Immunohistology and Molecular Studies of Sweat Gland Tumors

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Introduction

Adnexal tumors are generally classified according to two principles: (1) benign versus malignant, and (2) line of differentiation: that is, which normal cutaneous structure the lesion most resembles: hair follicle, apocrine/eccrine gland, or sebaceous gland. Although such a classification scheme seems simple at first glance, the reality is that there is still considerable controversy on how to catalog many lesions [1]. Furthermore, tumors of cutaneous sweat glands are uncommon, with a wide histopathological spectrum, complex classification, and many different terms often used to describe the same neoplasm [2].

It is important to understand the basic structure and the physiological function of human sweat glands in order to study the neoplasms that originate from them. Moreover, expression of individual cytokeratins and other markers in normal eccrine and apocrine glands is outlined in Table 2.1. The human body has $3–4 \times 10^6$ sweat glands, two types of which are generally recognized, namely, eccrine and apocrine sweat glands [3]. The average density of eccrine and apocrine sweat glands varies according to the person and anatomic site. The sites of maximum distribution of eccrine glands are the palms, soles, axillae, and forehead, while apocrine glands are most numerous in the axilla and anogenital area [4]. In addition to the eccrine and apocrine glands, two other skin sweat glands have recently been described: the apoeccrine and the mammary-like glands of the anogenital area [5, 6].

Normal Apocrine Glands

Apocrine sweat glands, which are derived from the folliculo-sebaceous-apocrine germ, are restricted to the axillae, anogenital and inguinal regions, the periumbilical and periareolar areas, and, rarely, the face and scalp. Apocrine glands become active at puberty and secrete a proteinaceous viscous sweat which has a unique odor. Specialized apocrine glands are found on the eyelids (Moll's glands) and in the auditory canal (ceruminous glands). The breast is sometimes regarded as a modified apocrine gland [7]. Apocrine glands are composed of a secretory glandular portion in the lower dermis and subcutis, a straight ductal component which is indistinguishable from the eccrine duct, and a terminal intra-infundibular duct which opens

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Table 2.1 Expression of cytokeratins and other markers in normal eccrine and apocrine glands (Data from [4])

	Eccrine gland				Apocrine gland			
	Dermal duct		Secretory coil		Dermal duct		Secretory coil	
Markers	Luminal cells	Basal cells	Secretory cells	Myoepithelial cells	Luminal cells	Basal cells	Secretory cells	Myoepithelial cells
CK4	–	–	–	–	NA	NA	NA	NA
CK7	–	–	+	–/+	+	–	+	+
CK8	–	–	+	–	–	–	+	–
CK10	+	–	–	–	+	–	–	–
CK13	–	–	–	–	NA	NA	NA	NA
CK14	+	+	–	+	NA	+	NA	+
CK15	NA	NA	NA	NA	–	NA	+	NA
CK18	–	–	+	–	–	–	+	–
CK19	+	–	+	–	+	NA	+	NA
CK 20	–	–	–	–	NA	NA	NA	NA
CAM 5.2	–	–	+	+	NA	NA	+	+
CK 1/5/10/14	+	+	–	–	+	+	NA	+
S100 protein	–	–	+	+	–	–	–	+

into the follicular infundibulum. The secretory part consists of large tubules with large, round to oval lumina, sometimes containing homogenous eosinophilic or pale basophilic material, the product of apocrine secretion. The luminal cells show an ample, eosinophilic, and finely granular cytoplasm, and are immunoreactive to low molecular weight keratin (LMWK), epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA). A conspicuous feature of apocrine secretory cells is their "decapitation" mode of secretion whereby an apical cap, formed at the luminal border of the apocrine cells, separates off from the cell and is discharged into the lumen. Another typical feature of these cells is the presence of intracytoplasmic small, brightly eosinophilic granules (zymogen granules) in a supranuclear location. Zymogen granules are PAS-positive and diastase resistant, and represent lysosomes that contain sialomucin, lipid, and iron. The cells in the secretory part are surrounded by a layer of spindled myoepithelial cells that express S-100 protein, p63, smooth muscle actin (SMA), and calponin [4]. Their contraction aids in the delivery of their secretory products. Peripheral to the myoepithelial cell layer lies a distinct basement membrane. The ductal component of the apocrine glands is composed of an inner luminal layer of small cells with scant cytoplasm and a peripheral layer of small cuboidal basophilic cells with round nuclei that expresses p63. A deeply eosinophilic homogeneous cuticle is recognized. Finally, the glandular epithelium of the apocrine glands often expresses gross cystic disease fluid protein 15 (GCDFP-15) and androgen receptors, which may be useful in the assessment of lesions suspicious of apocrine carcinoma [2].

Normal Eccrine Glands

Eccrine sweat glands, smaller than apocrine sweat glands in size, are distributed all over the body surface but not on the lips, external ear canal, clitoris, or labia minora. Eccrine glands secrete hypotonic sweat consisting mostly of water and electrolytes. Their main function is the control of body temperature [3]. The eccrine unit is composed of a secretory portion and a ductal component. The secretory coil lies in the lower reticular dermis and is composed of two populations of epithelial cells: clear cells, which contain

glycogen in their cytoplasm, and dark cells, which contain vacuoles filled with mucin. Both types of luminal cells are surrounded by a discontinuous myoepithelial cell layer that stains for S-100 protein, SMA, calponin, and p63. S-100 protein also stains the luminal epithelial cells [4]. The transition from the distal portion of the secretory coil to the proximal fragment of the duct is abrupt and is known as the ampulla. The ductal component, indistinguishable from an apocrine duct, is composed of two parts: the intradermal duct and the intraepidermal component (acrosyringium). The intradermal duct is composed of two layers of small cuboidal basophilic cells with round nuclei and there is an eosinophilic homogeneous cuticle lining the luminal aspect of the inner cell layer. The cells in the excretory coil express positivity for LMWK, EMA, and CEA, as well as S100 protein and p63 in the basal layer only. The intraepidermal duct (acrosyringium) has a characteristic spiraling course, is composed of a single layer of luminal cells, and has an acellular eosinophilic cuticle. This intraepidermal duct is surrounded in the lower part by two or three layers of outer cells. In the middle squamous layer, ductal cells comprising the acrosyringium start to keratinize, demonstrating keratohyaline granules, and the cuticle is no longer visible. Acrosyringeal cells stain for high molecular weight keratin (HMWK) and cytokeratin (CK) 14. Finally, skin tumors with eccrine differentiation often express positive immunohistochemical staining for estrogen and progesterone receptors [8], this has important clinical implications, as affected patients may be partially treated with hormonal therapy [9].

Apoeccrine Glands

Apoeccrine sweat glands have been proposed to represent a third, separate category of human sweat glands [10], although this is still controversial and requires further study. It has been suggested that these glands develop during puberty from the eccrine sweat glands (transformation or transgression of eccrine glands into apocrine glands) or from eccrine-like precursor sweat glands. Apoeccrine glands are mostly found in the axillary region, and within lesions of nevus sebaceus of Jadassohn (NSJ) [5]. Their presence would explain the existence of some adnexal lesions that have both eccrine and apocrine differentiation, as has been proposed in some examples of syringocystadenoma papilliferum (SCAP) or Fox–Fordyce disease [11].

Mammary-Like Glands

Cutaneous mammary-like glands (MLG) are now recognized to be a normal component of the skin in the anogenital region, including the perianal skin. MLG are unique in having features of apocrine, eccrine and mammary glands, and the previous assumption that these glands represent ectopic/accessory breast tissue lying along the milk line (mammary ridge) is now believed to be incorrect. Many adnexal lesions of the anogenital area are now recognized to be of MLG origin, and a helpful feature in attributing MLG origin to an adnexal tumor is the presence of normal MLG in the deep dermis and subcutaneous fatty tissue, in the vicinity of the lesion of interest, with a transition zone between benign and lesional areas [12, 13].

In this chapter a detailed practical approach to the most important general features of benign and malignant sweat glands tumors of the skin is intended, striving to maintain a common and acceptable terminology in this complex subject. For this purpose, we will follow the classification scheme outlined in Table 2.2. Furthermore, a comprehensive and functional approach to the use of immunohistochemistry in the diagnosis of sweat gland neoplasms is also described. The most relevant monoclonal antibodies, for use with immunoperoxidase techniques, in the diagnosis and classification of sweat gland tumors are listed in Table 2.3. Finally, molecular studies will be discussed where appropriate.

Table 2.2 Classification of sweat gland tumors

Differentiation	Benign	Malignant
Apocrine	Hidradenoma Spiradenoma/Cylindroma Syringocystadenoma papilliferum Adenoma of the nipple Ceruminous gland adenomas Moll's gland adenomas Hidradenoma papilliferum Myoepithelioma	Hidradenocarcinoma Spiradenocarcinoma/Cylindrocarcinoma Syringocystadenocarcinoma papilliferum Apocrine carcinoma Extramammary Paget's disease Mucinous carcinoma Endocrine mucin-producing sweat gland carcinoma Hidradenocarcinoma papilliferum Aggressive digital papillary adenocarcinoma
Eccrine	Poroma Syringoma Syringofibroadenoma	Porocarcinoma
Eccrine and apocrine	Apocrine/eccrine hidrocystoma Apocrine/eccrine nevus Tubular adenoma Benign mixed tumor	Syringoid carcinoma Microcystic adnexal carcinoma Adenoid cystic carcinoma Malignant mixed tumor of the skin

Table 2.3 Most relevant antibodies in the diagnosis of sweat gland tumors

Antibody	Role in the diagnosis of sweat gland tumors
Carcinoembryonic antigen (CEA)	Indicates ductal differentiation of both apocrine and eccrine type. It is expressed in the secretory and excretory portions of the eccrine gland. In apocrine glands is positive at the luminal edge of the excretory duct, but in negative the secretory portion
Epithelial membrane antigen (EMA)	Expressed in both the secretory portion and the excretory duct of eccrine and apocrine glands
CAM5.2	Reacts with the apocrine gland and supposedly the duct, and the eccrine secretory coils, but not the eccrine duct
MNF116	Detects the low and intermediate molecular weight keratins (5, 6, 8, 17, and 19), stains the basal cells of the epidermis and adnexae. It is found in all epithelial tumors, including adnexal ones
34βE12/CK903	It recognizes CK1, CK10, and CK14, which are expressed in ductal and squamous epithelia, basal cells, and myoepithelial cells. Reacts with basal cells from normal eccrine ducts and some apocrine gland tumors
Antibodies to individual keratins	Not of much assistance in routine diagnosis, but they have given a valuable insight into the possible derivation and/or differentiation of various eccrine tumors
Gross cystic disease fluid protein 15 (GCDFP-15)	Intense immunoreactivity in the luminal edges of the secretory tubules and the excretory ducts of the eccrine and apocrine glands
Human milk fat globulin 1 and 2 (HMFG-1, HMFG-2)	Expressed in the normal apocrine glands and tumors with apocrine differentiation
Vimentin, α-smooth muscle actin, s-100 protein, p63, calponin	Markers of myoepithelial cells which are seen in most sweat gland tumors considered to differentiate toward the secretory coil of sweat glands, and in most of the traditional apocrine tumors
Estrogen, progesterone and androgen receptors	Usually expressed in the apocrine sweat glands and tumors with apocrine differentiation
p53	Present in some sweat gland carcinomas; rarely present in benign tumors
Ki-67	The mitotic rate is an important indicator of malignancy
CD44	Strongly expressed in the eccrine coil secretory cells, it has not proved a useful marker of sweat gland differentiation in tumors
Ferritin	Demonstrates ferritin in the outermost layer of the eccrine and apocrine ducts
IgA and secretory component	Detect antigen in the lumen and on the surface of the epithelium of sweat glands
IKH-4, EKH-5, and EKH-6	Stain the secretory coil of the eccrine glands
SKH1	Reacts with the secretory portion and coiled duct of the eccrine gland and the secretory portion of apocrine glands

Cysts and Hamartomas

Apocrine Hidrocystoma, Eccrine Hidrocystoma, and Apocrine Cystadenoma

According to the latest WHO classification of cutaneous tumors, apocrine hidrocystomas are cystic adenomas that arise from the apocrine secretory coil, whereas eccrine hidrocystomas represent retention cysts of the eccrine duct [14]. It can be difficult to distinguishing between apocrine hidrocystoma and eccrine hidrocystoma in cases with compression of the epithelial lining of the apocrine hidrocystoma due to cyst distension by excessive secretions.

