

# PARANEOPLASTIC DERMATOSES



Natalia Fernández Chico  
Hospital Universitari de Sabadell  
January 29, 2010



# CUTANEOUS MANIFESTATIONS OF INTERNAL NEOPLASMS

1. Skin metastases
2. Genodermatoses
3. Paraneoplastic dermatoses

# PARANEOPLASTIC DERMATOSES

## CONCEPT

**“Benign dermatoses that appear in relation  
to an internal neoplasm”**

# PARANEOPLASTIC DERMATOSES

- Coexistence of an internal neoplasm and cutaneous inflammatory reaction.
- Unknown etiopathogenesis in most cases. Proposed theories:
  - Synthesis of hormones, cytokines, or growth factors by tumoral cells.
  - Immunologic response due to a crossed reactivity between tumor antigens and skin antigens.

# PARANEOPLASTIC DERMATOSIS

## CURTH'S CRITERIA (1976)

- ✓ Synchronic onset
- ✓ Parallel course
- ✓ Frequent association
- ✓ Tumor specificity
- ✓ Rarity of the dermatosis

# PARANEOPLASTIC DERMATOSES

## Classification

- ✓ Disorders of the epidermis
- ✓ Figurate erythema
- ✓ Neutrophilic dermatosis
- ✓ Interface dermatitis
- ✓ Disorders of the dermis
- ✓ “Deposit” disorders
- ✓ Others

# PARANEOPLASTIC DERMATOSES

## DISORDERS OF THE EPIDERMIS

✓ Acanthosis nigricans

✓ Acanthosis palmaris or *Tripe palms*

✓ Leser-Trelat sign

✓ Acquired ichthyosis

✓ Bazex syndrome

## ***TRIPE PALMS***

- Thickening of the dermatoglyphs
- Rough, velvety appearance similar to tripe
- Sometimes associated to Acanthosis nigricans
- 90% associated to neoplasms (stomach and lung)



# **BAZEX SYNDROME**

## **(Acrokeratosis paraneoplastica)**

- Psoriasiform dermatitis with acral distribution
- Male predominance (9:1)
- Usually precedes the diagnosis of the neoplasm by months or years
- Associated to squamous carcinoma of the upper aerodigestive tract
- Associated to metastases in the cervical lymph node chain

# BAZEX SYNDROME

## COURSE

Three stages:

- Acral hyperkeratosis in the fingers and toes, margins of the pinnae, bridge of the nose, cheeks.
- More patent violaceous plaques, palmoplantar involvement.
- Extension to other, more proximal areas: elbows, knees, trunk...

# BAZEX SYNDROME

## ASSOCIATION TO NEOPLASMS

- 100% associated to neoplasms
- 80% associated to neoplasms in the upper aerodigestive tract
- 64% squamous carcinomas
- 50% cervical lymph node metastases

# ACANTHOSIS NIGRICANS

- Bilateral, symmetrical brown-gray plaques.
- Evolution to velvety, warty plaques.
- Fold involvement: axillae, groin, back of the neck, intergluteal fold, submammary fold.
- A “benign” condition in 80% of cases.
- Two major groups:
  1. Benign: congenital or associated with obesity, endocrine disorders, or drugs.
  2. Malignant: associated with neoplasms.


# ACANTHOSIS NIGRICANS

- Malignant acanthosis nigricans should be suspected:
  - In the absence of a family history, obesity, or endocrine disorders.
  - Abrupt onset of lesions after the age of 40-50 years.
  - Rapid evolution.
  - Involvement of atypical areas: lips, oral mucosa, palms (*tripe palms*), flexor surface of the fingers, eyelids.
  - It is associated with an abdominal (most often gastric) adenocarcinoma in 90% of cases.

# LESER-TRÉLAT SIGN

- Seborrheic keratoses:
  - Multiple lesions
  - Eruptive emergence
  - Abrupt increase in number and size
  - Pruritus
  - Association with *Acanthosis nigricans*
  - Associated with gastrointestinal tumors, lymphomas.

# ACQUIRED ICHTHYOSIS

- *Ichthys* = fish
  - Generalized ichthyosis
  - Absence of family history
  - > 20 years of age
- 
- Association with hematological neoplasms, basically:  
Hodgkin's lymphoma 70%-80%, non-Hodgkin's lymphoma, multiple myeloma, other, ....

