The skin: a window into systemic diseases

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- Up to 20% of patients with cancer have cutaneous manifestations - OFTEN UNDER-RECOGNIZED
- Sometimes the skin lesions are the presenting sign

They may be:
- Paraneoplastic dermatoses
- Skin manifestations in patients with inherited syndromes and underlying malignancies
- Chemotherapy or immunosuppressive treatment effects
- Cutaneous metastases (or direct extension)

Paraneoplastic dermatoses

Merck's manual:
Paraneoplastic syndromes are symptoms that occur at sites distant from a tumor or its metastasis.

- Heterogenous group of non-inherited skin conditions that represent a remote effect of a neoplasm rather than being caused by tumor growth and invasion.
**Paraneoplastic dermatoses**
- Usually the clinical onset and the course of cutaneous disorders precede or have a parallel evolution with the internal neoplasm
- May herald a new or recurrent neoplasm
- Often under-recognized (their histology is not necessary different from similar clinical entities not associated with malignancy)

**Pathogenesis**
- Not completely understood
- Considering the wide range of muco-cutaneous lesions, it is unlikely to have an uniform etiology
- Likely associated with a variety immune and cytokine-mediated aberrations, as well as the possibility of tumor-induced host immunologic response

**Paraneoplastic dermatoses**
- *Early recognition* is of a paramount importance considering that they may precede the diagnosis of malignancy, signal a severe immuno-suppressed status and purport a great impact in overall morbidity, prognosis and mortality of these patients.
- Improved prognosis with earlier therapy
- Respond to tumor treatment
Paraneoplastic dermatoses

- Wide variety of manifestations:
  - Reactive erythemas
  - Papulosquamous
  - Vesiculo-bullous disorders
  - Proliferative reactions
  - Vasculitis
  - Neutrophilic dermatoses
  - Dermal depositions
  - Other

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Hypothyroidism: Chronic renal failure, multiple myeloma
Myasthenia: Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease
Case studies:
- stronger casual relationship with the underlying malignancies
- specific enough on clinical and histologic grounds for practical dermatologic and dermatopathologic recognition
CASE 1

- 69-year-old male with painful blisters and erosions on trunk and extremities and later on the oral mucosa, oropharynx and nasopharynx
Paraneoplastic pemphigus

- Anhalt (1990) - paraneoplastic pemphigus
  - distinct form of pemphigus associated with lymphoreticular malignancies

- Atypical pemphigus, “erythema multiforme with pemphigus-like antibodies”, paraneoplastic autoimmune multiorgan syndrome (PAMS)

- Polymorphous skin eruption (bullae with erosions)
- Oropharynx involvement
- Stomatitis (SJS-like)
- Conjunctival involvement (2/3)

- Bronchiolitis obliterans (high mortality risk)
- Autoantibodies also deposited in kidneys, heart, muscle
Paraneoplastic pemphigus

- **Clinical**: 6 clinical variants: BP-like, cicatricial pemphigoid-like, PV-like, EM-like, GVHD-like, LP-like

- **Histology**: unique combination of suprabasilar acantholysis with apoptosis, vacuolar changes with or without lichenoid inflammation (PV-like + EM-like +/- LP-like). Sometimes, subepidermal blister (BP-like)

**Immunoprecipitation**: Antibodies to *plakin* proteins - 250 kDa-desmoplakin I, 210 kDa-desmoplakin II and *envoplakin*, 190 kDa-*periplakin*

**DIF**: polyclonal IgG, C3 in intercellular spaces + granular C3 along BM

**IIF**: Rat bladder epithelium (desmplakins without desmogleins)- positive test for IgG
Paraneoplastic pemphigus

- 2/3 with known malignancy; 1/3 without
- 80% linked to 3 neoplasms:
  - Non-Hodgkin's lymphoma (42%)
  - CLL (29%)
  - Castleman's pseudolymphoma (10%)

Less common:
- Retroperitoneal sarcomas (6%)
- Thymomas (malignant and benign, 6%)
- Waldenstrom's macroglobulinemia (6%)

**Our patient:** diagnosed with CLL after the diagnosis of paraneoplastic pemphigus was rendered.

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Paraneoplastic pemphigus

- **Mandatory focused search** in 1/3 without malignancy (imaging, CBC, SPEP)
- **Recalcitrant to therapy**, does not follow a parallel course with the underlying malignancy
  1. Benign and resectable (thymoma or Castleman's) ⇒ resection improves PNP
  2. Malignant neoplasms: treatment will not improve disease

