COLLEGE of AMERICAN PATHOLOGISTS

ARCHIVES
of Pathology & Laboratory Medicine

EARLY ONLINE RELEASE

Note: This article was posted on the *Archives* Web site as an Early Online Release. Early Online Release articles have been peer reviewed, copyedited, and reviewed by the authors. Additional changes or corrections may appear in these articles when they appear in a future print issue of the *Archives*. Early Online Release articles are citable by using the Digital Object Identifier (DOI), a unique number given to every article. The DOI will typically appear at the end of the abstract.

The DOI for this manuscript is doi: 10.5858/arpa.2018-0189-RA

The final published version of this manuscript will replace the Early Online Release version at the above DOI once it is available.

Skin Adnexal Tumors in Plain Language

A Practical Approach for the General Surgical Pathologist

Edward H. Fulton, MD; Jennifer R. Kaley, MD; Jerad M. Gardner, MD

• ***Context.***—**Skin adnexal tumors, those neoplasms deriving from hair follicles and sweat glands, are often a source of confusion amongst even experienced pathologists. Many well-described entities have overlapping features, tumors are often only partially sampled, and many cases do not fit neatly into well-established classification schemes.**

Objectives.—**To simplify categorization of adnexal tumors for the general surgical pathologist and to shed light on many of the diagnostic dilemmas commonly encountered in daily practice. The following review breaks adnexal neoplasms into 3 groups: sebaceous, sweat gland-derived, and follicular.**

Data Sources.—**Pathology reference texts and primary literature regarding adnexal tumors.**

Conclusions.—**Review of the clinical and histopathologic features of primary cutaneous adnexal tumors, and the diagnostic dilemmas they create, will assist the general surgical pathologist in diagnosing these often challenging lesions.**

(*Arch Pathol Lab Med*. doi: 10.5858/arpa.2018-0189-RA)

As a general guideline, one might consider the possibility of an adnexal tumor when there is an epithelial proliferation in the dermis or subcutis that looks different from common epidermally-derived lesions like basal cell or squamous cell carcinoma, or is otherwise challenging to classify. In our dermatopathology practice at a tertiary academic medical center, we see adnexal neoplasms relatively often in consultation, and yet we still frequently encounter adnexal tumors that defy precise classification and do not nicely fit into one diagnostic box.

How should pathologists proceed once they have identified a possible skin adnexal tumor but are unsure of its precise classification? Before going straight to immunohistochemistry (IHC), the authors suggest using the following algorithmic approach based on hematoxylin-eosin (H&E) sections. Adnexal proliferations can be divided into 3 major groups on the basis of whether they show histologic differentiation resembling sebaceous glands, sweat glands/ducts (eccrine and/or apocrine), or hair follicles. In general, sebaceous proliferations are often the easiest to recognize because of their characteristic vacuolated sebocytes and because there are relatively few different entities in the sebaceous group. So rule out sebaceous proliferations first. Sweat gland tumors are a much larger category, but they are unified by the presence of sweat duct formation; these can range from small duct lumens within individual tumor cells all the way up to large dilated cystic spaces comprising much of the volume of the entire tumor. If there are no sebocytes or sweat ducts, then the last step is to consider the possibility of a hair follicle proliferation. This is often the most difficult category to recognize in our opinion, as follicular proliferations represent the most diverse group of adnexal tumors with the most histomorphologic overlap. Each group is discussed in more detail below. Supplemental images and educational videos about skin adnexal tumors corresponding to this article are available free online at https://goo.gl/sK71Lp (or scan the QR code in Figure 1).

SEBACEOUS TUMORS

Sebaceous proliferations are usually easy to recognize because of the vacuolated, bubbly, mature sebocytes that are present in varying proportions in most sebaceous lesions. Ideally, a mature sebocyte will possess 3 criteria: sharply marginated round cytoplasmic vacuoles, vacuoles that are optically clear (white) and do not contain mucin or other material, and vacuoles that scallop/indent into the nuclear membrane. The optically clear vacuoles in sebocytes are what remain after lipid material in the cytoplasm is processed for paraffin embedding. By IHC, these cells will stain with epithelial membrane antigen (EMA), adipophilin, and androgen receptor. Nuclear staining for factor XIIIa (clone AC-1A1) has also been shown to be a sensitive and specific marker of sebaceous cells (Figure 1, A and B).[1,2] In some sebaceous lesions, particularly sebaceous carcinomas, mature sebocytes may be very focal and difficult to find.

Sebaceous Hyperplasia

Clinically, sebaceous hyperplasia appears as one or more yellow papules, often with a central "dell" or depression, usually on the face of an adult. They may mimic basal cell carcinoma (BCC). Histologically, they look like mature, normal adult sebaceous glands, but only much larger (and

Accepted for publication August 13, 2018.

From the Department of Pathology, University of Arkansas for Medical Sciences, Little Rock.

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Jerad M. Gardner, MD, Department of Pathology, University of Arkansas for Medical Sciences, 4301 W Markham St, Little Rock, AR 72205 (email: jmgardner@uams.edu; Twitter: @JMGardnerMD).

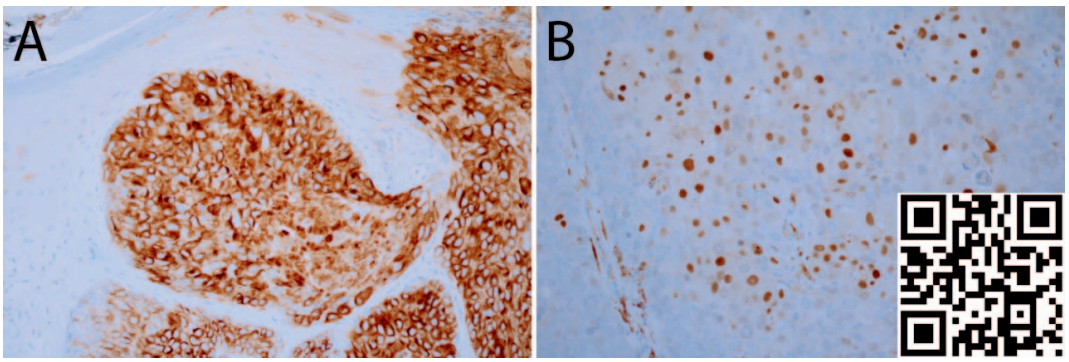

Figure 1. *Epithelial membrane antigen (A) and FXIIIa (clone AC-1A1) (B) staining in mature sebocytes within a sebaceous adenoma (original magnification ×200 [A and B]). Supplemental images and educational videos about skin adnexal tumors corresponding to this article are available free online at https://goo.gl/sK71Lp (or scan the QR code in Figure 1).*

forming a papule). Importantly, there is only a thin peripheral layer of basaloid cells (Figure 2, A through C). These enlarged sebaceous glands often empty directly onto the skin surface without connection to a hair follicle. Sebaceous hyperplasia is not associated with Muir-Torre syndrome (MTS).

Sebaceous Adenoma

Clinically, these appear as yellow papules, usually on the face of an adult. They may mimic BCC. Histologically they consist of circumscribed dermal sebaceous lobules, often connected to the epidermis (though not always). The central sebocytes are white/mature, but toward the periphery the sebocytes are less mature and usually have a pink-grey color owing to fewer lipid droplets and thus more visible cytoplasm. The peripheral basal cell layer is often several layers thick: if the basaloid component comprises more than 50% of the lesion, lesions are (somewhat arbitrarily) termed *sebaceomas* (Figure 2, A through C). Sebaceous adenomas may be associated with MTS (see below section on Sebaceous Neoplasms and Muir-Torre Syndrome).

Sebaceoma

As mentioned above, this is essentially a variation of sebaceous adenoma in which the basaloid component predominates and comprises 50% or more of the lesion. The lesion is still circumscribed and arranged into lobules. It may have some mitoses, but they should not be numerous or atypical. Thinking about the basaloid cell population in sebaceoma as homologous to the proliferative basal layer of a normal sebaceous gland should help observers accept and rationalize the presence of occasional mitoses in benign sebaceous lesions (Figure 3). Numerous mitoses, nuclear atypia, or infiltrative growth should prompt concern for sebaceous carcinoma. When we see a few atypical features

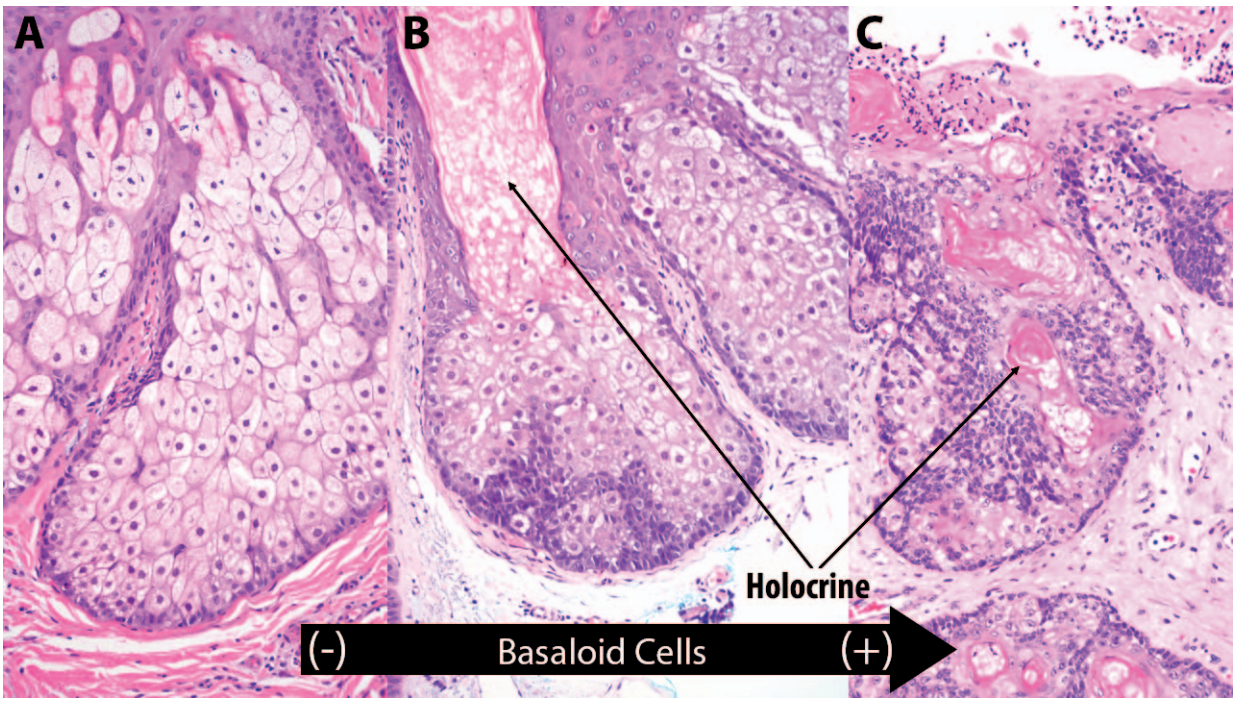

Figure 2. *A normal sebaceous lobule (A), a sebaceous adenoma (B), and a sebaceoma (C). Basaloid cells are limited to 1 to 2 layers at the periphery of normal sebaceous lobules, whereas they are increased in sebaceous adenomas and predominate (comprise more than 50% of the lesion) in sebaceomas. All 3 may show holocrine secretion (hematoxylin-eosin, original magnification ×200 [A through C]).*

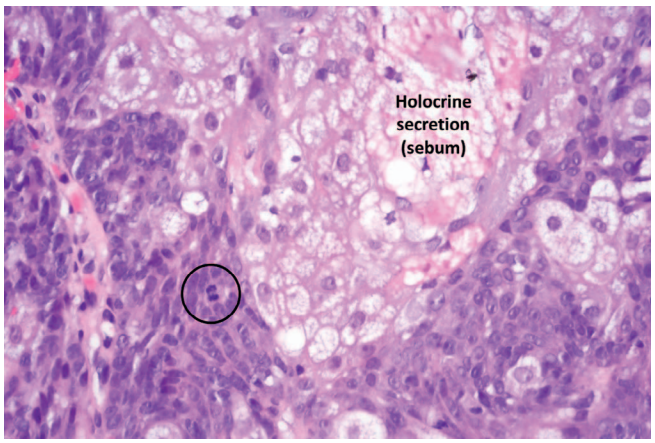

Figure 3. *Sebaceous adenoma. Scattered mitoses (circled) are acceptable in the basaloid component of benign sebaceous lesions. Sebum should not be overinterpreted as tumor necrosis (hematoxylin-eosin, original magnification ×400).*

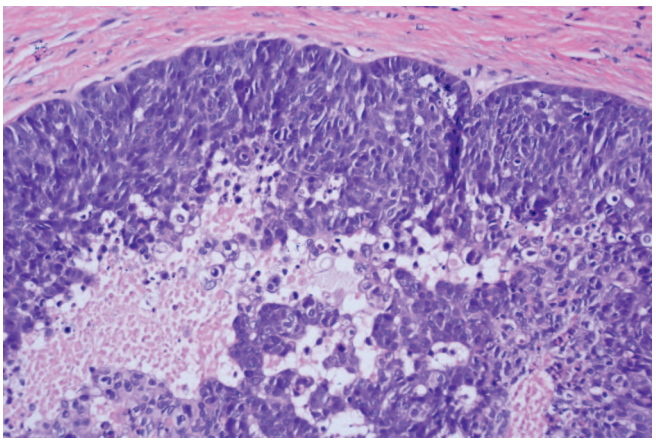

Figure 4. *Sebaceous carcinoma. Crowded, hyperchromatic atypical basaloid cells with focal sebaceous differentiation. Mitoses and apoptotic cells are abundant (hematoxylin-eosin, original magnification ×200).*

in sebaceous adenoma or sebaceoma but feel it falls short of sebaceous carcinoma, we usually append the diagnosis "with atypia" and add a comment recommending complete excision (especially if the lesion is transected at the base of a shave biopsy). For conventional sebaceous adenomas or sebaceomas that lack atypical features, complete excision is not mandatory in our opinion, even if margins are positive.

Basal cell carcinoma can show varying types and degrees of adnexal differentiation (sebaceous, eccrine/apocrine, or follicular). If a lesion has classic features of BCC, especially peripheral palisading with stromal clefting and stromal mucin, but also has scattered sebocytes, we tend to designate the lesion "basal cell carcinoma with focal sebaceous differentiation" rather than "sebaceoma." A general rule of thumb: if the sebaceous cells were removed from the lesion, would the remaining lesion be diagnostic for BCC? If the answer is "yes," then the lesion is probably a BCC with sebaceous differentiation rather than a sebaceoma or other sebaceous tumor. Normal sebaceous glands can sometimes become entrapped within BCC, squamous cell carcinoma, or other cutaneous epithelial neoplasms; it is important not to mistake these for true sebaceous differentiation within a tumor.

It should also be noted that normal sebaceous glands secrete sebum via holocrine secretion (mature sebocytes die and their remnants form sebum). This process is often recapitulated within sebaceous tumors, and it can lead to overinterpretation as tumor necrosis, leading to overdiagnosis of malignancy. We usually regard the pink remnants of vacuolated sebocytes found in the cystic spaces of many sebaceous neoplasms as sebum-like material rather than as true tumor necrosis. In our experience, true tumor necrosis in sebaceous neoplasms usually manifests as sheets of necrotic *basaloid* cells. Additionally, if there is true tumor necrosis in a malignant sebaceous lesion, there will usually be other malignant features as well; consequently, we urge caution against in making a definitive diagnosis of sebaceous carcinoma on the basis of necrosis alone (Figure 3).

Sebaceous Carcinoma

Sebaceous carcinomas are malignant tumors with sebaceous differentiation. They can be split into 2 clinical groups with essentially identical histologic features: *peri*ocular sebaceous carcinoma and *extra*ocular sebaceous carcinoma.

