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Unilateral Generalized Morphea is a Rare Variant of Localized Scleroderma

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Abstract
Localized scleroderma (LS) is a rare connective tissue disorder generally involving the entire dermis and usually limited to the subcutaneous tissue. However, it may progress to large indurated plaques, growth retardation, muscle atrophy, and even to flexion deformities or poorly healing ulcerations. LS has been classified as plaque, generalized, bullous, linear, and deep forms exhibiting different clinical subtypes. Recently, an unusual case of unilateral generalized morphea (UGM) in childhood extending from the middle dermis to the subcutaneous fat tissue has been reported. We here describe four young patients exhibiting a similar subtype of LS.

All patients demonstrated a prominent unilateral skin involvement starting in childhood or adolescence. Histology revealed prominent accentuation of intradermal involvement. Except for positive anti-nuclear antibodies, no specific antibody pattern could be observed. In presenting these clinically homogenous cases we hereby introduce UGM as an extreme variant of the linear form of LS in childhood. As the onset of UGM usually occurs in pediatric patients, pediatricians should be cognizant of the presentation of this uncommon condition. Treatment with combined low-dose methotrexate and pulsed high-dose corticosteroid therapy might represent a promising treatment option for UGM.

Key words: localized scleroderma; unilateral generalized morphea; fibrosis; low-dose methotrexate; pulsed high-dose corticosteroids

Scleroderma represents a chronic disease of the connective tissue characterized by fibrosis and hardening of the skin. In general, scleroderma is clinically divided into two distinctive diseases: systemic sclerosis (SSc) and localized scleroderma (LS). In SSc, skin, lungs, gastrointestinal tract, kidneys, and heart may be involved. Autoimmune phenomena such as increased anti-nuclear antibodies (ANA) occur in up to 90 % of the patients suffering from SSc [1, 2]. LS is restricted to the dermis and/or underlying tissue lacking the involvement of internal organs. Serological findings accompanying LS include a variety of abnormal immune reactions, e.g. ANA, anti-single-stranded DNA antibodies (anti-ssDNA) or rheumatoid factor (RF) [3, 4]. Within this entity, five clinical subtypes are described: plaque morphea, generalized morphea, bullous morphea, linear morphea, and deep morphea [5]. Moreover, LS, particularly when occurring in childhood, may contribute to progressive and long-lasting induration of the skin and subcutaneous tissue, growth retardation, muscle atrophy and, in severe cases, even to flexion deformities and poorly healing ulcerations [6]. Although the exact prevalence of SSc and LS is not well established, SSc in childhood appears to be a rarity. By contrast children more frequently develop linear morphea than do adults.

Because of the impact on growth in children and the possible result in major facial or limb asymmetry, flexion contractures, and disability, a sufficient therapeutic management is necessary, especially in pediatric patients [7]. Treatment options include a variety of topical, systemic, physical, phototherapeutic, and even surgical regimens.

Recently, Nagai et al. reported the occurrence of deep unilateral generalized morphea (UGM) in childhood [8]. We here add four unusual cases of UGM in childhood/adolescence and suggest combined low-dose methotrexate (15 mg of MTX weekly) and pulsed high-dose glucocorticosteroid (intravenous prednisolone 1000 mg for three consecutive days once a month) therapy (PCMT) as a promising therapeutic option.

Case Reports

Case 1

A 14-year-old girl was referred to our out-patient clinic in 2000. She was first diagnosed with plaque morphea at the age of 13. At clinical examination the patient presented with wide-spreading plaques of sclerosis and atrophy of the skin, unilateral affecting the right arm, leg and torso. The right limb circumference was smaller than the left by 7 cm. Laboratory results showed elevated ANA of 1 : 1250 (< 1:80), circulating immune complexes (CIC) of 16.7 µg/mL, positive histone H1, slightly positive histone H3 autoantibodies and an increased rheumatic factor (RF) up to 800.0 U/mL. The patient's family history revealed that her grandfather suffered from SSc. Previous therapy, including 15 sessions of high-dose ultraviolet A1 (UVA1), intravenous therapy with ceftriaxon, and oral glucosteroids did not improve skin lesions. We started oral MTX 15 mg per week and oral low-dose prednisolone 5 mg daily administered for a period of 18

months, accompanied by additional low-dose UVA1 irradiation and lymphatic drainage. Within the first year of treatment, no further progression was seen, skin status softened and flexibility increased.

