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Relative frequency of solitary melanocytic lesions of the oral mucosa

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BACKGROUND: Solitary pigmented lesions of melanocytic origin are uncommon in the oral mucosa. These lesions include the oral and labial melanotic macule, oral melanocytic nevus, oral melanoacanthoma, oral melanoma and atypical melanocytic proliferation. The purpose of the study was twofold: to report a large series of solitary melanocytic lesions from one source, and to determine the relative frequency of these lesions.

METHODS: The study was based on a systematic search of the files of the Pacific Oral and Maxillofacial Pathology Laboratory, University of the Pacific, San Francisco for solitary pigmented melanocytic lesions (benign and malignant) accessed during the years 1984–2002.

RESULTS: Of the 89 430 biopsies accessed during the 19-year period, 773 (0.83%) cases of solitary pigmented melanocytic lesions in the oral mucosa were identified. Oral and labial melanotic macules were the most common melanocytic lesions comprising 86.1% of the entire group and 0.7% of the total number of accessed biopsies. The vermilion border and gingiva were the most common sites (31.1% and 31.0% respectively). Oral melanocytic nevi comprised 11.8% of the entire melanocytic group and 0.1% of the total number of biopsies. The most common site was the palate (44%). Intramucosal nevi were the most common (64%), followed by compound nevi (16.5%) and common blue nevi (16.5%). Junctional nevi were uncommon (3.0%). Oral melanoacanthoma comprised only 0.9% of the entire melanocytic group and 0.008% of the total number of biopsies. Oral melanoma and atypical melanocytic proliferation were the least common lesions each comprising 0.6% of the entire melanocytic group and 0.006% of the total number of biopsies. The most common site for oral melanoma was the palate (60%).

CONCLUSION: The palate was the most common location for both melanocytic nevi and oral melanoma. Thus, all melanocytic lesions in the palate should be viewed with caution and biopsy is recommended to rule out melanoma. Further studies are required to elucidate the entity of oral atypical melanocytic proliferation.
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Keywords: melanoacanthoma; melanocytic proliferation; melanoma; melanotic macule; nevus; oral; pigmentation; pigmented

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Introduction

Pigmented lesions of the oral mucosa can be classified clinically as (1) multifocal and sometimes diffuse macular pigmentation, including entities such as physiologic (racial) pigmentation, disease-associated melanosis, smoking-associated melanosis, drug-induced melanosis and heavy metal pigmentation; and (2) solitary focal pigmentation including entities such as oral melanotic macule, amalgam tattoo, melanocytic nevus, melanoacanthoma, and melanoma (1, 2).

Histologically, in some multifocal or focal lesions, pigmentation is the result of increased melanin production, while in others it is caused by exogenous foreign materials.

Solitary pigmented lesions of melanocytic origin are uncommon in the oral mucosa. These lesions include the oral and labial melanotic macule, oral melanocytic nevus, oral melanoacanthoma, oral melanoma, and atypical melanocytic hyperplasia. Review of the literature revealed no information regarding the relative frequency of these lesions.

The purpose of this study was twofold: to report a large series of solitary pigmented melanocytic lesions from one source, and to determine the relative frequency of these lesions.

Material and methods

The files of the Pacific Oral and Maxillofacial Pathology Laboratory of the University of the Pacific, School of Dentistry at San Francisco, California, USA served as a source of material for this study. The laboratory serves the communities of Northern California. Files were systematically searched for all solitary pigmented

melanocytic lesions (benign and malignant) accessed during a 19-year period from January 1984 to the end of December 2002.

The search of solitary pigmented melanocytic lesions included oral melanotic macule, labial melanotic macule, ephelis, benign lentigo, junctional nevus, compound nevus, intramucosal nevus, common blue nevus, cellular blue nevus, combined nevus, spindle and epithelioid cell nevus (Spitz nevus), melanoacanthoma, atypical melanocytic hyperplasia/proliferation, melanoma *in situ*, and melanoma.

Prepared slides and demographic data from the biopsy files were reviewed.

Lip lesions involving the skin were excluded from the study, as well as cases in which there was a suggestion of racial pigmentation, a component of systemic disease, or a syndrome. No patient had a history of human immunodeficiency virus (HIV) infection.

