Scleroderma Spectrum Disease

435 medicine teamwork

Lecture objectives:

- Background
- Scleroderma
- Sjogren's Syndrome
- Inflammatory Myopathies

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References: Doctors' Slides, Kumar, Master The Boards

[Important | Notes | Extra | Editing file]

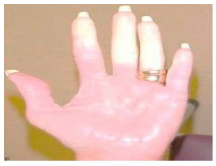
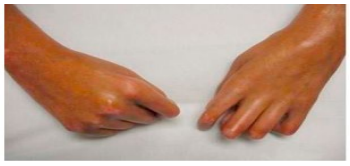
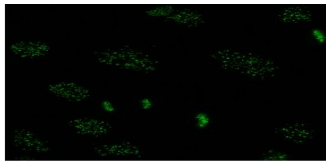
Scleroderma Spectrum Diseases

- Scleroderma Spectrum diseases are: a group of **heterogeneous** diseases that have a predominant feature and share other common features.
- They are rare, difficult to treat & associated with significant morbidity and mortality.

1- Scleroderma or Systemic Sclerosis (SSc):

❖ SSc is **characterized** by **skin thickening**, **vasculopathy** (Raynaud's Phenomenon) and **autoantibody production**.

- Scleroderma is a disease that has 3 different components and it's important to know that because when you're going to manage the patient you're gonna manage him symptom by symptom or organ by organ.

- They have interstitial lung disease, pulmonary hypertension, arthritis.

❖ Types are classified *based on* ***cutaneous involvement*** into: (Starts in the finger then spread proximally and the face is involved in both types)

Diffuse (30% of cases)	Limited (70% of cases)
(It starts with the fingers and/or toes and once you have involvement proximal to the elbow or to the knees it is diffuse)	(It starts with the fingers and/or toes and the involvement is distal to the elbows and knees)
- Associated with more **internal organ** involvement - **Worse** prognosis.	- Often **more indolent** (Always associated with hand thickening) - Has a higher risk of **pulmonary hypertension**
Anti-topoisomerase / RNA polymerase III antibodies	**Anti-centromere antibodies**
Clinical features: • The skin changes develop more rapidly. • Early involvement of other organ: • GIT involvement • Renal involvement • Lung disease *(mentioned below)*	**Clinical features:** Usually starts with Raynaud's Phenomenon many years before any skin changes happen. • The skin is thickened, bound down to underlying structure and the finger taper (sclerodactyly). • *Characteristic* facial appearance: 'beaking' of the nose, radial furrowing of the lips and limitation of mouth opening. • Known as CREST Syndrome (**C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia)

Autoantibodies:

Scl-70 (anti-topoisomerase) **Most specific test**	Associated with diffuse subset, Interstitial Lung Disease (ILD) , Reduced risk of Pulmonary Arterial Hypertension (PAH).
Anti-centromere	Associated with limited subset, PAH, and Digital Ulcer (DU). (Extremely specific for CREST Syndrome)
RNA polymerase III	Associated with SRC, malignancy associated SSc and mortality.
Scl-PM	Associated with **myositis** overlap.
ANA	positive in 85% to 90%, but nonspecific.

2013 Criteria for the Classification of Systemic Sclerosis.

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

- First item in criteria whether the sub-type is diffused or limited the score remains 9, but you have to eliminate any other causes that might imitate scleroderma such as Nephrogenic Systemic Fibrosis (allergic reaction to Gadolinium with MRI in patients with renal failure) or Graft Versus Host Disease (Post bone marrow transplantation they have severe GI and skin manifestations)

Organ involvement in SSc: (when you treat, you will treat each organ one by one)

- SSc is a disease that is difficult to evaluate, treat, and monitor.
- It's very **heterogeneous**, usually diagnosed late and there is **no** single drug that treats everything.
- Pathogenesis in each organ involved is not the same: could be Neurovascular, Fibroproliferative, or Inflammatory.
- A strategy should be adopted to evaluate each manifestation and organ involved on a regular basis.

