Primary Cutaneous Apocrine Carcinoma Versus Metastasis, A Plea to the Dermatopathology Community

To the Editor:

We have read with interest the report by Cangelosi et al on a rare cutaneous adnexal tumor with an unusual presentation.

In the report, the authors mentioned a metastatic breast carcinoma as their first challenging diagnostic alternative, because the patient had a history of invasive ductal carcinoma of the breast. Among the antibodies included in their immunohistochemical panel, they used mammaglobin, which failed to stain the tumor.

The authors also mentioned how the tumor showed conspicuous glandular differentiation, and although it was not shown at high power, it seems to us that figure 3A demonstrates some decapitation secretion in the ductular structures. This is not incompatible with the diagnosis proposed by the authors of porocarcinoma (a tumor thought in the past as "eccrine"). Recently, some groups have demonstrated apocrine features in poroid neoplasms.

The differential between cutaneous metastases from breast carcinoma and a primary cutaneous adnexal tumor is one of the most difficult tasks in the field of dermatopathology, and immunohistochemistry has only been partly helpful in solving this conundrum. In some instances, the expression of certain markers, may give a clue to the possible primary cutaneous tumor. That is the case of p63, one of the most promising markers in this respect. However, that is not always the case with cutaneous apocrine carcinoma (CAC), one of the most elusive primary cutaneous malignancies. CAC does not usually express p63, and its metastases are also commonly negative for such a marker.

In the past, it was suggested that the expression of estrogen receptors (ER)−, progesterone receptors (PR)−, and androgen receptors (AR)−, was very suggestive of an apocrine phenotype. However, Robson et al studied a large series of CACs and demonstrated that 62% were ER+, 60% were PR+, and 36% were AR−.

Something similar happened to the marker for gross cystic disease fluid protein 15 (GCDFP-15). It was once thought as a useful marker to detect neoplasms of mammary origin. In fact, many of the CACs reported have shown a weak and focal expression of GCDFP-15, or have failed to show any expression of the marker at all. This is despite the fact that GCDFP-15 is considered as a very specific marker for apocrine differentiation. Nevertheless, in a series, GCDFP-15 failed to mark 4 ductal breast carcinomas, whereas it marked the only CAC studied.

Other markers are, as well, of relative help when facing a possible CAC. Cytokeratin (CK) 5/6, for instance, is usually expressed strongly and diffusely by primary cutaneous adnexal neoplasms. On the contrary, only a small percentage of cutaneous metastases express CK 5/6 and they usually do it weakly. Nevertheless, we now know that breast carcinoma can express CK 5/6 and it usually carries a bad prognosis.

CK7 is another marker commonly used to differentiate between a primary cutaneous adnexal tumor and a metastasis: Focal CK7 expression is suggestive of a primary adnexal tumor, whereas diffuse immunostaining is mainly seen in metastases. Nevertheless, some have not found it useful, unless used as a part of an antibody panel. Moreover, CK7 can be strongly and diffusely expressed by primary CAC.

Epidermal growth factor receptor is another example in this long list. It was once demonstrated as more frequently expressed in sweat gland carcinomas than in breast carcinomas. Nevertheless, some series have demonstrated expression of epidermal growth factor receptor by up to 22% of their cases of primary mammary carcinomas.

One of the reasons why the differential diagnosis between metastatic breast carcinoma and primary CAC is so complex is that, as some authors have recently insisted, that the mammary gland is nothing but a modified apocrine gland. Despite this, there are some immunohistochemical clues that may help to solve this complicated problem.

We have recently used mammaglobin in a small series of CACs, with promising results in the differential with a metastatic breast carcinoma. In our study, breast carcinomas expressed diffusely and intensively the marker, whereas CAC showed only scattered positive cells. Nevertheless, nearly half of our breast carcinomas also showed the same immunostaining pattern as CAC. We therefore concluded that the marker had a great value when positive, then favoring a metastasis. On the contrary, a negative staining or one with only scattered positive cells would not be conclusive.

Our biggest limitation was the few number of CACs studied, because this is not a common tumor. For instance, a recent publication, involving several institutions from all over the world, achieved to collect 24 cases of CACs. Despite this difficulty, immunostaining with mammaglobin on a larger series of CACs would be of great interest to corroborate or deny the pattern of staining that we found. We have expectations about the possible forthcoming results.

