Morphea (Localized Scleroderma)

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Classification and Epidemiology of Morphea

Morphea, also called localized scleroderma, is a chronic autoimmune disease characterized by inflammation and sclerosis of the skin. Morphea, like scleroderma, is characterized as a sclerosing skin disorder, due to characteristic histological findings shared by both disorders, including sclerosis of the dermis and sometimes subcutis in the absence of fibroblast proliferation. However, morphea differs from scleroderma demographically and clinically. In contrast to scleroderma, involvement of internal organs in morphea is unusual and very different from that in scleroderma, and the diagnosis does not carry the same implications in terms of morbidity and increased mortality. Thus, it is the opinion of the authors that the term "localized scleroderma" should be avoided to limit unnecessary evaluation and anxiety for patients and confusion among providers. For the purposes of this chapter, we will exclusively use the term "morphea."

The clinical features of morphea are single or multiple sclerotic or indurated cutaneous plaques that are often dyspigmented (hypo- or hyperpigmented) and may have an erythematous border, depending on their stage of evolution. These plaques vary in appearance, depending on the subtype of morphea (Table 8.1) and activity of disease (see *Assessment of disease activity* and *Stages of morphea lesions*). Notably, cutaneous features of scleroderma, including Raynaud's phenomenon, mat-like telangiectasias, sclerodactyly, acrosclerosis, decreased oral aperture, and nailfold capillary changes, are not seen in morphea.

The major subtypes of morphea include circumscribed or plaque-type, linear, generalized, pansclerotic, and mixed forms. Clinical images of the morphea subtypes are presented in Fig. 8.1. The classification scheme presented herein was developed by the Committee on Classification Criteria

for Juvenile Systemic Sclerosis, composed of members of the Pediatric Rheumatology European society (PRES), the American College of Rheumatology (ACR), and the European League Against Rheumatism (ELAR) [1] (Table 8.1). Although there are many reported classifications of morphea, the authors have found this to be the most clinically relevant. The classification of morphea is based on the morphology of the skin lesions, as histopathology is similar in all the forms of morphea, and there are no known biomarkers for morphea subtypes. Histology is useful, however, in excluding other entities in the differential diagnosis (see *Differential diagnosis of morphea*).

Variants and Related Entities When linear morphea occurs on the upper face, especially the paramedian forehead, it is often called en coup de sabre (ECDS) (Fig. 8.2a, b). When it involves the lower face or produces hemifacial atrophy of deeper tissues, it is called progressive hemifacial atrophy (PHA), also known as Parry-Romberg syndrome (PRS) (Fig. 8.2c–f). Whether these conditions represent an entity different from morphea has been a subject of considerable debate, but recent literature suggests that they are part of the morphea disease spectrum [2] in the sense that PHA represents deep involvement of the facial tissues with resultant residual atrophy.

Overlying lichen sclerosus, changes may be seen in morphea lesions of all subtypes (Fig. 8.3). This observation has led to controversy over whether these represent two independent processes or whether changes similar to lichen sclerosus occur in morphea. Eosinophilic fasciitis (EF) has also been considered by some to be a variant of morphea, as about a third of patients with EF have findings typical of classic plaque-type morphea [3].

Other entities such as bullous morphea and guttate morphea have been described in case reports and case series [4–13]. Examination of reports of bullous morphea reveals that bullae were largely present in areas of dense sclerosis in dependent areas [7]. This suggests that the bulla is a secondary

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Table 8.1 Classification of morphea

Morphea subtype	Modifiers	Clinical
Circumscribed	Superficial	Single or multiple oval/round lesions; pathology limited to the dermis
	Deep	Single or multiple oval/round lesions involving the dermis and subcutaneous tissue, fascia, or muscle
Linear	Trunk/limbs	Linear lesions; possible primary site of involvement in the subcutaneous tissue without involvement of the dermis; may involve the subcutaneous tissue, muscle, and/or bone
	Head	En coup de sabre (ECDS), progressive hemifacial atrophy (PHA), linear lesions of the face and scalp (may involve the underlying bone)
Generalized		
1. Coalescent plaque		≥4 plaques in at least 2 of 7 anatomic sites (head-neck, right/left upper extremity, right/left lower extremity, anterior/posterior trunk); Isomorphic pattern: coalescent plaques inframammary fold, waistline, lower abdomen, proximal thighs; symmetric pattern: symmetric plaque circumferential around the breasts, umbilicus, arms, and legs
2. Pansclerotic[a]		Circumferential involvement of majority of body surface area (sparing the fingertips and toes), affecting the skin, subcutaneous tissue, muscle, or bone; no internal organ involvement characteristic of scleroderma
Mixed		Combination of any above subtype:: linear – circumscribed

[a]While Zulian and Laxer categorized pansclerotic morphea separately, it is the opinion of the authors that this subtype can be classified under the broader heading of generalized morphea, as the features of pansclerotic morphea fulfill criteria for generalized morphea in terms of the extent of involvement. The classification was further modified by the authors from the original by clarifying the level of pathology of the various subtypes (Adapted with permission from Laxer and Zulian [110])

change related to edema in dependent areas or lymphatic obstruction due to sclerotic changes in the skin, rather than a primary process [7, 11, 14]. Therefore, it is the opinion of the authors that bullae should not warrant a designation as a separate subtype. Similarly, guttate lesions likely represent a variant of circumscribed morphea.

Epidemiology and Clinical Course Morphea has an estimated incidence of 2.7/10000 with a female to male ratio of 2–3:1 [15]. Existing studies suggest that morphea occurs most frequently in Caucasians, though population-based studies are needed to confirm this finding [16–18]. The reported frequency of different subtypes varies likely due to differing classification systems. However, linear morphea is more common in the pediatric population [15, 19], while the generalized and plaque subtypes predominate in adults. The clinical course is not well described, with periods of disease activity ranging from 3 to 6 years, and reactivation occurring after periods of remission in some patients [20]. Patients with pediatric-onset disease may also experience persistent disease and/or recurrences in adulthood [21, 22]. A retrospective evaluation of long-term outcomes of adults with pediatric-onset morphea from the Morphea in Adults and Children (MAC) cohort revealed that 89 % of patients (24/27) developed new or expanding lesions over time, suggesting that patients may need lifelong evaluation and repeated courses of treatment to prevent morbidity [21] (Fig. 8.4).

Studies examining recurrence rates after treatment with methotrexate and/or systemic steroids report recurrence 6–19 months after discontinuation of therapy in 10–44 % of patients [23–26]. Studies evaluating long-term outcomes after methotrexate therapy vary greatly in methods and duration of follow-up, so comparison of recurrence is difficult [23, 27]. Recurrence has also been described in patients after successful treatment with UVA-1 phototherapy at rates as high as 46 %, which may exceed those rates described with methotrexate. Median time to recurrence ranges from 10 months up to 20–30 months for those treated with UVA-1 and methotrexate, respectively [22, 23, 27–29]. These findings emphasize the need for regular monitoring of patients with morphea for signs of new disease activity even after successful treatment (see *Assessment of disease activity in morphea*).

Factors associated with recurrence in previous studies have included longer duration of disease before treatment

Fig. 8.1 (**a**) *Plaque-type morphea*. Circumscribed hyperpigmented plaques are present on the posterior legs of this patient with morphea. (**b**) *Generalized morphea on the trunk*. Hyperpigmented sclerotic plaques are present on the chest and abdomen. (**c**) *Generalized morphea on the extremities*. Symmetric, hypopigmented, sclerotic plaques are present on the legs of this patient with generalized morphea. (**d**) *Linear morphea*. Linear lesions of both the extremity and trunk are seen in this patient. Note that early linear lesions may not completely coalesce and may be confused with plaque-type morphea if not carefully examined. Note that on the trunk, linear lesions characteristically obey the midline. (**e**, **f**) *Pansclerotic morphea*. Note sheets of contiguous sclerosis, encompassing the majority of the body surface area (**e**) and characteristically sparing the fingertips, stopping at the metacarpophalangeal joints (**f**)

Fig.8.1 (continued)

[28], older age of onset in the pediatric population [25], and the presence of linear morphea of the limbs [25, 30]. However, these associations have not always been replicated across studies. Prognostic markers have not yet been identified for recurrent or chronic disease in the form of prospective longitudinal studies, but retrospective reviews and cross-sectional studies have implicated that increased duration of disease before treatment may be associated with increased likelihood of recurrent disease [28]. Preliminary analysis from the prospective MAC cohort has revealed similar recurrence rates between pediatric and adult patients and across subtypes of morphea. The only variable associated with recurrence in this cohort has been disease duration, in that patients with longer disease duration have been more likely to recur.

Etiology and Pathogenesis of Morphea

The etiology and pathogenesis of morphea is not well understood. Most pathological events ascribed to morphea have been extrapolated from research in scleroderma, as the two disorders are assumed to arise from a similar etiology [31]. Morphea, like other autoimmune disorders, likely arises from a genetic background of increased immune disease susceptibility, combined with other causative factors, such as trauma or environmental exposures, which modulate the expression of disease.

