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# Questions raised by a case of adult-onset linear nodular scleroderma

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## Abstract

Morphea presenting clinically with nodular or keloidal skin changes is extremely rare. Nodular scleroderma or keloidal morphea presenting in a linear distribution is even more uncommon. We present an otherwise healthy young woman with unilateral, linear, nodular scleroderma and review the somewhat confounding earlier literature in this area. To date, this young woman's skin changes have proven refractory to oral hydroxychloroquine and ultraviolet A1 phototherapy. Several aspects of this case including the patient's family history of Raynaud disease, her nodular sclerodermatous skin lesions, and the presence of U1RNP autoantibodies raised concern about her management with respect to future risk of developing systemic sclerosis.

*Keywords: hydroxychloroquine, keloidal, linear, morphea, nodular, phototherapy, scleroderma, UVA1*

## Introduction

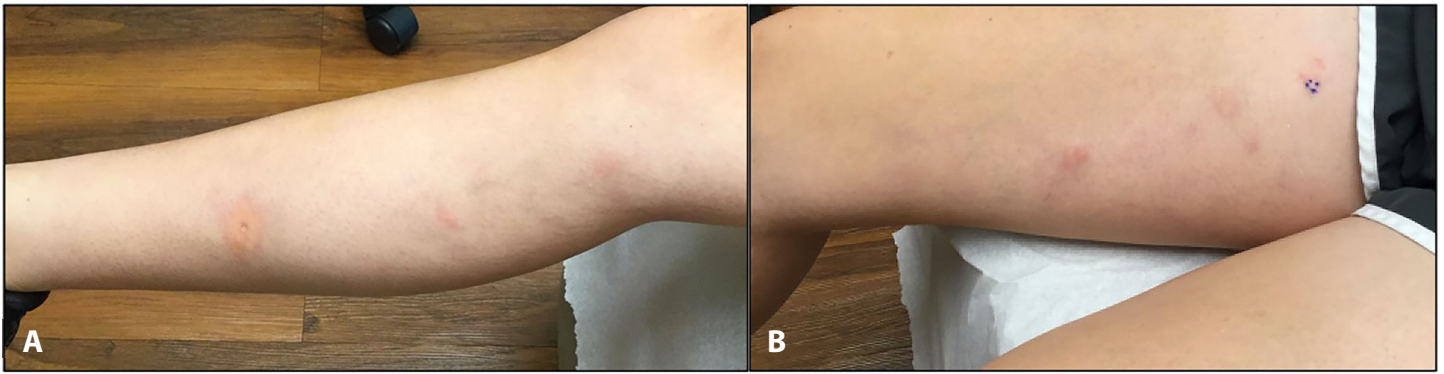
Morphea, historically referred to as "localized scleroderma" or "circumscribed scleroderma," is a rare autoimmune inflammatory fibrosing disease of the skin and subcutaneous tissue [1]. It is characterized by thickening and hardening of the skin resulting from autoimmune vascular changes, increased production of collagen, and extracellular matrix proliferation [1]. Morphea has historically been classified clinically to include the following

more commonly encountered phenotypes: plaque, generalized, linear, and profunda. Less commonly encountered phenotypes include bullous, pansclerotic, and keloidal/nodular morphea.

We report an otherwise healthy young adult woman who presented with a linear distribution of firm subcutaneous nodules extending from the medial right calf upward to the right medial thigh that had features of morphea on skin biopsy. Questions concerning the diagnosis and future prognosis of our patient arose following a review of the rather complicated previously published literature in this area. In this report, we share the results of our discussions concerning the optimal short- and long-term management of patients presenting in this manner.

## Case Synopsis

A previously healthy 27-year-old woman presented for evaluation of a one-year history of slowly progressive tender lumps in the skin of her right leg. The lumps initially appeared on her right medial calf as two adjacent lumps and slowly spread upward to her right thigh. The patient denied any seasonal variation of the lesions. Review of systems was negative for any clinical evidence of systemic sclerosis or autoimmune connective tissue disease. The patient's family and social history were unremarkable except for her mother who had Raynaud disease, but no clinical or laboratory evidence of systemic sclerosis.



