Scleroderma: Nomenclature, etiology, pathogenesis, prognosis, and treatments: Facts and controversies

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Abstract *Scleroderma* refers to a heterogeneous group of autoimmune fibrosing disorders. The nomenclature of scleroderma has changed dramatically in recent years, with morphea (localized scleroderma), limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, and systemic sclerosis sine scleroderma encompassing the currently accepted disease subtypes. Major advances have been made in the molecular studies of morphea and systemic sclerosis; however, their etiologies and pathogenesis remain incompletely understood. Although morphea and systemic sclerosis demonstrate activation of similar inflammatory and fibrotic pathways, important differences in signaling pathways and gene signatures indicate they are likely biologically distinct processes. Morphea can cause significant morbidity but does not affect mortality, whereas systemic sclerosis has the highest disease-specific mortality of all autoimmune connective tissue diseases. Treatment recommendations for morphea and systemic sclerosis are based on limited data and largely expert opinions. Current collaborative efforts in morphea and systemic sclerosis research will hopefully lead to better understanding of the etiology and pathogenesis of these rare and varied diseases and improved treatment options.
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What is in a name?

Scleroderma is a disease label fraught with misunderstandings. In recent years, the nomenclature of scleroderma has been replaced by more precise terminology, characterizing disease subsets defined by clinical findings, serologic data, and prognosis. The subsets include localized scleroderma (ie, morphea), limited cutaneous systemic sclerosis (LcSSc; previously referred to as CREST syndrome), diffuse cutaneous systemic sclerosis (DcSSc), and systemic sclerosis sine scleroderma. Experts in the field of adult localized scleroderma prefer to refer to this clinical entity as morphea, to decrease miscommunication with patients and referring physicians (patients and doctors alike hear *scleroderma* and assume the diagnosis is systemic sclerosis, which leads to unnecessary stress). In general, experts in the field of pediatric localized scleroderma prefer to keep the scleroderma moniker to stress the morbidity associated with the linear variants of this disease in their patient population.

Patients with LcSSc and DcSSc almost universally will have positive antinuclear antibodies (ANA), Raynaud's phenomenon, and nailfold capillary changes.[1,2] Patients with LcSSc develop sclerosis of the skin distal to their elbows and knees and have facial involvement. Patients with DcSSc develop proximal, in addition to distal, sclerosis. Patients with LcSSc are more likely to have anti-centromere antibodies, whereas patients with DcSSc are more likely to have anti-topoisomerase I (anti-Scl70) or anti-RNA polymerase III antibodies.[1,2] Patients with LcSSc and DcSSc are

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approximately equally likely to develop interstitial lung disease (ILD), but patients with LcSSc are at higher risk for fibrosis of their pulmonary artery leading to pulmonary artery hypertension (PAH).[1,2] Patients with DcSSc are at higher risk for renal crisis than their LcSSc counterparts.[1,2]

Morphea is a diverse disease as well, with distinct clinical presentations: circumscribed morphea (with superficial and deep variants), linear morphea (with trunk/limb variant and head variant), generalized morphea, pansclerotic morphea, and mixed morphea.[3] Linear morphea is more likely to affect children and involve underlying structures including soft tissue, bone, and when on the head and neck, the central nervous system.[3] Patients with generalized morphea are more likely to have positive autoantibodies and systemic symptoms including myalgia, arthralgia, and fatigue.[3–6] To date, no studies have assessed the differences in the pathophysiology of morphea subtypes.

Etiology and pathogenesis: Are morphea and systemic sclerosis the same disease on one continuous spectrum, or separate diseases?

The etiologies and pathogenesis of morphea and systemic sclerosis are incompletely understood at this time. A combination of factors is postulated to be involved. It is currently thought that patients who develop morphea or systemic sclerosis have an underlying genetic predisposition to these conditions, and then are exposed to an environmental factor that initiates the inflammatory and fibrotic cascades. To date, no studies on specific genetic alterations have been performed in morphea; however, patients with morphea have higher rates of autoimmune diseases in their families than expected in the general population.[3,5,7] Several large genome-wide association studies have been performed in patients with systemic sclerosis revealing association of systemic sclerosis with multiple genetic loci including HLA class II gene region, *IRF5, CD247, BANK1, STAT4, TNFSF4,* and *BLK* genes.[8] For a comprehensive review of these studies, please see Romano et al.[8]

