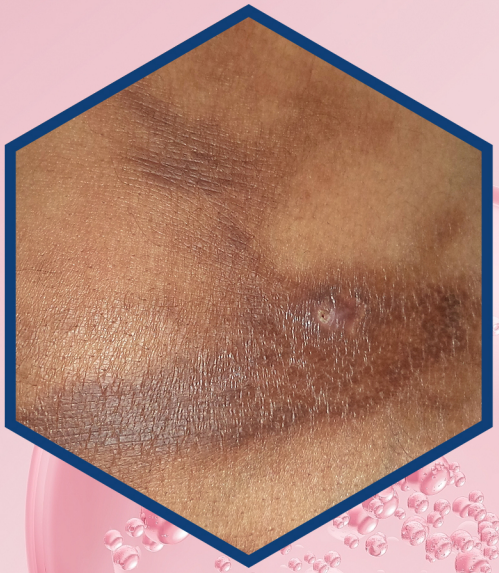
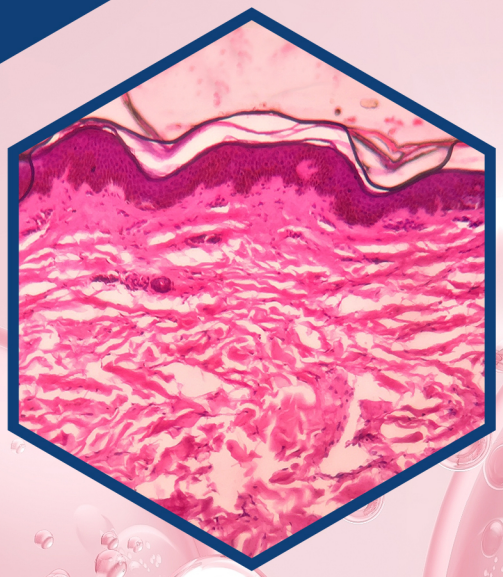
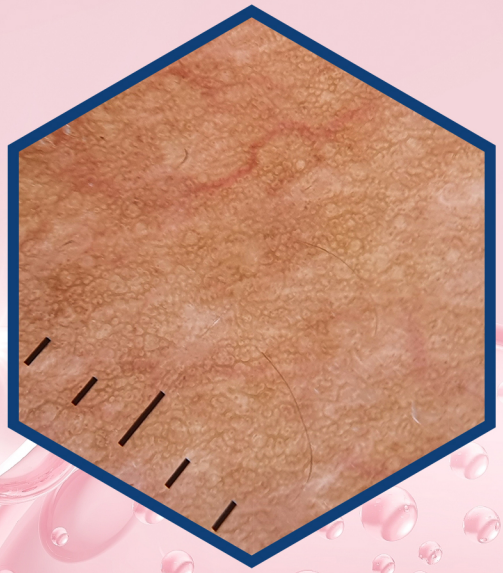
MORPHEA AND RELATED DISORDERS







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Morphea and Related Disorders

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FOREWORD

I feel privileged to write this foreword for the book titled “Morphea and Related Disorders”, edited by Dr. Tasleem Arif unquestionably one of my most exceptionally brilliant students. Dr. Tasleem did his postgraduation in dermatology under my supervision as the head of the Postgraduate Department of Dermatology, Venereology, and Leprosy at Government Medical College Srinagar, Jammu and Kashmir, India. Throughout his post-graduation, Dr. Tasleem manifested a profound interest in Morphea and related disorders, leading him to select these disorders as the focal point of his thesis.

This remarkably comprehensive book efficaciously addresses the missing gaps in our understanding of the range of these disorders.

Focus on the classification of Morphea, a comprehensive account of topics like linear atrophoderma of Moulin, Idiopathic Atrophoderma of Pasini and Pierini, Parry-Romberg syndrome, and Extragenital Lichen sclerosus makes it interesting for the readers thereby transforming it into an invaluable resource book for dermatologists as well as rheumatologists

I congratulate Dr. Tasleem for coming forth with a book on a spectrum of disorders that are still an enigma for the practicing dermatologist.

Iffat Hassan
Government Medical College Srinagar, Jammu and Kashmir, India

PREFACE

The aim of this book titled "Morphea and related disorders" is to give a comprehensive and detailed description of morphea and some of the disorders related to it. Morphea as a subject, has not been addressed adequately as other topics in dermatology like pigmentary dermatoses, bullous disorders, psoriasis, atopic dermatitis, etc. Patients of morphea are mainly managed by dermatologists and rheumatologists though other specialties like pediatrics, internal medicine, gynecology and obstetrics, and orthopedics are also involved in managing such patients. There have been several debates regarding various aspects of morphea especially its terminology, classification, etc. Unfortunately, I couldn't come across a single book, which has exclusively addressed morphea in total. Moreover, there has been plenty of confusion regarding certain conditions like Linear atrophoderma of Moulin, Parry Romberg syndrome, Idiopathic atrophoderma of Pasini and Pierini, Eosinophilic fasciitis and Lichen sclerosus; whether they constitute subtypes of morphea or they are separate disease entities. Thus, there existed an unmet need for a book giving an in-depth understanding of morphea and to give a compendious account of such bewildering conditions. Through this book, I have tried to address such issues.

The inspiration for writing the book on this subject came in 2012 during my dermatology residency programme when I was assigned thesis related to scleroderma. My research was based on both localized (morphea) as well as systemic (systemic sclerosis) forms of scleroderma. Since, the enrollment of my first patient for thesis research, I have been collecting data, figures, etc. as a preparation for this unique book project. So in other words, the drafting for book has been for the last 2-3 years but the actual preparation has been there for a decade. One of the major boosts to my confidence to write on this subject came from New England Journal of medicine (NEJM). Every physician is well aware of the impact and reputation which NEJM has in medical science. My basic research on morphea and systemic sclerosis was published in 2015 in BMC Gastroenterology Journal. That research was reviewed by NEJM in their journal watch and they concluded their journal watch based on findings of our research. That gave me an impetus to write on scleroderma. Since then, I have consistently made research on scleroderma and published around 25 research articles related to it. With such numbers and expertise in scleroderma, I felt probably I can attempt to edit and author a book on morphea. The everlasting prayers of my parents for my success have been a pillar in shaping my career.

Being the solo editor as well as author/co-author of 12 chapters (out of 20 chapters) of this book, the journey of this book for the past 2-3 years has seen lots of ups and downs. One of the major reasons was Covid-19. Apart from that, this era has been full of trials to me and my family. We have faced practically some calamities. At one stage, the circumstances became so difficult that I felt I will not be able to edit or author this book. But massive credit goes to my wife, Dr Marwa Sami, who knew what this book means to me. Despite our strenuous and back-breaking conditions, she kept me motivating and giving me timely reminders to complete this book. I don't feel this book could have been accomplished without her continuous motivation.

There are several features which add uniqueness to this book. Probably, the first book which has been written exclusively on morphea describing it's all parameters ranging from etiology to treatment. There are individual chapters' on topics like linear atrophoderma of Moulin, Parry Romberg syndrome, Idiopathic atrophoderma of Pasini and Pierini, Eosinophilic fasciitis, Lichen sclerosus and Pediatric morphea. Even in the most advanced textbooks of dermatology, we can hardly find any substantial account on such topics. Every chapter begins

with a table having the main substance summarized in the form of chapter synopsis. Learning points in the form of a table are provided at the end of each chapter so that readers can conclude what they have learnt from the chapter. The text of each chapter is enriched with ample number of boxes and tables to enhance the readability. Boxes are provided to summarize the content of a particular section for quick revision. This book will serve as reference book to dermatologists, rheumatologists and physicians ranging from resident to professor as well as practicing physicians. Ultimately, I am hopeful that readers will unveil several horizons related to morphea and its related disorders while reading this book.

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DEDICATION

This book is dedicated to:

……If anyone killed an innocent human, it would be as if he killed all mankind; And if anyone saved a life, it would be as if he saved the life of entire mankind……

(The Glorious Quran; Chapter 5: Verse 32.)

As an editor and author/co-author (of 12 chapters out of 20) of this book, if only one human gets correctly diagnosed and treated as a result of this book, I will feel that I have done my job.

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CHAPTER 1

Introduction and History

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Chapter Synopsis.
• Scleroderma is a spectrum of disorders characterized by thickening and/ or hardening of the skin and fibrosis of the involved tissues. It is divided into localized and systemic forms. The localized form is called morphea and the systemic form is the systemic sclerosis.
• The terms 'Localized scleroderma' and 'morphea' are not synonymous though they have been frequently used interchangeably.
• Morphea is differentiated from systemic sclerosis by the absence of sclerodactyly, vascular symptoms in the form of Raynaud's phenomenon, abnormalities of the nail fold capillaries, and specific internal organ system involvement like gastrointestinal tract, lung, and kidneys.
• Clinically, morphea is characterised by round or oval, irregular or linear plaques that are initially dull red or violaceous or brownish, smooth and indurated/sclerosed but later turn atrophic.
• Previously, morphea was considered a self-limiting disease. Currently, there is ample evidence to suggest that it can have a protracted, relapsing–remitting course. Certain types of morphea if left untreated, can cause significant cosmetic and functional disability.
• Several treatment options are available for morphea which include topicals, phototherapy, and systemic agents.

Keywords: Anti-nuclear antibody, Diffuse cutaneous systemic sclerosis, Fibrosis, Flexion contractures, Generalized localized scleroderma, Idiopathic atrophoderma of Pasini and Pierini, Keloid of Alibert, Lichen sclerosus, Limited cutaneous systemic sclerosis, Linear atrophoderma of Moulin, Localized scleroderma, Methotrexate, Morphea, Parry Romberg syndrome, Raynaud's phenomenon, Sclerosis, Scleroderma, Sclerodactyly, Systemic sclerosis, Systemic scleroderma.

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INTRODUCTION

Morphea is a group of chronic inflammatory diseases which is characterized by sclerosis of the skin as a result of excessive collagen deposition in the dermis and subcutaneous tissue [1]. The word scleroderma has been widely used to account for any condition where there are skin lesions associated with sclerosis of the skin. However, to be precise, the term scleroderma is used to connote a spectrum of disorders, which are characterized by sclerotic skin lesions as their primary disease process and presentation. These include a localized and a systemic form. The localized type which has been inappropriately termed as '*localized scleroderma'*, denotes a group of related disorders characterized by varying degrees of sclerosis, fibrosis and atrophy in the skin and subcutaneous tissues, that can occasionally extend deep into the fascia, muscle, bone and brain. However, the term *localized scleroderma* is not appropriate and a more apt term "Morphea" has been introduced in the literature to account for the confusion created by the term localized scleroderma'. Firstly, under the umbrella term of *localized scleroderma*, other disorders can be incorporated into it whose primary manifestation is not scleroderma; scleroderma is one of their secondary manifestations. There is a long list of such diseases which can have lesions similar to *localized scleroderma,* notable among them are chronic graft-versus-host disease, lipodermatosclerosis, porphyria cutanea tarda, *etc.* Secondly, among the types of morphea, there is an entity called generalized morphea which can be read as '*generalized localized scleroderma*' if we use the term *localized scleroderma* instead of morphea. The term "*generalized localized scleroderma*" will be a source of confusion to the authors as well as to the readers. Hence, this term *localized scleroderma* is discouraged and that is the reason throughout this book the term morphea will be preferred instead of *localized scleroderma*. On the other hand, the systemic form of scleroderma is systemic sclerosis (SSC), which, in addition to sclerotic skin lesions, is characterized by the presence of sclerodactyly, vascular symptoms in the form of Raynaud phenomenon, abnormalities of the nail fold capillaries, and specific internal organ system involvement like gastrointestinal tract, lung, kidneys, *etc.* Though the process of development of sclerosis in the skin may follow similar mechanisms in the two diseases (morphea and systemic sclerosis); these are considered as two distinct entities with different antibody profiles, prognosis and treatment.

SSC has been further classified into two subtypes: limited cutaneous systemic sclerosis (LcSSC) and diffuse cutaneous systemic sclerosis (DcSSC). The former affects the distal extremities leading to sclerodactyly. It is associated with a long preceding history of Raynaud phenomenon, telangiectasias, and gastrointestinal involvement, and conveys a risk of isolated pulmonary artery hypertension. On the contrary, DcSSC is differentiated from LcSSC by proximal (above the knee

and elbow and trunk) involvement of the skin. Though patients with DcSSC also suffer from sclerodactyly, they have a shorter history of onset of the Raynaud phenomenon, telangiectasias, and gastrointestinal involvement. These patients are at increased risk of interstitial lung fibrosis and renal crisis. These two subsets also have contrasting specific antibody profiles [2 - 5].

Morphea is an uncommon, autoimmune disease though relatively benign, characterized by round or oval, irregular or linear plaques that are initially dull red or violaceous or brownish (Fig. **1.1**), smooth and indurated/sclerosed but later turn atrophic. They are histologically characterized by sclerosis of the dermis and/or subcutaneous tissue (Fig. **1.2**) [1]. They are commonly confined to the skin and subcutaneous tissues; less commonly they can extend deeper and involve fat, fascia, muscle, bone and joints and rarely involve the eyes and brain. Like most of the other autoimmune diseases, morphea has been reported as more common in females. Though autoantibodies such as antinuclear antibody (ANA), antihistone, and anti-ssDNA can be found in the patients of morphea; however the SSC-specific autoantibodies such as anticentromere, anti-topoisomerase, and anti-RNA polymerase antibodies are rarely found in these patients. In addition, the organ system involvement that is typical of SSC, viz., gastrointestinal tract involvement, lung involvement and scleroderma renal disease does not occur in morphea. Though, nearly one-fifth to one-quarter of patients with morphea have been reported to experience extracutaneous manifestations but the SSC-specific organ system involvement doesn't occur in morphea. Previously, morphea was considered a self-limiting disease. However in the last decade, many reviews have been published on morphea and there is ample evidence to suggest that a protracted, relapsing–remitting course may be common in morphea. Certain types of morphea if left untreated, can cause significant cosmetic and functional morbidity. Though the disease itself doesn't seem to increase the chance of mortality; however, the disease can lead to significant morbidity as a result of flexion contractures, limb and facial asymmetry, extracutaneous manifestations, eye and CNS involvement; and psychological disability [6 - 9].

The treatment of morphea has been updated. Currently, there are several treatment options available for morphea which include topicals, phototherapy, systemic drugs, and recently biologicals. The choice of agent for treatment will depend upon several factors like the type of the morphea, the extent of the disease, the activity of the disease, the presence of deformities, *etc.* In the treatment of severe morphea, methotrexate in combination with systemic steroids and ultraviolet A1 light phototherapy has been the most effective treatment option [7].

CHAPTER 2

Classification

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Chapter Synopsis.
• Morphea comprises a group of distinct conditions that primarily involve the skin and subcutaneous tissues.
• Involvement of internal organ systems like lungs, gastrointestinal tract, kidneys and heart is usually absent in morphea.
• There are several types of morphea. Each type has a different clinical presentation and level of tissue involvement. However, the common denominator among the types of morphea is the presence of skin thickening (induration) with an increased amount of collagen in the lesion.
• Due to the broad clinical spectrum, several attempts have been made to classify morphea. However, to date no universally accepted classification system has been proposed which can account for all the heterogeneity seen in the clinical spectrum of this disease.
• Conditions like linear atrophoderma of Moulin (LAM), Idiopathic Atrophoderma of Pasini and Pierini (IAPP), Lichen sclerosus (LS), Eosinophilic fasciitis (EF) and Parry-Romberg syndrome (PRS) are related to morphea. Their relation with the morphea has been a topic of debate. These conditions need to be discussed thoroughly.

Keywords: Bullous morphea, Circumscribed morphea, Deep morphea, Disabling pansclerotic morphea, En coup de sabre, Eosinophilic fasciitis, Guttate morphea, Generalized morphea, Idiopathic atrophoderma of Pasini and Pierini, Keloidal morphea, Lichen sclerosus, Limited plaque morphea, Linear morphea, Mixed morphea, Morphea en plaque, Nodular morphea, Parry-Romberg syndrome, Plaque morphea, Progressive hemifacial atrophy, Subcutaneous morphea.

