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REVIEW

Diagnosis and Management of Cutaneous Manifestations of Autoimmune Connective Tissue Diseases

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Abstract: The cutaneous features of autoimmune connective tissue disease pose a unique challenge to patients and clinicians managing these conditions. In this review, we outline the key elements of diagnosis and treatment of cutaneous lupus erythematosus, dermatomyositis, systemic sclerosis, and morphea. This article also aims to present an update on gold standard as well as new and emerging therapies for these conditions. Overall, dermatologists can play a key role in diagnosing and treating autoimmune connective tissue diseases and this review intends to provide an up-to-date toolkit to guide clinical dermatologists in this endeavor.

Keywords: cutaneous lupus erythematosus, dermatomyositis, systemic sclerosis, morphea, eosinophilic fasciitis

Introduction

Cutaneous manifestations of autoimmune connective tissue disease (CTD) are common and often paramount to diagnosis, prognosis, and management. As such, dermatologists can play a critical role in early disease recognition accelerating crucial work up and management to improve patient outcomes. However, recognition of disease morphology, distinguishing autoimmune connective tissue disease from disease mimics, and approaching the oftentimes multifaceted workup and management of patients with connective tissue disease can present a challenge for even experienced clinicians. In this review, we provide an update on the literature discussing the diagnosis, workup, and management of patients with cutaneous lupus erythematosus, dermatomyositis, systemic sclerosis, and morphea. In doing so, we aim to provide clinical dermatologists with an accessible, up-to-date toolkit to improve comfort with their approach to patients with these disease states.

Cutaneous Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) can either occur in the context of systemic lupus erythematosus (SLE) or independently of SLE. The association of CLE with SLE depends on the subtype of cutaneous lupus. The current classification system for CLE divides the disease into three major subtypes: (1) Acute cutaneous lupus erythematosus (ACLE), (2) Subacute cutaneous lupus erythematosus (SCLE) and (3) Chronic cutaneous lupus erythematosus (CCLE). While the female-to-male incidence of SLE is as high as 15:1 for adults, this ratio drops to 2–3:1 for CLE.[1–4] Pathophysiology for CLE is complex, but environmental exposure in genetically predisposed individuals is thought to play a prominent role in disease onset. Ultraviolet radiation is a predominant trigger and is thought to induce apoptosis leading to altered clearance of fragmented DNA, with autoantigen recognition promulgating disease manifestations.[5]

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Diagnosis

The diagnosis of CLE is made primarily on a clinical basis dependent upon characteristic history and exam findings. Importantly, disease location and morphology can be used to determine the specific subtype of CLE which can help to inform risk of SLE association, prognosis, disease monitoring, and treatment.

ACLE is the subtype of cutaneous lupus most strongly associated with SLE, with greater than 90% of ACLE patients meeting criteria for SLE in one large cohort study.[6,7] ACLE can present with localized, or more rarely, generalized cutaneous disease. Localized ACLE is most commonly characterized by the pathognomonic transient, photosensitive malar "butterfly" rash of lupus characterized by erythematous to violaceous macules or edematous plaques overlying the malar cheeks.[8] In contrast to many butterfly rash mimics, including dermatomyositis, rosacea, and seborrheic dermatitis, the malar rash of ACLE strikingly spares the nasolabial folds (Figure 1). The malar rash of lupus can also be distinguished from rosacea by the lack of papules and pustules. Generalized ACLE presents with an erythematous morbilliform or eczematous appearing eruption, typically involving sun-exposed areas on the arms, hands and chest ("V-neck" area), which may sometimes resemble a drug eruption.[9] Erythema on the dorsal hands characteristically spares the knuckles and instead affects the interphalangeal skin, helping to distinguish generalized ACLE from Gottron papules in dermatomyositis.[1,10] In severe cases, patients may develop tense bullous lesions, often referred to as "bullous lupus erythematosus". Being almost universally associated with SLE, patients with ACLE will commonly have a positive ANA and ds-DNA characteristic of systemic lupus erythematosus.[11,12]

SCLE is a subtype of cutaneous lupus that often presents initially with erythematous macules or papules which later evolve into either psoriasiform (papulosquamous SCLE) or annular plaques (annular SCLE). Papulosquamous SCLE is more hyperkeratotic in nature while the annular variant of SCLE commonly presents in a polycyclic fashion with violaceous to erythematous annular plaques with trailing scale (Figure 2). These patients will frequently report photosensitivity with lesions most commonly appearing on the shoulders, upper extremities and "V" distribution of the thorax.[6,8] In contrast to ACLE, the face is typically spared. Overall, approximately 50% of patients with SCLE have been shown to meet criteria for SLE.[8] Importantly, drug-induced SCLE is also common. As such, a thorough review of medications is important when SCLE is suspected. Drug-induced SCLE is more likely to occur in older patients with hydrochlorothiazide, calcium channel blockers, and angiotensin-converting enzyme inhibitors being the most common culprits. Proton pump inhibitors and chemotherapeutic agents have also been implicated as relatively common triggers.[6,13] Importantly, however, a long list of medications have been reported as possible culprits of this disease.[14–19] While not required for diagnosis, a study of 296

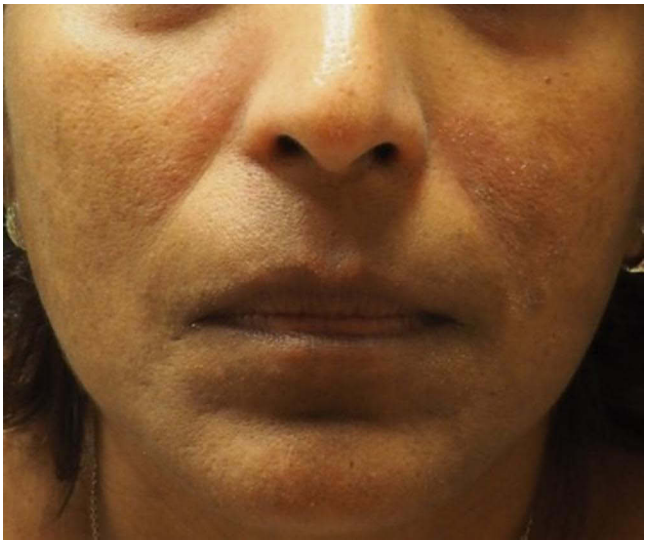

Figure 1 Acute cutaneous lupus erythematosus (ACLE) characterized by violaceous to erythematous patches and thin plaques involving the malar cheeks. Importantly, this pathognomonic "butterfly rash" of lupus strikingly spares the nasolabial folds helping to distinguish ACLE from disease mimics.

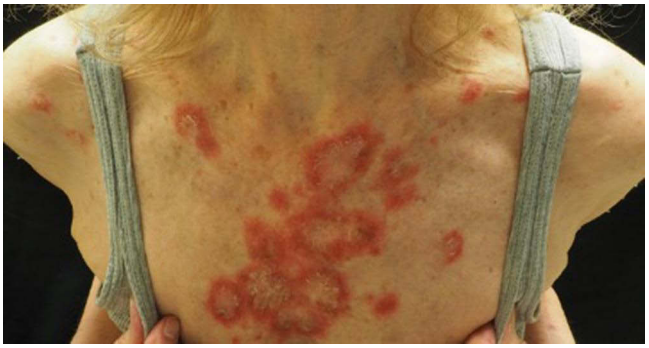

Figure 2 Annular subacute cutaneous lupus erythematosus (SCLE) characterized by polycyclic violaceous annular plaques with trailing scale in photo distributed anatomic sites (eg, upper chest).

SCLE patients found that 70% had a positive ANA.[20] Anti-Ro/SSA autoantibodies are also highly associated with SCLE.[21,22]

Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus (CCLE). This subtype of CLE has a predilection for the face, scalp, and ears (particularly conchal bowls) (Figure 3), however, can also occur as disseminated lesions in a minority of patients.[1,23] DLE frequently presents as erythematous to violaceous plaques with overlying hyperkeratotic scale, follicular plugging, and central atrophic scarring. When the scale is removed, the underside will display horny follicle-sized plugs known as the "carpet tack sign".[23,24] This sign is a helpful non-specific clinical finding for diagnosing DLE. Early disease detection is important, particularly when the face and scalp are involved as DLE presents a high risk for permanent dyspigmentation, scarring and irreversible scarring alopecia. DLE is less commonly associated with SLE than the other two major subtypes of cutaneous lupus with a 5–10% association for patients with more localized disease. However, concurrent SLE has been shown to occur in up to 28% of patients with disseminated disease.[23,25]

Other less common forms of CCLE include lupus panniculitis (lupus profundus), chilblain lupus, and tumid lupus (lupus tumidus). Lupus panniculitis may occur independently or concurrently with superimposed DLE and presents as subcutaneous indurated plaques or nodules in fat prone areas of skin (ie, cheeks, upper arms, breasts, thighs, and buttock). Lupus panniculitis is a lobular panniculitis, resulting in depressed areas of lipoatrophy upon resolution.[6] In a retrospective study of 61 patients with lupus panniculitis, 21% of patients had a coexisting diagnosis of SLE, however only 6.5% of patients developed SLE after or at the same time of lupus panniculitis onset.[26] Importantly, as opposed to

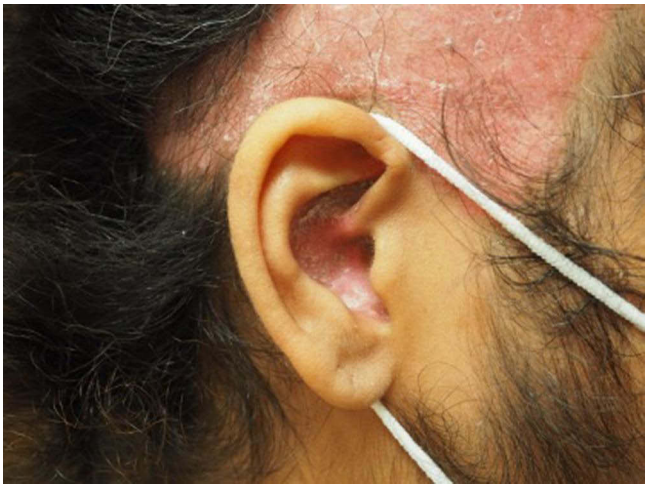

Figure 3 Discoid lupus erythematosus (DLE) has a predilection for the conchal bowls, face, and scalp, and presents with erythematous to violaceous scarring plaques with overlying adherent scale and follicular plugging.

other subsets of cutaneous lupus which can largely be diagnosed clinically based off morphology, lupus panniculitis is predominantly considered a biopsy diagnosis. Biopsy can help to differentiate lupus panniculitis from other types of CTD associated panniculitis and lupus panniculitis mimics such as subcutaneous panniculitis-like T-cell lymphoma.