The diagnosis of oral melanotic macule or labial melanotic macule was accepted only where there was a clinicopathologic correlation between the clinical feature of a discrete pigmented macule and the histologic features of increased pigmentation in the basal cell layer and/or the lamina propria (3). Lesions that exhibited only the histologic features without the clinical manifestation of focal pigmentation, were termed 'basilar melanosis' and excluded from the study.

Melanocytic nevi were re-evaluated and classified according to accepted criteria in the literature (4) as well as oral melanoacanthoma (5). Cases of melanoma *in situ*, invasive melanoma, and atypical melanocytic hyperplasia/proliferation were re-evaluated and classified according to the criteria suggested by the WESTOP workshop (6).

Results and comments

Of the 89 430 cases accessed during the 19-year period, 773 (0.9%) were identified as solitary pigmented melanocytic lesions of the oral mucosa. Table 1 shows the relative frequency of these lesions. Oral and labial melanotic macules were the most common lesions comprising 86.1% of the entire group. Oral melanocytic nevi comprised 11.8%, and oral melanoacanthomas only 0.9%. Oral melanoma and atypical melanocytic proliferation were the least common lesions (0.6% each). It was of interest to note that during the period of the study, 1622 cases of amalgam tattoo were identified comprising 1.8% of the total cases accessed during the 19-year period.

Oral and labial melanotic macules

Melanotic macule is a small, well-circumscribed, brown-to-black macule that occurs on the lips and mucous membranes. The lip lesion is termed a labial melanotic macule and the intra-oral lesion an oral melanotic macule (1, 3) (Figs 1 and 2).

In the present study, 665 cases of melanotic macules were identified. This is the largest series from one source reported in the literature. This number comprised 86.1% of the total number of melanocytic lesions and 0.7% of the total number of accessed biopsies. The prevalence of 0.7% is higher than 0.4% noted by Kaugars et al. (7) and 0.5% noted by Buchner and Hansen (3).

Table 1 Relative frequency of oral solitary melanocytic lesions

	n (%)
Melanotic macules	665 (86.1)
Oral	458
Labial	207
Oral melanocytic nevi	91 (11.8)
Ordinary	
Junctional	3
Compound	15
Intramucosal	58
Common blue nevus	15
Oral melanoacanthoma	7 (0.9)
Oral melanoma	5 (0.6)
Invasive	2
Invasive with *in situ* component	3
Oral atypical melanocytic proliferation	5 (0.6)
Total	773 (100)

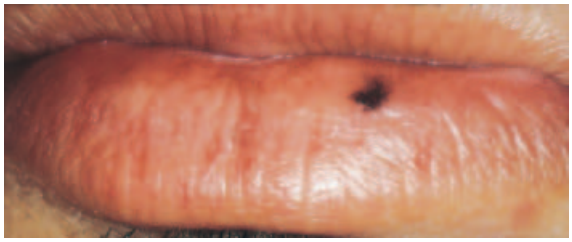

Figure 1 Labial melanotic macule.

Figure 2 Oral melanotic macule (buccal mucosa).

Location

Table 2 shows the location of the oral and labial melanotic macules. The vermilion border (31.1%) and

Table 2 Location of oral and labial melanotic macules

Location	*Number of cases (%)*
Vermilion border	207 (31.1)
Lower	195
Upper	12
Labial mucosa	8 (1.2)
Lower	7
Upper	1
Gingiva[a]	206 (31.0)
Mandible	64
Maxilla	142
Palate	124 (18.6)
Buccal mucosa[b]	76 (11.4)
Tongue	22 (3.3)
Retromolar pad	11 (1.7)
Floor of mouth	11 (1.7)
Total	665 (100)

[a]Including alveolar ridge.
[b]Including mucobuccal fold.

Table 3 Location of melanotic macules in various studies

	Location (%)			
Study	*Vermilion border*	*Gingiva*	*Palate*	*Buccal mucosa*
Buchner and Hansen (3) (105 cases)	30.5	22.8	12.4	16.2
Kougars et al. (7) (353 cases)	33.0	22.2	21.6	18.6
Present study (665 cases)	31.1	31.0	18.6	11.4

the gingiva (31%) were the most common sites, followed by the palate (18.6%), and buccal mucosa (11.4%). Of the lesions in the vermilion border, 94% were on the lower lip. In the gingiva, most lesions (69%) were in the maxilla, mainly in the anterior area. Few lesions were identified on the tongue, retromolar pad and floor of the mouth.

