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Reviews

Leiomyoma of the Oral Cavity: A Light Microscopic and Immunohistochemical Study with Review of the Literature from 1884 to 1992

Ernest Baden, John L. Doyle and David A. Lederman

Leiomyoma is the most common benign neoplasm in the uterus and stomach but is rare in the oral cavity. There were only 5 oral cases in a series of 7748 leiomyomas of all sites. Benign smooth muscle neoplasms are classified into leiomyoma (solid leiomyoma), angiomyoma (vascular leiomyoma) and epithelioid leiomyoma (leiomyoblastoma). 6 cases diagnosed as leiomyoma were retrieved from the files of two oral biopsy services over the past 25 years. A light microscopic study including trichrome and phosphotungstic acid haematoxylin (PTAH) stains, and an immunohistochemical study with the following markers: desmin, muscle specific actin, myoglobin, vimentin, S-100 protein, neuron-specific enolase, factor VIII and Ulex europeus were done with suitable controls. The haematoxylin and eosin and Masson's trichrome stains supported a diagnosis of leiomyoma in all 6 cases but PTAH was positive in only 3 of them. The immunohistochemical study confirmed the diagnosis of leiomyoma in 3 cases. The other 3 were identified as granular cell tumour, myofibroma and neurofibroma, respectively. The review of the literature contributed the following data: mean age was 41 and median age 39 in 134/142 patients. A male sex prevalence 72/137 patients (54.0%) was noted. The lips were the most common site with 39 cases (27.46%) followed by the tongue 26 (18.30%), cheeks and palate 22 (15.49%), gingiva 12 (8.45%), and mandible 8 (5.63%). Prognosis of oral leiomyomas is excellent. Immunohistochemistry is a precise and reliable method for definitive diagnosis of oral leiomyoma.
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INTRODUCTION

LEIOMYOMA IS the most common benign neoplasm of the uterus and stomach [1] and is rare in the oral cavity. The first case of oral leiomyoma was reported by Blanc in 1884 [2]. In a series of 7748 leiomyomas of all sites only 5 cases were in the oral cavity [1]. When all benign tumours of the oral cavity were considered, leiomyoma accounted for only 0.42% compared to lipomas which had an incidence of 2.4% [3].

Soft tissue leiomyomas (leiomyoma cutis) were next in frequency to those of the uterus and stomach [1]. They tend to occur early in life and show a clear female predominance [4], whereas in the oral cavity, they occur later in life and have a male predominance.

These benign smooth muscle neoplasms are classified as: leiomyoma (solid leiomyoma), angiomyoma (vascular leiomyoma), and epithelioid leiomyoma (leiomyoblastoma, bizarre leiomyoma).

Only a few immunohistochemical studies of oral and head and neck leiomyomas have been published [5–7].

The purpose of this study was to evaluate the reliability of routine (haematoxylin and eosin) and special stains [trichrome and phosphotungstic acid haematoxylin (PTAH)] for the histopathological diagnosis of oral leiomyomas, to define their immunohistochemical characteristics, and review the literature from 1884 to 1992.

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MATERIALS AND METHODS

An archival search for cases diagnosed as leiomyomas or related neoplasms for the past 25 years was made in two oral biopsy diagnostic services. After a review of the available slides, 6 cases with available paraffin blocks were selected for the study.

The paraffin blocks were recut and 5 μ sections were mounted on glass slides with poly-L-lysine. Haematoxylin and eosin, Masson's trichrome and Mallory's PTAH were done on all 6 cases.

The avidin–biotin complex (ABC) method was used for the immunohistochemical study. The slides were deparaffinised and dehydrated to absolute alcohol. Endogenous peroxidase was quenched with 1.0% H_2O_2 in absolute methanol for 5 min. Hydration was completed in phosphate buffered saline (PBS) at pH 7.4 for 10 min (three changes). Normal serum was used to reduce non-specific staining for 20 min. The sections cut for Ulex europeus antigen identification were covered with UEA-1 lectin dilution 1/100 and incubated overnight. All sections were again washed with PBS. Primary antiserum was applied

