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Morphea through the Ages

Introduction

Morphea, also referred to as localized scleroderma, is an immune-mediated fibrosing condition affecting the skin with variable extension to underlying structures. It presents most commonly in children between 2-14 years old, and adults in the fourth decade of life[1].

Pathogenesis

Our understanding of the pathogenesis of morphea is constantly being updated as we gain greater understanding of the disease. Microvascular injury in a predisposed individual is the first step in the pathogenesis of morphea, with multiple potential triggers implicated, including infections, drugs, and trauma[1]. Cell adhesion molecules and interleukin-8 (IL-8) attract the lymphocytic infiltrate and activation of the T helper type 1 (Th1)/Th17 pathway leading to early inflammatory plaques. Multiple cytokines including IL-2, IL-6, IL-4 and IL-13 are involved, with increased levels correlating with the severity of disease in generalized and linear forms[2]. IL-4 and IL-6 levels have also been shown to decrease in parallel with disease improvement. Activation of the Th2 pathway leads to fibrosis and damage. Conflicting evidence exists about the role of transforming growth factor (TGF-β) in the pathogenesis of morphea.

Clinical Presentation

There are many different subtypes of morphea, and the appearance of plaques varies accordingly. In the inflammatory phase, plaque-type morphea lesions can be ovoid or linear, with varying degrees of erythema and induration depending on the depth of involvement (**Figure 1**). In children, early inflammatory plaques on the face can mimic a capillary malformation or sinus pericranium, a congenital venous anomaly in which epicranial veins connect to intracranial dural sinuses. Indurated circumscribed plaques may have a similar appearance to necrobiosis lipoidica or pretibial myxedema.

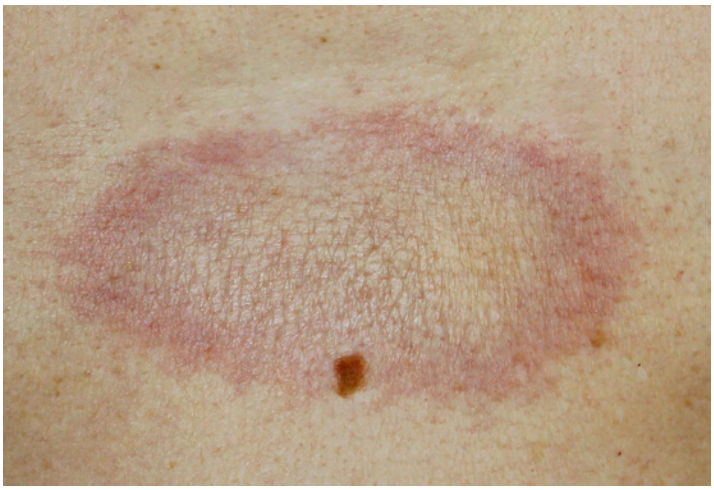

Figure 1. *Photo of morphea on patient's abdomen.*

Plaques may progress over time to become more sclerotic and then finally atrophic, with hyper- and hypopigmentation being the most prominent features in burnt out lesions. Not all plaques transition through these 3 classic phases (early inflammation, subsequent sclerosis and final atrophy). In deep forms of morphea, epidermal changes may be absent.

Diagnosis and Work-up

Consensus guidelines for the diagnosis and treatment of localized scleroderma have been published, including the 2019 EULAR consensus guidelines for juvenile localized scleroderma and the 2017 European Dermatology Forum guidelines[3,4].

The diagnosis of morphea can usually be made clinically, with biopsy required in cases that present with less-than-classic symptomology. Several classification systems have been proposed for morphea (**Table 1**)[5]. The Peterson classification consists of five groups: plaque, generalized, bullous, linear, and deep. The Laxer Criteria, proposed in 2006, differs in that it lacks a bullous variant and classifies deep involvement as a subtype of circumscribed morphea. Finally, the criteria proposed by the European Dermatology Forum has 6 subtypes and includes eosinophilic fasciitis. The most common presentation of morphea in children is linear, whereas in adults it is plaque. The Laxer criteria successfully classified 95% (n=900) patients in a recent study compared to 56% (n=533) and 52% (n=487) using the Peterson criteria and European Dermatology Forum classification respectively[5].

