Lesions and syndromes: Cutaneous markers of systemic problems

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“In medicine and psychology, a syndrome is the association of several clinically recognizable features, signs (observed by a physician), symptoms (reported by the patient), phenomena or characteristics that often occur together, so that the presence of one feature alerts the physician to the presence of the others. In recent decades, the term has been used outside medicine to refer to a combination of phenomena seen in association.

The term syndrome derives from its Greek roots (σύνδρομος) and means literally "run together", as the features do. It is most often used to refer to the set of detectable characteristics when the reason that they occur together (the pathophysiology of the syndrome) has not yet been discovered. A familiar syndrome name often continues to be used even after an underlying cause has been found, or when there are a number of different primary causes that all give rise to the same combination of symptoms and signs. Many syndromes are named after the physicians credited with first reporting the association; these are "eponymous" syndromes (see also the list of eponymous diseases, many of which are called "syndromes"). Otherwise, disease features or presumed causes, as well as references to geography, history or poetry, can lend their names to syndromes.”

-Wikipedia, Syndrome, 9.12.2010

The Muir-Torre syndrome
Fig. 6.—An early kerato-acanthoma lesion showing hyperplasia of sebaceous glands and hyperkeratosis with plugging of several adjacent follicles. H. and E. (× 25.)

Fig. 7.—A fully developed kerato-acanthoma in which numerous follicles have coalesced to form a large central crater with overhanging edges. H. and E. (× 3.)
Muir-Torre syndrome

- Autosomal dominant condition
- Variant form of the hereditary non-polyposis colorectal carcinoma or Lynch syndrome
- Produced by germline defects in several genes coding for DNA mismatch repair proteins.
  - Two most commonly encountered mis-match repair proteins that are defective are hMSH2 and hMLH1
  - A defect in a mismatch repair protein results in so-called microsatellite instability
  - Microsatellites are repeated DNA sequences (often comprised of repeats of the bases C and A)

Muir-Torre syndrome (con’t)

- Microsatellite instability can silence tumor suppressor genes
- Most common carcinomas are colon, bladder, female genital tract, renal
- Colonic carcinomas behave less aggressively
Sebaceous hyperplasia
Sebaceoma
Cystic sebaceous neoplasm
TABLE 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical diagnosis</th>
<th>Location of CST</th>
<th>Histopathology</th>
<th>MSI</th>
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<tr>
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<td>9 (197)</td>
<td>Cancer, unknown</td>
<td>Back</td>
<td>Cystic sebaceous adenoma</td>
<td>(+)</td>
<td>2/5</td>
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</table>

*Correlation with the histology of cystic sebaceous tumors in patients with CST (1/5)."
FIG. 1. Multiple sebaceous tumors of the nasal region (Patient 1).

FIG. 2. Cystic sebaceous adenoma (Patient 1).

FIG. 4. A. Cystic sebaceous adenoma with a central opening to the sinocutaneous tract (Patient E). B. Cut section with a small rim of uninvolved sebaceous cells at the periphery, and a broad zone of uninvolved fully differentiated sebocytes toward the center.
FIG. 3. Cystic sebaceous adenoma (Patient 2).

FIG. 5. A, Protruding cystic sebaceous tumor (Patient 4) with a thickened cyst wall and a higher proportion of immature sebocytes. B, Part of the thickened cyst wall with an irregular proliferation of immature sebocytes.

Cowden’s syndrome
Cowden’s syndrome

- Also called multiple hamartoma syndrome
- Multiple cutaneous lesions, usually trichilemmomas (in 85% of patients), and visceral cancers
- Named after a patient, Rachel Cowden
- Trichilemmomas, also gingival, labial and lingual papillomatosis giving gingival mucosa with a "cobblestone" appearance, scrotal tongue, wart-like acral keratoses.
- Cowden fibroma= sclerotic fibroma
- Cutaneous lesions often appear in early 20s.

