الجمعية الخيرية لرعاية مرضى الروماتيزم
Charitable Association for Rheumatic Diseases

جامعة الملك سعود
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SCLERODERMA SPECTRUM DISEASE

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Agenda

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

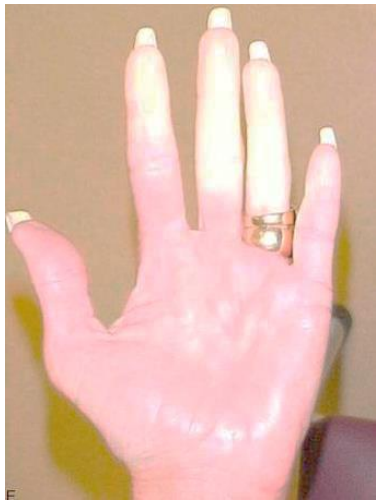
Background

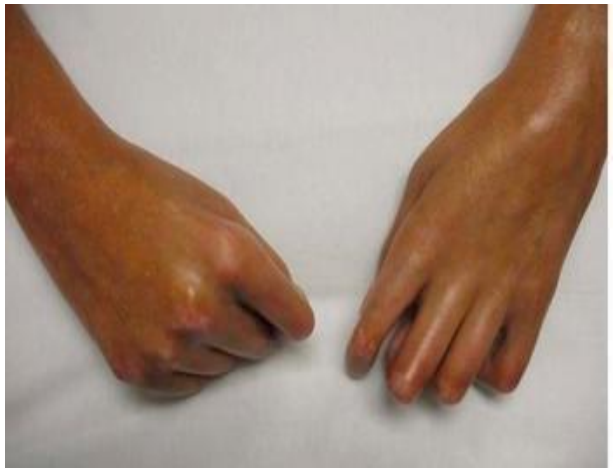
- Scleroderma spectrum diseases are a group of heterogeneous diseases that has a predominant feature and share other common features.
- They are rare.
- Difficult to treat.
- Associated with significant morbidity and mortality.

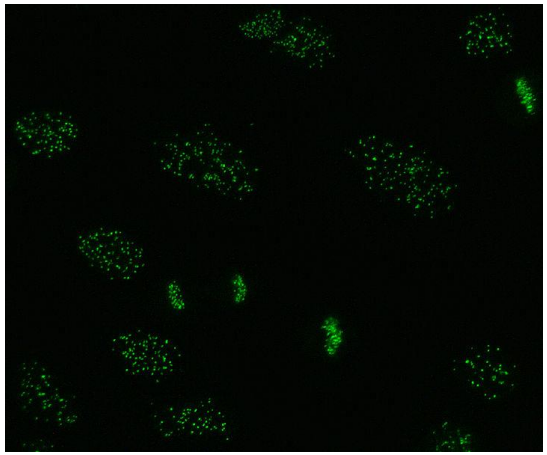
Scleroderma or systemic sclerosis (SSc)

SSc

- SSc is characterized by skin thickening, vasculopathy and autoantibody production.







Types

- Based on cutaneous involvement, it is classified to diffuse and limited.
- Diffuse disease is associated with more internal organ involvement, Anti-topoisomerase/RNA polymerase III antibodies and a worse prognosis.
- Limited form is often more indolent, has a higher risk of pulmonary hypertension, and anti-centromere antibodies

Autoantibodies

- Scl-70 (topoisomerase): is associated with diffuse subset, ILD, and reduced risk of PAH.
- Anti-centromere: limited subset, PAH and DU.
- RNA polymerase III: associated with SRC, malignancy associated SSc, and mortality.
- Scl-PM: associated with myositis overlap.

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	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

Organ Involvement in SSc

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

Skin the Largest and Most Important Organ in SSc (and all women)

Skin Involvement

- Skin involvement has been considered a reflection of internal organ involvement.
- The level of skin involvement predicts severe disease and mortality.
- Skin loosening occurs 5 years after the onset of the disease.
- Treatment is usually initiated when active skin inflammation is apparent or progressive skin thickening.

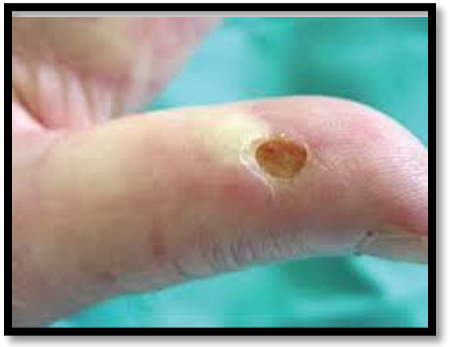
Skin Involvement

- SKIN INVOLVEMENT ALWAYS STARTS IN THE FINGERS AND TOES AND EXTENDS PROXIMALLY.
- 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

