Lecture (3)
Cutaneous Manifestations Of Systemic Diseases

Objectives: not given.

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Color index: slides, doctor notes, extra explanation.

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Introduction

Skin is the gate of the body, some systemic diseases or malignancies can have skin manifestations.

In this lecture we are going to study specific diseases and how they present in the skin, the lecture contents will be classified into:

1- Connective tissue diseases.
2- Endocrinological diseases.
3- GIT and metabolic disease.
4- Neurocutaneous diseases and Behcet's syndrome.
5- Causes of pruritus without skin diseases, nail changes, and when to do HIV testing for skin diseases.

Connective Tissue Diseases

There are three main connective tissue diseases:

A. Systemic Lupus Erythematosus (SLE).
B. Dermatomyositis.
C. Scleroderma.

Systemic Lupus Erythematosus

SLE is an autoimmune multisystem inflammatory disorder, there is genetic, environmental and hormonal factor involvement.

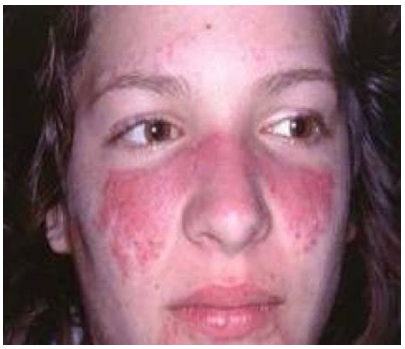
SLE has positive ANA and Anti-dsDNA tests.

Types of SLE include:

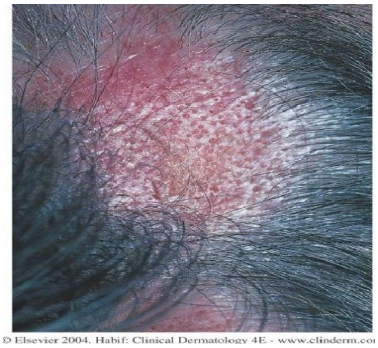
A. Spontaneous SLE.
B. Discoid Lupus.
C. Subacute Cutaneous Lupus.
D. Neonatal Lupus.
E. Drug-induced Lupus.

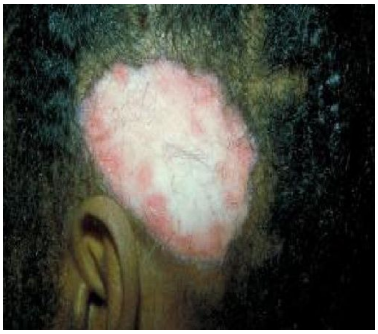
Skin characteristics of SLE are:

A. Facial photosensitivity.
B. Butterfly erythema(malar rash).
C. Oral and nasopharyngeal ulcers.
D. Alopecia.
E. Raynaud's phenomenon(found in 20% of the cases).

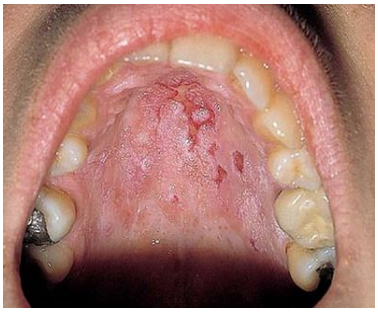


Malar rash





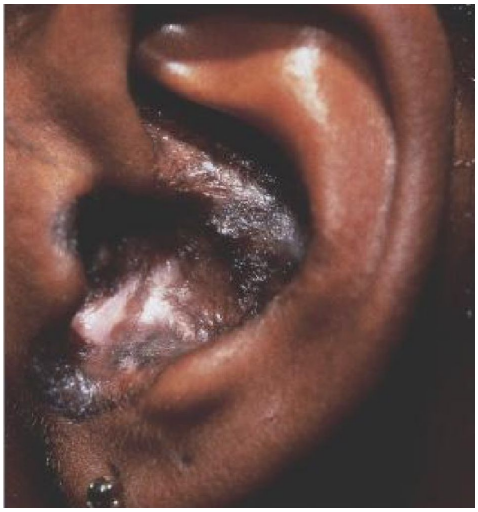
Alopecia (when there is involvement of the skull, hair will disappear forever)



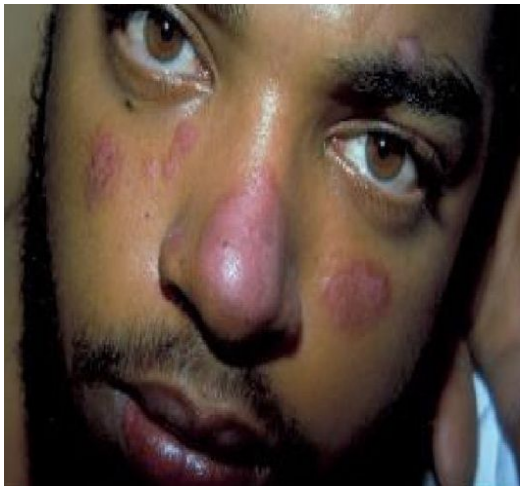
Oral ulcers in SLE

B. Discoid lupus:

Usually there is discoid lesions that are present in the skull, round scarring in light exposed areas and no systemic involvement.
Description of lesions in discoid lupus is very important.

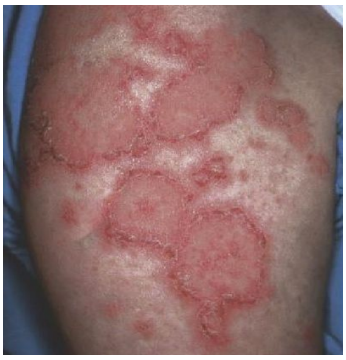


Follicular lesion that is characteristic of discoid lupus

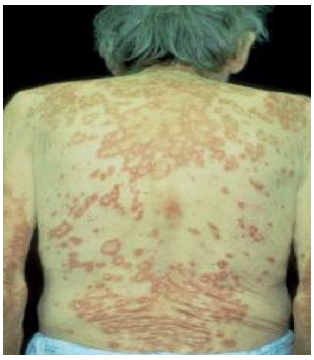


C. Subacute Cutaneous Lupus:

Has a papulosquamous or annular presentation, Associated with photosensitivity, does not cause scarring and usually ANA-negative but Anti Ro Positive.

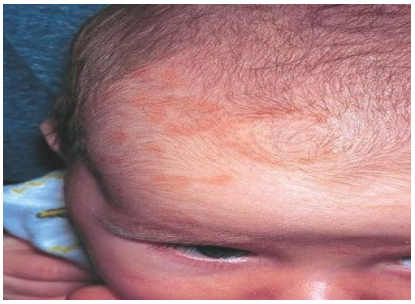


Subacute Cutaneous Lupus



D. Neonatal Lupus:

It appears in the first month when there is an active disease during delivery, lesions are annular or papulosquamous with a photodistribution, lesions commonly appear in the skull(neonatal lupus is the third differential in skull lesions appearing in an infant), the disease is anti Ro positive and is associated with congenital heart block (complete and permanent) the patient usually needs a pacemaker.



Involvement of the skull in Neonatal Lupus

E. Drug-induced Lupus:

Procainamide and Hydralazine are the commonest causes for development of this condition, drug-induced lupus is usually anti-histone positive.

