



Cutaneous Manifestation Of Systemic Diseases

Objectives :

- To highlight the relation between skin manifestations and common systemic disorders.
- To understand various skin clues and their importance in investigating and managing different systemic diseases.
- This lecture is not meant to be inclusive but to highlight important aspects in their diagnosis and management.

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Sources: *doctor's slides and notes FITZPATRICK color atlas +433 team male + 434 team*

[**Color index** : **Important** | **Dr's Notes** | **Males' Notes** | **Extra**]

Systemic diseases:

Endocrine diseases	Gastrointestinal diseases	Renal diseases	Hyperlipidemia
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> Cutaneous manifestations of endocrine diseases:

A. Diabetes mellitus		
<p>Acanthosis Nigricans</p>	<ul style="list-style-type: none"> → Velvety hyperpigmentation of the intertriginous/flexural areas (body folds and creases) and less often, extensor surfaces. → Commonly associated with insulin resistance and Obesity. → Increased insulin, which binds to insulin-like growth factor receptors to stimulate the growth of Keratinocytes and dermal Fibroblasts. → More common in Hispanics and people of African descent. → Can be associated with an internal malignancy (gastric adenocarcinoma). → Tx: Weight reduction and treat the underlying cause “decrease insulin resistance”. 	
<p>Acrochordrons “Skin tags”</p>	<ul style="list-style-type: none"> → Very common. → Soft papules, skin colored, pedunculated papules. → On the eyelids, the neck, the axillae and groin. → Asymptomatic. → Can get irritated or infected. → Mostly associated with obesity and insulin Resistance. → If numerous usually on top of acanthosis nigricans. → Tx: Cosmetic removal. 	
<p>Diabetic Dermopathy</p>	<ul style="list-style-type: none"> → The most common cutaneous sign of DM. → Brown atrophic macules and patches on the legs. → Hyperpigmented papules and plaques on Shins. → Possibly precipitated by trauma. → Men are affected more often than women. → Possibly related to diabetic neuropathy and vasculopathy. → They usually do not require treatment and tend to resolve after a few years with improved blood glucose control. 	

**Necrobiosis
Lipoidica
Diabeticorum**

- **Plaque with violaceous to red-brown, palpable peripheral rims and yellow-brown atrophic centers with telangiectasia.**
- The most common site is the **shins**.
- Ulceration can occur following trauma.
- **Histopathology: shows tiered granulomatous Reaction.**
- The proportion of patients with DM varies from 15% to 65%.
- Only 0.03% of patients with DM have NLD.
- Pathogenesis is unknown.
- Tx: Control of blood glucose does not have significant effect. Can improve with **topical/intralesional steroids, tacrolimus, phototherapy, cyclosporine, and rarely surgery.**



**Bullous
Diabeticorum**

- A rare condition associated with DM.
- **Tense blisters develop on normal-appearing skin in acral sites (feet, lower legs, hands).**
- There is frequently an association with **peripheral neuropathy**.
- Spontaneous healing usually occurs within 2 to 6 weeks.
- **Heals without scarring.**



**Scleredema
Diabeticorum**

- More common in males, often obese, with longstanding, uncontrolled diabetes, that have frequently suffered complications of diabetes (neuropathy, nephropathy, retinopathy, atherosclerosis).
- Presents as **woody induration and thickening of the skin** of the mid upper back, neck, and shoulders.
- **Thickening of the hands with tiny papules on fingers and stiff joints.**
- **Pebbled knuckles (or Huntley papules)** are multiple minute papules, grouped on the extensor side of the fingers, on the knuckles, or on the periungual surface **Generalized asymptomatic thickening of the skin (diabetic stiff skin).**
- Diabetic stiff hand syndrome, also known as diabetic cheiroarthropathy, is a disorder in which finger movement becomes limited as the hands become waxy and thickened. "Pic;Prayer sign"
- **Scleredema on upper back and neck.**
- Can be associated with infection and **monoclonal gammopathies.**
- Control of diabetes does not affect the course of scleredema.



