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Uncommon Oral Pigmented Lesions: A Case-Based Diagnostic Approach

Nadir Görülen Oral Pigmente Lezyonlar: Vaka Temelli Tanısal Yaklaşım

Oral Pigmented Lesions

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ABSTRACT

Oral pigmented lesions constitute a diagnostically heterogeneous group of conditions ranging from physiological pigmentation to potentially life-threatening malignancies. Accurate identification requires a meticulous assessment of clinical, radiographic, and histopathological features, supported by comprehensive patient history. This study presents a case series comprising three distinct pigmented oral lesions—oral malignant melanoma, imatinib-induced mucosal pigmentation, and oral melanocytic nevus—to underscore the clinical diversity, diagnostic complexity, and differential considerations inherent to such lesions. Each case illustrates unique etiopathogenetic mechanisms and highlights the necessity of distinguishing between melanocytic and non-melanocytic origins. Through this case-based approach, the study advocates for heightened clinical vigilance and interdisciplinary collaboration to improve diagnostic accuracy and patient outcomes in the context of oral pigmented lesions.

Keywords: Oral Pigmented Lesions; Differential Diagnosis; Malignant Melanoma; Drug-induced Pigmentation; Oral Nevus

ÖZET

Oral pigmente lezyonlar, fizyolojik pigmentasyondan yaşamı tehdit edebilen malignitelere kadar uzanan geniş bir klinik spektrumda yer almakta olup, tanısal açıdan heterojen bir grup oluşturmaktadır. Bu lezyonların doğru şekilde değerlendirilmesi; detaylı klinik muayene, radyografik görüntüleme, histopatolojik inceleme ve kapsamlı hasta öyküsünün birlikte ele alınmasını gerektirir. Bu çalışmada, malign melanom, imatinib kaynaklı mukozal pigmentasyon ve oral melanositik nevüs olmak üzere üç farklı pigmente lezyon olgusu sunularak, bu klinik tablolardaki etyopatogenez, ayırıcı tanı güçlükleri ve multidisipliner yaklaşım gereksinimi vurgulanmıştır. Bu olgu temelli yaklaşım, oral pigmente lezyonların tanı sürecinde dikkatli klinik değerlendirme ve disiplinlerarası iş birliğinin hasta prognozunu iyileştirmedeki rolünü ortaya koymaktadır.

Anahtar Kelimeler: Oral Pigmente Lezyonlar; Ayırıcı Tanı; Malign Melanom; İlaç İlişkili Pigmentasyon; Oral Nevüs

Introduction

Pigmentation of the oral mucosa may present with diverse clinical appearances, ranging from localized macular discolorations to widespread involvement, or from minor nodular elevations to sizable masses.[1] Considering that oral mucosa reflects not only physiological diversity but also various pathological conditions,[2,3] diagnosing pigmented oral lesions can be challenging, requiring careful evaluation of their characteristics and a thorough review of the patient's medical, dental, and personal history for accurate diagnosis.[1,3,4] The clinical history, symmetry, borders, uniformity of color of the lesion and changes in the lesion's appearance play a critical role in establishing the differential diagnosis during a comprehensive clinical evaluation.[5] Given the wide spectrum of potential conditions, it is imperative that clinicians maintain a high index of suspicion and employ a systematic approach to evaluation. Therefore, a thorough understanding of both the clinical presentations and underlying pathophysiological mechanisms is essential for effectively managing patients with pigmented lesions of the oral mucosa.

Pigmented oral lesions encompass a broad range of etiologies, including physiological pigmentation, drug-induced changes, nevi, and malignant neoplasms. Early and accurate differentiation among these entities is crucial for appropriate management and prognosis.

This case series aims to highlight the diagnostic challenges associated with uncommon oral pigmented lesions—specifically oral mucosal melanoma, imatinib-induced pigmentation, and melanocytic nevus-through a structured, case-based diagnostic approach. By integrating clinical, histopathological, and radiographic findings, this report underscores the importance of an interdisciplinary perspective in identifying and managing such lesions.

Case Reports

Case 1

A 61-year-old female patient presented to the clinic with a complaint of a painful lesion on lower labial attached gingiva. She noticed small patches of pigmented area 6 months ago, which increased to the present size and gradually became painful. The patient's medical history was noncontributory, and she was not under any medications. There was no familial history of carcinomas. Intraoral examination revealed a well-defined, smooth-surfaced, dark reddish/purple lesion on the labial attached gingiva at the region of the right lower first and second incisor teeth and the canine (Figure 1a). Lymphadenopathy of the submental lymph nodes was detected during extraoral examination. No pathology was observed on the patient's panoramic radiograph (Figure 1b).

