FEATURE ARTICLE

CE 1.5 Contact Hours

Localized Scleroderma in the Pediatric Population

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ABSTRACT: Localized scleroderma is an uncommon condition that affects the skin and underlying tissues. Although the pathogenesis is not well understood, lesions of localized scleroderma develop from an initial inflammatory reaction that results in collagen deposition, fibrosis, and atrophy. Healthcare providers need to be alert for skin discolorations or atypical ecchymosis appearances that do not resolve. Prompt diagnosis and treatment, particularly in pediatric patients, are necessary to reduce the risk of growth disturbance, extremity length differences, permanent damage to the skin, accessory structures, joints, and facial atrophy (Careta & Romiti, 2015). Delayed treatment is associated with worse outcomes (Martini et al., 2018). Consensus-based recommendations provide effective treatment options; however, more studies are required in the pediatric population as, to date, there is only one randomized controlled trial in this population (Constantin et al., 2018).

Key words: Circumscribed Morphea, Consensus Treatment Plan, Generalized Morphea, Linear Morphea, Localized Scleroderma, Pansclerotic Morphea

Scleroderma is a term used to describe a connective tissue disorder that results in cutaneous sclerosis and possible systemic involvement. There are two categories of scleroderma: systemic and localized. Systemic sclerosis is an autoimmune disorder involving connective tissue and can have many signs and symptoms, including immunologic disturbances, essential vasomotor disturbance, atrophy of skin, atrophy of subcutaneous tissue, atrophy of muscle, atrophy of internal organs, and fibrosis (Adrovic, Sahin, Barut, & Kasapcopur, 2018; Zulian, 2017). It is generally accepted that localized scleroderma (LSc) does not progress to systemic sclerosis; however, the two distinct autoimmune disorders may infrequently coexist (Giuggioli et al., 2018).

LSc, also referred to as morphea, is an uncommon fibrosing disorder that affects the skin and its underlying tissues. The terms "morphea" and "localized scleroderma" can be used interchangeably; however, LSc is typically preferred among pediatric dermatologists and rheumatologists (Constantin et al., 2018). The exact pathophysiology is not completely understood; however, the disease results in a disparity of the production of collagen and its destruction (Careta & Romiti, 2015; Fett & Werth, 2011b; Martini et al., 2018). LSc can be associated with systemic symptoms such as arthralgias, fatigue, and malaise (Fett & Werth, 2011b). LSc is set apart from systemic sclerosis by the fact that it almost exclusively has cutaneous involvement and lacks sclerodactyly, nailfold capillary changes, and Raynaud's phenomenon (Fett & Werth, 2011a; Florez-Pollack, Kunzler, & Jacobe, 2018; Zulian, 2018). Often, there can be involvement of the underlying muscle in LSc, but there rarely is internal organ involvement (Constantin et al., 2018). The type and extent of the lesions determine the course and outcomes for people affected by LSc (Zulian, 2018). Diagnosis can be difficult because of the rarity of the disease; however, early diagnosis is crucial, as delayed diagnosis in our pediatric patients can lead to increased morbidity from this potentially debilitating condition (Constantin et al., 2018).

PATHOGENESIS

The lesion of LSc initially reveals an inflammatory reaction, then matrix deposition (including collagen), followed by fibrosis, and, finally, atrophy (Constantin et al., 2018; Zulian, 2017). In addition, cytokines (which increase collagen synthesis) have been found in elevated levels in the LSc lesions (Zulian, 2017). LSc can affect the skin, subcutaneous tissue, underlying bone, and central nervous systems when present on the head and face (Fett & Werth,

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2011a; Florez-Pollack et al., 2018; Zulian, 2017). Although the etiology is not clear, trauma, medications, radiation, autoimmunity, infection, and microchimerism have all been associated with the formation of LSc (Fett & Werth, 2011a; Zulian, 2017). Abnormal fibroblast function also may be a contributing factor (Martini et al., 2018; Timpane, Brandling-Bennett, & Kristjansson, 2016; Zulian, 2018).

EPIDEMIOLOGY

LSc is considered a rare fibrosing disorder with incidence rates of 0.4–2.7 per 100,000 people in people of all ages (Fett & Werth, 2011a; Martini et al., 2018). It is more common in female patients at a rate of 2.4–4.2:1 and is more prevalent in Whites who comprise 72.7%–82% of people afflicted with the disorder (Fett & Werth, 2011a; Zulian, 2017). The true incidence is estimated to be higher, as some cases never present to healthcare providers or are misdiagnosed (Zulian, 2018). Specifically in the pediatric population, the prevalence rate has been reported at 3.4 cases per million per year in children ages 16 years or younger, with an average age of onset of 7.3 years (Aranegui & Jiménez-Reyes, 2018; Zulian, 2017; Zulian et al., 2019). Similarly, both children and adults with LSc have an increased prevalence of familial autoimmune disorders as well as higher levels of anxiety and depression (Aranegui & Jiménez-Reyes, 2018; Fett & Werth 2011a). LSc in children is rare but occurs 10 times more frequently than systemic sclerosis (Zulian, 2018).

