# Morphea

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**Key Points**

- Distribution and spread of sclerosis can help distinguish generalized morphea from systemic sclerosis (SSc).
- Approximately half of patients with plaque morphea will experience spontaneous regression after 3 years.
- Linear morphea may involve deeper tissues and may result in contractures and other extremity abnormalities that impart worse long-term outcomes than other subtypes.
- Methotrexate, sometimes in combination with glucocorticoids, is the preferred systemic option to treat progressive subtypes of morphea.

## Interdisciplinary Introduction

Morphea is an inflammatory disorder characterized by sclerosis of the dermis and subcutaneous fat. While it shares histopathological characteristics with systemic sclerosis (SSc), it is a distinct entity with a generally better prognosis. (See Chap. 6 for a full discussion of SSc.) It is important to distinguish the two entities to provide accurate prognosis and to avoid causing unnecessary anxiety for patients.

## Nomenclature

Inconsistent nomenclature has contributed to confusion about the relationship between morphea and SSc. Outside the dermatologic literature, morphea has been referred to as localized scleroderma and circumscribed scleroderma, among other misleading names. To minimize confusion, we will use the term morphea exclusively wherever possible.

## Epidemiology

There are no large population-based epidemiology studies evaluating the burden of disease in morphea, and the existing small retrospective studies may underestimate true incidence and prevalence of the disease. According to the best available data, morphea is rare, with an incidence of 0.4–2.7 per 100,000 people and a prevalence of up to 200 per 100,000 by age 80 [1, 2].

Adults and children have the same overall prevalence [1, 3], but prevalence of morphea subsets differs by age. Linear morphea, for example,

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is the most common subset in children and comprises 65% of cases in this demographic [4]. Both the en coup de sabre (ECDS) and progressive hemifacial atrophy (PHA) variants of linear morphea have median onset at age of 10 and 13.6 years, respectively [5].

There is a female to male predominance in morphea of approximately 3 to 1 [1]. Morphea is somewhat more common among whites than other races [1, 3].

## Pathogenesis

The etiology of morphea appears to involve complex interactions between the vascular, immune and inflammatory systems, as well as the extracellular matrix, which lead to excessive collagen deposition with end organ damage and dysfunction [6–8]. Specifying this fibrotic pathway and its upstream drivers is essential to developing effective therapies in morphea. Current hypotheses suggest that morphea is an autoimmune disease that may be initiated by an environmental trigger in genetically susceptible individuals.

### Evidence for Autoimmunity

Several associations suggest that morphea is an autoimmune disease. Morphea is associated with personal and family history of autoimmune disease, including systemic lupus erythematosus, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, Hashimoto thyroiditis and myasthenia gravis [3, 4]. Moreover, autoimmune serologies are often positive in morphea. A positive ANA has been reported in 20–80% of morphea patients [1, 9, 10]. Dharamsi et al. observed a prevalence of 12% for anti-histone antibodies and 8% for anti-single-stranded DNA antibodies in their cohort [10]. Additional autoantibodies reported in morphea patients include anti-fibrillin-1, rheumatoid factor, anti-cardiolipin and anti-topoisomerase II alpha [1, 11]. Of note, morphea patients are negative for autoantibodies specific for SSc, i.e., anti-centromere, anti-Scl-70, and anti-RNA polymerase III [3].

### Genetic Susceptibility

The genetics of morphea have not been fully elucidated, although there is evidence to suggest genetic susceptibility in some patients. Approximately 20 familial cases of morphea have been reported. Most kindreds include a parent and a child, but morphea has also been reported to occur in monozygotic twins [12, 13]. Additionally, in a study of Major Histocompatibility Complex class I and II alleles, Jacobe et al. observed specific risk alleles for morphea. The strongest associations were with *DRB1*04:04* (in HLA class II) and *HLA-B*37* (in HLA class I) [14].

### Environmental Triggers

As in many autoimmune diseases, environmental triggers may play a role in a subset of morphea cases. Suggested triggers include trauma, infection, drugs, vaccinations and radiation therapy [1, 11]. In a cohort of 750 children, 13% of children reported some kind of environmental trigger [4]. These included mechanical factors (67%, most commonly trauma, as well as insect bites or vaccinations), infections (25%), drugs (5%), and psychological distress (3%) [4]. Similar findings have been observed in adults: 16% of patients in one cohort noted triggers including surgery, penetrating trauma, injections, herpes zoster, radiation therapy, diagnostic x-ray, and extreme exercise [15].

