Εντοπισμένο σκληρόδερμα και μιμητές συστηματικής σκληροδερμίας (scleroderma-like disorders)

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Classification of scleroderma-like disorders

- Localized scleroderma.
- Disorders with mucin deposition: scleromyxedema, Buschke scleredema, nephrogenic fibrosing dermopathy.
- Disorders with monoclonal gammopathy: scleromyxedema, POEMS syndrome, myeloma with scleroderma-like changes, Buschke scleredema.
- Disorders with eosinophilia: diffuse fasciitis with eosinophilia, eosinophilia-myalgia syndrome, toxic oil syndrome.
- Disorders with defined metabolic/biochemical/endocrine abnormalities: insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), carcinoid syndrome, porphyria, phenylchetonuria, nephrogenic fibrosing dermopathy.
- Chronic graft-versus host disease.
- Chemically induced scleroderma-like disorders: eosinophilia-myalgia syndrome, toxic oil syndrome, polyvinyl-chloride disease, organic solvents, epoxy resins exposure.
- Drug induced scleroderma-like disorders: bleomycin, injections of pentazocine, progestin, vitamin B12, vitamin K, cocaine, D-penicillamine, peplomycin, interferon-β1a, uracil-tegafur, paclitaxel, methysergide, gemcitabine.
- Physical injury (trauma, vibration stress, radiation)
- Inherited progeroid syndromes (Werner's syndrome)
- Heterogeneous group of hereditary disorders with skin thickening (melorheosthosis, stiff skin syndrome, porphyria cutanea tarda, phenylketonuria), or tight skin (restrictive dermopathy, scleroatrophic Huriez syndrome).

Foti R, et al. Autoimmun Rev. 2008;7:331-9.

LOCALISED SCLERODERMA (MORPHEA)

Epidemiology

Uncommon disorder that affects adults and children

Annual incidence approximately 3 per 100,000

- 50 to 65% of cases develop in adults
- Mean ages of disease onset are 45 years and 10 years, respectively.
- Females are more susceptible to morphea than males (female-to-male ratio 2.6:1)
- disease activity typically persists for three to six years

cosmetic disfigurement or functional impairments due to atrophy or contractures often remain after the resolution of active disease

Sehgal VN et al. Int J Dermatol 2002; 41:467
Christen-Zaech S et al. J Am Acad Dermatol 2008; 59:385

Pathogenesis

- environmental factors (e.g., radiation, infections, skin trauma, exposures)

- Vascular dysfunction – reduced numbers of dermal capillaries, abnormalities in basal lamina and endothelial cell damage

- Autoimmunity

- Th2-associated cytokines (i.e. IL-4), are increased in skin lesions.

IL-4 upregulates the production of transforming growth factor (TGF)-beta by T lymphocytes and other cells. TGF-beta stimulates fibroblast production of collagen and other extracellular matrix proteins.

- Increased autoantibody levels in some patients with morphea, particularly those with the generalized or linear variants

Injury to the vascular endothelium → release of cytokines that upregulate the expression of vascular adhesion molecules, (VCAM-1, ICAM-1), and E-selectin → recruitment of T-lymphocytes (IL-4, IL-6, and TGF-beta) → collagen overproduction

Badea I et al. Rheumatology (Oxford) 2009; 48:213.
Fett N et al.J Am Acad Dermatol 2011; 64:217.

➢ Initially: inflammatory, erythematous patch

or edematous plaque.

- pain or itching may precede.

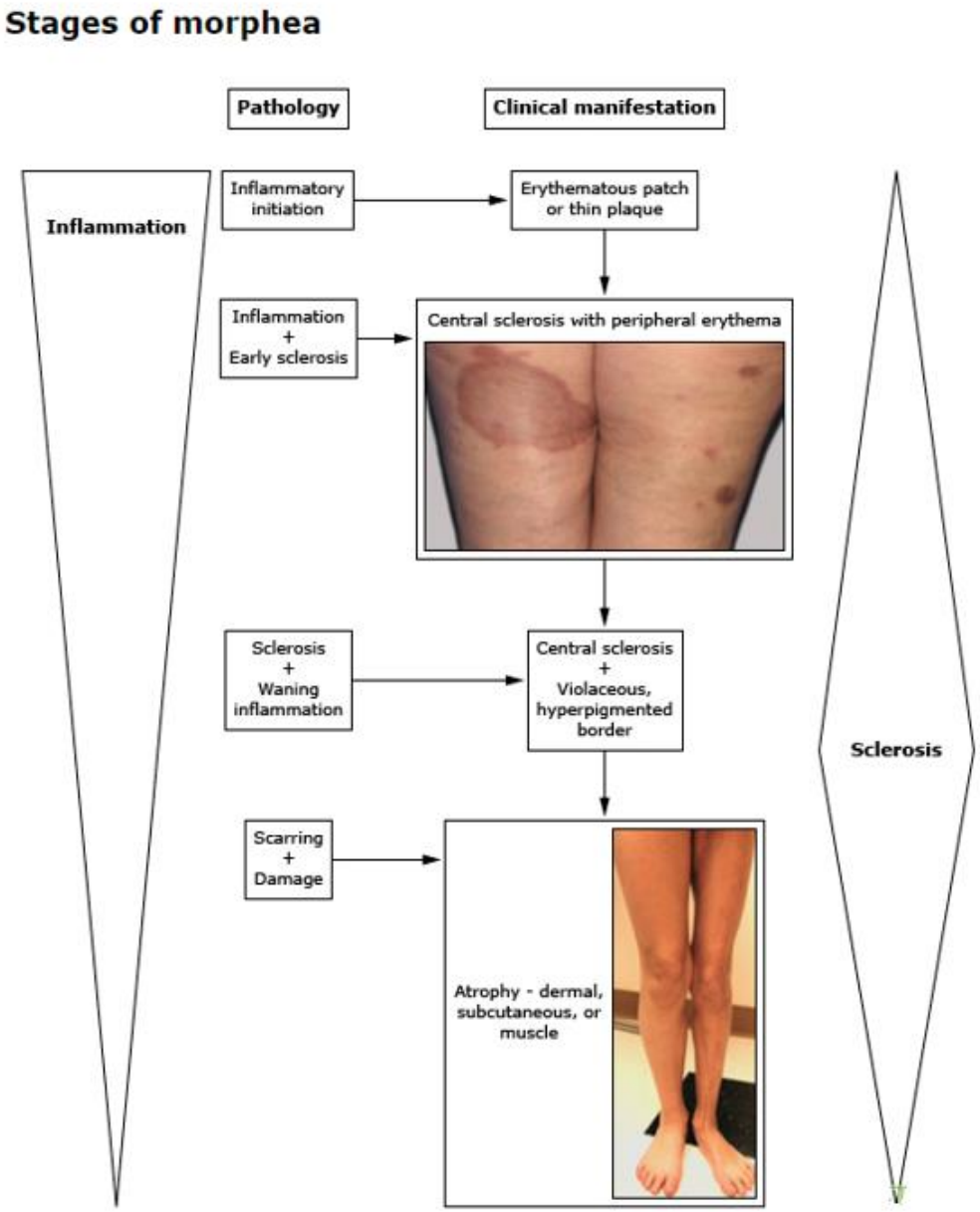
➢Sclerosis usually begins in the center of inflammatory lesions, leaving an erythematous or violaceous border.

- Hypopigmentation, hyperpigmentation,

alopecia secondary to loss of hair follicles.

➢Later stages, sclerotic plaques soften and transform into hypopigmented or hyperpigmented atrophic plaques (cigarette-paper like skin)

- deep morphea may result in deep indentations after the resolution of active disease.



Mertens et al. Am J Clin Dermatol.2017;18:491–512

Histopathology

- inflammatory stage

interstitial, periadnexal, and/or perivascular, inflammatory cell infiltrate composed primarily of lymphocytes and plasma cells.

eosinophils, mast cells, and macrophages may be present; inflammation may extend into the subcutaneous tissues.

- atrophic phase

loss of inflammatory cell infiltrate, less sclerosis, and an absence of appendageal structures.

Telangiectasia may be evident.

Mertens et al. Am J Clin Dermatol.2017;18:491–512
Walker D et al. J Am Acad Dermatol 2017; 76:1124.

Types of localized Scleroderma

- Circumscribed –most common manifestation of morphea in adults (65%)
- Generalized (10%)
- Linear (most common subtype of morphea in children) (6%)

en coup de sabre (a form of linear disease) (3-4%)

Parry-Romberg syndrome

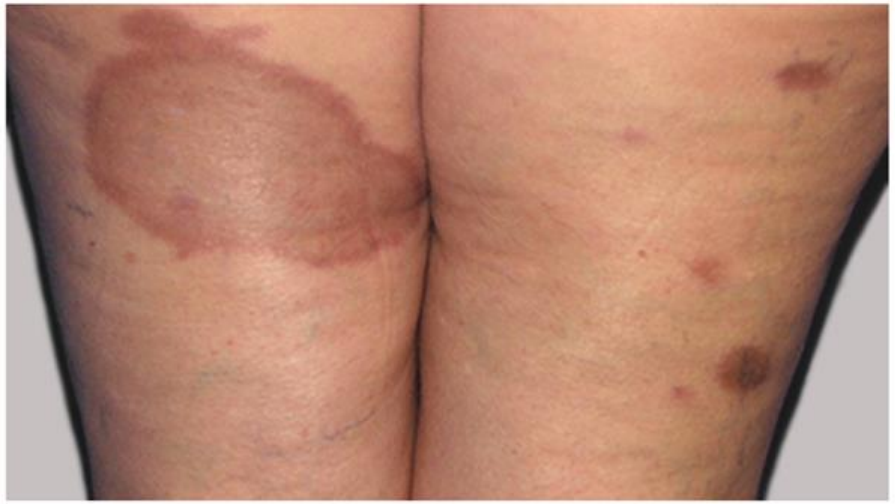
Deep morphea: involvement of the deep dermis and subcutaneous tissue and sometimes of underlying fascia and muscle

Mertens et al. Am J Clin Dermatol.2017;18:491–512

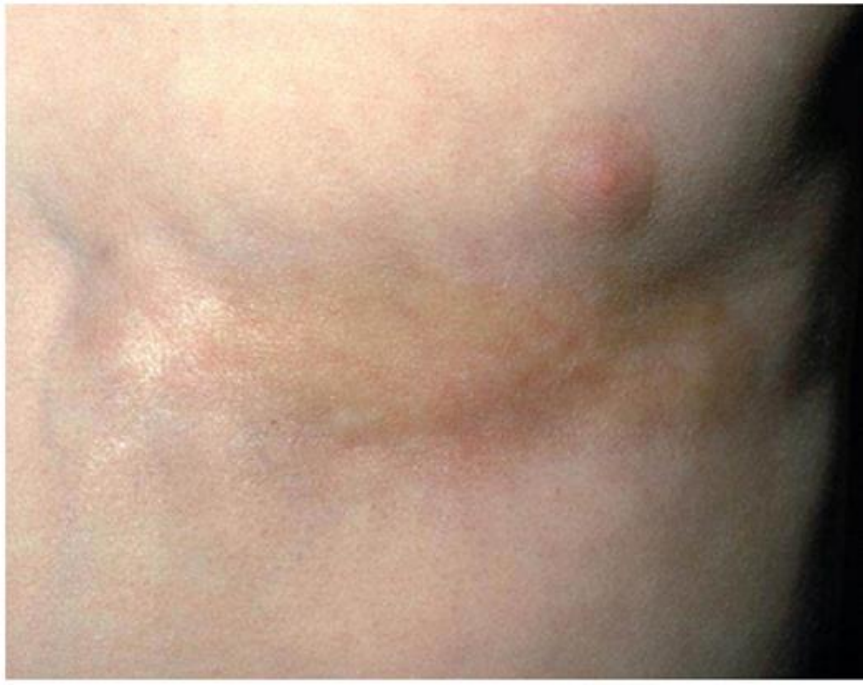
Circumscribed (plaque) morphea

single or multiple, well-defined, oval to round plaques

Inflammatory morphea



Circumscribed morphea



Generalized morphea

≥4 morpheaform plaques involving at least two different anatomic sites.

In contrast to systemic sclerosis, lesions usually begin on the trunk before spreading acrally; Raynaud's phenomenon is absent; the fingers and toes are spared.

- Symmetric type

These lesions are more frequently deep and associated with limited range of motion in underlying joints and pain.

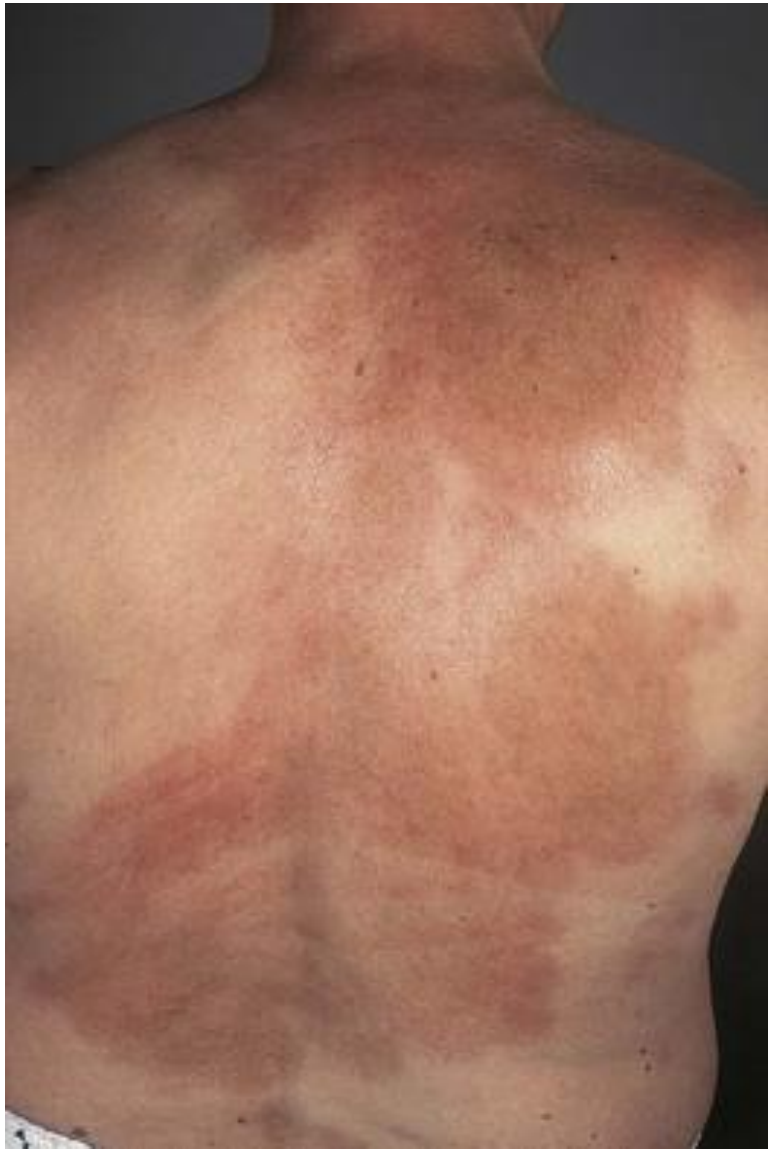
- Isomorphic type

almost exclusively in postmenopausal women. Lesions are distributed in areas of chronic friction (ie, waistband, bra straps, inguinal creases etc). Lichen sclerosus is more common; limited range of motion is rarely encountered, but genital involvement is more common

- Pansclerotic generalized morphea

deep morphea lesions occur in a generalized, circumferential distribution and involve the majority of the body surface area, excluding fingers and toes

Martens J et al. J Am Acad Dermatol. 2017;18:491-512
Teske N et al. J Am Acad Dermatol 2018;78:351.



