**Nodular swelling of the buccal mucosa**

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**CLINICAL PRESENTATION**

A 78-year-old white woman was referred to the Oral Medicine Service of Araraquara Dental School—UNESP, Brazil, for diagnosis and management of a nonulcerated submucosal nodule on the left side of the buccal mucosa (Figure 1A). According to the patient, it has been present for about 1 week. Clinical examination revealed a fluctuant nodular submucosal mass and slightly symptomatic on palpation. The lesion measured approximately 2 cm in greatest dimension, and it was covered by normal-appearing mucosa. Regional lymphadenopathy was not detected. Her medical history was noncontributory, and the patient did not report fever, weight loss, malaise, and fatigue.

**DIFFERENTIAL DIAGNOSIS**

Considering the clinical presentation and localization of the current lesion, differential diagnoses were focused on benign neoplasms of mesenchymal or glandular origin, as well as reactive lesions. Furthermore, due to the rapid growth of the lesion, malignant neoplasms of salivary gland, lymphoid, and mesenchymal origin were also considered.

**Benign mesenchymal tumors**

In the current nonulcerated nodular lesion, the diagnosis of submucosal mesenchymal neoplasms of neural (schwannoma, neurofibroma), adipocytic (lipoma), fibroblastic (solitary fibrous tumor), smooth muscle (leiomyoma), and myofibroblastic (myofibroma and nodular fasciitis) origin should be considered.

This abstract was presented as a poster on July 07, 2015, at the 23rd Brazilian Congress of Oral Medicine and Pathology, held in São Paulo, Brazil.

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Received for publication Aug 9, 2015; returned for revision Dec 2, 2015; accepted for publication Feb 6, 2016. © 2016 Elsevier Inc. All rights reserved.

http://dx.doi.org/10.1016/j.oooo.2016.02.005

Schwannoma and neurofibroma are benign peripheral nerve sheath tumors. Intraoral involvement accounts for approximately 1% of these tumors located in the head and neck region.1,2 Between 20% and 60% of oral neurofibromas are associated with neurofibromatosis, being that approximately 3% to 15% of these cases present potential for sarcomatous transformation. Intraoral schwannomas and neurofibromas show a predilection for the tongue, followed by the buccal mucosa, palate, floor of the mouth and lip.1 Although they can arise at any age, the average incidence is between 20 and 50 years, being more common in females.2 These tumors manifest as an asymptomatic nodular swelling.1 Microscopically, schwannoma shows a well-defined and encapsulated tumor mass comprising Schwann cells, whereas neurofibroma is an ill-defined mass and composed of Schwann cells, perineural cells, and endoneural fibroblast-like cells.2 Lipoma is a benign mesenchymal neoplasm that comprises about 1% to 4% of all benign tumors of the oral cavity.3,4 Clinically, it appears as a low-growing, painless, well-defined mass yellow in color. An elastic consistency may be evident, depending on the amount of fibrous tissue.3 The sites more frequently involved are the buccal mucosa and tongue, especially in males over 40 years of age.3,4 Microscopically, lipomas show a well-circumscribed mass composed mainly of mature adipocyte separated by thin vascular fibrous septae.3 Solitary fibrous tumor (SFT) is a spindle-cell neoplasm of fibroblastic origin and occurs most commonly in the pleura.3 To date, approximately 80 cases of oral SFT have been reported in the English language literature. The buccal mucosa is frequently affected, followed by the tongue, gingiva, palate, and lip. Oral SFT typically shows a low-growing asymptomatic submucosal mass of varying size, affects patients in their sixth decade of life, with equal gender predilection.5 Histopathologically, SFT shows densely cellular areas alternating with hypocellular areas in a collagenous stroma. The tumor cells show immunoreactivity for CD34, CD99, and bcl-2.5 Leiomyoma is a benign smooth muscle tumor, being commonly found in uterine myometrium (95%), and less than 1% is detected in the head and neck region. Oral leiomyoma accounts for about 0.05%, and clinically it appears as an asymptomatic submucosal mass, most
frequently affecting the lips, followed by the tongue, buccal mucosa, palate, gingiva, and mandible.\(^6,7\) It has a slight male predilection and a peak incidence between 40 and 49 years of age.\(^7\) Angioleiomyoma is the most common variant affecting the oral cavity (64% of all cases), followed by the solid and epithelioid variants.\(^6\) Histopathologically, consists of a circumscribed mass composed by spindle-shaped cells with eosinophilic cytoplasm and cigarlike shaped nuclei admixed with variable vascular stroma.\(^6,7\)

