Abstract

Background: Calcinosis cutis is a rare condition associated with different diseases, which is difficult to manage. Aims and Objectives: In this retrospective study, the epidemiology of calcinosis cutis and the effectiveness of various treatment regimens in its management were assessed in a single center. Materials and Methods: The data of 34 patients suffering from calcinosis cutis (male:female = 12:22; mean age = 48.6 ± 18.6 years) treated at our department between 2003 and 2016 were analyzed retrospectively. Results: Dystrophic, idiopathic, metastatic subtype, and calciphylaxis occurred in 70.6%, 11.8%, 5.9%, and 11.8% of the cases, respectively. Underlying diseases of dystrophic calcinosis included autoimmune connective tissue disease, skin trauma, cutaneous neoplasm, and inherited disorder in 58.3%, 20.8%, 12.5%, and 8.3% of the cases, respectively. Extremities were most frequently affected (n = 18). In the management, diltiazem was most frequently used in monotherapy with partial response in five of eight cases. Other drugs in monotherapy or in combination were administered in single cases. Surgical treatment resulted in least partial response in all of the cases followed (n = 7). Conclusion: Dystrophic was the most common subtype and autoimmune connective tissue disease was the most frequent underlying disease. We conclude that lower doses of diltiazem have only partial efficiency, and surgical therapy is at least partially effective in localized calcinosis.

Key Words: Calcinosis cutis, diltiazem, epidemiology, surgical therapy, treatment

Introduction

Calcinosis cutis is a rare condition associated with different diseases.[1] It can be subdivided into four subtypes: dystrophic, metastatic, iatrogenic, and idiopathic.[2] Some authors classify calciphylaxis as the fifth subtype of calcinosis.[3] It can be treated with pharmacotherapy, surgical, or combined therapy based on the clinical characteristics.

In this retrospective study, we assessed the epidemiology of calcinosis cutis and the effectiveness of various treatment regimens in its management in a single center. The aim of this study was to extend our knowledge of this barely investigated disease and to share clinical experience with the therapeutic possibilities.

Materials and Methods

In this retrospective case series study, we retrieved the data of cases encoded as calcinosis cutis by the International Statistical Classification of Diseases and Related Health Problems code of calcinosis from the medical data recording and text retrieval system at our department between November 1, 2003 and October 31, 2016. The Institutional Review Board reviewed and approved our research. Diagnosis of calcinosis cutis was made by clinical examination and proven by radiography, ultrasonography, and/or histological examination of a skin biopsy specimen. Dermoscopy was not performed in the diagnosis and assessment of calcinosis itself; it was only applied in the assessment of certain underlying diseases (basal cell carcinoma). We carried out nonlinear microscopy imaging of skin biopsy specimens collected from these patients. A femtosecond pulse Ti–sapphire laser with a central excitation wavelength of a 796-nm and a 460/50-nm band-pass emission filter was used. We classified calcinosis cutis retrospectively as dystrophic, metastatic, iatrogenic, idiopathic calcinosis, or calciphylaxis based on the patient history, underlying disease, laboratory, and histopathologic findings. Location of calcinosis was categorized as extremities (including the shoulders, upper arm, forearm, thighs, and calves, excluding hands

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and feet), hands and feet, trunk (including the chest, back, waist, and abdomen), buttocks and groin (genital area and hips), and head (neck, face, and scalp). Patients were treated either with pharmacotherapy, surgical or combined surgical and pharmacotherapy. Drugs administered in the treatment of calcinosis in this series included diltiazem, amlodipin, sodium thiosulfate, rituximab, cinacalcet, and phosphate binders. Response to therapy was categorized as complete in case of total resolution of the lesion with no recurrence of the healed lesion, partial response in case of regression or recurrence of the healed lesion, and no response in case of persistence or progression of the lesions.[4]

**Results**

In our study, 34 patients had calcinosis cutis (male: female = 12:22), mean age was 48.6 ± 18.6 years (range 11-85 years). Diagnosis was confirmed by histological examination of a skin biopsy specimen, radiography, ultrasonography, and by two of these methods in 14, 5, 2, and 11 cases, respectively. During the nonlinear microscopy imaging, we also observed that calcium salt deposits in the dermis produce strong endogenous two-photon fluorescence at laser excitation wavelength of 796 nm [Figure 1]. Only dystrophic cases were examined with this method. Epidemiologic characteristics of the population (sex, mean age at the onset of calcinosis), underlying diseases, time interval to onset of calcinosis, and localization of calcinosis are shown in Table 1. Examples of clinical manifestation and histopathologic findings of cutaneous calcinosis are shown in Figures 2 and 3.