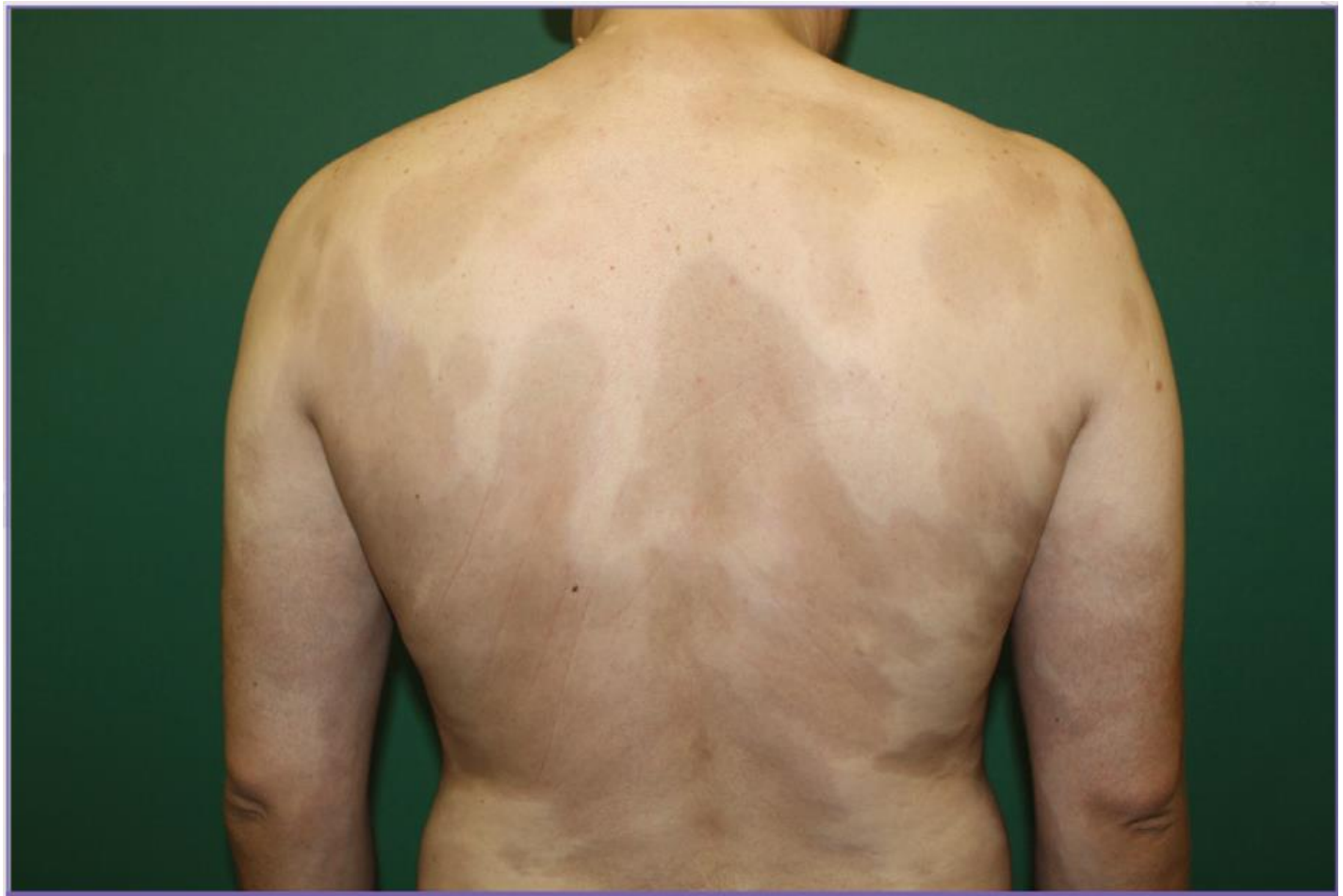
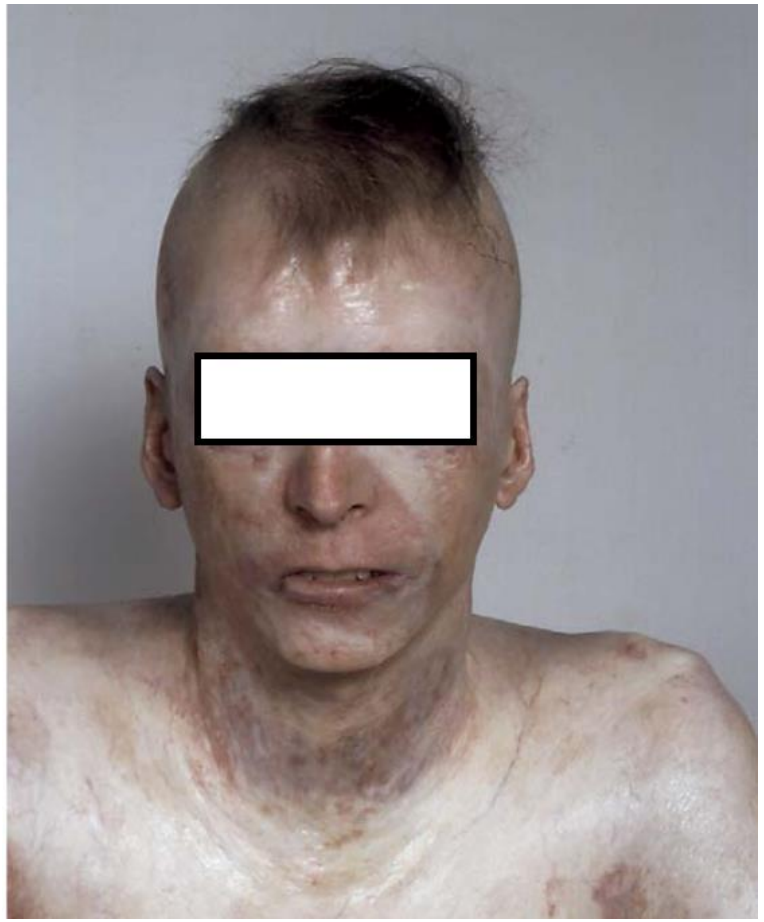
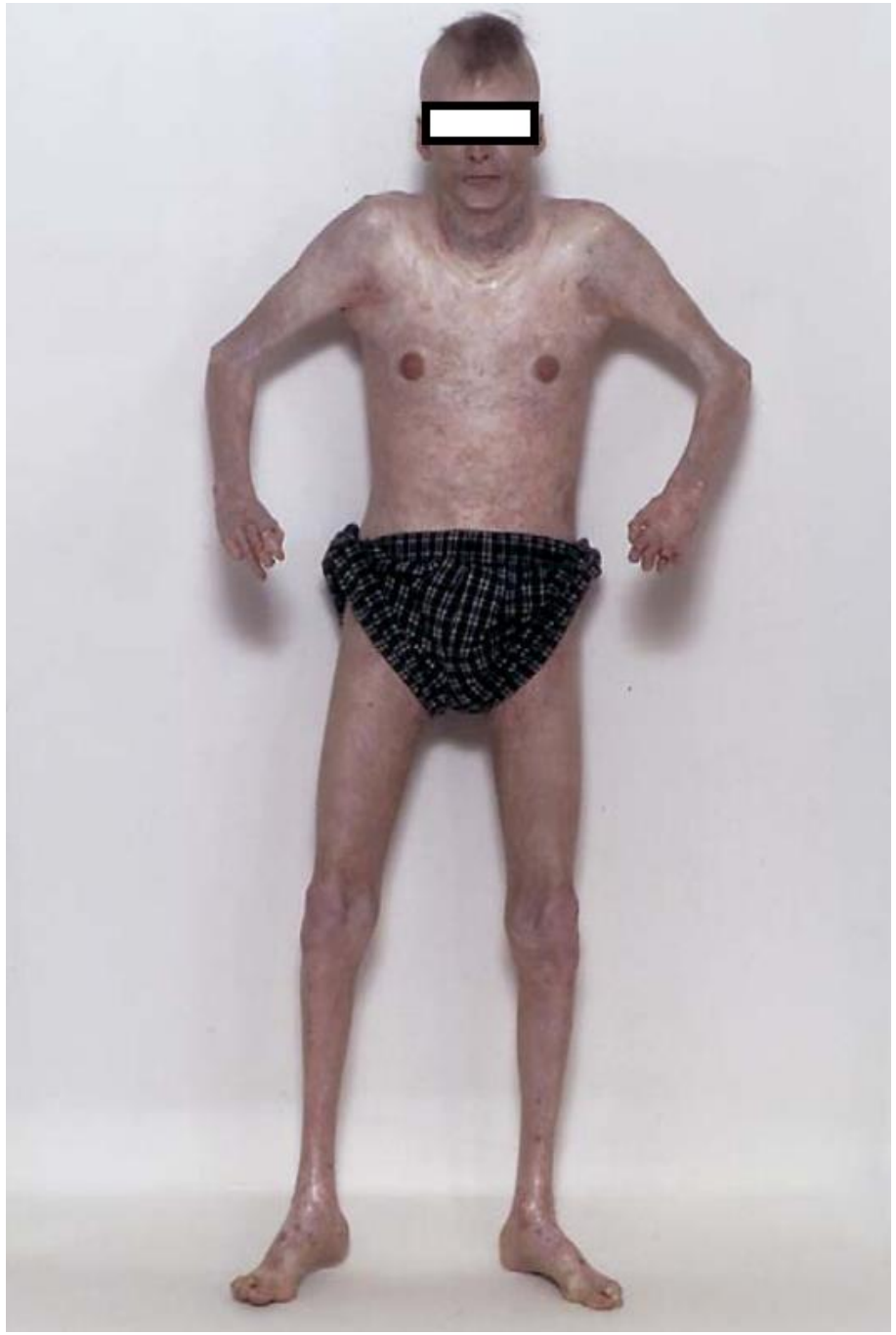
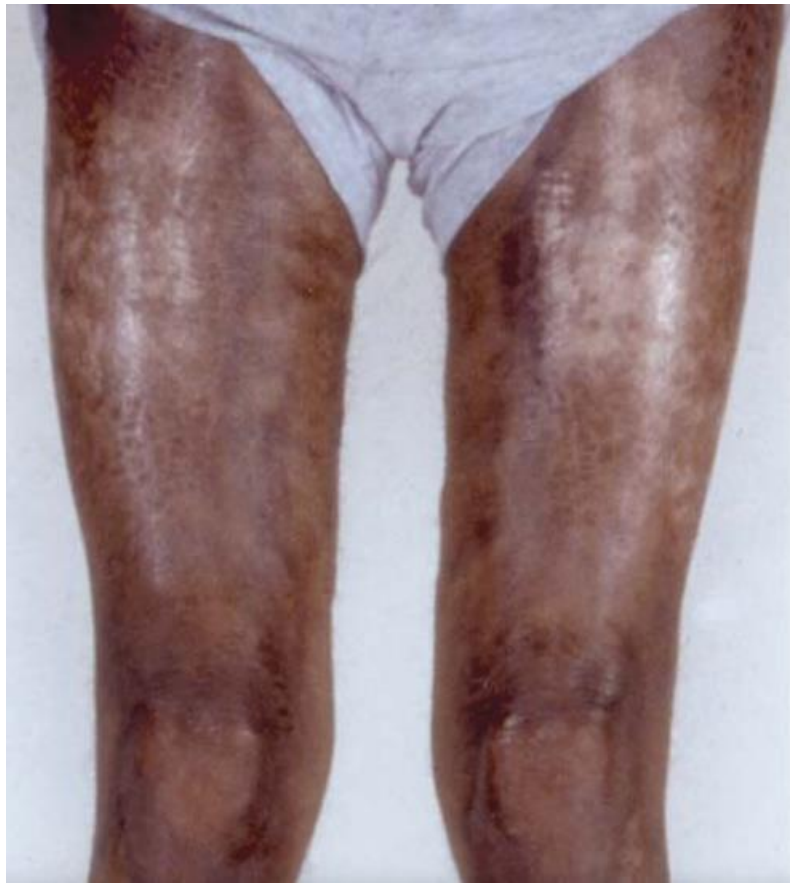


Figure 2. Generalized morphea







Pansclerotic generalized morphea

Henderson Maragh S et al. J Am Acad Dermatol. 2005;53:S115-9.

Linear Scleroderma

- Linear morphea —morpheaform plaques arranged in a linear distribution. Lesions occur on the extremities or face but also appear on the trunk. Single or multiple sites of involvement.

Involvement of deep tissues (subcutaneous tissue, muscle, or bone) can lead to significant deformities, including muscle weakness, joint contractures, and in growing children, limb length discrepancies.

- En coup de sabre — affects the head and neck.