INTRODUCTION

Morphea, inappropriately also called as, localized scleroderma, comprises a group of distinct conditions that primarily involve the skin and subcutaneous tissues.

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Lesions clinically range from very small plaques limited to the skin only, to diseases that have the potential to cause significant physiological and aesthetic deformities, with a wide range of extracutaneous manifestations. Based on the specific subtype and localization, structures near the skin that include fascia, muscles, fat, bones and joints can also get affected. Involvement of internal organ systems like the lungs, gastrointestinal tract, kidneys and the heart is usually absent in morphea. Morphea should be viewed as a distinct entity from systemic sclerosis because of its almost exclusive cutaneous involvement and absence of visceral organ involvement except in rare instances. The differences between morphea and systemic sclerosis have already been discussed in chapter 1.

There are several types of morphea. Each type has a different clinical presentation and level of tissue involvement. However, the common denominator among the types of morphea is the presence of skin thickening (Induration) with an increased amount of collagen in the indurated lesion at any stage of disease evolution [1, 2]. Due to its broad clinical spectrum, several different attempts have been made to classify morphea. However, to date, no universally accepted classification system has been proposed which can account for all the heterogeneity seen in the clinical spectrum of morphea. Despite several classification systems which have categorized the disease, there are still controversies among authors as to which conditions should be included within the spectrum of morphea. This is particularly relevant with the three related atrophic variants *viz.*, linear atrophoderma of Moulin (LAM), Idiopathic Atrophoderma of Pasini and Pierini (IAPP) and Parry-Romberg syndrome (PRS). A similar fate is faced by Eosinophilic fasciitis and Lichen sclerosus (LS). There has been controversy regarding bullous morphea and deep morphea. Whether the two should be kept as separate subtypes or not. Another headache to the system of classification is what constitutes generalized morphea as it has been defined in different ways by different authors. In this chapter, the authors will describe the various classification systems that have been suggested for morphea. However, in view of the lack of a single universally accepted classification system of morphea, the author has suggested a simple classification which can avoid most of the controversies by taking some suggestions from the already published classification systems. That classification system will be followed throughout this book.

CLASSIFICATION BY O' LEARY *ET AL*.

The earliest attempt to classify scleroderma was made by O'Leary and Nomland. They published their clinical study of 103 cases of scleroderma in 1930. They broadly classified scleroderma into two types: 1) Generalized forms of

scleroderma (associated with a varying degree of systemic involvement), 2) Localized forms of scleroderma, usually without systemic manifestations. Localized scleroderma is further divided into two types Table (**2.1**). A) Morphea and B) Other types [3, 4]. The classification of localized scleroderma is described as follows:

Table 2.1. Classification of localized scleroderma by O' leary *et al.*

Localized Scleroderma	
I. Morphea	**II. Other types**
Localized	Linear
Generalized	Localized forms associated with hemiatrophy including en coup de sabre

Morphea

Localized

According to them, a localized variant of morphea comprised of cutaneous patches having a variable size of 2 to 20 cm. These patches were having varied clinical presentations ranging from the classically sclerosed, carnauba wax-colored plaque to hyperpigmented atrophic areas present over the trunk and extremities. These lesions have signs of inflammation and later involute of their own.

Generalized

In generalized morphea, numerous plaques are present which at times may involve the entire trunk, though they didn't give the definite criteria to diagnose generalized morphea. These plaques have pigmentation, atrophy and sclerosis depending upon the stage of evolution of the disease. The prognosis of this type was considered good.

Other Types

Linear

In this type, there are linear bands or streaks of waxy/sclerosed skin involving a limb. It may or may not be associated with plaque morphea.

Localized Forms Associated with Hemiatrophy

This subtype may present with a small indurated plaque on the forehead or scalp and can include linear morphea en coup de sabre. There can be atrophy of bone or muscle of the face in collaboration with the involvement of upper or lower limbs or both. Though there is hardly any risk of mortality, there is variable morbidity

CHAPTER 3

Epidemiology

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Chapter Synopsis.
• Knowledge of the epidemiological aspects of any disease is of paramount importance in order to acquire a better understanding of the concerned disease condition.
• There is limited knowledge available in the literature on the detailed epidemiology of morphea, despite continuous research efforts.
• Rarity of morphea can be understood by its very low incidence rate reported in the literature, ranging from 0.3 to 3 cases per 100,000 population.
• Morphea can present at any age. However, it has been reported to have bimodal age of onset, with two peaks.
• The mean age of onset of morphea in the pediatric population is between 6-9 years. On the contrary, the mean age of occurrence in adult population has been reported to be between 20 and 40 years of age.
• There is a need to undertake large-scale population studies in order to get a detailed understanding of the epidemiology of morphea.

Keywords: Adult morphea, Autoimmune, Bimodal age, Caucasian race, Circumscribed morphea, Collagen vascular disease, Co-morbidity, Congenital morphea, Epidemiology, Female preponderance, Generalized morphea, Incidence and prevalence, Linear morphea, Localized scleroderma, Morbidity, Morphea, Morphea profunda, Pansclerotic morphea, Pediatric morphea, Plaque morphea, Psychological and physical disability.

INTRODUCTION

Morphea is a rare localized connective tissue (collagen vascular) disease presenting with different clinical forms. A detailed description of this disease,

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especially its epidemiology, is missing in the literature, mainly because of the rarity of this dermatoses. So far, very few studies have been dedicated to exclusively describe various epidemiological aspects of this rare skin condition. In this chapter, an attempt has been made to give a brief overview of the epidemiology of morphea, after a thorough review of the related literature. There is an absolute need to conduct large-scale population-based studies, in order to further understand the details of the epidemiological aspects of this rare dermatological condition.

MAGNITUDE OF MORPHEA AS PUBLIC HEALTH PROBLEM

Being a rare skin condition, morphea is expected to have less incidence. But at the same time, owing to chronicity, it has a relatively higher prevalence. Just to refresh the existing knowledge, it is appropriate to mention here that the incidence is the number of new cases occurring in a population over a period of time and the prevalence is the number of old and new cases present in the population at a point of time.

The rarity of morphea is reflected by its very less incidence rate reported in the literature, ranging from 0.3 to 3 cases per 100,000 population, with a slight variation between different studies [1 - 6].

In one of the best analytical studies on this topic to date from Olmsted County, Minnesota, wherein an attempt was made to register all patients with morphea from 1960 to 1993, the annual incidence rate of 27 per million (2.7 per 100,000) population was reported [7].

A general look at the literature shows that the overall incidence of morphea appears to have been increasing over time, most likely, because of better awareness among the patients who report it earlier and also better/ advanced diagnostic tools available now, than it was previously [8]. These aspects are summarized in Table **3.1**.

AGE OF INVOLVEMENT

Although morphea can present at any age, it has been reported to have a bimodal age of onset, with two peaks. The peak age for onset in the pediatric population is 6-11 years [4, 9 - 11], and that for adults, it is 44-47 years [4, 10, 11].

Although morphea has been described in infants and even neonates, the mean age of onset of the disease in the pediatric population is between 6-9 years [9, 12 - 15]. In children, morphea occurs at least 10 times more often than systemic sclerosis [16].

Table 3.1. Magnitude of morphea as a public health problem [1-8].

Incidence and Prevalence	The incidence of morphea is very less owing to the rarity of the disease condition, but because of its chronic nature, it has a considerable prevalence rate.
Average incidence rate	The average incidence rate ranges from 0.3-3 per 100,000 population, with some inter-study variations.
Annual incidence rate	One of the best analytical studies on this topic to date from Olmsted County, Minnesota, reported an annual incidence rate of 2.7 per 100,000 population.
Overall incidence	The overall incidence of morphea has increased with time, attributable to better patient awareness who report it earlier and due to the availability of advanced diagnostic tools now.

The mean age of occurrence in the adult population is between 20 and 40 years of age, with a slight variation between different studies [17 - 19]. Similarly, the age group of 20-29 years was most commonly affected in a study from India [5, 20].

Congenital forms, with a presentation at birth, have also been reported in the literature [15, 21, 22].

As a general statement, it can be stated that the prevalence of morphea increases with age [8]. The age-related aspects of morphea have been mentioned in (Box **3.1**).

Box 3.1: Age of involvement in morphea [4, 8, 10, 11, 15, 16, 21, 22].
• Morphea has bimodal age of onset. The peak age for onset in the pediatric population is 6-11 years while in adults, it is 44-47 years.
• In children, morphea occurs at least 10 times more often than systemic sclerosis.
• Cases of congenital morphea have also been reported.
• As a general rule, the prevalence of morphea increases with age.

CLINICAL ASPECTS OF MORPHEA VERSUS AGE GROUP

Although no specific age group is more susceptible or immune to the development of a particular clinical subtype of morphea, there is enough evidence in the literature that some clinical subtypes of morphea are more common in adults than in the pediatric age group and vice versa [23].

Circumscribed (plaque) morphea, which is the most common subtype of morphea, has been found to usually affect adults between 40 and 50 years of age [4, 6, 24]. In the Olmsted County study, 56% of patients had plaque-type of morphea [7].

CHAPTER 4

Predisposing Factors

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Chapter Synopsis.
• Morphea is a chronic inflammatory and fibrotic skin condition that classically presents as hyperpigmented sclerotic plaque with lilac-colored borders.
• The exact etiology of morphea is not known but many factors have been proposed to initiate the fibrotic cascade.
• Both genetic and environmental factors like infection, trauma, radiation, drugs and chemicals, vaccination, *etc.* underlie the pathogenesis of morphea.
• Several types of trauma have been implicated in the causation of morphea like blunt trauma, mechanical compression, and friction, penetrating trauma, trauma due to radiation, *etc*.
• The presence of autoantibodies and a high prevalence of personal and familial autoimmune diseases point to the autoimmune nature of the disease.

Keywords: ANA, Autoimmunity, Chemicals, Drugs, Endocrine dysfunction, Etiology, Fibrosis, HLA, Infection, Localized scleroderma, Microchimerism, Morphea, Predisposing factors, Pregnancy, Radiation, Risk factors, Thyroid disorder, Trauma, Triggers, Vaccination.

INTRODUCTION

Morphea, often inappropriately referred to as localized scleroderma, is an inflammatory skin condition affecting the dermis and subcutaneous tissue leading to varying degrees of sclerosis and atrophy. Unlike systemic sclerosis, internal organ fibrosis is not seen in morphea but cutaneous sclerosis, joint contractures, and restricted mobility have a substantial impact on the quality of life of affected

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patients. The pathophysiology of morphea involves increased collagen deposition and vascular changes in a background of autoimmunity [1]. A wide range of factors (Fig. **4.1**) may act as triggering events in the causation of morphea (Box **4.1**, **4.2**). This chapter will discuss these predisposing factors in detail.

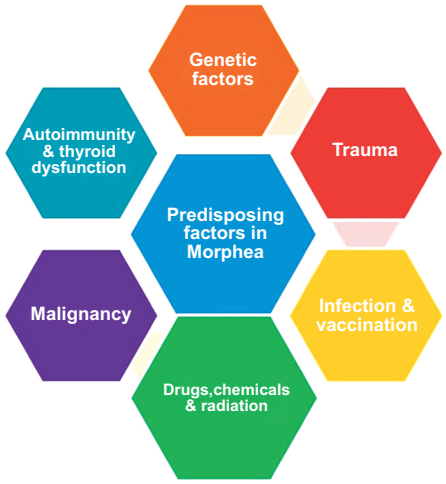

Fig. (4.1). Various predisposing factors implicated in the development of morphea.

GENETIC FACTORS

The role of genetics in morphea is suggested by HLA predisposition and familial occurrence in many cases [2 - 4] (Box **4.1**). Jacob *et al.* reported that certain HLA class I alleles like HLA DRB1*04:04 and HLA-B*37 confer increased susceptibility, particularly in linear and generalised subtypes [2]. X-chromosome inactivation has also been demonstrated in the pathogenesis of morphea [5]. The blaschkoid involvement in linear morphea indicates regional genetic susceptibility which can be attributed to cutaneous mosaicism [6, 7]. The role of micro RNAs (miRNAs) in the pathogenesis of morphea is emerging. Skin and serum of patients with morphea have been found to have downregulated antifibrotic miRNA-7 and miRNa-196a, which contributes to the overexpression of type I collagen [8, 9].

Box 4.1: Genetic factors involved in morphea.
HLA class I alleles HLA DRB1*04:04 and HLA-B*37
Downregulation of antifibrotic miRNA-7 and miRNa-196a
X-chromosome inactivation
Cutaneous mosaicism in linear morphea

EXTERNAL FACTORS

A variety of external factors and stimuli act as triggering factors in patients genetically predisposed to the development of morphea (Box **4.2**).

Box 4.2: Predisposing factors causing morphea.
Trauma
Infection
Vaccination
Drugs
Chemicals
Malignancy
Thyroid disorders
Autoimmunity
Radiation
Pregnancy

Trauma

Morphea has been reported following an array of traumatic events including physical injury, mechanical compression and friction, *etc*., (Box **4.3**).

Box 4.3: Types of trauma implicated in the development of morphea.
Blunt trauma
Penetrating trauma
Mechanical compression (slim belt, *etc.*)
Chronic friction due to clothing (brassiere, waist band, *etc.*)
Injection site trauma
Trauma due to waxing of hair
Surgical trauma
Radiation trauma

Blunt trauma, injection site trauma, following waxing for excessive hair, and use of slim belt have been reported as triggering factors in different reports [1, 10 - 17]. A survey of the Morphea in Adults and Children (MAC) cohort studied the role of skin trauma in morphea. In this survey, morphea was reported to occur as an isomorphic phenomenon and also as an isotopic response following surgery, penetrating trauma, injection, herpes zoster, radiation and extreme exercise.

CHAPTER 5

Pathogenesis

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Chapter Synopsis.
• Morphea is a disease of variable clinical presentation characterized by an increase in collagen deposition and extracellular matrix production.
• It is believed to be an autoimmune disease triggered by an extraneous agent in genetically susceptible individuals.
• Patients of morphea have an increased susceptibility to other autoimmune and rheumatological diseases. HLA-B*37 and HLA-DRB1*04:04 have been linked to increased susceptibility to morphea.
• The likely role of mosaicism is proposed in linear morphea which follows the lines of Blaschko.
• Epigenetic factors such as DNA methylation and histone acetylation may act as a link between genetic and extraneous factors in disease pathogenesis.
• Morphea is associated with several autoantibodies, but their role in pathogenesis and disease activity is not as specific as in SSC.
• Trauma, radiation, infections, and drugs may trigger morphea in susceptible individuals.
• Vascular endothelial injury is one of the earliest and most important steps in the pathogenesis of morphea.
• Keratinocytes produce several factors that lead to dermal fibrosis. Epidermal-dermal signalling pathways assist in the same.
• The early phase of inflammation is mediated by Th1 cytokines followed by the phase of induction of fibrosis characterized by Th17 cytokines. The final phase of sclerosis is mediated by Th2 cytokines.
• Myofibroblasts are the cells primarily responsible for fibrosis. The process of fibrosis goes on unchecked in morphea under the influence of several growth factors and activating signals.
• Morphea and SSC share common pathogenic features. However, there are differences in the triggering factors, genetic susceptibility, autoantibodies and cytokine levels.

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Keywords: Autoantibodies, Autoimmune disease, Borrelia, Chemokines, Chimerism, Cytokines, Cytomegalovirus, Dendritic cell, Endothelial injury, Epigenetics, Extracellular matrix, Fibroblasts, Genetic susceptibility, Human leucocyte antigen, Insulin-like growth factor, Interleukins, Matrix metalloproteinase, Mesenchyme, Micro-RNA, Mosaicism, Positional identity, Radiation, Sclerosis, T-helper cell, Transforming growth factor-β, Trauma, Tumor necrosis factor-α.

