Systemic connective tissue diseases

LECTURE IN INTERNAL MEDICINE FOR V COURSE STUDENTS

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Plan of the Lecture

Systemic connective tissue diseases

- Definition
- Classification
- Mechanisms
- Selected systemic connective tissue diseases
  - Marfan syndrome
  - Systemic lupus erythematosus
  - Scleroderma
  - Sjögren syndrome
  - Mixed connective tissue disease
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic and treatment guidelines

https://s-media-cache-ak0.pinimg.com/236x/01/00/a6/0100a6ca7539b8c4f99a369a2bb1c3a8.jpg

Definition

- Systemic connective tissue diseases (systemic autoimmune diseases, collagen diseases, collagen vascular diseases , SCTD) refer to a group of chronic autoimmune inflammatory disorders involving the protein-rich connective tissue that supports organs and other parts of the body, first of all the joints, muscles, skin, and other organs and organ systems, including the eyes, heart, lungs, kidneys, gastrointestinal tract, and blood vessels.
- There are more than 200 disorders that affect the connective tissue.

http://www.webmd.com/a-to-z-guides/connective-tissue-disease

Classification

Heritable SCTD

- ***Marfan syndrome***
- Peyronie's disease
- Ehlers-Danlos syndrome
- Osteogenesis imperfecta
- Stickler syndrome
- Alport syndrome
- Congenital contractural arachnodactyly
- Loeys–Dietz syndrome

Acquired SCTD

- ***Systemic lupus erythematosus*** (SLE)
- Rheumatoid arthritis
- ***Sjögren syndrome***
- Psoriatic arthritis
- Dermatomyositis (DM)
- Polymyositis (PM)
- Anti-synthetase syndrome
- ***Mixed connective tissue disease***
- Scurvy

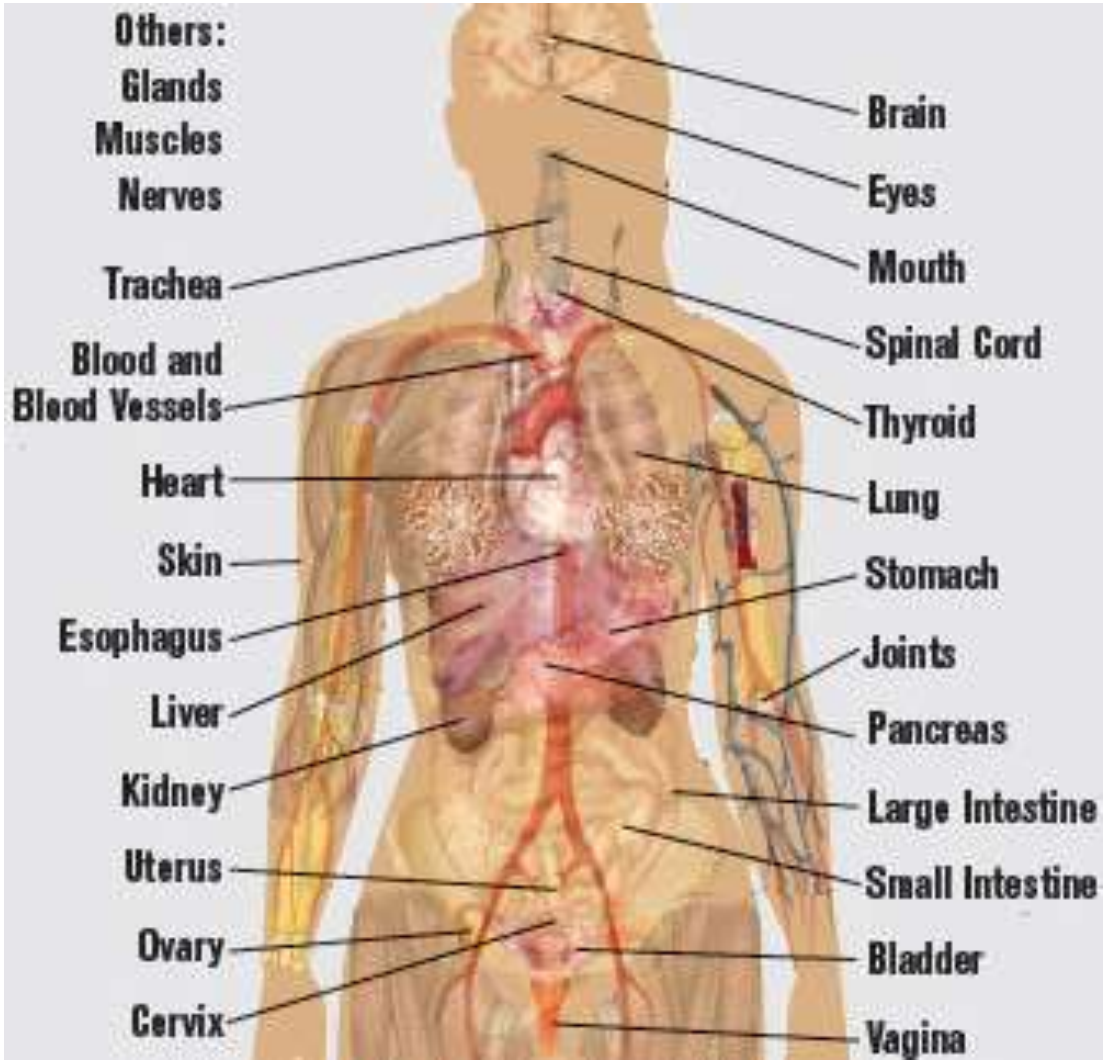
https://en.wikipedia.org/wiki/Connective_tissue_disease

Mechanisms
(The Connective Tissues Abnormalities)

- SCTD have the connective tissues of the body as a target of chronic autoimmune progressive inflammation.
- However, the mechanisms of SCTD are diverse, the connective tissues abnormalities include impaired angiogenesis as well as immunological alterations, e.g. B-lymphocytes and T-lymphocytes activation , self-antigens apoptotic modification and immune response against them, widespread lymphocytic and plasmacytic infiltration, activation of Toll-like receptors, etc. with abundant fibrinoid deposits.
- SCTD characterized by varying tissue distribution with different pattern of organ involvement.

http://rheumatology.oxfordjournals.org/content/45/suppl_3/iii1.full http://emedicine.medscape.com/article/335815-overview#a4

Mechanisms
(Body Systems Affected by SCTD)



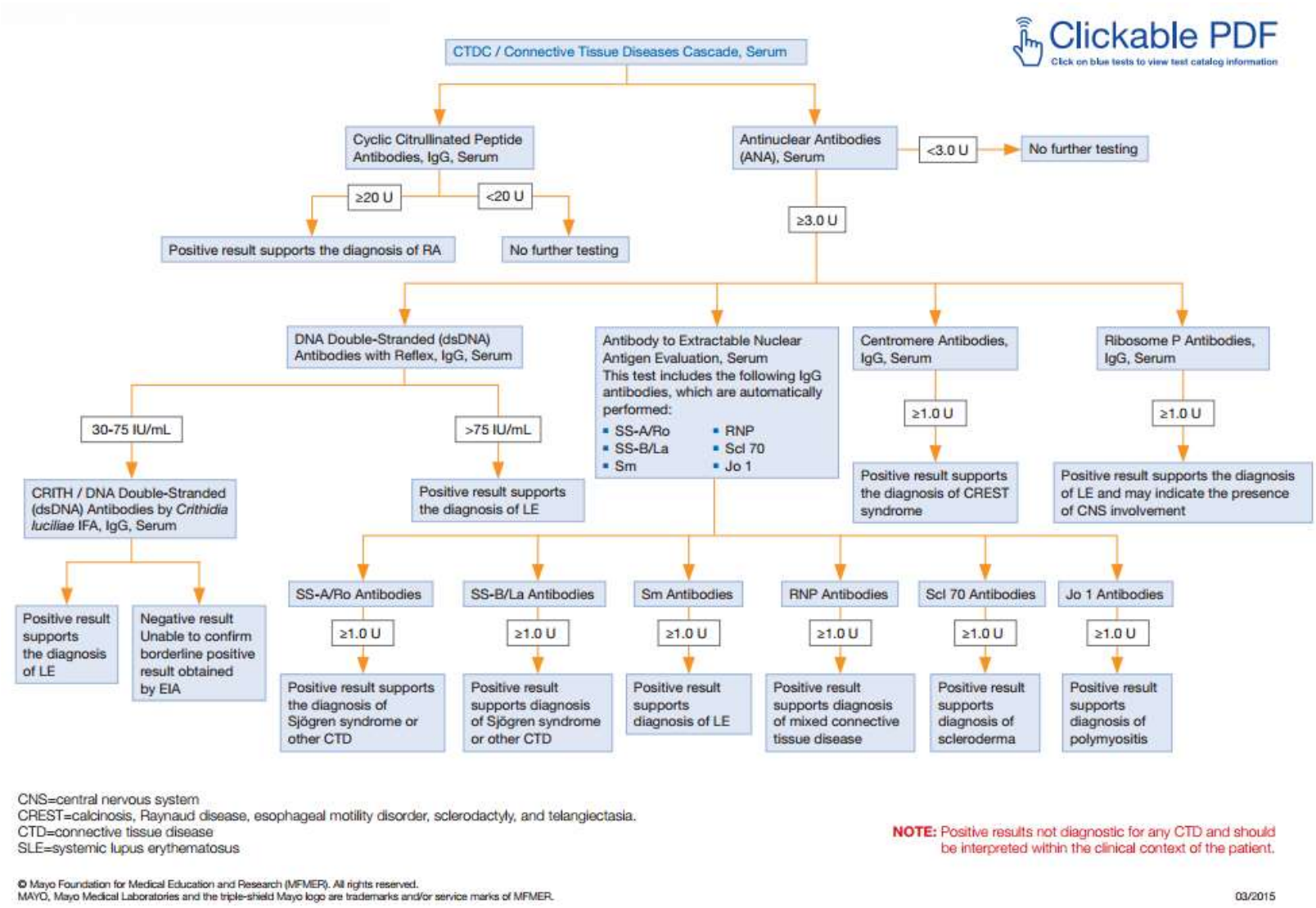
http://www.lifeextension.com/~/media/lef/images/magazine/mag2014/images/mar2014_smad_05.ashx

