Ασκηση 22

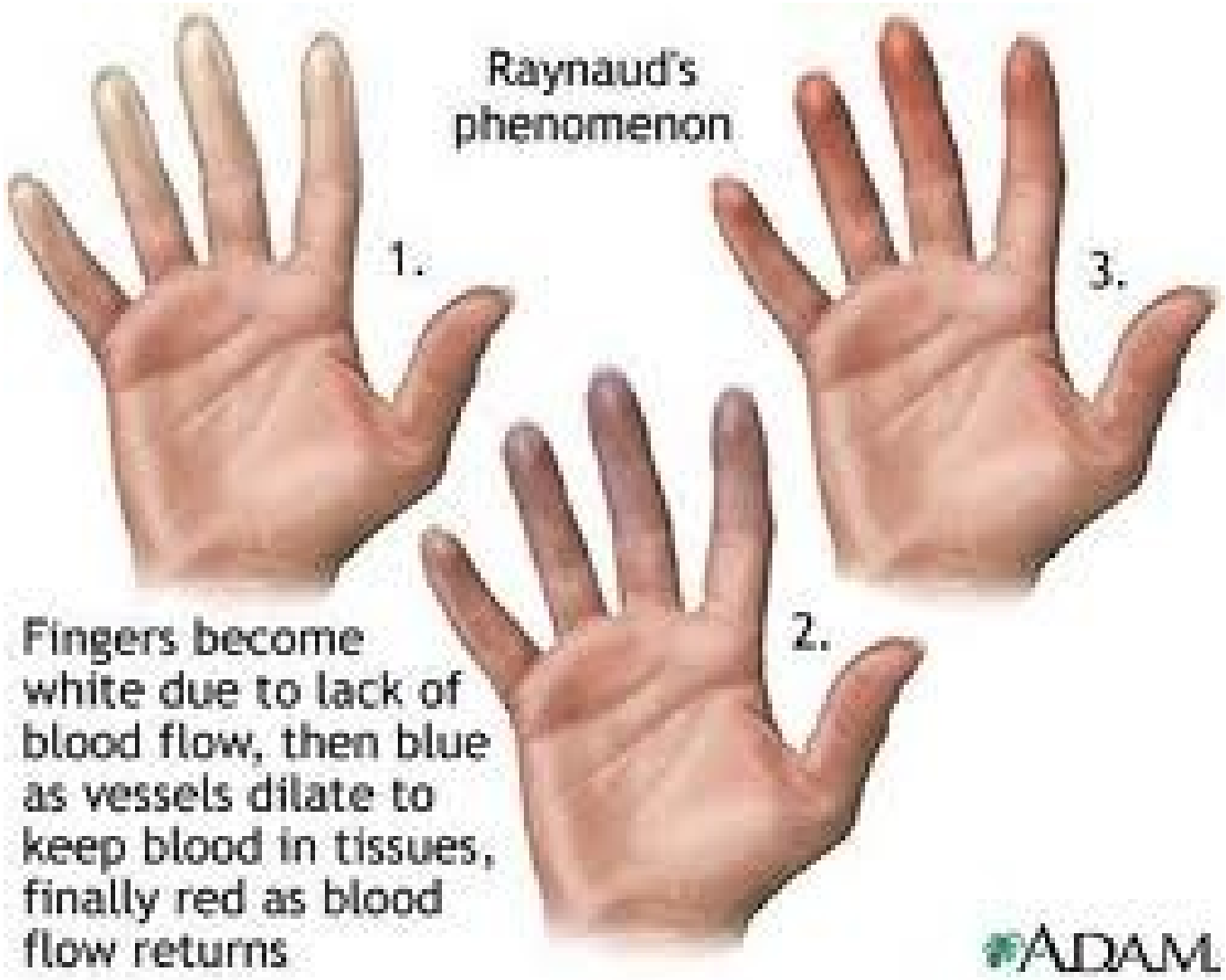
Συστηματικό σκληρόδερμα - Δερματομυοσίτις- Μικτή νόσος συνδετικού ιστού

Κατσιμπρή Πελαγία

Ασκηση 22

- Άντρας 60 ετών, συνταξιούχος.
- **Αιτία εισόδου:** Έλκη δακτύλων και κυάνωση χεριών στο κρύο.
- **Παρούσα νόσος:** Από 2ετίας αναφερόμενη κυάνωση χεριών στο κρύο και έλκη δακτύλων με δύσκολη επούλωση .
- **Ατομικό αναμνηστικό:** Αρτηριακή υπέρταση, κολπική μαρμαρυγή.
- **Συνήθειες και τρόπος ζωής:** Μέτριος καπνιστής εώς προ 20ετίας.