Laboratory investigations should include markers of systemic involvement and baseline bloodwork for possible systemic treatment if indicated. Screening for extracutaneous manifestations, present in up to 25% of patients, should be directed based on the location of the morphea and signs or symptoms.

Several autoantibodies are more common in patients with morphea, however testing for these is only recommended if clinical suspicion exists for concurrent autoimmune conditions6. Elevated antinuclear antibody (ANA) levels are reported in 23–68% of patients, usually defined as titres at minimum >1:80. The combination of positive ANA with positive anti-histone or anti-single-stranded DNA (anti-ssDNA) was associated with more severe disease in a cohort of 187 adults and children with linear morphea, defined by functional limitations, extensive body surface area involvement, and high skin damage[7]. Rheumatoid factor, which is elevated

Peterson 1995	Laxer 2006	European Dermatology Forum 2017
Plaque Guttate Lichen Sclerosis, keloidal Atrophoderma of Pasini & Pierini	Circumscribed Superficial Deep (+/- epidermis involved)	Limited Superficial Guttate Plaque
Linear - En coup de sabre - Parry Romberg - Trunk	Linear - En coup de sabre - Parry Romberg - Trunk	Linear - En coup de sabre - Parry Romberg - Trunk
Generalized 2 sites or more	Generalized 4 plaques 3 cm 2 sites (min)	Generalized 4 plaques, 2 sites (min) Pansclerotic
Deep Profunda/subcutaneous, eosinophilic fasciitis, Pansclerotic	Pansclerotic Circumferential	Deep
Bullous	Mixed	Mixed
		Eosinophilic Fasciitis

***Table 1**: Classification Systems of Morphea; adapted from Prasad et al.[5]*

in 3-16% of patients, was most common in a pediatric cohort of 750 patients and correlated with arthritis and musculoskeletal manifestations[6,8]. Inflammatory markers are seldom elevated, although an increase in erythrocyte sedimentation rate (ESR) can be seen in children with joint involvement[9].

Lichen sclerosis may coexist with morphea, both genital (n=8) and extragenital (n=19), as reported in up to 6% of patients with morphea based on a cohort of 472 adults and children. These data suggest that, compared with lichen sclerosis in the general population, lichen sclerosis was significantly more frequent in patients with moprhea as indicated by an odds ratio of 18.1 in this cohort of patients. , Patients with morphea may benefit from careful screening questions and physical exam for concomitant lichen sclerosis[10].

Abnormal findings in the central nervous system (CNS), eyes, and teeth have been associated with morphea affecting the head across multiple studies11. A wide range of CNS findings have been reported in patients with morphea of the head, the most common being white matter lesions ipsilateral to skin plaques but reports also include contralateral anomalies. Patients with anomalies are not always symptomatic. Guidelines recommend a brain MRI for screening in this population[3,4]. Imaging should include contrast, but vascular imaging is unlikely to help, and repeat imaging should be ordered if there is a change in symptoms[11].

Ocular manifestations are also most common in patients with facial lesions or those with CNS manifestations, and include anterior uveitis, episcleritis, enophthalmos, and lagophthalmos[11]. A baseline ophthalmologic assessment with slit-lamp exam and ongoing re-assessment every 6-12 months is recommended.

Dental changes including shortened roots, missing secondary teeth, and alveolar resorption have been reported on imaging in patients with en coup de sabre (ECDS) or Parry-Romberg Syndrome (PRS)[11] (**Table 2**).

Although imaging is not routinely recommended for localized morphea of the head, it may be helpful as the use of MRI has been reported to demonstrate the extent or activity of disease beyond what is appreciable on clinical exam[12].