**Figure 1.** Unilateral linear array of firm subcutaneous nodules and small plaques extending from **A)** the right medial calf, to **B)** the right medial thigh.

Physical examination revealed an indurated, ivory-colored plaque on the right medial calf in the area reported to be the site of the patient's first lesion. Also, on the right medial calf were multiple firm, tender, well-demarcated nodules in a linear distribution that extended proximally to the right medial thigh and right lower abdomen (**Figure 1**). There was an 8mm hypopigmented dermal papule on the right medial thigh where the patient's most recent lesions had appeared. There were no obvious skin changes on other areas of the patient's body. The continuous, linear, band-like confluent areas of induration typical of linear morphea in children were not present in our patient.

Laboratory studies including a complete blood count, comprehensive metabolic panel, and urinalysis were unremarkable. An antinuclear antibody assay was reported to be marginally positive at a titer of 1:80 by indirect immunofluorescence. A systemic sclerosis autoantibody panel including PM Scl-100, U3 RNP, RNA Polymerase III, Scl-70 antibodies was negative except for the presence of U1RNP autoantibodies.

Finger nailfold videocapillaroscopy was performed using an optical probe videocapillaroscope equipped with a  $\times 200$  magnification contact lens and connected to image analysis software (Inspectis AB, Solna, Sweden). The results failed to identify the microvascular abnormalities of systemic sclerosis or dermatomyositis.

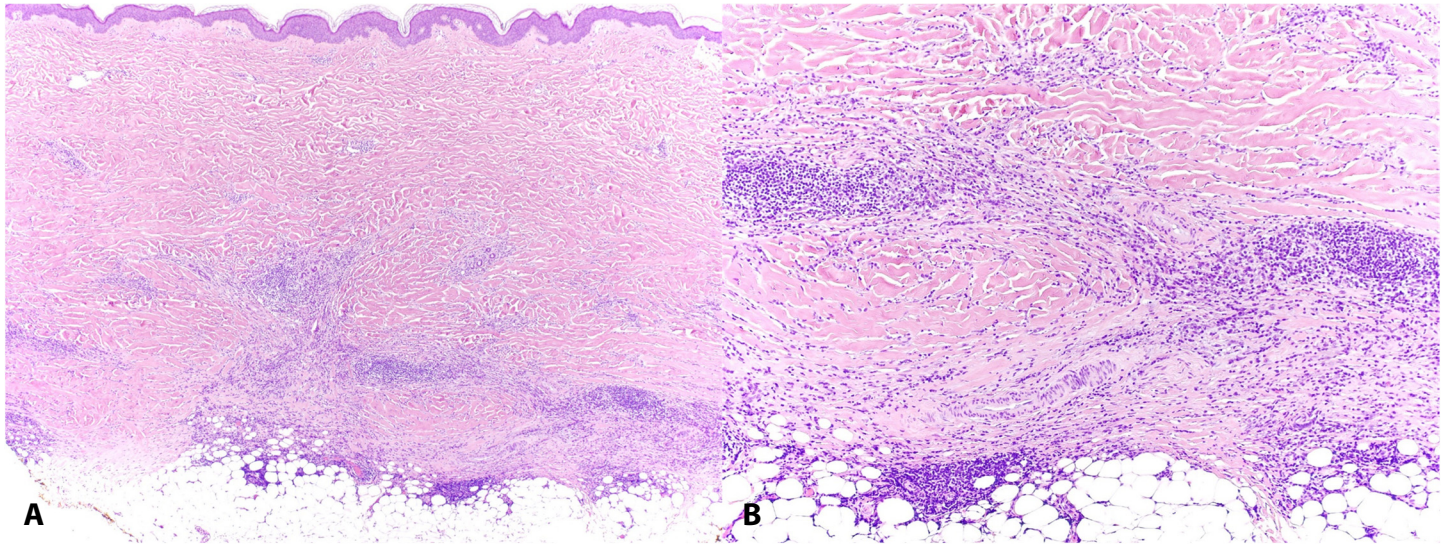
The histopathological findings from a prior skin biopsy of the right calf were reported as displaying changes suggestive of morphea. A repeat lesional biopsy from the right medial proximal thigh for

routine histopathology was performed during our initial evaluation in our clinic. The histopathologic findings were consistent with inflammatory morphea showing dermal sclerosis with interstitial lymphoplasmacytic inflammation and no significant inflammation of the panniculus (**Figure 2**).

