Localized scleroderma: clinical spectrum and therapeutic update*

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Abstract: Scleroderma is a rare connective tissue disease that is manifested by cutaneous sclerosis and variable systemic involvement. Two categories of scleroderma are known: systemic sclerosis, characterized by cutaneous sclerosis and visceral involvement, and localized scleroderma or morphea which classically presents benign and self-limited evolution and is confined to the skin and/or underlying tissues. Localized scleroderma is a rare disease of unknown etiology. Recent studies show that the localized form may affect internal organs and have variable morbidity. Treatment should be started very early, before complications occur due to the high morbidity of localized scleroderma. In this review, we report the most important aspects and particularities in the treatment of patients diagnosed with localized scleroderma.

Keywords: Autoimmune diseases; Collagen diseases; Immune System Diseases; Epidemiology; Localized scleroderma; Signs and symptoms.

INTRODUCTION

Two categories of scleroderma are known: systemic sclerosis (SSc), characterized by cutaneous sclerosis and visceral involvement (especially the esophagus, lung and vascular system); and localized scleroderma (LoS), which classically presents benign and self-limited evolution and is confined to the skin and/or underlying tissues. Localized scleroderma or morphea is a chronic connective tissue disease of unknown etiology.[1] Several types of morphea exist and each has different clinical manifestations and levels of connective tissue involvement (Chart 1). Morphea is characterized by skin thickening with increased quantities of collagen in the indurative lesion.[2] This entity is subdivided into linear scleroderma, plaque morphea, deep morphea, bullous morphea, and generalized morphea.[3,4,5] Each one of these subtypes may affect the face with varying intensity. LoS is the most common subtype of scleroderma in childhood. LoS categories are not mutually exclusive, since different subtypes may occur associated in the same patient.

LoS is a rare disease with an incidence of around 0.3 to 3 cases per 100,000 inhabitants/year.[6] It is more common in Caucasian women, with a ratio of 2-4 women to 1 man. Prevalence is similar in children and adults.[6-9] The peak incidence occurs in the fifth decade of life in adults, whereas 90% of children are diagnosed between 2 and 14 years of age.[8-11]

The literature suggests that LoS is not an exclusively cutaneous disease.[12] There is evidence of involvement of internal organs, association with other connective tissue diseases and exceptional transitional forms for SSc, especially in adults with the localized form of the disease.[13,14]

CLASSIFICATION

The most widely used classification in the literature is the Mayo Clinic Classification (in its simplified form), due to its objectivity and comprehensiveness.[15] According to this classification, there are five groups LoS, namely:

1. Plaque morphea,
2. Generalized morphea,
3. Bullous morphea,
4. Linear scleroderma - including subtypes that involve the head and face, linear scleroderma 'en coup de saber' (LScs) and progressive facial hemiatrophy (PFH),
5. Deep morphea.

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Chart 1: Description of the different manifestations of localized scleroderma

Classification	Subtypes	Features of lesions	Tissue involvement	Main location
Plaque morphea	Superficial	Oval lesions	Limited to epidermis and dermis	Trunk
	Deep		Deep induration Dermis and SC tissue Variable - fascia and muscle	
Linear morphea	Trunk and limbs	Linear induration	Dermis and SC tissue (may affect bone and muscle)	Trunk and limbs
	Head (LScs)		Frontoparietal dermis (muscle, bone and CNS)	Face and scalp
	PFH		Dermis, SC tissue, muscle, cartilage and bone	
Generalized morphea		4 or more indurated plaques > 3 cm	Limited to the dermis and rare in the SC tissue	Diffuse (not on the face or hands)
Mixed morphea			Combination of 2 or more subtypes	

SC: subcutaneous; CNS: Central Nervous System

LOCALIZED SCLERODERMA - SUBTYPES

Plaque morphea

The most frequent form of LoS in adults is the plaque morphea, which is well-circumscribed and typically confined to the dermis.[7,15,16,17] It is characterized by limited, round or oval shaped areas of hard and shiny skin, and affects one or more anatomical regions, most frequently the trunk and proximal extremities (Figure 1). In the earliest phases, a characteristic violaceous halo can be seen around the plaque ("purple ring"); this corresponds to the inflammatory phase of morphea.

