



Published by  
Department of Dermatology and  
Venereology, Universitas Udayana

# Differences in the diagnosis of sweat gland tumors with other histopathologically similar skin tumors



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## ABSTRACT

Sweat gland tumors are still relatively rare compared to other skin tumors. The clinical features of sweat gland tumors are non-specific and are rarely encountered in daily diagnostic practice. This article aims to explain the features of benign sweat gland tumors based on clinical and histopathological features. Many sweat gland tumors have overlapping clinical features with other tumors, whether from other adnexal tumors or even malignant tumors. Fulton et al. divided eccrine and apocrine gland tumors into six groups based on the similarity of the basic histopathological features, which could help clinicians better establish benign sweat gland tumors. The histopathological examination could complement history taking and physical examination to establish benign sweat gland tumors.

**Keywords:** apocrine, eccrine, sweat gland, tumor, histopathology.

**Cite This Article:** Sari, M., Fadila, A. 2022. Differences in the diagnosis of sweat gland tumors with other histopathologically similar skin tumors. *Bali Dermatology and Venereology Journal* 5(2): 42-49. DOI: 10.15562/bdv.v5i2.103

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Submit: 2022-10-17

Accepted : 2022-10-27

Publish: 2022-11-30

## INTRODUCTION

Adnexal tumors (ATs) are tumors arising from the skin's adnexal tissues, sebaceous glands, eccrine & apocrine sweat glands, and hair follicles that are mostly benign and have rare incidences.<sup>1-4</sup> Adnexal tumors might be solitary or sporadic that could be asymptomatic or a signal of several genetic syndromes (Cowden syndrome, Muir Torre syndrome, Birt-Hogg-Dubé syndrome, Brooke-Spiegler syndrome).<sup>3</sup>

Sweat gland tumors are still relatively rare compared to other skin tumors. However, among other ATs, sweat gland tumors have the highest prevalence (56%) compared to tumors originating from hair follicle differentiation (28%) or sebaceous glands (16%). The clinical features of sweat gland tumors are non-specific and are rarely encountered in daily diagnostic practice. The histopathological features of sweat gland tumors are variable. It has a complex classification system and could have different names for each disorder. Therefore it is not easy for clinicians to establish a diagnosis of eccrine and apocrine sweat gland tumors.<sup>1,5</sup> This literature review aimed to explain the features of benign sweat gland tumors based on clinical and histopathological

features.

## REVIEW

Skin adnexal proliferation is broadly distinguished based on two principles: from its differentiation line, which are sweat glands (eccrine and apocrine), sebaceous glands, and hair follicles, and from its nature which is benign or malignant tumors.<sup>1,3,5</sup> Sweat gland tumors have relatively broad histopathological features but have in common the presence of ductal or glandular differentiation of eccrine and apocrine glands. Fulton et al. divided eccrine and apocrine gland tumors into six groups based on the similarity of the basic histopathological features described in Table 1.<sup>2</sup> Some benign and malignant skin tumors which have similarities in their histopathology examination with adnexal tumors will be explained.

### Adenoma with well-differentiated aggressive digital papillary adenocarcinoma (ADPA)

Adenomas are tumors with glandular (ductal and lamina) differentiation, both eccrine and apocrine, with tubular, cribriform, papillary, mixed, or other patterns that do not belong to these

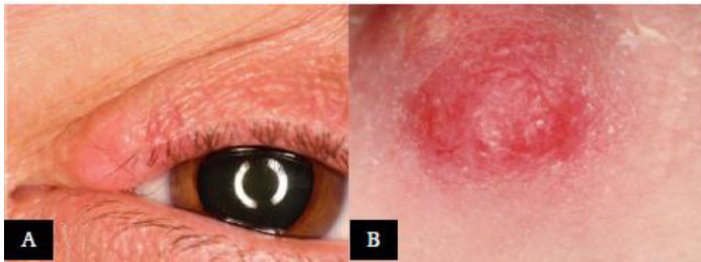
patterns. The clinical feature of adenoma is atypical: skin-colored or reddish papules or nodules, clearly demarcated and without ulceration (Fig. 1). Some cases of adenoma appear together with nevus sebaceous.<sup>6</sup>

The most common location of adenoma predilection is in the head and neck area, where elderly women are the most common group affected by this tumor.<sup>7</sup> Complaints regarding adenoma depend on the lesion location. Eyelid adenoma gives complaints of focal madarosis and telangiectasia, whereas nipple adenoma gives complaints of discharge and nipple erosion.<sup>8,9</sup>