Mechanisms
(Different Diseases associated with Specific Autoantibodies)

Disease	Autoantibody
• Systemic Lupus Erythematosus	• Anti-dsDNA, Anti-SM
• Rheumatoid Arthritis	• RF, Anti-RA33
• Sjögren Syndrome Systemic Sclerosis	• Anti-Ro(SS-A),Anti-La(SS-B)
• Polymyositis/Dermatomyositis Mixed Connective Tissue Disease	• Anti-Scl-70, Anti-centromere
• Wegener's Granulomatosus	• Anti-Jo-1
	• Anti-U1-RNP
	• c-ANCA

rheumatology.oxfordjournals.org/content/45/suppl_3/iii1.full

Diagnosis
(Connective Tissue Disease Cascade (CTDC))



https://en.wikipe http://www.mayomedicallaboratories.com/it-mmfiles/Connective_Tissue_Disease_Cascade__CTDC_.pdf dia.org/wiki/Rheumatoid_arthritis#Signs_and_symptoms

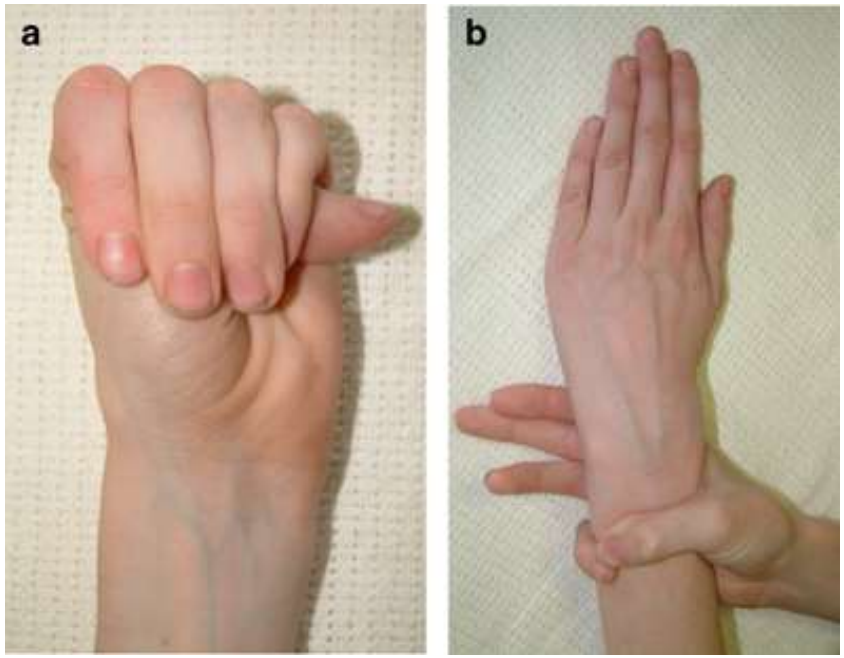
Marfan syndrome
(Definition)

- Marfan syndrome (MFS) is a spectrum of disorders caused by a heritable genetic defect of connective tissue that has an autosomal dominant mode of transmission.
- The defect itself has been isolated to the *FBN1*gene on chromosome 15, which codes for the connective tissue protein fibrillin.
- Abnormalities in fibrillin cause a myriad of distinct clinical problems, of which the musculoskeletal, cardiac, and ocular system.

Pharaoh Akhenaton

https://stottilien.files.wordpress.com/2014/01/echnaton.png https://en.wikipedia.org/wiki/Marfan_syndrome rheumatology.oxfordjournals.org/content/45/suppl_3/iii1.full

Marfan syndrome
(External Signs)



a) the Steinberg sign
b) the Walker-Murdoch sign

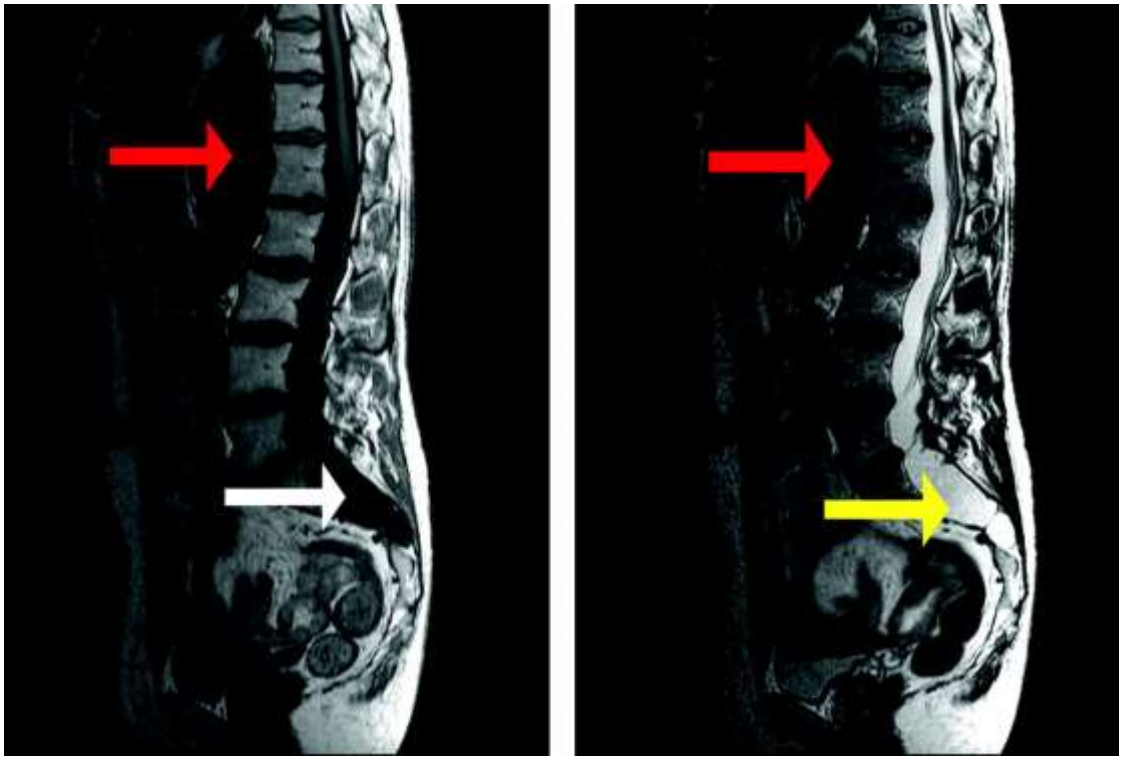
www.somospacientes.com/wp-content/uploads/2013/04/S%C3%ADndrome-de-Marfan.jpg mayoclinic.org/diseases-conditions/marfan-syndrome/symptoms-causes/dxc-20195415