Myofibromas are benign myofibroblastic tumors, with approximately 50% of them occurring in cutaneous tissues of head and neck region.\(^8,9\) Oral soft tissue myofibroma is relatively rare, with approximately 44 cases reported in the English language literature, frequently affecting the tongue (32%), followed by the buccal mucosa (18%). There is a slight predilection for the female gender (ratio 1:1.6), with age ranging from birth to 70 years (mean, 21.7 years).\(^9\) Clinically, a painless, firm, solitary swelling usually covered by normal mucosa is observed, and it may mimic other soft tissue tumors of neurogenic and smooth muscle origin. Besides, myofibroma can demonstrate a slow or even a rapid growth rate, making the diagnosis challenging.\(^8,9\) Microscopically, a spindle cell proliferation exhibits a biphasic pattern around irregular blood vessels (hemangiopericytic pattern).\(^9\) In difficult cases, immunohistochemistry, associated with careful morphologic analysis, is useful. Likewise, this is valid for all other tumors previously mentioned.

Nodular fasciitis (NF) is a benign myofibroblastic proliferation that frequently occurs in the subcutaneous tissues of the upper extremities, as well as head and neck region. NF occurs equally in both genders, predominantly between the ages of 20 and 40 years.\(^10,11\) Unfortunately, NF is not uncommonly misdiagnosed as sarcoma, owing to its rapid growth (few weeks), and microscopically by exhibiting high cellularity and high proliferative activity. To date, approximately 45 cases of oral NF have been reported in the English language literature, being the buccal mucosa the most common location.\(^11\)

**Reactive lesions**

Despite having no history of trauma, a diagnosis of mucocele was also considered. Mucocele is a common reactive lesion of the oral mucosa, resulting from ductal obstruction, and typically shows a mass with translucent aspect, and it frequently affects the lower labial mucosa.\(^12\) Microscopically, the mucocele exhibits mucus extravasation surrounded by a wall of granulation tissue.\(^12\) Fibrous hyperplasia (FH) is the most frequent reactive lesion of the oral cavity, and it clinically appears as a pedunculated or sessile growth as a result of trauma or local irritation.\(^13\) FH can be found in the buccal mucosa along the bite plane, as it was described in the current case. Microscopically, FH is characterized by large collagen fibers deposition.\(^13\) In the current case, these reactive lesions were considered as less probable diagnoses.
Benign and malignant minor salivary gland tumors

Minor salivary gland tumors represent 10% to 20% of all salivary gland tumors. Most lesions occur in the palate, followed by the buccal mucosa, and lips. Pleomorphic adenoma (PA), mucoepidermoid carcinoma (MEC), and adenoid cystic carcinoma are the most frequent histologic types of intraoral minor salivary gland tumors. In a series of 546 cases of minor salivary gland tumors in a Brazilian population, 305 (55.9%) and 241 (44.1%) were benign and malignant tumors, respectively. This study showed that 33 of 57 benign tumors affecting the buccal mucosa were PAs; and 17 of 41 malignant tumors affecting the buccal mucosa were MECs. Overall, the highest incidence occurs between the fifth to seventh decades of life, with female gender predilection. Minor salivary gland tumors usually occur as an asymptomatic, firm and ulcerated, or nonulcerated submucosal mass. Microscopically, PA is composed of both epithelial and myoepithelial elements; MEC presents mucous cells together with epidermoid and intermediate cells, whereas adenoid cystic carcinoma exhibits distinct architectural patterns described as tubular, cribriform, and solid.