Figure 149 Massive eruptive xanthomatata in a young man with type-2 diabetes mellitus.

CONTD....

• **Prayer Sign:**


Patient is unable to approximate the palmar surface of phalangeal joints despite of maximal effort.



• **Palm Print Test:**


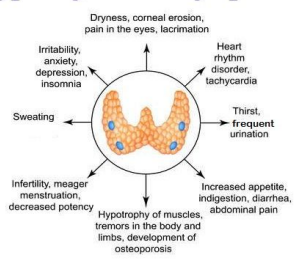
Degree of inter-phalangeal joint involvement can also be assessed by scoring the ink impression made by the palm of dominant hand.



<p>Acquired Perforating Dermatitis</p>	<ul style="list-style-type: none"> → A skin disorder occurring in patients with chronic renal failure, DM or both. → Histopathology: Characterized by the transepidermal elimination of both collagen and elastic fibers. → They present as 2-10 mm, firm, Pruritic hyperkeratotic papules, often umbilicated papules occurring on the trunk and extremities. → Tx: Topical keratolytics, phototherapy, topical/systemic retinoids, topical/intralesional steroids and oral antihistamines, and cryotherapy. 	
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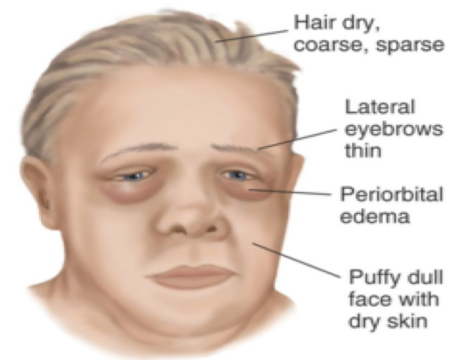
<p>Bacterial and Fungal infections</p>	<ul style="list-style-type: none"> → Pyodermmic infections such as impetigo, folliculitis, carbuncles, furunculosis, ecthyma, and erysipelas can be more severe and widespread in diabetic patients. → Erythrasma, caused by <i>Corynebacterium minutissimum</i> mostly on axillae and groin. malignant otitis externa, often caused by <i>Pseudomonas aeruginosa</i>. → Tinea pedis (can lead to cellulitis) and onychomycosis. → Candidal infections like perleche on corners of mouth, and on vulva. → Rare infections like mucormycosis by <i>Phycomycetes</i> and anaerobic cellulitis by <i>Clostridium</i> species. 	
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B. Thyroid disorders

<p>Hyperthyroidism</p>	<ul style="list-style-type: none"> → Warm, moist skin. → Palmoplantar hyperhidrosis. → Pruritus. → Diffuse, non-scarring alopecia. Increased risk of alopecia areata. Premature hair graying, alopecia with fine soft thinned scalp hair. → Facial flushing. → Hyperpigmentation of the skin, vitiligo. → Nail changes: Plummer’s nails, onycholysis, clubbing. Brittle nails. <p><u>Pretibial myxedema:</u></p> <ul style="list-style-type: none"> ● Cutaneous induration of the shins due to mucin deposition. ● Most commonly associated with Graves disease. ● Skin-colored to brown, waxy, indurated nodules/plaques with characteristic peau d’orange appearance. ● Pretibial myxedema: is the most characteristic features of thyrotoxicosis appearing as shiny waxy papules and plaques having orange-skin appearance on the chin of the tibia. 	 <p style="text-align: center;"><i>Hyperthyroidism Symptoms</i></p> 
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Hypothyroidism

- Coarse, rough, dry skin and Pallor.
- Pruritus.
- A yellowish hue to the skin due to Carotenemia.
- Diffuse hair loss with dull, coarse, brittle hair.
- Loss of the lateral 1/3 of the eyebrows.
- Myxedematous facies.
- Autoimmune disease – vitiligo, alopecia areata.
- Slow growing ridged and brittle nails.
- Delayed wound healing.