Table 1. *Antibodies used for immunohistochemistry*

Reagent	Source	Dilution
Anti-desmin	Dako Co. California	1:50
Anti-muscle specific actin	Sigma Co.	Prediluted
Anti-myoglobin	Dakopatts Denmark	1:200
Anti-vimentin	Dako Co.	1:500
Anti-S 100 protein	Dakopatts Denmark	1:100
Anti-neuron-specific enolase	Dako Co.	1:50
Anti-Factor VIII	Dako Co. California	1:700
Ulex europeus	Dako Co. California	1:100

and the slides incubated according to the time required for each marker (Table 1). The slides were then washed in PBS for 10 min. This was followed by incubation with diluted biotinylated antibody solution for 20 min (either goat anti-rabbit IgG or horse anti-mouse IgG). The sections were again washed for 10 min in PBS buffer and then incubated with Vectastain ABC reagent for 30–60 min. The slides were again washed in PBS for 10 min and then reacted with diaminobenzidine (DAB) 1 mg/ml from 2 to 7 min by checking under the microscope for development. The slides were washed under tap water, counterstained with haematoxylin, dehydrated and mounted with Permount.

Negative controls using normal rabbit and mouse serum were prepared. Positive control tissues were intestine and skin. Built-in controls were also present in the normal tissue surrounding the neoplasms.

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RESULTS

The haematoxylin and eosin and Masson's trichrome stains supported a diagnosis of leiomyoma in all 6 cases but PTAH was positive in only 3 cases.

The immunohistochemical study gave the following results: muscle-specific actin (MSA) was positive in 3 cases, myoglobin in 2 cases and desmin weakly positive in 1 case. All of the 3 cases were negative with S-100 protein and neuron-specific enolase (NSE).

The three remaining cases were negative with all of the above muscle fibre markers, except for focal staining with desmin in one which was strongly positive for S-100 protein and neuron-specific enolase supporting a diagnosis of granular cell tumour. The other 2 cases were strongly reactive for vimentin. One of these also showed focal staining for the S-100 protein and NSE markers suggesting a diagnosis of neurofibroma. The other vimentin positive case was negative with S-100 protein and NSE but focally was marked by MSA, therefore, suggesting a myofibroma, lesion closely related to leiomyoma.

The endothelial cells of all cases were marked with Factor VIII and Ulex europeus.

Immunohistochemistry confirmed the diagnosis of leiomyoma in 3 cases and identified the other three as granular cell tumour, myofibroma and neurofibroma, respectively.

DISCUSSION

The "irritation fibroma", a reactive lesion is by far the most common spindle cell "tumour" of the oral soft tissues. Spindle cells present a wide morphological spectrum readily explained by their histogenesis from undifferentiated mesenchymal cells during embryogenesis. Since both fibroblasts and leiomyocytes are spindle cells, and, it may be difficult to distinguish between them when only haematoxylin and eosin stained sections are available. Neurofibromas closely resemble fibromas, and some granular cell tumours may consist primarily of spindle cells. The myofibroma is closely related to the leiomyoma, and like the latter is rare in the oral cavity. Its histopathology is indistinguishable with routine stains from either fibroma or leiomyoma. Masson's trichrome stain is not reliable, dependant upon proper fixation and technical use of the reagents may given false positive results. This study showed that all 6 cases were positive with Masson's trichrome, using controls suggesting the lesions to be leiomyomas. PTAH was more specific. The three leiomyomas stained positive in contrast to the three other cases which were negative. However, interpretation of PTAH stain may be difficult in some cases as evidenced in these cases. Immunohistochemical markers are even more specific when properly selected and performed under standardised and controlled conditions. A diagnosis of leiomyoma was confirmed in 3 cases, and three other neoplasms were correctly identified as granular cell tumour, myofibroma and neurofibroma, respectively.

A review of the literature from 1884 to 1992 disclosed [1, 2, 4–6, 8–17, 19–101] 142 cases which documents the rarity of leiomyoma of the oral cavity. If one considers that the majority of oral leiomyomas were diagnosed on the basis of haematoxylin and eosin, and one of the trichrome stains, PTAH being used infrequently, the actual number of oral leiomyomas may be substantially less.

The mean age in 134 of a total of 142 cases was 41 years, the median age 39 years and the range from 2 months to 85 years. In 8 cases the age was not given. In an analysis of five reviews of oral leiomyomas [9–13] the mean age ranged from 39 to 46 years. Oral leiomyomas were found to be more common in males (54.0%) (72/137 patients) compared with females (46.0%) (65/137 patients). The sex was not known in 5 cases (Table 2). The male predominance was confirmed by two reviews [9, 13] to be slight in two others [11, 12] and an equal ratio of male to female found in one [10].

