REVIEW

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Pathogenesis and treatment modalities of localized scleroderma

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Key words: *localized scleroderma; morphea; sclerodermia circumscripta; Borrelia burgdorferi; treatment.*

Summary. *Localized scleroderma is a chronic inflammatory disease primarily of the dermis and subcutaneous fat that ultimately leads to a scar-like sclerosis of connective tissue. The disorder manifests as various plaques of different shape and size with signs of skin inflammation, sclerosis, and atrophy. This is a relatively rare inflammatory disease characterized by a chronic course, unknown etiology, and insufficiently clear pathogenesis. Many factors may influence its appearance: trauma, genetic factors, disorders of the immune system or hormone metabolism, viral infections, toxic substances or pharmaceutical agents, neurogenic factors, and Borrelia burgdorferi infection. Various therapeutic modalities are being used for the treatment of localized scleroderma. There is no precise treatment scheme for this disease. A majority of patients can be successfully treated with topical pharmaceutical agents and phototherapy, but some of them with progressive, disseminated, and causing disability localized scleroderma are in need of systemic treatment. The aim of this article is not only to dispute about the clinical and morphological characteristics of localized scleroderma, but also to present the newest generalized data about the possible origin, pathogenesis, and treatment modalities of this disease.*

Introduction

Localized scleroderma (*morphea*, *sclerodermia localisata*, *sclerodermia circumscripta)* is a chronic inflammatory skin disease, which manifests as a disorder of cellular immunity, microcirculation and abnormal collagen synthesis. This triad of components slowly causes sclerosis of the skin and sometimes even movement disorders.

There are only few data about the epidemiology of localized scleroderma. During the period from 1960 to 1993, the incidence rate of localized scleroderma in Olmsted County, Minnesota, was 27 per million inhabitants (1). The prevalence increases with age, being approximately 500 per million at the age of 18 years and 2200 at the age of 80 years (2). However, usually disease onset occurs at young age (at the age of 20–40 years), and about 15% of patients are children up to the age of 10 years (3). The disease is rare in blacks (3). Localized scleroderma is more prevalent in women than men, with a female-to-male ratio of 2–3:1 (3, 4).

Localized scleroderma is usually a relatively harmless disease. However, in about 10% of patients, scar formation may lead not only to cosmetic defect, but also to significant disfigurement or growth retardation and handicap of the affected individuals for their entire life (1). Appropriate treatment with topical or systemic drugs and phototherapy may be helpful for about 60% of patients with localized scleroderma (4). In this article, we will discuss the clinical and morphological characteristics, etiology, and pathogenesis and treatment modalities of localized scleroderma.

Etiology and pathogenesis

The pathogenesis of localized scleroderma has not been completely delineated. There is increasing evidence that sclerosis represents the end stage of the disease and results from an increased synthesis of collagen types I and III. According to literature data, three major components are involved during the development of sclerosis: damage of small vessels, activation of T lymphocytes, and production of altered connective tissue. The morphological changes affect principally capillaries and small arterioles 50–500 μm in diameter (4). The initial changes include expression of adhesion molecules and endothelial swelling, followed by thickening of the basement membrane and hyperplasia of the intima. Activated T cells that release cytokines – interleukin 4 (IL-4) and transforming growth factor β (TGF-β) – accumulate around affected vessels (5).

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They induce abnormal collagen synthesis by fibroblasts (6).

In most cases, the etiology of localized scleroderma is unknown. Many factors may influence its appearance: trauma, genetic factors (HLA system antibodies DR5, DR8, DR11), immunological, hormonal, viral, toxic (aromatic hydrocarbon, silicon, etc.), neurogenic (stress) or vascular factors, pharmaceutical agents (penicillamine, L-tryptophan), and *Borrelia burgdorferi* (*B. burgdorferi*) infection (4).