Marfan syndrome
(Pectus Carinatum Deformity)

Pectus carinatum also called pigeon chest, is adeformity of the chest characterized by a protrusion of the sternum and ribs.

http://www.londonorthotics.co.uk/media/22949/pectuse-cs1-before_boxpromo.jpg

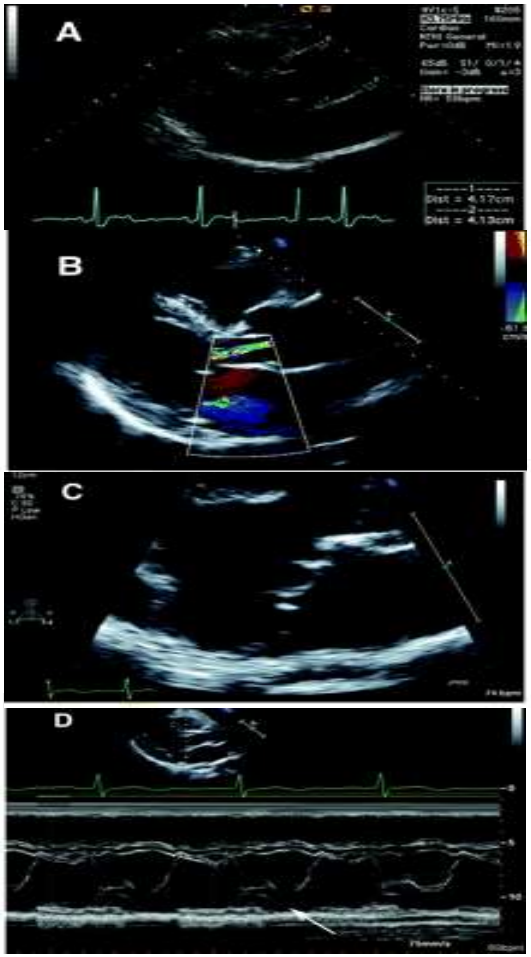
Marfan syndrome
(Dural Ectasia)



T1- and T2-weighted sagittal MR images of the lumbar spine reveal enlargement of the thecal sac (yellow arrow) with mild scalloping of the lumbar vertebral bodies and marked focal thinning of the sacrum (white arrow). An enlarged flow void anterior to the spine (red arrow) is related to dilation of the descending aorta

http://www.neurology.org/content/71/17/1378/F1.expansion.html

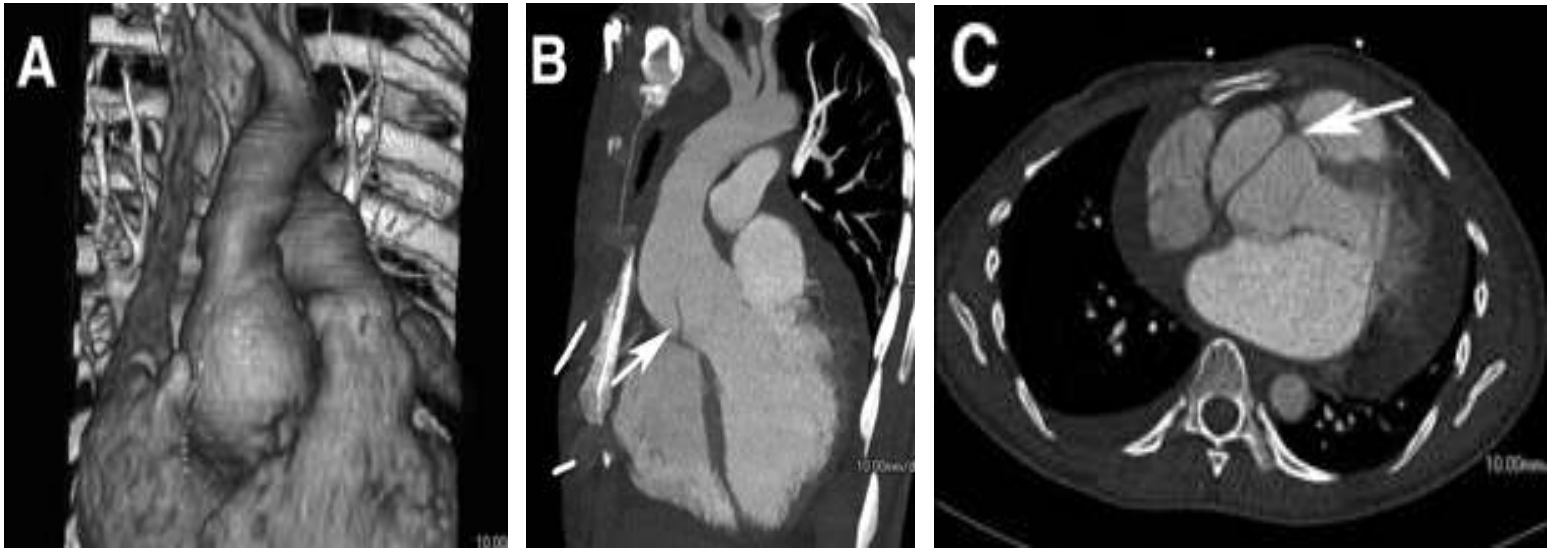
Marfan syndrome
(Echocardiography)



A) Two-dimensional echo image in the parasternal long axis demonstrates dilation of the aortic root in a MFS patient.
B) Color Doppler echo shows mild regurgitation through an otherwise normal aortic valve, which results from the dilatation of the root.
C) MFS patient with moderate mitral valve prolapse, demonstrated in 2-dimensional echo images.
D) Classic M-mode demonstration of prolapse of the posterior mitral valve leaflet (arrow).

http://circ.ahajournals.org/content/117/21/2802#T1

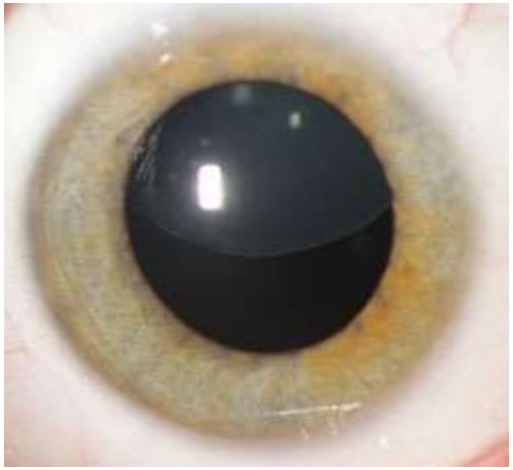
Marfan syndrome
(Computed tomography)



- A) Volume-rendered computed tomographic angiography image demonstrates the dilatation of the proximal aortic root and ascending aorta.
- B and C) Computed tomographic imaging demonstrates evidence of acute type A dissection (arrows).

http://circ.ahajournals.org/content/117/21/2802#T1

Marfan syndrome
(Ectopia Lentis)



- Ectopia lentis is a shift in the location of the lens inside the eye.
- The lens moves from its centered location in the eye so that the person is not looking through the center of their lens.
- This dislocation is caused by weakness in the connective tissue that holds the lens in place (zonules).

http://www.aapos.org/terms/conditions/68

Marfan syndrome
(Diagnostic Criteria)

- The diagnosis of MFS relies on a set of defined clinical criteria (the Ghent nosology) revised in 2010.
- The criteria puts more weight on the cardiovascular manifestations of the disorder.
- Aortic root aneurysm and ectopia lentis (dislocated lenses) are now cardinal features.
- In the absence of any family history, the presence of these two features is sufficient for the unequivocal diagnosis of Marfan syndrome.
- In the absence of one of these two cardinal features, the presence of an FBN1 mutation of positive systemic score is required.

http://jmg.bmj.com/content/47/7/476.abstract

Marfan syndrome
(Diagnostic Criteria: In the Absence of Family History)

- Aortic Root Dilatation Z score ≥ 2 AND Ectopia Lentis = Marfan syndrome
- Aortic Root Dilatation Z score ≥ 2 AND FBN1 = Marfan syndrome
- Aortic Root Dilatation Z score ≥ 2 AND Systemic Score ≥ 7pts = Marfan
- Ectopia lentis AND FBN1 with known Aortic Root Dilatation = Marfan syndrome

http://jmg.bmj.com/content/47/7/476.abstract

Marfan syndrome
(Diagnostic Criteria: In the Presence of Family History)

