An overview of hair follicle tumours

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Abstract
Tumours derived from/differentiating towards the hair follicle are relatively rare and the nomenclature is somewhat confusing. A seemingly difficult task of classifying and stratifying various follicular tumours can be made easier by grouping various follicular tumours according to lines of differentiation pertaining to the specific anatomical compartments within the hair follicle. This review paper aims to improve the understanding of follicular tumours and provide several key points in order to facilitate their diagnosis.

Keywords follicular; hair germ; infundibular; isthmic; matrix; trichilemmal

Introduction
Tumours derived from or differentiating towards the hair follicle represent a subgroup of cutaneous adnexal tumours. Even though basal cell carcinoma (BCC) is included in follicular tumour sections of certain textbooks due to features shared by BCC germ cells and follicular matrix cells, it is classified as keratinocytic and not appendageal in the 2018 WHO classification. Therefore, it is safe to say that follicular tumours are relatively rare, like other adnexal tumours. Follicular tumours display a wide and often overlapping morphological spectrum, brought on not only by the number of different structures within the hair follicle but also by the hair follicle cycle. These characteristics of the hair follicle often make follicular tumours difficult to understand for the beginners in the field, and sometimes result in considerable diagnostic difficulties for the practicing pathologist.

General diagnostic considerations
The most important diagnostic task is to determine whether a follicular tumour is benign or malignant and, if malignant, whether it is prone to recur or metastasize (fortunately, the latter being quite rare). Architectural (infiltrative vs. circumscribed) and cytological features (high mitotic count, pleomorphism) are quite useful for this categorization, yet not sufficient alone without a thorough knowledge of specific entities.

Hair anatomy/embryology-based classification of follicular tumours facilitates the diagnosis because the nomenclature of follicular tumours is descriptive and sometimes inconsistent. It is a classification that categorizes the entities based on the anatomic part of the follicle whose morphology they recapitulate. There are essentially four parts of the follicle from deep to superficial: the hair bulb, the suprabulbar zone (the stem), the isthmus and the infundibulum. The suprabulbar zone extends between the bulb and the insertion of arrector pili muscle. It is followed by the isthmus whose upper limit is the opening of the sebaceous duct. The infundibulum is the uppermost part of the follicle, spanning the distance between the sebaceous duct opening and the epidermal surface.

There are several classifications which are fundamentally quite similar, with most differences being in the number of categories. For the purpose of this review, we will use a relatively simple division into 5 categories, based on the predominant pattern of differentiation, starting from the most superficial part of the follicle:

- tumours with infundibular differentiation
- tumours with isthmic differentiation
- tumours with trichilemmal (outer root sheath of the hair stem & bulb) differentiation
- tumours with hair bulb (matrical and biphasic) differentiation
- tumours with panfollicular differentiation

Tumours with infundibular differentiation
The infundibulum is characterized by epidermal-resembling keratinocytes (containing a palisaded basal layer, a spinous and a granular layer) and laminated keratin. We will focus on trichoadenoma, as other entities in this group are cysts or hamartomas and not truly neoplastic (dilated pore, naevus comedonicus).

Trichoadenoma, also called “trichoadenoma of Nikolowski”, is a collection of keratinous dermal cysts, typically well-circumscribed, with little variation in cyst size (Figure 1). It bears an adenoma-like architecture on scanning power, but has no glandular components and is clearly not an adenoma. Cysts are filled with laminated infundibular keratin, and the epithelium contains all epidermal layers. Occasionally, the epithelium may be composed of pale pink isthmus-like cells and the keratin is more compact, or the surface of cysts is somewhat crenulated resembling the sebaceous duct. A foreign-body granulomatous reaction surrounding the cysts is frequent. The tumour is entirely benign in behaviour.

The main differential diagnoses are microcystic adnexal carcinoma (MAC) and desmoplastic trichoepithelioma (DTE). Some MACs are associated with larger cysts containing laminated keratin, resembling trichoadenoma at first glance; however, MAC is a deeply infiltrative tumour with desmoplasia that shows a substantial proportion of tumour strands and solid cell aggregates. Care should be taken to avoid this misdiagnosis, as treatment for MAC requires extensive surgery. DTE shows some cysts with infundibular-type keratin. However, follicular germ papilla-like structures are also identified and the stroma in the background is desmoplastic.

