Morphea (Localized Scleroderma) — Symptoms and Prognosis

See online here

Morphea or localized scleroderma is a rare disorder with characteristic clinical features. The treatment of this disease involves the use of long-term immunomodulators. In this article, we will learn about the clinical features including the different types of morphea, pathophysiology, laboratory diagnosis, treatment using different modalities, and the prognosis of morphea.

Definition of Morphea

Localized scleroderma/ circumscribed scleroderma, also known as morphea, is an idiopathic disorder that is characterized by excessive collagen deposition leading to
thickening of the dermis and/or subcutaneous tissue.

The disease leads to sclerotic changes in the skin in specific areas, following inflammation, in the absence of systemic involvement. This entity is different from systemic sclerosis. In fact, it is ten times more common than systemic sclerosis. The disease activity typically persists for 3 – 6 years. Functional or cosmetic impairments, secondary to atrophy or contractures, often persist after the active disease subsides.

Epidemiology of Morphea

- Morphea is a rare disease especially between the ages of 20-50 years with two thirds being younger than 18 years. The incidence falls between 0.4 and 2.7 per 100,000 people per year. In the case of children, 90% are diagnosed between 2 – 14 years of age. The mean age of children at the onset of the disease is 7.3 – 8.3 years.
- It is more common in whites and females (ratio of 2 – 4 women to 1 man); however, the prevalence is equal in children and adults.
- It has a female to male ratio of 3:1.

Etiology of Morphea

No single clear etiology has been identified. Some studies indicate that it may be triggered by bacterial or viral infections (for example, B. Burgdorferi). Genetic factors have also been implicated. However, only 4.7% concordance has been observed between twins; and family studies have shown only 1.6% frequency among first-degree relatives.

Trauma may act as an activator or initiator of progressive facial hemiatrophy, a type of morphea. Lesions form along the Blaschko's lines by a group of vulnerable cells. Romberg postulated that the probable etiology might be the disruption of sympathetic fibers; this supports the presence of skin lesions on the territory of trigeminal nerve branches. Autoimmune etiology is supported by the elevation of antinuclear antibody levels, association with diseases like rheumatoid arthritis, transverse myelitis, and the presence of CSF oligoclonal bands. Response to immunosuppressive therapy is also in favor of this etiology.

Radiation, and some drugs such as cocaine, balicatib, bisoprolol, bleomycin, D-penicillamine, bromocriptine, carbidopa, pentazocine etc. are also associated with the etiology of morphea.

Some chemicals, such as perchloroethylene, trichloroethylene, organic solvents, pesticides, epoxy resins, and silicone, can also cause morphea.

Pathology and Pathophysiology of Morphea
Morphea is an autoimmune connective tissue disease. The underlying pathway by which increased collagen production and deposition takes place is not completely understood. However, as per the endothelial theory of the pathogenesis of morphea, injury to the endothelium releases cytokines (IL-4 and IL-6) result in the expression of vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule (ICAM-1) and E-selectin, eventually recruiting eosinophils, CD4+ T cells, and macrophages.

These inflammatory mediators lead to the upregulation of profibrotic molecules, such as TGF-β by T-cells, increases the production of collagen. Additionally, increased expression of insulin-like growth factor (IGF) is observed in patients with morphea that increases collagen production and extracellular matrix deposition. Inflammation, vascular changes, and an imbalance between collagen formation and destruction (decreased in morphea) are important features of morphea.

**Symptoms of Morphea**

Based on the clinical features of morphea, Peterson et al. classified the disease into five types:
1. **Plaque-type**

2. **Generalized type**: Patients were classified to have this type if two or more body areas were involved.

3. **Bullous type**: Presence of bullae on the plaques

4. **Linear type**.

5. **Macular type/confluent patches**.

6. **Deep type**: This type includes subcutaneous morphea or morphea profunda, eosinophilic fasciitis and pansclerotic morphea.

