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Case Report

Is focal melanotic lesion potentially malignant? A case report

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الملخص

الميلانوما هي آفة خبيثة تصيب الخلايا المنتجة للميلانين التي تُرى غالباً في الجلد. وهي تنبع من السلائف المصطبغة عند ٣٥-٥٠٪ من الحالات. مع أن التصبغ الميلانيني في الفم كثير الحدوث، ولكن سرطان الخلايا المنتجة للميلانين كالميلانوما نادر الحدوث. وقد تنشأ الميلانوما من تصبغ موجود مسبقا، ولكن لم يسبق التعرف على آفات سالفة محددة. والمواقع الشائعة للميلانوما في الفم هي لثة الفك العلوي والحنك. نسجل هنا حالة ميلانوما تحولت من نسيج صبغي مزمن في لثة الفك السفلي والغشاء المخاطي الدهليزي مما يشير إلى الطبيعة الخبيثة المحتملة للبقع الصبغية في الفم.

الكلمات المفتاحية: استفحال إنتاج الميلانين في منطقة محددة؛ البقع الميلانينية؛ سرطان الخلايا المنتجة للميلانين في الفم؛ اللثة؛ الغشاء المخاطي الدهليزي

Abstract

Malignant melanoma is a lesion of melanocytes that is commonly observed on cutaneous surfaces. In 35–50% of cases, it originates from a pigmented precursor. Although oral melanocytic pigmentation is very common, melanocytic malignancies such as melanoma, are rare. Oral melanoma may arise from pre-existing pigmentation, but definitive precursor lesions have not been identified. Common sites for oral melanoma are the maxillary gingiva and palate. We report a case of malignant melanoma that transformed from a long-standing, focal, pigmented lesion on the mandibular gingiva and vestibular mucosa, suggesting the potentially malignant nature of focal oral melanotic lesions.

Keywords: Focal melanosis; Focal pigmented lesion; Malignant melanoma; Melanoplakia; Oral malignant melanoma; Potentially malignant lesion

Introduction

Malignant melanoma is a neoplasm of melanocytic origin, which may arise *de novo* from melanocytes within otherwise normal skin or mucosa or within benign melanocytic lesions. About 1% of all melanomas arise in the oral mucosa, constituting about 0.5% of all oral malignancies.[1]

Unlike cutaneous melanoma, which has a well-established aetiopathogenesis related to sun exposure and precursor lesions such as congenital nevi, dysplastic nevi, and Hutchinson's freckle, the exact aetiology is not defined for oral melanoma. The various aetiologic factors proposed include continuous exposure of the maxilla to the irritants and carcinogenic compounds in cigarette smoke and immunocompromised status. Other factors include cytogenetic defects, pre-existing lesions, growth factors, mechanical trauma, eating disorders, and chronic irritation from ill-fitting denture use.[2]

Most oral melanomas arise *de novo*, but about 30% are preceded by benign, focal oral pigmentation.[3] Focal mucosal pigmentation can be in the form of melanoplakia, melanotic

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macule, melanocytic nevi, or melanoacanthoma. Histologically, these lesions may show increased melanin pigmentation or increased melanocytic proliferation. The presence of benign, flat, pigmented lesions that histologi-cally show melanocytic proliferation with certain atypical features may represent the radial growth phase of melanoma, which may continue for years before entering into vertical phase with metastasis to the underlying connective tissue.

The most commonly affected sites are the palate and maxillary gingiva. Mandibular involvement is rare. In the case reported herein, the whole of the mandibular arch including the gingiva, mandibular vestibule, tongue, floor of the mouth, alveolar ridge and buccal mucosa were involved. This case was preceded by a benign, focal, melanotic lesion for years before development of ulceration, which showed induration and rolled out borders, rare features not usually observed in malignant melanoma.

