Lecture 32

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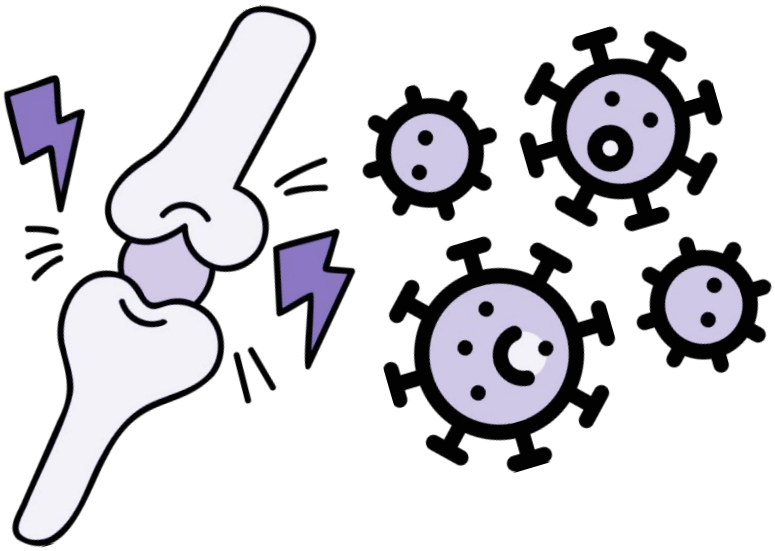

Reviewed By
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Scleroderma Spectrum Disease

Objectives:

- ★ To recognize the pathogenesis of scleroderma spectrum diseases
- ★ To recognize the clinical findings and investigation of scleroderma spectrum diseases
- ★ To recognize the management of organ involvement of each disease

Color index:

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Doctor's notes Textbook Important Golden notes Extra

Scleroderma or systemic sclerosis (SSc)

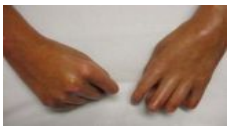
Scleroderma spectrum diseases

A group of heterogeneous diseases that has a predominant feature and share other common features. They are rare, difficult to treat and associated with significant morbidity and mortality.

- **Systemic sclerosis (SSc)** is a disease that is difficult to evaluate, treat and monitor. It is very **heterogeneous** and usually diagnosed late. There is no single drug that treats everything.
- Pathogenesis in each organ involved **is not the same** it could be (Neurovascular / fibroproliferative / inflammatory).
- A strategy should be adopted to evaluate each manifestation and organ involved on a regular basis.

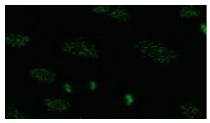
Systemic sclerosis is characterized by:

Skin thickening



Vasculopathy

Autoantibody



◀ The ACR/EULAR 2013 Criteria for the Classification of Systemic Sclerosis:

Item	Subitems	Weight
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 MCP joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (Only count the higher score)	Digital tip ulcer	2
	Fingertip Pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
PAH and/or interstitial lung disease (Maximum score is 2)	Pulmonary arterial hypertension Interstitial lung disease	2
Raynaud's phenomenon	-	3
Scleroderma related antibodies (Any of anticentromere, anti-topoisomerase-I [anti-Scl-70], anti-RNA polymerase-3). **(MAX SCORE IS 3)**	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	3

To have SSc, there should be **NINE** points in total. For Example:

1. If the **FIRST** criteria is present **ALONE**, that **equals** 9 points = SSc. (So, the first criterion alone is sufficient for the diagnosis)
2. Sclerodactyly of the fingers + Fingertip Pitting scars + PAH = 4 + 3 + 2 = 9 = SSc

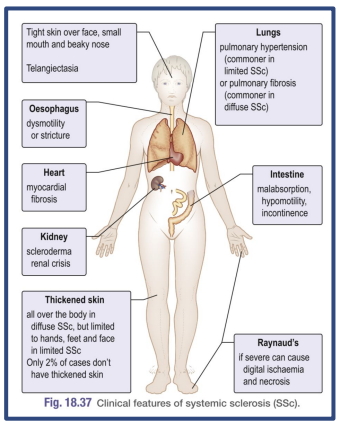
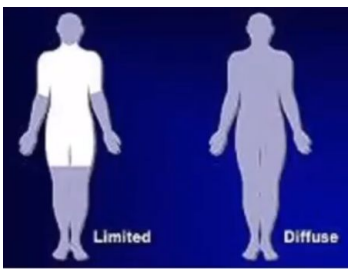
Scleroderma or systemic sclerosis (SSc)

◄ Types of SSc

Based on Cutaneous involvement, SSc is classified into 2 types[1]

Diffuse Diffuse Cutaneous Scleroderma (DcSSc) I 30% of cases	Limited Limited Cutaneous Scleroderma (LcSSc) I 70% of cases
• Associated with **more internal organ involvement** • Has a **worse prognosis** • **Anti-topoisomerase (Anti-Scl-70)** • **RNA polymerase III antibodies.**	• Skin involvement restricted to sites **distal to the elbow or knee** (apart from the face) • Often more indolent (Takes a long time before it becomes clinically apparent) • Has a **higher risk of pulmonary hypertension** • **Anti-centromere antibodies.**

★ **Edematous in onset,** skin sclerosis rapidly follows.
• **Raynaud's phenomenon** usually starts **just before or concomitant** with the **edema**.
• **Diffuse swelling** and stiffness of the fingers is rapidly followed by more extensive skin thickening, which can involve most of the body in the severest cases.
• Later, the skin becomes atrophic.
	• **Raynaud's phenomenon** starts **many years** (up to 15) **before** any skin changes.
	• The skin is tight over the fingers and often produces flexion deformities
	• **Has a Characteristic face features:**
	  ○ 'beak'-like nose
	  ○ small mouth (microstomia).

