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

Editing file

Color index

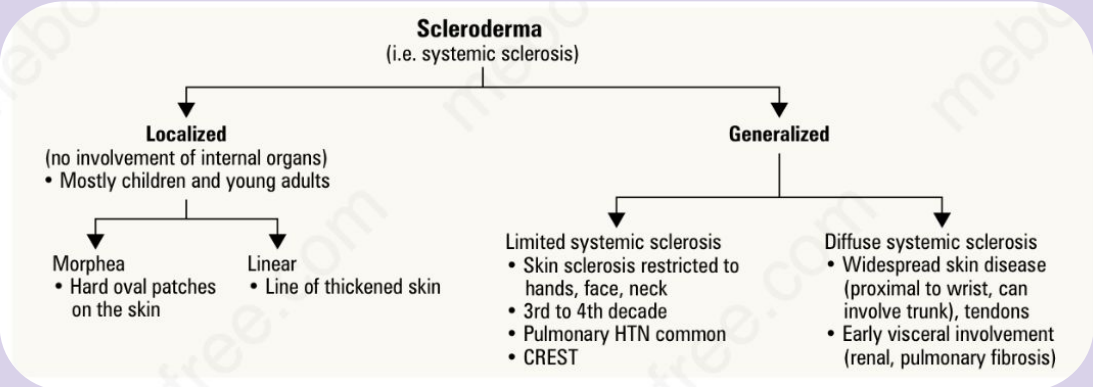
Original text
Females slides
Males slides
Doctor's notes 438
Doctor's notes 439
Text book
Important
Golden notes
Extra

Lecture Outline:

In this lecture we are going to talk about 3 different diseases

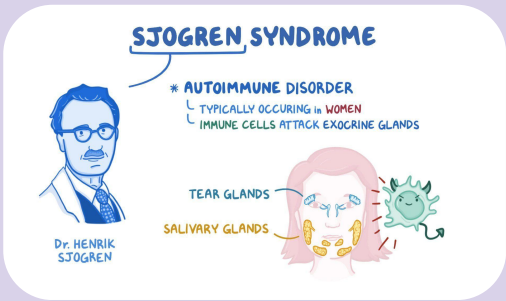
★ Scleroderma (systemic sclerosis) التصلب الجلدي

Non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction causing fibrosis



★ Sjogren's syndrome متلازمة شوغرن

Autoimmune condition characterized by dry eyes and dry mouth, caused by lymphocytic infiltration of salivary and lacrimal glands



★ Idiopathic inflammatory myositis الاعتلال العضلي الالتهابي

Autoimmune disease characterized by proximal muscle weakness +/- pain

OLYMYOSITIS/DERMATOMYOSITIS

Table 19. Classification Criteria for PM/DMM*

Criteria	Description
1. Symmetric proximal muscle weakness	Typical involvement of shoulder girdle and hip girdle
2. Elevated muscle enzymes	↑ CK, aldolase, LDH, AST, ALT
3. EMG changes	Short polyphasic motor units, high frequency repetitive discharge, insertional irritability
4. Muscle biopsy	Segmental fibre necrosis, basophilic regeneration, perivascular inflammation (DMM), endomysial inflammation (PM) and atrophy
5. Typical rash of dermatomyositis	Required for diagnosis of DMM (see below)

efinite if 4 present, probable if 3 present *NEJM* 1975;292:403-407

Dr: Clinical manifestations are the most important in Rheumatology.

Scleroderma or systemic sclerosis (SSc)

التصلب الجلدي

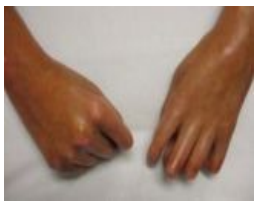
Scleroderma spectrum diseases

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.

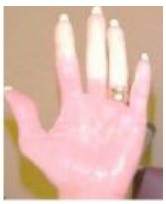
- **Systemic sclerosis (SSc)** is a disease that is difficult to evaluate, treat and monitor. It is very **heterogeneous** and usually diagnosed late. There is no single drug that treats everything. Each organ involved has a different treatment
- Pathogenesis in each organ involved **is not the same** 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:

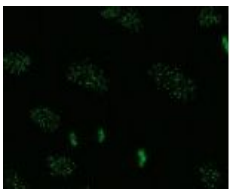
Skin thickening



Vasculopathy



Autoantibody



◄ Pathophysiology of SSc:

Dr: Systemic sclerosis has 3 pathological pathways that you need to understand:

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, renal crisis & pulmonary hypertension.
3) **Autoimmunity and inflammation**: development of autoantibodies that cause inflammatory manifestations such as arthritis and myositis.

