The diagnosis of cutaneous adnexal neoplasms is perceived by practicing pathologists as challenging not only because there is a constantly increasing number of described entities but their nomenclature is complicated or conflicting and finally, in may instances, they are difficult to classify. The goal of this presentation is to provide a practical approach to diagnose these tumors, with a special emphasis on the aspects that have a significant impact on patient’s management and prognosis. The main topics that will be discussed and exemplified with cases from our current practice will try to answer to the following questions: Is this a benign or a malignant neoplasm? Is this a primary adnexal neoplasm or a cutaneous metastasis of an internal malignancy? Is it possible that this tumor may represent the cutaneous expression of a certain syndrome or may be associated with internal malignancies?

The most important criterion to differentiate between malignant and benign adnexal tumors is the presence or absence of an infiltrative growth pattern. This is especially true for tumors of follicular origin in which is not uncommon to identify in benign neoplasms, a high mitotic rate or even cytologic atypia. A benign cutaneous adnexal neoplasm has usually smooth borders, are symmetric and well-circumscribed. In contrast the malignant tumors have infiltrative borders, extend in deep dermis without the interposition of a dense fibrotic stroma, have atypical mitoses and more frequently necrosis en masse. As previously noted, the presence of the cytologic atypia can be misleading. For example, one of the most locally aggressive cutaneous adnexal neoplasms, microcystic adnexal carcinoma, is usually characterized by a bland cytology. In contrast, some of the poromas of pilomatrixomas may exhibit cytologic atypia but still behave as benign neoplasms. As an example, a case of a cutaneous mixed tumor with a deceptively bland cytology but that was widely metastatic will be presented.

One of the most common problems is encountered in the setting of small incomplete biopsies, where the tumor contour cannot be entirely evaluated. For example, in the case of a microcystic adnexal carcinoma, a superficial shave biopsy will not offer any insight regarding the extension and tumor invasion and may be interpreted as a syringoma. Also we have encountered superficial biopsies of hidradenoma but in which hidroadenocarcinoma arose and was not represented in the original biopsy.

An important caveat is one particular lesion for which the location is essential in determining its behavior, namely, aggressive digital papillary adnexal adenocarcinoma. It was originally described in 1987 as a variant of sweat gland carcinoma occurring typically on hands, fingers and toes. Importantly the overall recurrence rate is approximately 30-40% and the rate of distal metastases (lung, lymph nodes) is approximately 14%. Sentinel lymph node biopsy in addition to local treatment can be also offered. Currently, the term of “aggressive digital papillary adenoma” was abandoned as all digital papillary neoplasms seem to have an aggressive biologic behavior and there are no reliable histologic or clinical features that can distinguish between these two entities. May be misdiagnosed for cutaneous metastases of tumors with papillary architecture (colon, thyroid, breast).

While the usual histologic picture for these tumors is the presence of epithelial nodules with glandular and papillary morphology, separated by dense fibrocollagenous stroma, in some cases a more solid growth pattern with back-to-back glands or poor glandular differentiation may be seen. Sometimes a spindle cell morphology or a myxoid background may be particularly
confusing, especially in small, limited biopsies. One such case of digital papillary adnexal adenocarcinoma with unusual histologic features will be presented, in order to increase the awareness of practicing pathologist dealing with cutaneous tumors with acral location.

Cutaneous metastases occur in up to 10% of patients with internal carcinomas. Their recognition is important since they portend a poor prognosis and can be the first sign of an internal malignancy. Most common primary tumors in women are breast (60-70%), GI, lung, and ovary in women while lung, GI, head and neck, and GU are most common in men. Less common are thyroid, adrenal, endometrium, prostate, and mesothelioma.

The most common metastatic tumors that resemble primary skin lesions are those with ductal differentiation (particularly microcystic adnexal carcinomas, hidradenocarcinomas, and eccrine/apocrine adenocarcinomas), tumors with a predominance of clear cells (xanthomas, trichilemmal carcinomas, hidradenocarcinomas, sebaceous carcinomas), and mucinous tumors. Based upon their morphologic features, those lesions may resemble carcinomas from the breast, gastrointestinal tract, lung, kidney, or ovary.

On histologic grounds alone, several features are traditionally used to distinguish between primary adnexal neoplasms and cutaneous metastases of internal malignancies. One of the features in favor of a primary cutaneous tumor is the connection to the epidermis or growth into skin appendages (i.e. in situ component). However, it is important to remember that tumors such as hidradenocarcinoma are strictly intradermal and do not connect with overlying epidermis, as well as the fact that epidermotropic metastases are not very uncommon. Another useful clue for a primary cutaneous tumor is the identification of the benign counterpart within the lesion (such areas of benign hidradenoma within a hidradenocarcinoma). One of the facts that are seldom noted in the literature is the more frequent presence of entrapped, “passenger” melanocytes within primary cutaneous lesions while they are rarely seen in metastatic tumors. Historically, one of most useful histologic feature for a cutaneous metastasis is the location of the tumor in deep dermis or subcutaneous tissue, multifocality and more frequent presence of lymphovascular invasion. However these histologic findings are not completely reliable and in many cases the patient clinical history may be helpful. A case of a distant epidermotropic metastasis of mucoepidermoid carcinoma of the salivary gland will be presented. Interestingly, the metastatic lesion and the primary salivary gland tumor were synchronous and therefore the differential diagnosis was very challenging.