B. burgdorferi infection has been showed to be a cause of erythema chronicum migrans, acrodermatitis chronica atrophicans, and lymphadenosis cutis benigna and has been implicated in the development of localized scleroderma. In 1987, Aberer et al. were the first to hypothesize about association between *B. burgdorferi* infection and localized scleroderma (7). Many techniques of analysis have been used to show the relationship between *B. burgdorferi* and localized scleroderma: indirect immunofluorescence assay and enzyme-linked immunosorbent assay (ELISA), histological investigations with special staining methods, cultivation of spirochetes, or their detection from lesions of patients with morphea using polymerase chain reaction (PCR). The research results have been contradictory. Researchers distributed into two groups: supporting and denying the significance of *B. burgdorferi* in the etiopathogenesis of localized scleroderma (Table 1).

Many reports relate localized scleroderma to *B.*

Table 1. Association between localized scleroderma and *Borrelia burgdorferi* infection

Investigator, year	The method of research	Number of cases	Positive results
Aberer et al., 1987 (7)	Serology	15	8
	Culture in Barbour-Stoennner-Kelly medium	1	1
	Avidin-biotin-immunoperoxidase staining and microscopy	8	3
Hoesly et al., 1987 (8)	Serology	57	7
Aberer et al., 1987 (9)	Avidin-biotin-immunoperoxidase staining and microscopy	13	4
Lecerf et al., 1989 (10)	Serology	21	1
Pinazo Canales et al., 1990 (11)	Serology	9	none
Ross et al., 1990 (12)	Steiner silver staining and microscopy	25	10
Aberer et al., 1991 (13)	Serology	30	14
Raguin et al., 1992 (14)	Serology	15	none
	Immunohistochemical staining and microscopy	14	none
	Culture	10	none
Schempp et al., 1993 (15)	Skin PCR	9	9
Buechner et al., 1993 (16)	Serology	10	10
Buechner et al., 1994 (17)	Serology	26	10
Ranki et al., 1994 (18)	Skin PCR	7	none
Wienecke et al., 1995 (19)	Skin PCR	30	none
Buechner et al., 1995 (20)	Serology	45	13
Dillon et al., 1995 (21)	Skin PCR	20	none
Breier et al., 1996 (22)	Serology	39	13
	Lymphocyte proliferation tests	39	11
De Vito et al., 1996 (23)	Skin PCR	28	none
Fujiwara et al., 1997 (24)	Skin PCR	19	5
Alonso-Llamazares et al., 1997 (25)	Serology	6	1
	Skin PCR	6	none
	Culture	6	none
Breier et al., 1999 (26)	Skin PCR	1	1
	Culture	1	1
Ozkan et al., 2000 (27)	Skin PCR	10	3
Svecova et al., 2000 (28)	Serology	32	11
Weide et al., 2000 (29)	Serology	53	3
	Skin PCR	33	none
Goodland et al., 2002 (30)	Skin PCR	16	none
Wojas-Pelc et al., 2002 (31)	Serology	50	14
Sommer et al., 2006 (32)	Serology	12	none
Espinoza-Leon et al., 2006 (33)	Serology (ELISA)	21	4
	Serology (ELISA and immunoblot)	4	none
Eisendle et al., 2007 (34)	Immunohistochemical staining with polyclonal antibody against *B. burgdorferi* and focus-floating microscopy	122	84
Zollinger et al., 2010 (35)	Skin PCR	49	1

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

burgdorferi infection. Histological and immunohistological detection of *B. burgdorferi* was reported in 0–40% of the cases with localized scleroderma, and cultivation of spirochetes from lesional skin succeeded in 5 patients (5 of 68) (29). Serological detection of antibodies against *B. burgdorferi* was described in 0–60% of patients with morphea in Europe and Asia and in 19% in the United States. DNA from *B. burgdorferi* was detected by PCR in 0–100% of the tissues of patients with localized scleroderma in Europe and Asia and in 0% in the United States (29). Recently, one study has found *B. burgdorferi* in 69% of cases of localized scleroderma (84 out of 122) using a new immunohistochemical staining with polyclonal antibodies against *B. burgdorferi* and special microscopy (focus-floating microscopy, FFM) (34). The specificity of this new method was equal to PCR testing (99.4% and 100.0%, respectively, for FFM and PCR), but sensitivity was higher (96.0% and 45.2%, respectively, for FFM and PCR) (36).

