Autoimmune skin diseases and the face

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Autoimmune Skin Diseases and the Face

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ABBREVIATIONS

ACE = Angiotensin-Converting Enzyme

ACLE = Acute Cutaneous Lupus Erythematosus

ADM = Amyopathic Dermatomyositis

ALT = Alanine Aminotransferase

AST = Aspartate Aminotransferase

CCLE = Chronic Cutaneous Lupus Erythematosus

CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index

CK = Creatine Kinase

DIF = Direct Immunofluorescence

DLE = Discoid Lupus Erythematosus

DM = Dermatomyositis

DSSI = Dermatomyositis Skin Severity Index

ELISA = Enzyme-Linked Immunosorbent Assay

EMG = Electromyography

HCQ = Hydroxychloroquine

HLA-B8 = Human Leukocyte Antigen B8

HLA-DR3 = Human Leukocyte Antigen DR3

HLA-DRw52 = Human Leukocyte Antigen DRw52

HLA-DQ1 = Human Leukocyte Antigen DQ1

IVIg = Intravenous Immunoglobulin

LDH = Lactic Dehydrogenase

LE = Lupus Erythematosus

PDAI = Pemphigus Disease Area Index

PF = Pemphigus Foliaceus

PV = Pemphigus Vulgaris

SCLE = Subacute Cutaneous Lupus Erythematosus

SLE = Systemic Lupus Erythematosus

UV = Ultraviolet

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SUMMARY

Autoimmune skin diseases and the face, *Author: Lea Klapan*

The prevalence of autoimmune diseases has increased in the last decade. In order to deal with the escalating figures, we need to know how to recognize them. One of the first indicators which can be noticed is when the condition appears on the skin, especially in the area of the face, due to its obvious and easily accessible location. This thesis deals with four important autoimmune diseases that, among other areas on and in the body, affects the face. They have been chosen due to their prevalence, deleterious effects imposed on the body and quality of life, but also, due to the convenient early symptoms developing on the skin; possibility for the early recognition, diagnosis and treatment. The autoimmune disorders which are about to be discussed in this thesis are: dermatomyositis, lupus erythematosus, morphea and pemphigus vulgaris.

Dermatomyositis is a rare inflammatory disease. It belongs to the group of inflammatory myopathies. It commonly affects the muscles with preceding skin symptoms. The rash that appears is red to purple in color and is usually found on the face (commonly on the eyelids, nose and cheeks) and on the knuckles of the hands. Dermatomyositis can affect adults as well as children.

Lupus erythematosus has a potential to affect many systems in the body, however skin involvement has been perceived as an isolated condition and therefore subjected to different handling. Cutaneous lupus erythematosus is a skin disease which may occur independent of or as an accompanying expression of systemic lupus erythematosus. It is divided into three main subtypes; acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). The types are characterized by photosensitivity and have a predilection to affect the face and sun exposed areas of the skin.

Morphea, a designated term for localized scleroderma, is a chronic condition of unknown etiology. It is the most common form of scleroderma, characterized by thickening of the skin. It can be further divided into subtypes, each with a different clinical manifestation and level of connective tissue involved. Each of the subtypes can affect the face.

Pemphigus vulgaris is the most common type in the group of pemphigus diseases. It is rare and causes painful blistering on the skin and mucous membranes. Blisters have tendency to spread widely and when ruptured, may become infected. Diagnosis is made on the basis of clinical picture and laboratory tests, among which direct immunofluorescence represents the golden standard. Treatment includes systemic corticosteroids and adjuvant therapy, most often azathioprine. Rituximab has been used more often in recent years.

Key words: autoimmunity, disease, face, dermatomyositis, lupus erythematosus, morphea, pemphigus vulgaris

SAŽETAK

Autoimune kožne bolesti i lice, *Autor: Lea Klapan*

Prevalencija autoimunih bolesti je u porastu, što ukazuje na veliku potrebu što brže i pouzdanije dijagnostike. Jedan od prvih indikatora koji pomaže u dijagnozi aktivne bolesti je pojava promjena na koži, ponajviše na koži lica s obzirom na dostupnost i vidljivost područja. U ovom radu opisati ćemo četiri važne autoimune bolesti, koje uz regiju kože lica zahvaćaju i druge organe. Obzirom na njihovu veliku prevalentnost, štetni učinak koji imaju na tijelo te kvalitetu života, no također zbog ranih promjena koje izazivaju na koži; što omogućuje rano prepoznavanje, uspostavljanje dijagnoze i terapije, odlučili smo se opisati dermatomiozitis, lupus eritematozus, morfeu i obični pemfigus.

Dermatomiozitis ubrajamo u skupinu bolesti zvane upalne miopatije autoimunog podrijetla. Karakterizira ga tipični osip na koži koji prethodi progresivnoj slabosti misića. Osip je crvenkasto do ljubičaste boje, najčešće na očnim kapcima, nosu i obrazima, te na zglobovima ruku. Javlja se u odraslih i djece.

Kožni lupus eritematozus može se pojaviti neovisno o ili u sklopu sistemskog lupusa. Razlikujemo tri tipa: akutni, subakutni te kronični kožni lupus eritematozus. Fotosenzitivnost je karakteristična za ovu bolest, kao i sklonost zahvaćanja lica te ostalih dijelova tijela izloženih suncu.

Morfea, lokalizirana sklerodermija, je rijetka kronična bolest nepoznate etiologije. Najčešći oblik sklerodermije karakteriziraju tipična zadebljanja kože. Razlikujemo nekoliko podtipova, svaki sa određenim kliničkim manifestacijama i različitim utjecajem na tkiva. Svaki podtip se može pojaviti na licu.

Vulgarni pemfigus najčešći je oblik unutar grupe pemfigusa. Rjedak je oblik, obilježen bolnim mjehurima na koži i sluznicama. Nastali mjehuri imaju tendenciju širenja te ukoliko dođe do njihovog pucanja, postoji mogućnost suprinfekcije. Dijagnoza se postavlja na temelju kliničke slike i laboratorijskih nalaza među kojima nalaz direktne imunofluorescencije predstavja zlatni standard za dijagnostiku. Liječenje uključuje sistemske kortikosteroide te adjuvantnu terapiju, najčešće azatioprin. Posljednjih godina sve se češće u terapiji primjenjuje rituksimab.

Ključne riječi: autoimunost, bolest, lice, lupus eritematozus, dermatomiozitis, morfea, vulgarni pemfigus

1. INTRODUCTION

Immune system in humans is a body's defence mechanism responsible for maintaining health and resisting development of diseases. It is composed of multitude of structures, agents and processes. In order to perform its role successfully, all of the parts must function appropriately. On a larger scale, immune system can be subdivided into two categories: innate and adaptive, also known as native and acquired, systems. In case when there is malfunctioning of any of the immune system's parts in a sufficient amount, disease arises. Disordered processes can contribute to emergence of autoimmune, inflammatory and neoplastic diseases.

Autoimmune conditions arise when there is an abnormal immune response to one's healthy tissues. The causation is often unknown; however, it is believed that genetics and environmental factors play a great role. Diagnosis most often consists of various laboratory testings, such as complete blood count, inflammatory markers and cytometry, together with clinical findings. Therapy is tailored to the individual and their final diagnosis.

2. DERMATOMYOSITIS

2.1. Introduction

Dermatomyositis (DM) is a rare condition that causes inflammation in both the skin and the muscles. The disease got its name from three separate Latin terms which mean skin (dermis), muscle (myos) and inflammation (-itis). In rare cases, only the skin is affected, without the muscular involvement. DM, together with polymyositis and inclusion body myositis, is categorized as idiopathic inflammatory myopathy. Known to have a bimodal age distribution, it affects children and adults with higher prevalence in the female sex and adults over the age of 50. DM is presumed to occur in genetically predisposed individuals due to a trigger, such as a malignancy, infection or medication, which generates an immune-mediated process. However, patients known to have juvenile dermatomyositis do not have an increased risk of malignancy, but do have an increased incidence of calcinosis cutis and associated small vessel vasculitis. There is a subset of patients in whom the cutaneous manifestations of dermatomyositis exist without objective evidence of muscle inflammation, referred to as amyopathic dermatomyositis, and formerly known as dermatomyositis sine myositis. Amyopathic dermatomyositis is defined as the finding of dermatomyositis in the absence of any clinical or laboratory signs of muscle disease for at least 6 months (formerly 2 years) after the onset of skin pathological conditions. (Gerami, 2006) The most common presentation is symmetric, proximal, extensor inflammatory myopathy and characteristic cutaneous eruption. (Bolognia, 2018) Hallmarks of the disease are myositis with necrosis, regeneration and perifascicular atrophy accompanied by a typical skin rash with heliotrope erythema, Gottron's sign, Gottron's papules and nail fold changes with splinter hemorrhage. (Volc-Platzer, 2015)

2.2. Classification

Table 1: Revised classification system for the idiopathic inflammatory dermatomyopathies

Dermatomyositis (DM)
Adult-onset:
Classic DM
Classic DM with malignancy
Classic DM as part of an overlapping connective tissue disorder
Clinically amyopathic DM
Amyopathic DM (ADM)
Hypomyopathic DM
Juvenile-onset:
Classic DM
Clinically amyopathic DM
Amyopathic DM
Hypomyopathic DM
Polymyositis
Isolated polymyositis
Polymyositis as part of an overlapping connective tissue disorder
Inclusion body myositis

Table 1 source: Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness?, J Am Acad Dermatol. 2002;46:626-36.