Φαινώμενο Raynaud

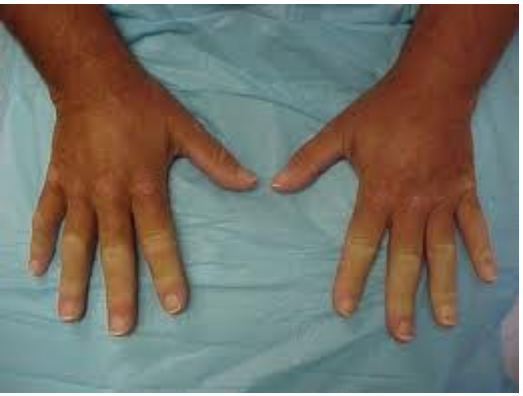


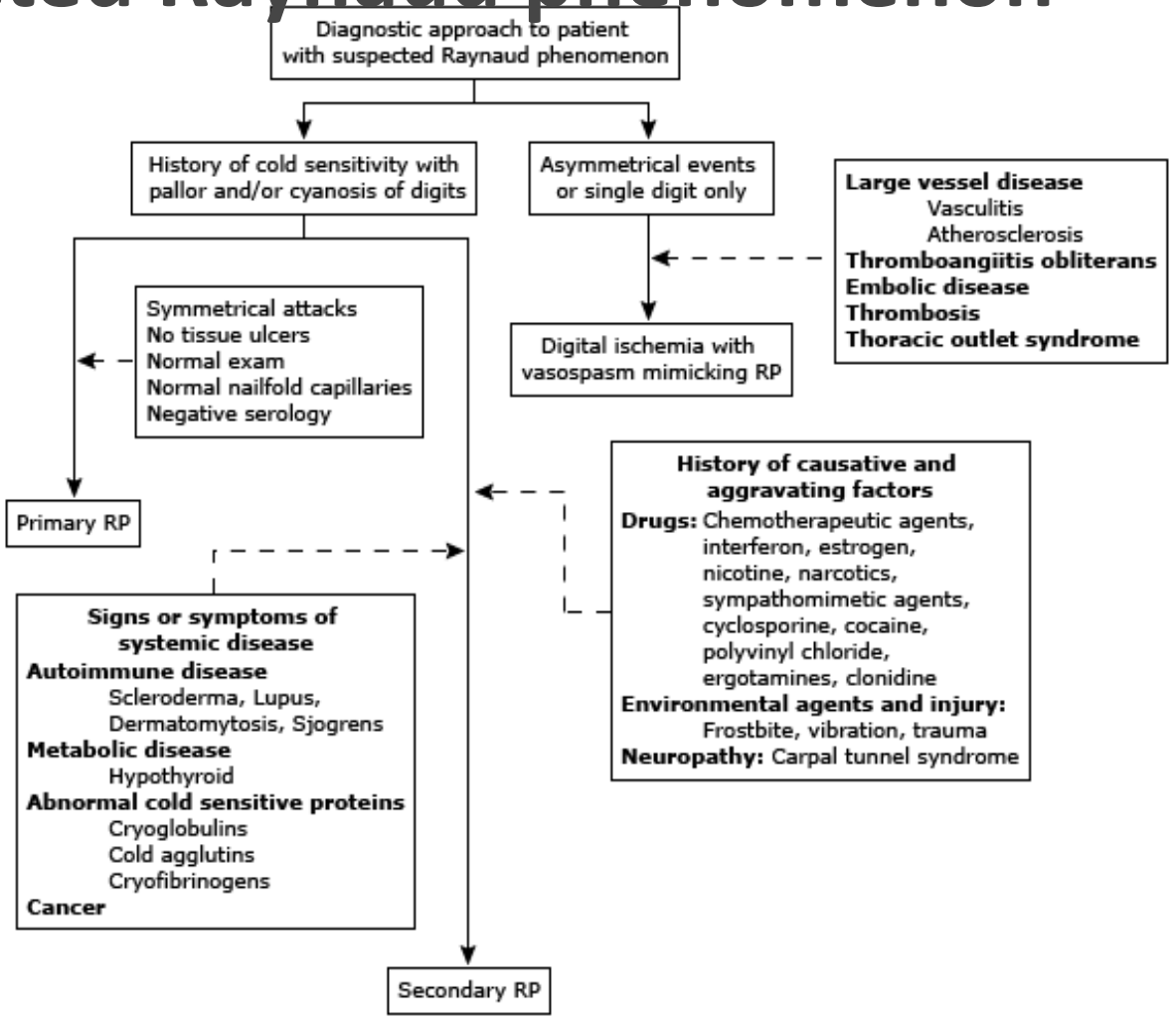
Disorders/factors associated with Raynaud's phenomenon

