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Skin involvement of juvenile scleroderma

Abstract

Pediatric scleroderma is a rare chronic inflammatory disease in children. It includes two major clinical entities, systemic sclerosis (SSc) and localized scleroderma (LS). The two forms have a common mechanism but their clinical manifestations differ. Skin involvement occupies an important place in diagnostic classifications due to the richness of dermatological clinical manifestations and their suggestive aspect of the disease. If the vital prognosis is often not compromised, the functional prognosis is strongly affected, sometimes with deleterious aesthetic problems. Very few pediatric publications have been produced. In this article, we report the different skin manifestations inherent to this disease, and their management in children.

Keywords: cutaneous sclerosis, localized scleroderma, children, morphea, skin disorder, systemic sclerosis

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Introduction

Juvenile scleroderma is a rare connective tissue disease characterized by inflammation, vascular abnormalities and fibrosis that can affect the skin, but also internal organs in the context of systemic involvement.[1] Skin involvement is the earliest, most frequent and most characteristic manifestation of scleroderma.

The dermatological manifestations of scleroderma include three subentities: localized scleroderma (LS), limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis. The most common form is localized juvenile scleroderma (JLS) ; considered benign, it can, however, cause unsightly effects.[2]

Localized scleroderma is a distinct entity from systemic sclerosis, due to the almost exclusive cutaneous damage and the absence of visceral involvement. Also known as morphea, it is defined by localized thickening and induration of the skin, but it can affect tissues at multiple levels ranging from subcutaneous fat, muscle, periosteum and bone. It is mainly observed in girls with an average age of onset of 9 years.[2,3]

Pathogenesis

The cause of scleroderma remains unknown, despite progress in science, several gray areas still remain to be clarified. Pathogenesis is likely multifactorial, involving genetic factors and environmental exposures (stress, microtrauma, chemicals, toxicants, and medications) leading to small vessel damage, release of profibrotic cytokines, and disruption of the balance between the production and destruction of collagen. This mechanism leads to vascular and immunological disorders. The early vascular phenomenon responsible for endothelial lesions with production of mediators promotes a dysregulated inflammatory cascade with production of several cytokines contributing to vascular remodeling and fibrosis lesions by accumulation of extracellular matrix substances.[4]

Indeed, pathogenic disorders begin with the expression of intercellular adhesion molecules-1 (ICAM-1) and glycosylation-dependent cell adhesion molecules-1 (GlyCAM-1) on the endothelium; leading to recruitment of several immunocompetent cells, in this case Th2 and Th17 cells with release of various cytokines (interleukin 4 (IL-4) and transforming growth factor β, etc.), mast cells and macrophages, leading to an endothelial-mesenchymal vascular system transition associated with proliferative tissue fibrosis.[4,5] The synthesis of modulators of vascular tone with excess endothelin stimulating the proliferation of smooth muscle cells and the accumulation of extracellular matrix components; contrasts with low production of nitric oxide and prostacyclins, causing disruption of the functions controlling tone and vascular permeability, and the physiological antithrombotic action of the endothelium.[4,6] The evolution of the lesions leads to capillary rarefaction, to a thickening of the vessel wall due to intimal proliferation and smooth muscle cells, and finally to the obliteration of small vessels which is responsible for hypoxia and d 'oxidative stress.[4,6,7]

Clinical presentation

Localized scleroderma, being by far the most common, is characterized by specific and circumscribed dermatological lesions.[2] Morphea classification depending on the subtype, severity, and site affected adjacent structures. The most widely used classification divides localized scleroderma into five general types: plaque morphoea, generalized morphoea, linear scleroderma, deep and mixed morphoea[8] (Table 1).