Bullous morphea

Bullous morphea is a rare form of morphea characterized by the appearance of bullae or erosions on morphea plaques.[18]

Deep morphea

The subtype classified as 'deep morphea' usually manifests itself as a single lesion on the upper trunk, near the spine.[19,20,21] The overlying skin may have a normal appearance, an atrophic appearance or be hardened, and will almost always be depressed or adhered to the deep plane. It is usually asymptomatic and is not associated with visceral involvement.[22,23] Deep morphea is usually not preceded by clinical evidence of inflammation, skin discoloration or sclerosis (Figure 2). Some authors conclude that PFH may be considered a variety of deep linear scleroderma.[22,24] Some cases of isolated deep morphea or similar injuries related to vaccine admnistration or intramuscular injection of vitamin K are described.[25,26]

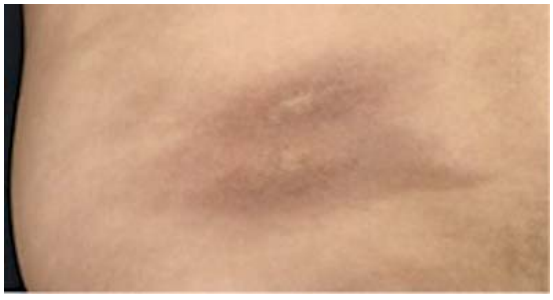


Figure 1: Plaque morphea lesion involving the trunk

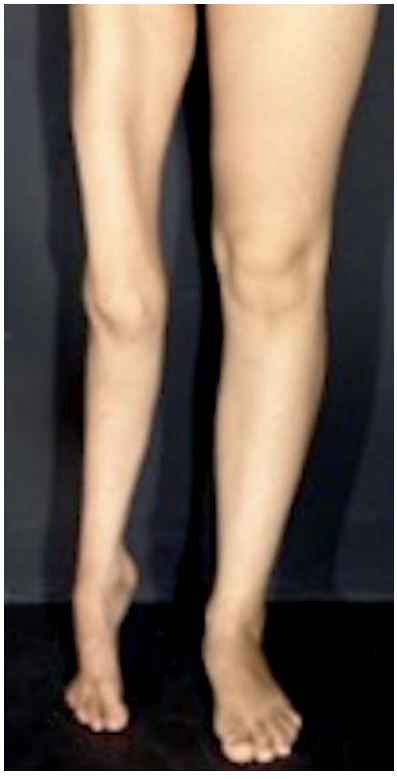


Figure 2: Patient with deep morphea involving the right lower limb

Generalized morphea

Generalized morphea is defined as morphea plaques involving more than 2 body sites. It is more frequent in women, and physical exercise has been cited as a triggering factor. The plaques are slightly inflamed, pigmented, ill-defined, thickened, adhered to deep planes, fascia and muscle, and most common on the trunk and extremities. Sclerosis onset is gradual and relatively fast over a period of months. Signs of acute inflammation such as edema and erythema may also be absent.[27]

Comprehensive literature review makes it possible to verify that clinical pictures similar to the clinical conditions described above are referred to indistinctly as generalized morphea and deep morphea.[28,29,30] Both terms are used to describe the same clinical situation in which the sclerotic process fundamentally affects the deep dermis and adipose tissue, but also the fascia and superficial muscle in an extensive manner. The term 'generalized morphea' refers to the extension that fibrosis may achieve, while the term 'deep morphea' is intended to describe the histological findings of superficial muscle, fascia, adipose tissue and deep dermis involvement in a clinically localized way.

Generalized morphea is different from SSc. Patients may develop sclerosis of the fingers, but usually do not present ulcerations, phalanx resorption, changes in capillaries of the nail fold or Raynaud's phenomenon, which occur in the SSc. The face is generally spared. In addition, the presence of flexion contractures of the joints and muscle-joint manifestations are common.[30] Pulmonary, esophageal, renal, or cardiac anomalies were occasionally documented.[7,9,11,12,30]

Linear scleroderma

Linear scleroderma is characterized by one or more linear streaks of cutaneous induration that may involve dermis, subcutaneous tissue, muscle and underlying bone. Linear scleroderma is often observed in children and adolescents, and is the most frequent form of scleroderma in childhood, affecting 40-70% of the children studied.[8,9,11] Approximately 67% of patients with linear scleroderma are diagnosed before age 18 years.[6] It is usually a single, unilateral lesion of linear distribution and involves the extremities, face or scalp. Lesions often follow Blaschko´s lines (Figure 3).

Linear scleroderma may affect the muscles and underlying bones, causing growth disturbance and ankylosis.[31,32] Children are more frequently affected than adults, but both sexes are affected equally. About 50% of patients with linear scleroderma have associated scleroderma in plaques.[33] "Mixed" forms such as localized scleroderma of the face (LoSF) associated with plaque morphea or linear scleroderma in other areas (most often on the trunk) are a peculiar form found in children and rarely seen in adults.[7] The duration of the disease is twice as long when LoS has an onset in childhood, and relapses and chronic disease activity are more frequently reported in these cases.[7]

LSF is not frequent. Jablonska et al. conducted a 20-year study of patients of the National Institute of Mexico City and found 30 patients dignosed with LSsc and 9 with PFH.[34]

When located on the scalp, it causes an alopecia plaque of linear distribution. The plaque is often atrophic and slightly depressed, and its skin is smooth, shiny, hard and sometimes pigmented. It is usually unilateral, affecting the parietal region, and it tends to deform the bone, causing depressed lesions described as LSsc. It may extend to the malar and nasal regions, and to the upper lip.

