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Case Report

Solitary fibrous tumor with malignant potential arising in sublingual gland

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A rare case is described of a solitary fibrous tumor (SFT) with malignant potential arising in the sublingual gland. A 59-year-old man presented with a 4-month history of a slowly enlarging painless mass in the center of the floor of the mouth. The tumor was a well-demarcated, firm mass with a multicystic lesion. The tumor exhibited highly cellular areas of spindle cells with patternless architecture alternating with hypocellular areas. The tumor cells were positive for CD34 and bcl-2 as well as vimentin, and negative for epithelial, myogenic, neurogenic and histiocytic markers. The tumor cells formed multiple satellite nodules around dilated ducts in the multicystic lesion, indicating infiltrative growth. In addition, areas exhibiting higher cellularity with increased mitoses were noticed in the satellite nodules, although cellular atypia was not obvious. These findings led to a final diagnosis of SFT with malignant potential. There has been no recurrence or metastasis for 27 months after the surgery. Solitary fibrous tumor of the salivary gland must be differentiated from various spindle cell neoplasms including myogenic, peripheral nerve sheath, fibroblastic and fibro-histiocytic spindle cell neoplasms, hemangiopericytoma and myoepithelioma. In addition to characteristic morphological features, an immunohistochemical positivity for CD34 and bcl-2 may aid in the diagnosis of SFT.

Key words: differential diagnosis, malignant, salivary gland, solitary fibrous tumor

Tumors originally described as localized fibrous mesothelioma or submesothelial fibroma have recently become known as 'solitary fibrous tumor (SFT)', as it has been demonstrated that they are not of mesothelial origin and can occur in extrapleural sites, including the head and neck region.[1–13] However, the involvement of salivary glands is uncommon.[4–8] Although a set of diagnostic criteria for SFT has been proposed, the broad range of morphological features shared with various spindle cell neoplasms, in addition to the rare occurrence in salivary glands, results in diagnostic difficulty.

We report an interesting case of SFT originating in the sublingual gland showing infiltrative growth and hypercellular, mitotically active areas, indicative of malignant potential. Histological and immunohistochemical characteristics of this tumor are described, along with a discussion of the differential diagnosis.

CLINICAL SUMMARY

A 59-year-old Japanese man presented with a 4-month history of a gradually enlarging, painless mass in the center of the floor of the mouth. On oral examination, there was a mass of elastic hardness, measuring 38 × 30 mm, covered by normal mucosa. Contrast-enhanced computed tomography (CT) scan revealed an enhancing mass with a low attenuation at a central region in the floor of the mouth (Fig. 1a) and a low density lesion suggesting retention of fluid in the left sublingual area (Fig. 1b). The connection between these two lesions was not obvious. There was no evidence of bony involvement. A clinical diagnosis was ranula or benign sublingual gland tumor with cystic change. When a biopsy was taken from the surface of the lesion of the floor of the mouth, mucous fluid oozed. The biopsy specimen was composed of scattered short spindle cells in collagenous fibrous tissue with chronic inflammatory cell infiltration and small blood vessels (Fig. 2). There was no mitotic figure. On the basis of the findings of clinical, CT scan and biopsy specimen, a tentative diagnosis