In morphea, several environmental factors have been postulated to be part of the etiology, including Lyme disease, trauma, radiation, medications, and viral infections.[9] Of these, radiation-induced morphea is most frequently described. Morphea occurs commonly on the chest wall after radiation treatment for breast cancer, with an estimated incidence of 1 in 500 patients.[9–11] The role of radiation in the induction of morphea is not completely understood. It has been postulated that radiation selects for activated fibroblasts, or induces an isomorphic response due to tissue trauma, or may increase the risk for presentation of self-antigens. In systemic sclerosis, postulated environmental factors include exposure to vinyl chloride, silica dust and organic solvents, medications (bleomycin, pentazocine, cocaine), and viruses (cytomegalovirus, parvovirus B19).[2,9]

The combination of genetics and a second environmental "hit" is thought to cause endothelial cell injury, resulting in up-regulation of cellular adhesion molecules (VCAM, ICAM, E-selectin) and chemokines (CCL2,5,7,17,22,27, CXCL8).[12,13] The cellular adhesion molecules and chemokines recruit inflammatory mononuclear cells, of which most are T-helper (Th) cells. The Th cells (Th1, Th2, and Th17) produce interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, IL-12, IL-13, IL-17, tumor necrosis factor (TNF)-α, interferon (IFN)-α and IFn-γ.[2,14,15] Production of these cytokines results in inflammation, and recruitment and activation of fibroblasts and myofibroblasts, resulting in fibrosis.[12,16,17] Kurzinski et al. postulate that the initial inflammatory phase is mediated by Th1 and Th17 cells and their associated cytokine profiles, with a shift in predominant cell phenotype to Th2 cells later in disease course, which results in sclerosis.[14]

Despite several shared pathogenic features, clinically morphea and systemic sclerosis are radically different diseases. The explanation for this distinct clinical disparity despite similar molecular pathogenic pathways remains unsolved. The following are pathogenic disparities between morphea and systemic sclerosis.

In a single study comparing subjects with morphea and systemic sclerosis, subjects with morphea were found to have higher levels of IL-2 and IL-6.[18] In an additional study comparing the effect of peripheral blood mononuclear cells (PBMC) from subjects with morphea and systemic sclerosis on cultured fibroblasts, the PBMCs from subjects with systemic sclerosis caused a decrease in matrix metalloproteinase-1 (a collagenase) and an increase in platelet-derived growth factor AA and BB, TNF-α, IL-13, and epidermal growth factor compared with those subjects with morphea.[19]

Autoantibody production is also disparate in morphea and systemic sclerosis. Greater than 95% of patients with systemic sclerosis will have a positive ANA,[2,20–22] whereas prevalences of ANA positivity in patients with morphea range from 20% to 80.[3–5,23–25] Anti-centromere antibodies, anti-topoisomerase I antibodies, and anti-RNA polymerase III antibodies are found almost exclusively in patients with systemic sclerosis.[2,224] In contrast, patients with morphea are more likely to have anti-single–stranded antibodies, anti-histone antibodies, and anti-topoisomerase II-α antibodies than patients with systemic sclerosis.[24]

Further data supporting the distinction between morphea and systemic sclerosis can be found in gene array studies. Recent data have revealed differences in gene signatures between patients with morphea, LcSSc, DcSSc, and healthy controls.[26] Gene array analysis revealed evidence for four separate gene signatures, subcategorized as inflammatory, proliferative/diffuse, limited, and normal-like.[26] These distinct gene signatures reveal that although all patients with morphea and systemic sclerosis present with increased collagen deposition, they are distinct diseases.

Finally, only nine patients who presented with morphea and later developed systemic sclerosis have been reported in the literature.[27–29] Examination for sclerodactyly, Raynaud's

phenomenon, and nailfold capillary changes at presentation is not thoroughly documented in all nine cases, raising the possibility that at least some of these cases were incorrectly diagnosed with morphea at presentation. Large cohorts of patients with morphea have reported no transitions to systemic sclerosis,[3,30] further supporting that morphea and systemic sclerosis are distinct diseases.