When the disorder completely affects the half of the face, it is classified as PFH or Parry-Romberg syndrome.[35,36,37] The process causes atrophy of the entire adipose tissue, and muscle and bone deformity, with no apparent changes in the skin. Onset of disease usually occurs at a mean age of 11 years. The course of

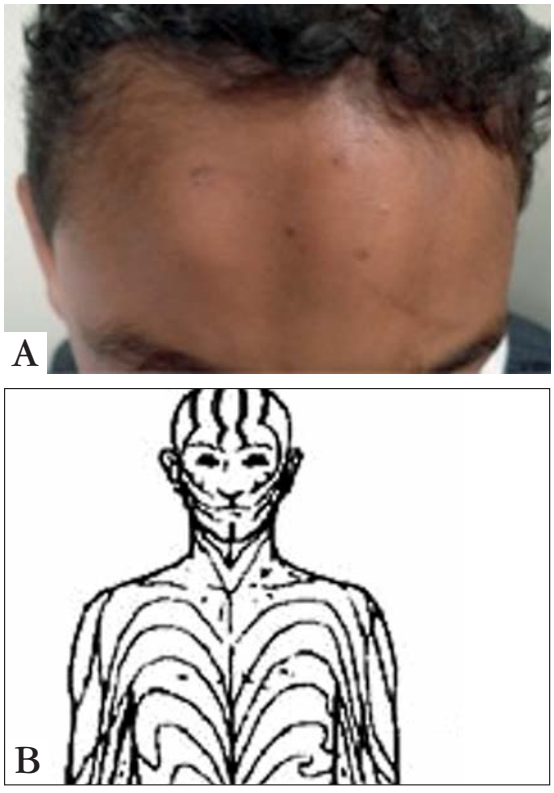


Figure 3: A. Patient with a linear scleroderma lesion (trilinear) on the forehead; **B.** Scheme of Blaschko´s lines

disease evolution takes place in a few years and is then followed by stabilization. There is a higher predominance in women (2-3:1).

High-severity was defined as presentation with pansclerotic or generalized morphea, LoSF and subtypes with evidence of high morbidity (e.g.: central nervous system involvement, extremity shortening, joint contracture). Moderate severity was defined as circumscribed deep morphea or linear scleroderma of the trunk or extremity without evidence of high morbidity. Low-severity patients are those with superficial circumscribed morphea (plaque lesions).[38]

Linear scleroderma "en coup de sabre" (LScs)

LScs is a rare and intriguing form of LoS, which was first described by Addison in 1854.[39] It has a slowly progressive course and is generally limited to the hemiface. LScs lesions often start with contraction and stiffness of the affected area, forming a depressed groove on the parietal region and extending to the scalp, developing an area of linear alopecia (Figure 4). The groove may extend to the nasal region, upper lip and, sometimes, to the gingiva. The ipsilateral tongue may be atrophic and the spacing and direction of teeth may be altered. The jaw may be involved and the bones of the skull may be affected. In case of deformity of the jaw, it may result in poor dental occlusion, poor teeth implantation, tooth root atrophy and delayed appearance of teeth.[37]

It affects mainly children and is more predominant in females than males (3:1). There is a higher incidence at the menarche. The average age of onset is around 13 years of age and phase of activity of skin lesions usually lasts 2-5 years.[10,32,40] Very little is known about its pathogenesis. Consequently, an effective therapy has not yet been found.

LScs is rarely associated with neurological and ophthalmological symptoms.[41,42] However, the pediatric population presents more extracutaneous changes (especially orthopedic, ocular and neurological) than the adult population.[8]

LScs is usually unilateral, but rare bilateral cases have been reported.[43-45]

Parry-Romberg Syndrome or Progressive facial hemiatrophy

The progressive facial hemiatrophy (PFH), also known as Parry-Romberg syndrome (PRS), was first described by Parry in 1825 and Romberg in 1846. It is rare disorder of unknown origin that usually develops between the first and second decades of life.[46,47] The disease has a slow, self-limited progression and usually progresses for 2 to 20 years until it becomes stationary. It is characterized by unilateral atrophy of the skin, subcutaneous tissue, muscle and underlying bony structures, most commonly affecting dermatomes of one or multiple branches of the trigeminal nerve. Atrophy may be preceded by cutaneous induration and discoloration of the affected skin, such as depigmentation or hyperpigmentation and cicatricial alopecia may be observed in affected areas of the scalp. In most cases, skin inflammation, induration and adherence are absent or minimal.[48,49,50] Involvement of the area below the eye region is more frequent (Figure 5).