Benign/reactive and malignant lymphoid proliferations

Follicular lymphoid hyperplasia is a rare benign lymphoproliferative process, with approximately 20 cases reported in the English language literature to date. It has been also named benign lymphoid hyperplasia, reactive lymphoid hyperplasia, and pseudolymphoma. Follicular lymphoid hyperplasia occurs most frequently in older female patients (mean age 61 years), usually presenting as a unilateral, painless, and slow-growing mass on the posterior hard palate and occasionally affecting the tongue. Buccal mucosa involvement appears to be rare. Histologically, the lesion is composed of multiple follicles with well-defined germinal centers.

Non-Hodgkin lymphomas (NHLs) represent the third most common group of malignant lesions of the oral
cavity, just behind squamous cell carcinomas and adenocarcinomas of salivary gland origin. In the oral cavity and oropharynx, NHLs account for 13% of all primary extranodal NHLs, commonly affecting the tonsils (about 70%). In the oral cavity, NHLs account for 2% to 3% of all malignancies, with most cases representing B-cell lymphomas, followed by T-cell and natural killer/T-cell lymphomas. Oral NHL occurs frequently between the fifth and seventh decades of life, with slight male gender predilection. The palate and tongue are commonly affected, followed by the buccal mucosa, floor of the mouth, and jaws. On clinical examination, oral NHLs may present lesions ranging from swellings to ulcerated masses, which can mimic reactive lesions such as pyogenic granuloma or giant cell lesion, as well as periodontal disease, osteomyelitis, squamous cell carcinoma, and salivary gland neoplasms.

### Malignant mesenchymal tumors

Sarcomas are rare malignant tumors of mesenchymal origin, usually classified considering their cell type origin, mainly based on microscopic and immunohistochemical findings, as well as cytogenetic changes. Although about 80% of sarcomas are derived from mesenchymal cells of soft tissues, a few of them have bony and cartilaginous origin. Soft tissue sarcomas account for about 6% of all malignant tumors in children and less than 1% of malignancies among adults.

In the head and neck region, soft tissue sarcomas are uncommon, being their frequency higher in pediatric patients than in adult patients (35% vs 10%). Clinically, soft tissue sarcomas of the head and neck region present as an infiltrative mass in the face, neck, sinonasal tract, and oral cavity, usually presenting a rapid onset and involvement of adjacent structures. The most soft tissue sarcomas are fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, undifferentiated high-grade pleomorphic sarcoma, and synovial sarcoma. About 20% of adult patients with head and neck soft tissue sarcoma present distant metastases. Recurrences occur within 2-year after the treatment, and the 5-year survival and local control rates are of 65% and 70%, respectively.

### DIAGNOSIS AND MANAGEMENT

In the case presented here, by considering the clinical findings and the abrupt onset of the current lesion, an incisal biopsy was performed. The histopathologic evaluation on the hematoxylin and eosin (H&E) stain revealed a nonulcerated lesion, presenting submucosal diffuse inflammation surrounding minor salivary glands, bundles of skeletal muscle fibers and adipose tissue (Figures 2A–2E). A mixed inflammatory infiltrate consisting of macrophages, plasma cells, lymphocytes, neutrophils and eosinophils, which involved the residual salivary gland parenchyma, with foci of acinar atrophy and necrosis, as well as myositis areas and remarkably nongranulomatous macrophage-rich sheets, were evident. Initially, the inflammatory process raised the suspicion of an infectious process. However, special histochemical stains, such as periodic acid-Schiff (PAS), Grocott-Gomori methenamine silver, acid-fast bacilli and Gram, were all negative. Thus, the clinicopathologic findings were consistent with the diagnosis of subacute necrotizing sialadenitis (SANS). The lesion healed completely after 4 weeks of follow-up (Figure 1B).