Genetics and Autoimmunity in Morphea Like many autoimmune connective tissue diseases, morphea is likely a complex genetic disease. Familial clustering has been reported, although rarely [18, 32, 33], and morphea is also associated with higher than expected rates of familial autoimmune disorders [18, 21, 34]. In retrospective studies, morphea patients

have demonstrated concomitant autoimmune disease, including psoriasis, systemic lupus erythematosus, multiple sclerosis, and vitiligo, at higher than expected frequency when compared with published population-based prevalence estimates [18, 34–36]. A population-based study examining a rheumatoid arthritis population in Sweden reported a higher risk of morphea among these patients with a reported standardized incidence ratio (SIR) of 2.40 [35]. A similar population-based study in Sweden also reported a higher risk of morphea among siblings of patients with multiple sclerosis with an SIR of 1.72 [36]. Morphea has been reported, in case studies, to coexist with other autoimmune diseases, including inflammatory bowel disease [37], autoimmune thyroid disease [38, 39], alopecia areata, type I diabetes mellitus [37], antiphospholipid syndrome [40], and necrotizing vasculitis [68]. Other types of inflammatory skin disorders can also be associated with morphea, such as psoriasis [41] and lichen planopilaris [42].

Of interest, the risk for morphea has been associated with the presence of specific HLA class I and II alleles, further implicating a possible underlying genetic predisposition for the disease. A large case-control association study of patients from the MAC cohort revealed strong associations with specific HLA class I and II alleles, including, most significantly, HLA-B*37, as well as another, DRB1*04:04, in common with a risk allele previously identified for systemic sclerosis [43]. Alleles conferring the greatest risk included HLA DRB1*04:04 and HLAB37 [43]. Risk alleles identified in this case-control study have also been associated with the risk in rheumatoid arthritis and autoimmune thyroid disease [44, 45], implying that there may be a common genetic susceptibility to these disorders.

Increasing evidence supports immune dysregulation as an important pathogenic event early in the course of morphea.

Early morphea lesions are characterized by the influx of large amounts of mononuclear lymphocytes (usually activated T-lymphocytes), plasma cells, and eosinophils [31]. This is likely the result of autoimmunity, as there is widespread autoimmune reactivity in morphea patients including elevated ANAs (see *Laboratory findings in morphea*), cytokines, and adhesion molecules [18, 21, 46]. Vessel damage and upregulation of adhesion molecules (ICAM-1, VCAM 1, and E-selectin) occur related to the inflammatory cell infiltrate in morphea, which facilitates local monocyte recruitment [47]. These adhesion molecules also facilitate the recruitment of T-lymphocytes that are capable of producing pro-fibrotic cytokines (IL-4, IL-6, and TGF-beta) and may contribute to the development to sclerosis [31, 48]. Of note,

Fig. 8.2 (**a**, **b**) *En coup de sabre morphea*. Depressed linear plaques are present on the foreheads of these patients. These lesions are often dyspigmented and may have more obvious dermal changes (**a**) or change predominantly in the subcutis. Interestingly, years after his initial period of activity on the forehead, this patient (**b**) also developed tenosynovitis. (**c**–**f**) *Progressive hemifacial atrophy* also known as Parry-Romberg Syndrome may be subtle (**c**), requiring additional exam maneuvers to detect. Asymmetry can sometimes be better appreciated using different facial expressions (**d**). When progressive, hemifacial atrophy may lead to more obvious lesions, as seen here on the chin, mandible, neck and tongue (**e**–**f**)

Fig.8.2 (continued)

Fig. 8.3 *Morphea and lichen sclerosus*. Sclerotic lesions of morphea with overlying areas of fine, hypopigmented, wrinkled skin are present. This lesion also has features of active inflammatory morphea with an erythematous border
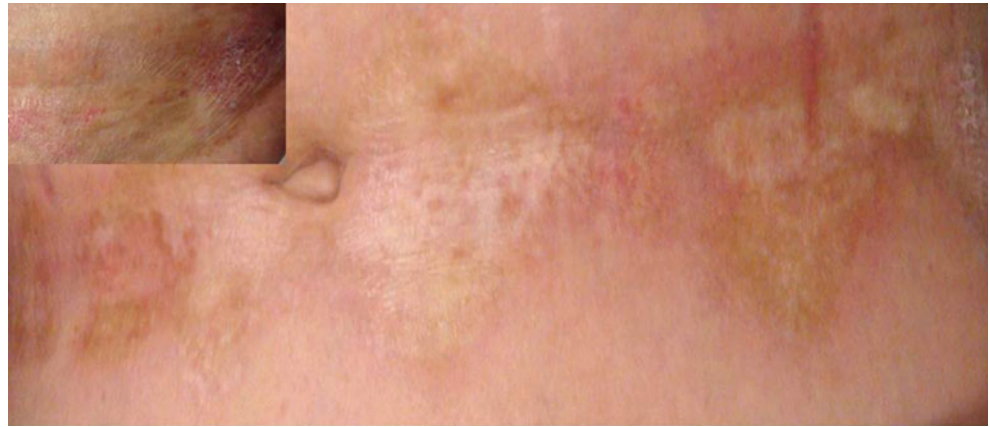

Fig. 8.4 *Chronic nature of morphea and sequelae*. Lesions began on the right leg at age five in this patient. Note muscle atrophy, limb length discrepancy, and pes planus foot deformity (**a**). In adulthood, the same patient had a recurrence of morphea in the form of active inflammatory lesions of the trunk, seen here on the abdomen (**b**), as well as a plaque that appeared on the shoulder (**c**)

increased levels of these vascular adhesion molecules have been detected in serum from patients with morphea [49]. These adhesion molecules are upregulated by cytokines classically associated with a Th2 immune response (IL-4, IL-1, and TNFs). Cytokines found in increased concentration in the sera and skin of morphea patients include IL-4, IL-6, and IL-8 [47, 50]. These cytokines, especially IL-4, upregulate TGF-beta, initiating a cascade of events that results in increased production of collagen and other extracellular matrix components via the induction of connective tissue growth factor, platelet-derived growth factor, and matrix metalloproteinases. Chimerism or nonself cells may also play a role in the pathogenesis of morphea by initiating a local inflammatory reaction [51].

In a recent study of 69 pediatric patients with morphea, interferon-gamma-inducible protein 10 (IP-10) levels were significantly elevated in the plasma of morphea patients

when compared with healthy controls. Immunohistochemistry staining of IP-10 was also present in the dermal infiltrate of a subset of morphea patients who had available skin biopsies. IP-10 levels were significantly elevated in those with active versus inactive disease and correlated with standardized disease outcome measures of activity, further suggesting that IP-10 may be a potential biomarker for disease activity in morphea [52].

Although large-scale studies examining gene expression profiles in morphea are lacking, Milano et al. [53] have used gene expression array analysis to establish a gene expression signatures for scleroderma skin subsets as compared to unaffected skin of the same patient. In their first study, they included the skin from three patients with morphea. They identified five significantly different gene expression clusters: diffuse proliferation, inflammatory, limited, and normal-like in scleroderma. Gene expression profiles from all three

biopsies of morphea skin fell into the inflammatory category, which was characterized by markers for an increase in immune response, response to pathogen, humoral defense, lymphocyte proliferation, chemokine binding, and chemokine receptor activity, and response to virus. These findings provide further evidence for an important role for immune dysregulation in morphea.

Taken together and extrapolating from research in scleroderma, these studies implicate an important role for interferons and Th1-skewed immune responses in early morphea, while Th2 cell lineages may become dominant in later disease as sclerosis predominates. Studies of this sort are necessary to identify pathways relevant to the pathogenesis of morphea and to pave the way for identification of biomarkers and therapeutic targets.

Histopathology of Morphea Histopathological changes in morphea evolve over the duration of individual lesions. The histopathological changes have been divided into indeterminate (early), inflammatory, mixed inflammatory and sclerotic, and sclerotic (late) stage morphea [54] (Figs. 8.5 and 8.6). Increased numbers of T-cells are present in the inflammatory stage compared with a normal skin. As in scleroderma, the inflammatory stage of morphea is characterized by dermal edema and by lymphocytic and histiocytic inflammatory cell infiltrates with plasma cells in a perivascular, periadnexal, and interstitial pattern. Eosinophils, mast cells, and macrophages may also be present. One finding particularly characteristic of morphea is the presence of an inflammatory cell infiltrate in the junction between the dermis and subcutaneous fat. From there, the inflammatory cell infiltrate may stream down the septa of the subcutaneous fat (Fig. 8.6c, d).

Recently, a cross-sectional study of the MAC cohort revealed a predilection for inflammatory cell infiltrate to occur in the border between the subcutis and the dermis. This was particularly true in cases where sclerosis followed a bottom-heavy pattern, characterized by hyalinized collagen bundles in the deep dermis and subcutis, sparing the papillary through the mid-dermis, a pattern which was typical of those with morphea profunda [55] (Fig. 8.6b). A biopsy with such changes, even in the absence of sclerosis, should alert providers to the possibility of early inflammatory morphea profunda. In contrast, in this the same study, a top-heavy pattern, characterized by collagen bundles exclusively in the papillary to superficial reticular dermis, was typical of those with lichen sclerosus overlap. Patterns of sclerosis varied equally in those with linear and plaque-type morphea between top-heavy, bottom-heavy, and full thickness patterns, with thickened collagen bundles throughout the dermis. Interestingly, among patients with generalized morphea, those with isomorphic pattern of distribution in patterns of chronic friction more often had top-heavy patterns of sclerosis, while bottom-heavy patterns predominated among those with symmetric patterns of distribution in generalized morphea. When inflammation was present, it consisted most often of lymphocytes (83/91, 91 %) and plasma cells (68/91, 75 %), but eosinophils were also noted with some frequency (17/91, 19 %).