One controversial environmental trigger implicated in morphea that deserves particular attention is infection, particularly with *Borrelia burgdorferi* [1, 11]. In a review of 19 studies from 1993 to 2007, six studies involving 40 patients showed an association between Borrelia and morphea, while 13 studies involving 240 patients failed to show the association [16]. Borrelia as a trigger for morphea in some patients is plausible but it remains unproven. Moreover, the association has not been observed in the U.S. In addition to Borrelia, a variety of viral infections have been noted as possible triggers, including CMV and hepatitis B and C [1, 11].

Drugs have rarely been implicated as a trigger in morphea [1, 17]. Implicated drugs and drug regimens include the following: balicatib, bisoprolol, bleomycin, peplomycin, D-penicillamine, bromocriptine, L-5 hydroxytryptophane plus carbidopa, L-5 hydroxytryptophane plus carbidopa and flunitrazepam, bromocriptine and clobazam, pentazocine and vitamin B12, vitamin K, and TNF alpha inhibitors [10, 17, 18]. Drugs that may cause local injection site reactions, including vaccines, represent a special case since they induce local trauma.

Morphea has also been reported to occur in association with radiation therapy [1, 11]. A recent review summarized 66 cases of morphea, which represented approximately 0.2% of breast cancer patients undergoing radiation therapy [18]. Morphea may occur within months of initiating radiation therapy, or as long as 20 years later [11]. When occurring in the setting of radiation, morphea may be mistaken for recurrent breast cancer or radiation dermatitis. It also tends to be painful and it does not respond well to usual therapies for morphea [19].

Further characterizing potential triggers in morphea may lead to insight into the underlying disease mechanism and therapeutic options.

## Histopathology

Skin biopsy is an important tool in the diagnosis of morphea. Histological examination can help characterize the degree of inflammation and depth of sclerosis, and it can help rule out other entities in the differential diagnosis (Table 5.1).

The key histopathologic findings in morphea include altered collagen in the dermis and subcutis as well as microvascular changes and inflammatory infiltrates in early lesions [1, 20]. Broad, sclerotic collagen bundles extend from the reticular dermis to the subcutis, replacing the subcutaneous fat (Fig. 5.1a, b). These changes give the gross specimen from a punch biopsy the characteristic so-called "squared off" or "cookie cutter" shape [11]. Additional findings include atrophy of adnexal structures including pilosebaceous units and eccrine glands, along with occasional endothelial cell swelling with thickening of small blood vessel walls. There is a perivascular lymphocytic infiltrate composed of both CD4+ and CD8+ cells, with some plasma cells and macrophages admixed.

**Table 5.1** Differential diagnosis of morphea

| |
|---|
| Chronic graft versus host disease (GVHD) |
| Lipodermatosclerosis |
| Injection site reactions |
| Porphyria cutanea tarda |
| POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) |
| Radiation dermatitis |
| Stiff skin syndrome |
| Cutaneous malignancies |
| Vitiligo |
| Port wine stains |
| Hypertrophic scar |

## Classification

Patients with morphea often are not diagnosed with the disease until 2 years into their course, which has implications for controlling the disease [21]. In part, this delay may result from a lack of published diagnostic criteria or widely accepted method of classifying the disease.

Existing classification schemes are typically based on morphology [1, 22]. We review two frequently cited classification schemes herein. Our proposed modified classification, with aspects drawn from both, is delineated in Table 5.2.

### Peterson Criteria (1995)

The Peterson criteria delineate five subtypes of morphea: (1) plaque, (2) generalized (involving >2 body areas), (3) bullous, (4) linear, and (5) deep [4]. In this scheme, guttate morphea, keloidal morphea, atrophoderma of Pasini and Pierni, and lichen sclerosus et atrophicus (LS) are classified as variants of plaque morphea. We have separated out these four conditions in our classification scheme to create a rare variants group.