Cowden’s syndrome (cont’d)

- Extracutaneous manifestations more often in women
- Fibroadenomas of the breast, breast adenocarinomas, thyroid adenomas and carcinomas of several types, ovarian, endometrial, urinary tract and gastrointestinal cancer. Skeletal abnormalities including macrocephaly, kyphosis, an arched palate, mental retardation and seizure disorders can all be part of the syndrome.
- Germline mutations in the PTEN (phosphatase and TENsin homologue) gene (chr. 10q22–23).
- About 15% of cases of Cowden’s syndrome have mutations in succinate dehydrogenase.
- Other syndromes associated with PTEN mutation include the Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Proteus syndrome.
Tricholemmal differentiation

1. At the isthmus:
   A peripheral layer of keratinocytes with palisading arrangement on a thick basement membrane, several layers of polygonal keratinocytes with large eosinophilic cytoplasm and abrupt keratinization without granular layer, resulting in compact, orthokeratotic and eosinophilic keratin.

2. At the lower segment:
   One or several layers of clear cells, with peripheral palisading over a thick basement membrane.
CLASSIFICATION OF FOLLICULAR PROLIFERATIONS ACCORDING TO THEIR TYPE OF DIFFERENTIATION

- Differentiation toward the infundibulum:
  - Nevus comedonicus
  - Dilated pore
  - Infundibular cyst
  - Folliculo-sebaceous cystic hamartoma
  - Trichodendroma

- Differentiation toward the isthmus (tricholemmal differentiation):
  - Tricholemmoma, inverted follicular keratosis
  - Tricholemmal cyst
  - Proliferating tricholemmal tumor
  - Tumor of follicular infundibulum
  - Filar sheath acanthoma

- Differentiation toward the mantle:
  - Fibrofolliculoma
  - Trichodiscoma

- Differentiation toward matrical cells:
  - Filomatrixoma
  - BCC with matrical differentiation
  - Filomatricarcinoma

- Differentiation toward germinative cells:
  - Trichoblastoma
  - BCC with follicular differentiation

- Differentiation toward the entire follicle:
  - Basaloid follicular hamartoma
  - Trichoepithelioma
  - Fibrous papule
  - Panfolliculoma

Tricholemmoma

Clinical features

- Small solitary papule with keratotic surface, usually on the face.
- Multiple tricholemmomas may be a cutaneous marker of Cowden’s syndrome.
- Ackerman considered tricholemmomas as old warts with tricholemmal differentiation.
Tricholemmoma
Histopathologic features

- Sharply circumscribed lesions composed of one or more lobules of epithelium with tricholemmal differentiation: peripheral layer of columnar cells with nuclear palisading over a thick basement membrane, resembling the outer root sheath.
- Lobules of clear or pale cells containing abundant glycogen within their cytoplasm.
- Areas of pseudocarcinomatous hyperplasia in desmoplastic tricholemmoma.
Desmoplastic trichilemmoma: histologic variant resembling invasive carcinoma


A clinical and histologic review of 22 patients (13 males, 9 females) with cutaneous lesions classified as desmoplastic trichilemmoma is reported. Typically, the lesions occur as solitary dome-shaped papules on the face during (at least) the fifth decade of life. The average age was 64 years (range 19-89) with a median age of 66.5 years. The most frequent clinical diagnosis was basal cell carcinoma, and the most common sites were the lip, eyebrow and nose. Two lesions occurred in examples of sebaceous naevus of Jadassohn. The proportion of desmoplasia varies, but is generally between 20% and 60% of the lesion. Ulceration is seen in a minority of lesions when present, is closely associated with underlying desmoplasia. Desmoplasia may be seen in small, as well as large, trichilemmomas, it generally occurs centrally but at times may be seen peripherally. The appearance of strands of epithelial cells entrapped in dense fibrous and hyalinized may mimic desmoplastic variants of squamous cell carcinoma and basal cell carcinoma. This appearance may be particularly troublesome when the desmoplasia occurs at the base of the biopsy specimen. Knowledge of this phenomenon and the search for more typical features of trichilemmoma such as clear cells and peripherally palisaded columnar cells upon a thickened, eosinophilic basal lamina membrane will allow the correct diagnosis to be made. We believe that the desmoplasia occurs as a secondary change in pre-existing trichilemmomas.
Sclerotic fibroma

- Well circumscribed, dermal or superficial subcutaneous mass
- Pauci-cellular
- Plywood sclerosis
- CD34+
FIGURE 1. Congenital Hand Lesion.