 Fig. 18.37 Clinical features of systemic sclerosis (SSc). 	**LcSSc also known as CREST syndrome:** **C - Calcinosis:** calcium deposits on the pressure points of the extremities **R - Raynaud's phenomenon:** spasm of the blood vessels in response to cold or stress **E - Esophageal involvement:** Acid reflux and decreased motility **S - Sclerodactyly:** Thickening and tightening of the skin on the fingers and hands. **T - Telangiectasia:** dilation of capillaries causing red marks on surface of skin

◄ Pathophysiology of SSc:

1) **T lymphocytes**, especially those of the Th17 subtype, **infiltrate the skin** causing abnormal **Fibroblast activation → collagen deposition** (primarily type 1) as well as fibronectin and glycosaminoglycans. This is more apparent in the **skin** and **lungs**
2) **Vasculopathy** and autonomic neuropathy leading to vascular complications like Raynaud's phenomenon[2], renal crisis & pulmonary hypertension.
3) **Autoimmunity and inflammation**: development of autoantibodies that cause inflammatory manifestations such as arthritis and myositis.

1. There is a third type called **sclerosis sine scleroderma** (ssSSc). it is a very rare subset characterized by the total or partial absence of cutaneous manifestations of systemic sclerosis with the occurrence of internal organ involvement and serologic abnormalities.
2. Raynaud's phenomenon is seen in almost 100% of cases.

Scleroderma or systemic sclerosis (SSc)

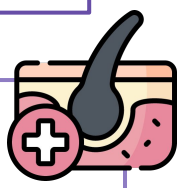
◀ AutoAntibodies

Scl-70 (topoisomerase)	Anti-centromere	RNA polymerase III
Associated with: • **Diffuse** subset • The **development** of **ILD** • **Reduced** risk of **PAH**	**Associated with:** • **limited** subset • **Pulmonary Arterial HTN** • **Digital ulcer**	**Associated with:** • **Scleroderma Renal Crisis** • **Malignancy** associated SSc • **Mortality.**

❖ **Scl-PM (scleroderma polymyositis):** Associated with myositis overlap

Skin Involvement in SSc

Skin | Lung | GI | Kidney | Others



- **Skin is the Largest and Most Important Organ in SSc** (and all women).
- **Skin involvement** has been considered a **reflection** of **internal organ involvement**.
- Skin involvement is seen in 99% of patients.
- The **level of skin involvement** predicts **severe disease and mortality**.
- Skin loosening occurs 5 years after the onset of the disease. At that time the patient may develop contracture and disability so it's imp to detect it And treat it early.

★ **SKIN INVOLVEMENT ALWAYS STARTS IN THE FINGERS AND TOES (distally) AND EXTENDS PROXIMALLY.**

  - **So no systemic sclerosis patient will have sparing of his hands.**

- **Contractures** of the fingers and **disability** are **preventable** with stretching exercise.
- Patients should be advised to **use emollients and creams** at all time.

Treatment of skin involvement

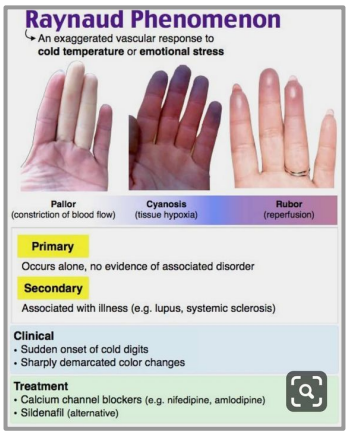
Treatment is usually initiated when **active skin inflammation is apparent** or **progressive skin thickening**.
Why do we treat the skin? To prevent joint contracture and disability in the hands.

Methotrexate	➢ **Mycophenolate mofetil** ➢ **Cyclophosphamide** ➢ **Rituximab**	Steroids
Avoid it if the patient has **interstitial lung disease** or **renal failure** because of its toxic effect.		High-dose corticosteroids (above 10 mg prednisolone daily) is a **significant risk** factor for **Scleroderma renal crisis** and is best to be avoided in patients with DcSSc.

Raynaud's Phenomenon and Digital Ulcers in SSc

Skin | Lung | GI | Kidney | Others

- **Raynaud's Phenomenon (RP)** and **Digital Ulcers (DU)** "Pain at the tip of the fingers" are 2 faces of the same coin. There is some difference between the underlying pathogenesis of both conditions.
- 95% and 50% of SSc have RP and DU respectively, but **RP tends to occur years before the diagnosis of SSc** unlike DU that usually occur in the first 5 years after the development of the non-RP manifestation.
- **Raynaud's Phenomenon:** is an **exaggerated response to cold or stress exposure** which will lead to peripheral vasoconstriction.
    - In normal people it last for few seconds
    - in patients with raynaud's phenomenon it can last for hours and days.
- Raynaud's Phenomenon in Systemic sclerosis patients can **complicate** into digital ulcer after developing ischemia.



