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Review article

Update on the treatment of calcinosis in dermatomyositis

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ABSTRACT

Calcinosis is a connective tissue disorder classified into the following four types: metastatic; idiopathic; iatrogenic and dystrophic. Dystrophic calcinosis can occur, for example, in dermatomyositis, mainly in juvenile dermatomyositis, and is characterized by an abnormal deposition of calcium salts in affected skin, subcutaneous tissues, and muscles or tendons, with normal serum levels of calcium and phosphate. The treatment of calcinosis in dermatomyositis remains a challenge, with few descriptions in the literature of low scientific evidence. So far, no therapy has proved to be highly effective in the combat and resolution of that comorbidity. The present study discusses the concept of calcinosis, particularly in dermatomyositis, as well as its treatment described in the literature.

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Atualização na terapêutica da calcinose em dermatomiosite

RESUMO

Calcinose é uma afecção do tecido conjuntivo classificada em quatro tipos: metastática, idiopática, iatrogênica e distrófica. Esta última é o que acontece, por exemplo, em dermatomiosite, principalmente na forma juvenil, e é caracterizada por uma deposição anormal de sais de cálcio em pele afetada, tecidos subcutâneos, músculos ou tendões, sendo os níveis séricos de cálcio e fósforo normais. O tratamento da calcinose em dermatomiosite continua sendo um desafio, havendo poucas descrições na literatura, de pouca evidência científica. Não se apresenta, até o momento, nenhuma terapia altamente eficaz no combate e resolução dessa comorbidade. No presente trabalho, abordamos o conceito de calcinose, particularmente em dermatomiosite, assim como o seu tratamento descrito na literatura.

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Concept of calcinosis

Calcinosis is a connective tissue disorder classified into the four following types: metastatic; idiopathic; iatrogenic and dystrophic.^{1,2} Metastatic calcinosis refers to the deposition

of calcium salts in normal tissues, with increased serum levels of calcium and/or phosphate, whose product is ≥ 70 .^{1,2} Idiopathic calcification occurs in normal tissues, with normal serum levels of calcium and phosphate.^{1,2} Iatrogenic calcinosis includes the hypersensitivity reaction, which usually begins with *livedo reticularis* rapidly progressing to

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the formation of skin ulcers and necrosis; it is more commonly reported in patients with chronic renal failure on hemodialysis.¹ Dystrophic calcinosis is the abnormal deposition of calcium salts in affected skin, subcutaneous tissue, and muscles or tendons, with normal serum levels of calcium and phosphate.^{2,3} Dystrophic calcinosis can occur, for example, in dermatomyositis (DM).

Calcinosis in dermatomyositis

In patients with DM, calcinosis is much more frequent in the pediatric age group, being present in 10%–70% of the cases.^{4–9} In adults, it is reported in about 20% of the patients,^{10,11} and can precede the diagnosis of DM or even appear years after that. Usually, calcinosis appears between the first and third years of the disease.⁶

In DM, calcinosis can present as follows: (a) hard nodules or plaques in subcutaneous or periarticular regions; (b) tumors; (c) deposits in the intermuscular fascia, leading to mobility limitation of the affected muscles; (d) severe dystrophic calcification similar to an exoskeleton; and (e) mixed form.⁴ Calcinosis can have a negative impact on the patients' quality of life, causing weakness, functional disability, joint contractures, muscle atrophy, skin ulcers, and, consequently, local pains and secondary infections.

Pathogenesis and risk factors

The etiopathogenesis of calcinosis in DM is unknown. Based on case reports, calcinosis is believed to result from the intracellular accumulation of calcium secondary to a change in cell membrane. It can be triggered by trauma and/or chronic inflammation,^{12,14–31} such as in cases nonresponsive to corticotherapy, in the presence of generalized cutaneous vasculitis, important muscle weakness, and persistent elevation in muscle enzymes.^{4–6,13–15}

The hypothesis of inflammation at the calcinosis site is plausible, because several authors have shown the presence of cells and pro-inflammatory cytokines, such as IL-1¹⁶ and TNF-alpha,¹⁷ and a variety of proteins related to mineralization, such as osteopontin, osteonectin, bone sialoprotein and hydroxyapatite,¹⁸ at the calcinosis site.¹⁷ It has also been associated with the presence of antibodies against the 140 kDa protein¹⁹ and with TNF-alpha-308A polymorphism.¹⁶

Fisler *et al.*²⁰ have studied 35 cases and reported an association between calcinosis and a delay in the diagnosis and/or beginning of treatment, increased muscle enzymes, and prolonged disease duration. Similarly, Pachman *et al.*¹³ have observed calcinosis and a delay in disease diagnosis. However, Sallum *et al.*⁶ have reported the association of the development of calcified nodules, systemic involvement of the myopathy and aggressive use of medicaments. Bowyer *et al.*⁴ have shown that inadequate initial therapy plays an important role in the development of calcinosis. In addition, as previously mentioned, calcinosis is less frequent in adults with DM, raising the possibility that age-dependent factors could influence the risk of developing ectopic calcifications.²¹

Treatment of calcinosis in dermatomyositis

The present study systematically review the treatments reported for calcinosis in DM. A literature search was conducted in the MEDLINE database by using the following terms: calcinosis and dermatomyositis.

