Calcinosis cutis arising in morphea: a case series

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Abstract

Calcinosis cutis, although common in systemic sclerosis, has been rarely reported in patients with morphea. We describe four patients with calcinosis cutis arising within morphea plaques, discuss their treatments and outcomes, and review previously published cases. Current management recommendations for concomitant morphea and dystrophic calcinosis cutis are based on limited data and expert opinion, which has primarily focused on reduction of active inflammation and reduction of symptoms related to calcinosis or ulceration. In most cases, no improvement of calcinosis was noted. The use of intralesional corticosteroids to active lesions in conjunction with systemic treatment, including methotrexate when indicated, appear promising treatments to halt progression of the disease. Surgical excision seems to be the most definitive treatment for calcinosis affecting morphea plaques, but the current literature lacks details regarding disease recurrence following operative management.

Keywords: morphea, calcinosis cutis

Introduction

Morphea, known alternatively as localized scleroderma, is an inflammatory, sclerosing disease of the skin and occasionally underlying tissue. Calcinosis cutis refers to insoluble calcium salt deposition in the skin and subcutaneous tissue. Although common in systemic sclerosis, calcinosis cutis has been rarely reported in patients with morphea [1-10]. Herein, we describe four patients with calcinosis cutis arising within morphea plaques and present their diverse clinical treatments and outcomes

Case Synopsis

Case 1

A 6-year-old girl presented with linear morphea on the right arm, extending from the shoulder to the right hand. It had been present since a few months of age. Histopathologic evaluation was consistent with morphea (histology slides and tissue no longer available). Her morphea remained superficial and asymptomatic for several years with intermittent use of calcipotriene 0.005% cream and clobetasol propionate 0.05% ointment. At nine years of age, she was first noted to have a few 0.5-1cm, firm, white papules within the morphea plaque on her right anterior shoulder, consistent with dystrophic calcification. At age 12 years, her morphea plaques thickened and several more white papules were noted within the firmest plaque on her anterior shoulder (**Figure 1**). She was treated with oral prednisone (1mg/kg/day) with taper over three weeks and two years of methotrexate 25mg by mouth once weekly. Over this period of time, her plaques softened and she did not develop new areas of calcinosis. Her range of motion remained full. At most recent contact, one year after finishing methotrexate, her disease remained quiescent.

Case 2

A 49-year-old woman with a 25-year history of generalized morphea was referred for a two-year history of painful, hard, white, ulcerating nodules

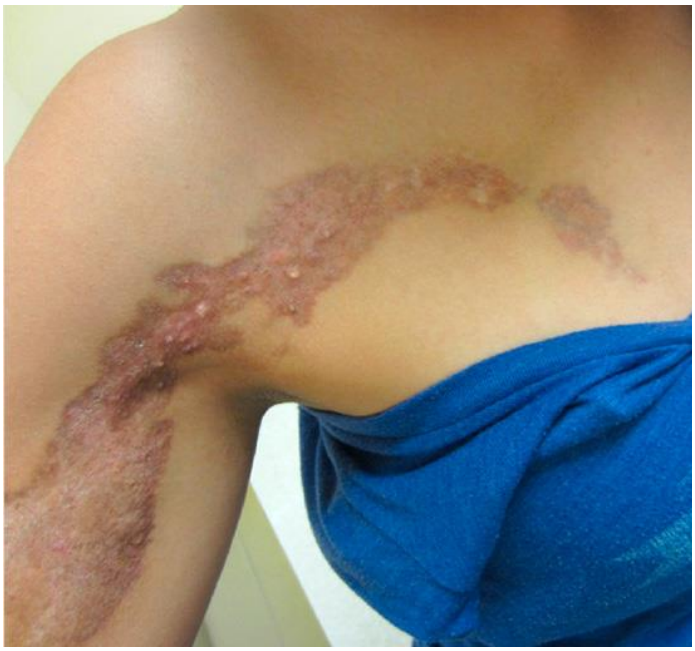

Figure 1. *Linear morphea and calcinosis cutis on the right shoulder and arm of a 12-year-old girl.*

within the morphea plaques on the abdomen and legs. Intralesional sodium thiosulfate approximately one year prior had resulted in increased pain and ulceration.

