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. 1.—Multiple facial nodules, some umbilicated and pigmented, with scarring at the sites of excision biopsy.
Fig. 6.—An early kerato-acanthoma lesion showing hyperplasia of sebaceous glands and hyperkeratosis with plugging of several adjacent follicles. H. and E. \( \times 25 \).
Fig. 7.—A fully developed kerato-akanthoma 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
Fig. 7. Case 5. Sebaceous adenoma, nose. Hematoxylin and eosin. × 14. (AFIP Neg. 73-3394.)
TABLE 1. Clinical findings in eight patients with MTS with CST: Current number in this study; in parentheses running number in genetic study (see ref. 1). +Current age. In Patient 4, metastatic colorectal cancer caused death at age 69. Internal tumors and skin tumors: in parentheses number of tumors. mx, multiple tumors.

<table>
<thead>
<tr>
<th>Number*</th>
<th>Sex</th>
<th>Ages (years)</th>
<th>Internal tumors</th>
<th>Skin tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (132)</td>
<td>M</td>
<td>89</td>
<td>Colorectal cancer (2')</td>
<td>Keratoacanthoma (2')</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Renal cancer</td>
<td>Basal cell carcinoma</td>
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<td></td>
<td></td>
<td></td>
<td>Colon adenomas (mx)</td>
<td>Solar keratoses (mx)</td>
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<td></td>
<td></td>
<td></td>
<td>Warts (mx)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sebaceous hyperplasias (mx)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sebaceous adenomas (mx)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spinal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cystic sebaceous adenoma</td>
</tr>
<tr>
<td>2 (134)</td>
<td>M</td>
<td>72</td>
<td>Colorectal cancer (2')</td>
<td>Proliferating cystic sebaceous tumor</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cystic sebaceous adenoma</td>
</tr>
<tr>
<td>3 (133)</td>
<td>M</td>
<td>46</td>
<td>Colorectal cancer</td>
<td>One unknown sebaceous tumor</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sebaceous hyperplasias (mx)</td>
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<td></td>
<td></td>
<td></td>
<td>Sebaceous adenomas (mx)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proliferating cystic sebaceous tumor</td>
</tr>
<tr>
<td>4 (162)</td>
<td>M</td>
<td>death</td>
<td>Colorectal cancer metastatic</td>
<td>Keratoacanthomas (mx)</td>
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<td>Squamous cell carcinoma (mx)</td>
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<td>Solar keratoses (mx)</td>
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<td></td>
<td></td>
<td>Sebaceous adenomas (mx)</td>
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<td></td>
<td>Cystic sebaceous adenoma</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Cystic sebaceous adenoma (2')</td>
</tr>
<tr>
<td>5 (MTS-K8)</td>
<td>M</td>
<td>54</td>
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<td>6 (MTS-K11)</td>
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<td></td>
<td>Colorectal cancer</td>
<td>Cystic sebaceous tumors (mx)</td>
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<td></td>
<td></td>
<td></td>
<td>Proliferating cystic sebaceous tumor (mx)</td>
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<td>7 (MTS-K13)</td>
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<td>59</td>
<td>Renal cancer</td>
<td>Keratoacanthomas</td>
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<td>8 (MTS-23)</td>
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<td>86</td>
<td>Colon cancer (3')</td>
<td>Sebaceous carcinoma</td>
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<td></td>
<td>Breast cancer</td>
<td>Sebaceous hyperplasias (mx)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Endometrial cancer</td>
<td>Sebaceous adenomas (mx)</td>
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<td></td>
<td></td>
<td></td>
<td>Solar keratoses (mx)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Proliferating cystic sebaceous tumor</td>
</tr>
</tbody>
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* Current number in this study; in parentheses running number in genetic study (see ref. 1).
### TABLE 2.

Cystic Sebaceous Tumors as Marker Lesions for the Muir-Torre Syndrome: A Histopathologic and Molecular Genetic Study.