INTRODUCTION

Morphea is a disease that shows wide variation in clinical presentation. The exact etiopathogenesis of the disease is still uncertain and is largely extrapolated from systemic sclerosis (SSC) as both diseases show increased collagen deposition and an increase in extracellular matrix production. The etiological and susceptibility factors of morphea have been discussed in the previous chapter. The discussion in this chapter shall be focussed on the pathogenesis of morphea. It is believed that the occurrence of morphea requires an external environmental insult in a genetically predisposed individual [1]. This insult leads to vascular changes and the release of several pro-inflammatory and pro-fibrotic cytokines involving epidermal signalling and mesenchymal drivers which ultimately produce skin sclerosis [2]. While the clinical features may show variability, the various subsets of morphea probably share inflammatory and fibrotic molecular pathogenetic mechanisms [2]. A greater understanding of disease pathogenesis and its subsets is important for insights into clinical features and targeted therapeutic solutions.

The pathogenesis of morphea involves the role of genetic factors, epigenetic factors, vascular factors, autoantibodies, and inflammatory cytokines. The role of both innate and adaptive immunity has been postulated. Environmental factors such as trauma, radiation, infections (*e.g.* Borrelia, Cytomegalovirus, *etc.*), and drugs are possible triggers for the occurrence of the disease. All these factors are discussed individually in the upcoming sections of this chapter. Fig. (**5.1**) describes the basic steps in the pathogenesis of morphea in the form of a flowchart.

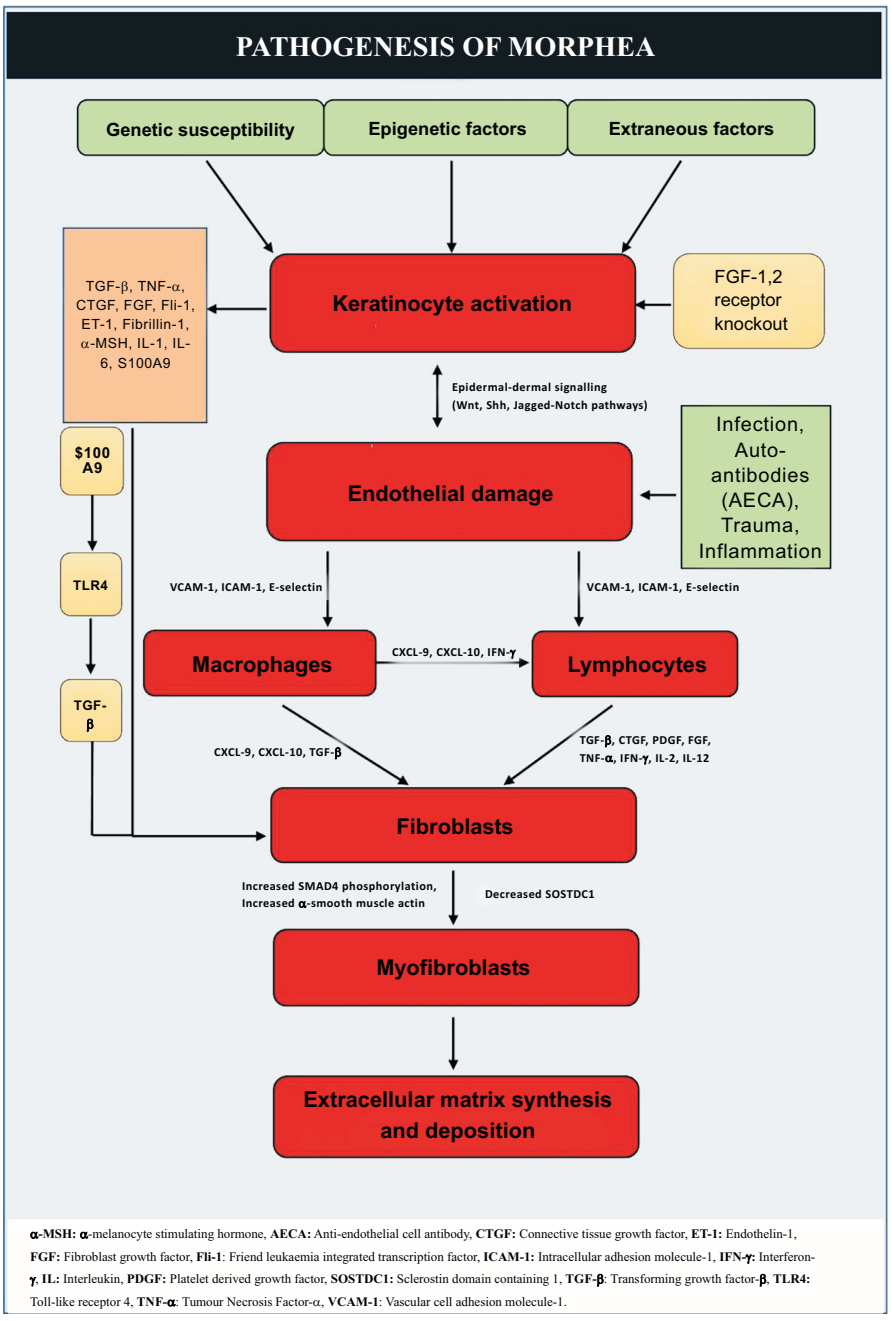

Fig. (5.1). The basic outline of the pathogenesis of morphea.

CHAPTER 6

Histopathology

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Chapter Synopsis.
• This chapter presents the best available knowledge on histopathological features of morphea that was retrieved from the earliest to the latest literature.
• The chapter begins with a brief introduction about the rationale for obtaining histopathological sample in morphea as well as the correct techniques for tissue sampling.
• It then presents histopathological findings that should be assessed and noted on the histopathological report.
• Individual features of different histologic variants of morphea and clinical variants of morphea that have special histopathological features are discussed.
• The chapter concludes with a detailed list of differential diagnoses that may resemble morphea histopathologically.

Keywords: Collagen, Collagen anomalies, Dermatopathology, Diagnosis, En coup de sabre, Fibrosis, Inflammation, Linear morphea, Line sign, Nodular morphea, Morphea, Morphea profunda, Mucin, Panniculitis, Pathology, Scleroderma, Sclerosing panniculitis, Sclerosis, Square sign, Superficial morphea.

INTRODUCTION

Morphea, or localized scleroderma, is a primary sclerosing skin disease, which may occasionally involve fat tissue, muscle, and fascia [1]. Skin biopsy is an adjunct to clinical examination in the work-up of morphea. Histopathological examination reveals depth of involvement and severity of inflammation [2]. These findings may assist clinicians in the choice of treatment modality [3]. In the light of the recent scientific reports, a low threshold for histopathological confirmation is recommended to better identify various clinicopathologic variants of morphea and related disorders [3].

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In clinical practice, four millimeter punch biopsy is the most commonly performed biopsy technique [2]. However, as several subtypes of morphea involve primarily subcutis or fascia, incisional or excisional biopsies of sufficient depth are indicated [4, 5].

In inflammatory lesions, specimens should be obtained at the erythematous rim; while in lesions without clinically overt inflammation, biopsy should be performed at the center of the lesion. The biopsy site should be noted for better clinicopathologic correlation [2].

REPORTING OF THE HISTOPATHOLOGICAL FINDINGS

Hematoxylin and Eosin Stain (H&E)

Hematoxylin and eosin (H&E) stained specimens are assessed for severity and histologic location of sclerosis and inflammation [2].

Severity of fibrosis is graded as mild (grade 1), moderate (grade 2) and severe (grade 3). To determine the histological grade of fibrosis, each of the four dermal layers (papillary dermis, and the superficial, median and deep reticular dermis) are assessed semi-quantitatively (none, light, moderate, and extensive) for fibrosis. Specimens with no fibrosis in papillary dermis and light fibrosis in superficial, or median or deep reticular dermis are reported as grade 1. Grade 3 fibrosis has two definitions: either severe fibrosis in deep and median reticular dermis irrespective of the extent of fibrosis involving papillary and superficial reticular dermis, or severe fibrosis in deep reticular layer along with moderate fibrosis in the remaining three dermal layers. Finally, grade 2 fibrosis is attributed to all cases, which do not have features of grade 1 or 3 fibrosis [6]. Histological grades of fibrosis are summarized in Table **6.1**.

Table 6.1. Histological grades of fibrosis.

Grade of Fibrosis	Papillary Dermis	Superficial Reticular Dermis	Median Reticular Dermis	Deep Reticular Dermis
Mild (grade 1)	None	None/light	None/ light	None/light
Moderate (grade 2)	Others	Others	Others	Others
Severe (grade 3)	Any	Any	Severe	Severe
	Moderate	Moderate	Moderate	Severe

Histologic location of sclerosis is assessed to determine the pattern of sclerosis. Fibrosis limited to papillary and superficial reticular dermis is defined as a top-heavy pattern, while fibrosis involving exclusively deep reticular dermis and subcutis corresponds to the bottom-heavy pattern. The full thickness pattern is characterized by sclerosis throughout the dermis [2].

Localization of inflammatory infiltrate is defined as perivascular and periadnexal if aggregates of more than 10 cells are observed around capillaries and adnexal structures, respectively. Other localizations include interstitial, dermal subcutaneous junction, septal or lobular parts of subcutaneous tissue. Severity of inflammation is graded as mild, moderate and severe. Mild and moderate inflammation is defined as the presence of a mild perivascular infiltrate and dense perivascular infiltrate, respectively. Severe inflammation is noted when the inflammatory infiltrate is as extensive as to form round, nodular collections located in perivascular, periadnexal, and/or interstitial space or at the dermal subcutaneous junction. Table **6.2** summarizes degrees of inflammation.

Table 6.2. Severity of inflammation.

Mild	Mild Perivascular Infiltrate
Moderate	Dense perivascular infiltrate
Severe	Dense infiltrate forming round, nodular collections located in perivascular, periadnexal, and/or interstitial space or at the dermal subcutaneous junction

Cell types (lymphocytes, plasma cells, and eosinophils *etc.*) observed in the inflammatory infiltrate should be reported. Of note, a cell type is documented only if more than 5 cells are observed at low power examination [2].

Special Stains

Mucin deposition is not considered as a typical feature of morphea, however it may be present. Results of the scientific studies are conflicting. On H&E stained sections, Jindal *et al.* reported the presence of interstitial mucin in 31 of 40 cases of morphea, while Yang *et al.* reported a sensitivity of 1% [7, 8]. Alcian blue stain and colloidal iron are special stains that are employed to detect the presence of mucin that is not readily seen in routine stains [9, 10]. Deposition of fair or slight amounts of mucin in deep dermis and interlobular septa was reported as a consistent finding in specimens of morphea and systemic scleroderma by Rongioletti *et al.* [10]. Mucin deposition in lower dermis and subcutis was described in cases of morphea profunda [9, 11]. Exceptionally, abundant mucin deposition in reticular dermis was reported in cases of nodular morphea [12, 13].

CHAPTER 7

Clinical Presentation

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Chapter Synopsis.
• All types of morphea usually begin with inflammatory-based processes followed by fibrotic-based stages.
• Circumscribed morphea is the most common clinical presentation of morphea and is subdivided into two subgroups (superficial and deep) based on level of fibrosis.
• Linear morphea is usually seen in children. It is characterized by band-like cutaneous sclerosis that can mostly result in depressed lesions.
• The linear morphea can involve frontoparietal area of the forehead and scalp, which is known as en coup de sabre due to its sword strike-like appearance. The deep involvement of en coup de sabre may imply underlying neurological, ophthalmological, and auditory complications.
• Pansclerotic morphea is a rare presentation of morphea that has been described as an extensive, progressive, full-thickness involvement of the skin including subcutis, muscle, fascia and bone. Pansclerotic morphea predominantly occurs in children and has rapid progression with an aggressive course.
• Generalized morphea has been defined in several ways. One of the widely accepted definition is that it is characterized by plaques of circumscribed morphea (at least four lesions larger than 3 cm) that involve more than two out of seven different anatomical regions (head/neck, two upper extremities, two lower extremities, anterior and posterior sites of trunk).
• Guttate, keloidal/nodal, and bullous morphea are rare forms of morphea.

Keywords: Circumscribed morphea, En coup de sabre, Guttate morphea, Generalized morphea, Ivory-colored, Keloidal/nodular morphea, Linear morphea, Lilac-colored, Lichen sclerosus, Mixed morphea, Pansclerotic morphea, Pseudo-cellulite appearance, Sword strike-like appearance.

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INTRODUCTION

Morphea is characterized by isolated patches/plaques of sclerosed skin. Morphea mostly affects the dermis, but it can also affect subcutaneous fat tissues and in rare cases extend to deeper tissues including fascia, muscle, and bones. There have been several classification systems of morphea and with time newer classifications are evolving [1]. In Chapter 2, various classification systems of morphea in a chronological way have been discussed and their merits and limitations have been highlighted. The list of few chronological classifications of morphea are presented in Fig. (**7.1**) [1, 3]. Circumscribed morphea, generalized morphea and linear morphea are the most common types of morphea while mixed type and keloidal/nodular types are less common clinical variants [2]. A simplified and holistic classification for morphea and 'morphea related disorders' has been presented in (Box **2.1**) (same as in chapter 2). This classification system will be followed throughout this chapter. The reason to follow this simplified and holistic classification in this book has been elaborated in depth in chapter 2. Readers are encouraged to refer to chapter 2 for further details.

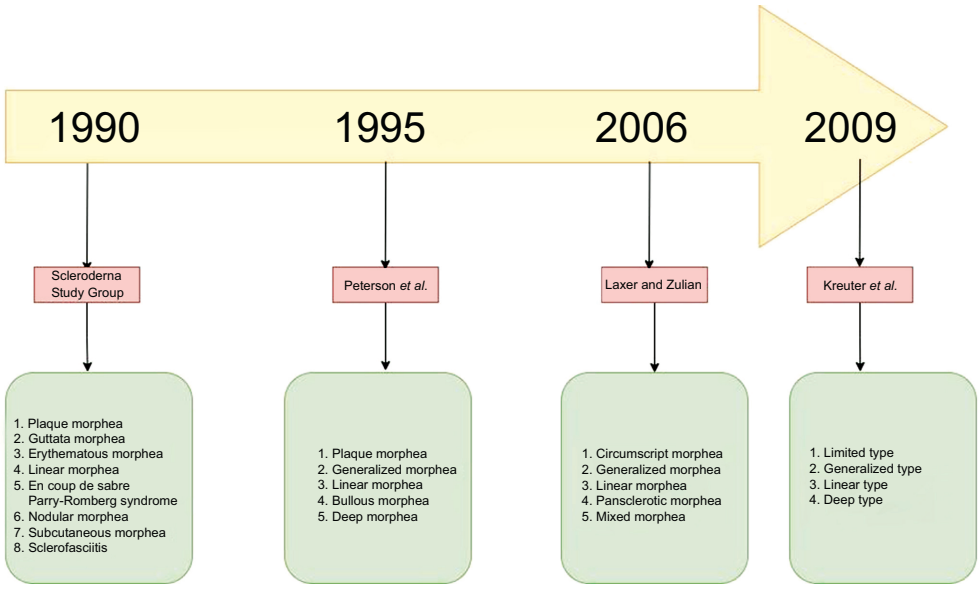

Fig. (7.1). Some chronological classifications of morphea.

Box 2.1. Holistic classification of morphea and related disorders.
I. Morphea
Circumscribed Morphea • Superficial variant • Deep variant **Linear Morphea** • Linear morphea involving trunk/ limbs • En coup de sabre **Generalized morphea.** **Pansclerotic morphea** **Mixed morphea** **Other types:** • Guttate • Bullous • Keloidal/nodular
II. Morphea-Related disorders
Idiopathic atrophoderma of Pasini and Pierini **Lichen sclerosus** **Parry Romberg Syndrome.** **Eosinophilic fasciitis.** **Linear atrophoderma of Moulin**

Morphea usually begins with inflammatory-based processes (Fig. **7.2**) followed by fibrotic-based stages resulting in indurated plaques (Fig. **7.3**). In the late stage, hyper-hypo pigmentation can be seen while lesions undergo atrophy (Fig. **7.4**). Levels of fibrosis in morphea may include subcutaneous fat tissue, muscle, fascia, bone, and even parts of the brain. However, skin softens in the majority of cases of morphea in months to years. In some cases, mild itching or pain can be seen at the site of the disease. Itching may also be related to the dryness of the skin. Morphea may present variably with respect to the type of lesion, color, number and spatial localization. The various clinical possibilities in the evolution of morphea are listed in (Table **7.1**).

