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## Laser therapy in superficial morphea lesions – indications, limitations and therapeutic alternatives

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### ABSTRACT



Morphea or localized scleroderma is an uncommon autoimmune and inflammatory disease which affects patients of any age. Even if morphea lesions present systemic symptoms as myalgias or arthritis, it is distinct from systemic sclerosis because it does not associate Raynaud's phenomena or sclerodactyly, which are encountered in systemic scleroderma. The most common form of morphea in children is `en coup de sabre`, which can alter the local anatomy by deep tissue involvement. In contrast, the most frequent form that affects adults is represented by circumscribed morphea. The initial lesions present an inflammatory phase that manifests in the form of erythematous plaques, sometimes accompanied by edema. In later stages, the inflammation decreases and the lesions become sclerotic to atrophic. Therapy is most beneficial when initiated in the inflammatory stage. Topical application of high potency steroids along with phototherapy demonstrates the best results in the active phase of the disease. Localized superficial morphea can be treated with the excimer laser (using ultraviolet type B light, in range of 308nm) if topical steroid administration shows no significant clinical improvement. Phototherapy with ultraviolet light is capable of decreasing inflammation and may also have immunomodulatory effects.

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### Introduction

Morphea or localized scleroderma is an uncommon fibromatous disease of the connective tissue in the skin and subdermal structures. The disease is characterized by the production of excess collagen deposits in the skin, causing its thickening [1]. The deposits of collagen usually involve the reticular dermis (in the classical form of morphea) but can expand into the subdermal layer [2]. Superficial morphea (SM) is a particular/uncommon entity characterized by a localized deposition of additional collagen in the papillary dermis and upper reticular dermis [3], being first described by McNiff in 1999 [4]. Patients who chose the excimer laser therapy

generally have followed a 6-8-week treatment with topical corticosteroids and often multiple sessions of UVA treatment, all these options being used for anti-inflammatory purposes. Basically, when patients receive recommendation for UVB or UVB narrow band, the excimer laser treatment represents a viable therapeutic alternative for dermatologists. In superficial morphea, the literature often describes multiple hyperpigmented and slightly indurated patches or plaques, distributed especially on the trunk and intertriginous areas [5]. Occasionally, purple borders may occur (suggesting the acute inflammatory phase), as well as minimal atrophy and hypopigmented areas in the hyperpigmentation spots [6].

The clinical diagnosis of morphea can be confirmed by histopathological examination which highlights the excessive bundle deposits of thickened collagen in the papillary dermis and reticular dermis. The purpose of the therapy is to improve induration and hyperpigmentation, to decrease inflammation, and to stop the progression of the lesions.

## Discussions

The term morphea was first used in Ancient Greece to describe the form or structure of objects. Nowadays, the entity of morphea refers to a chronic autoimmune disorder related to unknown conditions, which has a genetic predisposition, and which is characterized by sclerotic changes in the skin. Another term for this disorder is "localized scleroderma."

It may be challenging to distinguish localized scleroderma from scleroderma. Scleroderma, better known as systemic sclerosis, is a distinct autoimmune connective tissue disorder that can involve cutaneous sclerosis and systemic manifestations other than those observed in morphea.

Morphea is a fairly rare disease that can develop at any age, but most often affects adults [7]. The ratio between genders reflects a 3:1 fraction in favor of female distribution [7]. The most frequent manifestation of the disease in children represents the linear form, while for adults the clinical expression is usually the circumscribed plaques form. Regarding prevalence related to ethnicity, Caucasians are more likely to suffer from the disease than African-Americans [8]. The clinical appearance of morphea could be as a single localized lesion, or a single lesion which can affect half of the forehead (en coup de sabre), or an extensive form affecting half of the body [9], or in the form of a disseminated disease with multiple localizations affecting the entire body [10]. The clinical course of the disease may follow two paths. More frequently, the disease activity may persist for 3-6 years. In fewer cases, the disease activity can become persistent and recurring.