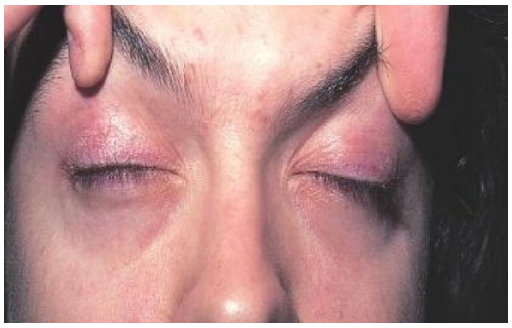
Dermatomyositis

Dermatomyositis is an idiopathic inflammatory myopathy, there is a genetic predisposition and an environmental trigger leading to humoral immune activation resulting in chronic inflammation.

Patients present with a characteristic skin rash and proximal muscle weakness(the patient will not say there is pain, instead the patient will say i feel tired).

Skin features in dermatomyositis:

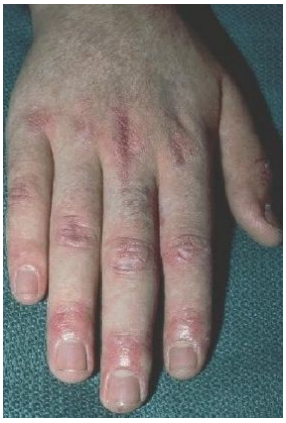
A. Heliotrope: Violaceous color over the upper eyelids(reddish discoloration usually in the upper eyelid, sometimes it will be edematous).
B. Gottron's papules: Flat- topped violaceous papules over knuckles of hands(it involves nails and joints but not the fingers).
C. Calcifications especially in kids.

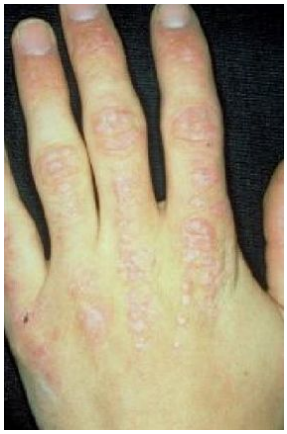


Heliotrope Rash

There is bilateral proximal muscle weakness with high CPK, positive EMG and muscle biopsy.

In adults especially over 50 years of age it is associated with internal malignancy. (A female above 50 newly diagnosed with dermatomyositis, you have to rule out ovarian cancer first, then other types of cancer).





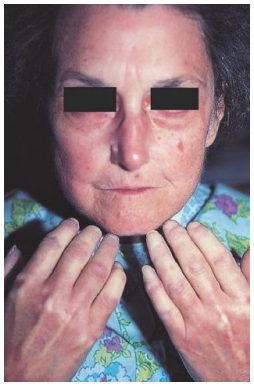
Gottron's papules

Scleroderma

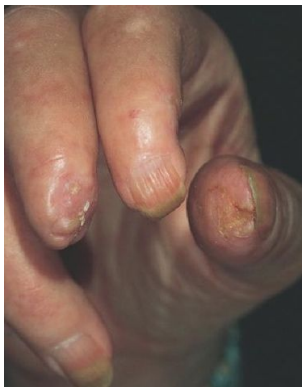
Scleroderma is a chronic connective tissue disorder with widespread fibrosis, it could be diffuse or limited.

Features of Scleroderma:

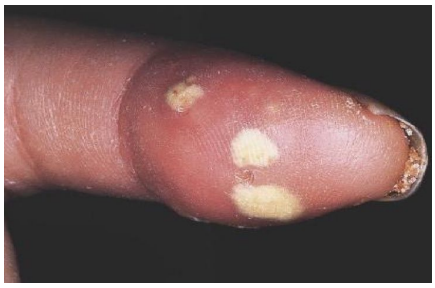
A. Tight and thickened skin.
B. Loss of forehead lines, beaked nose, small mouth, radial furrowing around the mouth.
C. CREST is a milder type of scleroderma, there is Calcification, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasia and positive anti-centromere with less systemic involvement.
D. In diffuse type there is more systemic involvement(Lung, GI, Kidneys) and positive anti scl-70.



Tight and thickened skin
Small mouth
Loss of forehead lines



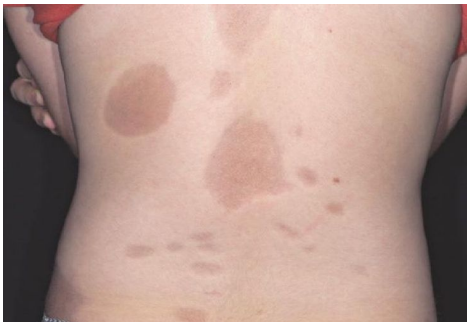
Sclerodactyly



Calcification
(usually at the tips of the fingers and painful even at rest).

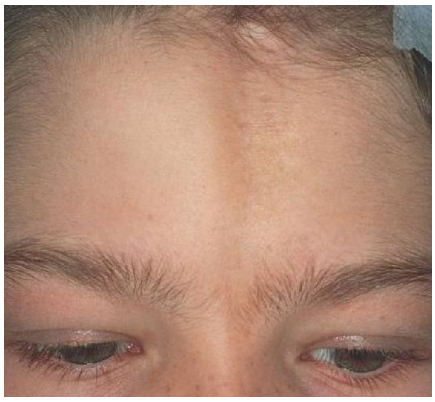
Other types of scleroderma include:

Morphea: A localized scleroderma without systemic involvement, there is a firm,white patch of skin surrounded by violaceous ring.



Morphea: usually present in the upper thigh and trunk

En coup de sabre: Linear scleroderma on the scalp and face which may give scarring alopecia and it may affect muscles or even bones.



En coup de sabre

Antibody Testing in connective tissue diseases (Important)

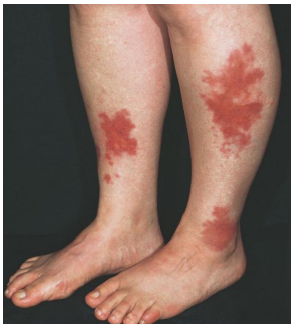
Antibody	Clinical Significance
ANA	Screening for SLE and other CTD
Anti-Centromere	Marker for CREST
Anti-Histone	Marker for Drug-induced Lupus
Anti-Smith	Specific for SLE
Anti-RNP	For Mixed CTD
Anto-Ro	Neonatal lupus, SCLE
Scl-70 Antibody	For Scleroderma
Anti dsDNA	For SLE

Endocrine Diseases

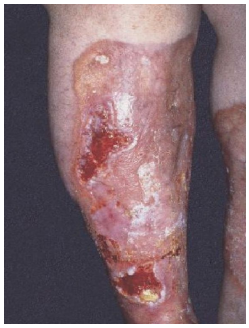
A. Diabetes Mellitus.
B. Hyperthyroidism.
C. Hypothyroidism.
D. Addison's Disease.
E. Cushing's Syndrome.