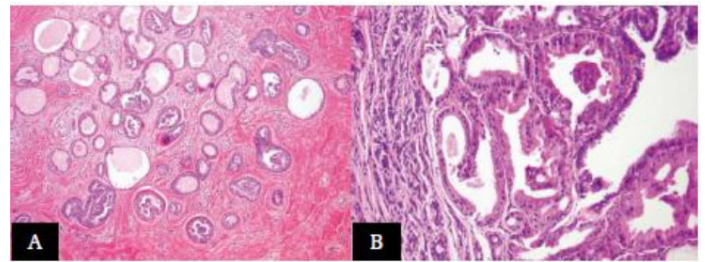
Histopathological features of adenomas are generally in the form of tumors with glandular differentiation in the dermis, well-defined, tubular, cribriform, papillary, micropapillary, or mixed growth patterns. The ducts in the adenoma are lined by two types of cells: secretory cuboidal luminal cells and cuboidal peripheral cells or squamous myoepithelial cells. Epithelial cells vary in size and shape (cuboid or squamous). The cytoplasm is pink or clear. Focal squamous and/or mucinous metaplasia might be seen (Fig. 2). Stromal adenomas have varying degrees of fibrosis and might be hyalinized. Further classification of adenomas is based on

**Table 1. Sweat gland tumor classification.<sup>2</sup>**

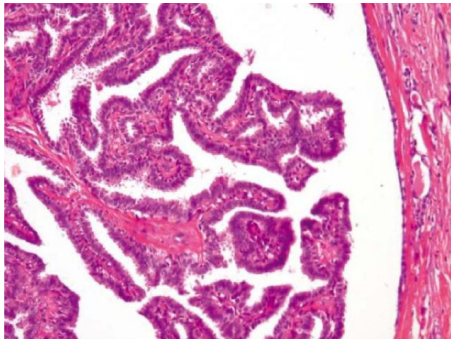
Pattern type	Pattern description	Examples
Pattern 1	Dermal cyst with cuboid or double columnar layer	Hidrocystoma, cystadenoma
Pattern 2	Pinkish/clear/squamous proliferation at the epidermis and/or dermis	Acrospiroma (hidroacanthoma simplex, poroma, dermal ductal tumor, hidradenoma) and malignant tumor
Pattern 3	Bluish basaloid proliferation at the dermis	Spiradenoma, microcystic adnexal carcinoma
Pattern 4	Tadpole/paisley tie	Syringoma, microcystic adnexal carcinoma
Pattern 5	Cystic chamber and papillary projection	Syringocystadenoma papilliferum, hidradenoma papilliferum, digital papillary adenocarcinoma
Pattern 6	Dermal tumor mixed with variable cords/chains/tubules and chondromyxoid stroma	A mixed tumor (chondroid, syringoma)



**Figure 1.** A. Adenoma (tubular apocrine adenoma) on the left upper eyelid as a reddish skin-colored and well-defined nodule deep in the dermis and without ulceration. Nodules adjacent to the lacrimal punctum appear as focal madarosis and telangiectasia.<sup>9</sup> B. Adenoma (tubular apocrine adenomas) on the left nipple appears as a reddish nodule with induration and discharge complaints.<sup>10</sup>



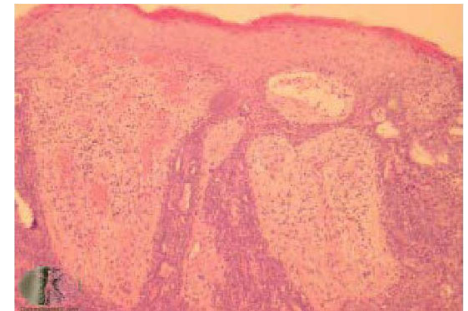
**Figure 2.** A. Eccrine adenoma showing a tubular and papillary pattern. The ductal structure is lined by two layers of cells: cuboidal epithelial cells on the inside and squamous cuboidal or myoepithelial cells on the outside. B. Apocrine adenoma shows epithelial cells lining the inside of the lumen with pink cytoplasm and apocrine-type secretions.<sup>7</sup>



**Figure 3.** Hidradenoma papilliferum showing papillary epithelial projections with visible fibrovascular nuclei within the cystic lumen.<sup>6</sup>



**Figure 4.** ADPA presented as masses on the right thenar, first finger base, and dorsum of the hand.<sup>10</sup>



**Figure 5.** The histopathological appearance of ADPA shows solid morphology of the ducts with focal areas of papillary formation. There are basaloid cells, enlarged atypical cell nuclei, large nucleolus, and an increased mitotic rate.<sup>7</sup>

the predominant growth pattern of tubular, cribriform, or papillary adenoma/hidradenoma papilliferum (Fig. 3).<sup>6</sup>

Well-defined adenocarcinomas should be distinguished from well-differentiated adenocarcinomas. One of the examples is well-differentiated aggressive digital papillary adenocarcinoma (ADCA), a rare

eccrine neoplasm with a recurrence rate of 50% and metastatic potential of 14% with or without recurrence.<sup>3,6,7</sup> Adenoma with well-differentiated aggressive digital papillary adenocarcinoma appears as a slowly growing solitary nodule (months to years), with its most common locations being the distal finger and thumb, with a