Chilblain lupus is a rare form of CCLE occurring most commonly on acral surfaces such as the fingers or toes. Lesions may resemble frostbite with patients often reporting their symptoms being worsened by the cold. On exam, this subtype will display painful dusky papules and plaques which are at risk for ulceration.[1] In patients with chilblain lupus, up to 20% of patients may go on to develop SLE.[27] Whereas spontaneous chilblain lupus generally has a mild progression and presents in middle-aged women, familial chilblain lupus typically has an onset in early childhood and the most frequent mutations identified are in the TREX1 gene.[28]

Lastly, tumid lupus appears clinically as dermal urticarial, erythematous, often annular plaques. Given its morphology, this subset of CLE is often misdiagnosed as urticarial vasculitis. Tumid lupus lacks secondary morphologic characteristics and is the least associated with SLE of all CLE variants, leading some to believe that this condition belongs as a separate disease process.[29] Due to the heterogeneous nature of cutaneous lupus, it is often difficult to quantitatively assess disease progression and response to treatment of cutaneous disease. The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was developed in 2005 as a tool to more accurately track skin disease in these patients.[30,31] While often used for clinical trials, CLASI can also be a meaningful tool for assessing clinical progress in practice.

Diagnosis of CLE can be made on a clinical basis for patients with classic disease history, location, and morphology. However, skin biopsy can be useful when diagnosis is in question, for certain subtypes of CLE (ie, lupus panniculitis as discussed above), and when attempting to rule out other conditions. Histopathology may show pilosebaceous atrophy and epidermal necrosis with dermal thickening (chronic subtypes) or basal layer vacuolation (subacute subtypes).[32] It is important to note that histopathology in CLE and dermatomyositis may appear indistinguishable and should not be used to distinguish between these conditions.[33] Direct immunofluorescence (lupus band testing) assesses for the presence of immunoreactants along the dermal-epidermal junction, but its value in diagnosis remains unclear and is not routinely performed.[6]

When a diagnosis of CLE is made, it is also important to assess patients for concurrent SLE. No current guidelines exist for SLE screening in patients presenting with CLE, but a comprehensive review of systems as well as a focused rheumatologic history is recommended along with physical exam and laboratory testing.[6] Initial laboratory workup for SLE for all patients with CLE in our practice include urinalysis, complete blood count, complement, antiphospholipid antibodies and antinuclear antibody (ANA) testing, followed by SLE-focused autoantibody evaluation (anti-smith, anti-double stranded DNA, anti-Ro/La). While the detection of certain autoantibodies is helpful in evaluating for SLE, no specific autoantibodies currently exist that can be used clinically to differentiate subtypes of cutaneous lupus.[23] That said, the strong association between SCLE and Anti-Ro/SSA autoantibodies may be useful in supporting this diagnosis.[6]

Multiple classification criteria based on various clinical and serologic features for SLE have been proposed over time including the commonly used 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria[34] and the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria.[6] It is important to remember that both of these tools serve as classification, rather than diagnostic criteria; however, they can help guide history taking and work up for patients with CLE. The 2012 SLICC classification criteria more thoroughly incorporates the cutaneous features of SLE and as such is the preferred classification criteria in many derm-rheum clinics (Table 1).[6,35]

Treatment

Treatment for CLE depends on subtype, severity of symptoms, and concurrence of SLE. Ultraviolet exposure and cigarette smoking are two of the strongest behavioral risk factors associated with disease flare for both CLE and SLE. Counseling around avoidance of both of these triggers is essential. Sun protection with broad-spectrum sunscreen (sun protective factor 50 or above) has been shown to prevent UV-induced skin lesions in patients with multiple subtypes of CLE.[36,37] Patients should also be counseled around the importance of sun protective clothing, sun avoiding behaviors (ie, seeking shade), and the benefit of sunscreen re-application as well as the benefit of physical over chemical blockers in sunscreen formulations. The effects of cigarette smoking on CLE are also well documented, both as a risk factor for

Table 1 Systemic Lupus International Collaborating Clinics (SLICC) Criteria*

Clinical Criteria	Immunologic Criteria
Acute cutaneous lupus	ANA**
Chronic cutaneous lupus	Anti-dsDNA**
Oral ulcers	Anti-Sm
Nonscarring alopecia	Antiphospholipid antibody
Synovitis/tenderness (≥2 joints)	Low compliment
Serositis	Direct Coombs test
Renal	
Neurologic	
Hemolytic anemia	
Leukopenia (<4000/mm^3)	
Thrombocytopenia (<100,000/mm^3)	

Notes: *Fulfilling criteria requires (1) the presence of ≥4 total criteria, with at least one criterion met from each category or (2) lupus nephritis along with ANA or anti-dsDNA antibodies. **Above reference range.

cutaneous symptoms in lupus erythematosus[38] and as a factor associated with poorer response to treatment for cutaneous disease.[38] As such, smoking cessation and avoidance should be considered a crucial component of treatment for CLE.

Topical therapies including, most commonly, topical corticosteroids and topical calcineurin inhibitors are a critical component of treatment for patients with most subtypes of CLE. For patients with more focal or mild disease, topical agents are considered first-line therapy and may allow for adequate control of disease. While there are very few studies exploring the efficacy of topical steroids in CLE, one study with 78 DLE patients reported complete resolution of cutaneous lesions in 27% and 10% of patients using fluocinonide 0.05% cream and hydrocortisone 1% cream, respectively.[39,40] In addition to topical application, intralesional steroid injections have shown efficacy for refractory disease in patients with DLE.[41]

Topical calcineurin inhibitors are another effective treatment with less risk for side effects than topical steroids. A randomized controlled trial (RCT) comparing tacrolimus with topical steroids for facial CLE found that tacrolimus was effective at improving skin disease with lower incidence of treatment-induced telangiectasia.[24,25] In practice, however, many providers use both topical steroids alternating with topical calcineurin inhibitors as a steroid sparing agent. However, many patients with CLE will have more widespread, severe, or rapidly progressive disease and for these patients topical agents alone may be insufficient.[1] In these patients, topical agents should be considered to be one aspect of a multifaceted treatment plan.

Antimalarials, such as hydroxychloroquine, quinacrine, and chloroquine, are effective first-line systemic treatments which serve as a mainstay of therapy for patients with CLE in combination with topical therapy. One meta-analysis has shown antimalarials to be most effective for ACLE in comparison to other subtypes.[42] However, antimalarials are considered first-line agents and are effective for all subtypes of cutaneous lupus requiring systemic therapy. Hydroxychloroquine is typically the antimalarial agent of choice for CLE, balancing efficacy and safety profiles.[43] Chloroquine can be considered as an alternative agent for patients with CLE who cannot tolerate or do not respond to hydroxychloroquine.[44,45] Quinacrine can be either added to hydroxychloroquine or chloroquine for patients with incomplete response or used as an alternative agent for patients with retinal toxicity.

While serious side effects are rare, retinopathy and cardiac arrhythmias are both possible adverse effects of hydroxychloroquine. Appropriate weight-based dosing of hydroxychloroquine (5 mg/kg/day) reduces the risk of retinal toxicity to <2% and is recommended in all patients.[46] Current screening guidelines recommend that patients started on hydroxychloroquine should receive optical coherence tomography and automated visual field testing from an eye care provider at baseline and then yearly no more than 5 years after beginning therapy with hydroxychloroquine.[46]

Electrocardiogram at baseline and shortly after initiation of hydroxychloroquine can also be considered, particularly in those taking other QTc prolonging medications.[47]

Systemic corticosteroids should not be used as a long-term immunomodulatory agent in patients with cutaneous lupus. However, short-term use, in conjunction with steroid sparing agents, can be considered for patients with severe, rapidly progressive, or refractory disease (ie, patients with rapidly progressive discoid lupus at high risk of permanent scarring and dyspigmentation). In a study of more than 1000 CLE patients, systemic corticosteroids were shown to be the most effective systemic agent with an efficacy rate of up to 94.3%.[48] The addition of systemic corticosteroids can be useful to gain rapid disease control for patients with severe disease. However, early plans should be made for gradual tapering and systemic steroid initiation in conjunction with other steroid sparing agents is recommended for patients with severe disease.[36]

Methotrexate (MTX) and mycophenolate mofetil (MMF) are both well-established second-line treatments for patients with more severe or refractory CLE. Additionally, these systemic agents have the added benefit of treating comorbid disease manifestations such as inflammatory arthritis (MTX) as well as lupus nephritis and interstitial lung disease (MMF) seen in SLE.[6] Methotrexate, dosed at 15–25 mg weekly, demonstrated significant improvement in 43 patients with refractory CLE, particularly in patients with SCLE and DLE.[49] MTX can be dosed orally, subcutaneously or intravenously and should be administered with daily folic acid supplementation to help prevent side effects. Increasing doses of folic acid as well as subcutaneous administration can help to mitigate gastrointestinal side effects associated with oral dosing. The typical dosing regimen used in our clinic is 10 mg weekly for 2 weeks followed by 25 mg weekly if two-week safety labs are within normal limits.

MMF has also shown benefit as an adjunctive treatment for patients with CLE refractory to antimalarials.[50] A systematic review further supported the use of MMF in refractory CLE,[51] although validation from larger RCTs is lacking.[1,35] In CLE, MMF is typically started at 500 mg twice daily with uptitration to 1 to 1.5 g twice daily dosing from there. Patients who cannot tolerate mycophenolate mofetil due to gastrointestinal side effects can be transitioned to comparable dosages of mycophenolic acid. When comparing the response rates between MTX and MMF for patients with CLE, there were no significant differences observed in a small cohort analysis.[52] Medication selection between the two treatments should be guided based on side effect profiles, disease course, and comorbid conditions.