- **Rheumatological diseases**

  Scleroderma SΛE, Polymyositis/dermatomyositis Sjögren's syndrome UCTD< MCTD>
- **Hematologic/oncologic**
- Paraneoplastic syndrome,Cryoglobulinemia, Cryofibrinogenemia, Cold agglutinin, Paraproteinemia, POEMS syndrome
- **Endocrine**
- Hypothyroidism
- **Vascular**
- Thoracic outlet syndrome, Emboli, Vasculitis, Prinzmetal angina, Atherosclerosis, Thromboangiitis obliterans
- **Neurological**
- Carpal tunnel syndrome, Migraine headache
- **Environmental**
- Vibration injury, Frost bite, Emotional stress
- **Drugs/toxins**
- Sympathomimetic drugs, Chemotherapeutic drugs, Interferons, Nicotine, Cocaine, Ergotamines, Polyvinyl chloride

Diagnostic approach to the patient with suspected Raynaud phenomenon





Ασκηση 22

- **Ανασκόπηση συστημάτων:**
- Αναπνευστικό: Χρόνιος ξηρός βήχας, κυρίως κατά τις πρωινές ώρες.
- Κυκλοφορικό: Δύσπνοια στην κόπωση από 12μήνου.
- Πεπτικό: Αίσθημα βάρους στο επιγάστριο με μετεωρισμό κι όξινες ερυγές, κυρίως το βράδυ.

Ουροποιητικό-νευροψυχιατρικό: Ουδέν

Ασκηση 22

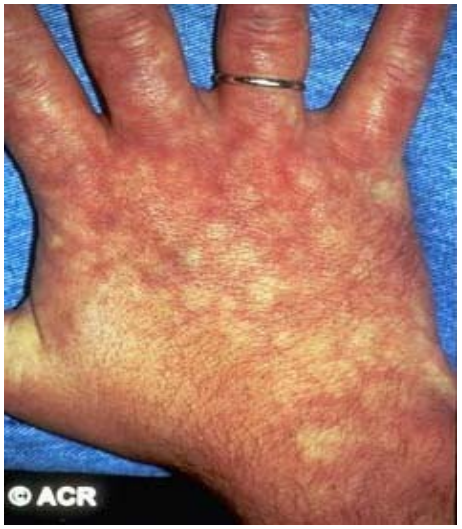
- **Αντικειμενική εξέταση:**
- Καλή όψη και θρέψη, απύρετος.
- Δέρμα: Τηλεαγγειεκτασίες στο στοματικό βλεννογόνο, κυρίως στην έσω επιφάνεια των χειλέων. Έλκη σε αποδρομή στο δείκτη και μεσαίο δάκτυλο του δεξιού χεριού, οιδηματώδη χέρια με σημεία αγγειοσύσπασης. Δικτυωτή πελίωση εμφανής στους μηρούς.
- Θώρακας: Τρίζοντες στο τέλος της εισπνοής στις βάσεις των πνευμόνων.
- Κυκλοφορικό: ΑΠ 145/85, σφύξεις 88/λεπτό, άρρυθμος σφυγμός, έντονος πνευμονικός δεύτερος ήχος, φυσήματα (-).
- Κοιλία-νευρικό-μυοσκελετικό: Ουδέν

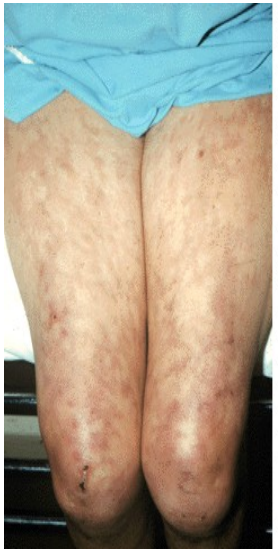
Δικτυωτή Πελίωση(livedo reticularis)

Πρωτοπαθής

Δευτεροπαθής

- Νοσήματα συνδετικού ιστού
- Περιφερική αγγειακή νόσος
- Υπεργλοιότητα
- Υπερπηκτικότητα
- Ενδοκρινικά νοσήματα
- Φάρμακα





Livedo reticularis
Livedo reticularis of the upper legs in a patient with systemic lupus erythematosus and Raynaud's phenomenon. This abnormality involved the thighs and arms in this patient, and was precipitated by the cold and cigarette smoking. Livedo reticularis is caused by capillary vasospasm and is often found among patients with antiphospholipid antibodies. Several small necrotic areas due to extensive vascular insufficiency are also present. Courtesy of Peter H Schur, MD.

Ασκηση 22

Εργαστηριακές εξετάσεις:

Hct=45,8 %, Hb=15 gr/dl, MCV=88 fl, Λευκά=6.300 (Π=60 %, Λ=28 %, Η=1 %),Αιμοπετάλια=220.000 /mm³

ΤΚΕ=5, CRP=0,3 mg/dl (ΦΤ<0.8 mg/dl)

TSH=0,89 μu/ml (ΦΤ=0,5-5 μg/dl), TPO/Tg (-)

RF (-), ANA=1/640, dsDNA (-)

ENA (+), anti-scl70 (+), anti-Ro/La/RNP/Sm (-)

AMA/ ASMA (-), ANCA p/c (-)

- Αέρια αίματος: pH 7,44, pCO2=40mmHg, pO2=81mmHg.
- Σπιρογράφημα: TLCO=70%(↓), λοιπά κ.φ.