Morphea can be seen as Wolf's isotopic response at the site of healed herpes zoster infection [4]. This type of involvement is rare and may imply underlying immunosuppression [5, 6]. Morphea can occur prior to or after the presence of granuloma annulare and autoimmune conditions such as lupus erythematosus, relapsing polychondritis, vitiligo, alopecia areata, and so on [7 - 10]. In addition, coexisting lichen sclerosus et atrophicus may be observed with morphea [11, 12]. Therefore, dermatologic examination of morphea should include signs and symptoms of such cutaneous diseases.

CHAPTER 8

Differential Diagnosis

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Chapter Synopsis.
• Morphea is the localized form of scleroderma characterized by the thickening of the skin and sometimes the underlying subcutaneous tissue.
• Morphea has diverse presentations in different subtypes, in different age groups, and in different stages.
• The differential diagnosis of morphea encompasses a wide spectrum from systemic sclerosis at one end to drug-induced morphea at the other end.
• Detailed history and examination together with histopathology and nail fold capillaroscopy help to differentiate morphea from other close mimics.
• The presence of Raynaud's phenomenon, sclerodactyly, calcinosis cutis, mat-like telangiectasia and autoantibody levels are the features that differentiate systemic sclerosis from morphea.
• Scleromyxedema is characterized by the deposition of mucin mostly in the skin and sometimes in the internal organs. Face, arms, and hands are mostly affected. In contrast to morphea, skin can be pinched and moved over the subcutis as mucin deposition is mainly in the papillary dermis.
• Scleredema is a fibro mucinous connective-tissue disorder associated with antecedent infections, diabetes or plasma cell dyscrasias. It is characterized clinically by woody hard induration of the skin. As compared to morphea, hands, and feet are typically spared in scleredema.

Keywords: Atrophic stage, Autoantibody, Calcinosis cutis, Circumscribed morphea, Comedo-like openings, Differential diagnosis of morphea, Drug-induced morphea, Early inflammatory stage, Generalized morphea, Interstitial mycosis fungoides, Linear morphea, Lilac ring, Morphea, Nail fold capillaroscopy, Neutrophilic panniculitis, Raynaud's phenomenon, Sclerodactyly, Sclerosis, Sclerotic stage, Systemic sclerosis.

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INTRODUCTION

Morphea is a disorder limited to the skin and subcutaneous tissue, sometimes extending to the deeper underlying structures. It is more prevalent in children and young adults. Clinically, morphea is characterized by one or more circumscribed oval asymmetric plaques. Usually, the lesions are present on the trunk, sometimes, on the limbs. Classically, there is no sclerodactyly, fingers are spared. Linear forms are more common on the limbs. Three different stages of the disease have been delineated.

In the inflammatory phase, the plaque is surrounded by a “lilac ring”. In the sclerotic stage, central sclerosis develops which heals with a hypo- or hyperpigmented atrophic stage. Morphea is a clinical diagnosis and there are no definite markers for proper diagnosis, disease activity and prognosis. As morphea encompasses a wide range of clinical phenotypes and has a different presentation in its different stages, it has to be differentiated from a variety of other diagnoses that it mimics.

DIFFERENTIAL DIAGNOSIS OF GENERALISED MORPHEA

Systemic Sclerosis

Generalized morphea may be difficult to differentiate from systemic sclerosis [1]. However, progression to systemic sclerosis is uncommon. Delay in the diagnosis of systemic sclerosis can lead to progressive systemic involvement and can have bad prognostic implications. Pansclerotic and generalized morphea present with diffuse and widespread sclerosis as seen in systemic sclerosis but spares the fingers and toes. Again one has to remember that morphea often called localized scleroderma and systemic sclerosis (systemic scleroderma) is different diseases, and it does not progress to systemic sclerosis over time. In such patients, where there is confusion, they should be evaluated for the presence of Raynaud's phenomenon, sclerodactyly, calcinosis cutis, telangiectasia and auto-antibody levels. Therefore, in systemic sclerosis, there is the presence of these differentiating points (Box **8.1**).

Box 8.1: Salient features of systemic sclerosis differentiating it from morphea.
Internal organ involvement.
Acrosclerosis/sclerodactyly
Raynaud’s phenomenon
Nail Fold Capillaroscopic Changes
Antibodies: Anti-centromere, Scl-70, and RNA polymerase-III

DIFFERENTIAL DIAGNOSIS OF CIRCUMSCRIBED MORPHEA

Clinical presentations of circumscribed morphea vary in the different stages- viz., early, sclerotic and atrophic stage, so do the differential diagnosis (Table **8.1**).

Table 8.1. Differential diagnosis of circumscribed morphea.

• Early Lesions	• Sclerodermoid/Atrophic Lesions
Acquired Port wine stain	Idiopathic Atrophoderma of Pasini and Pierini
Granuloma annulare	Lipodermatosclerosis
Mycosis fungoides (interstitial type)	Morpheaform dermatofibrosarcoma protuberans
Early Sweet syndrome	Radiation fibrosis
Interstitial and granulomatous dermatitis	Reflex sympathetic dystrophy
Erythema migrans	Scleromyxedema
Erythema nodosum migrans	Cheiroarthropathy due to diabetes mellitus
Annular lichenoid dermatitis of youth	Carcinoid syndrome
Hypertrophic scars or keloids	Porphyria cutanea tarda (PCT)
Connective tissue nevi	Nephrogenic systemic fibrosis (NSF)
	Pretibial myxedema
	Morpheaform Basal Cell Carcinoma
	Scleredema
	Anetoderma
	Stiff skin syndrome
	Restrictive dermopathy

Early Stage Circumscribed Morphea

Early circumscribed morphea presents as an erythematous plaque without apparent thickening of the underlying structures and without classical histopathological features, so it is not very easy to distinguish it from other common conditions.

Interstitial Mycosis Fungoides (IMF)

In the literature, there are several case reports where the initial histopathological diagnosis of IMF later turned out to be morphea on close follow-up [2]. Initially, the collagen deposition may not be evident in the histopathology and it may be difficult to differentiate morphea from mycosis fungoides which shows cellular proliferation. Immunohistochemistry helps to differentiate between the two

CHAPTER 9

Assessment of Disease Severity

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Chapter Synopsis.
• As the validation of new outcome measures in morphea are becoming available, however; a good histopathological correlation may provide additional information regarding disease activity and the depth of involvement. Thus, the role of skin biopsy in morphea can't be ignored.
• Several scoring tools have been validated in morphea to elucidate the clinical assessment. This will help in determining the appropriate time for treatment, especially systemic immunosuppressive therapy.
• Infrared thermography (IT) is a non-invasive technique that detects infrared radiation. It provides an image of the temperature distribution across the body surface and has been shown to be of value in the detection of active lesions with high sensitivity (92%).
• Active morphea is universally inflammatory. Features that suggest activity include new onset lesions, peripheral extension of older lesions, erythema and induration, localized warmth, pruritus and lilac ring surrounding the lesions.
• A cutometer measures skin elasticity and relaxation. The measurement is dependent upon anatomic site, age, sex, and edema. The probe measures the rate at which it is able to pull skin in and the rate at which the skin returns to baseline.
• Durometer is a device to measure skin hardness. The measurement is dependent on patient's sex, age, edema and location. The durometer measurements have low inter- and intra-observer variability.
• Cone beam computed tomography (CBCT) is used in linear morphea of the face (especially oral mucosal morphea). The CBCT scanner uses a 2D detector and a cone-shaped X-ray beam which scans the affected region providing both 2D and 3D images. It is cost effective, fast when compared to MRI, and the radiation dose is relatively less than a routine CT.

Keywords: Cone beam computed tomography, Clinical activity, Colour doppler, Cutometer, Durometer, Elasticity, Hardening, High-frequency ultrasound, Infrared thermography, Laser doppler flowmetry, Localized scleroderma.

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Localized scleroderma cutaneous assessment tool, Localized scleroderma skin severity index, Localized scleroderma skin damage index, Morphea, Outcome measures, Physician global assessment, Skin scoring tools, Skin thickness, Surface area measurement.

INTRODUCTION

Morphea is an inflammatory skin disorder that is characterised by excessive collagen deposition in the skin, dermis, and/or subcutaneous tissue, leading to skin thickening and hardening, often extending to the fascia, muscles, and even bone. This can result in potential functional and cosmetic sequelae including dyspigmentation, facial deformities, contractures, impaired joint mobility and deformities. In children, this can cause serious growth restrictions of the affected area [1, 2]. The disease may be relatively mild and the clinical presentation can vary from isolated superficial skin lesions to multiple plaques with a deeper component. The pleomorphic presentations can result in numerous subtypes/variants: plaque morphea, linear morphea, bullous morphea, deep morphea, and generalized morphea; also, eosinophilic fasciitis, morphea profunda and pansclerotic morphea of children. The clinical course of morphea may be static or progressive to skin thickening or atrophy [3].

Although the validation of new outcome measures in morphea is valuable, a good histopathological correlation may provide additional information regarding the depth of involvement and activity (inflammation) in cases where the clinical examination is inconclusive and ultrasound or magnetic resonance imaging (MRI) is not readily available [4]. Thus a biopsy in morphea not alone helps in the diagnosis but also in assessment.

It is important to assess the disease severity in a patient with morphea to decide on the appropriate line of management, as the condition carries a huge impact on the quality of life of the affected individual and their families. Morphea is more commonly reported in children than in adults and extracutaneous manifestations are also not rare. In early morphea, the lesions are erythematous, swollen and warmer than the surrounding skin. Gradually the central part of the lesion appears porcelain white with a surrounding lilac ring. In later stages as fibrosis and sclerosis ensue, the lesions are atrophic and hypo- or hyperpigmented, while their temperature is close to that of the surrounding skin [5]. A proper history and clinical examination will give the initial clue in staging the phase of the disease. Several scoring tools have been validated to elucidate the clinical assessment which will help in determining the appropriate time for treatment, especially systemic immunosuppressive therapy.

The commonly used skin scoring tools include the LoSCAT (Localized Scleroderma Cutaneous Assessment Tool) which is a scoring system that includes a Skin Severity Index (LoSSI) and a Skin Damage Index (LoSDI). Although this method does not evaluate the real size of the lesions, it can be performed by physicians in daily practice without the need for special equipment.

Though tried in few studies, the cutometer which measures the cutaneous elasticity, and the durometer which measures the skin's hardness, have their limitations. Infrared rmography (IT) is a non-invasive technique that detects infrared radiation and provides an image of the temperature distribution across the body surface. It has been shown to be of value in the detection of active lesions with high sensitivity (92%) but moderate specificity (68%). High-frequency ultrasound can detect several abnormalities such as increased blood flow related to inflammation as well as increased echogenicity due to fibrosis and loss of subcutaneous fat. The main limits of this tool are its operator dependency and the lack of standardisation [6]. Other methods such as laser Doppler flowmetry and cone beam tomography need better validation to be used as an outcome measuring tool in morphea.

CLINICAL AND HISTOLOGICAL ASSESSMENT OF DISEASE ACTIVITY

The clinical manifestations of morphea are dependent on the subtype, depth of involvement and phase of progression of the lesions. Morphea is characterised by an early or active phase and a late fibrotic phase. A thorough physical examination helps in the assessment of disease activity. Correctly identifying and quantifying disease activity and damage in different subtypes of morphea is essential for its appropriate management [2].

Active Morphea

Active lesions are important to identify as they are highly treatment responsive. Active morphea is universally inflammatory and features suggesting activity include new onset lesions, a peripheral extension of older lesions, erythema and induration, localized warmth, pruritus, and a lilac ring surrounding the lesions [7, 8]. Deep morphea lesions are poorly circumscribed tethered erythematous plaques, with varying amounts of edema/induration, and may not always have surface changes. Linear depressions (groove sign) may be present. Functional impairment and pain also suggest deep involvement. When there is an overlap of sclerotic lesions, the peripheral erythema in such lesions represents activity, while the deeply sclerotic skin represents damage [9].

CHAPTER 10

Associated Diseases

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Chapter synopsis.
• Morphea is a skin disorder characterized by early inflammation followed by fibrosis.
• It has been thought that morphea is a disease confined only to the skin. However, several reports demonstrated the association between morphea and other cutaneous and systemic disorders.
• Diseases associated with morphea may be autoimmune or inflammatory, cutaneous or extracutaneous disorders.
• Various concomitant inflammatory/autoimmune diseases that have been reported in morphea patients include psoriasis, vitiligo, alopecia areata, inflammatory bowel disorders, type I diabetes mellitus, Meniere's disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, mixed connective tissue disease, and antiphospholipid syndrome.
• Concomitant familial disorders which have been described in cases of morphea include rheumatoid arthritis, scleroderma, systemic lupus erythematosus (SLE), psoriasis, vitiligo, lichen sclerosus et atrophicus, thyroiditis, insulin-dependent diabetes mellitus, inflammatory bowel disease, myasthenia gravis, multiple sclerosis and sarcoidosis.
• Psoriasis, vitiligo and SLE are more prevalent in morphea cases than in the general population.

Keywords: Adult morphea, Antihistone antibodies, Anti-ssDNA antibodies, Antinuclear antibodies, Associated diseases, Autoimmune diseases, Autoantibodies, Childhood morphea, Connective tissue disorders, Familial, Family history, Fibrosis, Generalized morphea, Inflammation, Localized scleroderma, Morphea, Morphea and vitiligo, Morphea and psoriasis, Rheumatologic diseases, Rheumatoid factor, Scleroderma.

INTRODUCTION

Morphea is generally thought to be a self-limited benign disease confined to the skin with musculoskeletal involvement typically including growth defects with

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shortening of the affected limb, scoliosis, thorax asymmetry and muscle atrophy [1 - 4]. However, there are many reports that described morphea as a systemic autoimmune condition which has manifestations outside the skin [5 - 7]. Several case reports describe morphea coexisting with other autoimmune diseases [8 - 12]. These may underscore the postulation that morphea and systemic sclerosis are two ends of a continuous disease spectrum [7].

The prevalence of systemic and autoimmune or inflammatory diseases associated with morphea had been studied with different outcomes in different populations. The presence of concomitant diseases may affect patient management because many patients are untreated or are treated with skin-directed therapy despite being candidates for systemic therapy.

DISEASES ASSOCIATED WITH MORPHEA

Concomitant Autoimmune/Inflammatory Diseases

Concomitant rheumatic or other autoimmune diseases were reported in 18% of cases with morphea in a cohort study involving 245 cases. These concomitant diseases were more prevalent in adults and in cases with generalized morphea than in children and patients with other morphea subtypes respectively [1]. It is unknown whether children with morphea will develop autoimmune disorders at an increased rate as they grow older [6].

Concomitant autoimmune diseases included psoriasis, vitiligo, alopecia areata, inflammatory bowel disorders, type I diabetes mellitus, Menier's Disease and multiple sclerosis. Concomitant rheumatic diseases included systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome, mixed connective tissue disease and antiphospholipid syndrome (Table **10.1**). The association of morphea with primary biliary cirrhosis, myasthenia gravis and Hashimoto’s thyroiditis has also been reported [1, 5 - 7, 10 - 12].

Table 10.1. Concomitant autoimmune and rheumatic diseases reported in morphea cases.

• Autoimmune Diseases	• Rheumatic Diseases
Psoriasis	Systemic lupus erythematosus
Vitiligo	Rheumatoid arthritis
Alopecia areata	Sjogren's syndrome
Inflammatory bowel disease	Mixed connective tissue disease
Type I diabetes mellitus	Antiphospholipid syndrome
Menier's disease	Spondyloarthropathy

(Table 10.1) cont.....

• **Autoimmune Diseases**	• **Rheumatic Diseases**
Multiple sclerosis	Still's disease
Coeliac disease	
Autoimmune thyroiditis	
Primary biliary cirrhosis	

Several disorders occurred with greater frequency in morphea patients compared to published population-based prevalence estimates including psoriasis (1.5 to 4.5 fold increase), SLE (5.8 fold increase), multiple sclerosis (7-8 fold increase), and vitiligo (3.5 fold increase) [13 - 15].