Apocrine hidrocystoma is a cystic lesion that despite its apocrine derivation it is rare at sites rich in normal apocrine glands. It is usually found as a solitary lesion on the head and neck area of middle aged patients, although multiple lesions have also been documented sporadically or as a feature of ectodermal dysplasia (Schöpf-Schulz-Passarge syndrome) and focal dermal hypoplasia (Goltz syndrome) [15–17]. Similar lesions on the eyelids are also known as Moll's gland cysts [18], and penile variants are now thought at least in part to represent median raphe cysts rather than true apocrine cysts. Apocrine hidrocystoma presents as an intradermal, dome-shaped, translucent, bluish-black cystic nodule measuring up to about 1 cm. Some patients report worsening in summer months or with excessive heat that decreases during the winter months [19].

Microscopically, apocrine hidrocystoma consists of a large unilocular or multilocular cystic space situated within the dermis. The cystic spaces are usually lined by a double layer of epithelial cells: an outer layer of flattened vacuolated myoepithelial cells and an inner layer of tall columnar cells with eosinophilic cytoplasm and basally located, round or oval vesicular nuclei. Decapitation secretion is usually present, and papillary projections of epithelium into the lumen are found in about one-half of cases. Occasionally, the cyst cavity is partially replaced by a papillary or adenomatous proliferation, and the term "apocrine cystadenoma" is used to refer to these lesions [20].

Immunohistochemistry reveals that apocrine hidrocystoma is a complex tumor, and that lesions with a proliferative component (apocrine cystadenoma) are different from the pure cystic form and have increased Ki-67 staining, especially in areas with a genuine papillary growth pattern. EMA and CEA are demonstrable in the luminal aspects of the epithelial cells, which themselves express various cytokeratins, including 34β E12 (CK1/5/10/14), CK7, CK8, CK18, CK19, and others [21]. It is said that simple epithelial cytokeratins are not expressed in the eccrine retention variant of hidrocystoma. Differentiation between eccrine and apocrine lesions is also said to be achieved by using human milk fat globulin 1 (HMFG-1) and GCDFP-15, which are usually only expressed by the apocrine sweat gland [22]. Finally, the myoepithelial layer can be highlighted with SMA, calponin, and p63. Staining with S-100 protein is variable.

Apocrine and Eccrine Nevi

Eccrine nevus (nevus sudoriferous, sudoriferous hamartoma) is a rare hamartoma of the eccrine unit which typically presents in childhood or adolescence and has a predilection for the upper extremities. Apocrine nevus is a congenital, benign, and persistent adnexal cutaneous hamartoma composed of ostensibly normal apocrine glands and ductal structures within a fibrous stroma. It is not uncommon to find an apocrine nevus component in lesions of nevus sebaceus of Jadassohn or SCAP.

Histologically, eccrine nevi have localized increased number and size of eccrine glands. The variant called eccrine angiomatous hamartoma has, in addition to the eccrine glands, adipose tissue and small capillaries. In apocrine nevi the apocrine glands are more numerous than in other areas of mature skin and display a disordered architecture. The overlying epidermis may be slightly hyperplastic with papillomatosis, and it may contain buds of basaloid cells, occasionally forming similar aggregates to basal-cell carcinoma (BCC). The apocrine glands proliferate in the reticular dermis and may extend into the subcutaneous fat in a circumscribed but unencapsulated fashion, where they present within a delicate fibrous stroma [23, 24].

Immunohistochemical studies of apocrine nevi show similar features to those of normal apocrine sweat glands, thus being positive for EMA and

CEA, LMWKs, such as CK7, and GCDFP-15,while negative for HMWKs and S-100 protein [25]. Moreover, p63 can be expressed by basal cells of excretory ducts and by myoepithelial cells of the secretory coils [24, 26]. Ki-67 demonstrates that apocrine nevi show a low proliferation potential, which is consistent with the clinically benign and stable nature of these hamartomas [24].

Syringocystadenoma Papilliferum

SCAP is a benign lesion that occurs most commonly on the scalp or forehead. About 30% of cases are associated with a congenital lesion, usually a nevus sebaceous of Jadassohn, and for this reason it is not always possible to be certain at what age the SCAP component developed [27]. Probably half are present at birth or develop in childhood [28]. It usually presents as one or several yellowish papules, sometimes arranged linearly, and with reduced or absent hair growth. The lesions increase in size at puberty, becoming papillomatous and often crusted.

Microscopically, SCAP is composed of ducts and papillary projections lined by two layers of epithelial cells: cuboidal at the periphery and columnar cells with abundant, basophilic cytoplasm in the luminal layer. A connection to the preexisting follicular infundibula may usually be found. The stroma of the papillary processes characteristically contains numerous plasma cells. There may be a background of features of nevus sebaceus of Jadassohn. The main diagnostic issues are the distinction from SCAP hidradenoma papilliferum and to detect features of associated nevus sebaceus of Jadassohn, because such lesions, although very rarely, may give raise to secondary malignant neoplasms

SCAP expresses AE1/AE3, CAM 5.2, EMA, and CEA (Fig. 2.1). The inner layer is

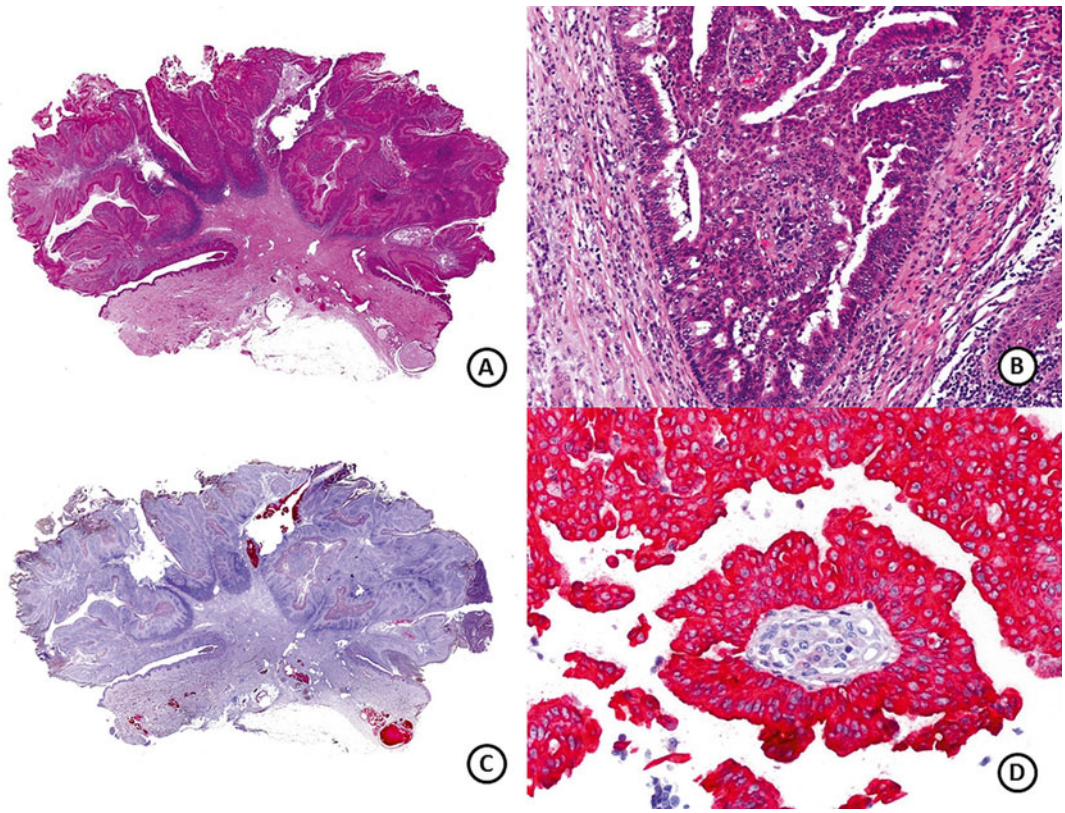

Fig. 2.1 (**a**): Syringocystadenoma papilliferum with prominent epidermal hyperplasia. (**b**) Papillary structures lined by two layers of epithelial cells and plasma cells in the stroma. (**c**) The same case immunohistochemically studied for CEA. (**d**) The epithelium lining the papillae exhibit CEA immunoexpression

positive for SMA. The results of markers of apocrine differentiation are variable. Some authors have found GCDFP-15 and HMFG-1 negative, while others have found GCDFP-15 and/or HMFG-2 present [29, 30]. The luminal cells constantly express CK7 and often CK19, whereas expression of other markers such as CK1/5/10/14, CK14, and CK5/8 is variable. The plasma cells secrete IgA and IgG and they are polyclonal.

Finally, genetic analysis using polymorphic markers at 9q22 (locus for the *PTCH1* gene) and markers at 9p21 flanking the tumor suppressor gene p16, showed LOH at 9q22 in 2 of 10 cases of SCAP, whereas 3 of 7 cases manifested allelic deletions at 9p21 [31].

Benign Tumors

Tubular Adenoma

According to the latest WHO classification of cutaneous tumors, "tubular adenoma" is the term used to encompass a spectrum of tumors including tubular apocrine adenoma and papillary eccrine adenoma, amongst others. Tubular adenomas are slowly growing, circumscribed nodules situated in the dermis or subcutaneous tissue, and have been described at a variety of sites including the scalp, face, eyelid, axilla, leg, and genitalia [32]. The last, however, may represent an adenoma of the anogenital MLG [33]. Those that present on the scalp often arise in a background of nevus sebaceus of Jadassohn and are sometimes associated with SCAP.

Histologically, tubular adenoma usually presents as circumscribed intradermal lobules of well-differentiated tubular structures that sometimes extend into the subcutis. Occasionally, the neoplastic tubules communicate with the overlying epidermis through duct-like structures or dilated follicular infundibula. The tubules exhibit apocrine features with an inner layer of cylindrical cells, often showing "decapitation" secretion, and a connective tissue stroma in which only small numbers of chronic inflammatory cells are present, in contrast to SCAP in which numerous plasma cells are usually found. However, cases of tubular adenoma have been reported with features of SCAP in the upper part of the lesion and probably these two lesions are more related than previously was thought [34, 35].

Immunohistochemical studies have shown that the luminal epithelial cells are positive for CEA, EMA, and various cytokeratins, including CK7 [36, 37]. The myoepithelial cells can be highlighted with SMA or S-100 protein. However, myoepithelial cell markers are often not expressed in the peripheral layer of atrophic distended tubules or in solid areas of immature squamous metaplasia. HMFG-1 and GCDFP-15 may also be expressed [36–38].

Hidradenoma Papilliferum

Hidradenoma papilliferum is a benign neoplasm that occurs almost exclusively in females, with predilection to the vulva and perianal region. Rare cases of hidradenoma papilliferum have been reported in males, and in extra-anogenital locations, particularly the head and neck area [39], but probably they represent examples of other adenomas with a prominent papillary component. It usually presents as a solitary, small and asymptomatic lesion. Human papilloma virus (HPV) has been suggested as having a potential role in the histogenesis of this neoplasm [40], although this observation needs further study.

Histopathologically, hidradenoma papilliferum arises from apocrine glands or possibly the anogenital MLG. It usually presents as a well-circumscribed solid or cystic dermal nodular lesion, not connected to the epidermis. It is formed of frond-like papillae or tubulopapillary structures that are lined by a two-cell layer: luminal cuboidal or low columnar epithelial cells with apical secretions, resting on an outer myoepithelial cell layer.

Immunohistochemically, the tumor cells often express LMWKs, EMA, CEA, HMFG, and GCDFP-15 [41, 42]. Furthermore, estrogen, progesterone, and androgen receptors are commonly expressed in hidradenoma papilliferum [43]. This and the presence of histomorphological features analogous to benign breast diseases

gives further evidence to a possible origin of hidradenoma papilliferum from MLG. The myoepithelial cells express S-100 protein and SMA.

Ceruminous Gland and Moll's Gland Adenomas

A ceruminous adenoma, also known as adenoma of the ceruminous gland and ceruminoma, is a benign neoplasm that arises from the ceruminous glands located in the external auditory canal. These tumors develop in a very specific location, as these glands are found within the outer one third to one half of the external auditory canal, more commonly along the posterior surface [44]. On the other hand, Moll's glands are presumed to be the origin of the few lesions with apocrine differentiation that occur on the eyelids. The most common is apocrine hidrocystoma, which has already been described above. But Moll's glands are also the origin of much rarer benign tumors grouped under the term "Moll's gland adenoma" [4].