Mammaglobin is a 93 amino acids protein, which originally was identified in breast carcinoma cell lines, and is secreted as a glycosylated peptide. Some have asserted that "mammaglobin does not seem to be a useful stain to distinguish breast from sweat gland carcinomas." The assertion by these authors was based on the expression of mammaglobin by 4/10 skin sweat gland carcinomas investigated. However, the expression was patchy (as in our study) in 2 cases. Moreover, the authors did not mention if the other 2 cases (which showed a diffuse pattern) were CACs or any other type of sweat gland carcinomas. This latter point is quite relevant: First, because CAC is usually the most difficult one to distinguish from a breast carcinoma. Second, because normal apocrine glands show a scattered expression of mammaglobin, whereas eccrine glands show strong cytoplasmic staining of the coiled cells. Therefore, it would be expected that allegedly eccrine tumors

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express mammaglobin in a strong way, whereas apocrine tumors do it in a scattered way. Nevertheless, to the best of our knowledge, the answer to that hypothesis is not known. Some reports on mammaglobin and sweat gland tumors have centered on allegedly apocrine tumors, such as hidradenoma papilliferum or apocrine hidrocystoma. Cylindroma did not show expression of mammaglobin or expressed the marker by a few small groups of cells. Therefore, this does not satisfactorily answer the question, because cylindroma has been alleged to be eccrine by some and apocrine by others.

We are planning to investigate some phenotypic and molecular aspects of CACs, which includes their mammaglobin expression. We need to collect as many cases as possible. Therefore, we would be grateful for any cases of CAC (paraffin block) which could be sent to our address during this current year, accompanied by minimal clinical information. Needless to say that all blocks will be returned.

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Sebaceous Carcinoma In Situ

To the Editors:

In a recent article, Kazakov et al described 5 cases of sebaceous neoplasms with architectural features of benignancy and cytological attributes of malignancy and stated that “the classification of such lesions as sebaceoma (with atypia) or sebaceous carcinoma remains unresolved.” This opinion is in contrast to that of Resnik, who reviewed the article and glass slides of the 5 neoplasms under discussion and did not agree with the authors’ assessment that these lesions cannot be classified as either sebaceoma or sebaceous carcinoma. In Resnik’s opinion, 4 of the 5 cases represent sebaceous carcinoma and 1 sebaceoma. Although we agree with
The Concepts of Carcinoma In-Situ and Carcinoma

To the Editor:

The correspondence titled “Sebaceous carcinoma in-situ”
touches upon an exceedingly important issue in dermato-pathology, that is, the differentiation of carcinoma in-situ from carcinomas that are no longer in-situ. That correspondence utilizes as a springboard for discussion both an article that presented a handful of neoplasms with sebaceous differentiation showing a discrepancy in criteria for determining malignancy/benignancy as assessed at scanning magnification from those discerned at high-power magnification and my published comments as reviewer of that work. Readers of this journal now have three different interpretations of the same collection of cases to contemplate: first, the original authors’ assessment that the neoplasms with sebaceous differentiation were not further classifiable as benign or malignant, second, my interpretation as reviewer of the original work that four were sebaceous carcinoma and one sebaceoma, and third, the conclusion that most, if not each of the five cases, are sebaceous carcinoma in-situ rather than sebaceous carcinoma. Irrespective of what this implies about the lack of uniform criteria for coming to a diagnosis for certain lesions in dermatopathology, the differentiation between carcinoma in-situ and carcinoma is not merely a semantic distinction for the following reason: carcinomas in-situ lack the capability to metastasize once they have been completely removed, whereas carcinomas that are not in-situ possess that potential. This difference has far-reaching implications for patients and clinicians who manage them.

How does a histopathologist make the determination that a carcinoma is in-situ? Drs Kramer and Chen utilize the features of “well circumscribed with smooth borders” as an indication that the carcinoma is “still confined in epithelium,” that is, it is an in-situ carcinoma. Judging from the size of the neoplasms with sebaceous differentiation that are being discussed, Drs. Kramer and Chen accept lesions that are strikingly larger, and even scores larger, than the original structures they purportedly have replaced (Fig. 1 reprinted from original article). In coming to a diagnosis of sebaceous carcinoma in-situ, Drs. Kramer and Chen use analogous findings to those for in-situ carcinomas in breast pathology. I apply different criteria for determining whether a cutaneous neoplasm is still in-situ. In my view, if a carcinoma alters the original cutaneous epithelial structure so that it can no longer be recognized as the original structure, it is no longer in-situ. The neoplasms being discussed (Fig. 1) show no evidence of

