Pediatric Morphea: A Case Report and Review of Current Treatment Options

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Abstract
Morphea, also known as localized scleroderma, is a rare, fibrosing skin disorder caused by the dysregulation of collagen production. We report a 10-year-old girl with a history of morphea since age 4, with plaques involving multiple body sites and some lesions overlying joints. Our treatment plan involved oral methotrexate and topical tacrolimus ointment, which we believe halted progression of the disease. In this report, we review current treatment options and emphasize appropriate management of morphea in the pediatric population.

Introduction
Morphea is a rare, fibrosing skin disorder with disabling potential when affecting areas overlying joints. It is very important to start treatment as early as possible, especially in the pediatric population. There are only a few randomized placebo-controlled studies analyzing the efficacy of methotrexate (MTX) in the treatment of morphea. However, therapies with the greatest evidence for efficacy include MTX and/or systemic corticosteroids. We present a case of a 10-year-old girl with a six-year history of morphea involving multiple body sites and overlying joints, treated with MTX and topical tacrolimus ointment. This report also reviews current treatment options in the management of pediatric morphea.

Case Report
A 10-year-old Hispanic female presented to our clinic with a six-year history of asymptomatic, dry, dyspigmented plaques involving multiple body sites, with marked size discrepancy between her left and right forearms and hands. Patient work-up for autoimmune disease previously completed in Puerto Rico included normal chest X-ray, electrocardiogram, echocardiogram, and retinal examination, with no evidence of systemic involvement. Laboratory findings included CBC and CMP within normal limits; positive anti-nuclear antibody (ANA), 1:1280 homogenous pattern; and positive anti-double stranded DNA (anti-dsDNA), 1:640. The patient was treated with 15 sessions of narrowband UVB (NBUVB) phototherapy, with no improvement of lesions. She was unable to continue phototherapy at the time due to insurance issues.

Reportedly, the lesions had been stable for two years prior to presentation. Clinical examination revealed firm, non-tender, atrophic white plaques with brown hyperpigmented borders affecting the left chest, mid-back, forearm, wrist and dorsal hand, and the right anterior shin and dorsal foot, with cutaneous induration of the right lower extremity evident (Figures 1a-d). The left forearm and hand were noted to be significantly smaller than the right, with tapering of digits and absence of nail-fold capillary changes (Figure 1a). On examination, the patient demonstrated normal joint mobility, full range of motion and muscle strength, and normal mouth-opening aperture. She denied Raynaud’s phenomenon, dysphagia, arthralgia, myalgia, headache, or history of seizures.

Laboratory work-up for systemic scleroderma included CBC, CMP, ANA, anti-topoisomerase I (Scl-70) antibody, anti-dsDNA antibody, anti-histone antibody, and procollagen type I intact N-terminal propeptide (PINP). Results revealed negative Scl-70 antibody (< 1.0 AI) and anti-dsDNA (2 IU/mL), while ANA was positive (1:160, homogenous pattern) and anti-histone antibody (4.2 U) and PINP (610 mcg/L) were highly elevated. Two punch biopsies were performed of lesions from the right lower extremity and left forearm. Biopsies showed findings consistent with morphea on histopathologic examination (Figure 2).

The patient was started on clobetasol 0.05% cream applied to affected areas twice daily but responded with minimal softening of lesions. Due to the potential disability involved with lesions overlying joints, we began this patient on methotrexate (MTX) 10 mg weekly with monthly lab monitoring; folic acid 1 mg daily, except on the day of MTX administration; and tacrolimus 0.03% ointment applied to affected skin daily. As of this report, the patient has had no complaints of side effects since starting MTX. Clinically,
lesions are softer to palpation and lighter in color. She continues to have full range of motion of all affected joints.

**Discussion**

Morphea is a rare, fibrosing skin disorder caused by the overproduction of collagen by fibroblasts, resulting in a thickening of the dermis, subcutaneous tissue, underlying bone, and rarely the central nervous system when present on the face and head.1,2 According to epidemiologic studies, disease incidence is estimated as 0.4 to 2.7 per 100,000 individuals, with a female-to-male ratio of 2 to 3:1 and equal prevalence in adults and children.3 A reported 90% of affected children present with morphea between 2 years and 14 years of age. Morphea is clinically differentiated from systemic scleroderma based on the absence of sclerodactyly, Raynaud’s phenomenon, telangiectasias, gastrointestinal involvement, and nail-fold capillary changes.1,2 Morphea has been associated with other connective tissue disorders, such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, juvenile dermatomyositis, polyosymyositis, and eosinophilic fasciitis, as part of an overlap syndrome.3

The morphea classification scheme is based on clinical criteria and includes five variants: circumscribed, linear, generalized, pan-sclerotic, and mixed.1,3 Linear morphea is the most common manifestation in pediatric populations, affecting 41.8% to 67% of children studied. It is characterized by linear induration involving dermis and subcutaneous tissue, which can be complicated by muscle atrophy, limb length discrepancies, and joint and bone deformity.2,4 Generalized morphea is a rare variant, occurring in 7% to 9% of morphea patients, that is typically limited to the trunk. Generalized morphea patients commonly are detected to have positive autoantibodies, particularly ANA, on autoimmune serology testing.2 Our patient fits the criteria for mixed morphea, defined as two or more variants and occurring in 15% of morphea patients, as her clinical picture is consistent with both linear and generalized morphea phenotypes.1,4