Serum autoantibodies in scleroderma

Antigen	ANA staining pattern	Approximate frequency in all patients (percent)	Clinical associations	Organ involvement
Scl-70 (topoisomerase-1)	Speckled	10-40	dcSSc	Lung fibrosis, isolated pulmonary hypertension less likely
RNA polymerase III	Fine speckled nucleolar	4-25	dcSSc	Renal, skin, pulmonary hypertension
U3 RNP (fibrillarin)	Nucleolar	1-5	dcSSc, poor outcome black men	Pulmonary hypertension, muscle
PM-Scl	Nucleolar	3-6	Overlap, mixed	Muscle
U1 RNP	Speckled	5-35	lcSSc, blacks, polymyositis overlap	Muscle
Centromere	Centromere (kinotochore)	15-40	lcSSc	Pulmonary hypertension, esophageal disease, "protection" from lung fibrosis and renal disease
Th/To	Nucleolar	1-7	lcSsc	Pulmonary hypertension, lung fibrosis, small bowel
Anti U11/U12	Nucleolar	1-5	lcSSc and dcSSc	Lung fibrosis
Anti-Ku		1-3	Overlap SSc	Muscle and joint involvement, SLE overlap

Characteristics and clinical associations of the different autoantibodies that may be seen in scleroderma. dcSSc and lcSSc refer to diffuse and limited cutaneous systemic sclerosis, respectively.

Adapted from: Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in systemic sclerosis. Nat Rev Rheumatol 2010; 6:112.

Ασκηση 22

- **<u>Αξονική τομογραφία θώρακος</u>:**

Αλλοιώσεις πνευμονικής ίνωσης με πάχυνση του διάμεσου ιστού στον αριστερό άνω και μέσο λοβό και λιγότερο στο δεξιό κάτω λοβό. Αλλοιώσεις με χαρακτηριστικά μελικυρήθρας σε αμφότερες τις βάσεις.

- **<u>Υπερηχογράφημα (Τρίπλεξ) καρδιάς</u>:**

Δεξιά κοιλία ελαφριά διατεταμένη, σημαντική διάταση του αριστερού κόλπου. Κλάσμα εξώθησης=60 %, TAPSE (μέτρηση πνευμονικής πίεσης)=32 mmHg (ήπια αυξημένη).

- The prevalence rates of scleroderma-like conditions range from 4 to 489 cases per million individuals.

- Incidence figures for SSc are 0.6 to 122 per million persons per year.

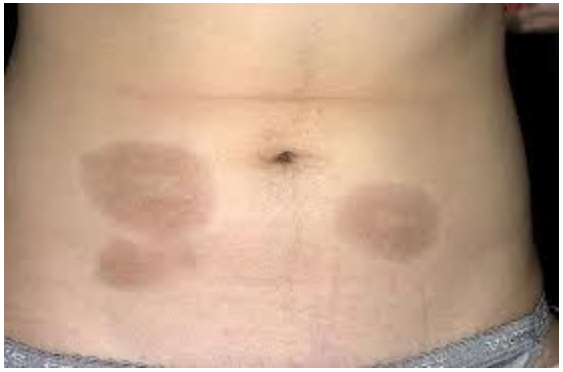
- There are regional differences in incidence. Higher rates are seen in the United States and Australia than in Japan or Europe, and in blacks than whites.

Scleroderma

- Subdivided into three groups:

1. systemic sclerosis
2. localized scleroderma
3. scleroderma-like conditions (heterogeneous group of diseases linked by the presence of thickened, sclerotic skin).

Localized scleroderma



- Divided into

1. Linear scleroderma (en coup de sabre) - most commonly occurs in childhood. Follows a dermatomal distribution on one side of the body.
2. Localized and generalized morpheae - characterized by patches of sclerotic skin that develop on the trunk and limbs at sites of previously normal texture. Generalized morphea typically spares the hands and face and is not associated with major vascular symptoms or with visceral disease. Unlike SSc!!

Systemic sclerosis

- Two distinct subsets:

1. diffuse cutaneous systemic sclerosis (DcSSc)
2. limited cutaneous systemic sclerosis (LcSSc).

Subsets are defined on the basis of the extent of skin involvement.