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pre-existing sebaceous lobules or follicular epithelium, therefore, I render a diagnosis of carcinoma rather than carcinoma in-situ. I fully accept that carcinomas in-situ may increase the dimensions of the pre-existing epithelial structure they occupy; however, in these neoplasms with sebaceous differentiation I see no evidence of such structures. I do not dispute the notion of sebaceous carcinoma in-situ; I just disagree with that assessment for these specific neoplasms. For me, the presence of sebaceous ducts and/or individual sebocytes is not confirmation of arising within pre-existing epithelium but instead findings indicative of sebaceous differentiation. I also do not use circumscription or smooth borders as distinguishing criteria between carcinoma in-situ and carcinoma because both of those features may also be seen in carcinomas that are clearly not in-situ, for example, some nodular pattern basal-cell carcinomas or squamous-cell carcinomas that extend into the deep dermis or subcutaneous fat. In no way am I implying that carcinomas in-situ do not extend into deep dermis or subcutaneous fat. Instead, I fully recognize that phenomenon and alert clinicians to it with a comment in the pathology report along the lines of “the lesion extends to the base of the sections/into subcutaneous fat via involvement of adnexal epithelium” because the depth of in-situ involvement has clinical relevance.

In sum, the differentiation between carcinomas that are in-situ and those that are no longer in-situ is more than an intellectual debate because of the different clinical implications of these diagnoses. The criteria I set forth for distinguishing between carcinoma in-situ and carcinoma may or may not be universally employed by dermatopathologists, but I have found that in daily practice they are easily applicable and serve clinicians and patients well.

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What is Extraocular Cutaneous Sebaceous Carcinoma In Situ?

To the Editor:

We thank Drs. Kramer and Chen for their interest in our article published in this Journal. The authors raise a valid question as to why the term in situ carcinoma cannot be applied to cutaneous sebaceous neoplasms. They also rightfully cite the definition of carcinoma in situ, which is a malignant epithelial neoplasm confined within the epithelium of origin. The main question is: What is the origin for cutaneous sebaceous carcinoma? Whereas in periorbital sebaceous lesions, it is accepted that sebaceous lesions arise from meibomian glands and glands of Zeis, sebaceous glands elsewhere in the skin practically never appear to give rise to a sebaceous carcinoma. In our files we have over 100 unequivocal extraocular sebaceous carcinomas, and in none of them is there evidence that the tumor has arisen from a preexisting sebaceous gland in a manner analogous, for example, to an invasive squamous carcinoma for which intraepithelial precursor lesions including actinic keratosis and Bowen disease (squamous cell carcinoma in situ) are typically found. We have seen a limited number of intraepidermal sebaceous carcinomas (Fig. 1), not extending beyond the epidermal basement membrane and lacking any association with sebaceous gland. Such lesions qualify as sebaceous carcinoma in situ and their features indicate that they have originated from epidermis, and that the original basement membrane at the dermoepidermal interface is intact. It is our view that the term “sebaceous carcinoma in situ” is valid only for a vanishing minority of sebaceous neoplasms and in most of these it is not possible to determine their precise origin (viz. sebaceous gland vs. epidermis) let alone assessing accurately whether the original basement membrane has been breached. Therefore, we would discourage the use of the term “sebaceous carcinoma in situ” for other sebaceous tumors.

Our article intended to highlight the existence of a small group of cutaneous sebaceous proliferations wherein the distinction between malignant and benign may be difficult and we accept that opinions on their classification may vary. The current approach in dermatopathology is to classify sebaceous lesions as benign or malignant. However, in sebaceous tumors attempting to classify accurately all lesions into either of these 2 categories may be an oversimplification of the problem. Some sebaceous tumors have a symmetrical silhouette similar to other benign adnexal tumors and they behave in a benign fashion despite having clearly malignant cytologic features. It is important to state that a similar situation can be seen infrequently in other adnexal tumors such as trichoblastomas and pilomatrixomas.

We disagree with Drs. Kramer and Chen that the 5 cases we reported are better classified as sebaceous adenoma. Sebaceous adenoma has completely different architectural and cytologic features. It has a distinctly multilobular architecture with several contiguous lobules usually showing connection to the overlying epidermis and replacing the squamous cells. The lobules vary in shape, sometimes even within a single lesion and there is a pushing, sharply

FIGURE 1. Sebaceous carcinoma in situ. The tumor is wholly intraepidermal and does not extend beyond the preexisting basement membrane (A). There are more and less differentiated areas (B).
The Dysplastic Nevus Controversy: It Is Not About the Nevus per se But One’s Belief in the Multistep Tumorigenesis Theory

To the Editor:

There has been long-standing controversy and heated debate concerning the validity of the term dysplastic nevus. In examining the pros and cons of the argument, one will find that the debate is not really about what one observes with his or her eyes both clinically and microscopically, but what one believes. Those who believe in the sequential multistep tumorigenesis theory will defend the term and concept of dysplastic nevus with might and passion. By contrast, those who do not believe in the multistep tumorigenesis theory will dismiss dysplastic nevus as a bogus term and concept.

