SKIN AND SYSTEMIC DISEASE

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THE SKIN

• The largest of the organs
• Weight: ≥9 Kg, Surface: 2 mm$^2$
• Multiple important functions
• Crucial for homeostasis
• «Cutaneous insufficiency» due to external factors or disease may lead to death (depends on the extent of involvement)
FUNCTIONS OF THE SKIN

• Protective (external insults, including solar radiation)
• Sealing (against loss of water and electrolytes)
• Defensive
• Barrier
• Repair
• Sensory (touch)
• Thermoregulation
• Immunologic
• Endocrine - Metabolic
THE SKIN

• External limit
• Border between external and internal environment (barrier and selective portal of entry)
• There is two-way interaction between skin and internal environment (body and psyche)
• Easy to examine by inspection
• “Window” to the internal environment
SKIN AND SYSTEMIC DISEASE: SCENARIOS

• Systemic disease with cutaneous manifestations
• Multi-systemic disease affecting many organs, including the skin
• Reactive skin diseases triggered by systemic disease (among other causes)
• Dermatoses associated with systemic diseases
• Skin involvement due to infiltration, spread, or deposition in the context of systemic disease
• Skin signs of cancer (paraneoplastic skin disorders)
• Pruritus of systemic aetiology
• Cutaneous drug reactions
SKIN AND SYSTEMIC DISEASE

• Skin signs or skin disease often lead to the diagnosis of systemic disease
• Cutaneous manifestations may possess a prognostic value
• Dermatologic disease may complicate therapy directed against internal disease
REACTIVE DERMATOSES OF MULTIPLE AETIOLOGY
REACTIVE DERMATOSES

- Erythema nodosum
- Erythema multiforme
- Stevens-Johnson syndrome - TEN
- Sweet syndrome
- Pyoderma gangrenosum
- Leukocytoclastic vasculitis
ERYTHEMA NODOSUM
ERYTHEMA NODOSUM
ERYTHEMA NODOSUM
ERYTHEMA NODOSUM: CAUSES

• Infections (bacterial, viral, fungal), most commonly TBC (adults), streptococcal (children)
• Sarcoidosis
• Drugs
• Inflammatory bowel disease (CD > UC)
• Adamantiades-Behcet disease
• Malignancies (hematologic > solid tumors)
• Pregnancy
• Idiopathic
ERYTHEMA MULTIFORME
ERYTHEMA MULTIFORME (MINOR)
ERYTHEMA MULTIFORME (MINOR)
ERYTHEMA MULTIFORME (MAJOR)
ERYTHEMA MULTIFORME
ERYTHEMA MULTIFORME (MAJOR)
ERYTHEMA MULTIFORME: CAUSES

- Infections (bacterial, viral, fungal), most often HSV and Mycoplasma pneumoniae
- Drugs
- Psychical factors
- Contact sensitization
- Collagen vascular disease
- Sarcoidosis
- Malignancies (hematologic)
- Pregnancy
- Idiopathic
SJS/TEN
SJS/TEN
TOXIC EPIDERMAL NECROLYSIS
SJS / TEN: CAUSES

• 10% < : SJS
  10–30%: SJS–TEN overlap
  30% > : TEN

• Drugs
• Infections (Mycoplasma pneumoniae)
SWEET SYNDROME
SWEET SYNDROME: CAUSES

- Acute febrile neutrophilic dermatosis
- Exanthem + fever + neutrophilia

- Idiopathic

- Malignancies: hematologic (AML) > solid tumors
- Infections (streptococcal pneumonia)
- Inflammatory diseases
- Drugs
LEUKOCYTOCLASTIC (HYPERSENSITIVITY) VASCULITIS
LEUKOCYTOCLASTIC VASCULITIS

- Small vessel vasculitis + leukocytoclasia
- Palpable purpura
- Drugs
- Infections (streptococcal, upper respiratory, HIV, HCV)
- Collagen-vascular diseases (RA, SLE, SS)
- Inflammatory bowel disease
- Malignancy (lymphoproliferative, HCL)
- Idiopathic
PYODERMA GANGRENOSUM
PYODERMA GANGRENOSUM: CAUSES