Ceruminous adenomas usually present as uncapsulated, but well circumscribed tumors. Connection to the epidermis is not usually seen unless the surface is ulcerated [44]. The tumor shows a dual or biphasic appearance, with glandular or cystic spaces showing inner luminal secretory cells with abundant granular, eosinophilic cytoplasm subtended by basal, myoepithelial cells at the periphery, adjacent to the basement membrane. The luminal cells often show decapitation secretion and yellow-brown, lipofuscin-like pigment granules (cerumen) in their cytoplasms [44]. Moll's gland adenomas usually show benign architectural and cytologic features with solid, solid-cystic, cribriform, or tubular-papillary patterns of growth. Remnants of Moll's glands can sometimes be seen in the vicinity of the neoplasm.

In ceruminomas, immunohistochemistry confirms the biphasic nature of the tumor. All cells are positive with pancytokeratin and EMA. The luminal cells are positive with CK7, while basal/myoepithelial cells are positive with CK5/6, p63, S100 protein, and SMA [44, 45]. CD117 can also be expressed in both populations. Finally, the tumor cells are negative with chromogranin, synaptophysin, and CK20 [44].

Nipple Adenoma

Nipple adenoma is a benign neoplasm that is often misdiagnosed as Paget's disease of the breast clinically or as ductal breast carcinoma histopathologically. It usually occurs in women around 50 years of age as a nodule under the areola or nipple. There is often erythema, erosion or ulceration of the epidermal surface, and sometimes, patients refer pain or discharge of a liquid material related to the menstrual cycle.

Microscopically, nipple adenoma presents as an endophytic, wedge shaped lesion, which usually opens to the epidermal surface or the follicular infundibulum. It consists of tubular elements lined by a double layer of epithelial cells, separated by fibrous septa. Inside the tubules, there is often an eosinophilic and homogeneous material that seems to correspond to apocrine secretion, and decapitation secretion can also be observed in the luminal cells lining the tubules.

Immunohistochemical studies have demonstrated that nipple adenoma does not express estrogen, progesterone, or androgen receptors, and the HercepTest is negative. SMA and p63 are expressed in the basal layer of the neoplastic tubules, supporting the benign nature of the lesion [46].

Apocrine Hidradenoma

Apocrine hidradenoma is a relatively common benign adnexal neoplasm which can have variable histomorphological patterns, reflected by the various terms that have been used to describe this entity: nodular hidradenoma, clear cell hidradenoma, eccrine acrospiroma, clear cell myoepithelioma, clear cell papillary carcinoma, solid-cystic hidradenoma, and apocrine hidradenoma. Apocrine hidradenomas usually present as solitary, skin-colored or reddish papules and/or nodules. They may be large, measuring up to 2 cm or more in diameter, and can occur at any anatomic location and any age.

Microscopically, the predominant growth patterns are solid and/or solid-cystic, seen together in about 90 % of cases, with variation in the ratio of the solid and cystic areas from case to case [4]. It is usually centered in the dermis and well circumscribed, but large tumors may involve the subcutis. It is composed of lobules of uniform eosinophilic or clear, glycogen-rich cells. Ducts can be seen throughout the lesion, some of them dilated and forming cystic areas and "decapitation" secretion is usually seen in some areas of the luminal border. In some cases, mucinous cells are also seen in that luminal border. Some areas may also show squamous differentiation (keratin pearls) or clear cell changes. The stroma is fibrous and may show extensive hyalinization or even keloidal appearance.

Ancillary studies are rarely needed for diagnosis, but immunostains may be helpful on occasions to highlight Glands and ducts when they are sparse, which helps in the distinction of hidradenoma from other clear cell tumors, such as tricholemmoma or cutaneous metastasis from renal cell carcinoma. Apocrine hidradenoma is a heterogeneous tumor with different staining profiles within the main cellular subtypes and architectural regions of the neoplasm. Immunohistochemistry usually demonstrates variability in the expression of the various keratin subtypes in different parts of the tumor, however, CK7, CAM5.2 (Fig. 2.2), and EMA/CEA (luminal border) are expressed in most tumors [47, 48]. Tumor cells are usually negative for S-100 protein (which reveals only Langerhans cells) [49].

Recent molecular studies have documented the presence of a chromosomal translocation *t*(11;19) in hidradenomas, that results in fusion of the mucoepidermoid carcinoma translocated 1

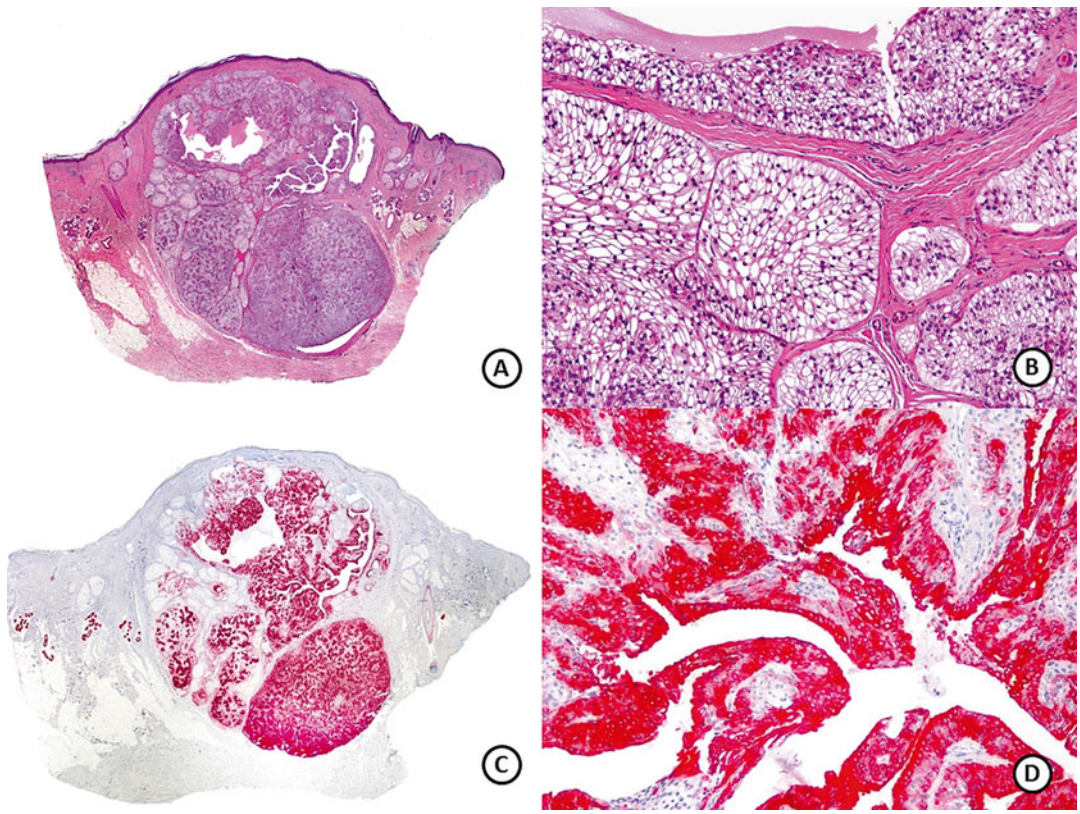

Fig. 2.2 (**a**) Apocrine hidradenoma. (**b**) Most of the neoplastic aggregates are composed of clear cells. (**c**) The same case immunohistochemically studied for CAM 5.2. (**d**) Strong expression for CAM 5.2 in the neoplastic epithelial cells

(*MECT1*) gene on chromosome 19p13 with the mastermind-like 2 (*MAML2*) gene on chromosome 11q21 [50, 51]. This translocation is said to be more common in cases with predominant clear cell differentiation, although it has also been observed in tumors with a mixed cell population, including cases completely devoid of clear cells. This translocation is not restricted to hidradenomas, and has also been described in salivary gland tumors, such as mucoepidermoid carcinoma and Warthin's tumor, as well as mucoepidermoid carcinoma of the cervix [50–52].

Cutaneous Mixed Tumor

Cutaneous mixed tumor is a rare, benign adnexal tumor of sweat gland origin, which is most commonly seen in the head and neck region of patients in the sixth and seventh decades. These tumors usually present as asymptomatic, slow growing masses, mostly affecting the nose, cheek and upper lip [53, 54]. Because of the presence of cartilage, mixed tumor of the skin has also been called "chondroid syringoma," but this term is best avoided as the neoplasm bears no resemblance to a syringoma and cartilage is not a constant feature. The etiopathogenesis of these tumors is unknown, and both an epithelial and a mesenchymal origin have been proposed [55].

Microscopically, cutaneous mixed tumors show both an epithelial and a mesenchymal component, similar to benign mixed tumors of the salivary glands, the so-called pleomorphic adenomas. They usually present as circumscribed nodules composed of bland epithelial cells, arranged in cords, ducts, or tubules. The stromal component is most often myxoid-cartilaginous, but can also be hyaline/fibrous, fatty, osteoid, or be minimal or absent. Cutaneous mixed tumors are classified into apocrine and eccrine types based on the histopathological appearance of the neoplastic tubules, because the eccrine variant shows round ducts lined by a single layer of epithelial cells, while apocrine variant exhibits elongated tubules lined by two layers of epithelial cells. Areas of follicular and/or sebaceous differentiation have only been described in the apocrine variant.

In the eccrine type of mixed tumor the cells express CEA, pancytokeratins, CK7, and S-100 protein [56], while in apocrine mixed tumor, hyaline cells are an accepted feature of myoepithelial differentiation and express actins, S-100 protein (Fig. 2.3), p63, and calponin [57]. Calponin, actins and p63 are negative in the eccrine variant of mixed tumor [57]. Gonzalez Guerra et al. [58] found that the neoplastic epithelium of the tubular structures of eccrine mixed tumor expressed strong immunoreactivity for calretinin, supporting a differentiation towards the secretory portion of the eccrine glands, while apocrine mixed tumor expressed calretinin only in the most keratinized areas of the ductal structures, which may represent areas of either ductal sebaceous differentiation or tricholemmal differentiation.

It has recently been demonstrated that rearrangement of pleomorphic adenoma gene 1 (*PLAG1*) leads to aberrant expression of its protein and is pathogenically relevant in the development of salivary pleomorphic adenomas. A genetic link between salivary pleomorphic adenoma and cutaneous mixed tumor has been subsequently established because most cutaneous mixed tumors express distinct nuclear immunostaining for PLAG1, with moderate or strong intensity in a significant number of neoplastic cells and positive gene rearrangement for *PLAG1* [59] and for EWSR1 [60] have been detected in cutaneous mixed tumors and cutaneous myoepitheliomas. These findings support the notion that salivary pleomorphic adenomas, cutaneous myoepitheliomas, and cutaneous mixed tumors are myoepithelial neoplasms, which are genetically related.

Syringoma

Syringomas usually present as multiple small, skin-colored papules around the eyelids, mostly in young women. Other locations are axilla, abdomen, and vulva. Histologically, they present as symmetrical and well-circumscribed lesions, confined to the upper dermis with no connection, with the overlying epidermis. They are composed of monomorphous cuboidal cells with small

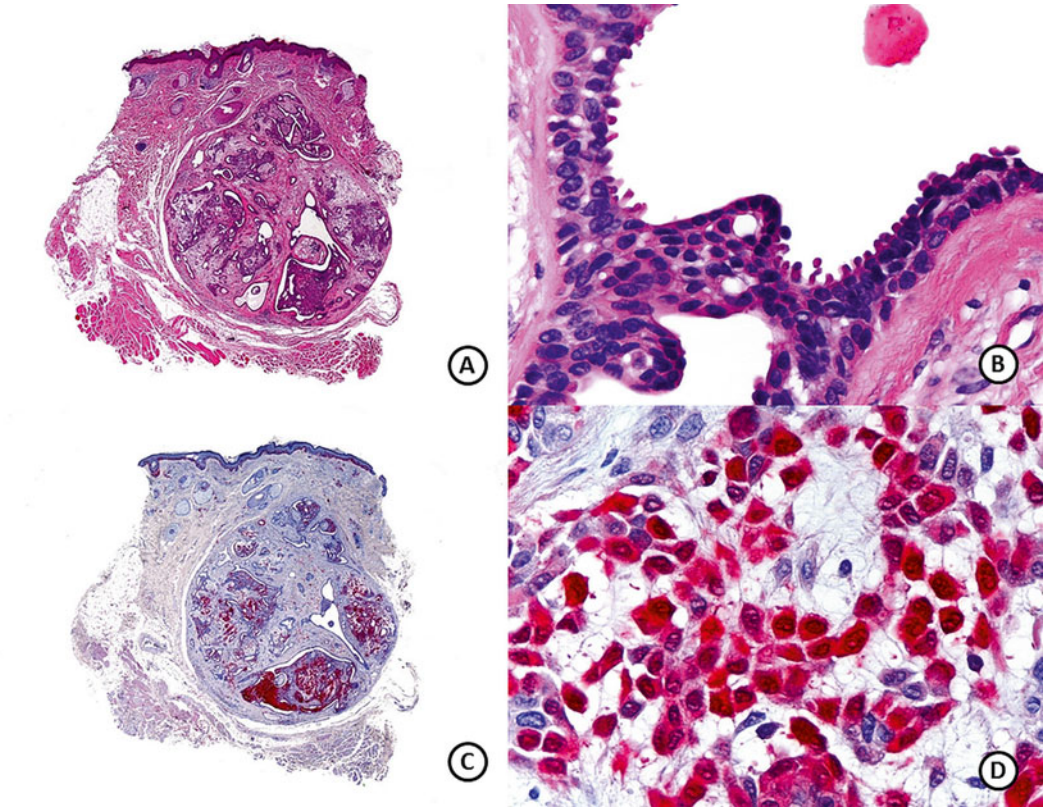

Fig. 2.3 (**a**) Apocrine mixed tumor. (**b**) Elongated tubular structures lined by two layers of epithelial cells with evidence of "decapitation" secretion in the luminal border. (**c**) The same case immunohistochemically studied for S100 protein. (**d**) Strong S100 protein immunoexpression in neoplastic myoepithelial cells

nuclei and inconspicuous nucleoli. Similar cells line ductal structures with small lumina, which may be empty or contain secretions. Calcification and granulomatous inflammation are sometimes observed [61, 62].

