12-Year-Old-Girl with a White Indented Plaque of the Frontal Scalp and Forehead

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Abstract

Morphea, or localized scleroderma, encompasses several skin conditions manifesting with sclerotic changes secondary to an idiopathic, autoimmune, inflammatory process. En coup de sabre, or "by the touch of the sword," is a form of localized linear scleroderma that affects the frontoparietal scalp and face and can result in secondary scarring alopecia. This type of morphea affects the dermal and subcutaneous layers but can extend to bone, sometimes affecting adjacent ocular and central nervous tissue. Morphea is a clinical diagnosis, initially presenting with inflamed edematous and erythematous patches before ultimately sclerosing to form bound-down indurated nodules or plaques. Unclear cases can be confirmed with a punch biopsy or a deep excisional biopsy. When morphea extends beyond the dermis, the extent of involvement should be evaluated with MRI or ultrasound. Without suspicion for other autoimmune conditions, testing for autoantibodies is not warranted given the low prognostic significance. Morphea treatment is based on how active and severe the condition is. Inactive disease lacks erythema, edema, peripheral induration, lesion expansion, or new lesion formation and can be managed with physical or occupational therapy and plastic surgery. Mild active disease can be managed with topical clobetasol, tacrolimus, vitamin D analogues, intralesional corticosteroids, and medium dose UVA phototherapy. Severe rapidly progressing morphea can be managed with

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methotrexate and systemic glucocorticoids. Refractory morphea can be managed with mycophenolate, cyclophosphamide, rituximab, abatacept, and tocilizumab.

Keywords

Morphea · Scleroderma · En coup de sabre · Autoimmune · Alopecia · Methotrexate Corticosteroids · TGFβ

A 12-year-old female reported a two-year history of a firm, white plaque that evolved on her scalp and forehead. The area on the scalp lacked hair and appeared depressed. Her mom reported that the area initially looked like a dark brown line, and they were told it was a birthmark (Fig. 18.1). The patient's medical history was significant for headaches and decreased visual acuity. She recently was fitted for new glasses. The patient was in distress over the cosmetic appearance of her skin and the hair loss, which prompted her evaluation.

On physical examination, a linear, indurated white, hairless plaque was observed extending from the frontal scalp into the central forehead. Eyebrows and eyelashes were of normal density. The fingernails were normal. The remaining skin exam was normal. A biopsy was performed and demonstrated thickened, hyalinized collagen bundles in the reticular dermis and subcutis. There was trapping of eccrine glands within the middle of a thickened dermis and a decreased number of adnexal structures and blood vessels.

Based on the clinical case description, what is the most likely diagnosis?

1. Alopecia areata
2. Dissecting cellulitis
3. Morphea
4. Tinea capitis

Fig. 18.1 Depressed, hyperpigmented patch on the forehead extending into the scalp. Image courtesy of Dr. Melissa Piliang and Janine Sot, MBA medical photographer

Diagnosis

Morphea

Discussion

Morphea, otherwise known as localized scleroderma, encompasses a group of skin diseases that present with sclerotic skin changes secondary to an idiopathic, inflammatory process [1, 2]. The five types of morphea include bullous, plaque, generalized, deep, and linear [3]. Localized scleroderma should not be confused with systemic sclerosis, which can affect internal organs without affecting the skin [4]. Unlike systemic sclerosis, morphea lacks sclerodactyly, nailfold capillary changes, and Raynaud's phenomenon [2]. Morphea has been shown to impact 3–27 individuals per 100,000 with women affected at a ratio 2.4–5 times greater than men [2]. Although the disease can affect patients at any age, it has a bimodal distribution with peaks around 7–11 and 44–47 years of age [2]. Alopecia secondary to morphea is often associated with en coup de sabre, a localized linear scleroderma that affects the frontoparietal area of the scalp as well as the face [5]. En coup de sabre presents as a white, linear, depressed, indurated, atrophic plaque with scarring alopecia [6]. It often resembles a scar from the strike of a saber or sword. The morphea of en coup de sabre affects the dermis and subcutaneous connective tissues but can also involve the muscles, cartilage, and bone, sometimes affecting the ocular and central nervous systems below the cutaneous lesions [3, 6]. Patients with morphea present with one or more plaques that are typically active for 3–5 years, although sometimes plaques can be more persistent [2, 7]. Unfortunately, even after active disease subsides, hyperpigmentation, contractures over joints, and atrophy can lead to persistent mobility impairment and disfigurement [1, 4]. Moreover, the course is relapsing and remitting, with about a 25% relapse rate, even after years of quiescence [8].