PRESENTATION

The clinical presentation of LSc can be different depending on the type or classification. Initially, patients present in an active (inflammatory) stage with erythematous to dusky violaceous plaques or patches (Fett & Werth, 2011a; Florez-Pollack et al., 2018). Patients may describe these lesions as a "bruise" that can develop over months or acutely, which may be pruritic and/or painful, while in the active phase (Florez-Pollack et al., 2018). As LSc progresses, the borders of the patches and plaques develop a characteristic "violaceous ring," whereas the center of these areas becomes white and sclerotic (Fett & Werth, 2011a; Florez-Pollack et al., 2018). When the plaque or patch is no longer in the active phase, the damaged area either becomes a white sclerotic plaque or the area may have postinflammatory hyperpigmentation, which then ultimately transforms into a shiny skin appearance with visible underlying vessels (Florez-Pollack et al., 2018). Inactive lesions present as hairless, anhidrotic plaques as a result of the excessive collagen deposition destroying the area hair follicles and eccrine glands (Fett & Werth, 2011a; Florez-Pollack et al., 2018).

DIAGNOSIS

Typically, the diagnosis of LSc is made by history and appearance of the skin lesions, supported by a complete history, review of systems, and comprehensive physical examination (Constantin et al., 2018; Timpane et al., 2016; Zulian, 2018). Laboratory testing is not routinely needed as complete blood count, urinalysis, and blood chemistries are commonly normal, and although biopsies can be done for confirmation, it is not mandatory to make the diagnosis (Constantin et al., 2018; Martini et al., 2018; Timpane et al., 2016; Zulian, 2018). Prompt diagnosis of LSc is necessary, as delaying treatment may lead to increased damage and loss of the ideal treatment period, yet LSc is misdiagnosed approximately 70% of the time upon initial presentation with as much as a 1- to 2-year delay in diagnosis (Constantin et al., 2018).

CLASSIFICATION OF LSC

The distribution of the skin lesions, in addition to associated findings, determines the classification of the five types of LSc. Historically, the classifications of LSc use its associated name, morphea (see Table 1).

- Generalized morphea has four or more plaques, which can be superficial or deep, that affect two or more anatomic sites that become confluent (Aranegui & Jiménez-Reyes, 2018; Zulian, 2017).
- Circumscribed (plaque) morphea is the most common and most benign classification of morphea in the general population. It occurs in the dermis but may involve the subcutaneous tissue or superficial panniculus (Aranegui & Jiménez-Reyes, 2018; Zulian, 2017). The plaques are few in number, are discrete, and involve two or less anatomic areas.
- Linear scleroderma is the most common type of morphea seen in pediatric population. The lesions are fibrotic and elongated and may lead to contractures, limb deformities, poor growth, and disabilities. When the scalp and face are involved, it is called "en coup de sabre" with lesions typically occurring on one side of the head and causing asymmetric facial development (Zulian, 2017). Those who present with a craniofacial distribution should have examination by an ophthalmologist and neurologist and have a magnetic resonance imaging as seizures, headaches, behavioral changes, or learning disabilities have been reported (Timpane et al., 2016; Zulian, 2017). Parry–Romberg syndrome is progressive hemifacial atrophy of tissue and skin located below the forehead with minimal or no superficial skin involvement (Zulian, 2017).
- Pansclerotic (deep) morphea is the most disabling and, fortunately, the least common form with full thickness being involved of the skin of face, scalp, trunk, and extremities sparing the toes and fingertips (Zulian, 2017).
- Mixed scleroderma is a combination of two or more of the above subtypes (Aranegui & Jiménez-Reyes, 2018; Zulian, 2018).

EVIDENCE-BASED TREATMENT

Because of the rarity of morphea and the difficulty in measuring outcome improvement, evidence-based therapies are

TABLE 1. Classifications of Localized Scleroderma (Morphea)

Classification	Distribution of Lesions	Associated Factors
Generalized morphea[a,b]	• Four or more plaques • Can be superficial or deep • Affect two or more anatomical sites • Become confluent	• None
Circumscribed morphea[a,b]	• Discrete and few in number • Affect two or less anatomical sites	• Most common and most benign
Linear morphea[a,c] (most common in the pediatric population)	• Fibrotic and elongated plaques	• May lead to contractures, limb deformities, poor growth, and disabilities
Linear morphea with craniofacial distribution	• Involving the scalp and/or face • En coup de sabre • Typically occur on one side causing asymmetric facial development[a]	• A craniofacial distribution requires examination by an ophthalmologist and a neurologist.[c,d] • Magnetic resonance imaging is needed.[c,d] •Parry–Romberg syndrome is a progressive hemifacial atrophy of tissue and skin below the forehead with no minimal or no superficial skin involvement.[c] •Seizures, headaches, behavioral change, or learning disabilities may occur.[c]
Pansclerotic (deep) morphea[a]	• Full thickness • Face, scalp, trunk, and extremities can be involved. • Toes and fingers not involved	• Least common and most debilitating
Mixed morphea[a]	• Combination of two or more classifications	• Dependent on type

[a]Zulian, 2018.
[b]Aranegui & Jiménez-Reyes, 2018.
[c]Zulian, 2017.
[d]Timpane et al., 2016.

minimal (Careta & Romiti, 2015; Fett & Werth, 2011b). Most studies have only included adult patients, with only one study specifically evaluating children (Zulian, 2018). However, Fett and Werth (2011b) conducted a comprehensive review of evidence-based treatment options for LSc including four randomized controlled trials (RCTs), four retrospective reviews, and three prospective reviews.