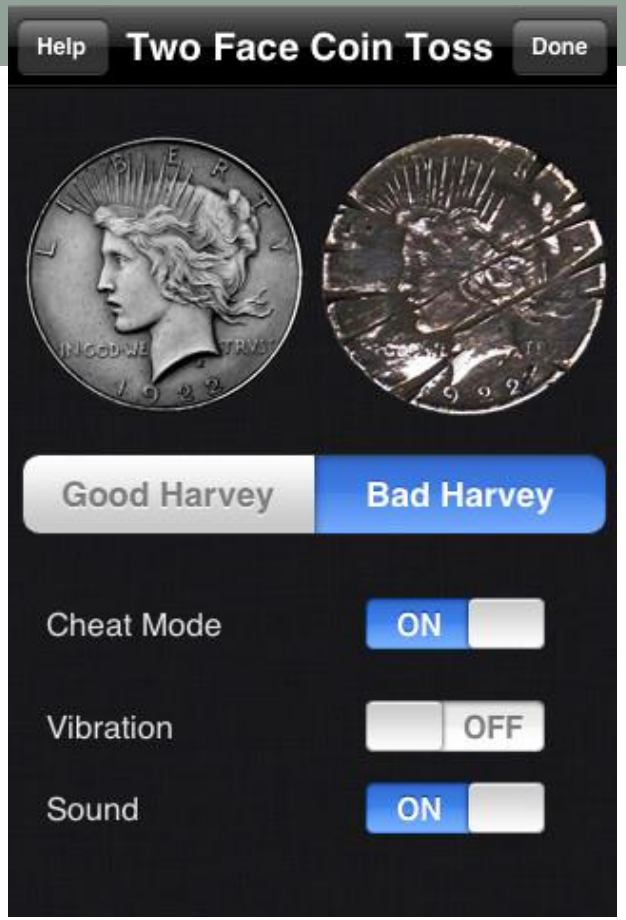
- Methotrexate (if no ILD or renal failure)
- Mycophenolate mofetil
- Cyclophosphamide
- Rituximab
- With some steroids

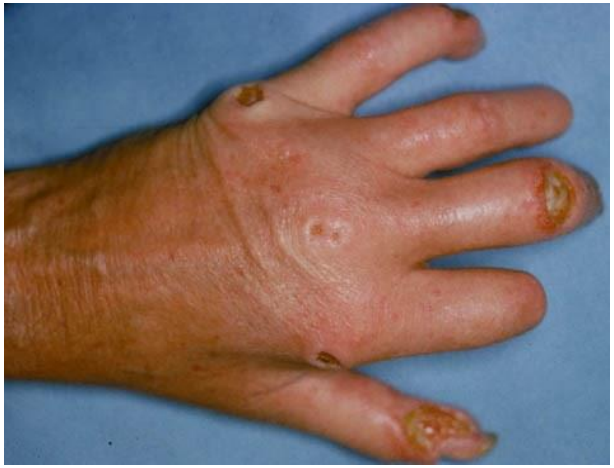
Raynaud's Phenomenon and Digital Ulcers (Pain at the tip of your fingers)



Raynaud's Phenomenon (RP) and Digital Ulcers (DU)

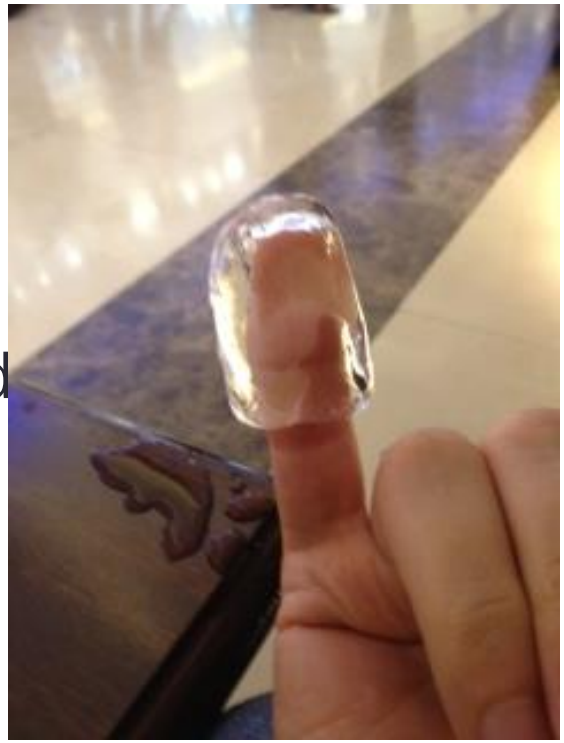
- RP and DU are 2 faces of the same coin.
- There is some difference between the underlying pathogenesis of both conditions.
- 95% and 50% of SSc have RP and DU respectively, but RP tends to occur years before the diagnosis of SSc unlike DU that usually occur in the first 5 years after the development of the non-RP manifestation.





Treatment Modalities in Secondary RP

- Never underestimate non-pharmacological treatment.
- Treat pain adequately.
- Calcium channel blockers are effective in treating RP with the cost of side effects and intolerance.
- Prazocin not working well.
- Efficacy of oral and IV prostaglandins.
- IV iloprost better than nifedipine.



Treatment of DU

- Aim of treatment includes: healing and prevention of new ulcers at the end of the study.
- Calcium channel blockers are commonly used but no evidence in healing 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 has a positive effect on healing and preventing ulcers.
- Prostacyclin has been shown to heal DU and prevent new ulcers.