Syringomas express CK6 and CK10, both are said to stain the straight duct, with CK6 being a marker for the inner ductal cells and CK10 being a marker for the middle tumor cells. Other cytokeratins variably expressed include CK1, CK5, CK11, CK19, and CK14 [63, 64]. Studies on expression of progesterone and estrogen receptors in syringoma, including those located on the vulva, show conflicting results. Progesterone receptors are expressed in most syringomas, supporting the view that they are under hormonal control, but the expression seems to be less frequent in cases on the vulva. Syringomas usually express CEA and EMA (Fig. 2.4) in the lumina of the ducts, and are usually negative for GCDFP-15 [65]. The expression of S100 protein family members has been also studied showing that syringomas are positive for S100A2, S1007, and S100P [66].

Spiradenoma, Cylindroma, and Spiradenocylindroma

Although originally considered to represent separate entities, the close relationship between spiradenoma and cylindroma became obvious after identification of lesions with hybrid features of both neoplasms, for which the term spiradenocylindroma was proposed, and nowadays, spiradenoma, cylindroma, and spiradenocylindroma are viewed as a morphologic continuum [4]. Although traditionally thought to be eccrine neoplasms, apocrine and

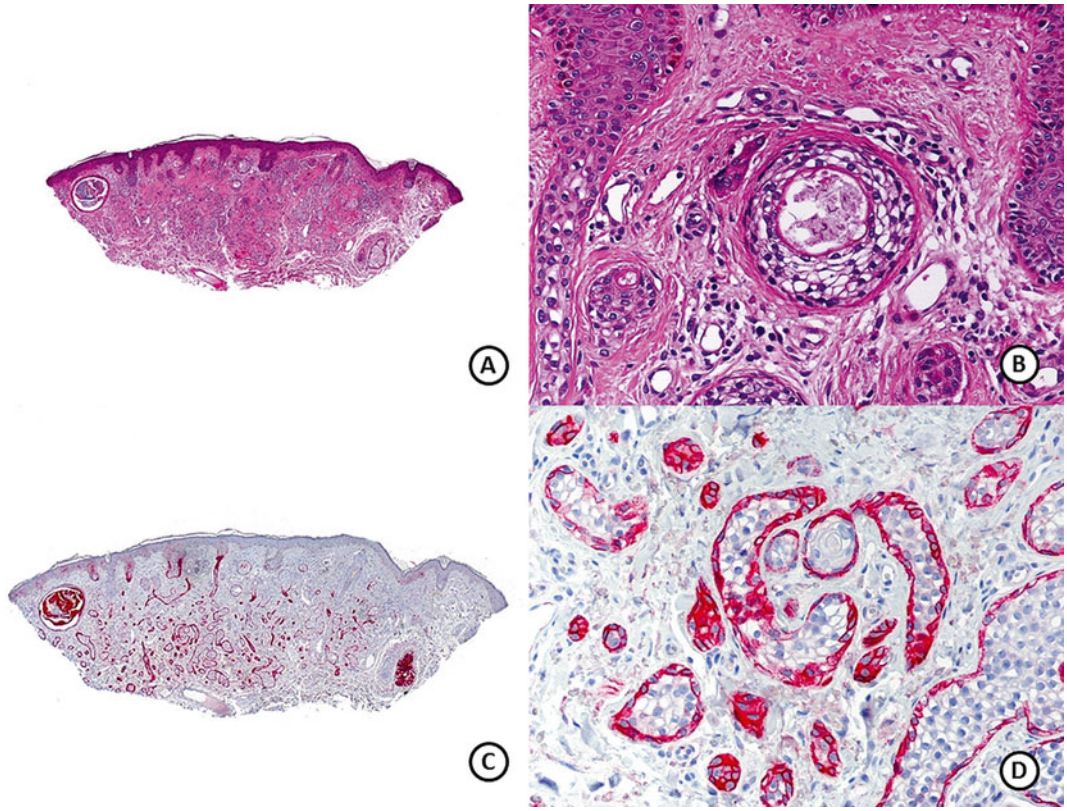

Fig. 2.4 (**a**) Clear-cell syringoma. (**b**) Ductal structures are lined by clear-cells. (**c**) The same case immunohistochemically studied for EMA. (**d**) The outer layer of some neoplastic epithelial aggregates express EMA

follicular differentiation has subsequently been shown in these three neoplasms suggesting that they differentiate along the lines of the folliculo-sebaceous-apocrine unit. All three neoplasms occur either sporadically or as a part of the Brooke–Spiegler syndrome in which they manifest as multiple lesions in various combinations with other adnexal neoplasms, mostly trichoblastoma [67–69]. They usually present as solitary, skin-colored or violaceous, small, asymptomatic nodules affecting adult to elderly patients in the head and neck area.

Microscopically, spiradenomas usually show one or several dermal circumscribed lobules of basaloid cells, with no connection to the epidermis. The nests are composed of two types of epithelial cells; one with a small, dark nucleus, mainly at the periphery of the cellular aggregates, and a second type with large and pale nuclei, sometimes located around small lumina with eosinophilic, PAS-positive, and diastase-resistant material. Spiradenomas tend to be more vascular and show more likely edematous and cystic stromal changes than cylindromas. Cylindromas typically show multiple small aggregates of basaloid cells surrounded by pink hyaline basement membrane material. Cylinders of hyaline membrane are often seen in the center of such aggregates. Two types of epithelial cells are usually found: a peripheral cell with a large basophilic nucleus and a tendency for palisading, and a larger centrally located paler cell with a vesicular chromatin pattern.

Spiradenomas and cylindromas express identical cytokeratin patterns. Neoplastic cells express CK5/6. In areas with ductal differentiation, luminal cells mainly express ductal markers (CK6, CK14, and CK19) and, less prominently, CK7 [70–74]. When immunostained for myoepithelial markers, these three tumors usually reveal patchy reactivity, with areas showing positivity for some of these markers alternating with

completely negative areas (Fig. 2.5) [74]. Basement membrane material seen around the nodules as well as intratumoral droplets stain for collagen IV [72, 73]. Staining for S-100 protein and CD1a reveals intratumoral dendritic cells thought to represent Langerhans cells [70]. Rare benign neoplasms manifest focal positivity for p53, limiting the use of this marker in the differential diagnosis from malignant lesions evolving from benign spiradenoma, cylindroma, and spiradenocylindroma [75].

Lesions occurring in the context of Brooke–Spiegler syndrome are associated with germ line and somatic mutations in the *CYLD* gene located on chromosome 16q [76]. Somatic mutations detected in neoplastic tissue in syndrome-associated lesions include both a sequence mutation and LOH at the gene locus. LOH at 16q has also been demonstrated in rare sporadic cylindromas and spiradenomas.

Poroma Group

These tumors usually originate from the outer cells of the intraepidermal (acrosyringeal) excretory ducts of eccrine the sweat gland. However, there are reports of poromas showing sebaceous, follicular and apocrine differentiation, and the term "apocrine" poromas has been used for those tumors [77]. Poromas usually occur in adults, with predilection to palms and soles, and less frequently the head and neck, and trunk regions. They are usually solitary and rarely multiple, and may present as superficial plaques or dermal nodules, with tendency to ulceration and bleeding.

Histopathologically, four main variants of poromas are recognized and distinguished according to their location in relation to the epidermis and the size of the neoplastic aggregates:(1) hidroacanthoma simplex, also known as intraepidermal poroma, composed of round nests

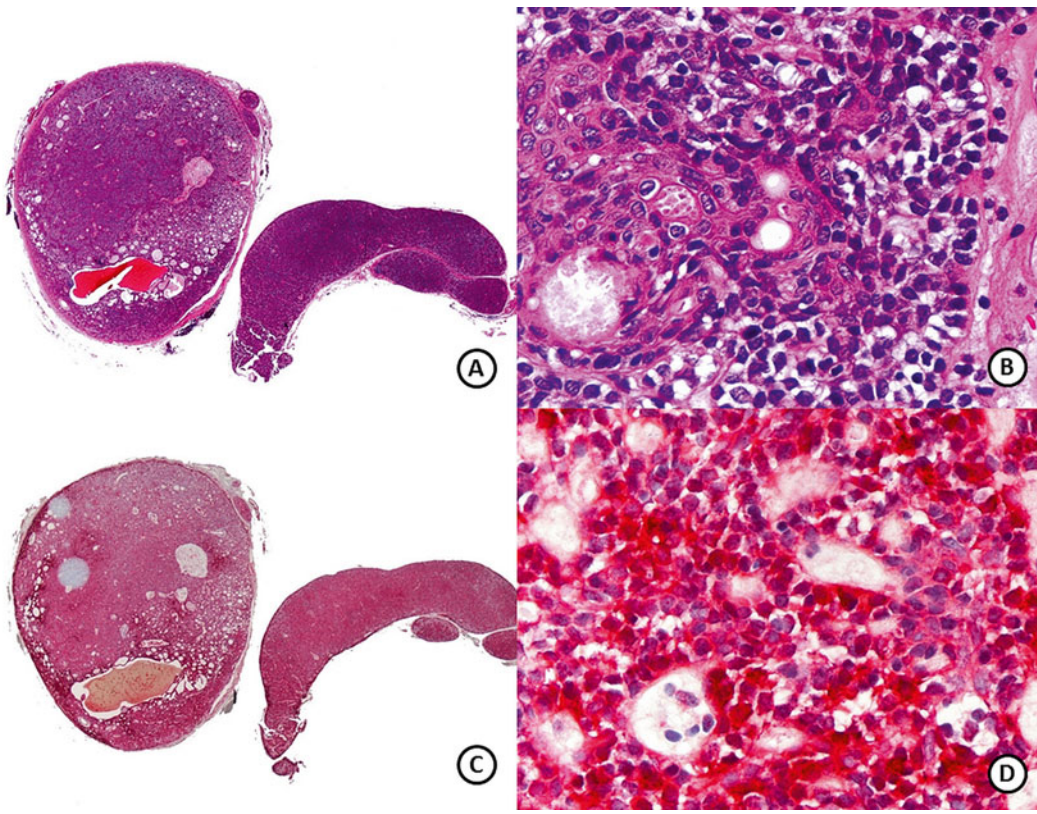

Fig. 2.5 (**a**) Spiradenoma. (**b**) Small ductal structures within the neoplastic aggregates. (**c**) The same case immunohistochemically studied for calponin. (**d**) Strong calponin immunoreactivity for neoplastic cells

of neoplastic cells confined within the epidermis; (2) classic poroma, composed of lobules of neoplastic cells involving both the epidermis and the dermis; (3) dermal duct tumor, characterized by small aggregates of neoplastic cells limited to the dermis, with few or no epidermal connection; and (4) poroid hidradenoma, characterized by single or few large solid neoplastic aggregates involving the dermis with cystic areas inside [78]. All poromas usually consist of solid sheets and nodules composed of two types of neoplastic cells: (1) Poroid cells, which are small basaloid cells, monomorphous and cuboidal, with a well-defined cell membrane, round nuclei and scant cytoplasm; and (2) Cuticular cells, which are larger than poroid cells, with ample eosinophilic cytoplasm, vesicular nuclei and evidence of primitive ductal differentiation in the form of small cytoplasm vacuoles. Well-formed ductal structures are also lined by cuticular cells. Areas of necrosis *en masse* are also frequently found. In intraepidermal lesions, neoplastic aggregates are sharply delineated from adjacent keratinocytes. Foci of squamous differentiation and clear cell change are sometimes seen. The intervening stroma shows abundant vascularization.

