Time to abandon the term angiomyolipoma for non-PEComatous angiomyomatous (or angiomatous) oral tumors with adipocytes

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Angiomyolipoma (AML) is the most common benign mesenchymal neoplasm of the kidneys with well-established clinical and morphological features. The oral and maxillofacial pathology literature contains several examples that identify angiomyomatous proliferations of the oral mucosa that contain an adipocytic component as analogous to classic renal AMLs although they differ significantly in their immunohistochemical phenotype. Herein, through review of the pertinent oral pathology literature and the detailed description of 2 lesions, one an oral angiomyoma with an adipocytic component and the other an apparently hamartomatous angioleiomyomatous proliferation with adipocytes, we provide, in our opinion, a solid argument against the use of the term AML for non-PEComatous oral tumors. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:492-497)
there are only 2 well-documented cases of oral PEComas, one reported by Koutlas et al.\(^2\) on the palate of a 46-year-old woman, the other by Accurso et al.\(^3\) on the lower lip of a 58-year-old male.

We describe 2 oral tumors presenting a mixture of blood vessels, smooth muscle cells, and mature fat cells, compare them with previously reported oral AMLs, and argue against the use of the term AML for non-PEComatous oral lesions.

**CASE 1**

A 78-year-old otherwise healthy male presented with a painless lump of the upper lip of 1-year duration. His medical history was noncontributory. Clinical examination showed a 0.7-cm round submucosal mass just left of the upper lip midline. On palpation it gave the impression of a fluid-filled cavity and was covered by normal mucosa. It was surgically excised with a provisional diagnosis of mucocele. The postoperative course was uneventful and 6 months after excision no recurrence has been reported.

**Fig. 1.** Tumor composed of thick-walled blood vessels with abnormal shape and bundles of intensely eosinophilic smooth muscle cells (hematoxylin and eosin [H&E], original magnification \(\times 100\)).

**Histologic sections showed a tumor composed of thick-walled blood vessels, bundles of intensely eosinophilic smooth muscle cells radiating from the vessels’ walls, and small group of mature fat cells (Fig. 1). The final diagnosis was angio(leio)myoma with an adipocytic component.**

**CASE 2**

A 19-year-old otherwise healthy female presented with an enlargement of the right cheek of unknown duration. Clinical examination revealed a freely movable submucosal mass of elastic consistency that was covered by normal mucosa. Ultrasonographically, it was consistent with lipoma. The tumor was surgically excised under local anesthesia. The postoperative course was uneventful and 4 years after surgery no recurrence has been reported.

**Fig. 2.** Tumor composed of blood vessels, bundles of smooth muscle cells, and groups of fat cells (H&E, \(\times 200\)).

On microscopic examination, an ill-defined and unencapsulated tumor was appreciated. It was composed of blood vessels, bundles of smooth muscle cells, and groups of fat cells (Fig. 2). Blood vessels were mainly thin walled and capillary size, whereas some medium-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Duration, y</th>
<th>Maximum dimension, cm</th>
<th>Follow-up, mo</th>
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<tr>
<td>Gutmann et al. 1975(^{11})</td>
<td>39</td>
<td>M</td>
<td>Hard palate</td>
<td>2</td>
<td>1</td>
<td>84 FOD</td>
</tr>
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<td>Yamamoto et al. 1995(^{12})</td>
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<td>F</td>
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<td>1</td>
<td>12 FOD</td>
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<td>F</td>
<td>Lower lip</td>
<td>10</td>
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<tr>
<td>Redman et al. 2001(^{14})</td>
<td>43</td>
<td>M</td>
<td>Palate</td>
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<td>Lower lip</td>
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<td>F</td>
<td>Hard palate</td>
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<td>1</td>
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<tr>
<td>Alvarez Alvarez et al. 2007(^{18})</td>
<td>43</td>
<td>F</td>
<td>Upper lip</td>
<td>6</td>
<td>2</td>
<td>48 FOD</td>
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<td>Koizumi et al. 2008(^{19})</td>
<td>52</td>
<td>M</td>
<td>Hard palate</td>
<td>n/a</td>
<td>n/a</td>
<td>a/a</td>
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</tbody>
</table>

\(n/a\), not available; M, male; F, female; FOD, free of disease.
sized vessels with muscular walls were seen in the periphery of the lesion. Discrete, small bundles of smooth muscle were close to but not associated with the vascular walls and groups of mature fat cells. Smooth muscles were enhanced by Masson trichrome stain. No epithelioid cells were present. The final diagnosis was angioleiomyolipomatous hamartoma.