Case report

A 73-year-old medically compromised man with no history of tobacco or alcohol abuse (diabetic and hypertensive since 36 years of age and has been receiving high-dose insulin and oral hypoglycemics for the former, as well as medication for the latter; history of myocardial infarction 15 years prior and on a antiplatelet regimen) was referred from an otolaryngologist for an opinion on an asymptomatic, grayish-black patch in the left buccal mucosa that developed 3 years prior, but did not show any changes according to the patient. The patient carried records from the last 3 years, in which the black, melanotic, pigmented lesion was mentioned involving the left mandibular buccal and lingual gingiva, vestibular mucosa, buccal mucosa and retromolar region. Unfortunately, a clinical picture of the lesion could not be retrieved from the otolaryngologist, but the patient presented a slide of the incisional biopsy specimen that showed increased melanin pigmentation in the basal layer with benign melanocytic proliferation [Figure 1]. The patient was diagnosed with melanoplakia, but showed clinically atypical features of asymmetry, border irregularity, colour variations and extensive size, and the patient was advised to undergo laser treatment. However, due to financial constraints and his asymptomatic nature, the patient refused to undergo the treatment. He has now been referred for an opinion regarding the lesion and for treatment of pain in the lower front region that developed 2 weeks ago. The patient also presented a history of using a maxillary partial denture from 2 years prior.

On extraoral examination, the left submandibular lymph node (level 1b) was palpable, measuring approx. 2 cm in diameter, firm in consistency, mobile and tender on palpation.

Intraorally, a solitary ulcer was observed in the left lower vestibule in the region of the left mandibular canine, and first and second premolars (33, 34, 35); it measured about 2×0.5 cm, was linear in shape with a raised edge, contained a black-pigmented floor, and the surrounding area showed a grayish-black plaque extending 5 mm around the ulcer with uniform pigmentation. The pigmentation extended medially on the buccal gingiva until the right mandibular canine (43) with areas of normal mucosa in between. The pigmentation was also observed extending posteriorly onto the alveolar ridge and vestibule in the region of the left mandibular molars (36, 37, 38) onto the retromolar area and further posteriorly onto the raphe, onto the soft palate medially, and onto the posterior buccal mucosa laterally. This pigmentation comprised varied intensities of colour with a grayish-black plaque extending to the retromolar region, and brown macular pigmentation on the raphe, soft palate, and posterior buccal mucosa. The brown macular pigmentation was also seen extending lingually on the gingiva from the left mandibular second premolar to the right mandibular first molar, in the floor of the mouth and on the ventral surface of the tongue. On palpation, the edge and base of the ulcer were indurated, bleeding, and tender [Figure 2]. Multiple erythematous macules of varying sizes were present on the posterior aspects of the hard and soft palates with ill-defined borders. The list of differential diagnoses for the palatal lesions was vast, including atrophic candidiasis, allergic stomatitis, chemical/thermal injury, infectious mononucleosis, macular lesions due to negative pressure of the denture, macular haemangiomas and telangiectasias, smoker's palate and erythroplakia. There was no history of deleterious habits like smoking or chewing tobacco, and no changes in the brand of toothpaste used or food items consumed. The patient presented with uncontrolled diabetes and wore dentures. Hence, the most probable diagnosis for the palatal lesions was atrophic candidiasis [Figure 3]. However, they were completely asymptomatic and were not the reason for the patient seeking dental opinion. The true cause for the pain was grave; the ulceration in the pigmented lesion produced reactive lymphadenopathy. The patient was given a provisional diagnosis of malignant melanoma involving the mandibular vestibule, alveolus, gingiva, floor of the mouth and ventral surface of tongue.