Treatment modalities in secondary Raynaud's Phenomenon

- Never underestimate non-pharmacological treatment. Patients should avoid cold by wearing gloves and warm clothes, and stop smoking.
- Treat pain adequately.
- **Calcium channel blockers (FIRST-LINE)** are effective in treating RP with the cost of side effects and intolerance.
- If the patient is not responding you can give IV prostaglandins or even Phosphodiesterase inhibitors
- IV iloprost better than nifedipine.
- Prazosin not working well.
- Efficacy of oral and IV prostaglandins.
- IV prostacyclin are used for severe disease and critical ischemia

Treatment modalities in Digital Ulcer

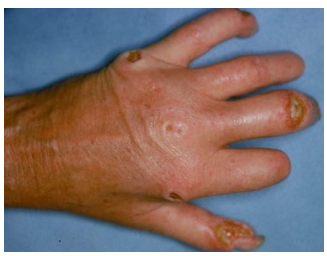
- Aim of treatment includes: **healing and prevention** of new ulcers at the end of the study.
- **CCB** are commonly used but no evidence in healing DU **(CCB has no role in DU)**
- **Endothelin receptor antagonist (bosentan)** has been shown to **prevent** new ulcers and is believed to be a disease modifying agent for SSc.
- **Phosphodiesterase inhibitors (e.g. Sildenafil and tadalafil)** have a positive effect on **healing** and **preventing** ulcers.
- **IV Prostacyclin** has been shown to **heal** DU and **prevent** new ulcers.
- it's very painful, if a patient presented to the ER with DU secondary to RP they will usually need opioids not paracetamol.

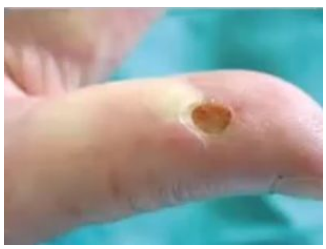
Phosphodiesterase inhibitors & IV prostaglandins:

- **Prevent** new ulcers
- **Improve (fasten)** the healing.

Endothelin receptor antagonist:

- Only **prevents** new ulcers
- **DO NOT** improve the healing.



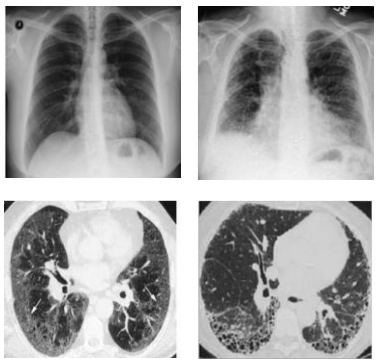


Interstitial lung disease in SSc

- **Interstitial lung disease (ILD):** a specific form of chronic, progressive fibrosing interstitial pneumonia leading to progressive loss of pulmonary function, and respiratory failure. It affect usually the bases of the lungs.
- ★ **Interstitial Lung Disease is the number ONE cause of mortality in patients with SSc.**
- It is very common, around 70% of patients tend to develop ILD at some time of the disease course.
- ★ **Common** in patients with **DcSSc** who have **topoisomerase 1 antibodies** (Scl70).
- **Who should be screened for ILD?** EVERYBODY.
  - Chest x-ray is not considered a good screening tool.
  - **High-resolution lung CT** is the **Gold standard**. it demonstrates fibrotic lung involvement.
- **Diagnosis** is made by a combination of imaging, physical exam and pulmonary function test (PFT).

★ Clinical findings in ILD:

1) Tachypnea	**3)** Cyanosis	**5)** Reduced chest expansion
2) Tachycardia	**4)** Clubbing	**6) Fine early inspiratory crackles**



Both patients have ILD, if we didn't perform HRCT the patient can be misdiagnosed due to normal CXR.

◀ Pulmonary function test (PFT) in ILD shows:

1. Low forced vital capacity (FVC)
2. Low forced expiratory volume in one second (FEV1)
3. Normal or high FVC/FEV1 ratio **(Restrictive pattern)**
4. **Low** diffusion capacity of carbon monoxide (**DLCO**) due to fibrosis

◀ Treatment Options:

❖ Most often with cyclophosphamide or azathioprine combined with low-dose oral prednisolone.

01

Cyclophosphamide
is up to today the **standard** of care used as treatment induction in ILD

02

Alternative could be:
Mycophenolate mofetil (MMF) or rituximab (RTX).
Used for induction

03

Maintenance includes:
Mycophenolate mofetil (MMF), Azathioprine (AZA) and Rituximab (RTX)

04

Steroids
Steroids are a part of induction and maintenance. High doses should be avoided.

Pulmonary Arterial Hypertension in SSc

Skin | **Lung** | GI | Kidney | Others

- **It is 6 times more common** in patients with **LcSSc**.
- Affects 8-13% of SSc (RHC criteria)
- **PAH is defined as Pulmonary Arterial Pressure ≥ 25 mmHg** with a Normal Pulmonary wedge pressure (≤ 15 mmHg) Because high PCWP indicates that the patient has heart failure
- PAH has become a very important cause of mortality along with ILD they are the cause of 8%-33% of death.
  - ➢ **PAH** is the **second** most common cause of death.

- These patients develop endothelial damage and hypertrophy → vasoconstriction → significant morbidity and mortality. So what are the **solutions to Reduce PAH-related Mortality and Morbidity?**

1 **Early detection**

2 **Aggressive treatment**

3 **Early referral for lung transplant**

Primary causes of death in 234 patients with SSc

	N	%
All death cases	234	100
SSc-related death cases	128	55
Pulmonary	78	33
Pulmonary fibrosis	45	19
Isolated PAH	33	14
Myocardial	33	14
Arrhythmia	14	6
Left heart failure	8	3
Right heart failure	5	2
Biventricular heart failure	4	2
Pericarditis (constriction and/or tamponade)	2	1
Renal	10	4
Renal crisis	10	4
Gastrointestinal	7	3

★ Clinical findings include:

- Desaturation
- **Tachycardia**
- **Palpable P2**
- **Parasternal heave**
- **Loud 2nd heart sound**
- **Signs of right sided heart failure** which include: **JVD**, **lower limb edema** and **ascites**.
- PFT may show isolated low DLCO

Note: Remember you can have pulmonary hypertension secondary to ILD which makes diagnosis and management more complex. It is important to look at the lung and heart together.