The later sclerotic stage of morphea is characterized histopathologically by thickened, acellular, homogenized-appearing collagen bundles that may involve all levels of dermis and/or subcutis (where collagen bundles stream downward through the septa) (Fig. 8.6e, f). The adnexal structures (hair, eccrine glands) are surrounded by dense fibrosis with loss of fat around the eccrine glands in chronic disease (Fig. 8.6g). In specimens from morphea profunda, the deep reticular dermis, subcutis, and/or fascia also show sclerotic changes. It is not uncommon for inflammation and sclerosis to coexist (Fig. 8.6a). The atrophic stage is characterized by loss of inflammatory cell infiltrate, decreasing sclerosis, and an absence of appendageal structures. Telangiectasia may be evident.

Triggers and Precipitating Factors The emergence of morphea following exposure to environmental exposures is intriguing and may provide clues for the pathophysiology of morphea. While there are no definitive associations, the

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Fig. 8.5 *Disease features in morphea*. (**a**) *Deep morphea*. The areas affected by deep morphea, also known as morphea profunda, may have a cobblestone appearance with subcutaneous atrophy. (**b–d**) *Inflammatory morphea*. An active plaque in the inflammatory stage is present on the left leg of this patient (**b**) note the violaceous border. There are also multiple early lesions present on the right. (**c**) Early morphea lesions may be subtle, as seen here on the patient's abdomen, where ill-defined indurated plaques with peripheral erythema indicate active inflammatory morphea. (**d**) This well-circumscribed plaque on the patient's breast exemplifies the erythematous border and central sclerosis typical of an early evolving morphea lesion. (**e**) *Sclerotic morphea*. This lesion demonstrates exuberant sclerosis centrally with surrounding hypopigmentation and erythema, likely indicating that the lesion is transitioning toward a more inactive state. Also note telangiectasias, which can occur in the surrounding atrophy and should not be mistaken for erythema indicating inflammation. (**f**) *Atrophoderma of Pasini and Pierini*. Preadolescent girl with several-year history of a large plaque and small patches of atrophy on the lumbar back. The lesions have a sharp drop-off with a "punched out" appearance and are not indurated clinically. (**g**) *Atrophy*. Severe subcutaneous atrophy is present in this patient with linear morphea in the atrophic stage, as well as postinflammatory hyperpigmentation changes and limb length discrepancy. (**h**, **i**) *Linear morphea of the extremity associated with disabling contractures*. Note contractures of the hands in children with long-standing linear morphea. Contractures can be a manifestation of damage occurring most commonly in linear lesions crossing joints, but may also be a component of other subtypes, including generalized morphea, when distributed over the joints
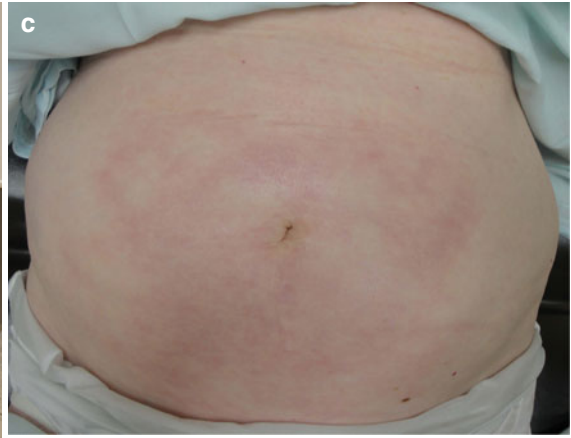
Fig. 8.5 (continued)

Fig. 8.6 (**a**) Skin biopsies of morphea have a characteristic "squared-off" shape because of the dense dermal sclerosis. There are patchy perivascular mononuclear cell infiltrates of lymphocytes, histiocytes, and occasional plasma cells, but otherwise the dermis is acellular compared with the normal skin. Flattening and atrophy of the epidermis are associated with underlying sclerosis. Hair follicles and sebaceous glands normally seen in a skin biopsy of hair-bearing skin are absent. (Magnification=2.5×). (**b**) This specimen shows a pattern of "bottom-up" sclerosis that can be seen in morphea before the entire dermis is involved. The sclerotic collagen is in the *lower half* of dermis, while the normal collagen is in the *upper half*. Dense collagen has replaced normal collagen from the *arrow down*. The *left upper corner* of the image also shows the edge of an atrophic hair follicle. (Magnification=5×). Sclerosis can also occur from the top down or may encompass the entire dermis, even extending into the subcutis and beyond in some cases. (**c**, **d**) Biopsies of active inflammatory morphea reveal perivascular, periadnexal, and interstitial inflammatory infiltrate. Also note the inflammatory cell infiltrate in the junction between the dermis and subcutaneous fat, streaming down through the septa of the subcutaneous fat. Though difficult to appreciate at this power, inflammatory infiltrate is typically composed of lymphocytes, plasma cells, and, occasionally, eosinophils. (**e**, **f**) Higher-power views of the non-sclerotic (**e**) and sclerotic (**f**) dermal areas show that the collagen in the sclerotic area has lost the fine fibrillar texture of normal collagen (Magnification=40×). (**g**) Encasement of adnexal structures by dense collagen with loss of the fat around eccrine glands is shown. Eventually, atrophy of hair follicles, sebaceous glands, and eccrine glands (*arrow*) occurs in long-standing morphea (Magnification=20×)
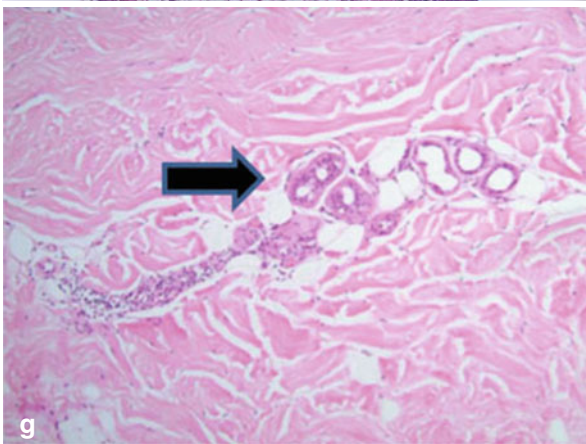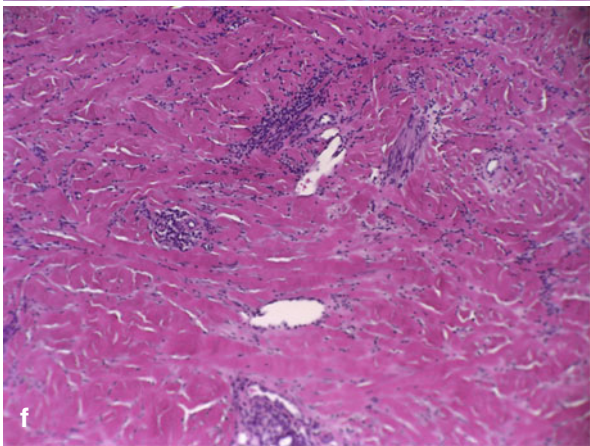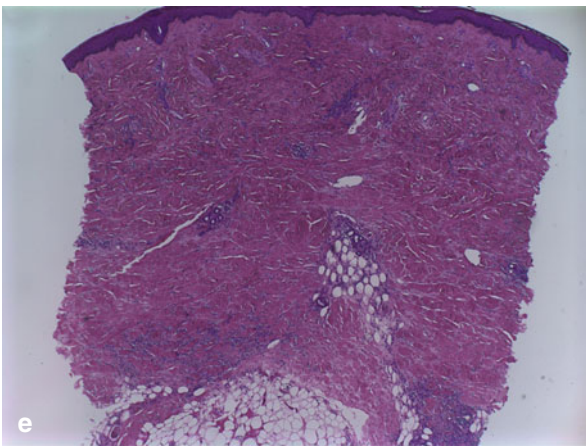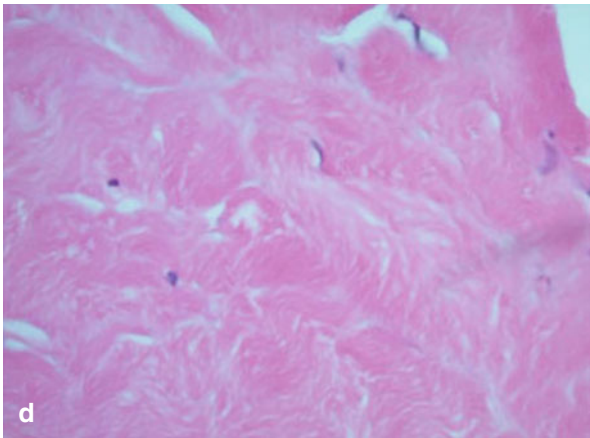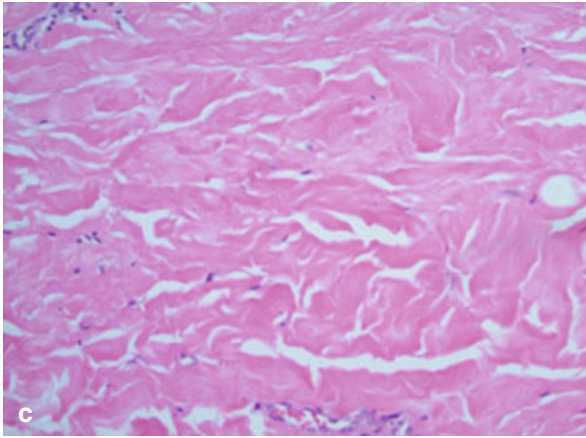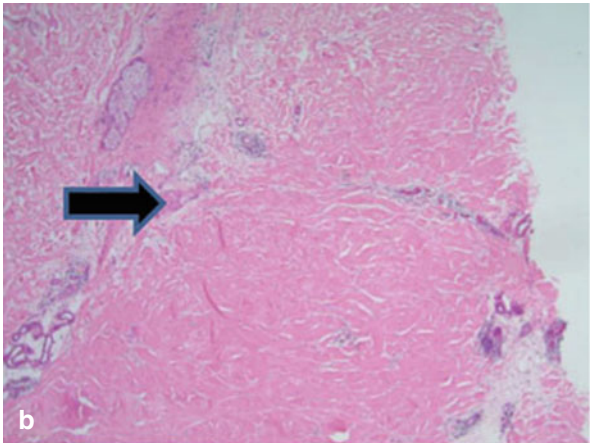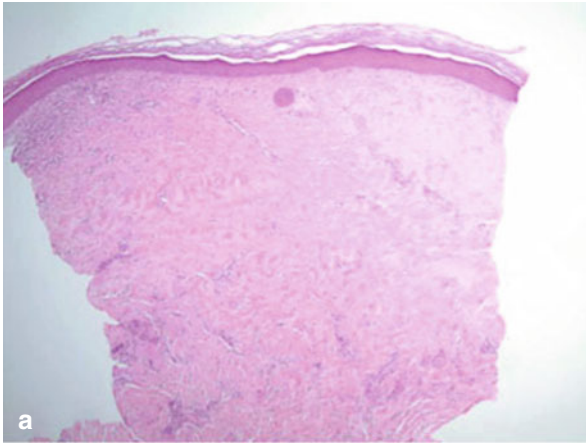
development of morphea lesions has been linked to local tissue trauma including radiation, surgery, insect bites, and intramuscular injections [56]. Although controversial, infectious agents have also been linked to pathogenesis. Studies in Europe had implicated a role for *Borrelia* infection in the pathogenesis of morphea, but this association has been largely discounted.