PFH may be clinically very similar to LSsc, and they may coexist in about 20-37% of patients, which makes it difficult to distinguish between them.[51,52] This percentage of coexistence is much higher than the one presented by LSsc with other forms of LS.[37,49] However, the PFH does present skin sclerosis at any of its stages.[46,47] Some authors have described patients with Lssc converting with time into PFH.[50,53-56] Age at the time of diagnosis is significant when the diagnosis is LSsc or PFH. Many authors consider LSsc and PFH to be the spectrum of a same disease.[45,57] Wartenberg described LSsc as an abortive form of PFH, whereas Wolf and Ehrenclou believed that PFH is not a distinct disease but a syndrome that may coexist with linear scleroderma or occur as a sequela of various conditions.[58,59] A histopathological criterion to distinguish both forms does not exist.[45]

Both LSsc and PFH may affect only the subcutaneous tissue (most often on the face) or affect the skin first and then the other deep tissues.[60]

Figure 4: Patient with LScs

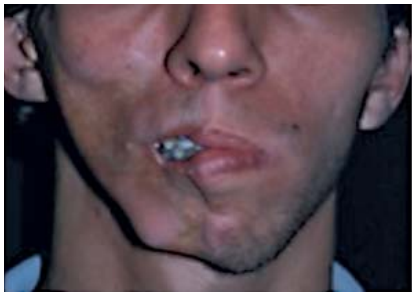


Figure 5: Patient with PFH

Pronounced cases of PFH seem to be associated with relevant CNS involvement, which is observed in patients with early onset of the disease or a history of trauma preceding the lesion.[24,36]

About 30-40% of patients with PFH present changes typical of morphea or linear scleroderma off the face area.[35,36,45,49]

The frequency of neurological complications is around 20% and the frequency of ophthalmic complications is around 15%. (Chart 2).[8,36,37,61]

ETIOLOGY

The pathogenesis of LSsc, PFH, LoS and SSc appear to be similar. There are references that indicate that it is triggered by viral or bacterial infection, such as by B. Burgdorferi.[56,62,63] Other studies deny this association.[60,64]

Genetic factors have been implicated.[56] However, it does not seem consistent, since only a 4.7% concordance between twins has been observed and family studies revealed only 1.6% frequency among first-degree relatives.[65-67]

Vascular abnormalities in scleroderma have also been reported.[52] Some studies believe that cerebral calcifications associated with scleroderma of the face represent calcified hemangiomas.[68] The presence of neurovasculitis was identified in different studies.[24,69-73]

Trauma is reported to act as an activator or initiator of PFH.[24,74-77] Some studies, however, do not believe that trauma is a trigger or predictor of severity in PFH.[60] The existence of bias cannot be ruled out due to the questioning about triggering factors to patients.

Since LSsc and PFH may involve the facial tissues and ipsilateral brain parenchyma, which have a share a common progenitor cell, there is a hypothesis of cortical dysgenesis, a malformation affecting one side of the rostral neural tube.[78,79,80] Some characterize it as a neurocutaneous syndrome in which cutaneous manifestations are induced by primary brain malformations.[54,55,70] A clone of vulnerable cells would develop the lesions following the Blaschko´s lines. Thus, some speculate about the possibility of genetic mosaicism being a determining factor for the linear distribution of the sclerosis process.[81] This theory would explain how multiple frontoparietal lesions may occur.[82]

Due to the description of skin lesions involving the area corresponding to the trigeminal nerve branches, Romberg suggested the disruption of sympathetic fibers as a possible etiology.[50]

Pathological evidence of intracerebral inflammation has already been illustrated in case reports with brain biopsy.[42,69,77,79,83]

Some changes that suggest autoimmune process are described as: elevation of antinuclear antibody; association with diseases such as LES, rheumatoid arthritis (RA) and SSc; association with transverse myelitis; and the presence of oligoclonal bands in CSF, with seizures and magnetic resonance imaging (MRI) showing brain lesions. [84-87] Resolution and improvement with immunosuppressive therapy also support this theory.[69,88,89]

After extensive literature review, the inflammatory process with a probable autoimmune substrate and the embryological origin of the disease, such as the genetic mosaicism, seem to be more clearly associated with the etiopathogenesis in patients with LoSF. Available data suggest that the mechanism of pathogenesis of scleroderma is complex. Vessels, immune system and extracellular matrix are affected and may contribute to the development of the disease.