- Ectopia lentis AND Family History of Marfan syndrome (as defined above) = Marfan syndrome
- A systemic score ≥ 7 points AND Family History of Marfan syndrome (as defined above) = Marfan
- Aortic Root Dilatation Z score ≥ 2 above 20 yrs. old, ≥ 3 below 20 yrs. old) + Family History of Marfan syndrome (as defined above) = Marfan syndrome

http://jmg.bmj.com/content/47/7/476.abstract

Marfan syndrome
(Diagnostic Criteria: Points for Systemic Score)

- Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hindfoot deformity = 2 (plain pes planus = 1)
- Dural ectasia = 2
- Protrusio acetabuli = 2
- pneumothorax = 2
- Reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (3/5) = 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae (stretch marks) = 1
- Myopia > 3 diopters = 1
- Mitral valve prolapse 1⁄4 1

http://jmg.bmj.com/content/47/7/476.abstract

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http://jmg.bmj.com/content/47/7/476.abstract

Marfan syndrome
(Physical activity)

- Probably permissible activities: bowling, golf, skating (but not ice hockey), snorkeling, brisk walking, treadmill, stationary biking, modest hiking, and doubles tennis.
- Intermediate risk: basketball (both full and half-court), racquetball, squash, running (sprinting and jogging), skiing (downhill and cross-country), soccer, singles tennis, touch (flag) football, baseball, softball, biking, lap swimming, motorcycling, and horseback riding.
- High risk: body building, weightlifting (non-free and free weights), ice hockey, rock climbing, windsurfing, surfing, and scuba diving.

https://en.wikipedia.org/wiki/Marfan_syndrome#Management

Marfan syndrome
(Management)

- Although future therapy directed at the fibrillin-1 gene or the TGF-β axis may ultimately prove most effective at preventing the aortic complications of MFS , β-blocker therapy currently remains the “standard of care” or if not tolerated calcium channel blockers, angiotensin converting enzyme
- (ACE) inhibitors or angiotensin II receptor antagonists (ARBs) can be use.
- Management of type A acute dissection of the aorta is a surgical emergency.
- The initial management patients with type B acute dissection of the aorta can employ standard medical approaches.
- Surgical repair of the severely regurgitant mitral valve is possible.
- In end-stage heart failure, orthotopic transplantation is an effective approach.
- Any spinal surgery should only follow detailed imaging and careful surgical planning.

http://emedicine.medscape.com/article/946315-overview http://circ.ahajournals.org/content/117/21/2802#T1

Systemic Lupus Erythematosus
(Definition)

- Systemic lupus erythematosus (SLE), also known simply as lupus, is a chronic autoimmune inflammatory disease that has protean manifestations and follows a relapsing and remitting course.
- Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, swollen lymph nodes, feeling tired, and a red rash which is most commonly on the face.
- More than 90% of cases of SLE occur in women, frequently starting at childbearing age.

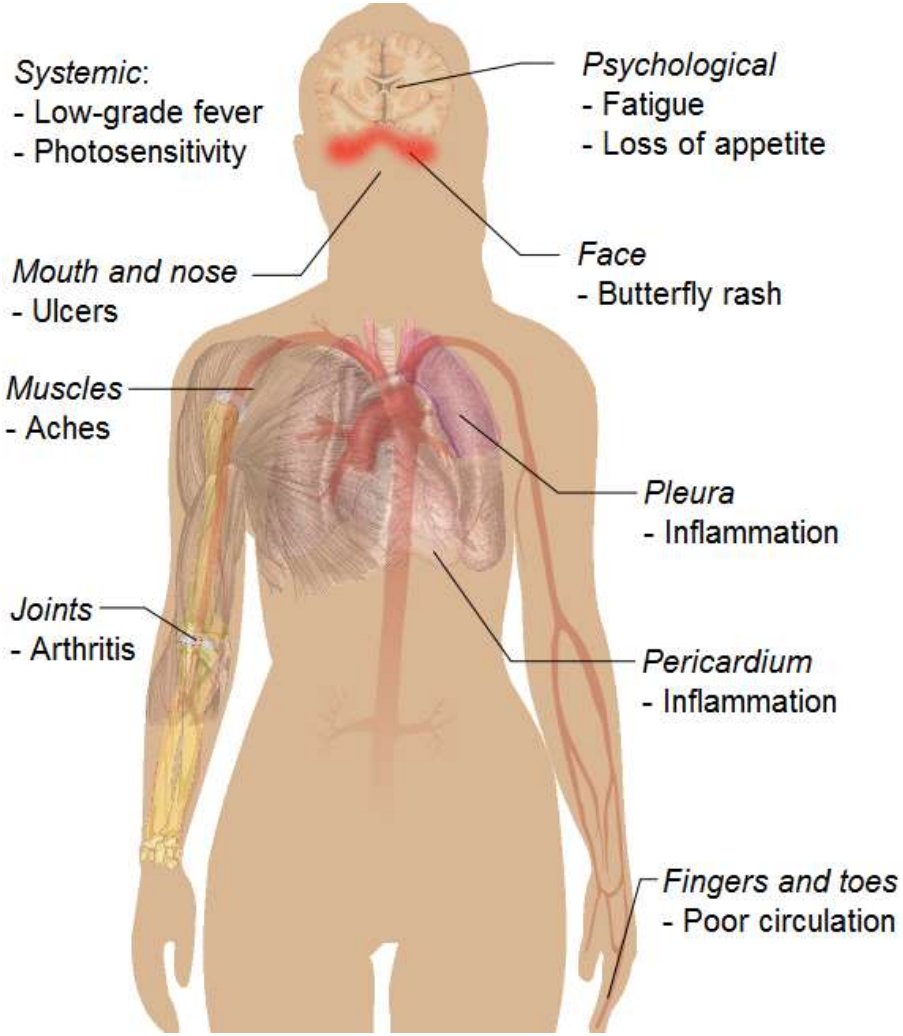
http://emedicine.medscape.com/article/332244-overview https://en.wikipedia.org/wiki/Systemic_lupus_erythematosus

Systemic Lupus Erythematosus (Manifestations)

- Constitutional (e.g., fatigue, fever, arthralgia, weight changes).
- Musculoskeletal (e.g., arthralgia, arthropathy, myalgia, frank arthritis, avascular necrosis).
- Dermatologic (e.g., malar rash, photosensitivity, discoid lupus).
- Renal (e.g., acute or chronic renal failure, acute nephritic disease).
- Neuropsychiatric (e.g., seizure, psychosis).
- Pulmonary (e.g., pleurisy, pleural effusion, pneumonitis, pulmonary hypertension, interstitial lung disease).
- Gastrointestinal (e.g., nausea, dyspepsia, abdominal pain).
- Cardiac (e.g., pericarditis, myocarditis).
- Hematologic (e.g., cytopenias such as leukopenia, lymphopenia, anemia, or thrombocytopenia).

http://emedicine.medscape.com/article/332244-overview#showall

Systemic Lupus Erythematosus
(Most Common Symptoms)



https://en.wikipedia.org/wiki/Systemic_lupus_erythematosus

Systemic Lupus Erythematosus
(Malar Rash)

The first criterion of SLE is a malar rash, also called butterfly rash, characterized by an erythema over the cheeks and nasal bridge (but sparing the nasolabial folds).

It lasts from days to weeks and is occasionally painful or pruritic.

http://2.bp.blogspot.com/-KB_jTj2IeVQ/U_6ePJ0Ll6I/AAAAAAAAAHU/t82ZVnCnxgQ/s1600/malar%20rash%20image.JPG

Systemic Lupus Erythematosus
(Photosensivity)

Photosensitive SLE rashes typically occur on the face or extremities, which are sun-exposed regions. Although the interphalangeal spaces are affected, the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints are spared.

http://emedicine.medscape.com/article/332244-overview

Systemic Lupus Erythematosus
(Discoid Rash)

- Discoid rashes are usually slightly elevated red or pink areas that form flakes or a crust on the surface of the skin and are rarely found below the chin, occurring most often on the scalp, and outer ear, and almost never on the legs.
- Rashes may be itchy and get larger, spreading outward and then leaving a central scar. In individuals with darker complexions, the central area can become de-pigmented; in all individuals the outer red area may become hyper-pigmented.

http://diseasesdefinition.com/wp-content/uploads/2014/12/Discoid-Lupus-Erythematosus.jpg

Systemic Lupus Erythematosus
(Oral Ulcers)

A 30-year-old male with systemic lupus erythematosus presented a palatal ulcer typical for lupus.