The pathogenesis of morphea is poorly understood but postulated to be multifactorial, including genetic, autoimmune, and environmental factors leading to microvascular injury, stimulating an imbalance between collagen production and degradation.2 Triggers such as mechanical trauma at lesional sites, suggesting koebernerizing phenomena or infection with Borrelia spp., particularly European strains, have been described in the literature.4,5 Morphea patients commonly have positive auto-antibodies, with a high prevalence of positive ANA titers, homogenous pattern; single-stranded antibody; anti-histone antibodies; anti-topoisomerase II alpha antibody; and rheumatoid factor.2

Excess collagen deposition is thought to be activated by vascular injury via factors previously described.3,5 In the vascular theory, endothelial injury causes a release of inflammatory cytokines and subsequent up-regulation of the expression of adhesion molecules and E-selectins. This up-regulation recruits T-cells that produce pro-fibrotic cytokines, mainly interleukin 4 (IL-4), interleukin 6 (IL-6), and transforming growth factor-beta (TGF-β), leading to increased collagen production and extracellular matrix deposition favoring a type 2 helper T-cell response. TGF-β also decreases protease production, primarily through inhibition of matrix metalloproteinases, and increases protease inhibitors, causing an imbalance of collagen production and breakdown, thus favoring fibrosis and a resultant hardening of the skin.

The diagnosis of morphea is based on clinical features. Lesions initially present as erythematous to violaceous hyperpigmented patches or plaques, which evolve to become white and sclerotic centrally with a characteristic hyperpigmented border.2 Older, non-active lesions are white sclerotic plaques that may present with post-inflammatory hyperpigmentation. Biopsy is confirmatory of cutaneous disease and should be obtained prior to initiating systemic treatment in children, if indicated. Biopsy also allows for the histopathological delineation of early versus late disease-stage process; morphea is more responsive to therapy in the early stage, while disease is active. Furthermore, biopsy can be used to differentiate morphea from other sclerotic diseases such as lichen sclerosus et atrophicus, in which systemic therapy would not be appropriate.

Morphea treatment is guided by clinical findings, which are most predictive of individual disease course and severity.1 Suggested treatment algorithms are based on morphea subtype.4 Evidence-based treatment options are limited due to morphea’s relative rarity, making it difficult to perform large, randomized controlled trials. Completed randomized controlled trials in 2006 and 2009 indicate narrowband ultraviolet B light (NB-UVB) phototherapy and topical 0.1% tacrolimus under occlusion, respectively, as safe and efficacious treatment options for morphea. Small prospective and retrospective studies also indicate calcipotriol in combination with betamethasone dipropionate, imiquimod, D-penicillamine, mycophenolate mofetil, cyclosporine, and photopheresis to be effective in treating children with morphea.6

Some children with morphea receive suboptimal therapy due to prescribing differences based on physician specialty as well as prescribing patterns that vary by age of disease onset.7 Studies indicate that general dermatologists are less likely to prescribe systemic immunosuppressives to children, while rheumatologists are more aggressive in their treatment and often prescribe systemic immunosuppressives. For best-practice disease management, general dermatologists may consider referral to a pediatric dermatologist when children present with severe morphea subtypes, particularly linear, as systemic immunosuppressive therapy is indicated.1,5 Similarly, phototherapy, which is an effective therapeutic option for morphea subtypes, is almost exclusively used by dermatologists and underutilized in other disciplines.6 Thus, morphea patients would benefit from comparative effectiveness studies and a multidisciplinary approach in developing treatment guidelines to be utilized uniformly across specialties.8

Determining the most appropriate treatment modality is complex and requires consideration of morphea subtype, disease extent and progression, and existing or potential physical deformity that can impede function. Determining phototherapy modality should also be based on these disease aspects in conjunction with study-based evidence and principles of phototherapy. Few published studies offer results reached by randomized trials or use of validated clinical score measurements, such as modified skin score (MSS) and ultrasound-measured dermal thickness.9

Phototherapy modalities utilized for morphea include psoralen UVA (PUVA), extracorporeal phototherapy, UVA-1, broadband UVA (BB-UVA), and NB-UVB. Level 1 evidence supports BB-UVA, UVA-1, and NBUVB as therapeutic options for morphea, while extracorporeal phototherapy and PUVA bath/cream are supported by level 2 evidence.7 Randomized comparison trials indicate medium dose (50 J/cm²) UVA-1 is more effective than NB-UVB in treating morphea as determined by the MSS; however, no significant difference was determined between low-dose (20 J/cm²) UVA and NBUVB.7 Studies comparing UVA-1 doses indicate variability in treatment efficacy. Thus, an optimum UVA-1 treatment dose still needs to be elucidated.7