Increasing evidence, however, exists for the role of trauma in the development of morphea lesions. In a study of 26 patients with severe juvenile localized scleroderma, four (15%) reported a history of trauma to the area, and one had a history of dental extraction ipsilateral to the area in which morphea developed [57]. There are many examples in the literature of injection-site morphea [56, 58], including the onset of morphea at the site of vaccinations as well as at the site of an insulin pump placement, observed by the authors. In a cross-sectional analysis of 329 patients in the MAC cohort, 52 (16%) had trauma-associated lesions at the onset of disease, most commonly chronic friction (isomorphic) and surgery/isotopic triggers [59]. These findings, if confirmed in future studies, might suggest that elective procedures and skin trauma or friction be avoided in morphea patients. However, necessary and lifesaving surgery, radiation, or other procedures should not be avoided merely due to a diagnosis of morphea.

Clinical Features of Morphea

Assessment of Disease Activity in Morphea The assessment of disease activity in morphea is important to clinical decision-making, as most treatments with proven efficacy are directed at the inflammatory stage of disease and will not be effective in predominantly sclerotic or atrophic lesions. The risk-benefit assessment of pursuing treatment for morphea lesions depends on the potential for functional or cosmetic impairment and symptom burden due to active lesions. It is therefore important to make an accurate assessment of lesion activity in each clinical examination, including clinical photographs to compare lesions to prior visits, since active disease may warrant intervention, while inactive disease may be carefully observed over time (see Fig. 8.10). Though imaging modalities such as ultrasound can be useful for assessing disease activity (see *Imaging methods*), active morphea lesions can usually be distinguished from inactive lesions by clinical features. Signs of disease activity (which have been established by expert consensus and validated) include new lesions, lesions that have expanded in size from previous visits, the presence of an erythematous or violaceous border around lesions, and possibly increased patient symptomology such as pain or itch at the site of lesions [60, 61].

Stages of Morphea Lesions Morphea of all subtypes can begin as erythematous patches or plaques and may be preceded by pain or itch. Later, hypopigmentation with skin thickening, which is a manifestation of sclerosis, begins to develop at the center of lesions. These lesions typically have an erythematous/violaceous border indicative of active inflammation and expansion (inflammatory phase) (Fig. 8.5b–d). Sclerosis develops centrally and may lead to a shiny white-yellow color, with surrounding hyperpigmentation, as lesions stop expanding (sclerotic phase) (Fig. 8.5e). The loss of hair follicles can lead to alopecia in areas of morphea.

As activity subsides, these sclerotic plaques will soften over the course of months to years and become atrophic with hyper- or hypopigmentation (atrophic phase). Sclerosis can lead to contractures and limitations in range of motion and may impede growth in the pediatric population, leading to limb length discrepancies. Limitation in range of motion may actually improve as the lesions progress from sclerosis into atrophy.

Atrophy produces varying features depending on the level of skin involvement: cigarette-paper atrophy (papillary dermis), cliff-drop atrophy (dermis), or deep indentations that alter the contour of the affected site (subcutis). Atrophoderma of Pasini and Pierini (Fig. 8.5f) is thought to be the residua of plaque-type morphea involving dermal atrophy, as the borders of these lesions are characterized by the cliff-drop appearance. When morphea affects the subcutis or deeper, long-term sequelae may include limb length discrepancies, limitations in range of motion, and contractures (Fig. 8.5g–i).

Depth of Involvement Assessment of the level of involvement in morphea is important to recognize potential comorbidities as well as to guide treatment (see Fig. 8.10). Morphea involving the superficial to the mid-dermis may be amenable to topical or phototherapy. Deep morphea, or morphea profunda, on the other hand, which involves the deep dermis, subcutaneous tissue, fascia, and/or muscle, will require systemic therapy to suppress disease activity when lesions are widespread or threaten function or cosmesis.

Deep involvement can occur with any subtype of morphea. Hemifacial atrophy, previously known as Parry-Romberg syndrome, represents deep morphea (morphea profunda) of the face that may or may not be accompanied by a more dermal linear or en coup de sabre (ECDS) lesion. Similar changes are seen in other anatomic sites with deep involvement (morphea profunda). Lesions in which the pathology is predominantly located in the deep dermis/subcutis are poorly circumscribed and may be accompanied by changes such as cobblestoning and altered contour in the sclerotic phase, as the skin becomes tacked down by sclerosis to underlying fascia (Fig. 8.5a).

A "groove" sign or depression may be present at the site of tendons and ligaments, and deep tissue loss may result in the atrophic phase. However, as deep involvement can occur without obvious superficial changes, it may be more reliably detected with careful palpation, biopsy, and/or imaging than by visual exam alone (see Figs. 8.9 and 8.10).

Data is lacking on the correlation between depth and involvement and amount of damage in morphea. However, a preliminary analysis of the MAC cohort revealed that the vast majority of patients who had functional abnormalities (including limited range of motion, contractures, limb length discrepancies in morphea-involved areas) also had deep involvement of their disease (80/86, 93 %). These results imply a possible connection between the depth of disease and potential for damage and further emphasize the importance of assessment of the level of involvement as part of the clinical evaluation of the patient with morphea (Fig. 8.10) [62].

Morbidity in Morphea Quality-of-life assessments show that individuals with morphea have better outcomes than those with disabling severe atopic dermatitis, with the exception of children and adolescents with the more severe forms of morphea affecting the face and limbs [63]. However, large cross-sectional studies of the MAC cohort have demonstrated that morphea patients do experience impairment of health-related quality of life that is greater than those with nonmelanoma skin cancer, vitiligo, and alopecia [64]. Notably, symptoms of pruritus and pain have been significantly associated with impaired quality of life in morphea, contrary to conventional wisdom that morphea is an asymptomatic disorder [64, 65].

A variety of internal disorders are reported to occur in patients with morphea, more frequently in the linear [34] and generalized or mixed subtypes [18], though they are different than the internal organ manifestations of scleroderma. The most commonly associated disorders include musculoskeletal and deep soft tissue abnormalities and neurologic and ophthalmologic problems. Malignancy is a rarely associated morbidity and may include squamous cell carcinoma in long-standing pansclerotic morphea [66]. Few systematic studies have been performed because of the infrequency of morphea and even more infrequent coexisting morbidities, so relatively little is known about the course and treatment of these disorders in the context of morphea [57].