Clinical findings

The characteristic lesion of localized scleroderma is a circumscribed sclerotic plaque with an ivory-colored center and, if the disease is in an active inflammatory stage, blue-pink or violaceous border. The lesion often begins as a peripherally expanding erythema. The center gradually becomes yellow or white and more or less hardened, but not bound to the deeper structures. After lesions persist for a fairly long time, atrophic skin changes may develop with loss of hairs and sweat glands, as well as hypopigmentation and hyperpigmentation. Many clinical variants of localized scleroderma are described (Table 2).

Diagnostics

Histological evaluation is the most important in the diagnosis of local scleroderma: at the beginning, features of inflammation (inflammation phase) and later features of sclerosis (sclerosis phase) can be assessed. Early on, there is a dense superficial and deep perivascular inflammatory infiltrate primarily composed of lymphocytes with a few plasma cells and eosinophils. Typically a much more pronounced inflammatory infiltrate can be observed at the junction between the dermis and the subcutaneous fat around the deep vascular plexus that often involves the subcutaneous fat and causes panniculitis and extends upward toward the eccrine glands. During inflammation phase, slight edema may be seen with swollen or thickened bundles of collagen. Later on, the inflammatory infiltrate disappears almost completely and collagen bundles become thickened, sometimes closely packed and arranged parallel to the epidermal surface. Elastic bundles usually lose their sinuosity and are outstretched. In this stage, the atrophy of adnexal structures and reduction in number usually can be observed.

Usually no specific changes are found in laboratory findings of patients with localized scleroderma. Sometimes peripheral blood analysis may show eosinophilia. Immunological testing is not specific as well. According to the literature, antinuclear antibodies (ANAs) are found in 47–76% of patients (31). Antibodies against deoxyribonucleic acid (anti-DNA) are found in isolated cases and more often in

Table 2. Clinical variants of localized scleroderma

Clinical variant	Clinical features
Morphea in plaque	One or several plaques can be observed
Morphea guttata	Many small sclerotic lesions
Morphea disseminata	Disseminated plaques that can be mistaken for systemic sclerosis
Morphea linearis	
En Coup de Sabre	The band-like sclerotic lesion typically develops in the frontoparietal region vertically in a paramedian position from the eyebrows to the scalp, where scarring alopecia evolves.
Morphea linearis of the limbs	Linear, band-shaped sclerotic lesions in a longitudinal direction develop predominantly on the extremities. These may pass over the joints and course limitations in joint motion and limb growth.
Atrophoderma Pasini et Pierini	Rare form. One or several round lesions with diffuse cyclamen-colored erythema develop. Virtually no sclerosis of the skin is seen; the lesion becomes atrophic and depressed with a sharp drop-off at the edge.
Morphea nodulare	Rare form. Nodular lesions reminiscent of keloids are seen
Morphea bullosum	Rare form. Bullae usually appear in a well-established plaque
Morphea profunda	Rare form. The sclerosis is located in the septal portion of the subcutaneous fat and deeper layers of the dermis. The skin is bound to deeper tissues such as fascias, has a rough or depressed surface
Morphea fascialis	Rare form. The sclerosis is located in the muscle fascia, usually affecting the flexural tendons on the forearm
Morphea pansclerotica	Very rare form occurring in children. Severe generalized skin lesions, multiple joint contractures, and other mutilating changes in internal organs develop

young patients (3, 4). Prinz et al. observed a highly significant association between localized scleroderma, serological evidence of *B. burgdorferi* infection, and high-titer antinuclear antibodies in 90 patients with morphea when disease onset was in childhood or adolescence (37).