Morphea is diagnosed clinically, with the history and physical exam resting as the cornerstones of the diagnosis [2]. Distinguishing morphea from systemic sclerosis is of paramount importance when making the initial diagnosis [7]. Initially, inflammatory morpheaform lesions present as edematous, inflammatory, erythematous patches and plaques that can be pruritic or painful [2]. Next, sclerosis expands from the center of the lesions, surrounded by an erythematous or violaceous border, before ultimately manifesting as bound-down, indurated nodules or plaques [2, 7]. Sclerotic lesions may result in the malformation, damage, or destruction of pilosebaceous units leading to cicatricial alopecia [9]. However, after months to years, the sclerotic lesions transition into softer, dyspigmented atrophic plaques associated with the inactive phase of the disease [2]. Deep, linear morphea is typically unilateral and can result in limb-length discrepancies in children [2]. When suspecting linear scleroderma, providers should evaluate the patient for signs of systemic sclerosis, such as Raynaud's phenomenon, sclerodactyly, and capillary nail fold changes

[7]. Histopathologic examination of biopsies and laboratory tests are not necessary in a majority of morphea diagnoses [2]. A skin biopsy should only be considered in cases of unclear patient presentation of morphea [2] In cases of deep morphea beyond the dermis, MRI should be used to evaluate soft tissue involvement and lesion depth and monitor musculoskeletal involvement [2]. Ultrasound is the preferred imaging modality to monitor disease activity in superficial morphea [2] Since the prognostic significance of autoantibodies is unclear, testing for them is not recommended [2].

While the cause of morphea is idiopathic, factors such as epigenetics, autoimmunity, and vascular dysfunction have been shown to play a role in its pathogenesis [2, 10]. Despite a lack of a particular gene being involved in morphea development, strong associations were found with the HLA class I allele HLA-B*37A and HLA Class II allele DRBI04:04 [2]. Additionally, patients with morphea are more likely to have a family history of autoimmunity [7]. Currently, no morphea-specific antibodies have been discovered [2]. Early morphea lesions have been shown to be teeming with mononuclear lymphocytes such as T lymphocytes, eosinophils, and plasma cells [2, 10]. Samples of affected skin have shown decreased dermal capillaries, irregularities in blood vessel basal lamina, and damaged endothelial cells, findings which point to vascular dysfunction as a component of localized scleroderma generation [7, 10]. The mechanism likely involves the activation of $CD4^+$ T_H2 cells, which secrete interleukin-4 (IL-4), subsequently activating T lymphocytes to secrete transforming growth factor ß (TGF- ß) [10]. The excess of TGF-ß stimulates fibroblasts to produce collagen and extracellular matrix proteins, directly contributing to sclerosis [10]. During the inflammatory phase, vascular endothelial damage triggers the release of cytokines that stimulate vascular adhesion molecule expression [7, 10]. Specific adhesion molecules that have been detected at higher levels in the serum of morphea patients include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin [7, 10]. Tissue damage also results in the secretion of chemokines, attracting leukocytes to extravasate into the dermis [3]. Subsequently, the lymphocytes produce profibrotic cytokines including IL-1, IL-4, IL-6, IL-8, IL-13, and TGF- ß, which activate fibroblasts, pericytes, and endothelial cells to differentiate into myofibroblasts [3]. The activated myofibroblasts produce collagen, fibronectin, and tenascin-c, thus activating more fibroblasts to differentiate into myofibroblasts and perpetuating the cycle of fibrosis [3].