2.3. Clinical Appearance

Dermatomyositis affects the skin and muscles. The rash on the skin usually appears before the muscle weakness starts; but it has been known that some people may only develop the skin rash without the muscular component of the disease. People who have DM can often feel tired and weak. Dermatomyositis usually affects the muscles which are involved in everyday movements like the neck, arms or hips. Due to inflammation the muscles may become weak, stiff, sore and tender to the touch. The most characteristic cutaneous DM features are the heliotrope rash (periorbital skin) (Image 1) and Gottron's papules (over bony prominences) (Image 2). The papules particularly affect the metacarpophalangeal, proximal interphalangeal and/or distal interphalangeal joints. Other potential affected locations are the skin overlying the elbows (Image 3), knees and feet, which are then referred to as Gottron's sign. The characteristic rash is often red or purple in color and is usually itchy, particularly if the skin of the scalp is affected which may be manifested as an erythematous psoriasiform dermatitis. If the fingernails are involved, they may be ragged and the skin around them may become inflamed and hypertrophic. The rash is frequently worsened by sunlight exposure and is therefore more obvious on sun exposed areas of the body. Other cutaneous manifestations which could appear as a result of the disease, however not characteristic, are malar rash and poikiloderma (combination of atrophy, disturbed pigmentation and telangiectasia) in a photosensitive distribution; such as extensor surfaces of the arms, 'V' of the neck, upper back (Shawl sign). More rarely occurring cutaneous manifestations include vesiculobullous lesions, eruption stimulating pityriasis rubra pilaris, vasculitis, erosive lesions and exfoliative erythroderma. Facial erythema which as a potential feature of DM must be distinguished from that of Lupus Erythematosus (LE), rosacea, atopic dermatitis and seborrheic dermatitis. A helpful distinguishing factor of DM from LE, is the mid-facial erythema which affects the nasolabial folds in DM which are classically spared in the LE. (Hertl, 2011)

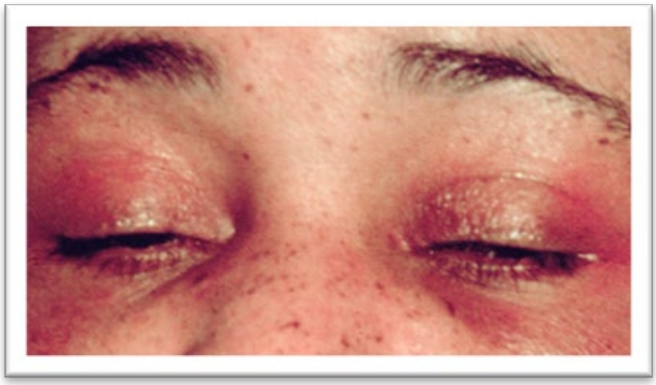


Image 1: Heliotrope rash can look patchy and uneven and is often accompanied by a swollen eyelid

Image 1 taken from: https://commons.wikimedia.org/wiki/File:Dermatomyositis11.jpg

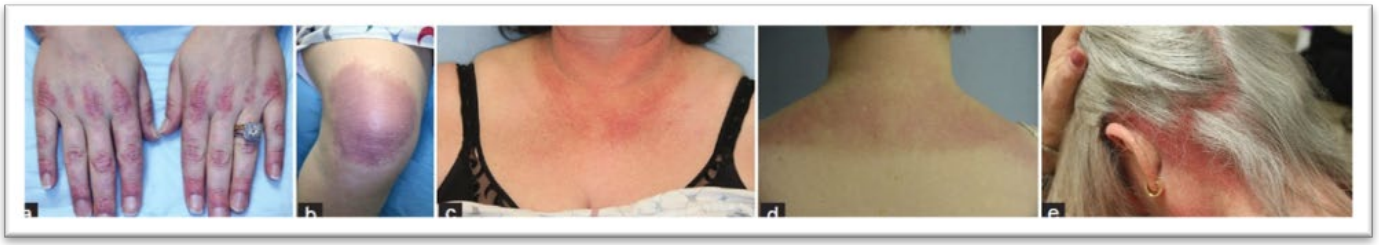


Image 2: (a) Gottron's papules: Violaceous, scaling papules on the skin overlying the joints and proximal nailfolds. (b) Gottron's sign: Violaceous patches overlying the knees. (c) "V neck" sign: Erythematous and hyperpigmented macules on the chest. (d) Shawl sign: Violaceous macules and patches on the upper back and shoulders. (e) Scalp disease in dermatomyositis: Deeply erythematous scaling plaques are seen diffusely on the posterior scalp

Image 2 taken from: http://www.e-ijd.org/viewimage.asp?img=IndianJDermatol_2012_57_5_375_100486_u2.jpg

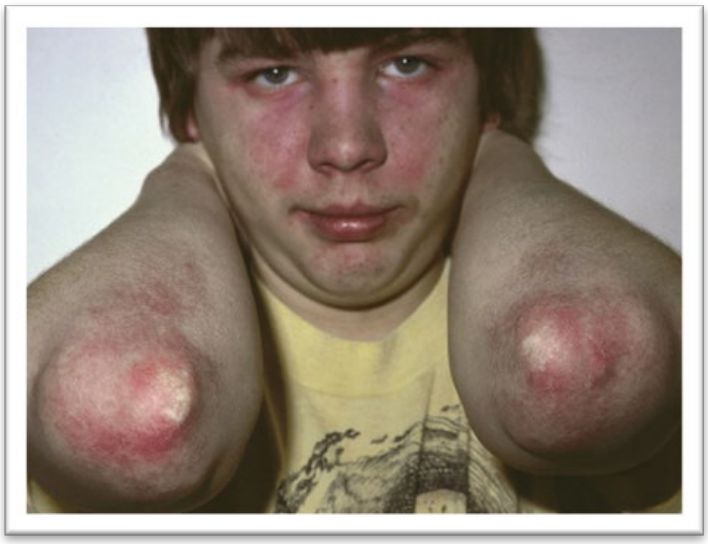


Image 3: Dermatomyositis – marked facial involvement

Image 3 taken from: Bolognia J.L.: Dermatology, Fourth Edition: Elsevier, 2017

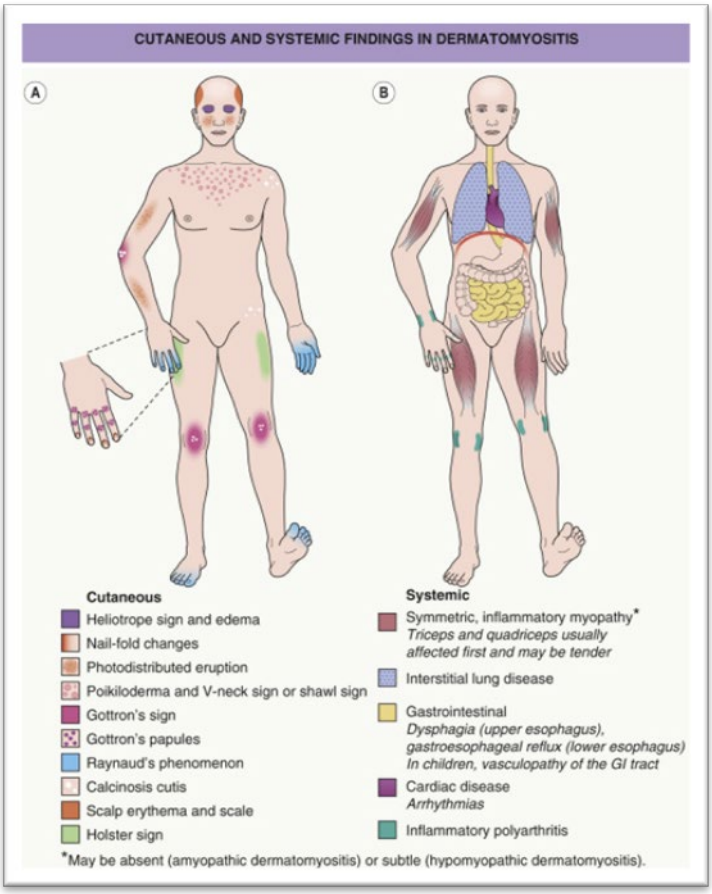


Image 4: Cutaneous and systemic findings in dermatomyositis

Image 4 taken from: Bolognia J.L.: Dermatology, Fourth Edition: Elsevier, 2017

2.4. Diagnosis

Diagnosis is suspected in patients with characteristic cutaneous findings. In order to confirm the suspicion and exclude other potential diseases, patients undergo testings and procedures such as blood tests, skin biopsies, MRI scans to look at the muscles, muscle biopsies, muscle ultrasound, or electromyography (EMG) to record the electrical impulses that control the muscles. Muscle involvement is suspected clinically and enzymatic testing often reveals elevated levels of muscle-derived enzymes which are mostly connected to their overwork, exhaustion or degradation; creatine kinase (CK), aldolase, lactic dehydrogenase (LDH), alanine aminotransferase (ALT), or aspartate aminotransferase (AST). Two validated instruments, the Dermatomyositis Skin Severity Index (DSSI) and the updated Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), can be used to determine the severity of the cutaneous disease of dermatomyositis. These indices should prove helpful in assessing therapeutic responses in future clinical trials. (Caroll, 2008) (Yassaee, 2010) Once the diagnosis has been confirmed, the patient should be evaluated to assess severity, prognosis and associated disorders. Patients should also be evaluated for esophageal, pulmonary and cardiac involvement. (Hertl, 2011)

