Solitary Fibrous Tumor with Entrapment of Minor Salivary Gland Tissue: An Unusual Presentation That Requires Exclusion of Pleomorphic Adenoma

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Abstract We report two unusual cases of solitary fibrous tumor (SFT) of minor salivary glands that microscopically mimicked pleomorphic adenoma. One of these lesions presented in the retromolar region and the other in the buccal mucosa. The microscopic features of these two tumors and their intimate relationship with regional mucous minor salivary glands posed a diagnostic challenge. Awareness of the morphological diversity of SFT coupled to a judicious use of appropriate immunohistochemical probes should prove valuable to accurately segregate SFT from pleomorphic adenoma.

Keywords Intraoral solitary fibrous tumor · Pleomorphic adenoma · Minor salivary gland neoplasm · Differential diagnosis

Introduction

Solitary fibrous tumor (SFT) is a rare benign spindle cell mesenchymal neoplasm that was originally described in the pulmonary pleura [1]. Today, SFT is considered a ubiquitous tumor, having been reported at many extra-pleural sites [2]. In the head and neck area, SFT has been reported in upper airways, nasal cavity, paranasal sinuses, orbit, all major salivary glands, thyroid gland, skin and meninges [3]. SFT infrequently involves the oral cavity with only approximately 70 cases reported in the English literature. Intraorally, the buccal mucosa is the most common site of involvement and the tumor develops as a slow-growing, asymptomatic, smooth submucosal growth of varying sizes that occurs in a wide age range [4].

Regardless of a pleural or extra-pleural location, SFT retains similar microscopic features. SFT appears as a well-circumscribed tumor showing a wide histological spectrum. However, in 1997, Chan [5] delineated a set of diagnostic criteria. The essential diagnostic features of SFT are those of a tumor characterized by the presence of hypercellular and hypocellular areas composed of bland, spindle or ovoid cells with scanty and poorly defined cytoplasm. The tumor cells are usually distributed haphazardly, but storiform and fascicular patterns of mesenchymal spindle cells are not uncommon and may suggest a neural genesis. The tumors cells may be intertwined amidst thin and thick collagen fibers. Areas of abundant stromal hyalinization and regions of vascular proliferation with a staghorn pattern may also be present. In addition, SFT displays a low mitotic activity [5].

The array of microscopic features displayed by SFT may pose a diagnostic challenge [5]. The present paper reports two exceptional cases of SFT of the oral cavity involving minor salivary glands. The microscopic findings were

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unusual and resembled those of pleomorphic adenoma with cystic changes and stromal hyalinization.

Case Reports

Case 1

A 45-year-old Caucasian female presented for evaluation of a non-ulcerated, sessile, pink nodular mass on the right retromolar region of 2 years duration. The lesion was firm and non-tender to palpation. The lesion measured approximately 1.5 cm in diameter (Fig. 1) and the patient denied a previous history of trauma. Physical examination of the patient failed to reveal abnormal head and neck structures. The patient's medical history was significant for seasonal allergies, arthritis of the knees, and hypertension treated with hydrochlorothiazide (25 mg d.), lisinopril (40 mg b.i.d.), atenolol (100 mg d.), and amlodipine besylate (100 mg d.). In addition, the patient reported a history of cigarette smoking for 4 years with a consumption of half a pack a day. Radiographic examination with a panoramic film showed normal anatomy of the maxillary sinuses, temporomandibular joint structures, and facial bones, and no evidence of mandibular or maxillary intraosseous or periosteal lesions.