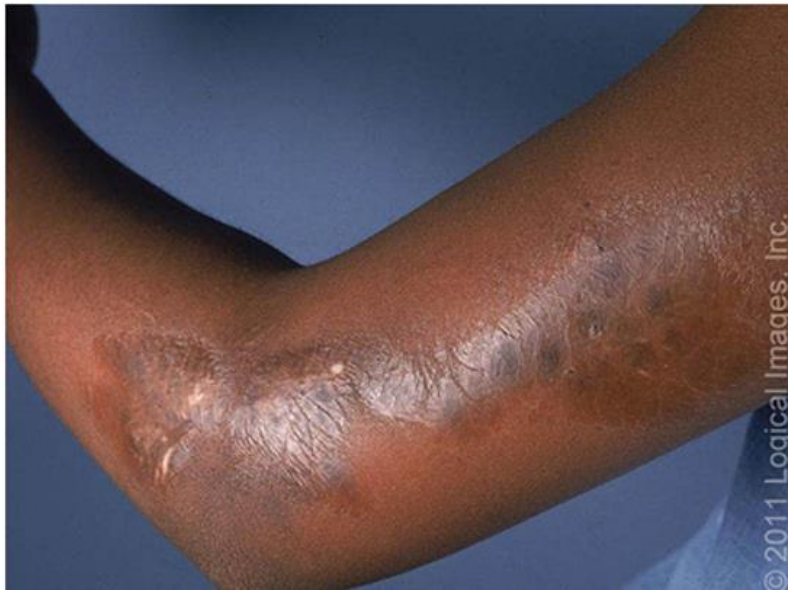
Hyperpigmented atrophic plaques that resemble the cut of a sword. The forehead is the most common site of involvement; lesions may extend onto the scalp (permanent alopecia), the temple and chin.

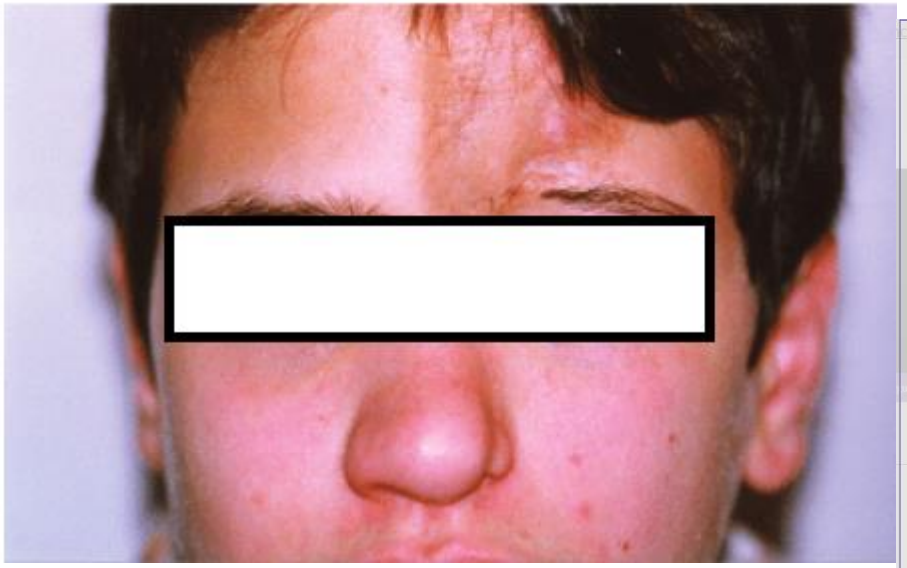
- Progressive facial hemiatrophy (Parry-Romberg syndrome)

unilateral atrophy of the skin, soft tissues, muscles, and/or bones of the face. Facial atrophy may be accompanied by classic, linear morphea lesions on the face or elsewhere.

Weibel L et al. Br J Dermatol 2008; 159:175
Tollefson MM et al. J Am Acad Dermatol 2007; 56:257.

Linear morphea





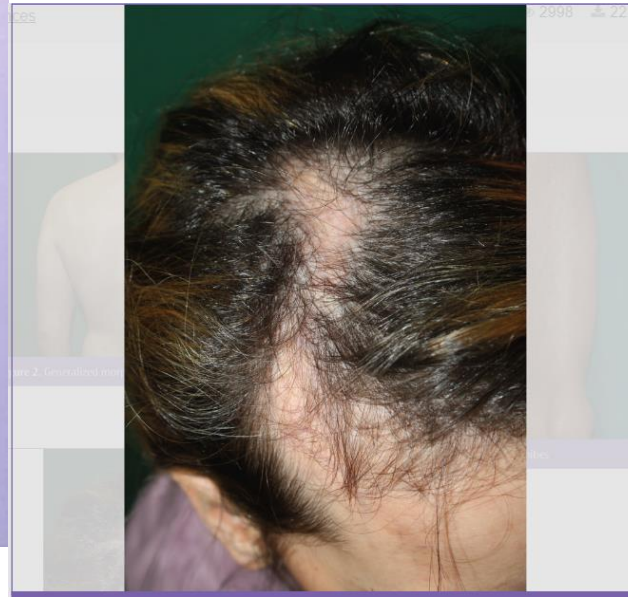
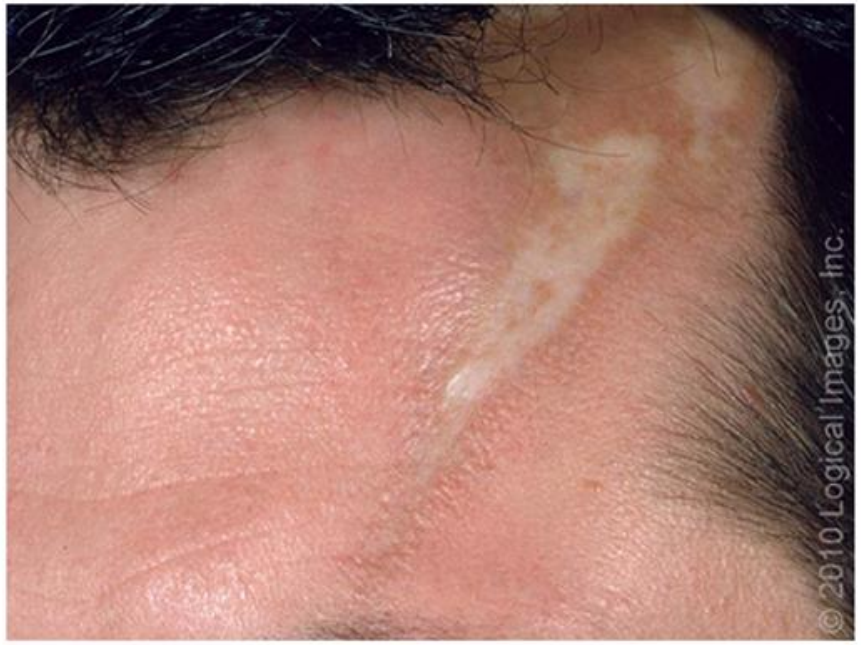
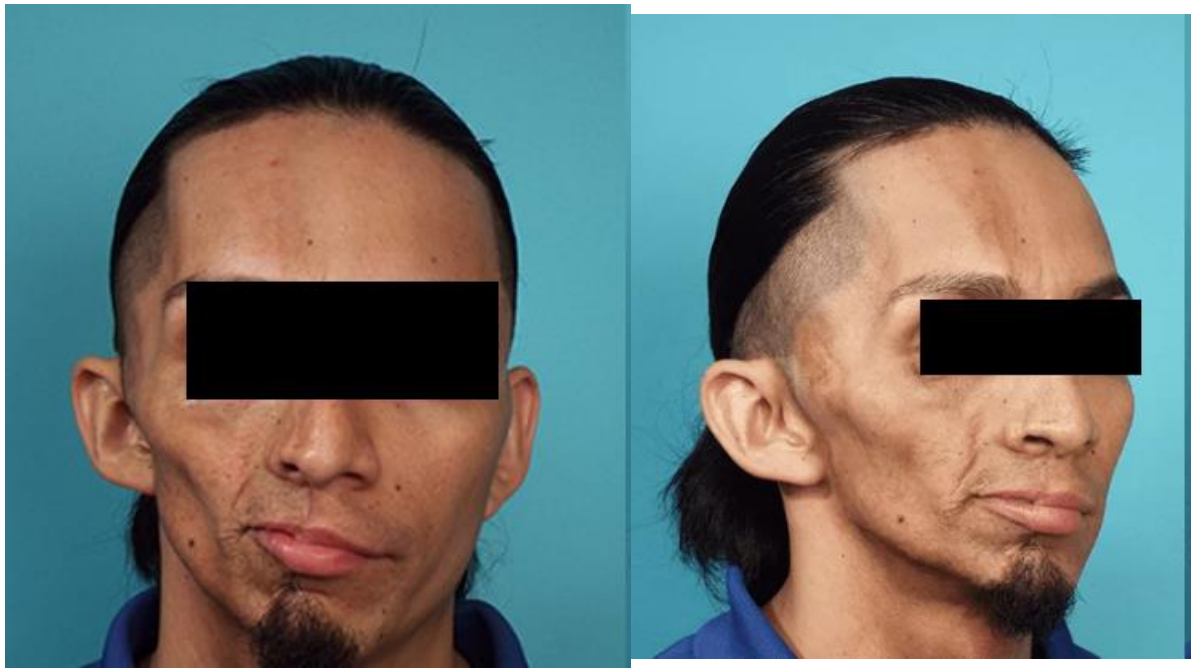


Figure 4. Linear morphea of the scalp causing cicatricial alopecia

En coup de sabre with secondary alopecia





Parry-Romberg syndrome

Extracutaneous manifestations

- Arthralgias, joint swelling, myalgias, limb contractures, and limited range, especially in generalized or deep morphea.
- Raynaud phenomenon typically is absent.

- Visceral involvement is extremely rare.

Dysphagia or dyspnea may develop secondary to the restrictive effects of extensive cutaneous sclerosis. Evaluation for pulmonary or esophageal abnormalities is not indicated in the absence of symptoms.

- Approximately 4% of individuals with linear lesions affecting the head have neurologic (seizures, headaches) or ocular complications (uveitis, episcleritis), adnexal abnormalities, dental malocclusion, altered dentition, destructive gingivitis, and atrophy of the tongue and salivary glands.

Marzano AV et.al Eur J Dermatol 2003; 13:171.

Laboratoty tests

- Serum autoantibodies — ANA positive in 18 to 68% of cases.

Other autoAbs include anti-ssDNA, anti-dsDNA, antihistone, anti-topoisomerase II alpha, antiphospholipid, and rheumatoid factor.

- Unclear clinical significance. Testing for autoAbs is not indicated unless another autoimmune disorder is suspected.

- Peripheral eosinophilia, hypergammaglobulinemia, increased ESR and CRP may occur with active disease of any type.

Arkachaisri T et al.J Rheumatol 2008; 35:2439.
Leitenberger JJ et al. Arch Dermatol 2009; 145:545.

Imaging studies

- MRI Not indicated for routine use
- MRI is indicated in cases morphea extending beyond the dermis (e.g. tightly bound-down quality on skin examination, muscle weakness, contractures, or limb length discrepancies) to assess lesion depth and involvement of soft tissue.

MRI findings include fascial thickening, fascial enhancement, articular synovitis, tenosynovitis, perifascial enhancement, myositis, enthesitis, bone marrow involvement, and subcutaneous septal thickening.

- Ultrasonography is an alternative to MRI.

Horger M, et al. AJR Am J Roentgenol 2008; 190:32.
Li SC et al. Rheumatology (Oxford) 2007; 46:1316.

Treatment

- Self-limited nature of morphea

- stable, limited dermal morphea

high-potency topical corticosteroid, intralesional corticosteroid injections, topical tacrolimus and topical vitamin D analogs as the initial treatment

- active extensive dermal morphea or spreading dermal morphea

phototherapy ultraviolet A1 (UVA1) or other forms of phototherapy (broadband ultraviolet A (UVA) and narrowband ultraviolet B (UVB).

not effective for deep morphea.

- Active rapidly progressing morphea and extensive and active morphea.

methotrexate ± systemic glucocorticoid therapy for highly inflammatory and rapidly progressive presentations.

- Physical and/or occupational therapy for patients at risk for or who show evidence of functional impairments.

Martens J et al. J Am Acad Dermatol. 2017;18:491-512

Eosinophilic Fasciitis (Shulman syndrome)

Etiology

- Unknown prevalence and incidence/ usually develops between 40 and 50 years old

Most cases are considered idiopathic.

In some cases related to:

- Strenuous exercise
- Initiation of hemodialysis
- Infection with Borrelia burgdorferi
- Physical factors such as radiation therapy and burns
- Chronic graft-versus-host disease (GVHD)
- Exposure to certain medications including statins, phenytoin, ramipril, subcutaneous heparin, and immune checkpoint inhibitor therapy (e.g. nivolumab and pembrolizumab)
- Autoimmune diseases including thyroid disease, primary biliary cirrhosis, systemic lupus erythematosus, Sjögren's syndrome
- Hematologic disorders like aplastic anemia, myeloproliferative disorders, myelodysplastic syndromes, leukemia, ,multiple myeloma

Pinal-Fernandez I et al. Autoimmun Rev 2014; 13:379.

- Initially symmetrical induration of the skin (erythema, non-pitting edema) and deeper perimuscular fascial planes.

- Later, symmetrical collagenous thickening of the subcutaneous fascia and induration with puckering that gives the skin the texture of orange peel (peau d'orange).

- Most commonly occurs on the extremities, neck, and trunk. Scleroderma of the fingers (sclerodactyly), the hallmark of systemic sclerosis, is absent in EF. Moreover, the skin of the hands and feet is generally spared.

- "groove sign"

Martens J et al. J Am Acad Dermatol. 2017;18:491-512

Histopathology

- Full thickness incisional biopsy of skin and subcutaneous tissues down to the muscle surface is required.