Different imaging techniques may be used in the diagnosis of localized scleroderma. The activity of scleroderma lesion is often assessed by thermography, laser Doppler flowmetry, or laser Doppler imaging: in active areas and areas of new lesions, the temperature and blood flow are increased (38, 39). Localized scleroderma on high-frequency (20–40 MHz) ultrasonographic evaluation usually presents as a regular increase of dermis echogenicity as a result of the accumulation of collagen fibers in this region and increase of the skin thickness (38, 40). Imaging techniques are of particular importance when assessing the efficacy of treatment of localized scleroderma (41).

Treatment

Various therapeutic modalities are being used for the treatment of localized scleroderma. There is no precise treatment scheme for this disease. A majority of patients can be successfully treated with topical therapy and phototherapy, but the progressive forms of the disease with intensely expressed skin sclerosis sometimes may need even systemic treatment (3). Most of data about the efficacy of treatment of localized scleroderma are based on single case reports or clinical trials without controls (Table 3).

Table 3. Treatment of localized scleroderma

	Treatment modalities	Efficacy	Level of evidence
Local	Topical corticosteroids	+	3
	Intralesional corticosteroids	+	3
	Vitamin A analogs	+	3
	Vitamin D analogs	+	3
	Testosterone	0	3
	Progesterone	0	3
	Intralesional interferon γ	0	2
	Topical immunomodulators	++	1
	Imiquimod	+	3
Systemic	Penicillin	++	3
	Penicillamine	++	3
	Methotrexate	++	2
	Hydroxy/chloroquine	+	3
	Corticosteroids	+	3
	Vitamin A analogs	+	3
	Vitamin D analogs	0	2
	Cyclosporine	0	3
Photo-therapy	Oral photochemotherapy	++	3
	Bath photochemotherapy	+++	2
	Cream photochemotherapy	++	3
	UVA1	+++	2
	Photodynamic therapy	++	3
	Extracorporeal photopheresis	+	3
	UVB	+	2
Others	Physical therapy	+	3
	Surgery	+	3
	CO_2 laser	+	3

Efficacy: +++, highly effective; ++, effective; +, moderately effective; 0, low efficacy or ineffective.
Level of evidence: 1, double-blind controlled trials; 2, clinical trial; 3, case reports.

Phototherapy. Phototherapy is the treatment with nature-identical ultraviolet radiation sources. The wavelength of the sun radiation ranges from 280 to 3000 nm. This is sectioned into ultraviolet radiation (UV), visible light, and infrared irradiation. Ultraviolet radiation is divided into UVC (200–280 nm, most of it is suspended in the ozone layer and it does not reach the surface of earth), UVB (280–320 nm), and UVA (320–400 nm) according to the wavelength. The effect of UV on the skin depends on the wavelength. The UVB radiation affects only in the upper layers of the skin and influences only keratinocytes and Langerhans cells. The UVA radiation penetrates more deeply into the skin and affects fibroblasts, dendritic cells, vascular epithelium, and inflammatory cells (mast cells, granulocytes). The UVA radiation also stimulates the production of inflammatory mediators, protein synthesis, and cell apoptosis.

In the medical literature, phototherapy for localized scleroderma was first described in 1994 (42). The efficacy of this treatment has been confirmed by various clinical trials. Phototherapy with psoralen (PUVA) activates metalloproteinase 1 (collagenase 1), which is important in collagen renewal (4). According to literature data, both bath PUVA and UVA1 phototherapy are effective treatments in most variants of localized scleroderma (43–45). It is safer and more effective than systemic treatment. Bath PUVA is more recommended for the late stage of localized scleroderma, when sclerotic changes predominate over inflammation. Satisfactory treatment results are achieved when 25–35 procedures over 3 months are performed (total UVA irradiation dose, 40–50 J/cm^2) (4). In view of the recent reports, UVA1 (340–400 nm) phototherapy can be more effective in early cases of localized scleroderma, when inflammatory changes predominate and progression of the disease is diagnosed (45, 46). The recommended total irradiation dose is 10–50 J/cm^2 (45). When the total UVA1 irradiation dose is 20 J/cm^2 or 50 J/cm^2, remission is achieved in 80% of cases or even more (45, 46). According to the results from study by Kreuter et al., narrowband UVB phototherapy also can be an effective therapeutic option in localized scleroderma, with a favorable risk/benefit ratio (45). However, according to their data, medium-dose UVA1 phototherapy was significantly more effective than narrowband UVB phototherapy (45).