C. Cushing's syndrome

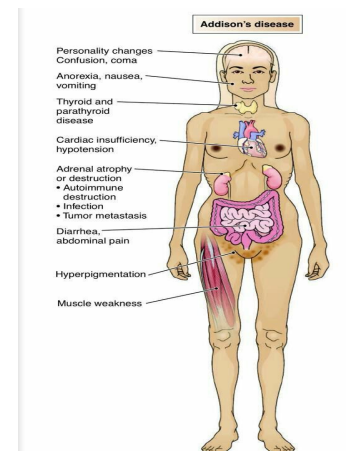
- Excessive glucocorticoid activity.
- Altered subcutaneous fat distribution: Moon facies, buffalo hump.
- Skin atrophy: Striae, prolonged wound healing, purpura and easy bruising.
- Telangiectasia on face.
- Clitromegaly and male pattern alopecia (**Hamilton pattern**).
- Infections: Tinea versicolor, onychomycosis, candidiasis.
- Adnexal effects: Corticosteroid-related acne, hirsutism.
- Caused by prolonged exposure to high levels of plasma glucocorticoid, adrenocortical hyperplasia, benign or malignant adrenal tumours, ectopic ACTH syndrome – secretion of ACTH by malignant or benign tumours arising in structures other than the pituitary or adrenal glands, exogenous steroid administration.

Cushing's Syndrome: Clinical Features:

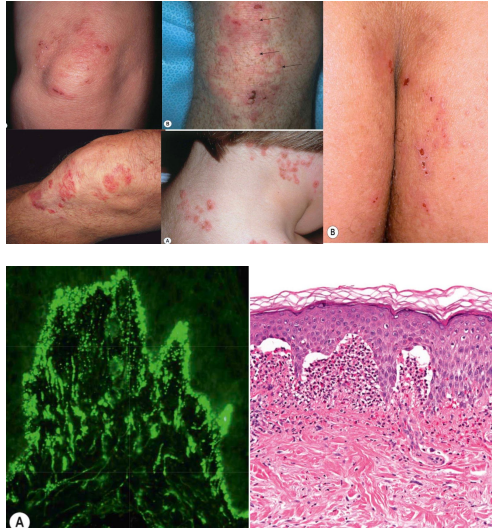

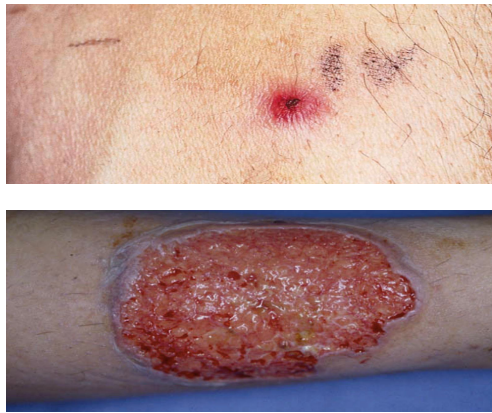


D. Addison's disease "Adrenocortical hypofunction"

- Insufficient Glucocorticoid Activity.
- Hyperpigmentation of the skin and mucous membranes due to high levels of circulating ACTH that binds to Melanocortin-1 receptor on the surface of the dermal melanocytes.
- Hyperpigmentation at Sun exposed skin, sites of trauma, axillae, palmar creases, old scars, nevi and mucous membranes.
- Loss of ambisexual hair in post-pubertal women.
- Fibrosis and calcification of cartilage including the ear (rare).



