THE UNIVERSITY OF NAIROBI
SCHOOL OF MEDICINE
DEPARTMENT OF INTERNAL MEDICINE
RHEUMATOLOGY SERIES

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SYSTEMIC SCLEROSIS

Definition

- A generalized disorder of connective tissue affecting skin and internal organs
- Characterized by fibrotic arteriosclerosis of peripheral and visceral vasculature
- Variable degrees of extra cellular matrix accumulation mainly of collagen. Occurs in both skin and viscera

Epidemiology

- Incidence – 20 cases per million population
- Prevalence – more than 150 pern million population
- F:M is 3-5:1 (2-4:1 in post menopausal)

Scleroderma: general principles

- Two major subtypes of scleroderma are defined based on the extent of skin thickening
    - Limited scleroderma (IcSSc)
    - Diffuse Scleroderma (dcSSc)
- Two types have different patterns of internal organ involvement and different atuto antibodies
- In general, IcSSc is a disorder of the blood vessels and dcSSc is a disorder of the inflammation

Clinical features

- Raynaud's phenomenon
- Tightening and thickening of the skin
- Involvement of internal organs including GIT, lungs, kidneys, accounts for morbidity and mortality
- Risk of internal involvement strongly linked to extent and progression of skin thickening

SSC SIMILARITIES

- In both types
    - 97% of individuals have positive ANA test (nucleolar pattern)
    - Skin thickening begins in the extremities and spreads towards the body
        - Sclerodactly
    - Raynaud's phenomenon
    - Skin tends to soften after 10-15 yrs
    - Rx is directed towards management of specific complications

Systemic sclerosis: preliminary classification criteria

- Major criterion
  - Proximal scleroderma
- Minor criteria
  - Sclerodactly
  - Digital pitting or scars or loss of substances from finger to pads
  - Bibasilar pulmonary fibrosis
- Major criterion or 2 minor criteria

Limited cutaneous systemic sclerosis (lcSSc, CREST variant)

- Skin thickening of arms and legs which does not extend above the elbows or knees
- Skin thickening over the face
- More severe raynaud's , often starting years before the onset of the thickening
- Telangiectasias of the skin
- Primary pulmonary HT
  - 25-50%
- Calcium deposits under the skin (calcinosis)
- GIT involvement – esophagus, stomach, colon
- Anti-centromere antibody – 50-60%
- Other antibodies

Diffuse cutaneous systemic sclerosis (dcSSc)

- Skin thickening of extremities, upper arms and legs, and trunk
- Most rapid skin thickening and highest risk of internal involvement is over first 3-5 yrs
- Milder raynaud's starting around same time as skin thickening
- Preceding carpal tunnel syndrome
- Pulmonary inflammation and fibrosis
  - 30-50%
  - Secondary PHT
- GIT involvement – esophagus, stomach, colon
- Kidney involvement – severe high BP, blood cell abnormalities, rapid kidney failure
- Cardiac involvement
  - Rhythm disturbances, heart failure
- Anti SCL 70 antibody positive
  - More lung involvement
- Anti SCL 70 antibody negative
  - Less lung and more kidney involvement

Other forms of scleroderma

- Mixed connective tissue disease (MCTD)
  - Lupus;/lcSSc/myositis/RA
  - Anti RNP antibody
- Myositis – scleroderma

    - PM-SCL antibody
- Eosinophilia myalgia syndrome
    - Contaminated L-tryptophan

Sequence of causes

- Damage to small blood vessels (vascular injury)
- Immune system activity
- Excessive scar tissue deposition (fibrosis) in organs and vessels
- Indirect and direct organ dysfunction

Blood vessel damage

- The trigger of the autoimmune process appears to be injury to the lining of small blood vessels (vascular endothelium)
- Causes of this vascular injury are unknown (infection?, chemicals?)
- Damaged blood vessels attract immune cells which adhere and migrate into tissues

Immune system dysfunction

- Once in the tissues, immune cells called T cells directly stimulates fibroblast to deposit collagen protein which is responsible for fibrosis or scarring
- Imbalance between chemical messengers promoting (TGF Beta) and inhibiting (Gamma INF) fibrosis