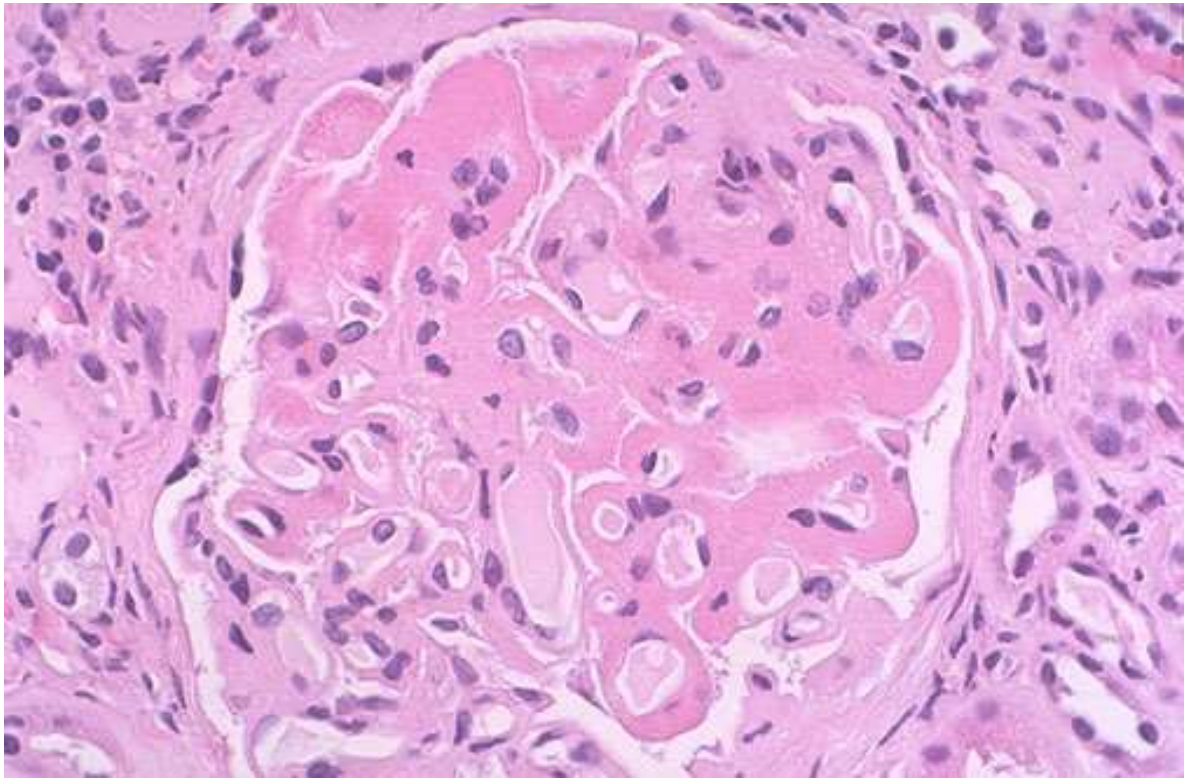
http://www.tannlegetidende.no/image/2015/F15-02-008.jpg

Systemic Lupus Erythematosus
(Serositis)

Serositis refers to inflammation of the serous tissues of the body, the tissues lining the lungs (pleura), heart (pericardium), and the inner lining of the abdomen (peritoneum) and organs within.

http://journal.publications.chestnet.org/article.aspx?articleid=1211826

Systemic Lupus Erythematosus
(Renal Disorder)



Glomerular disease with SLE is common, and lupus nephritis can have many morphologic manifestations as seen on renal biopsy.

http://library.med.utah.edu/WebPath/RENAHTML/RENAL120.html

Systemic Lupus Erythematosus
(Laboratory Tests)

- Antinuclear antibody (ANA) testing and anti-extractable nuclear antigen (anti-ENA) form the mainstay of serologic testing for SLE, although ANA screening yields positive results in many connective tissue disorders and other autoimmune diseases, and may occur in normal individuals.
- Subtypes of antinuclear antibodies include anti-Smith and anti-double stranded DNA (dsDNA) antibodies (which are linked to SLE) and anti-histone antibodies (which are linked to drug-induced lupus); anti-dsDNA antibodies are highly specific for SLE.
- Other tests routinely performed in suspected SLE are complement system levels (low levels suggest consumption by the immune system), electrolytes and kidney function (disturbed if the kidney is involved), liver enzymes, and complete blood count.
- The lupus erythematosus (LE) cells are only found in 50–75% of SLE cases, and they are also found in some people with rheumatoid arthritis, scleroderma, and drug sensitivities.

https://en.wikipedia.org/wiki/Systemic_lupus_erythematosus#Diagnosis

Systemic Lupus Erythematosus
(The American College of Rheumatology Revised Classification)

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occurs in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterised by tenderness, swelling or effusion
Serositis	a. Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or b. Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria >0.5 g per day or >3+ if quantitation is not performed or b. Cellular casts: may be red cell, haemoglobin, granular tubular, or mixed
Neurological disorder	a. Seizures: in the absence of offending drugs or known metabolic derangements (eg, uraemia, acidosis, or electrolyte imbalance) or b. Psychosis: in the absence of offending drugs or known metabolic derangements (eg, uraemia, acidosis, or electrolyte imbalance)
Haematologic disorder	a. Haemolytic anaemia with reticulocytosis, or b. Leucopenia: <4000/mm^3, or c. Lymphopenia: <1500/mm^3, or d. Thrombocytopenia: <100 000/mm^3 in the absence of offending drugs
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titre, or b. Anti-Sm: presence of antibody to Sm nuclear antigen, or c. Positive finding of antiphospholipid antibodies based on: (1) an abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilisation or fluorescent treponemal antibody absorption test
Antinuclear antibody	An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome

http://www.eular.org/myuploaddata/files/sample%20chapter20_mod%2017.pdf

Systemic Lupus Erythematosus
(the European League Against Rheumatism (EULAR) released recommendations for the treatment of SLE)

- In patients without major organ manifestations, glucocorticoids and antimalarial agents may be beneficial.
- NSAIDs may be used for short periods in patients at low risk for complications from these drugs.
- Consider immunosuppressive agents (e.g., azathioprine, mycophenolate mofetil, methotrexate) in refractory cases or when steroid doses cannot be reduced to levels for long-term use.

http://emedicine.medscape.com/article/332244-overview#showall

Systemic Lupus Erythematosus
(Medications)

- Biologic disease-modifying antirheumatic drugs (DMARDs): belimumab, rituximab, IV immune globulin.
- Nonbiologic DMARDS: cyclophosphamide, methotrexate, azathioprine, mycophenolate, cyclosporine.
- Nonsteroidal anti-inflammatory drugs (NSAIDS): e.g., ibuprofen, naproxen, diclofenac.
- Corticosteroids: e.g., methylprednisolone, prednisone
- Antimalarials: e.g., hydroxychloroquine.

http://emedicine.medscape.com/article/332244-overview#showall

Systemic Lupus Erythematosus
(Adjunctive therapies)

- No diet-based treatment has been proven effective.
- Patients should be reminded that activity may need to be modified as tolerated.
- Stress and physical illness may precipitate SLE flares.
- Persons with SLE should wear sunscreen and protective clothing or avoid sun exposure to limit photosensitive rash or disease flares.
- Vitamin D supplementation may improve endothelial function.

http://emedicine.medscape.com/article/332244-overview#showall

Systemic Lupus Erythematosus
(Multisystemic Approach)

- Rheumatologist.
- Infectious disease specialist.
- Neurologist.
- Pulmonologist.
- Cardiologist.
- Gastroenterologist.
- Nephrologist.
- Dermatologist.
- Hematologist.
- High-risk obstetrician.

http://emedicine.medscape.com/article/332244-overview#showall

Scleroderma (Definition)

- Scleroderma (systemic sclerosis (SSc)) is a rare chronic disease of unknown cause characterized by diffuse fibrosis, degenerative changes, and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower GI tract, lungs, heart, and kidneys) .
- Common symptoms include Raynaud phenomenon, polyarthralgia, dysphagia, heartburn, and swelling and eventually skin tightening and contractures of the fingers.
- Lung, heart, and kidney involvement accounts for most deaths.

http://www.merckmanuals.com/professional/musculoskeletal-and-connective-tissue-disorders/autoimmune-rheumatic-disorders/systemic-sclerosis