Immunohistochemical studies in poromas demonstrate positivity of ductal structures for EMA, CEA, and GCDFP-15. The neoplastic cells are immunoreactive for MNF116 and AE1/AE3 cytokeratins, but not for CAM5.2. Staining for CK7 is variable (Fig. 2.6). Poroid cells are positive for CK14 and are negative for CK10. In contrast, cuticular cells are positive for CK10, CK6, CK1 and /5/10/14, CK10/11, simple epithelial keratins (CK7, CK8/18, and CK19), and "basal" keratins (CK5/8 and CK14) [79]. The cuticular cells have been shown to have similar keratin expression patterns in "eccrine" and "apocrine" poromas. Cuticular cells are often positive for p53, but this feature alone should not be interpreted as a sign of malignant transformation [80].

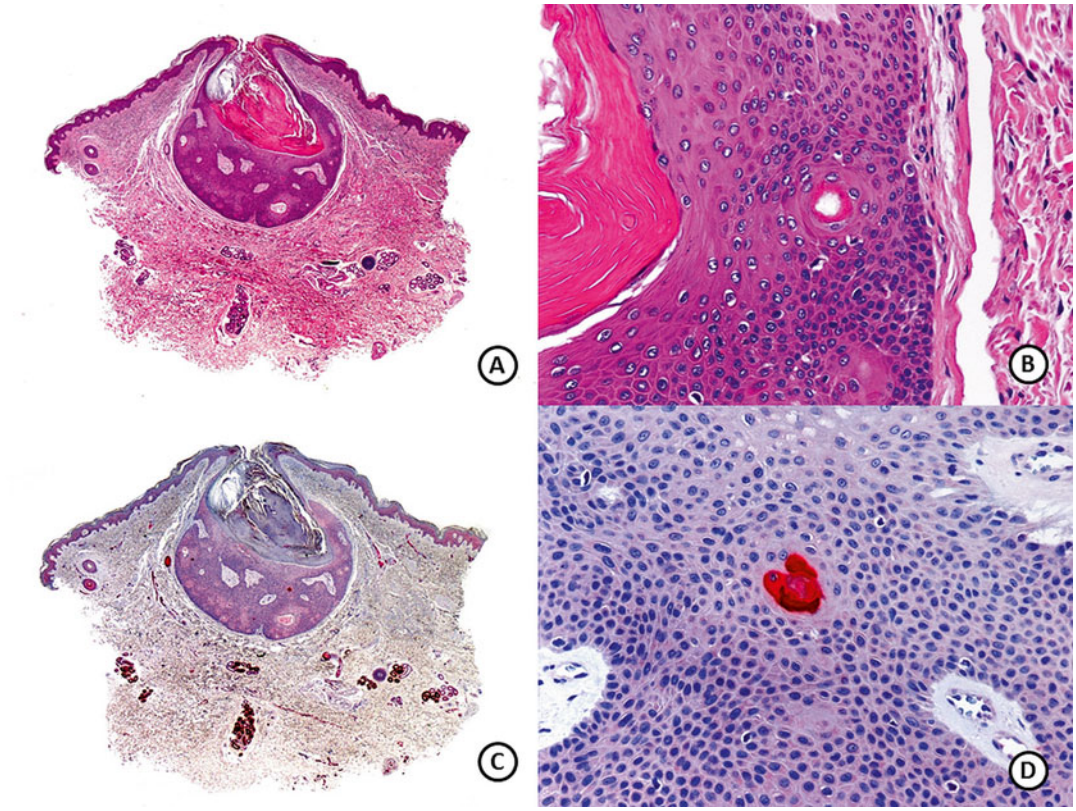

Fig. 2.6 (**a**) Poroma. (**b**) Ductal structures lined by cuticular cells within neoplastic aggregates of poroid cells. (**c**) The same case immunohistochemically studied for CK7. (**d**) Ductal structures show CK7 immunoreactivity

Three of seven studied poromas showed loss of heterozygosity in the *APC* gene, but the meaning of this genetic anomaly remains uncertain [81].

Myoepithelioma

Myoepitheliomas are exceedingly rare cutaneous tumors that arise in the dermis, subcutaneous fat or soft tissues. They are derived from myoepithelial cells which are found in the skin as a discontinuous peripheral layer around eccrine and apocrine glands. Analogous to salivary gland tumors, cutaneous myoepitheliomas are composed of myoepithelial and stromal components of mixed tumors, but lack the ductal epithelial component. Cutaneous myoepitheliomas usually present as firm, well-circumscribed, skin-colored or violaceous nodules ranging in size from 0.5 cm to 2.5 cm [82], although tumors located within deeper soft tissue may present as larger masses measuring up to 12 cm. [83].

Microscopically, cutaneous myoepitheliomas present as unencapsulated, circumscribed nodules consisting of a pure population of myoepithelial cells with no evidence of glandular or ductal differentiation as is seen in the more commonly encountered mixed tumor. They are situated in the dermis or subcutis, and composed of a variety of cell types, including spindle-shaped, epithelioid, histiocytoid, and plasmacytoid (hyaline) cells [84]. The cells usually have pale eosinophilic cytoplasm and relatively monomorphous ovoid nuclei with inconspicuous nucleoli. Some tumors have very little stroma, while others have a myxoid or collagenous hyalinized stroma.

Immunohistochemistry shows that the tumoral cells often express vimentin, EMA, S100 protein, and a wide spectrum of cytokeratins, although keratin staining is quite variable [85]. Myoid differentiation markers such as SMA (Fig. 2.7),

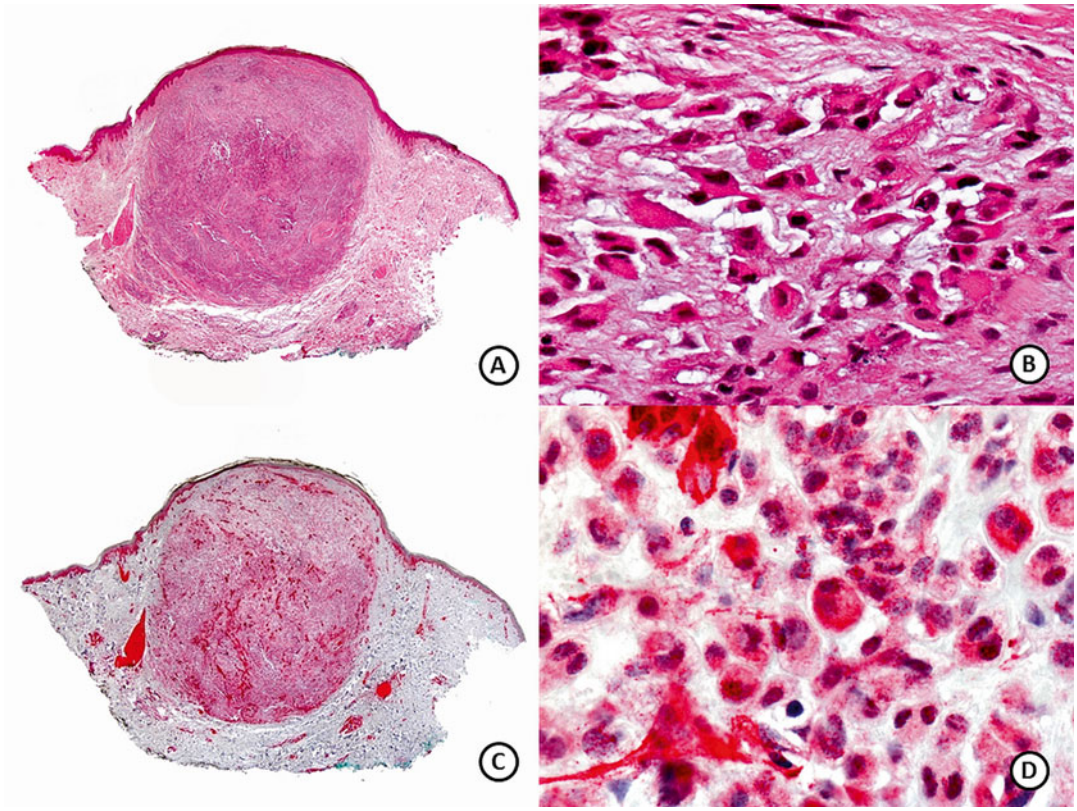

Fig. 2.7 (**a**) Cutaneous myoepithelioma. (**b**) Neoplastic cells showing eosinophilic cytoplasm and eccentric nuclei. (**c**) The same case immunohistochemically studied for SMA. (**d**) Strong immunoreactivity of neoplastic cells for SMA

muscle specific actin and calponin, as well as other markers like (HHF35) and glial fibrillary acid protein (GFAP) are seen inconsistently [86]. Desmin, synaptophysin, and chromogranin are usually negative [4].

Malignant Tumors

Syringocystadenocarcinoma Papilliferum

Syringocystadenocarcinoma papilliferum (SCACP) is an extremely rare cutaneous adnexal neoplasm representing the malignant counterpart of SCAP from which it usually evolves [1]. To date, less than 30 cases have been reported, and of those, only three had locoregional metastases [87–89]. The majority of cases reported were located in the head and neck region, or less commonly the perineal area and extremities of middle aged to elderly individuals. Clinically, SCACP presents as an enlarging flesh-colored to hyperpigmented exophytic nodule ranging in size from 0.5 to 13 cm [90].

SCACP is characterized histologically by disorderly arranged papillary projections, cytologic atypia and loss of the double layered epithelium [2]. Most tumors have been associated with nevus sebaceus of Jadassohn.

Although there is no definitive immunohistochemical profile for SCACP, this tumor is often positive for CEA and GCDFP-15. The in situ component may be positive with calponin, SMA and p63, which stain the peripheral myoepithelial cell layer. Moreover, p63 expression favors a primary sweat gland neoplasm of the skin rather than a cutaneous metastasis from a visceral adenocarcinoma [91, 92]. The epithelial cells stain with CK7 which may also be used to identify intraepithelial pagetoid spread [93]. An increased Ki-67 staining has been reported [4].

Cribriform Carcinoma

Cribriform carcinoma is a rare but distinctive histopathologic variant of cutaneous apocrine carcinoma that was originally described by Requena et al. in 1998 in a series of five cases [23, 94]. This neoplasm appears in adults and seems to be more common in females. The preferred sites of cribriform carcinoma are the lower and upper limbs.

On histopathology, the neoplasm usually shows no connection with the epidermis or adnexal structures and appears as a relatively symmetric, well-circumscribed dermal nodule, which involves the full thickness of the dermis and sometimes extends to the subcutaneous fat. The tumor is composed of multiple interconnected solid aggregations of epithelial cells that are punctuated by small round spaces in the fashion of a sieve. The cells show round or oval, hyperchromatic, slightly pleomorphic nuclei, inconspicuous or absent nucleoli, granular chromatin, and scant eosinophilic cytoplasm [23, 94].

The neoplastic cells are positive for different cytokeratins including MNF116, AE1/AE3, CAM5.2, and CK7as well as for CEA and EMA (Fig. 2.8), the last two staining the ductal component more intensely. However they are negative for CK20, GCDFP-15, and S-100 protein. Smooth muscle markers as SMA, muscle-specific actin, and calponin can be detected in the spindle cells of the stroma, which probably correspond to myofibroblasts, but not in the neoplastic cells [94].

Cutaneous Mucinous Carcinoma

Primary cutaneous mucinous apocrine carcinoma with neuroendocrine differentiation usually presents as a solitary papule, nodule, or plaque, typically affecting middle-aged or elderly individuals. It may occur anywhere, but has a predilection to involve the head and neck region, in particular the eyelids and scalp. The tumors are usually slow growing.

Hematoxylin and eosin-stained sections of this tumor show a nodular tumor involving the dermis with no connection to the epidermis. The tumor consists of solid, cystic or cribriform nests "floating" in pools of mucin, separated by thin fibrous septa. Neoplastic cells can show a low degree of atypia but mitotic figures are uncommon [95, 96].