EXTRACUTANEOUS MANIFESTATIONS

The extracutaneous involvement in LoS is considered to be extremely unusual by many authors.[12,13,32,56,57,90,91]

Development of skin disease usually precedes systemic manifestations, which usually occur a few months after the onset of LoS.[69,70] Systemic symptoms and signs may not occur in parallel with the cutaneous disease activity.[70]

The following extracutaneous involvements are described in patients with LoS: arthritis and other joint limitations, ocular involvement, neurological involvement, localized hair loss at the affected site, Raynaud's phenomenon, fascia or muscle involve-

Chart 2: Comparison of PFH and LSsc

Findings	PFH	Scleroderma "en coup de sabre"
Face	Unilateral atrophy	Unilateral, frontoparietal sclerotic band
	Minimal or absent induration or previous inflammation	Usually preceded by skin induration
	Cutaneous atrophy (normal hair and absent sclerosis)	Usually does not extend below the eyebrow
	Associated with dysplasia of the underlying bone, tongue, gingiva and unilateral palate	Important, depressed, hyperpigmented, shiny cutaneous sclerosis involving the scalp
		Frequently causes deformity and contractures
		Softening of lesions takes place over time

ment (documented by biopsy or imaging studies), gastroesophageal reflux (GERD), esophagitis (documented by upper gastrointestinal endoscopy), abnormal pulmonary function test (PFP), restrictive lung disease, cough or dyspnea, specific abnormalities on computed tomography (CT) or chest X-ray (CXR), vasculitis, arrhythmia, deep involvement of the breast tissue and others.[7,44,92-94] Dentition changes are described in LSsc and PFH, and my lead to malocclusion as well as tongue atrophy.[7,44,93]

Over 20% of patients with LoS develop extracutaneous manifestations such as arthritis, seizures, and uveitis.[11,17] Neurological complications are the most common association of systemic manifestations in LSsc.[71,95]

The most frequent neurological involvement associated with scleroderma are complex partial seizures. In 16% of cases neurological symptoms precede cutaneous manifestations and, apparently, there is no correlation with the severity of brain changes and skin condition.[95,96,97] In spite of brain abnormalities detected on imaging studies, neurologically asymptomatic patients are described. Brain abnormalities are ususally found to be ipsilateral to the skin lesions.[71,72,88,89,95] The actual prevalence of neuroimaging abnormalities has not been determined. Neurological imaging examination is usually only performed in symptomatic patients and subclinical manifestations are often not diagnosed.

A study conducted at the Department of Dermatology of the Hospital das Clinicas, University of São Paulo, assessed radiological brain changes in 12 patients with localized scleroderma of the face by performing magnetic resonance imaging (MRI) of the skull, before and after 3 years of follow-up. Brain changes were found in 75% of the evaluated cases and there was no change or progression in radiological images after 3 years of follow-up.[98]

Ocular abnormalities reported in the literature were divided into: involvement of adnexal structures, anterior segment involvement, posterior segment involvement, and ocular-CNS involvement.[36, 61,73,99,100] Ocular involvement is not common in children with LoS, being present in about 3.2% of children and 10% of adults. Prevalence of ocular involvement is 14% in LScs, which affects the cephalic segment, and one third in patients with PFH. This manifestation usually has an early onset.[61]

In a study conducted by Christianson HB et al., Arthralgia was reported in 44% of 191 patients with plaque morphea and in 40% of 44 patients with generalized morphea.[101] Several dermatological diseases, including lichen planus, vitiligo and alopecia areata have been associated with morphea.[8]

Due to the possible early onset and persistence of LoS for years, morbidity may be substantial. Children with LoS have a higher risk of growth disturbance, including extremity length differences, joint contractures and facial atrophy. In a follow-up study of LoS patients with onset in childhood, 25% reported mild to moderate disability after 20 years.[6] Another study of adults with childhood-onset LoS, more than 50% of patients reported permanent sequelae, including limited range of motion, deep tissue atrophy and extremity length differences.[102]

Therefore, orthopedic complications that interfere with mobility or cause severe joint contractures are common in linear scleroderma involving the limbs, especially in children. These are rarely observed when the disease begins in adulthood.[7]

In general, the greater the extension and depth of the sclerodermiform process, the greater is the likelihood of having an associated visceral anomaly. It occurs especially in the subtypes: linear scleroderma, generalized morphea and deep morphea.

Raynaud's phenomenon is usually associated with abnormal nail capillaroscopy, which suggests connective tissue disease. In a study conducted by Marzano et al. with 113 adult patients with LoS, Raynaud's phenomenon was found in 7% of the subjects. 87.5% of patients had positive antinuclear factor (ANF) and 50% had anti-centromere antibody (ACA). Prevalence in the 126 children studied was found to be 2%.[7]

Raynaud's phenomenon is considered a risk factor for the development of systemic disease. Therefore, careful follow-up of these patients is mandatory.[7]

The incidence of autoimmune diseases and prevalence of autoantibodies are increased in patients with linear scleroderma, when compared with healthy control group.[17] Cases of insulin-dependent diabetes mellitus (DM), Hashimoto's thyroiditis, Graves' disease and ulcerative colitis have been described.[8,103-105] It has also been reported that patients with morphea have an increased family risk of autoimmune disease.[8,9]

In a cohort study conducted by Zulian et al. the most frequent associations of extracutaneous manifestations found were: joint/neurological, ocular/neurological and Raynaud's phenomenon/joint. The authors recommend special attention in evaluating involvement of the joints, eyes and central nervous system in patients with LoS.[17]

The finding of more than one extracutaneous manifestation does not seem to represent a risk for development of SSc. Prevalence of evolution of linear scleroderma to SSc is around 0.9 to 1.3%.[12,106] However, the disease seems to be more aggressive in patients with extracutaneous involvement than in those with cutaneous involvement alone, based on the presence of systemic inflammation and more frequent need for immunosuppressive therapy. In these patients, the

involvement of organs is lighter than in SSc patients and poses no risk to life.