Thalidomide and lenalidomide are non-immunosuppressive agents with significant benefit used commonly as third-line agents (in conjunction with antimalarial therapy and/or MTX/MMF) for CLE.[36] Both of these drugs have shown efficacy in small clinical trials, however patients can relapse after withdrawal of therapy.[53,54] Given their known teratogenicity, patients must be enrolled in the thalidomide/lenalidomide Risk Evaluation and Mitigation Strategy (REMS) program prior to prescription and routine pregnancy tests must be monitored for patients of child-bearing potential. Peripheral neuropathy can be treatment-limiting, which is more pronounced in thalidomide than lenalidomide. Additionally, close monitoring for cytopenias and transaminitis is especially important for any patient being started on lenalidomide.

Retinoids can also be considered as an additional treatment option for patients with refractory hyperkeratotic CLE. One small randomized double-blind trial demonstrated a similar efficacy of approximately 50% between patients with CLE treated with acitretin (n = 28) and HCQ (n = 15).[55] Smaller case reports and case series have also demonstrated improvement in patients with CLE treated with isotretinoin. Overall, retinoids can be considered as an adjunctive treatment, particularly for patients with more hypertrophic or hyperkeratotic variants of CLE.[56] However, use is limited by the need to avoid acitretin in women of child bearing potential.

Dapsone can be considered as an adjunctive agent for bullous lupus. However, this medication has poor efficacy for other subtypes of CLE.[1]

Belimumab is a novel therapy for SLE that functions by blocking B lymphocyte survival and stimulation, and has been shown to improve skin disease in some studies, among other symptoms of SLE.[57,58] In a case series of 5 SLE patients with refractory disease, the addition of intravenous belimumab to standard therapy of systemic steroids and HCQ demonstrated clinical improvement in an average time of 8–12 weeks.[59] However, while belimumab has shown efficacy in SLE, the data supporting belimumab use in CLE are limited. In a retrospective study of belimumab use for patients with histologically-confirmed CLE, only 50% of patients exhibited a CLE response.[60]

Anifrolumab is a novel monoclonal antibody to the type I interferon receptor subunit 1 which has demonstrated efficacy for SLE in recent clinical trials. Anifrolumab has been shown to significantly improve skin disease in SLE as well as other systemic symptoms of SLE, suggesting this agent may be used with increasing frequency for patients with more refractory disease.[61]

Dermatomyositis

Dermatomyositis (DM) is a rare, autoimmune, idiopathic, inflammatory, myopathy characterized by a pathognomonic pattern of skin findings. In addition to skin and muscle involvement, patients with dermatomyositis are also at risk for other systemic disease manifestations (ie, interstitial lung disease) and the disease is thought to be associated with malignancy in approximately 15–27% of cases.[62] DM is more common in women, with a mean age at diagnosis of 44 years.[63] Etiology is still under investigation, but upregulation of the interferon pathway is thought to contribute, possibly in relation to external triggers such as malignancy, infections, drugs, or ultraviolet radiation.[64,65] DM occurs in two subtypes: (1) Classic DM (CDM) with cutaneous findings and symmetric proximal muscle weakness and less commonly (2) clinically amyopathic DM (CADM) which displays skin symptoms without muscle disease. Juvenile dermatomyositis (JDM) is the classification given for DM diagnosed in children. JDM and adult DM share the same hallmarks of disease, but JDM lacks an association with malignancy and interstitial lung disease while carrying a higher risk for severe muscle disease, calcinosis cutis, and joint contractures.[66] Recognition of pathognomonic skin findings is critical for prompt diagnosis of DM to allow for appropriate disease management and to assess for underlying malignancy in adults.

Diagnosis

The diagnosis of dermatomyositis is primarily made on a clinical basis based on characteristic features in the patient's history and physical exam.[67] For CDM, The Myositis Association guidelines require the presence of at least one characteristic skin feature in addition to symptoms of muscle disease.[68] Pathognomonic cutaneous findings for DM include Gottron papules (pink to violaceous to hyperpigmented macules and papules on the dorsal hands, most commonly located over the metacarpophalangeal joints) (Figure 4) and heliotrope rash (violaceous or erythematous discoloration of the upper eyelids with or without associated edema). Other classic skin findings include Gottron sign (erythematous to violaceous macules, papules, or plaques overlying the elbows or knees), "shawl" sign (erythema or poikiloderma over the posterior neck, back and shoulders), "V" sign ("V-shaped" macular erythema or poikiloderma on the anterior neck and chest) and "holster" sign (scaly erythema or poikiloderma of the lateral thighs). Patients also tend to display photosensitivity and pruritus, particularly of the scalp, which can become severe. Periungual erythema, nailfold capillary change, and cuticular dystrophy is almost universally present. Dermatoscopic examination of the nailfolds is important for diagnosis with dilated capillary loops alternating with areas of dropout and cuticular hemorrhage seen in most patients (Figure 5). In a study with 29 DM patients assessing nailfold capillaroscopic changes, 69% of patients exhibited enlarged capillaries, 31% with avascular areas, and 37.9% with hemorrhages.[69] Patients with DM may also display mid-facial erythema, which, in contrast to the malar rash of lupus, does not spare the nasolabial folds.[39,42,70] The Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) is a standardized and validated instrument using the cutaneous manifestations listed above to assess disease progression and response to treatment.[71]

Skin biopsy is not required for the diagnosis of DM for patients with characteristic skin disease but can be helpful if skin findings are ambiguous or unclear. In these settings, biopsy can be helpful for ruling out other diseases that may resemble DM, such as seborrheic dermatitis, atopic dermatitis, and papulosquamous disorders.[67] Histopathology cannot, however, distinguish between DM and cutaneous lupus erythematosus (CLE) as both will display vacuolar interface dermatitis with increased dermal mucin.[33]

Dermatomyositis can be associated with a positive antinuclear antibody (ANA) in approximately 60% of patients.[72] Importantly, ANA-negative DM is associated with an increased malignancy risk within 3 years of diagnosis compared to ANA-positive disease, and patients with ANA-negative disease may warrant more frequent cancer screening.[73] In addition, myositis-specific antibodies (MSAs) have been found to be present in roughly 20% of patients with DM. While MSAs cannot be used for diagnosis, these autoantibodies have important prognostic value in determining risk factors for systemic disease and malignancy (Table 2).[64,74]

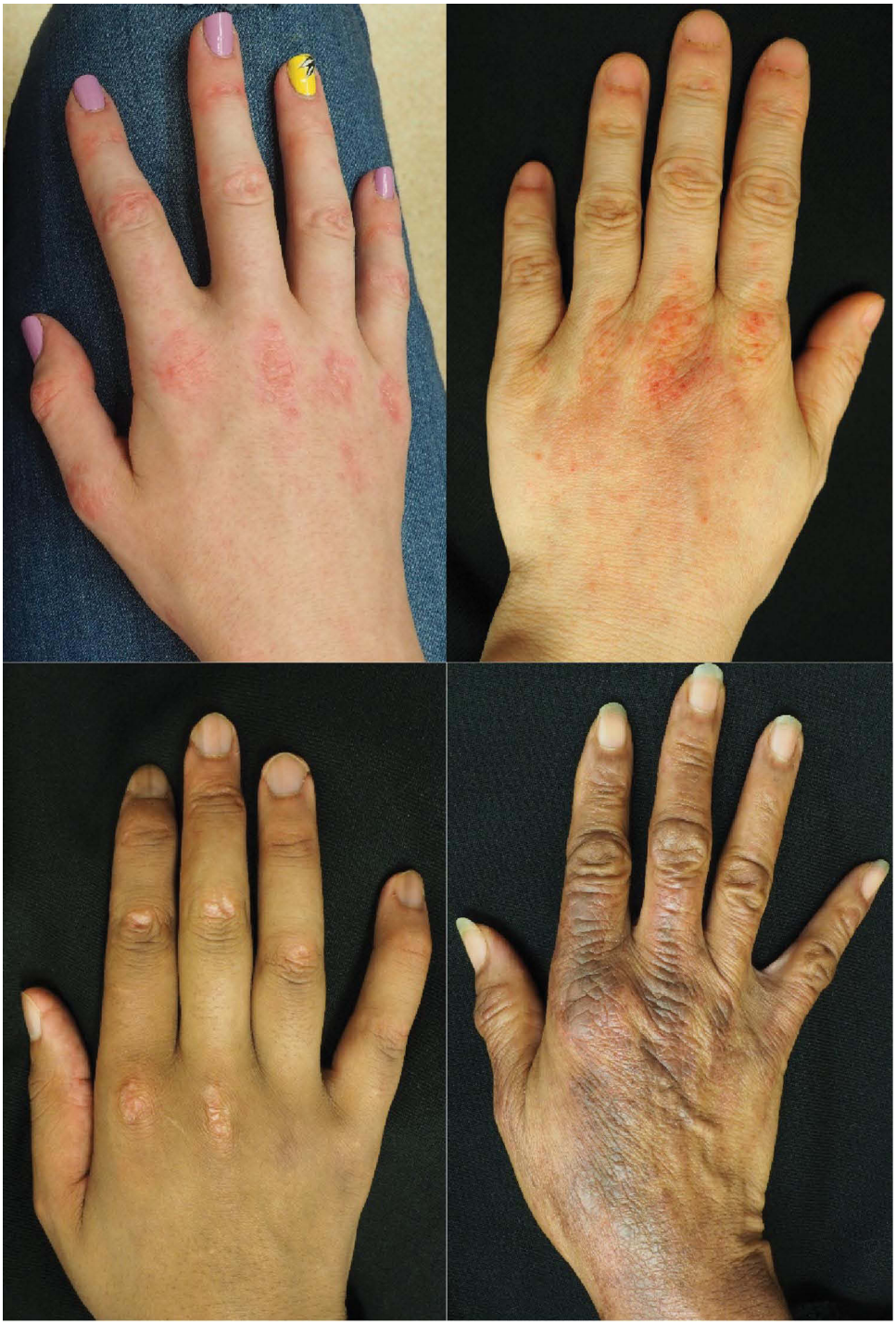

Figure 4 Gottron's papule appearance varies across skin tones presenting as pink to violaceous to hyperpigmented macules and papules over dorsal hands with predominance over metacarpophalangeal joints.