- *Musculoskeletal and soft tissue complications*. The most common extracutaneous finding in morphea patients is arthritis/arthralgias, which have been reported in 12 % of pediatric patients with morphea (Fig. 8.7a) [34]. Both articular and soft tissue/bony abnormalities are typically associated with linear morphea. Other musculoskeletal complications include joint swelling, myalgia, and limb contractures [18] (Fig. 8.4a). Individuals with facial linear
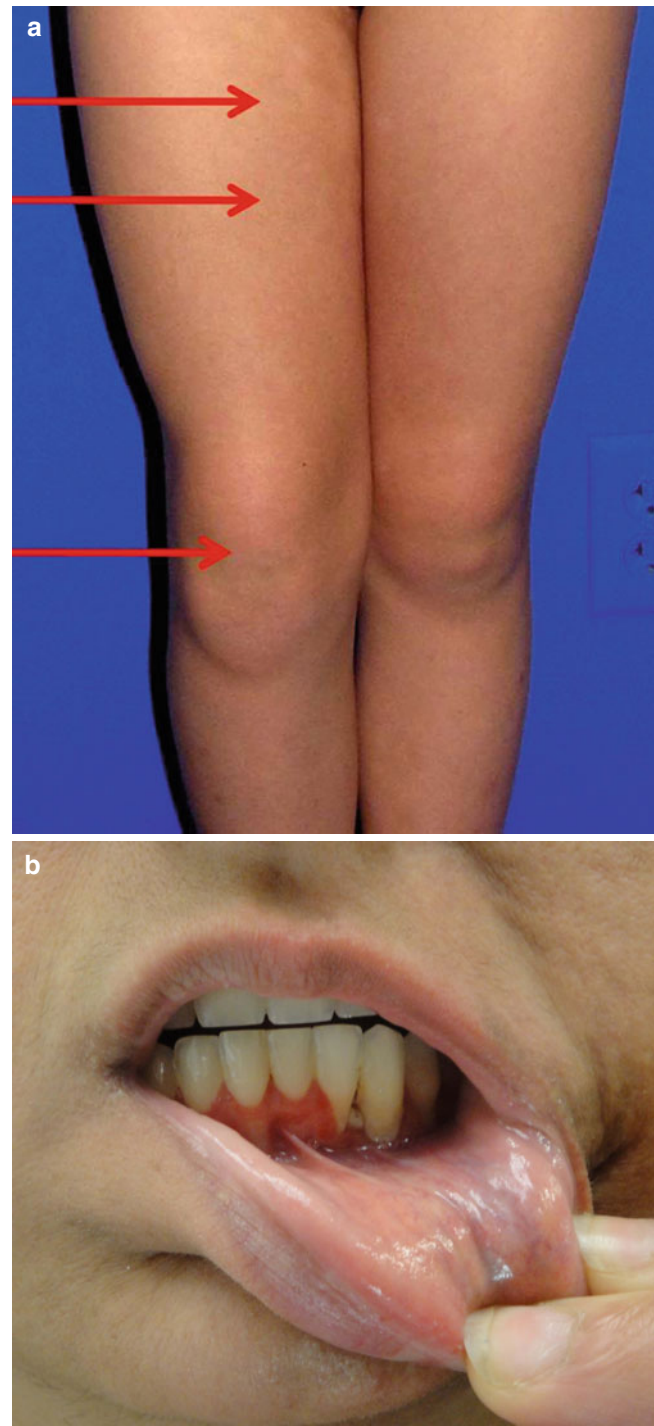
Fig. 8.7 *Morbidity in* morphea. (**a**) *Arthritis in morphea*. A swollen right knee with effusion (*lowest arrow*) is present in this patient with morphea (*upper areas*). Notably, this patient also had spondyloarthropathy. (**b**) *Gingival changes in morphea*. Gingival changes, in the form of a kind of destructive gingivitis, are seen in this patient with linear morphea of the face. Referral to oral maxillofacial surgery may be warranted to determine need for intervention once lesions are inactive

morphea can have dental abnormalities [66] including gingival involvement (Fig. 8.7b) and even ipsilateral tongue hypoplasia. Musculoskeletal changes including fascial thickening and enhancement, articular synovitis, tenosynovitis, perifascial enhancement, and myositis have been detected using MRI in morphea patients, particularly those with pansclerotic morphea, and have been observed in some cases even when involvement was not expected based on the exam [67]. However, the clinical significance of such findings has yet to be determined, and the authors would not recommend routine imaging in morphea patients without signs or symptoms of musculoskeletal involvement.

- *Neurologic complications*. Neurologic involvement was reported in 4 % of pediatric patients with morphea [34] and is more common in patients with linear morphea of the head. Complications include seizures, headache, and peripheral neuropathy among others. Intractable partial seizures [68], epileptic encephalopathy [69], status migrainosus [70], and central nervous system vasculitis [71, 72] have all been reported in association with morphea. Kistger et al. reviewed 54 patients with craniofacial scleroderma who also had neuroimaging (head CT or MRI) for neurologic symptoms. They found some common atypical features on imaging including atrophy, calcifications, and T2 hyperintensities. Others have described abnormal MRI results in patients with Parry-Romberg syndrome [73]. The clinical significance of such abnormal findings has yet to be determined, and at the current time, there is not sufficient evidence to recommend imaging in the morphea population in the absence of neurologic manifestations by history or physical examination.

- *Ophthalmologic complications*. Ocular involvement was reported in 2 % of pediatric patients with morphea [34]. Ocular involvement in morphea is also more common in patients with linear morphea that affects the face, although it has also been reported to occur in patients without facial lesions [74]. Associated ophthalmologic abnormalities may include enophthalmos, anterior uveitis, episcleritis, glaucoma, xerophthalmia, keratitis, and strabismus [74].

- *Other manifestations*. Genital involvement has been reported in association with morphea, particularly the generalized subtype, though to date, the frequency of such changes is not well described. Patients with genital involvement will often complain of pruritus, as well as dyspareunia, dysuria, and pain with defecation. Importantly, patients will not typically volunteer these symptoms without specific inquiry by providers [75, 76]. From the literature, the most common changes in the genital area include lichen sclerosus changes of porcelain-like polygonal macules, as well as more typical classical plaque-type morphea lesions with areas of waxy induration, and even labial fusion [75–78]. Patients with

reported genital involvement have typically been postmenopausal women with the generalized subtype of morphea, though lichen sclerosus changes have also been reported with some frequency in plaque-type morphea [75, 78]. Review of the MAC cohort database revealed genital changes were present in 3.5 % of all participants (14/433), though this represented almost 10 % of patients with the generalized subtype of morphea (13/149, 8.7 %). Similar to reports in the literature, those affected were all women and were typically postmenopausal (13/14, 92.8 %). Similar to previous reports, genital involvement in the MAC cohort was primarily seen in patients with the generalized subtype of morphea, typically with features of lichen sclerosus overlap (13/14, 92.8 %).

- *Malignancy*. Rare cases of malignancy are reported in morphea lesions, such as squamous cell carcinoma of the lip that developed in an individual with pansclerotic disabling morphea [66]. The etiology is likely similar to carcinoma developing in chronic venous insufficiency ulcerations and burn scars. Providers should take care to exclude cutaneous metastasis in lesions of morphea involving the breast (see *Differential diagnosis of morphea*).

Laboratory Findings in Morphea Individuals with all subtypes of morphea, particularly those with deep involvement, may have peripheral eosinophilia and presence of markers of inflammation and autoimmunity (though this is relatively uncommon). The most common of these markers are positive antinuclear antibody (ANA) and/or rheumatoid factor and presence of anti-ssDNA and antihistone antibodies (AHAs), which suggest a predisposition to autoimmunity, but do not reliably correlate with disease activity or severity [16, 37, 38]. In one nested case-control study, morphea patients had a higher prevalence of ANA (63/187, 34 %) and AHA positivity (22/187, 22 %) as compared to matched healthy controls. There was a similar prevalence of ssDNA antibodies in cases (15/187, 8 %) and controls (10/149, 7 %). Of those morphea patients with positive ANA, most had speckled pattern (52/63, 81 %) at high titer (>1:1,280), though few patients with ANA positivity had extractable nuclear antigen (ENA) antibodies (7/63, 11 %), implying the possible presence of an unidentified antigen in morphea. The presence of these autoantibodies, however, has not reliably correlated with any measures of clinical activity. Thus ANAs and AHAs have limited clinical utility except in linear morphea, where their presence may be associated with greater disease burden and functional impairment [79].

There are no laboratory tests that confirm the diagnosis of morphea, which is made on clinical features with confirmatory histopathology. Biomarkers predictive of activity or prognosis are also lacking. Thus clinical assessment remains the mainstay of diagnosis and evaluation.

Differential Diagnosis of Morphea

Many morphea patients experience delay in diagnosis and treatment because providers fail to recognize this relatively rare disease [80]. The development of morphea can be insidious and subtle, and initial misdiagnosis, particularly by non-dermatologists, occurs frequently [80]. Morphea can mimic other cutaneous diseases, including atrophic conditions, vascular lesions, dyspigmenting disorders, and even more common skin lesions such as bruises and scars (see Table 8.2) [81–83]. Early morphea lesions have been periodically confused with port-wine stains in the pediatric population [83, 84], because early lesions may present as erythematous linear patches with minimal sclerosis. Histology can be useful to distinguish these entities, and lesions should also be monitored for changes over time, as induration, atrophy, and sclerosis may develop over time and reveal the correct diagnosis [83].