Risk factors for developing the disease have been described in various studies. The immune component, which has an abnormal response to different triggers, is thought to be the key element in the pathogenesis of morphea. Different kinds of infectious episodes are related to the onset of this inflammatory disorder of the skin. As an example, studies performed in Europe have revealed a connection between *Borrelia* infection and morphea lesions [10,11]. These studies have noted high levels of antibodies against *Borrelia burgdorferi* in patients suffering from morphea. Another finding demonstrated the presence of these microorganisms in biopsies performed from lesions of morphea. Other studies question this outcome and claim that a certain type

of morphea lesions could be caused by certain species of *Borrelia* found only in Europe and Asia, but not identified in the USA [12]. There have been reported cases of morphea after administration of biological therapy with ustekinumab, a human monoclonal antibody which blocks interleukin (IL)-12 and IL-23 via P40, more specifically their common protein subunit [13]. Other factors in the etiology of morphea include cutaneous radiation, skin trauma such as surgery or injections, and insect bites [14,15].

Regarding pathogenesis, morphea is usually described as an autoimmune-mediated inflammatory disease. The inflammatory infiltrate shown in morpheic lesions is composed from T lymphocytes, plasmocytic cells, and eosinophils. Laboratory tests performed on morphea patients have revealed high levels of autoimmune antibodies, especially antinuclear antibodies. The key element in the pathogenesis of morphea is the increased production of collagen types I and III. This production is generated by platelet-derived growth factor, connective tissue growth factor, and matrix metalloproteinases [16]. All these factors decrease gamma interferon, a suppressor of collagen synthesis.

The morpheic lesions develop insidiously and arise as erythematous edematous plaques due to the initial inflammatory process. In time, the center of the lesion becomes sclerous and the periphery of the lesion highlights a violaceous border. Sclerotic lesions are characterized by follicular atrophy and hypo/hyperpigmentation, and eventually the lesions become atrophic.

Subtypes of morphea include circumscribed (plaques) morphea lesions, linear, deep, and generalized. The circumscribed form is most common in adults and it presents with indurated round-oval plaques. The linear form, which mostly affects children, occurs with morpheic form plaques arranged in linear distribution. En coup de sabre lesions involve morpheic lesions to the cephalic region. It resembles the cut of a sword and manifests as a linear atrophic plaque. Although it usually affects the forehead, its progression to the scalp may induce scarring alopecia. The generalized morphea is manifested by the presence of at least 4 plaques, on at least two anatomical sites. Contrary to the systemic sclerosis, generalized morphea does not involve Raynaud's phenomenon, sclerodactyly, and capillary changes observed at capillaroscopy [17]. The deep morphea subtype refers to the deep dermis and subcutaneous tissue involvement.

Systemic symptoms related to morphea include carpal tunnel syndrome and muscular and skeletal involvement such as arthritis and myalgias. En coup de sabre lesions may produce neurological and ocular complications. The coexistence of SM with other skin

diseases is uncommon. Saleh and Colab reported the case of a patient who presented both psoriasis vulgaris and MS [18]. There are reports of association between morphea and viral hepatitis C [19].

Regarding differential diagnosis, several disorders have raised, and continue to raise, differential diagnostic difficulties. Therefore, numerous controversies occur regarding the relationship between superficial morphea and Pasini-Pierini atrophoderma. Some authors consider both entities to be similar or even identical, especially regarding the atrophic phase of morphea [20, 21], whereas other authors distinguish between the two diseases. This hypothesis is sustained not only by the anomaly of the elastic fibers, the sclerosis of collagen bundles, and the presence of active inflammation in the regressed lesion of superficial morphea, but also by "the Sign of the rock" that is characteristic for atrophoderma [22-24]. The most important differential diagnosis regarding morphea lesions is lichen sclerosus et atrophicus. Lichen sclerosus et atrophicus represents a different entity, characterized histo-pathologically by epidermal thinning or atrophy, follicular hyperkeratosis, vacuolar change of the basal layer, dermal edema, and marked loss of elastic fibers [25-27]. The diagnosis of morphea is primarily based on cutaneous biopsy of the lesions performed for histopathological examination. The histopathological examination reveals the presence of thick bundles of collagen in the dermis. In superficial morphea, the modifications of collagen fibers can be observed in the papillary dermis and possibly in the superficial reticular dermis, while in the classical form of morphea, the excessive deposition of collagen bundles are also visible in the reticular and deep dermis. The histopathological examination must also specify the density of the fibroblasts and the density of elastic fibers, which can be performed after special colorations with Verhoeff – Van Gieson (VVG), Orceine, and Trichrome [27, 28]. The biopsy should be performed taking into account the resulting ulceration that can be difficult to treat and which can even become infected.

