Morphea: progress to date and the road ahead

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Abstract: Morphea is a rare autoimmune condition causing inflammation and sclerosis of the skin and underlying soft tissue. It is characterized by periods of activity (inflammation admixed with fibrosis), ultimately resulting in permanent damage (pigment change and tissue loss). Damage resulting from unchecked activity can lead to devastating, permanent cosmetic and functional sequelae including hair loss; cutaneous, soft tissue and bony atrophy; joint contractures; and growth restriction of the affected body site in children. This makes the early identification of activity and initiation of appropriate treatment crucial to limiting damage in morphea. To this end, recent investigative work has focused on validation of clinical, biomarker, imaging, and histologic outcomes aimed at accurately quantifying activity and damage. Despite promising results, further work is needed to better validate these measures before they can be used in the clinic and research settings. Although there has been recent approval of less toxic, targeted therapies for many inflammatory skin conditions, none have been systematically investigated in morphea. The mainstays of treatment for active morphea are corticosteroids and methotrexate. These are often limited by substantial toxicity. The paucity of new treatments for morphea is the result of a lack of studies examining its pathogenesis, with many reviews extrapolating from research in systemic sclerosis. Recent studies have demonstrated the role of dysregulated immune and fibrotic pathways in the pathogenesis of morphea, particularly interferon (IFN) gamma related pathways. Active morphea lesions have been found to display an inflammatory morphea signature with CXCR3 receptor ligands, as well as a distinct fibrotic signature reflecting fibroblast activation and collagen production. CXCL9 and 10 have been associated with increased measures of disease activity. While immune dysfunction is thought to play the primary role in morphea pathogenesis, there are other factors that may also contribute, including genetic predisposition, environmental factors, and vascular dysregulation. There remains an essential need for further research to elucidate the pathogenesis of morphea and the mode of action of dysregulated upstream and downstream immune and fibrotic pathways. These studies will allow for the discovery of novel biomarkers and targets for therapeutic development.

Keywords: Localized scleroderma; morphea; pathogenesis; evaluation; treatment

Introduction

Morphea, also known as localized scleroderma, is in an autoimmune disorder characterized by inflammation and sclerosis of the skin and underlying soft tissues. The estimated incidence of the disease is 0.4 to 2.7 per 100,000 people, although population based studies are lacking (1,2). Morphea affects adults and children equally, with females more susceptible to the disease than males (1,3-5). Morphea is a distinct from systemic sclerosis, or scleroderma, another autoimmune connective tissue disorder, in that it has unique demographic and clinical features and lacks the
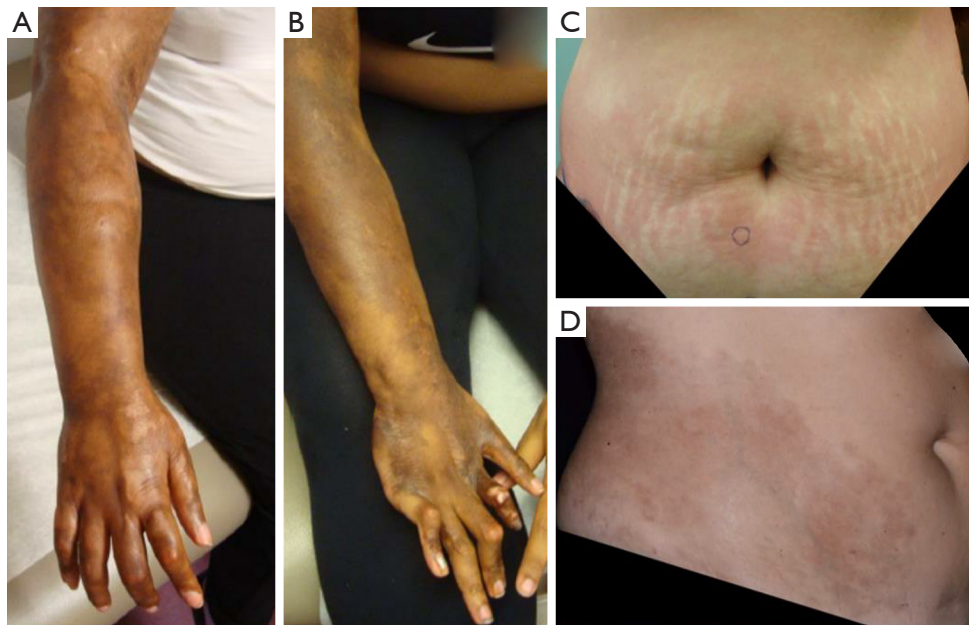
Figure 1 Morphea is characterized by periods of activity (A,C) and damage (B,D). (A) Right arm affected with significant inflammation, evidenced in swelling of digits and forearm. (B) Damage from morphea including joint contractures and hyperpigmented sclerotic plaques. (C) Active, inflammatory plaque on abdomen with striae. (D) Morphea damage with hyperpigmented, sclerotic plaques, atrophy.

autoantibodies specific to systemic sclerosis, despite having similar histology (6,7). Extracutaneous manifestations of morphea are uncommon, and include neurological and musculoskeletal findings distinct from those found in systemic sclerosis (3).

Morphea is characterized by relapsing and remitting periods of activity, marked by inflammation and fibrosis, and damage which produces atrophy. Unchecked disease activity in morphea can lead to permanent deformity and functional impairment, and thus early diagnosis and treatment are imperative to minimize damage (8). Several subtypes of morphea exist, each with different clinical manifestations and degree of involvement of the subcutaneous soft tissues (6,8). The pathogenesis of morphea is incompletely understood and is an evolving area of research. Studies suggest a multifactorial etiology involving dysregulated immune and fibrotic pathways, with additional contributing factors including genetic predisposition, traumatic or environmental factors, and vascular dysregulation (6,9,10).