Calonje, Eduardo; Fletcher, Christopher; Mentzel, Thomas

FIGURE 1. Circumscribed lesion on the left palm.

FIGURE 2. Congenital Hand Lesion.

Calonje, Eduardo; Fletcher, Christopher; Mentzel, Thomas

FIGURE 2. Low-power view showing an exophytic lesion.

FIGURE 3. Congenital Hand Lesion.

Calonje, Eduardo; Fletcher, Christopher; Mentzel, Thomas

FIGURE 3. Spindle cell proliferation with a storiform growth pattern.


Calonje, Eduardo; Fletcher, Christopher; Mentzel, Thomas

FIGURE 4. The spindle cells show uniform appearance with tapering nuclei and indistinct cytoplasm.
Gardner’s syndrome

- Multiple and often unusual cutaneous cysts
- Gastrointestinal polyposis, osteomas of the mandible and skull
- A phenotypic variant of Familial Adenomatous Polyposis.
- Adenomatous Polyposis Coli–APC) located on chr. 5q21-22

APC

- Encodes a protein that inhibits the Wnt signalling pathway by binding to and then down-regulating beta-catenin.
- APC mutations produce stop codons in the gene, leading to truncation of the protein. With the loss of APC function, beta-catenin accumulates in the cytoplasm, leading to problems in cell migration and differentiation.
- Affected patients often have over 100 colonic polyps, and an increased risk of small bowel and colon cancer. Sigmoidoscopy starting at age 12 and procto-colectomy and terminal ileostomy at young adult age have been advocated as preventive measures.
Cutaneous lesions in Gardner’s syndrome

- Infundibular-matrical hybrid cysts
- Pilomatricomas
Matrical differentiation

- Round, monomorphous epithelial cells with vesicular nuclei, scant cytoplasm, prominent nucleoli, many mitotic figures and scattered dendritic melanocytes
- “Shadow” cells: Abortive attempts of hair shaft formation.

Pilomatrixoma

Clinical features

- Frequent in children on the head, neck and upper extremities.
- Nodular, firm well-circumscribed lesion
- Multiple pilomatrixomas may be associated with myotonic dystrophy, Turner’s and Gardner’s syndrome.
- Rare variants: Giant, anetodermic, perforating, etc.
**Pilomatricoma**

**Histopathologic features**

- Cystic neoplasm with three types of neoplastic cells: matrical, transitional and shadow cells.
- Many mitotic figures in matrical cells ("proliferating pilomatricoma").
- Frequent calcification and ossification of shadow cells.
- Foreign body granuloma around shadow cells.
- Melanin in 25% of the cases.
- Rare findings:
  - Extramedullary hematopoiesis
  - Transepidermal elimination: Perforating pilomatricoma
  - Anetodermic changes
  - Matricoma: Multiple discrete neoplastic aggregations of matrical and shadow cells
  - Melanocytic matricoma: Pilomatricoma with abundant dendritic melanocytes scattered within the aggregations of matrical cells
  - Pilomatricoma-like changes in the cyst wall of infundibular cysts in patients with Gardner's syndrome

**Pilomatrixcarcinoma**

**Histopathologic features**

- General architecture of malignant neoplasm: Ulceration of the epidermis, necrosis en masse, etc.
- Most of the neoplastic aggregations are composed of basophilic matrical cells, with pleomorphic vesicular nuclei and numerous mitotic figures.
- Focally, matrical differentiation in the form of shadow cells.
Birt-Hogg-Dubee syndrome

Clinical features

- Fibrofolliculomas and trichodiscomas on the face: Asymptomatic skin-colored papules on the face. Most cases develop in the third decade of the life.
- Renal tumors, often bilateral. Oncocytoma, chromophobous carcinoma.
- Spontaneous pneumothorax, pulmonary cyst, emphysema.

