A case of a generalized symptomatic calcinosis in systemic sclerosis

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Abstract
Calcinosis consists of abnormal calcium deposition in soft tissues, which appears often in patients with limited systemic sclerosis, being one of the criteria of CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome. With a long evolution, the aim of the treatment is to control the symptoms and prevent complications. In this article, we present the challenging management of a profuse lesion of calcinosis in a patient with systemic sclerosis. We describe the case of a 52-year-old woman with systemic sclerosis and CREST syndrome who was admitted in our Department with multiple painful and disabling tumoral masses, situated in nearly all joints. The interscapular vertebral tumoral mass was excised and the defect was closed. Histopathological examination revealed cutaneous calcinosis, probably associated with CREST syndrome, a type of scleroderma. Postoperative results were favorable and no local complications were encountered. Six months follow-up revealed no evidence of recurrence. Despite the size and the invasion of the tumor in the muscle, complete resection was possible with an adequate reconstruction; the postoperative result being acceptable. With a lower response to medication, surgical treatment is considered the only option for treating symptomatic lesions of calcinosis in order to improve quality of life.

Keywords: calcinosis, CREST syndrome, systemic sclerosis, autoimmune disease.

Introduction
Systemic sclerosis is a rare, autoimmune disease with a progressive evolution, affecting the connective tissue of the skin and internal organs, through inflammation, fibrosis and vasculopathy [1]. The disease is more common among women than men (4/1), with an onset age of 30–50 years [2].

The clinical forms of systemic sclerosis are limited and diffuse. The limited systemic sclerosis affects 60% of the patients [3], a part of them developing in time CREST syndrome, an acronym that describes calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia [4].

The pathology of the disease is not totally understood, several cell lines being involved: fibroblasts, endothelial cells and lymphocytes (B- and T-) [5, 6]. These cells initiate an early vascular phase that is followed by an inflammatory infiltrate and fibrosis [2]. Genetic factors have been also incriminated, especially genes of the immune system and connective tissue which induce an activation of the immune and vascular response [1, 7]. Collagen and other extracellular matrix proteins are overproduced and accumulated in almost all tissues producing fibrosis of the affected organs [8].

The cutaneous manifestations appear due to deposition of compact collagen fibers and others proteins in the reticular dermis that produce atrophy of dermal appendages with skin fibrosis, calcinosis and cutaneous ulcers [9]. This increased accumulation of proteins determines an extent of the hypoxic state with inflammation and further depositions [1]. Clinical manifestations depend on the involved sites; usually the initial symptoms are vascular with appearance of a Raynaud’s syndrome of the fingers. Other symptoms include peripheral microvascular constriction, tightening of the skin, fingers swelling and contractures, polyarthralgia and dysphagia [9].

Even though the major impact of the health is due to vascular involvement and progressive fibrosis of the internal organs, skin manifestations are almost always present, their extension being associated with a poor prognosis [9, 10].

Aim
We describe the case of a middle-aged female patient with limited systemic sclerosis and generalized calcinosis
discussing the challenging management of a profuse calcified lesion.

Case presentation

A 52-year-old woman was referred to our Department of Plastic Surgery by the Department of Rheumatology, with multiple tumoral masses situated bilaterally in the interscapulovertebral region. The tumors appeared five years ago and increased in size, being associated with pain at passive and active movements of the shoulders. Local ethical agreement and informed consent of the patient were obtained.

The patient’s past medical history revealed that she was diagnosed five years previously with systemic sclerosis with a limited cutaneous involvement for which she had recurrent hospital admissions. Her cutaneous and vascular manifestations included sclerodactyly, digital ischemia, ulcers and Raynaud phenomenon. She had musculoskeletal involvement with arthralgia, myositis and tenosynovitis and joints contractures due to severe calcinosis. The gastrointestinal tract and pulmonary system were also affected, the patient being diagnosed with gastroesophageal reflux and interstitial lung disease. She had also some cardiac problems as moderate mitral insufficiency and multiple episodes of paroxysmal supraventricular tachycardia for which a catheter ablation of the slow pathway was performed. The patient had osteoporosis and a discopathy of the cervical and lumbar spine at L5, having total hysterectomy eight years ago. She was under treatment with an immunosuppressive drug (Methotrexate), folic acid, calcium channel blocker, beta-blockers, peripheral vasodilators, antiacids and pain medication.