Patients with limited cutaneous systemic sclerosis may display features of the CREST syndrome (**c**alcinosis cutis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia).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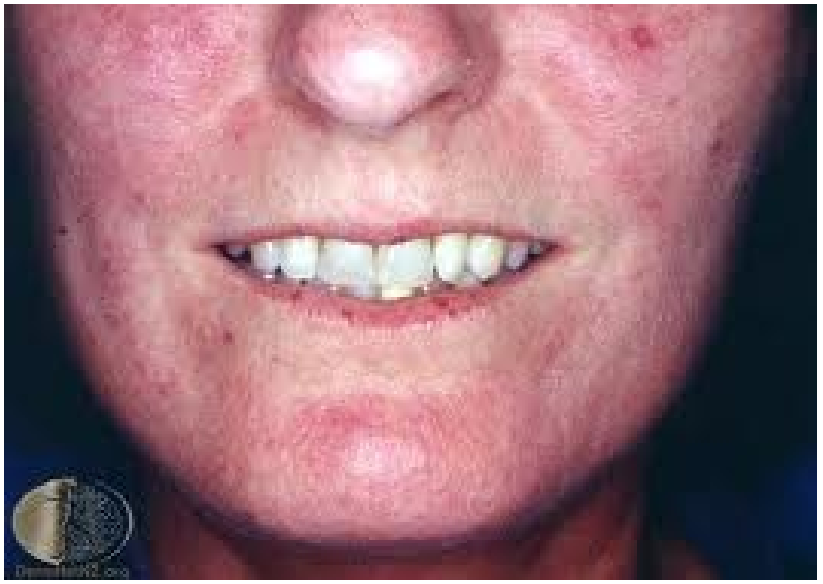
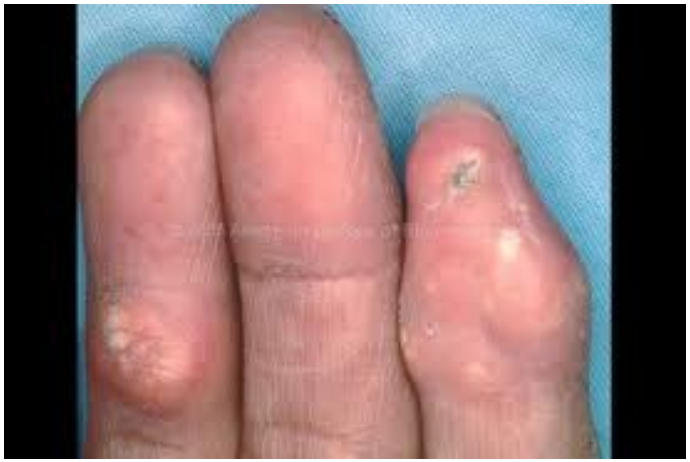




Classification of systemic sclerosis

Limited cutaneous scleroderma
Raynaud phenomenon for years, occasionally decades
Skin involvement limited to hands, face, feet, and forearms (acral distribution)
Nailfold capillary pattern typical of scleroderma predominantly nailfold capillary loops with capillary drop-out
A significant (10 to 15 percent) late incidence of pulmonary hypertension, with or without skin calcification, gastrointestinal disease, telangiectasias (CREST syndrome), or interstitial lung disease
Renal disease rarely occurs
Anticentromere antibody (ACA) in 50 to 60 percent but other patterns also occurring in 5 to 10 percent (especially anti-PM-Scl and anti-Scl-70)
Diffuse cutaneous scleroderma
Raynaud phenomenon followed, within one year, by puffy or hidebound skin changes
Truncal and acral skin involvement; tendon friction rubs
Nailfold capillary pattern typical of scleroderma with dilatation (early), dilatation and drop-out (active), and tortuosity with drop-out (late)
Early and significant incidence of renal, interstitial lung, diffuse gastrointestinal, and myocardial disease
Anti-Scl-70 (30 percent) and anti-RNA polymerase-I, II, or III (12 to 15 percent) antibodies
Scleroderma sine scleroderma
Presentation with pulmonary fibrosis or renal, cardiac, or gastrointestinal disease
No skin involvement
Raynaud phenomenon may be present
Antinuclear antibodies may be present (anti-Scl-70, ACA, or anti-RNA polymerase-I, II, or III)
Environmentally induced scleroderma
Generally diffuse distribution of skin sclerosis and a history of exposure to an environmental agent suspected of causing scleroderma
Overlap syndromes
Features of systemic sclerosis that coexist with those of another autoimmune rheumatic disease such as systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, vasculitis, or Sjögren's syndrome.
Pre-scleroderma
Raynaud phenomenon
Nailfold capillary changes (early or active pattern typical) and evidence of digital ischemia
Specific circulating autoantibodies - anti-topoisomerase-I (Scl-70), anti-centromere (ACA), or anti-RNA polymerase-I, II, or III or other hallmark scleroderma reactivity

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

- The diagnosis of systemic sclerosis is suggested by the presence of skin thickening and hardening (sclerosis) that is not confined to one area.
- The diagnosis is supported by the presence of extracutaneous features and characteristic serum autoantibodies.
- The assessment of skin involvement includes *estimation of skin thickness, pliability (hardness), and fixation to underlying structures (tethering).*
- ***The modified Rodnan skin score*** is commonly used as an outcome measure in clinical trials - rates the severity of these features from 0 (normal) to 3 (most severe) in 17 distinct areas of the body.