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Both cases were studied immunohistochemically using the streptavidin-biotin-peroxidase processing of the Ventana BenchMark XT fully automated slide preparation system (Ventana Medical Systems Inc., Tucson, AZ) and using the iView DAB detection kit (Ventana). Appropriate positive and negative controls were used according to the instructions of the antibodies’ manufacturers. In both cases the smooth muscle component was intensely positive for smooth muscle actin (asm1, 1:100; Novocastra, Newcastle upon Tyne, UK) (Fig. 3, A and B). Case 1 was positive for desmin (DER-11, 1:100; Novocastra) (Fig. 4) and case 2 negative. Adipocytes stained for S-100 protein (polyclonal, 1:100; Novocastra) (Fig. 5), whereas Factor VIII-related antigen (BGX016A, 1:50; Biogenex, San Ramon, CA) outlined the vessels. No reactivity was seen for HMB-45 (HMB45-CE, 1:25; Novocastra) and Melan-A (A103, 1:25; Dako, Carpinteria, CA).

DISCUSSION
Eble\(^6,\text{p21}\) has stated that “the name angiomyolipoma is one of the most accurately descriptive (terms) in pathology.” Thus, it is reasonable that it is applied to tumors showing a variable proportion of abnormal thick-walled blood vessels, spindle and epithelioid smooth muscle cells, and fat cells. Bonetti et al.\(^10\) in 1994 established renal AML as a member of the PEComa group of tumors that are characterized by their immunoreactivity for both melanocytic and smooth muscle markers, in particular HMB-45 and muscle-specific actin.\(^1,3,5\) Consecutive studies showed that HMB-45 is not diagnostic of renal and extrarenal AMLs, as HMB-45–negative AMLs were found in the

Fig. 3. A (Case 1), Smooth muscle bundles positive for actin (ABC-hematoxylin, original magnification ×200). B (Case 2), Smooth muscle bundles positive for actin (ABC-hematoxylin, original magnification ×400).

Fig. 4. Smooth muscle bundles positive for desmin (ABC-hematoxylin, original magnification ×200).

Fig. 5. (Case 2) Adipocytes exhibiting S-100 reactivity (ABC-hematoxylin, original magnification ×200).
CD10.30 negative but featured positivity for Melan-A and other reported oral example was reportedly HMB-45 revealed also immunoreactivity with this antibody. The oral AMLs or to site-specific differences.13,17 The former HMB-45 negativity to the scarcity of epithelioid cells in such description40 among the more than 100 cases of an adipocytic component and although there is only one of the head in the study of Hachisuga et al.39 featured in angiomyomas. Sixteen of 48 (33.3%) angiomyomas with a fat component re-

HMB-45 staining varied, being more prominent in ep-
thesioloid cells.29 However, elongated spindle cells re-

vealed also immunoreactivity with this antibody. The other reported oral example was reportedly HMB-45 negative but featured positivity for Melan-A and CD10.30

In case 1, tumor circumscription and growth of the smooth muscle cell component circumferentially to thick-walled blood vessels is consistent with angio-

myoma (vascular leiomyoma) with mature fat cells. Fat cells of previously reported “oral AMLs” were also mature. They were found singly12,18 or in small groups,11,14,16,18 and anisocytosis was described in one case.13 Groups of mature adipocytes are not uncommon in angiomyomas. Sixteen of 48 (33.3%) angiomyomas of the head in the study of Hachisuga et al.39 featured an adipocytic component and although there is only one such description40 among the more than 100 cases of oral angiomyomas reported so far, it is possible that small groups of adipose tissue have been overlooked, as they should not be of diagnostic importance.