- Inflammatory bowel disease
- Polyarthritis (seronegative or seropositive)
- Hematologic diseases (leukemia, preleukemic state, monoclonal gammopathies)
- Hepatic diseases (hepatitis, primary biliary cirrhosis)
- Myeloma
- Rheumatologic diseases (LE, Sjogren syndrome)
- Idiopathic
LIVEDO RETICULARIS

Causes:
• Obstructive vasculopathies
• Vasculitis
• Connective tissue disease
• Neurological disease
• Infection
• Malignancy
• Drugs
PRURITUS AND SYSTEMIC DISEASE
PRURITUS: CAUSES

Skin diseases
• atopic dermatitis, eczema, contact dermatitis
• psoriasis, LP
• autoimmune bullous diseases
• mycosis fungoides
• urticaria, mastocytosis,
• scabies, insect bites

Systemic diseases
• chronic renal insufficiency (hemodialysis)
• Hepatic/biliary
• Endocrine – DM
• Hematologic (anemia)
• paraneoplastic
Drug-induced
  Senile
  Pregnancy
  Neuropathic
  Psychogenous
  Idiopathic
SKIN AND RHEUMATOLOGIC DISEASES
SYSTEMIC LUPUS ERYTHEMATOSUS: SKIN MANIFESTATIONS

• Malar rash (butterfly rash) (ACR criterion)
• Photosensitivity (ACR criterion)
• Discoid lupus erythematosus (ACR criterion, 25%, milder disease)
• Subacute lupus erythematosus
• Diffuse alopecia
• Ulcers/mucocutaneous involvement
• Other: Raynaud phenomenon, livedo reticularis, panniculitis (lupus profundus), bullous SLE, vasculitis, urticaria, telangiectasia
SYSTEMIC LUPUS ERYTHEMATOSUS

- BUTTERFLY RASH
- PHOTOSENSITIVE RASH
DISCOID LUPUS ERYTHEMATOSUS
DERMATOMYOSITIS: SKIN MANIFESTATIONS

• Erythema «heliotrope» of the mid face
• Eruption of the eyelid margins - Periorbital edema
• Malar rash (rare)
• Eruption on the dorsal hands (over the knuckles – Gottron’s papules)
• Periungual changes of the finger nailfolds (dilated capillary loops)
• Diffuse alopecia
• Violaceous erythema or poikiloderma atrophicans et vasculare (anterior chest, upper back)
• Violaceous erythema of the extensor surfaces
DERMATOMYOSITIS

HELIOTROPE ERYTHEMA

GOTTRON’S PAPULES
DERMATOMYOSITIS

DIFFUSE ALOPECIA

PHOTOSENSITIVE POIKILODERMA
SYSTEMIC SCLEROSIS: SKIN MANIFESTATIONS

• Raynaud phenomenon
• Central skin sclerosis (major criterion): arms, face, neck
• Sclerodactyly, erosions and atrophy of fingertips (minor criterion)
• Areas of hyperpigmentation and hypopigmentation
• Nail-fold capillary dilatation or distraction
• Telangiectasia
• Atrophic changes of ala nasi and lips – facial amimia
• Cutaneous calcification
SYSTEMIC SCLEROSIS
SYSTEMIC SCLEROSIS: RAYNAUD PHENOMENON
RHEUMATIC FEVER

- Erythema marginatum (trunk)
- Skin nodules
RHEUMATOID ARTHRITS: CUTANEOUS FINDINGS

• Palisading granulomas
  - rheumatoid nodules
  - superficial ulcerating rheumatoid necrobiosis
  - rheumatoid papules

• Vascular reactions
  - PPPD (capilaritis)
  - vasculitis (small, large)

• Neutrophilic dermatoses
  - pyoderma gangrenosum
  - rheumatoid neutrophilic dermatosis
  - Sweet syndrome
SKIN FINDINGS IN SYSTEMIC DISEASES
SYSTEMIC AMYLOIDOSIS

• **Primary**
  - multiple myeloma, plasmacytic dyscrasia
  - idiopathic

• **Secondary**
  - inflammatory disease
  - infection

• **Skin and mucosal lesions:**
  - Purpura (periorbital)
  - Petechiae, echymoses
  - Waxy, yellowish nodules and plaques
  - Macroglossia
  - Alopecia
  - Nail changes
  - Skin discoloration (pallor, jaundice)
PRIMARY SYSTEMIC AMYLOIDOSIS
WEGENER GRANULOMATOSIS
(GRANULOMATOSIS WITH POLYANGIITIS)
KAWASAKI DISEASE

