CASE REPORT

In Situ Melanoma of the Gingiva Associated with Dense Inflammation and Pigment Deposition: A Potential Diagnostic Pitfall in Evaluating Stromal Invasion

Bruno Tavares Sedassari¹ · Nelise Alexandre da Silva Lascane² ·
André Luis Santana de Freitas² · Mário Cláudio Mautoni² ·
Mirian Nacagami Sotto³ · Marina Helena Cury Gallottini¹ ·
Suzana Cantanhede Orsini Machado de Sousa¹ · Décio dos Santos Pinto Jr.¹

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Abstract Melanoma is a highly aggressive neoplasm in which the neoplastic cells display melanocytic differentiation. Less than 1 % of all melanomas arise in the mucosal surfaces of the oral cavity, with purely in situ lesions being exceedingly rare tumors, but with a favorable prognosis compared with invasive lesions. We describe the clinical, histopathological and immunohistochemical findings in an uncommon case of in situ mucosal melanoma of the oral cavity with intense tumor-associated pigment deposition and inflammation complicating the morphological assessment of infiltrative areas.

Keywords Immunohistochemistry · Mucosal melanoma · Oral mucosa · Skin tumors

Introduction

Melanoma is a highly aggressive malignancy in which the neoplastic cells display melanocytic differentiation. About 15 % of all melanomas arise in head and neck, mainly in sun-exposed skin. Intraoral lesions are rare, comprising less than 1 % of all melanomas [1, 2]. With the maxillary gingiva and palatal mucosa as the most common intraoral sites of occurrence, most cases are diagnosed between the

5th and 7th decades of life and there is no sex predilection [1, 3].

On clinical presentation, oral mucosal melanoma shares aspects with its cutaneous counterpart and variable brown to black surface pigmentation, irregular borders, and ulceration are common features [1, 4]. Under histopathological examination, most cases are frankly invasive tumors, particularly owing to delay in diagnosis, with very few cases diagnosed as purely in situ lesions [1, 2, 5]. Morphological aspect is quite variable and is usually characterized by a combination of cell types with melanin pigment present in about a half of cases [3].

Although identification of melanin pigment is a helpful clue in diagnosing mucosal melanomas, its presence in excess may complicate the microscopic interpretation of important morphological details, including the distinction between exclusively in situ melanomas from infiltrative lesions with junctional activity. Herein, we describe an uncommon case of heavily pigmented gingival in situ melanoma with infiltration of melanophages and inflammatory cells in the lamina propria, highlighting the diagnostic challenges that such microscopic features may imply.

Case Report

A 51-year-old caucasian woman was referred for evaluation of a growing black patch with irregular borders located in the mandibular gingiva (Fig. 1a). She denied any other symptom. With the clinical hypothesis of melanoma, a wide incisional biopsy was performed removing lesional tissue from the lingual gingiva between the teeth #46 and #47.

✉ Nelise Alexandre da Silva Lascane
ne_lascane@hotmail.com

¹ School of Dentistry, Oral and Maxillofacial Pathology, University of São Paulo, São Paulo, Brazil

² School of Dentistry, Stomatology, Santa Cecília University, Rua Oswaldo Cruz, Santos, SP CEP: 11045-907, Brazil

³ School of Medicine, Dermatopathology, University of São Paulo, São Paulo, Brazil

Fig. 1 **a** Clinical aspect of the mucosal in situ melanoma presenting as a gingival black patch with irregular borders. **b** Gross appearance of the specimen submitted to pathological examination. **c** At low-power, mucosal fragment with an asymmetric distribution of melanocytes and pigment, which is present within the epithelium and the underlying connective tissue. **d** atypical melanocytes with the cytoplasm filled with melanin granules. The cells are configuring irregular clusters and individual cells may be seen in superficial

regions of the epithelium. **e** Atypical melanocyte with elaborated dendritic processes (*arrow*). There is an area in which the limit between the epithelium and connective tissue is obscured by the confluence of single melanocytes. **f** Pagetoid spread with nests of neoplastic cells in the stratum corneum. **g** Immunohistochemistry to HMB-45 and Melan A (*inset*) highlighting the melanocytic proliferation confined to the intraepithelial region