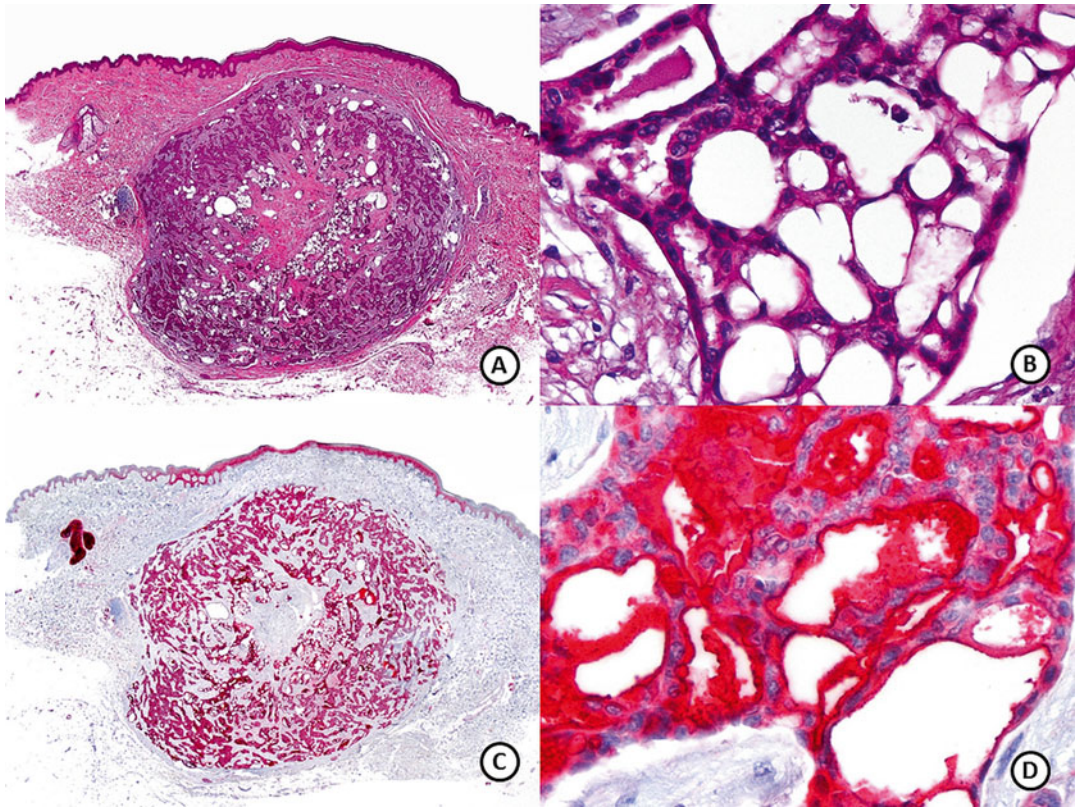

Fig. 2.8 (**a**) Primary cutaneous cribriform carcinoma. (**b**) Small ductal structures within solid aggregates resulting in a cribriform pattern. (**c**) The same case immunohistochemically studied for EMA. (**d**) EMA shows stronger expression in neoplastic cells lining ductal structures

On immunohistochemistry, neoplastic cells show positive expression of CK7, EMA, estrogen and progesterone receptors, and are negative for CK20 [97, 98]. Neuroendocrine markers such as chromogranin, synaptophysin, or neuron-specific enolase, show variable and sometimes focal expression [99–101]. The differential diagnosis with metastatic mucinous carcinoma, especially with metastatic mucinous breast carcinoma, may be extremely difficult, even with immunohistochemistry. Both tumors express CK7, hormone receptors, and some neuroendocrine markers. Some authors have suggested that the presence of an in situ component surrounded by myoepithelial cells highlighted by p63 and CK5/6 at the periphery of the tumor may be an additional criterion in favor of a primary carcinoma [97, 102, 103].

Endocrine Mucin-Producing Sweat Gland Carcinoma

Endocrine mucin-producing sweat gland carcinoma (EMPS) is an uncommon low-grade sweat gland carcinoma with an infiltrating growth pattern. It develops mostly in women and shows a predilection for the periorbital region [104–113]. Histopathologically, the neoplasm shows analogous features to endocrine ductal carcinoma/solid papillary carcinoma of the breast. EMPS shares some clinical and morphological similarities to primary mucinous carcinoma of the skin. The tumor is characterized by large monomorphous epithelial cells with little nuclear pleomorphism and only a few mitotic figures. In some areas, neoplastic cells are arranged in a rossete-like pattern.

This solid- cystic tumor shows mucin within cystic small spaces, cribriform areas and expresses the neuroendocrine markers synaptophysin, chromogranin (Fig. 2.9) and neuron specific enolase in varying staining intensities [104–113]. The tumor cells are also positive for estrogen and progesterone receptors.

Hidradenocarcinoma Papilliferum

Hidradenocarcinoma papilliferum is an extremely rare neoplasm, with very few reported cases in the literature [114–116]. Owing to the paucity of observations, the clinical features of hidradenocarcinoma papilliferum are not well established, but there do not appear to be obvious differences from long-standing hidradenoma papilliferum in which focal areas of ductal carcinoma in situ (DCIS) may be an incidental finding.

Histologically, DCIS ex-hidradenoma papilliferum appears as a typical hidradenoma papilliferum in which 1 or more foci of crowded epithelial cells may be found, showing pleomorphic hyperchromatic nuclei and abnormal mitotic figures. Retention of myoepithelial cells around such areas is indicative of DCIS.

Immunohistochemically, demonstration of a preserved peripheral myoepithelial layer around the dysplastic epithelium is a prerequisite for the diagnosis of DCIS. The proliferating index (Ki-67) is higher in the areas of DCIS compared with the benign portions of the neoplasm, but there has been no p53 expression in the few cases examined [117].

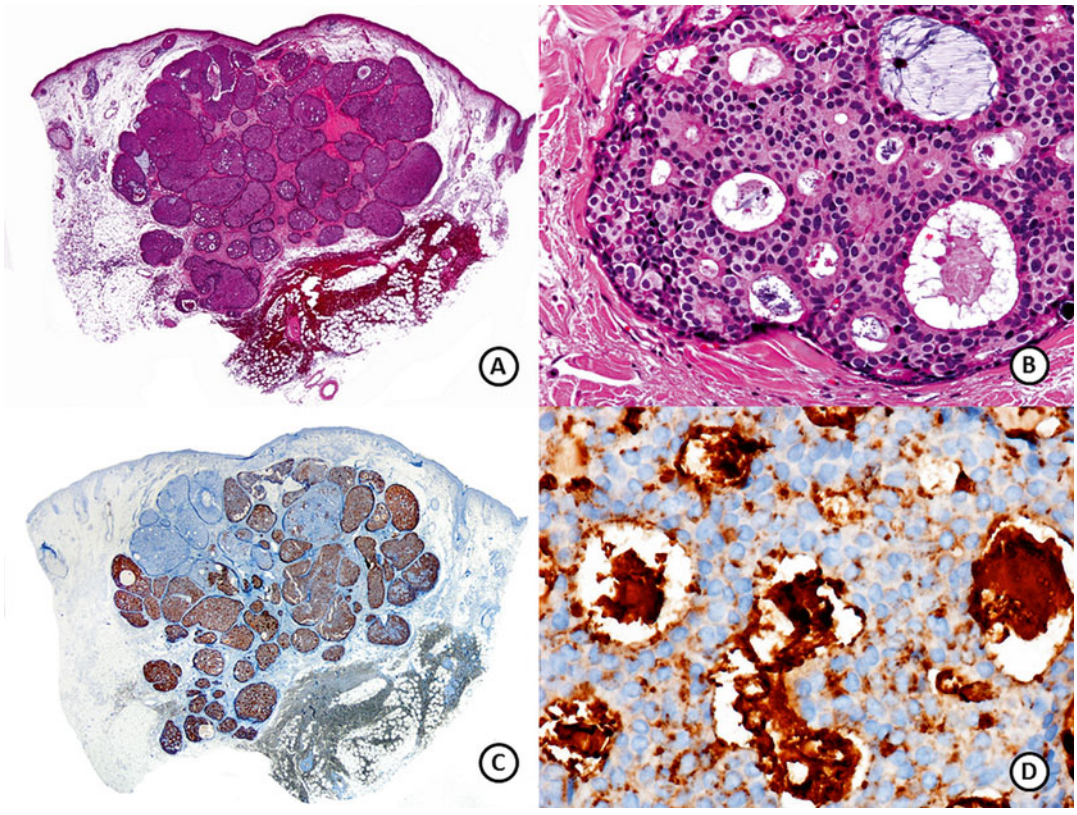

Fig. 2.9 (**a**) Endocrine mucin-producing sweat gland carcinoma. (**b**) Neoplastic aggregates showing ductal structures some of them containing mucin within the lumina. (**c**) The same case immunohistochemically stained for chromogranin. (**d**) Chromogranin is expressed in the cytoplasm of neoplastic cells and in a stronger way within the lumina

Digital Papillary Adenocarcinoma

Digital papillary adenocarcinoma (DPA) is an uncommon cutaneous malignancy first described by Helwig in 1979 with the term "aggressive digital papillary adenoma" [118, 119]. Because of the lack of histopathologic criteria to allow the distinction between adenoma and adenocarcinoma and predict the clinical behavior of these tumors, the term "aggressive digital papillary adenoma" was later abandoned and the lesion was considered a carcinoma. However, the aggressive course of the neoplasm has also been questioned recentely [120, 121]. It often occurs as a single, mildly painful mass and almost exclusively occurs on the volar site of the fingers and toes and on the adjacent skin of the palms and soles [120].

Microscopically, the tumor usually involves both the dermis and the and/or subcutis, and the silhouette of the lesion may be nodular and/or infiltrative. There is usually a combination of solid, solid cystic, cribriform, and tubular growth patterns. Papillary projections into luminal spaces are common, but may on occasion be rare or absent. The stroma may be variably fibrotic. The spectrum of histologic appearances ranges from obvious carcinoma to adenoma-like well-differentiated tumors.

Immunohistochemical studies have shown positivity for S100 protein, CEA, and cytokeratins [119], and may be useful in the differential diagnosis of DPA from metastatic adenocarcinoma. A recent immunohistochemical study of a series of 31 cases of papillary carcinoma demonstrated diffuse positivity for MNF116 pan-cytokeratin, whereas CEA and EMA highlight the luminal border of the tubules. SMA and calponin highlight a myoepithelial layer around tubular/glandular structures, as did p63 and podoplanin [122]. One approach is to investigate the expression of basal epithelial markers such as 34βE12 and p63, which may serve as a good indicator for primary cutaneous origin as well as in situ growth of this neoplasm. Proliferation index with Ki-67 is usually high (Fig. 2.10).

Ceruminous and Moll's Gland Carcinomas

Ceruminous carcinomas are rare malignancies usually presenting with a mass or pain in the outer ear canal of middle aged patients. Tumors are large for the anatomic site [123]. Histopathologically, the tumors are classified as ceruminous adenocarcinoma, NOS, ceruminous adenoid cystic carcinoma, and ceruminous mucoepidermoid carcinoma. The ceruminous adenocarcinoma may be difficult to distinguish from ceruminous adenoma. They usually demonstrate an infiltrative pattern with moderate to severe nuclear pleomorphism, increased mitotic index and rarely necrosis.

Reported examples of Moll's gland adenocarcinomas have shown variable features. Some have been predominantly solid, whereas others have displayed mostly tubular or ductal growth, but all have malignant architectural features. With respect to cytologic appearances, both low-grade and high-grade lesions have been described. In rare examples, evolution from a preexisting benign Moll's gland lesion has been suggested [4].