Case 2

Recently, a 23-year-old female presented to our outpatient clinic. Six years ago, at the age of 17, she remarked thickening of her skin on the right half of her body, followed by decreasing flexibility and unilateral Raynaud`s phenomenon. Therapy with chloroquine and low-dose oral glucocorticosteroids was unsuccessful. On clinical examination, hyperpigmentation and generalized sclerosis of the right limbs, the right torso and right cheek could be observed. Laboratory findings revealed increased ANA (1:2560) and positive anti-smooth muscle antibodies (ASMA). Low-dose UVA1 phototherapy for 30 sessions did not improve her skin condition. Consequently, we initiated PCMT. Within six months, further progress could be stopped and skin status markedly improved.

Case 3

A 38-year-old female attended with extensive atrophic areas of skin located on the right limbs and torso. The right limbs´ circumference measured less than left (12 cm of difference), a stretching deficit of the right fingers, muscle atrophy of the right calf and a hardening of the right palma could be observed. Although first signs of sclerosis had already been observed at the age of eight, there were still new progressing areas. Laboratory findings revealed increased ANA of 1:2560, anti-mitochondrial antibody (AMA) of 1:80, elevated RF of 800 U/ml, positive histone H2A, H2B, H3 and H4 autoantibodies, and increased level of human type III procollagen (PIIIP) of 1.0 E/mL (0.3-0.8 E/mL). During the last 30 years, no treatment had been performed. We decided to initiate PCMT for six months. Low-dose UVA1 phototherapy and physiotherapy was administered as an adjunct therapy. Within the last two years, no new active areas occurred, and altogether the skin softened, flexibility of ankles increased and the patient felt a clear relief from symptoms.

Case 4

In 2002, a 20-year-old female presented with multiple hyperpigmentated, partly sclerotic or indurated maculae and plaques located on the left abdominal region, left breast, left upper and lower limbs, left neck, and the left back (Fig. 1). On the left lower leg a decrease of the perimeter including a marked atrophy of the soft tissue was observed, the left foot measured less than the right with a contraction of the forth and fifth digits (Fig. 2). First eruptions already occurred during childhood at the age of four years. Autoantibody screening revealed ANA of 1:1280, positive ASMA, and disputably positive antibodies to extractable nuclear antigens. We initiated PCMT, and during treatment and subsequent follow-up examinations, skin status stabilized without any clinical signs of further activity. Meanwhile, therapy was reduced to the use of

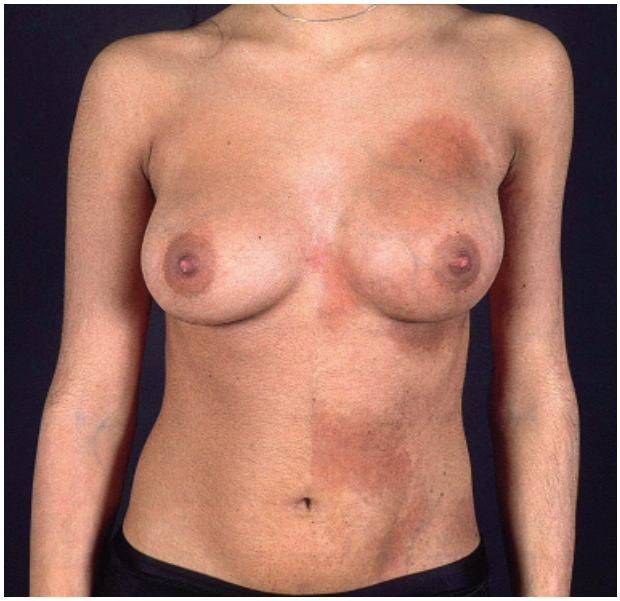

Fig. 1. Clinical aspects of one patient (case 4) with the diagnosis of unilateral generalized morphea. Note the remarkable accentuation of the left trunk with sclerotic and atrophic areas.