Principles of phototherapy proven in numerous studies indicate UVA (higher wavelength) penetrates deeper into the dermis than NBUVB (lower wavelength). The concept of selecting phototherapy modality based on extent of dermal involvement and depth of wavelength penetration has been previously demonstrated in psoriasis and cutaneous T-cell lymphoma studies.10,11 Thus, by similarly applying this principle, morphea extending to deeper cutaneous tissue would respond best to BB-UVA/UVA-1 as opposed to NBUVB, which is more appropriate for treating early, superficial lesions. The average length of phototherapy treatment by which disease improvement can be appreciated is between 10 weeks and 20 weeks. A clear benefit of phototherapy is the ability to effectively treat individuals with widespread disease. However, patients with morphea extending into the subcutaneous tissue, fascia, or muscle are

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Figure 2. Biopsy taken from left forearm revealing perivascular and interstitial lymphocytic infiltrate in the reticular dermis with thickening and hyalinization of collagen bundles.
not good candidates for phototherapy and require systemic therapy.

Systemic therapy with agents like MTX, mycophenolate mofetil, D-penicillamine, and cyclosporine should be highly considered in children with progressive or extensive cutaneous disease with lesions affecting the face or overlying joints, increasing the risk of developing both physical deformity and functional impairment. Children with severe morphea subtypes or children who exhibit progressive disease and have failed topical or phototherapy treatments would benefit from referral to a pediatric dermatologist for systemic management. D-penicillamine in combination with systemic corticosteroids was once considered the treatment of choice for severe morphea variants such as linear or generalized morphea in the pediatric population. Since 2000, systemic therapy with MTX in combination with systemic corticosteroids has become the first-line therapeutic option. In a retrospective study of 136 pediatric patients with morphea, MTX was prescribed to 39 patients at an initial dosage of 0.3 mg/kg/wk to 0.5 mg/kg/wk with folic acid 1 mg/d except on the day of MTX administration. MTX improved lesions in all patients except for one patient with morphea profunda and three patients with progressive hemifacial atrophy. Adverse effects of MTX were limited to gastrointestinal discomfort in five patients and increased hepatic transaminase in one patient.

Zulian et al. studied the long-term therapeutic role of MTX. The prospective study followed children with linear, generalized, and mixed morphea subtypes previously enrolled in a double-blind, randomized controlled trial. Patients were treated with oral MTX (15 mg/m²/wk) for at least 12 months and prednisone (1 mg/kg/d, with maximum dose of 50 mg) as a single morning dose for three months with gradual taper over one month compared to oral prednisone alone. The study also assessed clinical remission and complete remission as defined by therapeutic response maintained while on medication for at least six months and response maintained after stopping medication for at least six months, respectively. A cohort of 65 patients included 31 patients who responded to MTX at 12-month follow-up, 15 patients on MTX who relapsed but responded to a short course of oral prednisone in a previous double-blind study, and 19 patients assigned to placebo (oral prednisone alone) who relapsed but subsequently were started on MTX in an open-label study. Of the 65 enrolled patients, seven were lost to follow-up, while 48 (82.8%) responded to MTX; of those responders, 35 (72.9%) achieved complete clinical remission for 25.6 or more months after a mean of 27.5 months of MTX treatment. Zulian et al. determined oral MTX with concurrent prednisone administered in the first three months to be efficacious in treating children suffering from severe morphea. Furthermore, systemic treatment should be initiated early in disease onset, especially in linear, generalized, pansclerotic, and mixed morphea subtypes. Additionally, MTX treatment for at least 24 months is recommended, as longer treatment duration may reduce the occurrence of relapse and incidence of disease flare following MTX tapering, a finding consistent with literature from Christen-Zaech et al.

According to a 2013 article by Bielsa, psoralen UVA or NBUVB should be initiated in patients with generalized morphea without joint contractures, and if unresponsive following 40 sessions or eight weeks of phototherapy treatment, MTX combined with systemic corticosteroids can be administered. Patients with extensive cutaneous involvement, facial lesions, or lesions overlying joints should initially be treated with MTX combined with systemic corticosteroids, and patients who do not respond should then be started on mycophenolate mofetil. If still not responsive, phototherapy may be initiated. Patients with limited cutaneous involvement can be treated topically with tacrolimus, calcipotriene in combination with betamethasone dipropionate, or imiquimod.

Conclusion
Few randomized placebo-controlled studies assessing the efficacy of MTX in morphea have been performed. However, therapies with the greatest evidence for efficacy include MTX and/or systemic corticosteroids, which are highly indicated for the treatment of progressive or linear, generalized, and mixed morphea subtypes in the pediatric population. Numerous retrospective studies indicate favorable response to MTX, with children exhibiting disease stabilization and often visible and palpable clinical improvement of skin lesions with minor adverse effects. Studies also support long-term maintenance MTX treatment for at least 24 months in children to best achieve prolonged and sustained disease remission.

A multidisciplinary approach in performing comparative effectiveness studies is necessary to better develop morphea treatment guidelines and prevent morphea patients from receiving suboptimal therapy due to prescribing differences amongst specialists.

References