Scleroderma (Manifestations)

- Skin and nail manifestations (swelling of the skin, telangiectasias, sclerodactyly, masklike face, subcutaneous calcifications, digital ulcers).
- Joint manifestations (polyarthritis, flexion contractures in the fingers, wrists, and elbows, etc.).
- Gastrointestinal (GI)manifestations (dysphagia, malabsorption, pneumatosis intestinalis, peritonitis, and biliary cirrhosis).
- Cardiopulmonary manifestations (lung fibrosis, leading to restrictive disease with eventual respiratory failure, pulmonary hypertension, heart failure, pericarditis, and heart arrhythmias).
- Renal manifestations (severe renal disease, usually heralded by sudden, severe hypertension with features of thrombotic microangiopathic hemolytic anemia).

http://www.merckmanuals.com/professional/musculoskeletal-and-connective-tissue-disorders/autoimmune-rheumatic-disorders/systemic-sclerosis

Scleroderma
(Sclerodactyly)

http://images.slideplayer.com/32/10064496/slides/slide_60.jpg

Scleroderma
(Masklike Face)

http://www.ijdvl.com/articles/2013/79/3/images/ijdvl_2013_79_3_439_110801_f5.jpg

Scleroderma
(Subcutaneous Calcifications)

http://www.pcds.org.uk/ee/images/made/ee/images/uploads/clinical/calcificacion06CREST_600_450_70_http:www.pcds.org.ukeeassetsimgwatermark.gif_0_0_80_r_b_-5_-5_.jpg

Scleroderma
(Digital Ulcers)

http://what-when-how.com/wp-content/uploads/2012/04/tmpE87_thumb222.jpg

Scleroderma
(Flexion Contractures In The Fingers)

https://handlab.com/resources/wp-content/uploads/2014/04/CP2-1.jpg

Scleroderma
(2013 ECR/EULAR Criteria)

Item	Sub-items(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 Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension Interstitial lung disease	2 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	3

* 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 scleroderma.

Sensitivity 91% Specificity 92%

http://www.rheumtutor.com/2013-acreular-classification-criteria-for-scleroderma/

Scleroderma
(Early Diagnosis - the VEDOSS Initiative)

The VEDOSS (Very Early Diagnosis Of Systemic Sclerosis) initiative in Europe identified the following features as being key to diagnosing scleroderma in the very early stage:

- Antinuclear antibodies.
- Scleroderma-specific antibodies.
- Scleroderma pattern on nailfold capillaroscopy.
- Puffy fingers in Raynaud's syndrome patients.

http://patient.info/doctor/systemic-sclerosis-scleroderma

Scleroderma (Management)

- There is no cure for scleroderma, and management consists of controlling symptoms and preventing complications.
- Non-selective immunosuppressive cyclophosphamide has been associated with improvements in both pulmonary function and skin involvement but efficacy may reduce beyond two years.
- Mycophenolate mofetil has also been used with improvements in lung function.
- Azathioprine and methotrexate alone may not be as beneficial but have been shown to be effective for skin involvement.
- T-cell targeted therapy which is being tested includes sirolimus, antithymocyte globulin, and basiliximab.
- Oral corticosteroids.
- Nifedipine, nitroglycerin, phosphodiesterase type 5 inhibitors, prostaglandins are the drugs for Raynaud's phenomenon.
- In all other cases symptomatic treatment only.

https://en.wikipedia.org/wiki/Systemic_scleroderma http://patient.info/doctor/systemic-sclerosis-scleroderma

Scleroderma
(Patient Support Groups)

- The Juvenile Scleroderma Network is an organization dedicated to provide emotional support and educational information to parents and their children living with juvenile scleroderma.
- In the US, the Scleroderma Research Foundation is dedicated to raise awareness of the disease and assist those who are affected.
- The Scleroderma Society is a UK charity founded in 1982 to provide support for both people with scleroderma and their families.

https://en.wikipedia.org/wiki/Systemic_scleroderma

Sjögren syndrome
(Definition)

Sjögren syndrome (Sjögren's syndrome (SS)) is a systemic chronic autoimmune inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs with sicca symptoms, such as xerophthalmia (dry eyes), xerostomia (dry mouth), and parotid gland enlargement.

http://emedicine.medscape.com/article/332125-overview

Sjögren syndrome (Glandular Manifestations)

- Sjögren syndrome typically presents as dry eyes and dry mouth, also referred to as xerophthalmia (or keratoconjunctivitis sicca) and xerostomia, respectively.
- Eye symptoms include dryness, grittiness, pruritus, and foreign body sensation.
- Oral symptoms include difficulty speaking, eating, or swallowing, and frequent sips of water may be needed.
- The patient's eye may show conjunctival injection .
- Early oral findings include decreased salivary pool and dry mucous membranes, which can progress to erythema, fissuring, and ulceration.
- The patient may also have multiple dental caries as a result of decreased salivary flow.
- Parotid glands may be tender or swollen.

http://www.aafp.org/afp/2009/0315/p465.html

Sjögren syndrome (Extraglandular Manifestations)

- Arthralgia or nonerosive arthritis characterized by tenderness, swelling, or effusion of peripheral joints.
- Gastrointestinal symptoms (reflux, dyspepsia, diarrhea, constipation).
- Autoimmune thyroiditis.
- Pulmonary disease (chronic cough, recurrent bronchitis with chronic diffuse interstitial infiltrates on radiography, abnormal spirometry, pulmonary alveolitis or fibrosis on computed tomography).
- Raynaud's phenomenon.
- Cutaneous vasculitis.
- Peripheral neuropathy.
- Lymphadenopathy (enlarged lymph nodes in cervical, axillary, or inguinal region).
- Renal involvement (proteinuria, renal tubular acidosis, interstitial nephritis, glomerulonephritis, abnormal urinalysis).
- Fever not associated with infectious process.

http://www.aafp.org/afp/2009/0315/p465.html

Sjögren syndrome
(Dry Eyes)

http://www.rheum-care.com/wp-content/uploads/2014/05/stock-photo-16982142-blood-capillary-human-eye.jpg

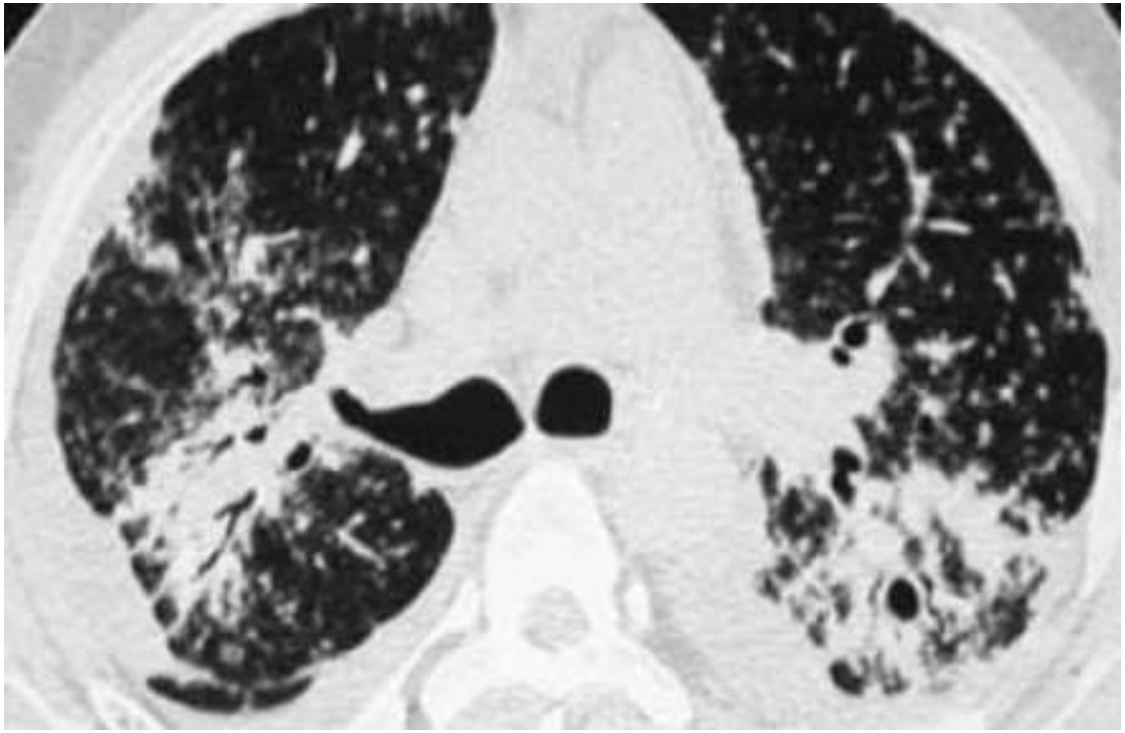
Sjögren syndrome
(Dry Mouth)

http://1.bp.blogspot.com/_PUjYKIyEP6g/TLvbsvFVfYI/AAAAAAAADTI/WZ0pX1oMZys/s640/nyc-dentist-blog-dry-mouth.jpg