The four RCTs included in the comprehensive review each evaluated the effects of a selected therapy as compared with either placebo or standard therapy. The effects of subcutaneous interferon-gamma, oral calcitriol, narrowband ultraviolet B light phototherapy, and topical tacrolimus were evaluated against either standard therapy or placebo. Results revealed that interferon-gamma and oral calcitriol were not effective in treating LSc but that narrowband ultraviolet B phototherapy and low-dose ultraviolet A1 phototherapy produced an improvement in plaque severity with similar efficacy. Topical tacrolimus ointment also was shown to decrease induration, dyspigmentation, skin thickness, telangiectasia, erythema, and atrophy when used for 12 weeks at twice-daily dosing.

Fett and Werth (2011b) also evaluated four retrospective reviews involving 119 patients that examined the effectiveness of methotrexate, in combination with systemic steroids, in the treatment of LSc. Adult dosing of methotrexate was 15–25 mg/week, and in children, it was 0.3–0.4 mg/kg per week. Adult dosing typically involved initial subcutaneous injections followed by oral administration, whereas pediatric dosing was via intramuscular administration. Intravenous pulse steroids were given initially, and then patients were transitioned to oral steroids. Seventy-nine percent of patients reported improvement with their symptoms with this treatment modality.

Finally, Fett and Werth (2011b) reviewed three prospective studies that specifically examined the effects of methotrexate therapy for LSc. Dosing and administration of methotrexate were similar to those in the retrospective studies, with adult dosing being 15 mg/week and pediatric dosing being 0.3 mg/week, with doses adjusted based on response. Again, steroids were concurrently used with high-dose bursts of intravenous methylprednisolone. There was a statistically significant improvement in adults, and nine of the 10 children involved in these studies showed improvement.

Retrospective and prospective reviews showed positive outcomes with the combination of methotrexate and steroids. However, in both study designs, disease flares were more common with the discontinuation of methotrexate therapy.

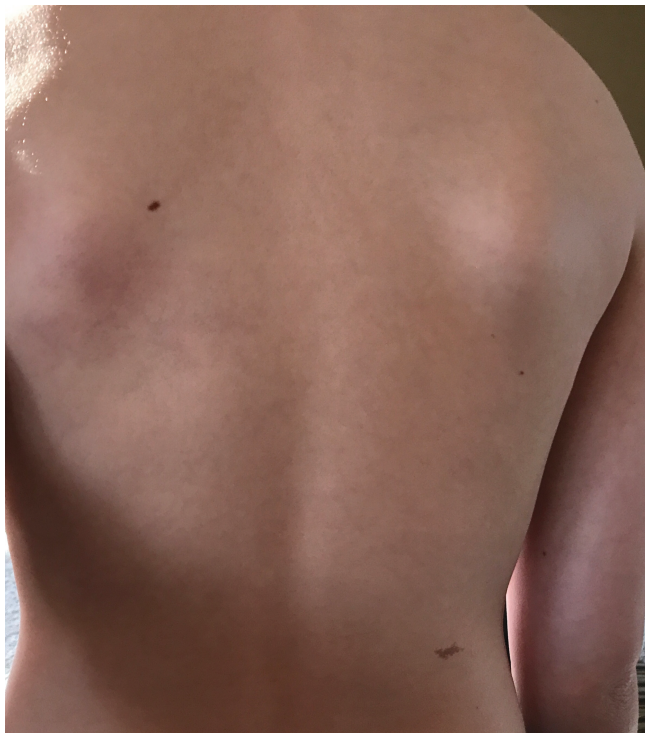

FIGURE 1. Left thoracic back lesion at time of initial presentation.

As there was a lack of control groups in these studies, results must be interpreted with caution (Fett & Werth, 2011a, 2011b).

Piram et al. (2013) conducted a retrospective study involving 52 pediatric patients diagnosed with linear morphea over a 20-year time span. Results showed that the limbs were involved twice as often as the face and more women than men were affected with linear morphea of the limbs at a rate of 4:1. Although the disorder would have long periods of inactivity than reactivation, linear morphea in these patients stabilized after 5.4 years; however, 31% of the patients in this study continued to have active disease after 10 years.