Grossly, the specimen consisted of an irregular soft tissue fragment with a central black area surrounded by a rim of tan, non lesional mucosa (Fig. 1b). The histopathological examination evidenced an asymmetric distribution of melanocytes and pigment, which was present within keratinocytes, melanocytes and melanophages (Fig. 1c–f). The epithelium displayed parakeratosis, acanthosis with elongation of the rete ridges and frankly atypical melanocytes with cytoplasm filled with melanin granules arranged in irregular nests. Single cells showing a lentiginous distribution or in confluence replacing the basal layer of the epithelium were also observed. The neoplastic melanocytes exhibited nuclear pleomorphism, elaborated dendritic processes and areas of pagetoid spread, with clusters and individual neoplastic cells identified in the stratum corneum. In many areas, the limits between the melanocytic proliferation in the basal region of the epithelium and the underlying lamina propria was unclear due to the confluence of single melanocytes, intense pigment deposition and dense infiltration of melanophages admixed with lymphocytes and plasma cells in the subjacent connective tissue, making it difficult to identify possible infiltrative foci.

Immunohistochemical analysis demonstrated that the neoplastic cells were strongly positive to HMB-45 and Melan A, and ensured that the neoplastic process was confined to the intraepithelial limits, excluding stromal invasion (Fig. 1g). No regressive area, satellite lesion or ulceration were observed. The final diagnosis of in situ melanoma of the gingiva was established based on clinical, histopathological and immunohistochemical aspects. The patient was submitted to complete surgical excision with tumor-free margins. Similar histopathological and immunohistochemical findings were found in the surgical specimen. After 12 months of clinical follow-up, no signs of local recurrence, local or distant metastasis could be found.

Discussion

Cutaneous and mucosal melanomas typically presents as pigmented lesions with irregular borders, surface, and color [3]. Although cutaneous and oral melanomas may share some clinicopathological features, the latter usually do not fit in any specific category described for its cutaneous counterparts (e.g., superficial spreading, nodular, lentigo maligna, and acral lentiginous), and a very few cases are detected as in situ lesions [1–3, 5, 6]. However, the morphological features described in the current case are similar to those of acral lentiginous type of cutaneous melanoma, and it seems to be a relatively common finding in oral mucosal melanomas [3].

Due to structural differences between the dermis and the mucosal lamina propria, the classic histopathological microstaging of Clark levels for cutaneous melanomas cannot be employed in mucosal lesions [5]. However, the presence and depth of invasion are inwardly associated with prognosis in head and neck mucosal melanomas [5–7]. The confluence of malignant melanocytes obscuring the basal region of the epithelium along with the presence of numerous melanophages and inflammatory infiltrate in the lamina propria of the present case may represent an important diagnostic pitfall, and distinguishing in situ from infiltrative tumors only on histopathological examination may be very difficult, particularly if the invasive areas are represented by few clusters of neoplastic cells or individual melanocytes in the epithelial-subepithelial junction (microinvasive mucosal melanoma) [5]. Despite the short-term favorable prognosis described for microinvasive mucosal melanomas, these lesions use to progress into widely invasive tumors and the clinician should be advised if any infiltrative focus is identified in association with an intraepithelial component of mucosal melanoma.