Upon clinical examination, we found a normal weight patient with a characteristic facies of “Byzantine icon” including thin lips, small mouth, thin nose and perioral wrinkles. She presented diffuse body hyperpigmentation with no skin thickening (Rodnan score 0/51). In the right hand, in the index and middle finger, were present scars of the fingertips associated with fingers acro-osteolysis (Figure 1).

Local examination of the posterior thorax revealed multiple nodular tumoral masses of 2/2 cm and 5/4 cm dimensions, situated bilateral in the interscapulovertebral region, well circumscribed with a firm, elastic consistency. Evaluation of the right acromioclavicular joint showed another tumoral mass of 2/2 cm with the same characteristics that limits the abduction of the right shoulder at 40°. The elbows had on the lateral epicondyles tumoral masses of 2/1 cm dimensions, with defined borders and solid consistency (Figure 2). There were also present some nodules on the volar surface of the radiocarpal joints and also on the dorsal surface of the left radiocarpal joint with an elastic consistency, which produced pain on active and passive movements.

Paraclinical examinations were performed using imaging techniques and laboratory tests. Radiographs of the thorax revealed multiple radiopaque masses in the soft tissue, in the interscapulovertebral region with a slightly evolution from the anterior evaluation. Radiographies of the elbow joints exposed multiple lobulated calcifications separated from the associated bone (Figure 3). Right shoulder radiography revealed multiple soft tissue periarticular calcifications associated with diffuse bone demineralization. The hand radiography showed amputation of the distal phalanges bilateral (without the right fourth finger) and multiple soft tissue calcifications on the radiocarpal joints, thumb bilateral and the right three and five fingers with the left fourth finger; no erosions were present.

To evaluate the structure of the tumoral masses situated in the elbow joints an echography was performed which displayed multiple nodular subcutaneous tumors, with a well defined border, which are spread in the left elbow over 10 cm length and have a minimum wall-echo shadow. Echocardiography of the left radiocarpal joint showed a distension of the flexors tendons with a minimum peritenoninous fluid.

Evaluation of the Raynaud syndrome was realized using a nailfold capillaroscopy that showed lower cutaneous transparency with structural alterations and disorganization of the capillary architecture, absent giant capillaries and presence of small hemorrhages.

Laboratory tests revealed moderate normocytic, normochromic anemia (hemoglobin 11.3 g/dL), elevated erythrocyte sedimentation rate (49 mm/h) and elevated C-reactive protein (43.67 mg/L). Antinuclear antibodies (ANA) and anti-Scl 70 antibodies were positive with negative anti-U1RNP antibodies and negative rheumatoid factor.

After the preoperative investigations, surgical treatment was decided. The operative time, under general anesthesia consisted in excision of a large, solid tumoral mass with a whitish necrotic aspect with numerous calcified nodules involving the deep structures including the muscle (Figure 4). Full hemostasis was achieved using a bipolar electrocautery. The wound was closed in layers and a drainage tube was placed.

Histopathological examination revealed morphological changes of the dermis and hypodermis. The epidermis had a normal histology in comparison with the superficial dermis where is observed significant accumulation of collagen forming thick bundles, homogeneous, with pronounced eosinophila, tending to compaction (Figure 5). A reduced fibroblastic component and a perivascular chronic infiltrate of lymphocytes are present (Figure 6). The structures of the pilosebaceous apparatus and of the sweat glands are under-represented.

Between deep dermis and adipose tissue of hypodermis there are present some calcium deposits in different stages of maturation. Distribution of these amorphous deposits is usually nodular (Figure 7) and less diffuse. The presence of the calcium deposits induces a mixed...
inflammatory response formed of macrophages, lymphocytes and foreign body-type multinucleated giant cells (Figure 8). The presence of these degenerative calcium lesions supports the diagnosis of an advanced type of scleroderma, associated with CREST syndrome.

The inflammatory component is disposed in the periphery of the calcium deposits, being included in a mass of dense connective tissue that appears to act as a barrier between the dystrophic calcium lesions and the surrounding tissues. Probably, the conjunctive barrier originated in the fibrous septa of the subcutaneous tissue. At this level, there are also present capillary vessels with pronounced hyperemia (Figure 9). Striated muscle tissue contains no calcification (on the studied material), their presence is noticeable to the epimysium (Figure 10).

To exclude Sjögren’s syndrome, a condition relatively frequent associated with scleroderma, we analyzed biopsy fragments from the mouth mucosa, containing minor salivary glands. Histopathological study has not revealed the presence of lymphocytic aggregates, invalidating thus a possible association with Sjögren’s syndrome (Figure 11).