Fig. 1 The patient presented with a nodule displaying an intact and smooth surface on the retromolar trigone (*white arrow*)

An excisional biopsy of the lesion was performed under local anesthesia with no complications. The specimen was fixed in 10% buffered formalin. The biopsy specimen measured $1.6 \times 1.0 \times 0.9$ cm and was of firm consistency and white color. Hematoxylin and eosin stained tissue sections revealed a specimen surfaced by an intact parakeratinized stratified squamous epithelium (Fig. 2). The subjacent stroma separated the epithelium from a circumscribed lesion composed mainly of hyalinized fibrous connective tissue with what appeared to be peripheral “pseudopods” and intermittent paucicellular and hypercellular areas populated by spindle cells with slightly wavy nuclei (Fig. 3). Focal areas with a hemangiopericytoma-like vasculature were noted at the periphery of the tumor. Toward the center of the lesion, a large cystic area lined by cuboidal epithelium with an intraluminal basophilic amorphous material was noted (Fig. 2). In addition, ductal structures with an intraluminal eosinophilic coagulum and peripheral clear cells, similar to those seen in pleomorphic adenoma, were also observed (Fig. 4). Sporadic mucous acini were seen amidst an abundant paucicellular hyalinized stroma. No evidence of malignancy was seen and tumor-negative surgical margins were observed.

A microscopic diagnosis of pleomorphic adenoma with unusual cystic areas and prominent stromal hyalinization was rendered. This diagnosis was later amended to solitary fibrous tumor after the utilization of immunohistochemical probes (tumor cells positive for CD34 (Fig. 5), and

Fig. 2 The specimen shows an intact stratified squamous epithelium. Circumscription of the lesion is noted and shows a prominent cystic structure with an intraluminal eosinophilic coagulum amidst a hyalinized stroma. In addition, neighboring lobules of mucous acini, some of them entrapped in the lesion, are noted. (Hematoxylin-eosin stain; original magnification $\times 10$)

Fig. 3 The tumor shows a proliferation of spindle cells arranged in a haphazard pattern with interspersed thick and thin collagen fibers. (Hematoxylin-eosin stain; original magnification $\times 100$)

Fig. 4 Congeries of ductal structures with an intraluminal eosinophilic coagulum are lined by cuboidal epithelium with an intermittent peripheral layer of clear cells. The paucicellular hyalinized stroma is clearly illustrated in this field. (Hematoxylin-eosin stain; original magnification $\times 100$)

vimentin; negative for pan cytokeratin, S-100, and HHF35).

The post-surgical recovery was uneventful and no evidence of recurrence has been documented at a 3-years follow-up.

Case 2

A 67-year-old Caucasian female presented for examination with the chief complaint of a swelling that involved her right cheek. The duration of the lesions was unknown. Intraoral examination showed a 2.0 cm submucosal mass in the anterior buccal mucosa (Fig. 6). On palpation, the lesion was found to be mobile and well demarcated.

Fig. 5 Positive signal for CD34 is demonstrated by the proliferating spindle mesenchymal cells. Numerous salivary ductal structures are also observed. (Original magnification $\times 100$)

There was no associated pain or paresthesia. Her medical history was unremarkable with not significant alcohol or tobacco usage.

After local infiltration, an excisional biopsy was performed. During the surgical procedure, the lesion appeared to be encapsulated. The lesion was removed intact from the surrounding tissue and was submitted for microscopic examination. The specimen was fixed in 10% buffered formalin. Gross examination showed a specimen measuring $2.0 \times 0.9 \times 0.8$ cm in its largest dimensions with a firm consistency and white color.

Fig. 6 The patient presented with an asymptomatic submucosal mass in the anterior right buccal mucosa (white arrow)

Fig. 7 Low power view showing a well-circumscribed tumor containing a large cystic structure similar to our first case (Fig. 2). Clusters of salivary gland acini are seen embedded towards the periphery of the tumor. Areas of stromal hyalinization are also observed. (Hematoxylin-eosin stain; original magnification $\times 10$)

Histopathologically, the specimen showed the presence of a circumscribed to encapsulated tumor (Fig. 7) composed of proliferating mesenchymal oval and spindle cells (Fig. 8), many of them with wavy nuclei reminiscent of neural cells, while others displayed plumped pale nuclei. Large conspicuous areas of stromal hyalinization were noted throughout the specimen, particularly around a large cystic space lined by cuboidal to pseudostratified columnar ductal epithelium (Figs. 7, 9). Numerous small ducts with an intraductal eosinophilic coagulum and peripheral clear cells, similar to those seen in “Case 1”, were also noted (Fig. 10). A scarce number of mucous acini were seen

