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REVIEW ARTICLE

Morphea and Eosinophilic Fasciitis: An Update

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Abstract Morphea, also known as localized scleroderma, encompasses a group of idiopathic sclerotic skin diseases. The spectrum ranges from relatively mild phenotypes, which generally cause few problems besides local discomfort and visible disfigurement, to subtypes with severe complications such as joint contractures and limb length discrepancies. Eosinophilic fasciitis (EF, Shulman syndrome) is often regarded as belonging to the severe end of the morphea spectrum. The exact driving mechanisms behind morphea and EF pathogenesis remain to be elucidated. However, extensive extracellular matrix formation and autoimmune dysfunction are thought to be key pathogenic processes. Likewise, these processes are considered essential in systemic sclerosis (SSc) pathogenesis. In addition, similarities in clinical presentation between morphea and SSc have led to many theories about their relatedness. Importantly, morphea may be differentiated from SSc based on absence of sclerodactyly, Raynaud's phenomenon, and nailfold capillary changes. The diagnosis of morphea is often based on characteristic clinical findings. Histopathological evaluation of skin biopsies and laboratory tests are not necessary in the majority of morphea cases. However, full-thickness skin biopsies, containing fascia and muscle tissue, are required for the diagnosis of EF. Monitoring of disease activity and damage, especially of subcutaneous involvement, is one of the most challenging aspects of morphea care. Therefore, data harmonization is crucial for optimizing standard care and for comparability of study results. Recently, the localized scleroderma cutaneous assessment tool (LoSCAT) has been developed and validated for morphea. The LoSCAT is currently the most widely reported outcome measure for morphea. Care providers should take disease subtype, degree of activity, depth of involvement, and quality-of-life impairments into account when initiating treatment. In most patients with circumscribed superficial subtypes, treatment with topical therapies suffices. In more widespread disease, UVA1 phototherapy or systemic treatment with methotrexate (MTX), with or without a systemic corticosteroid combination, should be initiated. Disappointingly, few alternatives for MTX have been described and additional research is still needed to optimize treatment for these debilitating conditions. In this review, we present a state-of-the-art flow chart that guides care providers in the treatment of morphea and EF.

Key Points

Progress has been made in elucidating the immunological pathways involved in morphea.

Disease monitoring by reliable and sensitive outcome measures is improved by the localized scleroderma cutaneous assessment tool (LoSCAT); however, especially for deep involvement, additional validated outcome measures are required.

This review provides two state-of-the-art algorithms that guide care providers with regard to (i) diagnostic work-up and disease monitoring, and (ii) treatment of morphea and eosinophilic fasciitis.

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1 Introduction

Morphea, also known as localized scleroderma, encompasses a group of idiopathic sclerotic skin diseases. Controversy exists with regard to nomenclature of the disease spectrum. In some countries, localized scleroderma is the preferred overarching term, because morphea is regarded as one of the subtypes of the wider disease spectrum. However, morphea is the preferred term in the United States (US), because localized scleroderma could lead to unwanted confusion with the term systemic sclerosis, a systemic disorder with a different plethora of clinical and pathological signs and symptoms [1]. For the purpose of this review, we will use the term morphea.

The spectrum of morphea consists of heterogeneous disease phenotypes. Solitary sclerotic lesions, which generally cause few problems besides local discomfort and visible disfigurement, reflect the mild side of the spectrum [2, 3]. Conversely, sclerosis can cause severe complications in the linear subtype; limb length discrepancies and joint contractures may occur [1, 4, 5].

This review encompasses a description of the clinical aspects of the morphea subtypes. Eosinophilic fasciitis (EF, also known as Shulman Syndrome), often regarded as part of the morphea spectrum, is included in this review. Additionally, we describe recent developments in understanding of disease pathogenesis and potential outcome measures. Lastly, we present two state-of-the-art flow charts, which guide care providers with regard to (i) diagnostic work-up and disease monitoring and (ii) treatment of morphea and EF.

2 Epidemiology, Classification and Presentation

2.1 Epidemiology

The rarity of morphea is reflected in the annual incidence rates which are reported to be between 3.4 and 27 cases per 1,000,000 [6–8]. Females are more frequently affected than males (ratio: 2.4–5.0 to 1) [1, 9–11]. The peak incidence is bimodal with peaks between 7 and 11 years for pediatric-onset disease [1, 10–13] and 44–47 years for adult-onset disease [10, 12]. The incidence and prevalence of EF is unknown. The disease predominantly affects patients in their fourth and fifth decade of life [14–16]. Only a few case reports describe childhood-onset disease [11, 14, 15, 17–21].

2.2 Classification

Multiple classification schemes have been proposed throughout the years. However, consensus with regard to one superior classification system is currently lacking. Classification by Laxer and Zulian [22] describes the following five subtypes: (i) circumscribed morphea (including a superficial and deep variant), (ii) linear morphea (including a limb/trunk variant and head variant), (iii) generalized morphea, (iv) the pansclerotic subtype, and (v) the mixed subtype (Table 1). Other classification systems include more uncommon subtypes such as guttate and bullous morphea [23, 24]. Secondly, these systems include diagnoses which are debated to be part of the morphea spectrum, such as atrophoderma of Pasini and Pierini, extragenital lichen sclerosis et atrophicus, and EF. In the

Table 1 Classification of morphea subtypes by Laxer and Zulian [22]

Main group	Subtype	Description
(I) Circumscribed morphea	Superficial	Oval or round circumscribed areas of induration limited to epidermis and dermis, often with altered pigmentation and violaceous, erythematous halo ('lilac ring'). They can be single or multiple
	Deep	Oval or round circumscribed deep induration of the skin involving subcutaneous tissue extending to fascia and may involve underlying muscle. The lesions can be single or multiple. Sometimes the primary site of involvement is in the subcutaneous tissue without involvement of the skin
(II) Linear morphea	Trunk/limbs	Linear induration involving dermis, subcutaneous tissue, and sometimes muscle and underlying bone, and affecting the limbs and the trunk
	Head	*En coup de sabre (ECDS)*: Linear induration that affects the face and the scalp and sometimes involves muscle and underlying bone
		Parry–Romberg or *progressive hemifacial atrophy:* loss of tissue on one side of the face that may involve dermis, subcutaneous tissue, muscle and bone. The skin is mobile
(III) Generalized morphea		Induration of the skin starting as individual plaques (four or more and larger than 3 cm) that become confluent and involve at least two out of seven anatomic sites (head/neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk, posterior trunk)
(IV) Pansclerotic morphea		Circumferential involvement of limb(s) affecting the skin, subcutaneous tissue, muscle and bone. The lesion may also involve other areas of the body without internal organ involvement
(V) Mixed morphea		Combination of two or more of the previous subtypes. The order of the concomitant subtypes, specified in brackets, will follow their predominant representation in the individual patient [i.e., mixed morphea (linear-circumscribed)]

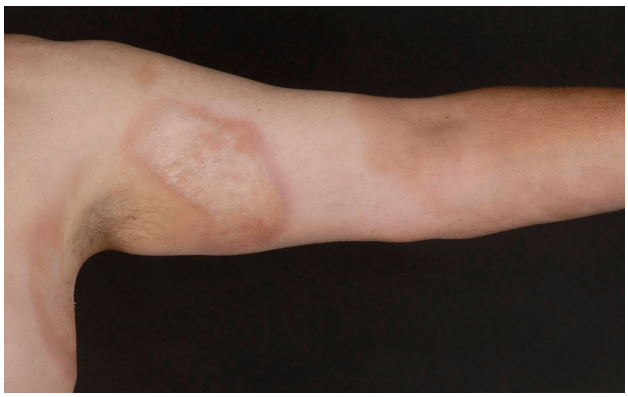

Fig. 1 Circumscribed superficial morphea (morphea en plaque). A *yellow-white* sclerotic plaque with an erythematous or violaceous border, the characteristic 'lilac ring'

authors' opinion, EF belongs to the spectrum of morphea, based on the fact that the largest case series reported concomitant morphea in 29–40% of the patients [14–16].