Morphea is an autoimmune inflammatory disorder in which the cutaneous atrophy begins to evolve after the inflammation phase fades. The treatment is often local and includes phototherapy. In more severe cases, systemic therapy may be instituted to prevent (at least in part) massive involvement of the skin and subcutaneous tissue, related to major disfigurement and functional impairment.

The most responsive forms of morphea to therapeutic effects are recent lesions with inflammatory signs. In such cases, topical treatment and phototherapy can improve the erythema and the regrowth of the hair follicles. In the active disease stage, the treatment aim is to limit formation of new plaques. Topical treatment options include high potency corticosteroids with their well-

studied adverse reactions and microbiome changes [29-31], topical calcineurin inhibitors, and topical vitamin D analogues [32-35]. Tacrolimus, a calcineurin inhibitor, has been shown to inhibit development of fibroblasts in vitro and in vivo [36-38], leading to a successful management in superficial new plaques of morphea.

Phototherapy has been used as monotherapy or in combination with topical medication. Long wavelengths such as ultraviolet type A (320-400nm) are beneficial in the treatment of sclerotic disorders, due to capability to penetrate under the epidermis layer, into the subcutis. Ultraviolet light type B such as UVB or narrowband UVB (280-315) has the penetrability level reaching the papillary dermis. The risk involved in using this type of treatment includes sunburn, erythema, and blistering. It has been proposed that UV increases the production of interferon gamma (which has the ability to decrease the synthesis of collagen) and also decreases collagen I and III from the morpheic lesions (through decreasing its synthesis) [37, 38]. Another effect of UV light in sclerotic diseases is related to the action of increasing collagenase enzymes [39-41] that induce collagen breakdown.

Phototherapy represents one of the most common treatments in morphea taking into account the clinical outcomes. Exposure of the cutaneous lesions to ultraviolet light has been proven beneficial over time. Mechanisms involving the decrease of collagen production or the increase in collagen enzymes have been observed in many studies. Presumably, fibroblasts augment the production of metalloproteinase extracellular matrix after exposure to UVA light [42, 43]. Another important finding suggests that exposure to UVA light decreases inflammatory cells that sustain the clinical expression of this disorder. Several studies show that after UVA radiation, there is a decrease in inflammatory cells as lymphocytic T cells, mast cells, and Langerhans cells [44]. UVB has shown the potential to enhance the receptor for  $\alpha$ -melanocyte-stimulating hormone, causing the release of metalloproteinase extracellular matrix [45]. Systemic therapy in morphea is usually necessary in patients with severe and disfiguring disease forms, or in patients diagnosed with generalized acute or progressive morphea. The use of methotrexate on such patients is required, but relapses may occur at cessation of the medication. It may be useful to combine methotrexate with systemic steroids.

Depth of lesion, lesion localization, and cosmetic considerations are important factors contributing to a lower quality of life in patients diagnosed with morphea. Physical and occupational therapy are required when generalized or deep morphea (affecting the subcutaneous fat or muscles) occur. Another option for patients who suffer from advanced cosmetic lesions (often on the face)

is represented by filler therapy. In patients with severe contractures, surgery may represent a viable therapeutic option [44-46].

## Conclusions

Morphea is an autoimmune inflammatory skin condition which affects both children and adults. It is characterized by an acute phase which involves an inflammatory process of the skin, in which the active plaques are increasing in size and present an indurated erythematous, violaceous border. Over time, the inflammation decreases in the center of the lesion and atrophy appears. The histopathological appearance of the lesions depends on the stage of the disease. The inflammatory infiltrate, localized perivascular and into the interstitial tissue, consists of T lymphocytes, mast cells, eosinophils and plasma cells. When sclerosis occurs, the histopathology examination reveals thickened collagen bundles into the papillary and reticular dermis up to the subcutaneous layer. The course of the disease is mainly chronic even though it is often asymptomatic. The most important characteristic for treatment is the ability to reduce the local inflammatory reaction and to stop the progression of the disease. In terms of atrophic lesions, treatments are limited, and sclerosis is very difficult to treat. Surgery of the lesions is an option as well as injections of fillers.

Our experience with the excimer laser, based on UVB 308 nm showed an important beneficial therapeutic effect mainly on the inflammatory lesions, characterized by erythematous plaques or edematous patches.

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