Fig. 8 Proliferation of oval and spindle cells with interspersed focal stromal hyalinization and a vascular proliferation suggesting a staghorn pattern. (Hematoxylin-eosin stain; original magnification $\times 100$)

Fig. 9 Higher power view showing the cystic space lined by a cuboidal to pseudostratified columnar ductal epithelium (Hematoxylin-eosin stain; original magnification $\times 100$)

entrapped amidst the proliferation of spindle cells. Some excretory salivary ducts showed oncocytic metaplasia. Surrounding the lesion, numerous unremarkable minor salivary gland acini of the mucous type, skeletal muscle fibers and lobules of adipocytes were observed. The tumor cells were immunoreactive to CD34 and vimentin, and negative for S-100, pan cytokeratin, and HHF35. Pan cytokeratin immunoreactivity highlighted the presence of entrapped salivary gland tissues (acini and ducts) as well as the epithelial lining of the cystic space (Fig. 11).

Based on the microscopic findings and the immunohistochemical profile, a final diagnosis of solitary fibrous tumor was rendered. No recurrence was noted at a 3-year follow-up.

Fig. 10 Ductal structures showing intraductal eosinophilic coagulum with prominent periductal hyalinization. Some ducts show the presence of peripheral clear cells. The resemblance to pleomorphic adenoma is striking. (Hematoxylin-eosin stain; original magnification $\times 100$)

Fig. 11 Higher power view of the tumor showing the pan cytokeratin immunoreactivity of the entrapped salivary gland acini, ducts and the epithelial lining of the cystic space (original magnification $\times 10$)

Discussion

Originally described as a “primary neoplasm of the pleura” by Kemperer and Rabin [1] in 1931, SFT has subsequently been reported to present in a variety of anatomic sites [5]. Pleural [6] and extrapleural SFT [7] may attain large size and can display malignant microscopic features and biological behavior. It has been reported that 13–23% of the pleural SFT are malignant [5]. In contrast, intraoral SFT, has an excellent prognosis associated with a benign clinical behavior [8].

Early reports uniformly regarded SFT as a tumor of mesothelial origin [9]. This view was gradually modified with the observation that SFT can affect other areas of the body [5]. Electron microscopy and immunohistochemistry have shown that SFT tumor cells are of mesenchymal origin [10]. Therefore, the World Health Organization (WHO) currently classifies SFT as an intermediate fibroblastic tumor [11].

The diagnosis of SFT may be difficult [4] in extrapleural locations due to its wide histological spectrum. Moreover, a small biopsy specimen will further hinder the ability of the pathologist to recognize this tumor despite a strict adherence to Chan’s criteria and the use of adequate immunohistochemical markers [2].

In the oral cavity, several benign, intermediate and malignant lesions must be differentiated from SFT [3, 8] (Table 1). When a spindle cell proliferation predominates, the microscopic differential diagnosis of SFT includes; leiomyoma, neurofibroma, benign nerve sheath tumors,

nodular fasciitis, low-grade sarcoma, and monophasic sarcoma [3, 8]. If a diffuse sclerosing pattern is observed, desmoplastic fibroma, sclerotic fibroma, and myofibroma should be considered [8]. In the presence of an abundant myxoid stroma, benign nerve sheath tumors, low-grade myxofibrosarcoma, low-grade liposarcoma, myxoid synovial sarcoma, and myxoid spindle cell lipoma should be included in the differential diagnosis [8]. Furthermore, SFT may exhibit the presence of multinucleated giant cells and thus, giant cell angiofibroma, a benign tumor considered by some as a subtype of SFT that has been rarely reported in the oral cavity [12], has to be ruled-out [3, 8].