➤ **Cutaneous manifestations of Gastrointestinal diseases:**

Gastrointestinal diseases:		
<p>Dermatitis herpetiformis</p>	<ul style="list-style-type: none"> ➔ An autoimmune blistering disorder that is often associated with a gluten-sensitive enteropathy. ➔ Small, severely pruritic, clustered vesicular papules or plaques that are symmetrically distributed over the extensor surfaces (elbows, knees, buttocks and shoulders). ➔ Worsening of the disease with dietary intake of Gluten. ➔ Considered A cutaneous manifestation of celiac Disease. ➔ Direct Immunofluorescence (DIF) of perilesional skin show granular IgA deposits in the dermal papillae. ➔ Tx: Dapsone, Gluten-free diet. 	
<p>Acrodermatitis enteropathica</p>	<ul style="list-style-type: none"> ➔ A rare autosomal recessive disorder that impairs dietary Zinc absorption in the GI tract. ➔ Usually starts manifesting as the infant is weaned from breast milk. ➔ Characterized by periorificial, acral dermatitis, alopecia and diarrhea, inflammatory rash, and hair loss. ➔ Scaly, erythematous patches and plaques similar to atopic dermatitis but progress to vesicles, crusts, erosions and pustules on the acral, perioral and perianal areas. ➔ Tx: Lifelong dietary Zinc supplementation. 	
<p>Pyoderma gangrenosum</p>	<ul style="list-style-type: none"> ➔ Painful ulcerative lesions with a well-defined undermined, violaceous border. ➔ Starts as a small red papule or pustule, that subsequently expands to form a large non-infectious ulcer. ➔ Positive pathergy test. ➔ Mostly associated with ulcerative colitis, Crohn's disease, Rheumatoid arthritis and leukemia. ➔ Tx: topical/intralesional steroids, systemic immunotherapy, biologics. ➔ Surgery is contraindicated. 	

Peutz Jeghers syndrome

- Autosomal dominant due to mutations in the STK11 gene.
- **Skin: Melanotic (brown) macules on mucosal surfaces** and less often on acral or perioral skin that first appear very early in life.
- Mucocutaneous hyperpigmentation together with GI polyposis.
- The skin findings first appear in infancy or early childhood and involve brown macules on the lips and buccal mucosa.
- **GI:** Hamartomatous polyps throughout the GI tract, most commonly in the jejunum. Bleeding may occur.
- 2-3% of patients develop GI carcinoma during their lifetimes.
- Increased incidence of breast, ovarian and GI cancers.



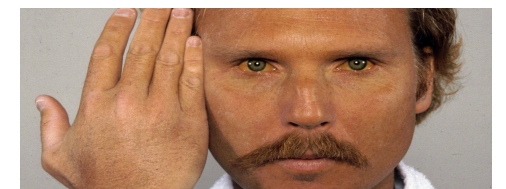
Porphyria cutanea tarda (PCT)/Dracula's or The Vampire Disease

- Porphyrias are inherited metabolic disorders resulting from a **deficiency of an enzyme in the heme production pathway**.
- PCT is the most common porphyria occurring in adults.
- **Deficiency in "Uroporphyrinogen decarboxylase"**
- Photosensitivity, skin fragility of sun-exposed skin after mechanical trauma, leading to erosions and bullae on the hands mainly.
- Healing of crusted erosions and bullae leaves milia, hyperpigmentation on the hands and other sun-exposed areas and atrophic scars.
- Facial Hypertrichosis, blisters, scarring with milia formation.
- Frequently associated with **Hepatitis C infection**.
- Tx: Phlebotomy, hydroxychloroquine, sun avoidance.
- Treatment by removal of possible triggers, including iron supplementation, alcohol, and estrogens.