After many years of neglect, substantial progress has been made in morphea research. The purpose of this review is to summarize new developments in understanding the clinical manifestations of morphea and their evaluation as well as management. We will also discuss the current understanding of the pathogenesis of morphea. Despite these promising

developments, further work is needed to better define clinical subtypes, extracutaneous manifestations, outcome measures and pathogenesis in order to better evaluate and treat patients with morphea.

Clinical manifestations of morphea

Morphea activity versus damage

Morphea is defined by periods of activity (inflammation and fibrosis) which leads to damage and atrophy. Activity in morphea is characterized histologically by an inflammatory dermal and subcutaneous lymphocytic infiltrate manifesting clinically as erythema, edema, and lesion extension, with patients reporting symptoms such as pain and pruritis (11). The fibrotic phase often initially overlaps with inflammation and is characterized by dense collagen deposition with admixed inflammatory cells manifesting as hardened yellow to white plaques with an erythematous or violaceous border. These mixed inflammatory and sclerotic lesions ultimately transition into an inactive phase characterized by resolution of inflammation with sclerosis progressing to atrophy of the dermis and sometimes underlying soft tissue. *Figure 1* demonstrates typical appearance of both active and inactive lesions. The pathological changes of morphea may affect

the dermis, subcutis, soft tissue, and sometimes bone. Fibrosis and resultant atrophy of the dermis, soft tissue, and bone can cause significant deformity and functional impairment, such as contractures, limb length discrepancy, or limitations in range of motion (8). Current standard of care therapies for morphea are immunosuppressive agents that aim to shut down disease activity, and thus early and accurate assessment of activity is crucial in preventing permanent cosmetic and functional sequelae.

Subtypes

Currently, a number of classification systems for morphea subtypes are in use. The first criteria created to classify morphea was the Mayo Clinic Criteria, published by Peterson *et al*. in 1995, which classified morphea into five subtypes: plaque, generalized, bullous, linear, and deep (12). In 2006, Zulian and Laxer published the Padua criteria, which outlined five different subtypes: circumscribed, generalized, linear, pansclerotic, and mixed, which does not include bullous morphea and deep morphea. The Padua criteria however does note that deep involvement can occur with circumscribed lesions (13). In 2017, the European Dermatology Forum proposed a classification system with five subtypes—limited which includes plaque, guttate, and superficial morphea, generalized type which includes generalized and pansclerotic subtypes, linear, deep, and mixed (2). Limitations exist within each classification system. First, authors of the classifications specialize either in adult or pediatric medicine and therefore do not see morphea patients across the lifespan. Second, the criteria were created primarily by either dermatologists or rheumatologists, who may have differing perspectives and experiences of morphea. This limits the ability to fully categorize morphea subtypes that may occur outside the authors area of expertise, particularly when it comes to extracutaneous manifestations or subtypes that occur more commonly in one demographic group. Also of concern, the existing classification criteria are the result of expert opinion, but were not prospectively examined using an unbiased analysis of demographic or clinical features of a large group of adults and children with morphea, making it difficult to determine how well these classification systems perform in defining demographically and clinically consistent subsets of morphea patients. The presence of different classification systems for morphea, each of which are actively in use, has produced ambiguity among clinicians and researchers in the definition and categorization of

subtypes, presenting a substantial barrier to multisite studies that are crucial in a rare disease like morphea. This also leads to confusion among clinicians who then are unable to accurately assess their patients.

Of all the different classification schemes, the Padua criteria likely performs the best at successfully capturing the most relevant disease subsets in morphea. In a recent large prospective cohort study of adult and pediatric-onset morphea patients, the Padua criteria correctly categorized 95% of patients (900/944), in comparison to other classification schemes which only correctly categorized 51–54% of patients (14). Furthermore, the groups created using the Padua criteria were found to have cohesive clinical and demographic features. However, there remain some ambiguities in the Padua criteria, such as how patients with multiple linear lesions who also meet criteria for generalized disease should be categorized, when patients with multiple linear lesions have been shown to be a distinct group with consistent demographic and clinical characteristics (15,16). Additionally, findings like deep involvement occur across linear, generalized, and circumscribed lesions and may be better considered a descriptor and not a separate subtype.

In order to increase the likelihood of uptake across different specialties and centers, refinement of the existing classification systems should be undertaken with a multidisciplinary group of relevant stakeholders using a consensus based process and ultimately validated by assessing performance in a heterogeneous group of morphea patients. It is vital that like patients are categorized consistently in terms of determining associated disease outcomes for both patient care as well as for multi-site collaborations for both observational and interventional studies.

Extracutaneous manifestations

Once believed to be exclusively a skin disorder, newer studies show that morphea is associated with extracutaneous manifestations distinct from those in systemic sclerosis (17-22). These include mucocutaneous, neurological, musculoskeletal, and ophthalmologic involvement (8).