In addition to histologic features and clinical information, immunohistochemical studies that might help in identification of tumor origin. As a note of caution, an enormous range of antibodies is now available and a large proportion is suitable for use with routine, formalin-fixed, paraffin-embedded tissues. Difficulties, however, are often experienced due to lack of specificity or poor sensitivity. It is essential that the practitioner be aware of the often wide range of cell types that may express any particular antigen and that the use of panels of immunohistochemical studies is more helpful than single stains.

In normal skin, the cells in the excretory coil of the sweat glands express low molecular weight keratin (LMWK), EMA, CEA, and GCDFP15, with scattered S100-positive basal cells. Eccrine cells usually express ER/PR while apocrine cells more commonly express androgen receptors (AR). Myoepithelial cells express S100, SMA, p63, and calponin.

Historically, gross cystic disease fluid protein 15 (GCDFP-15), estrogen receptor (ER), and progesterone receptor (PR) have been used as markers for breast differentiation. However, it is important to note that GCDFP-15, ER, PR, and Her2/neu have all been shown to be expressed also in cutaneous adnexal neoplasms, an expected finding since the breast is a modified apocrine gland. For this reason, these markers should be used with significant caution to help distinguish primary lesions from metastatic breast tumors. A challenging case of a patient with a remote history of breast carcinoma and presenting with a leg mass that was predominantly dermal, had histomorphologic features of adenocarcinoma and was positive for CK7, ER, PR,
suggesting the possibility of a metastasis. However, the tumor was also diffusely positive for p63 and raised the possibility of a primary adnexal neoplasm. The re-excision showed also an intraepidermal component and a connection of the tumor with overlying epidermis, supporting the diagnosis of porocarcinoma.

CK 5/6 and CK7 have been found to be less reliable as differentiating markers of primary cutaneous adnexal tumors versus cutaneous metastases, but still helpful when used in a panel of markers. Cytokeratin 5/6 is expressed in most primary cutaneous adnexal neoplasms, and only in a minority of metastatic adenocarcinomas. CK7 is relatively equally expressed in primary cutaneous adnexal neoplasms and cutaneous metastases (lung and breast). However it is mostly focal in the primary neoplasms while showing strong and diffuse expression in the metastases.

Gastrointestinal metastases (intestinal adenocarcinomas) usually show necrosis in the glandular lumina (“dirty” necrosis). Strong CK20 expression and lack of CK7 expression favors a metastasis from an intestinal primary over a primary cutaneous (usually CK7 positive and CK20 negative). Although CDX-2 is fairly specific for a gastrointestinal origin, it has been reported in ovarian mucinous tumors, and rare tumors of the lung, bladder, and head and neck. Both adnexal tumors and lung adenocarcinomas usually are CK7+ / CK20-. A number of primary pulmonary adenocarcinomas and thyroid neoplasms express TTF-1.

Eccrine carcinomas derived from sweat glands, microcystic adnexal carcinomas and hidradenocarcinomas in particular, can commonly mimic adenocarcinoma metastatic to the skin from a variety of primary sites, most commonly breast, lung, gastrointestinal tract, or ovary. We and others recently suggested that p63 can be used as a marker to distinguish primary adnexal tumors from metastatic adenocarcinoma to the skin: p63 is generally expressed in cutaneous adnexal tumors and is lacking in the metastatic adenocarcinomas (breast, gastrointestinal tract, lung). It is important to mention that p63 immunohistochemical study cannot be used to distinguish primary and metastatic squamous cell carcinomas (with lung or head and neck origin) or metastatic urothelial carcinomas since is routinely seen in normal basal cells of skin and other stratified epithelia, as well as in prostatic and respiratory epithelium. p63 is also a marker for myoepithelial cells of the breast. In primary cutaneous tumors the nuclear p63 labeling is seen in the outer layer of the proliferating basaloid cells, but not in the luminal cells of eccrine carcinomas while hidradenocarcinomas displays a more diffuse labeling of neoplastic cells.