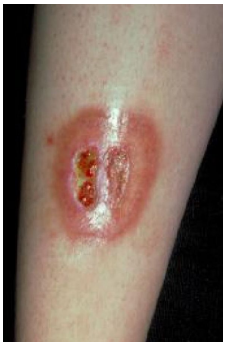
Diabetes Mellitus

Necrobiosis Lipoidica diabeticorum (NLD): Asymptomatic shiny atrophic red or yellowish plaques with telangiectasia over their surface + ulceration, usually seen on the shins. The condition may predate frank development of diabetes by several years, and it may develop at any stage of diabetes weather controlled or not, the severity of NLD is not directly related to the severity of diabetes.
NLD increases the risk of fungal and bacterial infections.
The risk of NLD development is low, but if NLD is present there is a 90% chance that the patient is diabetic.
Treatment for this condition is topical steroids, immunomodulators, phototherapy and laser if there is no ulcer, once ulcer is present, it's treated as a wound.



NLD without ulceration





NLD with ulceration

Hyperthyroidism

Skin features in hyperthyroidism:

A. Smooth warm moist (due to increase sweating) skin.
B. Pretibial myxedema (asymptomatic red plaques over shins).
C. Thin & fine hair.
D. Onycholysis.
E. Clubbing.

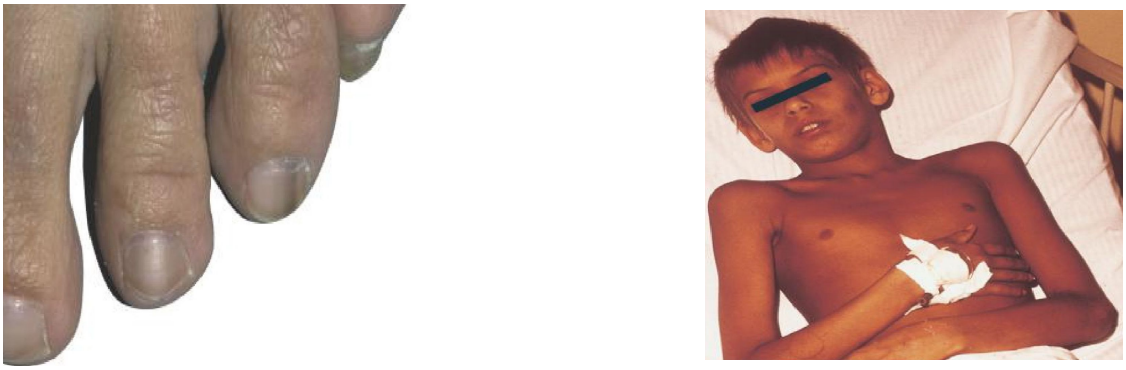
Hypothyroidism

Skin features in hypothyroidism:

A. Dry cold skin.
B. Edematous skin (myxedema).
C. Hair loss of lateral third of eyebrows.
D. Brittle hair or nails.

Addison's Disease

Skin manifestation in Addison's disease are hyperpigmentation at sun exposed skin, sites of trauma, axillae, palmar creases, old scars, nevi and mucous membranes.

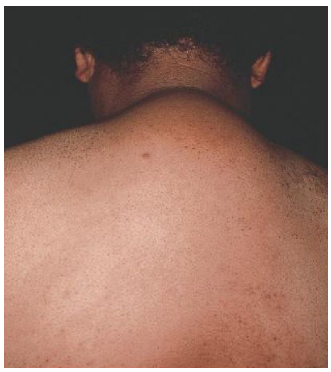


Hyperpigmentation in Addison's diseas

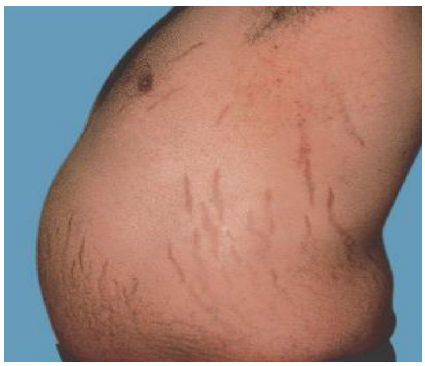
Cushing's Syndrome

Skin features in Cushing's Syndrome:

A. Rounded face with fullness of cheeks (Moon face).
B. Buffalo hump (fat deposition over upper back).
C. Central obesity with thin arms & legs & "lemon with sticks".
D. Atrophy of skin.
E. Striae.
F. Purpura, Hirsutism and Acne.



Buffalo hump



abdominal striae

GIT Diseases

A. Chronic Liver Disease.
B. Acrodermatitis enteropathica.
C. Peutz-Jeghers Syndrome.
D. Hereditary haemorrhagic Telangiectasia.
E. Pyoderma Gangrenosum.
F. Hyperlipidemia.

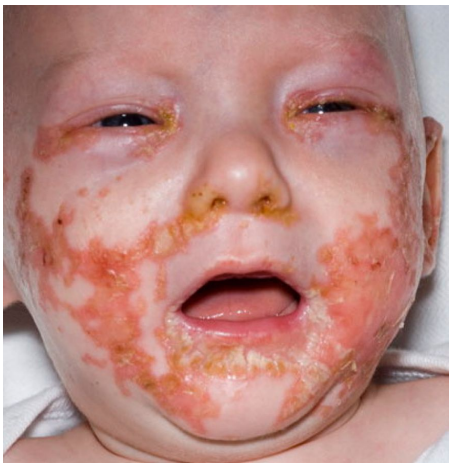
Chronic Liver Disease

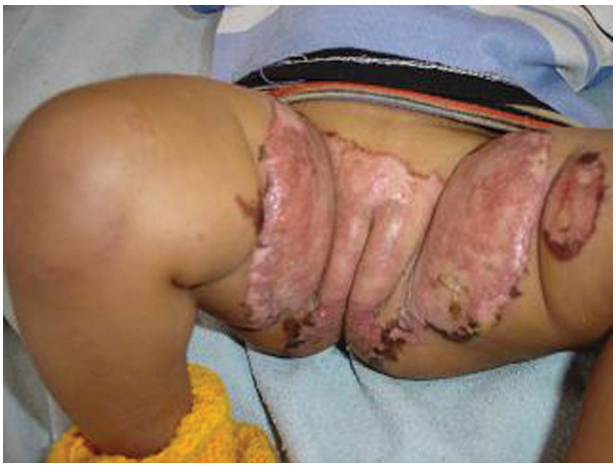
Skin features seen in chronic liver disease:

A. Jaundice.
B. Spider Telangiectasia, Collateral veins.
C. Acne, Purpura, Striae, Palmar erythema.
D. Gynecomastia.
E. Dupuytren's contracture, white nails.

Acrodermatitis enteropathica

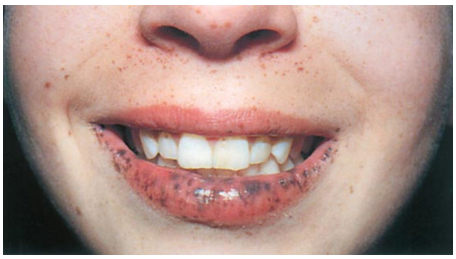
This condition occurs when an infant lives beyond one year with no source of feeding other than breastfeeding, it is a zinc deficiency disease, it present as erythematous erosive rash around orifices (mouth, anus, ears) and around hands & feet as well. There is alopecia and nail dystrophy, and it is associated with diarrhea and abdominal pain. In this disease look for zinc levels and alkaline phosphatase because it's zinc dependant.