The multistep tumorigenesis theory assumes that tumor develops via a sequential multistep process, such as from normal melanocytes to hyperplasia to nevus to dysplastic nevus and eventually to melanoma. Many believe this is true and hold the view that the multistep tumorigenesis theory has been proven scientifically. It is therefore appropriate to examine the literature critically in this regard.

When the term dysplastic nevus was first introduced by Greene et al in 1980, they believed that dysplastic nevi were precursors of cutaneous melanoma and stated that they “fit nicely into the schema of progression from hyperplasia to dysplasia to neoplasia that is accepted in many epithelial tumor systems, both experimental and human.”1 Here “the schema of progression” refer to the sequential multistep tumorigenesis theory often attributed to Leslie Foulds. However, acceptance does not equate with scientific proof. The reference Greene et al cited in support of their above statement is a review article dedicated to Leslie Foulds by Farber and Cameron published in 1980.2 If one reads this article critically, one will find that there was really no solid data in support of the multistep tumorigenesis theory. It was more speculative rather than evidence based.

The frequently cited contemporary article in support of the multistep tumorigenesis theory is a paper published by Fearon and Vogelstein in 1990.3 Vogelstein and colleagues have devoted decades in an attempt to validate the multistep tumorigenesis theory at the molecular level using colorectal neoplasia as a model system. They proposed a genetic model for colorectal tumorigenesis with a diagram depicting progression from normal epithelium to hyperproliferative epithelium to early adenoma to intermediate adenoma to late adenoma to carcinoma and then to metastasis with corresponding genetic alternations (Fig. 3 in the paper). This diagram has been reproduced and cited as evidence in support of the multistep tumorigenesis theory in popular textbooks, such as Rosai and Ackerman’s Surgical Pathology.4 However, if one carefully reads the original article,5 one will find this article is really mis cited, the data did not validate the multistep tumorigenesis theory at all. The authors stated in that article that their proposal of the genetic model for colorectal tumorigenesis is “rudimentary” and actually indirectly refuted the multistep tumorigenesis theory by declaring that “accumulation, rather than order, is most important.”

I was a firm believer of the multistep tumorigenesis theory. However, after critical review of literature, I came to a conclusion that there are no solid data supporting this theory. Most, if not all, tumors develop via a nonsequential stochastic process. At the molecular level, neoplasms are basically genetic diseases, involving alteration in DNA, such as deletion, substitution, insertion, or translocation. These genetic alterations are nonsequential and stochastic. There are no intermediate lesions between nevus and melanoma, only lesions that we are unable to classify into either of these categories based on histopathologic criteria. Dr. Bernard Ackerman summed it up well in these words: “In the realm of melanocytic neoplasms, there are only four possible answers: nevus, melanoma, melanoma in association with a nevus, and ‘I don’t know.’”6

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Uncertainty in Diagnosis

To the Editor:

Mark A. Hurt is opposed to statements such as Elder and Xu’s “Melanocytic Tumor of Uncertain Malignant Potential” because “a diagnosis is a statement of certainty,” whereas “certainty is a concept that refers to the identification of facts that, taken together, mean something specific, given a context of knowledge in a given discipline in a given timeframe in which the knowledge was discovered.” Does Dr. Hurt believe that a competent astrologist’s report deserves the label of certainty? The “Hurt’s certainty” of Hurt looks like belief to me. Although it would be nice to know what was in physicians’ minds when they diagnosed melanomas, ordered and performed amputations for lesions now called Spitz nevi—some may have been skeptical as the well circumscribed Spitz nevi do not look clinically like typical melanomas—this is not the Psychology Review. The identification of typical histologic features of melanoma means malignancy in our accepted standard of practice, but we cannot know how many of our “melanomas” are benign lesions having acquired after UV exposure, trauma, or inflammation, misleading histologic features of malignancy, or how many of our “nevi” are nevoid melanomas excised by a wise dermatologist before metastatic spread. Melanocytic Tumor of Uncertain Malignant Potential is not a statement of certainty but a statement of truth, unfortunately of limited value. A diagnosis of malignant melanoma means a range of outcomes, that is, the difference between “malignant” and the statements of risk or potential such as “Uncertain Malignant Potential” Hurt want to banish as meaningless is not that big. The practical difference has shrunk because melanoma excisions are more conservative, adjuvant systemic agents have yet to be successful, and denial of insurance coverage for pre-existing condition is now prohibited in the United States.