Periocular sebaceous carcinomas make up most cases of sebaceous carcinoma (~75%). They present most often in the upper eyelid, but also in other areas near the eye. The clinical presentation varies widely, mimicking other skin cancers or even inflammatory processes like chalazion. Periocular sebaceous carcinomas are less likely to be associated with MTS,[3] and a strong association with *TP53* mutations suggests that they may have a unique pathogenesis relative to other sebaceous carcinomas.[4,5] They carry about a 25% risk of metastasis and eventual mortality.

Extraocular sebaceous carcinomas are those that occur away from the eye; these tumors are more likely to be associated with MTS (see below discussion of sebaceous neoplasms and Muir-Torre syndrome), particularly when located away from the head and neck.

Both periocular and extraocular sebaceous carcinomas may exhibit aggressive behavior. A large retrospective review found similar 5-year overall survival in both groups: 75% for sebaceous carcinomas with orbital involvement versus 68% for sebaceous carcinomas not involving the orbit ($P = .66$).[6] Periocular sebaceous carcinomas with involvement of both upper and lower eyelids or with pagetoid invasion of the overlying epithelia of the eyelids may have a higher risk of aggressive behavior.[7,8]

The histopathology of sebaceous carcinomas is variable. They may have an irregular lobular growth pattern, diffuse sheets of basaloid cells, or infiltrative growth. Sebocytes may be abundant or very scarce. Some sebaceous carcinomas look similar to sebaceoma with abundant basaloid cells but with marked atypia and numerous and/or atypical mitoses (Figure 4). Others may appear similar to squamous cell carcinoma and can show prominent keratinization. Poorly differentiated sebaceous carcinoma in particular can be very difficult to distinguish from poorly differentiated squamous cell carcinoma, as obvious sebocytes can be very scarce. Sebaceous carcinoma should be in the differential for any carcinoma arising near the eye, especially if poorly differentiated. Two main difficulties arise in the diagnosis of sebaceous carcinoma; well-differentiated sebaceous carcinomas are obviously sebaceous in nature, but the difficulty lies in determining if they are truly malignant or are merely a benign sebaceous neoplasm;

Table 1. Immunohistochemistry of Sebaceous Tumors

Immunohistochemistry Target Antigen	Function
EMA	Usually shows strong positivity and highlights cytoplasmic vacuoles of more mature sebocytes. SCC and BCC can also express EMA,[22] as can other adnexal neoplasms. Recognizing the vacuolated pattern on EMA staining is the most important feature.
Adipophilin	Strongly highlights cytoplasmic vacuoles in more mature sebocytes.[23]
Factor XIIIa (clone AC-1A1)	Nuclear staining of normal and neoplastic sebocytes uniformly shows strong nuclear staining for factor XIIIa, but only with the AC-1A1 clone (Figure 1). Staining is best seen in more mature vacuolated sebocytes rather than in the basaloid cells. SCC and many other clear cell neoplasms are usually either negative or only weakly to moderately positive; use background normal sebaceous glands as an internal control and as a reference for judging strong intensity of staining.[1,2]
p63 and p40	p63 and p40 are expressed in the basaloid germinative cells of normal sebaceous glands,[24–26] and in our experience, the basaloid cells of benign and malignant sebaceous neoplasms, as well.[25,27]
CK7	CK7 shows positivity in most sebaceous tumors, although a subset may show negativity.[28]
CEA	Sebaceous tumors are usually negative for CEA.[29]
Ber-EP4	Usually shows negativity in sebaceoma, but positivity in the vast majority of basal cell carcinomas[30] (an important caveat is that squamatized areas of BCC may lack Ber-EP4 expression).[31]

Abbreviations: BCC, basal cell carcinoma; CEA, carcinoembryonic antigen; CK7, cytokeratin 7; EMA, epithelial membrane antigen; SCC, squamous cell carcinoma.

identifying numerous or atypical mitoses, cytologic atypia, and infiltrative growth are keys to making a diagnosis of sebaceous carcinoma in these cases. Poorly differentiated sebaceous carcinomas are obviously malignant, but the difficulty lies in determining if they are truly sebaceous in nature or are merely a poorly differentiated squamous cell (or other) carcinoma; identifying focal sebaceous differentiation, by H&E features or immunohistochemical staining, namely, nuclear positivity for factor XIIIa (clone AC-1A1) and "vacuolated" EMA staining (detailed in Table 1), is key to establishing a diagnosis of sebaceous carcinoma in these cases.

Nevus Sebaceus

Nevus sebaceus (sometimes incorrectly spelled "nevus sebaceous") is a hamartomatous proliferation of epidermis and adnexal structures (as with several other entities in dermatopathology, the word *nevus* here has nothing to do with melanocytic nevus or melanocytes). Although not a true sebaceous neoplasm, we include nevus sebaceus under the sebaceous heading here because of its name and the fact that it often possesses prominent sebaceous glands. It usually presents clinically as a pebbled hairless plaque on the face or scalp that is present at birth and that subsequently enlarges over time. As androgen hormone levels increase during puberty, the lesion takes on a more yellow "greasy" appearance due to enlargement of the sebaceous glands within the lesion. Histologically, nevus sebaceus can be identified at low power by a variable amount of papillomatous thickening of the epidermis (often resembling seborrheic keratosis) coupled with markedly diminished or completely absent hair follicles within the center of the lesion. This latter feature is particularly noticeable in lesions located on the scalp. Sebaceous glands are usually increased in number, and they often empty directly onto the surface of the skin rather than into an associated hair follicle like a normal sebaceous gland. In young children (prepuberty), the sebaceous glands are usually small and immature with much less vacuolated lipid content. During and after puberty, these sebaceous glands dramatically enlarge and become more lipidized owing to the influence of androgen hormones. Some cases of nevus sebaceus also possess apocrine glands (or eccrine glands with apocrine features). Apocrine glands are usually restricted to certain anatomic sites (mostly the anogenital region, axillae, and eyelids); thus, the presence of apocrine glands in the dermis in other anatomic sites should always raise the possibility of nevus sebaceus. Nevus sebaceus may harbor other tumors, mostly benign adnexal tumors including trichoblastoma, trichilemmoma, and syringocystadenoma papilliferum. When benign, precise classification of these is not of clinical importance. The authors sometimes use verbiage such as "nevus sebaceus with a variety of benign adnexal tumors" in cases with numerous secondary adnexal proliferations. Secondary malignant tumors are quite rare in nevus sebaceus in our experience, but include true BCC (most tumors resembling BCC within a nevus sebaceus may actually represent benign trichoblastomas),[9,10] squamous cell carcinoma, and apocrine carcinoma.[11]

Sebaceous Neoplasms and Muir-Torre Syndrome

Some sebaceous adenomas, sebaceomas, and sebaceous carcinomas are associated with MTS.[12,13] Sebaceous hyperplasia has no association with this syndrome, nor does nevus sebaceus. Muir-Torre syndrome is a variant of hereditary nonpolyposis colorectal cancer syndrome (also referred to as Lynch syndrome). It is the result of a germline mutation in one of several DNA mismatch repair (MMR) genes, most notably *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Unlike classic Lynch syndrome, where *MLH1* mutations predominate, *MSH2* is the most common germline-mutated MTS-associated gene. A second hit to the other allele of the mutated mismatch repair gene results in microsatellite instability and may lead to subsequent development of cancer.

MMR protein expression in sebaceous lesions can be assessed by IHC. Like in classic Lynch syndrome, because MMR proteins are paired in the cell, loss of one may affect the presence of another. MLH1 is paired with PMS2; as the dominant partner, if MLH1 is lost, PMS2 is also lost (but not vice versa). Similarly, MSH2 and MSH6 are partners; as the dominant partner, if MSH2 is lost, then MSH6 is also lost (but not vice versa).[14] The combination of positive and negative staining should yield enough information to identify the putative defective gene (Figure 5, A through D). It should be noted that benign sebaceous tumors in patients with MTS behave no differently than sporadic

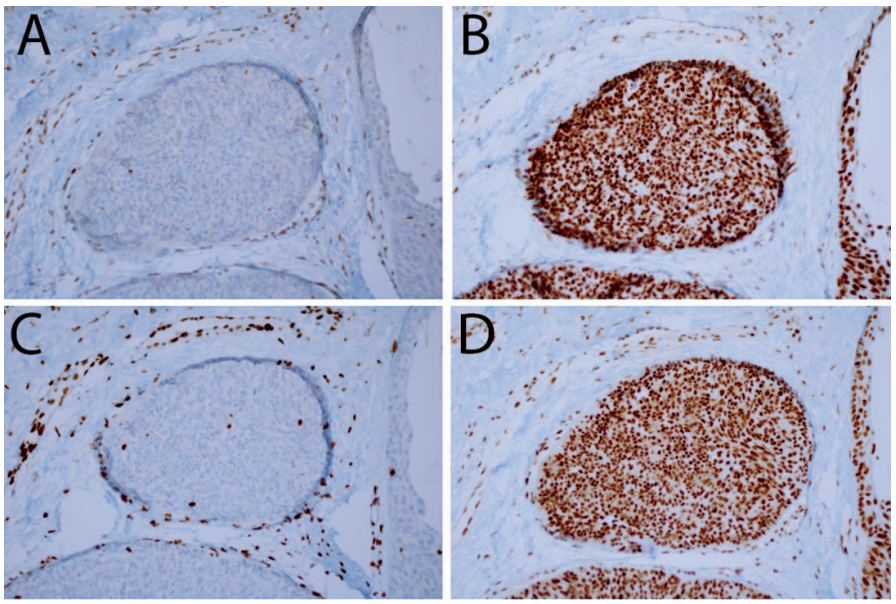

Figure 5. *Mismatch repair (MMR) protein interrogation by immunohistochemistry in a sebaceous adenoma. In this example, MSH-2 (A) and MSH-6 (C) staining are lost, while PMS-2 (B) and MLH-1 (D) staining are retained. This aberrant pattern of staining is compatible with* MSH2 *gene mutation, the most common MMR gene mutation in Muir-Torre syndrome (original magnification ×40 [A through D]).*

benign sebaceous tumors (ie, a sebaceous adenoma is benign regardless of whether it is sporadic or Muir-Torre associated). Practically speaking, in the authors' experience, most sebaceous neoplasms seen in our practice appear to be sporadic and unassociated with MTS.

There are varying opinions about how and when to test for MTS in patients with sebaceous neoplasia. As mentioned above, immunohistochemical stains for 1 of the MMR gene proteins can be performed and will show loss of nuclear staining when the corresponding gene is defective. This seems like a simple solution; however, loss of nuclear staining is often seen in *sporadic* cases of sebaceous neoplasia (where there is somatic but not germline mutation of 1 of the MMR genes). Up to two-thirds of sebaceous neoplasms will have defective MMR proteins by IHC,[15] but only a minority of these patients will actually have MTS.[16,17] Consequently, even if a sebaceous neoplasm has loss of a nuclear MMR protein(s) by IHC, the patient is still statistically unlikely to have MTS.

Ultimately, there is no clear consensus opinion regarding MMR protein testing of sebaceous lesions by IHC; because of the high rate of aberrant MMR protein expression (ie, loss of nuclear staining) in sporadic sebaceous neoplasms, we do not routinely perform MMR protein IHC testing in our practice unless requested by the treating physician. In our experience, most treating physicians with whom we work rarely or never request MMR IHC testing on sebaceous neoplasms. The authors add the comment "sebaceous neoplasms are sometimes associated with Muir-Torre syndrome" to all diagnoses of sebaceous carcinoma, sebaceous adenoma, and sebaceoma to help ensure that anyone receiving the report is aware of the potential syndromic association.

Some features raise additional consideration for MTS: multiple sebaceous neoplasms, particularly on extrafacial sites,[18] a sebaceous adenoma with cystic change,[19] and extraocular sebaceous carcinoma, particularly in patients younger than 50 years.[20] We are not aware of a definitive link between young age and MTS for sebaceous adenomas or sebaceomas. However, in our experience, most sebaceous neoplasms occur in adults older than 50 years. The presence of a sebaceous adenoma or sebaceoma in a younger adult is unusual. The authors believe that young adults who develop a sebaceous neoplasm may merit additional workup to exclude the possibility of MTS. This is because a subset of patients with MTS presents with sebaceous neoplasms before (sometimes by many years) the development of internal visceral malignancy. In one study, the median age for detection of internal visceral malignancy in patients with MTS was 50 years.[21] Diagnosis of MTS at a younger age could thus potentially allow for earlier detection and treatment of internal visceral malignancy. In individuals of reproductive age, a diagnosis of MTS may be important in family planning, as well. The treating physician and patient can decide together whether or not to pursue further MTS workup for the patient, based on their individual medical scenario and personal wishes. For those patients who choose to pursue further workup, consultation with a genetic counselor and/or gastroenterologist may be of value.

A number of immunohistochemical stains have been used to characterize sebaceous tumors[1,2,22–31]; they are outlined in Table 1.

SWEAT GLAND TUMORS

Sweat gland tumors are unified by the presence of ductal or glandular differentiation recapitulating various different parts of eccrine and apocrine glands and ducts. However, despite this unifying feature, they can show a relatively wide range of histopathologic features. We have attempted to arrange them into groups below based on 6 common histologic patterns (Table 2).

Pattern 1: Dermal Cyst With Double Cuboidal/Columnar Lining

Hidrocystoma

Hidrocystomas are the simplest benign sweat gland tumors; they usually clinically present as small, translucent papules on the upper cheek near the eye, more commonly in women. When biopsied, they often "pop" and deflate, releasing the sweat trapped inside. Histopathologically, they consist of single or multiple dilated cysts in the dermis lined by an attenuated layer of double cuboidal cells (indicative of their sweat duct derivation). The lining may be eccrine or

Table 2. Sweat Gland Tumors by Basic Histologic Pattern		
	Pattern Description	**Included Lesions**
Pattern 1	Dermal cyst with double cuboidal/columnar lining	Hidrocystoma, cystadenoma
Pattern 2	Solid pink/clear/squamoid proliferation in epidermis and/or dermis	Acrospiromas (hidroacanthoma simplex, poroma, dermal duct tumor, hidradenoma) and malignant counterparts
Pattern 3	Blue basaloid proliferation in dermis	Spiradenoma, cylindroma, and malignant counterparts
Pattern 4	Tadpole/paisley tie	Syringoma, microcystic adnexal carcinoma
Pattern 5	Cystic spaces and papillary projections	Syringocystadenoma papilliferum, hidradenoma papilliferum, digital papillary adenocarcinoma
Pattern 6	Dermal nodule with variable mixture of cords/chains/tubules and chondromyxoid stroma	Mixed tumor (chondroid syringoma)

apocrine, but as with most sweat gland tumors, the distinction between eccrine and apocrine differentiation is not clinically important.

Cystadenoma

When the lining of a hidrocystoma becomes thicker or more complex (beyond the usual attenuated double layer of cuboidal cells), the term *cystadenoma* is used. In our opinion, the change is vaguely reminiscent of the proliferative epithelium seen in usual ductal hyperplasia in the breast. This lesion is benign, and the epithelial cells should still be bland.

Pattern 2: Solid Pink/Clear/Squamoid Proliferation in Epidermis and/or Dermis +/− Cystic Change

Acrospiromas

Acrospiromas are a family of tumors so named because of their theoretical differentiation toward the acrosyringium (the portion of the sweat duct that passes through the epidermis).[32] On low power they tend to have an eosinophilic squamoid appearance, and closer examination usually reveals ductal lumen formation. The ducts are sometimes massively dilated to form large cystic spaces. If one imagines the cellular substance of an acrospiroma as being pink modeling clay, molding it into different shapes would yield different tumor names within the acrospiroma family (Figure 6). If it is entirely intraepidermal: hidroacanthoma simplex. If it is hanging from the epidermis like a shower curtain or extending long fingers downward: poroma. If it forms multiple superficial dermal nodules that loosely fit together (sometimes imparting a "carpal bone" appearance): dermal duct tumor. If forming 1 or several large deep dermal nodules, often with cystic spaces: hidradenoma. Any of these tumors may have clear cell change, in some cases being so abundant as to mimic metastatic renal cell carcinoma or other clear cell tumors. The subtypes of acrospiroma are explored below. These tumors may have overlapping features with one another (eg, hidradenoma sometimes connects to the epidermis and resembles poroma in the superficial aspect of the tumor). The authors attempt to classify these by which subtype they fit best with overall. Subclassification is mostly for academic interest and is not usually of clinical significance.