This finding was also supported by other studies. Qureshi et al, studied 15 metastatic carcinomas to skin including 14 adenocarcinomas and 1 urothelial carcinoma. Only one of the adenocarcinomas had partial p63 expression, but as the authors mention, the case was actually represented by a poorly differentiated esophageal carcinaoma. In a more recent report of Sariya et al reports that when used as a single marker, a positive p63 stain has the highest sensitivity (96%) for primary adnexal tumors and a negative p63 stain has the highest positive predictive value for a metastasis. Kanitakis et al also reported that the large majority (88.5%) of primary skin tumors express p63 while 89% of the metastatic tumors to skin are p63-negative. Ivan et al also demonstrated that strong p63 expression is retained in the rare cases of metastases of cutaneous adnexal tumors with sweat duct origin to other skin sites or lymph nodes. Therefore, using p63 in a panel of immunohistochemical studies, may help in the differential diagnosis of metastatic adenocarcinoma to skin from primary cutaneous tumors with ductal differentiation.

Podoplanin (D2-40) has been also suggested that is not expresses by metastatic tumors with various origins (lung, breast, gastrointestinal or genitourinary tracts) but is positive in primary adnexal neoplasms. Calretinin, a calcium-binding protein expressed in mesothelial, epithelial and stromal cells, has been found positive in both metastatic tumors but also in some cases of primary cutaneous neoplasms. Thus, with the exception of the rare metastasis of mesothelioma to the skin, any lesions in the skin expressing calretinin are likely to be primary adnexal tumors.
Apocrine carcinoma is a unique and rare entity that is characterized by a deep seated infiltrative nodule of tubules, glands, and solid patterns of growth with abundant eosinophilic cytoplasm that, at least focally, shows apical snouting. This tumor is histologically and immunohistochemically identical to metastatic breast apocrine carcinoma and can only be distinguished by close clinical correlation.

Primary cutaneous mucinous carcinoma is an uncommon but well recognized sweat gland carcinoma of probable eccrine differentiation. It presents as an isolated, slow-growing nodule most commonly on the head and neck in older men. These neoplasms are particularly problematic because they are generally histologically identical to metastatic mucinous carcinomas, most commonly of the gastrointestinal tract, breast and rarely, ovary. Gastrointestinal mucinous tumors metastatic to the skin generally retain CK20 expression, which is not seen in primary cutaneous mucinous sweat gland carcinomas. Strong CDX-2 expression has been well documented in gastrointestinal metastases to other visceral organs, and has been observed in isolated cases of mucinous cutaneous metastases of intestinal origin by the authors. There has been only limited investigation into CDX-2 expression in mucinous tumors involving the skin. A recent study reported CDX-2 expression in 100% of four mucinous cutaneous metastases of gastrointestinal malignancies and in one of two cases of primary cutaneous mucinous carcinoma. Therefore, we hesitate to rely on this marker as its utility has not yet been fully determined in routine diagnostic work. We recommend looking for the “dirty necrosis” that characterizes intestinal adenocarcinoma, as well as the use of CK20 and CK7 immunohistochemistry. If an in situ component of the primary mucinous carcinoma does exist in the cross-sections examined, the basal cells will label for p63, helping for the differential diagnosis.

A special attention will be paid to the diagnosis of sebaceous carcinoma since it carries a significant rate of local recurrence and even distant metastasis and can be easily misdiagnosed, especially when is poorly differentiated or in small, superficial biopsies. Detailed description of histologic criteria for this diagnosis will be provided along with a review of special stains or immunohistochemical studies currently available to assist us in the differential diagnosis, such as Oil Red O, EMA, androgen receptors, D2-40, CK19, adipophilin, etc. Examples from our referral practice of challenging sebaceous lesions will be presented in the context of differentiating them for other tumors that either have focal sebaceous differentiation or have clear cell changes mimicking sebocytes.

Association of the sebaceous neoplasms with Muir-Torre syndrome (MTS) will be discussed and reveal histologic clues for this associations since is generally accepted that the sebaceous lesions in this context are often difficult to classify, showing overlap features between all the prototypic forms of sebaceous neoplasms, ranging from hyperplasia to sebaceous carcinoma. Muir-Torre syndrome (MTS) is an autosomal dominant disease defined by the coincidence of at least one sebaceous skin tumor and one internal malignancy. About half of MTS patients are affected by colorectal cancer. In a subgroup of MTS patients the disease has an underlying DNA mismatch-repair (MMR) genes defect (most often hMSH-2 and hMLH-1) and microsatellite instability and thus is allelic to hereditary nonpolyposis colorectal cancer (HNPPCC). The sebaceous lesions in patients with MTS can often precede or occur concurrently with the visceral neoplasms. The early recognition of those lesions and their differentiation from sporadic sebaceous gland tumors are critical for proper patient management.
SELECTED REFERENCES (not specific order)
Wallace ML, Longacre TA and Smoller BR. Estrogen and progesterone receptors and anti-gross cystic disease fluid protein 15 (BRST-2) fail to distinguish metastatic breast carcinoma from eccrine neoplasms. Mod Pathol. 1995;8:897- 901.