• Acute febrile vasculitis of childhood
• Diagnosis is based on the presence of fever lasting >5 days and 4 of 5 of the following: edema or reddening of palms and soles, polymorphous rash, oropharyngeal changes, bilateral and painless bulbar conjunctival injection, and acute nonpurulent cervical lymphadenopathy
KAWSAKI DISEASE
DERMATOLOGIC MANIFESTATIONS OF BEHCET DISEASE

- **Classic triad**: recurrent oral apthous ulcers + genital ulcers + uveitis

- **Cutaneous manifestations** (58.6-97%):
  - erythema nodosum (nodules may ulcerate!)
  - subcutaneous thombophlebitis
  - pseudofolliculitis (sterile acneiform pustules and papules)
  - cutaneous hypersensitivity (EM, PG, SS)

- Positive pathergy test
- Abnormalities of nail fold capillaries

- Mucosal and cutaneous manifestations important diagnostic criteria in all proposed systems
BEHCET DISEASE: ORAL ULCERS

MINOR

HERPETIC

MAJOR
BEHCET DISEASE

PSEUDO-FOLLICULITIS

POSITIVE PATHERGY TEST
BEHCET DISEASE

SUBCUTANEOUS THROMBOPHLEBITIS

STERILE PUSTULE
BEHCET DISEASE

GENITAL ULCER

ORAL ULCERS
SKIN AND NUTRITIONAL DEFICIENCIES
SCURVY (VITAMIN C DEFICIENCY)
PELLAGRA (NIACINE DEFICIENCY): PHOTOSENSITIVE DERMATITIS
DERMATITIS ENTEROPATHICA (ZINC DEFICIENCY)
SKIN SIGNS OF INTERNAL MALIGNANCY
PARANEOPlastic DERMATOSES:
CRITERIA (H. Curth)

• *Concurrent onset*: neoplasm discovered at the time of diagnosis of dermatosis, or shortly before or after

• *Parallel course*: treatment of malignancy results in clearance of dermatosis, and if malignancy recurs then dermatosis relapses

• *Uniform site or type of neoplasm*: neoplasm of specific cell type and/or within a specific organ or tissue

• *Statistical association*

• *Genetic linkage*
PARANEOPLASTIC DERMATOSES: STRONGLY LINKED TO CANCER

- Acanthosis nigricans
- Bazex’s acrokeratosis
- Carcinoid syndrome
- Erythema gyratum repens
- Hypertrichosis lanuginosa
- Glucagonoma syndrome (necrolytic migratory erythema, angular cheilitis, glossitis)
- Ectopic ACTH syndrome (generalized hyperpigmentation)
- Neutrophilic dermatoses (pyoderma gangrenosum, Sweet’s syndrome)
- Paget’s disease of the breast
- Paraneoplastic pemphigus
- Sign of Lesser-Trelat
- Tripe palms
ACROKERATOSIS PARANEOPLASTICA (BAZEX)
ERYTHEMA GYRATUM REPENS

Delage M, Naouri M. NEJM 2010
ACANTHOSIS NIGRICANS
MIGRATORY NECROLYTIC ERYTHEMA
MAMMARY PAGET’S DISEASE
HYPERTRICHOSIS LANUGINOSA
TRIPE PALMS

Stavrianeas NG, Katoulis AC et al. Dermatology 1999
DISORDERS STATISTICALLY ASSOCIATED WITH CANCER

• Dermatomyositis
• Extramammary Paget’s disease
DISORDERS POSSIBLY ASSOCIATED WITH CANCER

- Dermatitis herpetiformis
- Exfoliative erythroderma
- Mycosis fungoides
- Porphyria cutanea tarda
- Acquired ichthyosis
- Multicentric reticulohistiocytosis
- Necrobiotic xanthogranuloma
- Leukocytoclastic vasculitis
SKIN AND ENDOCRINOLOGIC/METABOLIC DISEASE
SKIN AND DIABETES

- Diabetic dermopathy
- Diabetic bullae
- Necrobiosis lipoidica
- Disseminated granuloma annulare
- Perforating dermatoses
- Scleredema adultorum of Buschke
- Acanthosis nigricans