In the daily practice of pathologists, most cutaneous and even mucosal melanomas can be diagnosed in routinely stained hematoxylin and eosin sections. However, we have demonstrated that to establish the diagnosis of in situ melanoma with dense underlying pigmentation and inflammation, immunohistochemistry against the melanocytic markers HMB-45 and Melan A have an imperative role in determining the exclusively intraepithelial character. In mucosal sites of the head and neck region, most melanomas are widely infiltrative lesions at the time of diagnosis with the microscopic findings of mucosal ulceration, infiltration of nerves, blood vessels, lymphatics and submucosal structures, as well as stromal response with desmoplasia and inflammation [1, 3, 5–7]. Furthermore, when faced with such lesions, the pathologist should bear in mind the peculiarities of head and neck mucosal surfaces. Inflammation obscuring the limits between the epithelium and lamina propria is a common finding in biopsies of gingival tissues. If associated with an intraepithelial component of a melanocytic lesion, it should be carefully interpreted as it may or may not represent stromal response secondary to tumor invasion. In this histopathological picture, immunohistochemistry can also be helpful if associated with clinical and microscopic aspects.

The real incidence of in situ mucosal melanoma of the oral mucosa is difficult to estimate, but it represents less than 5 % of all intraoral mucosal melanomas [1, 3, 5–7]. Added to this rarity, the natural history of in situ melanoma is not clear, particularly those of mucosal surfaces, but it is considered to progress into invasive disease with time [8]. However, if disease is identified and treated early, it is potentially curable [9]. A literature research (MEDLINE)

Table 1 Clinical features, management, follow-up, and outcome of previously reported cases of in situ mucosal melanoma of the oral region, as well as those of the presented case

	Age	Sex	Site	Management	Follow-up (months)	Outcome
Tremblay et al. [10]	16	M	Palate	Surgical excision	NA	NA
Prasad et al. [5]	NA	NA	Oral mucosa	Surgical excision	NA	Recurrence. Development of invasive disease and distant metastasis
Magliocca et al. [9]	48	M	Palate	Surgical excision	42	No evidence of disease
Spith et al. [11]	67	M	Palate	Topical chemotherapy with imiquimod	13	No evidence of disease
Kemp et al. [12]	74	M	Upper buccal, palatal and gingival mucosa	Surgical excision	15	Multiple recurrences
Luna-Ortiz et al. [13]	47	F	Gingiva and palate	Surgical excision	24	No evidence of disease
	58	M	Palate	Surgical excision	8	No evidence of disease
Hajar-Serviansky et al. [14]	40	M	Lower lip	Surgical excision	NA	NA
Park et al. [15]	72	M	Upper labial mucosa	Surgical excision	1	Recurrence. Development of invasive disease and nodal metastasis
Smith et al. [3]	32	F	Palate and gingiva	NA	NA	NA
Presented case	51	F	Gingiva	Surgical excision	12	Free of disease

M male, F female, NA not available

reveals ten additional reported cases of in situ melanoma affecting the oral mucosa. The information about clinical data, management, and patient's outcome found in such cases, as well as those of the presented case, are summarized in Table 1. In general, most patients are men and the mean age at the initial presentation is 55 years (range 16–74 years). The most commonly affected anatomic sites are the palate and gingival mucosa, followed by the lip and buccal mucosa. The involvement of contiguous sites is common. Surgical excision seems to be curative, however some patients experience multiples recurrences within few months with eventual development of invasive disease and metastasis [3, 5, 9–15]. Thus, local control seems to be a therapeutic challenge in some cases.

In conclusion, in situ mucosal melanoma of the oral mucosa is an exceptionally rare lesion and its accurate microscopic diagnosis may be complicated by the presence of intense pigment deposition, melanophages and inflammatory cells in the underlying connective tissue. In cases with areas suspected of stromal invasion, the exact immunolocalization of neoplastic melanocytes by using melanocytic markers may be essential. Besides this, the pathologist should be acquainted with regional peculiarities of the oral mucosa when diagnosing such lesions. As the treatment may differ, separating intraepithelial melanomas from those with invasion is important. Finally, in situ mucosal melanomas are susceptible to recur and progress with invasion and metastasis, and long-term clinical follow-up is advised.

Compliance with Ethical Standards

Conflict of interest No conflict of interest to disclose.

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