On examination, the abdomen, thighs, and lower legs revealed more than one dozen, 3-8cm, brown, atrophic, bound-down plaques (**Figure 2A)**. Within the plaques were approximately ten, 0.5-1cm ulcers with pink borders and firm, subcutaneous, irregular, white nodules. A punch biopsy from the abdomen revealed broad and sclerotic collagen bundles and mixed infiltrate surrounding calcification with dermal fibrosis and vertically oriented blood vessels (**Figure 2B)**. She was started on doxycycline 100mg by mouth twice daily, then pentoxifylline 400mg by mouth three times daily was added two months later. With this regimen, the ulcers on her lower extremities healed. At the patient's request her doxycycline dose was decreased to once daily after approximately four months of treatment. She was referred for surgical removal of the large, recalcitrant calcified plaques on her abdomen, but at the time of publication she has not yet scheduled this surgery. Her plaques remain stable.

Case 3

A 53-year-old woman with a five-year history of circumscribed deep morphea on the right hip was referred for worsening pain from firm nodules within her morphea plaque. Examination revealed an approximately 20cm, brown, very firm plaque over the right lateral hip, with approximately six, 1-2cm, rock-hard nodules within it (**Figure 3A)**. A prior biopsy showed sclerosing septal and lobular panniculitis with plasma cells, eosinophils, and calcium deposition, consistent with morphea and dystrophic calcification (**Figure 3B)**. Topical clobetasol propionate 0.05% cream was not helpful. She was treated with methotrexate 15mg by mouth

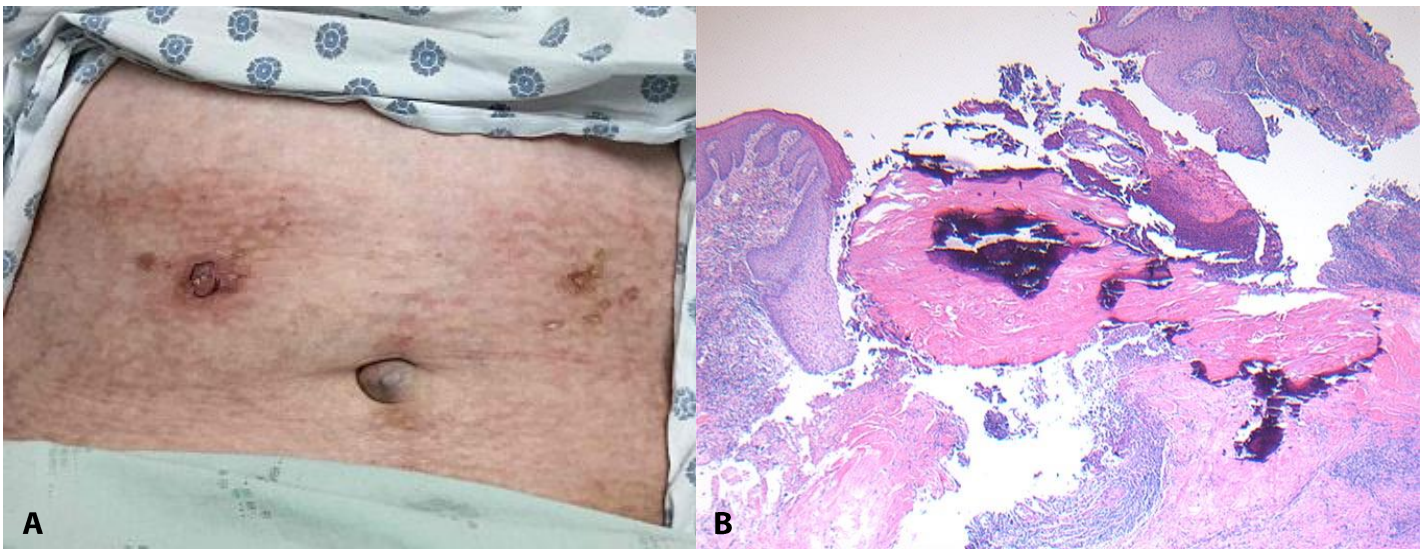

Figure 2. ***A)*** *Ulcers overlying calcinosis cutis within morphea plaques on the abdomen of a 49-year-old female. The marker outline present on the right abdomen was in preparation for biopsy.* ***B)*** *H&E stain demonstrating epidermal hyperplasia, broad and sclerotic collagen bundles, and mixed infiltrate surrounding calcification, 2.5×.*