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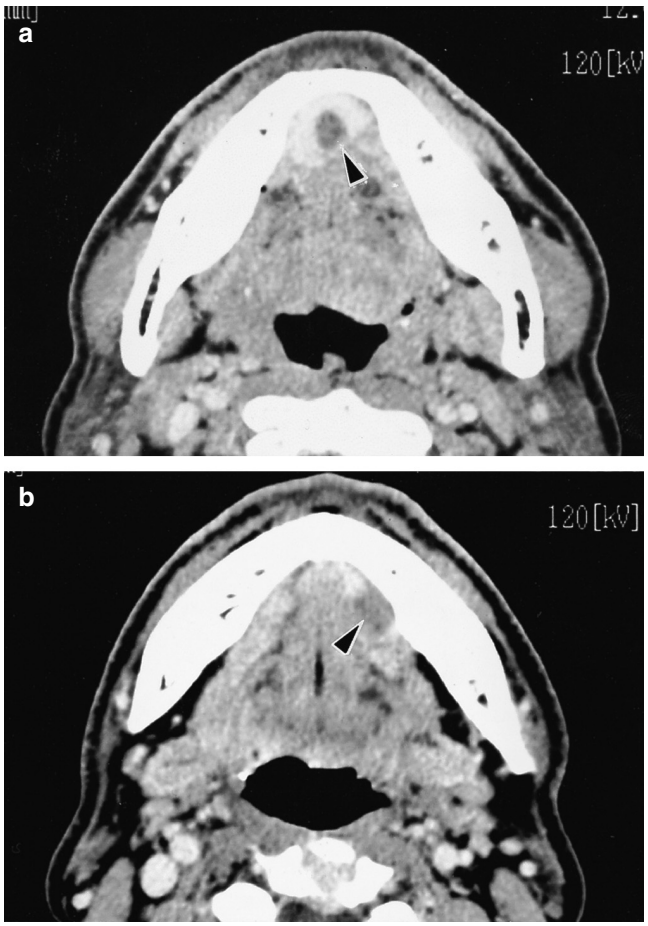

Figure 1 Contrast-enhanced computed tomography scan demonstrating (**a**) an enhancing mass with a low attenuation at a central region in the floor of mouth; and (**b**) a low-density lesion in the left sublingual area. Arrowheads point to the lesions.

of a fibrous wall of ranula was made. Excision of the lesion was performed. During surgery, a well-demarcated firm mass and a multicystic lesion corresponding to an enhancing mass and a low-density lesion on CT examination, respectively, were identified adjacent to the sublingual gland. As the microscopic examination demonstrated that the tumor showed an infiltrative growth and was present at the edges of the surgical specimen, additional resection with adjacent soft tissue was performed. The presence of the tumor was confirmed in the resected tissues. The patient is well without recurrence and signs of metastasis 27 months after the surgery.

PATHOLOGICAL FINDINGS

Macroscopically, the tumor was composed of a firm mass accompanied by a multicystic lesion corresponding to a low-density lesion in the left sublingual area on CT examination (Fig. 3). The cut surface of the firm mass was solid and grayish-white, and showed a cystic space containing a jelly-like material in the central area (Fig. 3). Histologically, the solid tumor was well demarcated, but not encapsulated, and entrapped sublingual gland tissues at the periphery (Fig. 4). The tumor exhibited highly cellular areas of plump, or spindle cells, with patternless architecture (Fig. 5a) alternating with hypocellular areas (Fig. 5b). Storiform-like arrangement of the tumor cells was occasionally observed, but there were no xanthoma cells or giant cells. The cellularity and the amount of collagen fibers varied from one area to another. In the hypocellular areas, the tumor cells were embedded in collagen bundles (Fig. 5b), which were often thick and keloid like. The histological findings of the biopsy specimen were essentially identical to those of the hypocellular areas. The tumor cells had oval nuclei and scant eosinophilic cytoplasm with ill-defined cell boundary. The blood vessels were abundant throughout the tumor; in the hypercellular areas, many capillary vessels with narrow spaces were prominent, in contrast

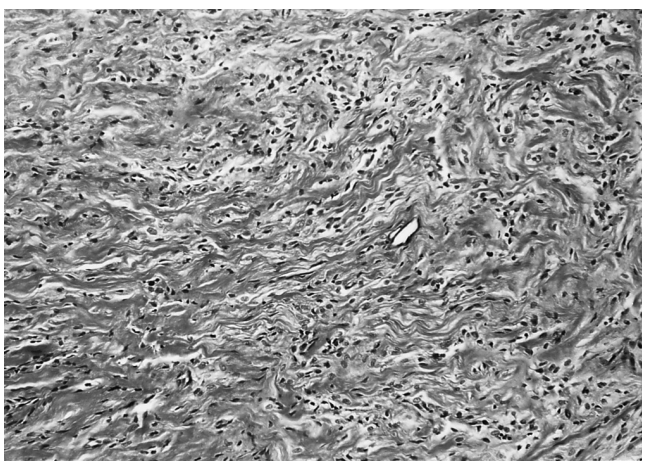

Figure 2 Biopsy specimen, which was composed of fibrous connective tissue with scattered fibroblast-like cells and small vessels.