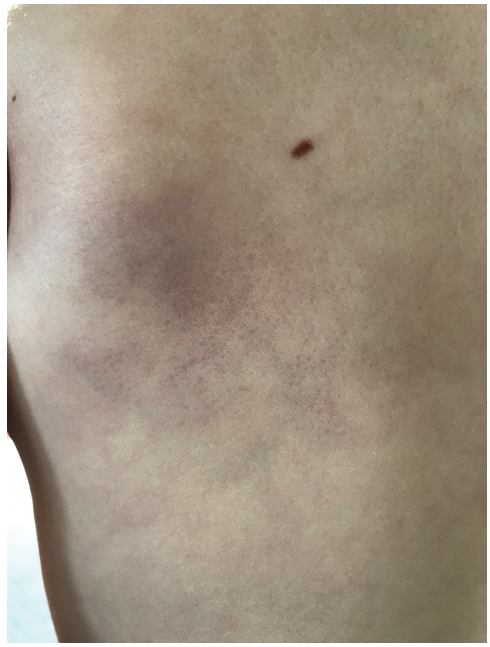

FIGURE 2. Left thoracic back lesion at time of initial presentation, closer view.

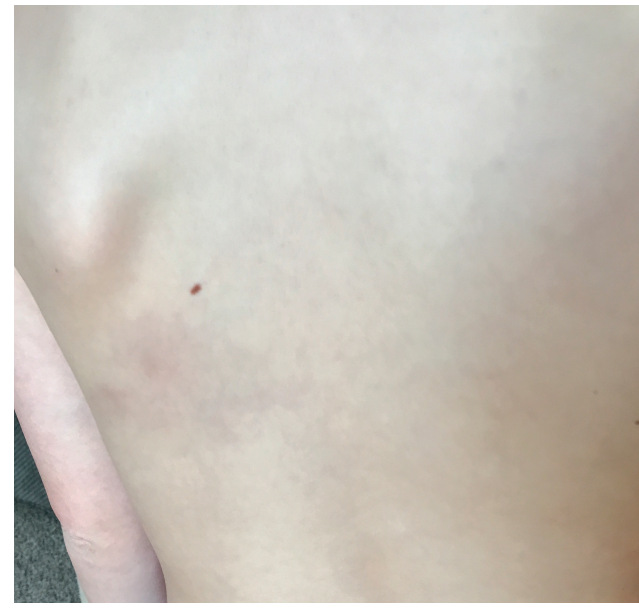

FIGURE 3. Left thoracic back lesion at time of presentation, closer view.

Zulian et al. (2011) conducted the only double-blind RCT with 70 pediatric patients ages 6–17 years with LSc to evaluate the efficacy and safety of methotrexate compared with placebo. Notably, both treatment and placebo groups received oral prednisone at 1 mg/kg per day for 3 months. Results indicated that patients who had been treated with methotrexate, in combination with oral

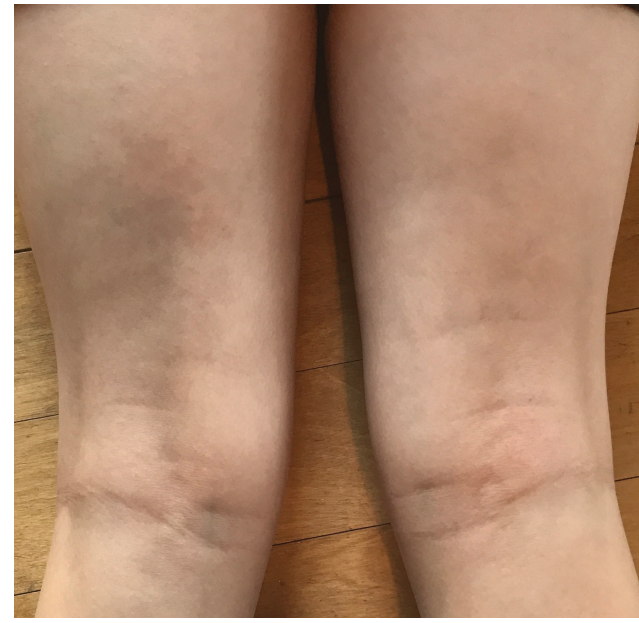

FIGURE 4. Left posterior thigh, prior to treatment.