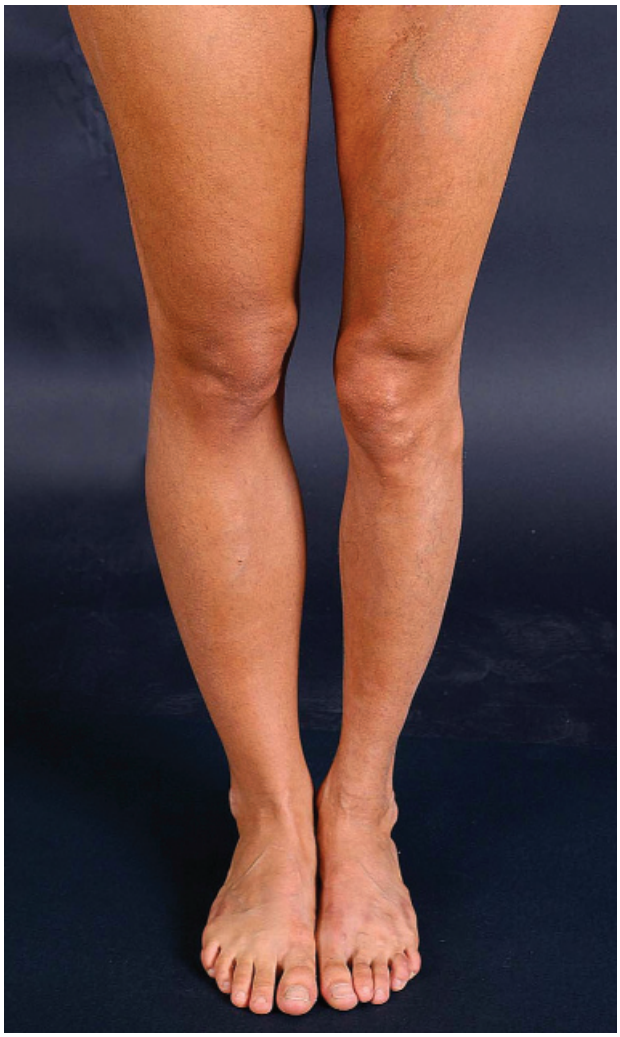

Fig. 2. Impressive difference of perimeter between both legs in the same patient.

emollients, physiotherapeutic strategies, and lymphatic drainage.

Discussion

A classification of LS proposed by Peterson et al. in 1995 suggests five major clinical subtypes including plaque, generalized, bullous, linear and deep morphea [5].

In plaque morphea, several clinical variants have been described comprising morphea en plaque, guttate morphea resembling extragenital lichen sclerosus, atrophodermia idiopathica et progressiva Pasini et Pierini (also named superficial morphea), and keloid morphea [5, 9]. Generalized morphea is defined by the occurrence of sclerotic lesions of increasing size in more than two anatomic localizations, often resulting in severe restrictions of the quality of life by decreased flexibility or, according to certain authors, even affection of internal organs when progressing towards SSc [10, 11]. Third, bullous morphea has been reported as a rare subtype associated with spontaneous blistering and tense subepidermal bullae [12]. The widespread entity of linear morphea additionally includes a number of different clinical aspects: linear scleroderma of the extremities, LS en coup de sabre as well as progressive hemifacial atrophy (also known as Parry-Romberg syndrome) [13]. Finally, deep morphea exhibiting an exceptional position by primarily involving deep dermal and subcutaneous architecture currently consists of four different variants: subcutaneous morphea, eosinophilic fasciitis (Shulman syndrome), morphea profunda, and disabling pansclerotic morphea of children [14-17].

Histopathological examination predominantly reveals dermal and subcutaneous sclerosis with thickened collagen bundles, a lymphoplasmacytic infiltrate as well as endothelial cell swelling [18]. The exact pathogenesis of LS still remains to be elucidated. Nevertheless, at least three possible independent or costimulatory pathogenic pathways have been suggested. Most sclerotic skin lesions leading to a loss of functional capabilities are thought to be characterized by the disproportional dermal deposition of collagenous fibers, partly an altered regulation and/or histomorphology of dermal vasculature and by an inappropriate activation of dermal fibroblasts, in most cases resulting from an induction of activated sclerotic / proinflammatory mediator-producing infiltrating T lymphocytes or related inflammatory cells [19-24].