The location of the melanotic macules in the present study was generally similar to other studies (Table 3), except that gingival lesions were more common and buccal mucosa lesions less common than in other studies.

Age of patients

Age at time of excision was known for 590 patients. Patients ranged in age from 4 to 98 years (mean 43.7), the highest incidence occurred in the fifth decade (23%). However, there were differences between intra-oral and labial lesions. While the highest incidence of intra-oral lesions was in the fifth decade (24.5%), with the mean age of 46 years, the highest incidence of labial lesions was in the fourth decade (24.7%), with the mean age of 38.6 years.

Other studies also show that the mean age at time of diagnosis of lesions of the lower lip is about 10 years earlier than that of intra-oral sites (7–9). A possible explanation is that a change in the lower lip is more noticeable to both the patient and general practitioner and therefore could be treated at a younger age (7).

Gender

There were 416 (66%) females and 214 (34%) males; female to male ratio was 1.9:1. The present study confirmed the reported predilection for females (3, 7, 10).

Histologically, labial and oral melanotic macules are characterized by increased production of melanin by basal melanocytes which are otherwise normal in number and distribution. Melanin pigment is also observed in melanophages in the upper portion of the lamina propria (3, 9, 10). In a quantitative study of the basal melanocyte population in cases of labial melanotic macules, an increase in the number of melanocytes in the basal cell layer was observed (11).

The etiology of labial and oral melanotic macules is not clear and it may represent a physiologic or reactive process. In many cases, it is a manifestation of a post-inflammatory pigmentation. Drugs, such as minocycline, could cause solitary pigmented macules (12). Fixed drug eruptions occur in the same location each time a specific drug is used and may be manifested as a dark pigmented macule on the tongue. This is commonly seen in patients who use antibiotics, phenobarbital, and heroin (13).

Treatment

The labial and oral melanotic macules are asymptomatic and have no malignant potential. No treatment or period of clinical observation is indicated if a diagnosis can be made on the basis of clinical features. Some lesions, however, develop relatively quickly and may be difficult to distinguish from melanoma. Any lesion in question should be excised and sent for histopathologic evaluation to rule out the possibility of melanoma. This is especially true for lesions of the palate where melanomas are most prevalent.

The labial and oral melanotic macules are usually solitary lesions but occasionally more than one lesion can be clinically observed. In patients with multiple melanotic macules, syndromes, such as Peutz-Jeghers, systemic diseases, such as Addison's disease, and pharmacologic agents, such as antimalarial medication, should be ruled out. Multiple melanotic macules have also been reported in patients infected with HIV. In some patients the lesions could be related to systemic therapy, but in others the cause remains unknown (14).

Oral melanocytic nevi

Oral melanocytic nevi are much less common in the oral mucosa than on the skin. While the mean number of melanocytic nevi on the skin of an adult Caucasian is about 30 (15), the total number documented oral melanocytic nevi in the literature are <300. Histologically, oral melanocytic nevi are classified into ordinary nevi (junctional, compound, intramucosal) and common blue nevus (4). Clinically, oral nevi are small, well-circumscribed macules but more commonly appear as slightly raised papules. They can be brown, bluish-gray, or almost black and occasionally appear non-pigmented (16, 17) (Figs 3 and 4).

Figure 3 Intramucosal nevus, palate.

Figure 4 Junctional nevus, palate.

In the present study, 91 cases of oral melanocytic nevi were identified. This number comprised 11.8% of the total number of melanocytic lesions and 0.1% of the total number of accessed biopsies.

Histologic type

Intramucosal nevi were the most common type (64%), followed by compound nevi (16.5%) and common blue nevi (16.5%). Junctional nevi were relatively uncommon (3%). No cases of combined nevus and Spitz nevus were identified.

Distribution of the histologic type of nevi in the present study was similar to the data in the literature, except that compound nevi were more common in the current study (16.5% compared with 9% in the literature) (18).

The present study also confirmed the finding that relative to the skin, common blue nevi are more common in the oral cavity (1).

Location

Table 4 shows the location of 91 nevi. The most common site was the palate (44%), followed by the buccal mucosa (22%), vermilion border (18%), gingiva (12%), and retromolar pad (4%). No lesions were found on the tongue or floor of mouth. It was of interest to note that the distribution according to location was different for the intramucosal and compound nevi when compared with the blue nevi. The palate was the predominant location for blue nevi (87%) and none were located in the buccal mucosa. However, 27% of the intramucosal and compound nevi were located in the buccal mucosa. These findings are in accordance with other series in the literature (18).