GENERAL MANIFESTATIONS OF SSc

Fatigue, arthralgias, and myalgias.

The frequency of these symptoms is uncertain.

In a study of 107 patients with established disease (median 10 years, range 1 to 37 years), the following were the most frequent symptoms:

Fatigue (76 percent)

Stiff joints (74 percent)

Loss of strength (68 percent)

Pain (67 percent)

Sleep difficulties (66 percent)

Skin discoloration (47 percent)

Less commonly noted symptoms were breathlessness, upset stomach, sore eyes, depression, nausea, and weight loss.

The level of fatigue in SSc is comparable to that in rheumatoid arthritis, sle, or cancer patients in active treatment.

The presence of fatigue was associated with poorer physical function and greater pain .

Causes of pain include skin-related discomfort, joint pain, Raynaud phenomenon, and ischemic digital ulcers.

Features of skin involvement

- The extent of skin induration varies. Almost all patients have skin involvement in the fingers (sclerodactyly), hands, and face.

During the first few months of disease, it may be difficult to make a firm diagnosis of systemic sclerosis. At this "inflammatory stage" of the disease, arthralgia and soft tissue swelling rather than skin induration may be more prominent mimicking rheumatoid arthritis or another connective tissue disease.

The presence of calcinosis cutis, hyperpigmentation, and/or cutaneous telangiectasia may be helpful in confirming the diagnosis but are *variable and often absent in early disease.*

Other prominent skin manifestations

1. Pruritus in the early stages
2. Edema in the early stages
3. Sclerodactyly
4. **Digital ulcers**
5. **Pitting at the fingertips**
6. Telangiectasia
7. Calcinosis cutis

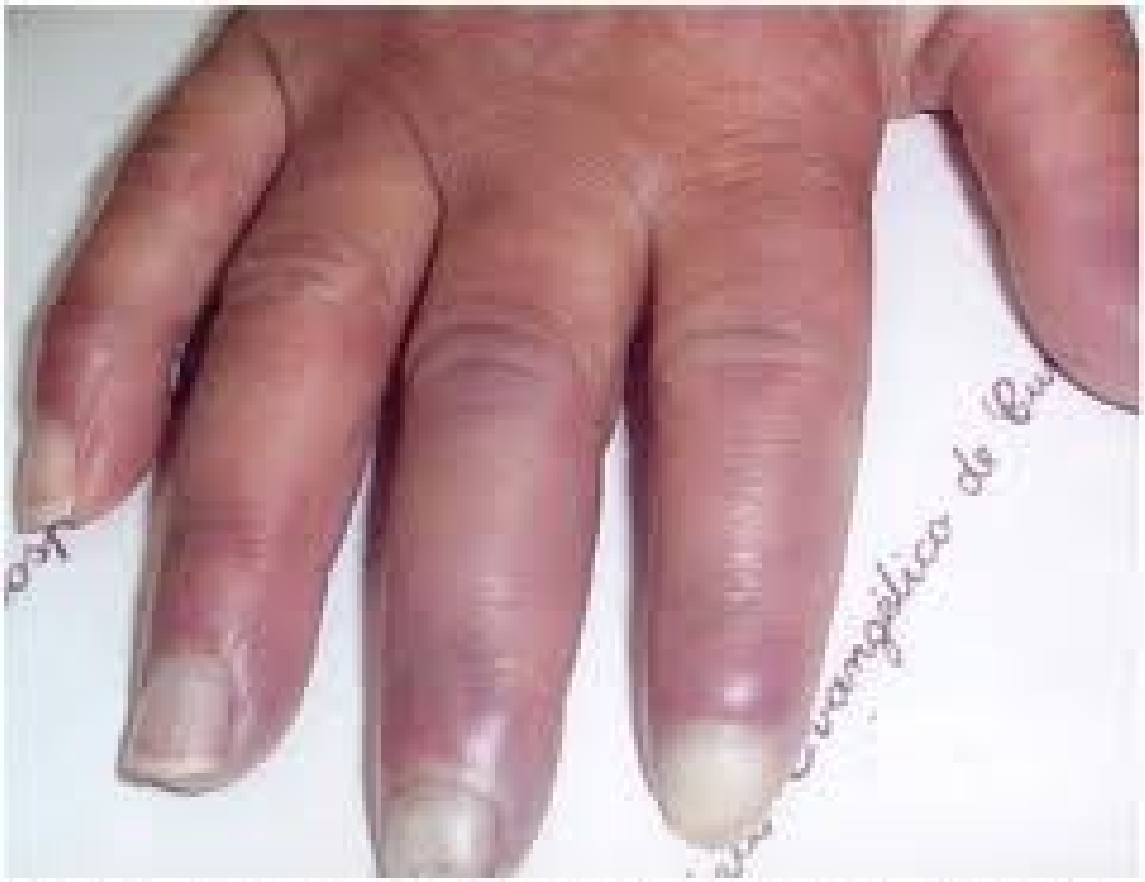


FIGURE 1: Raynaud´s phenomenon. The narrowing of the digital pulps and hypotrophy is suggestive of long-term Raynaud´s