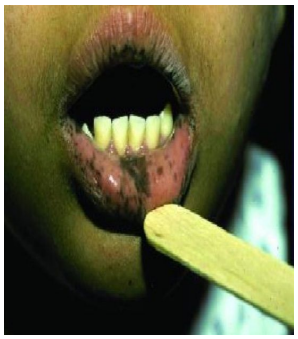




Peutz-Jeghers Syndrome

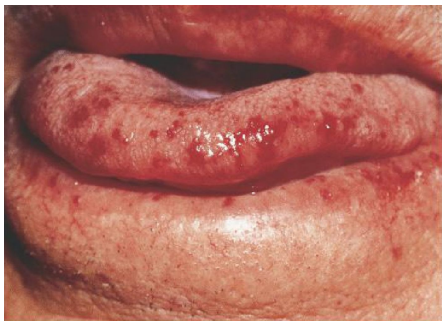
This syndrome present in the skin as small brown macules on the lips and buccal mucosa. It may present as small intestinal polyps, rarely these polyps can be premalignant.





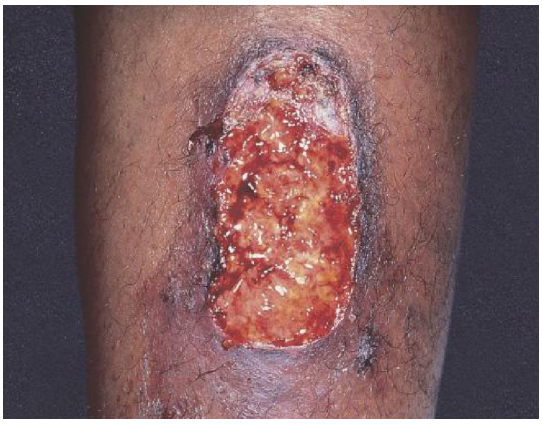
Hereditary haemorrhagic Telangiectasia

There is telangiectasia (dilated capillaries) over lip, tongue, nose, fingers and toes. Patients have a history of recurrent epistaxis and it is associated with recurrent upper GI Bleeding.



Pyoderma Gangrenosum

This is an acute painful leg ulceration that goes beyond the skin and is surrounded by violaceous border, it is commonly associated with inflammatory bowel disease, sometimes with rheumatoid arthritis and leukemia.



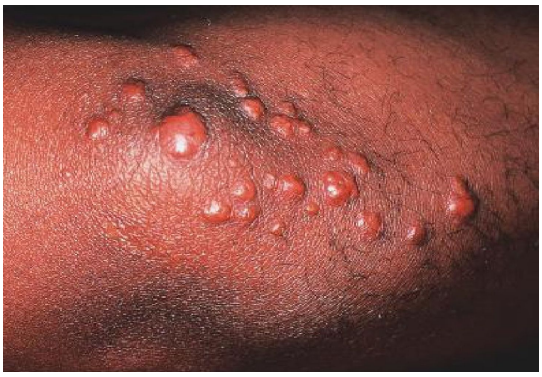
Violaceus ulcer going beyond the skin (Characteristic for pyoderma gangrenosum)

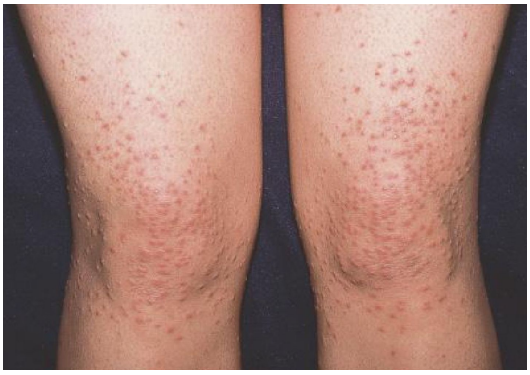
Hyperlipidemia

Present with different types of xanthomas, yellow color is characteristic.
Xanthoma may be an indicator to a primary hyperlipidemic status due to genetic abnormality, or a secondary hyperlipidemic status due to hepatic, renal, pancreatic or endocrine disease. Sometimes it may present in normo-lipidemic status.

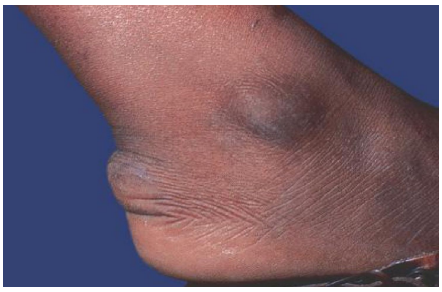
Types of xanthoma: (won't be asked about their systemic features)

A. Eruptive: small papules appear in crops over buttocks & extensors.
B. Tendinous: nodules over tendons e.g. extensor tendons of hands & feet and Achilles tendon.
C. Palmar crease xanthoma: present on the palms.
D. Tuberous(Fungating): papules and nodules over knees and elbows.
E. Xanthelasma: Bilateral symmetrical over both eyelids.

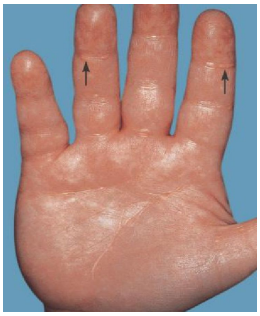




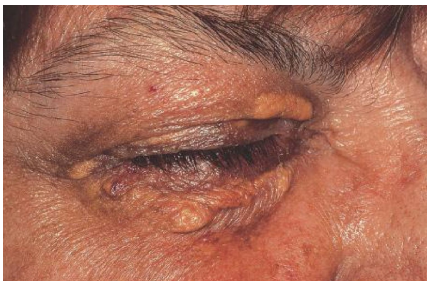
Tuberous xanthoma



Tendinous xanthoma



Palmar crease xanthoma



Xanthelasma

Neurocutaneous diseases

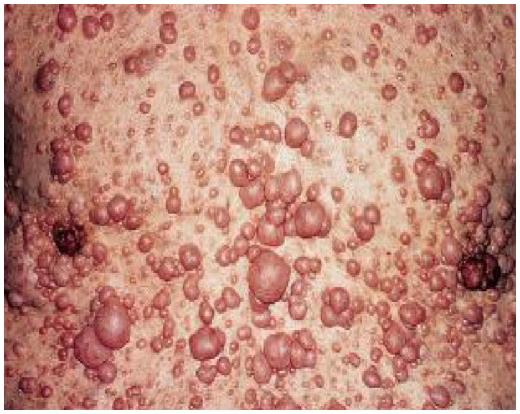
A. Neurofibromatosis.
B. Tuberous Sclerosis.

Neurofibromatosis

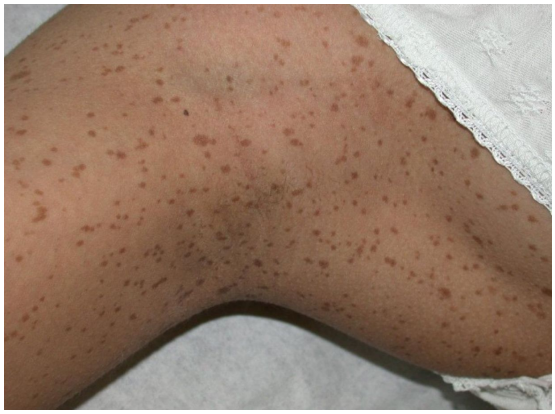
Autosomal dominant condition associated with ophthalmological and neurological complications such as tumors(meningiomas,gliomas), seizures and mental retardation.