As this classification was subject to controversy, Laxer and Zulian proposed a new classification in 2006 involving five types: **circumscribed, linear, generalized, pansclerotic**, and **mixed variants** of morphea.

**Morphea has two stages**: the first stage presents with an erythematous-violaceous plaque; the center of this plaque is typically sclerotic and white, whereas the borders that are active have a reddish appearance (lilac ring). As the disease activity abates, the plaques that are sclerotic remain with damaged adnexae.

The most frequently encountered type is **circumscribed morphea**; it may be deep or superficial or both and typically involves the truncal area. It may evolve in regions that had a history of trauma in adult patients; usually, the breasts are involved, nipples typically being spared.

Generalized morphea is rarer and is difficult to distinguish from systemic sclerosis; these patients, however, do not exhibit **sclerodactyly** or features of *Raynaud’s phenomenon*.

**Among children**, the most common entity is linear morphea. The distribution of lesions...
strongly correlates with the lines of Blaschko. In 25% of cases, bilateral disease may be detected. Usually, the paramedian aspect of the forehead is involved in en coup de sabre and is usually associated with alopecia and typically is found along the Blaschko lines. Progressive hemifacial atrophy, also called Parry-Romberg syndrome, may have minimal cutaneous changes but significant atrophy of the subcutaneous tissue.

Joint contractures and muscle atrophy are present in individuals with linear limb morphea. Tense bullae may be present on the plaques in bullous disease. The regions affected in deep morphea are panniculus, deep dermis, superficial muscle, or fascia, which can result in the patient becoming functionally disabled. The skin is usually normal in eosinophilic fasciitis, a type of deep morphea, as the inflammatory infiltrate involves only the fascia. Moreover, hematologic malignancies may have an association with eosinophilic fasciitis.

In pansclerotic morphea, the patient is markedly debilitated. It may even involve the bony tissue, apart from subcutaneous tissues. Muscle atrophy, non-healing ulcers, and joint contractures are also seen in this dreaded form of the disease. The ulcers may go on to develop squamous cell carcinomas in some cases.

If a patient presents with a combination of two or more subtypes, it may be labeled as mixed variant morphea.

**Diagnosis of Morphea**

The diagnosis of morphea is primarily clinical. Laboratory aids are helpful in many cases to confirm the diagnosis. A definitive diagnosis is difficult in the early stages of the disease.

*Image:* “Panoramic radiograph showing asymmetry with smaller condyle and coronoid process, short roots on affected side when compared to the right side.” by Khan M, Khan M, Negi R, Gupta N – J Clin Exp Dent (2014). License: [CC BY 2.5](https://creativecommons.org/licenses/by/2.5/)
In the **early inflammatory or erythematous stage**, the findings are non-specific and hence the diagnostic difficulty. In this stage, the inflammatory infiltrate is typically lymphohistiocytic and contains fibroblasts. Along with the inflammatory infiltrate, newly synthesized **collagen fibers** may be seen growing into the adipose tissue. As the inflammation subsides and the disease progresses into the **fibrotic stage**, the **adipocytes** are gradually and progressively replaced by dense dermal fibrosis. In this stage, a definite histopathological diagnosis can be made. The histological findings at this stage include **eosinophilic sclerotic collagen in the dermis** with almost no inflammatory infiltrate. The adnexae are eventually substituted with fibrotic changes.

**Laboratory Findings**

**Eosinophilia** is present in 7 – 10% with generalized or linear morphea; more patients with deep morphea have eosinophilia. **Hypergammaglobulinemia** may be seen in conjunction with severe skin disease. Also, acute-phase reactants and CPK may be increased in deep morphea.

**ANA positivity** is present in 23 to 63%. Anti-Scl-70, dsDNA, and ACA antibodies are positive in less than 5%; however, ACA and **rheumatoid factor positivity** were seen in nearly 15%. Some reports indicate a high prevalence of anti-histone antibodies in individuals with linear scleroderma. A high prevalence of **anti-topoisomerase II alpha** (in up to 85%) was also reported in patients with localized scleroderma.