◀ How to diagnose PAH in SSc:

- The **First** investigation to order is **echocardiography**.
- The **Gold** diagnostic tool is **right sided heart catheterization.**

◀ Treatment of PAH

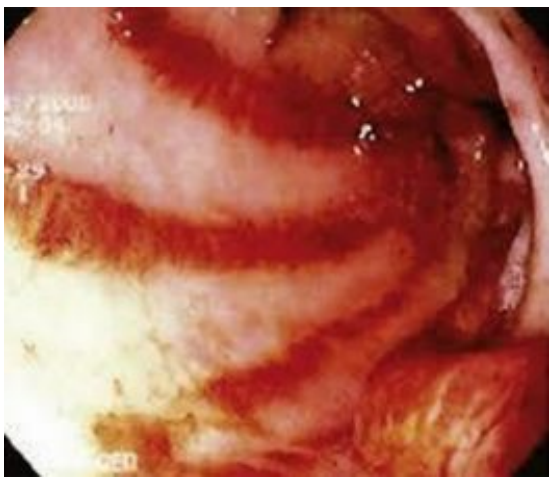
General info	• Pulmonary hypertension is treated with oral vasodilators, oxygen and warfarin. • Advanced cases should receive prostacyclin therapy (inhaled, subcutaneous or intravenous) or the oral endothelin-receptor antagonist, bosentan.	
Drugs	**Endothelin Receptor Antagonists:** **Bosentan,** Ambrisentan, Macitentan, Sitaxentan	• Phosphodiesterase Inhibitors • Prostacyclins

GI Involvement in SSc

◀ Gastrointestinal System Involvement:

GIT is the **most common** internal organ to be involved (95-99%) which includes:	
Mouth	• Reduced mouth opening in the mouth apparatus.
Esophagus (most common)	Dysmotility and reflux leading to strictures, they commonly present with dysphagia. • Treat reflux with **PPIs** & **lifestyle modifications.** • Metoclopramide or domperidone may help patients with symptoms of dysmotility/pseudo-obstruction.
Stomach	Gastroparesis, **watermelon appearance** with telangiectasia it is called gastric antral vascular ectasia (**GAVE**).
Small bowel	Blind loop syndrome complicated by bacterial overgrowth manifesting as chronic diarrhea and **malabsorption**. • Primary treatment is sequential **antibiotics** but stomas and Total parenteral nutrition can be offered in advanced cases
Large bowel	Chronic constipation, **fish mouth diverticula.** • Treatment includes **laxatives**
Anorectal incontinence	**Fecal incontinence** is a devastating complication and difficult to manage • One option could be to clear bowel frequently before going out and some pelvic floor exercises

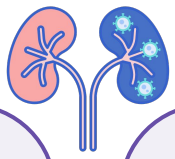
Barium enema showing **white based diverticula**, on **endoscope they look like fish mouth**



gastric antral vascular ectasia (GAVE), watermelon appearance

Scleroderma Renal Crisis (SRC) in SSc

Skin | Lung | GI | **Kidney** | Other



- **Mostly** in patients with **DcSSc.**
- SRC was the leading cause of death in systemic sclerosis patients till the introduction of **ACE inhibitors.**
- **Patients with SSc usually have low BP, once you see high BP, suspect SRC.**
- ★ **Precipitating factors include:** high dose **steroids**, **cyclosporin** & **pregnancy**.
- Anemia in SSc is usually **iron deficiency** because of blood loss from the bowel, telangiectasia, chronic diarrhea and reduce uptake. Once you see **microangiopathic hemolytic anemia** suspect SRC.

The **primary histopathologic** changes in the kidney are localized in the small arcuate and interlobular arteries and the glomeruli.

The characteristic finding is:

- **intimal proliferation** and **thickening** that leads to **narrowing** and **obliteration** of the vascular lumen, with concentric **"onion-skin"** hypertrophy
- This will lead to activation of the **aldosterone-renin-angiotensin pathway.**

◀ Clinical lab findings

- Any new onset HTN with a **BP of >150/85 or 20 mmHg** increase from baseline is critical to recognize.
- Normotensive renal crisis can occur
- Urinalysis might show **proteinuria** and **hematuria** but **no RBC cast.**
  - Casts are a feature of glomerular diseases, and renal crisis is not a glomerular disease. So if you see casts in a patient with SSc, you should put in mind that the patent may be having an overlap with either vasculitis or lupus
- **High creatinine is almost universal**
- Anemia with **positive hemolytic workup** points to **microangiopathic hemolytic anemia**
  - (High **LDH**, High **bilirubin**, **Schistocytes** on peripheral blood film, reticulocytosis, low haptoglobin)

◀ Treatment

- Treatment is **control of BP by reducing it 10 mmHg every 24 hours**
- ★ **Best (and only) drug: Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)**
- Even if progress to ESKD, 40% might recover and get back to near normal function.

Other organ Involvement in SSc

Skin | Lung | GI | Kidney | **Others**

Arthritis: similar to RA with erosions and joint destruction.

Myositis: manifested by weakness with no pain and high muscle enzymes.

Cardiac: Myocardial fibrosis leading to conduction abnormalities, cardiomyopathy and accelerated coronary artery disease.