Patient present with:

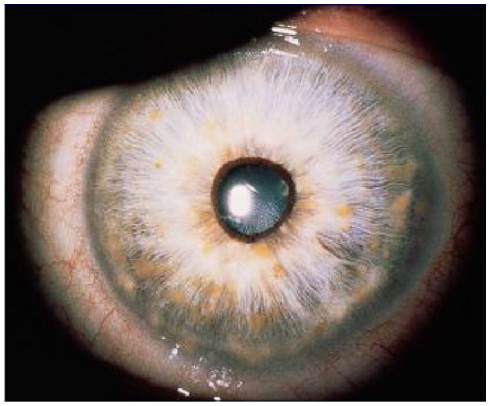
A. Café-au-lait macules (light brown).
B. Neurofibromas (soft pink or skin-colored papules and nodules).
C. Axillary or inguinal freckling.
D. Optic glioma.
E. Lisch nodules (iris hamartoma, seen by slit-lamp examination).



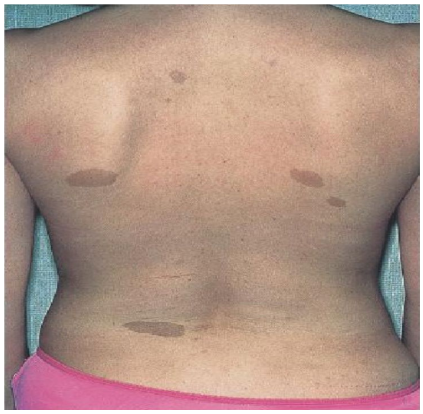
Neurofibromas



Axillary freckling



Lisch nodules



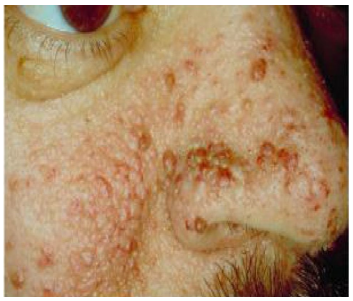
Café-au-lait macules

Tuberous Sclerosis(Epiloia)

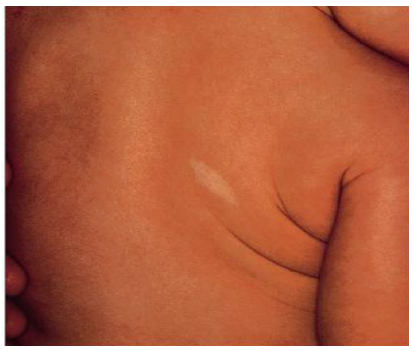
An autosomal dominant condition, patients present with cognitive impairment and retardation, epilepsy and skin lesions.
Epiloia stands for: Epi=epilepsy, Loi=low intelligence, A=adenoma sebaceum.
Retinal hamartomas, renal angiomyolipomas, rhabdomyomas of the heart may also present.

Skin features in tuberous sclerosis:

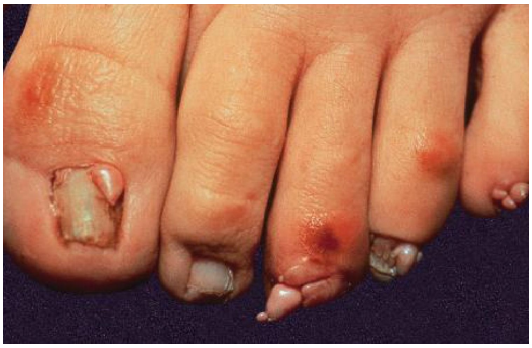
A. Adenoma sebaceum(angiofibroma): red rubbery papules around the nose, on the chin and over the cheekbones.
B. Ash-leaf hypopigmentation: oval area of hypopigmentation, this is the earliest sign of tuberous sclerosis, it always involves the trunk.
C. Periungual fibroma: multiple papules and nodules around the nails.
D. Shagreen patch: skin colored plaque on the trunk with “orange-peel” surface.



Adenoma sebaceum



Ash-leaf hypopigmentation



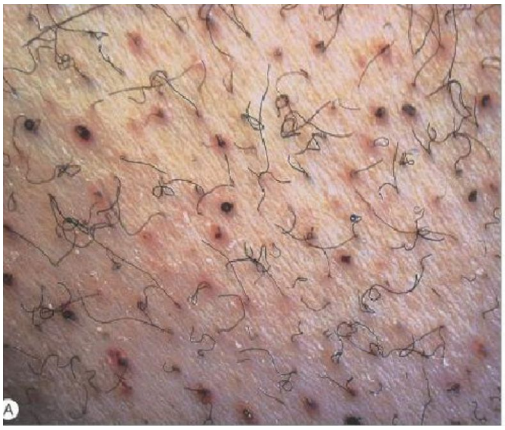
Periungual fibroma

Behcet’s syndrome

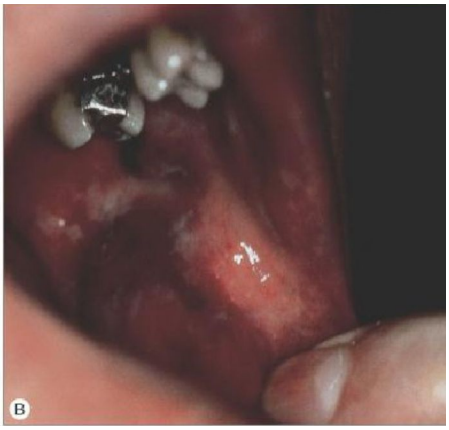
This is an autoimmune multisystem vasculitic disease with an unknown cause. It is manifested in the skin as cutaneous pustules and sterile painful oral (most common) and genital (mainly scrotal) ulcerations, there is also arthritis (knees and ankles are common sites), eye involvement with iritis, CNS involvement as meningoencephalitis and intracranial HTN.

Scurvy

This is a vitamin C deficiency disorder characterized by bleeding gums, easy bruising, purpura(perifollicular around the hair follicles) and it can cause loss of teeth.
Diagnosis is made when there is low Ascorbic Acid (Vit.C) in Leukocyte.



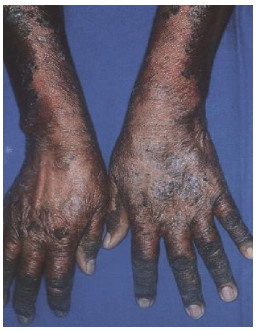
Perifollicular purpura



Gum bleeding and tooth loss

Pellagra

A nicotinic acid deficiency disease. (4 D's)
1- Dermatitis (photodermatitis).
2- Dementia.
3- Diarrhea.
4- Death.



Pruritis

In pruritis you have check TSH,CBC,Iron,Malignancy,CXR,Hepatic function and Renal function (Creatinine and Uric Acid).

Causes of generalized pruritus <u>without</u> skin lesions:

A. Skin dryness (the most common).
B. Endocrine: DM, hypo & hyperthyroidism.
C. Haematological: Polycythemia rubra vera, iron deficiency anemia.
D. Malignancy: e.g. Lymphoma.
E. Hepatic: Primary biliary cirrhosis.
F. Renal: Chronic renal failure (The commonest manifestation of CRF is pruritis).
G. Neurological: e.g. Tabes dorsalis.
H. Others: e.g. Psychogenic, drugs, idiopathic.