EXTRACUTANEOUS ORGAN INVOLVEMENT

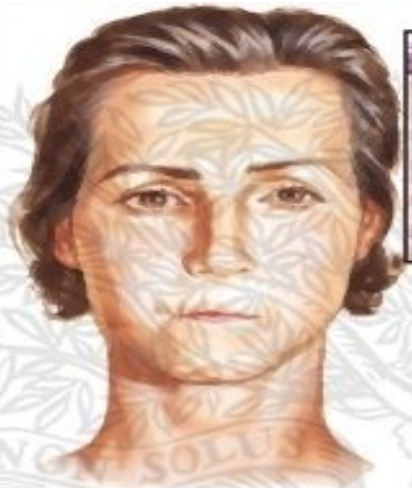
- **Gastrointestinal involvement -**can involve any part of the g.i.t. >50% patients. Most commonly due to chronic gastroesophageal reflux, also chronic esophagitis and stricture formation, Barrett's esophagus, and abnormal motility.

- **Musculoskeletal disease-**Swelling of the hands, arthralgia, myalgia, and fatigue. Joint pain, immobility and contractures develop as the result of fibrosis around tendons and other periarticular structures. Palpable and/or audible deep tendon friction rubs. Destructive joint disease in a patient with SSc may suggest an overlap syndrome with rheumatoid arthritis.

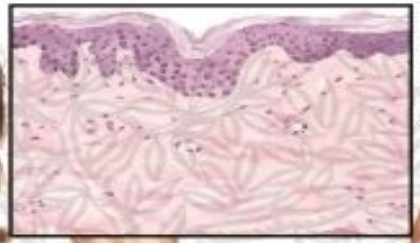
- **Neuromuscular involvement**

1. Cranial nerve entrapment, peripheral, cutaneous, and autonomic neuropathies
2. Myopathy and inflammatory myositis
3. Less commonly headache, seizures, stroke, radiculopathy, and myelopathy

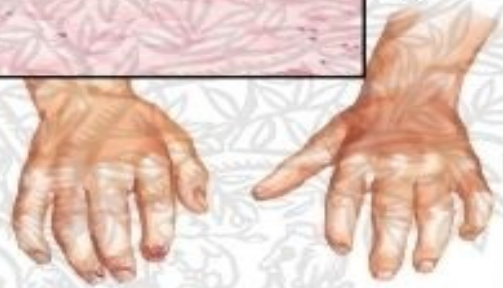
- **Genitourinary** Erectile dysfunction in men common. Women also have sexual dysfunction and dyspareunia .



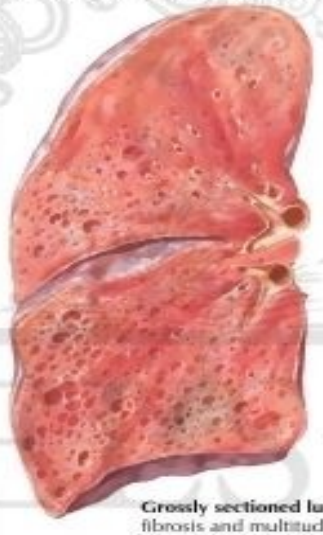
Characteristics. Thickening, tightening, and rigidity of facial skin, with small, constricted mouth and narrow lips, in atrophic phase of scleroderma



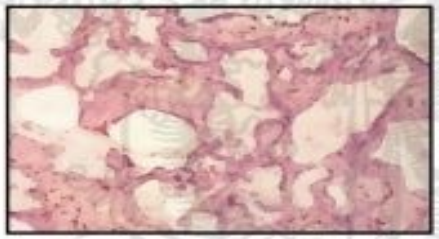
Typical skin changes in scleroderma: extensive collagen deposition and some epidermal atrophy



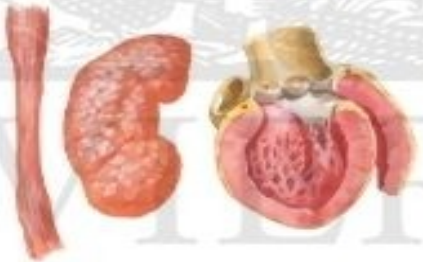
Sclerodactyly. Fingers partially fixed in semiflexed position; terminal phalanges atrophied; fingertips pointed and ulcerated



Grossly sectioned lung. Extensive fibrosis and multitudinous small cysts. Visceral pleura thickened but not adherent to chest wall



Microscopic section of lung. Fibrosis with formation of microcysts, many of which represent dilated bronchioles.