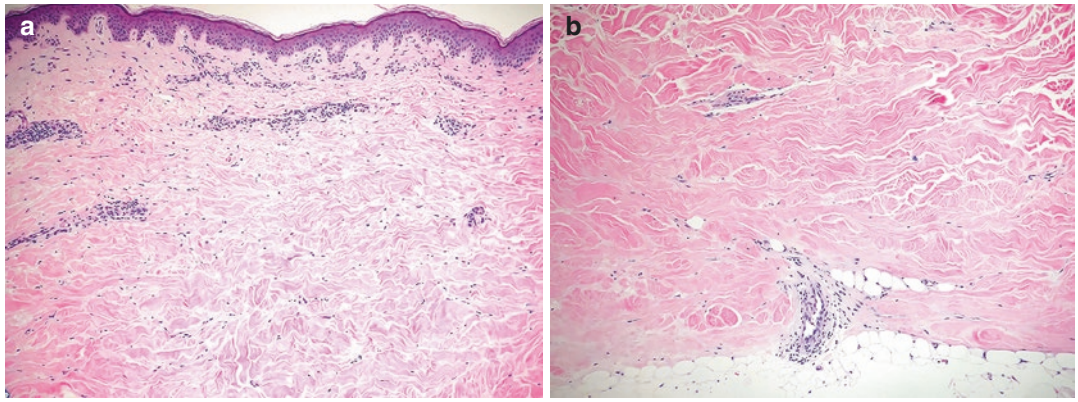



**Fig. 5.1** (**a**, **b**) Histopathology of morphea. (**a**) Low power: There is marked sclerosis with diminished space between collagen bundles throughout the reticular dermis. A concurrent perivascular and interstitial infiltrate is present (H&E, × 100). (**b**) High power: Strikingly sclerotic collagen bundles are present at the juncture between the dermis and subcutis. Perivascular lymphocytes and rare plasma cells are present (H&E, ×200). (Courtesy of Silvija P. Gottesman, MD)

**Table 5.2** Morphea subsets. Proposed modified criteria, based on the classifications by Peterson (1995) and Laxer and Zulian (2006)

| Variant | Frequency | Characteristics |
|---|---|---|
| 1. Plaque morphea | 40–50% (adults) | Asymmetric, round-oval, sclerotic plaques, 2–16 cm<br>Lilac borders<br>Hyperpigmented |
| 2. Generalized morphea | 10% | >4 individual indurated plaques >3 cm, involving >2 of 7 anatomic sites (head-neck, left upper extremity, right upper extremity, left lower extremity, right lower extremity, anterior trunk, posterior trunk) |
| 3. Linear morphea<br>(Includes en coup de sabre, Parry-Romberg, progressive facial hemiatrophy) | 20% in adults (65% in children) | Sclerotic plaque in linear configuration |
| 4. Deep morphea<br>(Includes morphea profunda, disabling pansclerotic morphea, eosinophilic fasciitis | <5% | Involves underlying fascia and muscle and may spare the overlying skin |
| 5. Mixed morphea | 15% | 2 or more subtypes |
| Rare/controversial variants:<br>Bullous morphea<br>Guttate morphea<br>Atrophoderma of Pasini and Pierini<br>Keloidal (nodular) morphea<br>Lichen sclerosis | <5% | |

Of note, although bullous morphea is included as a separate category in the Peterson classification criteria [22], there were no cases of bullous morphea in their population study [4]; we have therefore included bullous morphea in our rare variants category.

## Laxer and Zulian (2006)

The Laxer and Zulian criteria describe subtypes of juvenile localized scleroderma (JLS), a term synonymous with morphea that is often used in the rheumatology literature [23]. (As discussed

above, instead of using the term JLS we will refer to this entity as morphea.) The Laxer and Zulian scheme includes five categories of morphea: (1) circumscribed, (2) linear, (3) generalized, (4) pansclerotic, and (5) mixed.

Within these five categories, circumscribed morphea, which is the same as plaque morphea, is divided into superficial and deep subtypes. Generalized morphea is defined as four or more individual indurated plaques >3 cm each, involving >2 of 7 anatomic sites (head-neck, each extremity, anterior trunk and posterior trunk); we believe this definition is an improvement over Peterson's and have incorporated it into our classification. Mixed morphea refers to the simultaneous presence of two or more morphea subtypes in a single patient. Of note the Laxer and Zulian classification does not include bullous morphea as a separate category.

## Clinical Features

We review the clinical features of morphea subtypes according to our modified classification. In addition to the cutaneous manifestations reviewed below, morphea patients commonly experience a variety of extracutaneous symptoms such as arthralgias, myalgias and fatigue [1, 3, 4, 10]

### Plaque Morphea

We define plaque morphea as three or fewer plaques on the trunk or extremities. The plaques are typically painless, round or oval, edematous, firm and indurated; they can range in size from a few centimeters to up to 30 centimeters [1, 9, 11]. Early, active lesions have a characteristic lilac to dusky violaceous erythematous color surrounding the plaque (Fig. 5.2a). As the lesions expand, they may develop yellow-white sclerotic shiny centers. As plaques of morphea age, they become sclerotic, with hyperpigmentation or hypopigmentation; there may be loss of hair and sweat glands within the plaques (Fig. 5.2b).