Tumours with isthmic differentiation
The isthmic portion of the follicle is characterized by an outer palisaded layer and 4–5 inner layers of pink keratinocytes without a well-developed granular cell layer, while the keratin is...
compact and homogeneous (so-called “trichilemmal”), as opposed to laminated infundibular keratin.

Tumours with isthmic differentiation include the tumour of the follicular infundibulum (anatomically, a misnomer), pilar sheath acanthoma and proliferating trichilemmal cyst (pilar tumour).

**Tumour of the follicular infundibulum (TFI)** is most frequently presents as a solitary scaled nodule in the head and neck of middle-aged and elderly persons. On histology, it is a fenestrated proliferation of keratinocytes with isthmic features, connected to the epidermis (Figure 2a). The epithelial strands that outline fenestrations are often arranged parallel to the skin surface. The behaviour is benign.

Dermal induction changes accompanying dermatofibroma and epithelial fenestrations in fibroepithelioma of Pinkus may resemble TFI. In cases with underlying dermatofibroma, TFI and epithelial fenestrations in fibroepithelioma of Pinkus may occur. The latter outlines fenestrations are often arranged parallel to the skin surface. The behaviour is benign.

**Pilar sheath acanthoma (PSA)** presents as a solitary small nodule with a central keratin pore, characteristically on the upper lip. Histologically, there is a cystic central indentation with infundibular appearance surrounded by well-circumscribed nodules of isthmic keratinocytes containing trichilemmal keratin (Figure 2b). Its behaviour is entirely benign.

Trichofofolliculoma architecturally resembles PSA, but it shows more lines of differentiation (panfollicular differentiation). Sometimes, the central cystic part is not present in the sections due to orientation/tangential sectioning. When the latter happens, well-circumscribed nodules with isthmic keratinocytes surrounding compact keratin should allow for the diagnosis of PSA to be made.

**Proliferating trichilemmal cyst (PTC, synonym = pilar tumour)** shows scalp predilection (around 90% of cases) and a marked female predominance. Its biologic potential spans from benign (majority of cases) towards atypical/low grade, and rare higher grade tumours. They are slowly growing, usually solitary, often large and multinodular, with deep extension. Some cases exhibit substantial ulceration and a rather dramatic clinical appearance. Histology suggests development from a simple trichilemmal cyst in many cases. Architecturally, lobulated solid tumor foci predominate over the cystic component. In benign cases, tumour outlines are smooth, pushing, without infiltrative growth (Figure 2c). There is typically no granular cell layer and central keratin is compact and homogeneous. Epithelial glycogen accumulation can be seen, as well as a foreign body-type reaction in the surrounding connective tissue.

A smaller proportion of cases have some malignant potential. In the largest study to assess malignant potential so far, Ye et al. stratified 76 pilar tumour cases with follow-up into three groups. The first group, consisting of tumours with moderate atypia, typical pushing growth and no invasive features showed entirely benign behaviour. The second group exhibited some locally infiltrative dermal/subcutaneous growth (no neural/vascular involvement or significant atypia) and had local recurrence in 15% of cases. Third group were tumours that showed marked nuclear atypia, atypical mitoses, necrosis and infiltrative growth pattern (including but not limited to cases with neural and vascular involvement). They were the least frequent and showed higher rates (50%) of recurrence/regional lymph node metastasis. In this case series no distant metastases were recorded. There have been some convincing reports describing extremely rare death from metastases; however, there are also several sporadic reports of visceral metastasis that lack convincing histological depiction.

**Tumours with trichilemmal differentiation**

For the purpose of this review, “trichilemmal” refers to differentiation recapitulating the outer root sheath of the hair stem & bulb. It is characterized by several layers of cells with pale to clear, glycogenated cytoplasm, surrounded by a palisaded cell layer with nuclei oriented opposite to a brightly eosinophilic basement membrane.

**Trichilemmoma** can be solitary or multiple. Multiple trichilemmomas are diagnostic of Cowden syndrome, an autosomal dominant multiple hamartoma syndrome associated with germ-line mutations in the PTEN tumor suppressor gene. Individuals with Cowden syndrome carry an increased risk of breast, thyroid, uterine and other malignancies. Besides multiple trichilemmomas, the condition is also characterized by a host of cutaneous lesions such as multiple acrochorda, acral keratosis, dermal hyperneury and vitiligo. Oral cavity is frequently affected, imparting a characteristic, diffuse cobblestone mucosal appearance. Solitary trichilemmoma is most frequent in the head and neck, especially the central part of face. It is composed of peripherally palisading clear cells with epidermal/hair follicle connection and smooth contours outlined by a brightly eosinophilic basement membrane (Figure 3a). Trichilemmoma is practically the only cutaneous epithelial tumour known to diffusely express CD34, which can be important in the differential diagnosis.