Except for 14 cases reported as having spontaneous resolution,^{1–4,9,22–24} calcinosis in DM tends to increase with disease progression. An early and aggressive therapeutic intervention against DM activity has been suggested to possibly reduce the musculoskeletal sequelae of the disease, including calcinosis itself.²⁰

However, so far, no consensus has been achieved about the effective treatment for calcinosis in DM, and the data available in the literature are based only on reports and/or case series, particularly in juvenile DM. The use of the following medications has been mentioned: bisphosphonates; probenecid; warfarin; aluminum hydroxide; colchicine; diltiazem; and infliximab.

Ambler *et al.*²⁵ have reported the case of an 8-year-old child with chronic juvenile DM, whose calcinosis was completely resolved after using alendronate (10 mg/day) for 12 months. The patient had previously received diltiazem (15 mg, 2x/day) and probenecid (500 mg, 2x/day), with no resolution of the calcinosis. Similarly, Mukamel *et al.*²⁶ have reported an improvement in calcinosis in a 6-year-old patient with juvenile DM by introducing alendronate (10 mg/day) for 12 months.

Mori *et al.*²⁷ have reported the use of etidronate (800 mg/day) in a 26-year-old patient with DM, who, in addition to calcinosis, had osteoporosis. Those authors have reported the regression of calcinosis three months after beginning drug therapy. In addition, a significant improvement was observed in densitometric values after a three-year follow-up. Nevertheless, Metzger *et al.*²⁸ have assessed the effect of etidronate in three patients with DM and calcinosis for 12 months, no satisfactory effect being observed.

The use of pamidronate has also been described.^{29,30} Three patients with juvenile DM received pamidronate at the dosage of 1 mg/kg/day for three consecutive days, repeated every month. A satisfactory response was observed in all cases, including one complete resolution of the calcinosis.

Based on the principle that probenecid might reduce the local inflammatory process, it has been used, but the results are controversial.^{8,9,31–33}

Fuchs *et al.*³⁴ have described a case of juvenile DM with calcinosis in the prepatellar region, accompanied by inflammation and localized cutaneous ulcer. An improvement in the cutaneous lesions was observed two months after using colchicine at the dosage of 1 mg/day.

Based on the theory of having an inhibitory effect on the calcium channels of the cell membrane, diltiazem has proved to be, mainly in cases of juvenile DM, a therapeutic alternative.^{35–39} Its dosages have varied from 30–180 mg/day, and that drug was introduced to patients whose treatments with bisphosphonate and aluminum hydroxide did not succeed. All cases described^{35–39} showed an excellent response in follow-ups ranging from 6–10 months.

Miyamae *et al.*⁴⁰ have assessed the beneficial effect of thalidomide in one 14-year-old female patient with juvenile DM

for ten years, who had previously undergone pulse therapy with methylprednisolone, cyclophosphamide, cyclosporine, azathioprine, probenecid, magnesium hydroxide, aluminum hydroxide, in addition to infliximab (suspended due to adverse effects) and etanercept for disease activity and calcinosis progression. Later, at the age of 12 years, thalidomide was introduced (1.3 mg/kg/day, orally, in the first month, and, then, 2 mg/kg/day), the response being satisfactory.

Older descriptions have evidenced good results with aluminum hydroxide for patients with juvenile DM, no adverse effects being reported.⁴¹⁻⁴⁴ Nakagawa *et al.*⁴² have reported a case with an almost complete resolution of calcinosis after eight months of treatment.

Vitamin K plays an important role in calcium binding with bones and tissues.²³ Based on this concept, Berger *et al.*⁴⁵ and Matsuoka *et al.*⁴⁶ have used low doses of warfarin to patients with juvenile DM and nodular calcinosis. Those authors have reported a reduction in the size of the lesions after using warfarin for three years.

Regression of cutaneous calcinosis following intralesional infiltration of corticosteroid has been described by Al-Mayouf *et al.*⁴⁷ in a 10.5-year-old patient, preceded by use of methotrexate and corticosteroid for disease activity. For the calcinosis located in one of the elbows, colchicine and pamidronate infusion every three months (total of five doses) were unsuccessfully used. Corticosteroid infiltration using the barbotage technique was performed, with consequent regression of the calcinosis.

Surgical procedures have been reserved to extensive areas of calcification,^{48,49} with incision and local drainage, and have shown satisfactory results.

In the era of biological therapy, infliximab has been used at the dosage of 3 mg/kg (same schedule for rheumatoid arthritis) to treat five patients with juvenile DM refractory to previously proposed treatments; all cases had a positive response, with calcinosis regression in periods ranging from 8–30 months after beginning treatment.⁵⁰ Arabshahi *et al.*⁵¹ have reported the use of abatacept (10 mg/kg, monthly, after fortnightly application in the first month) and sodium thiosulfate (topic, initially at 3%, and, then, at 10%, fortnightly) to a 14-year-old patient with juvenile DM for three years, refractory to corticosteroid, tacrolimus and intravenous human immunoglobulin, who had progressive calcinosis and ulcerated cutaneous lesions. The therapy instituted determined a reduction in musculocutaneous inflammation and calcinosis regression.

In conclusion, the treatment of calcinosis in both adult and juvenile DM remains a challenge, with few descriptions in the literature of low scientific evidence. So far, no therapy has proved to be highly effective in the combat and resolution of that comorbidity.

Conflicts of interest

The authors declare no conflicts of interest.

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