Hemochromatosis

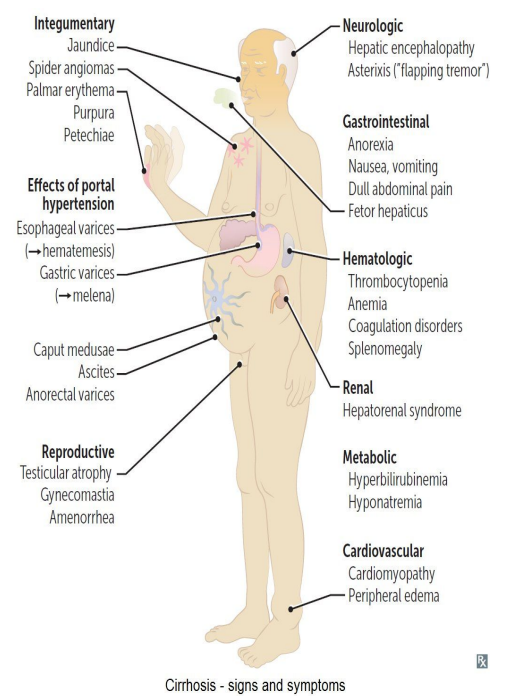
- Autosomal recessive disorder characterized by the **abnormal accumulation of iron in several organs leading to organ toxicity**.
- Cutaneous pigmentation is one of the earliest signs of the disease, most pronounced on sun-exposed areas (face).
- Appears as **metallic gray or bronze-brown color** that is generally diffuse.
- **Other findings:** Skin atrophy, ichthyosis-like changes, koilonychia and **partial hair loss** (most often in the pubic region).
- Tx: Phlebotomy and chelating agents.



Liver cirrhosis

Clinical features: Some of the associated abnormalities are the following:

- Jaundice
- Pruritus: This is related to obstructive jaundice and may precede it.
- Spider angioma/naevi: these are often multiple in chronic liver disease.
- Palmar erythema
- Purpura/Petechiae
- Caput medusae
- Loss of body hair.
- Pigmentation with bile pigments and sometimes melanin.
- White nails: these associate with hypoalbuminemia.
- Porphyria cutanea tarda.
- Xanthomas: in primary biliary cirrhosis.
- Hair loss
- Generalized asteatotic eczema: it may occur in alcoholics with cirrhosis who have become zinc deficient.



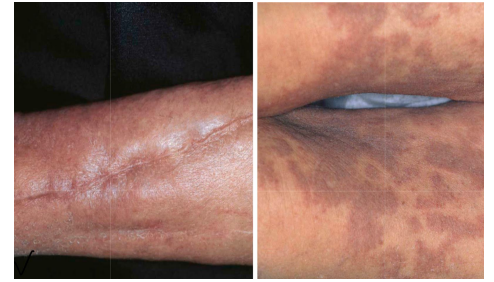
➤ Cutaneous manifestations of Renal diseases:

Manifestations associated with uremia:

<p>Xerosis/Dry skin</p>	<ul style="list-style-type: none"> → 50-90% of dialysis patients. → Can improve with routine use of emollients. → Some patients may develop acquired ichthyosis. → The exact cause of xerosis in ESRD remains unknown. 	
<p>Pruritus/Itchy skin</p>	<ul style="list-style-type: none"> → Affects 15-49% of patients with chronic renal failure and 50-90% of the dialysis population. → Uremia is The most common metabolic cause of pruritus. → <i>Manifestations of pruritus include:</i> Excoriations, prurigo nodularis, lichen simplex chronicus. → Resolved after transplantation. → Tx: Antihistamines, emollients, phototherapy, thalidomide, gabapentin. 	
<p>Half-and-Half nails</p>	<ul style="list-style-type: none"> → 40% of patients on dialysis. → NOT pathognomonic for renal failure. → Disappears several months after transplantation. → Dark (Reddish-brown) distal band and a white proximal band. → More common on fingernails but could be seen on the toenails. 	

Nephrogenic Systemic Fibrosis:

- Fibrosis of the skin and internal organs.
- Caused by exposure to gadolinium-based contrast agents used in imaging in patients who have **renal insufficiency on dialysis**.
- Large areas of thick, woody, indurated skin with fibrotic nodules and plaques on the extremities and trunk, **similar to scleroderma**.
- **Tx:** Extracorporeal photochemotherapy, immunosuppressive therapy, phototherapy, IVIG, **topical steroids, retinoids, and photopheresis**.