**Desmoplastic trichilemmoma** is a variant that has no association with Cowden syndrome. It is very important because it is a mimicker of malignancy. The periphery of the lesion looks like a typical trichilemmoma, while the center is sclerosed, composed of narrow and irregular epithelial cords embedded in a densely hyalinized PAS-positive, diastase-resistant stroma (Figure 3b). The cells in the desmoplastic areas have a more squamoid appearance.

Due to its infiltrative growth, desmoplastic trichilemmoma needs to be distinguished from trichilemmal, squamous and basal cell carcinoma. The pseudo-infiltrative part of desmoplastic trichilemmoma is central, not peripheral as in carcinomas, the
epithelial cords are surrounded by hyalinized stroma and do not exhibit true cytological atypia. Additionally, the periphery exhibits typical trichilemmoma features. In doubtful cases, especially in shave biopsies, CD34 can be very useful in the distinction, as carcinomas are negative for this marker. However, caution is necessary as some or most of the squamoid cells in the desmoplastic area can be negative for CD34. Classical trichilemmoma is most commonly confused with eccrine tumours such as hidroacanthoma simplex and eccrine poroma. Lack of ductal differentiation (which can be confirmed by negative reaction for EMA and CEA) and presence of trichilemmal differentiation should allow distinction to be made.

*Trichilemmal carcinoma* (TC) is regarded by some authors\(^{13,14}\) as a clear cell variant of squamous cell carcinoma, and the original concept proposed by Headington\(^{15}\) is contested. However, the neoplasm is recognized in the WHO classification of skin tumours. TC is relatively rare and found in the sun-exposed skin of the elderly. Histologically, it shows a lobular growth of atypical, PAS-positive clear cells with occasional subnuclear vacuolization and connection to hair follicles, but no

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**Figure 2**

a) Tumour of the follicular infundibulum. Anastomosing epithelial strands connected to the epidermis; (inset) isthmic-type epithelium. b) Pilar sheath acanthoma. Nodules of isthmic-type epithelium with central keratin (inset). c) Proliferating trichilemmal tumour. Well-circumscribed, predominantly solid tumour with central trichilemmal keratin; (inset) homogeneous keratin and isthmic-type epithelium.

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**Figure 3**

a) Trichilemmoma. Warty architecture with hyperkeratosis; (inlet) trichilemmal differentiation in the form of clear, peripherally palisading cells surrounded by a thickened basement membrane. b) Desmoplastic trichilemmoma. Outline of typical trichilemmoma with a sclerotic center; (inset) central part, narrow epithelial cords in a hyalinized stroma. c) Trichilemmal carcinoma. Nodules composed of atypical cells with trichilemmal differentiation.
thickening of the basement membrane (Figure 3c). Nucleoli are prominent, mitoses are frequent, and there are foci of trichilemmal keratinization. There can be focal CD34 expression, consistent with outer root sheath differentiation. TC typically exhibits low-grade behaviour, therefore a tumor-free margin is very important.

TC needs to be distinguished from desmoplastic trichilemmoma, and also from clear cell hidradenocarcinoma. The latter is more aggressive in behavior and shows ductal differentiation highlighted by CEA and/or EMA staining. Desmoplastic trichilemmoma lacks pleomorphism and mitoses exhibited by TC.

**Tumours with hair bulb differentiation**

The hair bulb consists of a crescent-shaped epithelial part - the matrix, which encases a central collection of mesenchymal cells - the follicular papilla. A layer of palisading follicular germinative epithelial cells in close association to papilla mesenchymal cells is found at the matrix/papilla interface. Tumours recapitulating the hair bulb can be divided into 2 categories. One represents the matrix (pilomatrixoma, melanocytic matricoma), and the other is biphasic epithelial/mesenchymal (trichoepithelioma, trichoblastoma), corresponding to the juxtaposed follicular germinative and mesenchymal cells of the papilla.