Hidroacanthoma simplex

This is a type of acrospiroma that is limited to the epidermis, with limited or no fingers of tumor pushing down into the dermis (the typical feature of poroma). The low-power appearance is quite similar to a clonal seborrheic keratosis, but with groups of small uniform bland "poroid" cells located within the epidermis. There is usually sharp demarcation from the adjacent normal epidermal keratinocytes. Small sweat ducts with a pink inner cuticle are usually present.

Poroma

This is a type of acrospiroma that presents as a sessile nodule, sometimes red and scaly. It is classically described on the sole or side of the foot, but it can occur in many other cutaneous sites. Histologically, poromas are composed of small, round, bland "poroid" cells that fill markedly elongated rete or tongues of tumor that push from the epidermis down into the underlying dermis. The tumor cells show abrupt demarcation from the overlying/adjacent epidermal keratinocytes, a useful diagnostic clue. A range of ductal differentiation is present within the tumor, including small cytoplasmic vacuoles, immature ducts (small round empty spaces lined by a pink homogenous cuticle layer), and more well-developed tubules (similar to normal eccrine ducts) embedded within the tumor. Larger dilated cystic ducts may also be present. The surface may be ulcerated. The stroma may be edematous and inflamed with

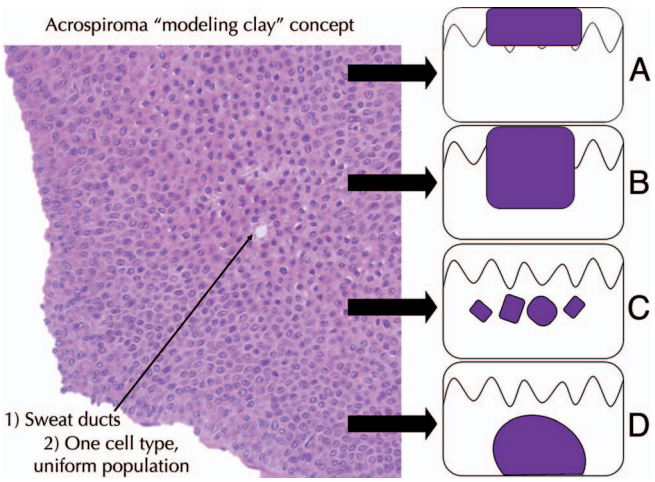

Figure 6. *Acrospiromas are the group of sweat gland tumors with differentiation toward the acrosyringium (the intraepidermal portion of the sweat duct). They have a uniform population of round to oval cells with foci of sweat duct formation. Conceptually, if this acrospiroma "clay" is molded into different shapes, it yields different tumor types within the acrospiroma family: hidroacanthoma simplex (A), poroma (B), dermal duct tumor (C), and hidradenoma (D) (hematoxylin-eosin, original magnification ×100).*

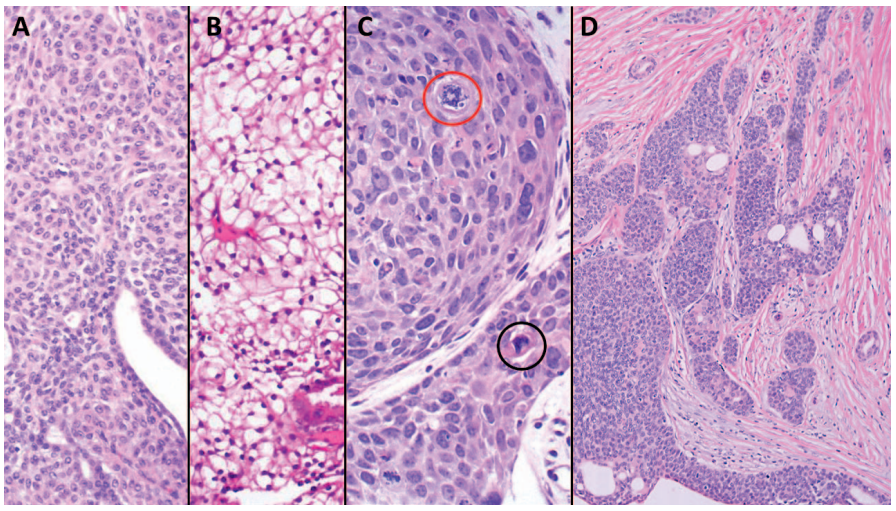

Figure 7. *Benign hidradenoma (A) with well-formed ducts. Note the lack of atypia, mitoses, or apoptotic cells. Hidradenomas may have extensive clear cell change (B), to the point that they look like clear cell renal cell carcinoma. Abundant and atypical mitoses (red circle), apoptotic cells (black circle), cytologic atypia (C), and infiltrative growth (D) are all features that support malignancy (C and D) (hematoxylin-eosin, original magnifications ×100 [A and B], ×200 [C], and ×40 [D]).*

dilated capillaries (these can resemble ducts at low power) and there may be dense pink basement membrane deposition also. Of note, pigmented poromas exist, displaying abundant melanin within tumor cells as well as admixed dendritic melanocytes: these can be clinically confused with nodular melanoma.[33] The presence of scattered single dendritic melanocytes evenly dispersed throughout the epithelial tumor cells is the characteristic pattern of "passenger" melanocytes that is seen in pigmented poroma, some seborrheic keratoses, and other epidermal neoplasms; these benign melanocytes should not be mistaken for the pagetoid spread of melanoma. The dendritic branching pigmented cytoplasmic processes, absence of nesting, even distribution throughout the epithelial cells, and absence of spread into the epidermis beyond the confines of the tumor are all clues to distinguish this benign passenger melanocyte phenomenon from bona fide melanocytic neoplasia.

Dermal Duct Tumor

This is a type of acrospiroma consisting of multiple small tumor nodules centered in the dermis with no connection to the epidermis. Many view these to be either poromas with limited connection to the epidermis (or a connection that is just not visible in the examined sections) and/or smaller, more superficial examples of hidradenoma with poroid cytologic features. These opinions reflect the similarity and relatedness of the acrospiroma group of tumors, and likely amount to semantics with no clinical significance. We do not use this diagnostic term often in our practice, as we believe most tumors in this category can usually fit into either poroma or hidradenoma, both of which are diagnostic terms more widely understood by dermatologists.

Hidradenoma

This is a type of acrospiroma presenting as a flesh-colored or erythematous nodule, usually in adults, that can occur anywhere. Histopathologically, hidradenomas consist of a circumscribed dermal nodule, often multilobulated, and sometimes with prominent clear cell and/or central cystic change. Some cases involve the subcutis. Many cases show focal or even extensive connection to the epidermis (showing overlapping features with poroma). Ductal structures may be small vacuole-like lumens, more obvious well-formed ducts (Figure 7, A), or, most commonly, large cystically-dilated ducts. Cuboidal or columnar cells, sometimes with apocrine differentiation, line the ductal spaces. Many sweat gland tumors produce dense pink basement membrane material in the intervening stroma; this finding is particularly prominent in some cases of hidradenoma.

Clear Cell Change: Clear cell change is a frequent finding in hidradenoma, and when extensive can mimic metastatic renal cell carcinoma (Figure 7, B).[34] Cystic spaces, basement membrane material, or direct connection to epidermis and/or adnexal structures are all features that, if present, support hidradenoma over metastatic renal cell carcinoma. Additionally, like most adnexal tumors, hidradenomas are positive for p63[35,36] and in our personal experience, also positive for p40, whereas renal cell carcinomas are negative for both p63 and p40.[37,38]

Atypia: When the overall appearance is that of benign hidradenoma, but there are focal atypical features (pleomorphism, large nucleoli, or increased mitotic activity) that fall short of obvious malignancy, the term *atypical hidradenoma* can be used. The authors use this designation occasionally, especially when the base of the lesion cannot be visualized on the biopsy, and thus the growth pattern (infiltrative versus noninfiltrative) cannot be reliably assessed. We usually recommend complete excision (if feasible for the anatomic site) and close clinical follow-up in this scenario. In their series of 10 cases, Nazarian et al[39] found that atypical hidradenomas are likely to recur locally (particularly if incompletely excised) but unlikely to metastasize.

Necrosis: In our experience, some cases of otherwise benign hidradenomas have small foci of necrosis. Nazarian et al[39] reported that several cases of atypical hidradenoma in their series had areas of necrosis, but we have had difficulty finding published data about the significance of focal necrosis in conventional hidradenomas in the absence of other atypical or malignant features. In our opinion, this is probably allowable in a benign hidradenoma provided a careful search for any other worrisome features is undertaken and the whole lesion is present for microscopic evaluation. Otherwise, it is probably prudent to recommend conservative complete excision of the lesion.

Hidradenomas in Breast: Hidradenomas can occur in the skin overlying the breast. When this happens, the differential often includes low-grade ductal carcinoma in situ (DCIS). Accurate clinical information regarding the precise location of the lesion (superficial—involving only skin/

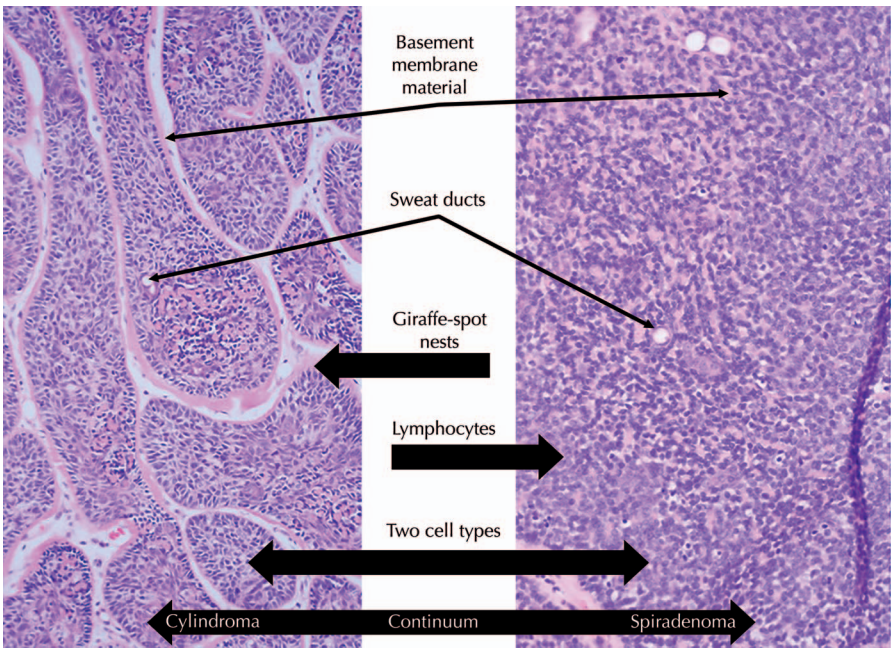

Figure 8. *Cylindroma (left) and spiradenoma (right) are 2 closely related sweat gland tumors. Sometimes, both cylindroma and spiradenoma components are present together in the same lesion (hematoxylin-eosin, original magnification ×40).*

subcutis—versus deep—involving breast parenchyma) can be of great help in making the distinction. The two can also be distinguished by IHC: hidradenoma, like most other primary cutaneous adnexal tumors, will usually be p63 positive, while low-grade DCIS should be p63 negative and estrogen receptor positive.

Malignant Acrospiromas

Malignant counterparts exist for the different members of the acrospiroma family. These tumors usually possess architectural similarities to their benign counterparts, albeit with the addition of cytologic atypia, brisk and/or atypical mitotic activity, and/or infiltrative growth pattern (Figure 7, C and D). Alternatively, obvious carcinoma can arise out of a background benign acrospiroma, giving a biphasic tumor with both benign and malignant components, but in our experience, this scenario is much less common. Malignant sweat gland tumors are very rare overall, but in our practice, we encounter malignant acrospiromas more frequently than most other types of malignant sweat gland tumors.

Porocarcinoma

Porocarcinoma has similar architectural features to poroma, but with the addition of marked nuclear atypia and brisk mitotic activity. It can closely resemble squamous cell carcinoma. Porocarcinoma can be distinguished from squamous cell carcinoma by identification of duct formation by tumor cells, but distinguishing true duct formation from entrapment of background normal intraepidermal sweat ducts (acrosyringia) or from nonspecific intracytoplasmic vacuoles can be quite difficult. Some studies have shown that strong expression of CD117 is supportive of porocarcinoma over squamous cell carcinoma.[40] Porocarcinoma can be in situ or invasive; porocarcinoma in situ that is limited to the epidermis without fingers protruding down into the dermis could technically be referred to as *malignant hidroacanthoma simplex*, but we find this terminology to be confusing to many treating physicians and thus we rarely use it in practice. True invasion can be difficult to distinguish from the tongues or fingers of in situ tumor that push deeply into the dermis in porocarcinoma. The presence of dermal desmoplastic response can be a useful feature that favors invasion in uncertain cases. When transected at the base in a partial biopsy, "porocarcinoma, at least in situ" can be a useful designation. In cases where it is uncertain if we are dealing with squamous cell carcinoma or porocarcinoma, we will often use terminology such as *carcinoma, invasive* or *carcinoma in situ* with a comment that squamous cell carcinoma is favored but porocarcinoma cannot be fully excluded (or vice versa). This helps the dermatologist to know that more aggressive behavior is possible and that treatment and follow-up should be planned accordingly.

Hidradenocarcinoma

This is the malignant form of hidradenoma. Sometimes there is a preexisting benign hidradenoma component from which the malignant component has arisen, but other times the malignant tumor appears to arise de novo. Hidradenocarcinoma has features similar to benign hidradenoma, including clear cell change and duct formation, but with the additional presence of marked nuclear atypia, brisk mitotic activity (usually greater than 4/10 high-power fields) including atypical mitotic figures, broad zones of necrosis, and/or infiltrative growth. In our experience, infiltrative growth is one of the most helpful features in distinguishing hidradenocarcinoma from benign hidradenoma. Hidradenocarcinomas have potential for local recurrence and/or metastasis.[39,41]

Pattern 3: Blue Basaloid Proliferation in Dermis Spiradenoma and Cylindroma

Spiradenoma and cylindroma are like siblings. They are both composed of the same types of cells, but these are arranged in different patterns. They sometimes coexist with both spiradenoma and cylindroma intermingled on the same slide (hybrid spiradenoma/cylindroma also known as "spiradenocylindroma") (Figure 8).