As the patient lacked sclerodactyly and other proximal skin changes concerning for systemic sclerosis, had no keloidal skin changes, and had no clinical or laboratory manifestations specific for systemic sclerosis, the patient was given an initial diagnosis of adult-onset linear nodular morphea. Consideration was given to an undifferentiated or overlapping connective tissue disease, especially mixed connective tissue disease (MCTD) given the patient's positive U1RNP autoantibodies. To date, however, the patient has shown no other signs concerning for the overlapping elements of MCTD, including systemic lupus erythematosus, polymyositis, and systemic sclerosis.

Intralesional triamcinolone injection therapy was discussed. However, given the multiplicity of nodules oral hydroxychloroquine therapy was chosen. The patient was started on hydroxychloroquine 400mg by mouth daily. After three months of hydroxychloroquine therapy the patient had not experienced improvement in the existing lesions and had developed a new nodule. After discussing other treatment options, she opted to begin ultraviolet A1 (UVA1) phototherapy while continuing hydroxychloroquine.

The patient underwent 20 treatments of medium-dose UVA1 phototherapy (set with a maximum of 50 Joules). Although the patient did not develop any



**Figure 2.** The punch biopsy of the right medial thigh nodule reveals thickened sclerotic collagen bundles and a dense lymphoplasmacytic infiltrate in the deep dermis and superficial subcutis at **A)** 40 $\times$ , and **B)** 100 $\times$ .

new areas of skin involvement while undergoing phototherapy, the UVA1 phototherapy did not produce a clinically significant improvement in her pre-existing skin lesions. Systemic immunosuppressive therapy with methotrexate was offered as an alternative treatment option, but the patient declined, given that her pre-existing lesions were stable and without evidence of newly occurring lesions.

### Case Discussion

The terms nodular morphea, keloidal morphea, nodular scleroderma, keloidal scleroderma, nodular localized scleroderma, and keloidal localized scleroderma have been used interchangeably without specific definitions for over a century. These various designations have been used to describe the rare patient who presents with nodules or hypertrophic keloidal plaques that upon skin biopsy show histopathologic features of morphea/localized scleroderma [2]. More recently, authors such as Rencic et al. have suggested that the clinical concepts of “keloidal morphea” and “nodular scleroderma” should be considered separately [3]. After elegantly reviewing the clinical and laboratory features of six of their own patients, as well as the previously published cases in this area, these authors proposed that “keloidal morphea” and “nodular

scleroderma” represent two clinically distinct variants of autoimmune scleroderma.

Nodular scleroderma has been described as predominantly affecting the upper trunk, neck, and shoulders of young-adult and middle-aged females in a non-linear fashion [2]. Interestingly, it has been described as occurring more frequently within the context of pre-existing systemic sclerosis than “skin-only” morphea [3].

Our case of adult-onset, unilateral, nodular scleroderma presenting as discrete nodules arranged in a linear array would seem to best fit into the clinical subgroup described by Rencic et al. as “nodular scleroderma” raising the possibility of an association with systemic sclerosis. We feel that our case has additional features that raise questions concerning the optimal clinical management of such patients over time.

This patient displayed some rather unique clinical features of nodular scleroderma. Firstly, the size of the nodules in our patient were larger than that which have been observed in nodular scleroderma patients reported in the past. In the literature review by Rencic et al, it is stated that “Clinically, nodular scleroderma is characterized by numerous, small, flesh-colored firm nodules....” with half of these patients having had papules and nodules ranging from 2mm to 20mm, which are significantly smaller compared to the larger nodular plaque measuring

40mm in our patient's case [2]. Secondly, the anatomic distribution of her lesions was unique, in that her nodules were unilateral, extending in a linear arrangement from the right lower abdominal wall to the right medial thigh and right medial calf, as opposed to the more common locations on the upper body.

