CASE REPORT

Metastatic oral malignant melanoma transformed from pre-existing pigmented lesions in mandibular gingiva: Report of an unusual case

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Abstract The objective of this study is to report the transformation of a 10-year history of melanotic mandibular gingival lesion into primary oral melanoma (POM) in a 37-year-old Taiwanese woman. The patient declined all treatments and died of widespread disease 15 months after POM was confirmed. The histology of initial biopsies was totally benign, but the size of lesion, irregular shape, and developing satellites of pigmentation at the periphery were clinically atypical. However atypical it was, this clinical appearance was unknown to the pathologists. This case demonstrates that oral melanoma can be preceded by a histologically benign-appearing flat pigmented lesion for an extended time. Therefore, a benign oral pigmentation should not be viewed as a harmless condition and regular periodical follow-up is necessary. We argue that the diagnosis and risk assessment of oral pigmented lesions require a team effort from both clinicians and pathologists to make an appropriate diagnosis and achieve a favorable prognosis.

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Oral melanoma transformed from melanosis

Introduction

Primary oral melanoma (POM) is extremely rare, accounting for 0.5% of all oral malignancies and 0.2–8% of all malignomas in Europe and the United States. The vast majority of melanomas in the head and neck are cutaneous melanomas, followed by ocular and mucosal melanoma involving the sinonasal cavity, oral cavity, pharynx, larynx, and esophagus. Cutaneous melanoma is generally seen on the skin of white people, whereas mucosal melanoma has been reported as having a higher incidence in Indians (16%), Japanese (11–14%), and Africans (4.6–8%) than in whites. Unlike the etiology of cutaneous melanoma that is linked to sun exposure, the risk factors for oral melanomas remain unknown. Tobacco use and chronic irritation may play some role, but the evidence is weak.

POM can appear in any age group with a mean age of 56 years and a male preponderance. The most frequently affected oral sites are the palate and maxillary gingiva. POM is described as being preceded by a pre-existing oral pigmentation 30–50% of the time; moreover, few cases of POM arising from benign melanosis and melanotic macules were histologically documented. Small pigmented lesions with an intact smooth mucosa can be confused easily with benign conditions such as melanotic macules, melanocanthoma, melanoacanthoma, melanocytic nevi, or smoker’s melanosis. The early radial phases of oral melanoma usually develop slowly over years. The finding that melanoma progresses from thin, radically growing lesions to thick, vertical growing lesions suggests that regression is associated with relatively early progression. Thus, they can enlarge and bleed, and local or distant metastases can occur until identification is completed. This study demonstrates a case of POM with widespread metastasis arising from a benign oral pigmentation.

Case presentation

In April 2002, a 28-year-old woman without any systemic diseases or a history of melanoma, smoking, or alcohol abuse presented with a thin melanotic mandibular gingival lesion that had existed over 2 years. The lesion was initially diagnosed histologically as a benign hyperpigmentation (Fig. 1A), but it was clinically atypical and somewhat worrisome because of its size, irregular shape, and the feathering of the pigmentation at the periphery in the labial and lingual gingiva of right mandibular teeth (Fig. 1A and B). It was treated with CO2 laser, but recurred quickly. The histology of second biopsies in December 2002 showed benign gingival melanosis (Fig. 1B). Several attempts were made to treat them with 755 nm Alexandra laser, 1064 nm laser, and 532 nm laser in the department of dermatology during the period of April 2003–August 2004, but the therapeutic response was poor. Since there was no increase in size or symptoms, she did not report for further treatment until tumor hemorrhage and a palpable chin lymphadenopathy occurred in August of 2010. The patient presented with an extensively growing melanotic lesion over the entire mandibular gingiva, ranging from left canine to right second molar, and extending to the lower lip, buccal mucosa, and mouth floor with an obvious submental lymphadenopathy (Fig. 2C and D). The panoramic, periapical radiograph and cone-beam computed tomography of the mandible revealed severe osteolysis beneath the tumor, especially around the incisors and symphysis area to the inferior border of the mandible (Fig. 2G and H). The third biopsy specimen showed plenty of atypical melanocyte hyperplasia with epithelium involvement consisting of intraepithelial dispersion of neoplastic cells (Fig. 1C and D). Further biopsy of a specimen from the submental mass revealed a lymph node with effaced nodal architecture replaced by neoplastic polygonal cells bearing vesicular nuclei, prominent nucleoli, and abundant brownish black pigments in the cytoplasm, which were proved by Fontana Masson stain to be melanin pigments (Fig. 1E–H). The neoplastic cells stained positive with S-100, HMB-45, and CD117. The metastatic foci showed more pleomorphic cell patterns than those seen in the primary sites, and metastatic malignant melanoma was confirmed. The whole-body positron emission tomography-computed tomography (PET-CT) study detected increased fluorodeoxyglucose (FDG) uptake and hypermetabolic lesions in the lower gum, lung, liver, and pelvis, compatible with POM and malignancy metastasis. An oncology group was consulted, but the patient declined all treatments.

Discussion

A literature review supported that POM can be preceded, for a variable period of time, by a flat pigmented lesion. The view of oral melanotic macule or melanosis considered as an innocuous lesion without a malignant potential began to change when few cases of the transformation of benign oral pigmentation into POM were reported by Taylor and Lewis in 1990, Kahn et al in 2005, and Kaehler et al in 2008. If so, should the melanin pigmentation of oral mucosa be considered a premalignant lesion like leukoplakia? What about oral melanosis that is frequently found in over half of Negroes and in other colored races? However, there have been no definite conclusion to date because of the underexploration of the subject.