Sjogren's Syndrome

- It is a systemic chronic inflammatory disorder characterized by **lymphocytic infiltrates** in **exocrine organs**[1]**.** Especially the lacrimal and salivary glands. There is an association with HLA-88/DR3
- **Most individuals with Sjögren's syndrome present with sicca (dryness) symptoms, such as:**

Xerophthalmia.
(dry eyes)
"keratoconjunctivitis sicca"

Xerostomia.
(dry mouth)

Vaginal dryness.
Loss of vaginal secretions leads to dyspareunia.

Parotid gland enlargement.
because of severe lymphocytic infiltration leading to obstruction

- **Others:**
  - There is a **high incidence of dental caries** and high risk of dental failure.
  - Conjunctivitis and blepharitis are frequent, and may lead to filamentary keratitis due to binding of tenacious mucus filaments to the cornea and conjunctiva
  - **keratoconjunctivitis sicca,** are due to a lack of lubricating tears, which reflects inflammatory infiltration of the lacrimal glands. It give the feeling of **"sand in the eyes".**

◀ Diagnosis criteria of primary Sjogren's Syndrome:

- **At least 4 of the criteria listed below (you MUST have number 1 or number 2)**

1	• **Positive minor salivary gland biopsy findings showing lymphocytic infiltration.**
2	• **Positive anti–SSA**[3] anti-sjogren syndrome A **or anti–SSB** anti-sjogren syndrome B **antibody results**
3	• **Oral signs (sialogram, scintigraphy or sialometry findings)**
4	• **Ocular signs (Schirmer test)**[2]
5	• **Oral dryness**
6	• **Ocular dryness**

★ **The best initial test is Schirmer test, while the most accurate is a minor salivary gland (labial) biopsy.**

- **Best initial test on blood:** SS-A and SS-B. These are also called "Ro" and "La" and are each present in about 65% of patients.
- **Rose Bengal staining:** Staining of the eyes shows punctate or filamentary keratitis.
- Antinuclear antibodies are found in 80% of cases.
- Rheumatoid factor is usually positive.

1. Salivary glands, lacrimal glands, skin glands, vaginal glands, etc..
2. A standard strip of filter paper is placed on the inside of the lower eyelid; wetting Of <10 mm in 5 min indicates defective tear production.
★3. This antibody is of particular interest because it can **cross the placenta** and **cause congenital heart block**

Sjogren's Syndrome

◀ Extraglandular manifestations of Sjogren's Syndrome:

1) Arthritis	**5)** Pancytopenia	9) **Demyelinating disease** (Eg. Multiple sclerosis) ★
2) Myositis	**6)** Palpable purpura	**10)** interstitial lung disease
3) Renal tubular acidosis type 1	**7)** Severe unexplained Fatigue	**11)** Interstitial nephritis
4) Raynaud phenomenon	**8)** Generalized osteoarthritis	**12)** arthralgia

◀ Treatment[1]

- The best initial therapy is to water the mouth.

Treatment of glandular manifestations of SS	Treatment of Extraglandular manifestations of SS
➔ Oral hygiene ➔ Avoid sugars ➔ Florid products ★ **Parasympathomimetics** (**pilocarpine**) will increase the secretion of salivary and lacrimal glands. ➔ Artificial eye and mouth moisturizers ➔ Creams and lotions ➔ Vaginal lubricants	➔ Treatment of all include immunosuppressive agents: ◆ Steroids ◆ MTX (except for ILD) ◆ Azathioprine ◆ Cyclophosphamide ◆ Rituximab ➔ **For Renal tubular acidosis**, you just need to give NaHCO3 (Sodium bicarbonate) supplement

◀ Complications

★ SS patients are at risk of developing **Non-hodgkin's B cell lymphoma** **20 times** more than the general population. **Malignancy is the most common cause of death.**

❖ Look for persistent lymphadenopathy (LAP) or **disappearance of RF** and weight loss.

An area for your notes

1. You can see that the Extraglandular manifestations are the inflammatory ones and require immunosuppression, while the glandular manifestation only require supportive treatment

Idiopathic inflammatory Myopathies

"This topic will be discussed in details in a separate lecture"

◀ Idiopathic inflammatory Myopathies

- Are a group of autoimmune myopathies that are characterized by muscle weakness due to muscle inflammation and damage.
- **Mainly in the proximal muscles** but it can progress to peripheral muscles.
- The onset is insidious and progressive.
- **Organ involvement:**
  - **Pharyngeal muscle** involvement can present as **dysphagia** and can lead to **aspiration pneumonia.**
  - **Chest wall weakness** can present as **dyspnea** and lead to **type II respiratory failure.**
  - Can affect the **heart** and lead to **cardiomyopathy**

Types of IMM[1]

- **Primary idiopathic polymyositis (PM)**
- **Primary idiopathic dermatomyositis (DM)**
- Polymyositis or dermatomyositis associated with malignancy
- Childhood polymyositis or dermatomyositis
- Polymyositis or dermatomyositis associated with another connective-tissue disease
- Inclusion body myositis extremely rare
- Miscellaneous (eg, eosinophilic myositis, myositis ossificans, focal myositis, giant cell myositis) extremely rare