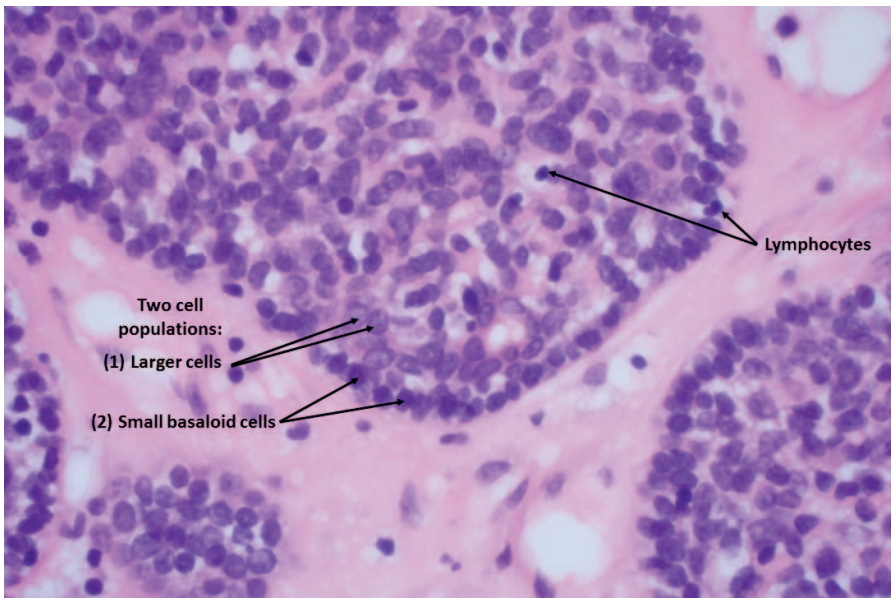

Figure 9. *Spiradenoma. Both spiradenomas and cylindromas have 2 cell populations: small basaloid cells at the periphery of nests, and larger ovoid cells with open chromatin toward the center of nests. Spiradenomas are also often peppered with lymphocytes (hematoxylin-eosin, original magnification ×400).*

Spiradenoma

Clinically, spiradenomas often present as painful nodules on the ventral surfaces of the body above the waist.[42] Histologically, they consist of multiple circumscribed blue dermal nodules with no epidermal connection. The blue basaloid appearance makes them easy to distinguish from most hidradenomas (which tend to be pink or clear) even at low power. The dermal nodules are composed of 2 populations of bland basaloid cells arranged into nests and trabeculae (Figure 9). Cells at the periphery of the nests and trabeculae have smaller, darker nuclei, and cells at the center have larger, vesicular, pale nuclei (this is the classic mantra for spiradenoma, although in practice, the distinction between these 2 populations of cells can sometimes be subtle). There is minimal atypia or mitotic activity. Sweat ducts and occasionally small cysts are present and usually easy to identify by the presence of bright pink eosinophilic cuticle lining the inside surface of the duct lumens. Basement membrane material (type IV collagen) is often abundant in the surrounding stroma. Dilated blood vessels are usually abundant as well, and there can be significant edema in the intervening stroma, imparting a very cystic or corded appearance with strands of tumor cells divided by broad zones of edematous stroma. A final helpful clue is that lymphocytes are usually scattered evenly throughout the nests and trabeculae of basaloid tumor cells. Spiradenomas are sometimes associated with Brooke-Spiegler syndrome (spiradenomas, cylindromas, and trichoepitheliomas) (*CYLD* gene mutation) or familial multiple spiradenomas,[43] but anecdotally most spiradenomas encountered in our practice are sporadic.

Cylindroma

Clinically, cylindromas present as red nodules that are sometimes painful. The vast majority occur on the head and neck, most commonly the scalp. There is striking female predominance.[44] They may be solitary or multiple; multiple tumors are often syndromic (see below).

Histologically, cylindromas consist of blue, basaloid, geometric micronodules of tumor cells in the dermis without epidermal connection. These micronodular nests of tumor cells mold together with one another in a pattern that is often compared to pieces of a jigsaw puzzle or a giraffe's spots. Cylindroma often lacks the sharp nodular circumscription seen in spiradenomas at low power. At higher power, however, each nest has a very similar appearance to spiradenoma, with dual populations of bland basaloid cells (peripheral cells with darker smaller nuclei and central cells with larger vesicular pale nuclei). Small sweat ducts are present. There is minimal atypia or mitotic activity. Cylindromas are remarkable for striking abundant basement membrane deposition, both in thick pink layers around each nest and as spherical pink droplets within nests.

The presence of numerous cylindromas covering the scalp has been described historically as "turban tumor" syndrome. This is now recognized as a variant form of Brooke-Spiegler syndrome (spiradenoma, cylindroma, and trichoepithelioma) caused by germline mutation in the *CYLD* gene.[43]

Spiradenocarcinoma and Malignant Cylindroma

These tumors are both exceedingly rare, much rarer than malignant acrospiromas in our experience. The diagnosis basically requires the presence of an obviously malignant carcinoma component arising from a histologically identifiable background component of benign spiradenoma or cylindroma, respectively. We have also observed cases where the obviously malignant cells were closely intermingled and mixed within the midst of a benign background spiradenoma.

Pattern 4: Tadpoles/Paisley Tie Syringoma

Clinically, these are small papules, often on the face, and sometimes present as multiple lesions. Histopathologically, they consist of a small dermal collection of obvious sweat ducts, some with a "tadpole" shape, in a dense sclerotic background. They are usually in the superficial dermis, although we have occasionally observed cases that extend into the deep dermis. They do not infiltrate into subcutis or deeper tissue in our experience. Even on a transected shave biopsy of a syringoma, it is usually easy to see that one is

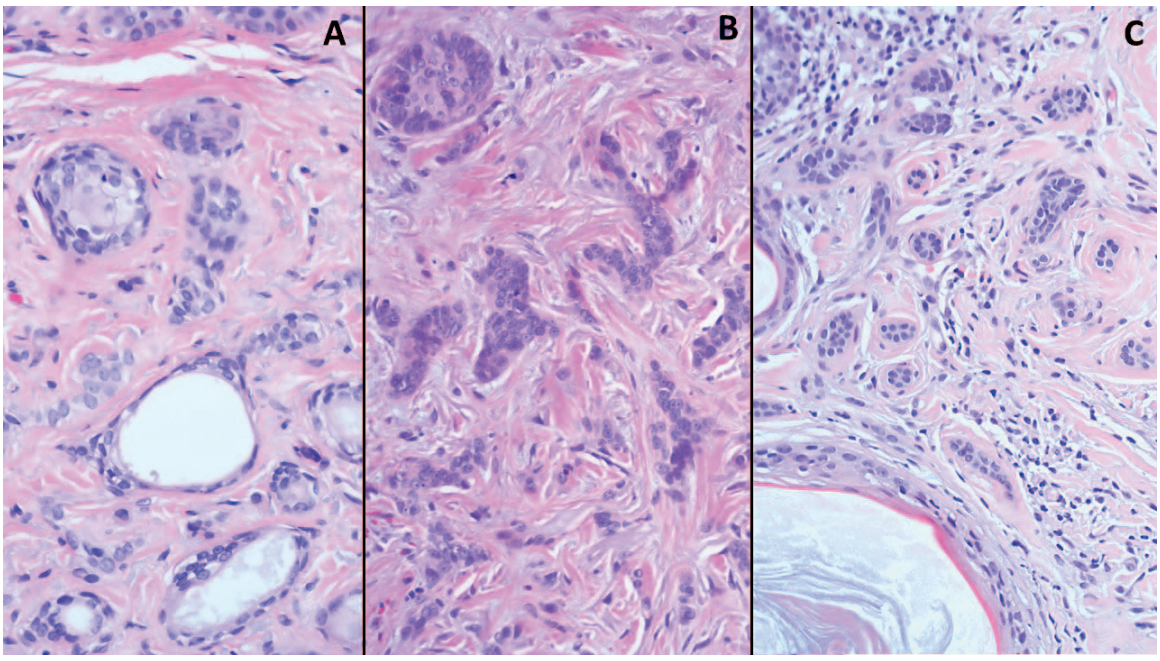

Figure 10. *Syringoma (A), morpheaform basal cell carcinoma (B), and desmoplastic trichoepithelioma (DTE) (C), here assembled side-by-side as if part of a single lesion, can have a similar histomorphologic appearance. Differentiating these entities from each other, and from microcystic adnexal carcinoma (MAC), can be challenging. Deep, infiltrative growth is the main factor that distinguishes MAC from syringoma and DTE (hematoxylin-eosin, original magnification ×200 [A through C]).*

dealing with a very small and localized process. Sweat duct lumen formation should be obvious and easy to identify, and the dense sclerotic background is also a very useful clue. Some syringomas have pale/clear cytoplasmic change, a finding that has been suggested to be associated with diabetes.[45]

Microcystic Adnexal Carcinoma

Clinically, microcystic adnexal carcinoma (MAC) usually presents as a firm flesh-colored plaque or nodule on the nasolabial/periorbital face of an adult.[46,47] While the lesion may clinically appear to be small, the infiltrative edges of the invasive tumor may extend well beyond the visible limit of the tumor seen on the skin surface and may also invade deeply into underlying subcutis or even deeper soft tissue. As a result, local recurrence is common. Although metastasis and mortality are rare, MAC can cause significant morbidity owing to the locally aggressive growth in a cosmetically sensitive anatomic site.[48,49]

Histopathologically, MAC is characterized by infiltrative growth. Thin cords of bland epithelial cells infiltrate the deep dermis, subcutis, and sometimes even the deep muscle. Perineural invasion is common. Duct formation is usually seen, but it may be focal or difficult to appreciate because the cords/tubules are tightly compressed, making the lumina very narrow. Sometimes more obvious ducts resembling those of syringoma are seen, but these are usually sparse and located deeper in the dermis. The superficial dermis usually contains small keratin-filled cysts; these are a useful clue to the diagnosis but are not specific, as they can also be seen in desmoplastic trichoepithelioma and other entities. Unlike syringoma, sweat duct formation is usually difficult to identify in the superficial dermis. If multiple sweat ducts with obvious lumens are visible on a superficial shave biopsy, it is more likely to be syringoma than MAC. Paradoxically, MAC is composed of cytologically bland tumor cells; it lacks most of the conventional malignant features seen in other carcinomas, such as pleomorphism, necrosis, and high mitotic rate. In fact, the presence of any of these histologically malignant features should prompt consideration of other forms of carcinoma (such as infiltrative squamous cell carcinoma or BCC) rather than MAC. If it looks cytologically "ugly," it is probably not MAC. If it looks like normal eccrine sweat ducts but they are invading the subcutis, the skeletal muscle, and/or the nerves, then it is much more likely to be MAC.

Microcystic Adnexal Carcinoma Differential Diagnosis: The classic differential diagnosis for MAC is desmoplastic trichoepithelioma, syringoma, and infiltrative/morpheaform basal cell carcinoma (Figure 10, A through C). Distinguishing between these lesions can be very difficult, especially on a superficial biopsy (Figure 11).[47]

Microcystic Adnexal Carcinoma Versus Desmoplastic Trichoepithelioma: Desmoplastic trichoepithelioma (DTE) has cords of banal cells and small, superficial keratin cysts just like MAC, but duct/lumina formation is lacking. As mentioned above, the ducts/lumina of MAC can be compressed and difficult to identify, particularly on superficial biopsy. Thus, the distinction of MAC from DTE is the most challenging in our opinion. Critically, DTE is small and confined to the dermis without deep infiltrative growth (Figure 11). Perineural invasion has been reported in DTE,[50] but perineural invasion in any infiltrative basaloid neoplasm should be cause for extreme caution. See the section on Desmoplastic Trichoepithelioma below for a discussion of an immunohistochemical algorithm for distinction of MAC, DTE, and BCC.

Microcystic Adnexal Carcinoma Versus Syringoma: Unlike DTE and MAC, syringoma has many duct lumina that are easily identified; they do not typically have thin cords of cells

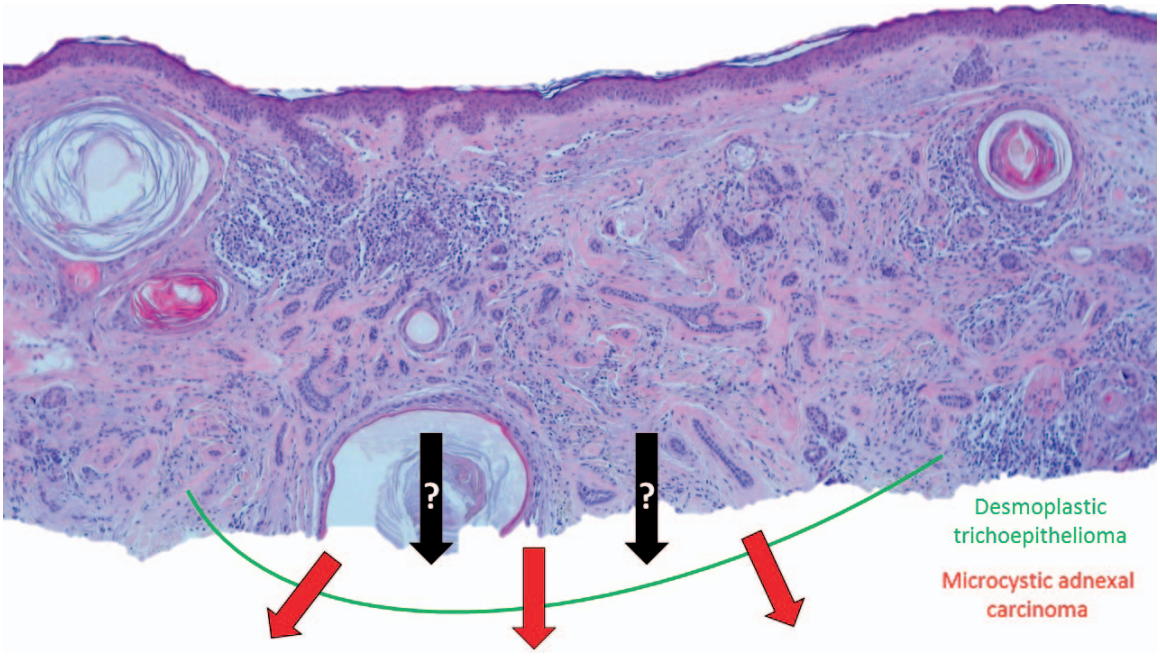

Figure 11. *This basaloid dermal tumor is an example of a case where the inability to see the base of the lesion precludes definitive distinction between microcystic adnexal carcinoma and desmoplastic trichoepithelioma (hematoxylin-eosin, original magnification ×20).*

in the absence of duct lumina. Multiple obvious sweat ducts present in the superficial dermis is a good clue for syringoma rather than DTE, MAC, or infiltrative BCC.

Microcystic Adnexal Carcinoma Versus Infiltrative BCC: The thin compressed cords of infiltrative BCC can have some similarity to MAC, but if the biopsy specimen is of decent size, larger nests of more obvious BCC are almost always present. Additionally, the characteristic stromal desmoplasia of infiltrative BCC is a very helpful clue. Infiltrative BCC and MAC can have similar clinical behavior; both have high risk of local recurrence and can be quite aggressive locally but have very low risk of metastasis or mortality. Keratin cysts are more often seen in MAC than in infiltrative BCC. See the section on Desmoplastic Trichoepithelioma below for a discussion of an immunohistochemical algorithm for distinction of MAC, DTE, and BCC.

Practical Approach to the MAC Differential Diagnosis: If the biopsy specimen is small and the diagnosis uncertain, the authors use the top line diagnosis "infiltrative basaloid neoplasm (see comment)," state which entity is favored, list the other entities in the differential diagnosis, and recommend conservative complete excision to visualize the whole lesion. A variety of immunostains have been reported to assist in sorting out this differential (discussed in the section on Desmoplastic Trichoepithelioma below), but in our experience, these are often difficult to interpret with certainty on small biopsy specimens and in the end we still often use descriptive language with recommendation for reexcision. In difficult cases, we find that a larger sample is usually much more useful than IHC in arriving at a more definitive diagnosis.

Pattern 5: Cystic Spaces and Papillary Projections

Syringocystadenoma Papilliferum

Syringocystadeonoma papilliferum is a benign sweat gland neoplasm that clinically presents as a warty or scaly ulcerated and bleeding plaque. They often arise on the scalp of children within a preexisting nevus sebaceus, but may occur in adults.[51] They have a very characteristic histopathologic appearance; the surface is exophytic with multiple downward extensions from the epidermis that open into dilated glandular channels with irregular branching architecture (Figure 12, A and B). Multiple papillae are present within the dilated glandular spaces, often appearing as islands floating in the midst of the spaces owing to tangential sectioning through the papillae. Numerous plasma cells are usually present in the fibrovascular cores of the papillae as well as within the adjacent dermis. Both the papillae and the dilated branching glandular channels are lined by a double layer of bland epithelium consisting of an outer layer of cuboidal myoepithelial cells and an inner layer of columnar cells, often with apical snouts.