2.5. Therapy

Patients who have conditions involving muscular problems should be advised to participate in exercise and rehabilitation programs because even in some patients who are responding appropriately to pharmacologic therapies for myositis, a large part of them will develop sustained disability. Studies have demonstrated that patients with inflammatory muscle disease who are participating in these types of programs have improved their muscle strength and endurance, and they have reported reduced disease activity. In addition, strength improvement has been noted even during active phase of the disease, rather than inducing flares in muscle involvement. (Hertl, 2011) Systemic corticosteroids have become the standard therapy for DM muscle disease or systemic involvement. The action of steroid therapy is lowering the immune response and reducing symptoms and/or signs of disease. Initially, a high dose is often used to control the symptoms before gradually tapering the dose over the time span of weeks to months. Long-term use of steroids has associated potential side effects including irritation of the stomach, thinning of the bones (osteoporosis), diabetes, cataracts, glaucoma and weight gain. Strong steroid ointments have been prescribed to treat the skin rash for all skin areas including the face. Even though it is not advised to use the ointment on the area of the skin, in the case of DM, benefits outweigh the risk. Other medications which have been shown to have an effect in DM are methotrexate, mycophenolate mofetil and azathioprine. They can be used on their own or in a combination therapy together with steroids to help the disease. Hydroxychloroquine may be useful for treating the skin rash. In some occasions, injections such as rituximab or intravenous immunoglobulin may be used. Patients who fail to respond to these immunosuppressants may respond to alternatives, which are pulse methylprednisolone therapy, combination immunosuppressive therapy, etanercept, infliximab, rituximab, oral tacrolimus, sirolimus, total body irradiation, or hematopoietic stem cell transplantation. (Hertl, 2011) Due to high photosensitivity of most patients with cutaneous lesions, daily usage of sunscreen is recommended, as well as protective clothing and sun avoidance. (Hertl, 2011)

3. LUPUS ERYTHEMATOSUS

3.1. Introduction

Skin is one of the main target organs known to be affected in lupus erythematosus (LE). Ever since systemic manifestations, without the involvement of the skin, was perceived as an isolated condition, the subject was handled differently in the dermatological, as well as rheumatological literature. Cutaneous lupus erythematosus is a skin disease which may occur independent of or as an accompanying expression of systemic lupus erythematosus. It is divided into subtypes; the three main types being acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). (Grönhagen, 2014)

3.2. SYSTEMIC LUPUS ERYTHEMATOSUS AND ACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a disease that has a potential to affect almost any organ system which, ultimately, results in a wide range of presenting symptoms. However, patients typically display classical manifestations; musculoskeletal, mucocutaneous or constitutional. Twenty percent of all SLE cases present with initial skin manifestations and 50-70% of all SLE will eventually show skin symptom during the course of their disease. (Hertl, 2011) ACLE is the main cutaneous manifestation of SLE, whereas other types appear to a much lower degree. Etiology of acute cutaneous lupus erythematosus (ACLE) is believed, as for other lupus erythematosus types, to be multifactorial; involving genetic, environmental and hormonal factors. Especially for ACLE, in genetically predisposed individuals, exposure to ultraviolet radiation is a frequent trigger. (Grönhagen, 2014)

3.2.1. Cutaneous manifestations

Common mucocutaneous manifestations (appearing in 80-90% of patients) (Image 5, Image 6) are: butterfly malar rash (erythematous rash appearing on the cheeks and nose bridge) lasting days to weeks, discoid scaly erythematous plaques on scalp, face, neck, recurrent oral ulcerations, patchy or diffuse alopecia (lupus hair) and photosensitive rash localized to back, neck, shoulders, extensor surfaces of arms, or generalized over wide body area. (Elsevier Point of Care, 2020) Acute cutaneous lupus erythematosus can be divided into localized ACLE and generalized ACLE. Most common is the localized form with the characteristic presentation of malar rash and erythematous macules which eventually become confluent. Generalized type occurs less often and commonly appears with systemic disease. The exanthem involves the trunk, extremities and UV-exposed parts of the body. Skin lesions appearing in ACLE generally heal without subsequent depigmentation and scarring. ACLE lesions, even though appearing in a similar distribution as CCLE, are different by being more transient, oedematous and erythematous. With the great possibility of characteristic cutaneous symptoms preceding the systemic impact, they should not be overlooked and disregarded, rather, brought to attention and dealt with, with appropriate treatment. As patients with ACLE are ones that most commonly suffer from the systemic disease, they are treated primarily by internal medicine specialists such as rheumatologists, immunologists etc. (Elsevier Point of Care, 2020)

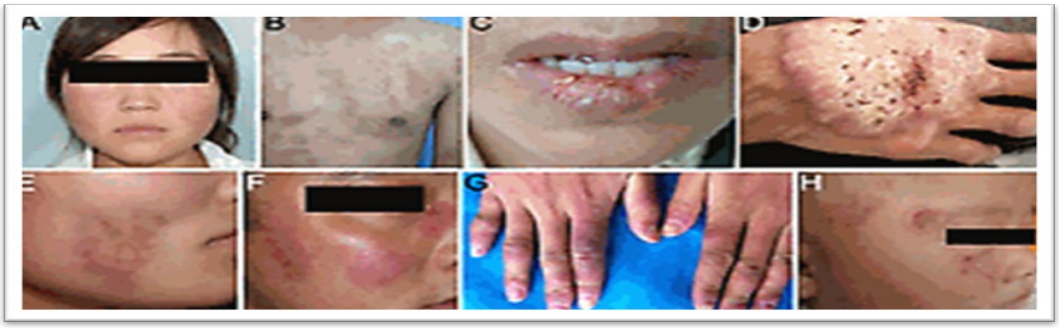


Image 5: Characteristic cutaneous manifestations

Image 5 taken from: Yu C et al: Immunologic and genetic considerations of cutaneous lupus erythematosus: a comprehensive review. J Autoimmun. 41:34-45, 2013

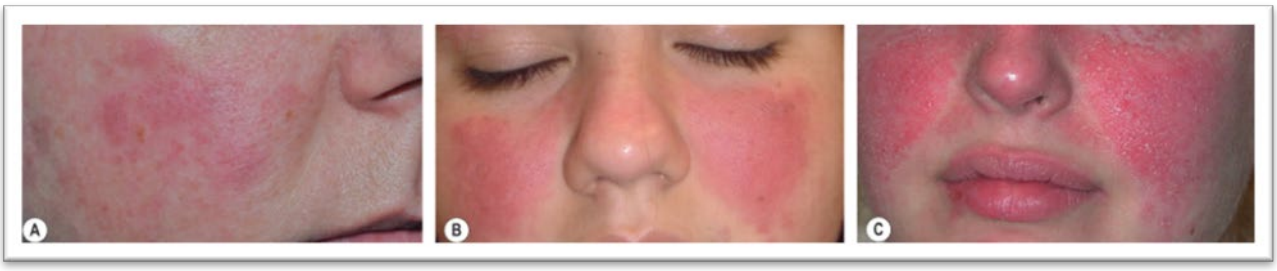


Image 6: Acute cutaneous lupus erythematosus (ACLE).
The facial erythema, often referred to as a 'butterfly rash,' may be variable (A), edematous (B), or have associated scale (C). The presence of small erosions can aid in the clinical differential diagnosis.
Image 6 taken from: Bolognia J.L.: Dermatology Essentials, Elsevier Inc., 2014

3.3. SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

3.3.1. Epidemiology and Laboratory Findings

Differentiation, especially between ACLE and SCLE, on histopathological level can be difficult. SCLE occurs primarily in young to middle aged women. (Walling, 2009) Female to male ratio is 4:1. Occurrence at any age is possible. Eighty-five percent of the initial SCLE cohorts was Caucasian and 15% was African American or Hispanic, whereas the latter two groups comprised approximately 50% of the regional populations. (Okon, 2013)

The Ro/SSA autoantibody is the characteristic laboratory marker, and most are positive for human leukocyte antigen (HLA) D3. ELISA is the assay technique of choice in most laboratories for determining Ro/SSA autoantibodies due to its high sensitivity. Other autoantibodies are present in SCLE with differing prevalence. From 12%–30% of cases may be drug induced. Medication-induced SCLE is traditionally most often related to hydrochlorothiazide due to its wide use, but proton pump inhibitors are increasingly recognized. (William, 2019)

3.3.2. Environmental Factors

Subacute cutaneous lupus erythematosus (SCLE) has been shown to occur in individuals who are genetically predisposed. It has been linked to persons with human leukocyte antigen B8 (HLA-B8), human leukocyte antigen DR3 (HLA-DR3), human leukocyte antigen DRw52 (HLA-DRw52), and human leukocyte antigen DQ1 (HLA-DQ1). (Brezinski-Wallace, 2020) Photosensitivity is seen as one of the major contributing factors for development of SCLE. UV light has been shown to affect the epidermis and dermis by inducing the release of inflammatory mediators, such as IL-1, TNF-alpha, IL-10 and oxygen free radicals. Additionally, drugs which are known to have a photosensitization as a side effect have been reported to induce SCLE lesions. Some drugs have been associated with the induction or exacerbation of SCLE lesions, estimated in up to 30% of patients. Among those are thiazide diuretics, calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors. (Hertl, 2011)