- **Is a life-threatening autoimmune skin disease**
  - Mortality 90%: sepsis, 30% from respiratory failure
CASE 2

- 55 year old male with recent significant weight loss and intertriginous pruritic, exudative pustulovesicles and erosions.
Differential diagnosis

- Nutritional deficiencies:
  - Acrodermatitis enteropathica
  - Pellagra
  - Necrolytic migratory erythema

- Other (GVHD, subacute LE, DM, PRP, photo-induced drug reactions)

Zinc studies- normal limits
CT- abdomen

Necrolytic migratory erythema

- Considered a diagnostic marker for glucagon-secreting (alpha-cell) pancreatic tumor
- Metastatic at presentation (>50%)
- Rare without tumor: chronic pancreatitis, cirrhosis, gluten-sensitive enteropathy, myelodysplastic syndrome

- Pathogenesis: excessive levels of glucagon promote aminoacid catabolism, deficiency of proteins and epidermal necrosis
Necrolytic migratory erythema

- Erythematous macules and papules, often in the groin, perioral, ankles, then blistering plaques, erosions
- Pain and intense pruritus are common
- DM (85%), weight loss, diarrhea, anemia, edema (hypoalbuminemia)

Clinical clues: anatomic distribution, waxing and waning, systemic symptoms

Necrolytic migratory erythema

- When suspected: CBC, LFT’s, glucagon levels, zinc, glucose tolerance, CT of abdomen
- Hyperglucagonemia (10-20X normal), glucose intolerance (90%)
- The dermatitis is unresponsive to conventional therapy, usually resolves quickly after the tumor is resected
CASE 3

- 62 year old male with recent onset of pruritic, concentric, erythematous bands with fine scale, with rapid extension, on trunk and extremities

Histology

- Gyrate erythema
  - Erythema gyratum repens
  - Erythema chronicum migrans
  - Erythema marginatum (rheumaticum)
  - Erythema annulare centrifugum
- Superficial perivascular tightly cuffed (coat-sleeve pattern) lymphohistiocytic infiltrate
- Endothelial cell swelling with RBC extravasation
- Focal spongiosis, parakeratosis
Distinctive dermatologic manifestations:
- Wood-grain appearance created by concentric mildly scaling bands of flat-to-raised erythema
- Fairly rapid migration (up to 1 cm/day)
- Intense pruritus
- Sites of predilection that include the trunk and extremities

Erythema gyratum repens

- 85% occur in the context of internal malignancy (some believe is 100% if the patient is followed long enough).
  - Lung adenocarcinoma (33%)
  - Esophageal adenocarcinoma (8%)
  - Breast carcinoma or metastatic tumors of unknown primary origin (6% each)
- More than 50% of cases, the cutaneous eruption may precede malignancy by at least one year
- Erythema annulare centrifugum: may be associated with lymphomas (Hodgkin and non-Hodgkin)
Case 4

- 50-year old female with periorbital violaceous patches and red-purple papules over knuckles, and periungual telangiectasia
Dermatomyositis

- Association with malignancy is controversial: 6-50%, only in adult forms

Hill et al; Frequency of specific cancer types in DM and PM: a population based study. Cancer Jan 2001:
- Goal: to determine risk of cancer after diagnosis of DM/PM
- Patients from 3 countries in Northern Europe with DM or PM, >15 yrs old, excluded patients with cancer history
- 32% (198/618) with cancer - 58% diagnosed after DM
- Conclusion: DM - three fold increased risk for all cancer types
- Risk of ovarian (10 X)>lung>pancreas cancer remained high and significant up to 5 yrs
- Ovarian cancer risk normalized > 5 yrs
- Risk of cancer higher among older patients
Case 5

- A 42-year old female presents with large, yellow indurated plaques on periorbital and chest areas.
Necrobiotic xanthogranuloma

- In 80% of cases associated with IgG monoclonal gammopathy, usually with kappa light chains
- Our patient - bone marrow revealed multiple myeloma
- Differential diagnosis: subcutaneous GA, rheumatoid nodule, necrobiosis lipoidica diabeteorum
Other proliferative reactions