The patient was advised to undergo Orthopantomogram (OPG) to determine bone involvement, but no significant findings were obtained. Chest X-ray and Ultrasound of the abdomen were conducted to determine metastasis, but no significant features were detected. The results of the blood investigations were as follows: haemoglobin (Hb), 12.9 gm%; total leucocyte count, 9100 cells/cu mm; neutrophils, 65%; lymphocytes, 30%; eosinophils, 3%; monocytes, 4%; basophils, 0%; RBC count, 4.16 million; PCV, 38%; MCV,

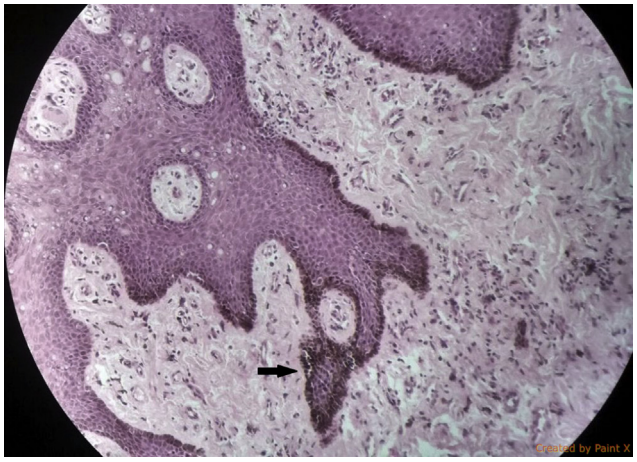

Figure 1: Histopathological image of H&E stained section showing increased melanin pigment and melanocytic hyperplasia. H&E, haematoxylin and eosin.

91 fl; MCH, 31 pg; MCHC, 33.9%; platelet count, 2.33 lakhs/cu mm; random blood sugar, **273 mg/dl**; blood urea nitrogen, 15.3 mg/dl; creatinine, 0.9 mg/dl; total protein, 8.4 g/dl; albumin, **3.1 g/dl**; alkaline phosphatase, **143 IU/L**; bilirubin, 0.8 mg/dl; serum electrolytes including Na^+, **130 mmol/l**, and K^+, 5.4 mmol/l; SGOT, **64 IU/L**; and SGPT, **77 IU/L**. The HIV spot test generated negative results, but **HBsAg test results were positive**.

Incisional biopsy of the lesion was performed from the left lower mandibular vestibule region, which showed stratified squamous epithelia with an abundance of infiltrating atypical melanocytes and some components growing into the underlying connective tissue. Atypical melanocytes were larger than normal and showed varying degrees of pleomorphism and hyperchromatism. The cells exhibited epithelioid or spindle shapes and were arranged in the form of loosely aggregated cords or sheets. An abundance of melanin pigmentation was also noted. These features were indicative of a malignant melanoma and signified the vertical growth phase as connective tissue invasion was observed [Figure 4].

Because of loco-regionally extensive disease, advanced age and medical comorbidities such as diabetes, hypertension, coronary artery disease and hepatitis B, surgical treatment and chemotherapy were not feasible. Thus, the patient was administered palliative treatment with antioxidants, nutritional supplements, analgesics and regular follow-up.

At the 3-month follow-up, there was extension of the ulcer medially with raised edges and increased depth. At the 5-month follow-up, the initially reactive level 1b lymph node became metastatic. It was 3 × 3 cm in size, hard in consistency and non-tender, but mobile. There was deepening of the ulcer with raised edges and feathering of pigmentation at the periphery with colour variations [Figure 5]. The haematological and biochemical parameters also deteriorated (alkaline phosphatase, **187 U/L**; SGOT, **79 IU/L**; Hb, **11.1 gm%**; RBC, **3.58 million cells/cu mm**;