Birt-Hogg-Dubé syndrome

- Several types of cutaneous lesions (usually stated as trichodiscomas, fibrofolliculomas and acrochordons) appear on facial skin, usually in patients in their twenties.
- The lesions are tiny papules, sometimes umbilicated, clinically resembling closed comedones. Occasionally, they can affect the trunk.

Birt-Hogg-Dubé syndrome, cont’d

- Mutations of tumor suppressor gene called BHD/FLCN, chromosome 17p11.2.
- Encodes folliculin, expressed in the skin and in several other tissues.
- Folliculin down-regulates mTOR activity
- Extracutaneous manifestations:
  - Spontaneous pneumothorax
  - Emphysema
  - Pulmonary cysts.
  - Renal tumors include oncocytopomas, chromophobe renal cell carcinomas and combinations of both cell types, or oncocytic hybrid tumors.
Fibrofolliculoma-Trichodiscoma

Histopathologic features

- Fibrofolliculomas and trichodiscomas seem to be the two ends of the spectrum of a single lesion.
- Fibrofolliculoma: Cords and strands of epithelial basaloid cells radiating from a follicular structure and surrounded by loose connective tissue.
- Trichodiscoma: Loose and finely fibrillary connective tissue surrounded by folliculosebaceous collarettes at both lateral margins.
Fibrofolliculoma
Tricodiscoma
Angiofibroma-like lesions in Birt-Hogg-Dubee syndrome
RENAL TUMORES

<table>
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<tr>
<th>GENERAL PATIENTS</th>
<th>PATIENTS WITH BHD SYNDROME</th>
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<tbody>
<tr>
<td>Clear-cell renal carcinoma (75%)</td>
<td>Chromophobe carcinoma (34%)</td>
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<tr>
<td>Papillary renal carcinoma (15%)</td>
<td>Renal oncocytoma (9%)</td>
</tr>
<tr>
<td>Renal oncocytoma (5%)</td>
<td>Hybrid tumors between chromophobe carcinoma and renal oncocytoma (50%)</td>
</tr>
<tr>
<td>Chromophobe carcinoma (5%)</td>
<td>Clear-cell renal carcinoma (9%)</td>
</tr>
</tbody>
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Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

- Cutaneous and uterine leiomyomas, and renal cell carcinoma
- Cutaneous lesions appear in young adults, increase in number with age
- Segmental leiomyomas are a marker for HLRCC
- Uterine leiomyomas appear in affected women, from their twenties to middle age
- The renal cell carcinomas include papillary, tubulo-papillary and collecting duct neoplasms, and often behave aggressively

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

- Enzymatic testing in skin fibroblasts
- Molecular genetic testing
Carney’s complex

- Autosomal dominant condition
- Angiomyxomas, epithelioid blue nevi, and mucosal lentigines
- Endocrine abnormalities, including neoplasms
- CNC1 gene located on chromosome 17q22-24 and the CNC2 gene mapped to 2p16 are considered responsible
- CNC1 gene, also known as the PRKAR1A gene, is a tumor suppressor gene that the type 1A regulatory subunit of c-AMP-dependent protein kinase A.

Carney’s complex, cont’d

- Superficial angiomyxoma
- Unlike banal cutaneous myxomas, those of Carney’s complex often feature the induction of hair follicular structures from the overlying epidermis, in the form of rudimentary follicular bulbs and papillae.
- Especially in external ear canal
- Atrial myxoma
Pigmented epithelioid melanocytoma

- Is it distinct from epithelioid blue nevus of Carney complex and from “animal type melanoma”?
- Protein kinase regulatory subunit R1α loss a possible marker for sporadic PEM
- Many cases with sentinel nodal involvement, few with distant metastases (Zembowicz, USCAP 2009)
The basal cell nevus syndrome (BCNS) is due to mutations in the patched or PTCH1 gene.