**Underlying disease**

In the most common dystrophic group (male:female=6:18), underlying disease was autoimmune connective tissue disease, skin trauma, cutaneous neoplasm, and inherited disorder in 58.3%, 20.8%, 12.5%, and 8.3% of the cases, respectively.

**Mean age at onset of calcinosis**

Mean age at onset of calcinosis was 49.9 ± 19.4, 42.5 ± 23.3, 36.5 ± 11.4, and 59.3 ± 5.6 years in dystrophic, metastatic, idiopathic calcinosis, and calciphylaxis, respectively. In autoimmune connective tissue diseases, mean age was 41 ± 16.2 years. Mean duration of the underlying disease until the onset of calcinosis was 13.2 ± 20.7, 3 ± 4.2, 1.25 ± 2.5, and 14 ± 6.1 years in the dystrophic, metastatic, idiopathic types, and calciphylaxis, respectively. Mean time interval to onset of calcinosis in the most common group (autoimmune connective tissue diseases) was 5.6 ± 4.7 years.

**Location of calcinosis**

Extremities were most frequently affected by calcinosis (n = 18, 52.9%).

**Treatment of calcinosis**

Patients were treated either with pharmacotherapy, surgical or combined therapy. Drugs were administered in monotherapy or in combination. The most frequently used medicine in the present case series was diltiazem. Eight patients received it in monotherapy (60–180 mg/day or 2% topically). All of them suffered from dystrophic calcinosis. Complete, partial, and insufficient response was observable in zero, five, and
Nevertheless, calcinosis cutis can be usually diagnosed by conventional histology with hematoxylin and eosin, von Kossa, or Alizarin red staining. Nonlinear microscopy is a novel noninvasive skin-imaging technique which was proven capable of ex vivo detection of microcalcification in pseudoxanthoma elasticum. Radiography, ultrasonography, computed tomography, or magnetic resonance imaging may also confirm the diagnosis of calcinosis. Calciphylaxis can be usually diagnosed by clinical examination appearing as painful, nonhealing, necrotic skin ulcers, and purpuras on the trunk, extremities, or genital area. Radiography or bone scintigraphy can confirm the diagnosis of calciphylaxis. In uncertain cases, skin biopsy may also be considered, although disturbed wound healing is a frequent side effect of this method. In the management of calcinosis, widespread calcified lesions require drug therapy. According to the literature, calcium-channel blocker diltiazem is most frequently used in the treatment of calcinosis, but depending on the clinical characteristics of the lesion and the associated symptoms, other drugs and therapeutic methods may be beneficial. Attenuation of the pain and disability associated with calcinosis could be a key feature of treatment.

### Discussion

Dystrophic, the most common type, calcinosis is caused by dermal damage; the metastatic one by alterations of the calcium-phosphate homeostasis; the iatrogenic one by unwanted medical action and the idiopathic one is of unknown origin. Calciphylaxis occurs mainly in the end-stage kidney disease. Calcification appears clinically as firm, asymptomatic, white, yellowish or flesh-colored papules, plaques, or nodules. Excretion of chalky material, pain, itching, ulceration, or infection may associate. Nevertheless, calcinosis cutis can be efficiently detected by conventional histology with hematoxylin and eosin, von Kossa, or Alizarin red staining. Nonlinear microscopy is a novel noninvasive skin-imaging technique which was proven capable of ex vivo detection of microcalcification in pseudoxanthoma elasticum. Radiography, ultrasonography, computed tomography, or magnetic resonance imaging may also confirm the diagnosis of calcinosis. Calciphylaxis can be usually diagnosed by clinical examination appearing as painful, nonhealing, necrotic skin ulcers, and purpuras on the trunk, extremities, or genital area. Radiography or bone scintigraphy can confirm the diagnosis of calciphylaxis. In uncertain cases, skin biopsy may also be considered, although disturbed wound healing is a frequent side effect of this method. In the management of calcinosis, widespread calcified lesions require drug therapy. According to the literature, calcium-channel blocker diltiazem is most frequently used in the treatment of calcinosis, but depending on the clinical characteristics of the lesion and the associated symptoms, other drugs and therapeutic methods may be beneficial. Attenuation of the pain and disability associated with calcinosis could be a key feature of treatment.