Among others which have been reported due to personal experience and with rarer occurrence are spironolactone, procainamide, sulfonylureas, omeprazole, ranitidine, hormonal therapies, etc. Medications found to be triggers for SCLE are different from those that induce classical SLE (e.g. hydralazine, procainamide, isoniazid, minocycline, sulfasalazine, etanercept). (Hertl, 2011)

3.3.3. Cutaneous Manifestation

The most common forms in which SCLE appears are annular/polycyclic or psoriasiform/papulosquamous (Image 7). The skin lesions usually start by development of red macules or papules which later progress to the two common aforementioned plaques. The distinct feature of this type is high photosensitivity; however, the resulting lesions very rarely appear on the skin of the face. The plaques are commonly found in photosensitive distribution on sun-exposed areas of the skin, such as the V of the lower neck and chest, shoulders, upper back, extensor arms, back of the neck, etc. After the resolution of the inflammation, the lesions clear by leaving hypopigmented areas, especially in the inactive centers of annular lesions. Rare presentations of SCLE have been reported including a morbilliform exanthem, exfoliative erythroderma, pityriasiform lesions, peculiar acral annular plaques, progressive generalized poikiloderma, sunlight induced papulonodular mucinosis, generalized erythroderma with acral bullae preceding SCLE and annular SCLE lesions that were eventually replaced by morphea. (Hertl, 2011)

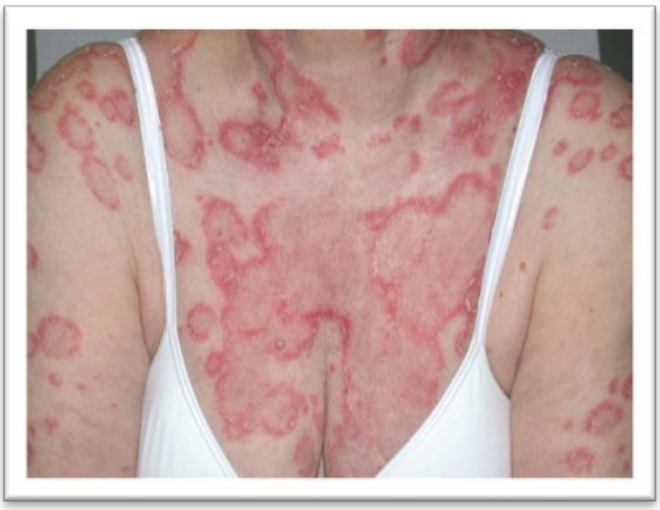


Image 7: Photosensitive annular-polycyclic or papulosquamous eruption distributed symmetrically on sun-exposed areas

Image 7 taken from: https://www.dermatologyadvisor.com/home/decision-support-in-medicine/dermatology/subacute-cutaneous-lupus-erythematosus-scle/

3.3.4. Therapy

Primarily, education of the patient is the most important. Evasion of the sun, UV light and photosensitizing drugs are the baseline measures that every patient with SCLE should undertake. Sun exposure during summer and midday hours is especially important to avoid. Sunscreens with high enough SPF should be applied regularly and in sufficient amounts, protective clothing, hats and vehicle window covers should be utilized. The most appropriate initial topical therapy for SCLE are the super potent topical class I agents. Tacrolimus applied topically may be beneficial in the area of the face and on lesions with less hyperkeratosis, especially due to unknown induction of side effects that are typical for topical steroids. Unfortunately, a high portion of patients do not respond sufficiently to topical therapy which increases the need for systemic therapy introduction. The most efficacious systemic agents proven to treat SCLE are antimalarials, of which hydroxychloroquine and chloroquine are mostly used. Other potential therapies which could be considered are thalidomide, dapsone, methotrexate, mycophenolate mofetil, retinoids, intravenous immunoglobulin, cyclosporine, clofazimine, interferon, immunosuppressive agents such as cyclophosphamide and rituximab. (Winkelmann, 2013)

3.4. CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS

3.4.1. Classification

Chronic cutaneous lupus erythematosus (CCLE) is two to three times more frequent than SLE. It consists of different clinical forms, among which discoid lupus erythematosus (DLE) is the most common. Lesions present in CCLE are long lasting, potentially for decades. Some of the main worrying factors of long-lasting DLE are disfiguring scarring leading to patient's emotional impact and increased risk for development of squamous cell carcinoma. The term DLE should nowadays encompass morphologically distinct plaques, regardless of systemic involvement. Rarely, DLE can be the first presentation which eventually results in systemic disease. The main distinguishing factor between DLE and SLE is the presence of scarring in DLE. One of the other distinguishing factors is the female to male prevalence ratio, which in DLE amounts to 3:2 to 3:1, whereas in SLE it appears to be 9:1. Additionally, the age of disease manifestation is slightly higher, averaging 20-40 years, than it is in SLE. (Hertl, 2011)

3.4.2. Pathogenesis

Table 2: Pathogenetically Relevant Factors for CCLE

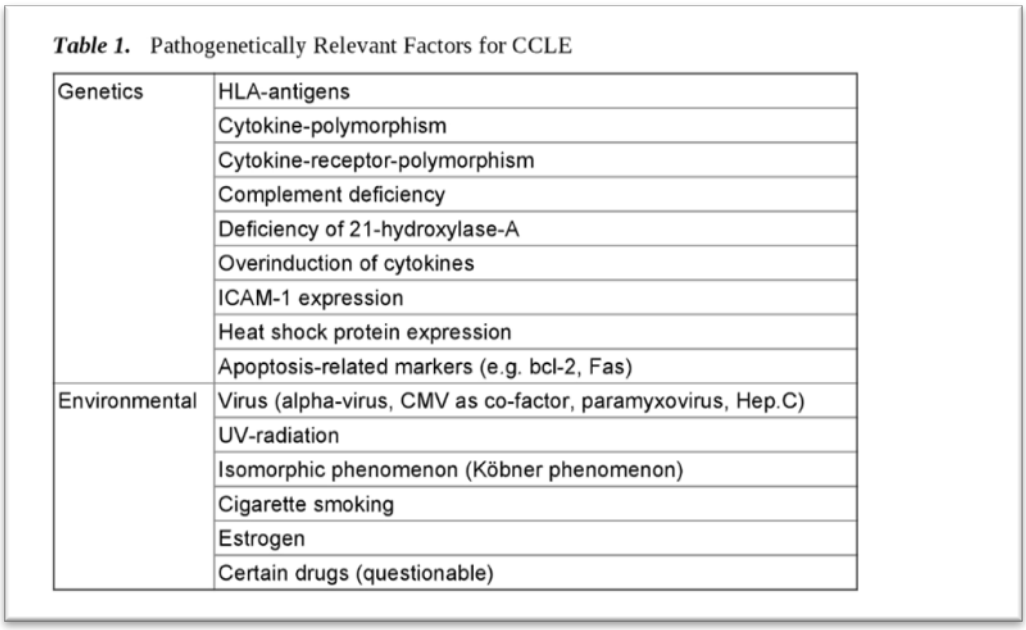


Table 1. Pathogenetically Relevant Factors for CCLE

Genetics	HLA-antigens
	Cytokine-polymorphism
	Cytokine-receptor-polymorphism
	Complement deficiency
	Deficiency of 21-hydroxylase-A
	Overinduction of cytokines
	ICAM-1 expression
	Heat shock protein expression
	Apoptosis-related markers (e.g. bcl-2, Fas)
Environmental	Virus (alpha-virus, CMV as co-factor, paramyxovirus, Hep.C)
	UV-radiation
	Isomorphic phenomenon (Köbner phenomenon)
	Cigarette smoking
	Estrogen
	Certain drugs (questionable)

Table 2 taken from: Hertl M.: Autoimmune Diseases of the Skin: Pathogenesis, Diagnosis, Management, 3rd edition Vienna: Springer, 2011

Detection of viral material like alphavirus or paramyxovirus in skin lesions is perceived as etiologic evidence for LE. Aggravation consequent to the cytomegalovirus infection, as well as a correlation with disseminated DLE lesions and SCLE with chronic hepatitis C virus were linked as possible etiologic factors. Evidence for viral induction can be judged as circumstantial due the known viral influence on the immune system; which acts by activating the proinflammatory cytokines which could trigger the disease, rather than the viral direct impact on the disorder. Distinct drugs do not seem to have an impact as disease inductors. Smoking has been found to have a negative influence on the therapeutic response to chloroquine, additionally, it contributes to the condition's persistence. While hormones were marked as almost irrelevant contributing factors, nonspecific injuries to the skin have shown to induce DLE lesions, leading to the manifestations at unusual locations. (Hertl, 2011) There has been a clear correlation between UV exposure (combination of UVA and UVB, or UVA and UVB separate exposure) and DLE. The course of action after exposure to UV (ultraviolet) light is induction of pro-inflammatory cytokines in keratinocytes and lymphocytes, which leads to induction of local inflammatory mediators which intensify the following feedback from the local level. The resident skin cells (endothelial, mast cells, fibroblasts) and migratory cells (e.g. monocytes, lymphocytes) become activated. (Hertl, 2011)