- Partial lypodystrophy
- Acral erythema
- Rubeosis
- Acral dry gangrene
- Neuropathic leg ulcers
- Eruptive xanthomas
- Carotenemia
- Hemochromatosis
NECROBIOsis LIPOIDICA
GENERALIZED GRANULOMA ANNULARE
ERUPTIVE XANTHOMAS
SCLEREREDEMA ADULTORUM (BUSCHKE)
## SKIN AND THYROID

<table>
<thead>
<tr>
<th>HYPERTHYROIDISM</th>
<th>HYPOTHYROIDISM</th>
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<tbody>
<tr>
<td>• Skin changes: pretibial myxedema, fine-smooth skin, warm-moist skin, hyperpigmentation)</td>
<td>• Skin changes: dry-coarse, cold-pale, boggy-edematous skin (myxedema)</td>
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<tr>
<td>• Hair changes: fine-thin hair, diffuse alopecia</td>
<td>• Hair changes: dull-coarse-brittle hair, slow growth, diffuse alopecia, alopecia of the eyebrows</td>
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<tr>
<td>• Nail changes: onycholysis, koilonychia, clubbing (thyroid acropachy)</td>
<td>• Nail changes: thin-brittle-striated, slow growth, onycholysis</td>
</tr>
<tr>
<td>• Dermatoses: vitiligo, alopecia areata, urticaria,</td>
<td>• Dermatoses: alopecia areata, ichthyosis, palmoplantar keratoderma, eruptive/tuberous xanthomas</td>
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PRETIBIAL MYXEDEMA
## SKIN AND ADRENALS

### CUSHING’S SYNDROME
- Altered subcutaneous fat distribution («moon facies», «buffalo hump», pelvic girdle fat deposition- thin extremities)
- Skin atrophy: global atrophy, multiple striae, cutaneous fragility, Batemann’s purpura
- Appendageal effects: steroid-induced acne, hirsutism

### ADDISON’S DISEASE
- Hyperpigmentation (MSH-like): diffuse, sites of trauma, axillary-perineum-nipples, nevi, mucous membranes, hair, nails
- Loss of ambisexual hair in women
- Vitiligo
- Chronic mucocutaneous candidiasis
CUSHING SYNDROME
ADDISON DISEASE
SKIN AND PULMONARY DISEASE
DISORDERS WITH PULMONARY AND CUTANEOUS MANIFESTATIONS

- Sarcoidosis
  - acute: erythema nodosum
  - chronic: papules, nodules plaques, lupus pernio
- Tuberculosis:
  - direct inoculation to the skin
  - spread to the skin
  - tuberculids
- Lymphomatoid granulomatosis
- Wegener’s granulomatosis
- Dermatomyositis, Scleroderma
- Blastomycosis
- Hereditary hemorrhagic telangiectasia
CLUBBING
TUBERCULOUS ULCER
VERRUCOUS CUTANEOUS TUBERCULOSIS
SCROFULODERMA
LUPUS VULGARIS
TUBERCULID: ERYTHEMA INDURATUM (BAZIN)
SARCOIDOSIS
SARCIOIDOSIS
LUPUS PERNIO
LUPUS PERNIO
SKIN AND RENAL DISEASE
SKIN CHANGES IN END STAGE RENAL DISEASE

- Pale color, sallowness
- Xerosis, ichtyosis
- Pruritus (hemodialysis)
- Uremic frost
CUTANEOUS DISEASE IN LONG-TERM IMMUNOSUPPRESSION

• Infections
• Neoplasms: porokeratosis, actinic keratosis, NMSC, Kaposi’ sarcoma
KAPOSI’S SARCOMA
CALCIPHYLAXIS

Marques Sa et al. An Bras Dermatol 2013
SYSTEMIC DISEASES WITH SKIN AND RENAL INVOLVEMENT