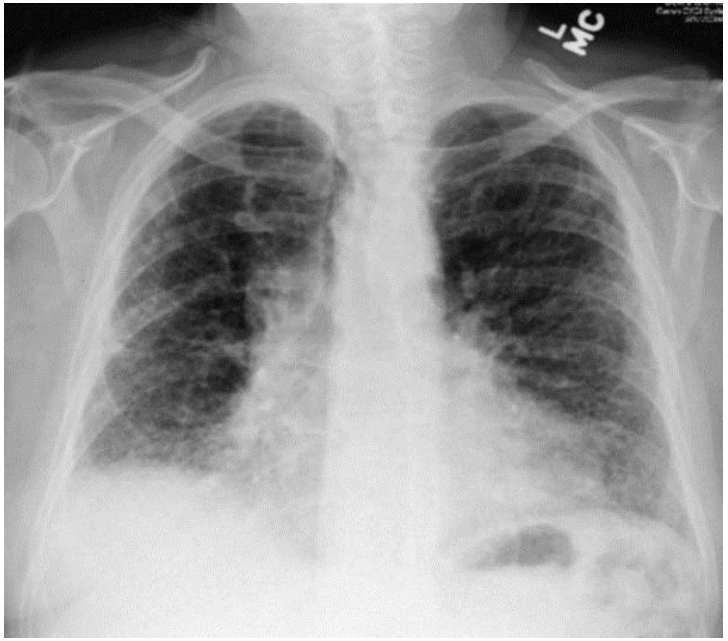
Interstitial Lung Disease

ILD

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

PFT in ILD

- Clinical findings in ILD:
- Tachypnea
- Tachycardia
- Cyanosis
- Clubbing
- Reduced chest expansion
- Fine early inspiratory crackles
- PFT in ILD shows
- Low forced vital capacity (FVC)
- Low forced expiratory volume in one second (FEV1)
- Normal or high FVC/FEV1 ratio
- Low diffusion capacity of carbon monoxide (DLCO)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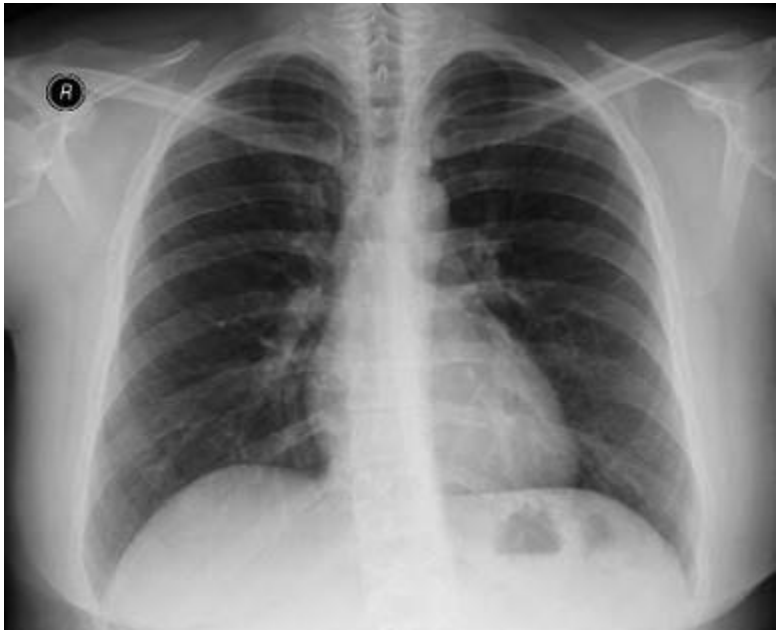
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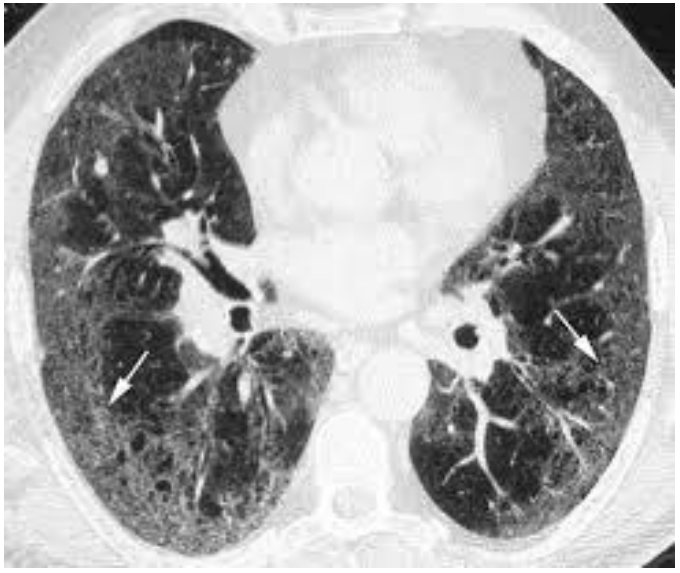
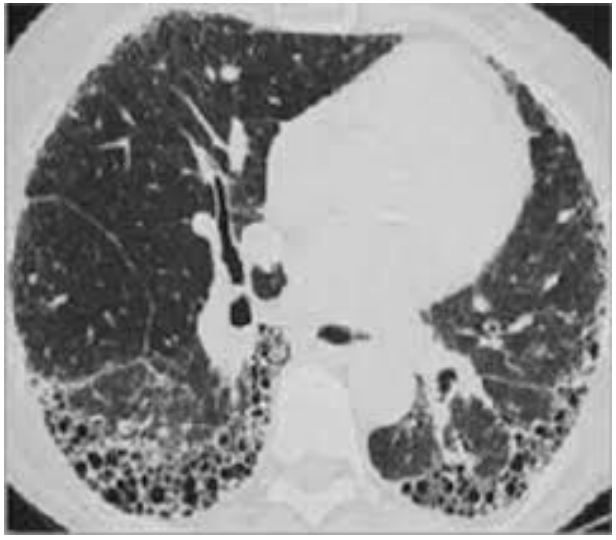




Treatment Options

- Cyclophosphamide is up to today the standard of care used as treatment induction in ILD.
- Alternative could be: MMF or rituximab.
- Maintenance includes: MMF, AZA and RTX.
- Steroids are a part of induction and maintenance.