Prognosis

Morphea does not increase mortality; however, it is associated with significant morbidity. Linear morphea, which is most common in children, can cause significant disfigurement. Linear morphea can also involve the underlying bone and growth plates, resulting in permanent limb-length discrepancy. Children who present with morphea on the head and neck are at increased risk for neurologic and ocular involvement.[31,32] In a large multicenter cross-sectional evaluation of 750 children with morphea, approximately 4% had neurologic disease manifestations (defined as seizures, headaches, peripheral neuropathy, vascular malformations, behavioral changes, neuroimaging abnormalities, electroencephalogram alterations, and central nervous system vasculitis).[31] Of the children labeled as having neurologic involvement, 88% had linear morphea and involvement was almost exclusively on the head and neck.[31] Of the 750 children, 3.2% developed significant ocular involvement (defined as sclerosis of adnexal structures, anterior segment inflammation, and anterior uveitis).[33] When only children with head and neck morphea were evaluated, approximately 14.2% had significant ocular involvement.[33] Anterior segment inflammation and anterior uveitis may be asymptomatic, and if left untreated, can result in irreversible vision loss. Therefore, it is recommended that children with morphea on the head and neck see an ophthalmologist every 3 to 4 months for 3 years after development of morphea.[33] Rarely (<1%) children developed pulmonary, cardiac, or renal involvement.[31] Data on adult morphea patient comorbidities is sparse. Adults with morphea have been reported to have an increased risk for concomitant autoimmune disorders. Both children and adults with morphea have higher levels of depression and anxiety than healthy, age-matched controls.[34,35]

Systemic sclerosis has the highest disease-related mortality of all autoimmune connective tissue diseases with a standard mortality ratio of 3.5, a median survival time after diagnosis of 11 years, and an absolute survival at 5 years of 77.9%.[36,37] Cardiopulmonary involvement (ie, ILD and PAH) accounts for the majority of the increased mortality in systemic sclerosis.[36,37] The median survival after diagnosis of PAH in the setting of systemic sclerosis is 2 years.[38,39] The median survival after diagnosis of ILD in the setting of systemic sclerosis is less than 5 years.[38] Mortality associated with renal crisis has decreased with the

advent of angiotensin-converting enzyme inhibitors.[40] Early intervention in ILD and PAH is thought to improve patient outcomes, and therefore patients with systemic sclerosis should have annual screening for these complications.[41–43]

Treatment

Treatment algorithms for systemic sclerosis and morphea are limited by the rarity of the diseases (which makes conducting trials with enough power to detect differences difficult), the difficulty in assessing disease improvement (validated outcome measures are lacking, which makes conducting therapeutic trials difficult) and the lack of universally used outcome measures (which makes conducting meta-analysis of trials impossible).

In systemic sclerosis, treatment is based on disease comorbidities. It is the responsibility of physicians caring for patients with systemic sclerosis to ensure they are being screened for ILD and PAH annually. Early detection and early treatment of these comorbidities decreases mortality[42] and patients with systemic sclerosis are not always routinely screened for these complications by other physicians caring for them.[44] Although treatment of ILD and PAH should happen under the care of a pulmonologist, as an integral member of their health care team, dermatologists should be involved in the screening for these comorbidities. Treatment of ILD and PAH is beyond the scope of this contribution; however, several reviews of treatment options have been recently published.[45–48]

Patients with LcSSc and DcSSc suffer from Raynaud's phenomonen with high frequencies. First-line therapy for Raynaud's phenomenon is dihydropyridine-type calcium channel blockers, usually nifedipine at doses of up to 20 mg four times daily.[45–48] For patients who develop digital ulcerations in the setting of Raynaud's phenomenon, the addition of bosentan (62.5 mg twice daily for 4 weeks, then 125 mg twice daily), or sildenafil (25 mg up to three times daily), or intravenous iloprost is recommended.[45–48]

Management of progressive skin involvement is dependent on additional comorbidities. In patients with concomitant myositis, arthritis, or overlap syndromes, methotrexate or azathioprine are recommended.[46–48] Patients with concomitant ILD should receive ILD-focused therapy, which is generally cyclophosphamide.[46–48] In patients with skin involvement only, mycophenolate mofetil or methotrexate are recommended.[45–48]

To date, there are no studies comparing subtypes of morphea and their response to treatments. Based on expert opinion, treatment of morphea should be based on disease subtype, area of involvement, activity of disease, and patient symptoms.[49–51] It is important to differentiate active morphea from burnt-out morphea. Active morphea (lesions with erythema, new lesions, expanding lesions) can be treated with topical or systemic immunosuppressives. Burnt-

out morphea, or morphea in the damage stage, is not treatable with immunosuppression.