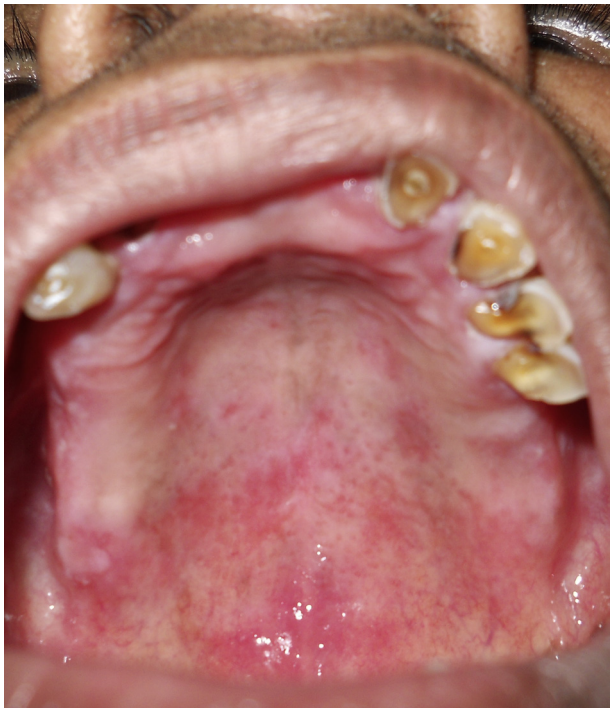

Figure 3: Photograph showing no pigmentation on the palate and mild atrophic candidiasis.

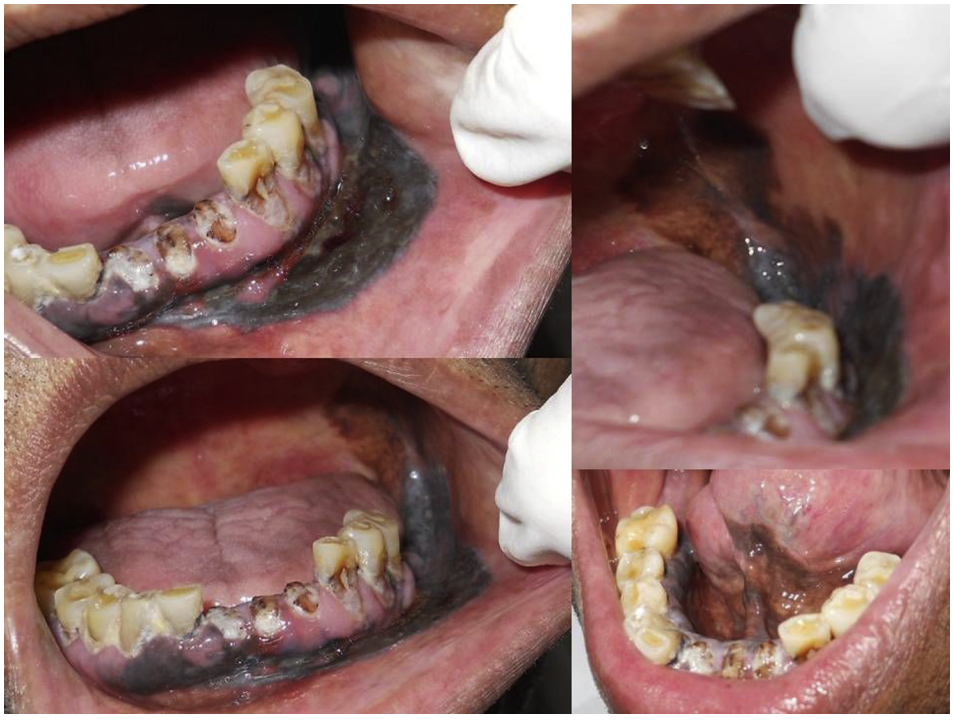

Figure 2: Photographs showing ulceration in the lower labial vestibule and extension of pigmentation over the mandibular arch including the tongue.

PCV, **31.6%**) due to worsening liver function owing to chronic hepatitis B and cancer-induced cachexia.

At the 6-month follow-up, the ulcer extended deeper with difficulty in eversion of the lips. The pigmentation also extended onto the buccal mucosa with irregular borders and showed variations in the intensity of black melanotic pigmentation. The depth of pigmentation also increased on the ventral surface of the tongue [Figure 6].

The patient did not report for follow-up visits and succumbed to death 1 year after the diagnosis.