Table 1 Classification of Localized scleroderma[8]

Limited Form
• Morphea (Plaque type) • Guttate morphea (Special form of morphea) • Atrophoderma of Pasini and Pierini (Special form of morphea)
Generalized Form
• Generalized localized scleroderma (affecting at least three anatomic sites) • Disabling pansclerotic morphea (Severe special form) • Eosinophilic fasciitis (special form predominantly affecting the fasciae)[1]
Linear Form
• Linear localized scleroderma (usually affecting the extremities) • Linear localized scleroderma en coup de sabre • Progressive facial hemiatrophy (Synonym: Parry-Romberg Syndrome)
Deep Form[2]
Mixed Form[3]

The most common form of LS is the plaque type morphea, it's mainly affects the trunk and upper limbs. It begins with a generally

circumscribed maculous lesion, circular or oval (Figure 1 & Figure 2). Lesions may initially appear erythematous, subsequently, they harden more in the center and take on a whitish or ivory hue. Active lesions are characterized by a purple halo « lilac ring » surrounding the fibrosing center. During the course of the disease, the sclerotic lesions often become softer again, sometimes also atrophic as well as hypo- or hyperpigmented[8,9] (Figure 3).

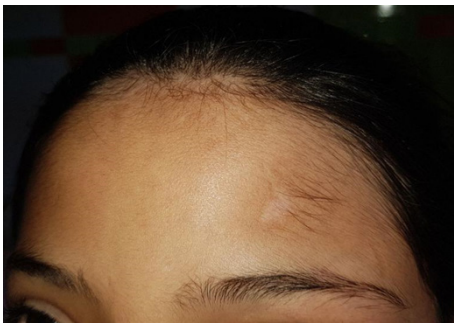

Figure 1 Morphea Skin.

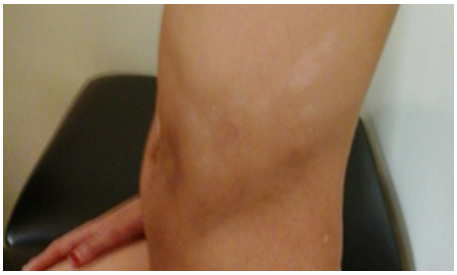

Figure 2 Morphea (Localized Scleroderma).

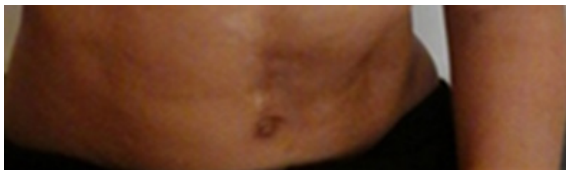

Figure 3 Morphea into sequellar plaque.

Banded sclerosis (linear scleroderma) is the most common subtype in children. Due to its site most often extending to the joints with possible locoregional joint deformation, it can cause functional disorders and limitation of movements, sometimes causing severe shortening of the limbs with the consequence of amyotrophy (Figure 4). Clinically, it is characterized by a hard sclerosing form in elongated bands that cannot be pinched.[8, 9,10] Generalized form of LS defined by the presence of at least 4 or more large lesions (>3 cm) affecting more than two different anatomical sites. It has a poor prognosis and resistance to treatment, its predilection site is the head and neck, the extremities and the anterior and posterior trunk[3,11] (Figure 5).

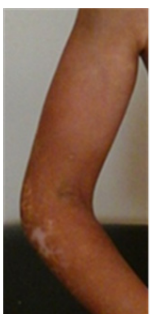

Figure 4 Linear scleroderma.

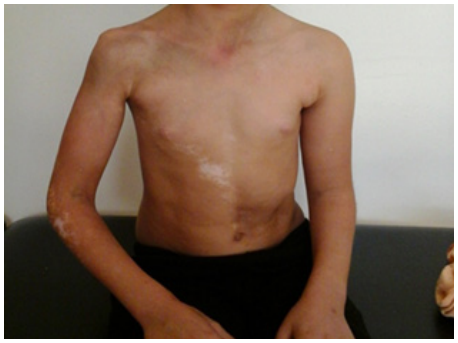

Figure 5 Generalized morphea with pigmentation disorder.

The best-known variant of linear LS, the « en coup de sabre » type. It is a particular entity characterized by its predilection facial site (Figure 6), which can extend paramedianly from the forehead, from the scalp to the eyebrow and which can cause significant unsightly damage and cause scarring alopecia.[3,8,12] (Figure 7).

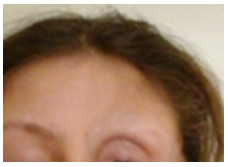

Figure 6 Morphoea en coup de sabre.