In addition, the nodules in our patient assumed a non-contiguous linear arrangement extending from the right lower abdominal wall to the medial right thigh and calf in a Blaschkoid distribution. Cases of keloidal morphea and nodular localized scleroderma published prior to 1975 were reviewed by Dr. Stephanie Jabłońska in Chapter 6 of her landmark textbook, *Scleroderma and Pseudoscleroderma*. In this textbook chapter, Dr. Jabłońska discussed eight of her own keloidal/nodular localized scleroderma patients that included three children. One case described a 14-year-old girl with keloid-like lesions observed to be arranged in a linear distribution on the shoulder region. In this child as well as our patient, the keloidal morphea/nodular scleroderma lesions appeared to be distributed along either Blaschko lines or dermatomal lines [4]. Since then there have been several additional published case reports of keloidal morphea/nodular scleroderma occurring in a linear distribution. In two reported cases, the scleroderma nodules appeared to have developed in pre-existing linear scleroderma indurated plaques [5, 6]. However, in our case the nodules were discrete and non-contiguously arrayed in a linear fashion.

It is currently believed that Blaschko lines demarcate the dorsoventral migration patterns of ectodermal development (data reviewed in Cheraghlou et al, 2020), [7]. Clinical localization of genetic skin diseases to Blaschko lines is now considered to be related to early, random, embryonic inactivation of X chromosomes in females resulting in epigenetic cellular mosaicism (i.e., lyonization). The X chromosome is enriched in genes involved in normal immunity and autoimmunity, including *TLR7* and *CD40L*. There is increasing evidence that partial/incomplete (i.e., "skewed") X chromosome inactivation might be a contributing factor to the female predominance of autoimmune disorders

such as lupus erythematosus and autoimmune scleroderma by an increased gene dosage mechanism (data reviewed in Syrett et al, 2019), [8].

Our patient presented without obvious symptoms or laboratory evidence to suggest the presence of systemic sclerosis. Besides the known development of nodular scleroderma lesions developing in patients with pre-existing systemic sclerosis, two additional features of this case suggest a potential for this patient to develop systemic sclerosis in the future. First, she had a marginally positive antinuclear antibody assay and U1RNP autoantibody. U1RNP autoantibody is the serologic marker for mixed connective tissue disease (MCTD). Mixed connective tissue disease and other overlap syndromes including undifferentiated autoimmune connective tissue disease can include an overlap component of systemic sclerosis. On a recent review of undifferentiated connective tissue disease, it was stated that approximately 50% of such patients will develop systemic sclerosis over time [9]. However, U1RNP autoantibodies have been reported to occur in patients with morphea/localized scleroderma without evidence of systemic sclerosis [10]. Thus, we will strongly encourage the patient to have periodic follow-up surveillance medical evaluations in the future to identify early features of systemic sclerosis.

The patient underwent therapy with hydroxychloroquine and UVA1 phototherapy without significant improvement of her pre-existing sclerotic skin lesions. However, she believed the severity of her disease was stable and declined further treatment. For slowly progressive cases such as this, systemic immunosuppressive monotherapy with methotrexate would be suggested [11]. Mycophenolate mofetil may also be considered as a well-tolerated and effective treatment in cases of morphea in which patients are intolerant or nonresponsive to methotrexate or methotrexate is contraindicated [12]. Newer evidence suggests that autoimmune fibrosis may involve specific cytokines of the Jak-STAT cascade. Inhibition of the Jak pathway with therapies such as tofacitinib has shown to decrease inflammation and even reverse fibrosis, thus offering alternative treatment options for these patients with recalcitrant morphea.

## Conclusion

Morphea and systemic sclerosis are rare sclerodermatous conditions and nodular forms of either disease are even more infrequent. Categorizing a patient with nodules showing sclerotic changes on histopathology can prove challenging, as demonstrated in this report. We encourage dermatologists to be aware of the specific features of both diseases, especially those that may

demonstrate signs of systemic involvement. In such cases, we feel that these patients should be followed closely, with careful evaluation for evidence of skin progression as well as new systemic symptoms.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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