Providers should consider common entities in their differential diagnosis, including lipodermatosclerosis and trauma-induced fat necrosis. Steroid atrophy can mimic morphea, as subcutaneous atrophy may result at the site of ste-

roid and other intramuscular injections, and injection of the scalp to treat other skin conditions can actually mimic linear morphea of the scalp. These entities can usually be differentiated from morphea by a careful history and physical examination, and, when necessary, a biopsy. Providers should also make sure to exclude more dangerous entities such as metastatic carcinoma in the appropriate settings (for instance, of lesions on the breast, overlying the site of known prior carcinoma). Post-radiation morphea can mimic radiation dermatitis, infection, or recurrent breast carcinoma (Fig. 8.8), and differentiating morphea from radiation dermatitis will depend on both clinical and histopathological features [85]. Special care should also be taken to distinguish morphea from scleroderma based on clinical features already described. Patients will often confuse the two entities, and misplaced concern over systemic disease damage to internal organs may impact negatively on patient quality of life [64].

The diagnosis of morphea is made clinically, but biopsy and histological examination may be useful to aid decision-making based on the depth of involvement (see Fig. 8.9). Biopsy should also be done to exclude potential malignancy

Table 8.2 Differential diagnosis of morphea

Most likely
1. Scleroderma (systemic sclerosis)
2. Lipodermatosclerosis
3. Eosinophilic fasciitis (may be a related process)
4. Trauma-induced fat necrosis (intramuscular injections)
5. Nephrogenic systemic fibrosis
6. Chronic graft-versus-host disease
7. Steroid atrophy
Consider
1. Lichen sclerosus (may be a related process)
2. Pretibial myxedema
3. Connective tissue nevi
4. Morpheaform basal cell carcinoma
5. Chemical-mediated sclerosing skin conditions (toxic oil syndrome, rapeseed oil)
6. Lyme disease (acrodermatitis atrophicans)
7. Phenylketonuria
8. Scleromyxedema
9. Pretibial myxedema
10. POEMS syndrome
11. Drug-induced sclerosing skin conditions: taxanes, IM injections, interferon-alpha
12. Lupus profundus
13. Port-wine stain
Always rule out
1. Carcinoma of the breast metastatic to the skin (*carcinoma en cuirase*)
2. Porphyria cutanea tarda
3. Dermatofibrosarcoma protuberans

POEMS *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, and *s*kin changes (Reproduced with permission from: Saxton-Daniels and Jacobe [111])
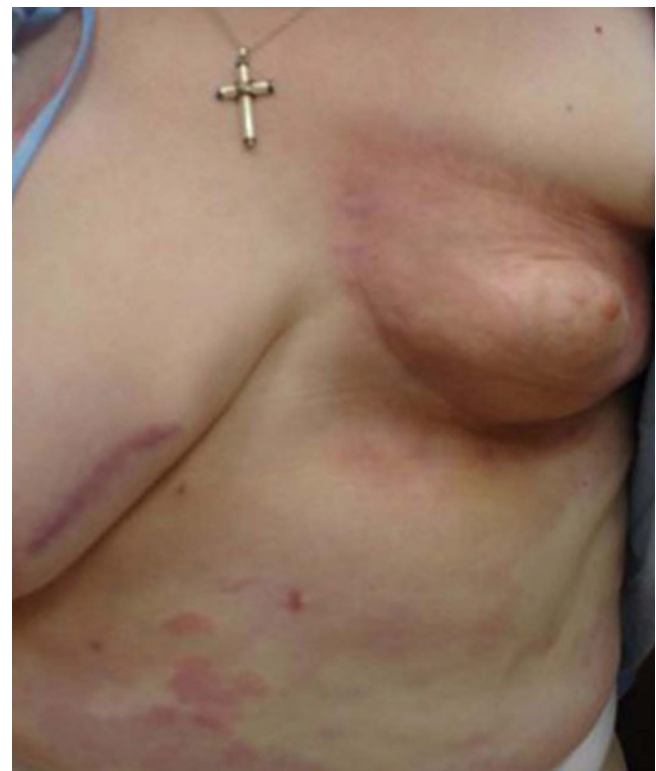

Fig. 8.8 *Postirradiation morphea on the breast*. Morpheaform changes occurred after breast reconstruction and radiation therapy in this patient with a history of breast cancer. Note the importance of a wider skin examination to differentiate this process from radiation dermatitis or recurrent carcinoma, as multiple morphea lesions are present on the trunk as well. Biopsy would be warranted in this case to rule out malignancy. Though postirradiation morphea has been reported, patients should not avoid necessary radiation or other lifesaving treatments due to a diagnosis of morphea

and in cases in which history and physical examination findings are not definitive, and pathology is needed to exclude disorders other than squamous cell carcinoma. Given the lack of accepted biomarkers, laboratory-based tests are not currently recommended for the evaluation of morphea in the absence of specific signs or symptoms that would otherwise prompt them (see *Laboratory findings in morphea*). Imaging is not recommended routinely for diagnosis, but may be useful to evaluate for depth of involvement or to monitor disease activity (see *Imaging methods* and Fig. 8.9).

Approach to the Evaluation of the Patient with Morphea

Approach to the patient with morphea depends on a number of factors, including disease subtype, disease activity, and depth of involvement, as well as patient symptomatology and the potential for cosmetic or functional impairment. Patients may benefit from a multidisciplinary approach to address functional and cosmetic issues as well as comorbidities when present (Fig. 8.9). As noted earlier, there are no

widely accepted biomarkers for morphea, so laboratory-based tests are not routinely recommended for the evaluation of morphea in the absence of specific signs or symptoms that would otherwise warrant them. Depending on features found on clinical examination or on patient complaints (muscle pain, limited range of motion, neurologic symptoms or deficits, etc.), imaging may be warranted to evaluate the depth of lesions and involvement of underlying structures (see *Imaging methods*).

Imaging Methods

- *Ultrasound* [86–89]. The most reliable assessment uses 20–25 MHz ultrasound (US). Ultrasound at 10–15 MHz – which is more readily available in the United States – is also useful [86, 87]. This modality has been more extensively used in making the diagnosis of morphea, but has been used more recently for measuring disease activity based on increased cutaneous blood flow and increased subcutaneous tissue echogenicity, and has been found to be a sensitive tool for monitoring localized scleroderma in the pediatric population
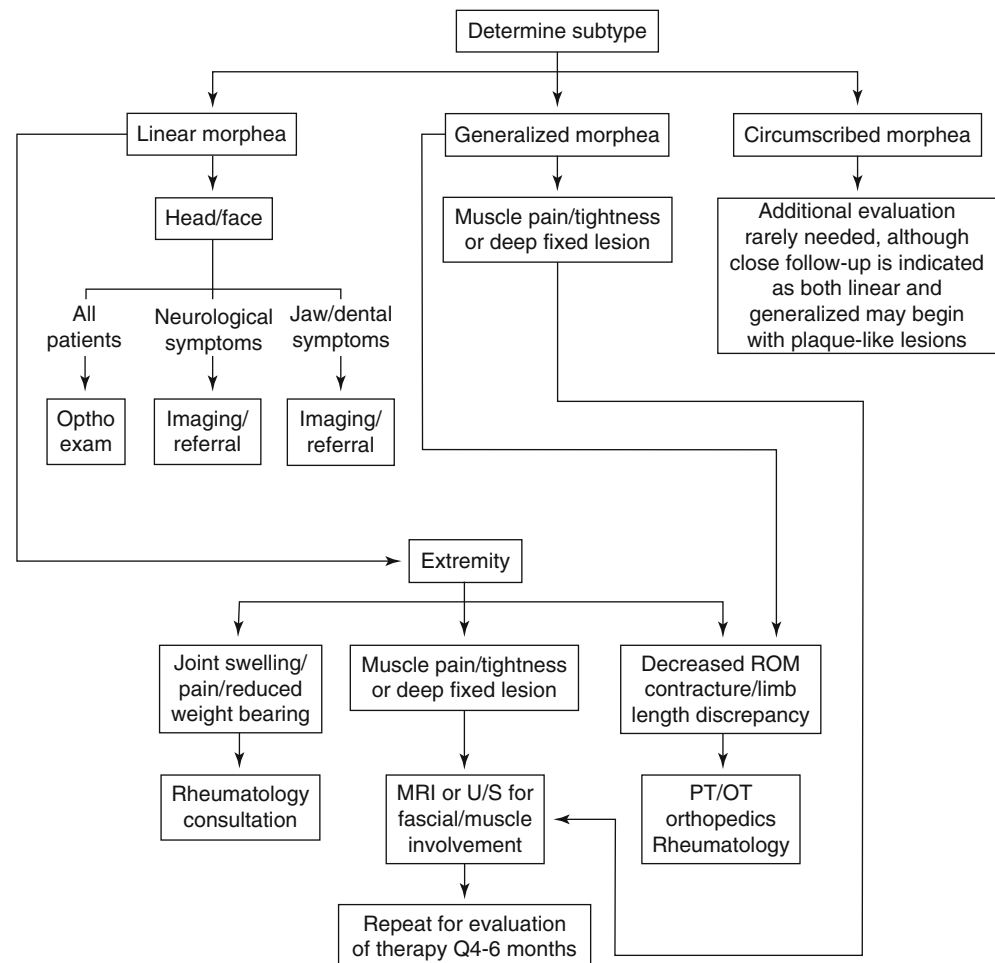

Fig. 8.9 Algorithm for the evaluation of patients with morphea (Reproduced with permission from: Jacobe H. Treatment of morphea (localized scleroderma) in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on 19 Dec 2014.) Copyright © 2014 UpToDate, Inc. For more information visit www.uptodate.com)

[86, 90, 91]. However, ultrasound assessment is operator dependent and lacks standardization.