### Generalized Morphea

Generalized morphea accounts for approximately 10% of the adult morphea patients [2]. We define generalized morphea as four or more individual plaques, each >3 cm, involving ≥2 anatomic sites, and sparing the face and hands [1, 22]. When the chest wall is involved, the nipples are characteristically spared [1]. Patients with generalized morphea often have extracutaneous symptoms, including mylagias, arthralgias and fatigue [3].

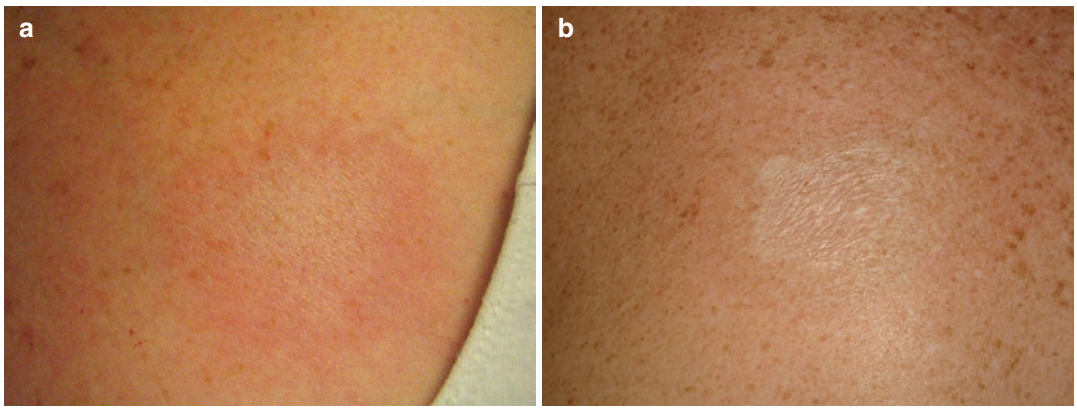
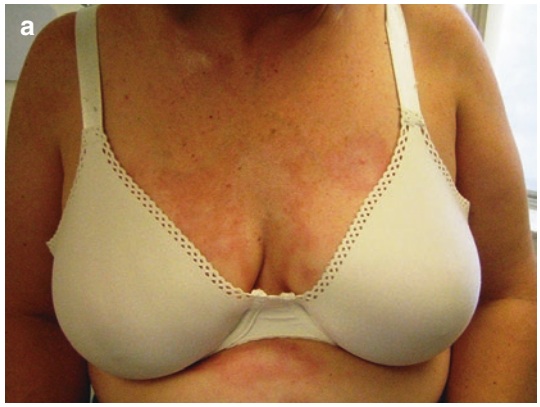



**Fig. 5.2** (**a**, **b**) Plaque morphea. (**a**) Acute plaque of morphea with an indurated sclerotic center and lilac colored erythema at the periphery. Chronic sclerotic plaque of morphea with a characteristic whitish color and a wrinkled appearance on the surface, which represents epidermal atrophy. (Courtesy of Amit Garg, MD)



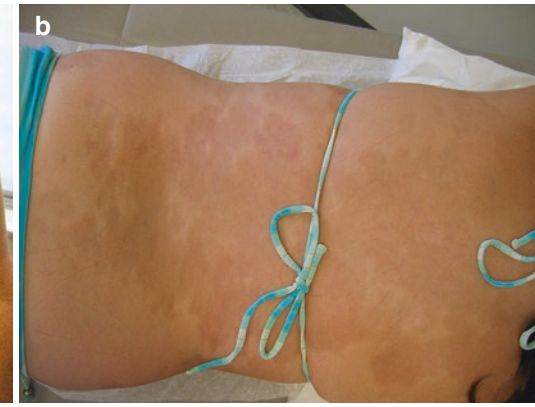




**Fig. 5.3** (**a**) Generalized morphea. Rounded indurated plaques with central sclerosis and peripheral lilac colored erythema on the trunk. Face and hands are spared. (Courtesy of Amit Garg, MD). (**b**) Generalized morphea. Multiple brownish colored indurated plaques coalescing to form larger plaques over the trunk. Face and hands are spared. (Courtesy of Amit Garg, MD)

The presentation of generalized morphea may initially appear concerning for SSc, but the two entities can readily be distinguished based on their clinical features. Generalized morphea typically begins on the trunk area (Fig. 5.3a, b) and spreads outward, sparing the face, hands and feet. In contrast, diffuse SSc typically begins on the hands and spreads proximally. In addition, patients with generalized morphea do not have Raynaud's phenomenon, nailfold capillary abnormalities, or sclerodactyly. (See Chap. 6 for a full discussion of SSc.)