Hidradenoma Papilliferum

Hidradenoma papilliferum is a relatively common benign sweat gland neoplasm that arises almost exclusively in the anogenital region of women. Like other cystic skin lesions, it often clinically presents as a skin-colored nodule. Histologically, hidradenoma papilliferum is a circumscribed cystic dermal lesion filled with multiple papillae. Each papilla is lined by a double layer of bland cuboidal to columnar cells. Apocrine snouts are sometimes present on the apical surfaces of the cells. The crowded papillae filling up the cystic space give a "maze-like" appearance at low power. Although this tumor usually lacks epidermal connection, we have observed occasional cases that did connect with the epidermis. Plasma cells may sometimes be present within the papillary cores, providing some overlapping features with syringocystadenoma papilliferum.

Digital Papillary Adenocarcinoma

Also known as "aggressive digital papillary adenocarcinoma," these tumors often present as nodules on the volar surface of the distal finger (or occasionally toe), usually of

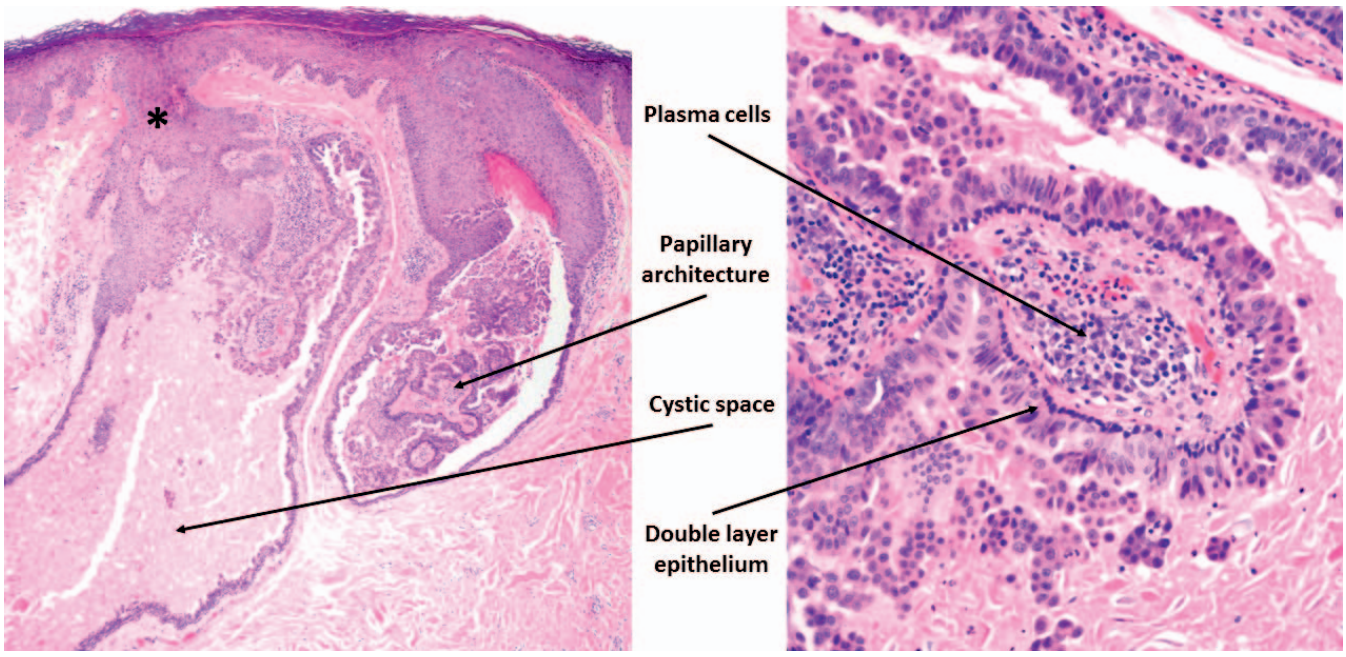

Figure 12. *Syringocystadenoma papilliferum. Note the plasma cells, papillary architecture, and double layer epithelium (B). Based on the plane of sectioning, an opening to the epidermal surface may not be visible (asterisk), imparting a cystic appearance (A) (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).*

middle-aged adults. There is a striking male predominance (7:1). Local recurrence is common unless the tumor is treated with wide excision or digit amputation. Metastasis to lung or regional lymph nodes may occur in a subset of cases, as well. Metastases may be late, and patients with metastatic disease may still survive for a relatively long period, so consequently long-term follow-up is recommended. Finally, assessment of traditional histopathologic features (high grade versus low grade) is not useful in predicting clinical behavior for this entity; even very bland, banal-appearing examples (that in the past were considered to be digital papillary adenomas) can recur or metastasize.[52,53]

Histopathologically, tumors consist of single or multiple deep dermal and/or subcutaneous nodules without connection to the epidermis. The tumor is often surrounded by dense fibrosis. Prominent central cystic areas are usually present, and a variable number of papillary and/or micropapillary structures protrude into the cystic spaces (Figure 13, A and C). Solid zones are also present in most cases, and these often show sheets of round or even oval to spindled cells, usually punctuated by tubules with cuboidal to columnar lining (Figure 13, B). These solid zones have a biphasic appearance that is vaguely reminiscent of biphasic synovial sarcoma in some cases (due to the plump spindle/round cells in sheets with scattered gland/tubule formation). Whorled squamoid foci are sometimes seen. The degree of atypia and mitotic activity can vary widely between cases, but most often cytologic atypia is mild to moderate and mitoses are not numerous. This can lead to a deceptively benign appearance. The presence of papillae is one the most important clues. Any tumor in the digit that resembles hidradenoma papilliferum (or the dermal aspect of syringocystadenoma papilliferum) should be regarded as digital papillary adenocarcinoma until proven otherwise. In gen-

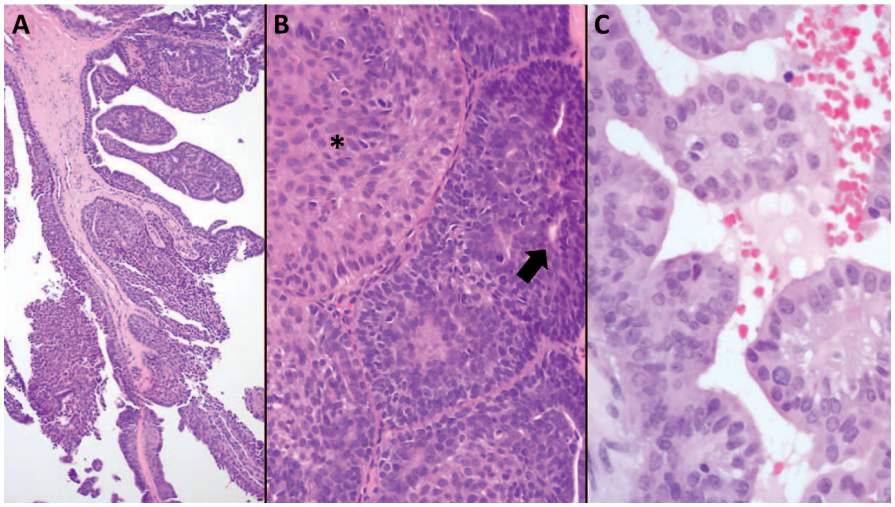

Figure 13. *Digital papillary adenocarcinoma. This malignant, papillary, sweat gland–derived tumor may have a deceptively bland cytomorphology (C). Papillary (A), solid zones (B, asterisk), and tubules (B, arrow) are apparent (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B], and ×400 [C]).*

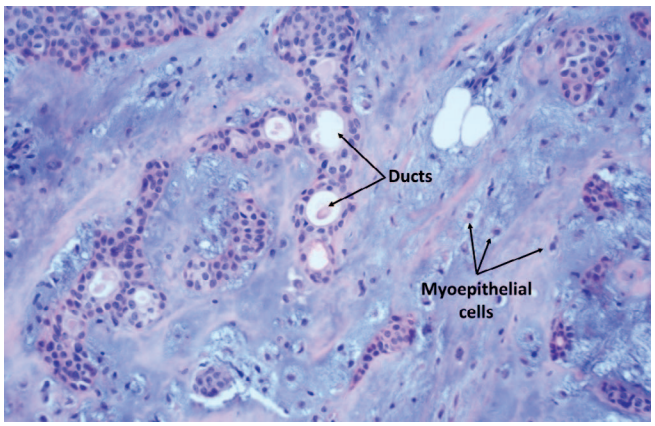

Figure 14. *Chondroid syringoma (mixed tumor). Duct formation and myoepithelial cells, which can have a variety of different histomorphologic appearances, are characteristic. The sheets of myoepithelial cells may have a chondroid appearance (as in this example), but this is not a consistent finding (hematoxylin-eosin, original magnification ×20).*

eral, for any adnexal tumor on the digits, always keep digital papillary adenocarcinoma in the differential diagnosis until it can be excluded with confidence by arriving at another diagnosis instead. If one is unsure, an expert consult is strongly recommended. Overdiagnosis of this entity could lead to an unnecessary digit amputation or other extensive surgical management; underdiagnosis could lead to inadequate treatment and potentially worse outcome. A lot is at stake for both the patient and the pathologist. We believe there is a lack of awareness of this entity among general pathologists, and the authors know of at least 1 medical malpractice lawsuit that was pursued over an alleged missed diagnosis of digital papillary adenocarcinoma.

Pattern 6: Dermal Nodule With Variable Mixture of Cords/Chains/Tubules and Chondromyxoid Stroma

Mixed Tumor (Chondroid Syringoma)

Mixed tumors are benign cutaneous nodules usually presenting on the head and neck of adults, although they may occur at essentially any cutaneous site. Histopathologically, the name *chondroid syringoma* is somewhat misleading; not all cases have true cartilage or even a chondromyxoid appearance. Furthermore, the glandular/ductal component usually does not truly resemble a syringoma. Like mixed tumor (pleomorphic adenoma) of the salivary gland, cutaneous mixed tumor is also composed of a mix of 2 components: epithelial cells and myoepithelial cells (Figure 14). These components can be arranged in a myriad of different histologic patterns. Most commonly, they form a relatively well-circumscribed dermal nodule composed of irregular, interconnected tubules and glands lined by bland columnar cells with an intervening myxoid stroma that contains variable numbers of myoepithelial cells. Apocrine, follicular, and/or sebaceous differentiation may be seen in the epithelial component, as well. The stroma is the part of the tumor that tends to show the greatest variation. The stromal background can range from myxoid to sclerotic and may include mature adipocytes as well as variable amounts of cartilage or even bone. Myoepithelial cells within the stromal component can show a wide range of cytologic features: round/epithelioid, spindled, plasmacytoid, or clear cell.

The myoepithelial cells in mixed tumor (and in myoepithelioma, which is likely on a spectrum with mixed tumor) usually coexpress S100 protein and cytokeratin (and/or EMA). Calponin is also expressed in most cases.[54] Other myoepithelial markers, such as p63 and SMA, may also show positivity, but tend to be less sensitive in mixed tumors and myoepitheliomas.[54,55] *EWSR1* gene rearrangements have been shown to occur in up to 44 % of cutaneous myoepithelial tumors.[56]

Myoepithelial Carcinoma/Malignant Mixed Tumor

This is the extremely rare malignant counterpart to mixed tumor. It can either take the form of carcinoma growing out of a benign mixed tumor precursor, or have the overall appearance of a mixed tumor but with the addition of infiltrative growth, marked nuclear atypia, tumor necrosis, and/or brisk/atypical mitoses. Determining malignant potential in mixed tumors of the skin and soft tissue can be challenging. In one study by Hornick and Fletcher,[54] the most reliable feature to support malignancy in mixed tumor or myoepithelioma was the presence of marked nuclear atypia. Unlike in its salivary counterpart, invasive growth pattern is insufficient for a diagnosis of malignancy, as nearly half of the cases in their series showed infiltrative margins but behaved indolently. Rather, the authors recommend that the presence of at least moderate cytologic atypia in an otherwise typical soft tissue myoepithelioma should warrant classification as carcinoma. We refer readers to that article and other recent articles for additional reading on this evolving area of pathology.[57]

A number of immunohistochemical stains have been used to characterize sweat gland tumors[24–26,35,36,58–65]; they are outlined in Table 3.

Metastatic Tumors Versus Primary Cutaneous Adnexal Neoplasms

Occasionally, primary cutaneous adnexal adenocarcinomas with sweat gland differentiation may raise suspicion for a metastatic adenocarcinoma from a visceral primary site. P63 is expressed in normal epidermal and adnexal basal and myoepithelial cells and has been shown to be a relatively sensitive marker for primary cutaneous carcinomas of all types (with the exception of mucinous carcinoma)—consequently, if p63 shows negativity, a metastatic adenocarcinoma should be a serious consideration.[24,25] In our experience, we have found p40 to have similar utility to p63 in this context, as Lee et al[26] have also reported previously. Of note, skin metastases from squamous cell carcinoma, urothelial carcinoma, and many salivary carcinomas will also be p63 and p40 positive, and thus these stains are not useful for distinguishing cutaneous primary versus metastasis in that context.[26]

Hair Follicle Tumors

Tumors with hair follicle differentiation are often very challenging to classify; understanding how follicular tumors correspond to portions of the normal hair follicle can be helpful. Frustratingly, many follicular tumors show overlapping features with one another and do not fit neatly into any singular diagnostic designation. The wide variety of evolving nomenclature and reclassifications of follicular proliferations over the years in the dermatopathology literature has added complexity to the situation. As Rapini succinctly puts it: "Classifying snowflakes is easier."[9(p319)] In this section, we will attempt to make follicular tumors at least somewhat

Table 3. Immunohistochemistry of Sweat Gland Tumors	
Immunohistochemistry Target Antigen	**Function**
EMA and CEA	Highlight duct lumens.
CEA	Luminal surface of secretory and duct-lining cells of eccrine glands; luminal staining of duct-lining cells only in apocrine glands.[58]
EMA	Indicates ductal differentiation of both eccrine and apocrine types.
CK7	Positivity in secretory cells of eccrine coil; positivity in duct and coil of apocrine glands.
CK5/6	Positivity in most primary adnexal carcinomas.[26]
p40 and p63	Positivity in most benign and malignant sweat gland tumors.[24–26,35,36] P40 may exhibit better specificity than p63 in distinguishing primary skin adnexal carcinomas from cutaneous metastases.[26]
GCDFP-15	Expressed in eccrine and apocrine sweat glands.[59]
Estrogen receptor/progesterone receptor	Often positivity in sweat gland neoplasms, especially tumors with apocrine differentiation.[60,61]
HER2	One study showed that a minority (only 3.5% of 85) of benign and malignant eccrine and apocrine neoplasms overexpress HER2.[62]
CK and S100	Positivity in myoepithelial cells. Myoepithelial cells are abundant in mixed tumor and are also present in a variety of other sweat gland tumors. Other myoepithelial markers may also show positivity, but have lower sensitivity.
CD117	Expressed by the secretory cells of normal sweat glands. Variable positivity in benign and malignant sweat gland neoplasms.[63]
SOX-10	Expressed in 100% of cylindromas and spiradenomas; variable positivity among other sweat gland neoplasms.[64]
DOG1	Expressed in most cylindromas; variable positivity among other sweat gland neoplasms.[64]
GATA3	Expressed in a wide variety of benign and malignant cutaneous epithelial neoplasms, including sweat gland neoplasms.[65]

Abbreviations: CEA, carcinoembryonic antigen; CK, cytokeratin; EMA, epithelial membrane antigen; GCDFP-15, gross cystic disease fluid protein-15.

easier to classify than snowflakes by arranging them into more simplified classification groups and by focusing on the practical issues that impact patient care and how we deal with these in our practice.

