

Letters to the Editor

CORRESPONDENCE RE: BONETTI F, MARTIGNONI G, COLATO C, MANFRIN E, GAMBACORTA M, FALERI M, ET AL. ABDOMINOPELVIC SARCOMA OF PERIVASCULAR EPITHELIOID CELLS. REPORT OF FOUR CASES IN YOUNG WOMEN, ONE WITH TUBEROUS SCLEROSIS. MOD PATHOL 2001;14: 563–8. AND TAZELAAR HD, BATTS KP, SRIGLEY JR. PRIMARY EXTRAPULMONARY SUGAR TUMOR (PEST): A REPORT OF FOUR CASES. MOD PATHOL 2001;14:615–22.

To the Editor: We read with interest the recent articles of Bonetti *et al.* (1) and Tazelaar *et al.* (2), describing two novel members of perivascular epithelioid cell (PEC) tumors. Bonetti *et al.* used the term “Abdominopelvic Sarcoma of Perivascular Epithelioid Cells” to describe a group of lesions having distinguishing features such as clinical presentation, metastatic spread, focal pseudopapillary pattern of growth, and frequent presence of intracytoplasmic melanin pigment. Tazelaar *et al.*, although they agree with the concept of “PEComa” (3), proposed the acronym PEST (Primary Extrapulmonary Sugar Tumor) for their neoplasm because of the similarities with clear cell “sugar” tumor of the lung and the putative aggressive behavior of some cases. In reading these papers, we got the impression that both the authors were describing the same lesion, but with two different names and in different locations. This became more clear when we compared their findings. In both papers, these lesions occurred in young to adult females (except for one male patient in Tazelaar *et al.*'s series) and were characterized by sheets of uniform, large epithelioid cells separated by a rich network of sinusoidal-type capillaries. The cells had abundant, clear to eosinophilic cytoplasm containing glycogen and showed a round to oval nucleus with occasional prominent nucleoli. A varying percentage of cells with intracytoplasmic brown pigment was present in two cases from Bonetti *et al.*'s series (identified as melanin pigment) and in one case reported by Tazelaar *et al.* (identified as hematoidin pigment). All the cases described by Bonetti *et al.* and one case by Tazelaar *et al.* behaved in a malignant fashion and displayed areas of necrosis, vascular invasion, and rare to numerous mitotic figures. Three cases from the Tazelaar *et al.* series were apparently benign (follow up median: 22.6 months; range 6–48 months), and histologically they showed only rare mitotic figures without necrosis. Immunohistochemically, all cases were strongly reactive for HMB-45, and two of four cases from the Bonetti *et al.* series stained with MART-1. One case reported by Bonetti *et al.* was associated

with tuberous sclerosis. Both authors considered in the differential diagnosis malignant tumors such as clear cell carcinoma of the kidney, malignant melanoma, and clear cell sarcoma. Moreover, both believed their cases showed many similarities with the malignant pigmented clear cell epithelioid tumor of the kidney recently described by Ribalta *et al.* (4). By this point, we were somewhat puzzled by the terminology adopted by the authors. What should we call morphologically similar lesions that we encounter in our practice? The group of pathologists of Verona first introduced the term PEComa to describe a family of tumors including angiomyolipoma (AML), clear cell “sugar” tumor of the lung, and lymphangiomyomatosis (LAM), all of which were composed of a pure proliferation of PECs and characterized by the same morphological, immunohistochemical, and ultrastructural features (3). The morphological features of PECs ranged from a smooth muscle spindle cell (LAM) to an epithelioid element (monophasic epithelioid AML), with classical AML representing the typical example of PEComa, in which all the morphophenotypes of PEC became evident. Although early papers described these tumors as being site-related (AML occurring in the kidney, clear cell “sugar” tumor and LAM in the lung), more recent reports considerably widened the spectrum of these lesions, identifying them in different extrarenal (5) and extrapulmonary (3, 6, 7) sites. Although once considered benign lesions, many case reports of malignant transformation of AML (8, 10) and clear cell “sugar” tumor (9) have been published. A recent review of renal epithelioid AML (10) confirmed the existence of malignant AML and showed that necrosis and mitoses (mainly atypical) seem to be predictive of a malignant clinical course. However, definitive minimal criteria for the diagnosis of malignancy cannot be assessed due to the paucity of cases reported. We believe that neoplasms originating from PECs, similarly to those derived from other cell types, can be benign or malignant, and the cases reported by Bonetti *et al.* and one case from Tazelaar *et al.*'s

series represent examples of malignant extrarenal PEComas.

Acknowledging the existence of a morphophenotypical modulation of PECs and the wide anatomical distribution of PEComas, we believe that extrarenal and extrapulmonary localization, focal papillary-like and pseudoglandular appearance, presence of melanin pigment, and malignant behavior should not be enough to justify new, confusing terminology.

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In reply: We would like to thank you for the interest shown in our work (1). The issue you address is indeed of great importance. The need for a well-defined and uniform terminology is of major importance to avoid confusion and allow the collection of a homogeneous group of cases.

However, some lesions composed of Perivascular Epithelioid Cells (PEC) have been only recently identified, and new data are accumulating rapidly. On the other hand, other lesions related to PEC have been described and are known with well-established names (*e.g.*, angiomyolipoma, lymphangiomyomatosis, etc).

The new lesions are of difficult denomination when the old terminology is used. This often leads to oxymorons such as Malignant Benign clear cell “sugar” tumor or extrapulmonary clear cell “sugar” tumor of the lung.