Treatment

The treatment of morphea largely depends on disease severity and activity. Certain features are associated with active, inflammatory morphea, including erythema, peripheral induration, lesion expansion, and new lesion formation [11]. If these clinical features are absent, then the morphea is in the inactive, “burnt out” phase. Currently, therapy is considered most effective when targeting the active stage of the disease [12]. Despite the lack of current medical treatments, patients can be

referred to physical therapy or occupational therapy if mobility is impaired due to excessively tight skin or joint contractures [13]. However, even in cases where lesions are removed or managed medically with systemic treatment, lesions can recur even several years later [14].

In cases of active morphea, treatment can be further stratified by the level of disease activity. When patients have a few active plaques without new lesion formation, then patients should undergo treatment with topicals such as corticosteroids, tacrolimus, calcipotriene, or intralesional injections of corticosteroids [15]. Adjunctive treatment with phototherapy can be considered with superficial and deep active morphea lesions [2]. In cases of rapid lesion formation or progressive deep morphea, patients should be started on long-term systemic methotrexate (12.5–25 mg/week) along with an optional prednisone bridge at 0.5 to 2 mg/kg daily for 2–4 weeks followed by a gradual taper over several months [15].

The current management recommendations are largely based on lower-quality evidence (1B-3) and there is much room for clinical trials to standardize existing or novel treatments [13]. It has been shown that methotrexate plus steroids result in superior outcomes relative to placebo plus steroids, but methotrexate plus steroids have not been shown to be superior to methotrexate alone [4, 16]. Methotrexate is well known for its role in suppressing folate metabolism by blocking dihydrofolate reductase [17]. Medium dose UVA_1 phototherapy has been shown to be more effective than narrow-band UVB in a randomized controlled trial and works by suppressing collagen synthesis [16]. Although oral calcitriol has failed to show efficacy beyond placebo, topical calcipotriene plus betamethasone showed relief in all 12 patients in one case series [18]. Vitamin D analogues have been shown to inhibit fibroblast proliferation and downregulate T cells [16].

Fortunately, several exciting novel agents may become used for morphea management in the future. The general classes of these medications fall into the categories of antifibrotics, anti-inflammatory agents, cellular and gene therapy agents, and senolytics [3]. One of the antifibrotic agents is fresolimumab, an anti-TGFβ monoclonal antibody, which has shown promise in early-stage trials in diffuse cutaneous systemic sclerosis [19]. Another similar agent is pamrevlumab, a monoclonal antibody against connective tissue growth factor (CTGF), a downstream marker of TGFβ. This drug increases vascular injury and inhibits the recruitment of inflammatory cells and fibroblasts. Currently, pamrevlumab is being tested in an ongoing trial for interstitial lung fibrosis [20].

Anti-inflammatory agents are often used for morphea because of their relative abundance. One example is the anti-IL-6 monoclonal antibody, tocilizumab, which has been shown to modestly affect skin scores in systemic morphea in a randomized clinical trial [3]. Interestingly, the PPARα agonist, fenofibrate, and the PPARγ agonist, pioglitazone, have been shown to have both anti-inflammatory as well as antifibrotic properties [3]. However, the amount of PPAR agonist activity these drugs have is high enough to raise safety concerns when used for morphea. Therefore, lanifibranor, a novel pan PPAR agonist with mild activity, was developed and has been shown to reduce skin fibrosis [3]. Lanifibranor is currently being investigated in an ongoing phase 2 trial for morphea and a phase 3 trial for NASH cirrhosis [21].

Topical crisaborole, a PDE-4 inhibitor, has been shown to decrease M2 macrophage differentiation and thus decrease skin fibrosis [3]. While crisaborole is being investigated in a phase 2 trial for morphea, there have not been any reports to date utilizing apremilast, an oral PDE-4 inhibitor, as a treatment for morphea [22]. Other well-known immunosuppressive agents that have shown efficacy in the treatment of morphea in randomized clinical trials include mycophenolate, cyclophosphamide, rituximab, and abatacept [4].