- edema of the deep fascia and lower subcutis and infiltration with lymphocytes, plasma cells, histiocytes, and eosinophils

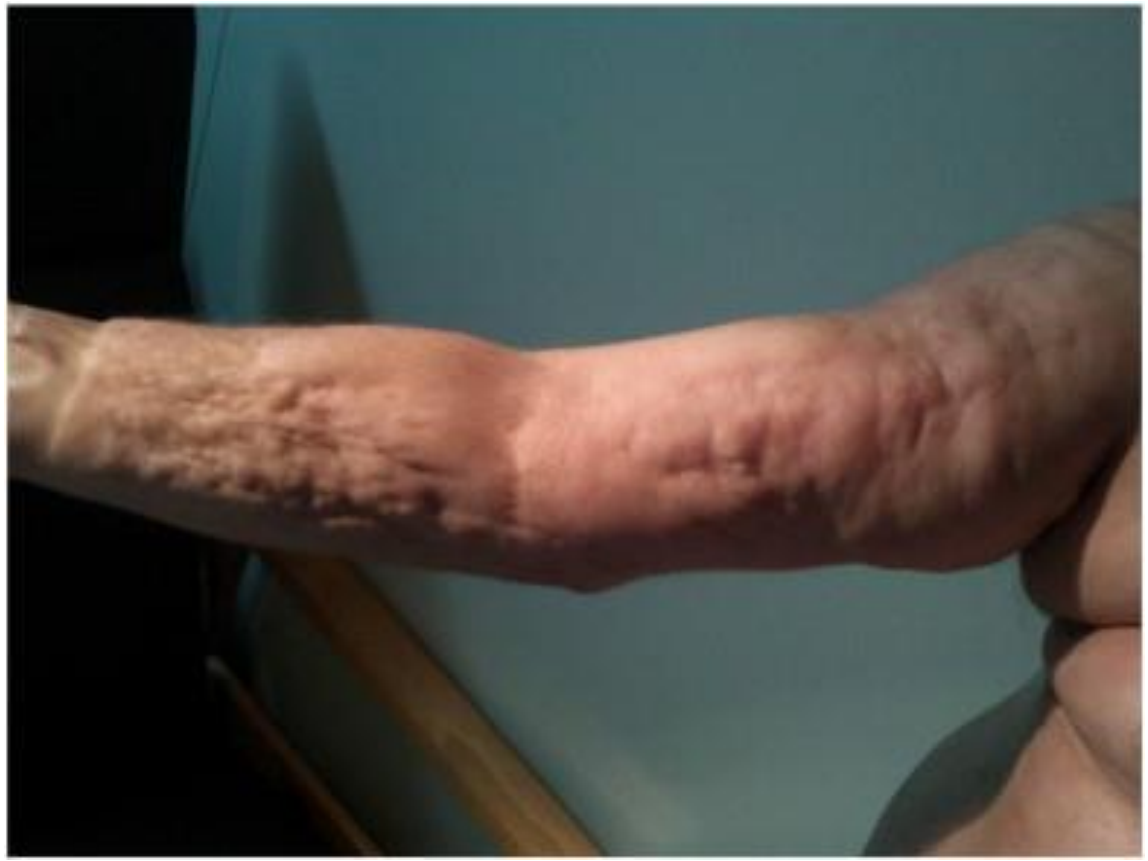
  eosinophil infiltrates are present in the majority of patients, but may also be absent.

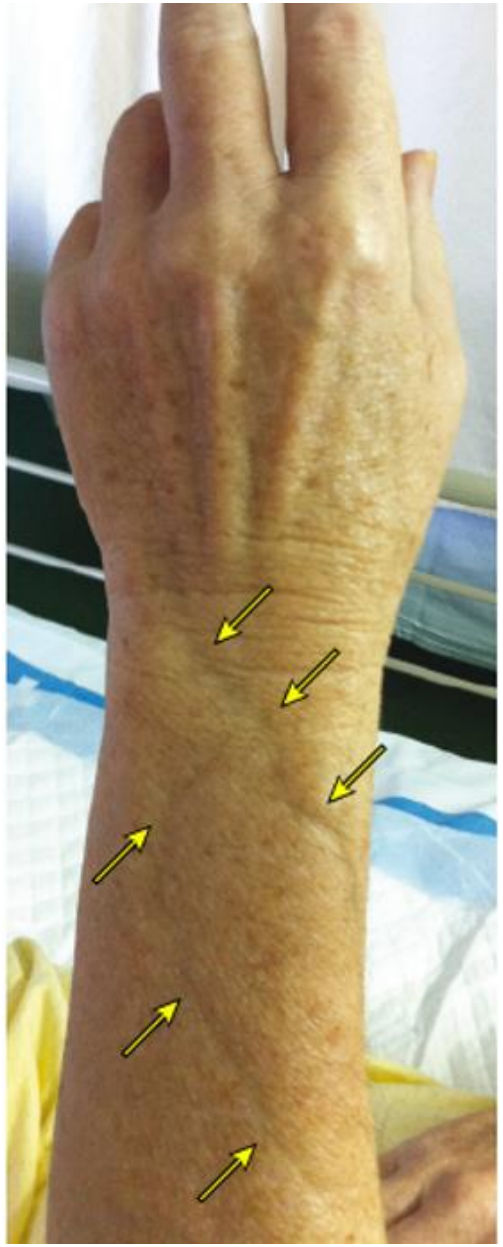
- As EF progresses, the fascia becomes thickened and sclerotic, with disappearance of inflammatory infiltrates.

- Degranulation of Infiltrating eosinophils and mast cells - elevation of cationic granule proteins and histamine in affected tissues and peripheral blood.

- Thickening and inflammation of the epimysium, perimysium, endomysium, and, to a lesser degree, even within muscle fibers. With routine histologic studies, difficult to distinguish from idiopathic inflammatory myopathies.

Long H et al. Clin Rev Allergy Immunol 2016; 50:189.
Huang KW, et al. Can J Neurol Sci. 1987;14:632–7.





''groove sign''

Pinal-Fernandez I, et al. Autoimmun Rev. 2014;13:379-382

Extracutaneous manifestations

- Inflammatory arthritis occurs up to 40% of pts with EF. Joint contractures and limited joint mobility may occur up to 50%.

- Muscle pain and muscle weakness are common symptoms. Deep skin and fascial involvement merging into perimyositis may occur.

- Neuropathies – cranial and peripheral neuropathies occur more often than would be expected. Carpal tunnel syndrome is a commonly described peripheral neuropathy associated with EF.

- Raunaud's and visceral involvement is rarely present in patients with EF. Occasional cases of pleural effusions, pericarditis, and renal involvement have been described.

Lakhanpal S et al. Semin Arthritis Rheum 1988; 17:221
Jones HR Jr, et al. J Neurol Neurosurg Psychiatry 1986; 49:324.

Laboratory findings

- The majority of pts have a peripheral blood eosinophilia in the acute phase.
- Peripheral eosinophilia is transient and does not correlate with disease severity.
- Over 50% of patients have elevated ESR and CRP as well as a polyclonal hypergammaglobulinemia.
- Serum ANA have not been reported to be present in EF with any consistency.
- Serum levels of creatine kinase (CK) are typically normal, even in patients with myalgia.

Lebeaux D, Sène D. Best Pract Res Clin Rheumatol 2012; 26:449.

TREATMENT

- Initially systemic glucocorticoids, prednisone 0.5-1 mg/kg per day (slow dose tapering) + methotrexate (15 to 25 mg once weekly)

- Duration of therapy once remission is achieved is 4 to 6 months, depending upon the clinical response.

  alternatives to methotrexate include mycophenolate or hydroxychloroquine.

- Refractory cases

Tocilizumab, baricitinib, sulfasalazine, azathioprine, infliximab, rituximab, intravenous immune globulin, dapsone, cyclosporine A, antithymocyte globulin, ultraviolet A (UVA) phototherapy, psoralen plus UVA (PUVA).

- Surgical fasciectomy in patients resistant to glucocorticoids. Surgical release may also be necessary for some patients with chronic carpal tunnel syndrome not responding to glucocorticoids.

Bischoff L,. et al. Int J Dermatol 2008; 47:29.
Wright NA, et al.JAMA Dermatol. 2016;152(1):97–9.

Eosinophilia myalgia syndrome

- A condition associated with use of L-tryptophan or 5-hydroxytryptophan supplements, used most commonly to treat insomnia (extremely difficult to differentiate from EF).
- The illness occurred in the USA and other countries in an epidemic form in 1989, and subsequent sporadic cases have been rare.

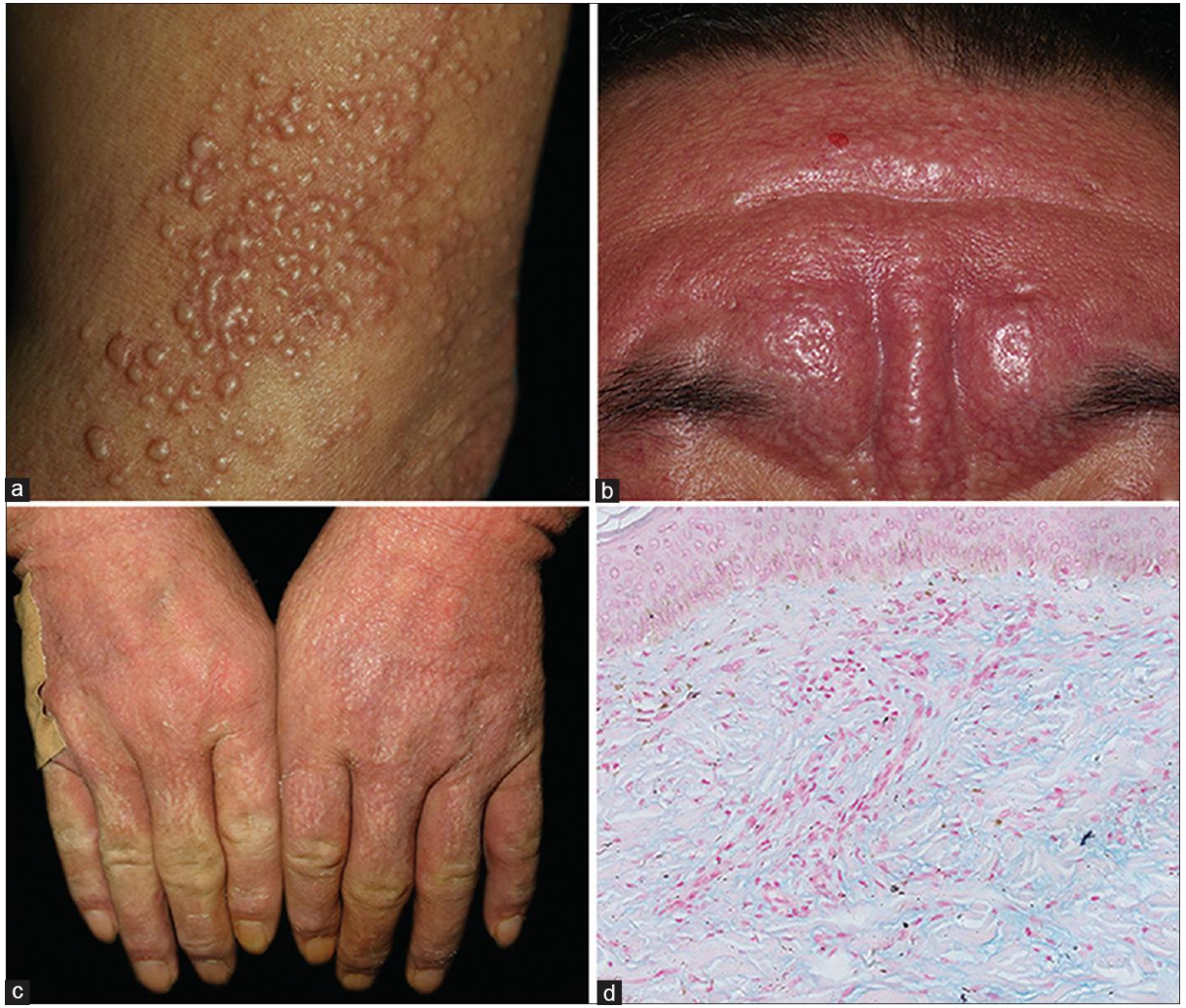
- Nonpitting edema evolving into induration with a peau d'orange appearance in EMS (similar to EF).
- Myalgias, often severe, are seen in EMS and remain a criterion for classification, whereas they are infrequent and mild in patients with EF.
- Visceral involvement, such as pneumonitis and neuropathy, may occur in patients with EMS, whereas these are uncommon in EF.