2.3 Clinical Characteristics

2.3.1 General Findings

Early, progressive morphea is characterized by erythematous or violaceous cutaneous lesions. As the disease progresses, sclerotic plaques develop at the center of these lesions. This leads to the appearance of a yellow-white sclerotic plaque with an erythematous or violaceous border, the so-called 'lilac ring' (Fig. 1). In some patients, development of hyperpigmentation is the predominant feature and sclerosis can be limited or absent (Fig. 2). In the majority of patients, skin softens in months to years. Consecutively, signs of residual damage, such as pigment alterations and cutaneous and subcutaneous atrophy, may develop. In most patients, the disease is self-limiting within 3–5 years. However, in some patients morphea remains progressive for multiple years or flares of disease occur frequently [1, 10, 25].

2.3.2 Circumscribed Superficial Morphea

In circumscribed superficial morphea, also known as 'morphea en plaque', involvement is limited to the dermis [9, 10, 13]. Solitary or few plaques predominantly affect the trunk, waist and submammary region. Circumscribed superficial morphea is the most common subtype in adults and generally causes few problems besides local discomfort and visible disfigurement.

2.3.3 Circumscribed Deep Morphea

In circumscribed deep morphea (morphea profunda), sclerosis reaching into the subcutis is present and may extend into the fascia and muscle. Deep morphea is a rare subtype in both the adult and pediatric populations (~5%) [1, 9, 10]. Lower extremities are often affected symmetrically, where sclerosis might cause contractures and lead to subcutaneous atrophy.

Fig. 2 Generalized morphea. Example of a patient with absence of induration, but extensive hyperpigmentation

2.3.4 Linear Morphea

In linear morphea, sclerosis may be limited to the dermis, but deeper involvement is often present. The 'band-like' cutaneous sclerosis (Fig. 3) frequently causes contractures [1, 4]. Additionally, limb-length discrepancies may occur [1] (Fig. 4). In the majority of patients, the disease remains unilateral. Linear morphea is the most common subtype in childhood-onset morphea (~65%) [11], but disease onset might occur during adulthood as well [4, 10]. Linear morphea of the limbs and trunk is characterized by a chronic disease course, as the disease may remain active after many decennia [26, 27] and recurrences are reported in a large proportion of both adults and children [4, 10, 25, 28, 29].

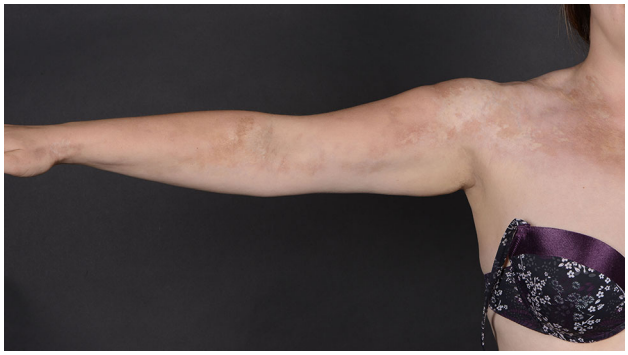

Fig. 3 Linear morphea of the upper extremity

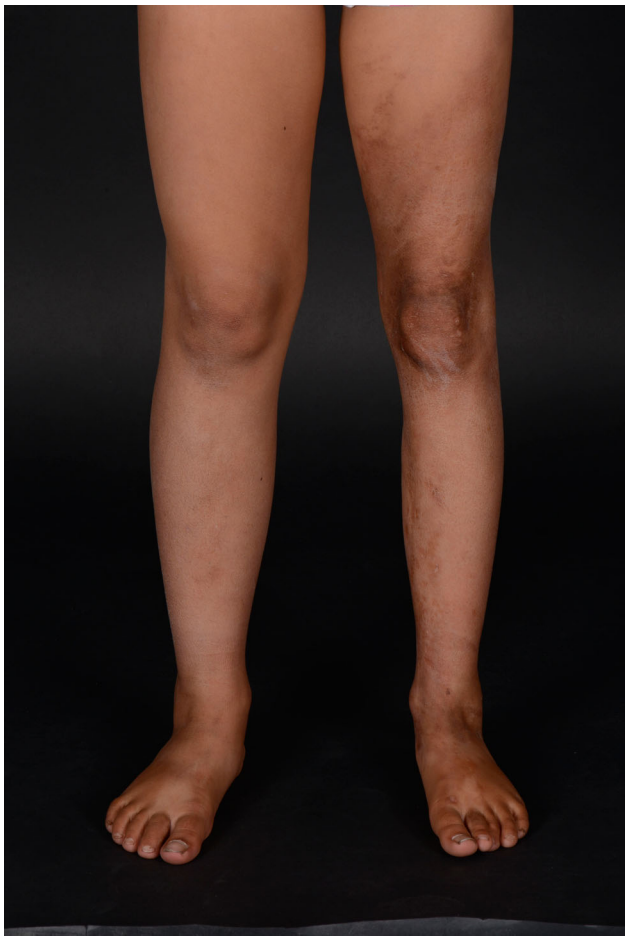

Fig. 4 Linear morphea of the lower extremity. Limb length discrepancy and subcutaneous atrophy in burned-out disease (left leg)

The 'en coup de sabre' (ECDS) subtype most frequently affects the paramedian forehead. Linear lesions may extent onto the scalp, where they cause alopecia (Fig. 5). This subtype might be accompanied by ocular [30, 31], neurological [1, 11, 32] and odontostomatologic [33–35] complications. Progressive hemifacial atrophy (Parry–Romberg

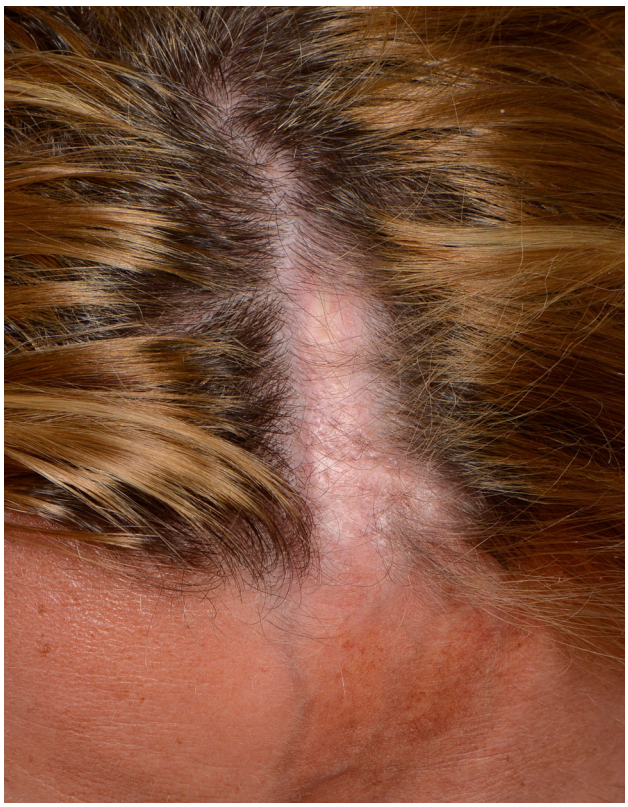

Fig. 5 Linear morphea on the paramedian forehead (en coup de sabre) crossing onto the scalp causing alopecia

syndrome) is characterized by diffuse unilateral subcutaneous atrophy of the face. This subtype is often regarded part of a spectrum with ECDS because 71% of the patients have overlaying cutaneous sclerosis [32, 36]. However, studies that investigate the connection between these two conditions are lacking.

2.3.5 Generalized Morphea

Generalized morphea is characterized by large superficial coalesced plaques on multiple body sites (Fig. 6). Generalized morphea is more frequently present in adults than children [9, 10, 13]. Sclerosis is usually present on the trunk, arms, and legs with sparing of the face, hands, and feet.