It is possible that the different terminology suggested might be due to the different areas of expertise of the pathologists describing these rare lesions. A pulmonary pathologist will prefer to call extrapulmonary clear cell sugar tumor (2) what a

uropathologist will probably call extrarenal epithelioid monotypic angiomyolipoma. Hopefully, new data will help us to better understand and classify these lesions in the near future. Although we believe that angiomyolipoma and pulmonary lymphangiomyomatosis are composed of PECs in different stages of modulation (3), we think that it is better to continue to name them with their well-established names, which identify their clinical and morphologic aspects and are well known by clinicians and pathologists.

On the other hand, we propose to name PEComas all other lesions composed of PECs, in the epithelioid, spindle, and lipid-rich forms.

The term PEComa is not committal as far as the biological behavior is concerned. The criteria for malignancy are not yet well defined. We are now collecting a large group of cases to better define the prognostic criteria. However, it is already apparent that a gray zone exists where prognosis cannot be defined with certainty.

The case described by Sale and Kulander (1988) (4), reporting a “benign” sugar tumor, which developed hepatic metastases after 10 years, should be a warning against an easy approach to the definition of the prognosis of these lesions.

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In reply: We appreciate the interest in tumor nomenclature shown by Drs. Nuciforo and O’Hara prompted by recent articles of Bonetti *et al.* (1) and us (8). We agree with their observation that the two articles describe the same lesions, *i.e.*, tumors composed primarily of perivascular epithelioid cells (PECs) having an HMB-45 positive immunophenotype. We also agree with the observation by Drs. Nuciforo and O’Hara that a melange of potentially confusing terms has been applied to these tumors. This raises an issue greater than just the “PEComa” one and leads to philosophical arguments about how to name new entities and whether to change old, familiar names as new knowledge is obtained. As poet Dana Gioia has said “to name is to know and to remember (2).” As a corollary, the goal of having an appropriate name should be to communicate succinctly to the clinician what the tumor is and how it is expected to behave. The name should be unique, unambiguous, and preferably easy to communicate. With this background, we are happy to share our thoughts about appropriate terminology for “PEC” tumors.

While the term “PEComa” is certainly unique, it was initially used by Zamboni and colleagues to describe “a family of lesions characterized by a pure proliferation of perivascular epithelioid cells” (9). In our opinion, the term “PEComa” is undesirable on several accounts. It is ambiguous, its form has little precedent in the literature, and a new term is being introduced when we believe that a satisfactory name for this tumor has existed for 30 years.

First, it is not clear whether the term should be restricted to tumors purely composed of “PECs” (as implied by Fig. 5 in Ref. 9) or whether the term should be more broadly applied to include angiomylipoma, and lymphangiomyomatosis as well, as apparently understood by Drs. Nuciforo and O’Hara in their letter—“. . .the term ‘PEComa’

to describe a family of tumors including angiomylipoma, clear cell ‘sugar’ tumor of the lung, and lymphangiomyomatosis. . .”

We are also unaware of any precedent in the solid tumor literature of nouns being derived from acronyms by adding the “-oma” suffix. For example, gastrointestinal stromal tumors are well recognized, but these have not been called “GIS-Tomas.” Although among hematologic diseases, the term “MALToma” is used colloquially, such terminology has not been incorporated into recent classification schemes (3, 4). In these examples, the letter “T” referring to “tumor” implies a neoplastic lesion, making an “-oma” redundant. By analogy, Bonetti and colleagues could have suggested the acronym “PECT” instead.

Additionally, when used restrictively, the term “PEComa” renames a well-established tumor type. Leibow used the term “sugar tumor” in 1971 (6) after having earlier used the non-unique name “clear cell tumor” in 1963 (5) to describe the same tumor. In the 1996 article in which the term “PEComa” was introduced, Bonetti and colleagues presented a pancreatic tumor composed of “PECs” and proposed naming this new entity “clear cell ‘sugar’ tumor of the pancreas. . .” (9). It is not clear to us either why Bonetti and colleagues apparently no longer use the term “sugar” tumor or use the term “PEComa” anywhere in their recent article (1). Instead, they have introduced yet another term for a neoplasm of such cells—“abdominal pelvic sarcoma of perivascular epithelioid cells” (1). Furthermore, the latter term suggests that malignant variants of such tumors may occur only in the abdominopelvic region. As reported by us, they can occur elsewhere (8).

Lastly, we should not underestimate the utility of easily pronounceable names for the purposes of verbal communication. In using the term “PE-

Coma” in conversation, should we say “peek-oma” or “peck-oma”?

In summary, in our opinion, there is a “PEC” family of tumors containing PECs that demonstrate HMB-45 reactivity. Examples of tumors composed purely of PECs are best given the unambiguous name “sugar tumor.” The modifier “primary extrapulmonary” was used by us to emphasize that these tumors are not restricted to the lung (and it resulted in the catchy acronym—“PEST”). However, we will acknowledge that the modifier would probably be unnecessary once there was more widespread knowledge that these tumors are not restricted to the lung. The terms angiomyolipoma and lymphangiomyomatosis should be retained for tumors or proliferations having the classic histologic features of each. The modifiers “epithelioid” could be applied when warranted (7). For any of the above, if malignant examples are encountered, adding the prefix “malignant” seems simplest, as is done with gastrointestinal stromal tumors.

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