➤ Cutaneous manifestations of Hyperlipidemia:

Hyperlipidemia:

Types of Xanthomas:

1. **Eruptive:** Small papules appear in crops over buttocks & extensors.
2. **Tendinous:** Nodules over tendons e.g. extensor tendons of hands & feet and Achilles tendon.
3. **Palmar crease xanthoma:** on palms.
4. **Tuberous:** Papules & nodules over knees and elbows.
5. **Xanthelasma:** Bilateral symmetrical over both eyelids.

Xanthelasma Palpebrarum

- ➔ **Most common cutaneous xanthoma.**
- ➔ Occurs mostly near the inner canthus (upper > Lower eyelid)
- ➔ Asymptomatic, bilateral.
- ➔ Can be associated with any type of primary hyperlipoproteinemia but can also occur without hyperlipidemia (50%).
- ➔ **Tx:** Surgical excision, laser, cryotherapy.
- ➔ Often treated with **topical trichloroacetic acid, electrodesiccation, laser therapy, and surgical excision.**



Tendinous/Tuberous Xanthomas




Tendinous xanthoma:

- ➔ Commonly seen on the achilles tendon, followed by the hand/feet, elbows/knees.
- ➔ The least responsive to treatment.
- ➔ Most seen in patients with familial hypercholesterolemia.

Tuberous Xanthoma:

- ➔ Firm, non-tender, cutaneous and subcutaneous yellowish nodules on the extensor surfaces.
- ➔ Mostly associated with familial dyslipoproteinemia.
- ➔ **May resolve after months of treatment with lipid lowering agents.**



Eruptive Xanthomas	<ul style="list-style-type: none"> → Painless, yellowish papules on an erythematous base, that present as grouped lesions on the extremities (knees), trunk, elbows and buttocks. → Usually associated with hypertriglyceridemia. → Could be seen in poorly controlled diabetes and acute pancreatitis. → Usually resolves in a few weeks after therapy. 	
Planar Xanthomas	<ul style="list-style-type: none"> → Yellowish-orange papules, patches or plaques. → Plane xanthomas of the palmar creases (Xanthoma striatum palmare) are almost diagnostic of dysbetalipoproteinemia. → Plane xanthomas of cholestasis may occur as a complication of liver disease (plaques on the hands and feet). → Plane xanthomas can occur in a normolipemic patient and could signal the presence of an underlying monoclonal gammopathy. 	
Verruciform Xanthomas	<ul style="list-style-type: none"> → Asymptomatic solitary plaques averaging 1 to 2 cm in diameter. → Occur primarily in the mouth but sometimes in anogenital sites. → Usually no associated hyperlipidemia. → Lesions persist for years. 	

➤ **Extra from males' team:**

Causes of generalized pruritus without skin lesions:

- **Endocrine:** DM, hypo & hyperthyroidism.
- **Haematological:** polycythemia rubra vera, iron def anemia Malignancy; e.g. Lymphoma.
- **Hepatic:** primary biliary cirrhosis
- **Renal:** CRF, The commonest manifestation of CRF is pruritus.
- **Neurological:** e.g. Tabes dorsalis.
- **Others:** Psychogenic, Drugs, Idiopathic.

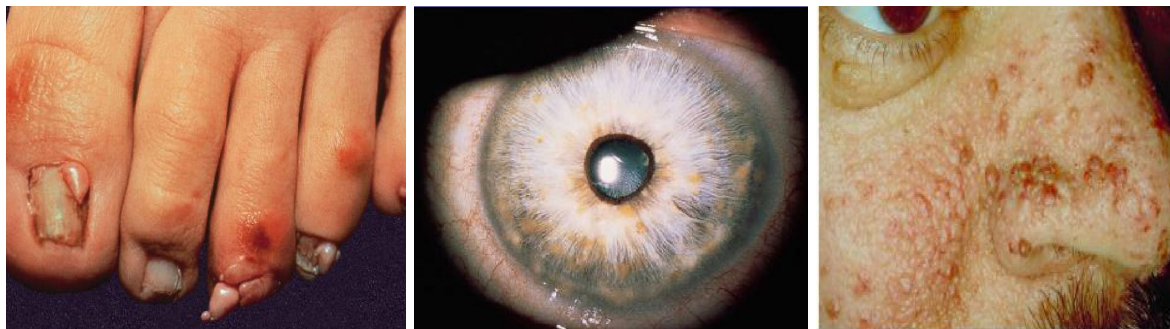
Neurocutaneous Disorders:

- Autosomal dominant
- Café-au-lait macules (light brown).
- Neurofibromas (soft pink or skin- colored papules and nodules)
- Axillary freckling(Crowe sign), the presence of the macules on the axillae.
- Optic glioma.
- Lisch nodules (iris hamartoma, seen by slit-lamp examination).
- Associated with Neurological complications e.g. tumors, seizures and mental retardation.

★ **Tuberous Sclerosis (Epiloia):** Epi = Epilepsy/Loi = Low intelligence /A= adenoma sebaceum

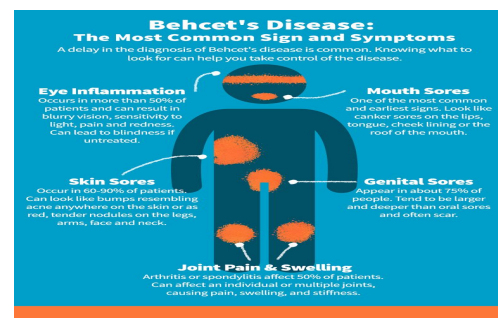
Skin Features:

- **Adenoma sebaceum (angiofibroma):** red papules around the nose and on chin.
- **Ash-leaf hypopigmentation:** oval area of hypopigmentation ***This is the earliest sign of TS.***
- **Periungual fibroma:** multiple papules & nodules around the nail.
- **Shagreen patch:** skin colored plaque on the trunk with “orange-peel” Surface.



Behcet's Syndrome:

- Oral ulcer (the most common).
- Genital ulcers (mainly scrotal).
- Iritis and arthropathy.
- May have CNS involvement.



Scurvy:

- Vitamin C deficiency, Bleeding gums.
- Can cause teeth loss (permanent complication)
- Easy bruising.
- Diagnosis : Low ascorbic acid (Vit-C) level in Leukocyte



Pellagra: Nicotinic acid deficiency 4 "D"s:

- Dermatitis (Photodermatitis).
- Death (if not treated).
- Diarrhea.
- Dementia.



Nails:

Koilonychia:

- ❖ Spoon- shaped appearance Causes:
- ❖ Iron deficiency anemia
- ❖ Thyroid disease
- ❖ Physiological; early childhood
- ❖ Dermatoses: Lichen planus, Alopecia Areata and others.



Clubbing:

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

Causes:

- Thoracic: Lung abscess, Lung CA.
- CVS: Congenital cyanotic heart disease.
- GIT:GI carcinoma, Inflammatory bowel disease Endocrine: Thyroid disease.
- Idiopathic.



Splinter Haemorrhages:

Causes:

- Bacterial endocarditis.
- Septic emboli.
- CTD.
- Trauma.
- Idiopathic.



MCQs:

Q1: Pruritus:

- Could indicate thyroid anomaly
- Pure cutaneous
- Always treated with topical steroids
- Not due to underlying disease

Ans: A

Q2: 42 years female has restricted ability to open her mouth and down tight skin over her hands. What is the most common systemic manifestation of Scleroderma?

- Renal.
- Cardiovascular.
- Pulmonary.
- Gastrointestinal.