Pulmonary Arterial Hypertension

PAH in SSc

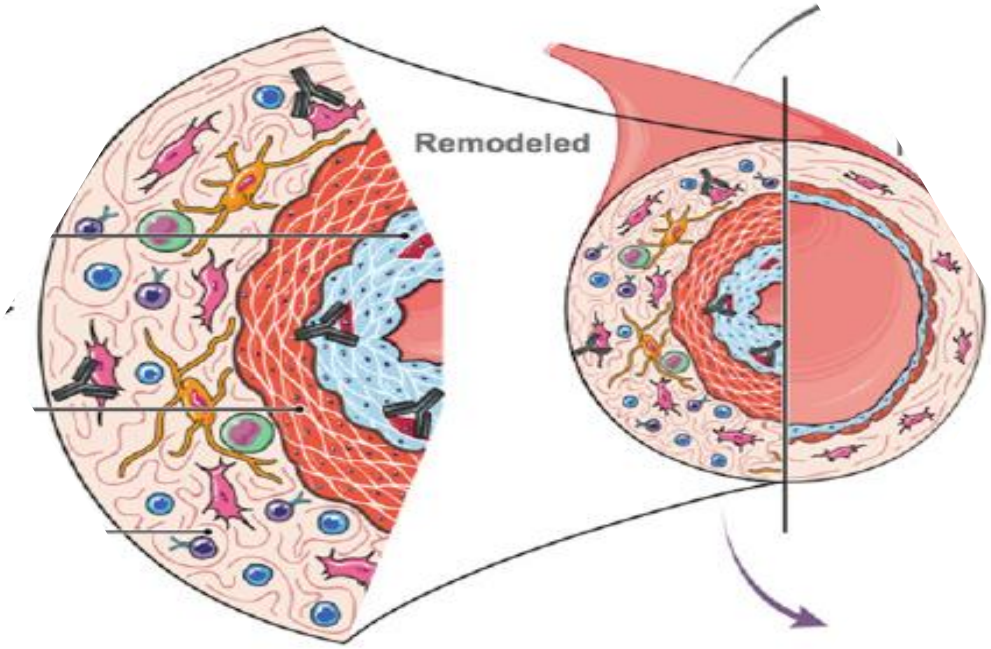
- PAH is defined as PAP ≥ 25mmHg with a pulmonary wedge pressure ≤ 15 mmHg.
- PAH has become a very important cause of mortality along with ILD they are the cause of 33% of death.
- Affects 8-13% of SSc (RHC criteria)

Table 1 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

Solutions to Reduce PAH-related Mortality and Morbidity

- Early Detection
- Aggressive treatment
- Early Referral for lung transplant



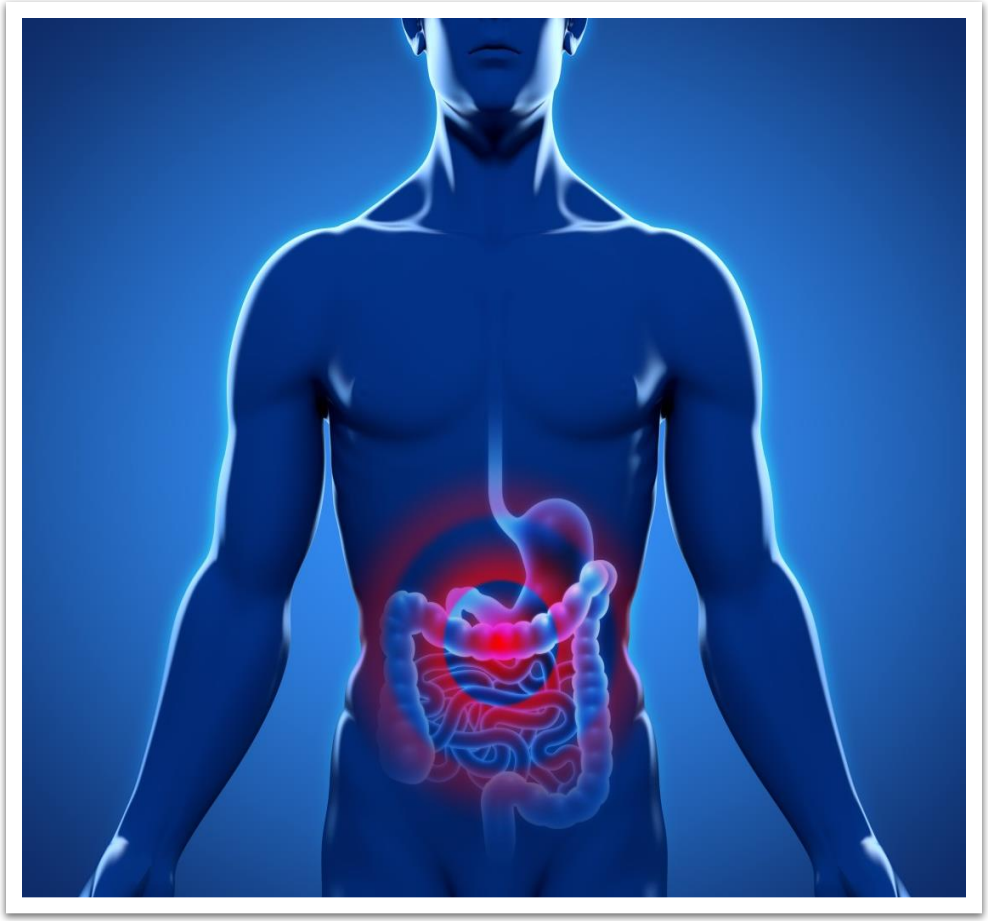
How to diagnose PAH in SSc

- Clinical findings include:
- Desaturation
- Tachycardia
- Palpable P2 and parasternal heave
- Loud 2nd heart sound
- Signs of right sided heart failure
- The first investigation to order is echocardiography.
- PFT may show isolated low DLCO
- The gold diagnostic tool is right sided heart catheterization.