Scleroderma or systemic sclerosis (SSc)

التصلب الجلدي

◄ Clinical manifestation

Systems	Features
Dermatological	- Painless non pitting edema → skin tightening - Ulceration, calcinosis, peringuinal erythema, hypo/hyperpigmentation, pruritus, telangiectasias - Characteristic face: mask-like facies with tight lips, beak nose, radial perioral furrows
Vascular	- Raynaud's phenomenon → digital pits, gangrene
GI (90%)	- Distal esophageal hypomotility → dysphagia - Loss of lower esophageal sphincter function → GERD, ulceration, strictures "any sphincter in you body can be affected" - Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss - Large bowel hypomotility → wide mouth diverticula
Renal	- Mild proteinuria, Cr elevation, HTN - Scleroderma renal crisis (10-15%), may lead to malignant HTN, oliguria, and microangiopathic hemolytic anemia
Pulmonary	- Interstitial fibrosis, pulmonary HTN, Pleurisy, pleural effusion
Cardiac	- Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias
Musculoskeletal	- Polyarthralgias "Resorbtion of distal tufts" (Radiological findings) - Proximal weakness secondary to disuse, atrophy, low grade myopathy
Endocrine	- Hypothyroidism

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

Dr: The classification criteria is not usually for diagnosis. It can be used to identify patient with unusual presentation.

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 Anti–topoisomerase I Anti–RNA polymerase III	3

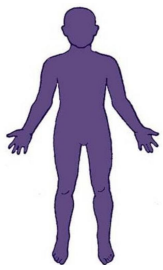
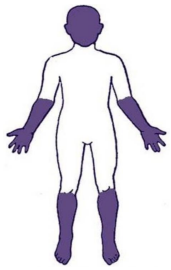
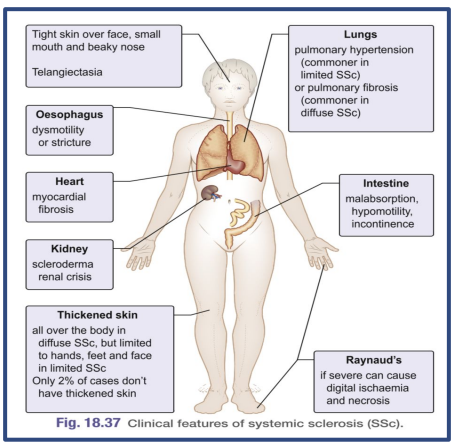
To have SSc, there should be **NINE** points in total. For Example:

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 تصلب الجلد المنتشر Diffuse Cutaneous Scleroderma (DcSSc) I 30% of cases	Limited تصلب الجلد المحدود Limited Cutaneous Scleroderma (LcSSc) I 70% of cases
Skin involvement	• Both distal and **proximal** to elbows and knees. (Affect the whole body) • **Edematous in onset,** skin sclerosis rapidly follows. • **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. 	• Often more indolent (Takes a long time before it becomes clinically apparent) • Skin involvement restricted to sites **distal to the elbow or knee** (apart from the face) • The skin is tight over the fingers and often produces flexion deformities. 
Organ involvement	• Associated with **more internal organ involvement thus it has a worse prognosis** • **Has a higher risk pulmonary (interstitial fibrosis) (ILD)**  Fig. 18.37 Clinical features of systemic sclerosis (SSc).	• Has a **higher risk of pulmonary hypertension** • **Has a Characteristic face features:** ○ 'beak'-like nose ○ small mouth (microstomia). • **LcSSc also known as CREST syndrome متلازمه كريست :** **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
Autoantibodies	• **Anti-topoisomerase (Anti-Scl-70)** • **RNA polymerase III antibodies.** most serious antibody.	★ **Anti-centromere antibodies.**
RP	• **Raynaud's phenomenon** usually starts **just before or concomitant** with the **edema**.	• **Raynaud's phenomenon** starts **many years** (up to 15) **before** any skin changes.