- *Magnetic resonance imaging* (MRI) [67, 92]. Although the MRI findings in morphea can overlap with other soft tissue abnormalities such as fibromatoses and myofibromatoses, the experienced radiologist can distinguish features of morphea including thickening of the dermis and increased signal intensity during the inflammatory stages, as well as changes in signal in the bone marrow with deeper involvement. MRI is particularly useful for evaluation of the depth of infiltration in morphea and sequential analysis of disease activity [92]. MRI has also been used to detect musculoskeletal involvement, including fascial thickening and enhancement, articular synovitis, and tenosynovitis, in patients with morphea, even some in whom musculoskeletal involvement was not suspected based on the history and exam [67] However, the clinical significance of such findings has yet to be determined, and at this point there is no evidence for pan imaging in the patient diagnosed with morphea without signs or symptoms concerning for musculoskeletal involvement. Imaging is best done after conferring with a radiologist to optimize the methods in which the patient is imaged and to ensure attention to possible features of morphea.

Therapeutic Options for Morphea

A majority of morphea patients experience delay in diagnosis of greater than 6 months, as well as quite varied treatment that appears to depend more on provider specialty than on disease characteristics or evidence for treatment modalities [80]. However, there are a number of therapeutic options with proven efficacy in morphea (Table 8.3). Each of these may be considered depending on disease subtype, activity, depth of involvement, and other patient considerations. The authors recommend using the evidence-based algorithm below when considering therapeutic options for patients with morphea (Fig. 8.10).

It is important to note that, contrary to conventional wisdom, morphea can be successfully treated with proper therapy and patient selection. However, providers should remember, and emphasize to patients, that the therapeutic end point in morphea is not the complete resolution of lesions but rather the loss of features of activity (reduction of erythema, halting progression of lesions or development of new lesions). Disease damage may actually increase for a time with treatment as lesions transition from inflammatory to atrophic or sclerotic stages (though skin thickening is likely to soften over time, even after treatment cessation). Providers should make sure to distinguish features of damage, such as dyspigmentation or atrophy, which can result in more visible

blood vessels and apparent erythema, from true erythema mediated by inflammation (this may be accomplished by examining areas of erythema with magnification and looking for the induration that accompanies inflammation).

The approach to the patient with morphea depends on the assessment of disease activity, depth of involvement, and the presence of other sequelae, which is typically based on clinical examination. Careful clinical photographs should be taken at each visit to monitor patient's lesions, as subtle changes indicative of disease activity may otherwise be missed. Clinical scoring measures, such as the LOSCAT, may also be useful for quantifying and monitoring progression of disease or efficacy of therapy [60, 93]. Histological examination may aid in initial therapeutic decision-making, as it can be difficult to determine the depth of involvement by clinical exam alone. In these cases, biopsy of the advancing edge of a lesion can be undertaken to provide insight into both activity and depth of morphea (see *Histopathology of morphea*).

Phototherapy There is substantial evidence for the efficacy of phototherapy in morphea, particularly for broadband UVA, narrowband UVB, and UVA-1 [94–99] (Table 8.3). UVB is more appropriate for lesions restricted to the superficial dermis, which are relatively thin on palpation and, on biopsy, have sclerosis and inflammation in the papillary and

Table 8.3 Treatments for morphea by the level of evidence

Treatment	Level of evidence
BB UVA	1,2
UVA-1	1,2
Calcitriol, oral (inefficacy 1)	1,2
MTX plus oral/IV corticosteroids	1,2
IFN-gamma (inefficacy 1)	1
PUVA bath	2
PUVA cream	2
ECP	2
Calcipotriene, topical	2
MTX monotherapy	2
PCMT	2
Tacrolimus, topical	2
Corticosteroids, oral	2
Hydroxychloroquine, mycophenolate mofetil, cyclosporine, bosentan, infliximab, imiquimod, antimicrobials, D-penicillamine, 585 nm long-pulse laser, wide surgical resection, orthopedic surgery, Apligraf	Minimal evidence (≥level 3)

BB broadband, *IFN* interferon, *ECP* extracorporeal photochemotherapy, *MTX* methotrexate

Level of evidence: *1*, indicates randomized controlled trial; *2*, uncontrolled trial, *3*, case report, case series (Adapted from content in Jacobe H. Treatment of morphea (localized scleroderma) in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on 19 Dec 2014.) Copyright © 2014 UpToDate, Inc. For more information visit www.uptodate.com)
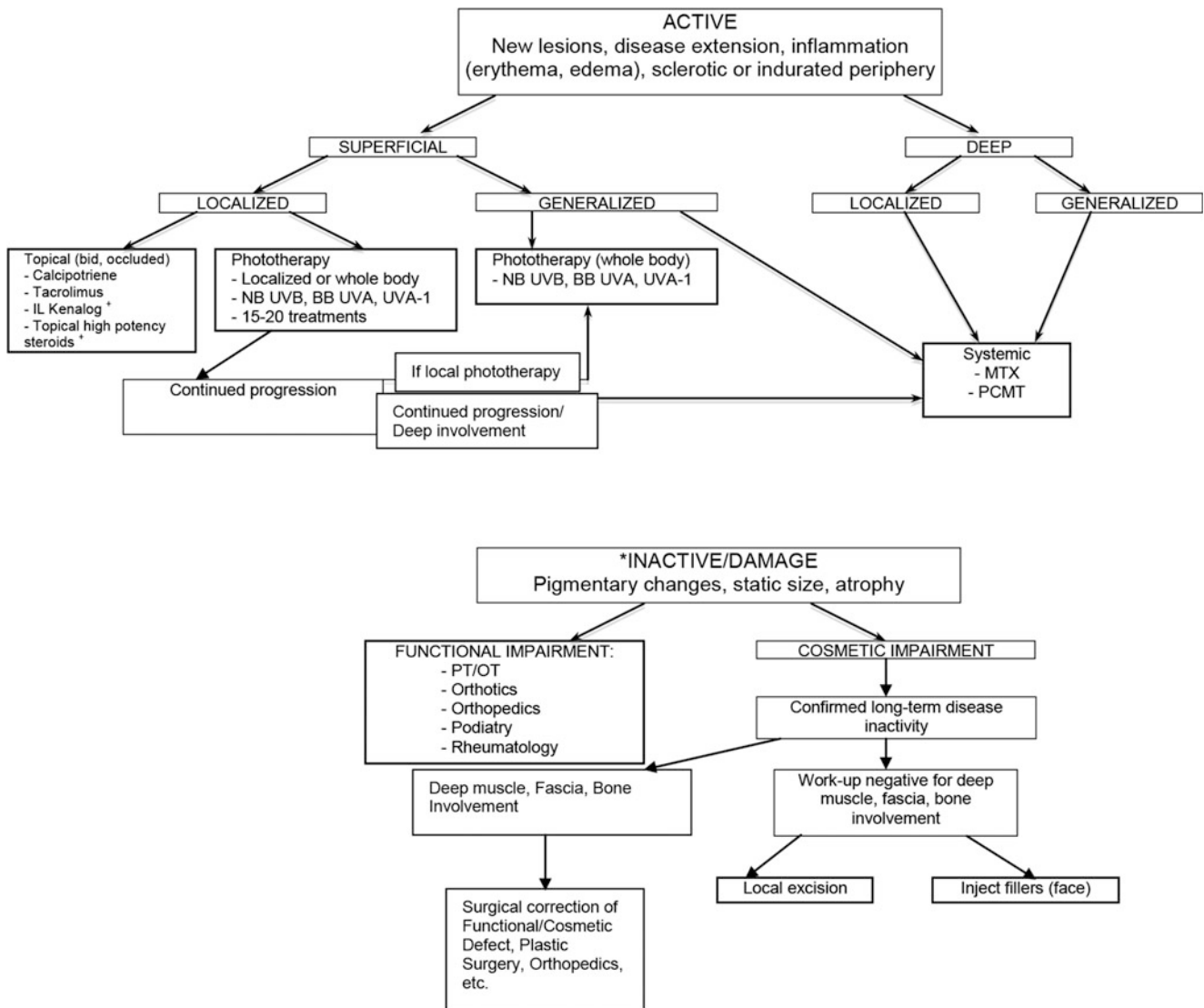
Fig. 8.10 Therapeutic algorithm for morphea based on existing evidence. Histological examination and/or MRI are encouraged to evaluate lesions for the depth of involvement and, likewise, determine appropriate treatment as well as evaluation of therapeutic efficacy. Superficial involvement is defined by histological evidence of papillary dermal involvement. Deep involvement is defined as sclerosis or inflammation of the deep dermis, subcutis, fascia, or muscle (Reproduced with permission from: Jacobe H. Treatment of morphea (localized scleroderma) in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on [19 Dec 2014].) Copyright © 2014 UpToDate, Inc. For more information visit www.uptodate.com). *There is very little evidence for any therapy addressing disease damage in morphea. The risk of disease reactivation is also unknown, but possible with the use of invasive procedures. Therefore, surgery and the like should only be undertaken after prolonged inactivity of disease. + There is no evidence for efficacy in the literature

superficial reticular dermis. UVA-based treatments can penetrate to a greater depth and are therefore more effective for deeper dermal lesions. UVA-1, in particular, has been shown to normalize dermal collagen and reduce inflammation in morphea and thus may be effective for disease in either inflammatory or sclerotic phase [95]. There is also evidence in the literature for the efficacy of broadband UVA phototherapy, which can be an appropriate alternative when UVA-1 is not available [94]. Improvement in disease, noted by the halting of lesion progression and the reduction of erythema, should be seen after 10–20 treatments. A trial can usually be stopped after 20–30 treatments if improvement is not seen in that period. Treatments are usually given three to five times weekly for a period of several weeks until this number of total treatments has been reached. Evidence suggests that patients may continue to improve even after the cessation of therapy, leading some to suggest an even greater number of treatments (30–50) for further therapeutic benefit. Optimum doses and regimen for UVA-1 phototherapy have yet to be determined; however, one randomized controlled trial has suggested that both low-dose (20 J per square centimeter) UVA-1 and medium-dose (50 J per square centimeter)

UVA-1 are equally effective, while medium-dose UVA-1 is more effective than narrowband UVB [96]. Phototherapy is not likely to be effective for lesions with deep involvement of the subcutis, fascia, or muscle and therefore should not be considered a primary therapy for such disease.