The hair follicle is the structure responsible for forming the hair shaft. Normal hair follicles have several layers going from inside (starting at the hair shaft) to outside (ending at the dermis): the inner root sheath (which has 3 layers), the outer root sheath, and a special fibrous root sheath/adventitial mesenchymal layer that wraps around the outside of the follicle and is contiguous with the hair papilla. The follicle can also be separated into multiple sections from superficial to deep: the infundibulum (which extends from the epidermal surface to the opening of the sebaceous duct), the isthmus (which extends from the opening of the sebaceous duct to the insertion of the arrector pili muscle), and the inferior follicle (which extends from the insertion of the arrector pili muscle to the hair bulb). There is also a germinative matrix, the cluster of proliferative round blue cells that make up the hair bulb; these cells give rise to the hair shaft itself. All of these parts can contribute to the histopathologic appearance of follicular tumors, and again understanding how the features of hair follicle tumors relate to normal follicular anatomy can be useful (Figure 15, A through E).

Trichofolliculoma

Trichofolliculomas are benign tumors that clinically present as small papules, usually on the face of an adult. They may have a tuft of small hairs protruding from a central opening. Histopathologically, trichofolliculoma is often regarded as the most well-differentiated follicular tumor, as it most closely resembles the configuration of a normal hair follicle. They are composed of a dilated central follicle that connects to the skin surface, with multiple small immature hair follicles that bud outward from central dilated follicle. In some cases, this epidermal connection is not visible owing to the level of sectioning, and in these cases the follicle will look more like a cyst. The central dilated follicle is lined by stratified squamous epithelium similar to that seen in the infundibulum of a normal hair follicle (ie, the lining resembles normal epidermis). The central dilated follicle may be filled with loose keratin and/or fragments of hair shaft. As with most benign follicular proliferations, dense fibrous stroma (homologous to the fibrous root sheath of a normal hair follicle) closely surrounds the periphery of the entire lesion. Trichofolliculoma is sometimes described as having a "hen and chicks" configuration, referring to many "baby" follicles that empty into a central dominant "mother" follicle.[9(p319)]

Fibrofolliculoma and Trichodiscoma

Trichodiscomas are benign hamartomas of the mesenchymally derived perifollicular fibrous root sheath. They typically occur on the face/head and neck. Histopathologically, they consist simply of a "ball" of fibrous root sheath material (ie, dense pink fibrosis) that may push aside normal local dermal structures, such as sebaceous lobules. The appearance is very similar to an angiofibroma (fibrous papule).

Fibrofolliculomas are exactly the same as trichodiscoma, except they have the additional feature of a central follicular structure with numerous thin basaloid epithelial strands extending into the fibrous component[66] (Figure 15, B). In our experience, most biopsy specimens that at first glance resemble trichodiscoma either end up being angiofibroma/fibrous papule or fibrofolliculoma after deeper sectioning. Additionally, angiofibroma/fibrous papule with an entrapped hair follicle very closely resembles fibrofolliculoma; the presence of not only a central follicle but also the thin

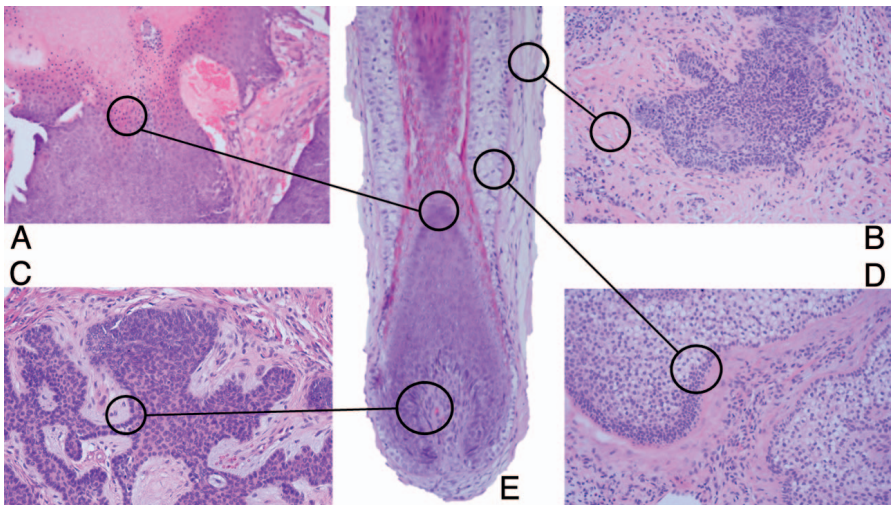

Figure 15. *The structures in a normal terminal anagen hair follicle (E) can be related to a variety of follicular tumors. In pilomatricoma (A), the transition from basaloid to "ghost" cells is analogous to hair shaft formation. In trichoepithelioma, papillary mesenchymal bodies (circled) are analogous to the normal mesenchymal follicular papilla (C). The fibrous component of fibrofolliculoma is analogous to the mesenchymally derived fibrous root sheath (B). The clear cell change and thick basement membrane of trichilemmoma is analogous to the follicular outer root sheath and vitreous layer (D). Understanding these relationships can assist in learning to classify these often challenging neoplasms (hematoxylin-eosin, original magnification ×40 [A through E]).*

strands of basaloid epithelium is the key to distinguishing fibrofolliculoma from angiofibroma/fibrous papule. The presence of numerous trichodiscomas, fibrofolliculomas, and acrochordons are associated with Birt-Hogg-Dube syndrome, an autosomal dominant syndrome associated with pulmonary cysts, spontaneous pneumothorax, and renal cell carcinoma.[67,68] Thus, if multiple such lesions arise in one patient, further clinical workup to exclude this syndrome may be worthwhile.

Trichoepithelioma

Trichoepitheliomas are benign hair follicle tumors that typically present as small flesh-colored papules in adults. Histopathologically, they consist of dermal proliferations of basaloid cells with peripheral palisading, arranged in nests or thin cords. They sometimes have a connection to epidermis or adjacent normal follicles. There is a dense pink fibrous stroma with bland spindle cells closely surrounding the tumor; this is homologous to the fibrous sheath that surrounds normal hair follicles. Papillary mesenchymal bodies may be seen, but are not always present; these are small aggregates of oval/round-to-spindled cells within the dense stroma that indent and invaginate into the basaloid epithelial nests (Figure 16). They are homologous to the mesenchymal hair papillae in the bases of normal hair follicles. Keratin cysts and calcifications are often present. Mucin pools may be seen within the nests in trichoepithelioma, but mucinous stroma with cleft artifact separating basaloid nests from surrounding stroma would favor basal cell carcinoma instead of trichoepithelioma (Figure 17, A through C).

Trichoepithelioma Versus BCC

The distinction between these 2 entities can be very challenging to make in some cases, particularly on a partial biopsy. To complicate matters, BCC can be keratotic or have follicular differentiation. The following features favor BCC over trichoepithelioma (Figure 17, A through C): (1) mucinous stroma, especially with cleft artifact, rather than dense pink fibrous cellular stroma; (2) desmoplastic stroma rather than dense pink fibrous cellular stroma; and (3) ulceration, deep infiltration, and/or perineural invasion.

Papillary mesenchymal bodies are often seen in trichoepithelioma and sometimes in trichoblastoma, but they are very uncommon in basal cell carcinoma.[69] We regard the presence of papillary mesenchymal bodies, particularly in the absence of the features of BCC above, as strongly favoring trichoepithelioma or other benign follicular proliferations over BCC.

Additionally, a variety of immunohistochemical stains have been described to help distinguish BCC from follicular tumors. Cytokeratin (CK) 20 has been used to highlight scattered passenger Merkel cells, which are retained in many follicular tumors but usually lost in BCC.[70] We have found CK20 in this context to be useful occasionally in difficult cases. Cytokeratin 15 (CK15), CD10, CD34, and bcl-2 have all been evaluated as potential markers for distinguishing trichoepithelioma from BCC, but the utility of these markers largely relies on the ability to interpret particular patterns of staining in the tumor epithelium and/or surrounding stroma[71(p1472),72–76]; the authors do not routinely use these markers in their practice (Table 4). Ber-EP4 is a very sensitive marker for BCC, but as it also stains trichoepithelioma and trichoblastoma, it is not useful in this context.[77]

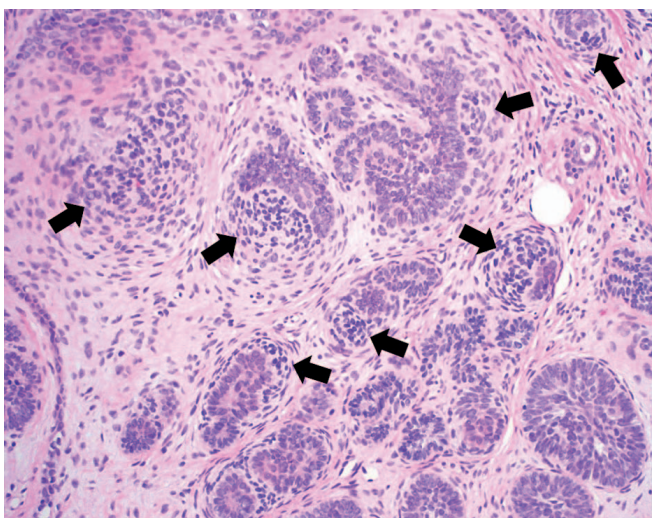

Figure 16. *Numerous papillary mesenchymal bodies in a trichoepithelioma. Stromal cells condense and bulge into the epithelial nests. Depending on the plane of section, they may have varying appearances (arrows) (hematoxylin-eosin, original magnification ×100).*

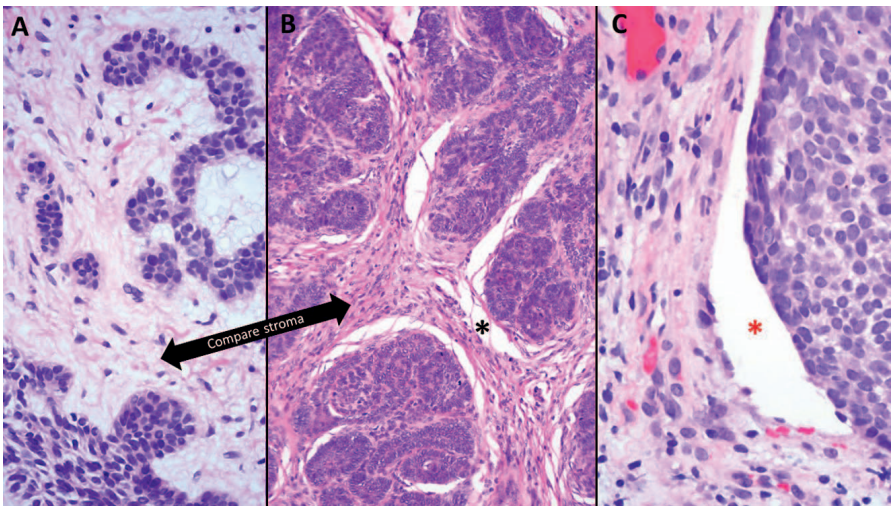

Figure 17. *Compare the myxoid stroma of basal cell carcinoma (BCC) (A and C) with the relatively cellular eosinophilic stroma of trichoepithelioma (B). Also, compare the true clefting between epithelial cells and stroma seen in BCC (C; red asterisk) to the stromal clefts that can be seen in trichoepithelioma (B; black asterisk). In trichoepithelioma, stroma still hugs onto the epithelial cells, and the clefts involve stroma only (hematoxylin-eosin, original magnification ×200 [A through C]).*

Finally, if the diagnosis is truly uncertain (especially if the specimen is a transected shave biopsy on the face of an older sun-damaged patient), the authors often render the following diagnosis: "Basaloid neoplasm, margin positive. Comment: This could represent a trichoepithelioma, but a basal cell carcinoma with follicular differentiation cannot be completely excluded." This way dermatologists are not obligated to treat, but have justification to do so if they wish, depending on the size of the lesion, their level of concern, and/or their confidence that the patient would return for follow-up visits if watchful waiting were used.

Desmoplastic Trichoepithelioma

Desmoplastic trichoepitheliomas are benign lesions that present as small papules, often with a raised border and depressed center, on the face of an adult. There is a strong female predilection (4:1). They do not typically share the syndromic associations of classic trichoepitheliomas.[71(p1550)] Histopathologically, they consist of thin cords and strands of bland basaloid epithelial cells set within a dense fibrotic dermis. Keratin cysts are often present. The appearance of DTE is very different from conventional trichoepithelioma. The major differential diagnosis for DTE includes MAC and infiltrative/morpheaform BCC. As discussed with relation to trichoepitheliomas, BCCs may be distinguished from benign follicular tumors by using a CK20 stain to look for scattered passenger Merkel cells; Merkel cells are often retained in benign follicular tumors and are often scarce or absent in BCC. Androgen receptor (AR) and CK20 may be used together as a panel to help distinguish desmoplastic trichoepithelioma (usually AR negative with CK20-positive Merkel cells present) from morpheaform (infiltrative) BCC (usually AR positive and lacking CK20-positive Merkel cells).[70] See the section on Microcystic Adnexal Carcinoma above for a discussion regarding distinguishing DTE from MAC, based on H&E features.

One proposed immunohistochemical algorithm for distinction of MAC, DTE, and morpheaform BCC uses BerEP4, PHLDA1 (pleckstrin homology-like domain, family A, member 1), CK15, and CK19.[78] In this study, all BCCs expressed BerEP4, while the vast majority of MACs were negative (DTEs were variably positive). All DTEs were PHLDA1 positive and all BCCs were PHLDA1 negative (MACs were variably positive). Twenty of 21 DTEs expressed CK15, whereas most BCCs and MACs were negative. CK19 showed variable positivity in all 3 entities, but more often positivity in MAC.

Trichoblastoma

Trichblastomas are benign tumors with differentiation toward the hair bulb portion of the hair follicle. They usually present as nodules on the head and neck, especially the scalp, of middle-aged to older adults.[71(p1475)] Tumors are slow growing, will often have been present for several years before biopsy, and are typically around 3 cm at presentation. They can sometimes become quite large (nearly 10 cm).[79] Histopathologically, they consist of dermal nodules, often extending into the subcutis, composed of blue basaloid cells in nests that can be arranged in a variety of patterns. The low-power appearance is similar to BCC. The tumor does not usually connect with epidermis or follicles. Cellular dense pink fibrous stroma, similar to that seen in trichoepithelioma, is typically present but in variable amounts. Papillary mesenchymal bodies are sometimes present, as well. Keratin cysts are only occasionally seen. Sometimes the nests of basaloid cells are larger, other times

Table 4. Immunohistochemical Findings in Basal Cell Carcinoma, Trichoblastoma, and Trichoepithelioma[a]

	Basal Cell Carcinoma	Trichoblastoma	Trichoepithelioma
bcl-2 (epithelium)	+ (diffuse)	± (peripheral)	± (70%; peripheral)
CD10 (epithelium)	+ (86%)	±	± (15%)
CD10 (stroma)	−	+	+ (92%)
CD34 (stroma)	±	±	+
Androgen receptor (epithelium)	+ (78%)	−	−

Abbreviations: +, positive, ±, positive or negative, −, negative.

[a] Table adapted from Table 31.1 in *McKee's Pathology of the Skin*, 4th ed.[71]

they are smaller and connected together by thin cords of basaloid cells (described as "antler-pattern"). Alternatively, the cells may be arranged in dramatic palisading rows (referred to as "ripple pattern" trichoblastoma; some authors have suggested that all "ripple pattern" trichoblastomas are actually sebaceomas).[80–83] Pigmented dendritic melanocytes may be scattered within the tumor (pigmented trichoblastoma).[84,85] The basaloid cells are uniform and lack pleomorphism, but mitoses are often easily identified and apoptotic bodies can also be present. Mitoses and apoptotic bodies alone are not evidence of malignancy.[86]

The main differential diagnosis for trichoblastoma is BCC. Mucin pools can be seen within tumor nests of trichoblastoma and can mimic the "adenoid pattern" of BCC, but mucinous/myxoid stroma with mucin-filled clefting artifact dividing the tumor nests from the stroma would usually favor BCC over trichoblastoma. The presence of a dense pink cellular fibrous stroma (especially if there are papillary mesenchymal bodies) is a very useful clue to the diagnosis of trichoblastoma over BCC. The lack of connection to epidermis is another feature favoring trichoblastoma over BCC. Again, as with trichoepithelioma, if the diagnosis is uncertain and the biopsy specimen is small/partial, it may be best to have the tumor completely excised to be cautious.