# PARANEOPLASTIC DERMATOSES

- ✓ Disorders of the epidermis
- ✓ **Figurate erythema**
- ✓ Neutrophilic dermatosis
- ✓ Interface dermatosis de interfase
- ✓ Disorders of the dermis
- ✓ “Deposit” disorders
- ✓ Others

# PARANEOPLASTIC DERMATOSES

## FIGURATE ERYTHEMA

✓ Necrolytic migratory erythema

✓ Erythema gyratum repens

# ERYTHEMA GYRATUM REPENS

- Rare, few cases reported.
- 100% cases associated with neoplasms: bronchial carcinoma, esophageal carcinoma.
- Clinical characteristics: urticarial, wavy, concentric erythematous bands that change in a few hours.

# NECROLYTIC MIGRATORY ERYTHEMA

- Erythematous plaques with polycyclic margins
- Buttocks, genitals, inguinal region, acral zones, periorificial
- Scabby peripheral margins (epidermal necrolysis)
- Glossitis, cheilitis

# NECROLYTIC MIGRATORY ERYTHEMA

- Association with glucagonoma in the context of a glucagonoma syndrome:
  - Weight loss, diabetes, anemia...
- Sometimes not paraneoplastic:
  - Cirrhosis of the liver
  - Chronic pancreatic disease
  - Celiac disease

# PARANEOPLASTIC DERMATOSES

- ✓ Disorders of the epidermis
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# PARANEOPLASTIC DERMATOSES

## NEUTROPHILIC DERMATOSES

- ✓ Sweet's syndrome
- ✓ Pyoderma gangrenosum

# **SWEET'S SYNDROME**

## **(Acute febrile neutrophilic dermatosis )**

- Acute erythematous rash with plaques or nodules that develop pseudovesicles
- Upper region of the trunk, face, and upper limbs
- Accompanied by:
  - Fever
  - Leukocytosis-neutrophilia
  - Rapid response to systemic corticosteroids

# SWEET'S SYNDROME

- Most are idiopathic types (prodromal: symptoms of acute upper respiratory tract infection)
- 20% are associated with neoplasms:
  - » No prodromal symptoms.
  - » Anemia, absence of neutrophilia.
  - » Blistery lesions, necrotic ulcers.
  - » Mucous membrane involvement.
  - » 85% hematological neoplasms: acute myeloid leukemia, lymphomas.
  - » Good response to oral corticosteroids irrespective of the course of the neoplasm.

# PYODERMA GANGRENOSUM

- One or more destructive ulcers that appear spontaneously or after minimal trauma.
- Two variants:
  - Typical type:
    - 50% idiopathic
    - Associated with inflammatory intestinal disease, rheumatoid arthritis...
  - Atypical type:
    - Associated with hematological diseases
    - Only 7% of cases are associated with neoplasms: acute myeloid leukemia, multiple myeloma

# PARANEOPLASTIC DERMATOSES

## INTERFACE DERMATITIS

- ✓ Dermatomyositis
- ✓ Paraneoplastic pemphigus

# DERMATOMYOSITIS

- Connective tissue disease of unknown etiology.
- Characteristic cutaneous eruption.
- Clinical and laboratory signs of proximal inflammatory myopathy of the extensor muscles (although there is also dermatomyositis *sine* myositis and hypomyopathic dermatomyositis).



## Classificación de Bohan y Peter de miopatías inflamatorias

- I. Polimiositis primaria idiopática
- II. Dermatomiositis primaria idiopática
- III. Poli y dermatomiositis asociada a neoplasia.
- IV. Dermatomiositis juvenil (o polimiositis)
- V. Síndrome overlap de polimiositis (o dermatomiositis) con otra enfermedad autoinmune.
- VI. Miositis por cuerpos de inclusión
- VII. Formas raras de miositis idiopática
  - Miositis granulomatosa
  - Miositis eosinofílica
  - Miositis focal
  - Miositis orbitaria

(Dr Monteagudo. Update on Systemic Autoimmune Diseases. CSPT, 2006)

# DERMATOMYOSITIS

## CHARACTERISTIC CUTANEOUS LESIONS

1. Violaceous erythema
2. Gottron's sign
3. Gottron's papules
4. Periungual telangiectasis and cuticle dystrophy
5. Poikiloderma
6. Mechanic's hands
7. Calcinosis cutis

