Oral melanoacanthoma and oral melanotic macule: a report of 8 cases, review of the literature, and immunohistochemical analysis

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ABSTRACT

Oral melanoacanthoma (MA) is a rare, benign pigmented lesion, similar to cutaneous MA, characterized by hyperplasia of spinous keratinocytes and dendritic melanocytes. The pathogenesis of oral MA remains uncertain, although its clinical behavior is suggestive of a reactive origin. The most common intraoral sites are the buccal mucosa, lip, palate and gingiva. The average age of presentation is 28 years, mainly in blacks, with a strong female predilection. The oral melanotic macule (MM) is a small, well-circumscribed brown-to-black macule that occurs on the lips and mucous membranes. The etiology is not clear and it may represent a physiologic or reactive process. The average age of presentation is 43 years, with a female predilection. A biopsy is recommended to distinguish these lesions from each other and from other oral melanocytic lesions. We depict four cases each of oral MA and MM, affecting Caucasian and Latin American mestizo patients. The clinicopathological features of these cases reflect its ample spectrum, and to the best of our knowledge, it is the first example of oral MA affecting a Caucasian boy reported in the English literature. Therefore oral MA and MM should be considered in the differential diagnosis of pigmented lesions in the oral mucosa in these populations.

Key words: *Caucasian, melanoacanthoma, melanotic macule, mestizo, oral pigmented lesion, pediatric patient.*

INTRODUCTION

The term melanoacanthoma (MA) was first used by Mishima & Pinkus in 1960 to describe a benign mixed skin tumor composed of basal and prickle cell keratinocytes and pigment-laden dendritic melanocytes (1). Only about 40 cases of oral MA have been reported in the English literature and it is considered as a reactive process unrelated to the neoplastic MA of the skin (2). Clinically, cutaneous MA occurs mainly in elderly white patients, its development is slow and usually shows roughened or papilllary surface. In contrast, oral MA affects almost exclusively black youngsters, develop quickly (3), and have a flat or slightly raised brown to black pigmented surface (4). These features, together with its tendency to affect mucosal sites exposed to trauma, the observed regression following biopsy or removal of offensive irritants (5), and the histological findings of chronic inflammation and slightly increased vascularity (6) favours a reactive nature. We previously reported a case of oral MA in a mestizo Guatemalan female patient, which demonstrates that this lesion can affect racial or ethnic groups other than blacks (7). Oral melanotic macule (MM) is a small, well-circumscribed, brown-to-black macule, and about of 665 cases has been reported in the English literature (2). Their etiology is not clear and it may represent a physiologic or reactive process. Thus, the aims of this article are to describe the clinicopathologic features of 4 cases each of oral MA and MM, the immunohistochemical (IHC) features of 2 cases of oral MA, to report the first case of oral MA affecting a Caucasian children and to discuss the differential diagnoses and treatment modalities of these conditions.

CASE REPORTS

CASE 1

On august 2005, a 7-year-old Caucasian Brazilian boy presented to the Oral Diagnosis Clinic (Orocentro), School of Dentistry, State University of Campinas, Piracicaba, São Paulo, Brazil, for evaluation and management of a pigmented macule discovered during routine dental treatment on the attached gingiva of the partial erupted mandibular left permanent canine. It measured 0,3 cm in the maximum diameter and appeared homogenous in pigmentation density (Fig. 1a).

CASE 2

On june 2006, a 25-year-old mestizo Mexican male presented to the Departamento de Atención a la Salud, Universidad Autónoma Metropolitana-Xochimilco., Mexico City, México, for evaluation of an pigmented dark-brown macule localized in the right buccal mucosa with evolution time of three months. It measured 1 cm in the maximum diameter (Fig. 1b).