It is generally accepted that systemic sclerosis (SSc) is distinct from morphea and that it is quite rare for patients to have both. However, a systematic review and meta-analysis of 5 studies involving 1,082 patients ranging in mean age from 36 to 55 years and predominantly female reported the coexistence of SSc and morphea to be between 2.4 and 7.4% of

Test Category	Specific tests	Utility
Bloodwork	CBC, CRP, ESR	Elevated ESR may be seen in children with joint involvement
	ANA, Anti-ssDNA, Anti-histone	Positivity of 2 associated with more severe disease
	Rheumatoid Factor	Associated with arthritis and Musculo-skeletal manifestations in children
Imaging	MRI Brain	Assess for CNS manifestations in patients with linear morphea of the head
	MRI body	Better assessment of activity/extent if unclear from clinical exam
	Panoramic radiographs	Assess for dental anomalies in patients with linear morphea of the head
Referrals	Ophthalmology	Assess for ocular manifestations in patients with Facial or scalp lesions
	Rheumatology	Assess for arthritis in patients with symptoms
	Dentistry	Assess for dental anomalies in patients with linear morphea of the head

***Table 2**: Potential Investigations/ Assessments that can be considered; courtesy of Cathryn Sibbald, MD*

patients[13]. Analysis also revealed that patients with both SSc and morphea tended to be ANA positive with Raynaud's phenomenon and the authors postulate that these characteristics, along with presence of nailfold scleroderma patterns in a patient with morphea, should prompt further screening for possible SSc.

Assessment

Multiple clinical tools have been investigated to assess the clinical severity and response to treatment, all with limitations.

One of the more common and validated scoring tools is the LoSCAT (Localized Scleroderma Cutaneous Assessment Tool), which includes a Skin Severity Index (LoSSI) and a Skin Damage Index (LoSDI)[14]. With this tool, markers of activity include new or enlarging lesions, erythema, and induration at the edges of plaques. Indices of damage include hyper- and hypopigmentation, subcutaneous and dermal atrophy, and central induration. Unfortunately, this tool does not include waxy white plaques which are also markers of active disease.. Photo-documentation is recommended along with the use of the LoSCAT assessment tool if possible[4].

Less commonly adapted tools include infrared thermography and high frequency ultrasound. In addition to the need for equipment, limitations of these tools include low specificity of thermography and lack of standardization for ultrasound, explaining their lack of inclusion in guidelines[3,4].

Treatments

Topical treatment regimens are listed in **Table 3**. Both guidelines(the 2019 EULAR consensus guidelines for juvenile localized scleroderma and the 2017 European Dermatology Forum guidelines) include topical treatments as first-line options for plaques that are limited in size and depth (not extending deeper than dermis) [3,4]. Calcipotriol, tacrolimus and corticosteroids are all included despite a paucity of evidence supporting their use, and occlusion is suggested to enhance the efficacy of all[4]. Other agents with limited evidence include imiquimod, crisaborole, and hyaluronidase.

Topical treatments should be continued for a minimum of 3 months, as clinical response in sclerosis can take anywhere from 8-12 weeks. After 3 months, topical corticosteroid-based regimens are recommended to be used intermittently as opposed to continuously[4].

Medication	Dose/ Frequency	Comments
Calcipotriol	0.005% cream twice daily	Modulates Tcells, Decreases collagen synthesis
Tacrolimus	0.1% ointment twice daily	Inhibits Tcell activation and cytokine production. May be more effective for early inflammatory plaques.
Imiquimod	5% cream 3x /week x 4weeks then 5x weekly	Induces local IFN, suppresses TGFB + collagen synthesis by fibroblasts
Cortico-steroids	Multiple options, high potency BID x 3 months continuous then intermittent	Anti-inflammatory, immune modulation. Very limited data but high consensus agreement for effectiveness and utility.
Crisaborole	2% ointment twice daily	Limits Macrophage differentiation and IL6 release (antifibrotic), decreased thickness in case series of localized plaques.
UVA	PUVA: 2-4 x weekly UVA1: 50-80J/cm2 3-5 x weekly Both: minimum 30 irradiations	Immune modulation, stimulates collagenase activity. Penetrates deeper than UVB but not below dermis.
NBUVB	5 x weekly for 8 weeks	Immune modulation
Hyaluronidase	Monthly x4	Degrades extracellular matrix, benefit for improving oral aperture opening

Table 3: *Topical treatments; adapted from LaChance et al.[2]*

Improvement in plaque morphea with phototherapy has been described using both UVA and UVB wavelengths[2]. UVA provides the advantage of potential collagenase activation and deeper penetration, although access may be limited in some centres.