**Skin Biopsy**

The stage of the disease and the depth of involvement decide the histological manifestations of morphea. Most pathological and morphological changes are seen in the transition between the subcutaneous tissue and the **dermis**; hence, the skin sample taken for biopsy should contain **subcutaneous tissue** for an accurate histopathological diagnosis. Skin surface depression results due to the obliteration of adipose tissue.

Histopathological findings alone are usually not sufficient to distinguish between morphea and systemic sclerosis. Thickened dermal collagen bundles with inflammatory infiltrate are features of the early inflammatory stage. Few inflammatory cells, replacement of the **adipocytes**, atrophy of the glands, and extension of collagen fibers between the adipocytes are the typical features seen in the later fibrotic stages.
Infrared Thermography

Although this modality picks up active disease, it has a low specificity for older lesions due to the **atrophy** of subcutaneous fat and skin. However, the use of **laser doppler flowmetry** in such cases can distinguish real active lesions from mere false-positives.

Magnetic Resonance Imaging (MRI)

The true extent of specific lesions may be evaluated best using MRI. **Dermal thickening** and subcutaneous tissue infiltration are associated with an increase in the signal intensity on **short tau inversion recovery (STIR)** images and T1-weighted gadolinium-enhanced images, and hypointensity on unenhanced T1-weighted images. Neuroimaging is advised in patients with linear scleroderma **en coup de sabre** variety, which is associated with complex **partial seizures, cerebral atrophy, intraparenchymal calcifications** and white matter lesions.
Atypical Neuroimaging Manifestations of Linear Scleroderma “en coup de sabre”: (A) Axial T2-weighted image, (B) axial FLAIR image showing new, extensive, patchy areas of T2 prolongation in the white matter of the left cerebellar hemisphere and (C) post contrast axial T1-weighted image demonstrating persistent mild diffuse leptomeningeal enhancement (small arrow) with new areas of nodular parenchymal enhancement (large arrow) in the left cerebellar hemisphere.” by M Allmendinger A, A Ricci J, S Desai N, Viswanadhan N, Rodriguez D - Iran J Child Neurol (2015). License: CC BY 3.0

Differential Diagnoses of Morphea

Usually, the diagnosis of morphea is straight-forward. In some cases, there may exist some ambiguity as outlined below.

**Cutaneous polyarteritis nodosa** may present as lilac reticulate lesions with mild induration. **Sarcoidosis** may also present with morphea-like lesions. Other differentials include macular vascular nevus, **scleroederma of Buschke**, **lipodystropia centrifugalis abdominalis infantilis** (may resemble morphea lesions on the abdomen), and atrophic morpheic plaques resulting from intramuscular injections of vitamin K or subcutaneous corticosteroid injections, and **melorheostosis**.

Therapy of Morphea

There are no causal treatments for morphea. However, there are several treatment options available that should be used in the active stage of the disease for maximum benefit. The treatment options may be grouped under topical drugs, phototherapy and systemic treatments.

Topical Drugs

**Corticosteroids**: Steroids with moderate to high potency may be used during the active phase for a maximum of **three months**. For linear lesions, intralesional steroids may be considered.

**Calcipotriol**: This agent may be used topically, twice daily (0.005% preparation). Its use is advocated in cases where the sclerosis is superficial. It causes softening of lesions due to its antiproliferative actions.

**Tacrolimus** (0.1%): If used topically in the early inflammatory stages, it can produce satisfactory results. It is an **immunosuppressive agent** acting by inhibiting the production of various interleukins (IL).