Skin involvement:

- **Skin** is the largest and most important organ involved in SSc.
- Skin involvement has been considered a reflection of internal organ involvement.
- It predicts severe disease and mortality. the more skin involved the higher the chance that internal organs are involved the more severe the disease
- It always starts in the fingers and toes and extends ***proximally.*** Contracture of the fingers and disability are preventable with stretching exercise. Patients are advised to use emollients and creams (and vaseline on wet skin) at all times.
- Skin loosening occurs 5 years after the onset of the disease.
- The diagnosis of scleroderma is primarily based upon the presence of characteristic skin changes.
- **Treatment** is usually initiated when active skin inflammation is apparent or progressive skin thickening. (So once you stop the inflammation with immunosuppressive agent fibroblast will be deactivated and there won't be collagen deposition)

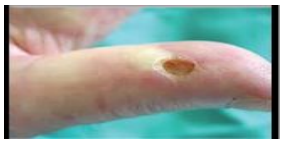
1.Methotrexate (if no ILD *Because it causes pneumonitis and can lead to pulmonary fibrosis* or renal failure) it slows the underlying process of limited scleroderma.	4.Rituximab
2.Mycophenolate	5.Some Steroids
3.Cyclophosphamide	(Stretching exercises also is advised because the more you stretch the more you maintain the joint range of movement. It decreases disability by 80%)

Raynaud's Phenomenon (RP) & Digital Ulcers (DU):

(the patient will have exaggerated response to temperature changes and the symptoms are: discoloration, paresthesia, and pain)

- **RP and DU are 2 faces of the same coin**. There is some differences between the underlying pathogenesis of both conditions.
- 95% and 50% of SSc have RP and DU respectively.
- RP tends to occur years before the diagnosis of SSc.
- DU usually occurs in the first 5 years after the development of the non-RP manifestation.
- **Treatment modalities in:**

Secondary Raynaud's Phenomenon	Digital Ulcer
- Never underestimate non-pharmacological treatment. - Treat pain adequately. - **Calcium channel blockers (CCB)** are effective in treating RP with the cost of side effects and intolerance. - **Prazosin** *not* working well. - Efficacy of oral and IV prostaglandins. - **IV iloprost** is better than nifedipine.	- **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. - **Endothelin receptor antagonist (bosentan)** *the only approved medication* has been shown to prevent new ulcers and is believed to be a disease modifying agent for SSc - **Phosphodiesterase inhibitors** (Sildenafil or

	Tadalafil) have a positive effect on healing and preventing ulcers. - **Prostacyclin** has been shown to heal DU and prevent new ulcers. 

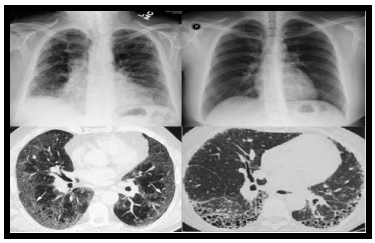
Interstitial Lung Disease (ILD): (Chest x ray is not diagnostic at all. Always go for High Resolution CT)

- ILD is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia leading to progressive loss of pulmonary function and respiratory failure.
- It usually affects the bases of the lungs.
- Diagnosis is made by a combination of imaging and pulmonary function test (PFT).
- EVERYBODY should be screened for ILD.

Clinical Findings in ILD	PFT in ILD shows
- Tachypnea - Tachycardia - Cyanosis - Clubbing - Reduced chest expansion - Fine early inspiratory crackles	- Low FVC - Low FEV1 - Normal or high FEV1/FVC ratio - Low diffusion capacity of carbon monoxide (DLCO)

Treatment:

- **Cyclophosphamide** is the standard of care used as treatment induction in ILD up to this day. (improves dyspnea and PFTs)
- Alternative could be: **MMF** or **rituximab**.
- Maintenance includes: **MMF**, **AZA** and **RTX**. (RTX is an anti-CD20)
- **Steroids** are a part of induction and maintenance.

