Nodular (keloidal) scleroderma: A case series of 5 patients

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INTRODUCTION

Nodular scleroderma (NS), is a rare variant of cutaneous scleroderma, mostly affecting young middle-aged women of African ancestry.[1] NS can occur in association with diffuse systemic sclerosis or as localized scleroderma (morphea).[2] Alternative name designations include nodular morphea and keloidal morphea. Though the exact pathogenesis of NS is not completely understood, an exaggerated and dysregulated pattern of fibrosis that recapitulates a hypertrophic scar or keloid in areas of the skin affected by scleroderma is seen. NS probably reflects an interplay between those genetic factors implicated in the formation of keloids and hypertrophic scars in concert with endogenous and exogenous factors that lead to the development of scleroderma.[3] Generally, the diagnosis rests upon a careful integration of the clinical features with the light microscopic findings. To the best of our knowledge, only 61 cases of NS have been reported in the literature. Herein, we describe a series of an additional 5 cases of NS.

Abbreviations used:

NS: nodular scleroderma
SLE: systemic lupus erythematosus
SMA: smooth muscle actin

CASE 1

A 35-year-old African American female, presented with multiple lesions on her chest and flank with associated symptoms of burning and itching. The patient had a 5-year history of scleroderma (diffuse systemic sclerosis) confirmed with a cutaneous punch biopsy 5 years prior to this current presentation. Her initial laboratory findings showed a positive antinuclear antibody exhibiting a distinct nucleolar pattern. Antihistone, rheumatoid factor, and other scleroderma-related antibodies (anticentromere, anti-topoisomerase I, and anti-RNA polymerase III) were negative. Previous treatments included tacrolimus 0.1% ointment, and clobetasol 0.05% ointment with minimal improvement, as well as hydroxychloroquine 200 mg twice daily. She was lost to follow-up but returned 5 years later with new lesions.

On physical examination, she presented with annular, indurated, hyperpigmented plaques on her chest and bilateral flank (Fig 1); she had taut acral skin with digital accentuation. No lymphadenopathy was present. Laboratory studies disclosed an elevated erythrocyte sedimentation rate as well as persistent positivity of antinuclear antibods. A biopsy of the left flank was performed showing a striking nodular fibrosing reaction reminiscent of a hypertrophic scar but with certain distinctive morphologic features including (Fig 2, *A*) a paucity of adnexal structures and a perivascular and perineural lymphocytic and plasmacytic infiltrate. There was a striking diminution in the expression of CD34 while there was acquisition of smooth muscle actin (SMA) staining within fibroblasts in the zones of nodular fibrosis (Fig 2, *B*). The biopsy was interpreted as NS.

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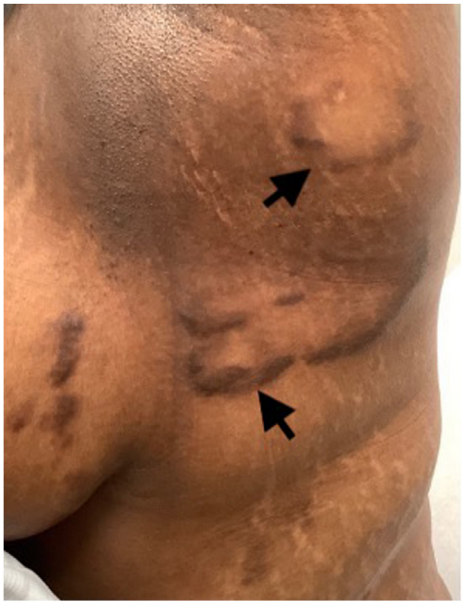

Fig 1. Annular hyperpigmented plaques (*arrows*) located on the right flank.

