Lecture note for

Coetaneous manifestation of connective tissue diseases

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التيم: 428 + نوت ب2

تم اضافه مرضين شرحت لقروب ب 1

ALL DISEASES OCCUR MORE IN FEMALES.

1. DERMATOMYOSITIS :التهاب الجلد والعضلات

DEFINITION:

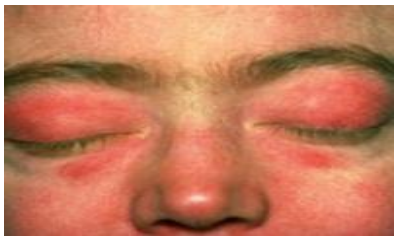
- It is a rare disorder of skin and muscle characterized by a specific rash and proximal weakness.
- Age: have a bimodal peak, a childhood onset and a 40-50 years peak
- Systemic manifestations may occur; therefore, a review of systems should assess for the presence of arthralgias, arthritis, dyspnoea, dysphagia, arrhythmias, and dysphonia

ETIOLOGY:

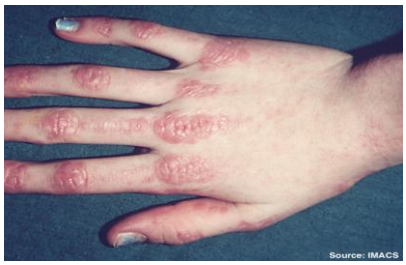
1. A genetic predisposition.
2. Immunologic abnormalities are common.
3. Infectious agents, including viruses (particularly Coxsackie virus, echovirus, human T-lymphotropic virus 1 [HTLV-1], and human immunodeficiency virus [HIV]), Toxoplasma species, and Borrelia species, have been suggested as possible triggers of the disease.
4. Other agents that may trigger the disease include penicillamine, statin drugs, quinidine, and phenylbutazone. (Important)

FEATURES: الفقره مهمه جدا جدا جدا

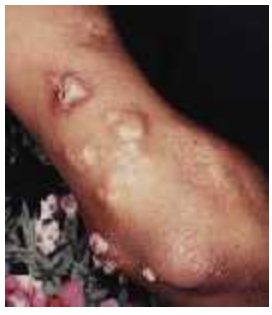
- The main symptoms include skin rash and symmetric proximal muscle weakness which may be accompanied by pain المريض لا يستطيع القيام من السرير او صعود الدرج



- violaceous macular rash in:
  a. Upper eyelid (particularly peri-orbital area, or cheek مهمه جدا)
  b. Described as heliotrope. with dilated blood vessels
- Gottron's papule مهمه – علامه مميزه



  a. erythematous rash & papule can be found in any joints especially in the dorsa on hands & fingers(cuticle might be roughened with loops of blood vessels on nail fold)
  b. N:B: at the joins itself not in between the joints like SLE
  c. What is the difference between Gottron papules and Gottron sign? Very Important
    i. Gottron's sign: a pink to reddish purple atrophic or scaling eruption often over the knuckles, knees and elbows.
    ii. Gottron's papules: are flat topped, polygonal violaceous papules over the knuckles (less common but highly characteristic).
- Shawl (or V-) sign:
  a. is a diffuse, flat, erythematous lesion over the back and shoulders or in a "V" over the posterior neck and back or neck and upper chest
  b. Which worsens with UV light exposure and may progress to poikiloderma (telangiectasia and atrophy, (dappled skin))
  c. Highly associated with lung disease
- Dysphagia occurs in 30% of patients, because of esophageal muscle involvement … and respiratory difficulties can occur. (diaphragm+ intercostals)
- Photosensitivity (IMPORTANT):
  a. Photosensitivity + telengactesia which could be a sign of malignancy (especially in GIT malignancy + and to some extent ovarian ca& prostate and breast)
  b. so it's important to screen malignancies in patients who are:
    i. older than 50 yrs
    ii. had a history of symptoms of malignancy
    iii. Proximal muscle weakness (triceps , quadriceps)