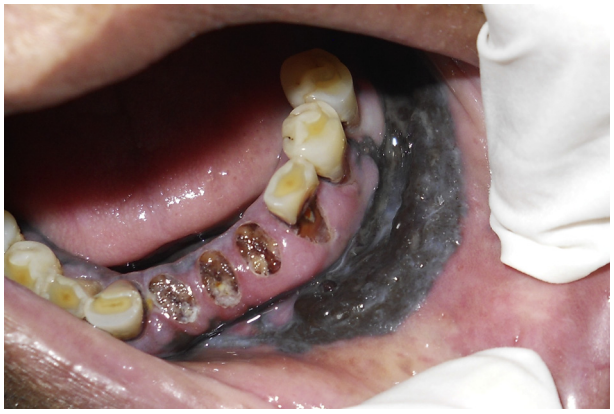

Figure 5: Photograph at the 3-month follow-up showing increased depth of ulcer and raised edge.

Discussion

Although primary oral melanomas are rare, melanocytic, flat, pigmented lesions are commonly observed in the oral cavity, which can be focal (melanotic macule, melanocytic nevi, melanoacanthoma, melanoplakia) or diffuse (endocrinal, smoker's melanosis, drug-induced). These lesions histopathologically show only basilar melanosis, apart from melanocytic nevi, demonstrating melanocytic proliferation into theques or clusters. Depending on the extent of such theques in the epithelium and/or connective tissue, they can be categorized as either junctional, intramucosal or compound. The transformation of a melanotic macule into malignant melanoma was reported by Kahn et al.[4] who suggested that melanocytic hyperplasia even in the absence of any atypia or dysplasia should be considered alarming as it may indicate a predisposition to melanoma and the presence of a melanotic macule may actually represent the *in situ* phase of melanoma. The benign melanocytic proliferation observed in the incisional biopsy specimen slide in our case also signifies that melanoplakia—when diagnosed 3 years ago—may have developed during the horizontal growth phase of melanoma. The lack of treatment then pushed its development into the vertical growth phase with tissue invasion and resultant ulceration, induration, and metastasis to the lymph nodes.

Melanocytic nevi represent the proliferation of melanocytes and their clustering at different levels. The transformation of melanocytic nevi into oral melanoma has not been documented. However, they are considered as precursor lesions for melanoma as they occur commonly on the palate, which is the preferred site for melanoma development. Additionally, atypical melanocytic hyperplasia similar to that seen in cutaneous dysplastic nevi may be observed in melanocytic nevi, which can predispose melanoma development. No evidence of increased risk of transformation of melanocytic nevi into melanoma was reported in the review of 119 cases by Meleti et al.[5] The probable reason was that all those 119 cases underwent complete excision and thus their potential to develop into melanoma if left untreated was not explored; the study also suffered limitations of short follow-up periods.

Melanoacanthoma is a benign, reactive lesion that greatly mimics melanoma due to rapid enlargement, but histologically, it does not show any atypia or melanocytic proliferation, and some cases may even involute after biopsy.[6]

Melanoplakia literally means "black plate" and is commonly a physiologic pigmentation that shows increased activity of melanocytes rather than increased proliferation. Physiologic pigmentation is usually present since childhood. However, any recent development of pigmented patches should be viewed with suspicion.

Various histological terminologies have been reported for precursor lesions such as atypical melanocytic proliferation, Pagetoid premalignant melanosis, premalignant melanocytic