Esophagus, kidneys, heart, skin, and other organs, as well as joints, may also be affected.

EXTRACUTANEOUS ORGAN INVOLVEMENT

- **Pulmonary involvement** >70% patients.

1. Interstitial lung disease
2. Pulmonary vascular disease leads to pulmonary arterial hypertension. (lcSsc)
3. Lung cancer

- **Renal disease-50%** Albuminuria, a mild elevation plasma Cr +/- HT

  Scleroderma renal crisis-most serious renal complication, occurs in 10 -15%, generally among early-stage dcSSc - poor prognosis.

- **Cardiac disease**

1. Pericardial disease
2. Myocardial disease -Patchy myocardial fibrosis distinguishable from the fibrosis of coronary atherosclerotic disease and is independent of 2o cardiac involvement of pulmonary hypertension.
3. Arrhythmias- Conduction system disease result from fibrosis of the myocardium and conduction system.

Clinical features of the major systemic Sclerosis subsets

Diffuse cutaneous	Early (<3 years after onset)	Late (>3 years after onset)
Constitutional	Fatigue and weight loss	Minimal, weight gain typical
Vascular	Raynaud's often relatively mild	Raynaud's more severe, more telangiectasia
Cutaneous	Rapid progression involving arms, trunk, face	Stable or regression
Musculoskeletal	Prominent arthralgia, stiffness, myalgia, muscle weakness, tendon friction rubs	Flexion contractures and deformities, joint/muscle symptoms less prominent
Gastrointestinal	Dysphagia, heartburn	More pronounced symptoms, midgut and anorectal complications more common
Cardiopulmonary	Maximum risk for myocarditis, pericardial effusion, intersitital pulmonary fibrosis	Reduced risk of new involvement but progression of existing established visceral fibrosis
Renal	Maximum risk period for scleroderma after 5 years	Renal crisis less frequent, uncommon after 5 years
Limited cutaneous	**Early (<10 years after onset)**	**Late (>10 years after onset)**
Constitutional	None	Only secondary to visceral complications
Vascular	Raynaud's typically severe and longstanding telangiectasia	Raynaud's persists, often causing digital ulceration or gangrene
Cutaneous	Mild sclerosis with little progression on trunk, face	Stable, calcinosis more prominent
Musculoskeletal	Occasional joint stiffness	Mild flexion contractures
Gastrointestinal	Dysphagia, heartburn	More pronounced symptoms, midgut and anorectal complications more common
Cardiopulmonary	Usually no involvement	Lung fibrosis may develop, but often progresses slowly, Anti-SCL-70 predicts increased risk of severe fibrosis. Maximum risk for developing isolated pulmonary hypertension and secondary right ventricular failure.
Renal	No involvement	Rarely involved, anti-RNA polymerase predicts increased risk of renal involvement.

Clinical manifestations of lung disease in scleroderma

Disease	Symptoms	Signs
Pulmonary fibrosis	Dyspnea Dry cough	Chest expansion Basal crepitations (rales) Clubbing (late, very uncommon)
Pulmonary hypertension	Dyspnea Ankle edema	Loud P2 Right ventricular heave
Pleural involvement	Pleuritic chest pain Dyspnea	Pleural rub Pleural effusion (rare)
Bronchiectasis	Cough with purulent sputum Dyspnea	Basal crepitations
Spontaneous pneumothorax	Chest pain Dyspnea	Resonant percussion Reduced breath sounds
Lung cancer (scar type), especially alveolar cell	Cough Hemoptysis	? Signs of collapse
Respiratory failure due to respiratory muscle involvement	Dyspnea Reduced chest expansion	Hypoventilation

Ασκηση 22

Κύρια σημεία:

1. Η διάγνωση του συστηματικού σκληροδέρματος είναι κλινική και βασισμένη στην χαρακτηριστηκή πάχυνση του δέρματος, το φαινόμενο Raynaud, και τη συμμετοχή σπλαγχνικών οργάνων. Στο συγκεκριμένο περιστατικό πρόκειται για πνευμονική προσβολή (κυρίως ίνωση και ήπια πνευμονική υπέρταση) και προσβολή πεπτικού (ΓΟΠ).
2. Η χρήση συγκεκριμένων αυτοαντισωμάτων βοηθά στο διαχωρισμό ανάμεσα στο περιορισμένο και διάχυτο συστηματικό σκληρόδερμα.
3. Η θεραπεία εκτός από συμπτωματική/βοηθητική και ανοσοκατασταλτική κατευθυνόμενη προς τα όργανα στόχους, τώρα στοχεύει στους παθογενετικούς μηχανισμούς της ίνωσης και της αγγειοπάθειας.
4. Η έγκαιρη διάγνωση του πρώιμου σταδίου της ενεργού φλεγμονής αυξάνει την αποτελεσματικότητα της ανοσοκατασταλτικής αγωγής.