2.3.6 Eosinophilic Fasciitis (EF)

The onset of EF is characterized by acute or subacute development of pitting edema and erythema. As the disease progresses, edema is gradually replaced by a *'peau d'orange'* aspect as deep sclerosis starts to develop (Fig. 7). Extremities are affected symmetrically, with exclusion of

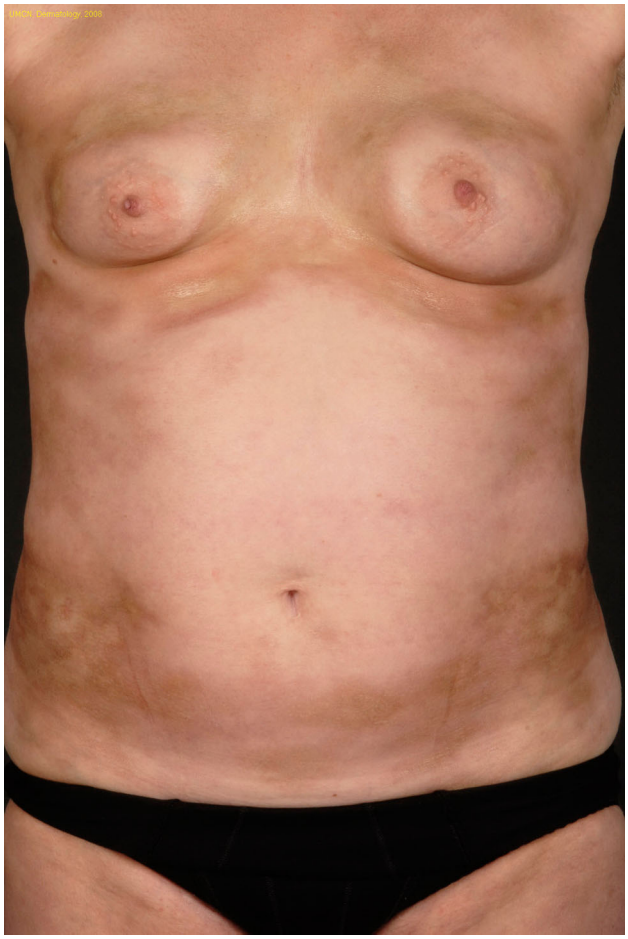

Fig. 6 Severe case of generalized morphea on the trunk with atrophy of both breasts

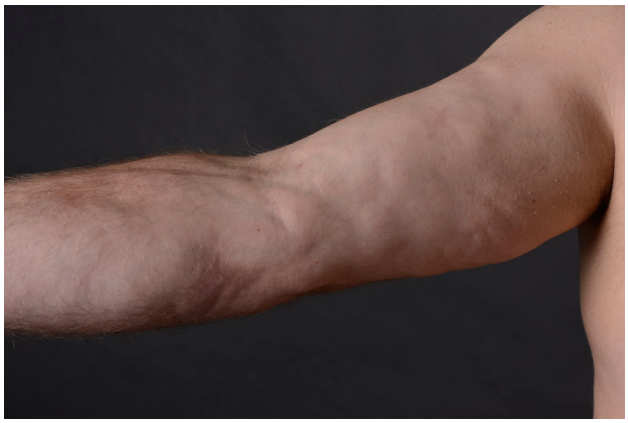

Fig. 7 Peau d'orange aspect on upper extremity in a patient with eosinophilic fasciitis

hands and feet. Neck and truncal involvement is reported in widespread disease. Cutaneous involvement may be accompanied by general symptoms such as weight loss, myalgia and asthenia [14, 15, 21].

3 Histopathology

3.1 Skin Biopsy in Morphea

Histopathological characteristics correlate with the clinical state of morphea. Evaluation of early active morphea, represented by a biopsy of the inflammatory border, reveals a perivascular infiltrate composed of lymphocytes and plasma cells, possibly accompanied by eosinophils and macrophages. Evaluation of sclerotic skin demonstrates thickened and homogenized collagen bundles at the papillary and reticular dermis. The abundant collagen bundles enclose eccrine glands and few dermal blood vessels with fibrotic walls and narrow lumina may be observed as the sclerosis progresses. Subcutaneous infiltration and sclerosis reflect deeper involvement.

We recommend a diagnostic skin biopsy only in case of an unclear clinical presentation of morphea. The clinical appearance of the biopsy site (inflammatory border versus sclerotic center) should be mentioned to the pathologists for optimal clinicopathological correlation.

3.2 Full-Thickness Biopsy in EF

A full-thickness biopsy, containing fascia and muscle, is the golden standard for the diagnosis of EF. Histology typically displays a thickened fascia infiltrated by lymphocytes accompanied by eosinophils, plasma cells, and macrophages [14, 15]. The presence of eosinophils is transient and may be absent if patients have prolonged disease or receive systemic corticosteroids (SCSs) or immunosuppressive drugs (ISDs). Adjacent myositis is frequently observed [37]. The presence of thickened dermal collagen fibers may reflect the presence of concomitant superficial morphea [14, 15]. More recently, magnetic resonance imaging (MRI) [38–40], ultrasound [41, 42], and positron emission tomography (PET) [43–45] have been reported to be helpful in establishing the diagnosis by decreasing the likelihood of sampling errors for deep biopsies or by visualizing the fasciitis.

4 Pathogenesis

4.1 Pathological Hallmarks of Morphea

The exact driving mechanisms behind morphea pathogenesis remain to be elucidated. However, extensive extracellular matrix (collagen) formation and autoimmune dysfunction are thought to be key pathogenic processes [46–48]. Likewise, these processes are considered essential in systemic sclerosis (SSc) pathogenesis. The similarities

between the two diseases have led to many theories about their relatedness. Based on this possible connection, most theories for morphea pathogenesis are deduced from SSc. Endothelial dysfunction, immune dysregulation, and excessive collagen deposition are regarded as key hallmarks for SSc pathogenesis [49, 50]. In recent years, research in SSc has led to some insight into these hallmarks and their inter-relationship. The evidence and relevance for these hallmarks in morphea pathogenesis are described in the following sections.

4.1.1 Vascular Dysfunction

For SSc, endothelial dysfunction is clinically reflected in the presence of Raynaud's phenomenon and visible changes on capillaroscopy (nailfold lesions) [51]. No such clinicopathological correlation exists for morphea. However, the propensity of pericyte hyperplasia in capillar and venular walls and increased capillary density in active morphea lesions have been reported [52].

4.1.2 Immune Dysregulation

4.1.2.1 Autoimmunity Autoimmunity is likely involved in the pathogenesis because of the presence of autoantibodies in a proportion of the morphea patients [9, 11, 53–58]. Secondly, the presence of concomitant autoimmune diseases in morphea patients and their relatives supports involvement of autoimmunity [5, 11, 13, 59]. Recently, a study including 211 morphea patients and 726 matched controls investigated HLA class I and II typing. The strongest associations with morphea were found with the HLA Class II allele DRB1*04:04 and class I allele HLA–B*37. Comparison of the risk alleles for the morphea cohort versus other autoimmune diseases revealed only one allele in common between morphea and SSc. However, many more alleles showed similarity with other autoimmune diseases such as rheumatoid arthritis [60].

4.1.2.2 Cytokines and Chemokines Increased serum levels of the adhesion molecules Vascular Cell Adhesion Molecule-1 (VCAM-1), Intracellular Cell Adhesion Molecule-1 (ICAM-1) and E-Selectin have been reported in morphea patients [61, 62]. These molecules might be involved in early recruitment of inflammatory cells such as T cells, monocytes, and other immune cells.

Initial studies demonstrated elevation of classic profibrotic T helper cell 2 (T_h2) cytokines IL-4 and IL-13 (and IL-2, 6, and 8) in serum of 48 morphea patients. Likewise, IL-4 and IL-13 elevation has been demonstrated in circulation, skin, and lung tissue of SSc patients [63–65]. Recently, a cross-sectional study performed a 29-plex Luminex, which included T_h1, T_h2 and T_h17 cytokines and chemokines on plasma of 69 pediatric morphea patients and 71 controls. Elevation of interferon-γ (IFN-γ)-induced protein 10 (IP-10, CXCL10), IL-12p70 and IFN-γ suggested a proinflammatory T_h1 predominance, whereas IL-17a elevation signified a proinflammatory T_h17 predominance. Elevation of these proinflammatory T_h1 and T_h17 cytokines and chemokines correlated with shorter disease duration. In contrast to the $T_h1/17$ predominance, T_h2 cytokines IL-4, IL-5, and IL-13 were not significantly elevated [66]. IL-17a gene upregulation has also been reported in peripheral blood mononuclear and skin samples from morphea patients. This study confirmed the correlation between IL-17a elevation and shorter disease duration [67]. Tumor necrosis factor-α (TNF-α), an effector cytokine affiliated with the T_h1 and T_h17 lineage was shown to be increased in active disease versus inactive disease [66]. The association of TNF-α levels and disease activity was also shown in a previous study [68].

In conclusion, it is unclear whether a $T_h1/17$ or T_h2 predominance is present in morphea. One postulated theory is T_h1 and T_h17 predominance in early, active disease and T_h2 predominance in the fibrotic phase of the disease.