**Imiquimod**: This agent causes induction of **interferon gamma (IFN-γ)** which, in turn, causes inhibition of transforming growth factor beta (TGF-β). This drug has been shown to reverse erythema, sclerosis and pigmentation; however, further studies are needed to evaluate its benefit.
**Phototherapy**

Induction of **interstitial metalloproteinases** is brought about by ultraviolet light and this forms the rationale behind the use of phototherapy in morphea. Usually, **UVA** is used as it has been shown to be more beneficial than narrow band **UVB**. **UVA1** at a dosage of 20 – 70 J/cm² are used for a total of 20 – 30 treatments.

![Figure 3](image)

**Figure 3**

*Image: “UVA1 phototherapy in localized scleroderma. Macroscopic aspects of LS displaying extensive sclerosis on the chest before (Fig. 3) and after low-dose UVA1 irradiation resulting in a remarkable softening (Fig. 4).” by Breuckmann F, Gambichler T, Altmeyer P, Kreuter A – BMC Dermatol. (2004). License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0)*

However, deep forms of morphea are not amenable to treatment using phototherapy; this is because UVA penetrates only until the dermis. Often, it takes **10 – 20 treatments** for results to become clinically evident. Furthermore, patients may continue to show improvement after stopping the treatment.

**Psoralen plus UVA (PUVA) and bath PUVA** may be of benefit.

**Systemic Treatments**

**Methotrexate** (MTX): Most evidence for treatment benefit exists for this drug. **Cytokines** such as IL-2, IL-4, and IL-6 contribute to the sclerotic changes seen in morphea. MTX inhibits these cytokines; hence, it is presently considered as the **first-line modality** for the treatment of severe forms of **morphea** (linear, generalized, and deep subtypes). It may be administered at a dosage of 15 – 25 mg/week (adults) and 0.3 – 0.4 mg/kg/week (pediatric).

It may be combined with **systemic prednisolone**, which may be tapered off in three months. Nearly 73% of patients continue to be in clinical remission for as long as 2 years if they are on MTX.
**Mycophenolate mofetil** (MMF): This drug is considered in patients who are already on MTX and steroids. The addition of MMF has been shown to be beneficial in these patients. It is an immunosuppressant, which acts by inhibiting the T- and B-cell proliferation.

**Physical therapy** is frequently advised, especially in linear morphea affecting the limbs, and generalized and **pansclerotic morphea**. It may be helpful in minimizing joint contractures.

![Image: “Clinical changes before and after treatment. (a) Note the ivory-white color at the beginning of the treatment. (b) Reduction in color and size at the end of treatment.” by Rodríguez-Castellanos M, Tlacuilo-Parra A, Sánchez-Enríquez S, Vélez-Gómez E, Guevara-Gutiérrez E – Arthritis Res. Ther. (2015). License: CC BY 4.0](image_url)

**Progression and Prognosis of Morphea**

Generally, plaque-like lesions **show improvement** over time. For **3 to 6 years**, the disease remains active in most cases; however, it may even last up to 25 years. **Pigmentation** may persist in around 30% of patients. **Calcinosis** may sometimes complicate linear lesions and may need surgical removal. **Contractures** can lead to restriction of motion of joints and claw-hand. **Facial hemiatrophy**, if present, usually persists; however, frontoparietal scleroderma usually shows resolution over time. The presence of **anti-Ku antibodies** in patients may indicate the rare possibility of progression to systemic sclerosis.

**Review Questions**

The solutions can be found below the references.

1. **Which of the following drug is considered the first-line choice for the treatment of linear morphea?**

   A. Methotrexate
B. Cyclophosphamide
C. Iphosphamide
D. Cyclosporine
E. Etoposide

2. Which of the following recently discovered antibody is present in up to 85% of patients with morphea?

A. Anti-Ku
B. Anti-Rho
C. Anti-La
D. Anti-Topoisomerase I
E. Anti-Topoisomerase II

3. The most common type of morphea is

A. Circumscribed
B. Linear
C. Generalized
D. En coup de sabre
E. Pansclerotic

References


Correct answers: 1A; 2E; 3A