Remember you can have pulmonary hypertension secondary to ILD which makes diagnosis and management more complex.

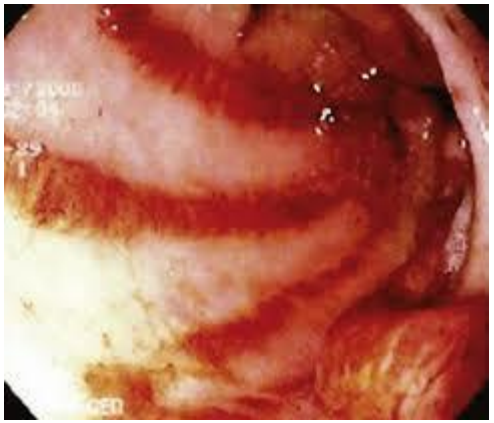
Treatment of PAH

- Endothelin Receptor Antagonists:
  - Bosentan
  - Ambrisentan
  - Macitentan
- Phosphodiestrase Inhibitors
- Prostacyclins



Gastrointestinal System

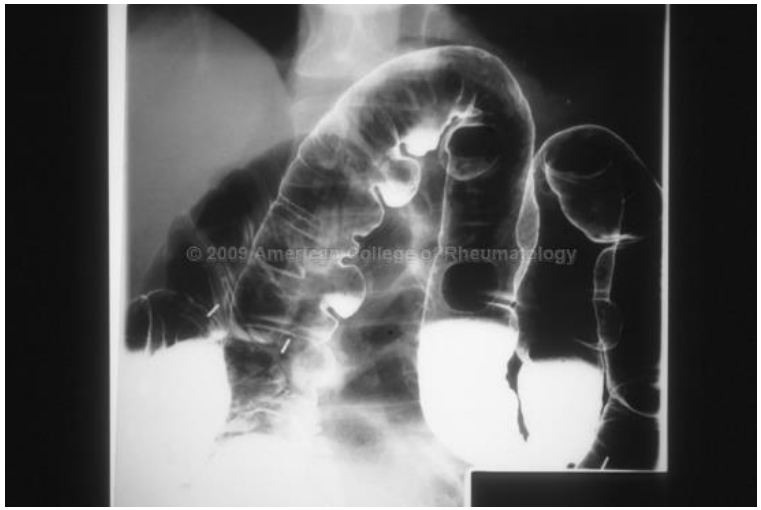
GIT Involvement



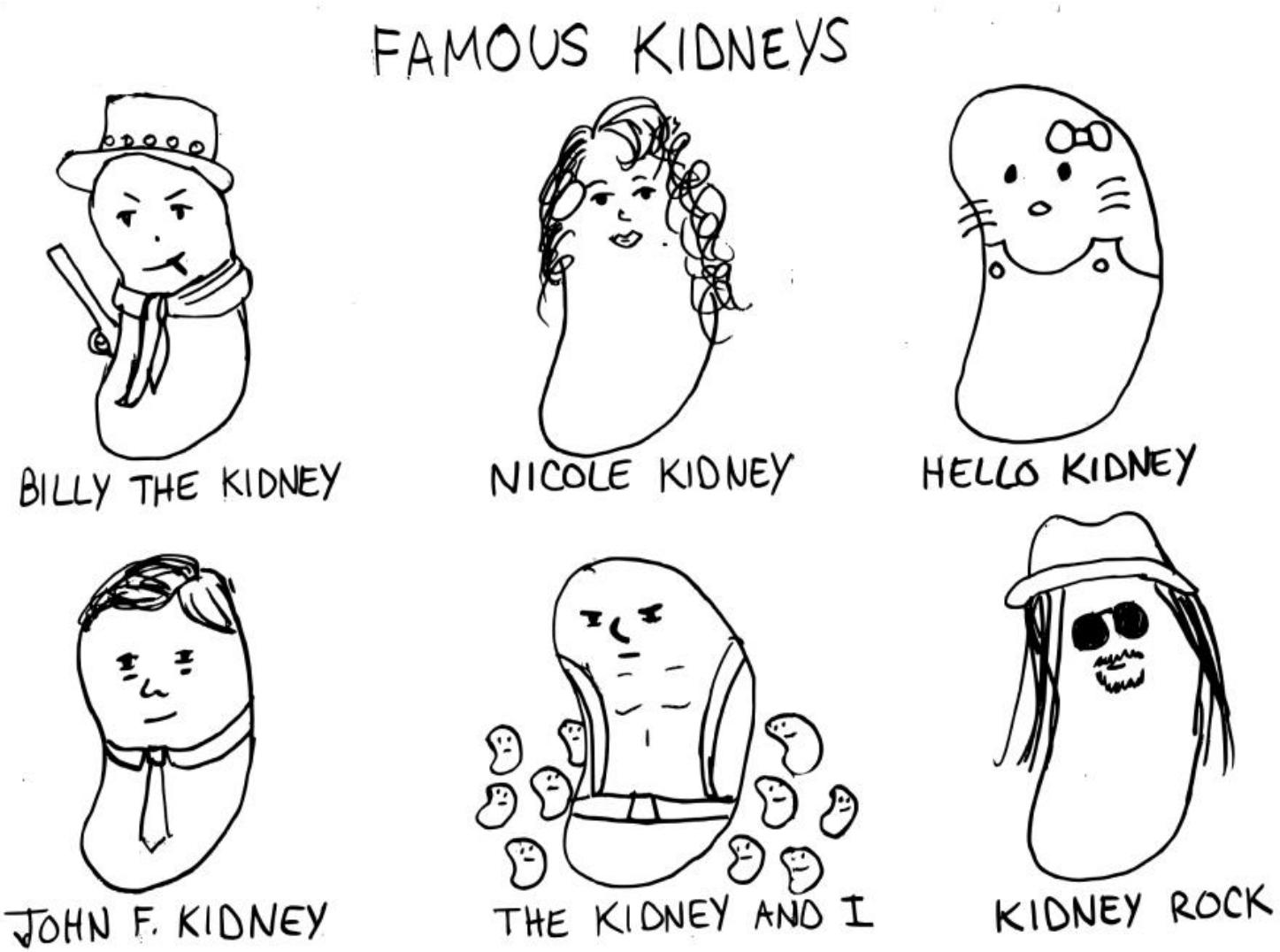
- GIT is the most common internal organ to be involved (95-99%) which includes:
- Esophagus: dysmotility and reflux leading to strictures
- Stomach: gasrtoparesis, watermelon appearance with telagectasia.
- Small bowel: blind loop syndrome complicated by bacterial overgrowth manifesting as chronic diarrhea and malabsorption.
- Large bowel: chronic constipation, fish mouth diverticulae.
- Anorectal incontinence