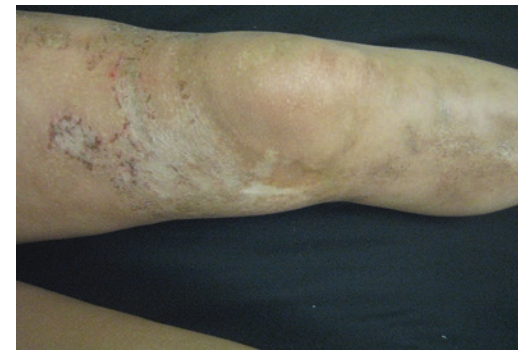


**Fig. 5.4** Linear morphea. Sclerotic plaques arranged linearly involving the leg and knee joint of an adolescent. (Courtesy of Amit Garg, MD)

## Linear Morphea

Linear morphea presents with a linear, indurated plaque that may follow the lines of Blaschko. It can involve a single limb (Fig. 5.4), multiple limbs, the trunk or the head. In addition to the skin, linear morphea may involve deeper tissues, including subcutaneous fat, muscle and bone. Plaques of linear morphea may result in contractures, atrophic limbs and limb length discrepancies. Partly for this reason, linear morphea is associated with worse long-term outcomes than other subtypes, both functionally and from a quality-of-life standpoint [24].

Two important types of linear morphea deserve special mention. En coup de sabre (ECDS; "the cut of the sabre") presents with an erythematous, sclerotic, atrophic linear plaque of morphea on the face, most commonly the paramedian forehead (Fig. 5.5). Progressive hemifacial atrophy (PHA, Parry-Romberg syndrome) affects the face and head and may also affect the eye and brain [4, 5]. In PHA, the overlying skin is normal but the deep facial structures on one side of the face, including bone, muscle and fat, fail to develop. The normal overlying skin allows PHA to be readily distinguished from ECDS.

It is important to note that both ECDS and PHA may be associated with ocular or neurological abnormalities, and thus it is of particular importance to identify patients having these sub-

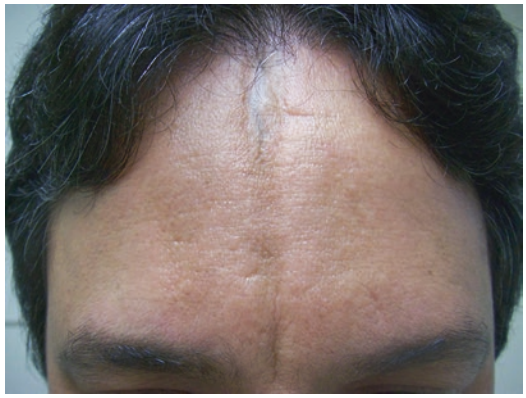


**Fig. 5.5** Linear morphea (en coup de sabre). A linear atrophic sclerotic plaque of morphea on the paramedian forehead. (Courtesy of Amit Garg, MD)

types to facilitate monitoring. In a cohort of 750 pediatric morphea patients, 23% had head-face localization (99 ECDS, 8 PHA, 6 a combination); of those, 21 patients (19%) had neurologic manifestations, including seizures, headaches, vascular malformations and behavioral changes [4]. Headaches, including migraine headaches, were the presenting sign in four ECDS patients in one study [25]. There were also neuroimaging abnormalities noted in ECDS patients, including white matter abnormalities, calcifications, and EEG abnormalities. Ocular findings in these variants have been found to include anterior uveitis, episcleritis, glaucoma and keratitis [4].

## Deep Morphea

Deep morphea (also called morphea profunda or subcutaneous morphea) involves underlying fascia and muscle and may spare the overlying skin [2]. Two variants of deep morphea, disabling pansclerotic morphea (DPM) and eosinophilic fasciitis (EF), deserve particular attention.

### Disabling Pansclerotic Morphea

DPM of children is a variant of deep morphea described in 1980 by Winkelmann and colleagues in a series of 14 patients (10 girls and 4 boys) [26]. The clinical features were varied: 12 of 14 patients had generalized morphea, and some had esophageal or pulmonary involvement. On biopsy, however, all patients shared the common finding of pansclerosis extending from the dermis down to the panniculus, fascia, muscle and in some cases also to bone. Nine patients had a progressive course unresponsive to therapy, and two patients died from complications of the disease. The Winklemann series highlighted the important point that while morphea typically takes a benign course, more fulminant presentations with worse outcomes are possible.