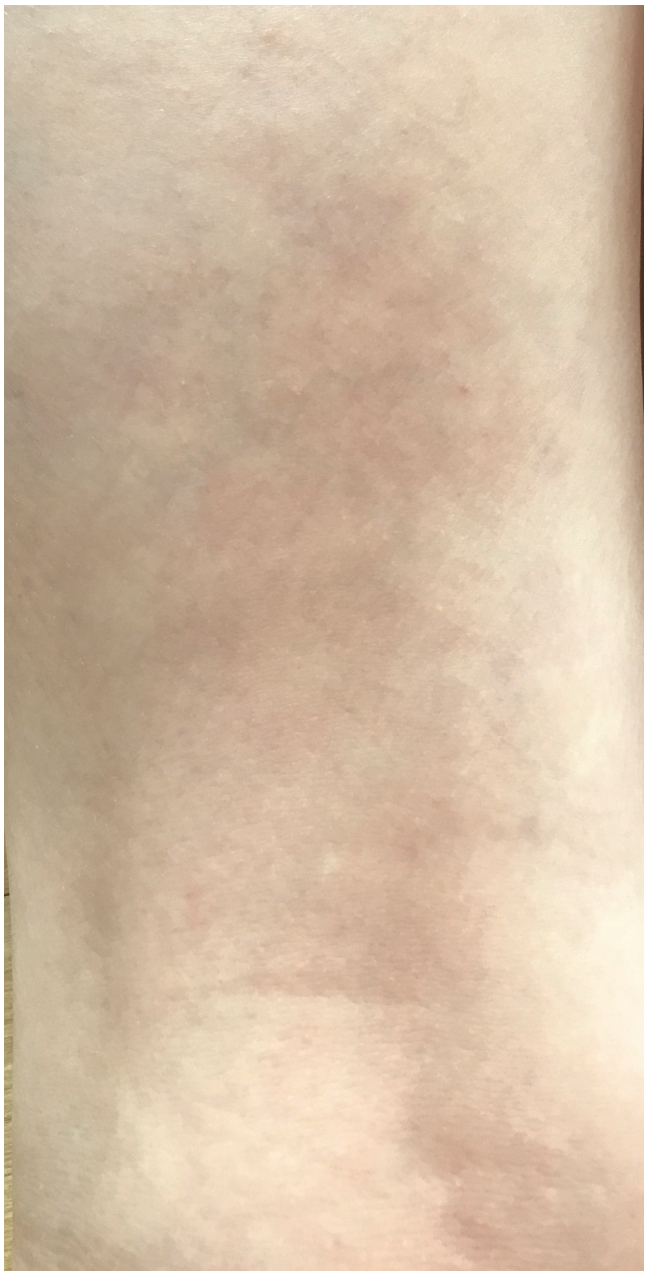

FIGURE 5. Left posterior thigh, prior to treatment, closer view.

prednisone, had significant improvements in lesion severity, number, and flares in comparison with the placebo group. Methotrexate was found to be well tolerated with only mild adverse events reported in 56.5% of the patients, with the most frequently reported being nausea (17.4%) followed by headache (10.9%).

Qayoom, Rather, Manzoor, and Samen (2019) recently conducted a prospective study where 21 patients with moderate-to-severe LSc were treated with a combination of intramuscular methotrexate in combination with intravenous steroids. Notably, the mean age of patients was 21 years, and nearly 50% of the sample was under the age of 18 years, with the youngest being 3 years old. Patients were placed on a treatment regimen of 30-mg/kg methylprednisolone at monthly pulses for 3 months and 0.2–0.4 mg/kg per week of intramuscular methotrexate for 12 months and were followed for 5 years between 2014 and 2019. Although the sample size was small, the conclusions supported previous research as the combination of systemic steroids and methotrexate resulted in a significant improvement in symptoms in both children and adults.

A consensus treatment plan was development for systemic therapy by a workgroup consisting of 10 pediatric rheumatologists, two dermatology consultants, and a lay advisor (Adrovic et al., 2018; Careta & Romiti, 2015; Li et al., 2012; Timpane et al., 2016). Notably, a general treatment approach is that no therapy is needed for a single circumscribed lesion. However, emollients, topical steroids, and calcipotriene may help with itching and dryness (Adrovic et al., 2018; Zulian, 2018; Zulian et al., 2019).

In patients with moderate-to-severe LSc, the treatment options include methotrexate alone, methotrexate and intravenous methylprednisolone, or methotrexate and oral prednisone (Adrovic et al., 2018; Li et al., 2012; Timpane

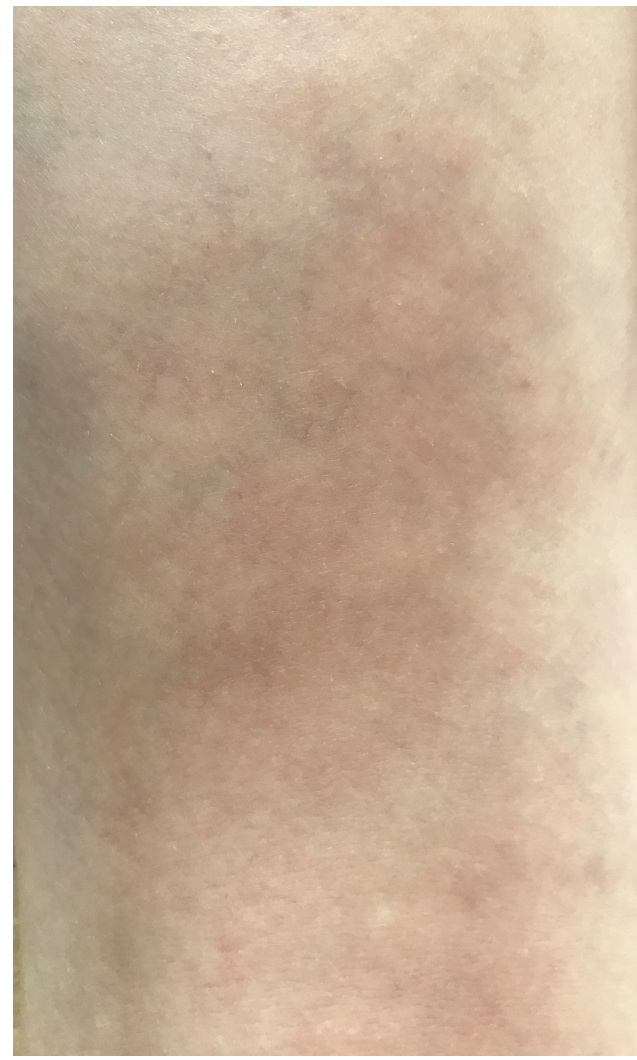

FIGURE 6. Left posterior thigh, prior to treatment, closer view.