# DERMATOMYOSITIS

## VIOLACEOUS ERYTHEMA

- Violet-coloured confluent macular erythema or exanthema
- Generally pruriginous
- Sometimes photoinduced
- Evolves toward poikiloderma
- No relation between activity and muscular involvement
- Distribution:
  - Eyelids (heliotrope erythema)
  - Center of the face, forehead
  - Scalp
  - Anterior neck and upper chest (V sign)
  - Posterior neck and upper back (cape sign)
  - Extensor surfaces of arms, forearms, hands, and fingers

# DERMATOMYOSITIS

## GOTTRON'S SIGN

- Violaceous erythema that affects the bony prominences
  - ✓ Interphalangeal and metacarpophalangeal joints
  - ✓ Knees
  - ✓ Elbows
  - ✓ Internal malleolus
- Bilateral and symmetrical distribution

# DERMATOMYOSITIS

## GOTTRON'S PAPULES

- Erythematous-violaceous maculopapules located on the dorsal aspects of the interphalangeal and metacarpophalangeal joints
- 
- In advanced stages, the central zone becomes whitened, depressed, and atrophic.

# DERMATOMYOSITIS

## MECHANIC'S HANDS

- Bilateral symmetrical confluent hyperkeratosis in the internal region of the thumb and external regions of the other fingers (most prominent in the index and middle fingers)
- Can sometimes extend toward the palmar surfaces
- Currently considered a marker of myositis

# DERMATOMYOSITIS

## MUSCULAR INVOLVEMENT

- Predominantly involves the scapular and pelvic girdles:  
myalgias, tiredness, weakness, and difficulties climbing stairs,  
rising from a chair, combing, shaving ....
- Later involves cervical and paravertebral musculature
- Occasionally dysphagia, dysphonia: rapid progression, poor prognosis.

# DERMATOMYOSITIS

## OTHER SYSTEMIC MANIFESTATIONS

- Articular involvement (25%): generalized arthralgias, morning stiffness, nonerosive arthritis affecting the small joints, hands, wrists, and ankles.
- Pulmonary involvement (15%-65%): interstitial pneumonitis (poor prognosis, association with anti-Jo1 antibodies).
- Cardiac involvement: conduction disorders, arrhythmias...

# DERMATOMYOSITIS & CANCER

- There seems to be a clear relation between dermatomyositis and cancer
- The most appropriate strategy to search for this neoplasm remains to be defined.
- No clear answers have been found for three important questions :
  - Is there a predictive factor or marker for neoplasms in dermatomyositis?
  - How should the possible neoplasm be studied?
  - How long should patients be followed-up to rule out the possibility of a neoplasm?

# DERMATOMYOSITIS & CANCER

## MOST COMMON TUMORS

- ✓ **Ovarian**
- ✓ Lung
- ✓ Gastrointestinal tract
- ✓ Pancreas
- ✓ Breast

# DERMATOMYOSITIS & CANCER

## PREDICTIVE FACTORS

- Clinical
  - Age
  - Necrotic skin lesions
  - Presence of interstitial lung disease: negative association
- Biological
  - Routine determinations: normal levels of CK, elevated ESR
  - Tumor markers: CA125, CA 19.9
  - Autoantibodies: anti-p155

# DERMATOMYOSITIS & CANCER

## SEEKING THE NEOPLASM

- Complementary tests
  - Clinical history
  - Blood test with tumor markers
  - Occult blood in feces
  - Thoracoabdominal CT
  - Gynecological examination, cytology, pelvic ultrasonography, and mammogram in women
- At least one thorough physical examination every year for the first 3-4 years

# PARANEOPLASTIC PEMPHIGUS

## CONCEPT

- *Pemphix* = blister.
- Autoimmune disease related to lymphoproliferative processes.
- Especially mucous membrane involvement.
- Polymorphous cutaneous eruption.
- +/- Lung involvement.
- High mortality.