4.1.3 Excessive Extracellular Matrix Formation

Development of cutaneous or subcutaneous fibrosis is the key characteristic of morphea. Fibrosis is a result of excessive collagen synthesis and decreased degradation. Transforming growth factor-β1 (TGF-β1) has been shown to increase the expression of several collagen types and other extracellular matrix components in morphea and SSc [69–71]. Additionally, TGF-β1 has inhibitory effects on matrix degradation. Therefore, TGF-β is regarded a key player in morphea and SSc pathogenesis. However, the processes leading to excessive TGF-β synthesis in morphea remain poorly understood. Recent reports in SSc showed TGF-β-dependent fibrosis development via toll-like receptor (TLR) signaling [72–75]. Most interestingly, some of these reports demonstrated endogenous ligands (mitochondrial DNA [72], fibronectin EDA (extra domain-A) [73] and tenascin-C [75]) for these TLRs. These findings integrate innate immunity and fibrosis development. The role of the innate immune system, via TLR signaling, in fibrogenesis remains to be investigated in morphea. However, a previous report of tenascin upregulation in morphea skin samples might hint towards involvement of the innate immune system in morphea pathogenesis [76].

4.2 Epigenetics

Low concordance rates of autoimmune diseases in monozygotic twins suggest additional pathogenic mechanisms besides genetic factors [77]. The field of epigenetics

investigates heritable changes that influence gene expression without altering the DNA sequence; these changes include DNA methylation, post-translational modification of histones and microRNAs (miRNAs) [78]. MiRNAs are short non-coding RNAs of 18–23 nucleotides that bind messenger RNAs (mRNAs) and thereby inhibit their translation or induce mRNA degradation. A study in 2013 was the first to report miRNA dysregulation in morphea. This study reported let-7a downregulation in morphea skin and circulation. Additionally, experimental let-7a overexpression, or inhibition, affected protein expression of type I collagen [79]. A second study reported miRNA-196a downregulation in serum and involved skin of morphea patients. Transfection of an miRNA-196a inhibitor into normal cultured fibroblasts upregulated type 1 collagen protein in vitro [80]. Lastly, a recent study reported upregulation of miRNA-155 in SSc and morphea skin. Most interestingly, this study showed the potential of miRNA as a therapeutic target by decreasing the dermal thickness, collagen deposition, and number of activated fibroblasts upon topical administration of a miRNA-155 blocking agent in a murine bleomycine-induced fibrosis model [81]. The potential of miRNA as a therapeutic option in humans is currently being investigated in a phase I trial with MRG-201, a molecule which mimics miRNA-29 activity (clinicaltrials.gov NCT02603224).

4.3 Environmental Factors

Multiple environmental factors have been proposed to be involved in morphea development. The role of friction, long-term pressure, or mechanical factors such as vaccination or other injections is repeatedly reported in 13–16% of morphea patients [1, 11, 82]. Secondly, morphea is an uncommon complication after radiation therapy. A recent literature review summarized 66 cases with radiation-induced morphea (RIM) [83]. Radiation may lead to secretion of T_h2 cytokines (Il-4 and -5), which leads to TGF-β-mediated fibrogenesis.

For multiple decades, studies have reported inconsistent results with regard to the association of *Borrelia burgdorferi* (*B. Burgdorferi*) and morphea. Results vary from detection of *B. burgdorferi* in case reports and large proportions of patients in case series [84–87], to complete absence of detectable *B. burgdorferi* in other studies [88–97]. The different techniques being reported, in combination with different borrelia strains present in different geographical locations, makes it difficult to come to a conclusion for a large group of morphea patients. In the authors' opinion, it is unlikely that *B. burgdorferi* is involved in morphea pathogenesis for a large proportion of patients.

Interestingly, recent case reports almost exclusively report TNF-α inhibitors in drug-induced morphea [98–101]. Conversely, two cases have described beneficial effects of infliximab in severe morphea cases [102, 103]. Moreover, elevation of TNF-α in circulation in active morphea endorses the role of this cytokine in the development of morphea [66, 68]. However, the exact role of TNF-α still remains to be elucidated. In addition to TNF-α inhibitors, multiple other drugs and injections have been implicated in cases of drug-induced morphea. A review including 15 cases of drug-induced morphea concluded that drug-induced morphea was extremely rare, drug withdrawal did not lead to remission in most patients, and some of the drugs could be directly linked to connective tissue metabolism [104].

4.4 Pathogenesis of EF

The pathogenesis of EF remains unknown. Numerous associations with potential etiological factors have been proposed in case reports. Most of these factors have also been reported in association with morphea (i.e., *B. burgdorferi* infection [105], radiation therapy [106], and insect bites [107]). The most commonly reported etiological factor for EF is strenuous exercise or trauma preceding disease onset. Two case series, consisting of 52 [15] and 63 patients [16], reported exercise to be suggestive for disease induction in 46 and 28% of the patients, respectively. However, the mechanisms leading to clinical phenotype remain unknown.

5 Laboratory Testing

5.1 Autoantibodies

To date, no morphea-specific autoantibodies have been discovered. This is in contrast to SSc, for which multiple specific autoantibodies (anticentromere, anti-topoisomerase 1 and anti-RNA polyisomerase III antibodies) have been reported and are routinely being screened in standard care [108].

Antinuclear antibodies (ANAs) have been reported in 5.9–68% of morphea patients [9, 11, 13, 54–56, 58]. Previous retrospective studies reported increased ANA frequencies in severe subtypes such as linear and generalized morphea [13, 54]. Recently, a prospective study with 187 morphea patients could not confirm differences in ANA prevalence between the different subtypes. This study reported ANAs to be present in 34% of the complete group, with ANA prevalences only varying between 33 and 36% in the different disease subtypes [53]. Additionally, this study showed single-stranded DNA antibodies (ssDNA abs) only to be present in 8% of the complete group and 13% in the linear subtype, versus 7% in controls. Retrospective studies reported ssDNA abs in 29–39% of the linear subtype [54, 55]. Antihistone antibodies (AHAs) are consistently reported to be increased in the linear subtype

(18–42%) [53, 54, 56], whereas conflicting results exist with regard to AHA and the generalized subtype [53, 56]. Lastly, antibodies to cardiolipin [11, 109–111], phospholipid [110], U1 ribonucleoproteins [112], U3 ribonucleoproteins [113], MMP-1 [114], and antinucleosome [58] have been described in morphea.

For morphea, autoantibodies remain of limited clinical use; no specific autoantibodies have been identified and no associations have been reported between any of the previously reported antibodies or titers and clinical activity or severity measures in the complete group of morphea subtypes.

In conclusion, we do not recommend testing of autoantibodies for diagnostic and disease monitoring purposes.

5.2 *Borrelia burgdorferi*

Section 4.3 encompasses a more detailed description of the role of borrelia in morphea development. Based on evidence, serological testing may be considered in atypical presentation of morphea.

5.3 Other Laboratory Tests

Inflammatory serological markers are upregulated in a minority of morphea patients and do not correlate with disease activity [11]. Therefore, we do not recommend routine testing of inflammatory serological markers.

5.4 Laboratory Tests for EF

Peripheral eosinophilia and elevation of inflammatory markers may be present in the early stages of EF. However, these findings are transient and may be absent in later stages of the disease or when patients receive SCS or ISD treatment. We recommend routine testing of absolute eosinophil counts and inflammatory markers in the initial phase of the disease and for the detection of disease reactivation [14, 15]. Autoantibodies may be detected in 15–20% of patients, whereas specific antibodies are absent in the majority of patients. Autoantibody testing may be useful in the differentiation versus SSc [14, 15]. In addition, anti-neutrophil cytoplasmic antibody (ANCA) testing can be performed in cases where eosinophilic granulomatosis with polyangiitis (EGPA) is considered as part of the differential diagnosis [115].

6 Outcome Measures

Validated outcome measures for disease activity and damage are essential for optimal standard of care. Secondly, data harmonization is crucial for comparability of study results. Recently, a comprehensive systematic review described tools for determining disease activity in morphea [116]. In the following sections, we describe the most promising outcome measures.