The association between morphea and non-segmental vitiligo has rarely been reported [16 - 20]. In addition, the co-occurrence of linear morphea and homolateral segmental vitiligo has also been reported [21]. A possible mechanism explaining this finding is cutaneous mosaicism as linear morphea following Blaschko's lines has been previously reported [22]. A decrease in T-regulatory cells leading to loss of tolerance can also be a common link [23].

Kim *et al*., reported a case who had generalized morphea lesions on the right and left sides of the back and linear morphea on the left side of the forehead, which was on the same side of the body where segmental vitiligo was located [24].

Van Geel *et al*, have also described a case with the simultaneous presence of segmental vitiligo, alopecia areata, psoriasis and a halo nevus and postulated a shared autoimmune-mediated process as the underlying mechanism [25]. Similarly, Bonilla-Abadía *et al.*, postulated an autoimmune mechanism to explain the association of morphea, vitiligo, autoimmune hypothyroidism, pneumonitis, autoimmune thrombocytopenic purpura, and central nervous system vasculitis [19]. In these reports, morphea becomes part of a multiple autoimmune syndrome (MAS), where there are three or more well-defined autoimmune diseases present in a single patient [26]. Therefore, it may be imperative to screen and follow up morphea cases for the development of other autoimmune diseases in the future.

Hydroxychloroquine was reported to be effective in blocking the progression of scleroderma and treating vitiligo. Hydroxychloroquine sulfate (200 mg/day) was used in a case with concurrent morphea and vitiligo. Skin lesions of morphea and vitiligo stabilized within 6 weeks. In addition, the vitiliginous lesions showed 70% repigmentation after 5 months from the start of medication. Skin lesions of morphea also showed no more progression. The patient tolerated the 7-month treatment period with no side effects [24].

CHAPTER 11

Extracutaneous Manifestations

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Chapter synopsis.
• Some patients with morphea have extra-cutaneous manifestations. Morphea should not be considered as exclusively limited to the skin but as a disease that may have other organ system involvement.
• Musculoskeletal manifestations have been reported in morphea. These include arthralgia, flexion contractures, arthritis, *etc.* MRI may be a useful tool for the detection of musculoskeletal involvement.
• Gastroesophageal manifestations are rarely reported in morphea. Most authors believe that routine workup for gastroesophageal manifestations is justified only in SSC. However, morphea patients symptomatic for gastroesophageal symptoms or having autoantibodies may be referred to a gastroenterologist.
• Cardiac involvement is common in SSC but it is exceedingly rare in morphea. Isolated cases of pericarditis and incomplete right bundle branch block have been reported in morphea.
• Ophthalmological involvement is not uncommon in pediatric morphea especially with linear morphea involving the face. Ocular monitoring is mandatory in those with skin lesions on the face and/or concomitant CNS involvement. Common ocular manifestations include eyelid abnormalities, eyelash abnormalities, lacrimal gland abnormalities, anterior uveitis, secondary glaucoma, episcleritis, strabismus, *etc.*
• Neurological symptoms and signs in linear morphea involving the face are protean and include seizures, headache, focal neurologic deficits, and movement disorders as well as neuropsychiatric symptoms and intellectual deterioration.

Keywords: Arthralgia, Arthritis, Autoimmune disease, Autoimmune thyroiditis, Cardiac manifestations, Dental anomalies, Epilepsy, Extra-cutaneous manifestations, Focal neurologic deficits, Flexion contractures, Gastrointestinal manifestations, Gastroesophageal reflux, Headache, Linear morphea ECDS, Morphea, Musculoskeletal manifestations, Neurological manifestations, Ocular manifestations, Squamous cell carcinoma, Thyroid abnormalities.

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INTRODUCTION

Several patients with morphea have extra-cutaneous manifestations and associated autoimmune diseases. Morphea should not be considered as exclusively limited to the skin but as a disease that may potentially develop systemic involvement. These patients should be studied more thoroughly and followed with close collaboration between the dermatologist and rheumatologist and other allied specialities.

EXTRACUTANEOUS MANIFESTATIONS

Though morphea is known as a dermatologic disease, in the literature the possibility of visceral involvement has also been reported, in the case of overlap with other autoimmune diseases or as possible evolution towards a systemic form; the latter possibility was described anecdotally in pediatric cases [1, 2]. Various extracutaneous manifestations of morphea have been discussed below:

Musculoskeletal Manifestations

Musculoskeletal complications (Box **11.1**) are reported in up to 40% of cases with morphea [3]. These include arthralgia, flexion contractures, arthritis and considerable impairment [4]. In recent years, the first data documenting a high prevalence of musculoskeletal involvement in patients with morphea have been published [3, 5, 6]. Furthermore, musculoskeletal manifestations may be an important argument for systemic rather than topical therapy. The recent German Society of Dermatology guidelines for the management of patients with morphea recommends treatment with methotrexate and prednisolone if the patient has a deep, linear or generalized form of morphea or if fasciae, muscles or bones are involved [7]. It has been shown that in patients with morphea, magnetic resonance imaging (MRI) is a useful tool for the detection of musculoskeletal manifestations [8]. MRI provides complementary information about the depth of involvement of underlying morphologic structures, contrary to the clinical examination, which generally reveals information about the superficial involvement in this disorder. The use of MRI makes it possible to objectively evaluate changes in fascial, muscular and joint disease.

Box 11.1: Musculoskeletal involvement in morphea.
Reported in 40 % cases of morphea.
The presence of musculoskeletal manifestations may indicate systemic therapy.
Arthralgia, flexion contractures, and arthritis are the usual presentations.

(Table 11.1) cont.....

In case of fascial, muscle or bone involvement, a combination of methotrexate and systemic steroids is recommended.
MRI is recommended for the detection of musculoskeletal manifestations.
MRI objectively evaluates changes in fascial, muscular and joint disease.

Gastrointestinal Manifestations

There is a scarcity of data regarding gastrointestinal involvement (Box **11.2**) in morphea. Zulian *et al.* [5] in their study reported gastroesophageal reflux in 1.6% of the patients. Zaninotto *et al.* [9] in their study recommended that esophageal tests may be useful in the evaluation of SSC; however, they did not recommend its routine use in cases of morphea. Esophageal involvement has been seen in some patients with pediatric morphea [10]. Patients of pediatric morphea who are symptomatic for gastroesophageal symptoms or having autoantibodies can be subjected to a meticulous history regarding gastroesophageal symptoms and referral to a gastroenterologist can be considered based on the patient's clinical profile [11].

Box 11.2: Gastrointestinal involvement in morphea.
Data regarding gastrointestinal involvement in morphea is scarce.
Gastroesophageal reflux has been reported in 1.6% of the patients in some case series while others have not found such abnormality.
Meticulous work-up for the gastroesophageal system is justified in SSC but seems to be unjustified in morphea.
Morphea patients who are symptomatic for gastroesophageal symptoms or having autoantibodies may be subjected to gastroesophageal evaluation.

Need for Upper GI Evaluation?

Esophageal manometry has been performed in children with morphea, showing nonspecific alterations without any changes typical of SSC [5]. Arif *et al.* [12] in their study concluded that esophageal involvement in SSC is very frequent while its involvement in morphea is very insignificant. In their study, they mentioned that every case of SSC needed a meticulous upper GI evaluation, whether symptomatic or not, however, such an evaluation in morphea seemed to be unjustified [12]. These facts and the lack of information on the natural history of this abnormality in asymptomatic children hardly support the recent recommendation for an extensive gastrointestinal evaluation of all patients with morphea [13].

CHAPTER 12

Disease Prognosis

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Chapter synopsis.
• Morphea is a chronic and relapsing skin disease; its course depends on the specific clinical variant.
• The typical course of morphea is self-limited and takes approximately 3- 5 years.
• The morphea prognosis is good, however, the disease may relapse. The relapsing course of the morphea is mainly observed in linear and generalized variants.
• The rapid progression of the disease is observed among patients suffering from generalized morphea and disabling pansclerotic morphea.
• The factor significantly associated with worse outcomes may be related to the prolonged time from diagnosis to treatment.
• Morphea affects the patient's quality of life, especially in adult and female patients.

Keywords: Circumscribed morphea, En coup de sabre, Extracutaneous complications, Generalized morphea, Functional disabilities, Joint contractures, linear morphea, Morphea course, Morphea prognosis, Morphea recurrence, Morphea relapse, Morphea plaque, Musculoskeletal complications, Pansclerotic morphea, Progression of morphea, Quality of life, Relapsing course of morphea, Unpredictable course, Worse prognosis.

INTRODUCTION

Morphea belongs to chronic and relapsing skin disorders [1]. The natural course of morphea, especially in localized forms, is usually mild and predictable, leading to mainly cosmetic consequences (dyspigmentation and/or telangiectasia which

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can be also of post-steroidal origin) [2]. However, its course and prognosis are mainly related to its clinical subtypes. Unpredictable course and worse prognosis may concern deep, linear forms as well pansclerotic morphea.

Morphea which involves subcutaneous tissue, muscle tissue and bones may lead to functional disabilities including joint contractures and limb length discrepancies. Approximately 20-40% of children may present extracutaneous complications, and musculoskeletal manifestations are the commonest [3, 4]. Internal organ involvement is rare, however possible, especially associated with the involvement of the central nervous system and the organ of vision. The aspects related to extracutaneous manifestations in morphea are described in detail in Chapter 11.

MORPHEA COURSE

The usual course of morphea is self-limited and takes approximately 3- 5 years [3, 4]. The typical plaque changes the morphology over time. In the initial active phase of morphea, it is characterized by an erythematous, violaceous border (lilac ring) and central induration, which becomes discolored and often turns into a yellowish-white (ivory) color [5]. Inactive lesions of morphea are mainly characterized by atrophy and dyspigmentation. Deeper skin involvement may be accompanied by hair loss. Although the disappearance of the erythema indicates that the inflammatory phase has subsided, what takes usually several months, sclerosis may resolve within years. The softening of the skin lesions in plaque morphea may take approximately 2.7 years after diagnosis and occurs in half of the patients. However, this process in deep forms of morphea may take even up to 5.5 years [6]. The decrease in induration indicates an improvement in the clinical condition, similarly to hair regrowth [2]. In deep and linear forms of morphea, tissue damage and atrophy appear at the beginning and may remain stable over time, despite the treatment. To limit and stabilize the disease, treatment should be introduced as early as possible [7, 8].

Adults with pediatric-onset morphea are less likely to present with active disease and are characterized by higher disease damage [measured by Physician Global Assessment of Disease Activity (PGA-A)] [9]. The most aggressive disease course was observed among children with linear subtypes and more than 10% of them presented with persistent activity lasting longer than 10 years [7]. In Parry-Romberg syndrome, the disease usually presents with a slow progression over a highly variable course ranging from 2 to 20 years [10]. The factor significantly associated with worse outcomes could be the prolonged time from diagnosis to treatment [7].

The rapid progression of the disease is observed among patients suffering from generalized morphea and disabling pansclerotic morphea [2, 4, 5]. According to Alimova *et al.* the generalized morphea as the initial presentation and positive baseline ANA may be associated with the worsening course of the disease [11]. Due to the progressive, extensive and deep sclerosis, the disease may lead to disability in a short period of time [12]. Hard-to-heal ulcers and calcification can be associated with dermatogenic contractures. Moreover, the occurrence of squamous cell carcinoma in the area of ulcers has also been described, especially within the lower extremities [13]. In (Box **12.1**) characteristic features of morphea related to its course are listed.

Box 12.1: Characteristic features of morphea course.
The usual course lasts 3-5 years.
The morphology changes over time.
The softening of skin lesions may take 2.7 – 5.5 years.
In linear and deep morphea, the disease damage may persist despite the treatment.
The most aggressive disease course regarding children is with linear subtype and may present with persistent disease activity.
The slow progression usually occurs in Parry-Romberg syndrome.
The rapid progression is usually seen in generalized morphea and disabling pansclerotic morphea.

MORPHEA RECURRENCE

Although long-term studies evaluating the recurrence risk in morphea are limited, especially in the adult population, the disease shows significant relapse tendency [1, 9, 14 - 16]. Florenz-Pollack *et al.* conducted a prospective study on a group of children and adults [17]. 66% of patients treated with methotrexate and 41% with UVA1 had achieved a complete response in a 1-year follow-up period. In that group of patients, almost one-third experienced disease flare-ups at an average of 1.7 years after remission [17]. The longer periods between remission and relapse have been reported by other researchers [7, 16]. Martens *et al.* observed that recurrence occurs more frequently in the juvenile population than in adult one (27% vs.17%, respectively) and the median time for morphea relapse was 26 -27 months. Moreover, they considered linear morphea of the limbs as the most frequently recurrent variant [16]. In other studies, the higher recurrence rate was related to generalized morphea [16]. After 5 years, the recurrence was observed in 44% of patients as a new activity in the area of previous morphea plaque [16]. In the study of Saxton-Daniels *et al.* the percentage of new or expanded lesions was even higher and accounted for 89% [14].

CHAPTER 13

Investigations

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Chapter synopsis.
• Clinical findings are usually sufficient to make a presumptive diagnosis of morphea. Several procedures and investigations are employed to confirm the diagnosis and to assess the depth of involvement, disease severity, and activity.
• Autoantibodies especially Anti-nuclear antibodies (ANA), Antihistone antibodies (AHA) and Anti single-stranded DNA (a-ssDNA) antibodies have been implicated as potential markers of disease severity. These antibodies are however infrequently present even in patients with severe forms of morphea.
• Skin biopsy shows a prominent lymphoplasmacytic inflammatory infiltrate at the dermal-adipose tissue interphase in early lesions and a more characteristic replacement of normal dermal and subcutaneous structures by abnormal collagen.
• Radiographic studies might be abnormal and are especially helpful if deeper tissues are involved.
• Infrared thermography, durometer and cutometer measurements are being investigated as outcome measures in morphea.

Keywords: Antinuclear antibody, Anti-histone antibodies, Collagen deposition, Cutometer, Durometer, Dermoscopy, Eosinophilia, High eccrine glands, Hypervascularity, Infrared thermography, Line sign, Magnetic resonance imaging, Mucinosis, Skin biopsy, Ultrasonography.

INTRODUCTION

In most patients of morphea, the diagnosis can be made based on the clinical findings alone. However, the significance of investigative studies to confirm the diagnosis and to determine the severity of the disease cannot be underestimated. Early clinical diagnosis of morphea is pivotal in minimizing functional and cosm-

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etic impairment that may occur in severe forms of morphea. Unlike systemic sclerosis, no specific serological parameters have been defined in morphea and screening for antibodies is probably relevant only if the presence of another autoimmune disease is clinically suspected. Also, there are no disease activity indicators for morphea. Monitoring of disease activity relies mainly on clinical findings. Some parameters have recently been defined as indicators of disease activity in morphea and may be utilized for assessment of disease activity on case to case basis. Histopathology would be relevant in cases with unclear clinical presentation. In addition, diagnostic techniques like ultrasonography, laser Doppler measurements, cutometer and durometer have been used for assessing the course of the disease and for assessing therapeutic efficacy in clinical studies. Such diagnostic techniques for the assessment of disease activity as well as disease severity have been already discussed in detail in chapter 9. In this chapter, only a brief overview of such techniques will be presented.

ROUTINE LABORATORY INVESTIGATIONS

Complete Blood Count

Blood counts are usually normal. However, patients in the early inflammatory phase of morphea and those with deep morphea may exhibit peripheral eosinophilia.

Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP)

ESR and CRP may be elevated in patients with active disease or those with extensive involvement.

Creatinine Kinase and Aldolase

Creatinine kinase levels in morphea are especially relevant in patients with suspected concomitant myositis. Elevated creatinine kinase and aldolase levels may indicate disease activity in juvenile localized scleroderma and are usually elevated in patients with new active skin lesions. In an observational analysis of children with juvenile localized scleroderma, creatinine levels were also found to be associated with muscle atrophy and extremity shortening [1].