Table 4 Location of oral nevi

Location	*Intramucosal*	*Compound*	*Junctional*	*Blue*	*Total*	*Percentage*
Palate	20	5	2	13	40	44
Buccal mucosa[a]	15	5			20	22
Vermilion border	11	3		2	16	18
Gingiva[b]	8	2	1		11	12
Retromolar pad	4				4	4
Total	58	15	3	15	91	100

[a]Including mucobuccal fold.
[b]Including alveolar ridge.

Age of patients

Tables 5 and 6 show the age range, age distribution, and mean age of 88 patients at the time the nevi were removed. The youngest patient was 3 years old, and the oldest 80 years (mean 30.5 years). The highest incidence was in the third and fourth decade, with almost half of the patients (46%) in this age group. The mean age for patients with junctional and

Table 5 Age distribution of oral nevi

Age group (years)	*Intramucosal*	*Compound*	*Junctional*	*Blue*	*Total*	*Percentage*
0–9	1	4	2		7	8
10–19	8	6	1	2	17	19
20–29	18	1		1	20	23
30–39	16	1		3	20	23
40–49	9	2		3	14	16
50–59	3			4	7	8
60–69				1	1	1
70–79				1	1	1
80–89	1				1	1
Total	56	14	3	15	88	100

Table 6 Age range and mean age of patient with oral nevi

	Age (years)	
	Range	*Mean*
Intramucosal	7–80	31.3
Compound	3–47	18.2
Junctional	7–14	9.3
Blue	14–73	43.3
Total	3–80	30.5

Table 7 Type of oral nevi by gender of patients

	Gender		
	Male	*Female*	*Total*
Intramucosal	22	36	58
Compound	4	11	15
Junctional	1	2	3
Blue	10	5	15
Total	37	54	91
Percentage	40	60	100

compound nevi was relatively low (9 and 18 years, respectively) and for patients with intramucosal nevi relatively high (31 years). The mean age for patients with blue nevi was 43 years. These findings are similar to other studies of oral nevi (18).

Gender of patients

Of the 91 oral nevi, 60% were in women and 40% in men (Table 7); female to male ratio was 1.5:1. It was of interest to note that while all types of ordinary nevi were more common in women, blue nevi were more common in men (67%). The present study confirmed the reported predilection of ordinary nevi in women and blue nevi in men (18).

Almost all oral melanocytic nevi are solitary lesions. However, Biesbrock and Aguirre (19) report an unusual occurrence of multiple intra-oral junctional nevi in the hard palate and maxillary tuberosity.

Treatment

Cutaneous melanomas have been shown to arise from pre-existing melanocytic nevi, however, the malignant potential of oral nevi has not been determined. Nevertheless, oral nevi and oral melanomas have several similarities. Both lesions occur most frequently on the palate, and nevi may represent the pre-existing pigmentation that is reported to precede the development of oral melanomas. Since oral nevi cannot be clinically differentiated from early melanoma, and are relatively uncommon lesions, excision of all lesions is both practical and advisable (1).

Oral melanoacanthoma

Oral melanoacanthoma is a rare acquired pigmented lesion characterized histologically by dendritic melanocytes dispersed throughout an acanthotic epithelium. Clinically, the lesion is flat or slightly raised, and either brown or black. The lesion tends to rapidly increase in size, may attain a size of several centimeters, and therefore mimics the radial growth phase of intra-oral melanoma (20).

In the files, seven cases of oral melanoacanthoma were identified, comprising 0.9% of the total number of melanocytic lesions and 0.008% of the total number of accessed biopsies. Clinical data of this rare lesion are presented in Table 8. Age range of the patient at presentation was 36–68 years (mean 44 years). Of the seven patients, four were women and three were men. Five (71%) were black and two (29%) were Asian. Four lesions were located in the buccal mucosa and one lesion each on the vermilion border of the lip, retromolar pad, and tongue.

Only about 40 cases of oral melanoacanthoma have been reported in the literature. Clinical features of the present series differ from the literature, especially with regard to patients' age and race. In the literature, oral melanoacanthomas have been reported at a mean age of 28 years, mainly in blacks (90%), with a strong female predilection (2.1:1), and located mainly in the buccal mucosa (65%) (21).