Mucocutaneous findings in morphea are seen in the form of genital and oral lesions. Genital lesions in morphea occur predominantly in post-menopausal women, and are associated with more superficial dermal morphea and accompanying extragenital lichen sclerosus lesions (23). Studies have shown that genital lichen sclerosus et atrophicus (LsA) and morphea lesions in extragenital sites

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may co-exist, thus supporting examination of genitalia in those with morphea and the extra genital skin in those with LsA, particularly in post menopausal women (24). Oral involvement has been reported mainly through case reports and case series in the context of facial linear morphea lesions, and can include abnormalities of dentition, loss of oral structures, functional impairments from sclerosis of tissue (i.e., decreased oral aperture), as well as arthritis and mechanical dysfunction with TMJ pain (25-31). Oral lesions tend to directly underlie the cutaneous and soft tissue morphea lesions, and often show abrupt demarcation at the midline similar to cutaneous lesions (25,27,30,32,33). In general, there is a dearth of large, systematic studies on the frequency and type of oral and genital involvement across morphea subtypes, and further work is required in order to better characterize mucocutaneous findings in morphea (24).

Neurologic involvement in morphea can take the form of various manifestations such as migraines, seizures, focal neurologic deficits, and movement disorders (34). Literature regarding neurologic findings in morphea is also primarily in the form of case reports and case series (20,34). Some reviews and reports suggest a role for neuroimaging in these patients, as MRI and CT which can demonstrate findings such as subcortical calcifications and brain atrophy associated with cutaneous lesions of morphea involving the head (35). However, the significance of these findings is uncertain as some patients present with severe symptoms and deficits with no changes on imaging, and some patients with imaging findings do not have significant neuroimaging findings (19,20,34). Additionally, there is uncertainly regarding whether these lesions respond to immunosuppressive agents or are better treated by directly targeting neurological symptoms, particularly in the absence of any sign of central nervous system (CNS) inflammation on evaluation. Thus, there remains a need for further study in this area.

Patients with localizing neurologic clinical manifestations such as hemiplegia or visual field deficits would benefit from prompt multidisciplinary evaluation with consideration of neuroimaging to rule out emergencies such as CNS or optic vasculitis (8). Current literature suggests that the severity of cutaneous morphea may not correlate with severity of nervous system involvement, i.e., there are cases of patients with subtle skin findings but striking MRI findings and severe neurologic manifestations (19,35-38).

Musculoskeletal manifestations of morphea can arise when the disease affects not only the skin but also underlying structures such as fascia, muscle, and even joints

and bone (13). When this occurs, morphea can be associated with severe pain, flexion contractures, and functional impairment due to decreased range of motion (39). Deep morphea lesions often have very subtle surface changes, and palpation can be more important than visual inspection to appreciate the extent of these lesions. It also may be difficult to fully evaluate activity in these deeper lesions, and given that unchecked morphea activity can lead to permanent functional sequelae, patients with these deeper manifestations of morphea may benefit from MRI to determine disease activity and damage (40,41). Although involvement of joints and areas underlying areas of morphea is the most common presentation, patients may also experience sacroiliitis, generalized synovitis, and inflammatory arthritis. Although musculoskeletal involvement has been more extensively reported in children with linear morphea, limitation of range of motion has also been reported in adults with generalized symmetric morphea. Little is known however about the association with findings like arthritis and the activity of the cutaneous lesions or their optimal treatment, while soft tissue involvement appears to be associated with deep cutaneous lesions and is linked with activity of the cutaneous disease (16). Thus it is important for patients with morphea, particularly with linear subtype or deep cutaneous involvement, to undergo a thorough examination of the musculoskeletal system and prompt evaluation by rheumatology, orthopedics, or physical medicine and rehabilitation as needed (8).

Ophthalmologic involvement of morphea is rare, and is generally associated with linear morphea involving the head. Literature regarding this is primarily in the form of case reports and a large international case series, which describe features such as diplopia related to involvement of periocular muscles and/or inflammatory changes such as uveitis and episcleritis (42). CNS involvement leading to ophthalmologic change has also been reported (43). Patients reporting visual changes or even patients with morphea lesions in close proximity to the periorbital region should be promptly referred to an ophthalmologist for evaluation (8).

Overall, the extracutaneous manifestations of morphea have not yet been systematically studied. Thus, their frequency among patients with morphea and their relationship to the activity of skin disease are not well known, and little is known about the response of extracutaneous manifestations to morphea treatment. This is an important evolving field of research in morphea, and there is a need for larger studies describing the frequency,

clinical findings, and association with morphea activity in the skin.

Diagnosis and treatment

The diagnosis of morphea can typically be made based on clinical findings, however biopsy of the lesions and imaging can help confirm the diagnosis or exclude other diagnoses. Treatment of morphea depends on clinical activity, depth of lesion involvement, and extent of disease, and primarily centers around limiting disease activity (8,44). Active lesions that are isolated to a limited surface area can be treated by topical or intralesional steroids, as well as calcineurin inhibitors such as tacrolimus. For patients with more generalized dermal involvement or rapidly developing new lesions, ultraviolet (UV) phototherapy can also be used.

Systemic therapy in morphea is indicated for those with moderate-severe disease, large body surface area involvement, deep involvement, or for lesions that may impact function/ cosmesis (facial lesions). The most widely investigated systemic therapies include combinations of methotrexate and corticosteroids. Mycophenolate mofetil is an emerging alternative to methotrexate for those who cannot tolerate or have contraindications to methotrexate (45). These medications maybe limited by lack of tolerance or toxicity in many patients, underscoring the need for less toxic therapy (46-52). Other systemic therapies used for morphea include bosentan, infliximab, tofacitinib, and abatacept (53). While these treatments show promise, current data is insufficient to confirm efficacy of routine use, and further study is necessary.

There are a wide variety of systemic therapies other than methotrexate, systemic glucocorticoids, and mycophenolate used for active morphea. Examples of these new and emerging treatments include bosentan, infliximab, tofacitinib, and abatacept (53). While these treatments show promise, current data is insufficient to confirm efficacy of routine use, and further study is necessary.