### Table 1: Demographic and clinical data of patients

| Subtype (no., %) | Underlying disease | Patients (no.) | Age at onset of calcinosis cutis, mean (range), years | Time interval to onset of calcinosis cutis, mean (range), years | Location of calcinosis cutis (no.) |
|-----------------|-------------------|---------------|---------------------------------|------------------|---------------------------------|
| Dystrophic (24, 70) | ACTD3 | SSc | 2 | 1 | 14 (41) | 39.7 (20-50) | 8 (4-12) | 0 | 3 | 0 | 1 | 0 |
|                 | SLE |            | 2 | 0 | 2 | 43.5 (35-52) | 7 (2-12) | 0 | 2 | 0 | 1 | 0 |
|                 | PSE |            | 2 | 0 | 2 | 46.5 (39-54) | 12.5 (0-25) | 1 | 1 | 0 | 0 | 2 |
| Metastatic (2, 6) | CRI | ....... | 0 | 1 | 1 | 2 (6) | 1 | 0 | 0 | 0 | 2 |
|                 | Hyperparathyroidism | ....... | 1 | 0 | 1 | 26 - 0 | 1 | 0 | 0 | 0 | 0 |
| Calciphylaxis (4, 12) | Scrotal calcinosis | ....... | 0 | 4 | 4 | 4 (12) | 36.5 (22-49) | 1.25 (0-5) | 0 | 0 | 0 | 4 |
| All together | ....... | ....... | 22 | 12 | 34 (100) | 49 (11-85) | 10.93 (0-57.3) | 5 | 18 | 7 | 8 | 4 |

**ACTD**: Autoimmune connective tissue disease, **SSc**: Systemic sclerosis, **DM**: Dermatomyositis, **JDM**: Juvenile dermatomyositis, **UCTD**: Undifferentiated connective tissue disease, **MCTD**: Mixed connective tissue disease, **OCTD**: Overlap connective tissue disease, **SLE**: Systemic lupus erythematosus, **PXE**: Pseudoxanthoma elasticum, **CRI**: Chronic renal insufficiency, **ND**: No data.
primary therapeutic aim rather than the radiologic improvement of the calcified lesions.\textsuperscript{[4]} Drugs can be applied in calcinosis and calciphylaxis in monotherapy or in combination with other drugs, surgical therapy, or other methods. Sodium thiosulfate can be the first choice in the pharmacotherapy of calciphylaxis;\textsuperscript{[13,14]} phosphate binders, bisphosphonates, and cinacalcet may also be beneficial.\textsuperscript{[14]} Surgical therapy can be the first choice in certain cases, especially in localized, painful, movement-restricting lesions.\textsuperscript{[15]}