3.4.3. Clinical appearance

The disease can be divided into multiple categories, with the most common division to localized and disseminated, both possibly having systemic manifestations or appearing without. Systemic manifestations can appear in 10-20% of patients, as they do not develop in the beginning of the disease; they are considered as progression to SLE. Localized DLE frequently involves head and neck, predominantly the scalp and ears. Generalized DLE, occurring above and below the neck, is rarer and commonly involves the extensor surfaces of forearms and hands. The most common form is the chronic discoid lupus erythematosus. Main characteristics are plaques which are sharply demarcated, elevated and erythematous with scales which may rarely ulcerate (Image 8). (Hertl, 2011) In the early stages the lesions are erythematous and hyperpigmented, can be painful to the touch and if left untreated can result in scarring and disfiguration, especially with the facial involvement. Lesions in DLE are mostly found in sun-exposed areas of the body, such as the face, ears, arms (Images 9-11), but can also affect areas which were not exposed to the sun. The prevalence of mucous membrane involvement in chronic CLE is about 25%. Within the mouth, the buccal mucosa is most commonly involved, whereas the palate, alveolar processes, gingivae, and tongue are less frequently involved. (Wallace, 2019) Involvement of the scalp can be found in about 60% of DLE patients. (Hertl, 2011) Localized form of DLE can be demarcated from the neck region above, while the generalized form implies to neck below distribution. Chilblain or perniotic lupus encompasses the violaceous patches and plaques, painful to the pressure, in the regions of the nose, ears, fingers, toes, knees and elbows. Chilblain lupus occurs when there is a temperature drop, and can be difficult to distinguish from frostbite. Lupus tumidus, one of the rare CCLE forms, is characterized by appearance of urticarial plaques due to excessive mucin deposition. Mucosal DLE, form involving the mucous membranes, involves most commonly the oral and buccal areas, but can also manifest in nasal, conjunctival and anogenital mucosal regions. They appear as erythematous patches which have a tendency to ulcerate which could potentially result in atrophy. (Hertl, 2011)

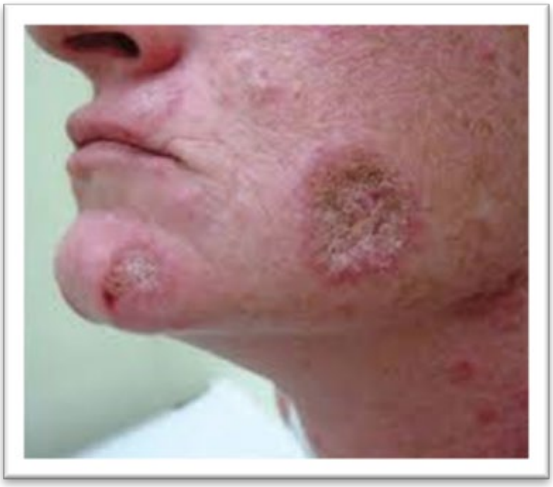
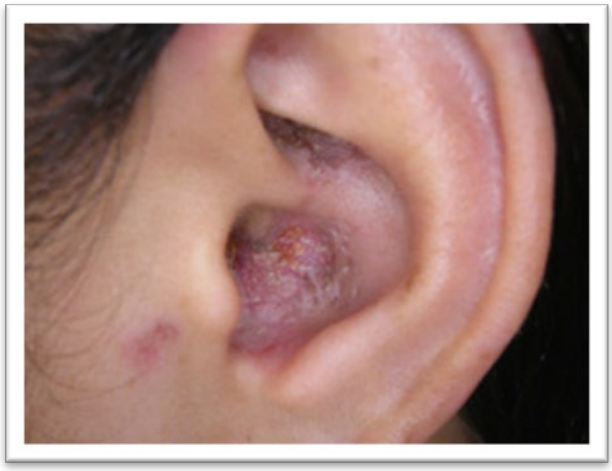
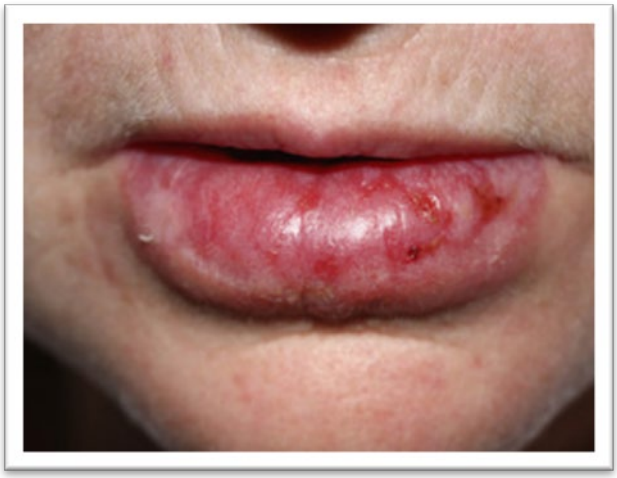
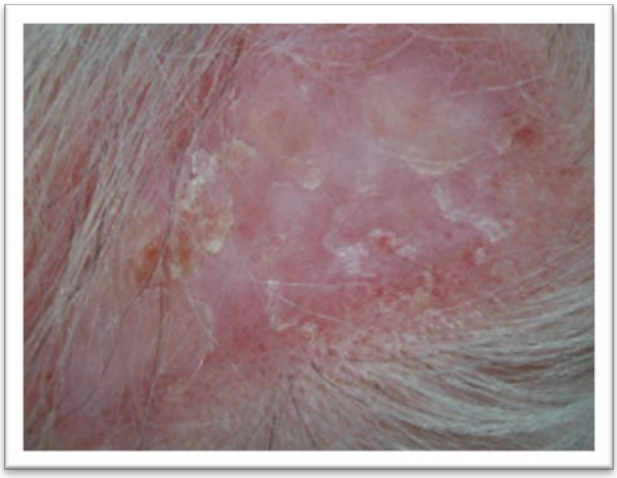


Image 8: Discoid lupus erythematosus, demonstrating coin-shaped plaques with dense peripheral inflammation and central scale

Image 8 taken from: Walling H.W., Sontheimer R.D.: Cutaneous Lupus Erythematosus: Issues in Diagnosis and Treatment: Am J Clin Dermatol 2009;10(6):365-81







Images 9 – 11: Chronic discoid lupus erythematosus of the ear, lip, on the scalp

Images 9-11 taken from: https://dermnetnz.org/topics/discoid-lupus-erythematosus/

3.4.4. Diagnosis

Patients with skin manifestations without systemic involvement will present to dermatologists. When it is suspected that internal organs are affected, patients are redirected to general practitioners or rheumatologists. Patient's history should have a focus on LE-related symptoms; e.g. photosensitivity, arthralgias, alopecia, Raynaud's phenomenon, morning joint stiffness, thrombosis, spontaneous abortions, atypical pneumonia, carditis and neurological disorders. Typical histology findings, depending on the stage of the disease, include epidermal hyperkeratosis, epidermal atrophy, thickening of the epidermal basement membrane, basal cell degeneration, mononuclear cell infiltration at the dermo-epidermal junction, adnexal structures and blood vessels. CLE diagnosis should be based on the findings of patient history, clinical exam, laboratory studies, serology, as well as histology and direct immunofluorescence (DIF) exam of skin biopsies if the histology is not diagnostic. (Okon, 2013) Serologically, DLE patients have a lower incidence of ANA, dsDNA, Sm, U1RNP, and Ro/SSA antibodies, as compared to other CLE subtypes. The cornerstone of CLE diagnosis is a lesional biopsy for histology. (Okon, 2013)

3.4.5. Therapy

Primarily, dermatologists try to prevent the formation and progression of lesions, and improve appearance of the skin by educating the patient, and utilizing the topical and systemic treatments. As a preventative measure, patients should avoid exposure to the sun and use protective measures such as hats and sunscreen with SPF50. Picking on the lesions should be avoided as this can lead to permanent scarring and development of new lesions. Treatment of CLE lesions should firstly begin with topical therapies, including steroids and/or calcineurin inhibitors, but should be advised to use with caution when applying to the face. Finding based on trials support the higher efficacy of high-dose usage over low-dose steroids, but due to known side-effects of steroid treatment, lowest potency needed for resolution should be used for the shortest duration possible. A variety of steroids is prescribed, depending on the area of the body where the therapy should be applied (e.g. scalp, thinner skin areas, thicker skin areas). Topical steroids are often prescribed as creams, whereas in cases of a more severe disease, ointments may be required. Systemic therapies, such as oral corticosteroids, are indicated in cases where there is widespread or scarring disease, or in cases refractory to topical treatments, but is generally avoided when not pressingly needed due to risks of side effects. Antimalarials remain the cornerstone of treatment, with methotrexate, acitretin, isotretinoin and dapsone being second-line agents, and azathioprine, thalidomide, mycophenolate mofetil, sulfasalazine and oral gold being third-line. (Lee, 2020) When systemic treatments are prescribed, topical agents are typically continued as adjunctive therapy. (Okon, 2013)

Table 3: Algorithm for cutaneous lupus erythematosus treatment. Localized disease is initially treated with topical agents (either corticosteroids or calcineurin inhibitors. Hydroxychloroquine is also often used, depending on the site or if there is scarring disease. Widespread or scarring disease treatment starts with topicals and hydroxychloroquine (HCQ). If this fails, quinacrine is added to HCQ. If this regiment fails, a switch to chloroquine can be made, while continuing quinacrine. If this fails, other options include mycophenolate mofetil or mycophenolate sodium, azathioprine, dapsone, retinoids and thalidomide can be considered. In this case of failure of these agents, experimental therapy can be considered