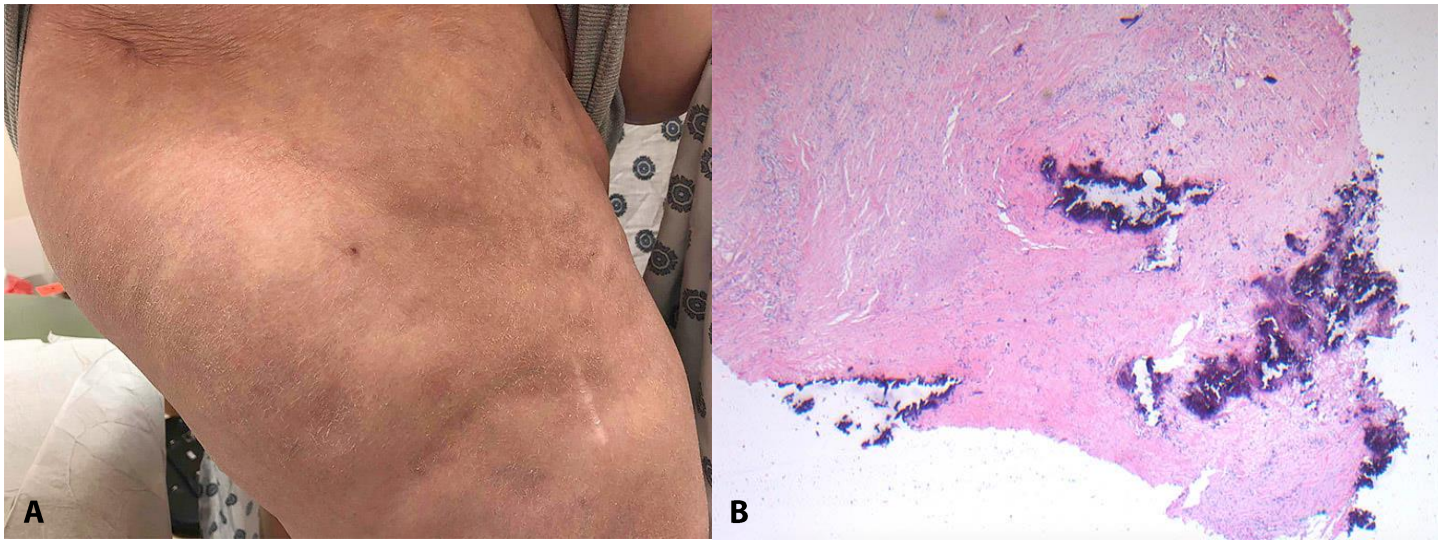

Figure 3. ***A)*** *Large morphea plaque with several areas of calcinosis cutis within it on the right lateral hip of a 53-year-old female.* ***B)*** *H&E stain demonstrating marked sclerosis in the deep dermis and prominent calcium deposition, 2.5×.*

once weekly for approximately six months with some improvement and softening of the deep sclerosis, but no improvement in the calcified nodules. She started treatment with mycophenolate mofetil 500mg twice daily but discontinued after three months owing to elevations in her liver function tests. She then discontinued all medications because of persistently high liver function tests requiring liver biopsy, which showed mild periportal chronic inflammation. At most recent correspondence, the patient remained off medical treatment for her morphea and was continuing to develop painful, calcified nodules within her morphea plaque.

Case 4

A 54-year-old woman presented with a one-year history of painful circumscribed morphea. Examination revealed two, 10cm, firm, red-brown, tender sclerotic plaques on her left and right lower back, as well as a paraspinal 3cm, violaceous, plaque (**Figure 4**). Prior biopsies were consistent with morphea but did not reveal calcinosis at that time. One biopsy site took a year to fully heal and extruded a white substance. Clobetasol propionate 0.05% ointment and tacrolimus 0.1% ointment resulted in no improvement. A subsequent computed tomography (CT) scan of the lower back identified calcification in the subcutaneous soft tissues within the morphea plaques and confirmed secondary calcinosis cutis. Intralesional triamcinolone 5mg/mL was injected into the thicker plaques monthly for approximately one-and-a-half years with reduction in pain and inflammation, but no change in calcification. She developed a few smaller morphea plaques and was started on minocycline 100mg by mouth daily six months prior to the time of writing. At last follow-up, two newer plaques had progressed and become more sclerotic with early calcification. The patient declined alternative systemic therapy because of the focal nature of her lesions and her overall satisfaction with intralesional triamcinolone and minocycline.