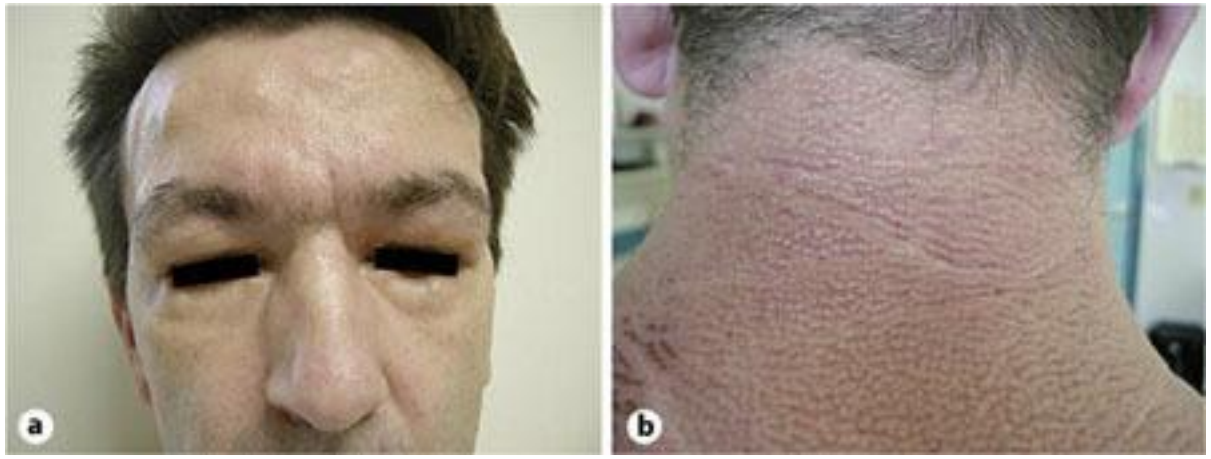
Allen JA, et al. Arthritis Rheum 2011; 63:3633

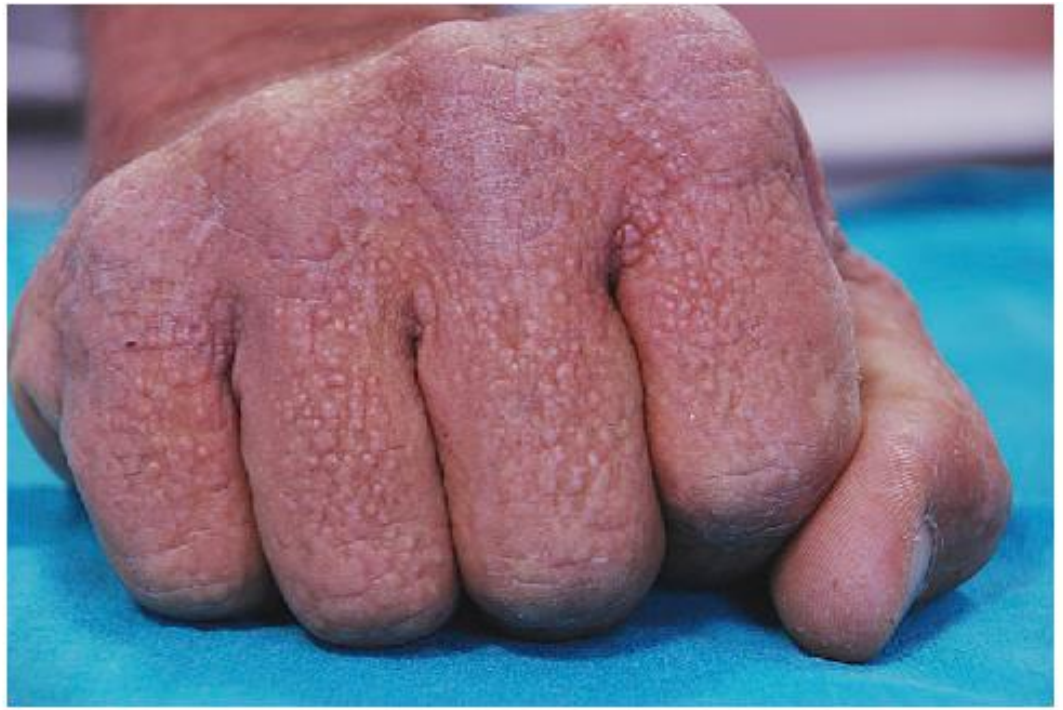
Scleromyxedema, (papular mucinosis)

- almost always (>80%) associated with a benign gammopathy, mainly IgG-λ
- thyroid disease should be ruled out
- Fibroblasts overproduce hyaluronic acid and mucin
- Skin biopsy: diffuse mucin depositions within the upper and mid reticular dermis (colloidal iron, toluidine blue or Alcian blue stains)
- infiltrative skin induration with formation of papules, usually not pruritic
- face ‘’leonine facies’’, upper trunk, distal forearms, dorsal hands, sclerodactyly
- arthralgias, destructive polyarthritis, decreased range of motion of the hands and wrists, reduced mouth opening
- Central and peripheral nervous system involvement frequent, sometimes leading to coma (dermato-neuro syndrome)
- esophageal dismotolity, scleroderma renal crisis-like, inflammatory myopathy, severe cardiovascular manifestations
- treatment include IVIG + corticosteroids, thalidomide, lenalidomide, bortezomib, melphalan, autologous stem cell transplantation

Claveau J-S, et al.Blood Cancer Journal. 2022; 12:58







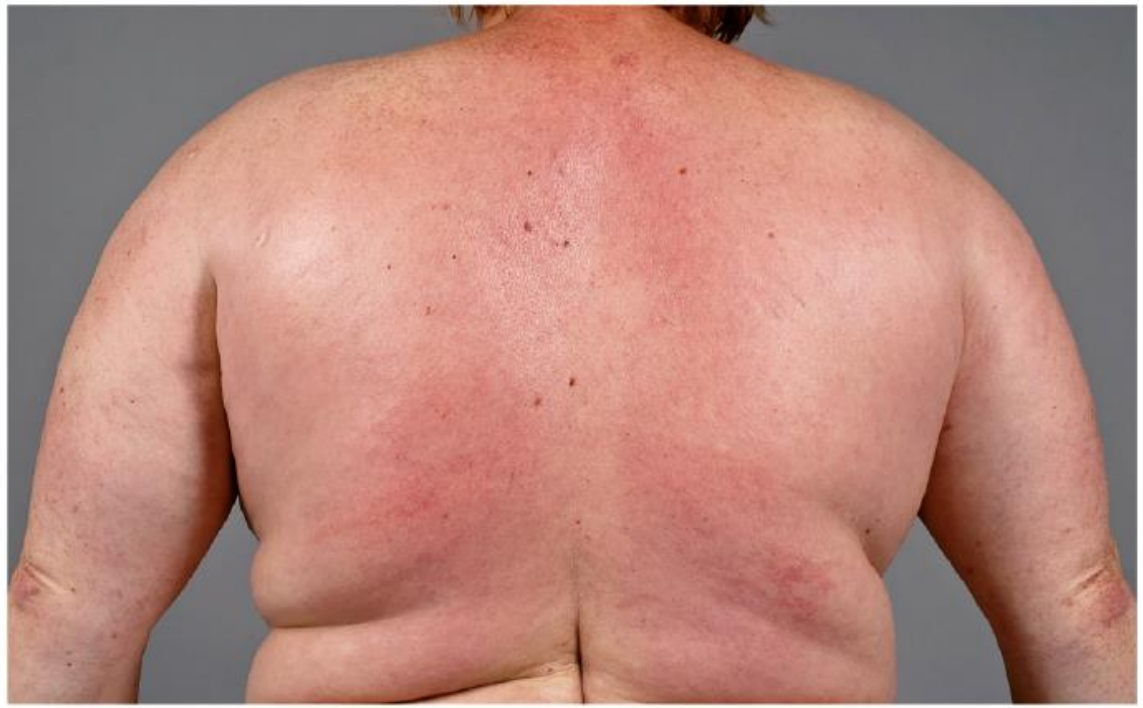
Scleromyxedema

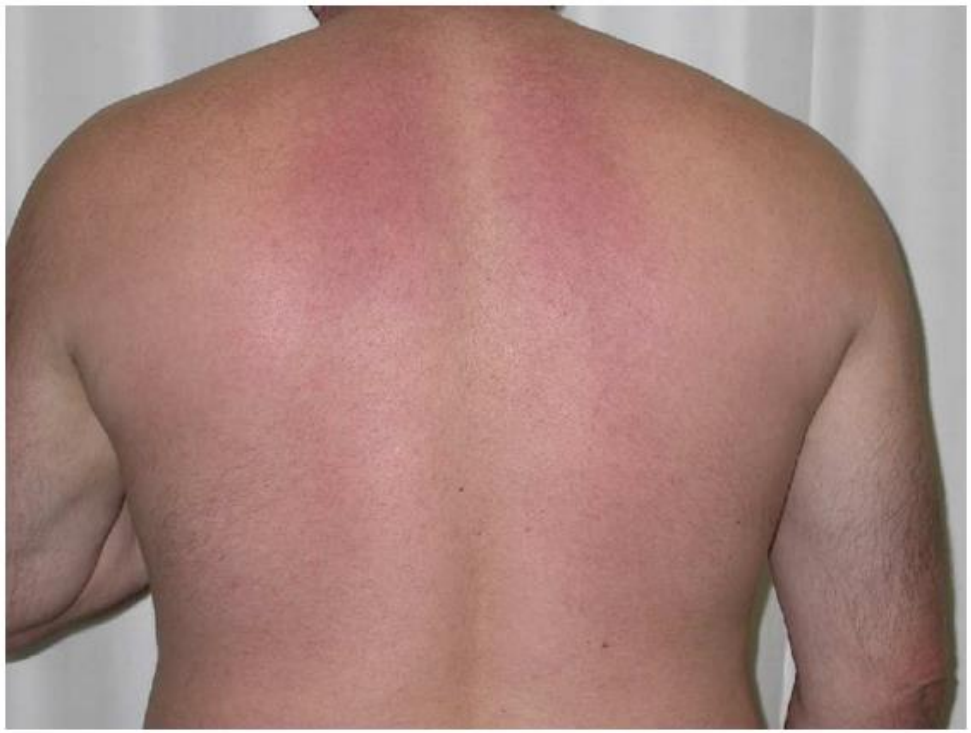
Scleredema(Buschke's)

- predominantly in men with diabetes mellitus (DM), but also associated with upper respiratory tract infections (streptococcus spp.) or monoclonal gammopathy (IgG-k) in the absence of DM.
- histology: abundant dermal mucin deposits and septal fibrosis

  the epidermis is usually normal and there is an absence of fibroblast proliferation
- slowly progressive symmetrical, non-pitting induration and thickening of the skin of posterior neck and upper trunk and shoulders, with erythema and peau d' orange aspect.
- extension to the face affecting facial expression is possible
- systemic involvement is rather infrequent.
- phototherapy, bortezomib and intravenous immunoglobulin, cyclophosphamide

Rongioletti F, et al.J Eur Acad Dermatol Venereol. 2015;29:2399–404





Scleredema

Nephrogenic systemic fibrosis

- related to organ deposition of gadolinium-based contrast agents, mainly gadodiamide, after MRI in patients with advanced renal failure (i.e. eGFR <30 mL/min/1.73 m^2)
- number of new cases declined dramatically since the cause was identified in 2006; disease can reveal itself years after exposure.
- histology: proliferation of fibroblasts with thickening of collagen bundles extending into the subcutis.

- clinically, firm and sometimes erythematous and itchy papules coalescing in plaques and / or deep nodules symmetrically distributed on the limbs and trunk, impaired joint flexibility

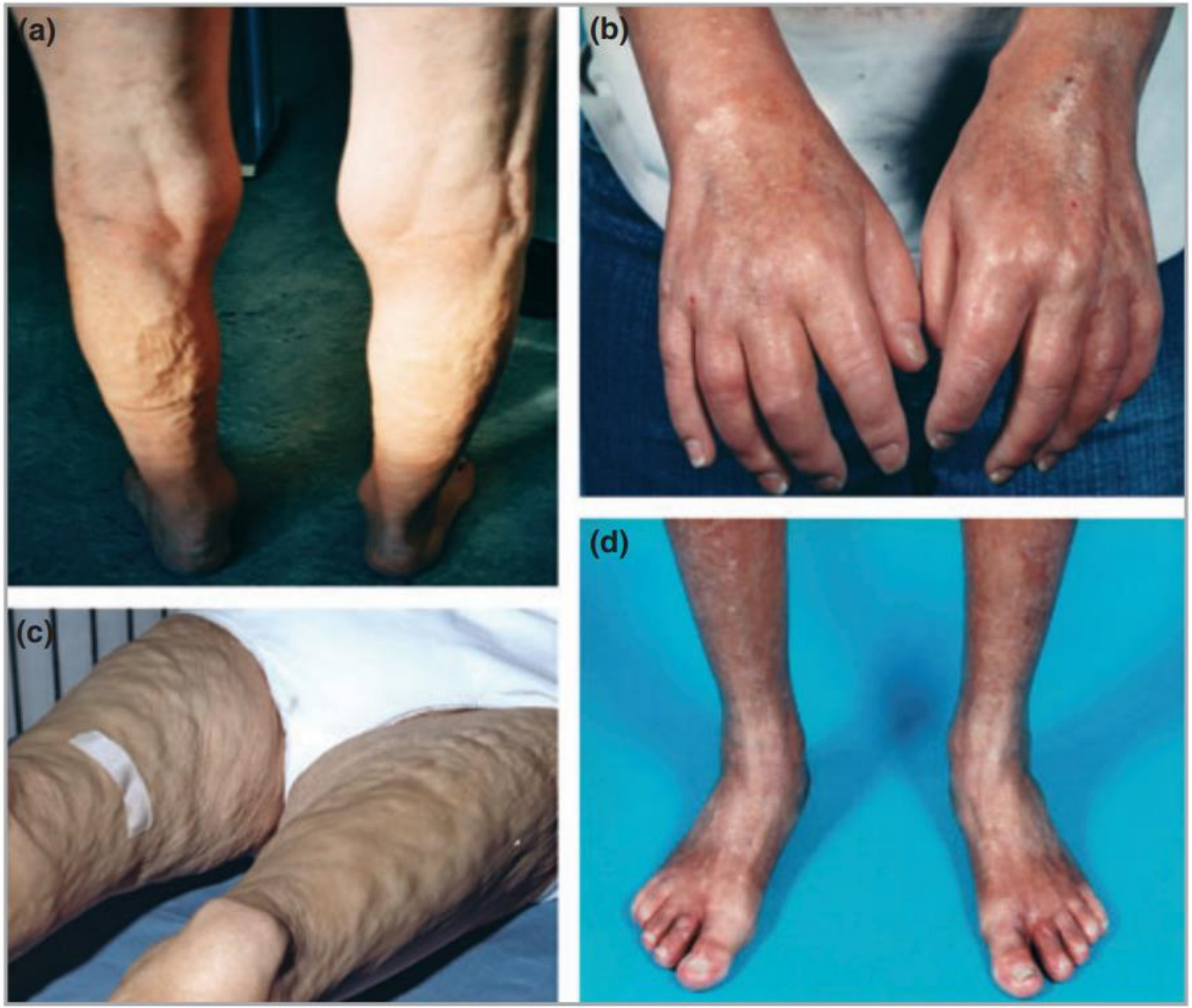
  a “cobblestone” or “peau d’ orange” aspect of the skin is often present

  face and fingers / toes are usually spared.

  systemic involvement affecting heart and lungs may occur.

- Treatment: corticosteroids, PUVA, immunomodulators, pentoxifylline, and extracorporeal photopheresis (ECP).