The major diagnostic dilemma lies mainly in distinguishing SFT from hemangiopericytoma (HPC) due to their overlapping histological features [13]. Both tumors share the “staghorn-like” vascular pattern and cellular morphology [4]. In addition, SFT and HPC have been reported to show similar immunohistochemical and ultrastructural profiles [14]. SFT and HPC display immunoreactivity for CD34, Bcl-2 and CD99 antigens [14]. Ultrastructural studies have demonstrated pericytic, fibroblastic, and myofibroblastic differentiation in both tumors [14]. These findings have led pathologists to consider HPC and SFT as a spectrum of the same entity [13]. Consequently, usage of the term hemangiopericytoma/solitary fibrous tumor to describe these lesions has started to populate the literature [13].

Rarely, SFT of the oral cavity may show entrapment of adipose tissue, skeletal muscle, and salivary gland tissue that may also complicate the microscopic diagnosis. The presence of adipose tissue has been described in several SFTs of the oral cavity. This finding has previously been reported in other areas of the body. In fact, the prominent entrapment of adipocytes prompted Weiss et al. [15] to coin the term lipomatous hemangiopericytic-solitary fibrous tumor. The differential diagnosis of a SFT of the oral cavity with adipose cells should include spindle cell lipoma and myxoid liposarcoma [8]. Interestingly, the presence of skeletal muscle fibers in SFT has not prompted the designation of these tumors as “myogenous producing” lesions. Rather, the presence of muscle fibers in SFT has been interpreted as a reflection of the intramuscular genesis of SFT. Similarly, it appears to be that the presence of minor salivary glands in some SFTs may represent the development of this tumor within the stroma of salivary gland parenchyma [8].

Only few cases of SFT of the oral cavity have reported the entrapment of minor salivary gland tissue within its substance. In 2004, Swelam et al. [16] documented a case of SFT in the lower lip involving minor salivary glands. They described the presence of several acini with dilated duct and cystic-like structures amidst hypocellular areas. However, examination of the photomicrographs illustrating

Table 1 Histopathological differential diagnosis of SFT [3, 8]

Benign lesion	Intermediate malignancies	Malignant lesions
Leiomyoma	Dermatofibrosarcoma protuberans	Low-grade sarcoma
Nerve sheath tumor		Monophasic and myxoid synovial sarcoma
Myofibroma		Low-grade myxofibrosarcoma
Nodular fasciitis		Low-grade liposarcoma
Spindle cell lipoma		
Desmoplastic fibroma		
Sclerotic fibroma		
Giant cell angiofibroma		
Benign fibrous histiocytoma		

that the putative “hypocellularity” actually showed hypercellularity. More recently, O’Regan et al. [8] reported two more cases of SFT of the oral cavity (lip and buccal mucosa) showing involvement of minor salivary gland tissues. These two cases were characterized by the presence of extensive periductal hyalinization. Our two cases showed a combination of the microscopic findings independently described by Swelam et al. [16] and O’Regan et al. [8]. These features include: circumscription of the tumors, extensive areas of stromal hyalinization, entrapment of acinar structures, and dilated ductal structures with the formation of large cystic areas. The presence of large cystic areas in SFT arising in the stroma of minor salivary glands is an interesting finding whose pathogenesis remains obscure. We can only speculate that these cystic structures originate from the persistence of salivary excretory ducts that become increasingly dilated by the accumulation of proteinaceous material that results in an oncotic pressure phenomenon that drives the formation of a cyst. In addition, we found that many ductal structures consisted of an inner lining of dark epithelial cells and a peripheral clear cell layer, many of them containing an intraluminal

eosinophilic coagulum, reminiscent of pleomorphic adenoma. This finding coupled to the presence of extensive areas of hyalinization with interspersed areas of spindle cell proliferation argued in favor of the presence of a benign salivary gland tumor such as pleomorphic adenoma. Table 2 summarizes the main findings of the five SFTs (including our two cases) arising in the stroma of minor salivary glands.