- **Multicentric reticulohistiocytosis**
  - Systemic granulomatous disease:
    - Cutaneous nodules (face, hands, nailfolds)
    - Severe symmetric destructive polyarthralgia of hands, knees, shoulders, “short fingers”
    - Arthritis mutilans in 50%
    - 2/3 with xanthelasma
    - Systemic infiltration: BM, heart, lung, kidney

- Distinct giant cells with “eosinophilic ground glass cytoplasm”, non-Langerhans derived

- 28% associated with neoplasia
- Controversial:
  - MRH progresses despite tumor therapy or remits without tumor treatment
  - No predominant consistent type of neoplasia
    - Leukemias and lymphomas most common
    - Breast, cervix, gastric
    - Ovarian, lung, colon
  - 75% precede cancer diagnosis (months-4 years)
  - Depending on level of suspicion, careful search/follow-up may be warranted
CASE 6

- A 30-year-old female with tender, violaceous edematous papules, nodules, bullous, ulcerated plaques on face, neck, and upper extremities
Sweet’s syndrome

3 Types:
1. Idiopathic form: preceded by URI
2. Drug associated: G-CSF
3. Malignancy associated (21%)
   - Female predominance (80%), age 30-50
   - Associated with fever, neutrophilia, prompt response to steroids

Sweet’s syndrome

- Hematologic malignancy (85%):
  - AML (42%)
  - Lymphoma (11%), MDS, CML, CLL, hairy cell leukemia, multiple myeloma
- Solid tumors: adenocarcinomas of GU tract (37%), breast (22%), GI tract (17%)
Suspect paraneoplastic Sweet’s if:
- Not preceded by URI
- Atypical, bullous, or ulcerated lesions
- Generalized involvement, including lower extremities
- Older patients
- Absent fever
- Recurrent episodes

Pyoderma gangrenosum
- Begins as painful papule or pustule, usually on lower extremities
- Extends to a tender irregular ulcer with necrotic base, undermined violaceous borders and peripheral advancing erythema
- Fever and toxicity
Pyoderma gangrenosum

Malignant association in 7%; presenting sign of acute leukemia - AML most common (23%), myeloma

Bullous variant commonly associated with malignancy

- Koester et al, bullous PG in myeloproliferative conditions, sign of transformation to acute leukemia, ominous prognostic sign.

CASE 7

- 42-year old male presents with tender, red pretibial plaques and nodules. Was clinically diagnosed with stasis dermatitis and pigmented purpuric dermatitis and no biopsy was performed. The lesions are growing and became more painful and the patient comes for a new evaluation.
**Foci of fat necrosis with ghost-like cells and calcifications**

- Basophilic granules in the cytoplasm of the necrotic fat cells
- Lamellar deposits around individual fat cells
- Polymorphous inflammatory infiltrate with rare giant cells

**Pancreatic panniculitis**

- **CT**: pancreatic mass (acinocellular carcinoma)
- High levels of amylase, lipase
- Fat necrosis occurs also in internal organs
- Hypocalcemia - life-threatening
- No clinical differences in the character of the subcutaneous nodules between the cases seen with pancreatic malignancy and those seen with benign pancreatic disease

**Other panniculitis**

- Chronic erythema nodosum – can be associated with non-Hodgkin lymphoma, carcinoma pancreas, colon, cervix
Paraneoplastic vasculitis

- Wide spectrum of vasculitis associated with neoplasia
  - 45% LCV
  - 37% PAN
  - 7% WG
- Majority hematologic malignancies (63%) but also seen in solid tumors
- Common association: hairy cell leukemia-PAN

Papulosquamous paraneoplastic lesions

- Acanthosis nigricans- 2.8%, gastric adenocarcinoma (60-90%)
- Acquired ichthyosis (non-epidermolytic palmoplantar keratoderma) - esophageal SCC
- Bazex syndrome (acrokeratosis paraneoplastica)
  - Violaceous papulosquamous eruption on ear helices, tip of nose, swelling and bulbous enlargement of distal phalanges
  - Male predominance (90%)
  - Underlying internal malignancy (100%): SCC of upper aerodigestive tracts (oropharynx, larynx or esophagus)
  - 47% - precedes the diagnosis of cancer
- Histology: NONSPECIFIC: mild perivascular inflammation, acanthosis, hyperkeratosis, focal parakeratosis and sometimes vacuolar degeneration of stratum spinosum