Distinguishing trichoepithelioma from trichoblastoma is fraught with difficulty, since both tumors show many of the same features. Both entities may actually exist on a spectrum. In our practice, we have often used the term *trichoblastoma* for larger deeper tumors that lack connection with the epidermis and *trichoepithelioma* for small superficial tumors that connect with the epidermis and/or with hair follicles. In any event, both are benign entities and the distinction is not usually of clinical importance.

Malignant Trichoblastoma

Malignant transformation can very rarely occur in trichoblastoma. There are several scenarios in which this can occur:

1. Low-grade trichoblastic carcinoma: This tumor looks like trichoblastoma, but has infiltrative growth into skeletal muscle. It may have local recurrence rarely per anecdotal reports, but does not appear to have metastatic potential. Some observers regard this as an "atypical trichoblastoma" as opposed to a true carcinoma.[87]
2. High-grade trichoblastic carcinoma: A poorly differentiated carcinoma arising out of a benign trichoblastoma (or trichoepithelioma). This is essentially a "carcinoma ex" trichoblastoma. The identification of the background benign trichoblastoma/trichoepithelioma is key to the diagnosis.[88]
3. Trichoblastic sarcoma: A trichoblastoma wherein the basaloid epithelial component has benign features but the cellular stroma has features of malignancy (pleomorphism, marked nuclear atypia, brisk mitotic activity).[89]
4. Trichoblastic carcinosarcoma: A trichoblastoma where both basaloid epithelial cells and spindled stromal cells have malignant features.[90]
5. Basal cell carcinoma arising out of trichoblastoma: The authors have also observed rare cases of obvious BCC arising out of an obvious background of benign trichoblastoma or trichoepithelioma.

Trichilemmoma

Trichilemmomas are common benign follicular proliferations that often present as papules on the nose, eyelid, or elsewhere on the face of an adult, often with a verrucous clinical appearance.[91] Indeed, the surface of a trichilemmoma usually has many features of a verruca microscopically: papillomatosis, hypergranulosis, foci of parakeratosis, and dilated vessels in the underlying rete. For this reason, some believe trichilemmoma to be a variant of verruca (studies looking for human papillomavirus in trichilemmoma have had varying results).[92,93] The epidermis is thickened and there are broad bowl-shaped lobules of clear glycogenated epithelial cells bulging/pushing down from the epidermis into the dermis. Basal layer palisading is usually present at least focally. Dense pink basement membrane material may be present in the dermis. The basal palisading, clear cells, and prominent basement membrane material of trichilemmoma is morphologically homologous to the outer root sheath of the lower portion of the normal hair follicle (Figure 15, D).

Trichilemmomas and Cowden Syndrome

Cowden syndrome is an autosomal dominant genetic disorder characterized by germline mutation of the *PTEN* gene, resulting in the development of various hamartomas, including trichilemmomas. These patients also have an increased risk of various internal cancers, including breast, thyroid, and endometrial cancers. The authors do not routinely mention Cowden syndrome association in a diagnostic report for trichilemmoma, unless there is a history of multiple trichilemmomas. Anecdotally, the vast majority of trichilemmomas encountered in our clinical practice are solitary incidental lesions with no Cowden syndrome association.

Desmoplastic Trichilemmoma

Benign trichilemmomas may sometimes have foci where cords of epithelial cells are haphazardly arranged within a desmoplastic (and sometimes mucinous) stroma (Figure 18). The cells in these cords can be squamoid, basaloid, or clear. These desmoplastic areas in trichilemmoma can easily mimic infiltrative basal cell (or squamous cell) carcinoma when superficially biopsied. Finding adjacent areas of conventional trichilemmoma can help avoid misdiagnosis. Since these are often on the nose/face, misdiagnosis as an infiltrative carcinoma can cause significant morbidity to the patient owing to unnecessary excess surgery. If the features are ambiguous and the biopsy specimen is small, a note that carcinoma cannot be fully excluded may be appropriate. When the diagnosis is obvious on the initial biopsy, the authors usually diagnose these simply as "trichilemmoma" (rather than "desmoplastic trichilemmoma") in the final diagnosis line of their reports. In our experience, the adjective "desmoplastic" can cause unnecessary anxiety for dermatologists, who often hear that word in the context of more aggressive lesions. Although trichilemmomas with a desmoplastic component may be confusing and challenging to diagnose for the pathologist, the finding is of no clinical significance and thus mentioning this pattern is not required in our opinion. If a case of desmoplastic trichilemmoma is sent to us for consultation because of the desmoplastic appearance, then we usually will mention the desmoplastic component but will be sure to add a comment that "despite

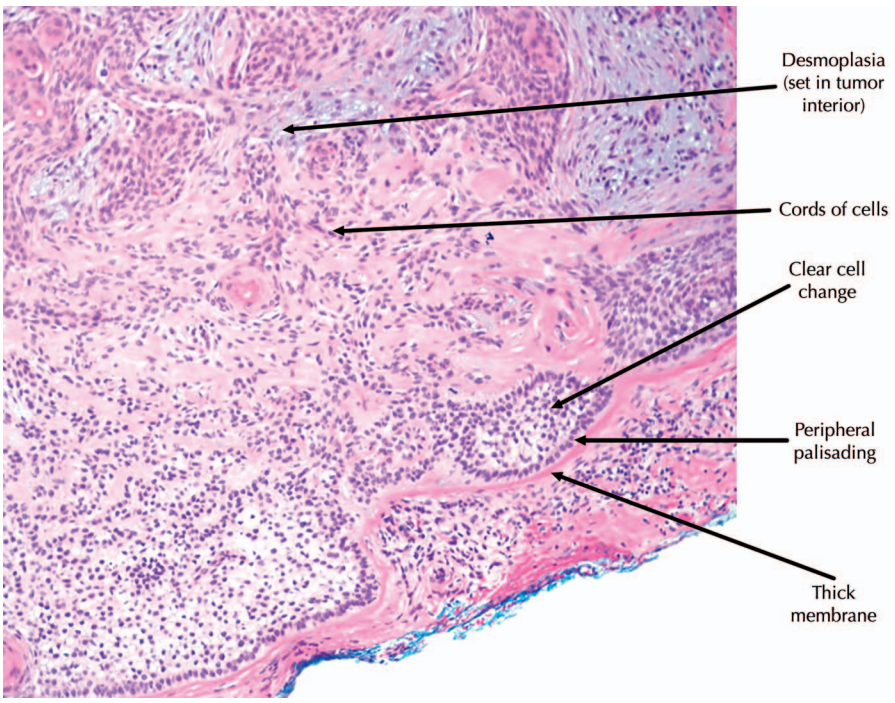

Figure 18. *Desmoplastic trichilemmoma. The base of the lesion has the classic appearance of trichilemmoma (thick basement membrane, peripheral palisading, and clear cell change), but there is desmoplasia toward the interior of the lesion (hematoxylin-eosin, original magnification ×100).*

the unusual appearance, this is a benign lesion and no further treatment is required."

Pilomatricoma

Pilomatricoma (also spelled "pilomatrixoma") is a benign tumor that clinically presents as a firm nodule, most often on the face (although they can arise on the trunk and extremities as well). Most occur in children and adolescents, but they can occur in any age group, including elderly patients. Histopathologically, they are characterized by varying amounts of 2 components mixed together in a disorganized fashion in the dermis: (1) anucleate pink "ghost" or "shadow" cells (sheets of dead keratinocytes in which the ghost/shadow outline of each individual cell can still be seen) and (2) aggregates or sheets of small round blue cells representing a germinative/matrical epithelial component (similar to the round blue cells seen in the hair bulb/root of normal hair follicles) (Figure 19, A through C). Some cases have abundant ghost cells with little or no obvious matrical round blue cell component. Others have abundant sheets of blue matrical cells and less prominent ghost cells.[94] Each nodule of the tumor is often surrounded by brisk granulomatous inflammation, fibrosis, and foreign body giant cell reaction to the keratin of the anucleate ghost

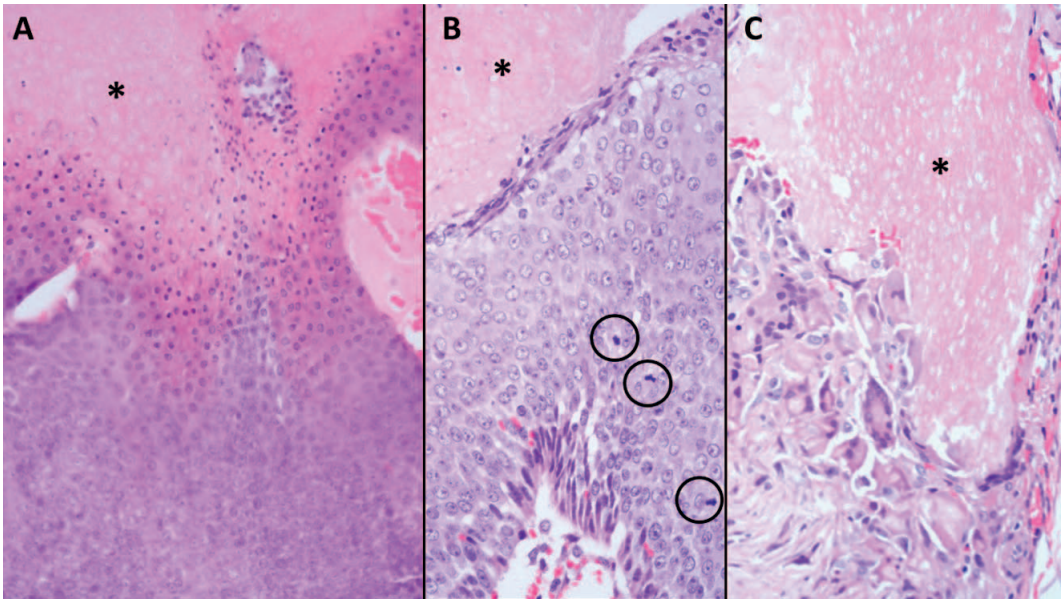

Figure 19. *Pilomatricoma. "Ghost" or "shadow" cells are indicated by the asterisks (A through C). Mitoses (circled) may be frequent in the basaloid component of the tumor and are permissible (B). A giant cell tissue reaction is commonly seen surrounding ghost cells (C) (hematoxylin-eosin, original magnification ×200 [A through C]).*

cells. Calcifications are often present, and metaplastic bone formation can occur. Mitoses may be quite frequent in the round blue cell matrical component of benign pilomatricoma, but nuclear pleomorphism should not be seen; conceptually, these round blue cells are homologous to the proliferative matrical component of the hair root, and so the permissibility of mitoses should not be surprising. Brisk mitotic activity alone should not be regarded as evidence of malignancy.

Multiple pilomatricomas may be a cutaneous sign of myotonic dystrophy.[95] Patients with Gardner syndrome (the extraintestinal variant of familial adenomatous polyposis) may have cutaneous cysts that show pilomatricoma-like changes.[96] In our experience, the vast majority of pilomatricomas in our practice are solitary and incidental with no syndromic association.

Malignant Pilomatricoma

Malignant pilomatricoma is very rare, occurring mostly in adults. In addition to high mitotic rate, malignant pilomatricomas usually possess atypical mitotic figures as well as marked nuclear atypia/pleomorphism and an infiltrative growth pattern.

The authors wish to thank Sara C. Shalin, MD, PhD, for her helpful assistance with the section on Muir-Torre syndrome. We also wish to thank Phillip H. McKee, MD, and Elsevier for permission to use a table from his textbook.

References

1. Clark LN, Elwood HR, Uhlenhake EE, Smoller BR, Shalin SC, Gardner JM. Nuclear factor XIIIa staining (clone AC-1A1 mouse monoclonal) is a highly sensitive marker of sebaceous differentiation in normal and neoplastic sebocytes. *J Cutan Pathol*. 2016;43(8):657–662.

2. Uhlenhake EE, Clark LN, Smoller BR, Shalin SC, Gardner JM. Nuclear factor XIIIa staining (clone AC-1A1 mouse monoclonal) is a sensitive and specific marker to discriminate sebaceous proliferations from other cutaneous clear cell neoplasms. *J Cutan Pathol*. 2016;43(8):649–656.

3. Lazar AJF, Lyle S, Calonje E. Sebaceous neoplasia and Torre-Muir syndrome. *Curr Diagn Pathol*. 2007;13(4):301–319.

4. Shalin SC. P53 staining correlates with tumor type and location in sebaceous neoplasms. *Am J Dermatopathol*. 2012;34(2):129–135.

5. Tetzlaff MT, Singh RR, Seviour EG, et al. Next-generation sequencing identifies high frequency of mutations in potentially clinically actionable genes in sebaceous carcinoma. *J Pathol*. 2016;240(1):84–95.

6. Dasgupta T, Wilson LD, Yu JB. A retrospective review of 1349 cases of sebaceous carcinoma. *Cancer*. 2009;115:158–165.

7. Rao NA, Hidayat AA, McLean IW, Zimmerman LE. Sebaceous carcinomas of the ocular adnexa: a clinicopathologic study of 104 cases, with five-year followup data. *Hum Pathol*. 1982;13(2):113–122.

8. Chao AN, Shields CL, Krema H, Shields JA. Outcome of patients with periocular sebaceous gland carcinoma with and without conjunctival intraepithelial invasion. *Ophthalmology*. 2001;108(10):1877–1883.

9. Rapini RP. *Practical Dermatopathology*. 2nd ed. Philadelphia, PA: Elsevier Saunders; 2012.

10. Ackerman AB, de Viragh PA, Chongchitnant N. *Neoplasms With Follicular Differentiation*. Philadelphia, PA: Lea and Febiger; 1993.

11. Dalle S, Skowron F, Balme B, Perrot H. Apocrine carcinoma developed in a nevus sebaceus of Jadassohn. *Eur J Dermatol*. 2003;13(5):487–489.

12. Shalin SC, Lyle S, Calonje E, Lazar AJ. Sebaceous neoplasia and the Muir-Torre syndrome: important connections with clinical implications. *Histopathology*. 2010;56(1):133–147.

13. Schwartz RA, Torre DP. The Muir-Torre syndrome: a 25-year retrospect. *J Am Acad Dermatol*. 1995;33:90–104.

14. Geiersbach KB, Samowitz WS. Microsatellite instability and colorectal cancer. *Arch Pathol Lab Med*. 2011;135(10):1269–1277.

15. Jessup CJ, Redston M, Tilton E, Reimann JD. Importance of universal mismatch repair protein immunohistochemistry in patients with sebaceous neoplasia as an initial screening tool for Muir-Torre syndrome. *Hum Pathol*. 2016; 49:1–9.

16. Roberts ME, Riegert-Johnson DL, Thomas BC et al. A clinical scoring system to identify patients with sebaceous neoplasms at risk for the Muir-Torre variant of Lynch syndrome. *Genet Med*. 2014;16(9):711–716.

17. Everett JN, Raymond VM, Dandapani M. Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm. *JAMA Dermatol*. 2014;150(12):1315–1321.

18. Lee JB, Litzner BR, Vidal CI. Review of the current medical literature and assessment of current utilization patterns regarding mismatch repair protein immunohistochemistry in cutaneous Muir-Torre syndrome-associated neoplasms. *J Cutan Pathol*. 2017;44(11):931–937.