Ans: D

Q3: Acrodermatitis enteropathica is:

- Autoimmune disease
- Autosomal recessive
- Iron deficiency
- Copper deficiency

Ans: B

Q4: What is the appropriate way to handle direct Immunofluorescence specimen:

- Take biopsy from the blister
- Take biopsy from perilesional skin
- Put the biopsy in formalin
- Formalin has no role in IF biopsy

Ans: B

Q5: Dermatitis herpetiformis:

- Common bullous disease
- Only Occurs in elderly
- Present as multiple non-pruritic vesicles
- Dapsone is very effective treatment

Ans: D

Q5: Which of the following is the most useful test to evaluate vesiculobullous lesions:

- A. Routine histology
- B. Direct immunofluorescence
- C. Culture
- D. Electron microscopy

Ans: B

Q6: A patient with ulcer and crohn's diseases, which cutaneous manifestation can present:

Ans: pyoderma gangrenosum

Q7:Half and half nails comes in patient complaining of:

- A. ESRD
- B. Vasculitis
- C. Hepatic necrosis

Ans:C and A

All can cause A more correct but C also not false

Q8: Cutaneous manifestation of hypothyroidism is:

- A. Pretibial myxedema
- B. Tendinous xanthomas
- C. Skin tags
- D. Myxedematous face

Ans:D

Q9: Acanthosis nigricans is common in: Obese people

Q10: 68-year-old male with poorly controlled DM. Which of the following xanthoma you will most likely see in him:

- A. Eruptive xanthoma
- B. Tendinous xanthoma
- C. Tuberos xanthoma
- D. Xanthelasma

Ans: A

Q11: Which of the following skin rashes is associated with diabetes mellitus:

- A. Acanthosis nigricans
- B. Palpable purpura
- C. Pretibial myxedema
- D. Striae

Ans: A

Q12: 8 months old infant presented with diarrhea, hair loss, and scaly erythematous patches and crusted erosions on perioral and perianal area. How you treat this infant:

- A. Zinc
- B. Corticosteroid
- C. Antibiotics
- D. Emollient

Ans: A

Q13: Which of the following is contraindicated in patients with Pyoderma gangrenosum:

- A. Cyclosporine
- B. Surgical debridement
- C. Systemic steroid
- D. Topical steroid

Ans: B

Q14: Carotenaemia with yellowish hue to the skin is seen in:

- A. Chronic renal failure
- B. Diabetes mellitus
- C. Hyperthyroidism
- D. Hypothyroidism

Ans: D

Q15: A 30-year-old insulin dependent diabetic female presented with a yellowish-brown atrophic plaque on her shins. Which of the following is the most likely diagnosis:

- A. Erythema nodosum
- B. Pretibial myxedema
- C. Necrobiosis lipoidica
- D. Granuloma annulare

Ans: C

Q16: 68 year old male with poorly controlled diabetes Which one of the following xanthoma you will most likely see in this patient:

- A. Eruptive xanthoma
- B. Tendinous xanthoma
- C. Tuberos xanthoma
- D. Xanthelasma

Ans: A

Q17: What is the most common metabolic disease causes pruritis:

- A. Uremia
- B. Hyperthyroidism
- C. Hypothyroidism

Ans: A

Q18: A 50–year-old female presented with symmetrical bilateral pretibial non-pitting oedema associated with skin colored waxy papules. Clinical features are associated with which one of the following diseases?

- A. Hypothyroidism
- B. Thyrotoxicosis
- C. Cushing’s disease
- D. Diabetes mellitus

Ans: B

Q19: A 25-year-old male known to have tuberculosis of the adrenal glands presented with increase pigmentation of the flexures and mucus membrane. Which of the following is the pathogenesis of this hyperpigmentation?

- A. Increase melanin production
- B. Increase ACTH hormone level
- C. Post-inflammatory hyperpigmentation
- D. Iron deposition in the dermis

Ans: B

Q20: In a 56 year old male with atrophic hyperpigmented papules and plaques on shins, the blood test you will request is:

- A. TSH
- B. Kidney profile
- C. Liver function test
- D. Fasting blood sugar

Ans: D

Q21: In a patient with celiac disease, who has small pruritic excoriated papules and vesicles on buttocks and elbows. Direct immunofluorescence will show granular deposits of:

- A. IgA
- B. IgE
- C. IgG
- D. IgM

Ans: A