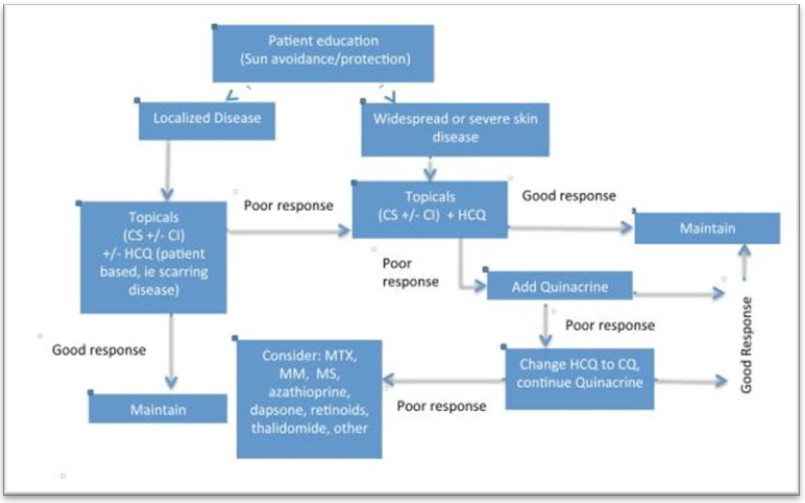


Table 3 taken from: Okon L.G., Werth V.P.: Best Pract Res Clin Rheumatol. 2013 Jun; 27(3): 391-404.

4. MORPHEA

4.1. Introduction

The word scleroderma is made up of two Greek terms; skleros which means hard, and derma meaning skin. The condition appears rarely and is affecting the connective tissues. It is characterized by cutaneous inflammation, in which there is collagen deposition in the skin as well as occasionally in other organs, resulting in sclerosis and systemic involvement. Scleroderma is subdivided into two categories; systemic – which affects the visceral compartment (especially esophagus, lung and vascular system) as well as inducing cutaneous sclerosis, and localized – which primarily affects the skin but can affect the underlying tissues as well. While systemic scleroderma typically affects older women and has characteristic manifestations such as hair loss, anhidrosis, facial telangiectasia, mouth opening limitations and xerostomia, localized scleroderma has a predominance in the younger age group. Localized scleroderma, by contemporary literature advised to be called morphea, is a chronic condition of unknown etiology. It is the most common form of scleroderma and is characterized by thickening of the skin and accumulation of collagen in the indurative lesions. Morphea can be further divided into subtypes, with each having a different clinical manifestation and level of connective tissue involved. Each of the subtypes can affect the face. (Hertl, 2011)

4.2. Clinical Appearance/ Classification of Morphea

Morphea is divided into 5 subtypes: plaque, generalized, bullous, linear and deep. The division is based on the type's extent, form and depth of cutaneous sclerosis. It is not uncommon for these subtypes to occur at the same time in one patient. (Hertl, 2011)

Plaque Morphea

This is the most common form of morphea. It can appear in all parts of the body with a higher predominance occurring in the trunk site. It is characterized by the presence of round or oval patches found on shiny and hard skin. If noticed in the inflammatory phase, a violaceous halo (Image 12)can be found around the lesions. Over time, from months to years, they soften, become atrophic and change pigmentation. The atrophic changes may progress to involve the dermis and/ or subcutaneous tissue which ultimately results in change of the skin surface producing wrinkling or induration. (Hertl, 2011)

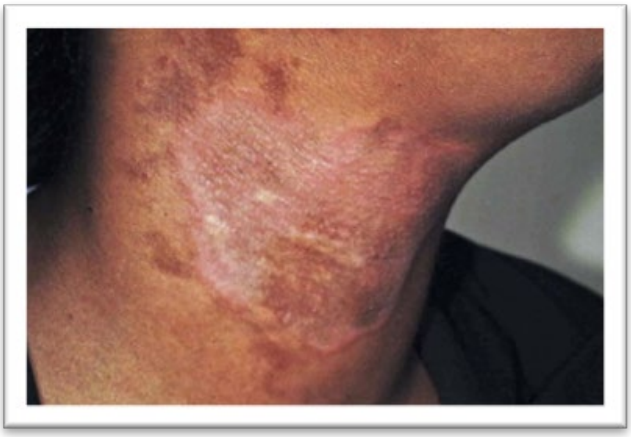


Image 12: Slightly raised, erythematous plaque in a patient with morphea
Image 12 taken from: Taliaferro S.J.: Collagen Vascular Diseases: Treatments for Skin of Color, Elsevier Inc 2011

Generalized Morphea

Form is deemed generalized when lesions are found on more than 3 sites. Most common areas of appearance are the trunk, upper thighs and lumbosacral region (Image 13). The appearance of plaques is described as slightly inflamed, pigmented, ill-defined, thickened and adhered to deep planes, fascia and muscle. There is female predominance and it is believed that physical activity can be a triggering factor. Generalized morphea, although not typical childhood disease, has been reported in children; in for example one case; it reportedly began at a BCG vaccination site. (Matsumoto, 2015) Disabling pansclerotic morphea is an aggressive variant of the generalized type and is of earlier onset, although it can appear later in adult life. (Maragh, 2005)

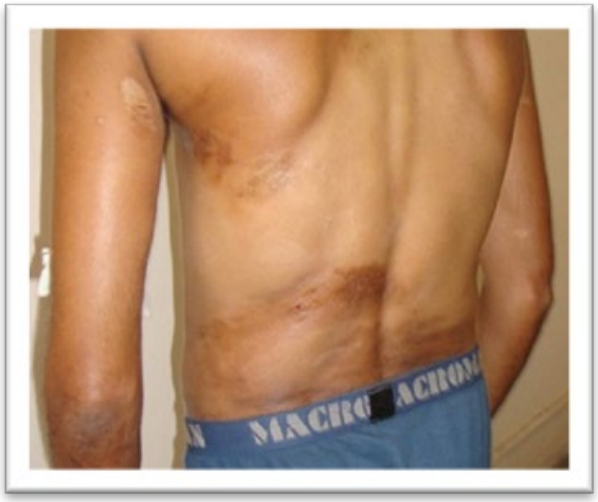


Image 13: Indurated sclerotic plaques on back and scapular area

Image 13 taken from: Balegar S, Mishra KD, Chatterjee S, Kumari S, Tiwary AK. Generalized morphea following radiotherapy for an intracranial tumor. Indian J Dermatol. 2016; 61(5):581.

Bullous Morphea

Rare form of morphea. Presence of tense subepidermal bullae (Image 14) or erosions on morphea plaques is characteristic for this type. Bullous morphea may appear alongside any other morphea subtype. The most common regions affected are believed to be lower extremities. (Hertl, 2011)

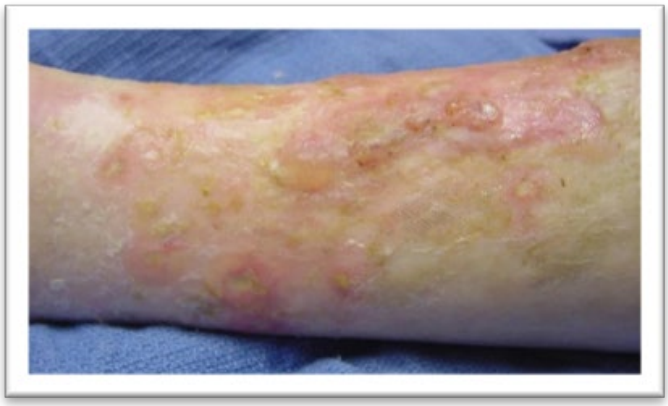


Image 14: Bullous morphea on the lower extremity

Image 14 taken from: Morphea, Atlas of Dermatology, 2010
http://www.dermaamin.com/site/index.php?option=com_content&view=article&id=212:bullous-morphea--&catid=2:b&Itemid=3

Linear Morphea

Linear scleroderma is characterized by one or more linear streaks of cutaneous induration that may involve dermis, subcutaneous tissue, muscle and underlying bone. (Careta, 2015) Features which are characteristic for this type of morphea are; collage deposition in the dermis and subcutis, vascular changes, as well as inflammatory cell infiltration. Due to the potential bone affliction, it can cause impaired growth and joint contractures, as well as cosmetic, functional and psychologic problems. This form is predominantly found in children. The inflammatory violaceous brim around the lesions is commonly absent. The appearance is generally found in the distribution of Blaschko's lines. Blashko's lines are the pattern assumed by many different nevoid and acquired skin diseases on the human skin and mucosae. (Jackson, 1976) The onset of linear scleroderma is sometimes abrupt and occasionally follows trauma. (Falanga, 1986) Its mean duration is longer than that of plaque-type morphea, and it is less likely to resolve as completely. Linear morphea can be even further subdivided into:

Acral linear morphea: Lesions are mostly found on the lower extremities. Characteristic indurations involve the dermis, subcutaneous tissue, muscle and bone. It is not uncommon for arthralgia and edema to appear before the lesions in affected areas. Most commonly manifested in children.