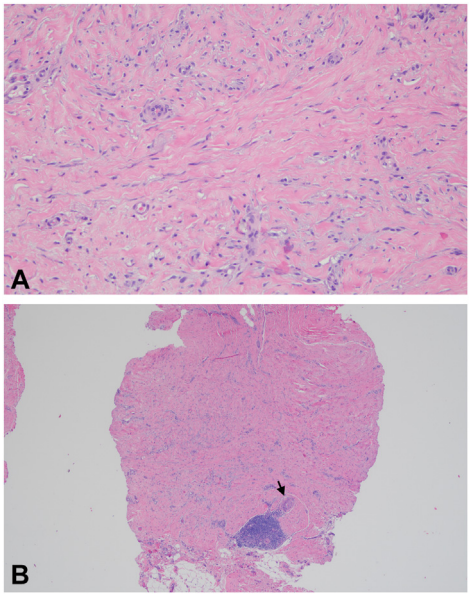

Fig 2. A, High-power magnification accentuating the nodularity and hypercellularity of fibrosis defining a pattern reminiscent of a hypertrophic scar. **B,** Low-power view of mid and deep dermal fibrosis. There is striking paucity of adnexal structure. Modest perivascular and perineural lymphocytic (*arrow*) and plasmocytic infiltrate is present in the dermis (hematoxylin and eosin).

The patient was subsequently advised to follow-up with her rheumatologist for further evaluation.

CASE 2

A 67-year-old Caucasian male, with a past medical history of interstitial lung disease and rheumatoid arthritis presented with subcutaneous nodules on the gluteal and thigh area that had been present for 2 months. An initial biopsy suggested findings of scleromyxedema. However, a repeat punch biopsy was performed to rule out rheumatoid nodules. Results from the repeated biopsy did indeed reveal sclerosis and mucin deposition; however, it also showed a pattern of paucicellular hyalinizing fibrosis in the deeper dermis and subcutis, showing the typical phenotypic profile that one encounters in scleroderma revealed by focal acquisition of smooth muscle staining amidst interstitial fibroblasts with a converse mirror image reduction in the expression of methotrexate was planned as the proposed treatment; however, the patient was lost to follow-up.

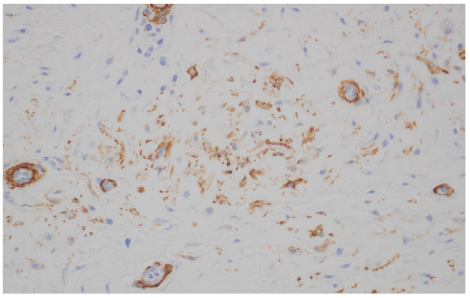

Fig 3. Focal acquisition of smooth muscle actin staining.

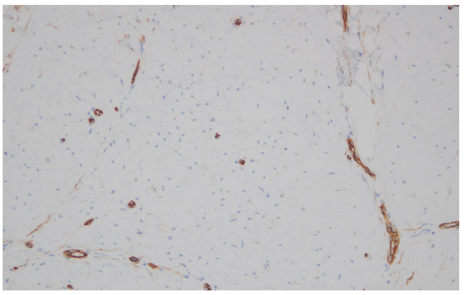

Fig 4. Marked reduction in the expression of CD34.

CASE 3

A 67-year-old Caucasian female with an over 40-year history of systemic scleroderma presented with worsening ulcerations on her fingertips. On physical examination, severe sclerodactyly with resorption of bilateral distal phalanx, ulceration of distal fingers, nail dystrophy was observed. She underwent symptomatic management with topical corticosteroids, oral pain management, and surgical closure of ulcerated areas. The patient was recommended to continue topical corticosteroid and given the option to start a trial of botulinum toxin A or prostacyclin analog, treprostinil. She underwent arthrodesis to immobilize the interphalangeal joints

of her right fourth and fifth digits due to worsening symptoms. A tissue sample was collected during the procedure and analyzed. The skin sample showed reactive epithelial changes including a hyalinizing pattern of fibrosis with many robust appearing activated myofibroblastic elements coursing through the sclerotic dermis. The SMA preparation shows acquisition of a SMA phenotype amidst the myofibroblastic appearing cells within the zones of sclerosis (Fig 3). The sclerosis differed from the paucicellular low density fibrocyte pattern of sclerosis seen in conventional scleroderma because of the keloidal hypertrophic scar-like reaction pattern. Overall, the collective findings are supportive of the patient's known diagnosis of systemic scleroderma.