| Table 2: Treatment data and response outcomes within the different calcinosis subtypes |
| Type | Disease | Sex | Age (years) | Time to onset (years) | Pharmacotherapy | Doses (mg/day orally) | Surgical therapy | Response |
|------|---------|-----|-------------|----------------------|----------------|-----------------------|-----------------|----------|
| Dystrophic | JDM | M | 20 | 0 | Diltiazem | 180 | - | PR |
|          | SSc | F | 50 | 12 | Diltiazem | 90-180 | - | PR |
|          | SSc | M | 49 | 8 | Diltiazem | ND | 2% Topical | PR |
|          | PXE | F | 54 | 0 | Diltiazem | 120 | - | PR |
|          | PXE | F | 39 | 25 | Diltiazem | 60-90 | - | PR |
|          | DM | F | 59 | 7 | Diltiazem | 90 | - | NR |
|          | DM | F | 38 | 0 | Diltiazem | 180 | - | NR |
|          | MCTD | F | 55 | 12 | Diltiazem | ND | - | NR |
|          | SSc | F | 20 | 4 | Amlodipine | 2.5 | - | NR |
|          | JDM | M | 11 | 3 | Rituximab | ND | - | PR |
|          | SLE | F | 35 | 12 | Diltiazem | 60 | - | PR |
|          | Sodium thiosulfate | | | | | 7500-12,500 (|/week intravenous) | 1000-8000 | |
|          | BCC | F | 85 | 0 | - | - | Yes | CR |
|          | BCC | M | 64 | 0 | - | - | Yes | CR |
|          | BCC | F | 36 | 0 | - | - | Yes | CR |
|          | Trauma | F | 65 | 61 | - | - | Yes | PR |
|          | Trauma | F | 74 | 71 | - | - | Yes | ND |
|          | Trauma | F | 53 | ND | - | - | Yes | PR |
|          | Trauma | F | 64 | ND | ND | ND | ND | ND |
|          | OCTD | F | 38 | 7 | ND | ND | ND | ND |
|          | SLE | F | 52 | 2 | ND | ND | ND | NR |
|          | Morphea | M | 30 | 0 | ND | ND | ND | NR |
|          | Trauma | F | 82 | ND | ND | ND | ND | ND |
|          | Trauma | M | 74 | 40 | ND | ND | ND | PR |
| Idiopathic | SC | M | 22 | 0 | - | - | Yes | PR |
|          | SC | M | 34 | 5 | - | - | Yes | ND |
|          | SC | M | 41 | 0 | - | - | Yes | ND |
|          | SC | M | 49 | 0 | - | - | Yes | ND |
|          | SC | M | 22 | 0 | - | - | Yes | PR |
|          | Morphea | M | 30 | 0 | ND | ND | ND | NR |
|          | Trauma | F | 82 | ND | ND | ND | ND | ND |
|          | Trauma | M | 74 | 40 | ND | ND | ND | PR |
| Metastatic | CRI | M | 59 | 6 | Sevelamer | 4800 | - | NR |
|          | hPT | F | 26 | 0 | ND | ND | ND | ND |
|          | CRI | F | 54 | 17 | Diltiazem | 180 | Yes | PR |
|          | CRI | F | 57 | ND | Diltiazem | ND | Yes | ND |
|          | CRI | F | 67 | 7 | Diltiazem | 60 | - | NR |
|          | CRI | M | 59 | 18 | Sevelamer | 800-7200 | Yes | NR |
|          | CRI | M | 59 | 18 | Sevelamer | 4800 | Yes | NR |
|          | CRI | M | 59 | 18 | Sevelamer | 4800 | Yes | NR |
|          | CRI | M | 59 | 18 | Sevelamer | 4800 | Yes | NR |
|          | CRI | M | 59 | 18 | Sevelamer | 4800 | Yes | NR |
|          | CRI | M | 59 | 18 | Sevelamer | 4800 | Yes | NR |

JDM: Juvenile dermatomyositis, M: Male, PR: Partial response, SSc: Systemic sclerosis, F: Female, ND: No data, PXE: Pseudoxanthoma elasticum, DM: Dermatomyositis, NR: No response, MCTD: Mixed connective tissue disease, SLE: Systemic lupus erythematosus, BCC: Basal cell carcinoma, CR: Complete response, UCTD: Undifferentiated connective tissue disease, OCTD: Overlap connective tissue disease, SC: Scrotal calcinosis, CRI: Chronic renal insufficiency, hPT: Hyperparathyroidism
Our epidemiologic results correspond to published data as we found dystrophic calcinosis to be the most frequent subtype and autoimmune connective tissue diseases to be the most frequent underlying disease. Calcinosis appeared years after the onset of the underlying disease; earlier onset was seen in juvenile dermatomyositis. Extremities were affected most commonly.

Nonlinear microscopy imaging revealed strong endogenous two-photon fluorescence of the calcium salt deposits enabling noninvasive detection of calcinosis cutis. In vivo nonlinear microscopy to assess this condition may be a powerful tool and possibly replace invasive diagnostic methods, which pose hazards due to impaired wound healing.

In the management of calcinosis cutis, there are no accepted therapeutic algorithm or a standard treatment, because the recommendations are based on single case reports and retrospective studies with relatively small element numbers. Thus, therapy should be tailored to each patient.