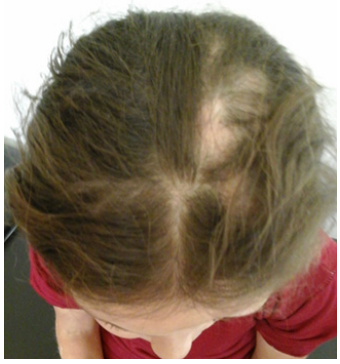

Figure 7 Scleroderma with alopecia.

Its clinical appearance is very suggestive of a scar that could be left by a sword blow. This type of scleroderma can hinder dental and palatal growth through bone and dental hypoplasia and fatty tissue, with loss of eyebrows, eyelashes and scalp areas (Figure 7).

Apart from dermatological damage and the aesthetic disorder that it can cause, several other complications are possible, notably associated visual and neurological disorders.[12]

Progressive facial hemiatrophy (PFH) (Parry-Romberg syndrome) is a condition related to li-near LS.[8] It is defined by an initial major and progressive atrophy, inexorably reaching a hemiface with muscle, bone and fatty tissue atrophy[13] (Figure 8).

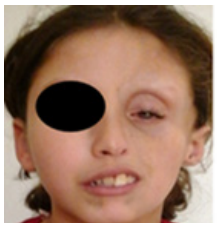

Figure 8 Progressive facial hemiatrophy (Parry Romberg Syndrom).

It is often active for several years with a poor aesthetic outcome with severe deformities and remodeling of the facial structure sometimes leading to pronounced facial asymmetry and serious ophthalmological lesions[13] (Figure 9).

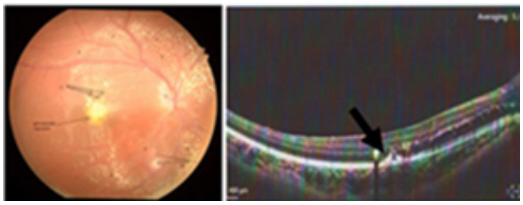

Figure 9 Neuroretinitis in Parry Romberg syndrome.

In localized scleroderma, hardening of the skin stops within two years of the onset of the disease, and the lesions do not spread to other parts of the body. However, the disease can sometimes last several years, and some plaques can become more marked (dark or light) even after the inflammatory process has stopped.

Systemic sclerosis (SSc) is a rare disease in children in which visceral manifestations can occur, particularly peripheral vascular, digestive, cardiopulmonary and renal manifestations.[14] It is characterized by microcirculation abnormalities and cutaneous or visceral fibrosis lesions.[15] Cutaneous sclerosis lesions are characterized by their clinical polymorphism.

Limited cutaneous systemic sclerosis is a form of systemic sclerosis characterized by the association of Raynaud's phenomenon with skin fibrosis of the hands, face, feet and forearms. There is no skin involvement of the torso, abdomen, back and thighs.[16] It causes sclerotic infiltration of the skin which takes on a shiny, tense appearance, the dermis thickens on palpation. This sclerosis begins on the fingers with an ascending topography (Figure 10). It can gradually lead to a limitation of finger extension but also a limitation of finger flexion (Figure 11).

Figure 10 Hand involvement in scleroderma.

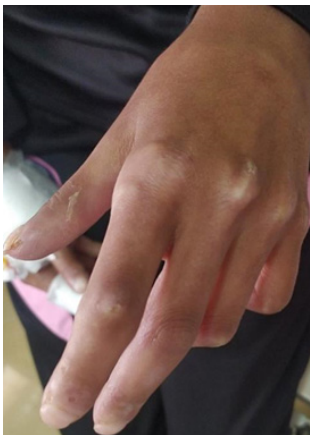

Figure 11 Typical sclerodactyl with flessum.

On the face, we describe a smoothed appearance of the skin, perioral radiated folds and a limitation of the mouth opening (Figure 12). The skin becomes waxy texture tight, hard and bound to subcutaneous structures. Raynaud's phenomenon is the most common sign and often the first sign of the disease. It has the particularity of being asymmetrical and can occur in summer[16,17] (Figure 13). Other signs usually appear a few years later.

