

Calcinosis cutis universalis associated with systemic lupus erythematosus: an exuberant case*

Calcinose cútis distrófica universal associada a lúpus eritematoso sistêmico: um caso exuberante

Ana Paula Gonçalves Carocha ¹
Gimelly Ribeiro Barreto ³
Mayra Carrijo Rochael ⁵

Daniel Moscon Torturella ²
Rogerio Ribeiro Estrella ⁴

Abstract: Calcinosis cutis is an uncommon disease of unclear pathophysiology that is often disabling. It is characterized by the formation of calcium deposits in the skin or subcutaneous tissue. It is classified into four subtypes: dystrophic, metastatic, idiopathic or iatrogenic. It may be seen in a variety of systemic diseases such as hyperparathyroidism and hypervitaminosis D, but is most commonly found in dermatomyositis, scleroderma and overlap syndromes and is a rare complication of systemic lupus erythematosus. The management of secondary complications and the success of therapy are constant challenges in the follow-up of these cases.

Keywords: Calcinosis; Systemic lupus erythematosus; rheumatic diseases

Resumo: Calcinose cutânea é uma doença incomum, de fisiopatologia incerta e, muitas vezes, incapacitante. Caracteriza-se pela deposição de sais de cálcio na pele ou tecido subcutâneo. É classificada em quatro subtipos: metastática, distrófica, idiopática e iatrogênica. Pode ser vista em várias doenças sistêmicas como hiperparatireoidismo e hipervitaminose D, ocorrendo com maior frequência na dermatomiosite, esclerodermia e síndromes overlap, sendo uma complicação infrequente no lúpus eritematoso sistêmico.

O manejo das complicações secundárias, assim como o sucesso terapêutico, constituem desafios constantes no seguimento destes casos.

Palavras-chave: Calcinose; Doenças reumáticas; Lúpus eritematoso sistêmico

INTRODUCTION

Calcinosis cutis is the formation of calcium salt deposits in the skin or subcutaneous tissue. When confined to a small area of the extremities and joints, it is described as calcinosis circumscripta. When diffuse, it is referred to as calcinosis universalis and affects the subcutaneous and fibrous structures of the muscles and tendons. It has been classified into four types: metastatic, dystrophic, idiopathic and iatrogenic.¹⁻¹¹

In systemic lupus erythematosus (SLE), the formation of ectopic calcium deposits is a rare finding. The first cases were described in 1961 and occurred at a mean of 9.8 years following diagnosis of SLE.^{8,12}

The present paper describes a case in which the patient developed exuberant dystrophic calcinosis cutis universalis thirteen years after having been diag-

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¹ Currently participating in postgraduate studies in Dermatology at the Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, Brazil.

² Currently participating in postgraduate studies in Dermatology at the Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, Brazil.

³ Medical student, Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, Brazil.

⁴ Adjunct Professor, Department of Dermatology, Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, Brazil.

⁵ Doctorate in Anatomopathology from the Universidade Federal Fluminense (UFF). Associate Professor, Department of Pathology, Division of Dermatopathology, Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, Brazil.

nosed with SLE. Treatment was initiated with diltiazem and aluminum hydroxide. The patient was followed up over 6 months; however, results were discouraging.

CASE REPORT

A 30-year old female teacher had received a definitive diagnosis of SLE thirteen years previously and was currently using prednisone 30 mg/day and hydroxychloroquine 400 mg/day, albeit irregularly. She reported that four years previously, erythematous, painful plaques that felt hard to the touch had appeared on her arms, legs and thighs. She denied having had any previous complaints compatible with myopathy.

Dermatological examination showed hardened, erythematous, violaceous plaques with telangiectasias and atrophic and ulcerated areas on her arms, buttocks and on the backs of her thighs (Figures 1 and 2). She also had livedo reticularis on her arms, buttocks, thighs and back. She had periorbital erythema and a rash in the malar region. There were erythematous papules on the interphalangeal and metacarpophalangeal joints of her hands.