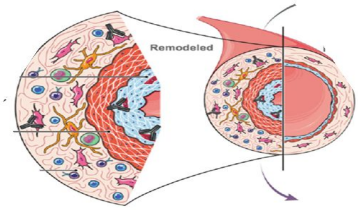


Pulmonary Arterial Hypertension (PAH):

- PAH is defined as PAP ≥ 25mmHg with a pulmonary wedge pressure ≤ 15 mmHg.
- PAH has become a very important cause of mortality along with ILD; they cause 33% of death.
- Affects 8-13% of SSc (RHC Criteria)
- Remember, you can have PAH secondary to ILD which makes diagnosis and management more complex.

Solutions to Reduce PAH-related Mortality & Morbidity.

- Early detection
- Aggressive treatment (early aggressive treatment will prevent those remodelings)
- Early referral for lung transplant



How to Diagnose PAH in SSc

- The first investigation to order is **Echocardiography.**
- The gold diagnostic tool is **Right sided heart catheterization.**

- PFT may show isolated low DLCO (Very low DLCO with normal PFT)

Clinical Findings in PAH	Treatment of PAH
- Desaturation - Tachycardia - Tachypnea - Syncope - Palpable P2 and parasternal heave. - Loud 2nd heart sound. - Signs of right sided heart failure.	- **Endothelin Receptor Antagonist:** - **Bosentan** - Ambrisentan - Macitentan - **Phosphodiesterase Inhibitors** - **Prostacyclins**

Gastrointestinal System Involvement:

- GIT is the most common internal organ to be involved (95-99%). (the most affected part is the esophagus. من الاشياء العجيبه they are in no risk to develop barrett's esophagus)
- It affects the whole tract:

- **Esophagus** → Dysmotility and reflux leading to stricture. - **Stomach**→ gastroparesis (Patient will have: early satiety, nausea, abdominal pain and weight loss), watermelon appearance with telangiectasia.	**Treatment of both includes:** - lifestyle modification. - Proton pump inhibitors. - Iron deficiency anemia treatment.
- **Small bowel** → blind loop syndrome complicated by bacterial overgrowth manifesting as chronic diarrhea and malabsorption.	**Primary treatment:** - sequential antibiotics. **Advanced case:** - Stomas and TPN can be offered.
- **Large bowel** → Chronic constipation, fish mouth diverticula.	**Treatment:** - Laxatives.
- **Anorectal**→ Fecal incontinence.	Devastating complication and difficult to manage but one option could be to **clear bowel frequently before going out.**

Kidney Involvement:

Scleroderma Renal Crisis (SRC):

- Patients with SSc usually have low BP, once you see ***high BP*** suspect SRC.
- The **primary histopathologic changes** in the kidney are localized in the small arcuate, 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. leading to the activation of the Aldosterone-renin-angiotensin pathway.
- Precipitating factors include: high dose aldosterone, cyclosporine, and pregnancy.
- Anemia in SSc is usually iron deficiency, once you see ***microangiopathic hemolytic anemia*** suspect SRC

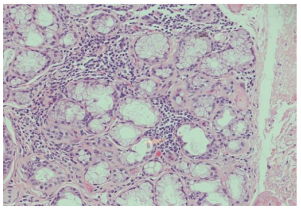
Clinical Findings	Treatment
- Any new onset HTN with a BP of > 150/85 or 20 mmHg increase from baseline is critical to recognize. - Normotensive renal crisis can occur. - Urinalysis might show proteinuria and hematuria **but no RBC cast**. (Suggest Glomerulonephritis due to SLE if it was present) - High creatinine is almost universal. - Anemia with positive hemolytic workup points to microangiopathic hemolytic anemia.	- Control BP by reducing it 10 mmHg every 24h - Best and ONLY drug ACEI. - Even if it progressed to ESKD 40% might recover and get back to near normal function.

Other Manifestations:

- **Cardiac** → Myocardial fibrosis leading to conduction abnormalities, cardiomyopathy, and accelerated coronary artery disease.
- **Arthritis**→ similar to RA with erosions and joint destruction.
- **Myositis**→ manifested by weakness with no pain and high muscle enzymes.