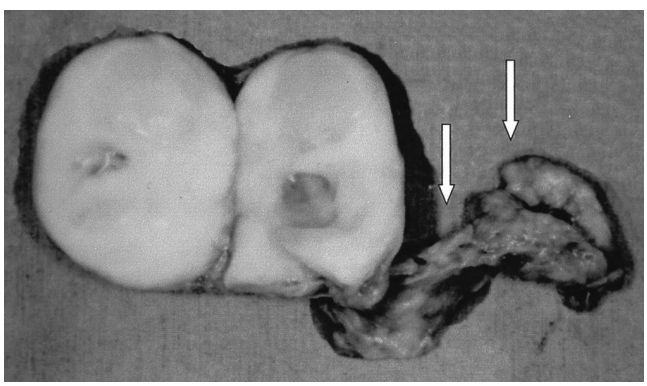

Figure 3 Macroscopic view of the tumor, showing a solid tumor with cystic change accompanied by a multicystic lesion (arrows).

Figure 4 Gross pathological findings of the excised solid tumor. The tumor entraps the remnants of sublingual gland tissues at the periphery.

to those with gaping spaces in the hypocellular areas. In the center of the firm mass, a myxoid area with cystic change was present. It was noticed that the tumor exhibited infiltrative growth in the multicystic lesion. Although, macroscopically, there was no solid tumor, the tumor cells formed multiple small satellite nodules around dilated ducts in the multicystic lesion (Fig. 6a). In addition, although cellular pleomorphism was not obvious, hypercellular areas with crowded nuclei and increased mitoses (more than four mitoses per 10 high-power fields) were noticed in the satellite nodules (Fig. 6b). In the solid tumor, findings suggestive of malignant change were not observed and mitotic activity was less than one per 10 high-power fields. Proliferating cell nuclear antigen (PCNA)-positive cells were also more frequently found in the mitotically active areas (Fig. 6c). The PCNA labeling index in these satellite nodules (7.1%) was higher than that in the solid tumor (2.2%).

Immunohistochemically, the tumor cells were intensely positive for CD34 as well as vimentin (Fig. 5c). α-Smooth muscle actin was also occasionally expressed, but cytokeratins, epithelial membrane antigen, desmin, myoglobin, factor VIII-related antigen, S-100 protein, glial fibrillary acidic protein (GFAP) and CD68 were completely negative. Bcl-2 was weakly expressed by most of the tumor cells. Immunohistochemical results are summarized in Table 1. On the basis of these histological and immunohistochemical findings, the final diagnosis of SFT with malignant potential was made.