Full blood count, erythrocyte sedimentation rate (ESR), clinical chemistry, antinuclear factor (ANF), anti-RNP, anti-Jo-1, anti-Mi and limb x-rays were requested and a punch biopsy was performed on the skin lesion on the patient's left arm. The abnormalities detected in the laboratory tests were: leucopenia $2.98 \times 10^3/\text{mm}^3$ leukocytes (normal range: $5-11 \times 10^3/\text{mm}^3$), ESR 40 mm/h (normal range: ≤ 20 mm/h), ANF 1/200 cytoplasmic dot staining pattern (normal range: $\geq 1/80$), alkaline phosphatase 233 U/L (normal range: $35-104$ U/L) and gamma GT 70 U/L

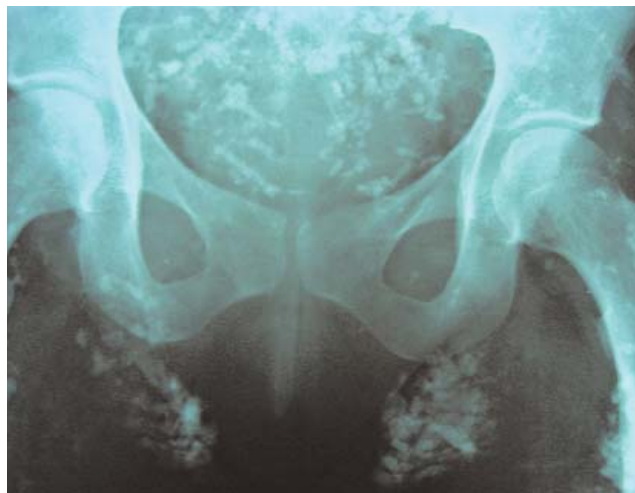


FIGURE 3: Multiple radio-opaque images, clearly outlined in the subcutaneous tissues corresponding to calcium deposits at pelvic radiography

(normal range: 8-41 U/L). Anti-DNA, anti-RNP, anti-Jo-1 and Anti-Mi were nonreactive. Serum creatinine phosphokinase (CPK) and transaminase (TGO and TGP) levels were normal. Serum calcium and phosphorus levels were 9.4 mg/dL and 3.4 mg/dL, respectively (normal range: calcium: 8.5 – 10 mg/dL, phosphorus: 2.5 – 4.3 mg/dL). Hand, elbow, knee and spleen x-rays showed multiple, clearly outlined radio-opaque images in the subcutaneous tissues (Figures 3 and 4).

Biopsy showed an intense inflammatory infiltrate throughout the entire dermis with numerous sites of calcification in the dermis and in the subcutaneous tissue, corroborating the diagnosis (Figures 5 and 6).



FIGURE 1: Hardened, erythematous, violaceous plaques with telangiectasias interspersed with atrophic and ulcerated areas and livedo reticularis on the buttocks and backs of the thighs



FIGURE 3: Ulcerated lesion with an erythematous base, releasing a hardened, whitish content composed of calcium salts



FIGURE 4: X-ray of the same lesion shown in Figure 3

DISCUSSION

Calcinosis is classified into four subtypes: metastatic, dystrophic, idiopathic and iatrogenic. The metastatic type occurs in normal tissue as the result of increased serum calcium and/or phosphorus levels and a calcium x phosphate product ≥ 70 mg/dL. Idiopathic calcinosis occurs in the absence of any tissue or metabolic abnormalities. Iatrogenic calcinosis occurs as the result of intravenous leakage of calcium gluconate or as calcium salt deposits in the skin following electromyography or electroencephalography. The dystrophic form of this condition occurs when calcium salts are deposited following damage or tissue devitalization in the skin, subcutaneous tissue, muscles or tendons in the presence of normal calcium and phosphorus metabolism and no visceral involvement.¹⁻¹¹ Calcium salt deposits in the skin and subcu-

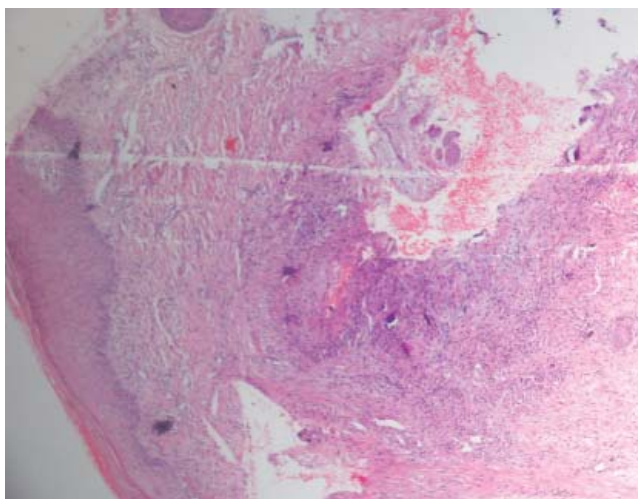


FIGURE 5: Skin with intense inflammatory infiltrate over the entire dermis and some points of calcification (hematoxylin-eosin, magnification x40)