Two novel miscellaneous agents are currently in the drug pipeline that are worth mentioning. First, there is a cellular and gene therapeutic agent called FCX-013, which is a modified autologous fibroblast [3]. In the ongoing trial, this agent has been injected directly into morphea plaques and then subsequently induced by a second oral agent to express matrix metalloprotease 1 (MMP-1), thus leading to targeted collagen breakdown [3, 23]. Secondly, a senolytic agent called dasatinib, a selective BCR-ABL and SRC tyrosine kinase inhibitor, has been shown to decrease senescence-resistant myofibroblasts. Furthermore, dasatinib has shown clinical improvement in a phase 1 trial of interstitial lung disease secondary to systemic sclerosis [3].

Although methotrexate is considered first-line management in severe morphea, not all patients are able to tolerate methotrexate due to various comorbidities. In cases of hepatic insufficiency, mycophenolate may be a safer alternative, as well as being the general second-line agent behind methotrexate [24]. In cases where patients with severe morphea have renal insufficiency, rituximab may be the favored choice, followed by mycophenolate or cyclophosphamide if renal dosing is accounted for [25, 26]. In cases of heart disease, methotrexate is still considered first-line and has been shown to have cardioprotective benefits in patients with rheumatoid arthritis [27]. For patients with lung disease, cyclophosphamide may be a reasonable option as it has been shown to have modest benefits in interstitial lung disease [28]. For patients without insurance, methotrexate is an affordable first-line drug. Similarly, in cases of deep tissue and musculoskeletal involvement, methotrexate is still the first-line treatment [2]. In cases of serious infection, immunosuppressive treatment may need to be held until after the infection resolves [29]. For pregnant patients, hydroxychloroquine has been found to be both safe and effective [30]. Meanwhile, children are treated similarly to adults, albeit with dose adjustments. Although managing and studying morphea can be difficult due to its relative rarity, often self-limiting course, variety of presentations, and the relative paucity of high-quality trials, there are many new agents that have the potential to revolutionize morphea management.

Linear morphea associated with the head and neck is at significant risk to contracture and cause deformity, thus requiring aggressive systemic therapy [1]. Therapy for en coup de sabre generally starts with methotrexate and a short course of systemic corticosteroids for 2–3 months [1]. If treatment is ineffective, options such as phototherapy (PUVA, UVA, or UVA1) or mycophenolate should be considered [1].

An important aspect in the treatment of morphea is patient education on the scarring nature of the disease. Patients should be counseled that treatment is aimed at

new, active lesions and involved skin may never return to its previous appearance [1]. The chronic, inactive lesions are often unresponsive to treatment and do not warrant systemic therapy [1]. Hair transplant can also be performed in patients who have a healthy, non-scarred patch of hair [9]. Hair transplantation is not as effective in scarred tissue due to the decreased blood supply [9]. Another possible option for future hair growth includes hair autografting followed by topical minoxidil 5% [31].

Key Points

- Morphea is an idiopathic, inflammatory autoimmune cutaneous and connective tissue condition that presents as white, linear, depressed, indurated, and atrophic plaques with scarring alopecia.
- Inactive morphea is devoid of features such as erythema, edema, peripheral induration, lesion expansion, and new lesion formation and can be managed with physical therapy, occupational therapy, and plastic surgery.
- Mild active morphea can be treated with topical clobetasol, tacrolimus, vitamin D analogues, intralesional corticosteroids, and medium-dose UVA_1 phototherapy.
- Severe morphea with rapid progression can be managed with methotrexate with or without systemic glucocorticoids.
- Refractory morphea can be treated with mycophenolate, cyclophosphamide, rituximab, abatacept, tocilizumab, and newer agents as they exit the pipeline.

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