AUTOANTIBODIES

The role of autoantibodies in morphea is not very clear but serological biomarkers in the form of autoantibodies may be used as a valid means to classify and differentiate morphea. The commonly used antibody markers in morphea include:

Antinuclear Antibody (ANA)

Antinuclear antibodies are found in 23-68% of patients with morphea [2]. Speckled and homogenous patterns are the most common. Although ANA positivity does not appear to vary with the different clinical subtypes of morphea, it does seem to be associated with disease severity with respect to the extent and depth of lesions, presence of extracutaneous manifestations and probability of disease relapses [3 - 5]. ANA can thus act as a potential biomarker for disease stratification and management in morphea.

Antihistone Antibodies (AHA)

Antihistone antibodies can be detected in 47-87% of patients with morphea. Similar to antinuclear antibodies, a positive correlation with the disease severity with respect to the number and size of lesions has been observed [6, 7]. Also noteworthy is the frequent association of AHA with the linear morphea subtype where it may correlate significantly with the extent of involvement and disease activity [3, 7, 8]. AHA do not appear to be predictive of disease relapses, unlike ANA.

Anti-single Stranded DNA Antibodies (a-ssDNA)

They are detected in nearly 50% of patients with morphea being most common in patients with generalized morphea and least in the circumscribed form. Anti-ssDNA antibodies may have a positive correlation with disease activity as well as severity. Musculofascial involvement and joint contractures have also been found more commonly in patients with antibodies to single-stranded DNA [9, 10].

Rheumatoid Factor (RF)

RF has been detected in 15 – 60% of patients with morphea, being more common in children with linear morphea. The presence of RF may correlate positively with arthritis and musculoskeletal involvement in morphea and should mandate clinical monitoring of such patients for the development of any musculoskeletal abnormalities or arthritis [11].

Antibodies to Extractable Nuclear Antigens (ENAs)

In 1-15% of patients with morphea, antibodies against the extractable nuclear antigens like anti-double stranded DNA (ds DNA), anti-SSA/SSB, anti-

CHAPTER 14

Treatment

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Chapter synopsis.
• The choice of therapy for morphea should be based on several factors: Relative activity of the disease, depth and the localization of involvement, and course. Subcutaneous involvement, rapid progression, and involvement of functionally/cosmetically sensitive areas or large body surface areas are all indications of systemic treatment.
• Although no specific therapy for morphea exists, a variety of therapeutic options are available. The treatment aimed at reducing inflammatory activity in early, active disease is more successful than attempts to decrease sclerosis in well-established or older lesions.
• Treatment options may be divided into topical and systemic therapy as well as ultraviolet (UV) phototherapy.
• Topical and UV phototherapy are usually appropriate in plaque-type morphea with limited extension, whereas generalized, linear, or deep types usually require systemic therapy.

Keywords: Adverse drug effect, Azathioprine, Broadband ultraviolet A, Calcineurin inhibitors, Calcipotriol, Corticosteroids, D-Penicillamine, Imiquimod, Interferon gamma, Localized scleroderma, Methotrexate, Morphea, Narrowband ultraviolet B, Mycophenolate mofetil, Phototherapy, Systemic treatment, Topical treatment, Tacrolimus, Ultraviolet A1, Vitamin D analogues.

INTRODUCTION

There are various therapeutic modalities for morphea; however, evidence in support of many of these therapies is limited. The activity of the disease, depth and extent of involvement, and the presence of functional impairment or cosmetic deformity determine the most appropriate treatment. The severity of the disease varies and is unpredictable, but the prognosis is usually good. Most morphea pati-

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ents might be successfully treated with topical therapy and phototherapy but the severe and progressive form of the disease might require systemic anti-inflammatory and immunosuppressive agents [1].

Treatment options for morphea might be divided into topical, phototherapy, and systemic therapy. The extent and severity of the disease should be taken into account before planning the treatment. All the treatments are more effective in the active, early phase of the disease Fig. (**14.1**).

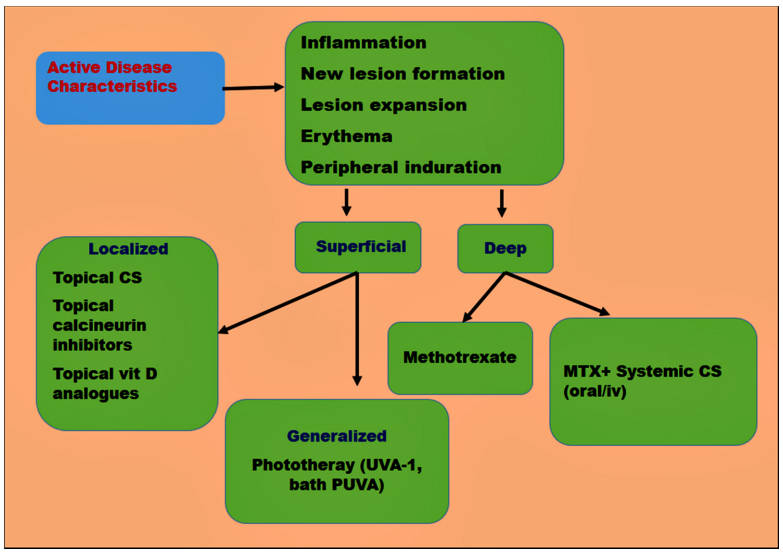

Fig. (14.1). Treatment options during the active phase of the disease.

TOPICAL THERAPY

Topical treatment is useful for the limited and superficial forms of morphea, such as plaque (circumscribed) morphea. Topical corticosteroids, vitamin D analogues, and topical calcineurin inhibitors are the mainstay of topical treatment, however, topical imiquimod, intralesional (IL) interferon gamma might be an alternative choice of treatment as well (Table **14.1**) [2, 3].

Table 14.1. Main topical treatment options in morphea and their mechanism of action.

Corticosteroids	Anti-inflammation, immunosuppression.
Calcipotriene	Antiproliferation, antiinflammation
Tacrolimus, pimecrolimus	Immunmodulator, immunsupression
Imiquimod	Immune response modifier
IFN-gamma	Antifibrosis

Topical/ Intralesional Corticosteroids

Once entered into the cell, topical corticosteroids bind to the cytoplasmic glucocorticoid receptor and are transported to the nucleus. The complex topical corticosteroid-glucocorticoid receptor binds to glucocorticoid response elements in the promoter region of a number of genes and modulates the transcription of a number of genes by inducing or inhibiting the transcription of specific mRNA and protein synthesis. These effects lead to the suppression of synthesis and release of prostaglandins and other inflammation mediators; release of the anti-inflammatory proteins; reduced release of inflammatory cytokines; inhibition of T cell activation; changes in the function of endothelial cells, granulocytes, mast cells, and Langerhans cells; and inhibition of the mitotic activity of epidermal cells and dermal fibroblasts.

Even though there are no studies proving the effectiveness of topical or IL corticosteroids in morphea, they are still used in cases with superficial lesions in the active phase of the disease (Box **14.1**). They can inhibit the further progression of the disease by diminishing the inflammation and softening sclerotic lesions. Therapy with high-potent corticosteroids should be performed in the active phase of disease for a maximum period of 3 months. Longer application of topical corticosteroids should be given as an interval therapy. Application under occlusion might be considered to increase the efficacy. Intralesional corticosteroids can be used in the active margin of the linear en coup de sabre subtype. Triamcinolone acetonide (40 mg) is the most commonly used agent by diluting 1:2 or 1:4 ratio with lidocain [2, 4].

Box 14.1. Topical corticosteroids for morphea.
Paucity of studies proving the effectiveness of topical corticosteroids.
Suited for the superficial lesions in the active phase of the disease.
Primarily act by their anti-inflammatory role. They can inhibit further progression of the disease by inhibiting inflammation and soften sclerotic lesion.
Moderate- to high-potent corticosteroids should be used in the active phase of disease and their application should be restricted to a total of 3 months.
Longer time therapy if needed, should be given as interval therapy.
Topical steroids under occlusion may increase the efficacy of treatment.
Intralesional corticosteroids may be used in the active margin of the linear morphea en coup de sabre.

Topical Vitamin-D Analogues

Vitamin D may exert inhibitory effects on fibroblast proliferation, collagen synthesis, and T lymphocyte activation. Topical treatment with calcipotriene

CHAPTER 15

Idiopathic Atrophoderma of Pasini and Pierini

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Chapter synopsis.
• Idiopathic atrophoderma of Pasini and Pierini (IAPP) is a rare disease of unknown etiology characterized by the presence of single or multiple well-defined atrophic plaques having an abrupt edge forming "cliff-drop" borders.
• The etiology is unknown. Genetic factors, neurogenic causes, immunological factors, somatic mosaicism, *B. burgdorferi,* and abnormal metabolism of dermatan sulphate have been proposed.
• IAPP usually affects individuals during the second or third decades of life and predominantly affects females. However, it can rarely occur in infancy or old age.
• Histopathologically, it is characterized by a normal epidermis with increased pigmentation in the basal layer. There is a mild perivascular mononuclear cell infiltrate and melanophages in the upper dermis. Collagen in the deeper dermis is edematous, clumped, and homogenized. The elastic tissue may show a spectrum that ranges from normal to severe diminution with the fragmentation of elastic fibers.
• The absence of signs of inflammation, 'lilac ring' appearance, sclerosis and induration in the lesions of IAPP differentiates it from morphea. Sclerosis which is prominent in morphea is absent or minimal in IAPP.
• IAPP has a benign course and lacks the complications seen in some forms of morphea. New lesions may develop while the existing lesions may enlarge variably over the next 10-20 years. However, existing lesions do not involute in IAPP.
• Several treatment options have been tried in IAPP but none have been found to be consistently effective. Oral tetracyclines, penicillin, hydroxychloroquine, standard recommended therapy for Lyme disease, potassium aminobenzoate, calcineurin inhibitors, PUVA, retinoids, steroids and phototherapy have shown variable efficacy.

Keywords: Abrupt borders, Anetoderma, Atrophoderma, Atrophy, Atrofodermia idiopatica progressive, Atrophic plaques, Atrophic scleroderma d'emblee, Atrophoscleroderma, Atrophoderma elastolytica discreta, Atrophic-scleroderma superficialis circumscripta, Atypical lilac-colored and non-indurated scleroderma.

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Blaschkoid idiopathic atrophoderma of Pasini and Pierini, Borrellia burgdorferi, Cliff- drop borders, Dermatan sulphate, Dyschromic and atrophic variation of scleroderma, Footprint in snow appearance, Fragmentation of elastic fibers, Idiopathic atrophoderma of Pasini and Pierini, Intra-collagenous edema, Inverted plateau, Linear atrophoderma of Moulin, Morphea, Morphea with an unusual degree of atrophy, Morphea plana atrophica, Mosaicism, Skin glycosaminoglycans, Sclerosis, Swiss cheese, Tetracycline.

INTRODUCTION

Idiopathic atrophoderma of Pasini and Pierini (IAPP) is a rare disease of unknown etiology which is characterized by the presence of single or multiple well-defined atrophic plaques. These plaques are characterized by slight depression of the skin with an abrupt edge causing what is known as “cliff-drop” borders. In contrast to morphea, these plaques do not show signs of inflammation, sclerosis, and induration [1]. The most commonly affected site is the trunk especially the back and abdomen. Proximal extremities can also get affected. Most commonly, plaques are present in a bilaterally symmetrical distribution, although lesions involving the body in an asymmetrical distribution have also been reported [2]. The plaques are generally round or ovoid in shape with their long axis parallel to the lines of cleavage and having a tendency to coalesce to form large, irregular-shaped plaques with convex borders [3].

HISTORICAL BACKGROUND

The history (Table **15.1**) of IAPP dates back to 1902-1904, when Brocq *et al.* termed it “atrophic scleroderma d'emblee” and Thibierge described a “dyschromic and atrophic variation of scleroderma” [4, 5]. In 1923, Pasini described a case report of a 21-year-old woman with a 4-year history of brownish-grey, “cyanotic” lesions on the trunk that was published in an Italian dermatology journal. These lesions were oval to round in shape. They were depressed below the surrounding normal skin. There was no associated inflammation. The lesions had spread from the upper back to the lower part of the back, flanks, and sacral regions. In addition, the patient had some lesions on the chest and a few lesions were present around the waistline. These plaques were flat, smooth, atrophic and depressed 1-2 mm below the surrounding normal skin. There was no induration and the sclerosis was absent. Follicular openings were fewer than normal. The affected skin was appearing thinner because of which one can view the deeper blood vessels. The border of the lesions had an irregular, slightly wavy shape and showed an abrupt transition from normal to diseased skin. He termed this entity “Atrofodermia idiopatica progressiva” designating it as a separate entity from that of morphea or

scleroderma [6]. This term by Pasini has been translated into English as "progressive idiopathic atrophoderma". Thirteen years later, in 1936, in Argentina, Pierini and Vivoli described a 19-year-old woman with similar lesions. She presented with multiple bluish, non-indurated patches of 3 years duration. These lesions were present on the right side of her chest and back in a zosteriform distribution. These skin lesions remained completely unaltered for the next 10 years [7]. Subsequently, Pierini observed over 50 such cases. His cases and several reports by other researchers can be seen in the Argentine literature [2]. Pierini classified this disorder into two types, a primary idiopathic form of atrophy and an atrophoscleroderma that was secondary to morphea. Since then, it has been described in the literature by various confusing terms such as "atrophoscleroderma superficialis circumscripta," "morphea with an unusual degree of atrophy," "morphea plana atrophica," and "atypical lilac-colored and non-indurated scleroderma" [2].

Table 15.1. Historical background of Idiopathic atrophoderma of Pasini and Pierini.

1902-1904	Brocq *et al.* coined the term "atrophic scleroderma d'emblee" and Thibierge described a "dyschromic and atrophic variation of scleroderma".
1923	Pasini described a case of a 21-year-old woman with a 4-year history of brownish-grey, "cyanotic" lesions on the trunk without inflammation, induration or sclerosis and termed it as 'Atrofodermia idiopatica progressiva'.
1936	Pierini and Vivoli described a 19-year-old woman with multiple bluish, non-indurated patches of 3 years duration present on the right side of her chest and back in a zosteriform distribution that remained completely unaltered for the next 10 years.
1958	Canizares *et al.*, introduced the entity into the American dermatologic literature and proposed the term "idiopathic atrophoderma of Pasini and Pierini". They suggested that this disease was unique and differed sufficiently from *morphea* and classified it as a separate entity.
2000	Yokoyama *et al.*, showed that skin glycosaminoglycans extracted from the lesions of patients with IAPP were different from those seen in typical lesions of morphea thus supporting the view that IAPP is different from morphea.

In 1958, it was Canizares *et al.*, who first introduced this entity into the American dermatologic literature. He reviewed findings achieved by Pierini and proposed the term "idiopathic atrophoderma of Pasini and Pierini". Canizares *et al.* suggested that the disease was unique and differed sufficiently from morphea and classified it as a distinct entity. Since the two authors deserve the credit for making the greatest contribution to the knowledge of this entity, hence the name IAPP [8]. In 2000, Yokoyama *et al.* investigated the skin glycosaminoglycans extracted from the lesions of patients with IAPP. They concluded that glycosaminoglycans in IAPP were different from those seen in typical lesions of morphea. This further added to the support that IAPP is different from morphea [9].

CHAPTER 16

Linear Atrophoderma of Moulin

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Chapter synopsis.
• Linear atrophoderma of Moulin (LAM) is a rare dermatologic disorder characterized by hyperpigmented atrophic plaques following the lines of Blaschko.
• Most of the reported cases have disease onset during childhood or adolescence. However, it can occur at any age.
• The etiopathogenesis of LAM is not clear. It is believed to be caused by a somatic mutation taking place early in embryogenesis resulting in a genotypic and phenotypic mosaicism. However, no gene responsible for LAM has been reported till date.
• Most often, lesions of LAM are not associated with preceding inflammation, induration, or sclerosis. Trunk has been the most common affected site followed by upper and lower limbs. Face and neck involvement occur rarely.
• Histologically, hyperpigmentation of the basal layer is the most characteristic finding. However, newer findings have been reported which include perivascular lymphocytic infiltrates, epidermal atrophy, decreased elastic tissue, altered dermal collagen, dermal atrophy, acanthosis, plasma cell infiltrate, and dilated dermal blood vessels.
• No definitive treatment for LAM exists. Several treatments have been tried with unsatisfactory results like oral potassium aminobenzoate (12g/day), penicillin, topical corticosteroids, heparin, phototherapy, combined PUVA and penicillin; vitamin E (400 IU/day) and topical clobetasol propionate.