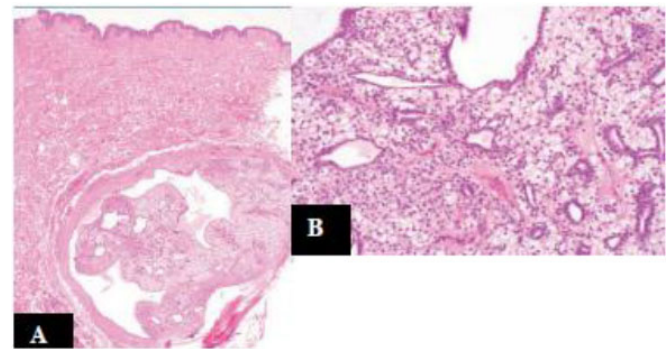
sex predilection most common in males and an age predilection most common in the 5<sup>th</sup> to 6<sup>th</sup> decades of age (Fig. 4).<sup>7</sup>

Histopathological examination of ADPA showed an infiltrative, destructive growth pattern with papillary projections, poor gland differentiation, necrosis, cellular atypia, pleomorphism, and papillary,

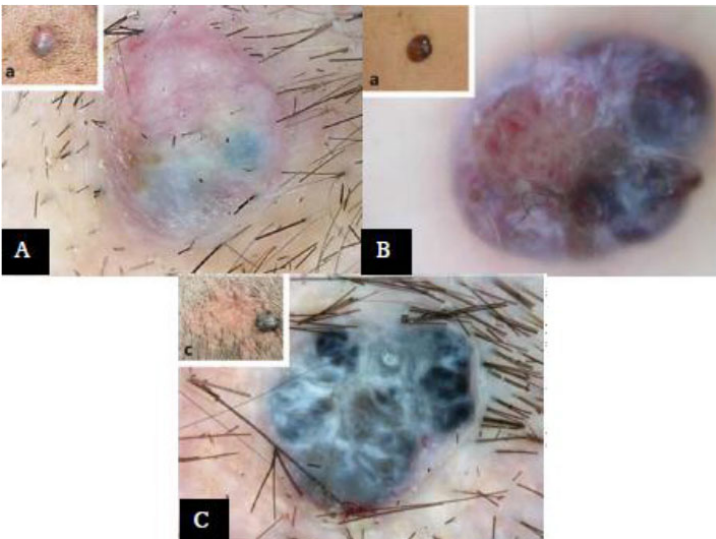




**Figure 6.** Nodular hidradenoma appears as a reddish nodule.<sup>7</sup>



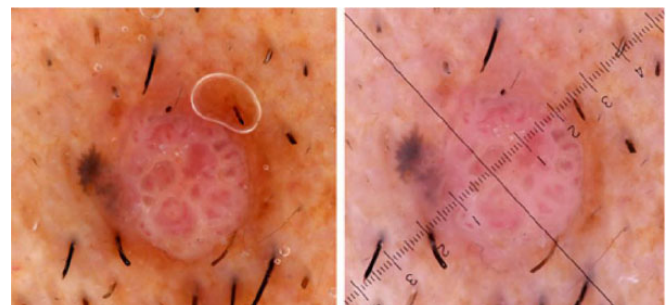
**Figure 9.** Hidradenoma. A. Tumor in the dermis, well-demarcated, not involving the epidermis, not encapsulated, solid, and cystic. B. Clear cells and cells with ductal and glandular differentiation could be seen.<sup>3</sup>



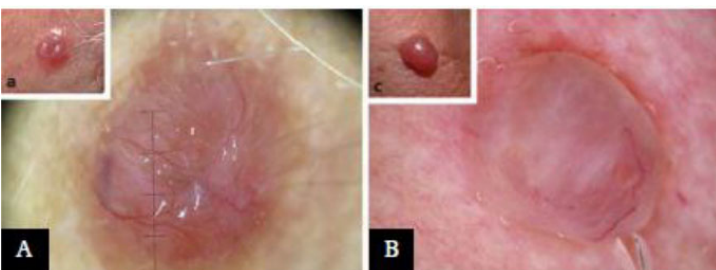
**Figure 7.** Pigmented hidradenoma. A. Reddish homogeneous area at the top and bluish homogeneous area at the bottom of the lesion. White structures and telangiectasias could also be seen. B. Bluish homogeneous areas with small "milky-red" areas with white structures and atypical polymorphous veins. C. Completely dark blue homogeneous area with white structures and telangiectasias.