Sjögren syndrome
(Arthritis)

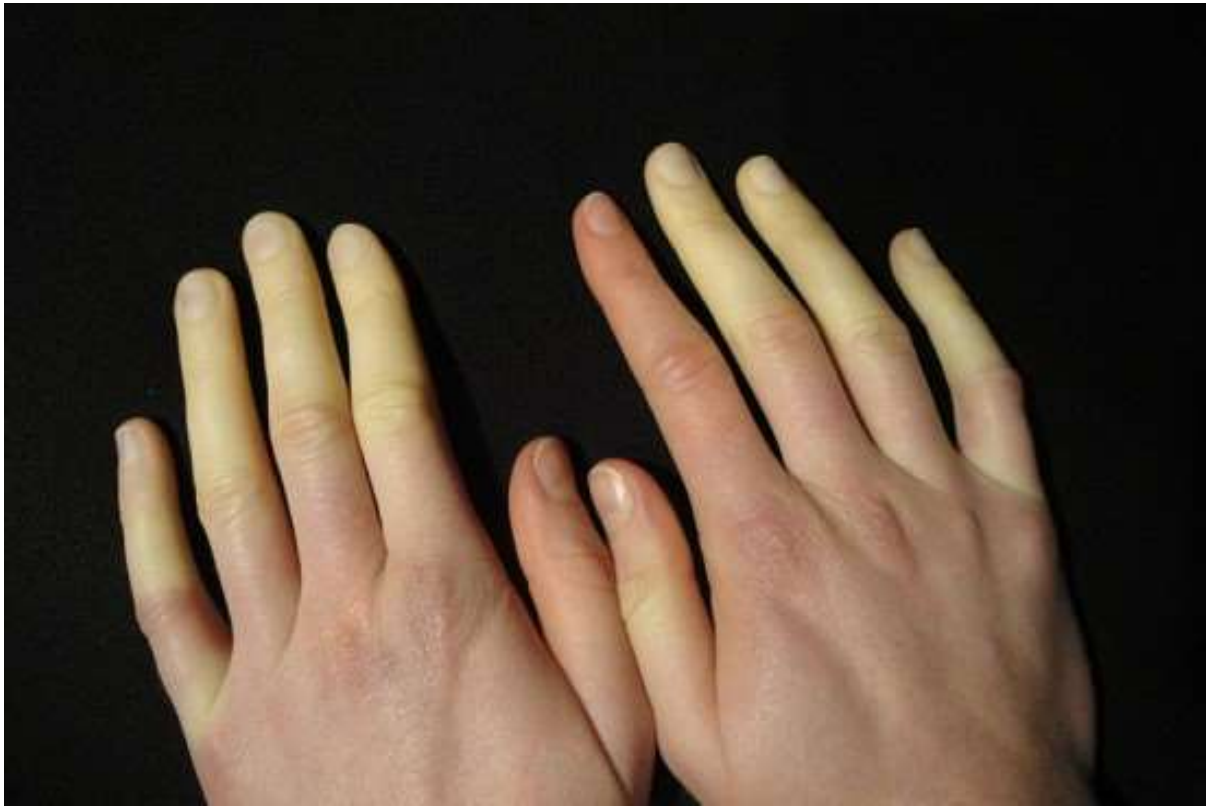
http://www.healthline.com/hlcmsresource/images/slideshow/secondary-sjogrens-syndrome-and-arthritis/285x285_Secondary_Sjogrens_Syndrome_And_Arthritis_Doctor_9.jpg

Sjögren syndrome
(Pulmonary Fibrosis)



http://www.radiologyassistant.nl/data/bin/w440/a5097977c62e89_sarc-fibrosis.jpg

Sjögren syndrome
(Raynaud's Phenomenon)



http://userfiles.steadyhealth.com/userfiles/articles/thumb_raynaud-syndrome.jpg

Sjögren syndrome
(Lymphadenopathy)

http://www.antimicrobe.org/images-Monographs/e27_TB_1.jpg

Sjögren syndrome
(Diagnostic Testing: Eye Symptoms)

- Eye symptoms are usually evaluated with the Schirmer test or the rose bengal test.
- The Schirmer test involves placing a sterile filter paper strip beneath the lower eyelid for five minutes. If the moistened area measures less than 5 mm, the test is positive.
- The rose bengal test usually is performed by an ophthalmologist; 1% rose bengal dye is instilled and the ocular surface integrity is evaluated by quantitatively scoring the staining of the conjunctiva. Rose bengal dye will stain devitalized corneal and conjunctival epithelial cells. The test will identify keratosclerosis (KCS) when minimal ocular symptoms are present. A routine slit-lamp evaluation can identify a diminished tear meniscus.

http://www.aafp.org/afp/2009/0315/p465.html

Sjögren syndrome
(Diagnostic Testing: Oral Dryness)

- Oral dryness can be evaluated objectively by nonstimulated whole saliva flow collection, in which the patient spits into a graduated test tube every minute for 15 minutes. Collection of less than 1.5 mL in 15 minutes is considered a positive result.
- Other tests include contrast sialography, which visualizes the salivary glands and ducts via contrast dye injection into the Stensen duct, and scintigraphy, which evaluates salivary gland function by measuring sequential uptake and excretion of technetium 99m.

http://www.aafp.org/afp/2009/0315/p465.html

Sjögren syndrome
(Diagnostic Testing: Biopsy)

- Although once considered the gold standard for diagnosis of Sjögren syndrome, minor salivary gland biopsy of tissue taken from the patient's lip is not always necessary.
- A positive biopsy is defined as at least one focus of dense, inflammatory infiltrate containing at least 50 lymphocytes per 4 mm^2.
- The lip biopsy may be useful in ambiguous cases or when therapy beyond symptom management is being considered.

http://www.aafp.org/afp/2009/0315/p465.html

Sjögren syndrome
(Patient education)

- Neither a cure nor a specific treatment is known to permanently restore gland secretion. Instead, treatment is generally symptomatic and supportive.
- Eye care: moisture replacement (artificial tears), goggles, cyclosporine, cevimeline, and pilocarpine.
- Vaginal dryness: personal lubricants.
- Musculoskeletal: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, intravenous immunoglobulin), disease-modifying antirheumatic drugs (DMARDs).
- Systemic: biologic disease-modifying antirheumatic drugs (DMARDs).
- Dental care: topical fluoride application to strengthen tooth enamel and frequent teeth cleanings by a dental hygienist.

https://en.wikipedia.org/wiki/Sj%C3%B6gren%27s_syndrome#Treatment

Sjögren syndrome
(Surgical Therapy)

- Occlusion of the lacrimal puncta can be corrected surgically.
- Electrocautery and other techniques can be used for permanent punctal occlusion.
- During surgery, the anesthesiologist should administer as little anticholinergic medication as possible and use humidified oxygen to help avoid inspissation of pulmonary secretions.
- Good postoperative respiratory therapy should also be provided.
- Patients are at higher risk for corneal abrasions, so ocular lubricants should be considered.

http://emedicine.medscape.com/article/332125-treatment#showall

Sjögren syndrome
(Patient education)

Educate patients with Sjögren syndrome on avoidance strategies and self-care issues for the treatment of dry mouth, eyes, skin, and vagina.

Sjögren syndrome
(American-European Consensus Sjögren Classification Criteria: 1)

I. Ocular Symptoms (at least one)

Dry eyes >3 months?

Foreign body sensation in the eyes?

Use of artificial tears >3x per day?

II. Oral Symptoms (at least one)

Dry mouth >3 months?

Recurrent or persistently swollen salivary glands?

Need liquids to swallow dry foods?