Diagnosis

Variable	Without muscle biopsy	With muscle biopsy	Definition
Age of onset			
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5	18 ≤ age (years) at onset of first symptom assumed to be related to the disease <40
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2	Age (years) at onset of first symptom assumed to be related to the disease ≥40
Muscle weakness			
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7	Weakness of proximal upper extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5	Weakness of proximal lower extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Neck flexors are relatively weaker than neck extensors	1.9	1.6	Muscle grades for neck flexors are relatively lower than neck extensors as defined by manual muscle testing or other objective strength testing
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2	Muscle grades for proximal muscles in the legs are relatively lower than distal muscles in the legs as defined by manual muscle testing or other objective strength testing
Skin manifestations			
Heliotrope rash	3.1	3.2	Purple, lilac-colored, or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital edema
Gottron's papules	2.1	2.7	Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli, and toes
Gottron's sign	3.3	3.7	Erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable
Other clinical manifestations			
Dysphagia or esophageal dysmotility	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the esophagus
Laboratory measurements			
Anti–Jo-1 (anti–histidyl-transfer RNA synthetase) autoantibody present	3.9	3.8	Autoantibody testing in serum performed with standardized and validated test, showing positive result
Elevated serum levels of creatine kinase (CK)* *or* lactate dehydrogenase (LDH)* *or* aspartate aminotransferase (ASAT/AST/SGOT)* *or* alanine aminotransferase (ALAT/ALT/SGPT)*	1.3	1.4	The most abnormal test values during the disease course (highest absolute level of enzyme) above the relevant upper limit of normal
Muscle biopsy features—presence of:			
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7	Muscle biopsy reveals endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibers, but there is no clear invasion of the muscle fibers
Perimysial and/or perivascular infiltration of mononuclear cells		1.2	Mononuclear cells are located in the perimysium and/or located around blood vessels (in either perimysial or endomysial vessels)
Perifascicular atrophy		1.9	Muscle biopsy reveals several rows of muscle fibers, which are smaller in the perifascicular region than fibers more centrally located
Rimmed vacuoles		3.1	Rimmed vacuoles are bluish by hematoxylin and eosin staining and reddish by modified Gomori trichrome stain

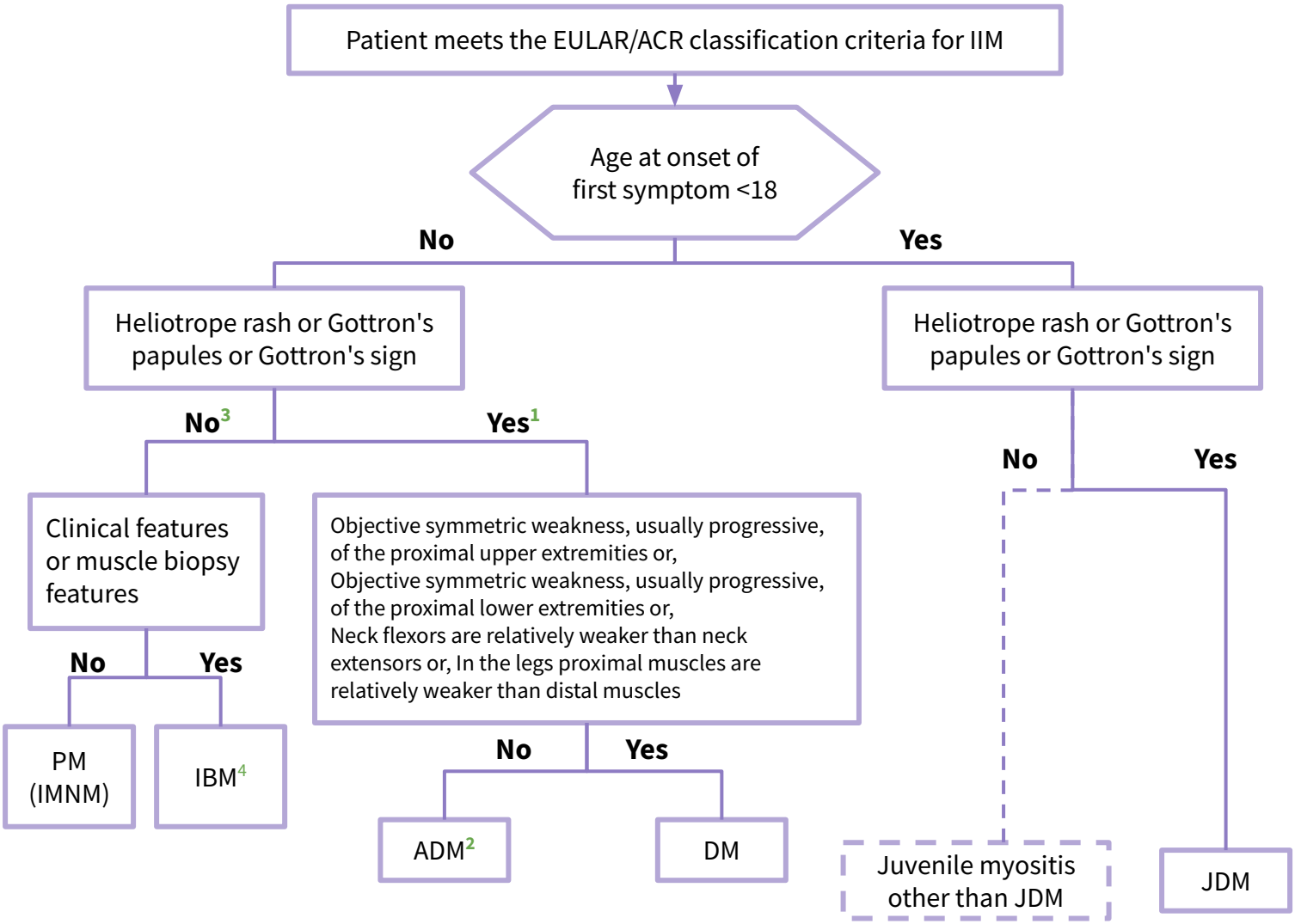
Diagnosis is made if the score is
Without biopsy ≥ 7.5
With biopsy ≥ 8.7