CASE 3-8

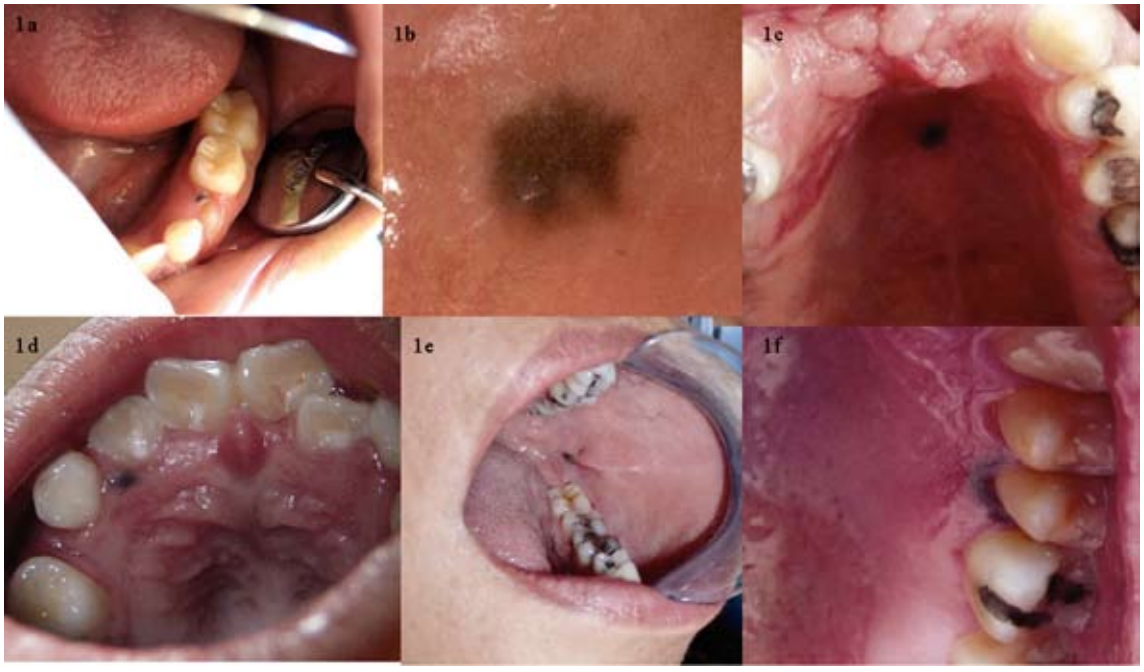
Between june 2003 to august 2006, six mestizo Guatemalan patients were referred to Oral Medicine Center of Guatemala City, Guatemala, for evaluation of pigmented lesions in the mouth.

A 33-year-old female presented a painless pigmented dark-brown macule, with evolution time of two years, on palatine attached gingiva of maxillary right first molar, and measured 0,6 cm in maximum diameter (Case 3).

A 40-year-old female presented a pigmented dark-brown macule on the hard palate and measured 0.5 cm in greatest diameter. The patient had an erythema in the underlying mucosa caused by a partial removable prosthesis. Fungal organisms were negative on cytological smear. An excisional biopsy was performed, using a 0,6 cm punch (Case 4) (fig. 1c) (7). An 8-year-old boy presented a pigmented lesion on the palatal gingival papilla between the right permanent lateral incisor and deciduous canine. It measured 0,3 cm in maximum diameter (Case 5) (Fig. 1d). An 8-year-old girl presented a pigmented macule on the palatine attached gingiva between the maxillary right permanent lateral and central incisors and measured 0,3 cm in maximum diameter (Case 6). A 43-year-old female presented a pigmented lesion on the left buccal mucosa at level of the occlusal plane, distal to the region of third molar and measured 0,4 cm in greatest diameter (Case 7) (Fig. 1e). A 50-year-old male exhibited a dark-brown macule on the lingual aspect of the attached gingiva of maxillary left second premolar, which measured 0,7 cm in greatest diameter (Case 8) (Fig. 1f).

In all cases, the clinical differential diagnoses included MM and/or melanocytic nevus. An excisional biopsy was performed and submitted for histopathological study. Fontana-Masson stain and IHC analysis for melanocytic markers S-100 (polyclonal, dilution 1:12000; Dako A/S, Glostrup, Denmark), HMB-45 (monoclonal, dilution 1:200; Dako A/S, Glostrup, Denmark), and Melan-A (monoclonal A103, dilution 1:800; Dako A/S, Glostrup, Denmark) were used to further illustrated cases 1 and 4.