Subsequent classification schemes have offered different definitions for DPM. In the Laxer and Zulian classification criteria, pansclerotic morphea (no longer referred to as "disabling") is defined as: "circumferential involvement of the limbs involving epidermis, dermis, subcutaneous tissue, muscle and bone; may affect other areas of the body with full depth sclerosis [23]." In their study of 750 children with morphea, two patients (0.3%) had DPM [4]; of these, one child developed severe atrophy of the right leg, ultimately resulting in auto-amputation. The second child developed a squamous cell carcinoma in a chronic leg ulcer and subsequently died. Other studies have found an association between DPM and recalcitrant skin ulcers as well as an increased incidence of squamous cell carcinomas [27, 28].

More recently, it has been recognized that DPM may occur in adults [29, 30]. Kim et al. reported 13 cases of adult DPM, representing a 3.6% prevalence in their adults and children cohort; mean age of onset was 54 years [30]. Seven were female and 6 were male; all patients had a generalized distribution with a more rapid onset and severe progression than in other subtypes [30].

### Eosinophilic Fasciitis

A second important variant of deep morphea is eosinophilic fasciitis (EF, also called Shulman syndrome). EF is characterized by rapid-onset, symmetric, subcutaneous sclerosis, typically involving the distal extremities but sparing the hands and feet [31]. There is limb edema, associated with discomfort and pain. After the edema subsides, the surface of the skin takes on a char-

acteristic "peau d'orange" appearance. Some patients may manifest a so-called "groove sign," in which a depression appears in the skin along the course of a vein. In about one third of patients, there is a history of antecedent intense physical exercise or trauma. The hands are not typically involved, and patients do not develop Raynaud's phenomenon.

A deep incisional biopsy to fascia is the gold standard for diagnosis of EF. MRI to assess for fascial inflammation may be helpful in supporting a clinical diagnosis of EF, guiding biopsy site selection, judging the extent of disease and monitoring response to therapy [32]. Associated laboratory findings include peripheral eosinophilia, elevated inflammatory markers and hypergammaglobulinemia [31]. Hematologic malignancies have been reported in EF patients. Different from forms of SSc, this condition tends to be responsive to oral glucocorticoids,

## Mixed Morphea

Mixed morphea is characterized by the simultaneous presence of two or more subtypes of morphea. The clinical features of each type are consistent with those reviewed above.

## Rare Variants

Our rare variants group includes five entities: bullous morphea, guttate morphea, atrophoderma of Pasini and Pierini, keloidal morphea, and lichen sclerosus et atrophicus. Bullous morphea is characterized by one or more tense blisters overlying a morphea plaque [22]. Guttate (or "drop-like") morphea appears as multiple, small (less than a centimeter) sclerotic papules that tend to be more superficial and lighter in color than those in other variants [9, 22]. Atrophoderma of Pasini and Pierini is characterized by multiple, depressed, atrophic, well-demarcated, hyperpigmented patches with a predilection for the posterior trunk [22]. A lack of sclerosis and dermal atrophy results in characteristic "cliff-drop borders" [22]. Some authors view this variant as burned-out morphea, while others characterize it as a distinct entity [33]. Keloidal (nodular) morphea is characterized by nodules indistinguishable from classic keloids, arising within a morphea lesion [1]. Lastly, lichen sclerosis (LS) is an idiopathic, inflammatory condition affecting the skin and mucosa, which manifests on the anogenital (85% of cases) as well as extragenital skin [9]. The eruption appears as sclerotic, white, flat-topped papules with atrophic overlying skin, fine wrinkling and follicular plugging. Studies have pointed to an association between all types of morphea and genital LS, though the frequency reported varies [34–36]. Lutz et al. found genital LS was present in 38% of morphea patients, as compared to 3% of controls [34]. Kreuter et al. noted a frequency 5.7% of LS in a retrospective study of their German morphea cohort of 472 [36]. These studies highlight the importance of genital exams in all morphea patients, particularly as genital LS may be asymptomatic and therefore patients may not be aware of it or bring it to the physician's attention. Untreated genital LS may cause unnecessary scarring, and vulvar LS carries a 5% increased lifelong risk of squamous cell carcinoma [35].

## Natural History

The natural history of morphea is variable and depends, to some extent, on subtype. In approximately 50% of patients with plaque morphea, plaques will spontaneously regress and soften 3 years into the course [2]. Similarly, deep morphea may soften in 5–6 years [2]. Those lesions that do spontaneously remit may also recur, sometimes years later: in one study, children had a recurrence rate of 27%, while recurrence in adults occurred in 17% [37]. In a small group of patients, lesions of morphea stay active and persist throughout life; this is the especially true of the linear and deep subsets.