The site distribution in our study [1, 2, 4–6, 8–17, 19–101]

Table 2 [1, 2, 4–6, 8–17, 19–101]. *Leiomyomas of the oral regions*

Total number of cases: 142	
Age in 134 patients	
Mean	41 years
Median	43 years
Range	2 months–85 years
Sex in 137 patients	
Male > female	
72	65

Table 3 [1, 2, 4–6, 8–17, 19–101]. *Sites of leiomyomas in the oral tissues*

Sites	Number	Per cent (%)
Lips	39	27.46
Tongue	26	18.30
Cheek	22	15.49
Palate	22	15.49
Gingiva	12	8.45
Mandible	8	5.63
Others	13	9.15

Total number of cases = 142.

was as follows: the lips were the most common site with 39 cases (27.46%), the upper lip (14 cases) and the lower lip (15 cases) were nearly equally involved. The exact location on the lips was not reported in 10 cases. The tongue was next in frequency with 26 cases (18.30%), followed by the cheeks and palate, both with 22 cases (15.49%), gingiva with 12 cases (8.45%), and the mandible with 8 (5.63%). Other locations accounted for 13 cases: mandibular anterior mucobuccal fold (4), floor of mouth (2), parotid (2), submaxillary gland (2), uvula (2), and tonsil (1) (Table 3).

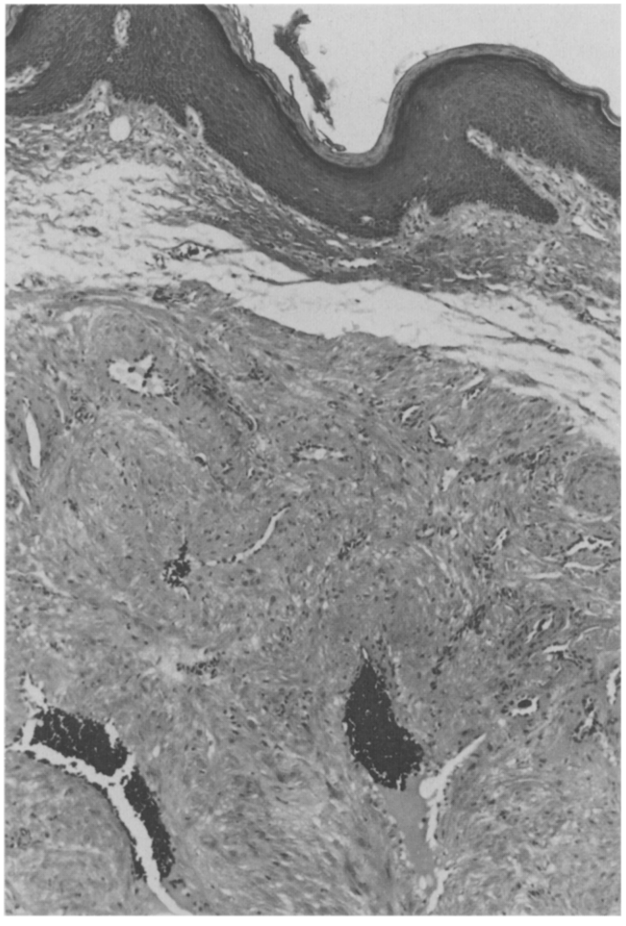

Fig. 1. Angiomyoma (vascular leiomyoma). Well circumscribed submucosal tumour consisting of numerous large vascular space within cohesive proliferation of closely packed spindle cells arranged in a circumferential, whorling and streaming pattern. Haematoxylin and eosin × 40.

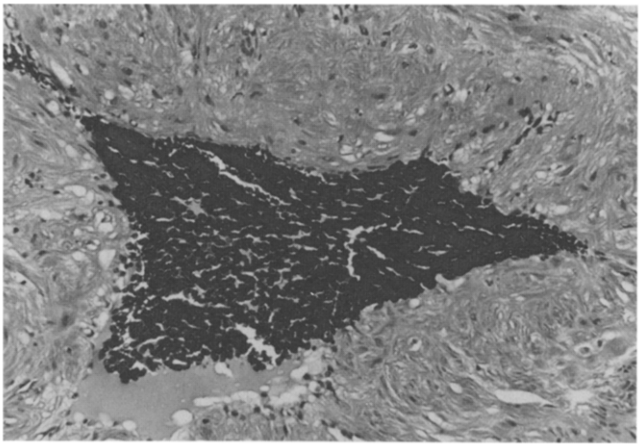

Fig. 2. Angiomyoma (vascular leiomyoma). Higher power of an irregular vascular space filled with erythrocytes. Endothelial-like cells blend into closely packed oval and spindle shaped cells arranged in a whorling, streaming and interlacing pattern. The nuclei are small and pleomorphic. Haematoxylin and eosin × 100.