An area for your notes

1. Proximal skeletal muscle weakness = Polymyositis. Proximal skeletal muscle weakness + skin rash = Dermatomyositis

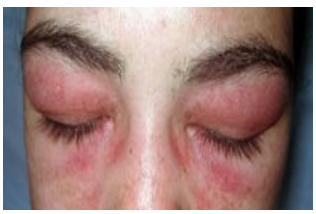
Idiopathic inflammatory Myopathies

◀ Algorithm for IIM

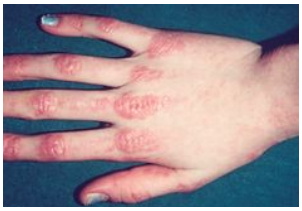


◀ Rashes of DM

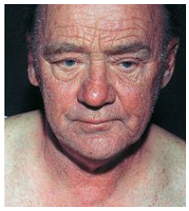
01 **Heliotrope rash**



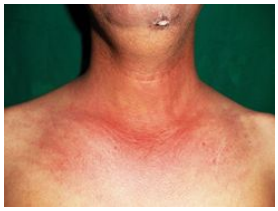
02 **Gottron's papules/sign**[5]



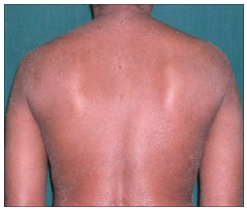
03 **Photosensitivity**



04 **Shawl rash** [7]



05 **Erythroderma**[6]



1. If the patient has skin manifestation + features of inflammatory myopathies, this is considered as Dermatomyositis
2. Amyopathic dermatomyositis (rare). It is similar to SSc where they have skin manifestations but there is no muscle involvement
3. If the patient doesn't have skin manifestation, but has the typical features of inflammatory myopathies, this is considered as Polymyositis
4. Inclusion body myositis.
5. Gottron's papules: on the knuckles & PIP joint. Gottron's sign: involves the elbows and knees
6. The most severe and serious, complete erythema of the body.
7. Around the neck and upper trunk.

Idiopathic inflammatory Myopathies

◀ Investigations

Muscle enzymes	CK, LD, AST, ALT, Aldolase. The **best initial test** is CPK and aldolase
MRI Muscle	Showing muscle edema
Muscle biopsy	Showing lymphocytic infiltration (Either CD4 or CD8, based on the subtype). Muscle biopsy is the **most accurate test** Establishing diagnosis and excluding other causes of myopathies.
EMG	Myopathic changes. Not very helpful
Autoantibodies	**Jo-1** the most common, occurs in around 40% of patients , Non-Jo-1 antibodies, Anti-SRP, Anti-Mi2
MOST IMPORTANT: RULE OUT OTHER CAUSES OF MYOPATHIES (Eg, hypothyroidism, hyperthyroidism, diabetes, cushing syndrome, Addison disease, statins ,etc)	

◀ Extramuscular manifestations

1. **Arthritis**
2. **Raynaud phenomenon**
3. **interstitial lung disease (antisynthetase syndrome)**[1]

◀ Treatment

★ **Steroids (Oral prednisolone is the treatment of choice)**

- Methotrexate
- Mycophenolate mofetil
- Azathioprine
- Rituximab
- **Intravenous immunoglobulins** if the patient has dysphagia or chest wall involvement (Heart, pharyngeal muscle, etc)

◀ Conclusion

- Scleroderma spectrum diseases are rare but serious diseases that are characterized by a specific organ involvement and many other common features.
- Therapies used to treat inflammatory manifestations are similar for all conditions.
- Morbidity and mortality are due to internal organ damage.

Box 18.38 Antinuclear autoantibodies and disease associations

Antibody	Disease	Prevalence
ds-DNA	SLE	70%
Anti-histone	Drug-induced lupus	–
Anti-centromeric	Limited scleroderma	70%
Anti-Ro (SS-A)	SLE	40–60%
	Primary Sjögren's	60–90%
Anti-La (SS-B)	SLE	15%
	Primary Sjögren's	35–85%
Anti-Sm	SLE	10–25% (Caucasian)
		30–50% (black African)
Anti-UI-RNP	SLE	30%
	Overlap syndrome	
Anti-Jo-1 (anti-synthetase)	Polymyositis	30%
	Dermatomyositis	
Anti-topoisomerase-1 (Scl-70)	Diffuse cutaneous SSc	30%

1: antibodies to tRNA synthetase enzymes. These people are more likely to develop pulmonary interstitial fibrosis, Raynaud's phenomenon, arthritis, and hardening and fissuring of skin over the pulp surface of the fingers (mechanic's hands).