Prognosis for patients with morphea is generally good. In one study, although 11% of morphea patients had some form of long-term disability related to joint involvement, overall survival rates were the same as the general popu-

lation and they had a normal life expectancy [2]. As discussed above, DPM is an important potential exception which warrants further study.

## Disease Assessment

A variety of non-conventional tools have been used to assess extent and activity of skin involvement in morphea, including computerized skin scores, durometers, cutometers, infrared thermography, ultrasound and MRIs [38–40]. There is an ongoing need for better quantitative disease measurements, especially those that may be used to measure improvement from treatment over time.

Many of the existing ancillary studies of morphea disease activity require specialized tools, training, time and expense to carry out and are neither widely available nor used routinely in the clinical setting. Skin scoring systems represent one of the best available disease assessment tools for morphea, because they require no specialized equipment and rely instead on physical examination and forms that can readily be completed and scored.

One of these is the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT), developed and validated by Arkachaisri et al., who integrated the modified Localized Scleroderma Skin Activity Index (mLoSSI) and the Localized Scleroderma Skin Damage Index (LoSDI) with the physician global assessment of disease damage; this tool has been demonstrated to have good inter- and intra-rater reliability [41, 42].

## Comorbidities

As reviewed above, morphea patients, especially those with generalized morphea, have been found to have higher rates of autoimmune and rheumatic disease than the general population [3]. The most prevalent of these comorbidities were psoriasis, systemic lupus erythematosus, multiple sclerosis and vitiligo [3].

Morphea patients of both sexes have a high incidence of genital LS. Additionally, in a large Swedish cancer registry that looked at incidence of female cancers (breast, ovarian, uterine, and other genital cancer) in patients with 33 different autoimmune diseases, morphea patients had the highest risk of "other genital cancers" with a standard incidence ratio of 35.88 [43]. Lastly, adults and children with morphea have higher rates of depression and anxiety than age matched controls [44].

## Approach to Screening and Monitoring

All morphea patients, including children, should have annual genital exams to evaluate for genital LS [34–36] (Table 5.3).

Children with linear morphea of the head (ECDS or PHA) require monitoring for ocular and central nervous system (CNS) involvement [1, 4]. Based on their finding that 14.2% of children with ECDS had ocular involvement, which was often asymptomatic even when requiring aggressive therapy to prevent irreversible damage,

**Table 5.3** Workup for morphea

| Morphea subset | Test/exam |
|---|---|
| All morphea patients (men and women, adults and children) | Annual genital exam to rule out LS |
| Patients with linear morphea of the face, head and neck (ECDS; Parry-Romberg; Progressive hemifacial atrophy) | Ophthalmologic screening every 3–4 months in the first 3 years to detect asymptomatic inflammatory eye disease<br>Consider MRI of the head to identify and track underlying brain involvement |
| Generalized morphea | Although these patients can experience some external chest constriction with breathing, they do not need a full systemic sclerosis (SSc) pulmonary workup, including pulmonary function tests and high-resolution computed tomography to rule out SSc-associated interstitial lung disease (See Chap. 6 for discussion of SSc management) |

Zannin et al. recommended ophthalmologic screening every 3–4 months for the first 3 years after diagnosis in patients with ECDS [45].

Monitoring for CNS involvement in patients with linear morphea of the head is less straightforward. In one series of 21 cases, 4 patients (19%) had abnormalities on head MRI, although abnormal imaging did not correlate with neurologic symptoms. The authors noted that abnormal imaging changed management in two asymptomatic patients [46]. Obtaining an MRI often requires sedation in children and may not always have management implications. As such, head MRIs in children with ECDS remain controversial.

## Principals of Management

Treatment of morphea has been attempted with a wide variety of topical and systemic modalities (Table 5.4), although evidence for efficacy is limited by the quality of available studies. In particular, treatment studies suffer from a lack of validated outcome measures, small sample sizes, and a lack of controlled trials. Those randomized, controlled trials that do exist are often underpowered [47]. We review our overall approach to treating morphea as well as evidence for use of available treatment modalities.