Fig. 1. Pigmented macule on the mandibular gingiva (a, case 1), affecting the buccal mucosa (b, case 2), and on the hard palate (c, case 4) microscopically diagnosed as melanoacanthoma; and on the maxillary interdental gingival papilla (d, case 5), affecting the buccal mucosa (e, case 7), and located on maxillary attached gingiva (f, case 8), microscopically diagnosed as melanotic macule.



RESULTS

The clinical features of the cases in this series are summarized in Table 1. Four patients were male and four were female. All except one were Latin American mestizo patients. The cases occurred over a wide age range (7–50 years), with an average age of presentation of 25,8 years. All the patients presented single lesions, most frequently located on the gingiva (5 cases), followed by buccal mucosa (2 cases) and hard palate (1 case). The size of the lesions ranged from 0,3 to 1,0 cm. The clinicians in these cases did not report that the lesions displayed a sudden onset.

Oral lesions presented each as an asymptomatic pigmented dark-brown macule with an intact mucosal surface and well-defined borders, except case 2. The clinical diagnoses included MM and/or melanocytic nevus.

Microscopical examination in cases 1 to 4, revealed a fragment of oral mucosa exhibiting parakeratinization, acanthosis and broadening of rete ridges. Benign melanocytes with clear cytoplasm and pigment-laden dendritic processes were scattered throughout the prickle layer of the surface epithelium (Fig. 2a and b), which was salient by means of Fontana-Masson stain (Fig. 2c). A mild chronic inflammatory infiltrate and melanophages were present in the lamina propria associated with increased vascularity (Fig. 2d).

Other areas exhibited a pigmented basal layer associated with a proliferation of heavily pigmented dendritic melanocytes in the basal and suprabasal layers of the epithelium. Case 2 exhibited intraepithelial and lamina propria eosinophil-rich focal areas. Based on these histological features the diagnosis was of oral MA.