GIT Involvement

- Small bowel: blind loop syndrome complicated by bacterial overgrowth manifesting as chronic diarrhea and malabsorption.
- Primary treatment is sequential antibiotics but stomas and TPN can be offered in advanced case .
- Large bowel: chronic constipation, fish mouth diverticulae.
- Treatment includes laxatives
- Anorectal: fecal incontinence is a devastating complication and difficult to manage but one option could be to clear bowel frequently before going out.



Kidney Involvement



Scleroderma Renal Crisis

- 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 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.
- Precipitating factors include high dose steroids, cyclosporin, pregnancy.
- Anemia in SSc is usually iron deficiency, once you see microangiopathic hemolytic anemia suspect SRC.

Clinical and Lab Findings

- Any new onset HTN with a BP of >150/85 or 20mmHg increase from baseline is critical to recognize.
- Normotensive renal crisis can occur
- Urinalysis might show proteinuria and hematuria but no RBC cast.
- High creatinine is almost universal
- Anemia with positive hemolytic workup points to microangipathic hemolytic anemia

Treatment

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

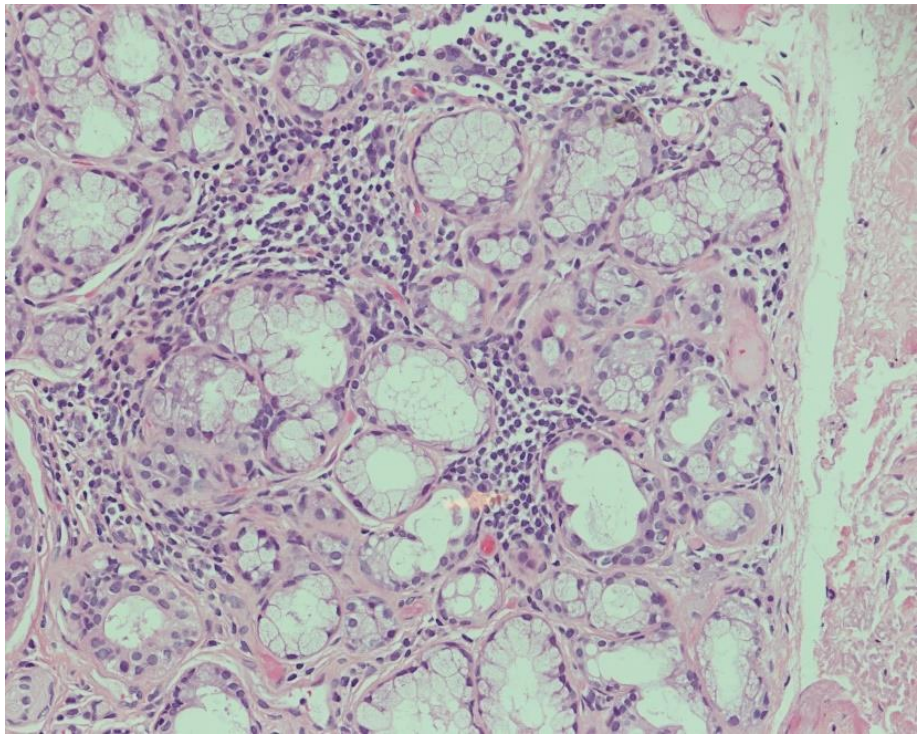
Other manifestations

- 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.