LABORATORY CHANGES

While in SSc certain serum changes (such as the presence of Scl-70) are considered markers of the disease, laboratory changes are variable in LoS and their relationship to the underlying disease is questionable. Topoisomerase 1 antibody, called Scl-70, is considered to be a serologic marker of SSc.[7]

The ACA (anti-centromere antibody) is considered a marker of the CREST syndrome, characterized by calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias.[7]

The number eosinophils and erythrocyte sedimentation rate (ESR) are found to be increased in case of disease activity or relapse.[7]

It is believed that ANF is positive in patients with mixed forms. When present in the LoSF, it would indicate more prolonged forms with complicated courses, but it is not correlated with disease activity.[7] ANF with homogeneous and speckled pattern is positive in 37-50% of patients with linear scleroderma.[6,32,56]

Therefore, the presence of systemic markers such as ANF, ACA and Scl-70 is not always a sign of systemic disease.[7,91] Autoantibodies such as centromere, Ro/La, RNP and Scl-70 may precede the development of systemic disease, and patients with these changes must be followed up for many years.[56]

The finding of rheumatoid factor (RF) is a risk factor for joint affection in patients with LoS. Positive RF cases should be monitored.[17]

Peripheral eosinophilia is commonly found in patients with generalized scleroderma, which may be very important. Increased gamma-globulin or immunological changes (such as the presence of ANF, anti-DNA single chain), and decrease in complement or antiphospholipid antibody may also be found.[30,33] Antihistone antibodies and increased procollagen type III serum levels have been proposed as indicators of severity in LoS. It is not uncommon to detect these anomalies in extensive and deep forms of morphea.[107-109]

ANATOMICO-PATHOLOGICAL SKIN CHANGES

Histology of scleroderma depends on two factors: stage of the disease and the depth to which the disease extends. In most situations, morphological changes are best seen in the transition area between the dermis and the subcutaneous tissue. Thus, the skin sample must contain subcutaneous tissue.

In the inflammatory phase or in the early lesions, which clinically exhibit erythematosus component, histology is not characteristic of scleroderma, and making a definitive diagnosis is difficult. In this phase, the presence of denser, homogenized collagen that is a little more eosinophilic, especially around vessels and adnexa is observed. The lymphohistiocytic inflammatory infiltrate with fibroblasts is periadnexal and perivascular, and the periadnexal fat cushion disappears or reduces. The colagen cords of newly formed collagen may already be seen invading the adipose tissue as pseudopods, and may be accompanied by inflammatory infiltrate. Both dermis and hypodermis vessels may show a tumefied endothelium with decreased lumen.[1]

In later lesions, scleroderma is installed and there is no clinical evidence of inflammation. It is characterized by intense fibrosis in the dermis, which progressively substitutes the adipose panicle. A definitive histological diagnosis is possible. At this stage, the dermal collagen is sclerotic, i.e., eosinophilic, homogenized and dense, and the inflammatory infiltrate is absent or discreetly confined around adnexae that already show atrophy. With the evolution of the disease, the tendency is that adnexae will be replaced by fibrosis (Figure 6). The vessels of the hypodermis show a thickened wall and significantly decreased lumen size. The replacement of adipose tissue by sclerotic collagen is best assessed when compared with a fragment of the contralateral normal skin. The destruction of the adipose tissue is clinically evidenced by the depression of the skin surface.[2]

In summary, scleroderma lesions are characterized by an initial inflammatory stage that is followed by a fibrosis stage and results in the replacement of normal dermis and hypodermis structures by abnormal collagen.[10]

THERAPEUTICS

The management of LoS is still unsatisfactory and there are very few randomized and controlled therapeutic studies.[45] Different therapeutic modalities have been suggested, including the use of topical

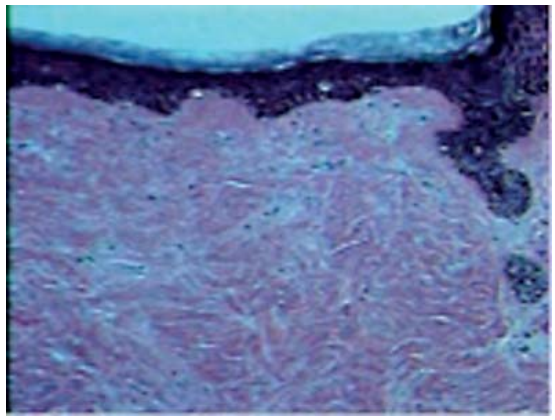


Figure 6: Histology of late-phase scleroderma

medications, immunosuppressive pharmacological agents, physical therapy and phototherapy.[110]

Treatment should be initiated at an earlier stage before complications occur occur due to the high morbidity of localized scleroderma, which leads to limitation of motion and deformities. To start or indicate one treatment modality, we should consider the presence or absence of disease activity.