6.1 Clinical Scores

The localized scleroderma cutaneous assessment tool (LoSCAT) is a composite of the modified localized scleroderma severity index (mLoSSI) [117] and localized scleroderma skin damage index (LoSDI) [118]. The mLoSSI assesses signs of disease activity (expansion of disease, presence of erythema, and skin induration). The LoSDI scores cutaneous and subcutaneous atrophy, and pigment alterations; signs which reflect disease damage. In addition to the LoSCAT, physician global assessment of disease activity (PhysGA-A) and damage (PhysGA-D) have also been investigated in the development of the LoSCAT score [117, 118]. The Dyspigmentation, Induration, Erythema and Telangiectasia (DIET) score poorly discriminates between disease activity and disease damage; similar scores can reflect either active or inactive disease [119, 120]. Lastly, several one- or two-dimensional clinical scores, such as the modified Rodnan skin score [121–123] (mRSS), the modified skin score (mSS, by Zachariae) [124, 125] and the computerized skin score (CSS) [126] have been described. These scores share the downside of only capturing skin sclerosis as a sign of disease activity. Therefore, based on current literature, LoSCAT in combination with PhysGA-A and PhysGA-D are the recommended clinical outcome measures for superficial morphea assessment.

6.2 Miscellaneous Outcome Measures

Ultrasound is widely reported for the assessment of morphea activity [116]. However, the downside of ultrasound is the wide variability in equipment reported between studies. The Localized Scleroderma Clinical and Ultrasound Study Group (LOCUS) has developed a standardized ultrasound imaging protocol, which should lead to data harmonization [127]. Another technique commonly reported is infrared thermography (IRT). Multiple studies have demonstrated correlations between lesion temperature and clinical activity status of the morphea lesions [116]. Lastly, durometry is a tool used to measure material hardness. Originally, durometry was described as a reliable method for the assessment of morphea skin hardness [124]. Recently, a study with 23 pediatric patients demonstrated that durometry was able to discriminate between affected and unaffected skin and that it was sensitive to detect change in lesions [128]. The usefulness of durometry remains limited as lesions located at bony surfaces, such as

scalp, and skin lesions are not suited to assessment with durometry [129, 130].

In conclusion, in superficial morphea, high frequency ultrasound and IRT are the most promising techniques for monitoring disease activity, in addition to the LoSCAT.

6.3 Outcome Measures for EF

To our knowledge, no outcome measures have been validated for EF. Therefore, we recommend the use of outcome measures known from SSc and morphea research. We recommend LoSCAT in combination with PhysGA-A and PhysGA-D, possibly accompanied by ultrasound and IRT, for the assessment of superficial involvement. Lastly, movement restrictions may be assessed by passive range of motion measurements.

7 Assessment of Musculoskeletal Involvement

Slow progression of musculoskeletal involvement may be notoriously difficult to measure between consecutive visits, but accumulated damage may be significant over a longer period of time. This emphasizes the necessity of additional imaging tools or biomarkers which reflect active deep disease.

7.1 Recommendations for Morphea

A retrospective study reported MRI findings in 43 morphea patients; MRI enabled confirmation of musculoskeletal abnormalities in all but one of the patients in whom musculoskeletal involvement was clinically suspected [131]. A recent retrospective study confirmed the potential of MRI in detection of musculoskeletal involvement [132]. More importantly, a longitudinal study reported MRI findings to be sensitive to changes in patients with deep morphea who were being treated with ISDs [133].

One study reported the additional value of electromyography (EMG) in detection of muscle dysfunction in patients with linear morphea [134]. Lastly, ultrasound has been reported in the monitoring of muscle involvement in deep morphea. However, the usefulness of this technique is highly operator-dependent [135]. In conclusion, the exact role of EMG and ultrasound requires further investigation. Based on the current evidence, we recommend MRI for monitoring of musculoskeletal involvement in morphea when indicated. However, we do not recommend routine MRI assessment.

7.2 Recommendations for EF

A retrospective study described serial MRI findings in six EF patients. Pretreatment MRI evaluation showed strong fascial enhancement, especially after intravenous (IV) administration of an extracellular gadolinium-based contrast agent. Post-therapy MRI evaluation during follow-up showed complete resolution of the characteristic MRI changes of the superficial and deep muscle fasciae in those patients who had complete clinical remission ($n = 5$) [40]. Another case series described MRI findings in six EF patients. Pretreatment MRI findings ($n = 6$) showed fascial thickening and hyperintense signal within the fascia in fluid-sensitive sequences. The post-therapy images ($n = 3$) showed marked improvement in two and mild but definite improvement in the other [136]. Case reports confirm the added value of MRI for both diagnostic purposes [137] and for the assessment of the fasciitis [39, 138]. In addition, ultrasound [41, 42] and positron emission tomography (PET) [43–45] have also been reported to be helpful for similar purposes. In conclusion, MRI may be considered for the assessment of EF.

8 Differential Diagnosis

8.1 Differentiation Diagnosis of Morphea

Evaluation of the differential diagnosis for the complete morphea spectrum is beyond the scope of this review and is described elsewhere [24]. Differentiation between morphea and SSc is commonly requested in an outpatient clinic. In the vast majority of patients, differentiation between the two diseases should be based on clinical findings and no additional testing is necessary in the absence of SSc suspicion.

Raynaud's phenomenon or gastrointestinal problems are early signs of SSc and should therefore be checked in the patients' history. Signs of SSc such as sclerodactyly, digital ulcers, pitting scars, puffy fingers, calcinosis cutis, telangiectasia, and diffuse facial sclerosis are rarely present in morphea and should be excluded by clinical examination.

Two studies investigated differentiating characteristics between morphea and SSc skin biopsies. These studies identified abundant cellular infiltrates in morphea compared with SSc, even in the sclerotic phase of morphea. However, most signs overlapped and differentiation remained difficult [139, 140]. Therefore, we do not recommend routine skin biopsies for the purpose of differentiation between morphea and SSc.

If SSc suspicion is present at any of the aforementioned steps, complete screening for SSc, including extensive laboratory testing, pulmonary imaging and functional testing, cardiac imaging, and nailfold capillaroscopy, is recommended [108].

8.2 Differential Diagnosis of EF

The initial presentation of EF is characterized by an acute or subacute onset of pitting edema, erythema, myalgia, and arthralgia, accompanied by elevated inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] and peripheral eosinophilia. After this initial inflammatory phase, sclerosis gradually starts to develop at affected body sites [15, 21]. The differential diagnosis of EF consists of morphea, SSc, scleroderma-like conditions, and miscellaneous diseases characterized by signs of inflammation and peripheral eosinophilia.

Differentiation between morphea and EF is mainly based on the characteristic distribution of cutaneous sclerosis in different morphea subtypes (i.e., linear morphea) [48]. In addition, histological demonstration of a fasciitis accompanied by eosinophils in the infiltrate support the diagnosis of EF [15]. However, histological differentiation with deep morphea, especially in the presence of widespread sclerosis, may be challenging. In such cases, clinical findings such as symmetrical distribution, a pronounced inflammatory phase, and detection of peripheral eosinophilia point towards EF.

Eosinophilic fasciitis and SSc are both characterized by initial inflammation, followed by cutaneous fibrosis. Facial and acral involvement are uncommon in EF and point toward SSc. In addition, presence of Raynaud's phenomenon, abnormal nailfold capillaroscopy, specific autoantibodies, and internal organ involvement are absent in EF and frequently found in SSc. Lastly, histopathological demonstration of a fasciitis supports the diagnosis of EF [108].

Eosinophilia-myalgia syndrome (EMS) [141], caused by L-tryprophane ingestion, and toxic oil syndrome [142], are two examples of scleroderma-like syndromes which may be difficult to differentiate from EF, even by full-thickness biopsies. However, internal organ involvement differentiates the conditions from EF. Likewise, hypereosinophilic syndrome (HES) [143] and EGPA [144] are also characterized by organ involvement. In addition, the absence of cutaneous sclerosis in both HES and EGPA should aid differentiation with EF.

Lastly, nephrogenic systemic fibrosis should be suspected in patients with advanced renal failure, or a history of gadolinium administration. In addition to the patients' history, involvement of the acra and absence of eosinophilia supports the diagnosis of nephrogenic systemic fibrosis.

9 Referral and Flow Chart

Figure 8 displays a flowchart which guides the care provider with regard to diagnoses and complication management.

9.1 Morphea ECDS and Progressive Facial Hemiatrophy (Parry–Romberg Syndrome)

Referral to an ophthalmologist should be considered to detect complications such as eyelid abnormalities, anterior uveitis, and episcleritis [30]. Odontostomatologic complications should be managed accordingly in cooperation with an oral maxillofacial surgeon and/or dentist [33–35]. Lastly, neurological manifestations consisting of seizures and headaches [145] may occur and referral to a neurologist could be considered to rule out central nervous system involvement [32, 146–150].