En coup de sabre: This type got its name due to the saber cut-like scar that it produces (Image 15). It is more likely to appear bilaterally than other linear forms. Lesions are mostly affecting the face and scalp, and are shown to generally follow one of two lines. The first descends vertically from the frontal scalp to the side of the nose, adjacent to the midline. The second starts close to the vertex and progresses forwards to the lateral forehead, and then medially towards the inner canthus. (Hassan, 2019) The pathway of sclerosis is thought to start from the outermost layer progressing inwards; from the skin to underlying fascia and bone. It is associated with facial hemiatrophy (Parry-Romberg syndrome) from which it can be distinguished. (Dervis, 2005) Some of the distinguishing factors being the presence of cutaneous sclerosis, cutaneous hyperpigmentation and alopecia which were seen to be more present in en coup de sabre than Parry-Romberg syndrome.

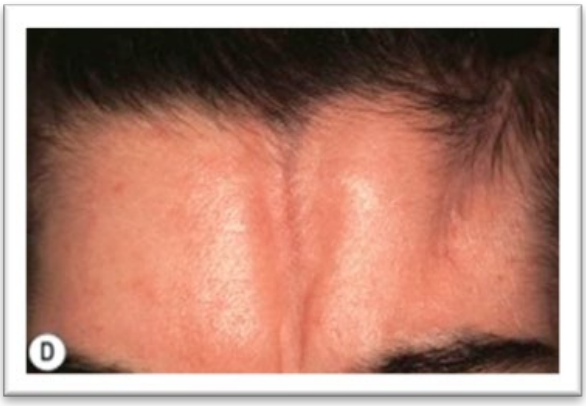


Image 15: *En coup de sabre* with linear paramedian depressions and sclerosis
Image 15 taken from: Bolognia, Dermatology Essentials, Elsevier Inc. 2014

Progressive hemifacial atrophy: Believed to be a primary atrophic disorder affecting the subcutaneous tissue, muscle and bone, with ocular changes and absent skin indurations distinguishing it from en coup de sabre. Lesions continue to extend and involve the cheeks, tongue and mandible. If the condition appears in early age, it can affect the mandible and maxilla resulting in hypoplasia causing prominent facial disturbances. (Deshingkar, 2012)

Deep Morphea

Deep morphea is commonly characterized by a single lesion, occurring in the subcutaneous tissue (fat, fascia or superficial muscles) (Image 16). It is usually asymptomatic, without visceral involvement, however, when a subcutaneous region of a part of the body is affected, the overlying skin can be of normal, atrophic or of hardened appearance, and is almost always adherent to the underlying structures. There have been cases linked to development of isolated deep morphea after vaccination and vitamin K injections, which are sometimes used therapeutically in certain hematologic conditions. (Torrelo, 2006) (Morell, 1995)

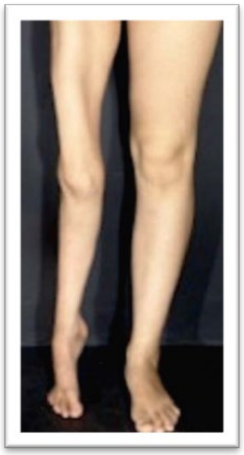


Image 16: Deep morphea involving the right lower extremity

Image 16 taken from: Mariana Figueiroa Careta MF, Romiti R. Localized scleroderma: clinical spectrum and therapeutic update. An Bras Dermatol. 2015; 90(1): 62–73.

4.3. Diagnosis

Clinical findings and histology are the base for diagnosis. There are no reliable laboratory markers to track disease activity. Active disease features the extension and/or appearance of lesions and the presence of a violaceous halo around the plaques, which can be noticed clinically. Serial tracking of eosinophilia, hypergammaglobulinemia and ANA titers may be of value in determining disease progress and activity. Neurologic findings such as seizures, migraine headaches, focal neurologic deficits, and asymptomatic MRI abnormalities are seen in some patients, predominately those with linear morphea of the head and neck. Musculoskeletal complications can include joint contractures, limb length and girth discrepancies, arthritis, and arthralgias, and these are most common in children with linear morphea of a limb. (Careta, 2015)

4.4. Therapy

Morphea has a tendency for recurrence and has been shown to spontaneously regress in the period of 3-5 years subsequent to its appearance. There is no therapy which has been widely accepted. Treatment is mostly chosen based off the clinical subtype and is urged to start as soon as possible due to the disease's tendency for having functional and cosmetic consequences. Topical and systemic immunosuppressants have been the mainstay of therapy due to the belief that the immune cell activation is the cause of skin sclerosis development. Other therapies which have shown result are UVA treatment of different dosages, both oral and topical calcitriol, - alone or used together with a psoralen cream and UVA, methotrexate, D-penicillamine and antimalarials. (Kliegman, 2020)

5. PEMPHIGUS VULGARIS

5.1. Introduction

Pemphigus is a term that encompasses a group of autoimmune skin and mucosal diseases, of which pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the most common. Immunoglobulin A pemphigus, pemphigus erythematosus, pemphigus vegetans and paraneoplastic pemphigus are some of the other types which belong to the group of pemphigus diseases. These diseases are characterized, on the histological level, by blisters in the epidermis occurring due to loss of intercellular connections and by circulating immunoglobulins which are targeting the surface of the keratinocyte cells. PV is found to be more common in people of Jewish, Mediterranean and Middle Eastern descent. The approximate age of onset is considered to be 40 years. Epidemiologic studies have detected a link between PV and other autoimmune diseases such as autoimmune thyroid disease, rheumatoid arthritis and diabetes type 1, showing greater prevalence of these in patients suffering from PV than in general population. Higher prevalence has also been linked to family members of PV patients indicating an underlying genetic susceptibility. (Parameswaran, 2015)

5.2. Etiology

The main difference between the two most common pemphigus types, is that in PV, the characteristic blisters develop in the deeper epidermal layer than they do in the PF case where the blisters occur in the more superficial, granular layer. The main antibody in PV is directed against desmoglein 3, which is found in deeper epidermal layers in contrast to desmoglein 1, which is the target in PF, found in more superficial layers. In about 80% of the patients with an active disease, there is presence of circulating antibodies which corresponds to the disease severity. Factors found to contribute to the disorder's development are phototherapy and several drugs, such as captopril, penicillamine, aspirin, calcium channel blocker and rifampin. (Lee, 2020)

5.3.Clinical Features

The primary finding in PV is a flaccid blister which has a tendency to burst easily. These lesions can be painful and/or pruritic, and appear anywhere on the skin (Image 17, Image 18), with the least likelihood of occurrence on the palms and soles. Due to the blisters' high fragility, the most common characteristic clinical finding are erosions which are quite large in size and spread easily. These erosions can extend to normal surrounding skin in cases when the roof of the blister remnants are pulled or when the periphery of active lesions are rubbed. The Nikolsky sign, which helps in differentiation between pemphigus and pemphigoid, is a phenomenon which describes the appearance of newly formed blisters in normal-looking skin, away from active lesions, by use of pressure or mechanical force. In approximately 60% of affected patients, the disease first appears on the oral mucosa which then progresses to generate changes on the skin. Mucosal membranes of the oropharynx and nasal mucosa are mostly affected in PV. Similarly to the skin, mucosal blisters are usually not intact leading to existence of painful erosions which results in odynophagia which could ultimately result in patient's hospitalization for disease control, fluid and nutrition replenishment. Painful oral lesions can precede the more generalized eruptions by 5 months to a year. (Ljubojevic, 2002)

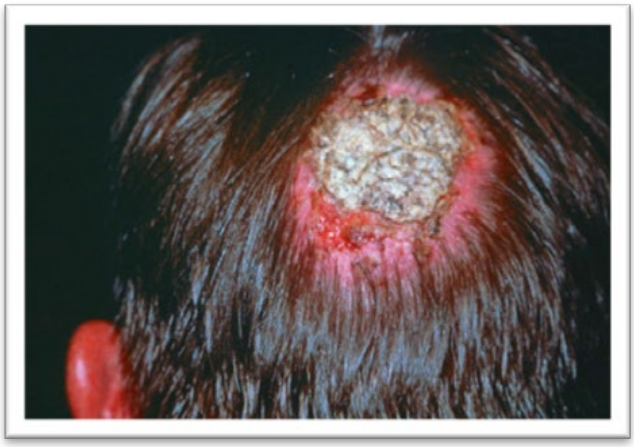


Image 17: Chronic pemphigus vulgaris of the scalp

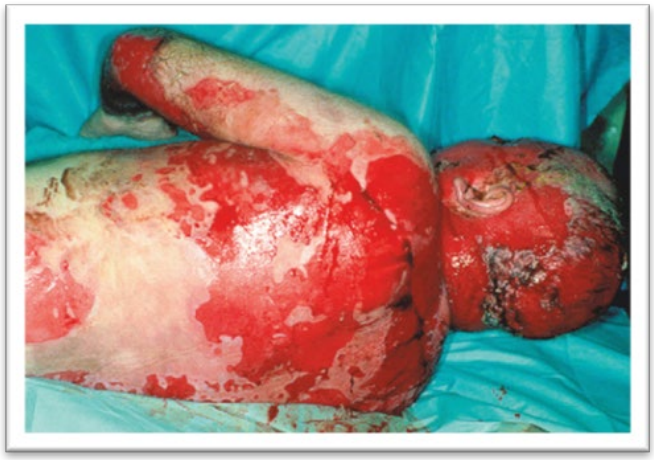


Image 18: Generalized cutaneous involvement

Images 17 and 18 taken from: James W.D.: Andrews' diseases of the skin, Edition 12, Elsevier, 2016