Isolated lesions of localized scleroderma can be successfully treated using photodynamic therapy.

Marked reduction of sclerosis is seen after photodynamic therapy 1–2 times per week for 3–6 months using 3% 5-aminolevulinic acid gel and irradiation dose of 10 J/cm^2 (47).

Topical treatment. The disease is generally self-limited; most cases require little or no treatment and many patients do well with simple emollients. The benefit of corticosteroids in the treatment of localized scleroderma is questionable. Mostly ultrapotent topical corticosteroids may be useful in superficial active lesions for reducing inflammation. Sometimes even corticosteroids of weak (1% hydrocortisone) or medium (0.1% mometasone, 0.1% betamethasone, etc.) potency 1–2 times per day may be rather effective for the treatment of isolated lesions of localized scleroderma (3, 4, 46, 48). Intralesional corticosteroids may also be effective, but usually are used if only a small number of lesions are present (3, 4). Triamcinolone (0.1–0.3 mL) diluted with local anesthetic at a ratio of 1:2 and injected to the margin of the lesion may suppress inflammation and stop progression of the disease (3, 4). Injections can be repeated once a week for 3 weeks (3, 4). Corticosteroids are ineffective in resolving sclerosis.

Derivatives of vitamin D and vitamin A are under study in localized scleroderma. In vitro, calcipotriol inhibits the proliferation of fibroblasts (4). A study by Cunningham et al. showed an improvement of localized scleroderma after treatment with topical calcipotriene (0.005%) twice a day for three months (49). However, placebo-controlled studies are needed to confirm the efficacy of calcipotriol for the treatment of localized scleroderma (50).

Ointments containing heparin or heparinoids have been recommended for the treatment of localized scleroderma (51). Preliminary reports on new therapies for localized scleroderma are also available. These include the use of tacrolimus 0.1% ointment applied 2 times per day by occlusive dressing with a significant clinical improvement of late sclerotic lesions and complete clearance of early inflammatory skin lesions in 3 months (52, 53). This medication is well tolerated and safe for the long-term treatment of localized scleroderma (52). Case reports are published about successful treatment of this disease using imiquimod (5% cream) (54, 55). A few patients were successfully treated with topical tocoretinate for 6 months to 3 years, and clinical as well as histological improvement of lesions of localized scleroderma was observed (56).

Systemic treatment. A wide variety of systemic therapies have been recommended for the treatment of localized scleroderma. Systemic treatment is usable only for the progressive and destructive variants of the disease.

Penicillin and other antibiotics are often prescribed, but no controlled study, establishing their efficacy, has been carried out. Regression of localized scleroderma during prolonged treatment with penicillin or penicillamine has been observed in adults and children (57). Penicillin in the range of 10–30 million IU per day for 2–4 weeks is helpful in about 5% of patients (4, 51). Penicillamine seems to be similarly effective but is used less often because of its potential side effects.

In linear forms of scleroderma, phenytoin has been recommended (initially 100 mg 2 or 3 times per day, later 100 mg for 1–3 years) (51). Antimalarial drugs have been helpful in individual cases (200 mg of chloroquine per day for 3–6 months or 250 mg of hydroxychloroquine per day) (51).

Oral corticosteroids (1–2 mg of methylprednisolone per day) may be helpful in the inflammatory stages of localized scleroderma, especially in some patients with either rapidly progressive linear or disabling types of the disease, but corticosteroids do not improve established sclerosis (4). Alternatively, 15–20 mg of methotrexate per week seems to be helpful in the acute phase of localized scleroderma (58, 59). Based on experience with other autoimmune diseases, some authors favor the combination of methotrexate and corticosteroids, especially in rapidly progressive types of localized scleroderma (60). Immunosuppressive treatment is recommended for several months up to one year. Cyclosporine has not been shown to be effective and should not be combined with any phototherapy that currently is the most effective therapy for localized scleroderma.