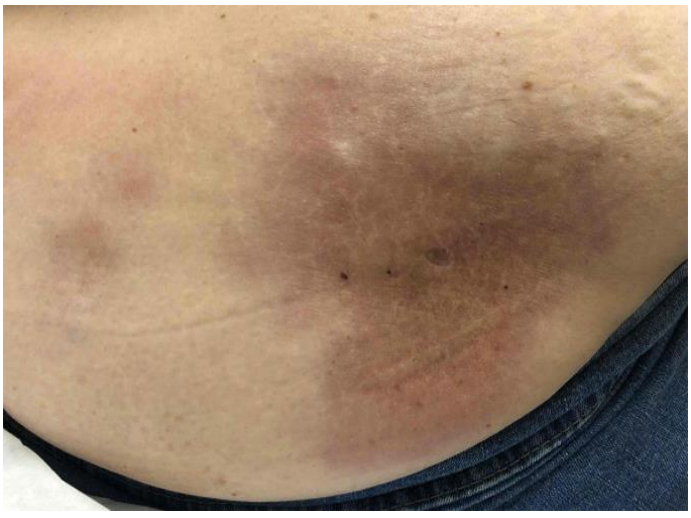

Figure 4. *Large, firm, tender morphea plaque containing calcinosis cutis on the right lower back of a 54-year-old female*

Case Discussion

Morphea is characterized by the disruption of normal tissue architecture through excessive collagen production and deposition [11]. Calcinosis cutis is separated into five subtypes: dystrophic, metastatic, iatrogenic, idiopathic, and calciphylaxis [12]. Dystrophic calcinosis describes deposition into already-damaged tissue and is the most common subtype of calcinosis cutis. It is frequently associated with various autoimmune connective tissue disorders, including systemic sclerosis [13]. Like morphea, systemic sclerosis is a sclerosing disease; unlike morphea, it can affect internal organs [11]. Some have postulated that microtrauma caused by the process of sclerosis induces dystrophic calcium deposition into affected areas of the body [12, 13].

Reports of calcinosis in the setting of morphea are rare. Upon review of the English literature, ten reports dating from 1979 to 2016 constitute the majority of evidence on calcinosis cutis arising within morphea lesions of linear, generalized, and circumscribed/plaque subtypes [1-10]. Of the 14 patients described including the four in this series, four were male and ten were female. The age at presentation with calcinosis ranged from 6 to 83, with an average age of 48. Diagnosis of calcinosis was made almost exclusively by biopsy, often supplemented by imaging with X-ray, ultrasound, and/or CT. Laboratory testing for disruption in calcium metabolism was performed in several of the previous cases and was unrevealing. Although plaque-type morphea is the most common morphea subtype overall, five of the 14 reported cases of calcinosis cutis arose within the linear variant of morphea, the most common subtype among children and adolescents. This group includes three of the four youngest patients reported.

Current management recommendations for coexistent morphea and dystrophic calcinosis cutis are based on limited data from case reports and expert opinion [15]. Treatment of patients with morphea and concomitant calcinosis cutis has primarily focused on reduction of active inflammation secondary to morphea and reduction of symptoms related to calcinosis or ulceration. In the majority of cases, no improvement of calcinosis was noted [3, 8, 9]. Oral methotrexate helped stabilize the disease in our pediatric patient, whereas doxycycline coupled with pentoxifylline halted disease progression in our patient with morphea of the abdomen and legs. Intralesional triamcinolone showed initial benefit in one of our patients, in whom disease was also suppressed with the addition of minocycline. However, these medical treatments did not improve calcinosis cutis or related symptoms. Surgical excision has been the most successful treatment modality for calcinosis in the cases documented (**Table 1**), [2, 4].

Calcinosis cutis can occur uncommonly in the setting of morphea and is believed to develop secondary to tissue damage. Various treatments have been attempted to address disease progression over the last several decades without an obvious single most effective treatment option. Based upon our current knowledge and existing data, treatment should aim to address underlying active morphea contributing to tissue damage and resultant dystrophic calcinosis. Surgical excision seems to be the most definitive treatment for calcinosis affecting morphea lesions, but the current literature lacks details regarding disease recurrence following operative management.