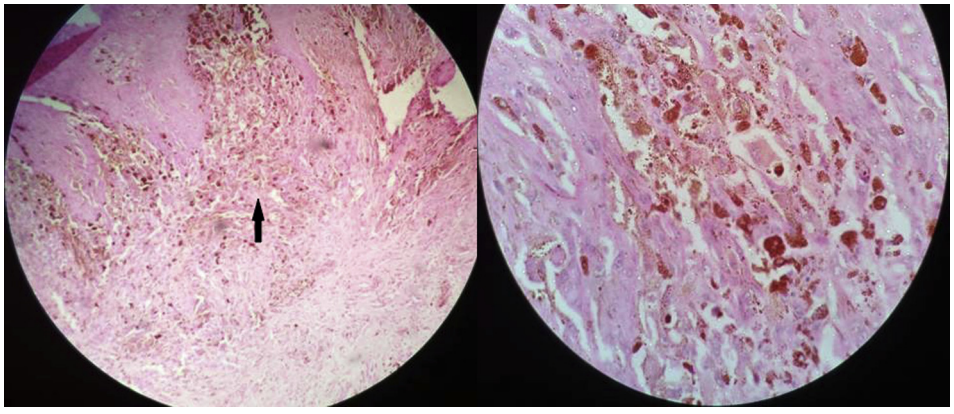

Figure 4: Photomicrograph of H&E-stained section showing atypical melanocytes invading the connective tissue in low-power view (10×). High-power view shows larger atypical melanocytes with varying degrees of pleomorphism and hyperchromatism, as well as increased melanin pigmentation (40×). The histological picture confirmed the diagnosis of malignant melanoma. H&E, haematoxylin and eosin.

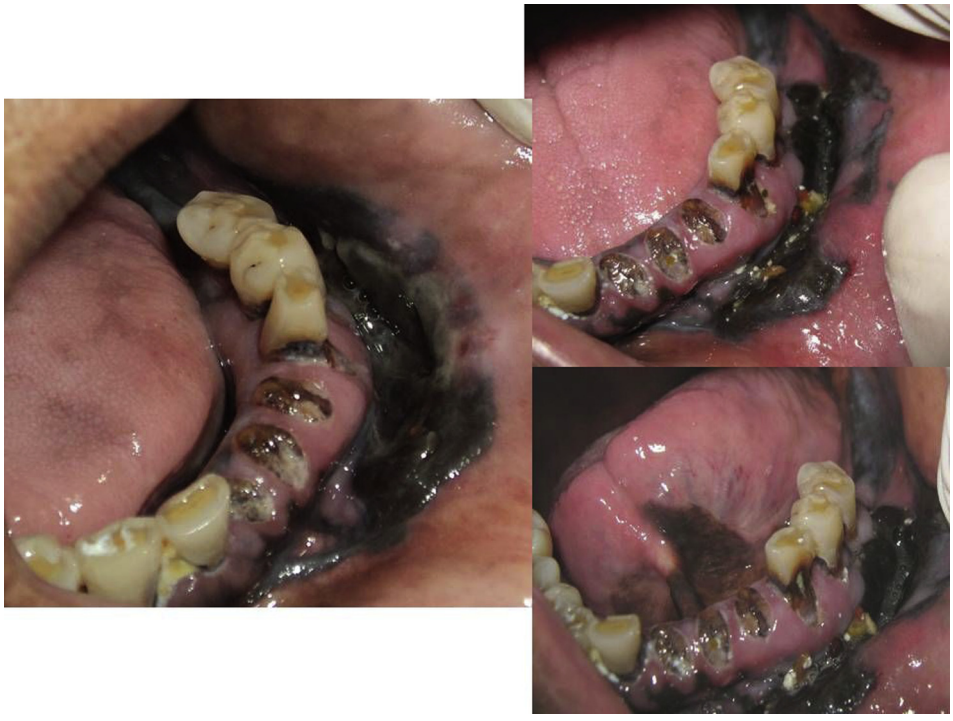

Figure 6: Photographs at the 5- and 6-month follow-ups showing extension and deepening of ulceration with feathering of pigmentation at the periphery and increased depth of pigmentation.

dysplasia, and melanoma *in situ* with similar features. However, no clinical correlations of these terminologies have been reported. The clinical appearance in our case was atypical, as it fulfilled the ABCDE criteria (asymmetry, border irregularity, colour variations, diameter >6 mm, evolution or surface elevation), but histologically, it only showed melanocytic hyperplasia without any atypical or dysplastic features. Tanaka et al.[7,8] allocated the classification of oral melanoma based on clinical features, unlike previous investigators who categorized oral melanoma into acral lentiginous varieties of cutaneous melanomas. The classification included pigmented nodular, non-pigmented nodular, pigmented macular, pigmented mixed (macular + nodular) and non-pigmented mixed types. Our case was classified as pigmented macular oral melanoma initially, which turned into an ulceration. This cannot be categorized into any of the types described. Hence, we suggest adding another type of pigmented ulcerated variety into the clinical classification of oral melanoma.