- Calcinosis of the skin or the muscle:
  a. In children, Dermatomyositis may leave severe restriction of limb movement because of muscle calcification. مهمه جدا – علامه مميزه
  b. firm, yellow or flesh-coloured nodules, often over bony prominences, they may become ulcerated

DIFFERENTIAL DIAGNOSIS:

1. Lupus erythematosus.
2. Mixed connective tissue disease.
3. Steroid myopathy. 4. Toxoplasmosis.

FORMS OF THE DISEASE:

1. Juvenile
2. Malignancy associated → need deep investigations in case of any suspicious signs
3. Primary
4. Dermatomyosis without myositis (only the skin)

PATHOLOGY: HISTOLOGICAL CHANGES SIMILAR TO SLE. THERE ARE:

- Free RBCs (from dilate blood vessels).
- Melanin
- Muscle fiber degeneration and internalization of sarcolemmal nuclei
- Thin atrophic epidermis with liquefaction in basal layer.

DIAGNOSIS: IMP

- Proximal muscle weakness (difficulty in combing hair, lifting heave objects, standing form a sitting position, climbing the stairs) with two of the three laboratory criteria.
- Raised circulating muscle enzymes:
    i. SGOT,
    ii. SGPT
    iii. CK (most specific) مهمه : يستخدم للتشخيص والمتابعه للعلاج
    iv. Aldolase
- Serology:
    a. Anti-Jo-1 (anti-histidyl-t-RNA synthase) in 30%. It is specific, and has a bad prognosis, because it is associated with pulmonary disease. very Important
    b. Anti-Mi-2 is highly specific for DM, but it lacks sensitivity because its
    c. Present only 25% of patients with DM, indicates good prognosis.
- Biopsy:
    a. Inflammatory cell infiltrations & necrosis of muscle cells
    b. biopsy is mainly taken from proximal muscle group especially extensors
- EMG

MANAGEMENT:

- Removal of malignancy if present improves muscle weakness.
- Topical steroids: if only coetaneous (Skin slowly improves)
- Systemic steroid: when the muscle is involved (doesn't improve the skin)
- Immunosuppressive agents may be of value (azathioprine, methotrexate…)

Follow up: for muscle by monitoring power & CK level.

*features common to all types of lupus erythematosus LE:

1. Lichenoid tissue reaction.2.epidermal hyperkeratosis.3.patchy thickening of the angular layer.

The presence and type of circulating auto antibodies is the major criterion for diagnosis.

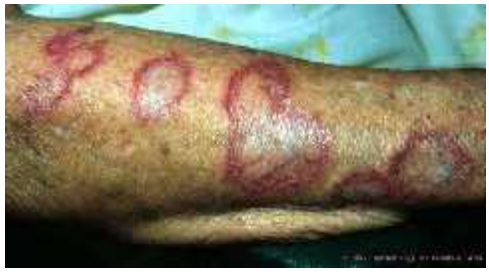
2. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

DEFINITION

- It is a genetically determined multi-system auto-immune disease characterized by diverse clinical features of unknown aetiology.
- The clinical manifestations include fever (90%), skin lesions (85%), arthritis, CNS, renal, cardiac, and pulmonary disease.
- Many of the clinical manifestations of SLE are caused by the effects of circulating immune complexes on various tissues or to the direct effects of antibodies to cell surface component

CLINICAL FEATURES:

- A systemic disease manifested on skin as macular rash affecting the face at T zone & spares the nasolabial folds, so called "butterfly area". Provoked by sunlight. مهمه جدا جدا
- In hands, it spares the joint area usually (between the joints)
- Hair loss:
  a. Patchy, diffuse hair loss is a recognized feature.
  b. But, permanent hair loss & scarring is unusual مهمه جدا,(usually seen in CDLE. See below)
  c. And the lesion is less florid
- SLE with photosensitivity, it will result in lichenification from sun exposure which may lead to skin lymphoma.
- Discoid rash: Erythematous patches or plaques with an adherent keratotic scale and follicular plugging, atrophic scarring hairless patches may occur in older lesions.
- Oral ulcers



DIAGNOSIS:

- Typical presentation (unwell, butterfly rash provoked by sun)
- To confirm Diagnosis: ANA (antinuclear antibody), anti double stranded DNA antibody.