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 occu of internal organ involvement and serologic abnormalities.
(Not important)

Scleroderma or systemic sclerosis (SSc)

◄ AutoAntibodies

Scl-70 (topoisomerase)

Associated with:
- **Diffuse** subset
- The **development** of **ILD**
- **Reduced** risk of **PAH**

Anti-centromere

Associated with:
- **limited** subset
- **The development of Pulmonary Arterial HTN**
- **The development of Digital ulcer**
- **Reduced risk of ILD**

RNA polymerase III

Associated with:
- **Scleroderma Renal Crisis**
- **Malignancy** associated SSc
- **Mortality.**

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

Skin Involvement in SSc

- **Skin is the Largest and Most Important Organ in SSc** (and all women).
- **Skin involvement** has been considered a **reflection** of **internal organ involvement**. (the worst the skin involvement the worst the 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.**

If you want to understand how Scleroderma patients feel: Try to wear a leather gloves 2 times smaller than your size.

◄ Treatment of skin involvement

- If you don't start treatment, patients will end up with major deformities.
- Why do we treat the skin? To prevent joint contracture and disability in the hands.
- Treatment is usually initiated when **active skin inflammation is apparent** or **progressive skin thickening**.

1) Lifestyle modifications
2) Non-pharmacological modifications:
- **Contractures** of the fingers and **disability** are **preventable** with stretching exercise.
- Patients should be advised to **use emollients and creams** at all time.

3) Pharmacological modifications:
- **Methotrexate** (used as a first line) Avoid it if the patient has **interstitial lung disease** (It can cause pneumonitis) or **renal failure** (because of its toxic effect)
- **Mycophenolate mofetil**
- **Cyclophosphamide**
- **Rituximab**
- **Steroids** 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

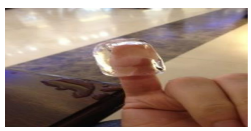
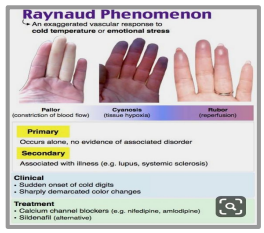
Raynaud's Phenomenon and Digital Ulcers in SSc

Skin | Lung | GI | Kidney | Others

- **Raynaud's Phenomenon:** is an **exaggerated response to cold or stress exposure** which will lead to peripheral vasoconstriction. In normal people it last for few seconds. However, in patients with raynaud's phenomenon it can last for hours and days. Dr. called it MI of the fingers.
- There are two types of Raynaud's Phenomenon:
  - Primary RF (idiopathic): affects 4% of the population, usually young women.
  - Secondary RF: caused by an underlying disease (SSc, Sjogren's syndrome, dermatomyositis, lupus, vasculitis)
- **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. The longer vasoconstriction, the more prone to ischemia.
- 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 in Systemic sclerosis patients can **complicate** into digital ulcer after developing ischemia.
- In RP there is only tissue ischemia while in DU there is tissue ischemia and damage

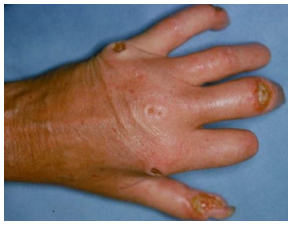
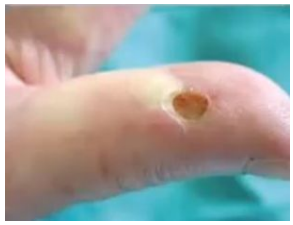
◀ Treatment modalities of secondary RP

- Never underestimate non-pharmacological treatment. Patients should avoid cold by wearing gloves and warm clothes, and stop smoking.
- Treat pain adequately. If you don't that will lead to more vasoconstriction
- **Calcium channel blockers**[1] **(FIRST-LINE)** are effective in treating RP with the cost of side effects and intolerance. (Amlodipine, Nifedipine, Diltiazem)
- If the patient is not responding you can give IV prostaglandins (iloprost) or even Phosphodiesterase inhibitors like sildenafil (for males)
- **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
- BBs are contraindicated, because we have alpha receptors in peripheral blood vessels.

◀ Treatment modalities of 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** (iloprost and epoprostenol) 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.

1- we can use ACEI or ARBs, But the most famous is CCB

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.**

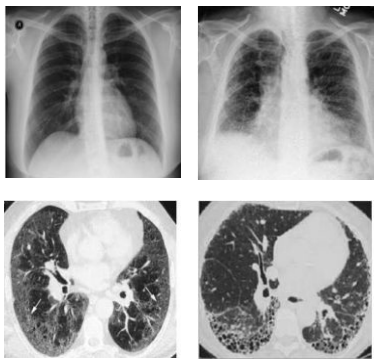
- It is very common, around 70% of patients tend to develop ILD at some time of the disease course.