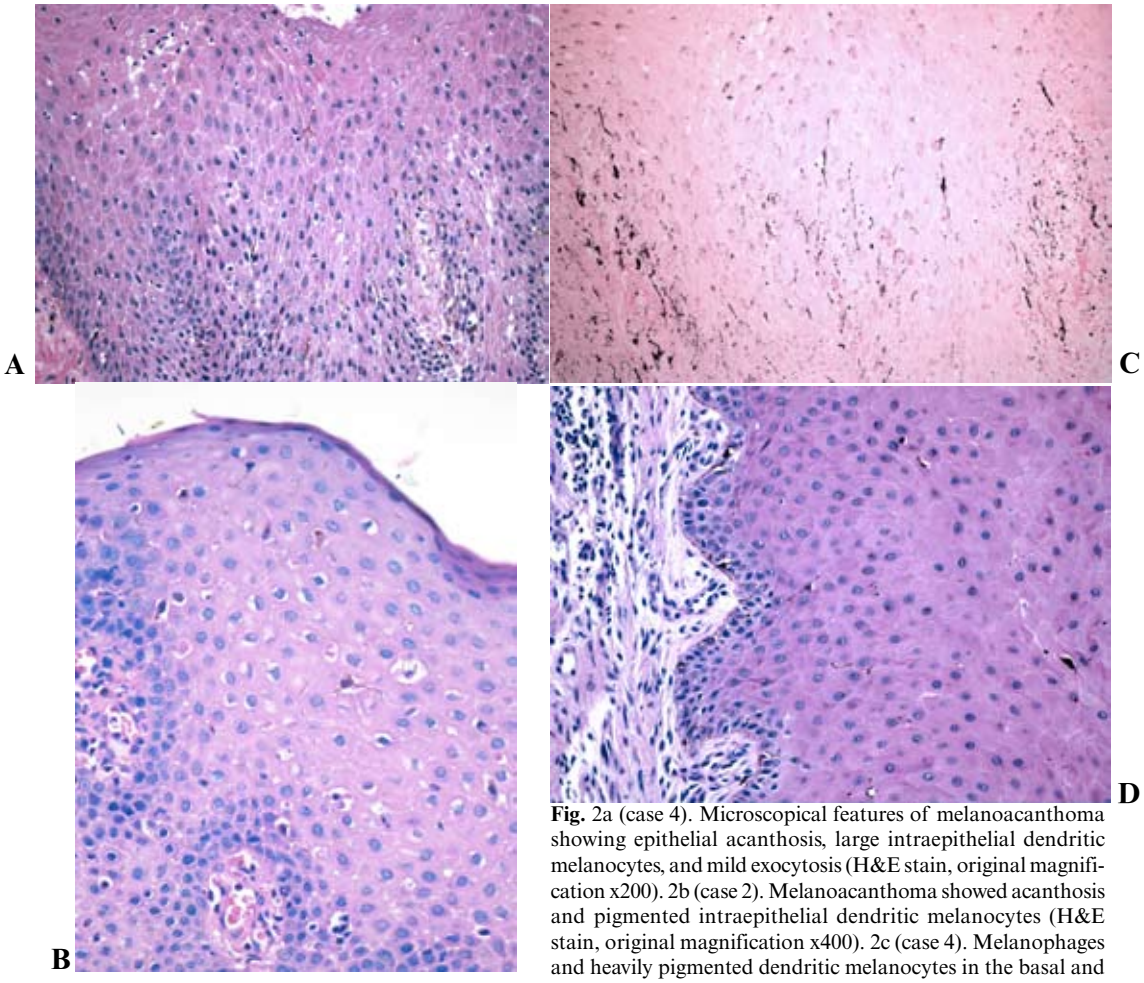


Fig. 2a (case 4). Microscopical features of melanoacanthoma showing epithelial acanthosis, large intraepithelial dendritic melanocytes, and mild exocytosis (H&E stain, original magnification x200). 2b (case 2). Melanoacanthoma showed acanthosis and pigmented intraepithelial dendritic melanocytes (H&E stain, original magnification x400). 2c (case 4). Melanophages and heavily pigmented dendritic melanocytes in the basal and suprabasal layers of the oral epithelium (Fontana-Masson stain, original magnification x200). 2d (case 1). Mild subepithelial vascular proliferation and chronic inflammatory infiltrate (H&E stain, original magnification x200).

On the other hand, the cases 5 to 8 showed a fragment of oral mucosa with parakeratinization, acanthosis and heavily pigmented basal layer. The lamina propria displayed a focal perivascular mild chronic inflammatory infiltrate and melanophages. Scarce and discrete pigmented dendritic melanocytes in the basal layer of the epithelium only in cases 5 and 8 were observed. Based on these histological features the diagnosis was of oral MM.

As many of the dendritic melanocytes were densely pigmented, a red chromogen, fast red, was used to differentiate the immunohistochemistry reaction product from the background melanin. The dendritic melanocytes of the cases 1 and 4 exhibited weak diffuse cytoplasmic immunoreactivity for S100 protein, HMB-45, and Melan-A (Fig. 3a, b).

After one year of follow-up in case 1 no recurrence was detected. There are no follow-up data in 7 cases.

