has been related to higher prevalence of diabetes mellitus⁹ and obesity.¹⁰ In a study Braden et al.¹¹ highlight increased BMI in patients with central calciphylaxis versus those patients with distal involvement (38 kg/m² vs 29.3 kg/m²; P < 0.005).

Another factor that may favor the development of this disease is anti-coagulant therapy with coumarinic agents such as warfarin, which promotes vascular calcification through inhibition of vitamin K-dependent γ -carboxylation of the matrix protein Gla¹² (an extracellular protein inhibiting vascular cal-

cification and promoting bone formation). In our patients there was a high prevalence of warfarin therapy (6/8 patients received this drug for different reasons), which might have worsened vascular calcification and promoted the occurrence of the disease.

Calcium-phosphorus metabolism impairments are less important in patients with proximal lesions than in those with distal impairment. Our patients did not present severe impairments of the calcium-phosphorus metabolism, all had properly controlled calcium-phosphorus product, and only 3 had severe hyperparathyroidism (PTH > 1,000 pg/mL). This suggests that calcium-phosphorus metabolism impairments are an important factor in vascular calcification in ESKRD patients, although they are not the determinant factor for the development of calcifying panniculitis.

Calciphylaxis with predominantly central involvement has been related with poorer prognosis and higher mortality than the distal form.^{4,8}

The characteristic changes of calciphylaxis, already described in the literature, such as calcification of the small vessels and endovascular hypertrophy associated to panniculitis and thrombosis,¹³ were confirmed in the histological samples of all of our patients.

There is currently no standard or universal therapy for calciphylaxis. Parathyroidectomy in patients developing calciphylaxis and presenting severe hyperparathyroidism may be beneficial,¹⁴ although its usefulness is controversial since many studies have shown not to modify the disease course.¹⁵ Surgical debridement or exeresis of the lesions has shown benefits in some series,¹⁶ although in our patients surgical intervention did not modify the poor progression. Currently, it is recommended to discontinue therapy with calcium supplements and vitamin D, to increase the dialysis frequency to 5-6 sessions/week, and to decrease the calcium concentration of the dialysis bath to 1.5-1 mEq/L,¹⁷ although these measures stabilize the lesions in a small number of patients. Other measures aimed at improving tissue hypoxia, such as hyperbaric oxygen or sodium thiosulfate¹⁸ (an antioxidant able to bind to the nitric oxide synthetase enzyme, besides acting as calcium chelator) have also been used. Recently reported in the literature are cases of patients treated with bisphosphonates, in which there was a regression of the lesions after starting therapy with sodium etidronate.¹⁹ We have used this treatment in one of our patients without observing improvement of the lesions or the survival. Recently, there have been cases treated with cinacalcet²⁰ with a good course, although there is currently still little experience with this type of drugs for treating calciphylaxis.

In spite of the current therapies, the disease prognosis still is very poor, with a mortality ranging 60%-80%. The most common death cause is sepsis from cutaneous origin, as it happened in 87.5% of our patients.

In summary, calciphylaxis is a disease with a very poor prognosis and high mortality, with no specific therapy with demonstrated efficacy to date. Female gender and obesity associated to diabetes mellitus and metabolic syndrome, anti-coagulant therapy, and excessive blood pressure control at the beginning of HD therapy may favor its occurrence, even in

the absence of relevant mineral metabolism changes. Given the current epidemics of DM, obesity, and metabolic syndrome, it is foreseeable that the number of patients on HD and calciphylaxis will increase. In these patients with obesity, DM and metabolic syndrome HD-associated hypotension should be avoided since it may be a factor promoting ischemia of the subcutaneous fat tissue.

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