MANAGEMENT:

- Potent steroid, to prevent scaring (but in the face when don't use super potent steroid because it may cause thinning of the epidermis, folliculitis &telangiectasias).
- Immunosuppressive drug (systemic steroid, cyclophsphamide, azathioprine, &chlorambucil)
- Sun avoidance and therapy with sunscreens, topical corticosteroids at night, and ant malarial agents is usually effective.
- Skin graft if it is in small area
- Maintenance with low dose steroid.

DRUGS ASSOCIATED WITH LUPUS ERYTHEMATOSUS

1.	**Chlorpromazine**	**2.**	**Hydralazine**
3.	**Methyldopa**	4.	**Penicillamin**
5.	**Anti- TNF**	6.	procinamide
7.	**Isonizide**	8.	Minocyclin
9.	**Quinidine**	10.	IFN-alpha, IFN-beta

3. CHRONIC DISCOID LUPUS ERYTHEMATOSUS (CDLE): VERY IMP!

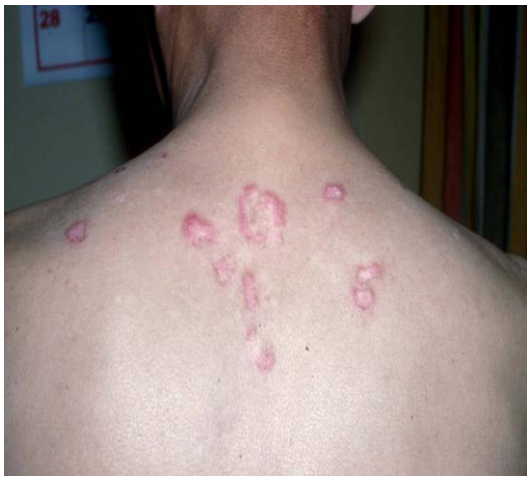
DEFINITION:

Chronic purely coetaneous (90% of cases) disorder characterized by red scaly plaque on light exposed areas (photosensitivity), which heal with scarring.

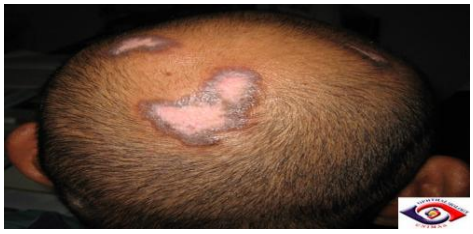
Serologic abnormalities are uncommon.

CLINCAL FEATURES:

- Chronic, raised, scarring, atrophy producing, photosensitive dermatosis.
- The disease is not common, but causes concern because the face is the most commonly affected site and because of permanent scarring that may be seen. (Usually multiple plaques).
- May occur in patients with systemic lupus erythematosus (SLE) and some patients (< 5%) with CDLE progress to SLE.
- Patients with DLE rarely fulfill 4 or more of the criteria used to classify SLE.



- The primary lesion
  a. An erythematous papule or plaque with slight to moderate scaling.
  b. As the lesion progresses, the scale may thicken and become adherent to underlying epidermis (carpet-tack sign), and run into hair follicle
  c. pigmentary changes may develop, with hypo pigmentation in the central or inactive area and hyper pigmentation at the active border.(annular plaque) مهمه جدا جدا
  d. Can occur anywhere; nasal bridge, scalp, inside the ear canal (very important site of involvement), checks, hands.
- ANA almost positive with systemic lupus BUT not always with discoid lupus
- Skin biopsy هي الاختبار الافضل لكشف هذا المرض – مهمه to confirm the Diagnosis
- In the scalp:
  a. it may cause scarring permanent alopecia so, we treat it aggressively by either:
    i. intralesional
    ii. systemic steroid



- Squamous cell carcinoma is a complication of old scar (over years)
- There is no systemic upset…In the winter months the problem become quiescent.