Table 7.2 Possible laboratory studies in the evaluation of pruritus. These laboratory tests should be performed according to the patient's history, in particular in cases of generalized pruritus of unknown etiology.

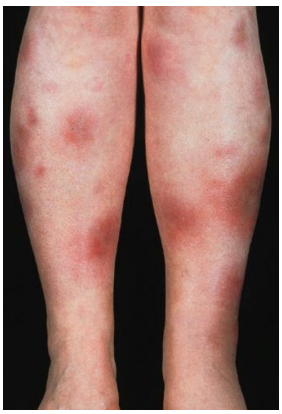
POSSIBLE LABORATORY STUDIES IN THE EVALUATION OF PRURITUS
• Erythrocyte sedimentation rate (ESR) • Complete blood cell count (CBC) with differential and platelet count • Blood urea nitrogen, creatinine • Liver transaminases, alkaline phosphatase, bilirubin • Fasting glucose • Thyroid function tests (thyroid stimulating hormone (TSH) and thyroxine levels) • Parathyroid function (calcium and phosphate levels) • Serum iron, ferritin • Chest radiograph • Stool for ova, parasites and occult blood
• Viral hepatitis screen • Serum protein electrophoresis • Serum immunofixation • Antinuclear antibodies (ANA), antimitochondrial antibodies
• Human immunodeficiency virus (HIV) • Allergy panel: total IgE, histamine, serotonin (plasma) • Prick tests of major atopy antigens and additives, patch tests • Urine for sediment, 5-hydroxyindolacetic acid (5-HIAA) and mast cell metabolites • Additional radiographic studies, e.g. abdominal CT scan • Anti-tissue transglutaminase antibody • Anti-smooth muscle antibody

Erythema Nodosum

These are multiple bilateral tender erythematous subcutaneous nodules over the shins, they are more common in female and obese people. It is a sign, not a disease.

Causes include:

A. Infectious: Streptococcus, tuberculosis, hepatitis, chlamydia.
B. Sarcoidosis.
C. Drugs: Oral contraceptive pills, sulfonamides.
D. Lymphoma & leukemia.
E. Pregnancy.
F. Behcet's disease.
G. Idiopathic.

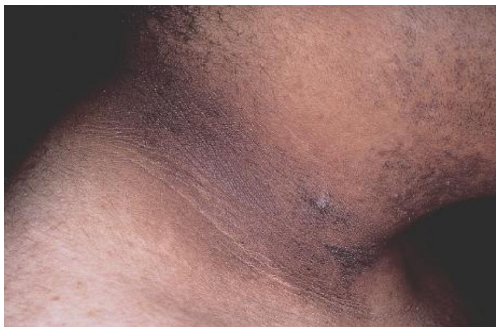


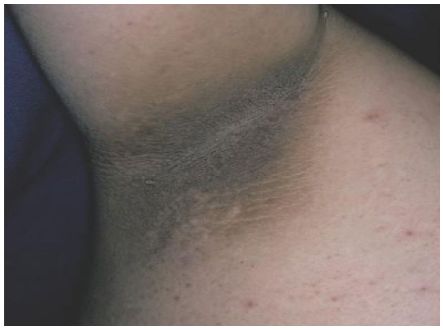
Acanthosis Nigricans

Brown hyperpigmentation & increased thickening of skin with velvety texture at neck, axillae and groin, when this condition is present check TSH. The condition could indicate stomach cancer.

Causes:

A. Obesity.
B. Endocrinopathy: Diabetes, thyroid disease, Insulin resistance.
C. Internal malignancy: The most common is adenocarcinoma of stomach.
D. Drugs: Nicotinic acid.
E. Familial.
F. Idiopathic.



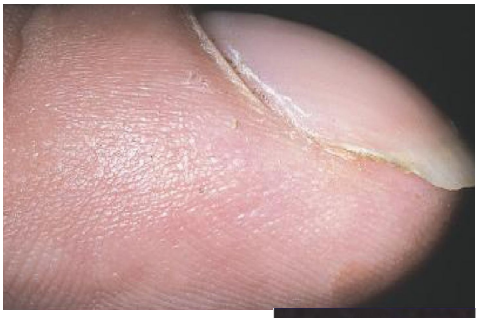


Nail Changes

Clubbing: Exaggeration of the normal nail curve associated with loss of the normal angle between nail and the posterior nail fold.

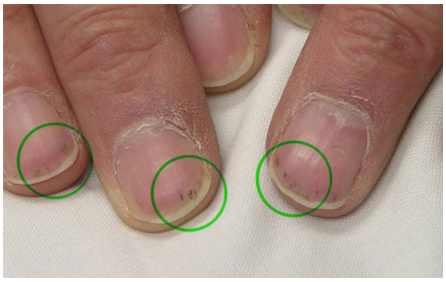
Causes:

A. Thoracic: Lung abscess, Lung cancer.
B. CVS: Congenital cyanotic heart disease.
C. GIT: GI carcinoma, Inflammatory bowel disease.
D. Endocrine: Thyroid disease.
E. Idiopathic.

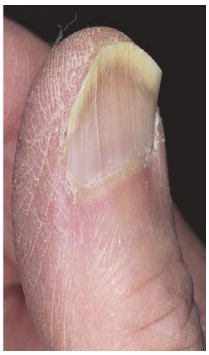


Splinter Hemorrhage:
Causes:

A. Bacterial endocarditis.
B. Septic emboli or distal thrombosis (starts with splinter hemorrhage).
C. CTD.
D. Trauma.
E. Idiopathic.



Koilonychia: Spoon-shaped appearance.



Causes:

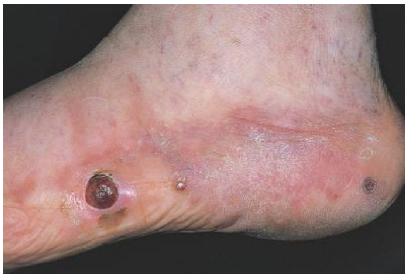
A. Iron deficiency anemia.
B. Thyroid disease.
C. Physiological: Early childhood.
D. Dermatoses: Lichen planus, Alopecia areata.

When to do HIV testing for skin diseases

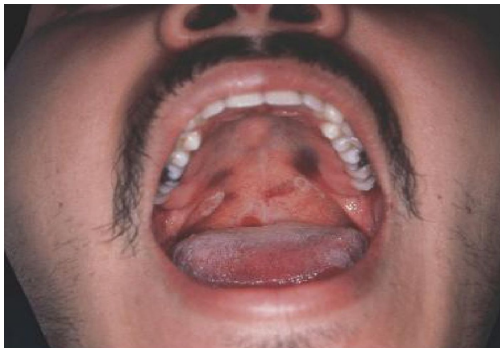
There are some skin conditions or manifestations that are associated with HIV, if these are present then HIV testing is necessary.