Another treatment for morphea is ultraviolet (UV) phototherapy, used for a variety of sclerosing and inflammatory conditions of the skin (54). Phototherapy options include Ultraviolet A1 (UVA1) and narrowband UVB (NBUVB). While both can be used for treatment of morphea, UVA1 is preferred when available as there is more evidence supporting its efficacy in morphea (54). Patients with extensive dermal morphea are good candidates for this treatment, as they have a large amount of body surface area involved, making topical therapy alone impractical.

In these cases, topical therapies can be used as an adjunct, with systemic immunosuppressive therapy held in reserve in case they cannot tolerate phototherapy. The relatively favorable side effect profile of phototherapy gives it an advantage over systemic immunosuppressants and thus is the preferred agent in these patients (54). Other procedures that have been reported to be effective in the treatment of some morphea patients include photodynamic therapy and pulsed dye laser therapy for sclerotic lesions, intralesional hyaluronidase injections for morphea-induced microstomia, and extracorporeal photochemotherapy for severe, generalized disease (31,54-60). Further research into these agents and procedures is warranted in order to more clearly define efficacy and indications for use before they should be used as first line agents.

Damage that results after active lesions progress to an inactive state include atrophy, pigment changes and functional impairment. Damage tends to remain stable or increase after successful management of active disease (61). Once lesions are clinically inactive, treatment centers around improving quality of life by addressing cosmetic and functional concerns. Sclerosis and atrophy due to morphea can lead to limb-length discrepancies, contractures, and limited range of motion. It is important to refer these patients to physical therapy, occupational therapy or specialties such as rheumatology or orthopedics early in order to reduce disability. In addition to functional impairment patients also suffer from cosmetic damage. Dermal fillers and surgical procedures, such as fat transfer, can help restore contour to lesions with significant atrophy. Recent studies have shown the utility of adipose tissue as filler for its ability to regenerate soft tissues and remodeling capacity provided by its unique cytokine and growth factor profiles (62). Despite these promising results, there is no evidence that fat transfer replaces the use of immunosuppressives in active facial morphea lesions. Therefore, fat transfer should only be used once active disease is demonstrably controlled with immunosuppressives or quiescent off therapy to avoid recurring tissue loss. Taken as a whole, treatment efficacy and benefit on life quality of interventions to mitigate damage are very poorly studied in morphea.

Refining outcome measures in morphea

Given that the clinical manifestations of morphea are dependent on subtype, depth of involvement and phase of progression of the lesions, an accurate understanding of the

entire disease picture is essential. Correctly identifying and quantifying disease activity and damage in different subtypes of morphea is key not only to appropriate management but also to conduct well designed studies. Thus, recent work has focused on validation of clinical, biomarker, and imaging outcomes aimed at accurately quantifying activity and damage. Validation and acceptance of these measures are important for future large, multisite clinical trials in morphea, which will be necessary given the rarity of the disease and will ultimately lead to better patient care.

Clinical outcome measures

Until recently, morphea was thought to be unresponsive to therapy largely because existing outcomes did not measure the effect of treatment on activity. Many previously reported outcome measures in morphea exclusively measured damage, and therefore remained unchanged even with successful immunosuppressive treatment, which exclusively improves activity and stabilizes damage (61). Patient-reported outcomes (PRO), which are critical to assessing the effect of therapy on patients, are equally challenging to quantify in morphea. This is because features of morphea, such as tissue loss and sensations of skin tightening, are not represented in traditional dermatology and rheumatology measures. These gaps need to be addressed in order to conduct well designed clinical trials (63).

The Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) is a promising clinical outcome for morphea, but important aspects of the measure need to be refined. The LoSCAT is the only clinical score for morphea incorporating both activity and damage, and is the only clinical measure in morphea developed using the rigor of the Outcome Measures in Rheumatologic Clinical Trials (OMERACT) principles (39,64-70). To date, the LoSCAT is the most fully validated clinical outcome in morphea and has strong support for use in measuring disease activity and damage in a clinical population. However, it has not been validated for discrimination in terms of long-term responsiveness to change and minimal clinically important differences (MCID) have not yet been defined (68). Thus further work needs to be done to further validate the use of the LoSCAT in sensitivity to change, as this is absolutely necessary for the planning and conduct of clinical trials in order to contextualize change in score beyond statistical significance. This will allow the LoSCAT to be used as an outcome in clinical trials to determine treatment response (71,72).

Patient reported outcomes are another important outcome to consider when designing clinical trials, even more so when evaluating the comparative effectiveness of new treatments and contrasting their impact on quality of life. Studies have shown that patients with morphea have significant impairment in quality of life, likely related to symptoms such as pain, itch, and fatigue, as well as worry about progression to systemic disease (15,64,73). However, surprisingly, even patients with clinically severe disease report only mild to moderate impact on life quality based on current patient reported outcome measures (64). This indicates that current skin based measures may not detect aspects of morphea relevant to patients and also may fail to capture disease heterogeneity, i.e., one patient may have hemifacial atrophy while another suffers from limitation of joint range of motion. Disease specific measures can overcome these difficulties, and thus the pediatric Localized Scleroderma Quality of Life Instrument (LoSQI) was developed as the only disease-specific measure in morphea, designed to measure the unique impact of morphea from the perspective of the patient (74). While the LoSQI is a promising step in the right direction for accurately assessing impact of morphea on patients, it thus far only has support for use in the pediatric morphea population. Further work needs to be done on adapting this for use in clinical trials with adults.