2- Sjogren's Syndrome (SS):

- It is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in **exocrine organs.**
- it's an autoimmune disorder secondary to antibodies predominantly against lacrimal and salivary glands. 90% of those affected are women.
- Most individuals with sjogren's syndrome present with Sicca symptoms, such as:



1. **Xerophthalmia (Dry eyes)** gives the feeling of "sand in the eyes" as well as burning and itching (keratoconjunctivitis).	**3. Vaginal dryness** loss of vaginal secretions leads to dyspareunia.
2. Xerostomia (Dry mouth) pts in constant need to drink water. loss of saliva will lead to rampant dental caries.	**4. Parotid gland enlargement**

Complications:

- SS patients are at risk of developing non-Hodgkin's B cell **lymphoma** (the most dangerous complication) 20 times more than the general population.
- Look for persistent LAP or disappearance of RF.

Criteria of SS:

Diagnosis of primary SS requires **at least 4** of the criteria listed below *(but you must have either 5 or 6 included as one of the criteria because the first 4 are not enough to diagnose the disease)*:

1. Ocular dryness	4. Oral signs (sialogram, scintigraphy or sialometry findings)
2. Oral dryness	5. Positive minor salivary gland biopsy findings.
3. Ocular signs (Schirmer test)	6. Positive anti-SSA (Sjogren's Syndrome A) or anti-SSB (Sjogren's Syndrome B) antibody results.

Extraglandular manifestations of SS:

Arthritis	Palpable purpura	Renal tubular acidosis type 1 (All rheumatic diseases can cause RTA 1)
Myositis	ILD	Interstitial nephritis
Pancytopenia	Demyelinating disease	Fatigue

Diagnostic Tests:

- 🔰 Best initial test → **Schirmer test:** in which a piece of filter paper is placed against the eye and then observed for the amount of wetness on the filter paper.
- 🔑 Most accurate test → **lip or parotid gland biopsy** they reveal lymphoid infiltration in the salivary glands.

Treatment of Glandular Manifestations	Treatment of Extraglandular Manifestations
- initial therapy is to water the mouth. - Oral hygiene - Avoid sugar - Florid products - Parasympathomimetics (pilocarpine) and cevimeline increase acetylcholine, the main stimulant to the production of saliva. - **Artificial eye & mouth moisturizers** - Creams and lotions - Vaginal lubricants	- **Treatment of all includes immunosuppressive agents:** - Steroids - MTX (Except for ILD) - Azathioprine - Cyclophosphamide - Rituximab - For RTA you just need to give NaHCO3

3- Idiopathic Inflammatory Myopathies(IIM):

The RAREST one , but once it comes يضيق صدري :(

What is it:

- They are a group of autoimmune myopathies that are characterized by muscle weakness mainly in the **proximal** muscles. **It is INSIDIOUS** and progressive.
- Once it hits the distal muscles, pharyngeal muscle, chest wall or the heart it is very bad
- Polymyositis (PM) is a rare muscle disorder of unknown etiology in which there is inflammation and necrosis of skeletal muscle fibres. When the skin is involved it is called dermatomyositis (DM). PM and DM affect adults and children and are more common in women.
- **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.
- **Antibody:** ***anti Jo-1*** (the most specific one)
- **Clinical features:**
  - Symmetrical muscle weakness and wasting affecting the proximal muscles of the shoulder and the pelvic girdle.
  - Patients have difficulty squatting, going upstairs, rising from a chair, and raising their hands above their heads
  - In DM: there are also characteristic skin changes: heliotrope (purple) discoloration of the eyelids and scaly erythematous plaques over the knuckles (Gottron's papules). **DM is associated with an increased incidence of underlying malignancy. (Ovary, Lung, GI, Lymphoma)**

Types of IIM: (what i want you to remember is Polymyositis & dermatomyositis الباقين موش مهمين)