Papulosquamous paraneoplastic lesions

- Sign of Leser Trelat
  - Eruptive SK
  - Adenocarcinoma- gastric most common (24%)
- Tripe palms: significant marker of malignancy
  - (91%), lung-gastric, GU cancers
- Acquired ichthyosis
  - Hodgkin’s lymphoma (70-80%)
TAKE HOME MESSAGES

• Paraneoplastic dermatoses are often under-recognized
• Similar histology and clinical features with entities not associated with malignancy
• May precede the underlying malignancy

• Early recognition of paraneoplastic syndromes is of a paramount importance:
  - herald a new or recurrent neoplasm
  - signal a severe immunosuppressed status
  - great impact in overall morbidity and prognosis

KEY POINTS

- Remember those highly associated with underlying malignancies:
  - Paraneoplastic pemphigus
  - Necrolytic migratory erythema
  - Bazex syndrome
  - Leser-Trelat
  - Necrobiotic xanthogranuloma

- Multiple adnexal tumors may be associated with visceral tumors
- 43-year old male with two slowly growing lesions on left shoulder and respectively on right forearm

Well-circumscribed cystic sebaceous neoplasm composed predominantly of sebocytes

Endophytic sebaceous neoplasm, with keratoacanthoma-like architecture
Diagnosis

SEBACEOUS ADENOMAS
(one with cystic and the other one with keratoacanthoma-like architecture)

Muir-Torre Syndrome (MTS)

■ 1968 - Muir & Torre - patients with both sebaceous tumors and intestinal malignancies
■ MTS:
  ■ sebaceous neoplasm
  ■ internal malignancy
  ■ family history
■ Mode of inheritance - AD with variable penetrance

Skin tumors in MTS

■ Sebaceous neoplasms
  ■ adenoma, epithelioma/sebaceoma, carcinoma (30 %)
  ■ difficult to classify “cystic sebaceous neoplasms” (KA-like, cystic)
  ■ other tumors with sebaceous differentiation reported
■ Keratoacanthomas
Muir-Torre Syndrome

- At least 3 of 4 MTS patients show microsatellite instability (MSI)
- MTS: a subset of hereditary non-polyposis colorectal carcinoma (HNPCC) syndrome
- Majority (> 90%) of MSI results from loss of MMR proteins MLH1 or MSH2
- MTS: loss of MSH2/MSH6>>>MLH1
- HNPCC: loss of MSH2=MLH1
- There are only case reports of PMS2 loss in MTS

Microsatellite Instability

- PCR-based assay is the gold standard
- IHC – may be used with variable sensitivity and specificity rates

Histologic clues for sebaceous lesions associated with Muir-Torre syndrome

- Usually the lesions are hard to classify
- Sebaceous adenomas or sebaceomas are more commonly associated with MTS than carcinomas or hyperplasia
- Extraocular location
- Multiple lesions
- Cystic appearance
- Keratoacanthoma-like architecture
Trichilemmoma

- Face
- Solitary or multiple lesions (Cowden’s disease)
- Clear cells
- Peripheral palisading
- Thick basement membrane
- Warty epidermis
Cowden disease

Cowden disease (multiple hamartoma syndrome) - autosomal dominant condition with variable expression that results from a mutation in the PTEN gene on chromosome arm 10q.

Hamartomatous neoplasms: skin and mucosa, GI tract, bones, central nervous system, eyes and genitourinary tract.

Skin and mucosa involved in 90-100% of cases: trichilemmomas, oral mucosal papillomatosis, palmoplantar keratoses.

Other cutaneous manifestations: vitiligo, lipomas, hemangiomas, neurofibromas, xanthomas.

Associated with the development of several types of malignancy: breast, endometrial and thyroid carcinomas.
PTEN immunohistochemistry

- Complete PTEN loss was noted in 5/6 (83%) CS-associated TL and 1/33 (3%) sporadic (non-CS) TL.
- Demonstration of complete PTEN loss in TL by IHC is strongly suggestive of association with CS, but retention of PTEN staining does not entirely exclude CS.


Fibrofolliculoma and trichodiscoma

Birt-Hogg-Dube syndrome – AD, chr 7p11, encodes a novel protein, folliculin

- multiple FF, TD, acrochordons
- Associated with RCC (papillary, chromophobe, oncocytoma)

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