**Pilomatricoma** is usually encountered in children and young adults in the head/neck, trunk and upper limbs. Most pilomatricomas are solitary. Multiple pilomatricomas have been documented in patients with Gardner syndrome, Turner syndrome, and a host of other very rare syndromes. It is usually documented in patients with Gardner syndrome, Turner syndrome, and a host of other very rare syndromes. The latter is more frequent in late lesions, with true osseous metaplasia and formation of calcium deposits. The latter is especially frequent in late lesions, with true osseous metaplasia and formation of calcium deposits. The latter is more frequent in late lesions, with true osseous metaplasia and formation of calcium deposits. The latter is more frequent in late lesions, with true osseous metaplasia and formation of calcium deposits. It appears that most cases pilomatrical carcinoma are low grade tumours, with rare metastases that are usually limited to the lymph node drainage area. However, a handful of cases reported in the literature have been associated with distant metastases.

**Trichoepithelioma and trichoblastoma.** These tumours show substantial morphological overlap and it has even been suggested that all neoplasms in this category should be classified as trichoblastomas. In general, “trichoepithelioma” is used for more superficial sporadic tumours and multiple small tumours located on the face that are part of the Brooke-Spiegler syndrome.

**Trichoepithelioma** is usually limited to the upper portion of the reticular dermis and may show occasional epidermal connection. It is composed of small lobules and infundibular keratocysts lined by basaloid, peripherally palisading cells which are cytologically essentially indistinguishable from BCC cells (Figure 5a). The surrounding stroma is generally more pronounced than in BCC, recapitulating “papillary mesenchymal bodies”, i.e. mesenchymal nodules forming the follicular hair germ papilla.

Multiple trichoepitheliomas occur as small papules in the central face, characteristically occupying nasolabial folds, cheeks, eyebrows or eyelids. They are found in multiple familial trichoepithelioma setting as an isolated finding, or accompanying cylindromas/spiradenomas in Brooke-Spiegler syndrome. Multiple familial trichoepithelioma is actually a phenotypic variant of Brooke-Spiegler syndrome, as they share both clinical/pathologic features and CYLD mutations. Rombo syndrome is a rare syndrome that may present with multiple trichoepitheliomas in combination with milia, verruciform atrophy, BCC, vellus hair cysts, peripheral vascodilatation, and cyanosis.

The main differential diagnosis for trichoepithelioma is BCC. Formation of papillary mesenchymal bodies points to trichoepithelioma, while ulceration, connection to the epidermis, peritumoural clefts and mucin deposition argue for BCC. Numerous

**Figure 4 a)** Pilomatricoma. Proliferation of peripheral basaloid and central ghost cells; (inset) interface between two cell populations. **b)** Pilomatrical carcinoma. Poorly differentiated carcinoma with ulcerated surface, composed of basaloid cells; (inset) a high power view highlighting ghost cells surrounded by atypical basaloid cells with numerous mitoses.
studies have tried to utilize various panels of immunohistochemical markers, such as CD34, CD10, epithelial membrane antigen, bcl-2, cytokeratin 15, cytokeratin 20 and D2-40 to aid in the distinction, with inconclusive results.\(^\text{21}\) If histological distinction cannot reliably be made on a superficial shave biopsy, it is prudent to recommend complete excision of the lesion.

Desmoplastic trichoepithelioma (DTE) shows some specific morphological and differential diagnostic features compared to conventional trichoepithelioma. It is usually a small and superficial papule with a central dimple located on the face of young adults. Lesions are superficial, fairly circumscribed and characterized by superficial infundibular keratocysts with focal calcification and thin strands of epithelial basaloid cells lacking peripheral palisading, embedded in a desmoplastic stroma (Figure 5b). Perineural involvement has rarely been reported in DTE\(^\text{22}\) that should not be equated with malignancy or lead to overtreatment.

The main differential diagnoses which can be extremely challenging in superficial partial biopsies, include morphoeic BCC (mBCC) and microcystic adnexal carcinoma (MAC). DTE does not show any peripheral palisading, retraction artefact, prominent mitotic activity or ulceration found in mBCC and contains keratocysts, unlike mBCC. DTE can also be distinguished from mBCC by the presence of scattered CK20-positive Merkel cells in tumour strands and negativity for androgen receptors. BerEP4 is not useful in the differential, being usually positive in both. DTE is never as infiltrative as MAC, even in the cases with perineural invasion described by McNiff et al.\(^\text{22}\) In addition, MAC usually does not exhibit superficial calcified keratocysts. Evidence of ductal differentiation in MAC by CEA/EMA staining, if present, can exclude DTE. A combination of CK15 and CK19 may also be used in the differential, as the immunoprofile is CK15+/CK19- in DTE and CK15-/CK19+ in MAC.\(^\text{23}\)