CASE 4

A 54-year-old Caucasian female with a past medical history of systemic lupus erythematosus (SLE) with secondary Sjogren and rheumatoid arthritis, presented with a pruritic erythematous rash on her right elbow for the past 11 months. She reported that the rash spread to her posterior neck in the past month. Patient applied saline solution to the affected areas with no improvement. Physical examination revealed firm dermal skin-colored papules on the right elbow and a linear array of firm skin-colored papules, with minimal scale on the posterior neck. Pinpoint vessels were present under the dermatoscope. A biopsy of both sites was performed revealing sclerodermoid-like reaction characterized by widened collagen bundles with a hyalinized nodular appearance reminiscent of NS. The CD34 preparation showed striking diminution within the zone of sclerosis and minimal staining for interstitial fibroblasts in zone of sclerosis indicating a loss of CD34 (Fig 4). Serum protein electrophoresis to evaluate for underlying plasma cell dyscrasia was negative. Based on the dermatopathology findings, the diagnosis of nodular scleroderma with overlying eczematous alterations was made and the patient was prescribed 0.05% fluocinonide cream to be applied twice daily.

CASE 5

A 49-year-old African American female, with a 37-year history of SLE presented with new lesions on her fingers. Patient was previously managed with hydroxychloroquine and nabumetone. Physical examination revealing blisters and tender papules on the dorsum of her right third and fourth digits were observed. A biopsy of her third digit was obtained and the results showed an unusual nodular keloidal-like pattern of fibrosis in concert with significant microvascular changes including extensive microvascular deposits of complement. Despite the history of SLE, the myxovirus-resistance protein A stain was negative including a notable lack of endothelial cell staining for myxovirus-resistance protein A. A diagnosis was made of NS possibly with concurrent nabumetone associated pseudoporphyria, somewhat reminiscent of sclerodermiform porphyria.

DISCUSSION

NS is a rare form of scleroderma characterized by indurated lesions that clinically resemble keloid scars. Previous reports describe the existence of less than 50 reported cases of NS; however, our review has identified a total of 61 reported cases of NS in the literature.[4] It was first described in 1854 by Thomas Addison as an "untrue keloid."[5] The terms "nodular" scleroderma, keloidal scleroderma, nodular morphea, and keloidal scleroderma have been used interchangeably to describe the same fundamental process which is one of nodular plaques resembling a hypertrophic scar clinically and to a certain extent histologically in the setting of scleroderma be it in the context of systemic sclerosis or cutaneous confined scleroderma (ie, morphea). Due to the diverse nomenclature, many authors have recognized subsets of NS represented by: (1) NS in the setting of systemic scleroderma and (2) NS with or without conventional lesions of morphea in the absence of systemic scleroderma. One might suggest using the term 'nodular/keloidal scleroderma' for those cases occurring in the setting of systemic scleroderma and apply the designation of nodular or keloidal 'morphea'[2] for cases confined to the skin. Clinically, NS presents as keloidal plaques or nodules favoring the neck, upper trunk, chest, limbs, and extremities.[2,6] The light microscopic findings are highly reproducible. Without any known history of systemic scleroderma or cutaneous confined morphea, the histology in fact does resemble a hypertrophic scar or keloid. However, among the clues are areas of deeper-seated fibrosis that recapitulate the more conventional pattern seen in scleroderma. In particular, the collagen bundles are of wider caliber, show a loss of their fibrillar architecture, and assume a parallel orientation to the long axis of the epidermis. In addition, there is a paucity of adnexal structure.[7] The typical perivascular and perineural plasmacytic infiltrate that one observes in classic morphea is seen in NS. Finally, the classic scleroderma phenotype within the dermal fibroblasts is an immunohistochemical hallmark of NS and defines a powerful diagnostic tool in confirming the diagnosis. The fibroblasts do not express CD34 and show focal acquisition of SMA staining, defining the classic

Table I. Demographic and clinical characteristics of the 5 patients with nodular scleroderma

Case	Race	Age	Sex (M/F)	Anatomic location	Key findings
1	African American	35	F	Chest, bilateral fanks	5-y history of diffuse systemic sclerosis; Annular plaques
2	Caucasian	67	M	Gluteal region and proximal thigh	Subcutaneous nodules
3	Caucasian	67	F	4th and 5th fingers	Over 40-y history of systemic scleroderma
4	Caucasian	54	F	Elbow, posterior neck	History of SLE, RA, and Sjogren Skin-colored papules in a linear pattern
5	African American	49	F	3rd and 4th fingers	History of SLE

F, Female; *M*, male; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus.

procollagen phenotype unique to scleroderma. Finally, the typical profound elastolytic pattern highlighted by an elastic tissue stain in the setting of a scar is not seen.