Criteria of disease activity include:

- Appearance of new lesions in the last 3 months (documented by the physician);
- Expansion of pre-existing lesion in the last three months (documented by the physician);
- Moderate or severe erythema or skin lesions with erythematous borders;
- Violaceous lesion or lesion border;
- Documentation of disease activity or progression to deep tissues by the doctor (by photography, MRI or ultrasonography (US);
- Increased induration of the lesion border;
- Worsening of hair loss on the scalp, eyebrows or eyelashes (documented by the physician);
- Increased creatine kinase (CK) in the absence of other changes;
- Skin biopsy demonstrating active disease.

The following parameters indicate clinical damage:

- Atrophy of the dermis;
- Atrophy of the subcutaneous tissue;
- Hyperpigmentation or hypopigmentation of the lesion;
- Lesion center with increased skin thickness.

Several clinical assessment methods have been published, such as the depigmentation, induration, erythema, and telangiectasia score; the modified Rodnan skin score (MRSS); and the Localized scleroderma Skin Severity Index (LoSSI).[111-113] All these methods assess activity and damage together, based on limited clinical parameters. The lack of validation of treatment response criteria limits the ability of clinicians to judge the effectiveness of treatments.

Currently, there is no consensus on the treatment of LoS and a variety of therapeutic strategies have been proposed. Most of the studies are case series. There are very few comparative or placebo controlled studies.[114-116] According to a study conducted by Li et al, in the United States and Canada in 2012, pediatric rheumatologists employ MTX or systemic corticosteroids to treat superficial, circumscribed morphea en plaque; dermatologists, on the other hand, usually prescribe topical agents and phototherapy to patients.[38,115,117-120]

Some therapeutic options are proposed for the treatment of LoS: D-penicillamine, topical or oral vitamin D, psoralen-UVA photochemotherapy, phenytoin, corticosteroids, methotrexate, cyclosporine and interferon.[121-124]

Several options are available for the topical treatment, which should be limited to more superficial and limited forms of morphea, such as plaque morphea. In the initial, more inflammatory phase, the use of high-potency topical corticosteroids is recommended. However, no study has demonstrated the real efficacy of this treatment.[115]

One pilot-controlled study with topical tacrolimus and including 10 patients with plaque morphea has been demonstrating efficacy.[125] The use of topical imiquimod 3 times weekly has been shown effective in reducing erythema and induration of morphea plaques in a study with 12 patients and a report of 2 cases.[111,126] The combination of calcipotriol with topical betamethasone has been demonstrated effective in a prospective study of 6 patients with plaque morphea.[127]

In an uncontrolled study, it was observed that scleroderma in children can be successfully treated with topical calcipotriol and low-dose UVA phototherapy.[128]

Li et al. established a consensus treatment plan (CTPs) for the first 12 months of activity of moderate to severe LoS. Based on scientific evidence, the plan only specifies the use of MTX or corticosteroids administered IV or orally. Mycophenolate mofetil (MMF) is suggested as an option for patients intolerant to MTX or who failed to respond to MTX.[129] This consensus was based on indices of activity, damage and efficacy of treatment, and was guided by members of the CARRA (Childhood Arthritis and Rheumatology Research Alliance).[92] Scheme is shown in chart 3.[127-136]