Keywords: Altered dermal collagen, Atrophoderma, Atrophy, Atrophic plaques, Basal hyperpigmentation, Blaschko lines, Blaschkose, Blaschkoid lichen planus, Hyperpigmented bands, Idiopathic atrophoderma of Pasini and Pierini, Linear atrophoderma of Moulin, Linear morphea, Mosaicism, Perivascular lymphocytic infiltrate, Postzygotic mutation, Potassium aminobenzoate, Skin biopsy, Skin ultrasound, Subcutaneous tissue, Twin spotting.

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INTRODUCTION AND HISTORICAL BACKGROUND

Linear atrophoderma of Moulin (LAM) is a rare dermatological disorder characterized by hyperpigmented depressed plaques following the lines of Blaschko [1]. It was first reported by Moulin *et al.* in 1992. They reported five patients in good health who were having unilateral hyperpigmented atrophic plaques along Blaschko lines (BL) which they couldn't attribute to any known skin disorder. The lesions were having variable amount of pigmentation and atrophy that exactly followed BL. The onset of the lesions was during childhood or adolescence falling in the age group of 6-20 years. All the five patients had unilateral lesions and were present on the trunk forming a recumbent "S" pattern. The lesions started from a point 3 to 6 cm away from the posterior midline and progressed anteriorly to end precisely on the anterior midline. Though the number of bands described was variable, similar pigmented atrophic lesions or pigmented lines were present on the limbs of the same side in 3 out of the 5 cases. Due to the asymptomatic nature of the lesions, they caused only a cosmetic concern for the patients. They were stable and didn't show tendency to progress during follow up period of 2-30 years. Histopathology from five skin biopsies which were done on 3 patients showed unremarkable epidermis except hyperpigmentation of the basal layer. The dermis didn't reveal any pigmentary incontinence, inflammation, alteration of connective tissue including collagen and elastin. In one patient, perivascular lymphocytic infiltrate was present. They believed that this clinical atrophy was related to the loss of subcutaneous tissue; however, a deep biopsy from both the affected skin and contralateral sides to assess the thickness of subcutaneous tissue was originally not performed. Moulin *et al.* suggested the term "blaschkose" to differentiate it from the term "blaschkitis" that has an inflammatory and acquired nature [2].

Two years later, it was Bauman *et al.* in 1994, who reported a patient with a similar disease that was published in a German journal. He coined the term linear atrophoderma of Moulin. According to them, LAM belonged to the group of acquired linear dermatoses that follow BL and suggested that LAM was a variant of idiopathic atrophoderma of Pasini and Pierini (IAPP) [3]. However, the term LAM is a misnomer as there is no atrophoderma, the atrophy in LAM has been attributed to the thinning of subcutaneous tissue rather than the dermis. The use of ultrasound probes to determine skin thickness has revealed that there is thinning of the subcutaneous tissue underlying the lesions of LAM. Hence, the atrophy in the lesions of LAM is due to a decrease in the subcutaneous tissue [4].

EPIDEMIOLOGY

LAM is a rare disease. All the reported cases have been sporadic cases or short case series not exceeding five cases. Currently, there is not a single study available for LAM from which the author can describe its epidemiological parameters. Owing to the paucity of cases of LAM, the author has searched for the published cases of LAM since 1992 till the drafting of this chapter. Despite the meticulous search in, the author could find only 48 published cases of LAM (Table **16.1**).

Table 16.1. Forty eight published cases of linear atrophoderma of moulin.

Case No	Year of Publication	Authors	Reference	Age	sex	Sites	Histopathology	Other comments
1	1992	Moulin *et al.* 1st of 5	[2]	8	m	T	Basal Hyperpigmentation; perivascular lymphocytic infiltrate	-
2	1992	Moulin *et al.* 2nd of 5	[2]	7	f	T	Basal Hyperpigmentation	-
3	1992	Moulin *et al.* 3rd of 5	[2]	15	m	T	Basal Hyperpigmentation	-
4	1992	Moulin *et al.* 4th of 5	[2]	20	m	T	Skin Biopsy not done	-
5	1992	Moulin *et al.* 5th of 5	[2]	6	m	T/UL	Skin biopsy not done	-
6	1994	Baumann *et al.*	[3]	22	m	T/UL	Basal epidermal ballooning; perivascular lymphocytic infiltrate; increased dermal collagen.	-
7	1995	Larrègue *et al.*	[37]	15	m	T	Increased dermal collagen.	-
8	1996	Artola *et al.*	[38]	5	f	T	Acanthosis and basal hyperpigmentation; increased dermal collagen; perivascular lymphocytic infiltrate	Treatment with oral potassium aminobenzoate 12g/day stabilized lesions

CHAPTER 17

Parry-Romberg Syndrome

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Chapter synopsis.
• Parry-Romberg syndrome (PRS) is a rare disease characterized by progressive hemi-facial atrophy of the skin and soft tissue and later causes atrophy of muscles and the underlying osteocartilaginous structures with or without neurological and other complications.
• The etiopathogenesis of PRS has not been clear till date. Several theories have been postulated which include autoimmune theory, vascular dysfunction, sympathetic dysfunction, genetic predisposition, trauma, infections, neural crest migration disorder, *etc.*
• The onset of PRS usually occurs during the first and second decades of life. After a span of 2-20 years, the disease usually "burns out" before acquiring stabilization.
• Histopathological examination usually shows atrophic epidermis, dermis, subcutaneous fat, skin adnexa, vessels, and/ or hair follicles. Whether, clinically patients have cutaneous sclerosis or not, histopathology will show homogenized and thickened dermal collagen bundles.
• Neurological, ophthalmological, dental and maxillofacial complications are usually present. Neurological complications are the most common extracutaneous manifestations; seizures and headaches being the most common presentations.
• The diagnosis of PRS is mainly based on typical clinical presentation and further supported by other investigations like skin histopathology and imaging modalities to look for related complications.
• There is no standard medical treatment currently available for PRS. Immunosuppressive therapies like systemic corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil, cyclophosphamide and other treatments like PUVA, hydroxychloroquine, plasmapheresis, *etc.* have yielded variable success.
• Surgical and aesthetic treatments include lipo-injection, fat grafting, soft tissue fillers, dermal fat grafts, bone paste cranioplasty, adipofascial flaps, bone grafts, biocompatible porous polyethylene implants. Nasal reconstruction, lip repair, eyebrow repair, eyebrow lifting, face-lift, lip augmentation, Z-plasty, and hair transplant have been carried out for a better aesthetic outcome.
• There is enough evidence to support that morphea en coup de sabre and PRS lie on the same spectrum of disease.

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Keywords: Autoimmune theory, Baraquer-Simons syndrome, *Borrellia burgdorferi*, Burnt-out phase, Cervical sympathectomy, Channelopathy, Congenital hemiatrophy, Dermal fat grafts, Enophthalmos, Facial asymmetry, Facial hemiatrophy, Fat grafting, Galeal flaps, Hyperactivity of the brain stem, Idiopathic hemifacial atrophy, Linear morphea en coup de sabre, Maxillofacial complications, Lipodystrophy, Neural crest migration disorder, Neurological complications, Parry-Romberg syndrome, Photographical evaluation, Primary hemifacial hypertrophy, Progressive facial hemiatrophy, Progressive hemifacial atrophy, Rasmussen encephalitis, Romberg syndrome, Sunken hemiface, Sympathetic dysfunction, Vascular dysfunction.

INTRODUCTION

Parry-Romberg syndrome (PRS) is a rare disorder characterized by progressive hemiatrophy of the skin and soft tissue of the face and later causes atrophy of muscles, cartilage, and the underlying bony structures with or without neurological complications [1, 2]. It was initially described by Drs Caleb Hillier Parry in 1825 and Moritiz Heinrich Romberg in 1846 [3, 4]. However, its current name progressive hemifacial atrophy (PHA) was coined by Eulenberg in 1871 [5]. PRS usually presents initially in children and young adults and gradually progresses over a variable time course which may range from 2 to 20 years, finally reaching a “burnt-out phase” and stabilizing for no apparent reason [6 - 10]. The highly variable signs and symptoms of the disorder coupled with the peculiar disease course put obstacles in elucidating the underlying pathophysiology of the disorder. Though, a specific etiology has not been described till date, several theories have been postulated to account for its causation. These include infection, trauma, sympathetic nervous system dysfunction, vascular abnormalities, inflammatory conditions, and autoimmune disorders, etc [1, 11 - 14]. Most often, it is restricted to one half of the face, however it can involve the arm, trunk, and leg [2]. It usually starts in the first decade of life although a late onset has been described in some cases [1, 2, 15]. Female preponderance has been noted in PRS. Though, it is assumed to be a sporadic disorder, rarely familial cases have also been described [16 - 18].

HISTORICAL BACKGROUND

Regardless of the etiology of PRS, evidence has suggested that the history of this disorder dates back to more than 2000 years (Table **17.1**).

Table 17.1. Historical background of Parry-Romberg syndrome.

2001	The history of PRS dates back to more than 2000 years. Appenzeller *et al.* conducted a study titled "Neurology in ancient faces" of 200 mummy portraits painted in color at the beginning of the first millennium. Two of them were found to have PRS. The diagnosis was based on facial features suggesting localized atrophy of the skin and subcutaneous tissues.
2017	Charlier *et al.* retrospectively described PRS in a major French revolution leader Mirabeau (1791).
1825	Late Caleb Hillier Parry presented the first description of Parry–Romberg syndrome.
1846	Moritiz Heinrich Romberg described the disorder.
1871	Eulenberg proposed the term "progressive hemifacial atrophy".
2015	Tolkachjov *et al.* used the synonyms for Parry–Romberg syndrome: idiopathic hemifacial atrophy, progressive hemiatrophy and Romberg syndrome.
2015	Nomura *et al.* suggested that progressive hemifacial atrophy (PHA) can progress in lupus profundus, lipodystrophy, morphea, and Parry–Romberg syndrome.

Appenzeller *et al.* conducted a study of 200 mummy portraits painted in color in 2001. They found two mummies to have this disease [19]. The diagnosis was suggested based on facial features of localized atrophy of the skin and subcutaneous tissues. PRS has been described in a major French revolution leader Mirabeau (1791) retrospectively by Charlier *et al.* in 2017 [20]. The description of first case of PRS was presented by "Collections from the Unpublished Medical Writings of the Late Caleb Hillier Parry" (1825) [3]. Moritiz Heinrich Romberg described the disorder in 1846 [4]. In 1871, it was Eulenberg who introduced the current nomenclature for this disorder: Progressive hemifacial atrophy (PHA) [5]. Tolkachjov *et al.* suggested synonyms for Parry–Romberg syndrome which include idiopathic hemifacial atrophy, progressive hemiatrophy (PHA) and Romberg syndrome [21]. Nomura *et al.* suggested that PHA could progress in morphea, lipodystrophy, lupus profundus, and PRS [22]. The term PHA has been used synonymously with PRS.

EPIDEMIOLOGY

The true incidence and epidemiologic parameters of PRS are not well known due to several reasons which include lack of standardized diagnostic criteria for the disease, rare occurrence of the disease and the overlap of clinical manifestations between PRS and morphea en coup de sabre (ECDS) [2, 23]. PRS is more prevalent in the female sex, similar to morphea. Chiu *et al.* have described a study of 32 pediatric patients, 66% of them were females [24]. Rogers carried out a review of 772 cases having Progressive facial hemiatrophy and found the female to male ratio of 3:1 [25].

CHAPTER 18

Lichen Sclerosus

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Chapter synopsis.
• Lichen sclerosus (LS) is a chronic mucocutaneous inflammatory disease, which involves genital and extragenital skin.
• The etiology of the disease is unknown but several factors including genetic factors, autoimmunity, hormonal factors, infections, and drugs have been suspected.
• The disease has a predilection for females, with the ratio ranging between 3:1 and 10:1. For extragenital involvement, male to female ratio is 1:1.
• Extragenital LS presents with polygonal porcelain-white papules and plaques accompanied by follicular delling and ecchymosis. The condition is most commonly located on the buttocks, thighs, breasts, submammary area, neck, back, chest, shoulders, axillae, and the flexural surface of the wrists.
• Histopathology reveals an atrophic epidermis with the basal vacuolar change, papillary dermal edema, homogenized collagen, and lymphocytic infiltrate beneath the edema.
• Diagnosis depends on clinical examination and is confirmed by histopathology.
• Treatment modalities include topical steroids, topical tacrolimus, phototherapy, antibiotics, and methotrexate among others.

Keywords: Atrophy, Autoimmunity, Corticosteroids, Chrysalis structures, Dermoscopy, Diagnosis, Differential diagnosis, Extragenital, Genital, Histopathology, Inflammation, Inflammoscopy, Lichen sclerosus, Lichenoid inflammation, Keratotic plugs, Malignancy, Methotrexate, Morphea, Phototherapy, Tacrolimus, Sclerosis.

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Tasleem Arif (Ed.)

INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory mucocutaneous disease of genital and extragenital skin. Etiology is poorly understood, however, the role of genetics, autoimmunity and infections, among others, is postulated. The disease commonly involves the anogenital region, where it is usually a scarring condition with a chronic progressive course. Thus, it may cause significant functional (dyspareunia, dysuria) and cosmetic problems (changing the appearance of genitalia). There is a risk of malignant transformation in approximately 5% of genital LS cases [1]. Extragenital LS is thought to affect 15-20% of all patients with LS [2]. Cutaneous LS most commonly involves the upper trunk and does not have a premalignant potential. However, it may cause diagnostic difficulties by simulating various dermatologic conditions including morphea, and is more treatment-resistant [1]. While there are numerous studies about female and male genital LS, studies focusing on extragenital form of the disease are scarce. Thus, this chapter will primarily focus on extragenital LS along with a discussion on genital LS when necessary, in order to define similarities and contrasts between the two forms.

HISTORICAL BACKGROUND

In 1887, the description of a patient with lichenification and pruritus of the vulva along with coalescent papules on the trunk and forearms, by Hallopeau, is usually considered to be the first clinical description of LS [3]. However, in 1875, Weir's report of a case presenting with oral and vulvar "ichthyosis" was possibly the first LS patient described [4, 5]. From his first case until 1898, Hallopeau continued to describe three new cases of LS, which he considered to be an atrophic form of lichen planus due to oral mucosal involvement [6]. From late 1800s to early 1900s, various independent scientists presented the same disease, under different names [3, 4, 7 - 14]. The synonyms used in dermatologic literature to designate LS are listed in (Table **18.1**). Of note, as can be seen in the (Table **18.1**), Breisky's definition of "kraurosis vulvae" in gynecologic literature had preceded Hallopeau's definition in dermatologic literature [7]. Kraurosis vulvae was not linked to LS until 1920 [5]. Similarly, urologic literature referred LS as "balanitis xerotica obliterans" by Stühmer's definition, which was only linked to LS in 1941 [5, 14]. Darier published the classical histopathological features of LS in 1892 [8]. As atrophy is not always present in LS lesions, International Society for the Study of Vulvar Disease proposed the term "lichen sclerosus" in 1976, and since then, this nomination has widely gained acceptance [15].

Table 18.1. Various synonyms of lichen sclerosus.