In the treatment of the dystrophic subtype, the most experienced is related to calcinosis associated to autoimmune connective tissue diseases, which is the most common underlying cause of calcinosis cutis. Pharmacotherapy should be continued for months to years. Calcium channel-blocker diltiazem is recommended in the first line with surgical excision of solitary, painful lesion. It was effective in doses of 240–480 mg/day; lower doses resulted in only partial resolution or were ineffective. In this study, we found that lower doses (60–180 mg/day) resulted in no or only partial response. For the treatment of larger lesions, bisphosphonates, probenecid, and aluminum hydroxide are also recommended in the literature. Bisphosphonates reduce serum calcium levels and inflammation; they were efficiently administered in some cases of calcinosis in systemic sclerosis and juvenile dermatomyositis. Aledronate was effective in doses of 10 mg/day and disodium etidronate in 10–20 mg/kg/day. Probenecid (1.25–2 g/day) was effective in some cases of calcinosis complicating juvenile dermatomyositis. Aluminum hydroxide decreases phosphate levels and reduces the size and symptoms of calcified lesions in some cases of systemic lupus erythematosus and juvenile dermatomyositis with calcinosis. but none of these patients had complete resolution of the lesions. For early, small lesions, warfarin, ceftriaxone, or intravenous immunoglobulin was shown to be beneficial. Warfarin inhibits calcium deposition in tissues; it was used efficiently for early calcinosis in systemic sclerosis in doses of 1 mg/day. Ceftriaxone (2 g/day) was used successfully in a case of calcinosis in morphea. Intravenous immunoglobulin (monthly 2 g/kg divided over 4 or 5 days) was used for calcinosis in CREST syndrome, dermamyositis and juvenile dermatomyositis occasionally with success. Based on our experience, we recommend surgical excision in dystrophic calcinosis cases if the underlying factor (e.g., trauma) does not persist any more or surgical excision is expected to be curative (e.g., basal cell carcinoma). Considering the side effects of pharmacotherapy, surgical therapy may also be applied for early, solitary lesions. Carbon dioxide laser is also mentioned in the literature as a potential therapeutic method for small calcified lesions and extracorporeal shock-wave lithotripsy for pain control in calcinosis. In the management of inflammation associated with calcinosis, anti-inflammatory colchicine or minocycline may be beneficial. Colchicine (0.6–1.8 mg/day) was effective in some patients suffering from dermatomyositis and systemic sclerosis. Minocycline (50–200 mg/day) had a therapeutic effect in some cases of systemic sclerosis. Anti-inflammatory thalidomide (50–75 mg/day, 1.3–2 mg/kg/day) had a positive effect in a case of juvenile dermatomyositis with calcification.

Intralesional corticosteroids have also alleviated the symptoms of inflamed calcified lesions in morphea and juvenile dermatomyositis. Rituximab (375 mg/m²/month, two courses) was occasionally effective in the treatment of calcinosis complicating CREST syndrome and systemic sclerosis due to control of inflammation. According to the literature, sodium thiosulfate was administered with success in dystrophic calcinosis topically (10%–25% in zinc oxide, twice a day, in occlusion). It has vasodilatory and anti-inflammatory effects and increases solubility of calcium hydroxide.

In the treatment of the metastatic subtype, sodium thiosulfate was administered with success in tumoral calcinosis topically (10%–25% in zinc oxide, twice a day, in occlusion) according to the literature. For idiopathic calcinosis, surgical excision or curettage is the first-line therapy, especially in the case of scrotal calcinosis. Intralesional corticosteroids have also alleviated the symptoms of inflamed calcified lesions of idiopathic calcinosis.

Iatrogenic calcinosis generally heals spontaneously in 2–6 months; surgical care may be required in some cases. In the management of calciphylaxis, sodium thiosulfate was the first choice applied intralesionally (1–4 ml of 250 mg/ml solution diluted 1:1 with 1% lidocaine weekly, 3–16 times) or intravenously (5–25 g, 3 times a week). When secondary hyperparathyroidism is present in calciphylaxis, calcimimetics may be an alternative option of parathyroidectomy in doses.
of 30–120 mg/day.\textsuperscript{[56-58]} Bisphosphonates may also be beneficial,\textsuperscript{[14,60,61]} and calcium-free phosphate binders may be used as an adjunctive therapy.\textsuperscript{[62]} We do not recommend the use of phosphate-binder sevelamer, as we found this drug ineffective in all of our three cases. Based on this study, diltiazem may also be beneficial in calciphylaxis in higher doses (≥180 mg), whereas we found it partially effective in one case (180 mg/day). Lower doses (60 mg/day) are not recommended based on our study. Surgical therapy is primarily indicated for localized, movement restricting, painful, ulcerated, or infected lesions,\textsuperscript{[1,12,15]} and for painful ulcers of calciphylaxis.\textsuperscript{[63]}

In a case of multiple calcified lesions, we experienced significant regression after regular aerobic sports activity. Further research on the effect of lifestyle improving blood supply and attenuating the formation of calcification need to be carried out to confirm efficiency.

Considering that our work was a monocentric retrospective case series study on a small population, further randomized controlled trials would be needed to confirm our findings and to improve therapeutic possibilities.

**Authors statement**

We confirm that where it was required and informed, written consent has been obtained from the patients. The studies have been performed according to the Declaration of Helsinki. All procedures have been approved by the institutional ethics committee.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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