Immunohistochemical analysis was performed to characterize and highlight the heterogeneous population of the inflammatory cells, through a broad panel of antibodies, such as shown in the Table I. The percentage of positive cells was determined by using the image computer analyzer (Dako’s Automated Cellular Imaging System; Dako, Carpinteria, CA). Two authors (J.E.L. and L.Y.A.) performed blinded analysis of randomly immunohistochemical slides independently. It was classified as −, negative; +/−, rare positive cells; +, ≤5% of positivity; ++, 5%–50%; ++++, >50%.

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| Table I. List of primary antibodies and immunohistochemical results |
|----------------------|------------------|------------------|-------|
| Antibody | Dilutions | Clone | Supplier | Results |
| CD1a | 1:400 | O10 | DakoCytomation | +/-- |
| CD3 | 1:800 | Polyclonal | DakoCytomation | ++ |
| CD4 | 1:200 | 4B12 | Leica Biosystems | + |
| CD8 | 1:600 | C8/144 B | DakoCytomation | ++ |
| CD11c | 1:500 | SD1 | Leica Biosystems | ++ |
| CD20 | 1:2000 | L26 | DakoCytomation | ++/− |
| CD34 | 1:100 | QBEnd/10 | Leica Biosystems | − |
| CD56 | 1:100 | CD564 | Leica Biosystems | +/− |
| CD57 | 1:500 | TB01 | DakoCytomation | +/− |
| CD68 | 1:3000 | KP1 | DakoCytomation | +++ |
| CD123 | 1:200 | BR4 MS | Leica Biosystems | +/− |
| CD138 | 1:500 | MI15 | DakoCytomation | + |
| CD163 | 1:500 | 1D6 | Leica Biosystems | +++ |
| CD207 | 1:200 | 1D26 | Monosan | +/− |
| CD303 | 1:500 | 12B3.13 | Dendritics | +/− |
| EMA | 1:500 | E29 | DakoCytomation | + |
| Granzyme B | 1:100 | GrB-7 | DakoCytomation | +/− |
| Perforin | 1:100 | 5B10 | Leica Biosystems | − |
| HLA-DR | 1:500 | TAL.1 B5 | DakoCytomation | +++ |
| S100 | 1:3000 | Polyclonal | Leica Biosystems | + |
| XIlA | 1:100 | E980.1 | Leica Biosystems | + |
| Ki-67 | 1:500 | MIB-1 | DakoCytomation | >7% |

−, negative; +/−, rare positive cells; +, ≤5% of positivity; ++, 5%–50%; ++++, >50%.
CD4, in diffuse pattern, whereas CD20+ B-cells were practically absent. These data suggest a predominance of cytotoxic T-cells (CD3+/CD8+) (Figures 3A–3C). EMA and CD138 immunostaining revealed focal aggregates of plasma cells; moreover, these markers highlighted the residual salivary gland component (Figures 3D and 3E). In consecutive serial sections, macrophages were strongly immunopositive for both CD68 and CD163, suggesting a M2-like phenotype (Figures 4A and 4B). This finding was also confirmed by CD11c positivity, a macrophage marker (Figure 4C). Human leukocyte antigen-D related (HLA-DR) highlighted, in addition to macrophages, a significant number of dendritic-like cells (Figure 4D).
Among these latter, submucosal dendritic cells were evidenced by XIIIa immunomarker (Figure 4E). Scarce S100+ dendritic-like cells were visualized (Figure 4F), whereas CD1a+/CD207+ Langerhans cells were practically absent. Interestingly, S100 positivity was also detected in some ductal cells and seromucous acini of the residual salivary glands. Furthermore, plasmacytoid dendritic cells (CD123+/CD303+) were occasionally seen. CD56, CD57, and granzyme B confirmed the presence of scattered cytotoxic lymphocytes. CD34 highlighted discrete fine blood vessels within the lesional stroma. Last, inflammatory cells expressing Ki-67 proliferation marker were meaningful (>7%), especially on macrophage and lymphocyte populations (Figure 3F).