Hurt defends the benign/malignant dichotomy against “the premise that all diseases exist on a spectrum and that the terms “benign” and “malignant” should be relegated to the dustbin of history to be replaced with the term “low risk,” “high risk” and various risks within these 2 extremes. Worse yet is the preposition that the spectrum consists of benign neoplasms “transforming” into malignant ones, which is a sure sign of a mind out of focus. My wife applauds the diagnosis but I still believe that congenital nevi can occasionally transform into melanomas. I even believe that these concepts— the benign/malignant dichotomy, the low-risk/high-risk spectrum—are too focused. I would say that neoplasms come in different flavors and that a good/bad dichotomy or a faint/strong spectrum are insufficient. The malignant Spitz tumors we cannot reliably identify seem different than conventional melanomas of same Breslow depth or same level of nodal involvement. Prognosis and mutations are not the same. Ackerman’s dichotomy—Spitz nevus/melanoma—is reductive. The next article in the same issue illustrates perfectly why uncertainty should be emphasized. Mistakes happen, even to great pathologists. In the lawsuit, the plaintiff experts often deny uncertainty. In Ackerman case a focus a melanoma in a benign nevus, they stated that the patient had a “85.6% chance of 8-year survival” and a “98% chance of cure.” If they know so much why don’t they provide such details in their own diagnostic reports? In a lawsuit I witnessed, an unknown “expert” provided a precise growth rate and quite high chance of survival had the melanoma been diagnosed some 4 months earlier at the first opportunity to do the biopsy. Instead of waiting for congressional action on medical malpractice, American Societies of Dermatology and Dermatopathology could evaluate the state of uncertainty in prognosis and diagnosis. Like the authorities occasionally trying to smuggle forbidden items through the controls, they could also disguise as another consultation slides of routine or difficult cases with known outcomes and establish average and individual error rates teaching a precious lesson especially to the weakest among us. Uncertainty should be acknowledged, evaluated, and reduced instead of hidden, ridiculed, or denied. This evaluation is difficult. Excision of nevi or melanomas for histologic evaluation influences their history in a manner reminiscent of Heisenberg uncertainty principle. However, molecular pathologists may be able to look for markers of melanomas in archival blocks and evaluate our false-positive and false-negative rates. The Hurt’s distinction between diagnosis and prognosis, potential, or risk is spurious. Only indicating a risk, tuberculin test, HIV-1 enzyme-linked immunosorbent assay or Venereal Disease Research Laboratory test are proper diagnostic tools because they are evaluative (relative costs, risks, sensitivity, and specificity indicate whether they are used as screening or confirmatory tests or superseded) and correspond to modern concepts of pathophysiology. Charlatans, shamans, traditional healers do make diagnoses, but their approach lack these features. On which side are we?

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Response of Mark A. Hurt, MD, to Dr. Dumas on “Uncertainty in Diagnosis”

To the Editor:

To answer Dr. Dumas directly, astrology is a mystical fantasy just as Melanocytic Tumor of Uncertain Malignant Potential (MELTUMP) is a mystical fantasy, made up from “whole cloth” to place the burden of the diagnosis on the lesion in question rather than the understanding of the interpreter. If “belief” means that one observes facts in nature then integrates those facts into concepts by a process of reason, then sure, a diagnosis is a form of belief; but it is reasoned belief based on a process of thought, based on facts in nature, rather than utter contempt for belief and for facts, which is what MELTUMP represents.

In contrast with the viewpoint of Dr. Dumas, MELTUMP is a statement of uncertainty, but it is not a diagnosis. This is the point, and this is why it should never be codified into the literature as a diagnostic concept.

As for the “transformation” of benign lesions into malignant ones, this is pure fantasy, too. Lesions do not “transform,” but individual cells do. Whatever occurs in cells that become ultimately a malignancy is utter conjecture at this point. It is, thus, not true that nevi become melanomas; else, there would be no point of the concept of a nevus: every melanocytic lesion would be a melanoma. In nature, there are only three possibilities: nevus, melanoma, and nevus in conjunction with melanoma. In the mind, there is a fourth possibility: I do not know.

I will grant one point to Dr. Dumas. There are lesions about which one is uncertain. I agree fully with this. The point that I do not agree with is the fact that the lesions of which I am uncertain have no natural history; they do. This is the problem: I do not know the natural history of some lesions I observe. This is not the same as a melanocytic lesion with an uncertain malignant potential; there is no such lesion.

I wonder if Dr. Dumas really read and thought about my article on “Diagnosis! (Not Prognosis, Not Potential, Not risk).” I don’t believe he did.

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