**Figure 10.** Trichilemmoma appears as a pigmented, focal nodule on patients with skin type Fitzpatrick-3.<sup>15</sup>

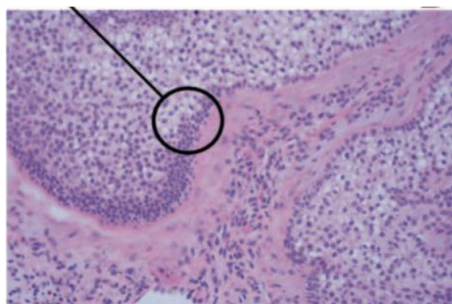


**Figure 11.** Trichilemmoma dermoscopy (polarized dermoscopy: left picture, unpolarized dermoscopy: right picture) shows a focal, pigmented macular component with converging radial lines, an unpigmented lesion with radially arranged peripheral vessels, and a white area with several centralized vessels.<sup>15</sup>

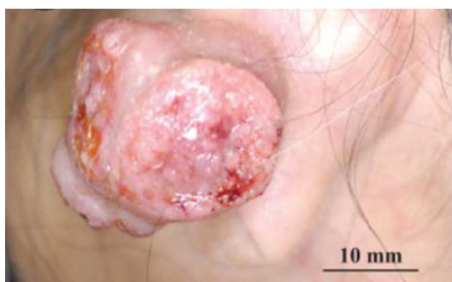


**Figure 8.** Non-pigmented hidradenoma. Figures A and B show reddish homogeneous areas with white structures and arborizing telangiectasias.<sup>12</sup>

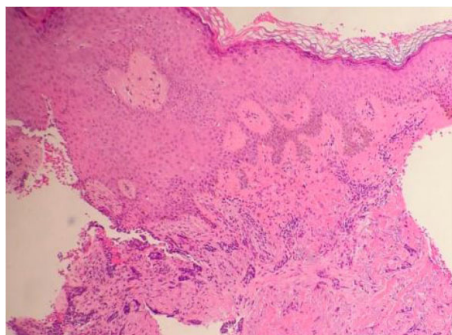




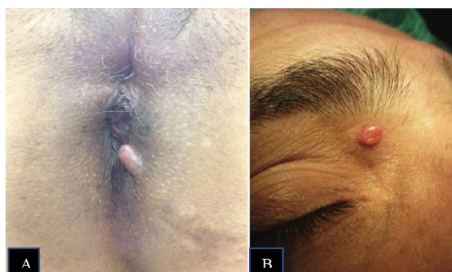
**Figure 12.** Histopathology examination of trichilemmoma shows clear cell changes and a thick basement membrane (analogous to the outer root sheath of a hair follicle and vitreous layer).<sup>2</sup>



**Figure 13.** Squamous Cell Carcinoma (SCC).<sup>18</sup>



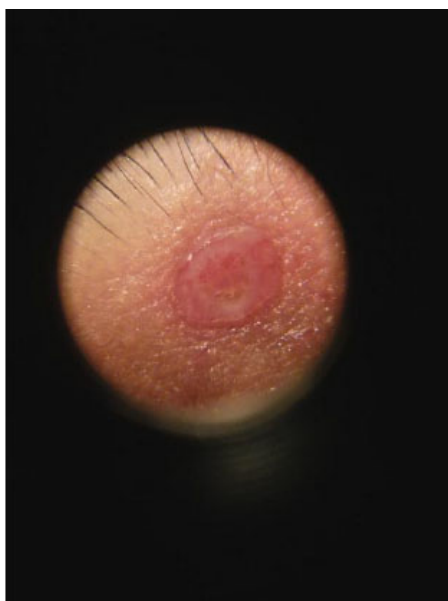
**Figure 14.** Desmoplastic SCC (H&E stain, 10× magnification).<sup>17</sup>



**Figure 15.** Hidradenoma papilliferum. A. Perianal HP shows a cystic nodule.<sup>21</sup> B. Ectopic HP of the eyelid.<sup>22</sup>



**Figure 16.** Hidradenoma papilliferum of the vulva shows a more extensive feature.<sup>18</sup>



**Figure 17.** HP dermoscopy showing telangiectasia on the surface of the nodule and central umbilication.<sup>22</sup>

cystic, or solid growth (Fig. 5). Areas of squamous cell differentiation could be found but are usually focal. Most well-differentiated ADPAs show less specific cell variations, which could complicate their diagnosis.<sup>6,7</sup> Immunohistochemical examination of ADPA shows mostly positive for p63, keratin7, keratin77 (eccrine gland specific), PHLDA1, and epithelial membrane antigens. Meanwhile,