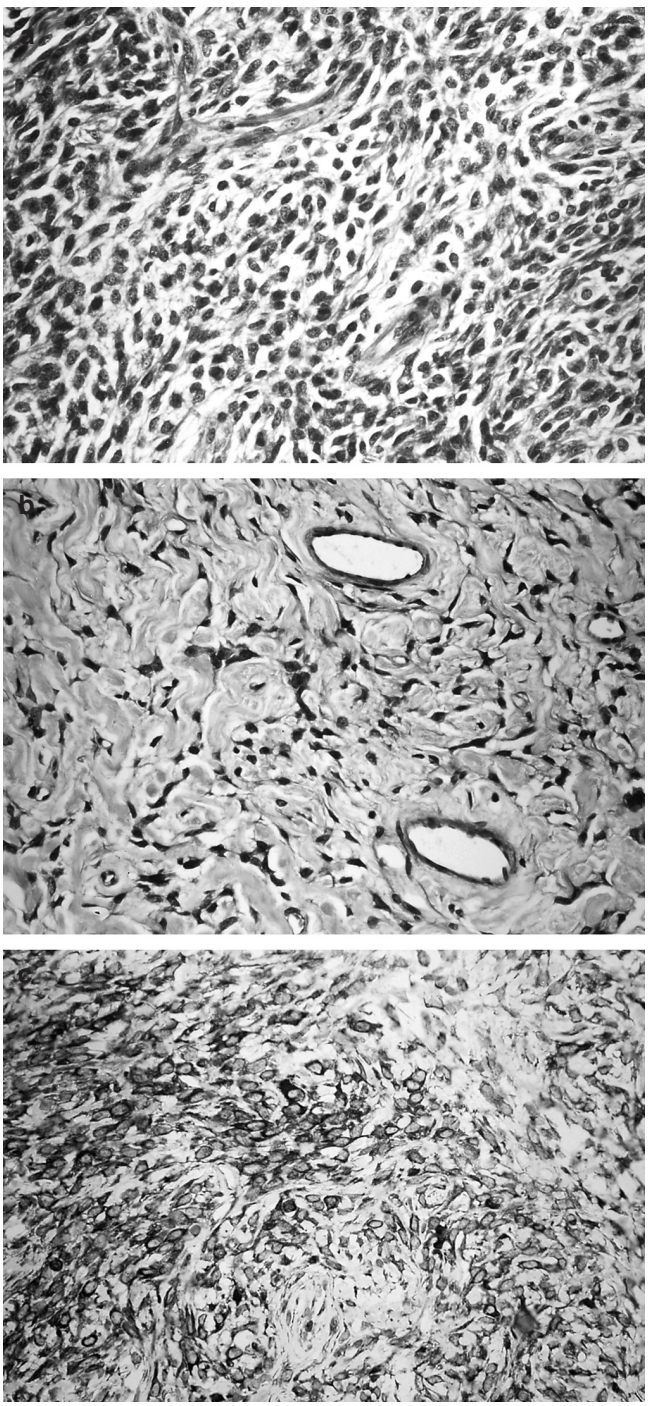

Figure 5 The tumor is characterized by (**a**) highly cellular areas of plump or spindle cells with bland oval nuclei and scant cytoplasm showing a haphazard arrangement; and (**b**) hypocellular collagenous areas with abundant blood vessels. (**c**) Most of the tumor cells intensely express CD34.

DISCUSSION

Solitary fibrous tumor was first described by Klemperer and Rabin in 1931[14] and thought to be associated only with a mesothelial-lined surface, but it most frequently arises in the pleura and occasionally in the pericardium or peritoneum. However, after El-Naggar *et al.* reported SFT that presented as an ethmoid sinus mass,[1] numerous examples histologi-