In a case series and review by Manganaro et al.,[9] it was mentioned that these lesions normally do not show ulcerations with indurated borders and palpable lymph nodes because of the prolonged radial growth phase with minimal or no invasion. Atypical melanocytes also show a pagetoid spread into the superficial layers of epithelia, resulting in uniform epithelial thickening rather than hyperplasia at a focal site. In contrast to this, our case showed palpable, hard lymph nodes with ulceration and indurated borders. This is likely due to the transformation of a prolonged radial phase into a rapid vertical phase with invasion into the underlying connective tissue.

The patient in our case did not have any deleterious habits and did not use denture that could have triggered the ulceration. However, the patient was systemically compromised. His uncontrolled diabetic status, elderly age and chronic hepatitis produced chronic immunosuppression that could have affected the immunosurveillance, predisposing him to the development of malignancy.

There has been a concern regarding the biopsy of pigmented lesions considering the concept of tumour seeding when an aggressive malignant lesion is manipulated. This can lead to local recurrence or regional or distant metastasis. Some authors have also postulated that the release of fibroblast growth factors during the healing of biopsy wounds may actually stimulate tumour outgrowth.[1] However, the current guidelines recommend excisional biopsy (i.e. complete removal of the lesion with a 1–2-mm margin). Studies have found reduced survival in patients who underwent incisional biopsy (i.e. removal of part of the lesion with neighbouring normal tissue) for cutaneous melanoma compared to excisional biopsy.[10,11] However, in the oral cavity, the size of the lesion and anatomical limitations may preclude excisional biopsy. This could be one of the reasons for reduced survival of only 15% for oral melanoma as compared to 21–40% for head and neck mucosal melanoma and 80% for cutaneous melanoma.[1,6]

The prognostic parameters defined for cutaneous melanoma, such as Clark's level of invasion and Breslow tumour thickness, are not efficient for oral melanoma due to the absence of clearly defined levels of papillary and reticular dermis, and the tumour thickness is usually >4 mm in almost all cases.

There are various tumour-associated antigens expressed in melanomas, the detection of which may actually predict the transformation of benign pigmentation into melanoma. These include HLA-restricted antigens, such as HMB-45,

MUC-18, gangliosides, FGF, and mutated p53, which are known targets for immunotherapy since melanoma is one of the most immunogenic tumour. Hence, if these could be conducted in the benign or radial growth phases, the complications may be reduced, and the 5-year survival rate could improve. However, these tests could not be performed in our case due to financial constraints and unavailability of resources.

In conclusion, focal melanotic lesions should always be viewed with suspicion and should be considered potentially malignant, such as leukoplakia or erythroplakia. Biopsy is always performed on these potentially malignant lesions to identify and grade the dysplasia as it determines the prognosis and chances of these converting into malignancy. Similarly, focal melanotic lesions must be biopsied, preferably via excisional biopsy, to identify melanocytic proliferation; if such hyperplasia is observed, even without the presence of atypical features, the radial phase of melanoma should be suspected and prompt treatment should be initiated before its transformation into the vertical phase on account of the poor prognosis of this aggressive malignancy. We also propose to modify the clinical classification of oral melanomas by adding a separate clinical variety of pigmented ulcerative types to the existing classification.

Conflicts of interest

The authors declare that there are no potential areas of conflict.

Authors' contributions

Dr Astha Chaudhry – Clinical case record and writing of manuscript. Dr Pulin Saluja – Description of the histopathological elements of the manuscript and review of the article. Dr Manjunath M. – Guiding the follow up for the case and overall review of the article.

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