Rutten, Arno; Burgdorf, Walter; Hugel, Heino; Kutzner, Heinz; Hosseiny-Malayeri, Hamid; Friedl, Waltraut; Propping, Peter; Kruse, Roland


<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical diagnosis</th>
<th>Location of CST</th>
<th>Histopathology</th>
<th>MSI</th>
<th>Germine mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (132)</td>
<td>Dermatolipoma</td>
<td>Upper back</td>
<td>Cystic sebaceous adenoma</td>
<td>(6/7) +</td>
<td>hMSH2</td>
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<tr>
<td>2 (134)</td>
<td>Cyst.</td>
<td>Lower back</td>
<td>Proliferating cystic sebaceous tumor</td>
<td>n.e.</td>
<td>(1677delT)</td>
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<tr>
<td>3 (133)</td>
<td>Cyst.</td>
<td>Upper back</td>
<td>Cystic sebaceous adenoma</td>
<td>(4/6) +</td>
<td>ND</td>
</tr>
<tr>
<td>4 (162)</td>
<td>Cyst, nodule</td>
<td>Trunk</td>
<td>Proliferating cystic sebaceous tumor</td>
<td>(4/5) +</td>
<td>1809delT</td>
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<tr>
<td>5 (MTS-K8)</td>
<td>(Rule out) carcinoma</td>
<td>Abdomen</td>
<td>Cystic sebaceous adenoma</td>
<td>(3/8) +</td>
<td>ND</td>
</tr>
<tr>
<td>6 (MTS-K11)</td>
<td>Not given</td>
<td>Cheek</td>
<td>Cystic sebaceous adenoma</td>
<td>(2/4) +</td>
<td>ND</td>
</tr>
<tr>
<td>7 (MTS-K18)</td>
<td>Cystic tumor</td>
<td>Trunk</td>
<td>Cystic sebaceous adenoma</td>
<td>(2/4) +</td>
<td>ND</td>
</tr>
<tr>
<td>8 (MTS-23)</td>
<td>Nodule</td>
<td>Upper back</td>
<td>Cystic sebaceous adenoma</td>
<td>(2/4) +</td>
<td>ND</td>
</tr>
</tbody>
</table>

CST, cystic sebaceous tumors; MSI, microsatellite instability (instable markers/all examined markers); NE, not examined; ND, not detected.
### TABLE 3.

**Cystic Sebaceous Tumors as Marker Lesions for the Muir-Torre Syndrome: A Histopathologic and Molecular Genetic Study.**
Rutten, Arno; Burgdorf, Walter; Hugel, Heino; Kutzner, Heinz; Hosseiny-Malayeri, Hamid; Friedl, Waltraut; Propping, Peter; Kruse, Roland


**TABLE 3.** Summary of the spectrum of histopathologic findings in CST

<table>
<thead>
<tr>
<th>Lesion Description</th>
<th>Histopathologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign cystic sebaceous adenomas</strong></td>
<td>- Regular differentiation of sebocytes towards the center</td>
</tr>
<tr>
<td></td>
<td>- High amount of sebum in the center</td>
</tr>
<tr>
<td></td>
<td>- No (or few) mitoses</td>
</tr>
<tr>
<td><strong>Proliferating cystic sebaceous tumors</strong></td>
<td>- More prominent proliferation of sebocytes</td>
</tr>
<tr>
<td></td>
<td>- Irregular differentiation of sebocytes towards the center</td>
</tr>
<tr>
<td></td>
<td>- Small focus of sebaceous cell</td>
</tr>
<tr>
<td></td>
<td>- Mitoses and focally atypical cells</td>
</tr>
</tbody>
</table>
Cystic Sebaceous Tumors as Marker Lesions for the Muir-Torre Syndrome: A Histopathologic and Molecular Genetic Study.
Rutten, Arno; Burgdorf, Walter; Hugel, Heino; Kutzner, Heinz; Hosseiny-Malayeri, Hamid; Friedl, Waltraut; Propping, Peter; Kruse, Roland.

FIG. 1. Multiple sebaceous tumors of the nasal region (Patient 4).
FIG. 2.