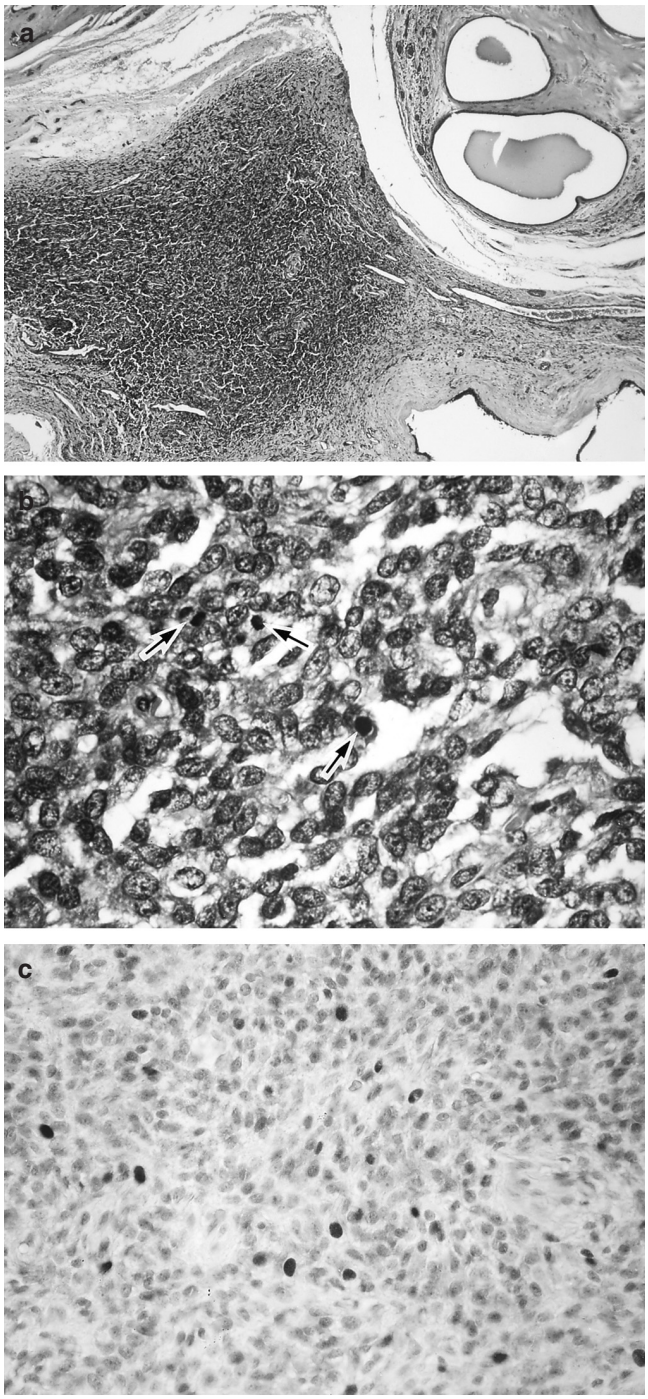

Figure 6 (**a**) In the multicystic lesion, the tumor cells form hypercellular satellite nodules around dilated ducts of sublingual gland. (**b**) Crowded nuclei and increased mitotic figures (arrows) are noticed. (**c**) Proliferating cell nuclear antigen is frequently detected in the nuclei of the tumor cells.

cally identical to a serosa-associated SFT have been described in various extraserosal locations including the head and neck region.[2–13] The ubiquitous occurrence of SFT in extraserosal locations appears to demonstrate that SFT is not of mesothelial origin, but a mesenchymal neoplasm.[15] Most of the immunohistochemical, ultrastructural and tissue culture studies have supported its mesenchymal origin. An immunohistochemical marker for SFT, CD34, which was originally recognized as a marker for primitive hematopoietic elements and later identified in endothelial cells, has also been shown in a variety of non-hematopoietic and non-endothelial cell tumors including SFT, giant cell angiofibroma and spindle cell lipoma. It is interesting that these tumors show considerable overlap between the histological, immunohistochemical and biological features. Recently, a novel family of interstitial dendritic cells characterized by fibroblastic features, one or more long cytoplasmic processes and CD34 positivity has been shown to be widely distributed throughout connective tissues.[16,17] It has been hypothesized that SFT and other CD34-positive spindle cell tumors may potentially share a common cell origin, namely this population of dendritic cells.

In the head and neck region, the involvement of the orbit, sinonasal tract, nasopharynx, major salivary glands, oral cavity (especially buccal mucosa) and thyroid has been reported. In the major salivary glands, only 11 cases that involved the parotid (seven cases), sublingual (two cases) or submandibular glands (two cases) of five men and six women ranging in age from 43 to 81 have been described.[4–8]

Because of its rarity and broad range of morphological appearances, SFT of the salivary glands can be confused with a variety of benign and malignant spindle cell neoplasms including fibroblastic tumor, fibro-histiocytic tumor, peripheral nerve sheath tumor, myogenic tumor, hemangiopericytoma and myoepithelial tumor. The extent to which a given histopathological feature is present can help determine the most appropriate diagnosis. In the present case, as the biopsy specimen contained only hypocellular fibrous area, we could not suggest the possibility of SFT at that time. It is also not easy to distinguish extrapleural SFT from non-neoplastic conditions with fibrosis in a small biopsy specimen. In contrast, because entrapment of normal salivary gland acini and ducts could be observed at the edges of the lesion, SFT of the salivary glands may be misdiagnosed as a more aggressive tumor. In the present case, the morphological features were identical to those of SFT in the pleura. It was composed of non-descriptive spindle cells dispersed among collagen bundles in a ‘patternless’ pattern. Cellularity of the tumor varied from area to area and was inversely related to the amount of collagen fibers.