9.2 Eosinophilic Fasciitis

Eosinophilic fasciitis manifests secondary to malignancy in a minority of patients (5–10%). Association with hematological malignancy is more common than association with solid neoplasms [14, 15, 151]. Various screening modalities, such as laboratory testing, X-ray, CT or PET scan, ultrasound and endoscopy, may be employed, dependent on the patient risk profile and additional signs of malignancy.

9.3 Musculoskeletal Complications

Musculoskeletal complications (arthralgia, contractures, and arthritis) are reported in up to 40% of morphea and EF patients [1, 5, 15]. We recommend consultation of a rheumatologist in the presence of musculoskeletal complications.

10 Treatment

Care providers should take disease subtype, degree of activity, depth of involvement, and quality-of-life impairments into account when initiating treatment. In most patients with circumscribed superficial subtypes, treatment with topical therapies suffices. In widespread superficial disease, phototherapy or systemic treatment with methotrexate (MTX) should be initiated. For deep involvement, MTX is considered first-line treatment. The addition of SCS should be considered in case of severe disease, rapid progression, or (looming) contractures. Figure 9 shows an algorithm which guides care providers in treatment decisions for the different subtypes, including EF.

10.1 Topical Therapy

10.1.1 Topical and Intralesional Corticosteroids

Topical corticosteroids (TCSs) are first-line therapy for superficial morphea. However, no studies have reported

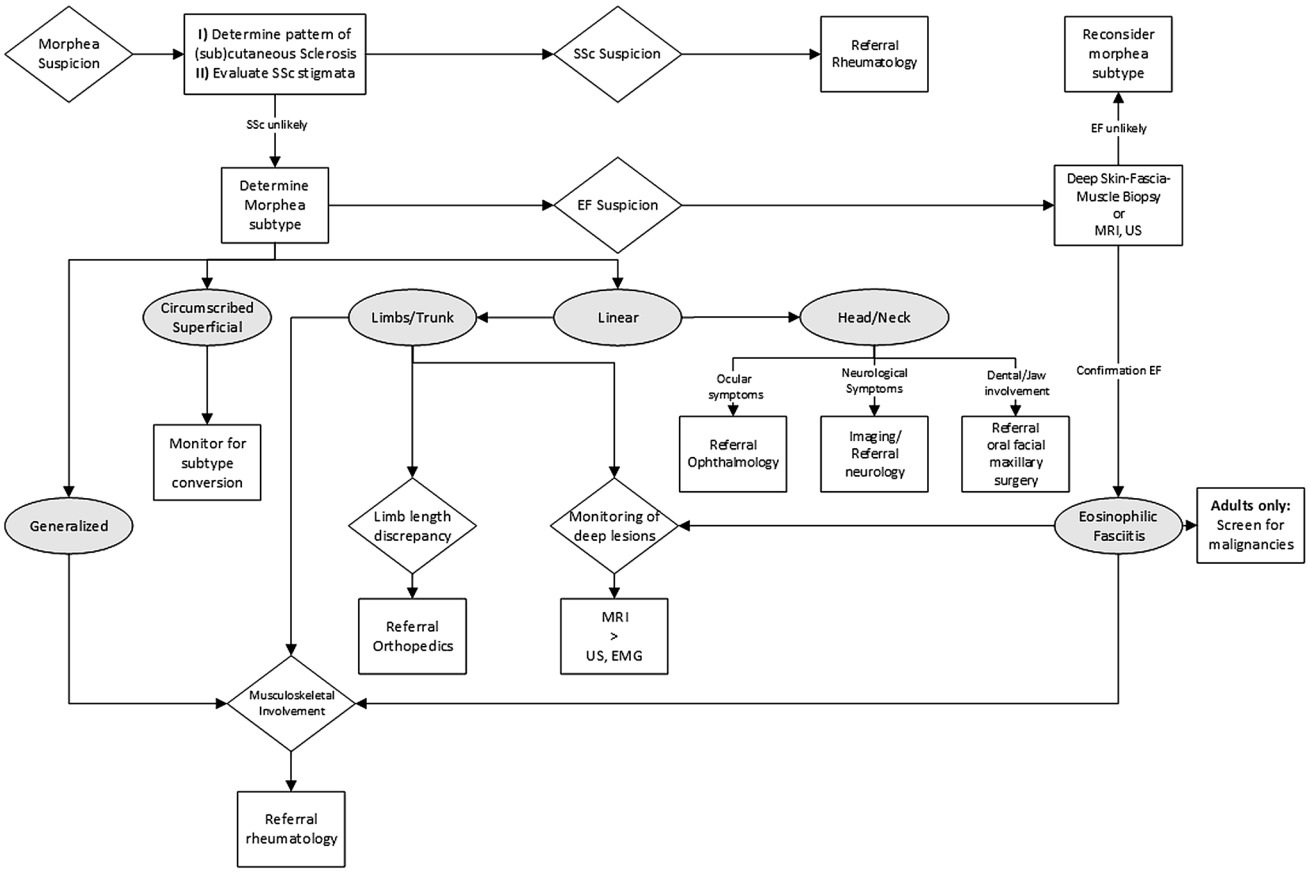

Fig. 8 Flow chart for considerations with regard to diagnosis and monitoring of morphea and eosinophilic fasciitis. *EF* eosinophilic fasciitis, *EMG* electromyography, *MRI* magnetic resonance imaging, *SSc* systemic sclerosis, *US* ultrasonography

efficacy of TCSs in morphea. Based on expert opinion, we regard TCS first-line treatment for superficial circumscribed morphea. We recommend a highly potent TCS once a day for up to 4 weeks or a moderately potent TCS once a day for up to 3 months. Additionally, long-term TCS therapy should be in the form of interval therapy [24]. As with TCS, there are no studies reported for intralesional corticosteroids.

10.1.2 Topical Tacrolimus 0.1% Ointment

A double-blind, randomized controlled trial (RCT) with tacrolimus 0.1% ointment reported significant improvement in durometry and clinical scores [152]. A 3-month open-label study with topical tacrolimus 0.1% ointment twice daily under occlusion demonstrated complete resolution of early lesions and softening of late sclerotic lesions [153]. Another open-label study reported improvement in 9 out of 13 patients with topical tacrolimus 0.1% ointment, twice daily without occlusion [154]. We recommend topical tacrolimus 0.1% ointment, either with or without occlusion, twice daily as an alternative or additional topical therapy for superficial morphea. Additionally, based on a recent case report, we do not recommend topical tacrolimus in radiation-induced morphea [155].

10.1.3 Topical Calcipotriol 0.005% Ointment

Two uncontrolled studies investigated topical calcipotriene 0.005% ointment, either with [156] or without occlusion [157]. These studies included 31 patients and both studies reported beneficial effects in all patients. Lastly, an uncontrolled study with six patients reported efficacy of combination therapy with betamethasone dipropionate and calcipotriol 0.005% [158]. Based on the literature, we recommend topical calcipotriol 0.005% ointment, once or twice daily, with or without occlusion as an alternative topical therapy for superficial morphea. Additionally, topical calcipotriol 0.005% ointment may be prescribed combined with TCS therapy.