Fig. 3. Angiomyoma (vascular leiomyoma). Fascicles of interlacing wavy spindle cells present well defined cell membranes, longitudinally arranged intracytoplasmic fibrils and oval cigar-shaped orthochromatic nuclei with one to two nucleoli. Haematoxylin and eosin × 400.

The five reviews of the literature disagreed with the above site distribution, because either they represented earlier studies with fewer cases, different selection criteria or omission of case reports.

The tongue was found to be the prevalent site in four [9–11, 13], followed by the palate in four studies [10–13] and the cheeks in one [9]. In third position were the cheeks in three reviews [10, 11, 13] and the tongue [12] and palate [9] in one, respectively. In sharp contrast with our findings, the lips were in 4th place in four of the five reviews [9–11, 13] and only one study confirmed our findings [12]. Four of the five studies reported that the lower lip was more commonly involved than the upper lip [9–11, 13], however we could not confirm this finding.

How do the reported data compare with a series of 562 leiomyomas of all sites [18]? Five hundred (89%) were found

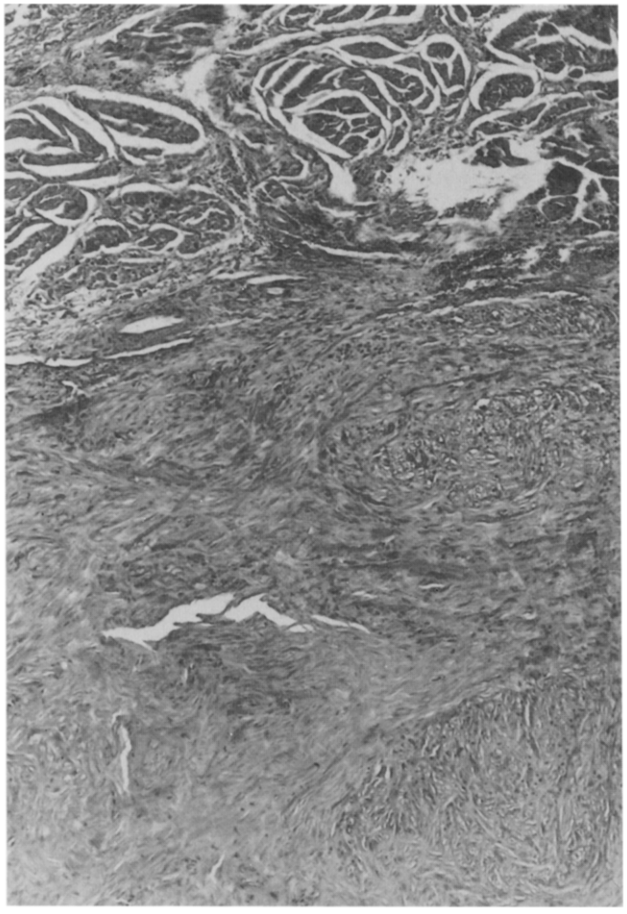

Fig. 4. Leiomyoma (solid leiomyoma). Well circumscribed submucosal tumour extending to bundles of striated muscle. A whorling to interlacing pattern of closely packed wavy spindle shaped cells is seen. Haematoxylin and eosin x 40.

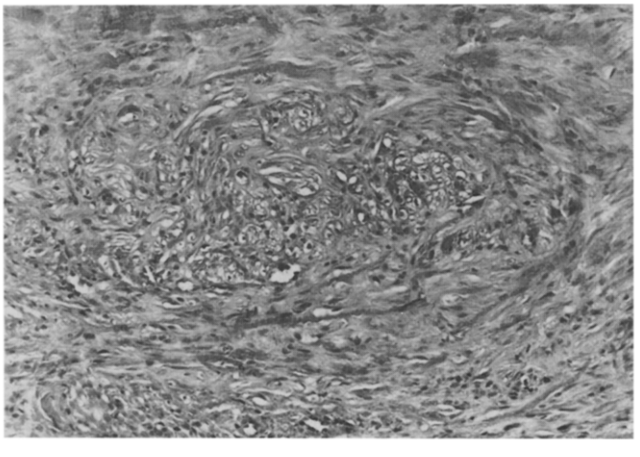

Fig. 5. Leiomyoma (solid leiomyoma). Cross-section of a nodule of closely packed whorling spindle cells interlacing with peripheral bundles of spindle cells. Haematoxylin and eosin x 100.