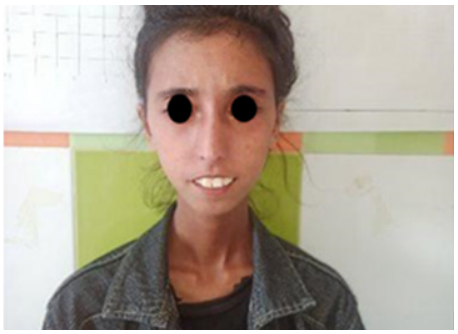

Figure 12 Scleroderma face (hardening of the skin may limit the opening of the mouth).

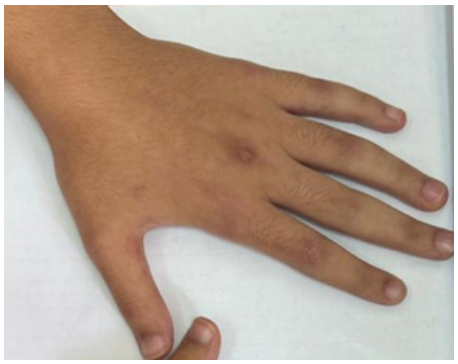

Figure 13 Raynaud's phenomenon.

Diffuse cutaneous systemic sclerosis is also a form of systemic sclerosis which is characterized by cutaneous fibrosis of the trunk and extremities associated with frequent and early multi-visceral involvement. Cutaneous fibrosis progresses rapidly and can spread throughout the body, limiting movement and causing significant muscle and joint pain. The hardening of the skin gives a frozen and expressionless appearance to the face (Figure 12), making it difficult to eat.[17]

Telangiectasias are sometimes present on the thorax, face, lips, tongue and fingers in a stellate form. They are the consequence of dilation of small vessels.

Digital ulcers are a common visible manifestation of the progressive vascular disease that characterizes the systemic sclerosis disease process. They are the consequence of damage to the small vessels of the hand with poor blood circulation to the Fingertips.[18,19] (Figure 14). The pathogenetic mechanism of digital ulcers is ischemic and can progress to necrosis and loss of fingers. But the mechanical or traumatic origin cannot be excluded, especially those facing the extensors of the hands (especially at the level of the small joints) or facing a pressure point against a bony relief. It sometimes persists after healing of an ulcer or pulp scar. They are often exquisitely painful.[19,20]

Pigmentation disorders such as areas of hyperpigmentation or depigmentation sometimes having a melanodermal appearance may be present during the progression of the disease (Figure 5).

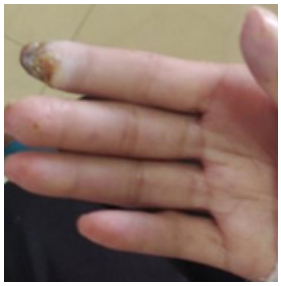

Figure 14 scleroderma Digital ulcer.

Calcinosis cutis is the deposition of insoluble calcium in the skin and subcutaneous tissues. They are often surrounded by an inflammatory reaction, most often localized at the level of the soft tissues (Fingertips, extension surface of the forearms or anterior surface of the knees).[17] Extensive calcinosis affects periarticular or even joint areas, muscles and tendons[17] (Figure 15) It is associated with longer disease duration, digital ulcers, acro-osteolysis. Whatever their form, calcinoses progress towards fistulization, with extrusion of the calcareous material.

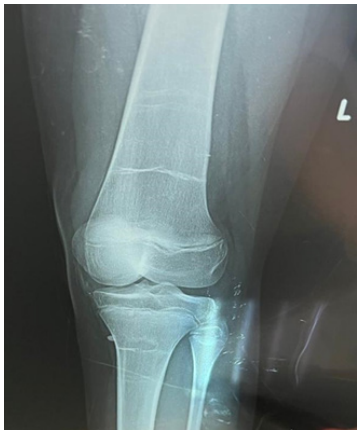

Figure 15 Periarticular calcinosis.

