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Clinical report

Calciphylaxis. A review of 9 cases☆

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ABSTRACT

Background and objective: Calciphylaxis is a cutaneous ischaemic vascular disease of small vessels with high morbidity and mortality. To date very few series of patients with this disease have been published, none from a Spanish hospital. The main objectives of this work are to analyse the demographic, clinical and histological profile of patients diagnosed in our department to identify risk factors and potential therapeutic strategies.
Material and method: We made a retrospective study of the cases seen in the dermatology department with a diagnosis of calciphylaxis and who had a confirmatory biopsy in the period between January 2010 to August 2015.
Results: Nine patients were studied, with an age range of 76–86 years. All had cardiovascular comorbidities and 67% had renal failure. A 33% mortality was observed.
Conclusions: Faced with a possible diagnosis of calciphylaxis, a complete blood analysis is mandatory to rule out other causes of skin ulcers. The management of these patients should be undertaken by a multidisciplinary team. We emphasize the role of sodium thiosulfate in the treatment of this condition.

Calcifilaxia. Estudio de 9 casos

Palabras clave:
Calcifilaxia
Hiperparatiroidismo
Tiosulfato sódico
Úlcera cutánea

RESUMEN

Fundamento y objetivo: La calcifilaxia es una vasculopatía cutánea isquémica de vasos de pequeño tamaño con una alta morbimortalidad. Hasta el momento actual han sido publicadas muy pocas series de pacientes con esta enfermedad, ninguna procedente de un hospital español. Los principales objetivos de este trabajo son analizar el perfil demográfico, clínico e histológico de los pacientes diagnosticados de calcifilaxia en nuestro servicio, para identificar posibles factores de riesgo y potenciales estrategias terapéuticas.
Material y método: Estudio retrospectivo de los casos vistos en el Servicio de Dermatología con diagnóstico de calcifilaxia con una biopsia confirmatoria, en el periodo de enero de 2010 a agosto de 2015.
Resultados: Se estudiaron 9 pacientes, con edades de 76-86 años. Todos tenían comorbilidades cardiovasculares y el 67% tenía insuficiencia renal. Se observó un 33% de mortalidad.
Conclusiones: Ante el posible diagnóstico de calcifilaxia debe realizarse una analítica sanguínea completa para descartar otras causas de úlceras cutáneas. El tratamiento de estos pacientes debe llevarse a cabo por un equipo multidisciplinar. Resaltamos el papel del tiosulfato sódico en el tratamiento de esta entidad.

Introduction

Calciphylaxis is a cutaneous small-vessel ischaemic vascular disease.[1] It is a rare entity, more common in patients with chronic kidney disease and, especially, in those on haemodialysis.[2] The main risk factors are hypercalcaemia, hyperphosphatemia, elevated calcium-phosphorus product, elevated parathyroid hormone

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Table 1
Summary of clinical data of patients.

	Sex and age	CKD	Comorbidity	PTH (pg/ml)	Vit D (ng/ml)	Ca/P (mg/dl)	Ca × P
1	86F	No	HBP, diabetes, atrial fibrillation, OAC, hypoalbuminaemia	22		7.8/2.9	22.6
2	76M	No	HBP, diabetes, ischaemic valvular and heart disease	70	14	10.2/3	30.6
3	89M	Yes	HBP, diabetes, valvular disease, taking CT due to autoimmune disease, myelomonocytic leukaemia, hypothyroidism, hypoalbuminaemia	60	24	8.8/4	35.2
4	77F	Yes	HBP, rheumatoid arthritis, taking CT	186	18	10.6/3.9	41.3
5	66F	Yes	HBP, diabetes, peripheral vascular disease, hypoalbuminaemia	108		8.3/2.9	24.1
6	84M	Yes	HBP, diabetes, AF, valvular heart disease, stroke, OAC, colon neoplasia	361	6	9/3.6	32.4
7	80M	Yes (HD)	HBP, diabetes, valvular and ischaemic heart disease, OAC	109	13	9.1/4.5	41
8	80M	Yes	Hypertension, diabetes, ischaemic heart disease, OAC, hypoalbuminaemia	170	9	8.2/2.3	18.86
9	66F	No	Diabetes, dyslipidaemia, ANCA+ vasculitis, taking CT	94	12	8.4/1.8	15.12

OAC: oral anticoagulants; ANCA: neutrophil cytoplasmic antibodies; Ca: calcium; CT: oral corticosteroids; CKD: chronic kidney disease; AF: atrial fibrillation; HD: haemodialysis; HBP: high blood pressure; F: female; P: phosphorus; PTH: parathyroid hormone; M: male.

