

Case Report

Oral soft-tissue angiolipoma: report of two cases of rare oral lipomatous lesion with emphasis on morphological and immunohistochemical features

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(Received August 20, 2012; Accepted November 19, 2012)

Abstract: Oral angiolipomas are exceedingly rare and little is known about their morphological and etiological features. Here, we report two cases of oral angiolipoma and discuss their clinicopathological and immunohistochemical features, focusing on endothelial markers. Both lesions presented mature adipocytes interspersed by small blood vessels containing fibrin thrombi. Immunohistochemical analysis showed numerous mast cells and expression of CD34, vascular endothelial growth factor, intercellular adhesion molecule-1, interferon- γ and interleukin 6 in most endothelial and stromal cells. Mast cell-endothelial cell interaction may be responsible for the reactive or neoplastic origin of the vascular proliferation of these entities. (*J Oral Sci* 55, 85-88, 2013)

Keywords: angiolipoma; oral; mast cell; endothelial cell; immunohistochemistry.

Introduction

Angiolipomas are benign adipocytic tumors predominantly found as painful multiple subcutaneous nodules on the forearm, trunk and upper limbs of young adults (1). Although these entities represent 6% to 17% of all lipomas, angiolipomas are rarely reported in the oral cavity and information about their epidemiological and clinicopathological characteristics is mostly derived from single case reports (1). The aim of the present study is to report two additional cases of oral angiolipomas and to discuss their most prominent clinicopathological and immunohistochemical features.

Case Report

Case 1: A 57-year-old male presented to the oral medicine clinic complaining of an asymptomatic swelling in the cheek lasting 1 year. Oral examination revealed a 15-mm slightly purplish painless exophytic pedunculated fibrous nodule covered by ulcerated mucosa in the right pterygomandibular raphe (Fig. 1A). Possible diagnoses included fibrous hyperplasia, fibrolipoma and schwannoma. The lesion was completely removed using a conservative surgical procedure under local anesthesia and his post-operative course was uneventful. Final diagnosis was non-infiltrating angiolipoma and 34-month follow-up

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Fig. 1 Ulcerated exophytic swelling on the right pterygomandibular raphe (A, case 1); clinical aspect of the affected area after surgical removal of the lesion (B, case 1); trans-surgical aspect of the lesion showing a purplish color (C, case 2).

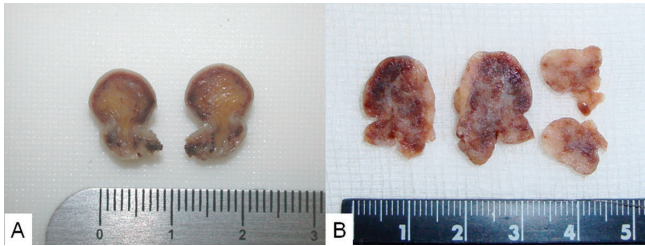


Fig. 2 Gross image of the post-fixed surgical specimens from case 1 (A) and from case 2 (B) showing a yellow-brownish aspect at cutting surface.

period revealed no signs of recurrence (Fig. 1B).

Case 2: A 29-year-old female was referred to the oral and maxillofacial surgery clinic with a 4-month history of a painless swelling in the masseteric region. Clinical examination revealed a 30-mm submerse well-defined mobile nodule, covered by normal oral mucosa, on the deep left lower posterior mucobuccal fold. Possible diagnoses included a benign mesenchymal neoplasm and lymphoid hyperplasia. The lesion was managed via an intraoral conservative surgical approach under local anesthesia. During surgery, it was observed that the lesion showed a purplish color and was very well-defined, being easily detached from the adjacent muscle and adipose tissue (Fig. 1C). Her postoperative course was uneventful. Final diagnosis was non-infiltrating angiolipoma and a 13-month follow-up period revealed no signs of recurrence.