Synonym	**Author/Year/Reference**
Oral and vulvar ichthyosis	Weir, 1875 [4]
Kraurosis vulvae	Breisky, 1885 [7]
Atrophic lichen planus (“lichen plan atrophique”)	Hallopeau, 1887 [3]
Sclerotic lichen planus (“lichen plan sclereux”)	Darier, 1892 [8]
Playing card scleroderma (“kartenblattförmige sklerodermie”)	Unna, 1894 [9]
White spot disease	Westberg, 1901 [10]
Lichen albus	Von Zumbusch, 1906 [11]
Lichen planus sclerosus et atrophicus	Montgomery and Ormsby, 1907 [12]
Dermatitis lichenoides chronica atrophicans	Csillag, 1909 [13]
Balanitis xerotica Obliterans	Stühmer, 1928 [14]

EPIDEMIOLOGY

Lichen sclerosus may affect patients of all ages and both sexes. However, there is a bimodal distribution of the age of onset. Women are mostly affected in premenarchal and postmenopausal periods [1]. In men, the first peak occurs during childhood while the second peak affects adult men in the late fourth decade [1, 16]. The disease has a predilection for females, with the ratio ranging between 3:1 and 10:1 [17]. For extragenital involvement, this ratio was reported as 1:1, while for extragenital bullous disease, it is similar to that of genital LS [18, 19]. Although reported in various ethnic groups, the condition is seemingly more common in Caucasians [20]. The prevalence of the disorder is difficult to determine owing to the fact that the patients may apply to various specialties, that not all physicians are conversant with LS, and that patients may not present to physicians because of embarrassment or because the disease does not cause any symptoms [1]. An estimated prevalence is between 1:300 and 1:1000 [20]. Extragenital LS affects about 15-20% of all patients with LS [18]. Isolated extragenital LS constitutes only 6% of LS [1]. Extragenital lesions occur more frequently in women, affecting 11% and 13% of women in different series [21 - 23], whereas extragenital disease is rare or absent in men [16, 24].

ETIOPATHOGENESIS

Etiopathogenetic factors involved in the development of LS are summarized in (Box **18.1**).

CHAPTER 19

Pediatric Morphea

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Chapter synopsis.
• Morphea is a rare autoimmune disease characterized by inflammation and limited sclerosis of the skin and underlying tissues.
• Pediatric morphea represents about 15% of all morphea cases and most frequently affects children aged 7-10 years, especially girls.
• The etiopathogenesis of morphea has not been fully revealed. However, it is assumed that genetic and environmental factors as well as immunological and vascular disorders are involved.
• Pediatric morphea is divided into five clinical types: linear, circumscribed, mixed, generalized, and disabling pansclerotic.
• The clinical course of the disease includes three stages: early inflammation, progressive sclerosis and atrophy.
• Management of morphea is based on the clinical type of the disease, its severity and activity, the extent of skin lesions, and the patient's age.

Keywords: Childhood morphea, Clinical types, Circumscribed morphea, Classification, Diagnosis, Deep morphea, Differential diagnosis, En coup de sabre, Extracutaneous manifestations, Generalized morphea, Lilac ring, Linear morphea, Juvenile localized scleroderma, Mixed morphea, Morphea in children, Monitoring, Morbidity, Management, Parry-Romberg syndrome, Pediatric morphea.

INTRODUCTION

Morphea is a rare autoimmune disease characterized by inflammation and limited sclerosis of the skin and underlying tissues (subcutaneous tissue, fascia, muscles, and bones). Morphea is most common among women (2,6-6 times more often), with the peak incidence among 40-50 years [1].

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Pediatric morphea represents about 15% of all morphea cases and most frequently affects children aged 7-10 years, especially girls [2, 3]. Nonetheless, rare cases of congenital morphea have been described (about 0.8% of all morphea cases) [4]. The estimated prevalence of pediatric morphea is 0.34-2.7 cases/100,000/year, however, the real incidence can be higher due to differential difficulties [5]. The clinical manifestation of pediatric morphea is varied based on the disease activity and the extent of tissue involvement [1]. The clinical course of the disease includes three stages: early inflammation, progressive sclerosis and atrophy [3, 6]. The most common clinical type of pediatric morphea (linear morphea) requires prompt immunosuppressive therapy, otherwise it may lead to irreversible orthopedic sequelae [2].The disease is typically diagnosed on the basis of its clinical picture, however, in case of any doubts, a histopathological examination should be performed [7].

ETIOPATHOGENESIS

The etiopathogenesis of morphea has not been fully elucidated. However, it is assumed that genetic and environmental factors as well as immunological and vascular disorders are involved (Fig. **19.1**) [8, 9]. Latest reports have shown human leucocyte antigens such as HLA-B*37, HLA-DR5, HLA-DR8, HLA-DR11; individual and/or a family history of autoimmune diseases predispose to the development of morphea [8, 9]. Moreover, epigenetic factors (*i.e.* decreased DNA methylation and histone acetylation, changed expression of individual miRNA molecules, *e.g.* miRNA-181b-5p, miRNA-223-3p, miRNA-210-3p, let 7i-5p, miRNA-21-5p) are no less important [10]. A number of external factors contribute to morphea onset in susceptible patients – *i.e.* injuries (surgery, injection, tooth extraction, vaccination, insect bites), repeated friction (especially along waistline, groins) and drug use (bisoprolol, bleomycin, D-penicillamine, TNF-α inhibitors) [9]. The above mentioned factors can activate keratinocytes for inflammatory mediators release, which then stimulate immune cells, including lymphocytes, endothelial cells and fibroblasts [9]. Consequently, the production of extracellular matrix increases, what clinically manifests as skin fibrosis and sclerosis [9].

CLINICAL PRESENTATION

According to Pediatric Rheumatology European Society, pediatric morphea is divided into five clinical types: linear, circumscribed, mixed, generalized, and disabling pansclerotic (Table **19.1**) [2, 11]. The differences between morphea in children and adults are presented in (Table **19.2**) [12].

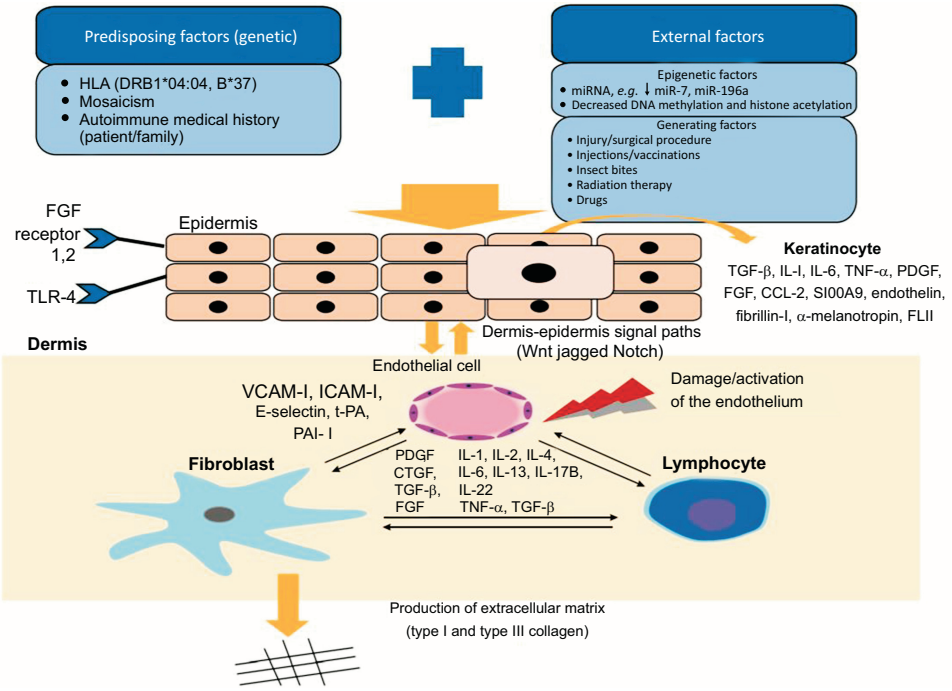

Fig. (19.1). The etiopathogenesis of morphea [8].

Table 19.1. Classification of pediatric morphea published by Pediatric Rheumatology European Society [2, 11].

Type of Morphea	Subtype of Morphea		Description	
Linear	Of extremities		linear, band-like sclerotic lesions occurring along Blaschko's lines	
	Of head and neck	En coup de sabre		
		Progressive facial hemiatrophy/		
Circumscribed	Superficial		Oval/round lesions of >1 cm in diameter, occurring in 1 or 2 different anatomical locations	Involving epidermis and dermis
	Deep			Involving deep layers of the skin, subcutaneous tissue, muscle
Mixed			linear + circumscribed linear + generalized	
Generalized			≥ 4 areas of skin induration, ≥ 3 cm in diameter, in ≥ 2 anatomic sites.	
Pansclerotic			Circumferential involvement of limb(s) affecting the epidermis, dermis, subcutaneous tissue, muscle and bone.	

CHAPTER 20

Eosinophilic Fasciitis

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Chapter synopsis.
• Eosinophilic fasciitis (EF) is a rare disease of sudden onset, characterized by edema, erythema, and rigidity of the limbs, in addition to thickening of the muscle fascia. It is characterized by the absence of sclerodactyly, Raynaud's phenomenon, and capillary changes in the nail folds.
• It was first reported by Shulman in 1974 with scleroderma-like changes associated with peripheral eosinophilia, hypergammaglobulinemia, and increased erythrocyte sedimentation rate.
• About 30 to 46% of patients of EF have a history of intense or unusual physical exercise or a history of trauma. Several drugs, including hemodialysis, radiotherapy, and graft-versus-host disease have also been implicated in its etiology.
• Diagnosis is primarily based on a well-taken history and good clinical examination. Clinically, there is symmetrical and woody edema associated with painful erythema of sudden origin, sparing face, hands, fingers, and feet.
• Histologically, thickening of the muscle fascia is observed, in addition to an infiltrate of lymphocytes, plasma cells, histiocytes, and eosinophils.
• Early diagnosis and treatment are extremely important for clinical response and complete regression of the condition. Spontaneous improvement can occur; however, most cases require drug treatment.

Keywords: *Borrelia burgdorferi*, Chronic synovitis, Eosinophilia, Eosinophilic fasciitis, Erythrocyte sedimentation rate, Fasciitis, Fibrosis, Groove sign, Hypergammaglobulinemia, Joint contractures, Localized scleroderma, Magnetic resonance imaging, Morphea, Peripheral eosinophilia, Scleroderma, Shulman syndrome, Stiffness, Tenosynovitis, Thickening of fascia, Valley sign.

INTRODUCTION AND HISTORICAL BACKGROUND

Eosinophilic fasciitis (EF) is a rare disease, characterized by a sudden onset of edema, erythema and stiffness of the limbs (thickening of the subcutaneous tissue,

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fascia and muscle) [1]. Also called as, Shulman syndrome, its first case was reported in 1974 by Shulman with scleroderma-like changes associated with peripheral eosinophilia, hypergammaglobulinemia, and increased erythrocyte sedimentation rate (ESR) [2]. The relationship between EF and systemic sclerosis (SSC), a disorder with similar clinical and histopathological features, is still not clear; and, although both have symmetrical hardening of the limbs, EF is characterized by the absence of sclerodactyly, Raynaud's phenomenon and capillary changes in the nail folds [3].

Shulman described two patients who presented with peripheral eosinophilia, swelling of the extremities, induration of the skin and soft tissues accompanied by joint contractures in the limbs [2]. In 1975, Rodnan *et al.* reported seven patients with similar signs and symptoms seen by Shulman the year before [4]. They found a large number of inflamed cells in the muscle, fascia and subcutaneous tissue in addition to the peripheral eosinophilia, which was 30% or more of leukocytes [5]. Barnes *et al.*, in 1979, published a study of 20 cases of EF, showing that the common histopathological alterations were thickening of fascia and perivascular inflammatory infiltrate [5].

EPIDEMIOLOGY

EF is a rare connective tissue disease, with fewer than 300 cases reported in the literature [1]. It affects men and women between 37 and 50 years of age and its etiology is not fully understood [5].

Yamamoto *et al.*, in 2020, examined 31 Japanese patients with EF. These authors observed a ratio of male: female of 2.3:1 and a mean age of 47.7 years. They also found some triggering factors associated with EF like muscle training, sports, walking or sitting for a long time, physical work, insect bite and drugs. They observed co-occurrence of morphea in 9 cases (29%), and malignancies in 3 [6]. Several characteristics of various published cases of EF have been summarized in (Tables **20.1** and **20.2**) [1, 5, 7 - 69].

Table 20.1. Some published cases of Eosinophilic Fasciitis [1,5,7 - 69].

Publication Number	Year of Publication	Authors	Refs.	Age	No of Patients	Sex	Sites	Histopathology	Other Comments
1	1976	Atherton *et al.*	7	49	1	M	T; UL	Normal epidermis with an increase of normal fibrous tissue.	-

(Table 20.1) cont.....

Publication Number	Year of Publication	Authors	Refs.	Age	No of Patients	Sex	Sites	Histopathology	Other Comments
2	1977	Krauser *et al.*	9	22	1	F	UL	Severe thickening of the deep fascia associated with lymphocytes and plasma cell infiltrate.	-
3	1978	Weinstein *et al.*	8	55	1	F	UL	Inflammation and thickening of fascia.	Associated with eosinophilia. Good response to treatment with steroids
4	1979	Lupton *et al.*	10	53/59	2	f/m	UL/LL	On histopathology, the fascia was four times thicker than the dermis and epidermis. In addition to an infiltrate composed of lymphocytes, plasma cells, histiocytes and eosinophils	Report of two cases of patients between 50-60 years of age with edema, erythema and hardening of limbs; started by physical exercise
5	1979	Barnes *et al.*	5	20-68	20	f/m	LL/UL	Thickening of muscular fascia with edema and inflammation. Lymphocyte infiltration is observed.	Of the patients evaluated, only 5 had an early diagnosis. All 20 individuals had biopsies showing the characteristic morphological changes of EF. The biopsies were taken from areas of active disease.
6	1979	Jarret *et al*	11	59	1	F	UL	The biopsy showed a thick sclerotic fascia with strong lymphocyte infiltrate, plasma cells, occasional histiocytes and some eosinophils.	Report of a case with clinical and histological characteristic of EF but with progression as scleroderma.
7	1979	Nassonova *et al*	12	26-52	6	m/f	LL/UL	The fascia was thickened in all cases. Inflammatory changes in the fascia of the perimysial tissue were observed in the muscle. Eosinophils were found in the fascia. Most cells were lymphocytes with a variable number of plasma cells. In most cases, the inflammatory infiltrates had a perivascular distribution.	-

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Tasleem Arif

Dr. Tasleem Arif was born in Soura area of Srinagar, Kashmir, India. He acquired his medical graduation from Sher-i-Kashmir Institute of Medical Science (SKIMS) Srinagar, Kashmir, India. He received MD in Dermatology, STDs and Leprosy from Govt. Medical College Srinagar, Kashmir. He worked as Assistant professor in the department of dermatology JNMC in Aligarh Muslim University (AMU), India. He has more than 140 research publications and several book chapters. He is the discoverer of the sign "Tasleem's water jet sign" in dermatology. He has also discovered an innovative technique to measure area of graft required for vitiligo surgeries. He has co-authored an article on Melasma Severity Index (MSI), a new melasma scoring system which has received a national award (Dr S. Premalatha Award-2016) by IADVL. He has won the title World Champion-2019 in Dermatology (Scleroderma) recognized by IASR. His thrust area of research is Scleroderma. He has more than 25 research publications dedicated to scleroderma. As a lead author, his famous research on "esophageal involvement in systemic sclerosis and morphea" has received recognition by NEJM in their journal watch. He has also discovered an Innovative technique for administration of Botox for axillary hyperhidrosis. He is the International Fellow of EADV and Life member of IADVL, ISPD, PDS, ACSI, CDSI, HRSI, IASSTD & AIDS, NSI, CODFI. He has served as reviewer for more than 15 top impact dermatology journals including JEADV, JDDG, Acta Derm Ven, Dermatol Ther, Journal of Rheumatol, European J Derm, Int J Dermatol, etc. He is on the Editorial board of more than 25 journals. Recently, he has been awarded by EADV with prestigious award "Imrich Sarkany Non-European memorial scholarship" at Berlin, Germany -October 2023. He is currently working as Dermatology Specialist in Dar As Sihha Medical Complex, Dammam, Saudi Arabia.