Summary

Diffuse SSc	• Associated with **more internal organ involvement** • Has a **worse prognosis** • **Anti-topoisomerase** / RNA polymerase III antibodies.		
Limited SSc	• Often more indolent (has a longer disease duration before diagnosis) • Has a **higher risk of pulmonary hypertension** • **Anti-centromere antibodies.**		
AutoAntibodies in SSc	**Anti-Scl-70 (topoisomerase)** • **Diffuse** subset • The **development** of ILD • **Reduced** risk of PAH	**Anti-centromere** • **limited** subset • **P**ulmonary **A**rterial **H**TN • **D**igital **u**lcer	**RNA polymerase III** • **Scleroderma Renal Crisis** • **Malignancy** associated SSc • **Mortality.**
Skin Involvement	• **Skin is the Largest and Most Important Organ in SSc** • The **level of skin involvement** predicts **severe disease and mortality**. • **SKIN INVOLVEMENT ALWAYS STARTS IN THE FINGERS AND TOES (distally) AND EXTENDS PROXIMALLY.**		
Raynaud's Phenomenon	• **Calcium channel blockers (FIRST-LINE)** • CCB has not role in Digital ulcer		
Interstitial Lung Disease	• **Interstitial Lung Disease is the number ONE cause of mortality.** • **High-resolution lung CT** is the **Gold standard**. • Restrictive pattern with low DLCO • Treated with cyclophosphamide		
Pulmonary Arterial Hypertension	• **PAH is defined as Pulmonary Arterial Pressure ≥ 25 mmHg** with a Normal Pulmonary wedge pressure (≤ 15 mmHg.) • The **First** investigation to order is **echocardiography**. • The **Gold** diagnostic tool is **right sided heart catheterization.**		
Scleroderma Renal Crisis	• **Patients with SSc usually have low BP, once you see high BP suspect SRC.** • **Precipitating factors include: high dose steroids, cyclosporin & pregnancy.** • **Best (and only) drug: Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)**		
Sjogren's Syndrome	• Xerophthalmia, Xerostomia , Vaginal dryness, Parotid gland enlargement • **The best initial test is Schirmer test, while the most accurate is a minor salivary gland (labial) biopsy.** • **Best initial test on blood:** SS-A and SS-B. • Risk of developing **Non-hodgkin's B cell lymphoma 20** times more		

Lecture Quiz

Q1: A 45-year-old woman presents to the rheumatology clinic with a three-month history of itchy, dry eyes and a persistently dry mouth. She also mentions that her fingers have been extremely cold, occasionally turning blue after going outside in the morning. Schirmer's test is positive. What is the most likely diagnosis?

A- Systemic sclerosis
B- Raynaud's disease
C- SLE
D- Primary Sjögren's syndrome
E- Secondary Sjögren's syndrome

Q2: A 24-year-old woman presents to her GP complaining of cold hands and feet. This has been ongoing for the past three months and is especially bad when she goes out in the mornings and may last for hours. On further questioning, she mentions that her hands sometimes turn blue or red and that gloves are unhelpful. She has otherwise been feeling well and has no past medical history. What is the most appropriate treatment?

A- Propranolol
B- Aspirin
C- Nifedipine
D- Subcutaneous injection of low molecular weight heparin
E- Prednisolone

Q3: A 42-year-old woman presents to accident and emergency with retrosternal discomfort. She was diagnosed with systemic sclerosis a year ago. Which of the following statements is true about systemic sclerosis?

A- Microstomia is only seen in diffuse cutaneous systemic sclerosis
B- Skin involvement is limited to face, hands and feet in limited cutaneous systemic sclerosis
C- Oesophageal dysmotility is only seen in limited cutaneous systemic sclerosis
D- Anti-double stranded DNA antibodies are normally detected in patients with systemic sclerosis
E- Raynaud's phenomenon occurs as a result of skin fibrosis (scleroderma)

Q4: A 60-year-old woman complains of dry mouth and a gritty sensation in her eyes. She states it is sometimes difficult to speak for more than a few minutes. There is no history of diabetes mellitus or neurologic disease. The patient is on no medications. On examination, the buccal mucosa appears dry and the salivary glands are enlarged bilaterally. Which of the following best describes the pathophysiology of the condition?

A- Previous exposure to group A streptococcal organisms have stimulated an autoimmune response that leads to cross-reactivity between host and organism with tissue destruction and reduced tear and saliva production.
B- T cells infiltrate exocrine glands and B cells become hyper-reactive. Auto-antibodies ensue including anti-Ro/SSA and anti-La/SSB. Both pro- and anti-apoptotic messages are sent to ductal and acinar epithelial cells.
C- Activated T cells and monocytes accumulate in the skin leading to induration for unknown reasons. This infiltration leads to structural abnormalities in various tissues and organs hence a reduction in normal functioning. Anti-topoisomerase-I and anti-centromere autoantibodies are commonly present.
D- Immune complexes form and deposit in vessel walls. Vasoactive amines including histamine, bradykinin, and leukotrienes are released, and vessel permeability is increased. Complement activation occurs and mononuclear cells are attracted causing infiltration and decreased gland function.
E- Necrotizing vasculitis of small arteries and veins leads to granuloma formation and decreased exocrine function of salivary and lacrimal glands.

Q5: The patient in the previous question has read extensively on the Internet about her probable diagnosis and wonders if more testing can be done to confirm the diagnosis. She is aware of the Schirmer test (quantitative tear production test) and has already had that done by her optometrist. She is on cyclosporine eye drops with some improvement in the gritty eye symptoms. What more could be done at this point to further confirm the diagnosis?

A- Give a therapeutic trial of prednisone 20 mg/d for 1 month.
B- Obtain a detailed family history of rheumatologic conditions in first-degree family members.
C- Biopsy the patient's lip and check autoantibody levels in the serum.
D- Check IgG and IgM antibodies against mumps.
E- Diagnostic/therapeutic trial of hard candy, sugarless gum, and warm soaks to the parotid glands for 1 month.

Q6: A 45-year-old woman has pain in her fingers on exposure to cold, arthralgias, and difficulty swallowing solid food. She has a few telangiectasias over the chest but no erythema of the face or extensor surfaces. There is slight thickening of the skin over the hands, arms, and torso. What is the best diagnostic workup?

A- Rheumatoid factor and anti-CCP antibodies
B- Antinuclear, anti-Scl-70, and anticentromere antibodies
C- Creatine kinase (CK) and antisynthetase antibodies (such as anti-Jo-1)
D- BUN and creatinine
E- Reproduction of symptoms and findings by immersion of hands in cold water

Answers: Q1:D | Q2:C | Q3:B | Q4:B | Q5:C | Q6:B

THANKS!!

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Send us your feedback:
We are all ears!