**DISCUSSION**

SANS was first described in 1990, as a self-limiting inflammatory process. The etiology of SANS is unknown, but traumatic, infectious, and allergic etiologies have been suggested. Including the current case, only 33 SANS cases have been reported in the English language literature. Of them, 21 occurred on the hard palate, four on the soft palate, four on the buccal mucosa, two on the tongue, one on the upper lip, and one on the tonsillar area. Interestingly, none of them was found affecting the major salivary glands. The majority of cases occurred between the second and third decades of life (mean age 26.7 years), affecting preferentially men (ratio 3:1). Commonly, this lesion presents as a localized nonulcerated painful swelling, usually not exceeding 2 cm in diameter. As previously mentioned, in four SANS cases, the buccal mucosa was affected, in three women and one man, with an age range of 30 to 78 years (mean age 57.2 years). Histologically, SANS is characterized by a diffuse infiltration of both acute and chronic inflammatory cells involving the parenchyma of minor salivary glands, which show ductal atrophy and acinar necrosis. Ductal squamous metaplasia is mild or absent. Interestingly, eosinophilia is a constant finding among the most reported cases of SANS, and it was also evidenced in the current case (Figures 2C–2E). Eosinophils are usually absent in necrotizing sialometaplasia (NS) and chronic sclerosing sialadenitis (CSS), which are the main differential diagnoses of SANS. Despite some authors consider SANS as usual subtype of NS, there are clinical and histologic features that suggest it to be a distinct entity. The major ones among them are that SANS presents as a nonulcerated swelling, which shows a subacute inflammatory infiltrate and the average duration before diagnosis is less than 1 week. In contrast, NS is characterized by an ulcerated swelling composed of chronic inflammatory infiltrate and squamous metaplasia, which has a duration of approximately 3 weeks. Moreover, different from SANS, NS cases are most frequently diagnosed in other locations, such as major salivary glands, nasal cavity, maxillary sinus, and larynx.

By analysis of the H&E staining, the current SANS case exhibited numerous macrophages, neutrophils, eosinophils, plasma cells, and lymphocytes. To the best of our knowledge, this is the first study that provided a detailed immunohistochemical profile of the inflammatory cell populations in SANS. Overall, the inflammatory infiltrate consisted predominantly of M2-like phenotype macrophages, followed by dendritic cells (myeloid origin) and cytotoxic T-lymphocytes. The higher number of CD3+ T-cells, associated with the practically absence of CD20+ B cells, suggested that SANS has a predominant cell-mediated immune response. Macrophages are capable of responding to environmental changes by altering their functional phenotype, depending on surrounding signals. M1 macrophages (CD68+/CD163+/HLA-DR+) are pro-inflammatory, and they are characterized by high levels of phagocytosis, inhibition of cell proliferation, and tissue damage. In the current case, it was observed that the vast majority of macrophages exhibited the M2-like phenotype (CD68+/CD163+/HLA-DR+), which is anti-inflammatory and responsible for the angiogenesis and the tissue repair. Finally, by considering the dendritic cell populations, this study found that the myeloid lineage was predominant over plasmacytoid lineage. In fact, CD123 and CD303 immunomarkers exhibited scarce positive cells. Myeloid dendritic cells play a major role in antigen presentation and are capable of induce T-cell immunity or tolerance, depending on their stage of maturation. In contrast, plasmacytoid dendritic cells produce a massive amount of interferon type I upon viral infection and have an immunomodulatory role in natural killer, T-cell, and B-cell responses. Therefore, our results suggest the participation of dendritic cell subsets in the pathogenesis of SANS. Future studies, including a large SANS series, are necessary for a better defining of their etiopathogenic mechanisms and its delineation from others reactive conditions affecting minor salivary glands, such as NS.

The authors thank the Pathology Digital Technologies Core (NTDP) at Pathology Department at Botucatu Medical School, UNESP, for technical support with digital whole slides.

**REFERENCES**


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