Cystic Sebaceous Tumors as Marker Lesions for the Muir-Torre Syndrome: A Histopathologic and Molecular Genetic Study.
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FIG. 2. Cystic sebaceous adenoma (Patient 1).
FIG. 4. A: Cystic sebaceous adenoma with a central opening to the skin surface (Patient 6). B: Cyst wall with a small rim of nonvacuolated immature sebocytes at the periphery and a broad zone of vacuolated fully differentiated sebocytes toward the center.
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Rutten, Arno; Burgdorf, Walter; Hugel, Heino; Kutzner, Heinz; Hosseiny-Malayeri, Hamid; Friedl, Waltraut; Propping, Peter; Kruse, Roland


Figure 4. Continued
FIG. 3.

Cystic Sebaceous Tumors as Marker Lesions for the Muir-Torre Syndrome: A Histopathologic and Molecular Genetic Study.
Rutten, Arno; Burgdorf, Walter; Hugel, Heino; Kutzner, Heinz; Hosseiny-Malayeri, Hamid; Friedl, Waltraut; Propping, Peter; Kruse, Roland

FIG. 3. Cystic sebaceous adenoma (Patient 2).
Cystic Sebaceous Tumors as Marker Lesions for the Muir-Torre Syndrome: A Histopathologic and Molecular Genetic Study.
Rutten, Arno; Burgdorf, Walter; Hugel, Heino; Kutzner, Heinz; Hosseiny-Malayeri, Hamid; Friedl, Waltraut; Propping, Peter; Kruse, Roland

Fig. 5. A: Proliferating cystic sebaceous tumor (Patient 3) with a folded cyst wall and a higher proportion of immature sebocytes. B: Part of the infolded cyst wall with an irregular proliferation of immature sebocytes.
Figure 5

Cystic Sebaceous Tumors as Marker Lesions for the Muir-Torre Syndrome: A Histopathologic and Molecular Genetic Study.
Rutten, Arno; Burgdorf, Walter; Hugel, Heino; Kutzner, Heinz; Hosseiny-Malayeri, Hamid; Friedl, Waltraud; Propping, Peter; Kruse, Roland


Figure 5. Continued
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.
Figure 1. The Mitogen-Activated Protein (MAP) Kinase and Phosphatidylinositol 3' Kinase (PI3K) Pathways.
Signals from receptor tyrosine kinases can promote proliferation through the MAP kinase pathway (left branch) and survival through the PI3 kinase pathway (right branch).
Infundibulum

Isthmus

Stem

Bulb

Lower segment
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
  - Trichoadenoma
- Differentiation toward the isthmus (tricholemmal differentiation):
  - Tricholemmoma, inverted follicular keratosis
  - Tricholemmal cyst
  - Proliferating tricholemmal tumor
  - Tumor of follicular infundibulum
  - Pilar sheath acanthoma
- Differentiation toward the mantle:
  - Fibrofolliculoma
  - Trichodiscoma
- Differentiation toward matrical cells:
  - Pilomatricoma
  - BCC with matrical differentiation
  - Pilomatrixcarcinoma
- Differentiation toward germinative cells:
  - Trichoblastoma
  - BCC with follicular differentiation
- Differentiation toward the entire follicle:
  - Basaloid follicular hamartoma
  - Trichofolliculoma
  - Fibrous papule
  - Panfolliculoma
**Trichoolemmoma**

**Clinical features**

- Small solitary papule with keratotic surface, usually on the face.
- Multiple trichoolemmomas may be a cutaneous marker of Cowden’s syndrome.
- Ackerman considered trichoolemmomas as old warts with trichoolemmal differentiation.
Detection of HPV DNA in Trichilemmomas by Polymerase Chain Reaction

Angela Rohwedder, Oliver Keminier, Carlo Hendricks, and Jörg Schaller

1Department of Medical Microbiology and Virology, Ruhr-University Bochum, Germany
2Department of Dermatology, Dermatohistological Unit, St. Barbara Hospital Duisburg, Germany
MULTIPLE TRICHOLEMMOMAS IN COWDEN SYNDROME
Trichoilemmoma

Histopathologic features

- Sharply circumscribed lesions composed of one or more lobules of epithelium with trichoilemmal 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 trichoilemmoma.
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 nevus sebaceus of Jadassohn. The proportion of desmoplasia varies, but is generally between 20% to 60% of the lesion. Ulceration is seen in a minority of lesions but 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 fibrosis and hyalinization 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 basement membrane will allow the correct diagnosis to be made. We believe that the desmoplasia occurs as a secondary change in pre-existing trichilemmomas.