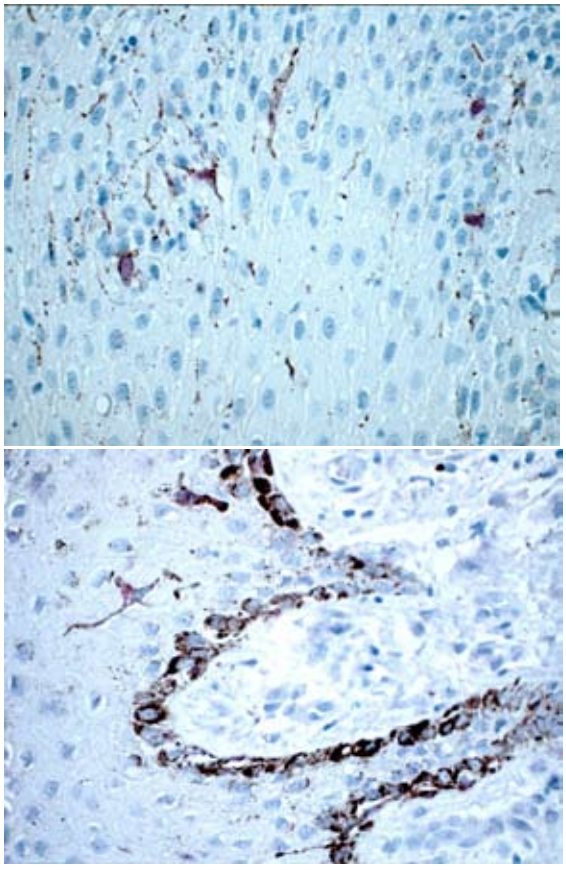


Fig. 3. IHC for S100 protein (a, case 4) and Melan-A (b, case 1) showing mild cytoplasmic immunoreactivity in the dendritic melanocytes (EnVision Systems, AP, original magnification x400).

DISCUSSION

Solitary pigmented melanocytic lesions of the oral mucosa include MM, MA, melanocytic nevus, atypical melanocytic hyperplasia/proliferation, and melanoma (2). Melanotic macules are the most common lesions, affecting mainly the vermilion border and gingiva, corresponding to 86,1% of solitary melanocityc lesions of the mouth (2).

According to the same authors, oral melanocytic nevi comprised 11,8%, while oral MA corresponded to only 0,9%. Oral melanoma and atypical melanocytic proliferation were the least common lesions, each comprising 0,6% (2). Our clinical differential diagnosis in these cases included oral MM and/or melanocytic nevus. As our patients were Caucasian or Latin-American mestizo we initially did not consider MA and a neoplasia was discarded on clinical grounds.

Only about 40 cases of oral MA have been reported in the literature. Most of the cases have affected adult blacks (90%; mean age of 28 years) with a female predilection (2,1:1), and most of these have been located in the buccal mucosa (65%) (8). Clinical features of the present cases differ from those previously reported with regard to patients' gender, race and location of the lesion, showing that oral MA may have an ample clinical presentation. When reviewing the literature we found that Matsuoka et al. (9) and Goode et al. (10) reported the youngest male cases of oral MA, which affected an 18 year-old black and a 26 year-old white patients, respectively. There are only two cases of oral MA affecting black female patients within the first decade of life, both involving the buccal mucosa (8,11). Therefore it seems that this study present the first report of oral MA affecting a Caucasian boy (case 1), involving the gingiva.

Oral MA is usually a solitary lesion but multiple and bilateral lesions in the buccal mucosa have been reported (8,12). The oral lesions generally regress after removal of traumatic irritants or after excisional biopsy. To emphasize the non-neoplastic nature of oral MA, Tomich & Zunt (6) suggested the term melanoacanthosis. We did not detect irritant factors that could be related to the lesion in the case 1. Nevertheless it is interesting to mention that the lesion was developed on stress-bearing surface in the attached gingiva during the mixed dentition at the level of the partial erupted left mandibular canine. The use of a partial removable prosthesis that caused erythema of the underlying mucosa, probably it is the irritant factor that could be related to the lesion in the case 4 (7). In the case 2, the lesion was located in the buccal mucosa at level of the occlusal plane, and probably could to be related to masticatory forces. According to Goode et al. (10) the inflammatory infiltrate of oral MA, shows eosinophilia associated with an increased vascularity and a mild chronic infiltrate. Our cases of MA exhibited mild increased vascularity and patchy chronic inflammatory cell infiltrate in the connective tissue, nevertheless eosinophils, except case 2, were absent.

Our results indicate that the main clinical and microscopical differential diagnosis is MM (Table 1). There are some clinical similarities between oral MA and MM.

Table 1. Clinical and histopathological characteristics of our cases diagnosed as MA or MM.