Muscle disease in DM usually presents simultaneously with skin involvement and patients will typically display gradual but progressive symmetric proximal muscle weakness. Common symptoms include difficulties with activities of daily living, such as getting up from a seated position and combing hair, as well as decreased neck strength and, in severe cases, dysphagia.[65,67] Amyopathic disease is a subset of classic DM and is characterized by an absence of clinical evidence or laboratory findings of proximal muscle weakness, and is thought to occur in approximately 20% of DM patients. Among this amyopathic cohort, 13% have been found to have hypomyopathic DM, characterized by laboratory

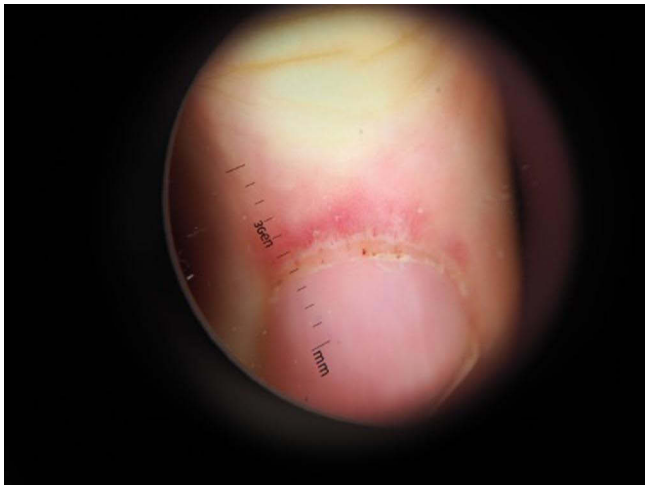

Figure 5 Nailfold capillary changes of dermatomyositis involve dilated capillary loops alternating with avascular areas and cuticular hemorrhage.

findings of muscle disease but with lack of subjective muscle weakness.[75] In regards to nomenclature, a patient with DM is considered provisionally amyopathic or hypomyopathic if they have no clinical evidence of muscle disease for greater than or equal to 6 months but less than 24 months.[76] Thus, patients should continue to be assessed for muscle weakness

Table 2 Common Myositis Specific Antibodies in Dermatomyositis

Myositis Specific Antibody	Characteristic Cutaneous Features	Systemic Associations	Prevalence in Dermatomyositis
Anti-melanoma differentiation-associated gene 5 (MDA-5)	• Ulcerative vasculopathy[82] • Cutaneous and oral ulceration, painful palmar papules, alopecia, panniculitis[83]	• Amyopathic • Increased risk for aggressive ILD	Asian: 11–57%[64,203] Caucasian: 0–13%[64,204]
Anti-Mi-2	• Classic dermatomyositis • Facial dermatosis, shawl sign, heliotrope rash, flagellate erythema, poikiloderma[82]	• Overall favorable prognosis • Good response to treatment • Decreased incidence of ILD and malignancy.[67]	2–38%[64,74,205]
Anti-nuclear matrix protein 2 (NXP-2)	• Mild skin disease • Subcutaneous edema[84] • Calcinosis and ulceration[85]	• More severe muscle disease and dysphagia[78] • Possibly increased cancer risk, particularly in males[79]	2–30%[64,206]
Anti-aminoacyl-transfer RNA synthetase (ARS)	• Mechanic's hands[86]	• Disease phenotypes vary by anti-ARS antibody, with those against non-Jo-1 ARS associated with earlier and more severe ILD and poor prognosis[87] • Association with anti-synthetase syndrome[67,81]	Up to 20% (anti-Jo-1)[64,207]
Anti-transcription intermediary factor 1γ (TIF1γ)	• Extensive skin disease • Facial dermatosis, shawl sign[82] • Ovoid palatal patch, palmar hyperkeratosis, psoriasiform plaques, atrophic hypopigmented patches with overlying telangiectasia[85]	• Increased malignancy risk[77] • Lower prevalence of ILD	Caucasian: 41%[208,209] Asian: 17%[209,210]
Anti-small ubiquitin-like modifier enzyme (SAE)	• Gottron papules, shawl sign, periungual erythema, V sign, Gottron sign[88]	• Correlates with cutaneous disease, progressing to myositis and potentially dysphagia.[77,80]	1–8%[211,212]

Abbreviations: CADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease.

at every visit and may be classified as confirmed amyopathic or hypomyopathic only after 24 months of monitoring.[64,76] A bilateral thigh MRI with myositis protocol can be used for patients for whom muscle involvement is equivocal based on clinical and serologic exam (ie, subjective muscle weakness but with muscle enzymes that are not elevated or only slightly elevated). Given the less invasive nature of this study, as well as the ability to track disease activity with time where needed, bilateral thigh MRI has arisen as the study of choice over muscle biopsy or electromyography in our, and many centers.

Screening for ILD is also important, with a recent meta-analysis showing a prevalence of ILD as high as 42% for patients with DM.[77] Recommended pulmonary screening includes an initial pulmonary function test (PFT) with carbon monoxide diffusion capacity at time of diagnosis with repeat testing every 3–12 months depending on previous findings and MSA status (ie, more frequent monitoring is recommended for patients at high risk for ILD such as patients with MDA-5 and anti-synthetase specific autoantibodies). Abnormalities on PFTs warrant a high-resolution chest computed tomography (CT) scan to assess the degree of disease activity.[64,78]

The association with possible underlying malignancy for adult DM is well established with the most significant risk found to be within the first 3–5 years of diagnosis.[62] Overall cancer incidence in DM is between 15% and 27%, with elevated risks for at least 11 types of malignancies.[79,80] For women, cancers with the greatest risk include breast, ovarian, and uterine cancer.[81] In a nationwide cohort study in Taiwan, cancers with the greatest risk associated with DM included nasopharyngeal carcinoma, followed by lung and breast cancers.[82] Universally accepted screening guidelines are lacking, but age appropriately cancer screening is recommended along with obtaining a complete blood count, liver function tests, urinalysis, fecal occult blood test and chest radiograph.[83] Additionally, given cancer is the leading cause of death in patients with DM, many experts recommend blind screening for patients using computed tomography (CT) or positron emission tomography (PET).[84,85]

Treatment

Treatment of the cutaneous manifestations of DM can be challenging, with skin disease often proving to be more recalcitrant than muscle disease. Most patients will require systemic therapy; however, behavioral changes and topical medications should be included as part of the treatment regimen. Year-round photoprotection is an important initial step in disease management as UV radiation is a known trigger of disease.[86] Akin to cutaneous lupus, patients should be counseled on aggressive techniques around UV protection including sun protective clothing, shade seeking behaviors, and physical sunscreens as even minimal UV exposure can lead to notable flares of disease.[64]

Topical corticosteroids can also be used as adjunctive treatment for relief of cutaneous symptoms including burning, pain, and pruritus. Topical calcineurin inhibitors are also commonly used as steroid-sparing agents to reduce the risk for cutaneous atrophy with prolonged topical steroid use. Both topical (pramoxine, menthol, camphor) and systemic (gabapentin, amitriptyline) antipruritic agents can also be prescribed to help mitigate pruritus while awaiting efficacy of systemic agents.[64,67]

Systemic corticosteroids are a crucial component of early treatment for patients with muscle disease in CDM while awaiting efficacy of steroid-sparing agents. While systemic steroids are also effective in treating skin disease, it is recommended to avoid systemic steroids for patients with amyopathic disease to mitigate risk factors associated with systemic steroid use. Patients with CDM should be started initially on high dose systemic corticosteroids until improvement of muscle disease is seen, and then steroids should be gradually tapered.[65] All patients started on systemic steroids should be started on steroid-sparing agents concomitantly to allow for more rapid tapering of systemic steroids. In addition, consensus guidelines for JDM recommend beginning systemic corticosteroids with MTX or intravenous immunoglobulin to reduce long-term steroid risks.[87]

Antimalarials were traditionally considered a first-line systemic treatment for the cutaneous manifestations of DM. However, their use in dermatomyositis is becoming less favored over time as antimalarials lack efficacy for both cutaneous and non-cutaneous symptoms. When used as a monotherapy, hydroxychloroquine results in remission of skin disease in only 11% of patients.[88,89] Additionally, approximately ⅓ of DM patients have been shown to develop cutaneous hypersensitivity reactions.[64,89] Because of this, antimalarials such as hydroxychloroquine are now used much more sparingly in the treatment of dermatomyositis.

MTX is a first-line steroid-sparing agent used for both skin and muscle disease in DM and has been shown to serve as an effective steroid-sparing agent for this disease.[90] In a study comparing MTX and cyclosporine A, 73% of patients treated with MTX showed clinical improvement after 6 months of treatment.[91] MMF is also considered a first-line agent for both skin and muscle disease and can also be considered in patients who have failed or cannot tolerate MTX. In a study of 12 DM patients with cutaneous lesions recalcitrant to traditional therapies, improvement was seen in 83% of patients following within 4 to 8 weeks of MMF treatment.[92] No head-to-head studies exist comparing MTX with MMF, but MTX is used more commonly as a first-line systemic agent, particularly given the malignancy risk for patients with dermatomyositis.[93] However, MMF is the preferred agent for DM patients at high risk for lung disease (particularly in those positive for MDA-5), as studies have shown MMF to be effective for treating and preventing progression of ILD.[94]

Intravenous immunoglobulin (IVIg) is an effective treatment for both muscle and skin disease in severe and refractory DM. The favorable results of IVIg in a recent phase III RCT ("ProDERM") led the US Food & Drug Administration to grant this medication orphan drug status for DM in July 2021. This trial enrolled 95 adult DM patients in which 47 patients received IVIg (2g/kg every 4 weeks). Results showed that IVIg was well tolerated and significantly effective at treating both muscle disease (primary outcome) and skin disease (secondary outcome) versus placebo.[95] IVIg can be used as both monotherapy and as an adjuvant to other systemic treatment.[64] In addition, IVIg is the preferred therapy for calcinosis cutis in JDM.[93]

Janus kinase (JAK) inhibitors have shown increasing evidence as an effective therapy in both CDM and CADM.[96,97] In the largest prospective clinical trial using tofacitinib monotherapy in ten patients with DM, the skin disease activity as measured by the CDASI improved from moderate to severe skin disease activity to mild in 70% of patients.[98] In another prospective study with 18 DM patients studying tofacitinib with concomitant glucocorticoid therapy versus conventional therapy, the former cohort exhibited a higher survival rate at 6 months as well as improved lung function.[99] Most studies to date exploring JAK inhibitor use in DM administered the drug as an adjuvant to other systemic therapies.[96]

Multiple trials for novel medications are currently underway, with a focus on mitigating the inflammatory pathway leading to disease. Apremilast is a phosphodiesterase 4 inhibitor which was recently shown to improve skin symptoms in a small phase 1b clinical trial for patients with refractory DM.[100] Another trial for a drug targeting the interferon inflammatory pathway in cutaneous disease is set to complete a phase 2 RCT in December 2022.[101,102] Finally, lenabasum is a selective cannabinoid receptor type 2 agonist which demonstrated benefit for cutaneous symptoms in a phase 2 RCT, but failed to replicate these findings in a recent phase 3 trial.[103,104]