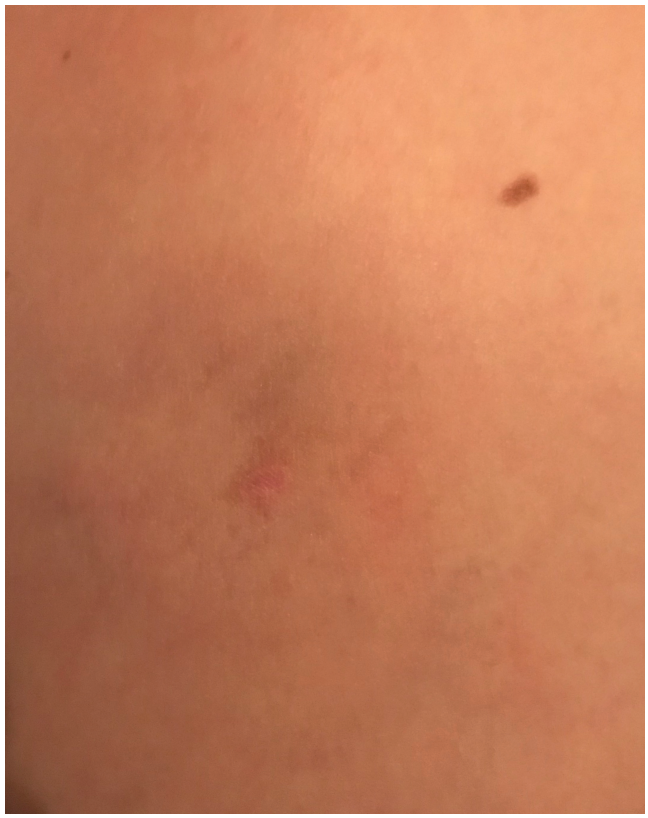

FIGURE 7. Left thoracic back lesion after treatment with oral methotrexate.

et al., 2016). Methotrexate, orally or subcutaneously, at 15 mg/m^2 once weekly (maximum dose of 25 mg weekly) for at least 1 year is the drug of choice when there is a risk for disability (Constantin et al., 2018; Florez-Pollack et al., 2018; Zulian, 2018. Glucocorticoids, such as prednisone of 1 mg/kg per day, with a maximum dose of 50 mg/day, or methylprednisolone of 20–30 mg/kg per day, with a maximum dose of 1000 mg/day, can be used as an adjunctive therapy during the first 3 months of treatment along with methotrexate (Zulian, 2018).

Prolonged remission has been reported when patients completed at least 2 years of treatment with either methotrexate alone or in combination with glucocorticoid steroids; however, there is not a universally accepted definition of what constitutes remission in LSc (Constantin et al., 2018; Zulian, 2018). For patients whom methotrexate is ineffective, the consensus plan does recommend mycophenolate mofetil dosed at 500–1000 mg/m^2, and if patients have resistant LSc, the biologics may be considered; however, there is a lack of clinical trials to support this option (Adrovic et al., 2018; Timpane et al., 2016; Zulian, 2018; Zulian et al., 2019).

PROGNOSIS

LSc tends to occur in an intermittent–recurrent course or a chronic course with sequelae (Aranegui & Jiménez-Reyes, 2018). The average duration of disease for children with LSc is at 13.5 years (Li et al., 2012). Recurrence rates of 28%–44% have been reported at an average of 16–20 months after methotrexate has been discontinued (Aranegui & Jiménez-Reyes, 2018; Careta & Romiti, 2015; Li et al., 2012). Because of risk of relapse, LSc should be treated aggressively with therapy continued for a minimum of 2 years (Martini et al., 2018; Zulian, 2017; Zulian et al., 2019). Continually active disease has been reported in 30% of adults with childhood onset (Careta & Romiti, 2015; Li et al., 2012). More than 50% of adult patients with pediatric onset of LSc were found to have resultant permanent damage from the morphea that included limited range of motion, limb-length discrepancy, deep atrophy, arthritis, joint contracture, "white" uveitis, and possibly brain involvement (Careta & Romiti, 2015; Constantin et al., 2018; Timpane et al., 2016; Zulian et al., 2011). In addition, the psychosocial factors that may occur with physical changes can decrease the quality of life in patients who have LSc (Adrovic et al., 2018; Constantin et al., 2018; Florez-Pollack et al., 2018).