POM is rare, but pigmented entities are relatively common in the oral mucosa with intrinsic and extrinsic sources. The differential diagnoses should include melanotic macules, nevi, melanocanthoma, smoker’s melanosis, amalgam tattoo, racial pigmentation, vascular blood-related pigments, and those related with systemic diseases such as Addison disease and...
Peutz–Jeghers syndrome. In other words, oral conditions with increased melanin pigmentation are common, but melanocytic hyperplasias are rare. Kahn et al suggested that melanocytic hyperplasia, even in the absence of epithelial hyperplasia or dysplasia, might be regarded as a sign of malignant change. Atypical melanocytes have been defined as melanocytes with hyperchromatic and angular nuclei, but with infrequent mitotic figures. A definitive precursor lesion for POM has not been identified; however, atypical melanocytic hyperplasia may represent a proliferative phase prior to overt melanoma occurs.

Figure 1  (A) Histology of the first biopsies (in September 2002) demonstrating hyperpigmentation of the basal layer of squamous epithelium, clusters of melanophages in the superficial stroma, elongated rete ridges without significant melanocytic activity, and no atypical melanocytes. (B) The second biopsy (in December 2002) of the recurrent lesion exhibiting a benign gingival melanosis with acanthosis, few brown pigments in the upper dermis, and chronic inflammatory cell infiltration. (C and D) The third biopsy (in August 2011) demonstrating malignant melanoma with atypical hyperplasia of melanocytes with epithelium involvement consisting of intraepithelial dispersion of neoplastic cells and existence of prominently pigment-laden atypical cells in the basal and submucosal area. (E–H) A biopsy of submental lymph node (in September 2011) demonstrating metastatic malignant melanoma with effaced nodal architecture replaced by neoplastic polygonal cells bearing vesicular nuclei, prominent nucleoli, and abundant melanin pigments in the cytoplasm. (G) The atypical melanocytes revealed strong cytoplasmic staining with Fontana Masson. (H) Neoplastic cells were immunoreactive to S100 during immunohistochemical staining. Hematoxylin–eosin stain: (A–C) 40×, (D) 200×, (E) 100×, and (F) 400×, Fontana Masson stain: (G) 400×; S-100 stain: (H) 400×.
The differential diagnosis of POM from benign melanosis, oral melanotic macule, labial lentigines, and racial pigmentation, or vice versa, was not always easy because of the lack of induration in the pigmented lesions, a small biopsy size, and underdiagnosis of \textit{in situ} lesions by both clinicians and pathologists.\textsuperscript{6,7,9} The final diagnosis of POM must be confirmed by positive immunohistological staining for S100, Melan-A, and HMB-45 or by cytoplasmic staining for Fontana Masson.\textsuperscript{1,6} Primary mucosal melanoma often exhibits a more aggressive behavior than its cutaneous counterpart.\textsuperscript{1,2} Approximately a third of patients have nodal involvement at presentation, and most afflicted individuals harbor multiple micrometastases prior to the clinical development of distant disease.\textsuperscript{1,7} Dentists and patients should learn the so called "ABCDE checklist" employed to identify cutaneous melanoma as the early markers of oral malignant melanoma (OMM) transformation, which includes the following: (A) asymmetry, (B) border irregularity or bleeding, (C) color variegations or ulcer formation, (D) diameter enlargement, and (E) elevation, a raised surface or erosion of bone. The histology of the first and second biopsies in this case was totally benign, but the clinical appearance was atypical because of the irregular periphery.

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\caption{(A and B) Clinical appearance of a melanotic mandibular gingival lesion with atypical outline and feathering of the pigmentation at the periphery (in April 2002). (C and D) Malignant melanoma with extensive growth over the entire mandibular gingiva, lower lip, buccal mucosa, and mouth floor (in August 2010). (E) Melanoma with an area of hypopigmentation in the labial gingiva of incisors (in December 2010). (F) Progressive melanoma with notable areas of depigmentation, resulting in mobile incisors (in February 2011). (G and H) Periapical film and CBCT showing severe bone destruction and moth-eaten osteolysis around mandibular incisors and the symphyses of mandible (in December 2010). CBCT = cone-beam computed tomography.}
\end{figure}
the developing satellites, and a larger size than that is usually associated with a melanotic macule. Therefore, a careful assessment of the patient’s clinical appearance and histology is necessary to make an appropriate diagnosis of oral pigmented lesions in its early *in situ* phase and achieve a favorable effect on prognosis.

Complete excision with adequate negative margins is prioritized in the treatment of choice for POM. Unfortunately, adequate local control is not a strong predictor for survival. Many patients with a presumptive radical excision of tumors develop a recurrence, which may be explained by the presence of atypical melanocytes in the surgical margins or the presence of satellites and the concept of “field cancerization” of POM. In addition, local failure may indicate a risk of metastasis. The advances in chemoradiotherapy and immunotherapy have produced some clinical response, but the conversion of transient remissions to stable cures remains challenging. Therefore, the prognosis of POM remains poor, and most patients died of metastatic lesions, with an overall 5-year survival rate of approximately 15% and a median survival rate of 18 months after initial diagnosis.

Laser technology is a medically acceptable method to treat many cases with benign pigmented skin or oral lesions, but its therapeutic effect was poor in our case. Could the laser therapy be a trigger factor for a benign melanotic lesion to become malignant? There has been no evidence on the issue to date to detect the relation of cause and effect.

Benign oral melanotic lesions are generally considered unlikely to become malignant, but our case demonstrates that this might not be true. Therefore, periodical follow-ups of patients with benign oral pigmentation are necessary.

### References