in the extremities, 48 (8.54%) in the head and only 14 in the trunk. The mean age was 47 years (range 12–84 years) and a clear female prevalence (1.7:1) was found. The site distribution in the head region was as follows: the ears were the most

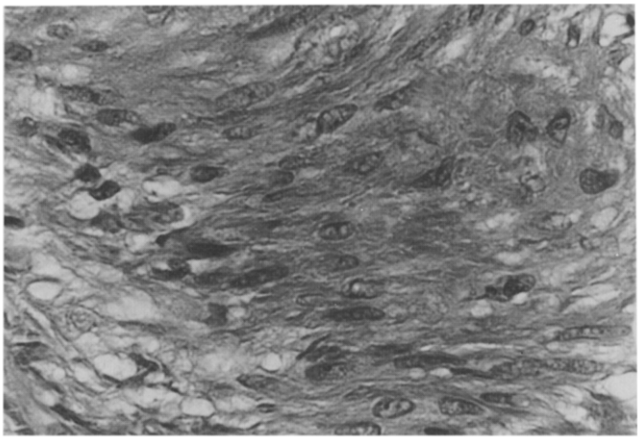

Fig. 6. Leiomyoma (solid leiomyoma). Higher power of palisading peripheral spindle cells. The cell membrane is ill-defined, wavy longitudinal cytoplasmic fibrils are noted. The nuclei are oval to cigar-shaped with well defined nuclear membrane, somewhat vesiculated chromatin and one to two small but prominent nucleoli. Haematoxylin and eosin x 400.

common site with 14 cases (29.2%), followed by the lips 11 cases (22.9%), nose and nasal cavity 11 cases (22.9%) and other locations like the face (3), mandible (2), cheek (1), hard palate (1), larynx (1) and parotid gland (1). Interestingly, the age was somewhat greater than in patients with oral leiomyomas. Also in this study, a clear preponderance of females was found for all sites. When only the head region was considered, a clear male prevalence was noted with 30/48 patients (62.5%) as compared to only 18 females (37.5%). Another interesting finding was that the lips were the second most common location in the above study, strongly supporting our results [18].

The site distribution may also be determined to some degree by the histogenesis of oral leiomyomas which are believed to arise from the tunica media of blood vessels, a histogenesis already proposed by Stout in 1938 [14]. Other origins like the circumvallate papillae [15], ductus lingualis [16] and heterotopic embryonal muscle tissue [17] have also been proposed. The frequency analysis of the various leiomyoma subtypes strongly supports a vascular histogenesis. Analysis of the 142 oral leiomyomas into the classic three subtypes: (1) leiomyoma (solid leiomyoma), (2) angiomyoma (vascular leiomyoma) and (3) epithelioid leiomyoma (leiomyoblastoma) clearly shows the predominance of angiomyoma (vascular leiomyoma) with 94 cases (67.0%), leiomyoma (solid leiomyoma) was next in frequency with 45 cases (31.7%) and only 2 cases of epithelioid leiomyoma (1.3%). No subtype was given in 1 case.

The prevalence of angiomyoma was confirmed by the other reviews with a range from 62.85% [9] to 75.34% [10].

The results of our immunohistochemical study agreed with the findings of three recent investigations [5–7], except that desmin was only weakly positive in the cases are studied. Vimentin was recognised but not specific in smooth muscle fibres.

The prognosis of oral leiomyomas was excellent. Recurrence is rare. Follow-up information was available in 48/142 cases (33.8%) ranging from 1 month to 8 years. 2 cases (4.2%) recurred after a few months. Follow-up information was available in 17/39 (44%) of the lip leiomyomas and none recurred after excision.