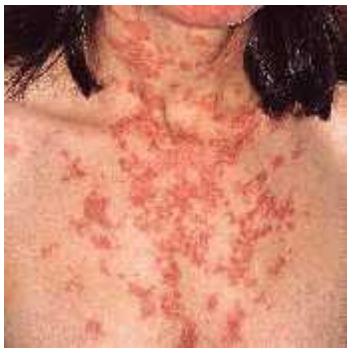
INVESTIGATION AND TREATMENT:

- Perform ANA to rule out SLE
- skin biopsy to confirm Diagnosis: best test
- Treatment:

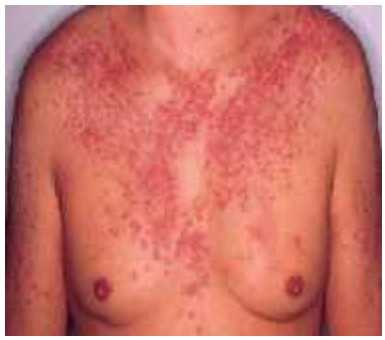
1. Protective clothing.
2. Moderate to strong topical steroid and intralesional steroid. → avoid the strong steroid if the lesions in the face , around the eye and the axilla to avoid atrophy مهمه جدا
3. Anti malarials like chloroquine and hydroxychloroquine(cause ocular toxicity)
4. Resistant cases: immunosuppressive (azathioprine, cyclosporine a, mycopheolate).
5. Oral gold and retinoid
6. Cosmetic camouflage(cover mark, derma blend)

4. SUB-ACUTE CUTANEOUS LUPUS (SCLE)

- it is coetaneous disease with some systemic involvement
- A strong association exists with anti-Ro (SS-A) auto antibodies
- it's a variant of LE in between SLE and discoid lupus in photosensitive patients with +ve Anti-Rho(60%) & Anti-LA(40%) but not ANA مهمه جدا



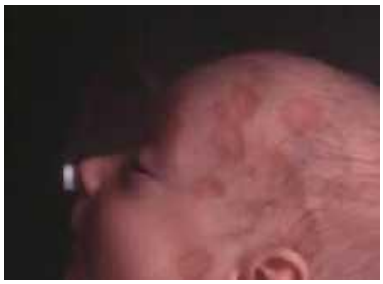
- Multiple red macule and plaques on exposed and covered skin persist throughout the year. Scaling and scarring are unusual.
- Upper part of trunk often involved with diffuse widespread lesions.
- Photosensitivity is prominent in about half of patients, its common in SCLE.
- Most have no other organ involvement except mild arthropathy.
- Differential diagnosis:
    a. Papulosquamous lesions may mimic psoriasis or lichen planus
    a. chilblains and erythema multiforume,
    b. light eruption
    c. Photosensitive drug eruption.



- Biopsy and immuoflurescence studies are helpful.
- Treated:
    a. Topical screens and systemic antimalarials.
    b. Systemic steroid may be needed.

5 NEONATAL LUPUS:

- Rare annular erythematous plaques with a slight scale characterize neonatal lupus erythematosus



- Appear predominately on the scalp, neck, or face (typically periorbital in distribution, but similar plaques may appear on the trunk or extremities.
- Usually for babies of Anti-Rho +ve mothers . مهمه جدا
- + ve Anti-Rho & Anti-La in 60% & 40% respectively.
- If patient has photosensitivity →sun block →
- You must refer patients with neonatal lupus to cardiologist (because of high risk to have complete heart block). مهمه جدا جدا
- Thrombocytopenia and hepatic disease may occur as frequently as cardiac disease.
- Risk: In women with anti-Ro antibodies only 1-2 % will have an infant with neonatal LE. The risk of a second child developing neonatal LE is 25%.

6. ANTIPHOSPHOLIPID ANTIBODY SYNDROME:

1. Associated with cerebrovascular accidents, MI, thrombotic episodes.
2. Patients have poor obstetric history with multiple miscarriages
3. patients have antiphospholipid antibody
4. Skin manifestations:
    a. Livedo pattern usually in the thighs.
    b. Ulcers, phlebitis and gangrene may be present.