Trichoblastoma has a predilection for the head and neck, trunk, genital/perianal region and proximal extremities. It can be large (3 cm or more), is well-circumscribed and occupies the entire dermis with occasional subcutaneous involvement. It has follicular hair germ differentiation, i.e. has both epithelial and mesenchymal component. The epithelial component grows in larger/smaller nodules, cribriform or trabecular structures, surrounded by specialized mesenchymal cells resembling the cells of follicular papilla (Figure 5c). Conventional BCCs do not show such typical epithelial/mesenchymal juxtaposition and marked peri-epithelial mesenchymal cell condensation. Trichoblastoma follows a benign course. Interestingly, Requena et al. recently described a multiple facial plaque trichoblastoma variant of presumed hereditary aetiology, but were unable to track down an underlying genetic alteration.\(^\text{24}\) Malignant variants may occur and are described below.

Cutaneous lymphadenoma\(^\text{25}\) (synonym adamantoid trichoblastoma) is a characteristic morphological subtype of trichoblastoma. It is well-delineated, un-encapsulated, with nests of large clear cells that are surrounded by peripheral palisading, infiltrated by numerous lymphocytes and embedded in a dense fibrous stroma. It should not be confused with lymphoepithelial carcinoma of the skin, an epithelial malignancy heavily infiltrated by lymphocytes.

Malignant trichoblastoma can have a malignant epithelial (trichoblastic carcinoma) or mesenchymal (trichoblastic sarcoma) component, or a combination of the two (trichoblastic carcinosarcoma) (Figure 5d). All of them affect the elderly. Sarcomatous transformation is even less frequent than carcinomatous transformation, with only a handful of cases described so far.\(^\text{26}\) “Trichoblastic carcinoma” has been used by the late Bernard Ackerman as a synonym for BCC; however,
we and other authors use it for malignant transformation of trichoblastoma. The most important diagnostic feature of malignant trichoblastoma is its grade. Low grade tumours resemble trichoblastoma but have infiltrative growth, involving deep soft tissue or skeletal muscle; high grade trichoblastic carcinomas show high grade cytomorphology together with infiltrative growth. The data on these two tumour types is limited, but it seems that low grade tumours exhibit only local recurrence, while high grade tumours may result in metastasis and death.22

As Brooke-Spiegler syndrome has been mentioned in this section, we will also refer to Birt-Hogg-Dubé (BHD) syndrome,28 a rare autosomal-dominant genodermatosis characterized by numerous, discrete 1–5 mm skin-coloured papules on the head and neck. It is caused by mutations in the FLCN gene29 that simultaneously carry predisposition for renal tumours, pulmonary cysts, bullous emphysema and spontaneous pneumothorax. Histology of the papules corresponds to fibrofolliculoma, a circumscribed proliferation of loose connective tissue around a well-formed follicle, and trichodiscoma, a collection of loosely-woven, follicle-associated connective tissue with admixed thin- and thick-walled blood vessels.

**Tumours with panfollicular differentiation**

Several differentiation lines can be found to a small extent in various follicular tumours; in tumours with panfollicular differentiation, it is a rule and it is generally quite pronounced. They are therefore considered hamartomatous by most authors.

**Trichofolliculoma**30 usually presents in the head and neck as a small (0.5–1 cm), solitary flesh-coloured nodule. One or more central white silky hairs can be seen growing from the nodule. On histology, a central cystic cavity is lined by infundibular type epithelium, and contains keratinous debris/shredded hairs. Numerous hair follicles with various anatomic lines of differentiation are spreading from the lining of the cavity towards the surrounding dermis (Figure 6). Trichofolliculoma not only recapitulates various anatomical lines of differentiation, but also different phases of follicle growth (anagen, catagen, telogen). Its behaviour is entirely benign. An extremely rare tumour called panfolliculoma can be included in this group because it shows multiple elements of the hair follicle, yet it predominantly resembles trichoblastoma with areas of more mature follicular differentiation.

**Practice points**

- Follicular tumours are rare and the terminology is confusing.
- A tumour classification based on anatomical lines of follicular differentiation is useful.
- Follicular tumour diagnosis may seem difficult, but is achievable with proper knowledge of the classification.
- Mitotic activity or infiltrative growth do not equal malignancy. Knowledge on which benign entities may display such features is crucial to prevent misdiagnosis.
- Multiple follicular tumours can be associated with genetic cancer tumour syndromes.