Immunohistochemically, the tumor cells were intensely positive for CD34 and vimentin. These findings fit the diagnostic criteria for SFT proposed by Chan.[18] The consistent positivity for bcl-2 has also been reported in SFT. The immunohistochemical features, such as the positivity for CD34, vimentin and bcl-2, and the negativity for desmin, actin, S-100 protein and CD68, may rule out myogenic, peripheral nerve sheath, fibroblastic and fibro-histiocytic spindle cell

Table 1 Immunohistochemical findings

Anti-	Source	Dilution	Results
CD34	Novocastra†	1:25	+
Cytokeratins (AE1/AE3)	Boehringer Mannheim‡	Prediluted	–
Epithelial membrane antigen	Dakopatts§	1:100	–
Vimentin	Dakopatts	1:50	+
α-Smooth muscle actin	Dakopatts	1:50	Focal
Desmin	Dakopatts	1:100	–
Myoglobin	Dakopatts	1:100	–
Factor VIII-related antigen	Dakopatts	1:200	–
S-100 protein	Dakopatts	1:400	–
Glial fibrillary acidic protein	Dakopatts	1:100	–
CD68	Dakopatts	1:50	–
bcl-2	Dakopatts	1:40	W+
Proliferating cell nuclear antigen	Dakopatts	1:100	
Solid tumor			2.2%
Satellite nodules			7.1%

+, Positive; W+, weak positive; –, negative.
† Newcastle, UK; ‡ Indianapolis, IN, USA; § Glastrup, Denmark.

neoplasms. The distinction of SFT from hemangiopericytoma is most difficult because of their striking morphological and immunohistochemical similarities. Generally, hemangiopericytoma shows homogeneously high cellularity and staghorn-like vessels throughout the lesion, whereas SFT shows varying cellularity and often thick and keloid-like hyalinization. In addition, hemangiopericytoma has been reported to be less consistently positive for CD34 than SFT. However, there is controversy as to whether hemangiopericytoma is a distinct clinicopathological entity or only represents a histological pattern, as hemangiopericytoma-like appearance may be observed at least focally in a diversity of tumors. Recently, some cases of hemangiopericytoma involving the major salivary glands reported before the recognition of extraserosal SFT have been reclassified as SFT. Further studies may be needed on the clinical and histopathological comparison between SFT and hemangiopericytoma based on the accumulation of many cases for settling this question.

Myoepithelioma has also to be considered within the differential diagnosis of SFT in the salivary glands. In fact, the first impression based only on the histopathological findings of the hematoxylin and eosin-stained surgical specimens led us to the misdiagnosis of infiltrating myoepithelioma of spindle cell type. However, the hypocellular areas with dense fibrosis observed in the present case are not features of myoepithelioma and the immunohistochemical findings, such as the positivity for CD34 and the negativity for cytokeratins, S-100 protein and GFAP, deny the diagnosis of myoepithelioma.

To our knowledge, all of the reported cases of SFT arising in the oral cavity and major salivary glands have been clinically and histologically benign. However, cases of malignant SFT have been reported both in the pleural and extrapleural sites. The same prognostic factors reported for SFT of the pleura, such as the presence of high cellularity, more than four mitoses per 10 high-power fields, pleomorphism, hemorrhage and necrosis, appear applicable to extrapleural SFT. However, difficulty of reliably predicting the biological behavior on the basis of these histological parameters has been described. In a large series of pleural SFT, 37% were classified as histologically malignant, but 45% of these tumors were cured by simple excision.[19] The most important prognostic factor is reported to be the ability to completely excise the entire tumor.

The present case showed infiltrating growth and formation of satellite nodules with areas of mitotic frequency and high cellularity. Chan described that the criteria of malignancy of SFT are the presence of two or more of the following features: high cellularity with crowding and overlapping of nuclei; cellular pleomorphism; and mitotic count more than four per 10 high-power fields.[18] Our case fulfils this criterion, therefore additional surgical treatment was performed. Vallat-Decouvelaere *et al.* found a higher rate of clinically malignant behavior than the previous series of extrathoracic SFT based on the analysis of their large series with long follow-up data.[20]

In the present case, the patient is well without recurrence and signs of metastasis 27 months after the surgery; however careful, long-term clinical follow up may be required for the determination of the biological behavior of SFT. We agree with the suggestion by Nascimento[15] that, because extraserosal SFT has been recognized only recently, tumors with histological features of malignancy should be regarded as potentially malignant and should be followed up closely even after a complete resection.