# PEMPHIGUS

## CONCEPT

Pemphigus: intraepidermic blister

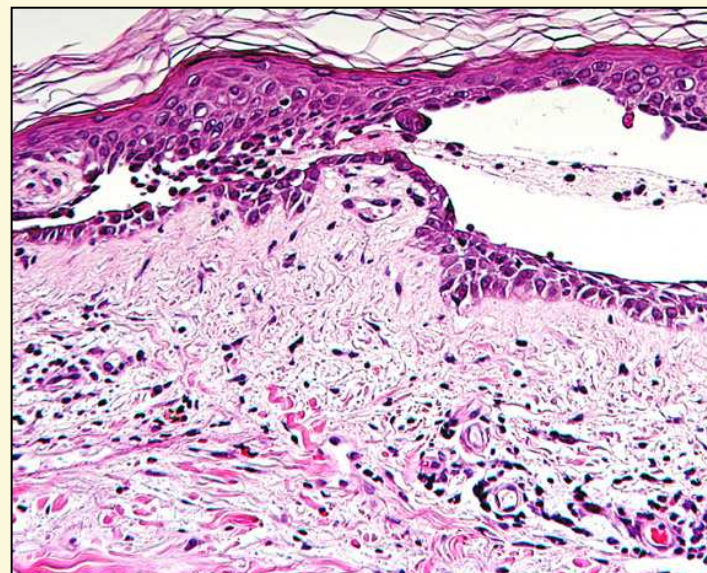


Soft bullae, short lasting, positive Nikolsky's sign

IgG antibodies directed  
against the surface of  
keratinocytes




Loss of cohesion



# PARANEOPLASTIC PEMPHIGUS

## CLINICAL PRESENTATION

- Constant, severe, untreatable mucous membrane involvement:
  - Especially the oral mucosa
  - conjunctiva and genitals
  - others: including the esophageal mucosa
- Mucosal lesions:
  - Intact bullae are rarely seen because they are fragile and break easily  **Erosions**
  - Very painful

# PARANEOPLASTIC PEMPHIGUS

## CLINICAL PRESENTATION

- Polymorphous skin lesions:  
pemphigus /pemphigoid and erythema  
multiforme-like
- Can appear at any location
- Can appear on normal skin or over an  
erythematous base
- Evolve to painful erosions that later become  
covered with scabs that tend not to heal



# PARANEOPLASTIC PEMPHIGUS

## MOST COMMONLY ASSOCIATED TUMORS

- ✓ 75%-80% hematological neoplasms:
  - ✓ Non-Hodgkin's lymphoma (42%)
  - ✓ Chronic lymphocytic leukemia (29%)
  - ✓ Castleman's disease (especially in children)
  
- ✓ Others:
  - ✓ Retroperitoneal sarcomas, thymoma, melanoma, Waldenstrom's disease...

# PARANEOPLASTIC DERMATOSES

## DISORDERS OF THE DERMIS

- ✓ Multicentric reticulohistiocytosis
- ✓ Necrobiotic xanthogranuloma

# PARANEOPLASTIC DERMATOSES

## “DEPOSIT” DISORDERS

- ✓ Amyloidosis
- ✓ Scleromyxedema

# PARANEOPLASTIC DERMATOSES

## OTHERS

- ✓ Hypertrichosis lanuginosa acquisita
- ✓ Pruritus

# HYPERTRICHOSIS LANUGINOSA ACQUISITA

- More common in women, ♀:♂ ratio 3:1
- > 40 years
- Fine whitish silky hair (lanugo)
- Starts on the face, later generalizes
- Progresses in weeks
- Strong association with cancer

# HYPERTRICHOSIS LANUGINOSA ACQUISITA

- Associated neoplasms:
  - ♀: colorectal and breast cancer
  - ♂: lung and colorectal cancer
- In general, the neoplasm has already spread at the time of diagnosis

# PRURITUS

- Localized: in general does not derive from systemic disease
- Generalized:
  - Specific skin lesions: pruritus secondary to skin disease
  - Without specific skin lesions (although there may be lesions from scratching, excoriations...): might derive from underlying systemic disease

# PRURITUS

## APPROACH

- Detailed clinical history:
  - Slow, progressive course
  - Interferes with sleep
- Physical examination:
  - Rule out dermatosis
  - Presence of lesions secondary to scratching
  - Rule out xerosis