7. LUPUS VULGARIS

(Also known as "Tuberculosis luposa") are painful coetaneous tuberculosis skin lesions with nodular appearance, most often on the face around nose, eyelids, lips, cheeks and ears

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8 SCELODERMA: (LOCALIZED – SYSTEMIC):

LOCALIZED SCLERODERMA

Localized scleroderma usually affects only the skin on the hands and face. Its course is very slow, and it rarely, if ever, spreads throughout the body (becomes systemic) or causes serious complications.

There are two main forms of localized scleroderma: Morphea and linear scleroderma.

MORPHEA

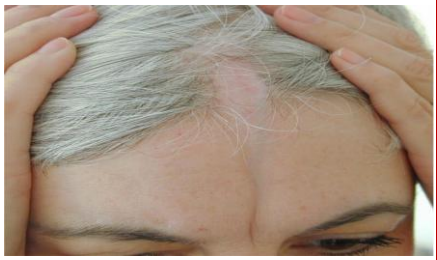
Purely coetaneous disorder seen most commonly in children or young adults and characterized by the spontaneous appearance of a scar like band or plaque on any body site.

Morphea is a rare condition also known as localized scleroderma

FEATURES:

- primary lesion:
    a. It is a disease characterized by patches of red or purple or white hot, firm skin.
    b. Appear mainly on the torso, arms, trunk, and legs with well marked red or violet margins.
    c. Calcification may develop within the lesion

- Unlike systemic sclerosis, Morphea lacks features such as Sclerodactyly, Reynaud phenomenon, nail fold capillary changes, telangiectasias, or progressive internal organ involvement.
- Morphea can present with extra-cutaneous manifestations, including:
  a. fever, lymphadenopathy, arthralgias, and central nervous system involvement
  b. Laboratory abnormalities, including eosinophilia, polyclonal hypergammaglobulinemia, and positive antinuclear antibodies.



- En coup de sabre ضربه السيف : بالفغانس (بالفرنسي):
  a. Is a type of linear scleroderma that presents on the frontal or frontoparietal scalp due to inflammatory disease (Morphea).
  b. depressed atrophic linear plaque cause alopecia and may cause growth irregularities of the skull in children مهمه جدا
- Histological features:
  a. In Morphea, there's loss of all skin appendages which is the major feature in histology علامه مميزه جدا وتفرقه عن المرض التالي.
  b. Collagen boundless are larger
  c. epidermis tend to be thin and atrophic
  d. Normal difference between the papillary and reticular dermis is lost.
- Diagnosed by clinical appearance and Biopsy.
- Management: no specific therapy:
  a. Potent corticosteroids (topical or intralesional)→ if active.
  b. Phototherapy. → if extensive (we could use systemic steroid also)
  c. Photo chemotherapy.
  d. Surgery
- N:B: Morphea + internal organ involvement = systemic sclerosis , it can affect the bone and muscle If it is so severe

SYSTEMIC SCLERODERMA:

- Progress accumulation of collagen, fibrosis, loss of mobility of the skin and other organs (respiratory and GI tract)
- Transforming growth factor beta 1 is thought to be involved in the pathogenesis.
- Females are more commonly affected.

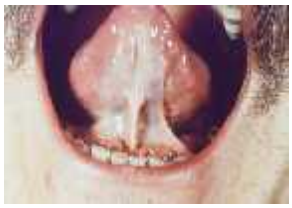
What is Reynaud's phenomenon?
It is digital ischemia that occurs on exposure to cold and / or as a result of Emotional stress.
Causes:
1- Rheumatic disorders (SS 85%, SLE 35%, DM 30%, RA, PAN).
2- Diseases with abnormal blood proteins (cryoprotein, Macroglobulins).
3- Drugs (β-adrenergic blockers, nicotine, and cyclosporine).
4- Arterial disease (atherosclerosis obliterans).
5- Carpel tunnel syndrome

FEATURES:

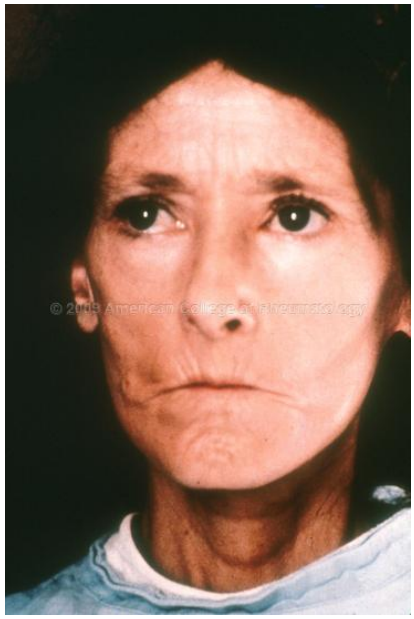
- Reynaud's phenomenon with triphasic colour changes, i.e. pallor, cyanosis, rubor, precedes sclerosis by months and years.
- In hands and feet:

- Initially swollen and tight shiny atrophic skin, which is bound firmly to the subcutaneous tissue
- Resorption of the distal phalanges and subcutaneous calcification may occur.
- Bony resorption and ulceration results in loss of distal phalanges.

- In mouth:
  - Sclerosis of sublingual ligament, uncommonly, painful indurations of gums, tongue
  - In X-Ray there is wide periodontal membrane.



- In face:
  - Line free forehead (**mask like**) patient looks younger than they are.
  - Small beaked nose
  - small mouth (microstomia)
  - Radial furrowing around the lips and telangiectasias in severe case.



- Sclerodactyly is a component of the CREST variant of scleroderma CREST is an acronym that stands for
  - C= Calcinosis,
  - R= Reynaud's phenomenon
  - E= esophageal dysmotility
  - S= Sclerodactyly
  - T= telangiectasias

DIAGNOSIS AND TREATMENT

- Pathology :
  - fat become closer to the epidermis
  - the pathological process involves fibrosis and vasculature, and Skin appendages is not involved مهمه جد (unlike Morphea which affect skin appendages also)
- Laboratory findings:
  - antiscleroderm70,
  - Anticentromere antibody: High incidence of anti-centromeric antibodies. It is specific. Very Important.
  - ANA
- Diagnosis :
  - Clinically made on facial appearance
  - Confirmatory tests: auto antibody screen, hand and jaw XR, barium swallow, and respiratory function test.

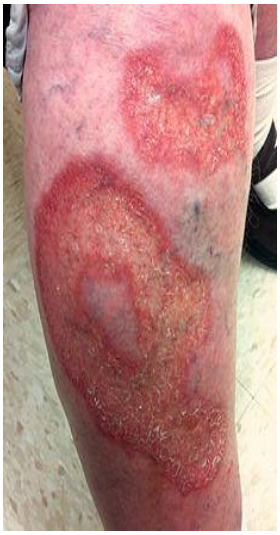
- Treatment
  - As the doctor said: the treatment is symptomatic IMP!!
  - Drugs used(as written in the book):
    - Immunosuppressives -in addition to steroids- (methotrexate, cyclophosphomide, cyclosporine a, photopheresis UVA).
    - Antifibrotics: (penicillamine, colchicicine, gamma interferon)
    - Vasodilators: Ca++ channel blockers مهمه(nifedipine ,prstacyclins).
    - Systemic steroids: in sever renal or respiratory involvement. (Renal involvement is the most serious complication).
    - Management of Reynaud's disease: Prostacyclins, nifepidine, ketanserin.

9 MIXED CONNECTIVE TISSUE DISEASES:

- Some features of both LE and systemic sclerosis. (Symptomatic treatment).
- The auto antibody is U1-RNP.

10 NECROBIOSIS LIPOIDICA (ASSOCIATED WITH DM).

- Shiny atrophic red to yellowish plaque with telangiectasias mainly over the shin.