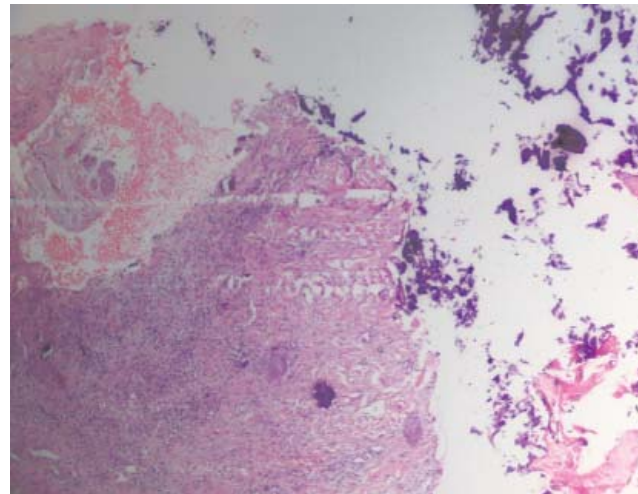


FIGURE 6: In this other section, note the extensive area of calcification at a greater depth (hematoxylin-eosin, magnification x40)

taneous tissue are found in a variety of rheumatic diseases, being most commonly associated with scleroderma, dermatomyositis and overlap syndromes and constitute a rare complication of SLE.¹⁻⁵

In lupus, calcinosis is a rare skin manifestation.^{1,2} It generally affects the patient a mean of 9.8 years following diagnosis of SLE.^{8,12} It is characterized by the presence of hard nodules of varying sizes, either mobile or affixed to the deep planes. They may form plaques and some lesions may ulcerate spontaneously, releasing their contents, which consist of a hardened whitish material, composed of calcium salts. In addition to the skin, the condition may affect the fascia and muscles, and the inflammatory process may result in incapacitating pain in some patients. It generally develops in regions of trauma such as the knees, elbows, fingers or buttocks. In some cases, other complications may develop such as chronic inflammation, infections and atrophy in addition to the issue of esthetics.^{1-3, 13, 14}

In this present case, calcinosis appeared thirteen years following the diagnosis of lupus. The lesions were compatible with calcinosis universalis based on the extent of the condition and the radiographic findings of the involvement of soft tissue and deeper planes. Histopathology confirmed this diagnosis. Calcium and phosphorus levels were normal and the hypothesis of mixed connective tissue disease was discarded (anti-RNP-negative). Although the patient had skin lesions that could be suggestive of dermatomyositis, she had not reported symptoms compatible with myopathy at any time during her disease. Muscle enzyme levels were normal and anti-Mi and Anti-Jo-1 were nonreactive; therefore, the possibility of this diagnosis was discarded. The fact that it was associated with collagenosis and that there were

no abnormalities in calcium metabolism characterizes the condition as dystrophic calcinosis. In agreement with cases reported in the literature, this patient had lesions in areas of trauma and on extensor surfaces^{1,2} with no clinical or laboratory signs of infection. In addition to the specific treatment for SLE, diltiazem and aluminum hydroxide were introduced.

The etiology of calcinosis has yet to be defined and various hypotheses have been made. Although tissue levels of calcium and phosphate were close to saturation levels, it is not usual for calcium salt deposits to occur due to local inhibitory mechanisms. Calcification may occur as the result of a tissue abnormality even when serum levels are normal. Changes in tissue structure, a reduction in vascularization, hypoxia, alterations resulting from the aging process and genetic predisposition may be involved in the formation of calcium deposits in the skin.² Tissue alkaline phosphatase activity inhibits calcium deposits through extracellular phosphate hydrolysis. When areas of trauma or inflammation are present, phosphate binds to the denatured proteins in dead cells, giving rise to new sites of calcification.¹ Various other local abnormalities such as alterations in collagen, elastin or subcutaneous fat may be involved in the process of ectopic calcium deposits.

Some investigators have suggested apoptosis as the principal mechanism in the formation of ectopic calcium salt deposits.¹⁵

Substances such as interleukins (IL-6 and IL-1) and tumor necrosis factor alpha (TNF-alpha) and the activation of tissue macrophages may also play an important role in the formation of calcinosis.

In the present case, diltiazem was initiated at a dose of 60 mg/day and increased, under close cardiologic monitoring, until reaching a dose of 240 mg/day. In addition, aluminum hydroxide was given at a dose of 60 mg/day.