★ **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. (useless)
  - **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 ★

- Tachypnea
- Tachycardia
- Cyanosis
- Clubbing
- Reduced chest expansion
- 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

- **PAH is defined as Pulmonary Arterial Pressure ≥ 25 mmHg** (normally 18-25 mmHg) with a **Normal** Pulmonary wedge pressure (≤ 15 mmHg) Because high PCWP indicates that the patient has heart failure
- **It is 6 times more common** in patients with **LcSSc**.
- Affects 8-13% of SSc (RHC criteria)
- 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 in PAH ★

- 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

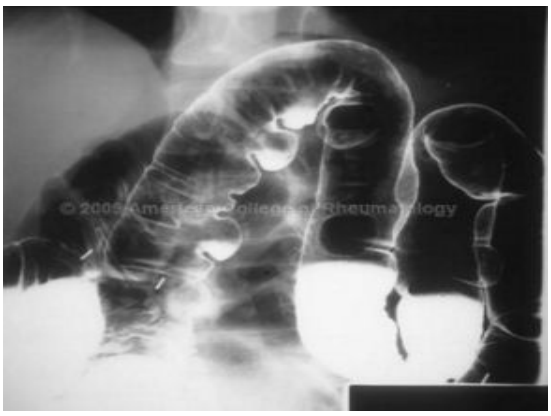
Skin | Lung | **GI** | Kidney | Others

"The least serious, but it's affect quality of life dramatically."

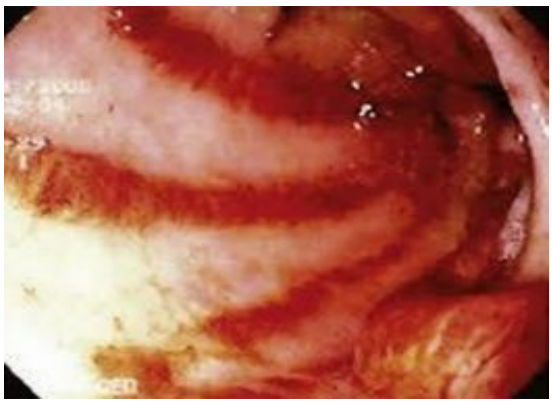
◀ Gastrointestinal System Involvement:

GIT is the **most common internal** organ to be involved (95-99%)

Part of GI tract	Manifestations	Treatment
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.** Avoids sleeping flat. - 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**)	**- Gastroparesis: Motility agents (metoclopramide, domperidone)**
Small bowel	- Blind loop syndrome complicated by bacterial overgrowth manifesting as chronic diarrhea and **malabsorption**	- Primary treatment is **sequential antibiotics (fluoroquinolones, amoxicillin)** 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



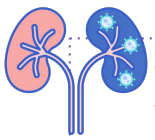
Barium enema showing **white based diverticula**, on **endoscope they look like fish mouth**



gastric antral vascular ectasia (GAVE), watermelon appearance

Scleroderma Renal Crisis (SRC) in SSc

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



The main mechanism of Renal crisis is the hyper activation of RAAS pathway in the kidney because of vasculopathy in afferent and efferent arteriole so, Patients with SSc usually have low BP, once you see high BP, suspect SRC.

- **Mostly** in patients with **DcSSc.**
- SRC was the leading cause of death in systemic sclerosis patients till the introduction of **ACE inhibitors.**
- 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.
- **Precipitating factors include:** high dose **steroids**, **cyclosporin** & **pregnancy**.

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 ESRD, 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.

"One of the rare but very serious presentation they can come with 3rd degree heart block, requiring a pacemaker."

Sjogren's Syndrome

متلازمة شوغرن

- 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

متلازمة شوغرن

◀ 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.