- Could be ulcerative.
- Check for diabetes because it strongly associate with it.(t may be called necrobiosis lipoidica diabeticorum (NLD))
- treatment :
  a) topical , injection (Rx for the underlying cause)
  b) For ulcerated lesion
     i) systemic +topical
     ii) cyclosporine مهمه
     iii) grafting(surgery)

11 PYODERMA GANGRENOSUM:

- Start as pustule then evolve to Ulcerative, necrotic ulcer become bigger with debridement. So you should not manage it with surgery in ER.
- Associated with IBD, hematologic malignancy (sweat gangrensum come with hematologic malignancy).
- Pathergy:
  a. Pathergy is a coetaneous phenomenon seen with both Behcet's disease and

pyoderma gangrenosum

b. In this condition a minor trauma such as a bump or bruise leads to the development of skin lesions or Pustules in the sites of trauma.
c. ulcers that may be resistant to healing
d. Either a subnormal response to an allergen or an unusually intense one in which the individual becomes sensitive not only to the specific substance but to others, so be careful and don't send the patient to surgery for excision which may extent the lesion.

- It was used for diagnosis in the past(in other word: Pathergy: when you prick the skin with sterile needle it will develop a pustule which will develop into ulcer لا تستخدم هذه الطريقه في الوقت الحالي)
- Forms :
  a. Primary : De novo غير معروف السبب
  b. Secondary : to IBS , leukemia …
- Treatment:
  a. High dose of systemic steroid. → if primary
  b. Treat underlying disease like IBD…
  c. Surgery is CONTRAIDICATED

12 LICHEN SCLEROSIS ET ATROPHICUS:

- it's atrophic (sclerosing or fibrosing) condition commonly of the vulva and anus frequently associated with Morphea
- It's a white atrophic glazed area of skin mainly affecting genitalia.
- In males:
  - It is called Balanitis xerotica obliterans
  - It could affect penis (rare) especially non circumcised men.
  - The disease may take the form of whitish thickening of the foreskin, which cannot be retracted easily.
- also it affects post menopausal women but it is more young women (commonest)
- They usually complaining of difficult urination(genital discomfort and bleeding)
- There is shrinkage of the genital tissue and increase melanin in the affected sites.
- Some lesions are asymptomatic; others may cause ulcer, pain or Pruritus.
- Extra genital lesions commonly around the neck and upper back.
- Incidence of about 3% malignant changes.
- Diagnosis
  - Clinically.
  - Biopsy may be required(loss of all appendages, epidermal atrophy,

homogenization of the collagen)

- Treatment: مهمه جدا : العلاج يكون ستيرويد ذو قوه عاليه جدا – مهمه
  - Unsatisfactory!
  - in male remove foreskin if it's affected
  - Supra potent steroid (not estrogen as the book said) usually not given for genital disease because they cause thinning & stria BUT in this case we have to give them to avoid risk of urethral constriction.

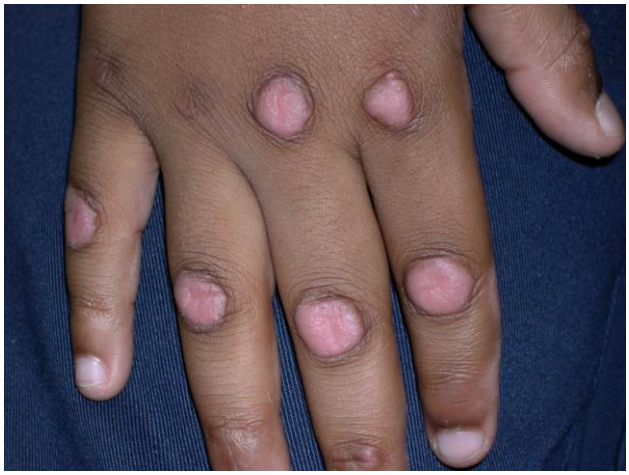
13 SWEET'S SYNDROME (SS)

Or acute febrile neutrophilic dermatosis is a skin disease characterized by the sudden onset of fever, leukocytosis, and tender, erythematous, well-demarcated papules and plaques which show dense infiltrates by neutrophil granulocytes on histological examination

➔ It associated with hematological disease

14- KNUCKLE PADS

Thickness of the skin over the hand joints



➔ It is familial
➔ The cause is unknown and no treatment for it