Since diltiazem is a calcium channel blocker, it reduces the entry of calcium into the cells and consequently blocks its accumulation, thereby reducing the formation of calcium deposits by optimizing the effect of the macrophages in clearing existing deposits.^{1,2}

Occasional success has been described with this drug, including a reduction in the progression of calcification with prolonged treatment and increasing

doses.

Aluminum hydroxide, a phosphate-chelating agent administered orally, acts by forming insoluble aluminum phosphate, which reduces bowel absorption of phosphate and contributes towards reversing the precipitation reactions associated with calcium deposits.¹

No side effects have been described in the literature; however, care should be taken since aluminum may accumulate and lead to osteomalacia, myopathy or dementia.²

Over a six-month follow-up period, results were discouraging and the patient developed secondary muscle atrophy, joint contractures and skin ulceration with episodes of secondary infection.

In general, treatment of calcinosis remains a challenge. No controlled studies have yet succeeded in defining the ideal treatment. In addition to aluminum hydroxide and diltiazem, which have been used to treat the condition, various other compounds such as probenecid, warfarin, colchicine and the bisphosphonates have also been tried; however, results have been highly controversial. Surgical removal of symptomatic lesions is considered as a last resort, since local trauma may stimulate calcification further, leading to a recurrence or exacerbation of the condition.^{1,13,14} Small, superficial lesions may be removed by CO₂ laser.

Cyclosporine, intravenous immunoglobulin, tacrolimus and TNF-alpha inhibitors are some examples of promising possibilities for treatment that are currently undergoing evaluation.² They are being used in patients with systemic autoimmune diseases of difficult control, and a reduction in secondary calcinosis has been achieved in some cases. □

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REFERENCES

- 1- Tristano AG, Villarroel JL, Rodríguez MA, Millan A. Calcinosis cutis universalis in a patient with systemic lupus erythematosus. *Clin Rheumatol*. 2005;25:70-4.
- 2- Boulman N, Slobodin G, Rozenbaum M, Rosner I. Calcinosis in rheumatic diseases. *Semin Arthritis Rheum*. 2005;34:805-12.
- 3- González CI, Calvo A, López N, Sarasibar H, Cires M, Jimenez F. et al. Calcinosis cutis: on one case. *An Sist Sanit Navar*. 2007;30:135-8.
- 4- Oğretmen Z, Akay A, Bicakci C, Bicakci HC. Calcinosis cutis universalis. *J Eur Acad Dermatol Venereol*. 2002;16:621-4.
- 5- Nomura M, Okada N, Okada M, Yoshikada K. Large subcutaneous calcification in systemic lupus erythematosus. *Arch. Dermatol*. 1990;126:1057-9.
- 6- Savin JA. Systemic lupus erythematosus with ectopic calcification. *Br J Dermatol*. 1971;84:191-2.
- 7- Powell RJ. Systemic lupus erythematosus with widespread subcutaneous fat calcification. *Proc R Soc Med*. 1974;67:215-7.
- 8- Kabir I, Lorincz LA. Chronic disseminated lupus erythematosus and calcinosis cutis. *Arch Dermatol*. 1965;92:328-330.
- 9- Tay CH. Cutaneous manifestations of systemic lupus erythematosus: a clinical study from Singapore. *Australas J Dermatol*. 1970;11:30-41.
- 10- Miteva L, Pramatarov K, Vassileva S. Calcinosis cutis in childhood systemic lupus erythematosus. *J Eur Acad Dermatol Venereol*. 2003;17:611-2.
- 11- Sornas SD, Padilha MHVQ, Machado TAR, Swenson AM, Kasbergen AC. Calcinose cutânea – relato de um caso. *An Bras Dermatol*. 2002;77:459-63.
- 12- Braverman IM. *Skin signs of systemic disease*. 3a ed. Philadelphia: Saunders; 1998. p. 255-377.
- 13- Wu JJ, Metz BJ. Calcinosis cutis of juvenile dermatomyositis treated with incision and drainage. *Dermatol Surg*. 2008;34:575-7.
- 14- Lipskeir E, Weizenbluth M. Calcinosis circumscripta: indications for surgery. *Bull Hosp Jt Dis Orthop*. 1989;49:75-84.
- 15- Kim KM. Apoptosis and calcification. *Scanning Microsc*. 1995;9:1137-75.

MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:
Ana Paula Gonçalves Carocha.
Rua Almirante Tamandaré, 67, apt° 1106 –
Flamengo – Rio de Janeiro, RJ, Brazil.
Phone: 21 9762 3527 / 21 2225 2649.
e-mail: anapaula.carocha@gmail.com

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