- **SEL**: malar erythema, DLE, diffuse alopecia, photosensitivity, vasculitis
- **Scleroderma**: Raynaud’s phenomenon, acral or diffuse sclerosis, CREST
- **Henoch-Schonlein purpura**
- **Polyarteritis nodosa**: nodules, livedo reticularis, palpable purpura
- **Wegener’s granulomatosis**: nodules, cutaneous granulomas, palpable purpura
- **Tuberculosis**: nodules, cutaneous granulomas, palpable purpura
- **Tuberculosis**: sarcoïdosis
- **Primary systemic amyloidosis**: pinch purpura, waxy skin, translucent papules
SKIN AND CARDIAC DISEASE
SKIN AND CARDIAC DISEASE

- Clubbing (hypertrophic osteoarthropathy)
- Cyanosis
- Pallor
- Edema
- Petechiae
- Splinter hemorrhages
- Janaway lesions, peripheral emboli
- Osler nodes
SKIN SIGNS OF CARDIAC DISEASE
SYSTEMIC DISEASES WITH SKIN AND CARDIAC INVOLVEMENT

- Primary systemic amyloidosis
- Behcet disease
- Carcinoid syndrome
- Cutis laxa
- Dermatomyositis
- Diabetes melitus
- Fabry’s disease
- Hemochromatosis
- Kawasaki disease
- SEL

- Homocystinuria
- LEOPARD syndrome
- Multicentric reticulohistiocytosis
- Neurofibromatosis 1
- Pseudoxanthoma elasticum
- Relapsing polychondritis
- Rheumatic fever
- Sarcoidosis
- Scleroderma
- Tuberous sclerosis
- Werner’s syndrome
SKIN MANIFESTATIONS OF HEREDITARY DISORDERS
EHLERS-DANLOIS SYNDROME
FABRY’S DISEASE
LEOPARD SYNDROME
NEUROFIBROMATOSIS TYPE 1
TUBEROUS SCLEROSIS
PSEUDOXANTHOMA ELASTICUM
SKIN AND GASTROINTESTINAL DISEASE
CUTANEOUS MANIFESTATIONS AND COMORBIDITIES IN CROHN’S DISEASE AND ULCERATIVE COLITIS

- Erythema nodosum (reflective of active disease)
- Small vessel vasculitis
- Pyoderma gangrenosum (typical or peristomal)
- Bowel associated dermatitis-arthritis syndrome

- Oral lesions: granulomatous infiltrates (CD), apthosis, angular cheilitis, pyostomatitis vegetans
- Metastatic Crohn’s disease
- Acquired acrodermatitis enteropathica-like lesions (Zn deficiency)

Comorbidities: Psoriasis, Hidradenitis suppurativa, Epidermolysis bullosa acquisita
SKIN DISEASES ASSOCIATED WITH GASTROINTESTINAL HEMORRHAGE

• Hereditary hemorrhagic telangiectasia
• Blue rubber bleb nevus
• Pseudoxanthoma elasticum
• Ehlers-Danlos syndrome (IV)
• Degos disease
• Scurvy
• Kaposi’s sarcoma

• Gardner’s syndrome
• Peutz-Jeghers syndrome
• Cowden’s disease
• Muir-Torre syndrome
• Cronkhite-Canada syndrome
SKIN MANIFESTATIONS OF LIVER DISEASE

• **Cirrhosis:**
  - spider angiomas
  - palmar erythema
  - dilated abdominal wall veins
  - Terry’s nails
  - Muehercke’s nails
  - hypotrichosis (axillae, pubis, chest)
  - gynecomastia
  - pruritus
  - jaundice

• **Hepatitis C:** vasculitis, urticaria, PCT, cryoglobulinemic purpura, pruritus, lichen planus (oral erosions)

• **Primary biliary cirrhosis:**
  - jaundice
  - diffuse hyperpigmentation
  - xanthomas (eruptive, planar, tuberous)
  - pruritus

• **Hemochromatosis («bronze diabetes»):**
  - diffuse hyperpigmentation

• **Wilson’s disease:**
  - Kayser-Fleischer ring
  - blue lunulae
SPIDER ANGIOMAS

Detry O, de Roover A. NEJM 2009
XANTHOMAS

Xanthelasma

Eruptive xanthomas

Tuberous xanthomas
NAILS IN LIVER DISEASE

Muehercke’s nails

Terry’s nails
CONCLUSIONS

• Skin findings may often lead to the diagnosis and guide patient’s management
• All physicians should be well-trained in Dermatology
• The role of the Dermatologic consultation in a General Hospital is crucial
Thank you for your attention!