Limited superficial plaque morphea is best treated with topical therapy or local phototherapy.[49,50] Treatment with twice-daily topical tacrolimus is supported by a randomized placebo-controlled trial.[52] Additional topical therapies that have shown benefit in prospective studies include topical imiquimod applied three to five times per week,[53,54] combination calcipotriol and betamethasone dipropionate applied once to twice daily,[55] and calcipotriene applied and occluded twice daily.[56] Topical steroids, anecdotally the most commonly used therapy for plaque morphea, may be effective, but to date there are no data supporting their efficacy as a solitary agent.

Phototherapy studies report improvement with narrow-band ultraviolet B (nb-uvb), UVA, low- and medium-dose UVA1, and PUVA.[57–70]

Deep plaque morphea may require local phototherapy (nb-uvb, UVA, low- and medium-dose UVA1, or psoralen plus UVA [PUVA]) or systemic immunosuppression.[50] If systemic immunosuppression is required, treatment with methotrexate in combination with a prednisone taper is supported by the strongest data.[71–74] In adults with morphea there is data showing improvement with methotrexate alone.[75]

Linear morphea of the extremities, as well as the head and neck, should be treated aggressively, particularly in children given the significant morbidity associated with untreated disease. Based on data from a randomized placebo-controlled trial, prospective case series, and expert opinion, linear morphea should be treated with methotrexate and a taper of systemic corticosteroids.[49–51,71–74] In some instances, linear morphea is a superficial process that does not involve the underlying tissues. In these cases, topical therapies noted above or phototherapy are appropriate treatment options.

Generalized morphea, due to the large surface area involved, is not usually amenable to topical therapy. Generalized morphea may present as superficial or deep subtypes. Patients with generalized morphea who are not at risk for joint contractures, can initially be treated with phototherapy (nb-uvb, UVA, low-and medium-dose UVA1, or PUVA). In patients who fail 2 to 3 months of phototherapy, or in patients who cannot attend phototherapy, methotrexate with or without a systemic corticosteroid taper is recommended.[49,50]

Patients with morphea who fail methotrexate or have contraindications to methotrexate may undergo a trial of mycophenolate mofetil.[49,51] Although the evidence for using mycophenolate mofetil in the treatment of morphea is weak,[76] it has a more favorable side-effect profile than other systemic immunosuppressives supported by similarly weak data (cyclosporine, imitinib, D-penacilliamine, cyclosphosphamide, TNF-α inhibitors, or extracorporal photopheresis).[77–83] Mycophenolate mofetil has been shown to have antifibrotic properties in both *in vitro* and *in vivo* studies,[84–90] and open-label trials have revealed statistically significant improvement in skin scores in subjects with diffuse systemic sclerosis and improvement in retroperitoneal fibrosis.[87,90] Mycophenolate mofetil also has been agreed on as a second-line agent to methotrexate by the Childhood Arthritis and Rheumatology Research Alliance Localized Scleroderma Workgroup.[51]

Conclusions

The term *scleroderma* has been replaced with morphea (which is further subdivided into circumscribed, linear, generalized, pansclerotic, and mixed subtypes), LcSSc, DcSSc, and systemic sclerosis sine scleroderma. Although all four conditions demonstrate activation of similar inflammatory and fibrotic pathways in their etiopathogenesis, important differences in signaling pathways and gene signatures indicate they are likely biologically distinct processes. Linear and generalized morphea can cause significant morbidity, but do not affect mortality. Systemic sclerosis has the highest disease-specific mortality of all autoimmune connective tissue diseases, the majority of which is due to cardiopulmonary involvement. Additional studies are required to determine the best treatments for systemic sclerosis and the different variants of morphea.

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