Serologically, various immunologic abnormalities such as ANA, antihistone and anti-ssDNA antibodies and RF have been detected in up to 80% of patients with severe generalized or linear scleroderma and a correlation with the clinical activity of disease has been hypothesized [25]. The pathological formation of autoantibodies may result from abnormal B cell function and indicate both hyperreactive alterations to T and B lymphocytes. Additionally, several interleukins (IL), such as IL-6, IL-8, soluble IL-2, and soluble adhesion molecules, as for example soluble CD30, are increased in LS and have been thought to indicate the course of disease [26]. However, sequential studies assessing the relative use of these markers over time are rare. Additionally, serum PIIIP, a marker for type III collagen synthesis, has been recommended for monitoring the extent of sclerosis in patients with SSc and LS [27].

On the basis of our patients' history, clinical representation with considerable accentuating the unilateral aspect, laboratory results, and histopathologic data the diagnosis of UGM was made which appears to be a rare variant of linear morphea. In 1996, Blaszyzyk et al. [28] described various subsets of childhood scleroderma which differed significantly from the adult forms and revealed a higher prevalence of LS in infancy. For example they reported three unusual cases of deep linear, primary atrophic scleroderma that was not preceded by inflammation and sclerosis involving the subcutis and deeper tissues [29]. In 2002, Nagai et al. [8] reported the first case of unilateral generalized involvement of morphea in a 6-year-old patient. In contrast to our patients, they found an accumulation of mid-dermal to subcutaneous thickened collagen bundles indicating deep penetration [8]. However, histopathologic findings in LS may vary significantly depending on the age of lesions. Laboratory investigations revealed positive ANA screening in our patients, whereas most AMA, ASMA, anti-double-stranded DNA antibodies (anti-dsDNA), CIC, RF, PIIIP, and fibrillarin autoantibody screening remained unspecific (Table 1). Progressing lesions of LS have been described to follow preformed dermal nerval and / or vascular structures [30]. On the other hand, the occurrence of sclerotic plaques along Blaschko's lines has

Table 1. Unspecific results of the laboratory screening in four patients diagnosed as unilateral generalized morphea childhood-ladolescence.

Antibody profile and age of onset in four patients with unilateral generalized morphea

	Anti-Histone	*ANA*	*AM A*	*ASMA*	*Anti-dsDNA (IU/mL)*	*CIC (ug/mL)*	*RF (U/mL)*	*Borrelia*	*PIIIP (E/mL)*	*Anti-Fibrillarin*	*Onset-age*
Case 1	Pos.	1 : 1250	neg.	neg.	< 1	16.7	800.0	neg.	neg.	Pos.	13
Case 2	neg.	1 : 2560	neg.	Pos.	14	3.2.	neg.	neg.	neg.	neg.	17
Case 3	Pos.	1 : 2560	1 : 80	neg.	82	neg.	58.4	neg.	1.0	neg.	8
Case 4	neg.	1 : 1280	neg.	Pos.	< 3	2.5	neg.	neg.	neg.	neg.	4

also been discussed [31]. Nevertheless no clear pattern could be established in our patients. Notably one patient (no. 2) of our study suffered from unilateral Raynaud-like phenomenon. Blaszyczyk et al. [28] stated that LS affecting the hands may not only cause contractures but is also able to induce vascular manifestations which differ from genuine Raynaud phenomenon in patients with SSc.

Topical therapy of LS includes corticosteroids and calcipotriene. Ultraviolet A irradiation alone or in combination with photosensitizing psoralen (PUVA) is another potential therapy option for LS [32]. Additionally, we were able to demonstrate the benefit of a therapeutic approach consisting of combined UVA1 irradiation and calciprotriol [33]. Systemic therapy should however be considered in extensive and recalcitrant forms of disease. To date, the use of MTX, systemic corticosteroids, and oral calcitriol represent common recognized therapeutical regimes [32]. In a recent study we reported the efficacy and safety of PCMT as a promising alternative in severe LS [34]. Three of the four patients described here also showed response to this treatment regimen, including reduction of inflammation and stopping of disease progression. Nevertheless, plastic surgery may be indicated in patients with marked atrophy, contractures, and facial deformities [31].

Conclusively LS is known to exhibit a wide spectrum of clinical presentations. Hence we interpret the findings in our four patients presented as a rare variant of linear morphea, namely UGM. According to our best experience treatment with PCMT might represent a promising therapeutical option which is possibly capable to prevent the development of deformities or functional disabilities in pediatric or adolescent patients.

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