REFERENCES

1 El-Naggar A, Ward RW, Ro JY, Ayala AG, Ordonez NG. Fibrous tumor with hemangiopericytic pattern, so-called 'localized fibrous tumor of pleura'. *Lab Invest* 1987; **56**: 21A.

2 Zukerberg LR, Rosenberg AE, Randolph G, Pilch BZ, Goodman ML. Solitary fibrous tumor of the nasal cavity and paranasal sinuses. *Am J Surg Pathol* 1991; **15**: 126–30.
3 Safneck JR, Alguacil-Garcia A, Dort JC, Phillips SM. Solitary fibrous tumour: Report of two new locations in the upper respiratory tract. *J Laryngol Otol* 1993; **107**: 252–6.
4 Gunhan O, Yildiz FR, Celasun B, Onder T, Finci R. Solitary fibrous tumor arising from sublingual gland: Report of a case. *J Laryngol Otol* 1994; **108**: 998–1000.
5 Hanau CA, Miettinen M. Solitary fibrous tumor: Histological and immunohistochemical spectrum of benign and malignant variants presenting at different sites. *Hum Pathol* 1995; **26**: 440–49.
6 Ferreiro JA, Nascimento AG. Solitary fibrous tumor of the major salivary glands. *Histopathology* 1996; **28**: 261–4.
7 Suster S, Nascimento AG, Miettinen M, Sickel JZ, Moran CA. Solitary fibrous tumors of soft tissue: A clinicopathologic and immunohistochemical study of 12 cases. *Am J Surg Pathol* 1995; **19**: 1257–66.
8 Brunnemann RB, Ro JY, Ordonez NG, Mooney J, El-Naggar AK, Ayala AG. Extrapleural solitary fibrous tumor: A clinicopathologic study of 24 cases. *Mod Pathol* 1999; **12**: 1034–42.
9 Kurihara K, Mizuseki K, Sonobe J, Yanagihara J. Solitary fibrous tumor of the oral cavity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87**: 223–6.
10 Perez-Ordonez B, Koutlas IG, Strich E, Gilbert RW, Jordan RCK. Solitary fibrous tumor of the oral cavity: An uncommon location for a ubiquitous neoplasm. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87**: 589–93.
11 Iwai S, Nakazawa M, Yoshikawa F, Amekawa S, Sakuda M. Solitary fibrous tumor of the buccal mucosa: Report of a case with immunohistochemical studies. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 461–5.
12 Lukinmaa PL, Hietanen J, Warfvinge G *et al.* Solitary fibrous tumour of the oral cavity: Clinicopathological and immunohistochemical characterization of three cases. *J Oral Pathol Med* 2000; **29**: 186–92.
13 Alawi F, Stratton D, Freedman PD. Solitary fibrous tumor of the oral soft tissues: A clinicopathologic and immunohistochemical study of 16 cases. *Am J Surg Pathol* 2001; **25**: 900–10.
14 Klemperer P, Rabin CB. Primary neoplasms of the pleura: Report of five cases. *Arch Pathol* 1931; **11**: 385–412.
15 Nascimento AG. Solitary fibrous tumor: A ubiquitous neoplasm of mesenchymal differentiation. *Adv Anat Pathol* 1996; **3**: 388–95.
16 van de Rijin M, Rouse CV. CD34: A review. *Appl Immunohistochem* 1994; **2**: 71–80.
17 Regezi JA, Nickoloff BJ, Headington JT. Oral submucosal dendrocytes: Factor XIIIa+ and CD34+ dendritic cell populations in normal tissues and fibrovascular lesions. *J Cutan Pathol* 1992; **19**: 398–406.
18 Chan JKC. Solitary fibrous tumor-everywhere, and a diagnosis in vogue. *Histopathol* 1997; **31**: 568–76.
19 England DM, Hochholzer L, McCarthy ML. Localized benign and malignant fibrous tumors of the pleura: A clinicopathologic review of 223 cases. *Am J Surg Pathol* 1989; **13**: 640–58.
20 Vallat-Decouvelaere AV, Dry SM, Fletcher CDM. Atypical and malignant solitary fibrous tumors of extrathoracic locations: Evidence of their comparability to intrathoracic tumors. *Am J Surg Pathol* 1998; **22**: 1501–11.