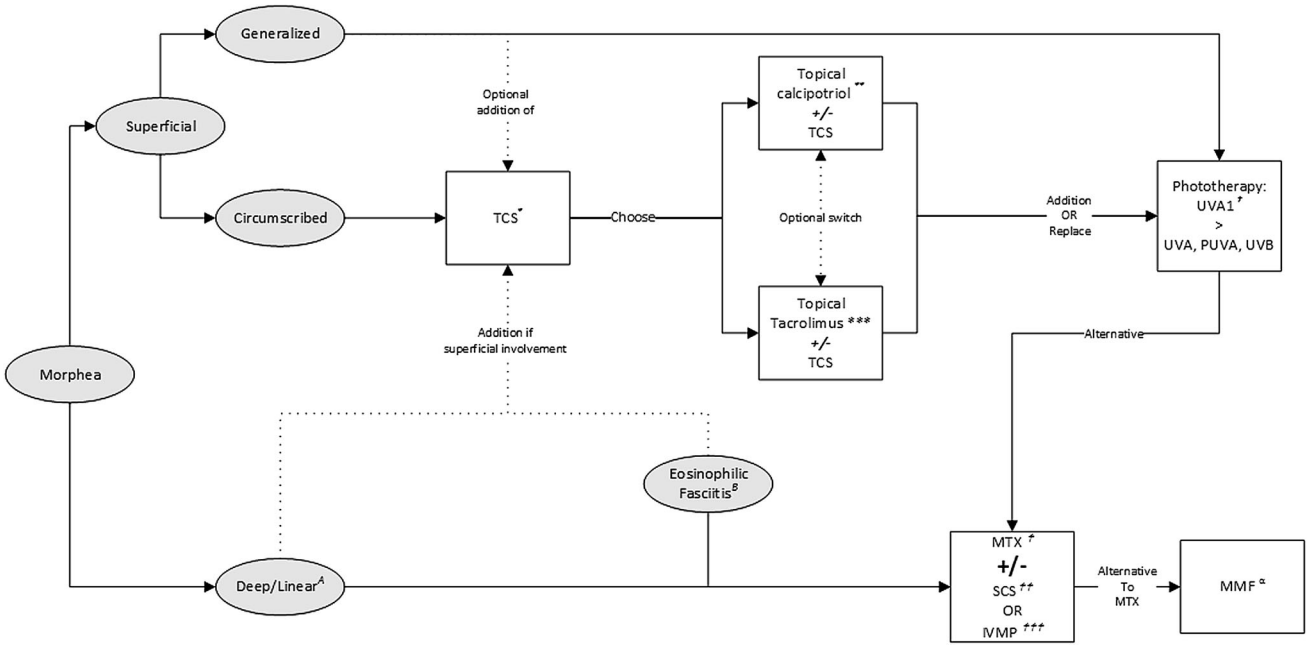

Fig. 9 Flow chart for the management of morphea and eosinophilic fasciitis. * Topical Corticosteroids (*TCS*): moderately potent TCS once daily for 3 months. Highly potent TCS once daily for 1 month. ** Topical calcipotriol 0.005% ointment: once or twice daily, with or without occlusion. Possibly in combination with TCS. *** Topical tacrolimus 0.1% ointment: once or twice daily, with or without occlusion. Possibly in combination with TCS. † Phototherapy: preferably UVA1; suggested dose: 60 J/cm^2 to a cumulative dose of 1460 J/cm^2. If UVA1 is unavailable or impractical, alternative modalities are broadband UVA, PUVA or UVB. † Methotrexate (*MTX*): adult starting dose 15 mg/week, max dose 25 mg/week; pediatric starting dose 15 mg/m^2, max dose 25 mg. Folic acid supplementation: 0.4–1 mg/day or 5–10 mg/week. †† Systemic corticosteroids (*SCS*): adult starting dose 0.5–1 mg/kg/day (max 60 mg) during a max of 3 months followed by tapering; pediatric dose: 1–2 mg/kg/day, max dose 60mg/day, followed by tapering. ††† Intravenous methylprednisolone (*IVMP*): adult dose 1000 mg/day for 3 days/month for 3–6 months, possibly followed by oral SCS. Pediatric dose 30 mg/kg/day for 3 days/month for 3 months, possibly followed by oral SCS. α Mycophenolate Mofetil (*MMF*, alternative to MTX): adult dose 1000 mg twice daily. Pediatric dose 600–1200 mg/m^2/day twice daily. A Deep/linear subtypes: treatment with MTX † monotherapy. Addition of SCS †† or IVMP ††† in case of rapidly progressive disease or in the presence of (looming) contractures. B Eosinophilic Fasciitis: standard induction treatment with oral SCS †† or IVMP ††† in combination with MTX †. *PUVA* psoralen plus broadband UVA, *UV* ultraviolet

10.1.4 Miscellaneous Topical Therapies

A proof-of-concept study with topical imiquimod 5% cream reported effectiveness, measured by decrease of DIET and visual analog scale (VAS) scores in nine pediatric patients [159]. A second prospective vehicle-controlled study with 25 adult patients confirmed these results. Imiquimod 5% cream was superior to vehicle in reducing DIET scores at months 3, 6, 9, and 12 [120]. Both prospective studies reported no study withdrawals and adverse effects were minimal. Lastly, several case reports and series confirm the beneficial effects of imiquimod 5% [119, 160, 161]. Despite these positive study results, German guidelines do not recommend the use of imiquimod 5% cream, based on the authors' experience [24].

Interestingly, an open phase II trial with 12 morphea patients reported significant reduction of mLoSSI and durometer scores at month 6 compared with baseline with 8% pirfenidone gel, three times daily. Pirfenidone gel was well tolerated and no side effects were reported [162].

10.2 Phototherapy

Several phototherapy modalities [ultraviolet (UV) B, psoralen plus broadband UVA (PUVA), broadband UVA and UVA1] have been investigated for morphea. Lower wave length phototherapy (UVA) has greater potency of tissue penetration than UVB and therefore has been studied more extensively.

10.2.1 UVA1

The treatment potential of UVA1 (wavelength of 340–400 mm) is superior to broadband UVA (320–400 mm), because of the lower risk for sunburn. This allows for higher dosage delivery with fewer side effects.

Three different UVA1 dose regimens exist and have been investigated for morphea: low dose (LD, 10–20 J/cm^2) [163–168], medium dose (MD, 30–50 J/cm^2) [121, 122, 167–170], and high dose (HD, 60–130 J/cm^2) [164]. One study demonstrated superior results for HD compared with LD-UVA1 [164]. Additionally, one randomized prospective study compared LD-UVA1, MD-UVA1, and UVB. This study showed superior efficacy of MD-UVA1 versus UVB but not versus LD-UVA1 [167]. Noteworthy, the first true randomized, blinded, and placebo-controlled trial with UVA1 is currently including patients (clinicaltrials.gov NCT01799174). The maximum dose investigated in a study consists of a cumulative dose of 3900 J/cm^2. At our center, we treat patients with 60 J/cm^2 3–5 times a week to a cumulative dose of 1460 J/cm^2. In contrast to the excellent short-term results with UVA1, a study of 37 adults showed 2-year and 3-year recurrence rates of 44.5 and 48.4% after UVA1 treatment, respectively [29]. No data exists with regard to effectiveness of repeated treatment with UVA1.

10.2.2 Miscellaneous Phototherapy Modalities

One study investigated broadband UVA (320–400 mm) in three dose regimens (5, 10, and 20 J/cm^2) for 20 sessions in 63 patients. All regimens were effective and none of them was superior to the other regimens [171]. Two prospective studies report beneficial effects of PUVA in 30 patients [172, 173]. Additionally, a retrospective single-center study confirmed these beneficial effects in 28 patients [174]. Lastly, one prospective study demonstrated equal effectiveness of UVB and low-dose UVA1 [167].

10.2.3 Summary and Recommendations

Based on the literature, we recommend UVA1 as first-choice phototherapy modality for adult patients. Although supported by less evidence, UVA1 phototherapy may also be used in a pediatric morphea. Despite the deeper penetration potential of UVA1, phototherapy should primarily be used for superficial subtypes of morphea. Additionally, it may be used as add-on therapy to systemic treatment in patients with both superficial and deep manifestations.

10.3 Systemic Treatments

10.3.1 Systemic Corticosteroids (SCSs)

One open study investigated an oral SCS (prednisone, starting dose 0.5–1 mg/kg/day followed by tapering) in 17 patients with severe morphea. Patients were treated for 5 to 70 months. This study reported a rapid response. However, in six patients (35%), disease relapse was observed after treatment discontinuation [175]. Additionally, a retrospective study with 28 adult patients reported a favorable response in 24 patients (86%) with an oral SCS (prednisone, starting dose 0.3–1.0 mg/kg/day). Patients were treated for 3–39 months. Similar to the first study, recurrence rate was 45% after treatment discontinuation [176]. High recurrence rates combined with an unfavorable long-term side-effect profile leads to the recommendation that oral SCS monotherapy is no viable long-term treatment option for morphea. Intravenous methylprednisolone (IVMP) has only been investigated in combination with MTX and will be discussed in the following section.

10.3.2 Methotrexate

MTX, with or without the combination of IVMP and/or oral SCS, is the most reported systemic treatment for morphea. Best evidence results from a double-blind RCT with 70 pediatric morphea patients, which investigated oral MTX (15 mg/m^2/week, max 20 mg) versus placebo for 12 months. Both arms received an oral SCS (prednisone, starting dose 1 mg/kg/day, max 50 mg, followed by tapering) for the first 3 months. Reported outcome measures consisted of a computerized skin score rate and IRT. Improvements in outcome measures at month 12 could only be observed in the MTX treatment arm, whereas the placebo arm showed worsening [28].