III. Ocular Signs (at least one)

Schirmer's test, (without anesthesia) ≤5 mm/5 minutes

Positive vital dye staining (van Bijsterveld ≥4)

IV. Histopathology Lip biopsy showing focal lymphocytic sialoadenitis
(focus score ≥1 per 4 mm^2)[2]

V. Oral Signs (at least one)

Unstimulated whole salivary flow (≤1.5 mL in 15 minutes)

Abnormal parotid sialography[3]

Abnormal salivary scintigraphy[4]

VI. Autoantibodies (at least one)

Anti-SSA (Ro) or Anti-SSB (La)

https://www.sjogrens.org/home/research-programs/healthcare-providers/diagnosis-criteria

Sjögren syndrome
(American-European Consensus Sjögren Classification Criteria: 2)

For a primary Sjögren diagnosis

a. Any 4 of the 6 criteria, must include either item IV (Histopathology) or VI (Autoantibodies)
b. Any 3 of the 4 objective criteria (III, IV, V, VI)

For a secondary Sjögren diagnosis

In patients with another well-defined major connective tissue disease, the presence of one symptom (I or II) plus 2 of the 3 objective criteria (III, IV and V) is indicative of secondary SS.

Exclusion Criteria

Past head and neck radiation treatment, Hepatitis C infection, Acquired immunodeficiency syndrome (AIDS), Pre-existing lymphoma, Sarcoidosis, Graft versus host disease, Current use of anticholinergic drugs

https://www.sjogrens.org/home/research-programs/healthcare-providers/diagnosis-criteria

Mixed Connective Tissue Disease (Definition)

Mixed connective tissue disease (MTCD), or undifferentiated connective tissue disease is a rare chronic autoimmune inflammatory connective tissue disorder characterized by the presence of high titers of a distinctive autoantibody anti-U1 ribonucleoprotein (RNP) what may be an overlapping group of connective tissue disorders (e.g., systemic lupus erythematosus, polymyositis, and scleroderma) that cannot be diagnosed in more specific terms.

http://rarediseases.org/rare-diseases/mixed-connective-tissue-disease-mctd/

Mixed Connective Tissue Disease (Manifestation)

- MCTD combines features of scleroderma, myositis, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, Raynaud's phenomenon, etc. and is thus considered an overlap syndrome.
- In the beginning stages, patients who have MCTD have symptoms similar to those of patients with other connective tissue disorders, including fatigue, muscle pain with no apparent cause, joint fever, Raynaud phenomenon, severe polymyositis, intense arthritis, aseptic meningitis, myelitis, gangrene, abdominal pain, neuropathy, hearing loss.

http://my.clevelandclinic.org/health/diseases_conditions/hic_Mixed_Connective_Tissue_Disease

Mixed Connective Tissue Disease
(The "classic" symptoms)

- Raynaud phenomenon.
- Swollen "sausage-like" fingers, sometimes temporary but at other times progressing into sclerodactyly (thin fingers with hardened skin and limited movement).
- Inflamed joints and muscles.
- Pulmonary hypertension (high blood pressure in the blood vessels of the lungs).

http://my.clevelandclinic.org/health/diseases_conditions/hic_Mixed_Connective_Tissue_Disease

Mixed Connective Tissue Disease
(Raynaud Phenomenon)

http://www.physio-pedia.com/images/3/34/Ray.png

Mixed Connective Tissue Disease
(Swollen “Sausage-Like" Fingers)

http://www.physio-pedia.com/images/7/70/PsAHands.jpg

Mixed Connective Tissue Disease
(Inflamed Joints and Muscles)

http://images.medicinenet.com/images/rheumatoid-arthritis-feet.jpg

Mixed Connective Tissue Disease
(Pulmonary hypertension)

http://www.scielo.br/img/revistas/rb/v41n3/en_12f8.gif

Mixed Connective Tissue Disease
(Alarcon-Segovia Diagnostic Criteria)

- Serological criteria: Positive anti U1 RNP at hemagglutination titer >1:1600
- 2. Clinical criteria:
- Oedema of hands
- Synovitis
- Myositis
- Raynaud´s
- Acrosclerosis
- Requirements:
- Serological
- At least 3 clinical features
- Association of hand oedema, Raynaud´s and acrosclerosis requires at least one other feature

http://www.medicalcriteria.com/criteria/reu_mctd.htm

Mixed Connective Tissue Disease
(Kusukawa Diagnostic Criteria)

- Common Symptoms
- Reynaud´s Phenomenon
- Swollen fingers or hands
- Presence of Anti U1 RNP
- Mixed findings
- A. SLE like
- Polyarthritis
- Pericarditis/pleuritis
- Lymphadenopathy
- Facial erithema
- Leucopenia/thrombocytopenia
- B. Scleroderma like
- Sclerodactyly
- Pulmonary fibrosis
- Esophageal dysmotility
- C. Polymyositis like
- Muscle weakness
- High creatine phosphokinase (CPK)
- Myophatic electromyogram (EMG)

Requirement for diagnosis: At least one common symptom, with positive U1 RNP antibodies and one or more findings in at least two of the three categories A, B, and C.

http://www.medicalcriteria.com/criteria/reu_mctd.htm

Mixed Connective Tissue Disease

(Standard Therapies)

- The treatment is based upon the specific symptoms present in each case.
- Many of the manifestations of MCTD appear to respond to therapy with corticosteroids such as prednisone.
- Mild forms appear to be controlled by nonsteroidal anti-inflammatory drugs (NSAIDs) or low doses of corticosteroids. When more severe involvement of major organs occurs, larger doses of corticosteroids may be of benefit.
- In some cases, drugs that suppress the immune system (e.g. disease-modifying antirheumatic drugs) have been used to treat individuals with MCTD.
- Calcium channel blockers may be used to treat Raynaud's phenomenon.
- Bosentan or sildenafil may be used to treat Pulmonary hypertension.

http://www.medicalcriteria.com/criteria/reu_mctd.htm

Prognosis

- The prognosis for patients who have SCTD is different for different diseases and varies from a benign course to severe progressive course.
- There are many possible outcomes, depending on the organs affected, the degree of inflammation, and how quickly the disease progresses.
- In approximately one third of patients the clinical symptoms go into long-term remission.
- One third of patients have a severe, progressive SCTD course.
- Persistent morbidity often is attributable to arthritis, easy fatiguability, and dyspnea on exertion.
- Most deaths from SCTD are due to heart failure caused by pulmonary arterial hypertension (PAH).

http://www.ncbi.nlm.nih.gov/pubmed/16084324

Prophylaxis

- Since the causes of SCTD are not known, there is no way of preventing these diseases, however, lifestyle and environmental factors if modified could assist in it.
- Progression some forms of SCTD could be prevented if treated aggressively prior to manifestations of symptoms, however, if such is the case, criteria would have to be determined for patient selection for this preventive treatment, and only those patients whose probability to develop clinical disease exceeds the established threshold, should be treated while asymptomatic.

http://www.arc.org.uk/arthinfo/medpubs/6529/6529.asp

Abbreviations

ACE – angiotensin converting enzyme

AIDS - Acquired immunodeficiency

ANA - antinuclear antibody

syndrome

anti-ENA - anti-extractable nuclear antigen

ARBs - angiotensin II receptor antagonists

CPK - creatine phosphokinase

DIP - distal interphalangeal joints

DMARDs - disease-modifying antirheumatic drugs

dsDNA - anti-double stranded DNA antibodies

EMG - myophatic electromyogram

EULAR - European League Against Rheumatism

KCS - keratosclerosis

LE - lupus erythematosus

MCP - metacarpophalangeal joints

MCTD - Mixed Connective Tissue Disease

MFS - Marfan syndrome

NSAIDS - nonsteroidal anti-inflammatory drugs

PAH - pulmonary arterial hypertension

PIP - proximal interphalangeal joints

RNP - anti-U1 ribonucleoprotein

SCTD - systemic connective tissue diseases

SS - Sjögren's syndrome

SSc - systemic sclerosis

VEDOSS - Very Early Diagnosis Of GI - gastrointestinal

Diagnostic and treatment guidelines

Marfan Syndrome

Medical Management of Marfan Syndrome

MARFAN DX: A Diagnostic Tool for Healthcare Professionals

Systemic Lupus Erythematosus (SLE) Treatment & Management

Systemic Lupus Erythematosus: Pathogenesis 20 and Clinical Features

Guidelines for clinical trials in systemic sclerosis (scleroderma)

Systemic Sclerosis

Diagnosis and Management of Sjögren Syndrome

Sjogren Syndrome Treatment & Management

Mixed Connective Tissue Disease