These conditions include:

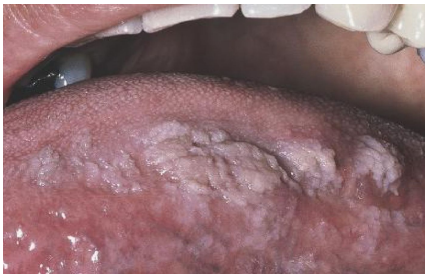
A. Oral hairy leukoplakia: corrugated white plaques on the lateral aspect of the tongue.
B. Kaposi's Sarcoma: a condition caused by HHV-8, characterized by blue macules, patches or nodules. The condition is in essence a vascular tumor and It is associated with low CD4 count, may resolve or diminish if CD4 count rises. Types of Kaposi sarcoma include the classic type (in elderly),Immunosuppression associated, HIV associated and the African endemic type. Sometimes there is metastasis to Lymph nodes , and Viscera.
C. Multiple mollsucum contagiosum in adult (on face).
D. Seborrheic dermatitis (extensive & refractory to therapy).
E. Severe extensive recalcitrant aphthous ulceration
F. Any STD.

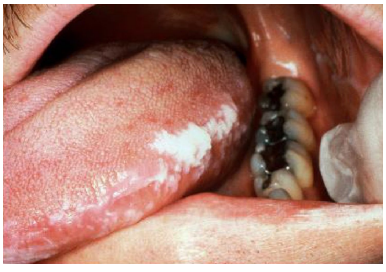


Kaposi's sarcoma



Mega aphthous ulcer

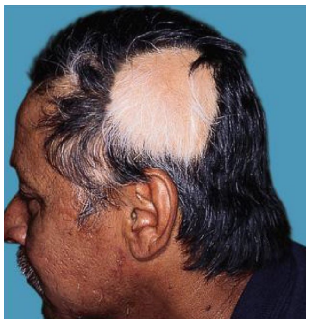




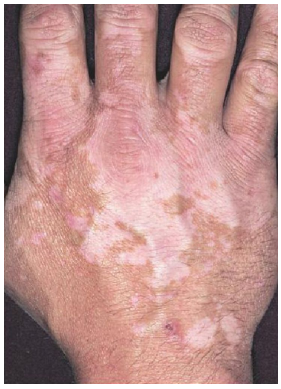
Association between systemic diseases and some skin diseases

There are some skin diseases that are associated with systemic diseases. Such as:

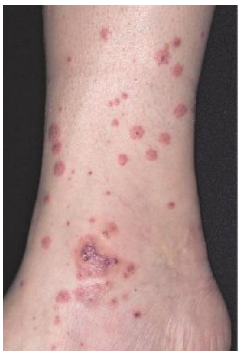
1- Lichen planus: associated with Hepatitis B and C.
2- Vitiligo and Alopecia areata: both are associated with autoimmune diseases like autoimmune thyroiditis,diabetes mellitus ,pernicious anemia, myasthenia gravis.



Alopecia areata



Vitiligo



Lichen planus

Purpura and Vasculitis

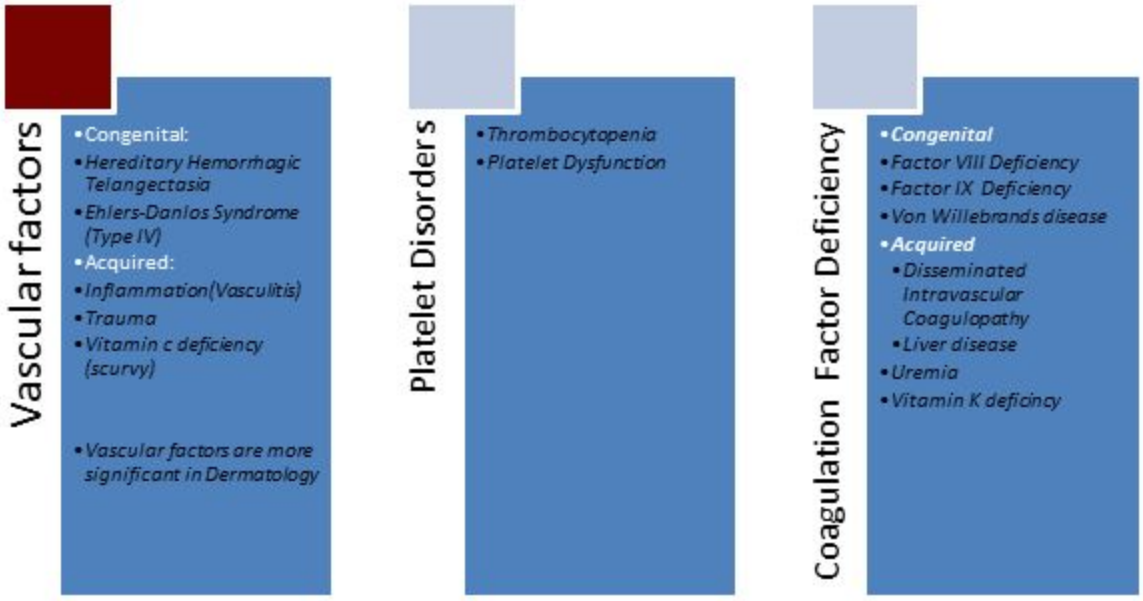
A) Purpura is a condition of red or purple discolored spots on the skin or mucus membranes that do not blanch on applying pressure. The spots are caused by bleeding underneath the skin usually secondary to **vasculitis** or dietary deficiency of vitamin C (scurvy).

Purpura is a clinical condition that is shortly described as “Persistent vascular macule that will not diminish while applying pressure” It is subdivided to :

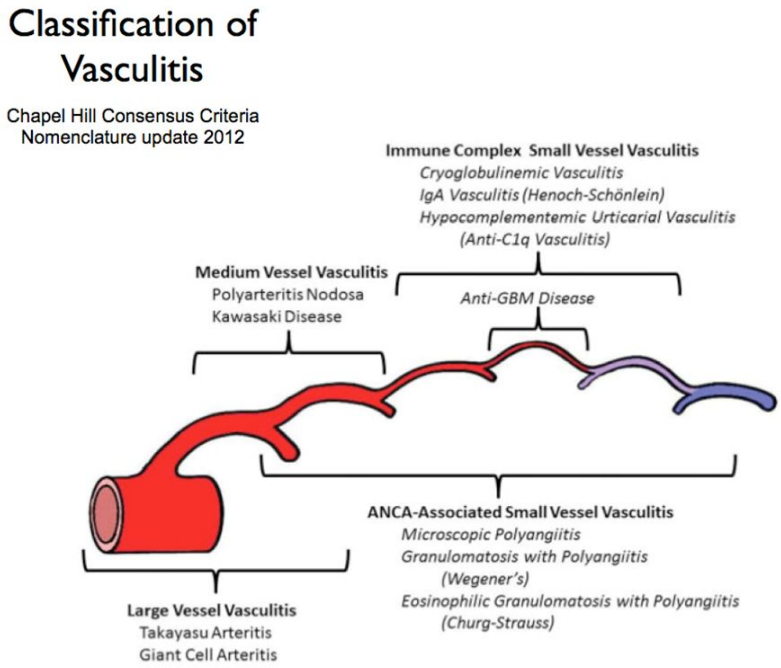
- Petechiae ≤ 4 mm.
- 1cm > Purpura < 4mm. *could be palpable or non-palpable.
- Echymoses ≥ 1cm.

In bedridden patients , purpura may appear on gravity-dependant areas of the body.