Malignant Mixed Tumor

Malignant apocrine mixed tumor is a rare tumor of the skin, most often found on the trunk and extremities, which are not the usual sites of the benign variant. Approximately 50 cases have been described to date. Although the majority of tumors have developed de novo, there are some documented examples which appear to have arisen within a preexistent benign mixed tumor. Clinically, the tumor is not distinctive and presents as a flesh-colored or erythematous nodule, predominantly affecting the distal extremities (the foot being the commonest site) [124]. Malignant mixed tumor is an extremely high-grade neoplasm with a metastatic rate of approximately 60 % and a mortality of roughly 25 % [124, 125]. The existence of a malignant counterpart of eccrine mixed tumor is controversial. Some of the reported malignant eccrine

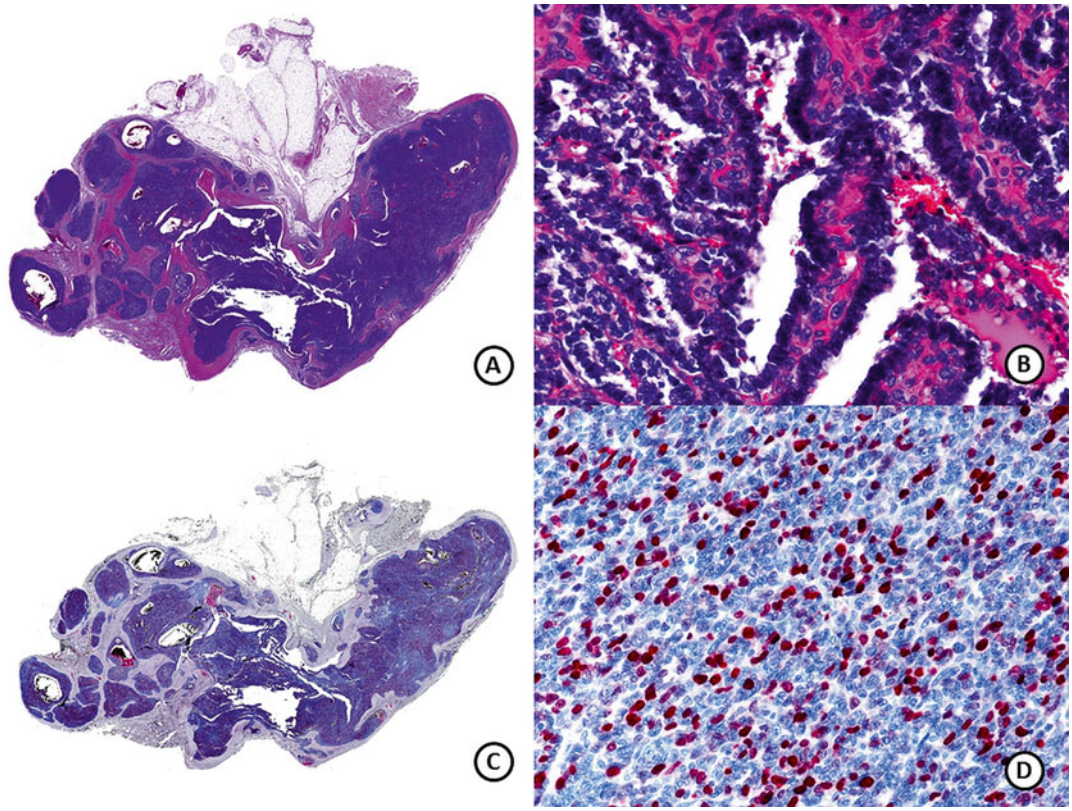

Fig. 2.10 (**a**) Digital papillary adenocarcinoma. (**b**) Papillary structures lined by atypical cells with hyperchromatic nuclei. (**c**) The same case immunohistochemically stained for Ki-67. (**d**) Numerous nuclei of neoplastic cells express Ki-67

mixed tumors of the skin have been found to represent malignant mixed tumors of the salivary glands involving the skin, and further studies are needed to clarify this issue [4].

Histopathologically, the tumors are composed of an epithelial and a mesenchymal component, the latter consisting of myxomatous and cartilaginous areas. The epithelial component predominates at the periphery of the tumor, where there are cords and nests of cuboidal or polygonal cells with some glandular structures. There is variable pleomorphism and scattered mitoses. Mesenchymal elements are progressively more abundant towards the center. Ossification is occasionally present. The histological appearance may be a poor indicator of the biological behavior of a particular tumor in this category, and the identification of a benign precursor lesion has only rarely been histologically documented [126, 127].

Immunohistochemically, the epithelial cells express pancytokeratin, AE1/AE3, CAM 5.2, EMA, CEA, and variably S-100 protein [128–130]. Intracytoplasmic lumina may be outlined with CEA. The luminal epithelial cells also show binding to the lectin *Ulex europaeus* [128–130]. The stromal cells are S-100 protein positive and variably express keratin. SMA and GFAP positivity has been variably reported as present or absent, while androgen receptors have not been detected.

Apocrine Adenocarcinoma

The term "primary cutaneous apocrine carcinoma" is a generic term that encompasses a wide spectrum of primary cutaneous carcinomas showing apocrine differentiation. Due to the complex nosology of apocrine carcinoma, in this chapter,

the term cutaneous apocrine adenocarcinoma will be restricted to malignant epithelial neoplasms that manifest unequivocal signs of apocrine secretion, but lack the defining microscopic features of the above mentioned well-defined lesions, such as digital papillary adenocarcinoma, mucinous carcinoma, syringocystadenocarcinoma papilliferum, and malignant apocrine mixed tumor. Also, the term will not be used to refer to other well-defined carcinomas associated with a specific glandular origin (Moll's glands, ceruminous glands, or anogenital mammary-like glands). The clinical features of this tumor are not distinctive, and lesions have been reported to occur in several areas with the axilla appearing to be the most commonly involved site.

Microscopically, the majority of the reported examples are characterized by a glandular, tubular, papillary, tubulopapillary, diffuse, or solid growth pattern centered on the dermis and subcutaneous tissue. In contrast to apocrine adenoma, the tumor is usually poorly circumscribed and frequently presents an infiltrating border. The epithelial cells have abundant eosinophilic cytoplasm, and decapitation secretion is invariably present. Pleomorphism and mitotic activity are variable features, but become more prominent in poorly differentiated variants. The tumor is commonly accompanied by a dense hyaline stroma.

Immunohistochemically, the tumor cells consistently express cytokeratins, including CAM 5.2, CK7, CK15, AE1/AE3, usually GCDFP-15 and variably CEA [131]. Controversial information has been published on the expression of S-100 protein, EMA, lysozyme, α_1-antitrypsin, and α_1-antichymotrypsin. In a significant subset of tumors expression of estrogen, progesterone, or androgen receptors is seen [131]. An in situ component is best identified by an intact peripheral basal/myoepithelial cell layer reactive for calponin, p63, and actin; however, this myoepithelial layer is lost in some cases [4, 32].

Porocarcinoma

Porocarcinomas are aggressive tumors with potential for local recurrence, and nodal and distant metastases [132]. They usually arise within preexisting benign poroid tumors, frequently located in the lower extremities. Histologically they are characterized by an asymmetrical, solid, and nodular growth pattern, with infiltrative or pushing borders. The neoplasm is composed of poroid and cuticular cells, similar to those of poroma, but with varying degrees of nuclear atypia, hyperchromatic nuclei, and prominent nucleoli. Both in situ and invasive forms have been described [2].

Immunohistochemistry shows that poroid cells are positive for CK7. EMA and CEA (Fig. 2.11) have been reported to be positive in the lumina of ductal structures [133, 134], however, poorly differentiated porocarcinomas with no luminal differentiation did not express CEA [132, 134]. The presence of scattered dendritic melanocytes, positive for S-100 protein and HMB-45, has been reported in both poromas and porocarcinomas [135]. Some authors have proposed that CK19 can be useful in the distinction of porocarcinoma from squamous cell carcinoma (SCC), as it is expressed in 67 % of porocarcinomas versus 18 % of SCC. S-100 protein is another useful marker in the differential diagnosis of this neoplasm from tumors with more prominent myoepithelial differentiation such as spiradenoma, apocrine hidradenoma, and cutaneous mixed tumors. In these tumors neoplastic aggregates of myoepithelial cells are positive with S-100 protein, whereas in porocarcinoma the positive cells are scattered dendritic cells [136]. The diagnostic role of other markers (p16, RB protein, beta-2-microglobulin) has been investigated, but they seem to have no relevance in routine practice [137, 138].

Extramammary Paget's Disease

Extramammary Paget's disease (EMPD) is an uncommon cutaneous malignant neoplasm arising in areas with high density of apocrine glands, most commonly in the vulvar and perianal region of middle-aged females, and less commonly the axilla. It has also been reported in areas with modified apocrine glands, such as the eyelids and external auditory canal. Apocrine gland origin or

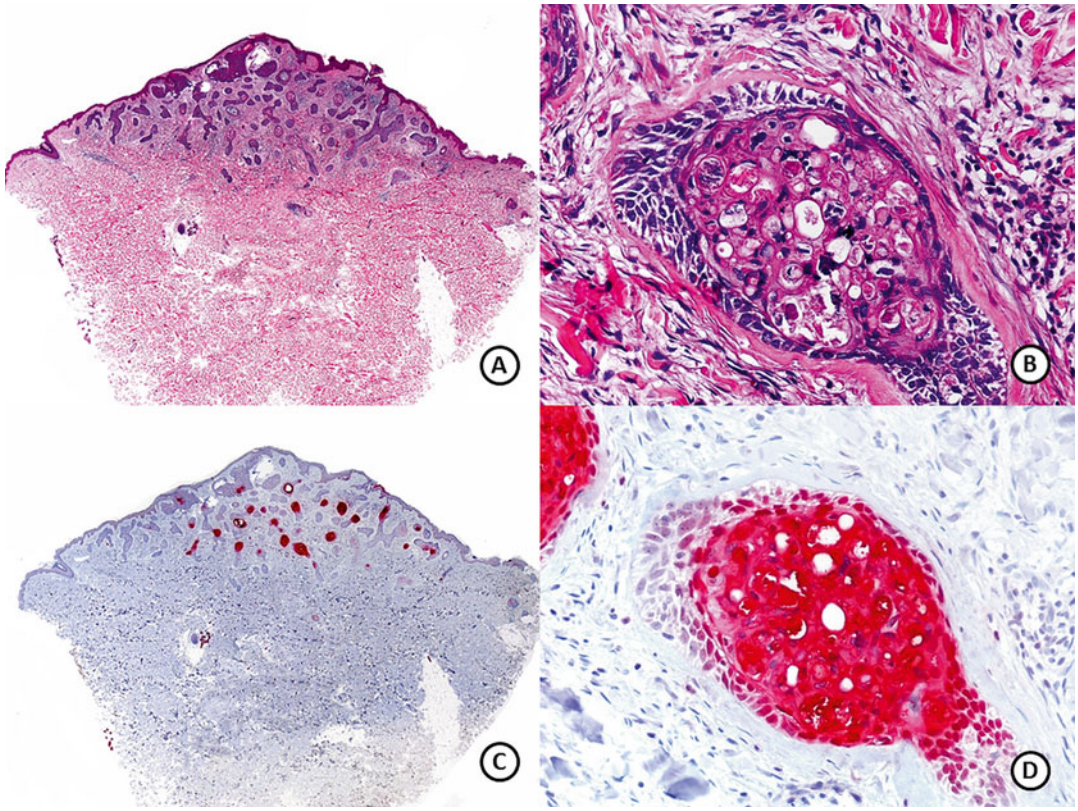

Fig. 2.11 (**a**) Porocarcinoma. (**b**) Some of the neoplastic aggregates show necrosis en masse, pleomorphic nuclei and small ductal structures. (**c**) The same case immunohistochemically studied for CEA. (**d**) CEA is expressed by most of neoplastic cells

apocrine differentiation of cells in EMPD has been generally accepted [2]. Lesions usually present as erythematous eczematoid slowly spreading plaques and erosive ulceration in older individuals. The size of the lesion usually correlates with its duration.

Histologically, there is a proliferation of single and small clusters of large cells within the epidermis, which have less defined intercellular bridges and exhibit glandular differentiation, occasionally showing intracytoplasmic luminal and ductal formation. The tumor cells in Paget's disease have abundant pale cytoplasm and large pleomorphic nuclei. Mitoses are usually present [7]. The epidermis is usually hyperplastic and there is often overlying hyperkeratosis and parakeratosis. A chronic inflammatory cell infiltrate is found in the upper dermis [8]. An underlying in situ or invasive adnexal carcinoma may be present. This may show apocrine differentiation, but in other cases it is not possible to determine the cell of origin.