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Daniel J. Santa Cruz, Cutaneous Pathology, St. John’s Mercy Medical Center, 615 S. New Ballas Road, St. Louis, MO 63141–8221, U.S.A.
Accepted July 17, 1989.
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
DOI: 10.1097/DAD.0b013e318159263d

FIGURE 1. Ceribiform lesion on the left palm.
FIGURE 2

Low-power view showing an exophytic lesion.
FIGURE 3

Spindle cell proliferation with a storiform growth pattern.
FIGURE 4. The spindle cells show uniform appearance with tapering nuclei and indistinct cytoplasm.
Gardner’s syndrome
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.
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
Birt-Hogg Dubee 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

Clinical features

• Autosomal dominant inheritance. Mutation in chromosoma 17p11.2, locus at the folliculin gene.
• 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-Dubee 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 oncocytes, 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.
Ackerman, Reddy, Soyer 2001

Fibrofoliculoma

Tricodiscoma
Angiofibroma-like lesions in Birt-Hogg-Dubee syndrome
Birt-Hogg-Dubé Syndrome
A Novel Marker of Kidney Neoplasia

Jorge R. Toro, MD; Gladys Glenn, MD, PhD; Paul Duray, MD; Thomas Darling, MD, PhD; Gregor Weirich, MD; Berton Zbar, MD; Marston Linehan, MD; Maria L. Turner, MD

Background: Birt-Hogg-Dubé syndrome (BHD) is a dominantly inherited predisposition for development of fibrofolliculomas, trichodiscomas, and acrochordons. Concurrent internal tumors, such as colonic polyps and renal carcinoma, have been described in patients with BHD.

Objective: To evaluate kindreds with familial renal tumors for cutaneous manifestations of BHD.

Design: One hundred fifty-two patients from 49 families underwent complete oral and skin examination. Skin lesions were identified by their clinical appearance, and the diagnosis was confirmed by results of histologic examination. Individuals underwent screening for familial renal neoplasms.

Setting: A tertiary referral research hospital.

Patients: Individuals with familial renal tumors and their asymptomatic at-risk relatives.

Main Outcome Measure: We determined whether any form of renal cancer is associated BHD.

Results: We identified 3 extended kindreds in whom renal neoplasms and BHD appeared to segregate together. Two kindreds had renal oncocytomas and a third had a variant of papillary renal cell carcinoma. Thirteen patients exhibited BHD. Seven individuals, including a set of identical twins, had renal neoplasms and BHD. An additional 4 patients (3 deceased and not examined) in these families had renal neoplasms but not BHD. Birt-Hogg-Dubé syndrome without renal neoplasms was present in 6 individuals. Thirteen patients with fibrofolliculomas and trichodiscomas presented clinically with multiple smooth skin-colored to grayish-white papules located on the face, auricles, neck, and upper trunk. Oral papules were present in 9 of 28 and acrochordons in 11 of 28 patients. Features of BHD not previously appreciated included dermal lipomas in 5, collagenomas in 4, and pulmonary cysts in 4 of 28 patients. Families with BHD did not display germline mutations in the von Hippel-Lindau gene or in the tyrosine kinase domain of the MET proto-oncogene.

Conclusions: Birt-Hogg-Dubé syndrome may be associated with familial renal tumors. Birt-Hogg-Dubé and renal tumors segregate together in an autosomal dominant fashion. Patients with BHD and their relatives are at risk for development of renal tumors. Therefore, patients with BHD and their relatives should undergo abdominal computed tomography and renal ultrasound screening for renal tumors.

Arêh Dermatol. 1999;135:1195-1202