Sjogren’s Syndrome (SS)

SS

- is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs.
- Most individuals with Sjögren's syndrome present with sicca symptoms, such as:
  - Xerophthalmia (dry eyes)
  - Xerostomia (dry mouth)
  - Vaginal dryness
  - Parotid gland enlargement



Criteria of SS

- Diagnosis of primary SS requires at least 4 of the criteria listed below (you must have 5 or 6):

1. Ocular dryness
2. Oral dyness
3. Ocular signs (Schirmer test)
4. Oral signs (sialogram, scintigraphy or sialometry findings)
5. Positive minor salivary gland biopsy findings
6. Positive anti–SSA or anti–SSB antibody results

Treatment of glandular manifestations

- Oral hygiene
- Avoid sugars
- Use florid products
- Parasympathomimetics (pilocarpine)
- Artificial eye and mouth moisturizers
- Creams and lotions
- Vaginal lubricants

Extra-glandular manifestations of SS

- Arthritis
- Myositis
- Pancytopenia
- Palpable purpura
- ILD
- Demyelinating disease
- Renal tubular acidosis type 1
- Interstitial nephritis
- Fatigue

Treatment of extra-glandular manifestations

- Treatment of all include immunosuppressive agents:
- Steroids
- MTX (except for ILD)
- Azathioprine
- Cyclophosphamide
- Rituxmiab
- For RTA you just need to give $NaHCO_3$

Complications

- SS patients are at risk of developing lymphoma 20 times more than the general population
- Look for persistent LAP or disappearance of RF

Idiopathic inflammatory Myopathies (IIM)

IIM

- Are a group of autoimmune myopathies that are characterized by muscle weakness mainly in the proximal muscles.
- It is insidious and progressive.
- 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

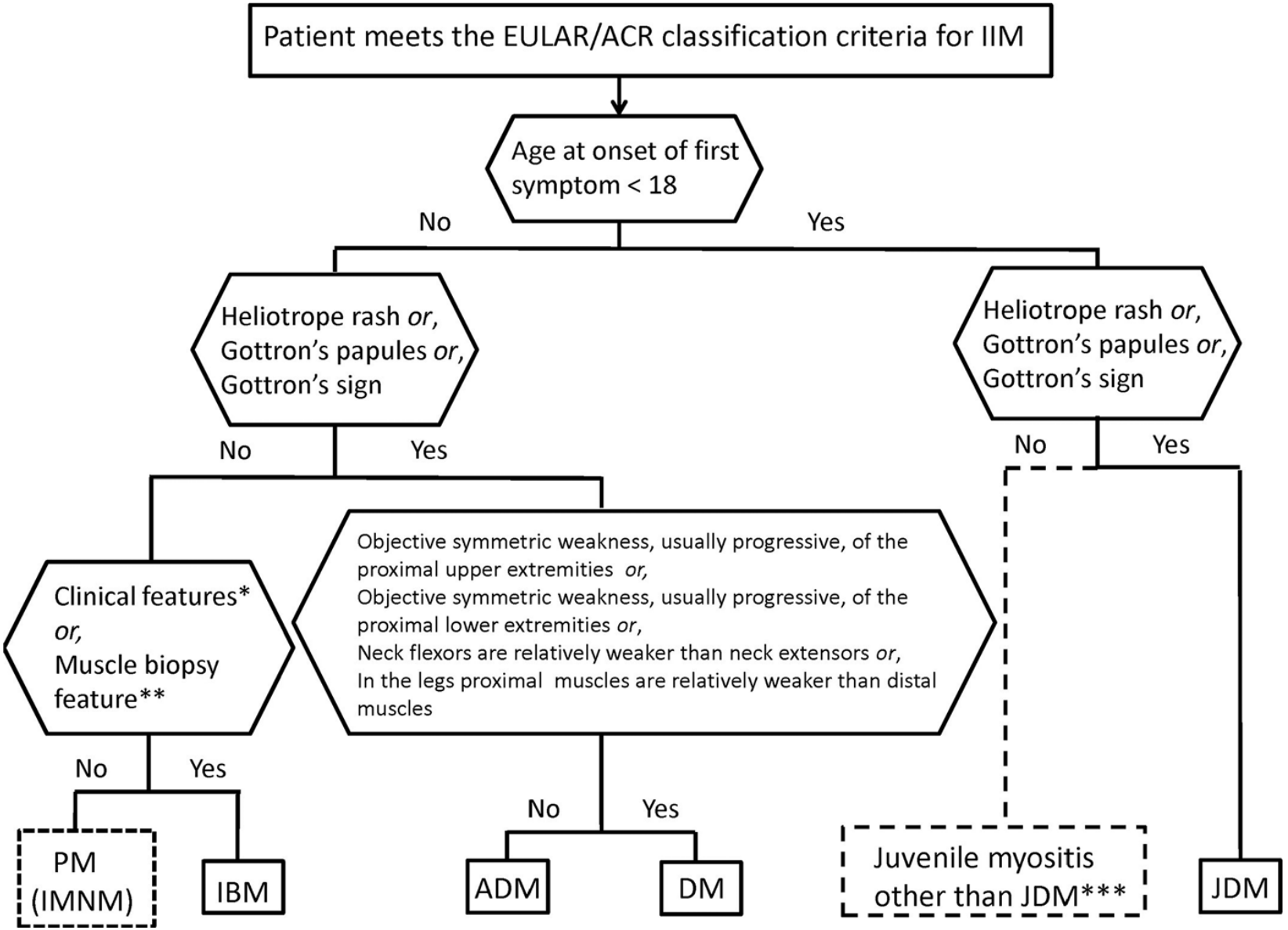
Types of IIM

I. Primary idiopathic polymyositis (PM)
II. Primary idiopathic dermatomyositis (DM)
III. Polymyositis or dermatomyositis associated with malignancy
IV. Childhood polymyositis or dermatomyositis
V. Polymyositis or dermatomyositis associated with another connective-tissue disease
VI. Inclusion body myositis
VII. Miscellaneous (eg, eosinophilic myositis, myositis ossificans, focal myositis, giant cell myositis)