Role of biomarkers

Biomarkers are needed in morphea that identify disease activity. While some patients present with clearly active or inactive disease, there are a significant number of patients who present with morphea lesions in which the level of activity is difficult to assess using clincal examination alone, making it difficult to know whether to initiate or escalate immunosuppressive therapy. Accurate and timely assessment of lesion activity is crucial to successful management of morphea patients, since the goal of morphea therapy is to eliminate disease activity in order to prevent permanent cosmetic and functional sequelae.

Studies on the role of biomarkers to indicate disease activity have focused on cytokine levels, as most patients with morphea have normal markers of inflammation such as erythrocyte sedimentation rate. While increased concentrations in numerous cytokines have been reported in the sera of patients with morphea, such as IL-2, IL-4, IL-6, IL-8, IL-13, IP-10, and TNF alpha, current evidence points towards downstream IFN-regulated pathway chemokines
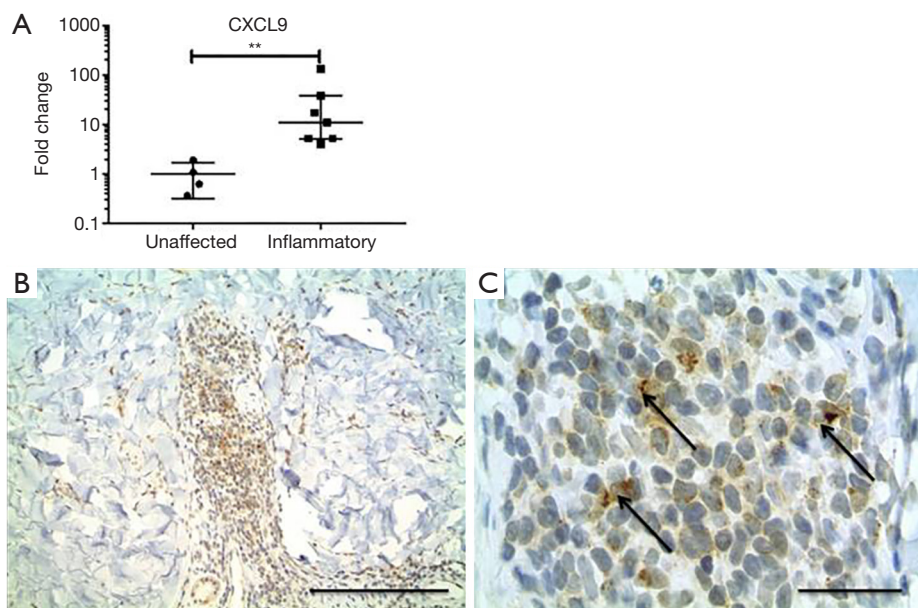
Figure 2 CXCL9 is increased in inflammatory morphea skin, supporting its role as a potential biomarker. (A) CXCL9 mRNA expression is increased in lesional, inflammatory skin when compared to site-matched unaffected skin. (B,C) CXCL9 is present in dermal interstitial infiltrates and stains dendritic appearing cells. Arrows indicate typical perinuclear cap staining pattern of CXCL9. Scale bar in B =100 mm; scale bar in C =25 mm. Reprinted from (80).

as the most promising biomarkers in morphea (75-81). CXCL9, along with other T helper type 1 cytokines, has been found at increased concentrations in morphea serum, and has been found to correlate with disease activity as measured by the LOSCAT in multiple independent studies (80,81). Further studies also indicate that CXCL10 may also have similar biomarker capabilities (81). *CXCL9* gene expression was also found to be increased in inflammatory lesional morphea skin, and co-localized with dermal macrophages, implicating the skin as the source of circulating cytokines (80,81). *Figure 2* demonstrates the elevation of CXCL9 in inflammatory morphea skin. Thus, current research indicates that IFN pathway dysregulation is associated with activity in morphea but how this dysregulation is related to the pathogenesis of morphea remains poorly studied.

Imaging measures of morphea

Recent studies have indicated that MRI may have a role as an objective outcome measure in morphea, particularly in the case of deep cutaneous or soft tissue involvement. High resolution MRI can demonstrate inflammation, sclerosis, and atrophy in morphea lesions, and has been shown to

be a useful adjunct to clinical examination when it comes to accurate assessment of disease activity and extent (41). *Figure 3* demonstrates MRI findings in morphea. This is particularly relevant for deeper morphea lesions extending to the subcutis, fascia, and muscle, which often present with subtle cutaneous manifestations. In fact, studies have shown that MRI can reveal clinically occult musculoskeletal involvement (82-84), demonstrating subclinical extension of lesions beyond visible margins (41). MRI has also been shown to demonstrate active disease that would otherwise be misclassified as inactive based on using the LoSCAT alone (41). Given how crucial it is to accurately assess activity when managing morphea patients, this further underscores the utility of MRI in conjunction with clinical evaluation for deep morphea. Future studies in MRI are needed to assess its responsiveness to change and to further define indications for imaging.