Systemic Sclerosis (Scleroderma)

Systemic sclerosis (SSc) is a rare connective tissue disease with both cutaneous and systemic manifestations of disease. Global incidence rates range between 8 and 56 cases per million annually with a higher propensity for women.[105,106] Among patients with SSc, greater disease severity has been noted in both men and African American patients.[106–108] The etiology of SSc is not well understood, but vascular injury prompting a dysregulated immune response and uncontrolled fibroblast activation leading to excess collagen deposition are thought to play a role.[109] Current hypotheses suggest exposure to viruses, environmental toxins or drugs may serve as disease triggers in genetically susceptible hosts.[110,111] Silica, vinyl chloride, paraffin, L-tryptophan, and rapeseed oil have all been associated with systemic sclerosis in prior studies.[112]

Diagnosis

SSc is a clinical diagnosis, and a careful skin exam for characteristic cutaneous manifestations is pivotal to early intervention and treatment. In 2013, The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) published a joint proposal for classification criteria of SSc, regarded as more sensitive and specific than previous classification criteria.[113] The ACR-EULAR classification system assigns points to both cutaneous (skin thickening on hands, fingertip lesions, telangiectasias, Raynaud phenomenon, nailfold changes) and systemic findings (pulmonary hypertension, interstitial lung disease), as well as serologic markers (anti-centromere, anti-ScL 70, anti-RNA polymerase III), and defines diagnosis in patients scoring ≥9. Cutaneous symptoms account for the majority of the ACR-EULAR criteria, underlying the importance of skin examination in diagnosing SSc.

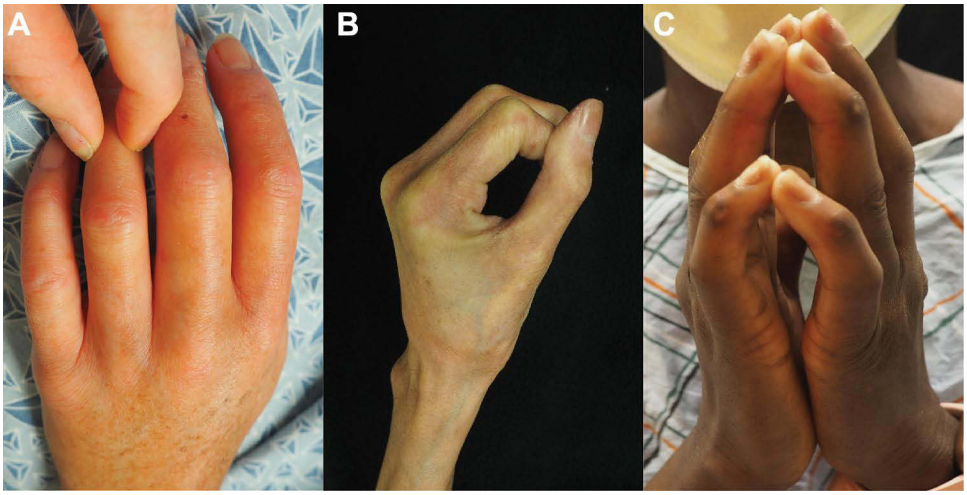

Figure 6 Cutaneous fibrosis starting at the distal fingers, as demonstrated by decreased skin mobility between the distal interphalangeal and proximal interphalangeal joints (**A**) is one of the hallmark features of systemic sclerosis. Over time, fibrosis extends proximally leading to difficulties forming a fist (**B**) and a positive "prayer sign" (**C**).

Cutaneous fibrosis affecting the fingers, hands and frequently the face is one of the hallmark findings for patients with SSc and as such is given significant weight in classification criteria and diagnosis.[106,113] Before thickening begins, patients may present initially with "puffy fingers", characterized by inflammation, edema, occasionally erythema and often pruritus and burning pain.[109] Patients will then progress to the "prolonged fibrotic phase" in which skin thickening occurs. Fibrosis begins on the distal fingers (sclerodactyly) and then extends proximally from there leading to difficulties making a fist and a positive "prayer sign" in patients over time (Figure 6). During this phase, compression of underlying joints can cause irreversible contractures and ulcers may occur due to trauma to fibrotic skin.[109] Patients with facial involvement may also display perioral skin tightening, leading to microstomia and anatomic changes leading to beak-shaped changes to the nose. Importantly, facial disfigurement has been ranked as the most significant factor affecting quality-of-life for patients with SSc.[114]

The extent of cutaneous fibrosis is used to subdivide SSc into four distinct clinical subtypes: (1) limited cutaneous SSc (LcSSc), (2) diffuse cutaneous SSc (DcSSc), (3) systemic sclerosis sine scleroderma and (4) SSc overlap syndrome.[106,115] Patients with LcSSc display sclerosis of the bilateral upper and lower extremities distal to the elbows and knees and sparing the trunk. Conversely, patients with DcSSc demonstrate skin fibrosis extending proximal to the elbows and/or knees, often involving the trunk. The facial changes of systemic sclerosis can be seen in both subtypes. Systemic symptoms occur in both LcSSc and DcSSc. Both subtypes may develop lung fibrosis and pulmonary arterial hypertension (PAH); however, interstitial lung disease is seen with higher frequency in patients with DcSSc while PAH is seen more commonly in patients with LcSSc. An increased risk for cardiac and renal involvement exists for DcSSc. The gastrointestinal tract is also commonly affected in both subtypes with varying degrees of severity.[106] In rare instances, patients will present with systemic findings of SSc without the typical cutaneous findings. This subtype is called systemic sclerosis sine scleroderma and occurs in 1.5–8.3% of SSc cohorts.[116,117] Lastly, SSc overlap syndrome is diagnosed in patients with signs and symptoms of SSc who also possess characteristics of other connective tissue diseases. Within this overlap subset, SSc occurs most commonly with features of Sjogren's syndrome and dermatomyositis/polymyositis, but may also present with symptoms of systemic lupus erythematosus and rheumatoid arthritis.[118]

Raynaud phenomenon (RP) is a common clinical finding in many connective tissue diseases and is the most common early manifestation of SSc.[119] Middle-aged patients, especially women, presenting with late onset or asymmetric RP should raise suspicion for SSc or other autoimmune diseases.[120] RP has been found to occur in 90–100% of patients with both LcSSc and DcSSc, and helps distinguish this condition from other fibrosing skin diseases.[106,119] This phenomenon is thought to occur secondary to microvascular injury and fibrosis in SSc and symptoms can be severe for many patients. While most frequently occurring in the fingers, symptoms can also occur in the toes, ears, nose, and tongue.[109] Those

with severe RP are at risk for ulceration, gangrene and digit loss, emphasizing the importance of early detection and treatment.

Nailfold changes in SSc are a common early finding and are a validated method of evaluating microvascular damage in these patients.[121,122] Capillaroscopy is an effective tool to help guide diagnosis, as patients with SSc will display unique capillary patterns which are present in a majority of patients.[123] Patients with this condition will display dilated nailfold capillaries and often show a mix of avascular and neoangiogenic areas. Capillaroscopy is particularly important when evaluating patients with RP to determine whether this finding is primary or secondary to connective tissue disease. While mild nailfold capillary dilation can occur in primary Raynaud's, more prominent abnormal nailfold changes are strongly suggestive of an underlying rheumatic disorder.

Telangiectasias are an important diagnostic feature of SSc and possess a distinctive morphology. As opposed to those seen in rosacea and liver disease, telangiectasias in SSc often appear matted and occur most commonly on the hands, face and upper trunk.[124,125] The number of whole-body telangiectasias in patients with SSc also has clinical significance as an association has been found with a higher degree of pulmonary hypertension and other vasculopathies in this condition.[125]

Calcinosis cutis is a common and potentially debilitating feature of SSc, thought to occur from calcium deposition in damaged tissue. In SSc, calcinosis typically occurs in the hands and fingers and is another potential cause of digital ulceration in this disease. Calcinosis can often be appreciated clinically; however, plain radiographs can also be used to assist with diagnosis. While a number of studies and case series have explored the use of medical therapies in calcinosis, including high dose diltiazem,[126] colchicine,[127] intravenous immunoglobulins,[128] and sodium thiosulfate,[129] overall outcomes with medical therapy have been variable.[130] Alternatively, optimizing medical management of the patient's underlying connective tissue disease is pivotal for patients with calcinosis and surgical excision can be explored as a definitive therapy for patients with severe symptoms.[130]

Patients with SSc often develop salt-and-pepper dyspigmentation, which can be one of the earliest manifestations of disease and have a major impact on quality of life, particularly for patients with skin of color.[131] This finding presents as diffuse areas of hyper- and hypopigmentation, often more prominent in sun-exposed areas, and will typically display perifollicular pigmentary retention (Figure 7).[132] Particularly in the absence of early fibrotic findings, patients with salt-and-pepper dyspigmentation can be misdiagnosed with vitiligo, with the risk of delaying diagnosis of systemic symptoms.[131] High levels of suspicion for SSc for patients with large patches of depigmentation with perifollicular pigmentary retention can assist with early diagnosis of disease.

Lastly, pruritus is a common feature of SSc, with one study reporting prevalence of 43% in a cohort of 959 patients.[133] Presence of this symptom has been associated with a larger degree of skin and gastrointestinal involvement as well as increased psychological burden and depression.[134] As such, pruritus also has a major impact on quality-of-life and patients should be screened for this system to ensure comprehensive care.

As discussed previously, SSc commonly manifests with systemic findings requiring prompt detection and management. Mortality in this disease is most likely to occur as a result of interstitial lung disease (ILD), pulmonary arterial hypertension (PAH) and direct cardiac involvement.[135] All patients with SSc should receive a high-resolution chest CT to assess for ILD at the time of diagnosis. Patients should also undergo initial pulmonary function testing (PFT) with

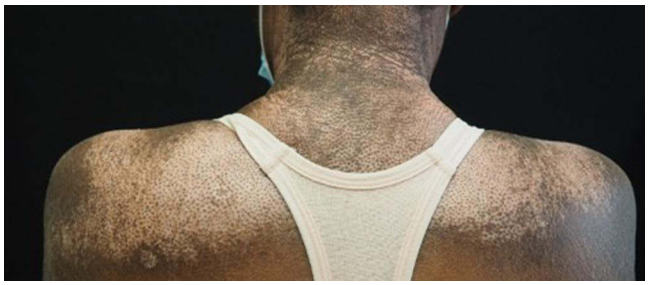

Figure 7 Salt-and-pepper dyspigmentation can be the presenting finding in patients with systemic sclerosis and a leading cause of body image dissatisfaction in patients with skin of color.