In the present series, the mean age was higher (44 years) and two patients (29%) were Asians. To the best of our knowledge, this is the first report in the English language literature of oral melanoacanthoma that occurred in Asians. The buccal mucosa was the most common location in the present series but lesions were also found on the vermilion border, retromolar pad and tongue. Furthermore, to the best of our knowledge, this is the first report of oral melanoacanthoma located on the tongue.

Oral melanoacanthoma is usually a solitary lesion but multiple and bilateral lesions in the buccal mucosa have been reported (21, 22). It is considered to be a reactive process unrelated to the neoplastic melanoacanthoma of the skin. The oral lesions generally regress after removal of traumatic irritants or after biopsy. To emphasize the non-neoplastic nature of oral melanoacanthoma, Tomich and Zunt (23) suggest the term melanoacanthosis and Horlick et al. (24) suggest the phrase mucosal melanotic macule, reactive type.

As oral melanoacanthoma grows at an alarming rate, incisional biopsy is indicated to rule out the possibility of melanoma. Once the diagnosis has been established, no further treatment is necessary. In some cases, the lesion has been reported to regress spontaneously after biopsy (21).

Oral mucosal melanoma

Melanoma is a malignant proliferation of abnormal melanocytes that usually originate on the skin and is extremely rare in the oral mucosa. Racial discrepancy is found in the incidence of oral melanoma. In Caucasians, it accounts for $< 1\%$ of all melanomas (25), while in the Japanese population it is more common, accounting for more than 10% (26). Clinically, oral melanoma is usually seen as an irregular, brown-to-black macule that progressively increases in size and at a later stage becomes papular or nodular. Some oral melanomas lack pigmentation and are termed amelanotic melanoma (27). In approximately one-third of the cases, oral melanomas are characterized by a prolonged radial growth phase followed by a vertical growth phase; whereas others exhibit a faster progression into a vertical growth phase (28, 29). Histologically, the radial growth phase represents *in situ* and superficial melanoma, and the vertical growth phase represent the nodular or invasive melanoma (6).

According to the recommendation of the WESTOP workshop in 1997 (6), oral mucosal melanomas should be considered separately from cutaneous melanoma and

Table 8 Clinical data of seven patients with oral melanoacanthoma

Case	*Age (years)*	*Gender*	*Race*	*Location*	*Appearance*	*Size (cm)*	*Duration*
1	36	F	Black	Buccal mucosa	Flat, brown	1.0	–
2	37	M	Black	Retromolar pad	Flat, brown	0.2	–
3	51	M	Asian	Tongue	Flat, black	0.6	Recent
4	24	F	Black	Buccal mucosa	Flat, black	2.0	Recent
5	63	M	Black	Buccal mucosa	Rough surface, slightly elevated	0.4	Recent
6	52	F	Asian	Lower vermilion	Flat, black	0.6	6 months
7	44	F	Black	Buccal mucosa	Flat, brown	1.0	–

Table 9 Clinical data of five patients with oral mucosal melanoma

Case	*Age (years)*	*Gender*	*Race*	*Location*	*Appearance*	*Size (cm)*	*Diagnosis*
1	67	M	Caucasian	Posterior buccal mandibular gingiva	Raised, brown	1.5	Invasive
2	54	M	Asian	Hard palate	Raised, black	2.0	Invasive with *in situ* component
3	48	M	Caucasian	Hard palate and alveolar ridge	Raised, black	2.5	Invasive with *in situ* component
4	61	F	Caucasian	Hard palate and alveolar ridge	Multiple, flat, raised black	3.5	Invasive with *in situ* component
5	22	M	Unknown	Dorsal tongue	Raised, black	1.3	Invasive

subclassified into *in situ* melanoma, invasive melanoma, and combined invasive melanoma with *in situ* component.

In the files, five cases of primary oral mucosal melanoma were identified. This number comprised 0.6% of the total number of melanocytic lesions and 0.006% of the total number of accessed biopsies. Table 9 shows the clinical data. There were two cases classified as invasive melanomas and one as combined invasive melanoma with *in situ* component. In two cases, most of the specimen revealed melanoma *in situ* and only in one focal area was micro-invasion noticed. No lesion appeared to be associated with pre-existing nevus.