19. Abbott JJ, Hernandez-Rios P, Amirkhan R, Hoang M. Cystic sebaceous neoplasms in Muir-Torre syndrome. *Arch Pathol Lab Med*. 2003;127(5):614–617.

20. Dores GM, Curtis RE, Toro JR, Devesa SS, Fraumeni JF Jr. Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: insight into Muir-Torre syndrome. *Cancer*. 2008;113(12):3372–3381.

21. Cohen PR, Kohn SR, Kurzrock R. Association of sebaceous gland tumors and internal malignancy: the Muir-Torre syndrome. *Am J Med*. 1991;90(5):606–613.

22. Sramek B, Lisle A, Loy T. Immunohistochemistry in ocular carcinomas. *J Cutan Pathol*. 2008;35(7):641–646.

23. Ostler DA, Prieto VG, Reed JA, Deavers MT, Lazar AJ, Ivan D. Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases. *Mod Pathol*. 2010;23(4): 567–573.

24. Ivan D, Hafeez Diwan A, Prieto VG. Expression of p63 in primary cutaneous adnexal neoplasms and adenocarcinoma metastatic to the skin. *Mod Pathol*. 2005;18(1):137–142.

25. Ivan D, Nash JW, Prieto VG, et al. Use of p63 expression in distinguishing primary and metastatic cutaneous adnexal neoplasms from metastatic adenocarcinoma to skin. *J Cutan Pathol*. 2007;34(6):474–480.

26. Lee JJ, Mochel MC, Piris A, Boussahmain C, Mahalingam M, Hoang MP. p40 exhibits better specificity than p63 in distinguishing primary skin adnexal carcinomas from cutaneous metastases. *Hum Pathol*. 2014;45(5):1078–1083.

27. Jain D, Mathur SR, Sharma MC, Iyer VK. Cytomorphology of sebaceous carcinoma with analysis of p40 antibody expression. *Diagn Cytopathol*. 2015; 43(6):456–461.

28. Ansai S, Arase S, Kawana S, Kimura T. Immunohistochemical findings of sebaceous carcinoma and sebaceoma: retrieval of cytokeratin expression by a panel of anti-cytokeratin monoclonal antibodies. *J Dermatol*. 2011;38(10):951–958.

29. Ansai S, Mitsuhashi Y, Kondo S, Manabe M. Immunohistochemical differentiation of extra-ocular sebaceous carcinoma from other skin cancers. *J Dermatol*. 2004;31(12):998–1008.

30. Fan YS, Carr RA, Sanders DS, Smith AP, Lazar AJ, Calonje E. Characteristic Ber-EP4 and EMA expression in sebaceoma is immunohistochemically distinct from basal cell carcinoma. *Histopathology*. 2007;51(1):80–86.

31. Yu L, Galan A, McNiff JM. Caveats in BerEP4 staining to differentiate basal and squamous cell carcinoma. *J Cutan Pathol*. 2009;36(10):1074–1176.

32. Pinkus H, Rogin J, Goldman P. Eccrine poroma: tumors exhibiting features of the epidermal sweat duct unit. *AMA Arch Derm*. 1956;74(5):511–521.

33. Mousawi A, Kibbi AG. Pigmented eccrine poroma: a simulant of nodular melanoma. *Int J Dermatol*. 1995;34(12):857–858.

34. Volmar KE, Cummings TJ, Wang WH, Creager AJ, Tyler DS, Xie HB. Clear cell hidradenoma: a mimic of metastatic clear cell tumors. *Arch Pathol Lab Med*. 2005;129(5):e113–e116.

35. Canedo T, de Almeida MP, Cuzzi T, Ramos-e-Silva M. Immunophenotypic aspects of cylindroma and nodular hidradenoma. *J Eur Acad Dermatol Venereol*. 2010;24(2):178–185.

36. Shin S. *A Comprehensive Guide to Core Needle Biopsies of the Breast*. 1st ed. Basel, Switzerland: Springer International Publishing; 2016:861.

37. Langner C, Ratschek M, Tsybrovskyy O, Schips L, Zigeuner R. P63 immunoreactivity distinguishes upper urinary tract transitional cell carcinoma and renal cell carcinoma even in poorly differentiated tumors. *J Histochem Cytochem*. 2003;51(8):1097–1099.

38. Hoang LL, Tacha D, Bremer RE, Haas TS, Cheng L. Uroplakin II (UPII), GATA3, and p40 are highly sensitive markers for the differential diagnosis of invasive urothelial carcinoma. *Appl Immunohistochem Mol Morphol*. 2015; 23(10):711–716.

39. Nazarian RM, Kapur P, Rakheja D, et al. Atypical and malignant hidradenomas: a histological and immunohistochemical study. *Mod Pathol*. 2009;22:600–610.

40. Goto K, Takai T, Fukumoto T. CD117(KIT) is a useful immunohistochemical marker for differentiating porocarcinoma from squamous cell carcinoma. *J Cutan Pathol*. 2015;43(3):219–226.

41. Souvatzidis P, Sbano P, Mandato F, et al. Malignant nodular hidradenoma of the skin: report of seven cases. *J Eur Acad Dermatol Venereol*. 2008;22(5):549–554.

42. Mambo NC. Eccrine spiradenoma: clinical and pathologic study of 49 tumors. *J Cutan Pathol*. 1983;10(5):312–320.

43. Hu G, Onder M, Gill M. A novel missense mutation in CYLD in a family with Brooke-Spiegler syndrome. *J Invest Dermatol*. 2003;121(4):732–734

44. Crain RC, Helwig EB. Dermal cylindroma (dermal eccrine cylindroma). *Am J Clin Pathol*. 1961;36(6):504–515.

45. Masutaka F, Hori Y, Nakabayashi Y. Clear-cell syringoma: association with diabetes mellitus. *Am J Dermatopathol*. 1984;6(2):131–138.

46. Ohtsuka H, Nagamatsu S. Microcystic adnexal carcinoma: review of 51 Japanese patients. *Dermatology*. 2002;204:190–193.

47. LeBoit PE, Sexton M. Microcystic adnexal carcinoma of the skin: a reappraisal of the differentiation and differential diagnosis of an under-recognized neoplasm. *J Am Acad Dermatol*. 1993;29(4):609–618.

48. Gabillot-Carre M, Weill F, Mamelle G, et al. Microcytic adnexal carcinoma: report of seven cases including one with lung metastasis. *Dermatology*. 2006; 212(3):221–228.
49. Burns MK, Chen SP, Goldberg LH. Microcystic adnexal carcinoma: ten cases treated by Mohs micrographic surgery. *J Dermatol Surg Oncol*. 1994;20(7): 429–434.
50. Jedrych J, Leffell D, McNiff JM. Desmoplastic trichoepithelioma with perineural involvement: a series of seven cases. *J Cutan Pathol*. 2012;39(3):317–323.
51. Sangma MM, Dasiah SD, Bhat VR. Syringocystadenoma papilliferum of the scalp in an adult male: a case report. *J Clin Diagn Res*. 2013;7(4):742–743.
52. Suchak R, Wang WL, Prieto VG, et al. Cutaneous digital papillary adenocarcinoma: a clinicopathologic study of 31 cases of a rare neoplasm with new observations. *Am J Surg Pathol*. 2012;36(12):1883–1891.
53. Duke WH, Sherrod TT, Lupton GP. Aggressive digital papillary carcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited). *Am J Surg Pathol*. 2000;24(6):775–784.
54. Hornick JL, Fletcher CD. Myoepithelial tumors of soft tissue: a clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. *Am J Surg Pathol*. 2003;27(9):1183–1196.
55. Jo V, Fletcher C. p63 immunohistochemical staining is limited in soft tissue tumors. *Am J Clin Pathol*. 2011;136(5):762–766.
56. Flucke U, Palmedo G, Blankenhorn N, et al. EWSR1 gene rearrangement occurs in a subset of cutaneous myoepithelial tumors: a study of 18 cases. *Mod Pathol*. 2011;24:1444–1450.
57. Jo VY, Fletcher CD. Myoepithelial neoplasms of soft tissue: an updated review of the clinicopathologic, immunophenotypic, and genetic features. *Head Neck Pathol*. 2015;9(1):32–38.
58. Maiorana A, Nigrisoli E, Papotti M. Immunohistochemical markers of sweat gland tumors. *J Cutan Pathol*. 1986;13(3):187–196.
59. Saga K. Histochemical and immunohistochemical markers for human eccrine and apocrine sweat glands: an aid for histopathologic differentiation of sweat gland tumors. *J Investig Dermatol Symp Proc*. 2001;6(1):49–53.
60. Swanson PE, Mazoujian G, Mills SE, Campbell RJ, Wick MR. Immunoreactivity for estrogen receptor protein in sweat gland tumors. *Am J Surg Pathol*. 1991;15(9):835–841.
61. Busam KJ, Tan LK, Granter SR, et al. Epidermal growth factor, estrogen, and progesterone receptor expression in primary sweat gland carcinomas and primary and metastatic mammary carcinomas. *Mod Pathol*. 1999;12(8):786–793.
62. Hiatt KM, Pillow JL, Smoller BR. Her-2 expression in cutaneous eccrine and apocrine neoplasms. *Mod Pathol*. 2004;17(1):28–32.
63. Nishida H, Daa T, Kashima K, et al. KIT (CD117) Expression in benign and malignant sweat gland tumors. *Am J Dermatopathol*. 2015;37(12):898–905
64. Lezcano C, Ho J, Seethala RR. Sox10 and DOG1 expression in primary adnexal tumors of the skin. *Am J Dermatopathol*. 2017;39(12):896–902.
65. Mertens RB, De Peralta-Venturina MN, Balzer BL, Frishberg DP. GATA3 expression in normal skin and in benign and malignant epidermal and cutaneous adnexal neoplasms. *Am J Dermatopathol*. 2015;37(12):885–891.
66. Misago N, Kimura T, Narisawa Y. Fibrofolliculoma/trichodiscoma and fibrous papule (perifollicular fibroma/angiofibroma): a revaluation of histopathological and immunohistochemical features. *J Cutan Pathol*. 2009;36(9):943–951.
67. Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol*. 1977;113(12):1674–1677.
68. Menko FH, van Steensel MA, Giraud S, et al. Birt-Hogg-Dube syndrome: diagnosis and management. *Lancet Oncol*. 2009;10(12):1199–1206.
69. Brooke JD, Fitzpatrick JE, Golitz LE. Papillary mesenchymal bodies: a histologic finding useful in differentiating trichoepitheliomas from basal cell carcinomas. *J Am Acad Dermatol*. 1989;21(3):523–528.
70. Katona TM, Perkins SM, Billings SD. Does the panel of cytokeratin 20 and androgen receptor antibodies differentiate desmoplastic trichoepithelioma from morpheaform/infiltrative basal cell carcinoma? *J Cutan Pathol*. 2008;35(2):174–179.
71. Calonje E, Brenn T, Lazar A, McKee P. *McKee's Pathology of the Skin*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2012.
72. Poniecka AW, Alexis JB: An immunohistochemical study of basal cell carcinoma and trichoepithelioma. *Am J Dermatopathol*. 1999;21(4):332–336.
73. Choi CW, Park HS, Kim YK, et al. Elastic fiber staining and cytokeratin 15 expression pattern in trichoepithelioma and basal cell carcinoma. *J Dermatol*. 2008;35(8):499–502.
74. Swanson PE, Fitzpatrick MM, Ritter JH, et al. Immunohistological differential diagnosis of basal cell carcinoma, squamous cell carcinoma, and trichoepithelioma in small cutaneous biopsy specimens. *J Cutan Pathol*. 1998; 25(3):153–159.
75. Kirchmann TT, Prieto VG, Smoller BR. Use of CD34 in assessing the relationship between stroma and tumor in desmoplastic keratinocytic neoplasms. *J Cutan Pathol*. 1995;22(5):422–426.
76. Pham TT, Selim MA, Burchette JL, et al. CD10 expression in trichoepithelioma and basal cell carcinoma. *J Cutan Pathol*. 2006;33(2):123–128.
77. Ansai S, Takayama R, Kimura T, Kawana S. Ber-EP4 is a useful marker for follicular germinative cell differentiation of cutaneous epithelial neoplasms. *J Dermatol*. 2012;39(8):688–692.
78. Sellheyer K, Nelson P, Patel RM. The immunohistochemical differential diagnosis of microcystic adnexal carcinoma, desmoplastic trichoepithelioma and morpheaform basal cell carcinoma using BerEP4 and stem cell markers. *J Cutan Pathol*. 2013;40(4):363–370.
79. Ogata T, Tanaka S, Goto T, et al. Giant trichoblastoma mimicking malignancy. *Arch Orthop Trauma Surg*. 1999;119(3-4):225–227.
80. Yamamoto O, Hisaoka M, Yasuda H, et al. A rippled-pattern trichoblastoma: an immunohistochemical study. *J Cutan Pathol*. 2000;27(9):460–465.
81. Misago N, Narisawa Y. Rippled-pattern sebaceoma. *Am J Dermatopathol*. 2001;23(5):437–443.
82. Graham BS, Barr RJ. Rippled-pattern sebaceous trichoblastoma. *J Cutan Pathol*. 2000;27(9):455–459.
83. Ohata C, Ackerman AB. "Ripple pattern" signifies sebaceoma (not trichoblastoma or "trichomatricoma"). *Dermatopathol Pract Concept*. 2001; 7(4):355–372.
84. Aloi F, Tomasini C, Pippione M. Pigmented trichoblastoma. *Am J Dermatopathol*. 1992;14(4):345–349.
85. Kanitakis J, Brutzkus A, Butnaru AC, Claudy A. Melanotrichoblastoma: immunohistochemical study of a variant of pigmented trichoblastoma. *Am J Dermatopathol*. 2002;24(6):498–501.
86. Bonczkowitz M, Weyers W, Schill WB. Proliferative activity of trichoblastoma in comparison to basal-cell carcinoma. *Am J Dermatopathol*. 1997; 19(5):508.
87. Laffay L, Depaepe L, d'Hombres A, Balme B, Thomas L, De Bari B. Histological features and treatment approach of trichoblastic carcinomas: from a case report to a review of the literature. *Tumori*. 2011;98:e46–e49.
88. Schulz T, Proske S, Hartschuh W, Kurzen H, Paul E, Wunsch PH. High-grade trichoblastic carcinoma arising in trichoblastoma: a rare adnexal neoplasm often showing metastatic spread. *Am J Dermatopathol*. 2005;27(1):9–16.
89. Rosso R, Lucioni M, Savio T, et al. Trichoblastic sarcoma: a high-grade stromal tumor arising in trichoblastoma. *Am J Dermatopathol*. 2007;29(1):79–83.
90. Kazakov D, Kempf W, Michal M. Low-grade trichoblastic carcinosarcoma of the skin. *Am J Dermatopathol*. 2004;26(4):304–309.
91. Hidayat AA, Font RL. Trichilemmoma of eyelid and eyebrow: a clinicopathologic study of 31 cases. *Arch Ophthalmol*. 1980;98(5):844–847.
92. Rohwedder A, Keminer O, Hendricks C, Schaller J. Detection of HPV DNA in trichilemmomas by polymerase chain reaction. *J Med Virol*. 1997;51(2):119–125.
93. Leonardi CL, Zhu WY, Kinsey WH, Penneys NS. Trichilemmomas are not associated with human papillomavirus DNA. *J Cutan Pathol*. 1991;18(3):193–197.
94. Kaddu S, Soyer HP, Hodl S, et al. Morphological stages of pilomatricoma. *Am J Dermatopathol*. 1996;18(4):333–338.
95. Chiaramonti A, Gilgor R. Pilomatricomas associated with myotonic dystrophy. *Arch Dermatol*. 1978;114(9):1363–1365.
96. Cooper PH, Fechner RE. Pilomatricoma-like changes in the epidermal cysts of Gardner's syndrome. *J Am Acad Dermatol*. 1983;8(5):639–644.