**Figure 18.** Syringocystadenoma papilliferum appears as a verrucous plaque on the scalp.<sup>3</sup>

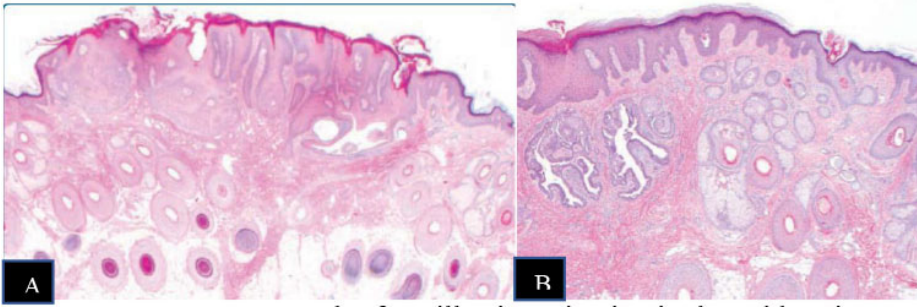
carcinoembryonic antigens, smooth muscle actin, S100 protein, estrogen, progesterone, and androgen receptors were positive in 50% of cases.

### Hidradenoma and trichilemmoma

Hidradenoma (nodular hidradenoma, eccrine acrospiroma, clear cell hidradenoma) is a common sweat gland tumor.<sup>3</sup> Hidradenoma is a tumor originating from the distal sweat gland and is clinically characterized by solitary skin-colored or reddish papules and/or rather large nodules that could reach 2 cm or more and are easily mobile (Fig. 6).<sup>3,6,11</sup> Hidradenoma could grow in any anatomical location and at any age in the form of solid nodules (nodular hidradenoma) or cystic (nodulocystic hidradenoma).<sup>6</sup> Nodular hidradenoma (NH, clear cell hidradenoma, eccrine acrospiroma, or solid cystic hidradenoma) is common in women aged 20-50 years and is commonly found on the scalp, face, and extremities.<sup>11</sup>

Hidradenomas show pinkish, bluish, or brownish homogeneous areas with white structures (including shiny white lines called a chrysalis) and blood vessels (telangiectasias and atypical polymorphous veins) on dermoscopy. Hidradenoma has two patterns: pigmented and non-pigmented. Pigmented hidradenoma pattern is a bluish or brownish heterogeneous area with the presence of variable white and vascular structures (Fig. 7). Nonpigmented hidradenoma pattern consists of a reddish homogeneous area throughout the lesion with variable white and vascular structures (Fig. 8).<sup>11</sup>

Hidradenoma is a tumor located in the dermis, clearly demarcated, and not encapsulated on histopathological



**Figure 19.** A. Tumor occurs as a result of papillae invagination in the epidermis. B. The left side of the image shows a papillary projection consisting of an inner layer arranged by columnar epithelium with secretions and an outer layer of myoepithelial cells.<sup>3</sup>



**Figure 20.** BCC might appear as a nodule (right image) or plaque (left image).<sup>6</sup>

examination. Large tumors could reach the subcutaneous layer, are not associated with the epidermis, and show a solid/cystic growth pattern with ductal differentiation.<sup>3,4,6</sup> This tumor consists of uniform lobes of eosinophilic cells or clear cells rich in glycogen and other cells such as epidermoid/squamous cells, mucinous cells, and oncotoc cells. Ducts could be seen throughout the lesion, some dilating and forming cystic areas filled with eosinophilic secretions. The tubular lumen and cystic space are lined by cuboidal ductal or columnar secretory cells. The nucleus is regular and slightly hyperchromatic. Mitosis is rare. Some areas might show squamous differentiation (keratinized pearls). The stroma might be fibrous and show extensive or sclerotic hyalinization but is usually focal (Fig. 9). Atypical adenomas might present as areas of focal atypia, poorly defined borders, nuclear pleomorphism, focal necrosis, and with increased mitotic activity.<sup>3,6</sup>

The histopathological appearance of a hidradenoma might resemble a trichilemmoma because of the clear cell changes. Trichilemmomas are

distinguished from hidradenomas by the presence of peripheral palisade and the absence of ducts.<sup>6</sup> Trichilemmomas are benign, solid tumors originating from the outer sheath cells of pilosebaceous follicles that appear as verrucous papules/nodules on the nose, eyelids, or other areas of the patient's face and neck of adult patients, both of their solitary and multiple nodules are flesh-colored (Fig. 10), with the highest sex predilection for males.<sup>3,13,14</sup> Multiple trichilemmomas involving the oral mucosa are found in patients with Cowden's syndrome (multiple hamartoma syndrome).<sup>3</sup>

Trichilemmoma shows a keratinized mass or "perivascular whitish halos", a central hyperkeratotic area with peripheral erythematous radial lines, and a "peripheral radiated red area", where all three findings are termed as "red iris-like structure" on dermoscopy. Several case reports reported dermoscopy of trichilemmoma showing an unpigmented lesion with radially arranged peripheral vessels and white areas with several centralized vessels (Fig. 11).<sup>15</sup>