Gross examination of the surgical specimen from case 1 revealed a brownish well-defined pedunculated soft-tissue specimen measuring $13 \times 9 \times 7$ mm. Cutting surface revealed a peripheral brownish zone adjacent to a central yellowish core (Fig. 2A). Gross examination of the surgical specimen from case 2 showed a $25 \times 13 \times 9$ mm brownish well-defined lobulated specimen that presented a mixed yellow-brownish cutting surface (Fig. 2B). Hematoxylin and eosin stained histological slides from both cases showed a well-demarcated proliferation of mature adipocytes interspersed by abundant randomly disposed small congested blood vessels on a dense fibrous connective tissue (Fig. 3A). Vessels were distributed in

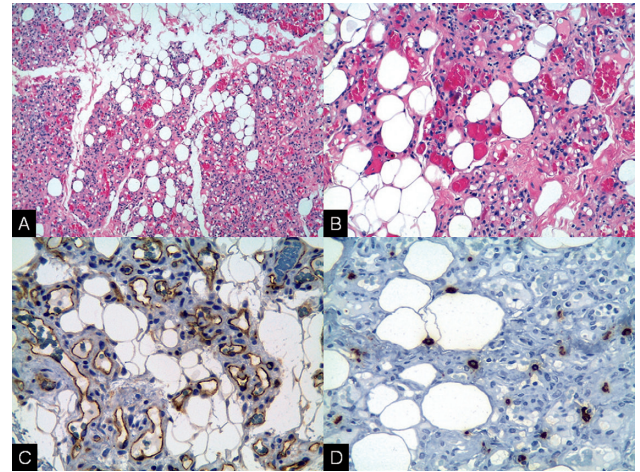


Fig. 3 Histological features from intraoral soft-tissue angiolipoma showing proliferation of both vascular and adipocytic components (A, HE 40 \times) and detail of the vascular component showing fibrin thrombi-containing blood vessels (B, HE 100 \times); immunostaining of endothelial cells by CD34 (C, Immunoperoxidase, 100 \times), and presence of numerous mast cells near adipocytes and blood vessels (D, Immunoperoxidase, 100 \times).

both the peripheral and central areas, including the outer limits of the connective tissue in case 1. Most vessels presented with fibrin thrombi (Fig. 3B) and endothelial cell hyperplasia was frequently observed, particularly in case 2. Some foci of hemorrhage as well as chronic inflammatory cells were sparsely distributed in both lesions, but mitosis and areas of necrosis were not seen.

Immunohistochemistry was performed in both cases using 3- μ m sections on silanized slides prepared using the streptavidin-biotin peroxidase technique. Primary antibodies directed against vascular endothelial growth factor (VEGF, mouse monoclonal anti-human VEGF, clone VG1, dilution 1:50; DakoCytomation, Glostrup, Denmark), mast cell tryptase (mouse monoclonal anti-human mast cell tryptase, clone AA1, dilution 1:10,000; DakoCytomation), intercellular adhesion molecule-1 (ICAM-1, mouse monoclonal anti-human ICAM-1, dilution 1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA), interleukin 6 (IL-6, mouse monoclonal anti-human IL-6, dilution 1:500; Santa Cruz Biotechnology), interferon-gamma (IFN- γ , rabbit polyclonal anti-human IFN- γ , dilution 1:200; Santa Cruz Biotechnology), tumor necrosis factor alpha (TNF α , mouse monoclonal anti-human TNF α , dilution 1:200; Santa Cruz Biotechnology) and CD34 (mouse monoclonal anti-human CD34, clone QBEnd/10, dilution 1:500; Biocare Medical, Concord, CA, USA) were used. The results showed that all endothelial cells in both cases were positive for CD34 (Fig. 3C). Mast cells were commonly found in both lesions and were localized around blood vessels and near adipo-