The patient made a good postoperative recovery with no local complications. Satisfactory functional and cosmetic results were achieved and six months follow up revealed no recurrence.

Figure 2 – Tumoral masses on the left elbow.

Figure 3 – Radiographic aspect of the left elbow with lobulated calcifications.

Figure 4 – Excision of the lesion involving the deep structures.

Figure 5 – Compacted aspect of the superficial dermis. HE staining, ×40.

Figure 6 – Perivascular inflammatory infiltrate in dermis. HE staining, ×100.

Figure 7 – Nodular distribution of calcium deposits within deep dermis and hypodermis. HE staining, ×40.

Figure 8 – Mixed inflammatory infiltrate in the interface between calcium deposits and hypodermis. HE staining, ×200.
Discussion

Calcinosi cutis often develops in patients with limited systemic sclerosis being associated with CREST syndrome [8]. It represents an abnormal calcium deposition in the skin and subcutaneous tissues independent of the serum levels of calcium and phosphorous [9], due to tissue hypoxia, mechanical stress or hypovascularity [11]. This produces inflammation and macrophage activation with alteration in various mediators balance causing increased influx of calcium to cells [8, 12]. Clinically is characterized by subcutaneous nodules or white papules of hard consistency, distributed symmetrically to the extremities and rarely to the trunk [13]. The lesions may ulcerate discharging a chalk-like material formed of calcium phosphate and calcium carbonate [14]. The remained lesion has a slow healing evolution being associated with numerous infections [13]. Calcinosi causes local pain, inflammation, irritation, ulceration with infections, muscle atrophy and joint contractures that leads to severe disability and morbidity [15]. Diagnosis is usually made clinically associated with plain radiographies, in some cases being necessary also an echography or a computed tomography [16]. Despite the symmetrical distribution of the subcutaneous nodules in the extremities, our patient had also a rarely distribution of a calcinotic mass to the posterior trunk. This dystrophic calcification might have been appeared due to mechanical stress and tissue hypoxia. Pharmacological therapy usually has lower results [9], as it had also with our patient who used Diltiazem and Colchicine. Other local treatments used for smaller localized lesions are extracorporeal shock wave lithotripsy and carbon dioxide laser with reduced results [17, 18]. The only effective treatment is considered the surgical therapy, which is used when other treatments failed or calcium deposits continue to expand being associated with functional joint impairment, nerve compression, recurrent infection and severe pain [12]. In some cases, the surgical therapy is only palliative due to common recurrences. Surgical treatment has also disadvantages requiring anesthesia and having the possibility of damaging the healthy tissue and the vascular network producing further ischemia [9].

CREST syndrome is a form of limited systemic sclerosis being associated with calcinosi, Raynaud phenomenon, esophageal dysfunction, sclerodactyly (tapering deformity of the fingers bones) and telangiectasia on the skin of the face and fingers, or inside the mouth, the presence of two being sufficient for a diagnosis [17, 19]. Our patient meets all the criteria of CREST syndrome with calcium deposits in the skin (histopathological examination), Raynaud syndrome (diagnosed using symptomatology and nailfold capillaroscopy), gastroesophageal acid reflux, thickening and tightening of the skin of the fingers and dilation of capillaries (telangiectasias) on the face and hands [20, 21]. The patient has also osteoporosis, which was aggravated in the last two years despite the medical treatment. The pathogenesis of calcinosi is not clearly understood, but it has been shown that its severity is not related with the severity of systemic sclerosis [3], although in our case calcinosi could have a negative impact, being an aggravating factor for osteoporosis [22, 23].

Although the concern of the disease is the progressive involvement of the internal organs [24], the patient’s main complaint was the presence of calcium tumoral masses in the skin, especially the one in the interscapulovertebral region that was associated with pain and difficulty in lying down.

Considering that no pharmacological therapy has demonstrated efficacy in the reduction of a large calcified
mass [25] and that the patient’s tumor did not responded to initial medical treatment, surgical treatment was decided to be the option for removing the calcinotic mass in order to improve the patient’s quality of life.

Conclusions

Even though there is a risk of recurrence and additional calcification due to surgical trauma, it is favorable to treat tumoral calcinosis before it progresses and become a large, ulcerated and disabling mass. Optimal treatment of calcinosis cutis is a challenge because the pathogenesis is unclear, no treatment being completely effective due to the higher rate of recurrences. Consequently, the management of complications became essential in order to lower morbidity and improve the quality of life.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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