The histopathological appearance

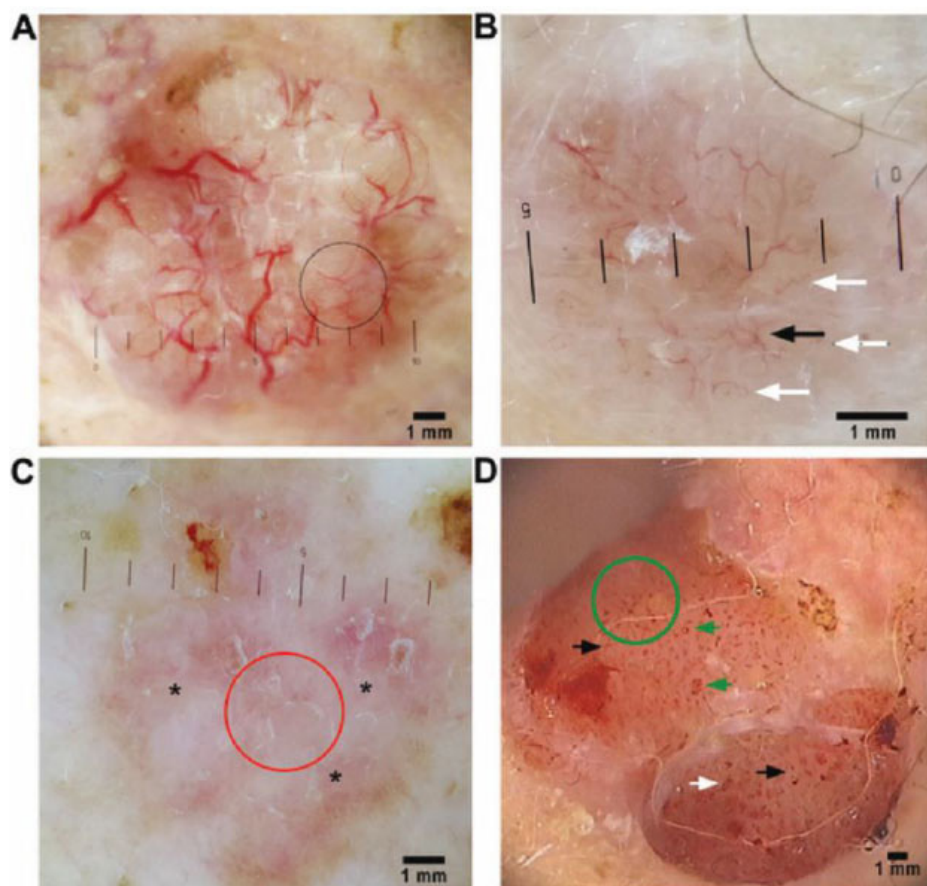
of trichilemmoma shows a verruca-like appearance, namely papillomatosis, hypergranulosis, focal parakeratosis, and dilated blood vessels on the surface of the rete.<sup>2</sup> The tumor is well-defined, with endophytic lobules extending from the epidermis to the dermis. The lobule consists of pale eosinophilic keratinocytes with peripheral palisade and is surrounded by a positive hyaline membrane with Periodic Acid-Schiff (PAS) staining.<sup>3</sup> Focal basal layer palisade, clear cells, and basement membrane material in trichilemmoma are morphologically homologous to normal hair follicle's lower outer root sheath (Fig. 12).<sup>2</sup> Verrucous hyperplasia and lobular formation with clear cells are diagnostic features of trichilemmoma.<sup>14</sup> Peripheral palisade and absence of ducts distinguish trichilemmoma from hidradenoma.<sup>7</sup> Immunohistochemical examination of trichilemmomas using CD34, CD10, and CK5/6, tumor cells showed negative CD34, but stromal cells showed positive diffuse CD34. CD10 and CK5/6 are positive on tumor cells.<sup>14</sup>