Table 3 Summary of French Recommendations for the Workup and Management of Systemic Sclerosis (SSc)[135]

Initial workup:	• Define phenotype: limited cutaneous SSc, diffuse cutaneous SSc, SSc sine scleroderma • Determine disease duration (since 1st non-Raynaud's symptom): <3 years or >3 years • Determine antibody status: ANA, anti-scl-70, anti-centromere, anti-RNA-polymerase III
Pulmonary	• Baseline high resolution CT chest • Pulmonary function tests with DLCO every 6 months for 3–5 years • Advanced workup and repeat imaging guided by symptoms
Cardiac	• Echocardiogram and electrocardiogram yearly • Advanced workup guided by symptoms
Gastrointestinal	• Workup guided by symptoms
Renal*	• Routine blood urea nitrogen, creatinine, urinalysis • Self-monitoring blood pressure first 3–5 years

Note: *If patient has positive anti-RNA-polymerase III antibodies or diffuse cutaneous SSc subtype.
Abbreviations: ANA, antinuclear antibody; CT, computerized tomography; DLCO, diffusing capacity for carbon monoxide.

frequent follow-up in those with DcSSc. Yearly echocardiogram and electrocardiogram are both recommended to assess for PAH and cardiac involvement.[135]

Gastrointestinal involvement is the most common systemic manifestation SSc, with evidence of this occurring in close to 90% of patients with both DcSSc and LcSSc.[106,136,137] Symptomatic patients most commonly present with signs of esophageal dysmotility, although any area of the digestive systemic can be affected with varying degrees of severity.[138] Initial screening involves obtaining a complete blood count and differential to detect anemia due to malabsorption or gastrointestinal bleeding, with further screening dependent on the presence of symptoms.[106,135]

Renal involvement should also be closely monitored in SSc and is more likely to occur in the DcSSc subtype. Serum creatinine and urinalysis are recommended screening for all patients, and those with DcSSc should undergo routine monitoring of blood pressure and creatinine levels.[106,135] In severe cases, patients may develop SSc renal crisis which typically carries a poor prognosis. Lastly, SSc can occasionally manifest with neuromuscular symptoms, particularly in patients with overlap syndrome. These symptoms include myopathy and symmetric proximal muscle weakness which warrant further workup.[106] While no set guidelines exist in the US for the workup of patients with SSc, recent guidelines published in France provide a comprehensive summary of recommended workup and management.[135] These recommendations are summarized in Table 3.

Skin biopsy is not generally indicated for the diagnosis of SSc, but may rarely be used to help confirm fibrosis in early or atypical presentations of disease.[106] Dermatopathology of SSc will typically display a square morphology with dense fibrosis, reduced adnexal structures, and lack of inflammatory cell infiltrate.[139]

The presence of autoantibodies play an important role in the diagnosis and prognosis of SSc. Anti-nuclear antibody (ANA) is positive in 90% of patients with this disease.[109] While many SSc-specific autoantibodies have been implicated, the presence of anti-centromere (ACA), anti-topoisomerase (anti-Scl 70), and anti-RNA polymerase III (anti-RNAP III) antibodies are seen with the greatest frequency in patients with SSc are all included within the ACR-EULAR classification criteria. Of these three, anti-Scl 70 and anti-RNAP III are both most strongly associated with DcSSc while ACA is more commonly associated with LcSSc.[135] In regard to cutaneous symptoms, anti-RNAP III is associated with rapidly progressive skin damage and skin malignancy.[106] Additionally, ACA is correlated with increased rates of PAH and anti-Scl 70 is associated with severe ILD.[135]

Treatment

Early treatment for patients with progressive fibrosis is essential to improve outcomes and minimize long-term complications associated with cutaneous fibrosis (ie, permanent joint contractures). Early disease is most amenable to treatment with anti-fibrotic agents as end stage or longstanding fibrosis is more recalcitrant to therapy and can be difficult to reverse. Cyclophosphamide was previously considered first-line for treating skin fibrosis and lung disease. However,

RCT data from the Scleroderma Lung Study II validated MMF as having improved tolerability with equal efficacy as cyclophosphamide in improving the cutaneous fibrosis of SSc.[140,141] In this study, 71.7% of patients treated with MMF experienced an improvement in their modified Rodnan Skin Score (mRSS) from baseline over the 24-month study period. In the wake of this study, MMF, with its anti-TGF-beta properties, has become the gold standard agent for treating cutaneous fibrosis for patients with SSc, particularly given the high risk of ILD. In this population, MMF in SSc is dosed at 2–3 grams daily with the greatest improvements in cutaneous fibrosis seen 6 months after initiation of therapy.

IVIg can be considered in patients with severe cutaneous fibrosis with sub-optimal response to first-line therapy. A single RCT has been conducted examining the effects of IVIg for skin disease in SSc.[142] This study enrolled 63 patients in Japan with DcSSc and initially administered a single course of IVIg at 400mg/kg/day for 5 days. While no significant improvement was noted after the initial course, patients were found to achieve improved skin scores following a second course of IVIg in the re-administration study. This RCT is supported by previous open label studies showing skin improvement after prolonged courses of IVIg,[143] as well as improvement of systemic disease manifestations such as myositis and gastrointestinal symptoms.[144] These studies suggest that IVIg should be considered for patients with refractory cutaneous fibrosis, particularly in those with visceral involvement.

Similar to IVIg, rituximab (RTX) is another systemic therapy that can be considered in patients with refractory disease with additional evidence supporting its therapeutic efficacy for systemic symptoms. A number of smaller clinical trials have studied RTX in SSc with skin outcomes frequently examined as an outcome measure. The majority of these studies reported a statistically significant improvement on skin disease at some point during the study period. Recently, the DESIRES clinical trial enrolled 54 patients with SSc (51 women, 5 men) randomized to receive weekly intravenous RTX (375 mg/m^2) or placebo for 4 weeks.[145] The study demonstrated a significant improvement in mRSS scores after 24 weeks for patients treated with RTX versus placebo. This study was the first clinical trial to assess skin disease as the primary endpoint and added robust data to support the use of rituximab as an alternative agent to consider for patients with severe cutaneous fibrosis.[101,145]

Methotrexate can also be considered as an adjunctive treatment for the cutaneous fibrosis seen in systemic sclerosis. Two RCTs have been published studying the effects of MTX on cutaneous fibrosis. Together, these studies enrolled a total of 100 patients with SSc, of which, 52 received MTX. One study administered MTX at 15mg/week intramuscularly for 24 weeks[146] while the second study gave an oral dose of 10mg/week for 12 months.[147] Both studies reported an improvement in skin symptoms for the MTX treatment group measured either by the total skin score[146] or mRSS.[147] Importantly, however, MTX does not have the same lung-protective features as MMF and should be considered to be an adjunctive therapy for cutaneous fibrosis for patients with SSc.

A number of targeted biologics are currently being studied for use in SSc and SSc-related skin disease.[148] Drugs targeting interleukin (IL) receptors include tocilizumab (IL-6), romilkimab (IL-4, IL-13) and rilonacept (IL-1R1). Of these agents, romilkimab and tocilizumab have both undergone phase 2 clinical trials with romilkimab demonstrating a statistically significant improvement in skin symptoms measured by the mRSS.[149] Lenabasum is another novel therapy, functioning as an agonist to type 2 cannabinoid receptor implicated in inflammation and tissue fibrosis. A phase II RCT of patients with early SSc treated with lenabasum, as an adjuvant to previous therapy, demonstrated significant treatment efficacy.[150] Skin improvement across various outcome measures (mRSS, physician global assessment and itch) were later seen in a follow up open-label trial.[161]

Aggressive management of Raynaud's phenomenon (RP) for patients with SSc is crucial to prevent complications such as ulceration and loss of digits. All patients should be counseled around behavioral modifications to mitigate RP including smoking cessation, warming the core, and avoiding triggers such as cold temperatures, nasal decongestants, and stimulants.[151] Regarding pharmacologic intervention, calcium channel blockers are widely regarded as first-line agents, followed by the addition of a phosphodiesterase type 5 inhibitor.[152] Recently, local injection with botulinum toxin has also been used to reduce vasospasm in treatment-refractory patients. Clinical trials have demonstrated benefit for SSc-related RP using botulinum toxin compared to both placebo[153] and prostaglandin analog infusions.[154] When they occur, ulcerations require prompt recognition and appropriate wound care to prevent infection, with some patients requiring surgical debridement. Intravenous prostaglandin/prostacyclin analogs should also be considered for patients at

risk for digit loss from severe ulceration. Finally, angiotensin receptor blockers, selective serotonin reuptake inhibitors, statins, endothelin receptor agonists and aspirin can also be considered for patients with refractory disease.[155,156]

The pathogenesis of pruritus in SSc is not well defined, but may be related to nerve fiber damage from underlying fibrosis and inflammation.[134] Treatment of cutaneous fibrosis with anti-fibrotic agents may improve pruritus in some patients. However, anti-pruritic agents, such as gabapentin, can be considered for patients for whom pruritus is more severe. A small case series has shown that low-dose naltrexone may be an effective treatment for some patients, but larger studies are likely needed.[157]

Of note, systemic corticosteroids should be avoided or used cautiously in SSc patients due to the risk for precipitating renal crisis.[109]

Morphea

Morphea is an immune driven sclerosing disorder of the skin and subcutaneous tissue. Although morphea was originally named "localized scleroderma" due to the similarities seen on biopsy of these two disease states, morphea and SSc are two distinct disease processes with morphea patients at no higher risk of progressing to SSc than the general population.[158–160] As such, patients with morphea lack the systemic disease manifestations seen in SSc such as Raynaud phenomenon, interstitial lung disease, and other visceral organ involvement.[159] Incidence of this condition is estimated to be between 3.4 and 27 per 100,000 with a higher propensity towards women.[161,162] Disease is thought to be related to inappropriate fibroblast activation causing localized overproduction of collagen leading to disease manifestations.[163]

Diagnosis

The diagnosis of morphea is typically made by the presence of clinical findings, although histopathology and radiologic imaging can be used to assist with diagnosis for patients with atypical presentations.[164,165] While multiple subtypes exist, classic morphology for morphea involves localized, erythematous to violaceus to hyperpigmented indurated plaques. Morphea can occur anywhere on the body, and often follow three distinct stages defined as (1) an early inflammatory stage, (2) a fibrotic phase, and (3) an inactive or "burnt out" stage.[160] The early inflammatory stage of morphea is often characterized by pink to violaceous patches or thin plaques which then progress to expand centrifugally becoming more fibrotic and indurated over time during the fibrotic phase. As plaques expand, morphea plaques often become hypo or hyperpigmented centrally with a violaceous hue at any active, advancing border. Burnt out morphea often becomes less indurated with time leaving behind hyper or hypopigmented patches or plaques. While morphea is classically asymptomatic, pruritus or tenderness can be experienced by some patients. Additionally, certain subtypes can cause mobility concerns, particularly in children, when deeper structures or joints are involved.