Our approach to treating morphea is guided by the following principles [38, 40, 47]. First, it is important to establish which category of disease the patient belongs to—i.e., plaque, linear, generalized, deep or mixed—because therapy may be tailored to subtype. It is particularly important to establish depth of the lesions, since superficial lesions may respond to topicals and phototherapy, while deeper lesions usually do not and often require systemic medications. Second, it is important to note number and location of lesions: greater number of lesions overall and the presence of lesions located over joints are indications for more aggressive therapy. Third, it is critical to distinguish lesions that are active (less than 6 months old), inflammatory, and growing, from those that are burned-out, scarred and fixed, since this may guide therapeutic approach. Finally, photography is helpful to document changes in lesions during therapy.

Regardless of subtype, residual damage may result in significant morbidity and sometimes disfigurement. Physical therapy is essential to maintaining mobility and strength, especially if patients develop contractures over joints. Cosmetic treatments including fillers, fat transfers, and reconstructions may be considered when it is clear the disease has remitted [48]. Further research is needed on the outcomes of these treatments.

**Table 5.4** Treatment of morphea

| Modality | | Subtype |
|---|---|---|
| Topical therapy | Class I topical corticosteroids bid for 8 to 12 weeks<br>Tacrolimus 0.1% ointment (Protopic)<br>Imiquimod 5% cream (Aldara)<br>Calcipotriene (Dovonex)<br>Calcipotriene/betamethasone dipropionate (Taclonex) | Plaque |
| UV phototherapy | NBUVB<br>UVA1 (low, medium, high doses)<br>Broadband UVA<br>PUVA | Linear<br>Generalized |
| Systemic therapy | Methotrexate in combination with systemic steroids<br>Methotrexate<br>Mycophenolate mofetil | Linear (ECDS; over a joint)<br>Generalized |
| Experimental | Pirfenidone gel<br>Fractional Carbon Dioxide Laser<br>Rituximab and methotrexate<br>HSCT | |

## Topical Therapy

Topical or intralesional corticosteroids are frequently used to treat morphea initially, but there is minimal evidence to support their use [9]. The highest quality studies are for genital lichen sclerosus, in which prospective and retrospective studies have shown that class I corticosteroids are effective in treating the condition [49, 50].

For lesions not responding to topical corticosteroids, topical tacrolimus 0.1% ointment (Protopic) may be used twice daily [51]. Other treatments that have been found to be effective in some studies include topical imiquimod 5% cream three times weekly, calcipotriene ointment, and a combination ointment of calcipotriol and betamethasone [52–54].

Pirfenidone 8% gel is a novel anti-fibrotic topical treatment which demonstrated improvement in the mLoSSI in a phase II trial conducted in 12 patients over 6 months [55]. Further studies are needed to clarify the optimal topical management in morphea.

## Phototherapy

With anti-inflammatory and anti-fibrotic properties, phototherapy may be an efficacious and safe treatment for morphea, especially in children and pregnant women [56]. Kerscher et al. introduced UVA1 therapy for morphea [57]. Subsequently, Kreuter et al. demonstrated that narrow-band UVB (NBUVB) was comparable to low- and medium-dose UVA1 [58].

There is no consensus in the literature on the optimal phototherapy modality for treatment of morphea, i.e., NBUVB, UVA1, broadband UVA or PUVA; rather, this choice is largely a function of body location, regional preference, and access to devices. We do not have UVA1 at our institution but have good success with NBUVB for superficial lesions and PUVA for deeper ones. In our experience it takes longer than 8 weeks to achieve an initial response, and we do not evaluate treatment success or failure until 3–6 months into therapy.

## Systemic Therapy

Methotrexate, sometimes in combination with glucocorticoids, is the preferred systemic option to treat progressive subtypes of morphea. Linear morphea in children and adults has been shown to respond to this combination in several trials, including a randomized controlled trial [38, 47, 59, 60]. The dose of methotrexate is 0.3–0.4 mg/kg per week in children or 15–25 mg/week in adults. The prednisone dose is 1 mg/kg daily. Pulse dosing of intravenous corticosteroids followed by a taper may also be used [38, 61]. If there is inadequate response to methotrexate and prednisone after 8–12 weeks, then mycophenolate mofetil may be considered [38]. Evidence for remaining systemic treatment options is anecdotal.

## Summary

Morphea is a rare sclerosing skin disease that is not associated with visceral organ involvement, although generalized, linear and pansclerotic subtypes may be associated with significant morbidity. Approximately half of patients will experience spontaneous regression, and prognosis for patients with morphea is generally good. Management involves establishing subtype, depth and extent of lesions, and activity of lesions. Methotrexate, sometimes in combination with glucocorticoids, is the preferred systemic option to treat severe or progressive disease. Physical therapy is an essential component of the management of patients with deep lesions and those with lesions overlying joints.

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