(PTH) and hypoalbuminaemia; obesity and diabetes mellitus; previous treatment with systemic corticosteroids, anticoagulants, derivatives of vitamin D and calcium salts. Although the development of calciphylaxis has been traditionally associated with chronic kidney disease patients, it can also occur in people without this condition.[3] The risk factors described in these patients are primary hyperparathyroidism, neoplasms, connective tissue diseases, protein C and S deficiency, and cirrhosis.

Although the pathophysiology of this entity is not yet well established, it appears that the different predisposing factors produce a rise of κ–β nuclear factor and consequently entail impaired bone mineralization and vascular calcification.[4]

Occurs more frequently in women after the fifth decade of life with erythema, increased local temperature and livedoid skin appearance, most often located in abdomen, buttocks and medial thighs. Necrotic sores and painful ulcers form progressively and usually have a torpid course with poor healing.

Definitive diagnosis requires a biopsy, which also serve to rule out other conditions that can produce similar lesions (atherosclerotic vascular disease, cholesterol embolization, nephrogenic systemic fibrosis, oxalosis, fulminans purpura, vasculitis, anticoagulant-induced necrosis, etc.).

Histopathological findings include: small and medium sized vessel calcification, f intimal hyperplasia, fibrin microthrombi, extravascular calcification, septal and lobular panniculitis, ulcers, necrosis of subcutaneous fat, etc. Von Kossa and Alizarin red staining are very useful for the identification of calcium deposits.[5]

Radiography of the affected area may prove useful to visualize an extensive calcification of soft tissue vessels.[2]

A multidisciplinary approach is essential for the proper treatment of these patients. Multiple therapeutic options[1] have been described but with little scientific evidence and limited effectiveness.

The prognosis is usually poor with a mortality rate of 60–80%, mainly due to the high risk of infection and sepsis.

To date, very few series of patients with this disease have been published,[6] none from a Spanish hospital. The research has focused mainly in patients with chronic kidney disease.

The main objectives of this work are to analyse the demographic, clinical and histological profile of patients diagnosed with calciphylaxis in our service, in order to identify potential risk factors and potential therapeutic strategies.

Materials and methods

We conducted a retrospective review of all cases seen in the Department of Dermatology diagnosed with calciphylaxis with a confirmatory biopsy in the period between January 2010 and August 2015. The main sources were the database of the Department of Pathology and the clinical history of patients. 9 patients were reviewed. All subjects underwent a complete medical history, physical examination, blood tests and skin biopsy. Calciphylaxis diagnosis was made taking into account all clinical and histological data. Besides a comprehensive assessment of the histological pieces was performed by an expert dermatopathologist (4).

Results

9 patients were studied in total. The ratio of male to female was 1.25:1, with an age range of 76–86 years (mean 78). The mean progression time of lesions to diagnosis was 10 weeks. Table 1 shows the clinical and laboratory data of patients and Table 2 shows the summary of the treatments received and their progression.

As for comorbidities, all patients had a cardiovascular risk factor and/or established cardiovascular disease. 44% were taking oral anticoagulants before diagnosis of calciphylaxis. 67% of patients had renal disease, of which 25% were treated with haemodialysis (patient 7). In the latter, the time of appearance after the start of dialysis was 3 years.

The lesions were located in the lower limbs and presented in most cases as very painful necrotic ulcers, with purplish adjacent skin and reticular pattern (Fig. 1).

As the calcium-phosphorus metabolism, all patients except case 1 had increased PTH, with a range of 60–361 pg/ml and an average of 131.11. The mean calcium × phosphorus product was 29.02 (range of 15.12–41.3).

The most common histological finding was ring-shaped calcifications of arterioles of medium and small calibre in all cases (Fig. 2). Calcification in capillaries is less frequent and requires von Kossa staining to be visible (50% of cases). Intimal hyperplasia and concentric fibrosis was observed with significant lumen reduction in all cases (Fig. 2). Another common finding was subcutaneous fat necrosis. We also observed epidermis and underlying dermis necrosis (70%). Extravascular calcifications were observed less frequently, including the involvement of a nerve trunk and calcification around the adnexum in case 1. Table 3 summarizes the main histological findings in each case.

All patients received local cures. 5 out of 9 patients (56%) underwent surgical debridement with good clinical response and one underwent a partial skin graft (patient 4), which became necrotic in subsequent weeks.

33% mortality was observed, with the death of 3 patients, 2 and 4 months after diagnosis of calciphylaxis. The causes of death were abdominal abscess (patient 3), sepsis (patient 5) and worsening of