Ultrasound is another tool that can be used for investigation of activity and depth of morphea lesions, and has promise as an outcome measure in morphea. Ultrasonography is easier to use and more cost-effective than MRI, and has been found to have high validity and reliability for evaluation of morphea. Ultrasound can differentiate all stages of morphea, including active disease, which appears
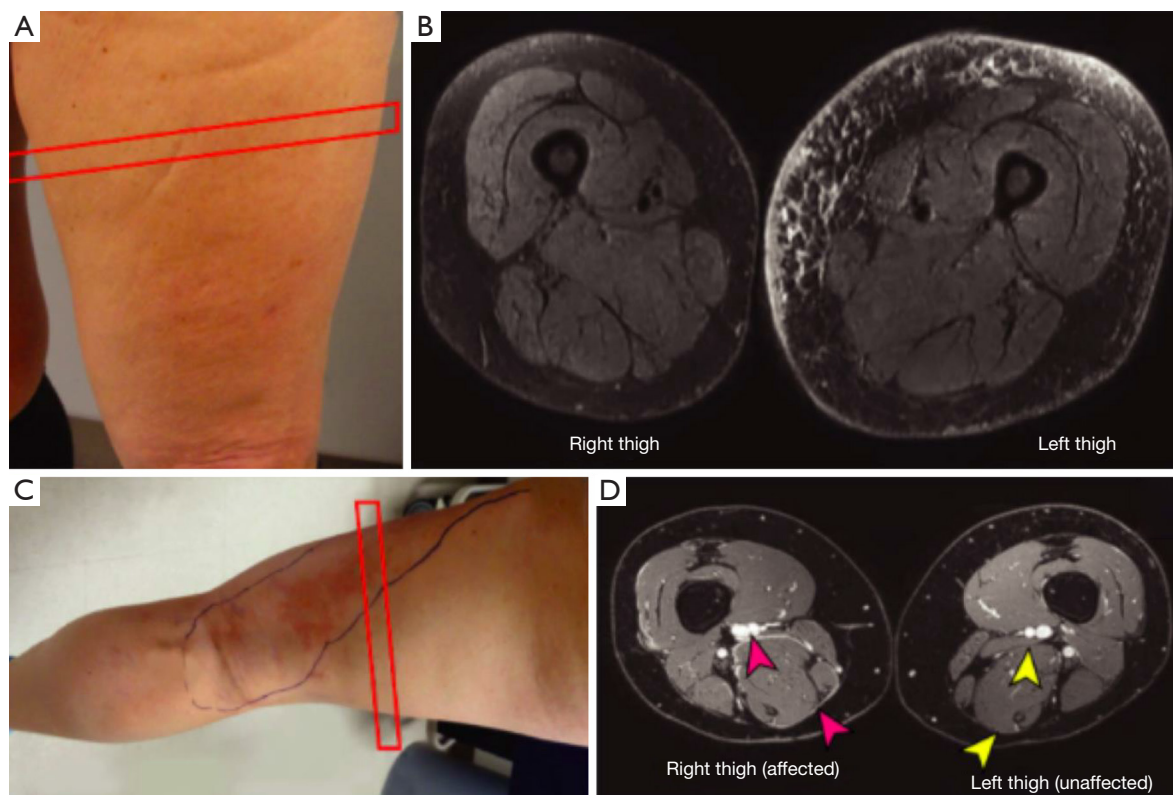
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Figure 3 MRI findings in morphea. Red boxes indicate area imaged. (A) Subtle morphea involving the left thigh. (B) Axial fat-saturated T2-weighted image of bilateral thighs, with hyperintense areas corresponding to morphea involvement. (C) Morphea of the lower right extremity. (D) Axial 3-dimentional subtracted postcontrast image of bilateral thighs showing fascial involvement as demonstrated by hyperintense signal on affected right thigh (red arrows), with unaffected left thigh (yellow arrows) presented for comparison. Reprinted from (80).

hyperechoic (sclerotic) or isoechoic (inflammatory), from inactive disease characterized by atrophy and damage, which appears hypoechoic (85). Ultrasound can also detect increased cutaneous blood flow, which is another sign of lesion activity (86). While results from ultrasonography have been correlated to clinical and histopathologic findings, further work needs to be done to validate this as an outcome measure. Additionally, it is important to collaborate with a musculoskeletal imaging expert with experience in morphea to get optimal information from the scan (including MRI and ultrasound) (8).

Three dimensional stereophotogrammetry (3D imaging) is a minimally invasive and radiation-free modality rapidly gaining popularity as the preferred method for quantifying information about facial soft-tissue, particularly in children, where quantifying facial features can be challenging (87). It has demonstrated a high degree of precision and accuracy across different platforms (87), and has been used in a variety of conditions affecting the face, including cleft

palate (88) and for postoperative monitoring to track fat graft retention and assess soft tissue volume of change (89). It has great potential for application in morphea affecting the head and neck, where facial asymmetry can be difficult to evaluate clinically, and the LoSCAT often falls short in correctly quantifying disease activity and damage. Advanced analysis of images can be used in conjunction with clinical assessment to provide information about vascularity and pigmentation to further monitor disease activity (90). 3D imaging is portable, fast, easy to use, and inexpensive, and has many applications in facial morphea. Further studies to validate this modality will continue to support its integration into clinical practice.

Histologic markers

Skin biopsy may provide additional information regarding depth of involvement and activity (inflammation) in cases where clinical examination is inconclusive or imaging is not

readily available (91). Pathological findings, particularly the pattern of sclerosis and degree of inflammation. For example, studies have shown that a bottom heavy pattern of sclerosis can be associated with pain and tightness, and that severe inflammation may be associated with pain and functional limitation (91). Histopathologic examination of morphea therefore has the potential to be used not only for diagnosis but also for assessment, assisting in clinical management by identifying disease activity and damage, and identifying patients who may require additional monitoring and treatment (91).