The combination of fibrosis and mucin in case 2 produced a morphology therefore reminiscent of scleromyxedema. The activated scleroderma associated fibroblast exhibits not only a procollagen phenotype with an increased production of collagen but can also elaborate other components of the connective tissue matrix such as hyaluronic acid.[8]

In middle aged and older individuals who develop scleroderma one must always consider its presentation as a paraneoplastic phenomenon best exemplified by scleroderma in the setting of an underlying plasma cell dyscrasia.[9] In case 4 the serum protein electrophoresis and immunofixation did not disclose a monoclonal gammopathy.[10] Case 5 had clinical and light microscopic features of nabumetone associated pseudoporphyria but the biopsy showed concomitant features of NS as well. In essence, the biopsy was consistent with sclerodermiform pseudoporphyria. While sclerodermoid variants of porphyria are well described in the literature, there are no prior reported cases of sclerodermiform pseudoporphyria Table I offers a comprehensive overview of the cases within this series and their key clinical findings.

Morphea has a female predominance and a higher prevalence in Caucasian populations compared to non-White racial-ethnic groups,[11] Kassira et al suggest that NS may present more commonly in African American patients.[1] A Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/82y374pbtx/1 summarizes the published data on NS. Out of the 20 papers that mentioned racial-ethnic background, most patients (n = 9) were of African descent (Caucasian n = 8; Asian n = 4; Hispanic n = 1). There was also a female predominance of NS, similar to that of morphea which is also reflected in this series of cases. Of the 5 patients with NS, 4 patients were female. Moreover, most cases of NS are with systemic sclerosis. In our series, only 2 of the 5 patients had systemic sclerosis; however, the other 3 patients had evidence of systemic multiorgan autoimmune disease in the context of SLE in 2 patients and rheumatoid arthritis in 2 patients. Hence our series establishes the association of NS with systemic autoimmune disease including but not limited to systemic sclerosis. Our patient's NS plaques were annular, which was one of the 2 shapes commonly described in the literature. More data is required to determine the frequency of annular sclerotic plaques as the predominant morphology of NS.

It has been postulated that NS or nodular morphea represents an exaggerated fibrosing reaction that mirrors the pathogenesis of hypertrophic scar formation and keloid development in a genetically predisposed patient who also has systemic scleroderma or localized cutaneous confined morphea.[2,12,13] Our series of cases illustrate an underrecognized clinical presentation of scleroderma in patients, particularly those with skin of color, and is an important cutaneous manifestation of systemic disease. This may be attributed to the misdiagnosis of NS with other scleroderma-like disorders that share similar clinical and pathologic features (ie, keloids, lichen sclerosis, granuloma annulare, scleromyxedema etc.). The diagnosis of NS should be included in the differential diagnosis of keloidal plaques that are annular and lack preceding trauma. It is paramount that physicians maintain a high index of suspicion for patients presenting with these features in order to prevent further cosmetic and functional sequelae.[14] Patients should be further evaluated with a skin biopsy for diagnostic confirmation and serological workup for systemic

sclerosis. Mainstay treatments for cutaneous and systemic scleroderma include topical or intralesional corticosteroids, topical vitamin D analogs and calcineurin inhibitors, mycophenolate mofetil, ultraviolet light therapy, methotrexate, and systemic steroids. However, 1 case of recalcitrant NS following cyclosporine treatment has been reported.[15] Oral Phosphodiesterase 4 inhibitors as an emerging treatment have shown promise; nonetheless, more evidence is required.[16]

Our case illustrates that NS is an important diagnostic consideration in patients presenting with spontaneous nodules or plaques resembling keloid scars, especially those that are annular. Given the paucity of previously published reports, it is likely that this cutaneous manifestation of systemic sclerosis is underrecognized.

Conflicts of interest

None disclosed.

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