CASE REPORT: PRESENTATION

A 10-year-old boy presented with his mother to a general dermatology clinic with a lesion of concern on the left

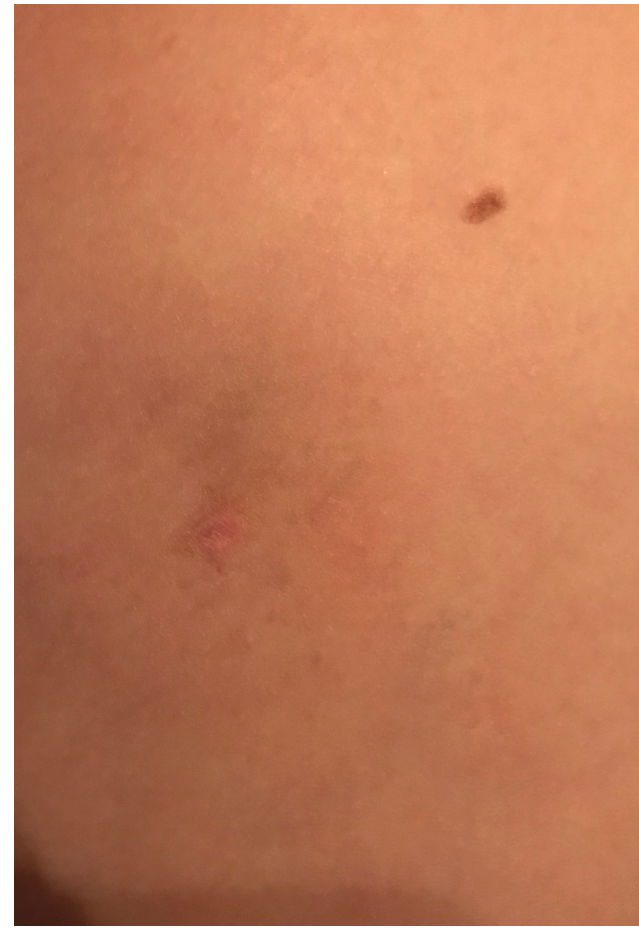

FIGURE 8. Left thoracic back lesion after treatment with oral methotrexate.

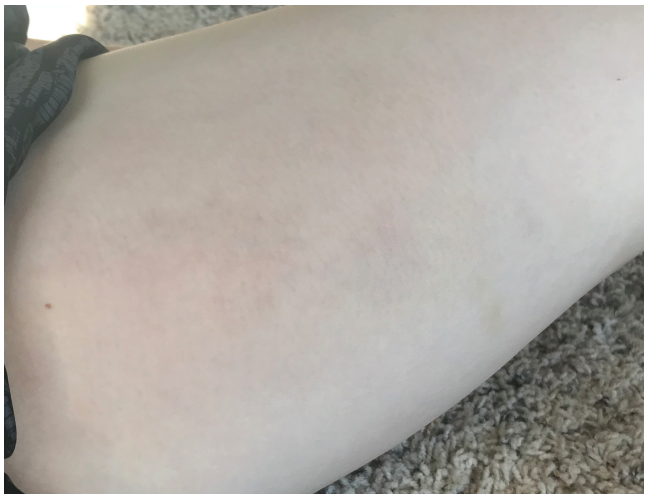

FIGURE 9. Left upper medial thigh, new lesions that presented while on oral methotrexate.

upper thoracic back. The mother had noticed what she thought was a bruise 4 months ago as the patient's football shoulder pads rested in the area. However, the bruise persisted 1 month after football season ended, and the mother brought her son to the dermatology clinic for evaluation. The patient and his mother denied any trauma, pain, or itching of the area. On physical examination, a circular plaque to the left lateral upper thoracic back measuring approximately 2.5 cm was found (see Figures 1–3). The area was a subtly pigmented purple/brown plaque with prominent underlying vessels. There was no pain with palpation or any deep involvement. Examination of the rest of the body revealed a second asymptomatic, subtly pigmented brown/purple hyperpigmented plaque that was more rectangular in shape. It measured 10 × 13 cm on the posterior aspect of the left thigh with subtle vessels underlying the plaque (see Figures 4–6). The mother states she did notice the thigh lesion 6 months earlier but did not give it any additional thought.

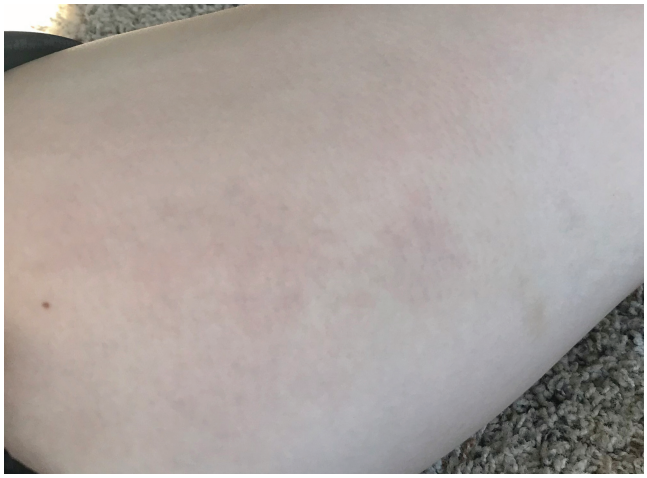

FIGURE 10. Left upper medial thigh, new lesions that presented while on oral methotrexate.