❖Causes of Purpura :



B) Vasculitis is a clinicopathologic process characterized by inflammatory destruction of blood vessels that results in occlusion or destruction of the vessel and ischemia of the tissues supplied by that vessel.



- **Large-vessel vasculitis:**

- Vessels affected: Aorta and the great vessels (subclavian, carotid).

- Presentation: Claudication, blindness, stroke.

- Serious and patients usually admitted in ER and therefore rarely seen in Clinics.

- **Medium-vessel vasculitis:**

- Vessels affected: Arteries with muscular wall.

- Presentation: Mononeuritis multiplex (wrist/foot drop), mesenteric ischemia, cutaneous ulcers.

- Ulcers, nodules and other systemic features might be present along with Purpura.

- **Small-vessel vasculitis:**

-Vessels affected: Capillaries, arterioles, venules.

-Presentation: Palpable purpura, glomerulonephritis, pulmonary hemorrhage.

Cutaneous small vessel Vasculitis :

- Is the most common type of vasculitis and it primarily affect postcapillary venules.

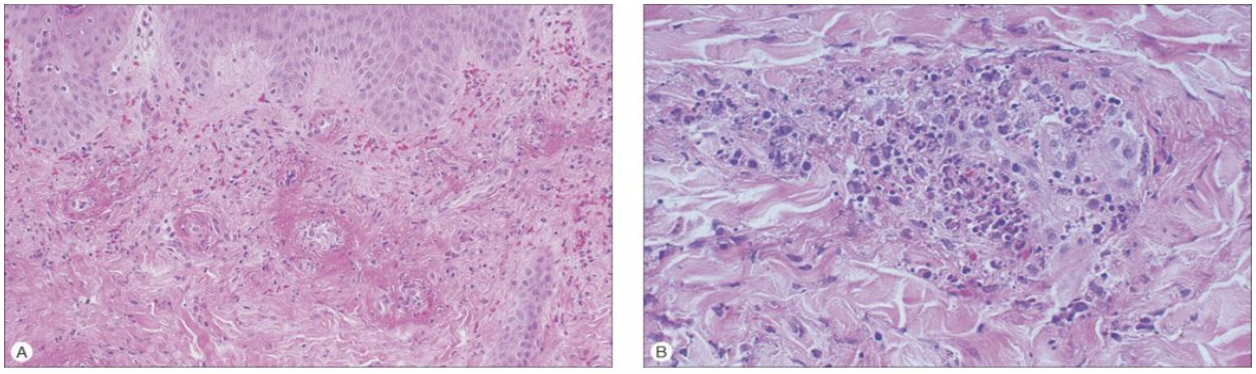
- Pathogenesis: Many forms of small-vessel vasculitis are felt to be caused by circulating immune complexes ,these lodge in vessel walls and activate complement system.

- Pathogenesis behind *Cutaneous small vessel vasculitis* can be : (important!)

1.Idiopathic. 2.Drug Induced. 3.Malignancy 4.Infectious 5.Autoimmune

- palpable purpura is the hallmark!
- pinpoint to several centimeters , predominate in Legs & ankles i.e. dependent areas.
- may not be palpable in the early stage.
- Papulonodular, vascular, bullous, pustular or ulcerated forms may develop, although they are more associated with *Medium vessel Vasculitis.*
- may be localized to the skin or may manifest in other organs, most commonly: joints, GIT, and the kidneys.
- Renal involvement present as “Glomerulonephritis”.
- The prognosis is good in the absence of internal involvement.

On Histology : Angiocentric segmental inflammation, endothelial cell swelling, fibrinoid necrosis of blood vessel walls and a cellular infiltrate composed of neutrophil with RBC extravasation.



- Venules are the targeted segments of the blood vessel in Small vessel Vasculitis, so inflammation has a pattern of: venule and then normal segment - venule - normal segment and so on .. understanding this helps in biopsy taking.

- **Work up:**

- Detailed History & Physical examination : History should focus on possible infectious disorders, prior associated diseases, drugs ingested , and a thorough review of systems.
- Always ask about Arthralgia abdominal pain and GI upset.
- CBC, strep throat culture or ASO titer, Hepatits B & C serologies, HIV , renal profile and ANA are a reasonable initial screen.
- Urinalysis for CBC, Protien and Casts.

- **Treatment : (Treat the underlying Cause)**

➔ Symptomatic treatment (if skin is only involved): rest ,NSAIDS ,Antihistamine
➔ Severe visceral involvement may require high doses of corticosteroids with or without an immunosuppressive agent
➔ Immunosuppressive agents for rapidly progressive course and severe systemic involvement.

Henoch-Schönlein purpura HSP

HSP is a prototype of *Small vessel Vasculitis* which occurs primarily in male children (peak age from 4-8) and young adults, but may occur at any age.

- Characterized by **intermittent purpura**, **arthralgia**, **abdominal pain**, and **renal disease.**

- Typically purpura appears on the extensor surfaces of the extremities and buttocks

- Become hemorrhagic within a day and fades in 5 days

- New crops appear over a few weeks.

- A viral infection or streptococcal pharyngitis are the usual triggering event.

- In about 40 % of the cases the cutaneous manifestations are preceded by mild fever, headache, joint symptoms, and abdominal pain for up to 2 weeks.

- May be associated with: pulmonary hemorrhage, abdominal pain and GI bleeding that on radiographs may show "cobblestone" appearance

- **Renal manifestations** may occur in 25% or more but only 5% end up with ESRD.

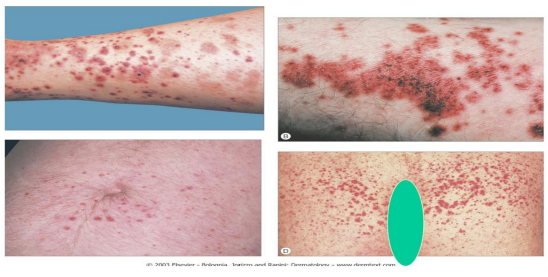
- The long-term prognosis in children with gross hematuria is very good; however, progressive glomerular disease and renal failure may develop in a small percentage

- **IgA** , C3 and fibrin depositions have been demonstrated in biopsies of both involved and uninvolved skin by **immunofluorescence techniques**

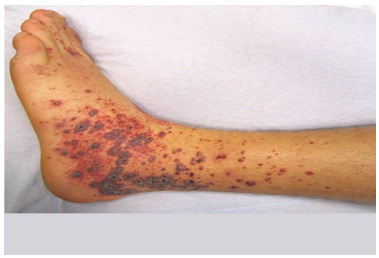
Common clinical cases :

1- a child presenting with severe ABDOMINAL PAIN and purpura on both legs and buttocks (asking about abdominal pain is very important).

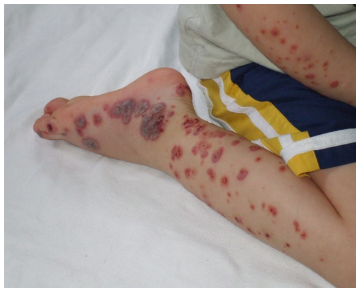
2- a patient presenting with Purpura, and a history FLU like symptoms 2-3 weeks before the lesion's manifestation.



Vasculitis



Purpura



Henoch-Schönlein purpura HSP