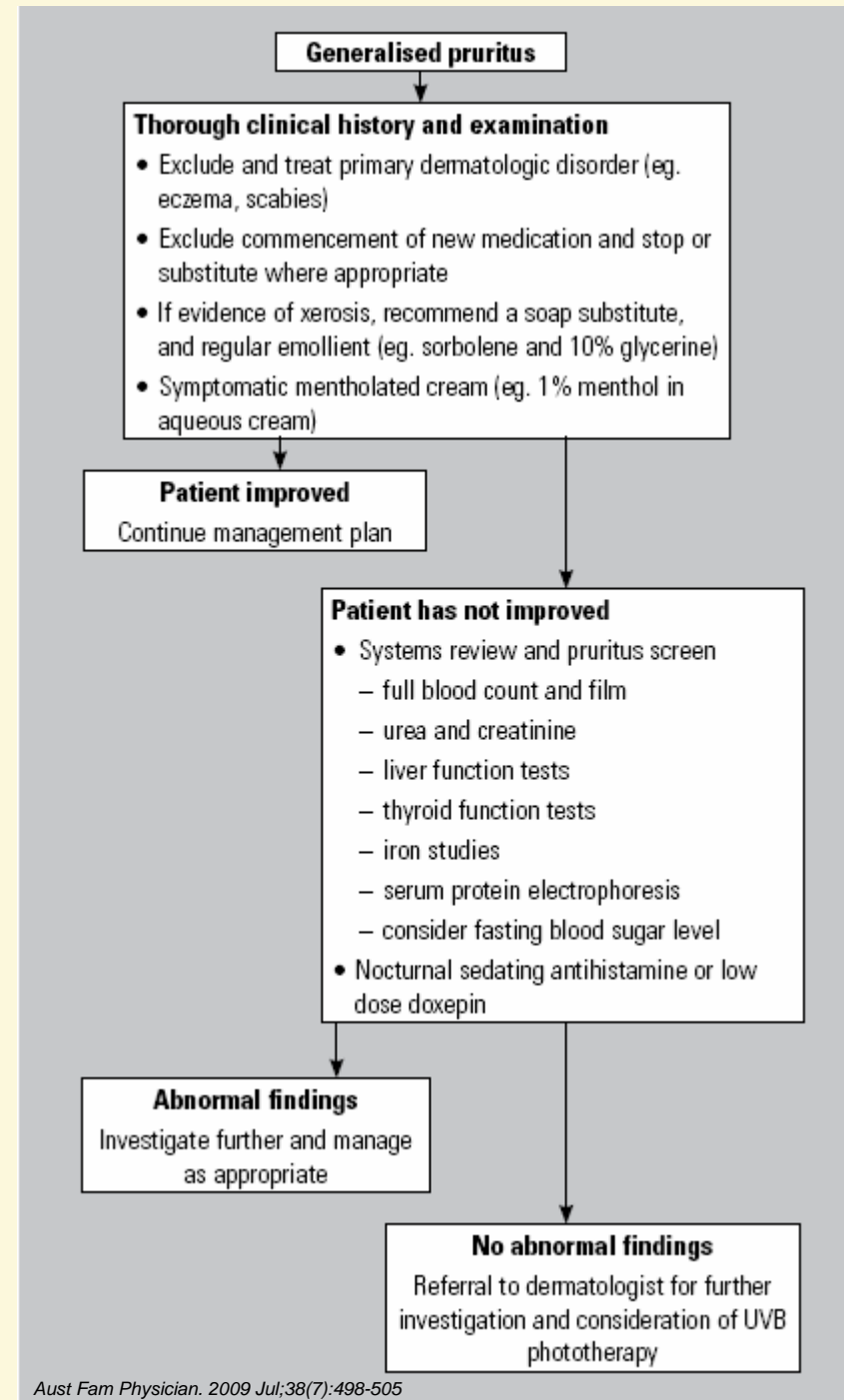
# PRURITUS

## SYSTEMIC DISEASES

- ✓ Hypothyroidism or hyperthyroidism
- ✓ Hyperparathyroidism or hypoparathyroidism
- ✓ Uremia
- ✓ Hepatic cholestasis
- ✓ Diabetes mellitus
- ✓ Ferropenia
- ✓ Parasitosis
- ✓ Hematological or solid neoplasms

# APPROACH

- In pruritus without an apparent cause:
  - Blood tests, ESR
  - Fe, ferritin
  - IgE
  - T4, TSH, PTH
  - Phosphate, calcium
  - Chest X-ray



# PARANEOPLASTIC DERMATOSES CONCLUSION

## SUSPECT A PARANEOPLASTIC DERMATOSIS IF:

- Abrupt onset of dermatosis in advanced age
- Rapid course
- Atypical clinical presentation
- More severe skin lesions

# PARANEOPLASTIC DERMATOSES

## CONCLUSION

- The following have a strong association with cancer:
  - Tripe palms
  - Bazex Syndrome
  - Erythema gyratum repens
  - Hypertrichosis lanuginosa acquisita
  - Paraneoplastic pemphigus
  - Malignant acanthosis nigricans
- Do not forget that the following are occasionally associated with cancer:
  - Sweet's syndrome
  - Pyoderma gangrenosum
  - Dermatomyositis
  - Pruritus

(although these have a benign counterpart)