The past medical history was positive for atopic dermatitis and bronchospasm, and there was no past surgical history. Medications included fluticasone nasal spray as needed, cetirizine 10 mg as needed, and albuterol inhaler as needed. There were no known drug allergies. Family history was noncontributory, no autoimmune disorders. Review of systems was unremarkable. Overall history and physical examination revealed an otherwise healthy 10-year-old boy.

A punch biopsy was performed to the thoracic back lesion, which showed perivascular and interstitial inflammation deep with slight alteration of dermal collagen. The inflammation was composed of lymphocytes, histiocytes,

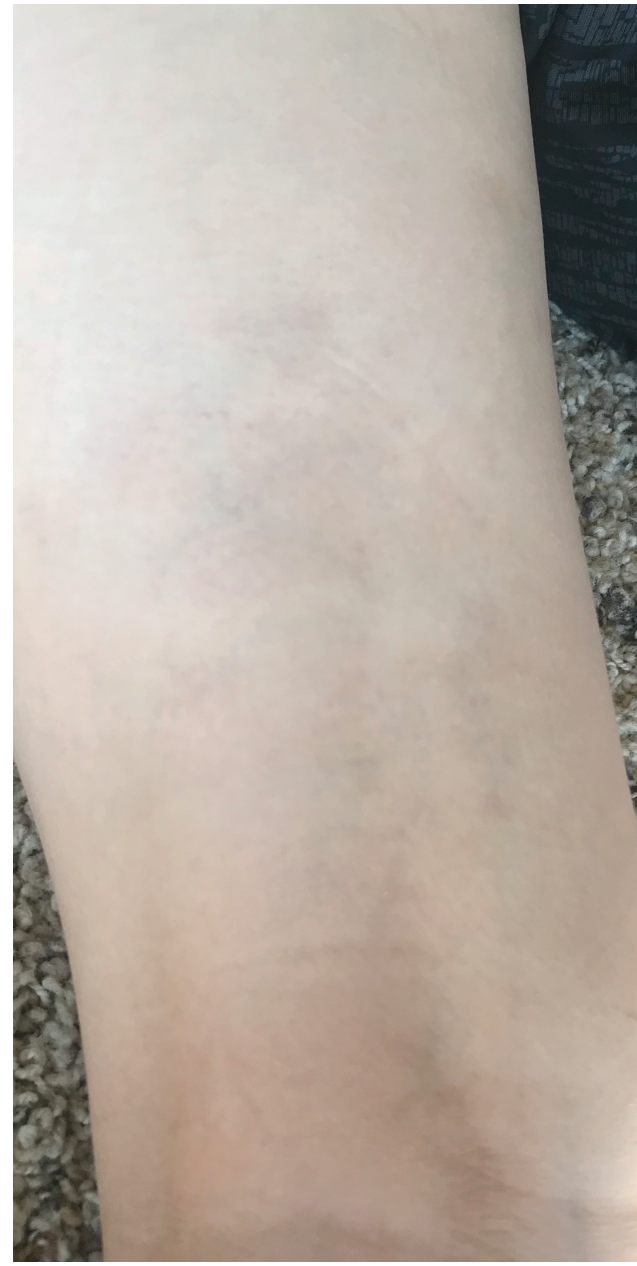

FIGURE 11. Left posterior thigh lesions progressing while on oral methotrexate.

and plasma cells. The dermatopathologist confirmed morphea in the inflammatory stages. The patient was ultimately diagnosed with mixed morphea, because of the linear scleroderma on the leg and circumscribed scleroderma on the back.

The patient was started on methotrexate 5 mg orally once weekly and referred to a pediatric dermatologist who continued the treatment with methotrexate with the addition of tacrolimus 0.1% ointment to affected areas daily. These lesions were appearing to improve (see Figures 7 and 8). However, at his 6-month follow-up appointment, it was noted that the plaques on the leg started to extend inferiorly to the posterior knee, to the medial left thigh, to the upper anterior portion of the left thigh, and into the left crural fold (see Figures 9–11). According to current recommendations by the consensus treatment plan, the treatment was changed from oral methotrexate at 5-mg weekly doses to 25-mg weekly doses by subcutaneous injection, with plans to continue for 2 years. Follow-up visits and monitoring for methotrexate with complete blood count and comprehensive metabolic panel will occur every 3 months as long as the disease continues to respond. The patient has tolerated the treatment well apart from some mild nausea.

CONCLUSION

Early and correct diagnosis of LSc in pediatric patients along with adequate treatment is critical to help reduce lasting effects of the disease. Following the recommendations, according to the consensus treatment plan, is necessary to achieve the best long-term outcomes. Because of the risk of relapse, it is important that treatment continue for at least 2 years. More research is needed to identify increased evidence-based treatment options and reduce morbidity particularly in the pediatric population. ■

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