Pleomorphic adenoma (PA) is notorious for presenting a gamut of histological variations that may lead the pathologist to diagnostic pitfalls, especially in incisional biopsies [17]. The classic microscopic features of PA consist of an epithelial proliferation with a myxoid background and many times, focal chondroid metaplasia. However, PA tends to show a morphological diversity that may simulate other benign and malignant tumors [17–19] (Table 3). For example, the epithelial component may show ductal formation and cribriform patterns that resemble adenoid cystic carcinoma. PAs with extensive myxoid background may be confused with soft tissue myxoma or neural tumors. In addition, a chondroid stroma may be erroneously interpreted as chondrosarcoma. Furthermore, a predominant spindle myoepithelial component needs to be segregated from neurogenic tumors [17, 20].

Similarly to PA, SFT can show diverse morphological features that may cause diagnostic difficulties. Examining multiple sections and the use of appropriate immunoprobes can ameliorate these difficulties.

The most consistent and reliable immunohistochemical marker for SFT is CD34 [4]. The CD34 antigen is strongly expressed in both, pleural, and extrapleural SFTs [4], including intraoral lesions [3]. Both of our cases showed a strong CD34 immunoreactivity. Bcl2 and CD99 markers have also been reported to be of value for the diagnosis of SFT. However, inconsistent expression of CD99 and lack of specificity of bcl2 in SFT lessens the value of these probes [3, 4, 8, 14]. CD34 has been used in pleomorphic adenomas to evaluate the stromal vascularization [21].

Some reports have described the cytogenetic alterations displayed by SFT and PA. SFT has been shown to display trisomy 8 and 21 [22, 23], while 70% of pleomorphic

Table 2 Reported cases of solitary fibrous tumor involving minor salivary glands

Author	Age (years)	Sex	Location	Size (cm)	Immunohistochemical findings			Follow-up
					CD34	Bcl2	CD99	
Swelam et al. [16]	65	F	Lower lip	2.0	3+	+	P	NED at 2 years
O’Regan et al. [8]	48	M	Left lip	1.5	3+	3+	Neg	Lost to follow up
	37	F	Left buccal mucosa	1.0	3+	3+	Neg	NED at 12 years
Present cases	45	F	Right retromolar region	1.5	3+	NA	NA	NED at 3 years
	67	F	Left cheek	2.0	3+	NA	NA	NED at 3 years

P positive, Neg negative, N/A not available, NED no evidence of disease

Table 3 Microscopic features of pleomorphic adenoma that may resemble other tumors. Modified from Speight and Barrett [18]

Microscopic features	Resemblance
Morphological diversity	Polymorphous low grade adenocarcinoma
Bilayered ducts and cribriform pattern	Adenoid cystic carcinoma
Bilayered ducts with clear outer cells	Epithelial-myoepithelial carcinoma
Sheets of epithelioid or basaloid cells	Basal adenoma or adenocarcinoma
Myxoid stroma	Myxoma, neural tumors
Chondroid stroma	Chondrosarcoma
Plasmacytoid cells	Plasmacytoma
Spindled myoepithelial cells	Benign neural tumors and spindle cell sarcomas
Squamous metaplasia	Squamous cell carcinoma
Oncocytic metaplasia	Oncocytoma
Lipometaplasia [19]	Benign lipomatous tumors
Ductal and spindle cell proliferation with interspersed hyalinization (our cases)	Solitary fibrous tumor

adenomas show abnormal karyotypes [24]. Thus, cytogenetic studies may be of value to differentiate these two tumors.

Intraoral SFT is usually treated by complete surgical excision and recurrence is unlikely. Two case series of intraoral SFTs, with extensive follow-up information, showed no signs of local recurrence and/or malignant transformation after treatment [3, 8]. In contrast, malignant and metastatic SFTs have been reported to occur in extraoral sites [6, 7]. Our two cases have demonstrated the expected biological behavior for intraoral SFT, with no evidence of recurrence at a three-year follow-up.

Our cases are unique not only because of their interglandular location but also because both mimicked pleomorphic adenoma at the microscopic level. Reporting this uncommon presentation of intraoral SFT should help the pathologist to resolve a potential diagnostic pitfall.

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