Variable	muscle biopsy	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 m			
Dysphagia or	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the esophagus
Laboratory mea			
Anti–Jo-1 (an autoantibod	3.9	3.8	Autoantibody testing in serum performed with standardized and validated test, showing positive result
Elevated seru lactate dehy aminotransf aminotransf	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 fe			
Endomysial in 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

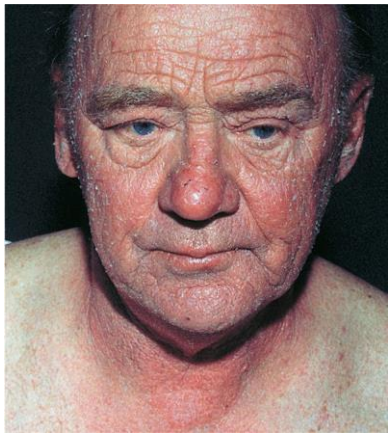
Diagnosis is made if the score is
Without biopsy ≥ 7.5
With biopsy ≥ 8.7

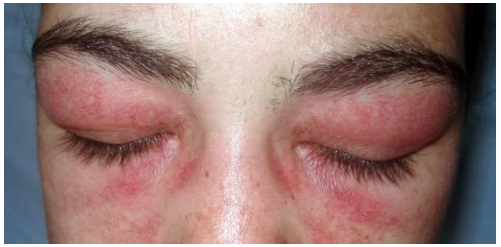
Algorithm for IIM

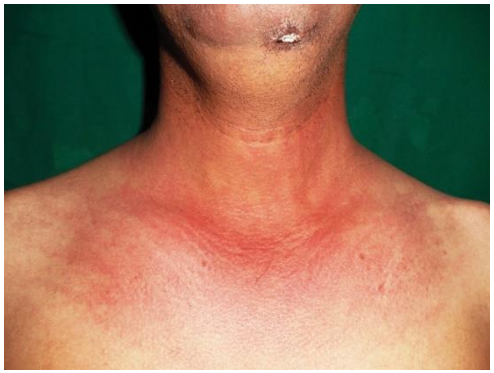


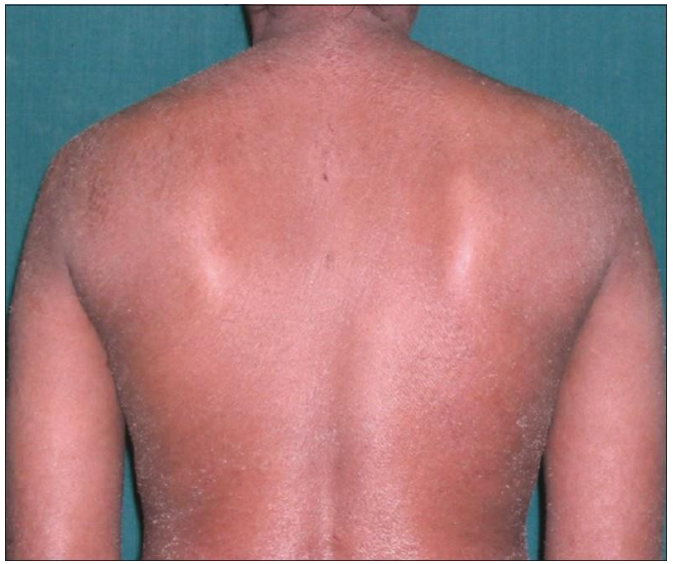
Rashes of DM

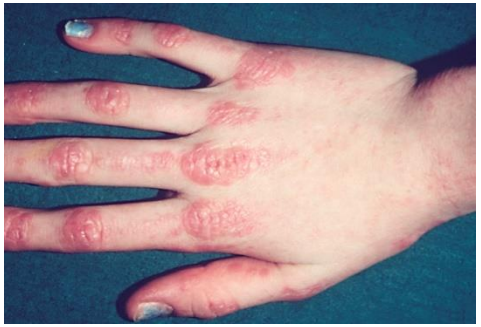
- Photosensitivity
- Heliotrope rash
- Gottron's papules/sign
- Shawl rash
- Erythroderma











Investigation

- Muscle enzymes
- CK
- LD
- AST
- ALT
- Aldolase
- MRI muscle: showing muscle edema
- Muscle biopsy: lymphocytic infiltration
- EMG: myopathic changes
- MOST IMPORTANT: RULE OUT OTHER CAUSES OF MYOPATHIES.

Autoantibodies

- Jo-1
- Non-Jo-1 antibodies
- Anti-SRP
- Anti-Mi2

Extra-muscular manifestations

- Arthritis
- RP
- ILD (antisynthetase syndrome)

Treatment of all manifestations

- Steroids
- Methotrextae
- Mycophenolate mofetil
- Azathioprine
- Rituximab
- Intravenous immunoglobulins

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.

THANK YOU FOR YOUR ATTENTION