With immunoperoxidase techniques Paget's cells stain for AE1/AE3, LMWK, and CK 7 (Fig. 2.12), with variable positivity seen for EMA and CEA. GCDFP-15, androgen receptors, and Her2/neu are also commonly expressed in EMPD, whereas estrogen and progesterone receptors are not [139–141]. Variable staining of cells has been reported for HMFG [142]. HER-2 protein is expressed in some cases. Prostate-specific antigen (PSA) is expressed in the pagetoid cells of many cases associated with an underlying adenocarcinoma of the prostate, but it may also be expressed in cases without an associated carcinoma [143]. Matrix metalloproteinases (MMP-7, MMP-19) are often expressed in cases with an underlying carcinoma [144]. Other

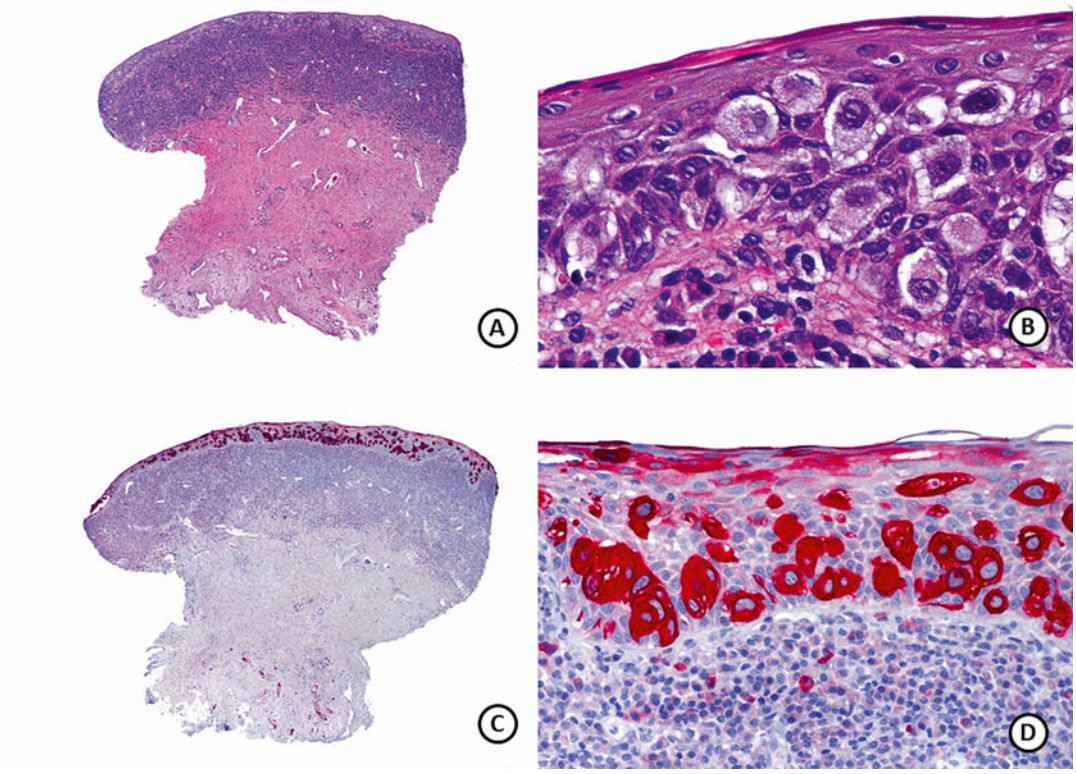

Fig. 2.12 (**a**) Extramammary Paget disease involving the glans penis. (**b**) Paget cells in pagetoid pattern involving the epithelium. (**c**) The same case immunohistochemically studied for CK7. (**d**) CK7 is expressed by Paget cells

proteins that can be expressed in Paget's disease include insulin-like growth factor-1 receptor, p-AKT, p-ERK1/2, Stat3, Stat5a, E-cadherin, cyclin D_1, and Bcl-xL [145–147]. Overexpression of p53 is correlated with stromal invasion. Ber-EP4 can aid in the differential diagnosis from Bowen's disease as it labels all cases of extramammary Paget's disease but none of the other pagetoid neoplasms [148].

Immunohistochemical expression of apomucin MUC1, MUC2, MUC5AC has been proposed as a helpful tool for histopathologic differential diagnosis among mammary Paget disease, extramammary Paget disease, and epidermotropic metastasis in the anogenital skin from adjacent visceral adenocarcinomas [149]. MUC1 is commonly expressed in most cases of mammary Paget disease. In contrast, MUC5AC is a unique mucin that is expressed in most cases of extramammary Paget disease, but not in mammary Paget disease. In cases of mammary Paget disease associated breast ductal carcinoma, both Paget cells and underlying ductal carcinoma exhibit the phenotype MUC1+MUC2−MUC5AC−. This mucin phenotype is also expressed by Toker cells. In patients with perianal Paget disease associated with rectal adenocarcinoma, Paget's cells express MUC2 constantly, but the expression of MUC1 and MUC5AC is variable. Cases of vulvar and scrotal intraepidermal extramammary Paget disease with no identifiable underlying malignancy express a uniform phenotype of mucin MUC1+MUC2−MUC5AC+, whereas cases of extramammary Paget disease associated with underlying apocrine carcinoma have a phenotype characterized by MUC1+MUC2−MUC5AC−, identical to that of normal apocrine glands. Bartholin's glands express a mucin phenotype identical to that of intraepidermal extramammary Paget disease. These results support that: (1) Mammary Paget disease may arise from either mammary glands or epidermal Toker cells;

(2) Intraepidermal extramammary Paget disease in the anogenital areas may arise from ectopic MUC5AC+ cells originating from Bartholin's or some other unidentified glands; and (3). Unique expression of MUC2 in perianal extramammary Paget disease indicates its origin from colorectal mucosa. In conclusion, the study of mucin gene expression is useful in the histopathologic differential diagnosis among mammary Paget disease, extramammary Paget disease and epidermotropic metastasis in anogenital skin from an adjacent colon adenocarcinoma.

Spiradenocarcinoma and Cylindrocarcinoma

Malignant neoplasms arising in preexisting benign spiradenoma and cylindroma, are rare, and approximately 100 cases having been reported to date [4]. The most common benign neoplasm giving rise to a malignant tumor is spiradenoma, followed by cylindroma. The microscopic appearances of these malignant tumors are heterogeneous, as is the terminology used by different authors. The lesions mostly occur as sporadic solitary neoplasms, or as a component of Brooke–Spiegler syndrome. Sporadic tumors occur mainly in elderly patients and usually involve the back, neck, and scalp, where they present as solitary tumors ranging in size from 2 to 17.5 cm. In Brooke–Spiegler syndrome patients, malignant lesions develop as large, rapidly growing, bleeding, or ulcerated tumors in a background of multiple, smaller, either grouped or confluent papules or nodules, which represent preexisting benign neoplasms [150, 151].

Histopathologically, features suggesting possible malignant potential include an infiltrating growth pattern and loss of mosaic appearance, hyaline sheaths, and biphasic cellular distribution. Nuclear pleomorphism, prominent nucleoli, and frequent or abnormal mitoses are also features seen in these malignant neoplasms.

Immunohistochemistry may be of help in highlighting ductal differentiation, the latter expressing EMA and CEA. The background population of tumor cells express CAM5.2, S-100 protein and GCDFP-15 expression with variable intensity [152]. Although immunostaining for p53 has been suggested to differentiate benign spiradenoma and cylindroma from their malignant counterparts, its utility is limited by its heterogeneous pattern of expression, especially the occasional lack of staining in clearly malignant areas and the occurrence, of focal weak positivity in the benign residual tumor or in unequivocally benign neoplasms [76].

Finally, cases associated with Brooke–Spiegler syndrome usually show a germ-line mutation of the *CYLD* gene. There appears to be no correlation between the germ-line mutation type and the clinical phenotype that would suggest malignant transformation [4]. Despite relatively frequent immunopositivity for p53, mutations of the *TP53* gene are rare in malignant lesions [76].

Microcystic Adnexal Carcinoma

Microcystic adnexal carcinoma (MAC), also called sclerosing syringomatous carcinoma or sclerosing sweat duct carcinoma is an uncommon malignant neoplasm, which is widely believed to be of eccrine origin. However, the presence of infundibular keratinous cysts and the description of apocrine and sebaceous differentiation has been described in many cases [2, 153]. This may suggest that both eccrine and apocrine variants of this neoplasm do exist. It typically develops on the mid-face of young, middle-aged, or elderly woman, and has a tendency toward persistent and local recurrence (approximately 50 %) [154], but not to metastatic potential [155, 156]. In particular, the upper lip and the glabella are the commonest locations.

Histopathologically, MAC is composed of a poorly circumscribed proliferation of non-atypical epithelial neoplastic cells infiltrating the dermis and subcutaneous tissue, with prominent perineural and intraneural invasion. The neoplastic cells are small, uniform, and basaloid, and show no or minimal cytological atypia and mitotic activity. Keratin-filled microcysts are often present in the superficial dermis. Tubular and ductal

structures lined by a single layer of neoplastic cells dominate the deeper parts of the lesion. The tumor stroma is characteristically sclerotic.

With immunohistochemistry, the tumor cells express AE1/AE3, and the ductal differentiation and intracytoplasmic lumen formation are positive for EMA and CEA [157]. LeuM1 is usually positive as wells as CD15, while Ber-EP4 (Fig. 2.13) and S100 protein show variable expression [158, 159]. The proliferation rate, as determined by Ki-67, is usually low [160].

Adenoid Cystic Carcinoma

Primary cutaneous adenoid cystic carcinoma (ACC) is a very rare malignant neoplasm affecting older adults, with a female predominance. It can occur in different anatomical sites, most commonly in the scalp [161]. The tumor has a 50% local recurrence rate, but metastasis to regional lymph nodes and distant organs is rare [162].

Histopathologically, ACC is indistinguishable from its salivary gland counterpart, and it usually presents as a dermal tumor that forms tubuloalveolar structures lined by atypical basaloid epithelia and associated with the formation of basophilic "cylinders" of myxoid matrix substance. Globules and cylinders of brightly eosinophilic basement membrane-like material complete the picture [163, 164]. Mitoses are typically inconspicuous. An important criterion in ACC in any anatomical location is the striking propensity of these tumors to manifest perineural infiltration.

Immunohistochemically, the tumor cells express low and high molecular weight keratin and broad-spectrum keratins. The presence of ductal differentiation can be confirmed with EMA and CEA, which are frequently expressed in the

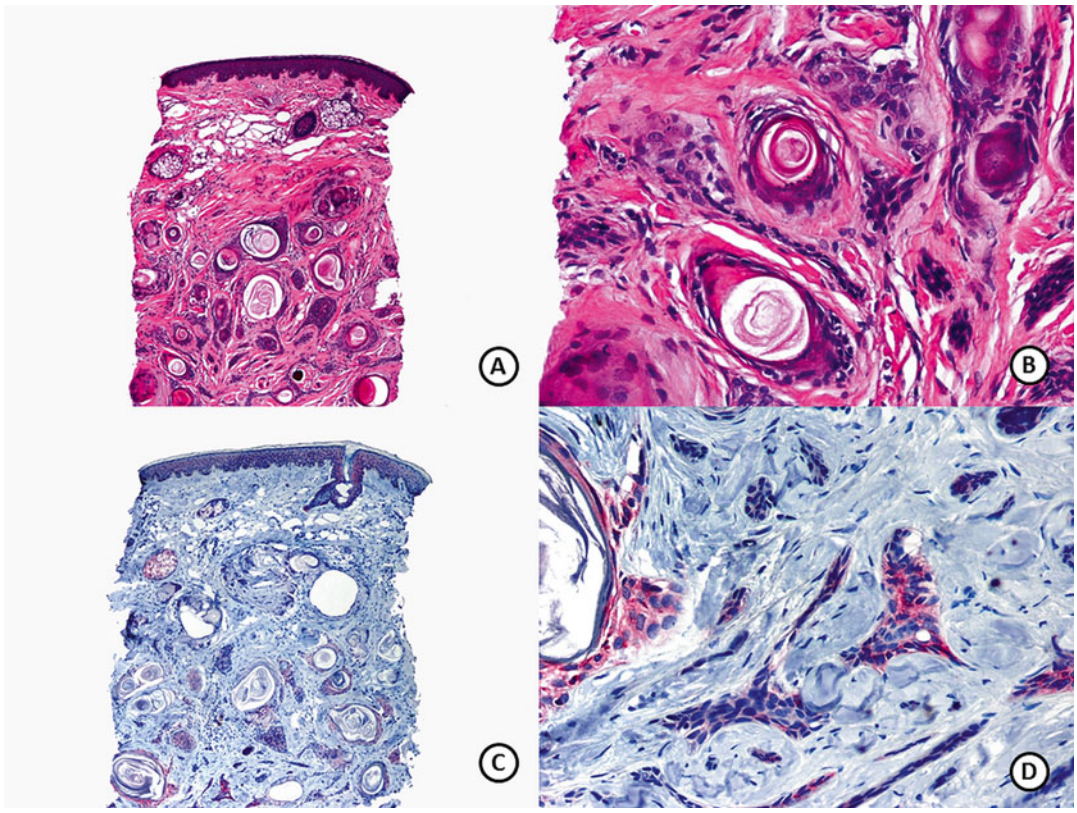

Fig. 2.13 (**a**) Punch biopsy of a microcystic adnexal carcinoma. (**b**) Solid aggregates and small keratinous cysts. (**c**) The same case immunohistochemically studied for BerEp4. (**d**) Weak immunoexpression of neoplastic cells for BerEp4

luminal surfaces and secretions. Myoepithelial differentiation (S-100 protein, actin, positivity) is a constant feature. The basement membrane material is composed of a mixture of collagens IV and V and laminin [165].

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