Bhargava V, et al. World J Nephrol 2021;10: 29-36



Nephrogenic systemic fibrosis

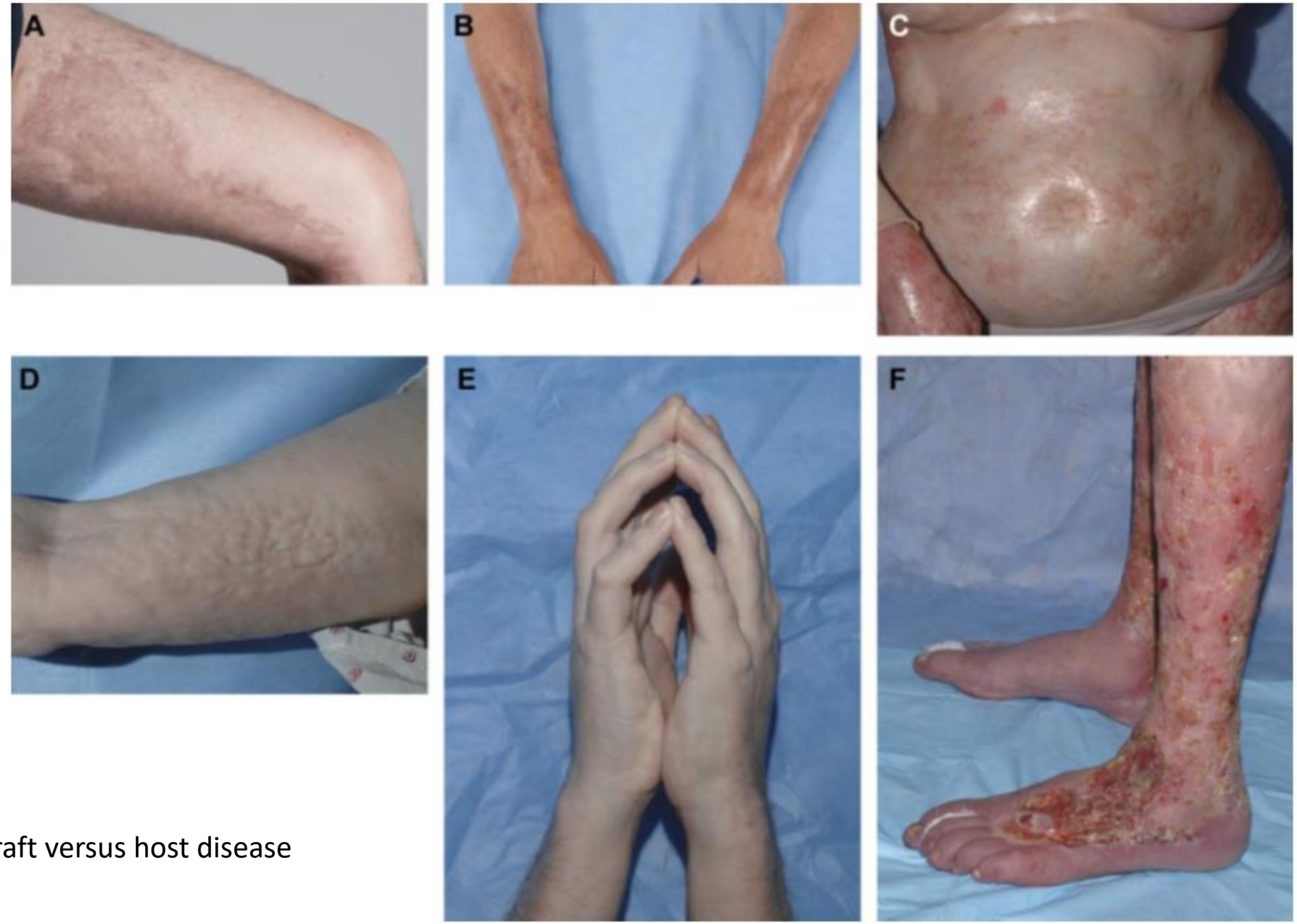
Chronic graft-versus host disease (GVHD)

- Skin sclerosis may be the product of excessive tissue repair resulting from immunologic injury by effector lymphocytes.

- sclerodermoid form-circumscribed firm plaques favoring the lower aspect of the trunk that may slowly spread/ progressive restrictive lung disease.
- occasionally, diffuse thickening resembling eosinophilic fasciitis or deep morphea-contractures, reduction of joint mobility.
- dystrophic changes of the nails, oral mucosal lesions, lichen planus-like lesions, scarring alopecia.
- Raynaud's phenomenon is rare.

- Topical steroids, CNIs, phototherapy, ECP, systemic steroids, mycophenolate, imatinib, rituximab, methotrexate, ibrutinib, JAK-inhibitors

Rodrigues K, et al. Am J Clin Dermatol. 2018;19:33-50



Graft versus host disease

Drug induced Scleroderma-like disorders

- symmetrical, mainly lower extremity lesions, sclerodactyly, contractures (resembling SSc or EF) or

  cutaneous lesions resembling morphea (morphea-like plaque).

- Usually no Raynaud, no visceral involvement

- Drug withdrawal, systemic glucocorticoids

Agents that may cause drug-induced scleroderma-like skin lesion.

Agents	Clinical characteristics
1. Chemotherapeutics	
Bleomycin	Scleroderma-like lesion
Taxane-based agents	Scleroderma-like lesion
Gemcitabine	Scleroderma-like lesion
Pemetrexed	Scleroderma-like lesion, morphea-like plaques
Uracil-tegafur	Scleroderma-like lesion
2. Immune checkpoint inhibitors	
Nivolumab	Scleroderma-like lesion (diffuse or limited form), morphea-like
Pembrolizumab	Progress to dcSSc from lcSSc, generalized morphea-like plaques
3. Analgesics	
Pentazocine	Deep fibrotic lesions with ulceration
Methysergide	Scleroderma-like lesion, lcSSc > dcSSx
Bromocriptine	Morphea-like lesion
Ketobemidone	Disfiguring fibrosis with multiple ulcerations
4. L-tryptophan	Eosinophilia-myalgia syndrome, Scleroderma-like lesion
5. Neurological drugs	
Carbidopa and l-5-hydroxy-tryptophan	Scleroderma-like lesion (with poikiloderma)
Levodopa/Carbidopa	Eosinophilic fasciitis
Ethosuximide	Morphea-like plaque, Scleroderma-like lesion
6. Appetite suppressants	lcSSc, morphea-like lesion
7. Other agents	
Vinyl chloride	Scleroderma-like lesion
Vitamin K_1/phytonadione	Morphea-like lesion, subcutaneous sclerosis
Penicillamine	Scleroderma-like lesion, keloidal lesion (nodular fibrosis), morphea-like
Fosinopril	dcSSc, eosinophilic fasciitis
Triamcinolone	Linear scleroderma-like atrophy
Interferon-alpha	lcSSc
Gadolinium-based contrast agents	Scleroderma-like lesion
Cocaine	lcSSc

Hamaguchi Y. Allergol Int. 2022;71:163-168

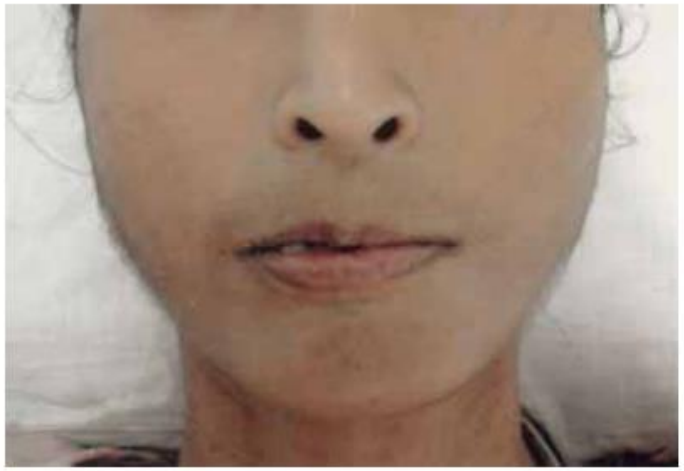


Fig. 1 : Clinical photograph of the face showing thickening of the skin, fish mouth, and beak like nose

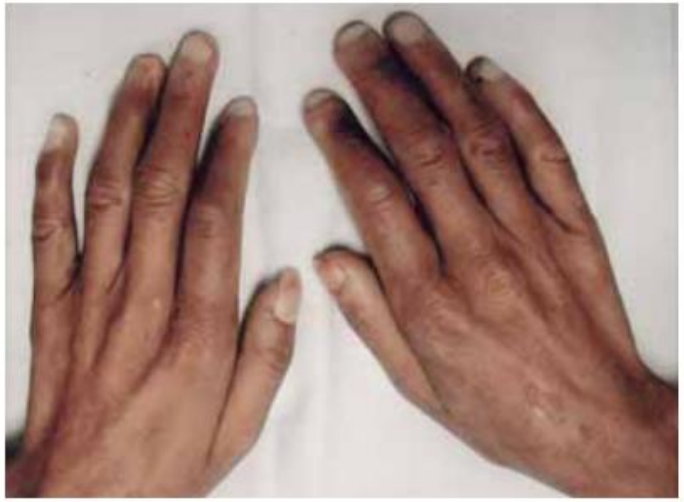
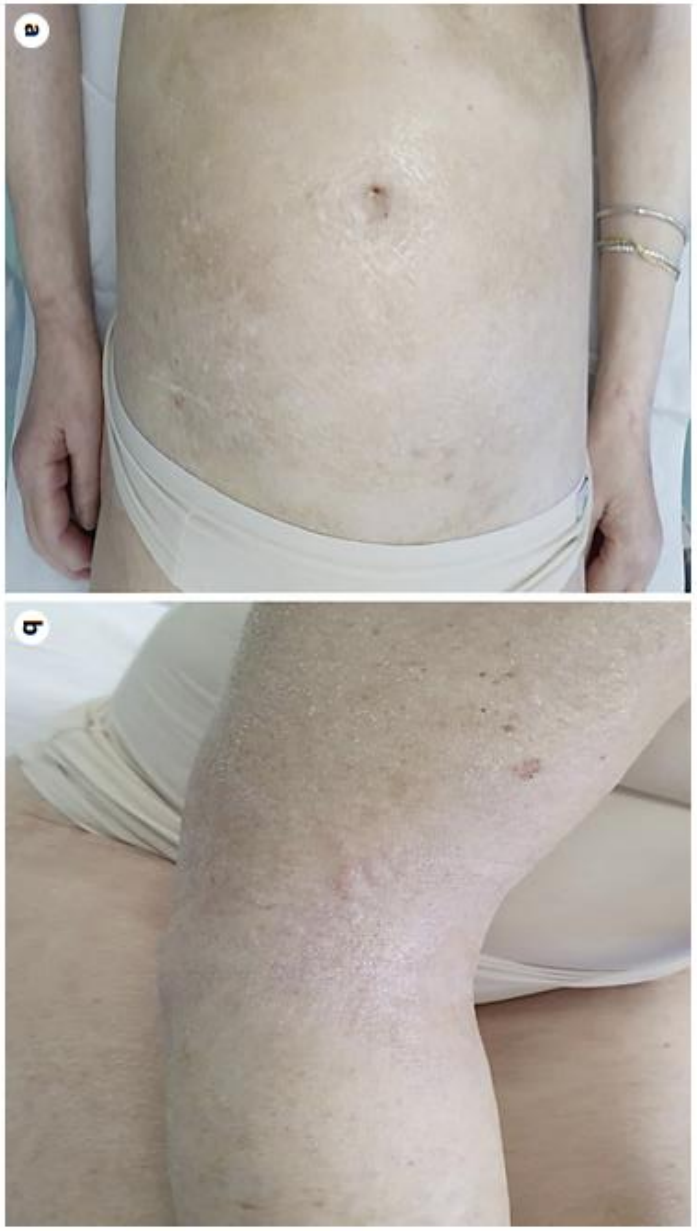


Fig. 2 : Clinical photograph of both hands showing thickened skin and bilateral sclerodactyly, clubbing of hands and resorption of terminal tufts

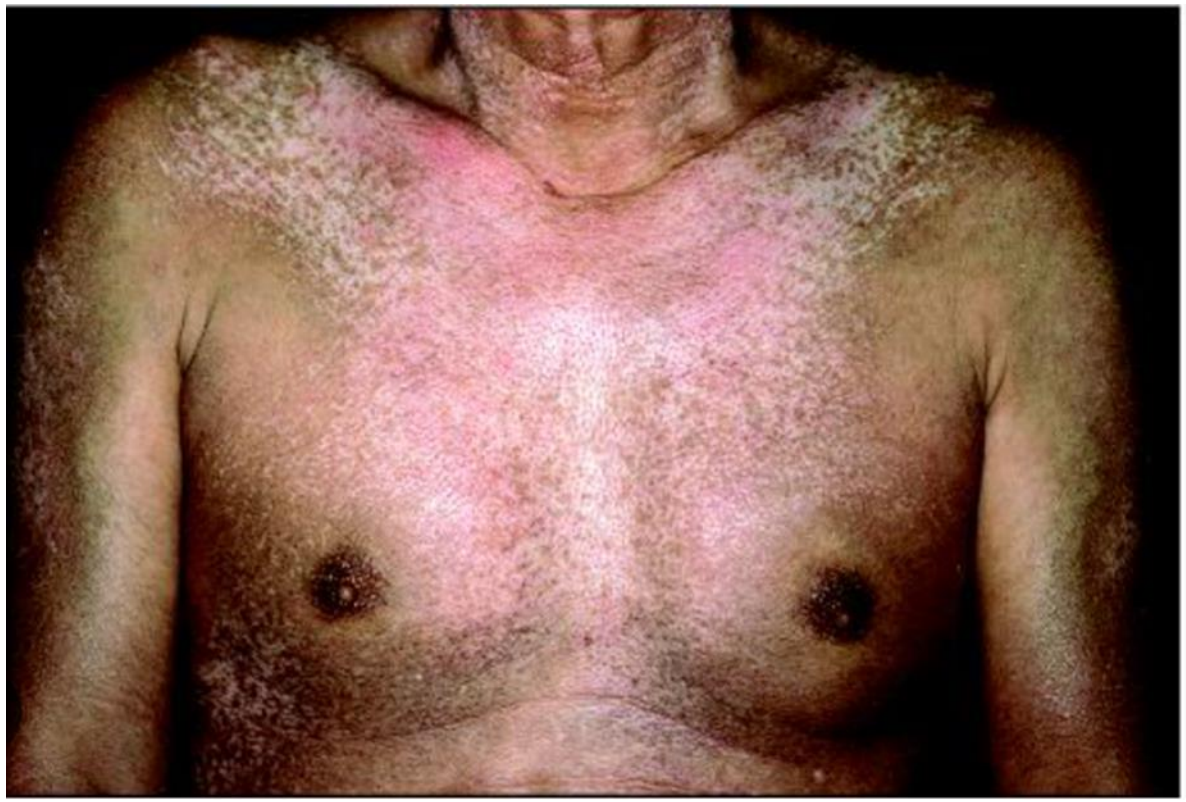
Bleomycin-induced scleroderma



Skin thickening after pembrolizumab

Amyloidosis

- Scleroderma-like amyloidosis is an extremely rare variant of light chain amyloidosis. Induration of skin can be widespread and can also involve extremities. Skin biopsy will show deposition of amyloid material in the dermis and sometimes hypodermis by Congo-red stain.