Another current area of study into potential histologic measures of morphea is regarding the altered distribution of dermal dendritic cells and vascular abnormalities that have been reported to relate the pathogenesis of morphea. Studies of morphea skin indicate that patients with morphea demonstrate a phenotypic change of CD34+ dendritic cells into SMA+ myofibroblasts with increasing disease extent and fibrosis (92). The degree of loss of CD34+ dendritic cells has been found to correlate with relative degrees of inflammation and sclerosis, and thus this has been proposed as a useful marker in predicting morphea severity and extent (92,93). Further studies have shown that treatments such as pulsed dye laser and UVA1 phototherapy are effective in improving indurated skin and reducing disease activity in morphea, and are also associated with an increase in the number of CD34+ cells (94,95). Taken together, these results underscore the potential use of histologic markers such as CD34+ dendritic cells as measures of disease in morphea, although further studies will be necessary to validate and refine these measures.

Pathogenesis of morphea

The precise pathogenesis of morphea is not completely understood. As with other autoimmune disorders, the main contributors to long-term morphea damage and disability are thought to be the extent and duration of the initial active phase, which likely drives subsequent damage-producing fibrosis (11). However, the dysregulated immune and fibrotic pathways that contribute to these changes have not yet been systematically studied. Current theories are often extrapolated from studies of systemic sclerosis due to a paucity of well-developed studies in morphea (96), although clinical evidence suggests that morphea has distinct disease characteristics, encompassing different demographics, clinical features (5,6,13,97) and response to treatment (7,46-48,98) than systemic sclerosis, and

further study independently into morphea is warranted. Although it is generally accepted that immune dysfunction is the principal component in the development of morphea (3,99-101), other factors are also thought to contribute to pathogenesis, including genetic predisposition, traumatic or environmental factors, and vascular dysfunction (3,7,9).

Immune dysregulation

There are several aspects of morphea that point to the role of autoimmunity in pathogenesis. Firstly, the natural history of the disease, with the clinically evident inflammatory stage preceding the development of sclerosis, supports the theory of immune dysfunction (8). Additionally, histopathologic studies demonstrate an influx of large numbers of mononuclear lymphocytes (primarily activated T lymphocytes), plasma cells, and eosinophils in lesional morphea skin, also supporting the role of autoimmunity (96). Morphea patients have also been found to have elevated cytokine levels, such as CXCR3 ligands as well as those associated with Th2 immune responses (80,96). For example, IL-4, which is produced by CD4+ Th2 lymphocytes, can upregulate the production of TGF beta, stimulating fibroblast production of collagen and other extracellular matrix proteins, and IL-4 has been detected at elevated levels in morphea patients (77). Some patients with morphea also have increased autoantibody levels, further supporting the role of immune dysfunction (3,100-102).

To date, most studies examining the autoimmune pathogenesis of morphea have consisted of reports of circulating chemokine profiles or antibodies, flow cytometry of peripheral blood, and immunostaining often in a limited number of samples or without controls (77,103-105). Recent observations have supported the role of dysregulated immune pathways, particularly IFN gamma, demonstrating that CXCL9 and CXCL10 levels are associated with increased clinical measures of disease activity (78-80,106-108). *Figure 4* demonstrates the elevation of these cytokines. Using microarray and bulk RNA sequencing on human skin samples, clinically early inflammatory morphea lesions have been found to display an inflammatory morphea signature, including chemokines CXCL9, CXCL10, CXCL11, and their receptor CXCR3, with cell-specific transcripts of infiltrating macrophages and T cell subsets (80,109). There have also been discoveries involving a fibrotic signature reflecting fibroblast activation and collagen production (110), which may enhance retention of inflammatory cells in the dermis of sclerotic lesions (111).
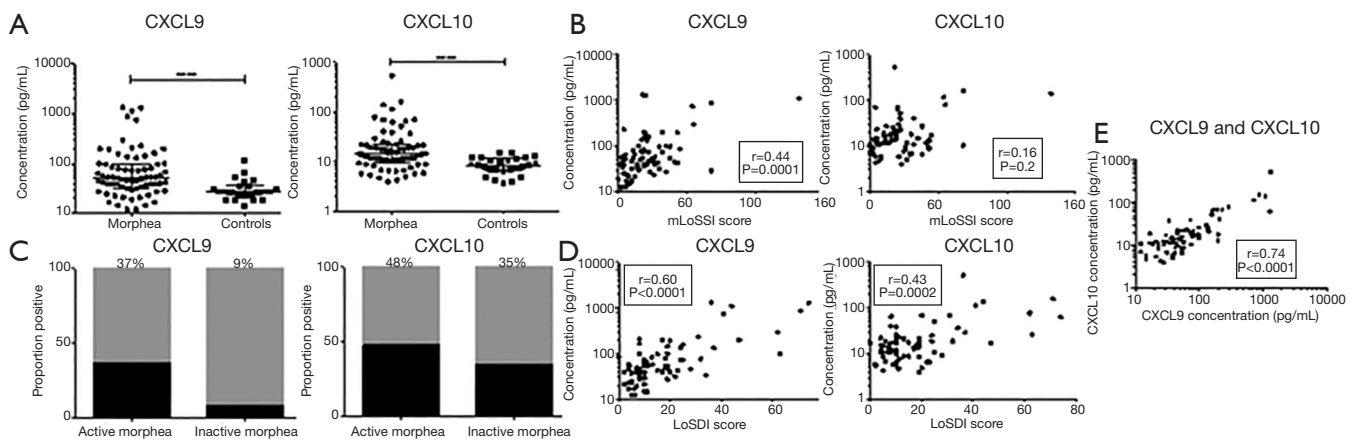
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Figure 4 CXCL9 and CXCL10 are elevated in morphea serum, emphasizing the role that the dysregulated IFN gamma pathway plays a role in the pathogenesis of morphea. (A) CXCL9 and CXCL10 are present at increased concentrations compared with control samples. (B,C) CXCL9 is increased in active morphea, decreases in inactive disease, and correlates with disease activity, but CXCL10 does not. (D) Both correlate with measures of disease damage. (E) CXCL9 concentrations correlate with CXCL10 concentrations. LoSDI, Localized Scleroderma Skin Damage Index; mLoSSI, modified Localized Scleroderma Skin Severity Index. Reprinted from (80).