Two prospective non-controlled studies investigated MTX in combination with IVMP [177] or oral SCS [178] in children. One study included ten pediatric patients who received subcutaneous MTX 0.3–0.6 mg/kg/week (max 20 mg/week), of whom nine patients simultaneously received IVMP (30 mg/kg for 3 days, monthly for 3 months). At the last follow-up visit, all patients who continued ($n = 9$) had inactive skin lesions [177]. The second study investigated subcutaneous MTX (1 mg/kg/week, max 25 mg) in combination with an oral SCS (prednisone 2 mg/kg/day, maximum 60 mg/day followed by tapering) in 36 pediatric patients. All patients demonstrated significant improvement in mLoSSI and PhysGA-A at a median of 1.77 months [178].

Two additional prospective studies investigated adult patients. One study investigated oral MTX (15 mg/week) in combination with IVMP (1000 mg for 3 days, monthly) for at least 6 months in 15 patients with severe morphea. In the majority of patients ($n = 14$), a significant decrease in mSS was observed, supported by histologic and ultrasound assessments [179]. Another uncontrolled prospective study investigated oral MTX (15 mg/week) monotherapy for 24 weeks in nine adult morphea patients [180]. Significant improvements in MSS and VAS for tightness were observed at week 24.

In addition to prospective trials, we identified 11 retrospective studies which report MTX with or without IVMP and/or oral SCS [1, 4, 25, 27, 32, 109, 181–185]. A total of 353 unique patients were identified (124 adults and 229 pediatric patients). Response rates to MTX with or without IVMP and/or oral SCS ranged between 80–94%. In contrast to the high short-term response rates, (long-term) disease recurrences are reported in 28–44% of the patients after MTX discontinuation [1, 25, 182, 184]. A prospective long-term follow-up study described that MTX treatment duration was a predictor for relapse, suggesting that longer treatment duration prevents disease relapse [186]. Lastly, some of the retrospective studies report superior response rates for combination therapy with MTX plus SCS compared with MTX monotherapy [4, 185]. However, these studies are prone to bias because of confounding by indication as a result of the retrospective design of these studies.

In conclusion, MTX is an effective treatment for morphea. However, no comparative studies between MTX monotherapy and MTX plus SCS have been reported. Therefore, no recommendations can be given as to whether MTX should be applied with or without SCS. However, either oral SCS or IVMP should be added to MTX in the case of severe disease, rapidly progressive disease, or in the presence of (looming) contractures. Recommended dosages are displayed in the legend of the flowchart (Fig. 9). Optimal timing of systemic treatment discontinuation remains a difficult aspect in therapeutic management.

10.3.2.1 Folic/Folinic Acid Supplementation A retrospective analysis of MTX treatment in 107 adult patients showed that folic acid (5–10 mg once a week) protected against MTX discontinuation due to adverse events [181]. Additionally, folic acid (0.4–1 mg/day) or folinic acid (5 mg/week) is recommended by Childhood Arthritis and Rheumatology Research Alliance (CARRA) [187].

10.3.3 Mycophenolate Mofetil (MMF)

Two studies reported MMF in severe refractory morphea. The first study retrospectively described ten MTX- and corticosteroid-refractory pediatric morphea patients who were treated with MMF (600–1200 mg/m^2/day). Six out of ten patients received MMF combined with MTX treatment. Arrest of disease progression was reported in eight patients (80%) a reduction of erythema in seven (70%), skin softening in nine (90%), and extracutaneous manifestations in four patients (40%). MMF was well tolerated in all patients [188]. The second study retrospectively described MMF in seven morphea patients (three adults and four children). Doses ranged from 500 to 2500 mg. This study reported disease remission in four patients (57%) and maintenance of disease remission in one patient (14%). In the remaining two patients (29%), MMF treatment was discontinued due to disease progression or side effects [189]. Despite the limited evidence for MMF in morphea, two studies showed extensive experience with MMF in large proportions of involved care providers [187, 190]. Based on current evidence, we recommend MMF (adults 1000 mg twice daily; children 600–1200 mg/m^2/day twice daily) as an alternative to MTX.

10.3.4 Miscellaneous Systemic Treatment Options

Recent case reports describe imatinib [191–194], infliximab [102, 103], rituximab [98], abatacept [195], the mTOR inhibitors tacrolimus [196] and everolimus [197], and mesenchymal stem-cell therapy [198] as alternative treatment options in severe morphea. The authors recommend restraint from the use of TNF-α inhibitors in the treatment of morphea as multiple reports show morphea can be provoked by these agents [98–101].

10.4 Recommendations for EF

Historically, HD SCS monotherapy (prednisone 0.5–2.0 mg/kg/day) was regarded as first-line treatment for EF [14, 15, 199]. However, multiple recent retrospective studies have shown superior response rates in patients who are treated with a combination of HD SCS and an ISD, especially for weekly MTX (15–25 mg/week) [14, 16, 200]. These studies are retrospective and thus prone to confounding by indication. Future prospective studies should investigate the additional (long-term) effect of MTX as was done for pediatric morphea [28].

Case series reported non- or partial responses to conventional treatment in a proportion of patients [14–16]. Until recently, only case reports or small case series described alternative treatment options [21]. However, a recent study prospectively investigated HD pulse IV MTX (4 mg/kg/month; median monthly MTX dose 288 mg) as an alternative treatment option in 12 patients with EF. The median mSS improved significantly after six pulses ($p = 0.001$). Additionally, the range of motion of affected joints and patient-reported outcomes showed significant increases. Treatment was well tolerated and adverse events could be managed accordingly. In this study, one patient had to be withdrawn due to an adverse event [201]. Another recent prospective study reported superior clinical improvement in severe EF patients treated with D-penicillamine (D-pen) plus oral SCS ($n = 10$) versus SCS monotherapy ($n = 6$). Disappointingly, four out of ten patients in the D-pen-arm had to discontinue treatment due to adverse events [202]. Lastly, the following alternative

treatments have been reported in case reports and series: infliximab [203], azathioprine [204, 205], sulfasalazine [206], cyclosporine [207], cyclophosphamide [208], rituximab [209], tocilizumab [210], sirolimus [211], PUVA [212], IV immunoglobulins [213], and bone marrow transplantation [214, 215].

We recommend a combination of SCS and MTX as first-line treatment for EF. Induction therapy may consist of HD oral SCS (prednisone 1 mg/kg/day, followed by tapering) or IVMP (1000 mg for 3 days monthly, followed by oral SCS) started simultaneously with weekly MTX (15–25 mg/week) maintenance therapy.

10.5 Treatment of Disease Damage

Multiple studies report effective strategies for correction of disease damage. However, timing of these correctional procedures is crucial, as disease flare has frequently been reported even after many years of disease quiescence [10, 26]. A recent study reviews the surgical treatment options for Parry–Romberg syndrome and ECDS and describes the debate with regard to timing of these procedures [36]. Autologous fat grafting in ECDS is reported in multiple case reports and series [216–221]. Lastly, one case report describes correction for limb-length discrepancy in linear morphea of a lower extremity [222]. In the authors' opinion, these procedures should only be performed in long-term quiescent disease by a care provider with (extensive) experience in this field. Lastly, although evidence is lacking, physical therapy should be considered in case of decreased range of motion of an affected joint or when postural deformities are present as a result of limb-length discrepancies.

11 Conclusions

Morphea and EF pathogenesis remains to be elucidated as well as the exact immunological relationship with SSc. This may lead to insight into the disease mechanisms behind these debilitating conditions and the identification of new therapeutic targets.

Progression has been made in standardization of outcome measures for morphea. Currently, LoSCAT is the most promising and frequently used outcome measure. This should lead to data harmonization and the potential to compare future studies.

Monitoring of deep involvement of morphea is one of the most difficult aspects of the disease. The lack of validated outcome measures for deep involvement emphasizes the need for new biomarkers.

Compliance with ethical standards

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Conflict of interest Jorre S. Mertens, Marieke M.B. Seyger, Rogier M. Thurlings, Timothy R.D.J. Radstake, and Elke M.G.J. de Jong have no conflicts of interest.

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