Dziadzio M, et al.Clin Rheumatol. 2006;25:3-15

POEMS syndrome

- rare paraneoplastic syndrome caused by a clone of aberrant plasma cells

(Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes)

- RP may be present in 20%.

- Skin sclerosis in acral regions in 10% of cases, more rarely on the trunk or in a diffuse manner

- Other skin changes

facial lipoatrophy

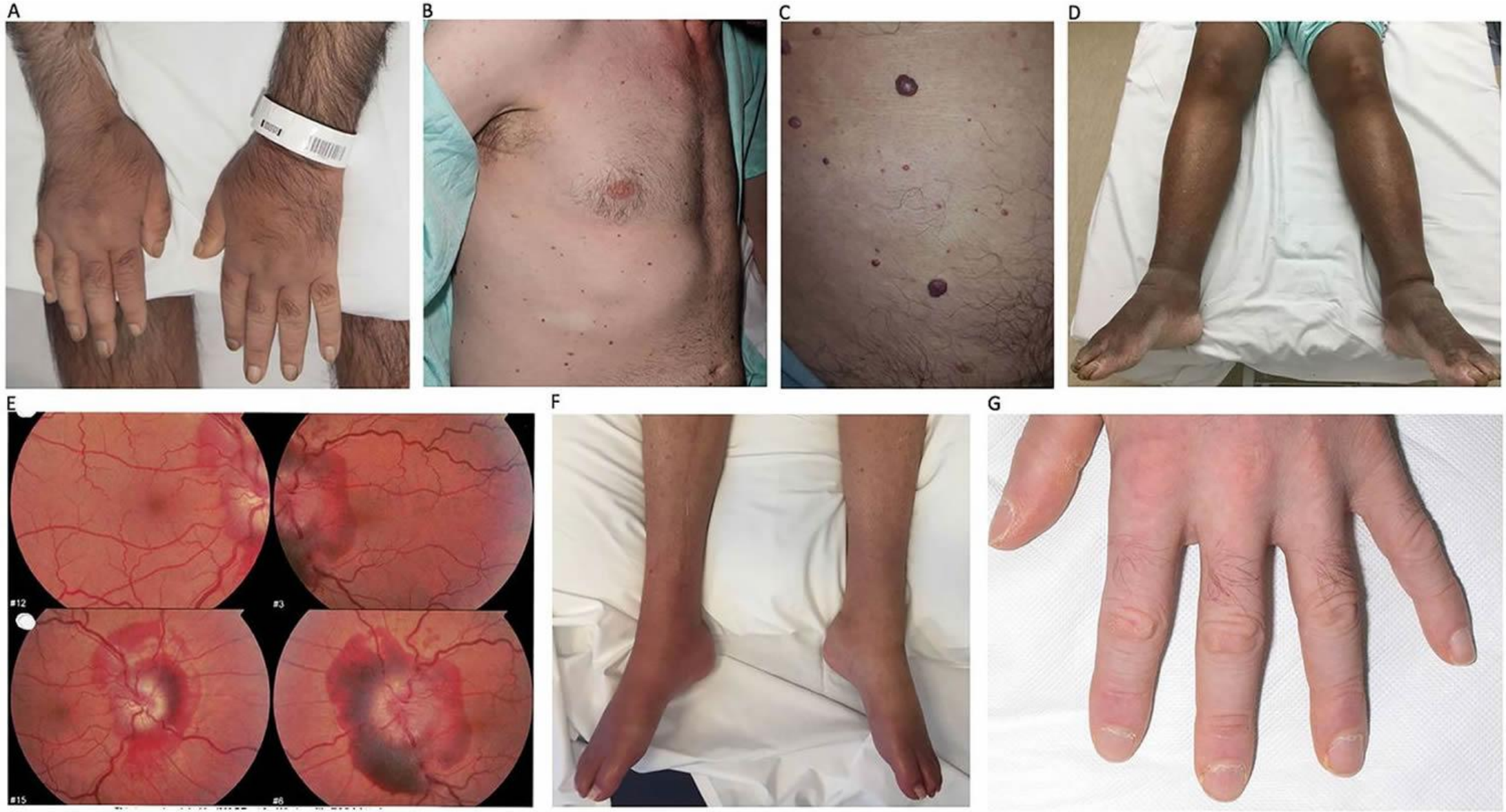
hyperpigmentation

hypertrichosis (often prominent on the extremities) and angiomatous papules (glomeruloid haemangiomas)

- radiation therapy (If 1 or 2 bone lesions and no bone marrow involvement)

systemic therapy (If >>2 bone lesions and bone marrow involvement) with Lenalidomide-based therapy followed by autologous stem cell transplantation

Dispenzieri A. Am J Hematol. 2019;94:812–27.

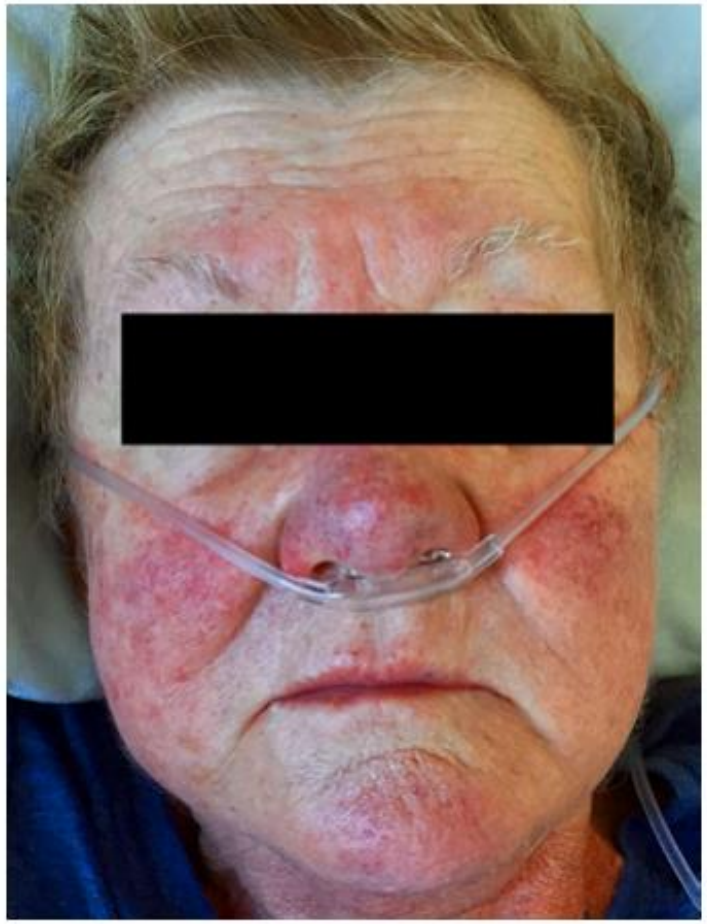


POEMS syndrome

Carcinoid syndrome

- Paraneoplastic syndrome caused by hormones like serotonin, and other mediators such as substance P and neurokinin-A secreted by neuroendocrine tumors.
- Usually flushing, erythema and rosacea of face and trunk
- Rarely, scleroderma-like cutaneous lesions; lower limbs more often involved before the upper limbs
- No acral distribution, no Raynaud's phenomenon or visceral involvement except endocardial fibrosis observed in carcinoid heart disease
- diarrhea, tachycardia, hypotension, fibrotic right-sided heart disease, bronchospasm, flushing, telangiectasia
- Poor prognosis; some cases respond to octreotide

Koch K, et al. Dermatopathology (Basel). 2019;6:99-104.



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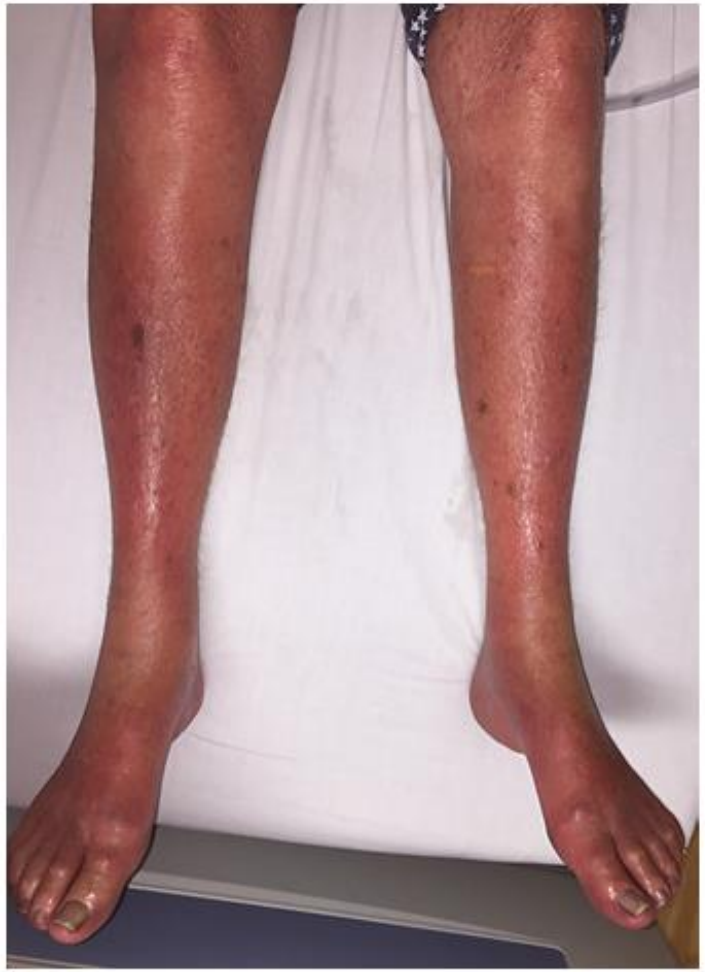


2

Fig. 1. Facial flushing of the cheeks, forehead and chin in carcinoid syndrome.
Fig. 2. Scleroderma-like erythema and tightness of the lower legs.

➢Toxic oil syndrome (TOS)

- A devastating disease firstly described in Spain in 1981 following the consumption of aniline-denatured and refined rapeseed oil that had been illegally sold as olive oil.
- Various sclerodermiform cutaneous lesions ranging from localized myxedema or plaque morphea to severe cases resembling eosinophilic fasciitis, generalized morphea or SSc, with generalized involvement of the arms and legs, sclerodactyly and muscle atrophy of the hands.
- No effective treatment (e.g. corticosteroids, azathioprine, penicillamine, plasmapheresis, vasodilators, NSAIDs)

➢Vinyl chloride disease and organic solvents (toluene, benzene, xylene)

- Raynaud's syndrome, scleroderma-like skin changes, circulatory disturbances in the extremities, thrombocytopenia, dermatitis, pseudo-clubbing of the fingers, (acrosteolysis).
- skin changes resemble morphea clinically and histologically

James TN. Clin Cardiol. 1994;17:463-70.

Phenylketonuria (PKU)

- rare autosomal recessive metabolic disease due to deficiency of phenylalanine hydroxylase.
- mental retardation, microcephaly, delayed speech, seizures, eczema.
- scleroderma-like changes may be observed usually within the first 2 years of life

predisposition for the proximal areas of the extremities, sparing the hands and feet.

- regression of lesions upon introduction of a low-phenylalanine diet

van Spronsen FJ,et al. Nat Rev Dis Primers. 2021;7:36
van Wegberg AMJ, et al. Orphanet J Rare Dis. 2017;12:162.

Genuine ‘’sclerodactyly’’

➢Porphyria cutanea tarda

- Metabolic disorder due to dysfunction of hepatic uroporphyrinogen decarboxylase (hereditary or acquired in association with hemochromatosis, HIV or hepatitis C infection)
- recurrent blisters on light-exposed areas leaving atrophic scars and milia, pigmentary changes and malar hypertrichosis
- diagnosis: clinical impression, skin biopsy and 24-hour urine collection for detection of porphyrins.
- treatment: withdrawal of alcohol and medications that may be involved; sun protection; phlebotomy (blood draws) is highly effective – 500 ml at 2-week intervals performed until hemoglobin values reach 10 g/dL or the serum iron 50-60 micro-grams/dL.
- antimalarial therapy has also been used with some success.

➢Diabetic cheiroarthropathy

- confluent tiny waxy papules on the dorsum of fingers are responsible for skin induration, leading to flexural joint contractures (long-standing juvenile-onset DM).
- Treatment: optimal glucose monitoring and control, NSAIDs, joint and muscle stretching exercises, physical/occupational therapy.

Singal AK. Mol Genet Metab. 2019;128:271-281
Hill NE, et al. Diabet Med. 2019;36:939-947.