Systemic medications are recommended for active lesions that are widespread, rapidly progressive, with potential of causing joint contractures, or located on the face[3,4]. A recent systematic review included 742 patients treated with systemic agents, with methotrexate and mycophenolate mofetil being the most commonly used immunosuppressants[15].

Methotrexate is considered a first-line agent in both children and adults. Systemic corticosteroids (methylprednisolone or prednisone) can be used adjunctively for the first 3-6 months of therapy. An evidence-based review of the use of systemic immunosuppressive therapies for the treatment of morphea included a comparison of the combination of methotrexate and steroids in children and adults with morphea, with all demonstrating better response with combination treatment[15].

Mycophenolate mofetil has demonstrated efficacy in patients who are refractory to methotrexate, in both pediatric and adult studies, with improvement documented in 87-91% of patients[16,17]. In patients who have contraindications or a lack of clinical response, multiple different systemic agents have been used, all with limited evidence, listed in **Table 4**.

Medication	Dose/ Frequency	Comments
Corticosteroids	30mg/kg/day methylprednisolone IV (max 1g) x3 days q1 month x3, or 0.5-2mg/kg/day prednisone x 2-4 weeks then tapered	Anti-inflammatory, immune modulation. Faster onset than Methotrexate.
Methotrexate	Children: 15mg/m2 weekly (oral or SC) Adults: 15-25mg weekly (oral or SC)	Anti-inflammatory effects via impaired synthesis of DNA, RNA, proteins
Mycophenolate Mofetil	Children: 600mg/m2 orally twice daily Adults: 1-1.5g orally twice daily	Inhibition of purine biosynthesis.
Hydroxychloroquine	Children: 5mg/kg/day Adults: 400mg/day	Immune modulation, anti-inflammatory
Abatacept	10mg/kg at days 0,14 and 28; then every 4 weeks	Anti-CTLA4 (modulation of selective T-cell co-stimulation), used with methylprednisone and methotrexate or mycophenolate
Tocilizumab	8-12mg/kg every 4 weeks (+/- 2 week dose after initial start)	Anti-IL-6R antibody (modulates fibroblast differentiation, collagen deposition)
Janus Kinase Inhibitors	Tofacitinib 5-10mg twice daily Baricitinib 2mg daily	Limit JAK-STAT signaling of IL-4, IL-6, IFN-γ
Apremilast	30mg orally twice daily (after starter pack titration)	Limits macrophage differentiation and IL-6 release (antifibrotic), improvement in adult cases of superficial plaques.
Dupilumab	Adults: 600mg then 300mg SC q2 weeks	Blocks IL-4RA (inhibits IL-4/13), Clinical trial ongoing in adults.

Table 4: *Systemic Treatments; adapted from Abduelmula et al.[15]*
SC: subcutaneous

Surgical interventions can improve volume, symmetry and contour in patients, and include grafting of fat, bone and cartilage, or injectable fillers such as hyaluronic acid[18]. The optimal timing for surgical intervention is not uniformly agreed upon, but in general most clinicians advocate for waiting until the disease is inactive to minimize any risk of reactivation or relapse[18].

Physiotherapy and manual therapy should be added to topical and systemic therapy in all types of morphea that result in restrictions of motion[4]. Massage and lymphatic drainage may also add benefit in sclerotic types of morphea.

Outcomes

The risk of relapse is as high as 30-45% in some cohorts[19,20]. Older age at disease onset is a prognostic risk factor for relapse, with other potential predictive risk factors including linear disease on the limbs, presence of extracutaneous manifestations, and elevated ANA levels. It is recommended that systemic treatments be continued for at least 24 months, although some experts advocate treatment to continue for 3 years[3,4].

Conclusion

More data is needed on long term outcomes, and hopefully current and future patient registries will help in gathering this important longitudinal data to help better inform treatment strategies as well as adding to current knowledge about pathogenesis and associations.

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