In conclusion, immunohistochemistry was a valuable,

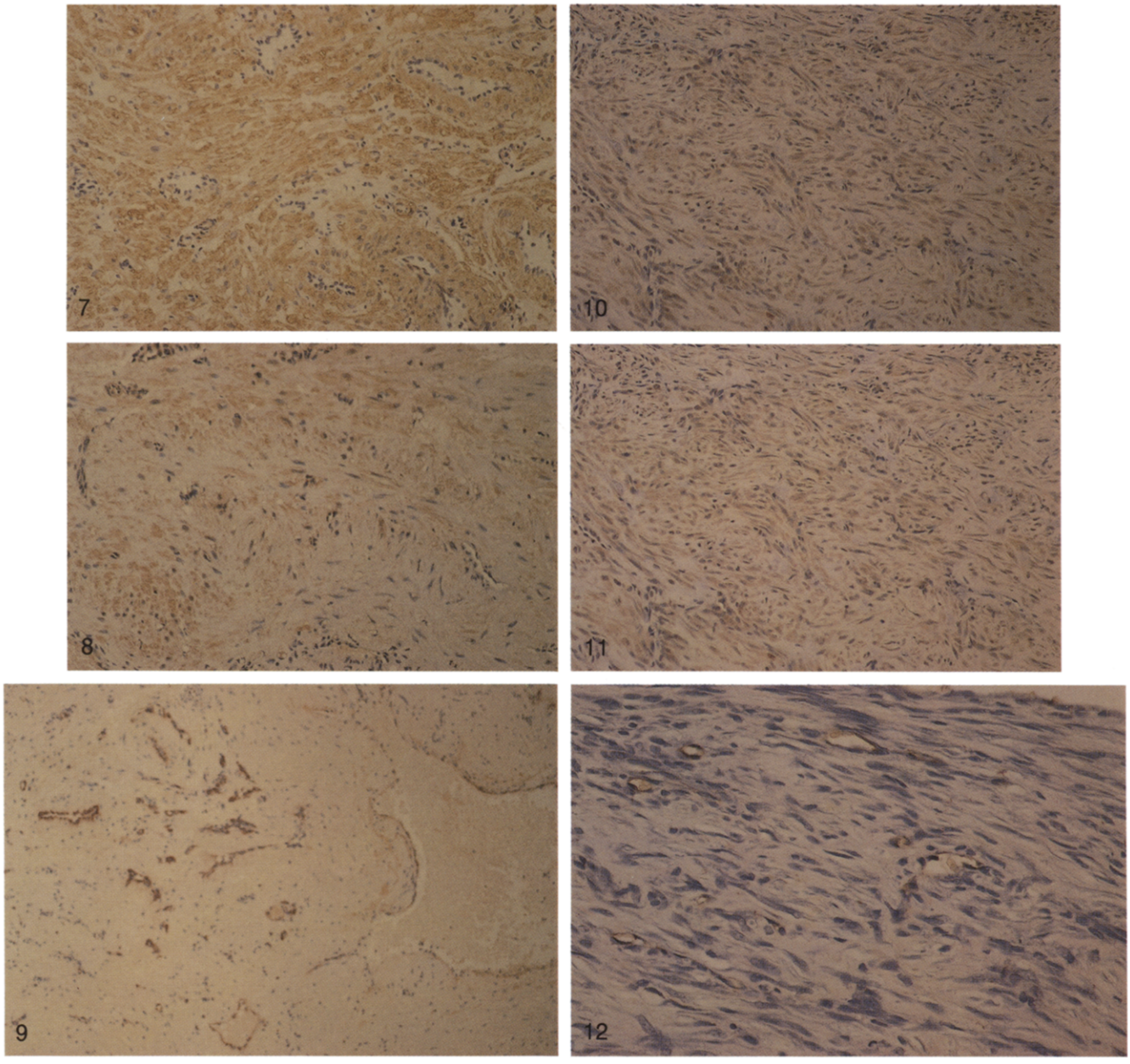

Fig. 7. Angiomyoma (vascular leiomyoma). The spindle cells are strongly marked with muscle-specific actin antibody. The surrounding connective tissue is negative. Muscle-specific antibody × 100.

Fig. 8. Angiomyoma (vascular leiomyoma). The spindle cells are positive with myoglobin antibody. Myoglobin antibody × 200.

Fig. 9. Angiomyoma (vascular leiomyoma). The endothelial cells of the blood vessels are marked, and the spindle cells are negative. Ulex europeus × 200.

Fig. 10. Leiomyoma (solid leiomyoma). The spindle cells are strongly marked with muscle-specific antibody. The connective tissue stroma is negative. Muscle-specific antibody × 200.

Fig. 11. Leiomyoma (solid leiomyoma). The spindle cells are positive with myoglobin antibody. Myoglobin antibody × 200.

Fig. 12. Leiomyoma (solid leiomyoma). The endothelial cells of the blood vessels are marked, the spindle cells are negative. Ulex europeus × 400.

precise and reliable method for definitive diagnosis of oral leiomyomas, especially in questionable cases. Marker studies were particularly valuable for the differential diagnosis of spindle-cell neoplasms arising in the oral cavity has been conclusively shown by our study.

The review of the literature showed that oral leiomyomas were rare, occurred more frequently in males and were most frequent in the lips. Angiomyoma was the most common subtype. Excision was curative and the overall prognosis was excellent.

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