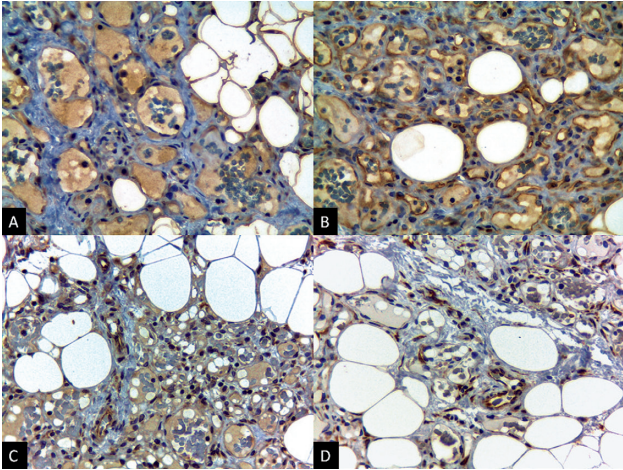


Fig. 4 Immunohistochemical expression of VEGF (A), ICAM-1 (B), IFN- γ (C), and IL-6 (D) in both endothelial and stromal cells in intraoral angioliipoma (A-D, Immunoperoxidase, 100 \times).

cytes (Fig. 3D). Counting of tryptase-positive cells in ten high-power fields revealed a mean of 16.3 mast cells per high-power field (40 \times) (mean of 16.5 mast cells/field in case 1 and 16 mast cells/field in case 2). Most endothelial cells were also strongly labeled with anti-VEGF, anti-ICAM-1, anti-IFN- γ and anti-IL-6 antibodies (Fig. 4 A-D). These antibodies also stained most stromal cells and inflammatory cells from both cases. TNF α expression was not observed in either case.

Discussion

Angioliipomas are a rare histological subtype of lipomas, representing less than 10% of all intraoral lipomas (2,3). Hamakawa et al. (1) reported one case of angioliipoma of the cheek and reviewed nine previously reported cases of oral soft-tissue angioliipomas. Subsequently, nine additional cases were reported in the English literature, raising the total number of reported cases from 1976 to 2012 to 19 (3-8). Male to female ratio from these intraoral angioliipomas was 1.4:1, in contrast to cutaneous angioliipomas and intraoral lipomas as a group, which either shows no sex predilection or a slight female predilection (2). Mean age of the affected patients was 37 years (range, 4 to 81 years), in contrast to other oral lipomas (and their variants), which usually affect adult patients in their fifties and sixties and to cutaneous angioliipomas which show a predilection for younger patients (2). These lesions presented a predominant predilection for the cheek/buccal mucosa (10 cases), followed by the lip (four cases). It seems that one of the cases in the present study is the first reported to affect the pterygomandibular raphe. Almost all cases were described as painless well-defined non-ulcerated submerse masses (1), but Ida-

Yonemochi et al. (4) reported an angioliipoma affecting the buccal mucosa with a polypoid morphology, similar to the pattern seen in case 1 from the present study.

Considering the intraoral angioliipomas reported from 1976 to 2012, there was a ratio of 3:1 for non-infiltrative to infiltrative subtypes. Mean age of the patients with non-infiltrative angioliipomas (28.2 years) was lower than the mean age of the patients affected by infiltrative angioliipomas (50.5 years), and mean size of the non-infiltrative lesions (3.1 cm) was also lower than the mean size of the infiltrative lesions (3.8 cm). Although there seems to be differences in these two parameters, the few reported cases preclude any definite conclusions. The two cases reported in the present study were classified as non-infiltrating lesions and were successfully managed through conservative surgical approaches. Most intraoral angioliipomas reported to date were managed through simple excision (with only four cases submitted to wide excisions) and, regardless of the surgical approach, there were no reported recurrences after a mean follow-up of 13 months (ranging from 4 to 36 months). This reinforces the benign nature of these tumors, similarly to both cases reported in the present study and other intraoral lipoma variants (2).