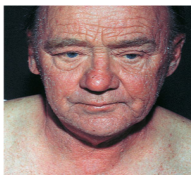
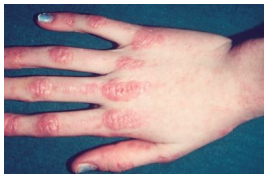
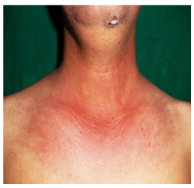
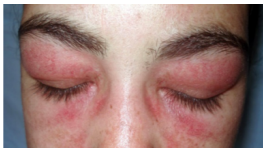
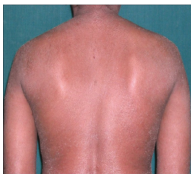
1. Primary idiopathic polymyositis (PM).
2. Primary idiopathic dermatomyositis (DM).
3. Polymyositis or dermatomyositis associated with malignancy.
4. Childhood polymyositis or dermatomyositis.
5. Polymyositis or dermatomyositis associated with another connective tissue disease.
6. Inclusion body myositis.
7. Miscellaneous (e.g. eosinophilic myositis, myositis ossificans, focal myositis, giant cell myositis.

Criteria for PM and DM:

Features
- 1. Symmetrical proximal muscle weakness
- 2. Muscle biopsy evidence of myositis
- 3. Elevation in serum skeletal muscle enzymes
- 4. Characteristic electromyogram pattern of myositis
- 5. Typical rash of dermatomyositis

Polymyositis
- Definite: all of 1–4
- Probable: any 3 of 1–4
- Possible: any 2 of 1–4

Dermatomyositis
- Definite: 5 plus any 3 of 1–4
- Probable: 5 plus any 2 of 1–4
- Possible: 5 plus any 1 of 1–4

Rashes of DM:

Photosensitivity.	Gottron's papules/ sign (very specific for DM).	Erythroderma.
Heliotrope rash.	Shawl rash.	

Extramuscular manifestations:

- Arthritis.
- RP.
- ILD (antisynthetase syndrome).

Investigations:

Most important: rule out other causes of myopathies.

- Muscle enzymes
- CK
- LD
- AST,ALT (In polymyositis ALT and AST are used in investigation. They are muscle enzymes. It is true that ALT is more specific to the liver but in severe muscle destruction you will have high ALT)
- Aldolase
- MRI muscle: showing muscle edema
- MRI biopsy: Lymphocytic infiltration
- EMG: myopathic changes

Diagnostic Tests:

- Best initial test ⟶ CPK and aldolase.
- Most accurate test⟶ Muscle biopsy

Treatment of all manifestations (اكثر مرضى يحتاجوا ستيرويد في وجه الارض)

- Muscle strengthening
- Steroids: *oral prednisolone is the treatment of choice.*

When patients are unresponsive or intolerant to steroids:

- Methotrexate
- Mycophenolate mofetil
- Azathioprine
- Intravenous immunoglobulins
- Rituximab
- Hydroxychloroquine helps skin lesions.

Conclusion:

- Scleroderma spectrum disease 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.**

MCQs

1-All the following are features of scleroderma expect:

A. Dysphagia
B. Raynaud's phenomenon
C. Skin contracture
D. Calcification in all long bones

2- A 35 years old lady complains dysphagia, Raynaud's phenomenon , sclerodactyly, investigation show antinuclear antibody, diagnosis is:

A. SLE
B. Systemic sclerosis
C. Mixed connective tissue disorder
D. Rheumatoid arthritis

3-A 14 year old girl on exposure to cold has pallor of extremities followed by pain and cyanosis. In later stages of life she is most prone to develop:

A. SLE
B. Scleroderma
C. Rheumatoid arthritis
D. Dermatomycosis

4-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 □
□

5- 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 □

6-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. Esophageal dysmotility is only seen in limited cutaneous systemic □sclerosis □
D. Anti-double stranded DNA antibodies are normally detected in patients □with systemic sclerosis □

Answer key:

1 (D) | 2 (B) | 3 (B) | 4 (C) | 5 (D) | 6 (B)