Patient	Age (years)	Race	Gender	Location	Clinical aspect	Size (cm)	Diagnosis
1	07	C	M	Mandibular gingiva	Flat, dark-brown	0,3	MA
2	25	LAM	M	Buccal mucosa	Flat dark-brown	1	MA
3	33	LAM	F	Maxillary gingiva	Flat, dark-brown	0,6	MA
4	40	LAM	F	Hard palate	Flat, dark-brown	0,5	MA
5	08	LAM	M	Maxillary gingiva	Flat, dark-brown	0,3	MM
6	08	LAM	F	Maxillary gingiva	Flat, dark-brown	0,3	MM
7	43	LAM	F	Buccal mucosa	Flat, dark-brown	0,4	MM
8	50	LAM	M	Maxillary gingiva	Flat, dark-brown	0,7	MM

C= Caucasian; LAM= Latino American mestizo, MA= melanoacanthoma, MM= melanotic macule.

MM is a small, well-circumscribed, brown-to-black macule that occurs commonly on the lips and gingiva, followed by the palate and buccal mucosa. Patients range in age from 4 to 98 years (mean 43,7), showing predilection for females (1,9:1). Histologically, it is characterized by in situ increased production of melanin by basal melanocytes, which are otherwise normal in number and distribution (13), or display increased numbers of melanocytes along the junctional zone in the case of the labial melanotic macules (14). Melanin pigment is also observed in melanophages in the upper portion of the lamina propria (13,14). These findings are in agreement with Sexton & Maize (14) who studied fifteen labial melanotic macules and ALL MM with the histopathological features present in cases 5 to 8. Moreover, a mild increased vascularity and patchy chronic inflammatory cell infiltrate in the connective tissue was observed in all our cases of MM and, interestingly, few pigmented dendritic melanocytes in the basal layer of the epithelium (cases 5 and 8) were observed. This finding suggests the possibility that melanocytes activation by unknown mechanism could be the link between oral MM and MA, and it could represent more a reactive than a physiologic process. Supporting this hypothesis, Horlick et al. (15) suggest that oral MA could be designated as mucosal MM, reactive type.

Melanocytic nevi are much less common in the oral mucosa than on the skin. Clinically, oral nevi are small, well-circumscribed macules or slightly raised papules. They can be brown, bluish-gray, or almost black and occasionally appear non-pigmented. Histologically, oral melanocytic nevi are classified as ordinary nevi (junctional, compound, intramucosal) and common blue nevus (16). The histological features in our cases excluded the diagnosis of oral melanocytic nevi.

Melanoma is very rare in the oral mucosa. 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. Histologically, the radial growth phase represents in situ and superficial melanoma, and the vertical growth phase represent the nodular or invasive melanoma (17). As oral MA grows rapidly, 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 excisional biopsy (8). Our cases did not show an alarming evolution, but a course of months, clinically more compatible with a benign pigmented lesion. Although most of our cases lack follow-up, no recurrence was observed in case 1 after one year of surgical excision.

A diagnosis of oral MA can be performed solely on the basis of the histological features. Nevertheless, in order to emphasize the presence of melanin Fontana-Masson stain can be used. The IHC profile of oral MA is essentially limited to the melanocytic markers, but it is not necessary for the diagnosis (8). IHC studies generally reveal diffuse nuclear and cytoplasmic immunoreactivity of the dendritic melanocytes with S-100 protein. These cells also exhibit moderate-to-diffuse cytoplasmic reactivity for HMB-45 (18). However, because of the heavy pigmentation of many of the dendritic cells, a reaction product may be difficult to visualize through the brown melanin. The use of a red chromogen (such as fast red) facilitates the interpretation of the IHC results.

In summary, we report 4 cases each of oral MA and MM, all but one affecting Latin American mestizo patients, indicating that these lesions can exhibit a similar and ample clinical presentation, and to distinguish among them and

other pigmentary disorders, the histopathologic analysis is indispensable. Oral MA and MM should be considered in the differential diagnosis when evaluating pigmented lesions of the oral mucosa in these populations.

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