Laboratory parameters

There are no characteristic serologic parameters in LS; and very few examination is required. The diagnosis of LS is usually based on clinical examination and in cases of uncertainty, skin and subcutaneous biopsy can aid the diagnosis.[21]

The basic laboratory tests of morphea includes a blood count that can objectively show hypereosinophilia in the active phase; an inflammatory assessment with an increase in sedimentation rate and C Reactive Protein in the initial phase.[21,22] The autoimmunity assessment can reveal the presence of rheumatoid factor, antinuclear antibodies and an absence of anti-Scl70 and anticentromere antibodies.[21]

The minimal morphological assessment includes a systematic ophthalmological examination and neurological exploration (brain imaging and electroencephalogram) in cases of linear facial morphea.[23] Other examinations depend on the clinic, in particular the use of MRI of the soft tissues in deep forms.[23]

The initial assessment for Raynaud's phenomenon in children requires a search for antinuclear factor and capillaroscopy, with a frequency of follow-up to be adapted according to the results.[23,24]

Systemic sclerosis is frequently characterized by highly specific antibodies, in its diffuse form (anti-topoisomérase I (anti-Scl-70) or anti-titopoisomerase-1 antibodies) and limited (anti-centromere antibodies).[8] An assessment of visceral damage (renal, esophagogastric, cardiac, pulmonary) and the search for an associated autoimmune disease is generally requested.

The particularity of juvenile systemic sclerosis is the low presence of anti-centromere antibodies and anti RNA polymerase III antibodies. However, anti-PMScl and anti-UIRNP antibodies found in overlap syndromes are very common.[23]

Therapeutic approach

The treatment of scleroderma in children is not well not well defined, it depends on the age of the patient, the functional and aesthetic impact, the activity of the disease and the area of the lesion. A severity score has been proposed to guide the management of the disease; Juvenile Systemic Sclerosis Severity Score which has been validated in children including skin involvement and various organ involvements.[25] There is no specific treatment for which effectiveness is assured. The majority of proposed treatments come from a few cases, knowing that prospective randomized pediatric studies are rare. In general, treatment of skin lesions depends on the depth and severity of the subtype. In recent years, it has relied on the use of the localized scleroderma skin assessment tool (LoSCAT), a simple and fast to use in daily clinical practice. It is composed of two indices : the Localized Scleroderma Skin Severity Index (mLoSSI) modified to measure disease activity and which takes into consideration new lesions, extension, erythema and thickening of existing lesions and the Scleroderma Skin Damage Index (LoSDI) assessing tissue damage.[26,27]

The use of certain drugs in children must carefully evaluate the benefit/risk ratio, and the doses and duration of treatment.

Treatment must be administered early and wisely, especially in a growing child. This is a crucial problem because although localized juvenile scleroderma is not a fatal disease, patients can develop serious functional sequelae such as joint contractures, limb growth abnormalities and psychological disorders.[26]

Some types of morphea may resolve spontaneously. Linear forms stabilize spontaneously after a few years, with a risk of unsightly after-effects when they are deep. Parry Romberg's hemiatrophies are currently difficult to stabilize and the after-effects are significant and leave excavated areas with significant loss of skin substance, thus harming self-image in children and especially adolescents.[28] These lesions can be treated surgically, in particular by autologous fat injections.

Recent studies in children show the effectiveness of systemic corticosteroids in combination with methotrexate (MTX) in patients with active juvenile localised scleroderma (JLS), particularly in progressive linear scleroderma and generalized or pansclerotic morphea. The use of steroids for the treatment of the active phase of the disease in children mainly in combination with MTX has been shown to be effective and well tolerated.[29,30]

Experts mainly suggest two administration regimens : oral prednisone at a dose of 1 to 2 mg/kg/day for a period of 2 to 3 months, followed by a gradual reduction, or pulsed high-dose intravenous methylprednisolone (30 mg/kg) with various administration schedules.[29,30]

MTX is the basic first-step treatment for JLS in a single weekly dose of 15 mg/m2 orally or subcutaneously. Once clinical improvement is achieved, MTX should be continued for at least 12 months before

gradually reducing doses.[31] In severe refractory cases or in the face of ineffectiveness or intolerance to MTX, mycophenolate mofetil (MMF) at a dose of 500 to 1,000 mg/m2 can be used.[31,32]

Circumscribed morphoea is generally of cosmetic concern only and should be treated with topical treatment. Treatment with topical tacrolimus and ultraviolet A phototherapy has been shown to be effective and decreases skin thickness, dyspigmentation, induration, erythema, telangiectasia, and atrophy.[33] However, studies have shown that neither interferon gamma nor vitamin D are effective.[34,35] D-penicillamine has been reported in some series as a treatment for morphea, but its real effectiveness has not been demonstrated.[36]