The end results: direct organ dysfunction

- Scar tissue that forms in organ tissues lead to direct organ dysfunction
    - Esophagus
    - Intestines
    - Heart
    - Lungs

Endothelin 1 (ET1)

- Released from cells in walls of damaged blood vessels
- Stimulates fibrosis
- Promotes scarring in tissues and in vessel walls
- Direct constricts blood vessels

Complications

- Raynaud's phenomenon
- Digital ulcers – auto amputation
- GIT problems – swallowing problems, GERD, GAVE (watermelon stomach), obstruction, malabsorption
- Lungs – fibrosis (leading cause of mortality in scleroderma), PHT
- Cardiac disease
- Kidney disease
- Calcinosis

Autoantibody association with scleroderma

- Anti – topoisomerase 1 (ScI 70) 20-40%
- Anti centromere 20-40%
- RNA polymerase 4-20%

Differential diagnosis

- Disorders with similar presentation
    - Inflammatory myopathy
    - SLE
    - RA
- Disorders with similar visceral features
    - Primary pulmonary HT
    - Primary biliary cirrhosis
    - Idiopathic intesitinal hypomotilitiy
    - Collagenous colitis
    - Idiopathic intestinal…

Raynaud's phenomenon

- Often painful color changes of digits with cold exposure or stress
    - White- blue – red
- May lead to formation of ulcers at finger tips and over joints
- The worse the pain, the worse the tissue ischaemia, and therefore the worse the risk of ulceration

Raynaud's general rx

- Don't smoke
- Keep core body temperature warm
- Baby aspirin
- May use vasodilators
- Avoid beta blockers
- Consider biofeedback

Vasodilators

- Dihydropyridine
- Calcium channel blockers
    - Felodipine
    - Nifedipine
    - Amlodipine
    - Long acting forms preffered
- Angiotensin receptor blockers
    - Losartan
    - Irbesartan
- Nitropaste
- Pentoxifylline

More RP rx

- Iloprost
    - Direct vasodilators (PG analogue)
    - 5 hour infusion daily for 5 days shown to reduce severity and frequency of attacks by 35-40% for 10 weeks after rx
- Viagra e.tc
- Above rx may be used in combination

Lung fibrosis

- Usually seen in dcSSc (30-80%)
- Can be caused by excessive scar tissue formation by fibroblasts or as the end results of lung inflammation
- Initial diagnostic tests are PFTs and CT scan of the chest
- If CT scan suggests inflammation…

Pulmonary HT

- May occur as a primary process in IcSSc (10-30%) or secondary to long standing lung fibrosis in dcSSc
- In IcSSc and MCTD, the process is similar to what happens to digital blood flow
- Diagnosis and monitoring
    - Screening tests – PFTs, echocardiogram
    - Monitoring – Echo
- Rx PTH
    - Continous IV epoporostenol
        - Direct vasodilator
    - Continous SQ treprosinil
    - Oral bosentan
    - Oral Viagra

Disease modifying therapies in systemic sclerosis

- Immunomodulatory rx
    - Cyclophosphamide
    - Methotrexate
    - Antithymocyte globulin
    - Cyclosporine A
    - Mycophenolate mofetil
    - Methotrexate
- Photopheresis for difuses cutaneous scleroderma
- Antifibrotic therapy
    - D-penicillamine
    - Interferons
    - Halufuginone
    - Recombinant human relaxin
    - Minocycline
- Vascular therapy
    - Oral vasodilators
    - Prostacyclin infusion

New rx horizons

- Immune system modulation
    - Rituximab – depletes immune B cells
- Abatacept
- Cyclophosphamide
- Anti-TGF beta antibody
- Relaxin

- Natural anti fibrotic hormone made in pregnancy
- Continuous sub cutaneous infusion

10 Commandments

1. Don't smoke
2. Keep core body temperature warm
3. An aspirin a day keeps a blood clot away
4. Avoid prednisone
5. Use an anti acid
6. Don't ignore new Blood pressure elevation
7. Don't ignore ulcers – they will only get worse
8. Don't ignore recommended routine screening tests
9. Don't ignore heart palpitations
10. Never give up hope