5.4. Diagnostics

Various testings are available, but skin biopsy remains the mainstay of diagnostics. The specimen taken should be sent for histochemical staining and direct immunofluorescence which is considered to be the golden standard for diagnosis. The characteristic laboratory findings are: light microscopy with findings of intraepithelial blisters with acantholysis; basal layer with single layer of intact cells (known as "tombstoning"), DIF with characteristic intercellular IgG and C3 deposition in "chicken-wire" lattice pattern, IIF tests for presence and titer of antibodies which should be used in conjunction with clinical, histopathological, and DIF evaluation; having estimated 90% positive predictive value and low negative predictive value; titers may correlate with disease state and can potentially be used for tracking progression and treatment response. Finally, ELISA (Enzyme-Linked Immunosorbent Assay) shows similar sensitivity but inferior specificity compared to IIF; antidesmoglein antibodies titers correlate with disease activity (however, there are a subset of patients with high anti-Dsg-3 antibodies but low disease activity). (Lee, 2020)

5.5. Treatment

A rating scale which is used to determine the severity of the disease, Pemphigus Disease Area Index (PDAI), integrates cutaneous with mucosal disease in well-defined anatomical locations, assesses number and sizes of lesions and also scores post-inflammatory hyperpigmentation of resolving lesions. (Grover, 2011) Because of the likelihood of potential lifethreatening infection due to secondary infections and metabolic disturbances, the condition should be treated approprately. Therapy starts with nonpharmacologic treatement which is considered supplemetary to the prescribed pharmacological; usage of mild soaps and emollients, ingestion of soft food and viscous lidocaine in patients with oral ulcers, avoidance of trauma in aims of stopping the spread and promoting containment of lesions. Systemic corticosteroids remain the gold standard treatment. In case of acute exacerbations, topical steroids are used for localized, while oral glucocorticoids for generalized conditions. Rituximab is extremely effective in recalcitrant pemphigus, when other treatments fail to control the disease. (Gregoriou, 2015) Adjuvant therapies are often initiated simultaneously with prednisone to minimize the side effects of prolonged corticosteroid therapy. These include azathioprine, mycophenolate mofetil, cyclophosphamide, dapsone, rituximab, intravenous immunoglobulin, and plasma exchange. These agents help reduce the risk of relapse. Adjuvant therapy such as immunosuppressants, anti-inflammatories, chemotherapeutic agents, and biologics are useful for disease control and to shorten the length of treatment with oral steroids in chronic disease states. The current treatment protocol states that the IV immunoglobulins are used for refractory diseases and in patients having contraindications to immunosuppressants. As a supporting argument to that and as a contributing presentation of support for its usage as an addition to standardized therapy, the article published in International Immunopharmacology states that; the multidrug protocol protects keratinocytes from autoantibody attack by systemic corticosteroids and mitochondrion-protecting drugs, selectively eliminates pathogenic autoantibodies by intravenous immunoglobulin (IVIg) and inhibits autoantibody production by cytotoxic immunosuppressors. Therefore, IVIg should be always added to the prednisone/rituximab regimen that does not eliminate circulating autoantibodies. To decrease risk for relapse to a minimum, PV should be maintained in full clinical remission until the critical mass of autoreactive plasma cells dies off. (Grando, 2020)

6. CONCLUSION

It was previously thought that autoimmune diseases are rare. With investigation, improved technology, newly gained knowledge, deeper understanding and insights, it has been estimated that nearly 8% of the world's population are diagnosed with some form of an autoimmune condition, 78% of whom are women. (Grando, 2004) In spite of new advances in diagnosing and treatments, there is still extensive lack of data which would explain the etiology of these diseases. Factors proven to have an impact are genetics and the environment. In order to prescribe an appropriate, effective treatment, doctors must be able to correctly diagnose the condition. Since multiple disorders have similar symptomatology and clinical picture, a physician has to be fully aware of all the potential differential diagnoses, their respective characteristics and attempt to exclude until confirming the correct one. Physicians have to conduct a thorough patient history and physical examination on account of knowing that they are the main source of information needed to make a diagnosis. Knowing that starting the therapy early on, in most disorders, has the greatest effect, no symptoms should be left unattended. A substantial amount of autoimmune conditions affect the skin, which should not be neglected and undermined. Knowing that most diseases that start off by impacting the skin progress to affect other regions of the body, such as the organs leading to deleterious effects, it is essential that they are diagnosed and treated early. Seeing how the face is the first part of the body we see in a person and the state of the skin is the mirror of internal processes, all changes should be noticed, kept track of and, eventually when diagnosed, appropriately treated. Due to the easy accessibility and convenient location of the skin of the face, no cutaneous change should be overlooked. As the quality of our skin contributes to our overall wellbeing, skin diseases do not just impose a threat to our health, but also to the quality of life in general. The diseases discussed in this thesis impose great burden on patient's lives. Due to their characteristic appearance, they should be recognized and treated early in aim of improving the patient's life in its entirety.

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Table 1: (Revised classification system for the idiopathic inflammatory dermatomyopathies) Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness?, J Am Acad Dermatol. 2002;46:626-36.

Table 2: (Pathogenetically Relevant Factors for CCLE) Hertl M.: Autoimmune Diseases of the Skin: Pathogenesis, Diagnosis, Management, 3rd edition Vienna: Springer, 2011

Table 3: (Algorithm for cutaneous lupus erythematosus treatment) Table taken from: Okon L.G., Werth V.P.: Best Pract Res Clin Rheumatol. 2013 Jun; 27(3): 391-404.

Image references:

Image 1: (Heliotrope rash can look patchy and uneven and is often accompanied by a swollen eyelid) Taken from: https://commons.wikimedia.org/wiki/File:Dermatomyositis11.jpg

Image 2: (Dermatomyositis clinical appearances) Taken from: http://www.e-ijd.org/viewimage.asp?img=IndianJDermatol_2012_57_5_375_100486_u2.jpg

Image 3: (Dermatomyositis – marked facial involvement) Taken from: Bolognia J.L.: Dermatology, Fourth Edition: Elsevier, 2017

Image 4: (Cutaneous and systemic findings in dermatomyositis) Taken from: Bolognia J.L.: Dermatology, Fourth Edition: Elsevier, 2017

Image 5: (Characteristic cutaneous manifestations of SLE) Taken from: Yu C et al: Immunologic and genetic considerations of cutaneous lupus erythematosus: a comprehensive review. J Autoimmun. 41:34-45, 2013

Image 6: (ACLE appearance) Taken from: Bolognia J.L.: Dermatology Essentials, Elsevier Inc., 2014

Image 7: (Photosensitive annular-polycyclic or papulosquamous eruption distributed symmetrically on sun-exposed area) Taken from: https://www.dermatologyadvisor.com/home/decision-support-in-medicine/dermatology/subacute-cutaneous-lupus-erythematosus-scle/

Image 8: (Discoid lupus erythematosus, demonstrating coin-shaped plaques with dense peripheral inflammation and central scale) Taken from: Walling H.W., Sontheimer R.D.: Cutaneous Lupus Erythematosus: Issues in Diagnosis and Treatment: Am J Clin Dermatol 2009;10(6):365-81

Images 9-11: (Chronic discoid lupus erythematosus of the ear, lip, on the scalp) Taken from: https://dermnetnz.org/topics/discoid-lupus-erythematosus/

Image 12: (Slightly raised, erythematous plaque in a patient with morphea) Taken from: Taliaferro S.J.: Collagen Vascular Diseases: Treatments for Skin of Color, Elsevier Inc 2011

Image 13: (Indurated sclerotic plaques on back and scapular area) Taken from: Balegar S, Mishra KD, Chatterjee S, Kumari S, Tiwary AK. Generalized morphea following radiotherapy for an intracranial tumor. Indian J Dermatol. 2016; 61(5):581.

Image 14: (Bullous morphea on the lower extremity) Taken from: Morphea, Atlas of Dermatology, 2010 http://www.dermaamin.com/site/index.php?option=com_content&view=article&id=212:bullous-morphea--&catid=2:b&Itemid=3

Image 15: (*En coup de sabre* with linear paramedian depressions and sclerosis) Taken from: Bolognia, Dermatology Essentials, Elsevier Inc. 2014

Image 16: (Deep morphea involving the right lower extremity) Taken from: Mariana Figueiroa Careta MF, Romiti R. Localized scleroderma: clinical spectrum and therapeutic update. An Bras Dermatol. 2015; 90(1): 62–73.

Image 17 and 18: (Chronic pemphigus vulgaris of the scalp) (Generalized cutaneous involvement) Taken from: James W.D.: Andrews' diseases of the skin, Edition 12, Elsevier, 2016

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Biography

Lea Klapan was born on May 3, 1995 in Zagreb, Croatia, where she finished both her primary and secondary education. She decided to pursue further education in medicine and enrolled to the Medical Studies in English at the University of Zagreb, which hosts a diverse array of students from all around the world. Additional to the clinical practices in Croatia, she had done clinical work in Germany and Switzerland. She is to graduate in July 2020.