For digital ulcers, treatment is based on local anesthesia (5% Emla anesthetic cream or 2% Xylocaine gel) with the use of nitrous oxide if local anesthesia proves insufficient. Other therapeutic tools are used depending on the type of wound and the stage of healing, in this case hydrocolloid dressings, hydrogels, alginates, hydrofibers, neutral tulles, interfaces, polyurethane films. In case of superficial superinfection, silver sulfadiazine dressings are recommended.[37]

Management of Raynaud's phenomenon depends on its severity ; most often certain vasodilators and calcium channel blockers give convincing results. In cases of severe and refractory Raynaud's syndrome, treatment with iloprost may be offered. In secondary prevention of digital ulcers, bosentan could also be of interest in adults.[38]

Children with head and neck morphea should have ophthalmologic examinations to monitor for asymptomatic involvement that may lead to irreversible damage.

Physiotherapy treatment, aimed at softening the skin and combating stiffness and joint contractures, remains the cornerstone of treatment. Psychological support is essential in severe forms with functional and aesthetic impact.

The advent of biotherapy has changed the course of certain forms of scleroderma refractory to usual treatment. Indeed, targeted therapy has been proposed as a potential therapeutic alternative for JLS refractory to methotrexate and/or mycophenolate mofetil. Organic products are generally well tolerated in children.

The use of tocilizumab, an antibody against interleukin (IL) 6 playing an important role in the pathogenesis of the disease, has been reported in a few pediatric series with convincing results in the localized form of the disease.[39] Other studies have demonstrated the effectiveness of abatacept, a protein that modulates lymphocyte activity and whose role would be musculoskeletal improvement with the limitation of cutaneous fibrosis in linear scleroderma in children.[40]

Concerning new biological agents such as JAK inhibitors, targeting the JAK-STAT pathway, their effectiveness has been reported in some pediatric cases of localized scleroderma. They could play a role in improving the fibrous process of recalcified morphea. Nevertheless, other randomized studies in children are useful to demonstrate their effectiveness on forms refractory to treatment and their tolerance in children.[41]

As the disease progresses, surgical reconstruction may be necessary for potentially functional and esthetic problems. This therapeutic recourse should only be carried out after the child has reached full growth and has stabilized with complete remission of disease activity. Generally, among adolescents, facial contouring improves self-image and quality of life.

Laser therapy offers a new and often effective treatment for stubborn skin conditions linked to autoimmune diseases. Concerning its use in juvenile cutaneous scleroderma, few reports have been made in the literature ; the majority of studies were single case reports or case series. It is therefore difficult to assess its benefit/risk ratio in children. Nevertheless, it can be an interesting therapeutic tool in certain cases of complicated and unsightly localized scleroderma lesions; but does not in any way slow down the progressive process of the disease and does not prevent the formation of new lesions. It can be considered as an adjuvant method to usual treatments in order to offer a better quality of life to patients.[42,43]

Evolution

The average duration of the illness is long and falls are frequent, sometimes long-distance. The complications are polymorphic and can be disabling. The medium and long term impact is potentially dermatological (atrophy, ulcerations, poikiloderma, necrosis, etc.) but also muscular (atrophy, adhesive myositis), joint and bone.

Indeed, children with localized juvenile scleroderma are at risk of growth disturbances (differences in limb length) and facial atrophy. The prognosis is very variable. The limited form is in principle accompanied by a better prognosis.

Conclusion

Juvenile scleroderma is a rare disease and presents a potentially cutaneous clinical expression. It is a fibrosing disease of the skin and underlying tissues whose pathogenesis is not yet completely understood, ultimately leading to an imbalance in the production and destruction of collagen. Despite its clinical polymorphism, skin damage must be quickly discussed by clinicians, with a view to early therapeutic management to prevent aesthetic and functional sequelae. Evidence-based treatment options in children are limited due to the rarity of the disease and the lack of randomized pediatric studies.

Acknowledgments

None.

Conflicts of interest

Authors declare there is no conflict of interest.

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