It was of interest to note that one invasive melanoma occurred on the dorsum of the tongue in a 22-year-old male. Both the location and young age of the patient are unusual for oral mucosal melanomas. Less than 30 cases of primary melanoma of the tongue have been reported in the literature (30). The age range of the other four patients (three men and one woman) was 48–67 years (mean 57.5 years). Three lesions were located in the hard palate and one in the mandibular gingiva. These findings are consistent with reported cases in the literature, namely that the mean age is 56 years, a greater incidence in men (2.8:1), and located mainly in the hard palate and maxillary gingiva (72%) (6).

Most oral melanomas present as solitary lesions, however, multiple or synchronous lesions have been reported (Fig. 5). This may be due to a 'field effect' rather than direct spread from a single primary lesion (6). Clinically, oral melanomas that present as multiple or with synchronous onset may give the erroneous impression of physiologic pigmentation (31).

Figure 5 Oral mucosal melanoma in the maxillary alveolar mucosa extending to the buccal mucosa.

Most mucosal melanomas exhibit an unrelenting progressive behavior. Patients with mucosal melanomas (both *in situ* and invasive lesions) generally have a poor disease course. The poor prognosis is believed to be due largely to the advanced nature of these melanomas at the time of definite diagnosis and treatment (31, 32). To improve prognosis, aggressive

Table 10 Clinical data of five cases of oral atypical melanocytic proliferations

Case	*Age (years)*	*Gender*	*Race*	*Location*	*Appearance*	*Size (cm)*
1	37	F	Unknown	Buccal mucosa	Flat, brown	0.6
2	76	F	Caucasian	Hard palate	Flat, black	0.8
3	30	M	Asian	Buccal mucosa	Flat, brown	0.7
4	37	F	Caucasian	Anterior maxillary gingiva	Flat, black	0.5
5	16	M	Caucasian	Lower vermilion	Flat, black	0.5

treatment should be initiated early in the natural history of oral melanomas. Surgery remains the primary treatment modality and radiation and/or chemotherapy may serve as adjuncts. Combination therapy may be advantageous in primary patient care because of the high recurrence rate associated with oral lesions. Vaccines derived from the patient's own tumor cells are being evaluated (32).

Oral atypical melanocytic proliferation

Oral melanocytic lesions in which the microscopic cytology or architecture is equivocal or difficult to interpret were termed by the WESTOP workshop (6) as atypical melanocytic proliferation. The designation indicates the presence of an unusual number of melanocytes with abnormal morphology at the epithelium-connective tissue interface. Changes are not severe enough to justify the diagnosis of melanoma *in situ*. It has been suggested that lesions designated as atypical melanocytic proliferation should be regarded as high risk and re-biopsied or clinically followed up indefinitely (33).

Five cases of oral atypical melanocytic proliferation were identified in the files comprising 0.6% of the total number of melanocytic lesions and 0.006% of the total number of accessed biopsies. Table 10 shows the clinical data. Clinically, lesions manifested as flat, brown-to-black macules, occasionally with irregular borders. No predominant site, age, or gender could be identified probably because of the small number of cases. Follow-up of these patients was unavailable. There is very little information in the literature regarding this entity (34, 35). Therefore, comparison of the present series to other studies could not be carried out.

Conclusions

There is no information in the literature regarding the relative frequency of solitary pigmented melanocytic lesions of the oral cavity. Analysis of 773 cases from one source revealed that:

1. Solitary pigmented melanocytic lesions are uncommon in the oral cavity and comprised only 0.9% of the total biopsies accessed. In comparison, the amalgam tattoo comprised 1.8%.
2. Oral and labial melanotic macules are the most common solitary pigmented melanocytic lesions (86.1%), followed by oral melanocytic nevi (11.8%), oral melanoacanthoma (0.9%), and oral melanoma and atypical melanocytic proliferation (0.6% each).
3. Of the melanocytic nevi, the most common type was the intramucosal (64%), followed by compound nevi (16.5%), and common blue nevi (16.5%). Junctional nevi were relatively uncommon (3%).
4. While the most common location for the oral melanotic macule was the gingiva, the palate was the most common location for both melanocytic nevi and oral melanoma. The buccal mucosa was the most common location for oral melanoacanthoma.
5. Mean age at diagnosis for melanocytic nevi was 30.5 years and for oral melanoma 57.5 years. However, there is no proof that oral melanocytic nevi are precursors of oral melanoma.
6. Further studies are required to elucidate the entity of oral atypical melanocytic proliferation. Especially needed are results of careful clinical follow-up of these lesions to reveal their relation to oral melanoma.

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