### Hidradenoma and squamous cell carcinoma (SCC)

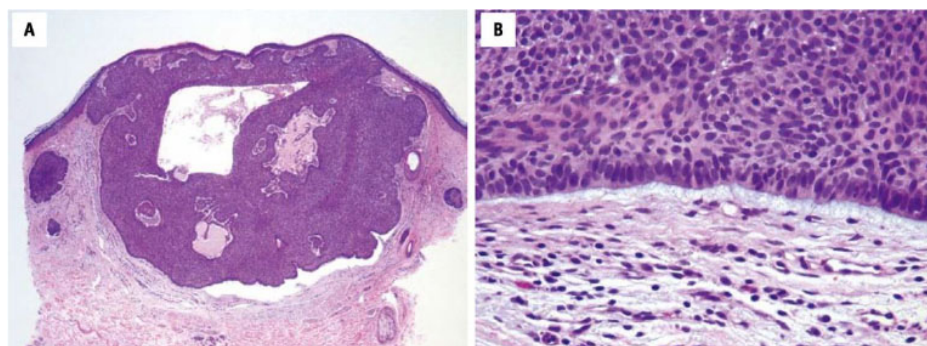
Hidradenoma with prominent squamous differentiation might resemble squamous cell carcinoma (SCC) on histopathological examination. However, SCC does not show ductal differentiation. SCC is a non-melanoma skin malignancy with a reported incidence of 20% of all skin malignancies. SCC incidence has increased drastically due to increased sun exposure, UV exposure intensity, increasing age, increasing public awareness of skin cancer and the increasingly sophisticated diagnosis of skin disorders by doctors, smoking, exposure to therapeutic UV rays (including PUVA therapy and tanning beds), Human Papilloma Virus (HPV) type 16, 31, and 34 infections, arsenic consumption, exposure to polycyclic aromatic hydrocarbons, immunosuppression, high fat and meat diet, chronic dermatosis history, and chronic ulcers. SCC has a larger lesion size than hidradenoma (>2 cm in diameter) and is often accompanied by lymphadenopathy (Fig. 13).<sup>16,17</sup>

On histopathological examination, SCC showed atypical cells in the dermis





**Figure 21.** BCC dermoscopy vascular view. **A.** Arborizing vessel, arborizing microvessels (black circle). **B.** Arborizing microvessels (black arrows) and short smooth telangiectasia (white arrows). **C.** Milky-pink background (black asterisk) and smooth short telangiectasia (red circle). **D.** Dotted (green circle), hairpin (white arrow), comma (black arrow) and glomerular vessels (green arrow).<sup>25</sup>



**Figure 22.** BCC. **A.** BCC appears as a nodular/nodulocystic tumor consisting of basaloid cells. **B.** At the periphery of the tumor nodule, the basaloid cells are arranged as a palisade, and a cleft separating the tumor from the dermal stroma contains a mucoid material.<sup>6</sup>

and an enlarged pleomorphic nucleus with atypical mitotic activity. Inflammation is usually seen in ulcerated lesions composed of lymphocytes, plasma cells, and neutrophils. Keratin is usually found in the dermis and surrounded by nests

of atypical cells with reduced stroma and lymphocytes. SCC might also exhibit desmoplastic features characterized by aggregates of moderately or poorly differentiated keratinocytes surrounded by a desmoplastic stroma of at least 30% of

the tumor volume (Fig. 14).<sup>3</sup>

### Hidradenoma papilliferum (HP) and SCC

Hidradenoma papilliferum (HP) is a benign, cystic, and papillary apocrine gland tumor. The most common age predilection for HP is middle age group women (30-49 years). However, several studies reported that 3-17% of HP patients are in their 6<sup>th</sup> decade.<sup>18,19</sup> The most common location for HP is the vulva, followed by the perianal, especially along the “milk line”.<sup>1,6</sup> Tumor location other than the anogenital region is referred to as ectopic HP and is most commonly seen in the head and neck region followed by the breasts, eyelids, external ears, scalp, eye area, nose, breast, chest, and abdomen (Fig. 15).<sup>20</sup>

Hidradenoma papilliferum presents as a single, symptomatic, asymptomatic, well-circumscribed, skin-colored or reddish-brown nodule with varying sizes (0.5 to 1 cm).<sup>20</sup> HP cases might mimic carcinoma (Fig. 16). Symptoms such as pain, burning sensation, vaginal discharge, bleeding, or pruritus are rare in long-standing tumors.<sup>18</sup> In some cases, ulceration and bleeding might occur.<sup>20</sup> HP dermoscopy shows multiple telangiectasias on the surface of the nodule and central umbilication (Fig. 17).<sup>22</sup>

Most cases of HP are benign, but some case reports regarding HP reported concomitant invasive vulvar squamous cell carcinoma, Paget’s disease, and melanocytic neoplasia. Several studies have identified HPV DNA type 16, 31, 33, 53 and 56 in HP.<sup>19,23</sup> HPV DNA is only present in a small number of cases. Therefore HPV pathogenesis as a causative agent of malignancy in HP still requires further research.<sup>19</sup> However, HPV as the causative agent in SCC has been demonstrated.<sup>17</sup>

Histopathologically, the appearance of stromal hidradenoma papilliferum is a well-defined pseudocapsule in the dermis with apocrine differentiation.<sup>18,19</sup> Tubular and cystic structures are seen within the cystic space of the tumor, which contains papillary structures (Fig. 3).<sup>1,18</sup> The cystic space, in some cases, is lined by a single layer of columnar cells with eosinophilic cytoplasm and hypochromic

nuclei. The HP lumen has two cell layers: cuboidal cells and myoepithelial cells.<sup>18</sup> Histopathological feature of HP is a papillary architecture with a luminal secretory cell layer surrounded by myoepithelial cells.<sup>3</sup> Malignant features are suspected if adenomatous hyperplasia is associated with cellular pleomorphism and an irregular papillary pattern without lumen formation.<sup>18</sup>

In some studies, squamous metaplasia has been noted in 1-16% of HP cases, mainly in irritation and recurrent infections caused by old lesions, and its histopathological features might resemble SCC.<sup>14,23</sup> Complex papillary gland pattern with stratification, and multiple degrees of pleomorphism and mitotic activity could stimulate carcinoma.