Additionally, pilot studies in an early fibrotic skin disease bleomycin mouse model have shown that CXCL9, but not CXCL10, along with receptor CXCR3, has been found to be necessary for fibrotic lesional development and therefore is mechanistically involved in pathogenesis (unpublished observation HJ).

Beyond CXCR3 ligands, other upstream and downstream pathways have also been implicated in the pathogenesis of morphea. IL-4/IL-13, IL-12, IFN gamma, and TGF beta are all cytokines that have been implicated in autoimmune fibrosis. These cytokines signal via the Jak-STAT pathway, and recent studies demonstrate that inhibition of this pathway can be therapeutic for this group of diseases (112). Jak inhibitors given to a small group of patients with recalcitrant morphea were found to lead to decreased inflammation and even reversal of fibrosis. Subsequent observations in a bleomycin-induced mouse model of morphea indicated that Jak inhibition prevented fibrosis and directly decreased collagen production, further implicating that this pathway is involved in morphea pathogenesis (112). Jak inhibitors are a promising potential targeted therapy, and further study will further highlight their utility in morphea.

Other factors contributing to disease pathogenesis

A variety of additional factors have been thought to play a role in morphea beyond immune dysregulation, including genetic predisposition, traumatic factors, and vascular dysregulation (6,9,10). The genetic contribution to morphea is suggested by reports of familial case clusters, the detection of increased rates of autoimmune disorders in family members of patients with morphea, and class I and II HLA associations (3,113). Environmental factors such as radiation, infections, skin trauma (i.e., surgical or through friction), and other exposures have also been proposed as contributors to disease expression (9). Observations in lesional morphea skin have revealed reduced numbers of dermal capillaries, abnormalities in basal lamina of blood vessels, and endothelial cell damage, supporting a role for vascular dysfunction in the development of morphea (7,96). In fact, studies have shown increased levels of vascular adhesion molecules in serum from patients with morphea (114). Thus, another possible contributor to morphea pathogenesis involves the vasculature, as it is hypothesized that the initial inflammatory stage of morphea leads to injury to the vascular endothelium, stimulating the release of cytokines that facilitate the recruitment of T lymphocytes capable of producing further profibrotic cytokines (7,96).

Future directions

There remains a critical need to define morphea pathogenesis more clearly in order to identify promising targets for mechanistic studies and therapeutic development. There remain few large scale studies on morphea

pathogenesis using transcriptional profiling, animal or *ex vivo* disease models, or molecular approaches. Further study using these state of the art approaches are necessary to gain a detailed, unbiased picture of upstream and downstream pathways in human skin that are likely implicated in morphea pathogenesis, particularly dysregulated IFN gamma mediated pathways, which appear particularly promising. Furthermore, many of the gene signatures being currently studied in morphea can be coupled to clinical measures of disease and have the potential to be used as biomarkers, allowing for prediction of disease course and therapeutic response.

Studying the mechanism of action behind the dysregulated pathways in morphea poses a clinical and pathologic challenge due to the clinical heterogeneity of the disease, as it often has variable anatomic patterning, morphology, and depth of tissue involvement (99). Moreover, the relative rarity of the disease makes it difficult to execute large studies correlating biological samples with accompanying clinical outcomes. Thus, there remains an important gap in knowledge that must be filled, as an improved understanding of the underlying molecular mechanisms of morphea is likely to allow for refining of outcome measures and the advent of novel targeted therapies, especially given that current, non-targeted treatments for morphea are often limited by substantial toxicity.

Conclusions

Morphea is an inflammatory skin condition characterized by activity (inflammation) presenting as erythematous and violaceous indurated plaques evolving to hyperpigmented lesions with central sclerosis and atrophy. There are several subtypes of morphea, and while a number of different classification systems exist, they are hindered by significant limitations and further work must be done to refine and clarify these schemes. For example, these schemes do not mention extracutaneous manifestations of morphea, a current evolving area of research.

Given that unchecked disease activity in morphea can lead to severe cosmetic and functional sequelae, it is crucial to identify activity and initiate treatment early. Thus, recent progress has been made in developing and refining outcome measures in morphea. Clinical, biomarker, imaging, and histologic outcomes have all been studied in order to allow for more accurate assessment of disease activity and severity. Despite promising results in this arena, further work

remains to thoroughly validate these measures before use in the clinical setting as well as for research purposes.

The present understanding of morphea pathogenesis is incomplete but points primarily towards the role of dysregulated immune and fibrotic pathways, with environmental triggers, genetic predisposition, and vascular dysfunction also playing a role. There remains a gap in knowledge in clearly elucidating the pathogenesis of the disease, and further study is necessary to provide a full understanding of the environmental, systemic, local, genetic and immunopathological factors underpinning morphea pathogenesis. This is particularly important given that current treatments for morphea revolve around the use of immunosuppressives such as corticosteroids and methotrexate to target activity, which are limited by significant adverse effects. A better understanding of disease pathogenesis will allow for refinement of outcome measures and development of therapeutic targets and novel biomarkers.

Footnote

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