Histological characteristics of angioliipomas reveal a well-demarcated, sometimes poorly-encapsulated, proliferation of mature adipocytes (usually representing at least 50% of the tumor mass) and interspersed connective tissue fibers showing an angiomatous proliferation composed of several small to medium sized congested blood vessels containing fibrin thrombi, and numerous mast cells (4). This angiomatous component tends to be more common in the subcapsular peripheral areas and most authors highlight the importance of fibrin thrombi-containing small blood vessels in the diagnosis of angioliipomas, noting that the simple presence of blood vessels in a benign lipomatous tumor is not a diagnostic criterion for angioliipomas (4). Angioliipomas do not present representative amounts of other mesenchymal elements, such as muscle and neural tissue, or pleomorphism and necrosis. Some of the previously reported cases did not include representative histological pictures of the typical microscopic features of angioliipomas and showed only the concomitant presence of mature adipocytes and blood vessels, some of these were congested and dilated. With regard to other histological variants, it is essential to fulfill all diagnostic criteria to consider the lesion as a specific subtype and this is crucial for understanding their true clinicopathological characteristics and biological behavior. Both cases published in the present study fulfilled all histological criteria for an intraoral

angioliopoma. Another interesting feature from both cases reported in the present study was the brown-yellowish gross color of the tumors, reflecting the mixture of the adipocytic and vascular components, in contrast to the yellowish gross color of conventional lipomas. When diagnosing intraoral angioliopomas, due to the presence of this angiomatous component, it is essential to exclude other histological differential diagnosis, such as a conventional lipoma with prominent blood vessels, hemangiomas with fat entrapment, and lymphangiomas and Kaposi sarcomas in close relationship to adipose tissue.

Pathogenesis of angioliopomas remains unclear, but history of trauma, lipomatous hormonal differentiation during puberty, fatty degeneration in hemangiomas and vascular proliferation in congenital lipomas have been suggested as possible associated causative factors (5,6). Most angioliopomas show a normal karyotype, suggesting that these tumors can represent reactive non-neoplastic proliferations. Ida-Yonemochi et al. (4) reported the presence of numerous VEGF-expressing mast cells around blood vessels in an intraoral angioliopoma, suggesting that secretion of this growth factor by mast cells could play an important role in the vascular proliferation in these tumors. Both cases reported in the present study reinforce this possible explanation as most endothelial cells, stromal cells and mast cells expressed VEGF.

Mast cells are associated with angiogenesis in different ways, including expression of basic fibroblast growth factor and VEGF, and several angiogenic factors have been shown to stimulate mast cell migration at sites of angiogenesis (9). The present study demonstrated that IL6 and IFN- γ , two inflammatory cytokines, were strongly expressed by both endothelial and stromal cells in oral angioliopomas, and that ICAM-1, a well-recognized intercellular adhesion molecule expressed in both endothelial cells and leukocytes, was also expressed in both cases. The concomitant expression of VEGF, IL6, IFN- γ and ICAM-1 in close relationship to mast cells and other sparse leukocytes in angioliopomas suggest that, at least partially, the morphological features encountered in these tumors could be associated with inflammatory stimuli modulated by mast cell-derived endothelial alteration and, consequently, leukocyte transmigration. However, as mast cell infiltration is a common feature in other lipoma variants, such as spindle cell lipoma (2), it remains uncertain why this pattern is found solely in angioliopomas.

Pro-inflammatory cytokines released by mast cells, including IL-6, IFN- γ and TNF α , can induce the expression of adhesion molecules by endothelial cells, such as

ICAM-1, and modulate the recruitment of leukocytes (10). Although the participation of these specific cells and cytokines in the pathogenesis of angioliopoma remains speculative, it is reasonable to consider that these interactions are important in the development of the vascular component in these lesions. Other studies focusing on mast cell-endothelial cell interaction and the expression of inflammatory cytokines in angioliopomas are encouraged for better comprehension of the exact nature (reactive or neoplastic) and origin of the endothelial proliferation of these lesions.

Acknowledgments

This work was supported by FAPERJ, Brazil (2011).

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