➢ fibroblastic rheumatism

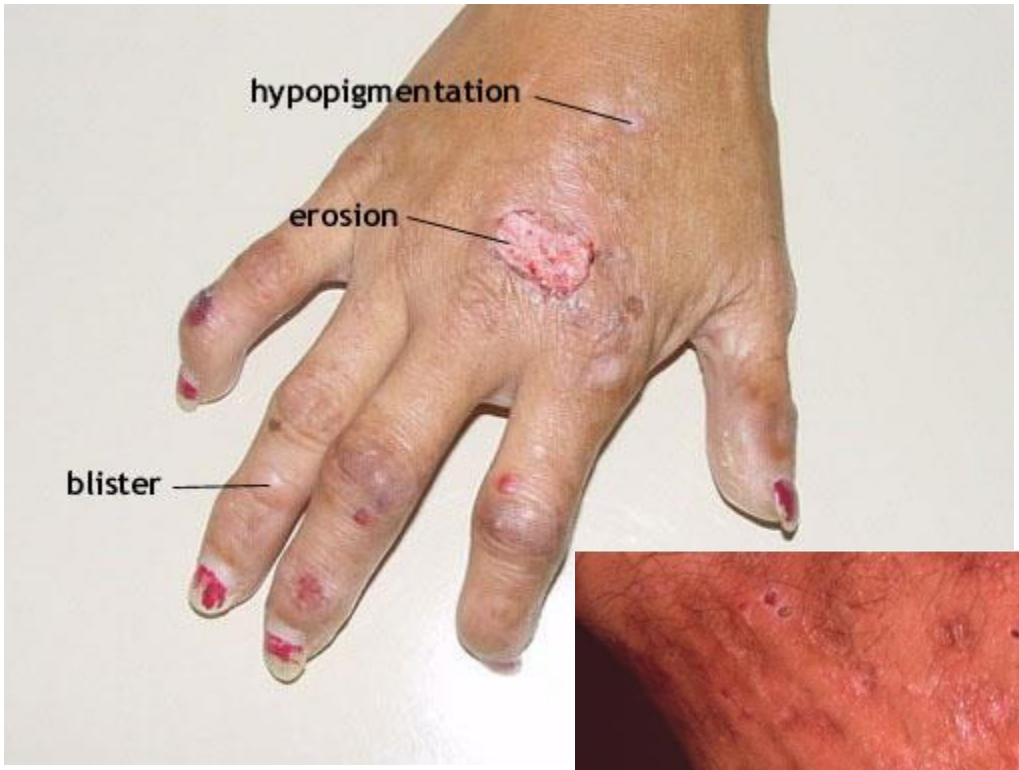
- rare dermatoarthropathy (40 cases world wide, mainly male adults) with a sudden onset, first described in 1980.
- multiple cutaneous nodules, typically in periarticular areas such as the hands, feet, elbows and knees, and symmetrical erosive arthropathy of both large and small joints.
- flexion contractures of the digits, sclerodactyly, Raynaud phenomenon, fever
- frequent relapses (over months to years) and progression to an erosive arthropathy, functional loss and permanent disability.
- (NSAID) therapy, systemic corticosteroids, MTX, hydroxychloroquine, interferon-alfa, and colchicine have been tried. MTX very efficient with marked improvement or resolution of joint pain and/or skin nodules.

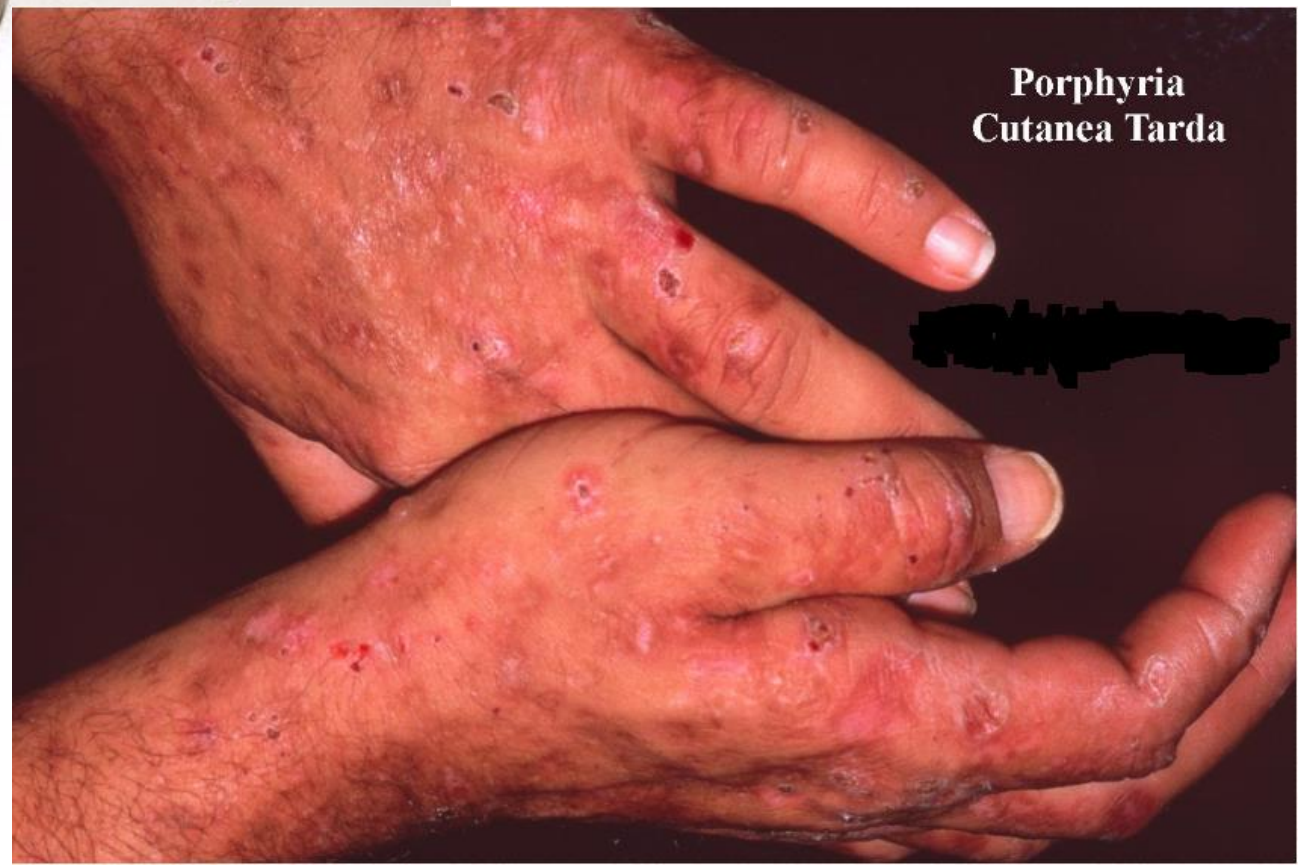
➢ Palmar fasciitis and polyarthritis (PFASP)

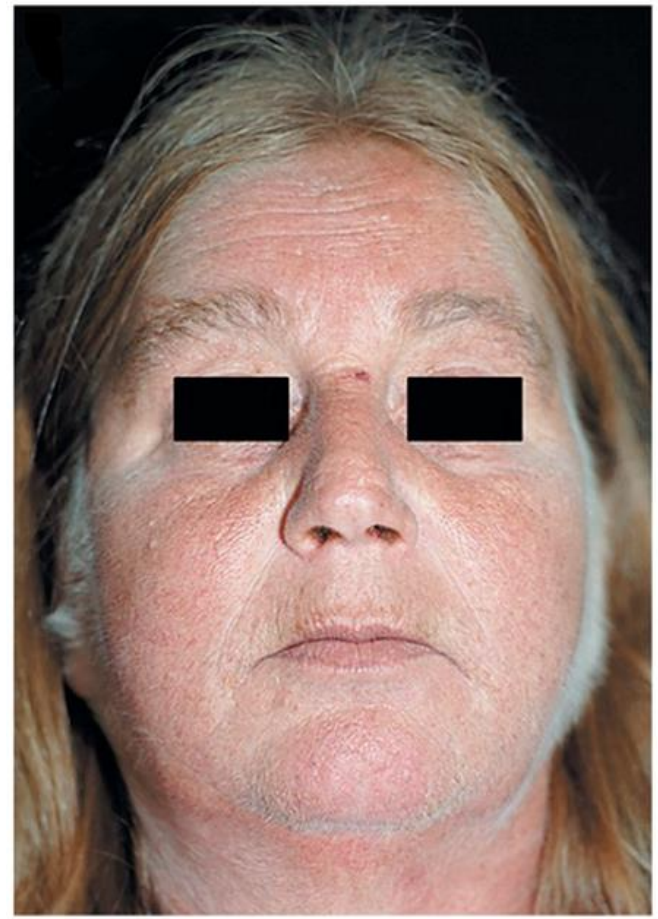
- paraneoplastic syndrome associated with ovarian and other cancers
- diffuse inflammation of the palmar fascia and tendon sheaths leading to flexion contracture of the hands without skin sclerosis / "woody hands"
- NSAIDs; ia or p.os steroids; if complete removal of the malignancy is possible, PFPAS can also undergo complete remission

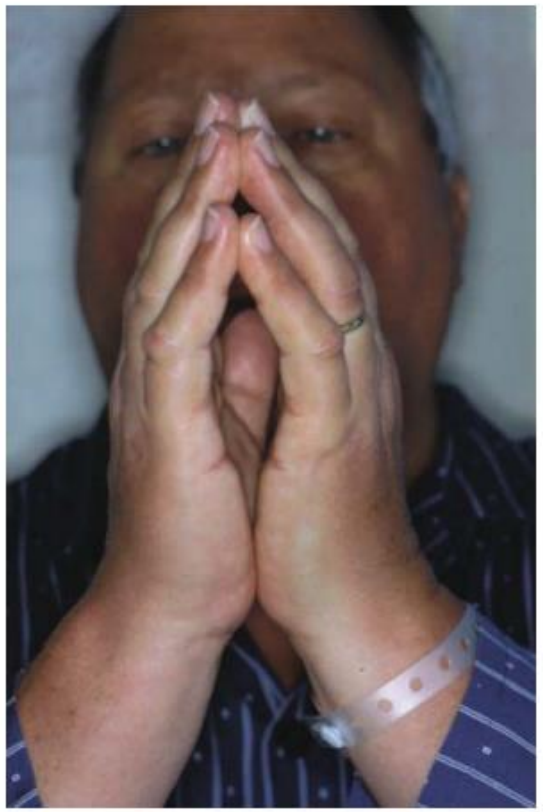
➢ rare genetic diseases such as Werner's syndrome (progeroid changes) or Huriez syndrome (keratoderma of the palm and soles).

Pieta A, et al. Rheumatol Int. 2022 Jun;42(6):1097-1103;
Manger B, et al. Semin Arthritis Rheum. 2014;44:105-11;
Oshima J, et al. Ageing Res Rev. 2017;33:105-114;
Patrizi A, et al. J Am Acad Dermatol. 1992;26:855-7.

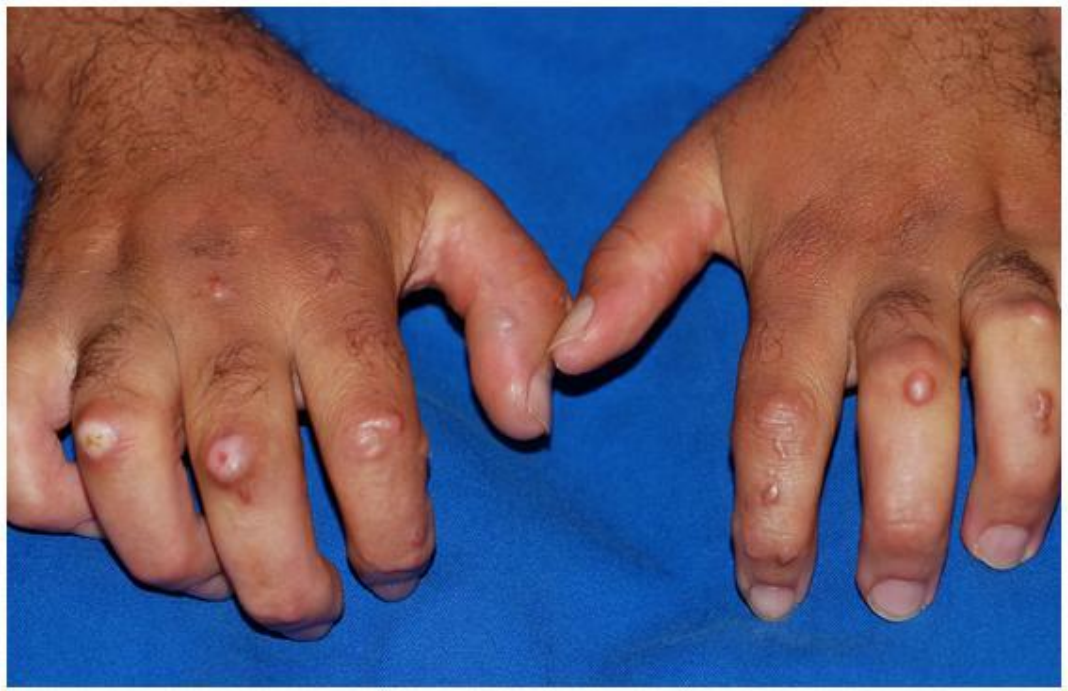

hypopigmentation
erosion
blister


Porphyria
Cutanea Tarda

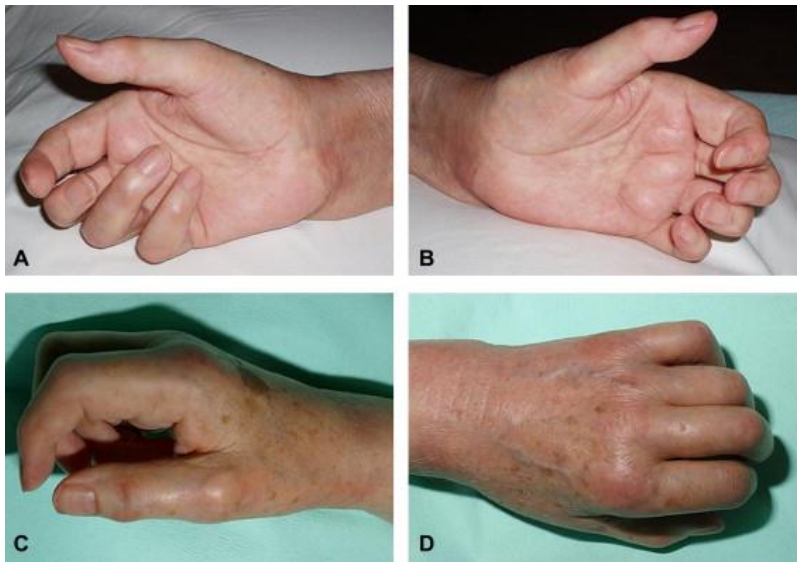




ure 24.5 The 'prayer sign', another feature of cheiroarthropathy.



Fibroblastic rheumatism



PFASP syndrome

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗ ΠΡΟΣΟΧΗ ΣΑΣ