Morphea is most commonly classified according to five subtypes: (1) circumscribed (plaque), (2) generalized, (3) linear, (4) pansclerotic, and (5) mixed.[160,166] These subtypes are diagnosed according to clinical characteristics of disease, location, and degree of fibrosis. While there may be overlap, classification can be useful for determining prognosis, work up, and recommended treatments.[165] Deep morphea (morphea profunda), keloidal morphea, and bullous morphea are considered disease descriptors and can occur across disease subtypes. In addition to these five subtypes, eosinophilic fasciitis is thought to be on the severe end of the morphea spectrum. Additionally, overlap between morphea and extragenital lichen sclerosus are not uncommon.

Circumscribed (plaque) morphea is diagnosed in patients with 1–3 circumscribed, round/oval plaques typically <3 centimeters in size (Figure 8). Circumscribed morphea can be either superficial (limited to the epidermis or dermis) or deep (extending into the fascia and possibly muscles).[166]

Generalized morphea is diagnosed when patients display 4 or more plaques larger than 3cm. Plaques in this subtype may become confluent and involvement of two distinct anatomic areas are required to make the diagnosis. Lesions typically appear symmetrically on the extremities, breasts, and abdomen, or on areas of chronic friction. Although joint involvement is less common for patients with generalized morphea than those with linear morphea, patients with generalized disease involving the extremities should be assessed for evidence of contractures or impacts on mobility.[164]

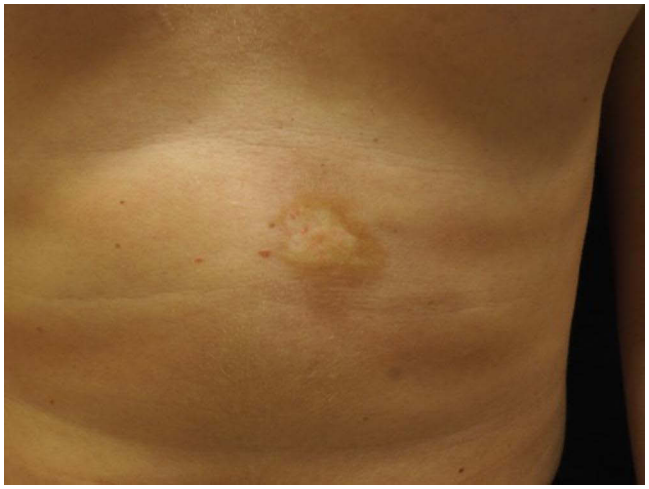

Figure 8 Plaque morphea is a subtype of morphea characterized by <3 plaques and <3 centimeters in size.

Linear morphea presents as linear plaques of morphea on either the head and face or extremities with the potential to involve deeper structures, causing functional impairment, neurological issues and cosmetic concerns.[167] As a result, prompt recognition and treatment is crucial to prevent permanent complications with mobility and/or disfigurement. This subtype is generally further subdivided based on facial or extremity involvement. Linear morphea affecting the face includes En Coup de Sabre (ECDS) which displays indurated linear plaques most commonly on the paramedian or temporal forehead and extending into the scalp with associated scarring alopecia (Figure 9).[166] Progressive hemi-facial atrophy (Parry-Romberg syndrome) is a subset of linear morphea leading to loss of subcutaneous tissue impacting one half of the face. Both subtypes of linear morphea impacting the face have the potential for involvement of underlying muscle, bone, eyes (with concomitant uveitis), and dental anomalies. Linear morphea present on the extremities may also impact muscles and bones and careful assessment for joint contractures or extremity shortening is crucial.[168]

Pansclerotic morphea is defined by morphea with fibrosis extending from the skin completely through the subcutaneous tissue, muscle and bone.[166]

Lastly, mixed morphea should be diagnosed in patients displaying a combination of more than one subtype of morphea.

Eosinophilic fasciitis (EF) is felt by many to be on the severe end of the morphea spectrum. Skin findings in EF typically show initial edema of the bilateral upper and lower extremities followed by bilateral, symmetric induration

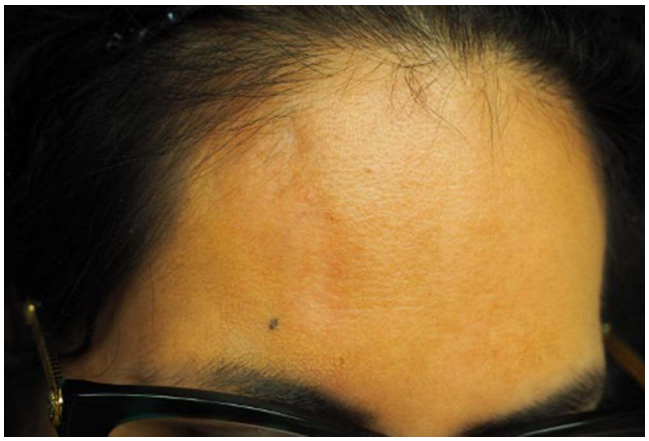

Figure 9 En coup de sabre is a subtype of linear morphea presenting as a hyper to hypopigmented indurated plaque extending linearly down the paramedian or temporal forehead.

leading to joint contractures in severe cases. EF is more likely than morphea to cause functional impairment, with progressive bilateral and symmetric fibrosis along the fascial plane leading to prominent functional impairment, especially for patients without early intervention.[169] An important diagnostic finding in EF is the "groove sign", in which affected extremities will show linear indentations tracking along superficial veins caused by subepidermal fibrosis (Figure 10).[169] Importantly, the location of fibrosis along the fascial plane in eosinophilic fasciitis leads to notable clinical difference that can help distinguish patients with eosinophilic fasciitis from patients with systemic sclerosis. Patients with eosinophilic fasciitis will have preserved mobility and laxity of the skin over the distal dorsal digits between the distal interphalangeal joints and the proximal interphalangeal joints (Figure 11) whereas patients with systemic sclerosis have dermal fibrosis starting at the distal fingertips and extending proximally leading to loss of mobility of this skin early in disease. Other important disease factors distinguishing eosinophilic fasciitis from systemic sclerosis include the presence of the groove sign and cobblestoning of the skin over the proximal extremities, giving patients with eosinophilic fasciitis a pseudo cellulite appearance in these locations (Figure 12). Patients with eosinophilic fasciitis also lack the facial involvement and RP seen in patients with SSc.

Historically, full thickness biopsy extending to the fascia was used for diagnostic purposes to confirm disease involvement in eosinophilic fasciitis.[170] However, recently, many derm-rheum experts have begun favoring MRI alone over deep tissue biopsy to avoids complications from poor wound healing in patients with this sclerotic disease.[171] Of note, MRI can be used both to confirm diagnosis as well as to track disease progression over time. Importantly, EF has also been shown to have an association with hematologic abnormalities such as eosinophilia and monoclonal gammopathy in some patients and patients should be screened appropriately.[172,173]

Overlap disease with extragenital lichen sclerosus (EGLS) is seen in roughly 4% of patients with morphea.[174] EGLS is characterized by epidermal atrophy leading to cigarette paper-like atrophic plaques, which may be asymptomatic or pruritic. Genital lichen sclerosus is also common in morphea patients, with a separate study revealing concurrent genital

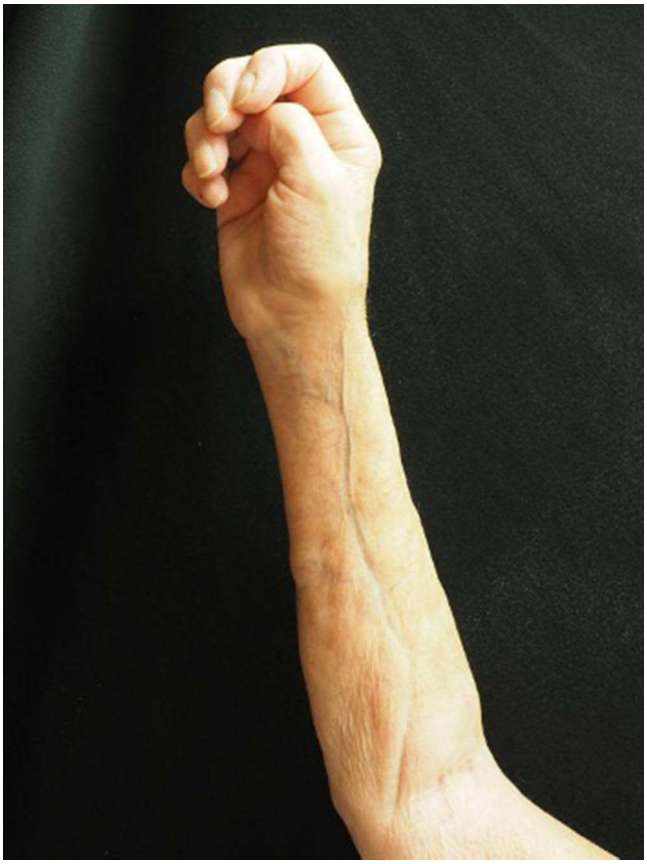

Figure 10 The groove sign of eosinophilic fasciitis is characterized by linear indentations of skin along the superficial veins of the forearm.