Retinoids can inhibit TGF-β, one of the key cytokines that promote collagen synthesis by fibroblasts (61). Treatment with the vitamin A derivatives – etretinate or acitretin – at doses of 10–50 mg per day is effective in localized scleroderma (62–64). The only disadvantage of this method is that the response to the treatment is noticed only after a few months.

Despite promising case reports, a double-blind, placebo-controlled study has not confirmed the clinical efficacy of oral calcitriol (1.25-dihydroxyvitamin D_3) in localized scleroderma. This vitamin D derivative has a pronounced anti-inflammatory effect and modulates fibroblast growth and TGF-β (65). Perhaps it would be useful to investigate more advanced derivatives that cause fewer side effects and test them for longer treatment periods.

In vitro both interferon γ and interferon α normalize pathogenic collagen production by fibroblasts. However, the clinical efficacy of these cytokines in localized scleroderma has not been confirmed (66).

Physiotherapy. Long-term physiotherapy is obligatory for patients in whom localized scleroderma threatens to impair mobility. Regular procedures 3–4 times per week are recommended: phonophoresis with corticosteroids, iontophoresis, regular

massages, technique of vibration, etc. In later stages of localized scleroderma, drainage of lymph, tissue massage, and undercurrent massage may be helpful. Remedial exercises always are useful.

However, in the case of persistent contractures, especially in linear localized scleroderma, reconstructive surgery may be needed.

Conclusions

Localized scleroderma may last from a few months to many years. The severity of the disease varies and is unpredictable, but the prognosis is usually good. With time, the inflammatory process diminishes, lesions soften, and sometimes even the sclerosis can lessen. The treatment of localized scleroderma is still controversial, and no specific treatment for the disease is available. Most of patients can be successfully treated topically with corticosteroids or other immunosuppressive agents, but occasionally systemic therapy is needed for disseminated, progressive, and destructive variants. Bath PUVA therapy is extremely effective for many forms of localized scleroderma and currently recommended as the treatment of choice, being safe and more effective than the systemic therapies discussed above. Further definition of the role of *Borrelia burgdorferi* in localized scleroderma is pivotal in making treatment recommendations.

Židininės sklerodermijos patogenezė ir gydymas

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Raktažodžiai: židininė sklerodermija, *Borrelia burgdorferi* infekcija, diagnostika, gydymas.

Santrauka. Židininė sklerodermija – tai neaiškios etiologijos jungiamojo audinio liga, odoje pasireiškianti įvairių formų ir dydžio plokštelėmis su odos uždegimo, sklerozės ir atrofijos požymiais. Ligos etiologija nežinoma, tačiau jos pasireiškimui gali turėti įtakos daugelis veiksnių: trauma, genetiniai veiksniai, imuninės sistemos veiklos arba hormonų apykaitos sutrikimai, virusinės infekcijos, toksinių medžiagų, vaistų ar neurogeninių veiksnių poveikis, *Borrelia burgdorferi* infekcija. Židininės sklerodermijos diagnostikai svarbiausias yra odos biopsijos histologinis tyrimas, kurio metu nustatomi uždegimo (pradinė uždegimo fazė) ir jungiamojo audinio pažeidimo (vėlyvoji sklerozės fazė) požymiai. Klinikinių laboratorinių ir imunologinių tyrimų rodmenys šiai ligai nėra specifiniai. Židininės sklerodermijos gydymui taikomi įvairūs gydymo metodai. Nėra tikslios šios ligos gydymo schemos. Daugelis pacientų gali būti sėkmingai gydomi vietiniais vaistais ar fototerapija, tačiau progresuojančioms ir organų funkcijos sutrikimus sukeliančioms ligos formoms gydyti kartais būtinas ir sisteminis gydymas. Šio straipsnio tikslas – ne tik aptarti židininės sklerodermijos klinikines ir morfologines savybes, bet pateikti naujausius apibendrintus duomenis apie galimą šios ligos kilmę, patogenezę bei gydymo metodus.

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