Vitamin D Derivatives Only one study provides level-1 evidence on the effect of vitamin D derivatives in morphea and actually showed no difference between oral calcitriol and placebo, with both groups improving equally [100] (Table 8.3). The authors also point out that this study was underpowered, making definitive conclusions about the efficacy of oral calcitriol difficult. Various uncontrolled trials and case reports have shown improvement in patients using topical vitamin D derivatives applied under occlusion. However, this improvement took place over a period of several months, during which time lesions might be expected to improve independently.

Immunomodulators

- *Methotrexate with or without corticosteroids*. The use of methotrexate monotherapy and methotrexate combined with systemic corticosteroids has been shown to be effective based on multiple prospective trials [2, 26, 29, 101–103] (Table 8.3). One double-blind randomized controlled trial has also shown that pediatric morphea patients treated with 15–20 mg weekly of methotrexate for 12 months, after induction with 1 mg/kg/day oral prednisone for 3 months, had lower clinical disease scores, decreased lesion temperature, and lower rates of relapse than those treated with prednisone induction alone (plus placebo) [29]. Relapse occurred within 12 months in 15 patients treated with methotrexate in addition to corticosteroids (32.6%) versus 17 of those treated with placebo only after steroids (70.8%). More specifically, new lesions developed in three methotrexate-treated patients (6.5%) versus four placebo-treated patients (16.7%) within 3–9 months. As the primary end point in the study was response to treatment within 12 months, it is difficult to determine the actual time for effect of this medication regimen. Similarly, optimum dose, route, and indications for the additions of corticosteroids to methotrexate, as well as duration of therapy, have not been definitively established. In most studies with combined therapy, including the randomized trial described, corticosteroids are used for induction therapy either orally or via intravenous pulse (IV methylprednisolone 30 mg/kg/day for 3 days per month or 1 mg/kg/day prednisone) over the first 3 months. Methotrexate is used as a steroid-sparing agent and initiated simultaneously (0.6 mg/kg/week in children or 15–25 mg/week for

adults), then maintained for a prolonged period (1–2 years) and gradually tapered. Consensus treatment plans for pediatric morphea have recently been established that detail these monotherapy and combined therapy approaches [61]. As evidence to date has not suggested a difference in disease processes between pediatric and adult morphea, it is likely that adults will respond similarly to this regimen. From the literature, most patients will respond in a mean of 2–5 months with this approach, with patients early in their disease course typically responding best. Importantly, relapse has been noted frequently after cessation of therapy (see *Epidemiology and clinical course*), indicating that therapy suppresses disease activity but is not curative [27].

- *Other immunomodulators*. Level 2 evidence supports the use of topical tacrolimus 0.1% ointment under occlusion for active, inflammatory superficial plaque-type morphea [104] (Table 8.3). Recent case series using oral mycophenolate mofetil indicate possible efficacy in patients who are refractory to methotrexate or have intolerable side effects [105]. Mycophenolate mofetil also may be effective as a treatment adjunct in children with morphea; in one retrospective analysis, ten patients with severe or methotrexate-resistant pediatric morphea experienced clinical improvement with mycophenolate mofetil that resulted in withdrawal or reduction of doses of corticosteroids and methotrexate [106]. Retrospective case reports on the use of oral cyclosporine, bosentan, infliximab, and topical imiquimod have reported some efficacy, but definitive studies are lacking (Table 8.3).

Antimicrobials Despite the widespread use of antimicrobials in morphea, including antibiotics and antimalarials, no published clinical trials of these agents exist [107]. Literature supporting the use of antimalarials is limited to a case series in which two patients improved with hydroxychloroquine, while simultaneously receiving methotrexate and corticosteroids [108]. In one retrospective review, 7 out of 11 patients had persistently active disease 3–153 months after initiating therapy with hydroxychloroquine [16]. At this time, the use of these agents in severe morphea is not indicated, pending more definitive evidence for their efficacy (Table 8.3).

Treatments Not Supported by Current Evidence The efficacy of the most commonly used treatment for morphea, topical corticosteroids, has never been formally evaluated [62, 80]. There have also been no studies investigating the use of intralesional steroids. In the authors' experience, intralesional steroids have been effective in treating circumscribed plaques of morphea or as an adjuvant for recalcitrant areas in patients receiving phototherapy or systemic treatment. Current evidence does not support the use of interferon-gamma in morphea [109], and the risks of penicillamine, including toxicities,

outweigh its potential benefits, which have not been well established. At this time, there is no sufficient evidence to support the use of these agents, especially in moderate-to-severe morphea, when other agents have proven efficacy (unless contraindications exist to their use) (Table 8.3).

Adjunctive Therapy A significant number of patients with morphea suffer irreversible sequelae that persist even after disease activity has subsided. Patients should be carefully evaluated for limitations in range of motion, contractures, limb length discrepancies, or other functional impairments. Treatment modalities may include physical therapy techniques for improving range of motion of affected limbs, stretching exercises for contractures, orthotics or shoe inserts to adjust for limb length discrepancies and to compensate for loss of subcutaneous fat, or even tendon release in some cases [16]. Referral to specialists, such as rheumatologists, physical therapists, orthopedists, oral maxillofacial surgeons, or plastic surgeons, may be helpful to maximize cosmesis and function and to minimize further damage. Importantly, studies to date are completely lacking in addressing this type of damage due to morphea.

Surgical Therapies There is limited evidence to support the use of surgical therapies for morphea. Importantly, these therapies should only be considered when morphea has been inactive, and a patient has been off treatment for a number of years. Patients should be monitored closely with serial examinations for reactivation, and collaboration with an experienced plastic surgeon is vital.

Summary

Morphea is a relatively uncommon idiopathic inflammatory disorder that leads to the development of sclerotic plaques in the skin. Though morphea may share common histopathological features with scleroderma, the disease differs demographically and clinically. Involvement of internal organs in morphea is unusual and very different from that in scleroderma. Morphea occurs in adults and children and preferentially affects females. The pathogenesis of morphea is not well understood, but is likely to involve autoimmunity, as well as genetic and environmental factors. Lesions typically begin as inflammatory patches that evolve into firm, sclerotic plaques. Involvement may be limited to the dermis or may extend to underlying subcutaneous fat, muscle, or bone. Atrophic changes often remain after resolution of lesion activity.

Morphea has a variety of clinical presentations. Circumscribed and generalized morphea occurs more frequently in adults, while linear morphea predominates in children. The identification of characteristic clinical findings often is sufficient for the diagnosis of morphea, but biopsy may be performed to exclude other entities or to obtain information on the depth of disease. Antinuclear antibody (ANA) levels are elevated in some patients with morphea; however, routine testing for autoantibodies is not indicated. Magnetic resonance imaging (MRI) or ultrasound can be used to assess the extent of involvement, in those patients for whom clinical examination suggests involvement deeper than the dermis, and may be useful for following disease activity during treatment.

The assessment of disease activity and depth of involvement guides therapeutic decision-making in morphea. Because of the self-limited nature of morphea, patients with limited plaque disease may elect to defer therapy. For patients with superficial (dermal) circumscribed disease who desire treatment, but do not have access to or prefer to avoid the frequent visits required for phototherapy, treatment options include high-potency topical corticosteroids, intralesional corticosteroids, a topical vitamin D analogue, topical tacrolimus, or imiquimod. For patients with superficial (dermal) forms of morphea who are able to receive phototherapy, treatment with UVA-1 is preferred; alternatives include broadband UVA, narrowband UVB, or PUVA. Phototherapy is unlikely to be effective for morphea involving the subcutaneous tissue, muscle, or bone. Rapidly progressive, severe, disabling disease requires systemic therapy, involving a combination of methotrexate and systemic corticosteroids. Morphea may cause joint contractures and other functional impairments secondary to deep tissue sclerosis. All patients should be clinically assessed for the development of these findings. Physical therapy is essential for patients who are at risk for or who show evidence for functional impairments.

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