This gene encodes a transmembrane protein that is part of the sonic hedgehog pathway, normally inhibiting smoothened (SMO) and thus slowing down GLI1 translocation to the cell nucleus.

Sporadic BCCs can have mutations in PTCH1 that render it ineffective, or mutations in SMO; either can result in increased GLI1 translocation. GLI1 translocation, in turn causes proliferation and inhibits differentiation. PTCH1 is also mutated in trichoepitheliomas, and PTCH1 knock-out mice develop trichoblastomas—hence, mutation is necessary but not sufficient for the formation of BCC in many cases.
Basal cell nevus syndrome (BCNS, Gorlin-Goltz Syndrome)

- Mutation in patched gene (ptchd)
- Basal cell carcinomas at early age
- Palmar pits
- Odontogenic keratocysts
- Infundibulocystic BCCs in clinically normal skin
- Anti-ptchd therapy in clinical trials (e.g. GDC-0449)
**Infundibular differentiation**

- Cystic lesions lined by epithelium similar to follicular infundibulum
- Basal layer, several layers of keratinocytes, a granular layer, and a cornified layer composed of laminated or basket-weave corneocytes
Cutaneous keratocysts of nevoid basal cell carcinoma syndrome


Four cysts were removed from two unrelated patients with nevoid basal cell carcinoma syndrome. Multiple sections from each cyst were studied. Two cysts showed histologic features similar to keratocysts that occur in the jaws of patients with this syndrome. The cysts were lined by a fessooned epithelium consisting of two to five layers of squamous cells that formed keratin without the presence of a granular cell layer. One cyst contained some lanugo hair and a small bud of follicular epithelium. This cyst was therefore similar to cutaneous steatocysts but did not have an identifiable sebaceous component. The second cyst was devoid of hair and adnexal structures and was indistinguishable from a jaw keratocyst. Two other cysts were typical epidermoid (infundibular) cysts. Although speculative, it is likely that some cutaneous cysts in patients with nevoid basal cell carcinoma syndrome are identical to jaw keratocysts and may be another cutaneous marker for this disease complex. (J AM ACADEM DERMATOL 14:572-576, 1986.)
Ultraviolet and ionizing radiation enhance the growth of BCCs and trichoblastomas in patched heterozygous knockout mice


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Brooke’s syndrome

• Aka Brooke-Spiegler syndrome, hereditary cylindromatosis, multiple familial trichoepithelioma
• Susceptibility to trichoepitheliomas, cylindromas, spiradenomas, pure or in combination
• Most lesions on head/neck

Brooke’s syndrome, cont’d

• Prediliction for face, scalp
• Entire scalp can be involved in cylindromatosis
• Rarely, cylindrocarcinomas, spiradenocarcinomas, trichoblastic carcinomas
Brooke’s syndrome, cont’d

- Familial cylindromatosis mapped to 16q12-16q13
- CYLD, a tumor suppressor gene identified in this locus, and then found in sporadic cylindromas
- CYLD interacts with NF-κB signalling pathway
**Basaloid follicular hamartoma**

**Clinical features**

- Clinical variants: Systematized, multiple, localized and linear.
- Generalized forms are familiar with autosomal dominant inheritance.
- Generalized variants may be associated with hypotrichosis and myasthenia gravis.
- In all clinical variants: Small papular lesions centered in hair follicles.
**Basaloid follicular hamartoma**

**Histopathologic features**

- Individual hair follicles are replaced by strands and branching cords of undifferentiated basaloid cells.
- Anastomosing basaloid cords
- Scant fibrous stroma
- Histopathologic differential diagnosis: Infundibulocystic BCC, trichoepithelioma and Pinkus fibroepithelioma: BFH has less stroma and interfollicular dermis is not involved.