Conclusion

Dystrophic calcinosis cutis may occur within plaques of morphea, but current evidence fails to provide support for any single treatment. We recommend that treatment should be individualized and focused on stabilizing active morphea, with consideration of expectant management in the asymptomatic, stable patient.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 1. *Summary of cases of calcinosis cutis arising in morphea plaques.*

Cases	Patient sex	Age at presentation	Location of morphea	Subtype of morphea	Years between morphea onset and calcinosis	Method of diagnosis	Treatment and response
Jinnin, et al. (2002), [6]	M	21	Arm	Linear	2	CT followed by skin biopsy	Topical corticosteroids → morphea improved, no change in calcifications
Gait, et al. (2009), [4]	F	72	Back	Plaque	3	Skin biopsy	Complete surgical excision of calcinosis; no discussion of healing or response
Reiter, et al. (2010), [3]	M	16	Bilateral arms, chest	Deep subcuta-neous	Not reported	Skin biopsy followed by X-ray	Aluminum hydroxide → disease progression IV ceftriaxone 2 g x 20 days (based on association of morphea with *Borrelia burgdorferi* in Europe) → stabilized morphea and diminished calcifications
Agarwal, et al. (2013), [2]	F	22	Arm	Linear	10	X-ray and CT followed by excisional biopsy	Surgical excision → complete healing after 6 weeks
Deza, et al. (2016), [1]	M	54	Shoulder	Plaque	<1	US and X-ray followed by skin biopsy	Expectant management → stable after 1 year
Holmes (1979), [9]	F	54	Buttocks, legs	General-ized plaque	33	X-ray followed by skin biopsy	Probenecid, aluminum hydroxide, diphosphonates, sodium ethylenediamine tetra acetic acid → no satisfactory response
Yamamoto, et al. (2002), [5]	F	52	Thigh	Linear	15	Skin biopsy	Topical corticosteroid, IM sodium aurothiomalate (gold), tocopherol acetate, retinol palmitate, IV alprostadil alfadex (PGE1) → no improvement, developed calcifications IL triamcinolone 20 mg/mL → erythema improved, no change in calcification or sclerosis
Vereecken, et al. (1998), [7]	F	67	Leg	Linear	40	Skin biopsy followed by X-ray, CT	Colchicine 1 mg daily → ulcerations healed, calcinosis stabilized
Hazen, et al. (1979), [8] and Hazen, et al. (1982), [10]	F	83	Face, scalp	Limited facial	13	Clinical exam	Potassium aminobenzoate, colchicine 0.6 mg three times daily, aluminum hydroxide-magnesium hydroxide, aluminum hydroxide → no improvement Hydroxychloroquine → improved

							initially, then worsened IL triamcinolone 20 mg/mL → improvement of some ulcers and calcification
	M	65	Face, scalp	Limited facial	20	Clinical exam	Zinc oxide ointment → ulcerations healed
Our cases presented	F	6	Chest, shoulder, arm	Linear	3	Clinical exam	Calcipotriene cream and topical corticosteroids → calcinosis developed, morphea worsened Oral prednisone + methotrexate 25 mg weekly x2 years → morphea improved and calcinosis stabilized
	F	49	Abdomen, legs	General-ized plaque	23	Skin biopsy	Doxycycline 100 mg twice daily x2 months → no improvement Pentoxifylline 400 mg three times daily added → ulceration healed, morphea and calcinosis stable Reduction of doxycycling to 100 mg daily → remained stable Surgical excision of calcinosis planned
	F	53	Hip	Plaque	1	Skin biopsy	Topical corticosteroids → no improvement Methotrexate 15 mg weekly x6 months → morphea improved, no change in calcinosis Mycophenolate 500 mg twice daily → no documented improvement No treatment → calcinosis worsened
	F	54	Back	Plaque	0	CT	Topical corticosteroids and calcineurin inhibitors → no improvement IL triamcinolone 5 mg/mL monthly → morphea improved with no change in calcinosis, then worsened with new plaques Minocycline 100 mg twice daily added → progression of morphea and early calcification