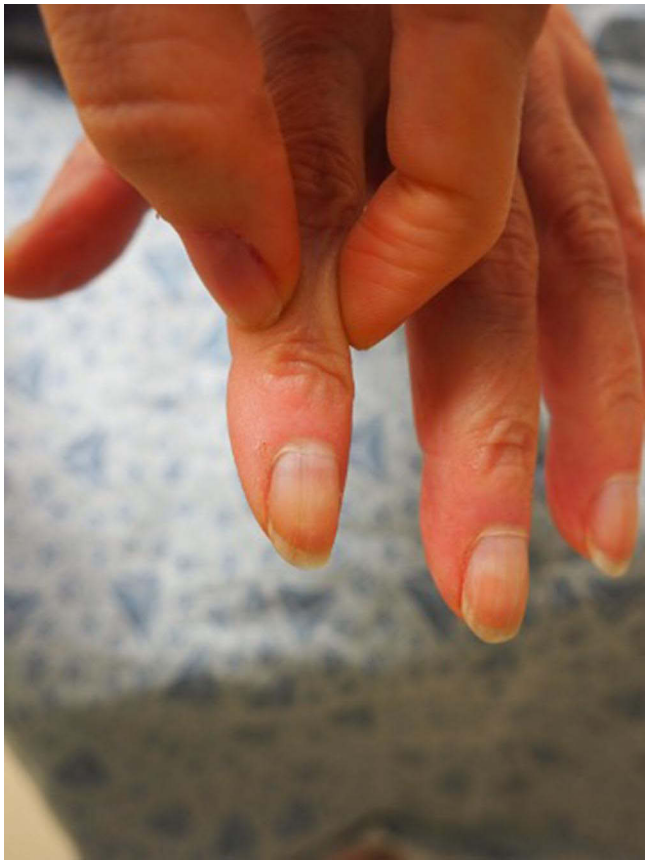

Figure 11 Preservation of mobility of the skin between the distal interphalangeal and proximal interphalangeal joints can help distinguish eosinophilic fasciitis from systemic sclerosis.

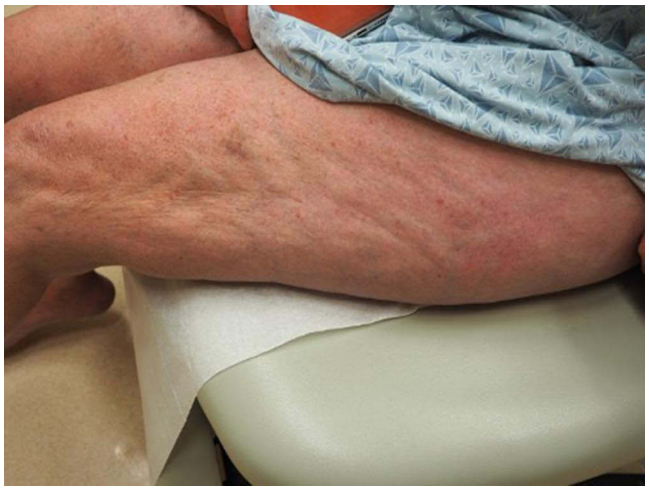

Figure 12 Fibrosis along the fascial plane in eosinophilic fasciitis can produce a puckering of skin of the proximal upper and lower extremities leading to a "pseudo-cellulite" type appearance.

lichen sclerosus in 38% of their patient cohort.[175] When morphea and EGLS present together, it is known as lichen sclerosus/morphea overlap. Given the similar clinical and histopathologic findings between these two conditions, some presume there may be a common pathological link and classify EGLS as a subtype of circumscribed morphea.[176] This

classification, however, is not universally agreed upon. When patients present with signs of EGLS, pelvic exam should be performed to rule out genital involvement.

While morphea is generally considered to be a clinical diagnosis, biopsy has utility when the diagnosis is uncertain. When morphea is suspected, full thickness biopsies extending into the subcutaneous fat are crucial to facilitated diagnosis.[164] Samples from the Inflammatory stage of disease will typically show lymphocyte and plasma cell infiltrate, potentially extending into the subcutaneous fat. More progressive sclerotic lesions often demonstrate thickened hyalinized collagen bundles throughout the dermis.[177] Deeper forms of morphea and eosinophilic fasciitis may require additional imaging studies, such as MRI, to appreciate the full extent of tissue involvement.

No autoantibodies with diagnostic or prognostic significance have been identified in patients with morphea to date. Importantly, given that morphea and SSc are two distinct entities, as described above, patients with morphea lack characteristic autoantibodies present in SSc and checking of these antibodies in patients with morphea is not recommended. A meta analysis looking at a large morphea cohort found that up to 50% of patients had elevated ANA, AHA, and anti-ssDNA. While not particularly helpful for diagnostic purposes, these three autoantibodies were associated with greater disease severity.[178] However, routine screening for these antibodies is not considered standard of care at this time.

As mentioned previously, as opposed to systemic sclerosis, systemic complications of morphea are rare. Potential systemic manifestations of disease include neurological complications (ie, neuromorphea), dental anomalies, or uveitis in craniofacial linear morphea, joint contractures in extremity subtypes of linear morphea, and/or concomitant inflammatory arthritis in any subtype of morphea. Patients with craniofacial subtypes of linear morphea should be screened with baseline brain MRI as well as dental and ophthalmology exam. Patients with extremity subtypes of linear morphea should be monitored for joint contractures with serial range of motion evaluations by physical therapy or rheumatology. Screening for concomitant inflammatory arthritis should be considered in all subtypes of morphea.[179,180]

Treatment

First-line treatment for morphea is dependent on subtype and severity of disease.

Non-progressive, localized disease without joint involvement or cosmetic concerns can be treated initially with topical or intralesional therapy. Large clinical trial data is lacking for the use of topical or intralesional corticosteroids, although case studies have reported some positive outcomes for this treatment option for patients with localized or plaque disease.[163,181] Other topical options include calcineurin inhibitors and calcipotriene.[182] Tacrolimus ointment has been studied most extensively among calcineurin inhibitors with a RCT showing superior efficacy to placebo over 12 weeks.[183] Calcipotriene ointment has also shown efficacy in a 3-month open label trial for treating circumscribed morphea.[184]

While topical therapy may be appropriate for patients with localized and non-progressive disease, most patients with more widespread or linear disease will require photo or systemic therapy.

Phototherapy is a treatment option for patients with generalized morphea, particularly for more superficial variants of diseased.[161] The lower side effect profile of phototherapy may also be preferred by some patients who are hesitant to consider systemic therapy. Phototherapy is thought to improve the clinical symptoms of sclerosing diseases both by immunomodulating B and T-lymphocytes and upregulating collagenase I activity within the skin.[160,185] Multiple treatment modalities exist, with evidence for ultraviolet A (UVA), ultraviolet B (UVB), and psoralen plus UVA (PUVA) all showing efficacy. UVA phototherapy has been most extensively studied for morphea[186] although no specific protocol has been specifically validated as superior and limited UVA phototherapy accessibility exists across the US. For this reason, NBUVB is used most commonly given its broader accessibility and favorable side effect profile in comparison to PUVA.

Methotrexate (MTX) has the most evidence supporting its use as a therapeutic in morphea and continues to be considered the first-line systemic agent for this disease.[187–189] Despite most studies focusing on the pediatric population, efficacy of MTX has also been validated in adults as both a monotherapy[190] and in conjunction with systemic corticosteroids.[191] Since noticeable clinical improvement with MTX monotherapy has been shown to take 3 months,[190] patients with rapidly progressive disease or disease with the potential to have a significant impact on mobility or cosmesis concomitantly with systemic corticosteroids early in their disease course. MTX given with systemic

corticosteroids has been studied extensively in children with morphea,[188] and strong consensus exists for its use early in the disease course for patients with linear and pansclerotic disease.[192] Importantly, decreased rates of relapse are seen in patients who are treated with methotrexate for 24 months prior to tapering.[189]

In patients for whom treatment with methotrexate is ineffective, not tolerated, or contraindicated, recent evidence supports the use of MMF or mycophenolic acid (MPA) as an effective alternative. A 2020 multicenter study examining a cohort of 77 patients with moderate to severe morphea found that MMF or MPA was generally well tolerated and effective in improving skin symptoms in 85% of patients.[187] Almost half of the patients in this study had previously failed or were unable to tolerate MTX. While no studies exist comparing MMF and MPA to methotrexate, both MMF and MPA can be considered as an alternative treatment option for patients requiring systemic management of their disease.

IVIg can also be considered for patients with progressive morphea who have not responded to or have contraindications to methotrexate and/or mycophenolate mofetil. While not extensively studied, IVIg has shown efficacy in small cohorts of both morphea[193] and eosinophilic fasciitis patients.[194] Of note, most of these studies examined IVIg in combination with other systemic agents.

JAK inhibitors, specifically tofacitinib, have been studied in small case reports of patients who had failed initial systemic therapy. In total, two patients with morphea and one with eosinophilic fasciitis received tofacitinib and all experienced significant clinical improvement during the documented treatment period.[195,196] More studies are needed to test the efficacy of JAK inhibitors in larger patient cohorts; however, early case series as well as mouse models of disease suggest JAK inhibition may be a promising therapeutic avenue for patients with morphea and eosinophilic fasciitis.[195,197]

Other emerging treatments currently being explored include dupilumab and abatacept. Dupilumab is an interleukin-4 (IL-4) receptor antagonist and is currently being studied in a phase 2 RCT for patients with morphea.[198] Abatacept is a selective co-stimulation modulator of T cells which has shown promising results in case reports of both adults and pediatric morphea patients. This treatment has been studied more extensively in children, with the largest pediatric study enrolling eighteen patients and finding that 83% responded by 12 months.[199] Similar results have been reported in small numbers of adults.[200,201]

In addition to medical management, physical therapy is recommended for patients with linear morphea when disease abuts or overlies joints, to decrease the risk for contractures. Patients with En Coup de Sabre or progressive hemi-facial atrophy subtypes of linear morphea may also benefit from consultation with plastic surgery.[202]

Conclusion

Cutaneous manifestations of autoimmune connective tissue disease, including cutaneous lupus, dermatomyositis, systemic sclerosis, and morphea are common and may serve as the antecedent trigger prompting patients to interface with the healthcare system. As such, dermatologists are uniquely positioned to recognize early manifestations of disease. This review is aimed at providing dermatologist with an understanding of the cutaneous features of disease as well as possible systemic complications, necessary work up, and approaches to treatment. In doing so, we hope to improve comfort with these disease states to improve outcomes for patients with connective tissue disease.

Patient Consent

Informed consent for the publication of all patient photographs and medical information was provided by all patients.

Disclosure

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