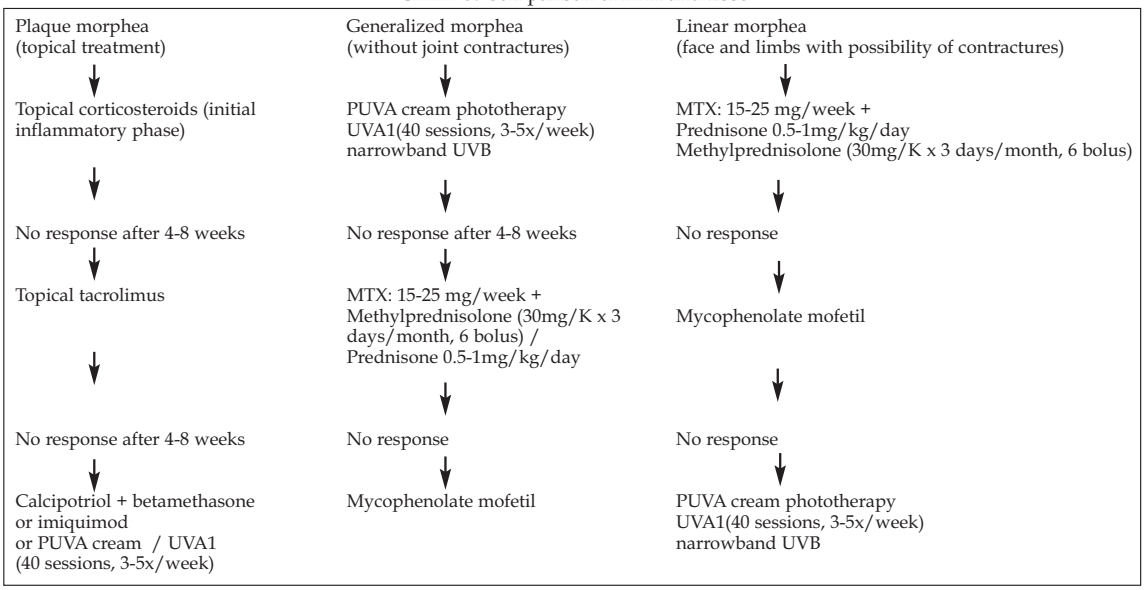
Thus, MTX can be used alone or in combination with oral or injectable corticotherapy.[117,119,125,130-133] The recommended dose is 1mg/kg/week, subcutaneously, and the maximum recommended dose is 25mg/week. 0.4-1 mg/day or 5mg/week of folic acid should be supplemented to the diet.[38]

Most studies report an 80% improvement rate with this therapeutic regimen.[130,131] Results were similar in patients treated with corticosteroids and MTX, when compared to those treated with MTX alone. The use of corticosteroids alone is effective, but the risk of relapse is higher.[134]

Recurrence rate ranges from 28 to 44% in 16-20 months after discontinuation of MTX. In adults with onset in childhood, this recurrence rate is around 59%.[102,117,135] Continuously active disease was reported in 30% of adults with childhood-onset LoS[102] and in 20% of patients with onset of LoS after 20 years of age.[6]

Based on its use in the treatment of LoS, other immunosuppressants are used in the treatment of morphea, such as D-penicillamine, which is little recommended owing to its poor safety profile.

Chart 3: Comparison of PFH and LSsc



Cyclosporine and extracorporeal photopheresis have isolated reports.[136-138] Significant improvements in cases of generalized morphea have been reported with the use of infliximab (anti-TNF alpha antibody) and imatinib (tyrosine kinase inhibitor).[139,140]

Another therapeutic option is the use of plastic surgery and physiatry techniques. Physical therapy is used in patients with sequelae from morphea (limited mobility of the extremities and joint contractures). No study demonstrates its actual utility. In any case, it does not seem to exacerbate the illness, therefore, it could be utilized in indicated cases.[115]

The management of facial atrophy, however, is challenging. Palliative reconstruction surgery is potentially beneficial for patients with disfiguring facial atrophy. The use of three-dimensional image may be useful in the preoperative period of bone reconstruction surgery.[141]

Ultraviolet radiation is an option that may be considered for the treatment of morphea. Possible options are: broadband ultraviolet light A (UVA combined or not with psoralen, narrowband UVA1 and UVB. The mechanism that could lead to a benefit in the management of morphea is unknown.[142,143] Experience with broadband UVA, associated or not with psoralens, is much smaller. A clinical improvement of 80% in treated patients has been reported.[143-145] Some authors suggest that treatment with PUVA (topical psoralen and UVA light) may be useful in the initial inflammatory stage of morphea.[146] There is less experience is with narrowband UVB. Its effectiveness is most often referred to in isolated cases and there are few controlled studies.[147]

Morphea may present tendency to progress and recur use, especially when the onset of disease occurs in childhood.[102] Nevertheless, LoS classically presents a self-limited course with a tendency to spontaneous regression after 3 to 5 years.[101] Plaque morphea rarely progresses to generalized or debilitating forms. However, the uncertainty about the extent of involvement and progression of scleroderma lesions on the face require prompt therapeutic intervention in the presence of lesions at this site, in order to prevent damages to organs or internal structures and serious aesthetic impairment.[148] Likewise, ELGS and HFP should always be treated early and intensively in order to minimize future sequelae. The use of various therapeutic options in the same patient throughout his life time is not uncommon.[149]

CONCLUSION

LoS seems not to be a exclusively cutaneous disease. When this disease is diagnosed, special attention should be taken to the involvement of internal organs, association with other connective tissue diseases and, more rarely, transitional forms to SSc. Treatment is challenging and difficult to evaluate as spontaneous regression of sclerotic lesions must always be considered.❑

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