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

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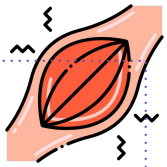
"This topic will be discussed in details in a separate lecture"

◄ Idiopathic inflammatory Myopathies [1]



- 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 in IIM

- **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 (rare)**

Types of IIM [2]

Dr: focus on PM and DM

- **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 (Not important)
- Miscellaneous (eg, eosinophilic myositis, myositis ossificans, focal myositis, giant cell myositis) extremely rare

You don't need to memorize it

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

1. I want you to understand that myopathy is a common feature of many disorders. Like metabolic disorder ,DM , hypo and hyperthyroidism, cushing's syndrome addison's disease, acromegaly. Then you go to drugs like statins , HIV medications. In neurology you have myasthenia gravis and metabolic myopathies and congenital myopathies. **So, muscle weakness does not have to be a myositis. when you see muscle weakness you have to consider everything before thinking about myositis (it affects 5-20 per 100,000 it's rare disease)**

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

Idiopathic inflammatory Myopathies

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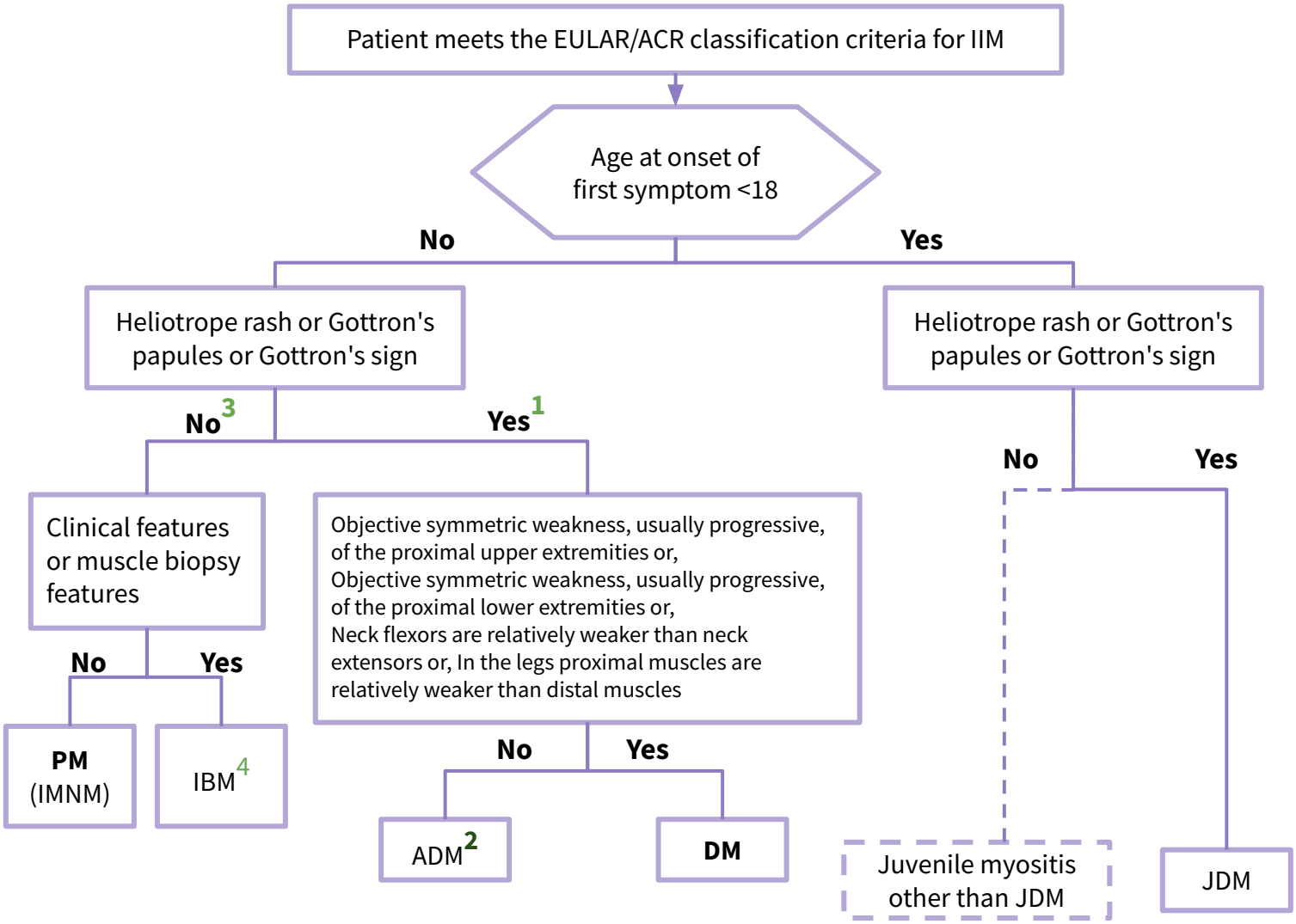
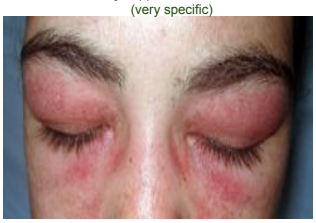
◄ Algorithm for IIM