An immunohistochemical examination might help differentiate HP and SCC. HP expressed CK7, EMA, CEA, and GCDFP-15.<sup>14</sup> SCC showed immunoreactivity for high molecular weight keratin, whereas HP did not. A positive GCDFP-15 supports HP diagnosis because it is positive for tumors of the apocrine and lacrimal glands. HP with squamous metaplasia and HP with associated SCC must be distinguished with extreme caution.<sup>18</sup>

### **Hidradenoma papiliferum dan siringokistadenoma papiliferum (SP)**

Syringocystadenoma papilliferum (SP) is a benign tumor with the scalp and face as the most common predilection. Its age predilections are newborn, childhood, or adolescence in the form of solitary or multiple yellowish, brown, or red papules that could resemble warts.<sup>3,6,24</sup> Syringocystadenoma papilliferum lesions could also occur in other areas of the head and neck. The trunk and extremities could also be affected, but the case is rarely reported.<sup>3</sup> Lesions might be linearly arranged with reduced or no hair growth. The lesions enlarge at puberty, become papillomatous, and often become crusted (Fig. 18).<sup>6</sup>

The SP has a distinct histopathologic feature and consists of invaginated papillae connected to the surface squamous epithelium (Fig. 19A). The epithelium covering the papillae consists of two layers: an inner layer consisting of

columnar cells and cuboidal cells, which are often seen with marked secretions, and an outer layer consisting of basal cells or myoepithelial cells (Fig. 19B). The center of the papilla, which is fibrous tissue, often contains a plasma cell infiltrate. On immunohistochemical examination, epithelial cells express cytokeratin, including CK7, EMA, and CEA. The myoepithelial inner layer is positive for smooth muscle actin.<sup>3</sup>

SP must be distinguished from HP because, in some cases, malignancy might arise from SP.<sup>6</sup> Histopathological features of SP include papillary structures connected to the epidermis with an infiltration of plasma cells in the middle of them. At the same time, HP does not show a prominent plasma infiltrate.<sup>3,6</sup>

### **Poroma and basal cell carcinoma (BCC)**

Basal cell carcinoma (BCC) is one of the histopathological differential diagnoses of poroma. BCC is a very common neoplasm with risk factors for sun exposure. It might occur in both sun-exposed and enclosed areas and patients with xeroderma pigmentosum, Bazex syndrome, basal cell nevus syndrome, a history of radiation exposure, and usually occurs in adult patients with predilections of 4<sup>th</sup> decade and male.<sup>6</sup>

BCC clinically presents as flesh-colored, erythematous, or pigmented papules or nodules, might ulcerate (rodent ulcers), or as chronic plaques (sclerosing BCC) (Fig. 20).<sup>6</sup> BCC dermoscopy shows leaf-like areas, large blue-grayish ovoid nests, short white streaks, "spoke-wheels" areas, blue and gray dots, and globules. In addition to these pigment criteria, specific vascular patterns prove useful for BCC diagnosis, especially when the structures mentioned above are absent. Relatively superficial blood vessels are easily accessible for dermoscopy examination (Fig. 21).<sup>25</sup>

BCC was histologically characterized by basaloid cells, peripheral palisade, mitotic features, apoptotic bodies, myxoid stroma, and peritumoral clefts (Fig. 22). Myxoid stroma and peritumoral cleft are the most helpful features to differentiate BCC from other basal cell tumors. Several secondary features that might be found in BCC are dystrophic calcification,

amyloid deposition, or an inflammatory reaction with or without features of partial regression.<sup>6</sup>

In contrast to BCC, poroma has no cell nucleus arranged as a palisade and no gaps between tumor cells and the surrounding stroma. The most important difference is in their cytology. Poromas are composed of small cuboidal cells with small nuclei showing a fine or open chromatin pattern, whereas basal cell carcinoma cells have elongated and hyperchromatic nuclei.<sup>6</sup>

## **CONCLUSION**

A histopathological examination could complement history taking and physical examination to establish a benign sweat gland tumor.

## **CONFLICT OF INTEREST**

This article has no conflict of interest to disclose.

## **FUNDING**

The authors state no funding is involved.

## **AUTHOR CONTRIBUTION**

All authors reviewed the results and approved the final version of the manuscript.

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