Authors have previously suggested that “oral AMLs”12,19,29,41 and skin AMLs42 are, in fact, vascular leiomyomas with a fat component. Absence of fat from the surrounding tissues14 and “lipoblastlike cells”12 have been stated as evidence against fat entrapment in vascular leiomyomas. However, adipose tissue is unanimously present in the oral mucosa and submucosa, whereas lipoblastlike cells are not a feature of renal AML. Immunohistochemically, fat cells were S-100 negative in one case of “oral AML” not tested for HMB-45,16 whereas in 4 other cases, they were S-100 positive.12,13 In renal AMLs, adipocyticlike cells may infrequently be S-100 positive and it is proposed that S-100(–), HMB-45(+) clear cells may represent PECs undergoing lipid degeneration.1,6

In case 2, the tumor was ill defined and vascular, similar to the angioymolipomatous hamartoma of the tongue reported by Ide et al.41 In contrast to the latter, however, the smooth muscle bands were close to, but not associated with, thin-wall capillary-size blood vessels, and medium-sized vessels with thick walls were seen only in the periphery of the tumor. Some authors11,19 characterize their “oral AMLs” as hamarto-

tos, too, but it should be noted that those publications appeared in an age that renal AML was believed to be a hamartoma. Furthermore, in one of those cases11 certain microscopic features are more reminiscent of venous or arteriovenous hemangioma with adipocytes and we feel that additional purported examples of “oral AMLs” may represent that entity.

Desmin negativity in some “oral AMLs” was con-
sidered indicative of perivascular origin of the smooth muscle component.12 There are, however, examples of desmin-positive oral “AMLs.”13,17,18 Heterogeneity for desmin is common in smooth muscle cells of blood vessels and is contributed to the antibodies applied,43 or the size and the anatomic location of the vessels.44

Although the diagnoses in our cases are straightforward, for the sake of differential diagnosis the possibilities of angiolipoma and myolipoma could have been considered. In angiolipoma, mature adipose tissue intermingles with thin-walled capillary-size vessels, as seen in case 2.45 A few cases have been reported in the oral cavity, but in none of them was there a smooth muscle component. Also, fibrin clots, considered diagnostic in angiolipoma, were not found in our case.45 As far as myolipoma is concerned, a rare oral example has been reported.46 Such tumors are composed of mature smooth muscle and adipose tissues. However, they lack the medium-sized thick-walled blood vessels seen in case 1, whereas in contrast to case 2 the smooth muscle component is dominant and arranged in short fascicles of slender smooth muscle cells forming a sievelike pattern with blending groups of mature adipocytes.47

Apart from the stated differences, and with the ex-
ception of a poorly documented alleged example arising in the lip of a 55-year-old woman,15 no reported cases of so-called oral AML have been associated with tuberous sclerosis complex. All tumors have behaved in a benign fashion, without recurrence after conservative excision. The vast majority of renal AMLs are benign neoplasms. However, they can predispose to life-threatening complications, the most significant being hemorrhage. Extrarenal AMLs reported in a variety of tissues and organs, including retroperitoneum, mediastinum, liver, adrenals, ovary, and lungs, are uncommon and can cause complications including hemorrhage and hy-
povolemic shock, and interference with major vessels as well as problems in surgical management.

In conclusion, it is our opinion that the term AML has been used deliberately in the oral and maxillofacial pathology literature to describe lesions characterized by smooth muscle or angiomatosus proliferations with an adipocytic component. Such cases are either vascular leiomyomas, venous/arteriovenous hemangiomas, or hamartomas. More importantly, many cases of oral “AML” have been discussed as counterparts of renal AML, a form of PEComa, although a myomelanocytic immunophenotype was not confirmed.

Thus, we fully agree with Hashimoto and Quade who discourage the use of the term AML for angiomatosus lesions with adipocytes, as there is no evidence of any relationship of such lesions with renal or retroperitoneal AML, or with tuberous sclerosis. The same argument applies against the use of terms such as mucocutaneous angiomyolipoma and angiolipoleiomyoma. More importantly, because a diagnostic term well known to clinicians and pathologists confers information relevant to the character, prognosis, and treatment of a lesion, we opine that the term AML be abandoned for non-PEComatous oral lesions because it is misleading.

The authors are indebted to Mr. Jonathan Henriksen (University of Minnesota) for his superb assistance with the illustrations.

REFERENCES


41. Beer TW. Cutaneous angiomyolipomas are HMB45 negative, not associated with tuberous sclerosis, and should be considered as angiomyolymphomas with fat. Am J Dermatopathol 2005;27:418-21.