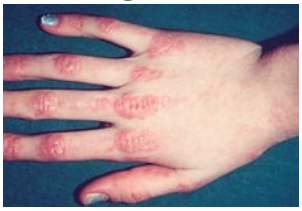


◄ Rashes of DM

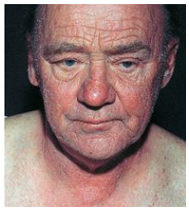
01 **Heliotrope rash (Pathognomonic)**
means it only happened in this condition (very specific)



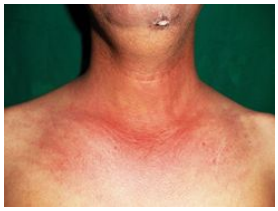
02 **Gottron's papules/sign[5] (Pathognomonic)**



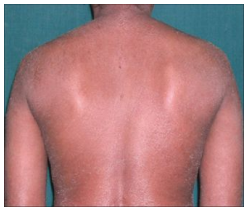
03 **Photosensitivity[8]**



04 **Shawl rash [7]**



05 **Erythroderma[6]**



1. If the patient has skin manifestation + features of inflammatory myopathies, this is considered as Dermatomyositis
2. Asymptomatic 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 painful erythema of the body. (patient can peel the skin like an orange)
7. Around the neck and upper trunk.
8. photosensitivity is an exaggerated response to sun exposure. (patient might have a sunburn from 5 min sun exposure)

Idiopathic inflammatory Myopathies

الاعتلال العضلي الالتهابي

◀ Investigations

Muscle enzymes[1]	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)**[2]

◀ 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. Muscle enzymes makes us differentiate between myositis and myopathy. Myopathy has abnormal muscle enzymes (not always but most of the time).
2. 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).

Take home Messages

This slide was added to remind you of the most important things to keep in mind after finishing the lecture

- SSc is characterized by skin thickening, vasculopathy and autoantibody.
- **Scl-70 (topoisomerase)** is associated with diffuse SSc, ILD and reduce risk for PAH.
- **Anti-centromere** is associated with limited SSc, PAH and reduce risk for ILD.
- Skin involvement in SSc always starts **distally** and treated with **methotrexate.**
- RP tends to occurs years before the diagnosis of SSc, treated with **CCB**.
- IV **iloprost** is used to heal and treat new digital ulcers in SSc.
- ILD in SSc is diagnosed by **HRCT** and treated with **cyclophosphamide** or mycophenolate mofetil.
- PAH in SSc is diagnosed with **right sided heart catheterization** and treated with **bosentan**.
- **microangiopathic hemolytic anemia** indicates scleroderma renal crisis.
- Sjogren's syndrome increases the risk of **non-hodgkin lymphoma**.
- **Heliotrope rash** and **Gottron's sign** are pathognomonic for dermatomyositis.

Doctor Summary + Cases

1 - In Scleroderma there is always predominant organ , but in some rare cases (<1%) we can see SSc without skin involvement. It's known as systemic sclerosis sine scleroderma (ssSSc).

2- Sjogren's Syndrome can initially present without dry mouth, but they come with demyelinating disease with skin rash.

3- similarity in myositis we have 2 features of 2 conditions were you don't have any muscle involvement but the patient has dermatomyositis. One of the conditions is skin involvement (patient come with rash and normal enzymes like Ck. this condition is called Amyopathic Dermatomyositis. The Anti-synthetase is another example were patients have minimal muscle involvement or no muscle involvement ,but they come with severe interstitial disease, arthritis and vasculitic skin rash.we treat these patient with large amount of steroids.

—----------

Why did they call it Anti-synthetase?

Because JO-1 and Non-Jo-1 antibodies are all synthetase anti-bodies.

- A patient with myositis came to the ER with respiratory failure he can come with type 1 respiratory failure and type 2 respiratory failure, what is the difference?

type 1: only hypoxia / *type 2*: hypoxia + hypercapnia

Any type 1 can progress to type 2. So, if someone has any chest wall problem he will come with type 2 because he can't breath + he can't wash out Co2.

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		
Digital Ulcer	• **Bosentan shown to prevent new ulcers** • **Phosphodiesterase inhibitors (sildenafil) have a positive effect on healing and preventing new ulcers**		
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 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.

Q4: 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.

Q5: 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:C | Q5:B

GOOD LUCK !

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