An incisional biopsy revealed a spindle cell tumor located beneath the epithelium, demonstrating immunohistochemical positivity for S-100 and SOX-10, and negativity for epithelial and endothelial markers, including Cytokeratin, p63, CD31, CD34, and ERG. The tumor exhibited a high Ki-67 proliferative index. These findings were interpreted as consistent with melanoma. Subsequent histopathological evaluation of the excisional

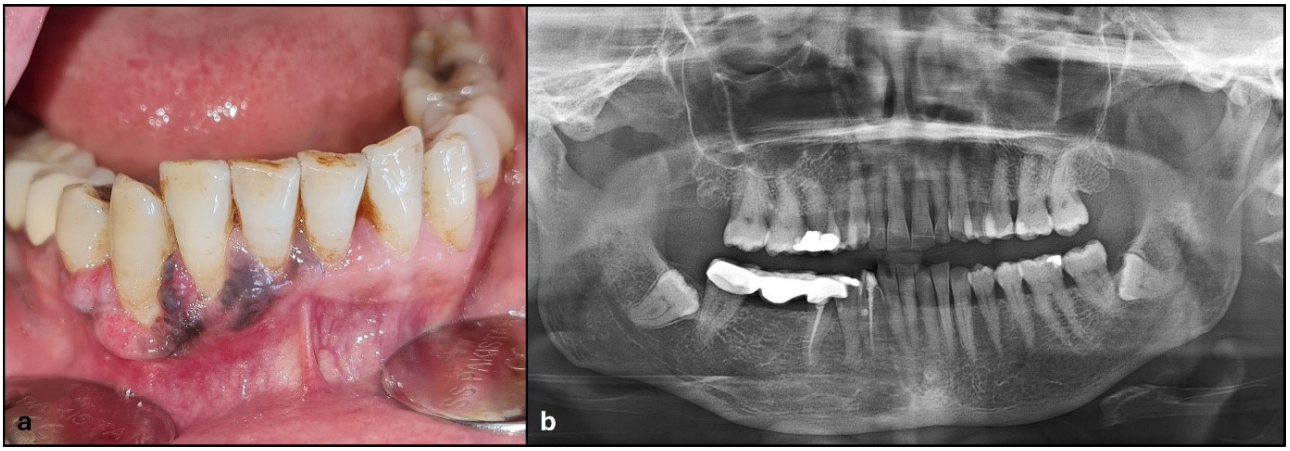

Figure 1. a-A well-defined, smooth-surfaced, dark reddish/purple lesion on the labial attached gingiva. Biopsy findings indicated malignant melanoma; **b**-No pathology was observed on the patient's panoramic radiograph

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biopsy specimen identified a malignant melanocytic neoplasm composed of spindle cells exhibiting high mitotic activity beneath a broad area of ulceration. Diffuse S-100 positivity was observed within the tumor (Figure 2). Molecular analysis was conducted to assess for KIT and BRAF mutations; however, no specific targetable mutations were detected in either gene region.

Following evaluation by the otorhinolaryngology team, induction chemotherapy was planned. However, no response was observed to neoadjuvant Optiva therapy administered by the medical oncology department. Consequently, the patient was referred for surgical excision of the tumor and is currently hospitalized for further management.

Oral mucosal melanoma (OMM) is characterized by the proliferation of malignant melanocytes at the interface between the epithelium and connective tissue, and may also occur deep within the connective tissue.[6] Although OMM constitutes approximately 0.2% to 0.8% of all melanoma cases and represents about 0.26% of oral tumors,[7] it is recognized as a highly aggressive form of melanoma with a poorer prognosis than its' cutaneous counterpart.[6,8,9] It is essential to distinguish OMM from other focal pigmentations such as amalgam tattoo, melanocytic nevus, melanotic macule, and melanoacanthoma in the differential diagnosis, as an early and prompt diagnosis of oral mucosal melanoma is important for the patient's prognosis.[8,10] (Figure 3)

Preferred treatment options of OMM include surgery, chemotherapy, radiotherapy, and immunotherapy,[7] but studies have demonstrated that recent surgical excision combined with immuno-chemotherapy can reduce or prevent lesion recurrence.[12] Despite multifaceted treatment modalities, the prognosis of OMM is notably poor, with a 5-year survival rate of less than 30%, primarily due to diagnostic delays and the occurrence of distant metastasis.[8,9,11,12]

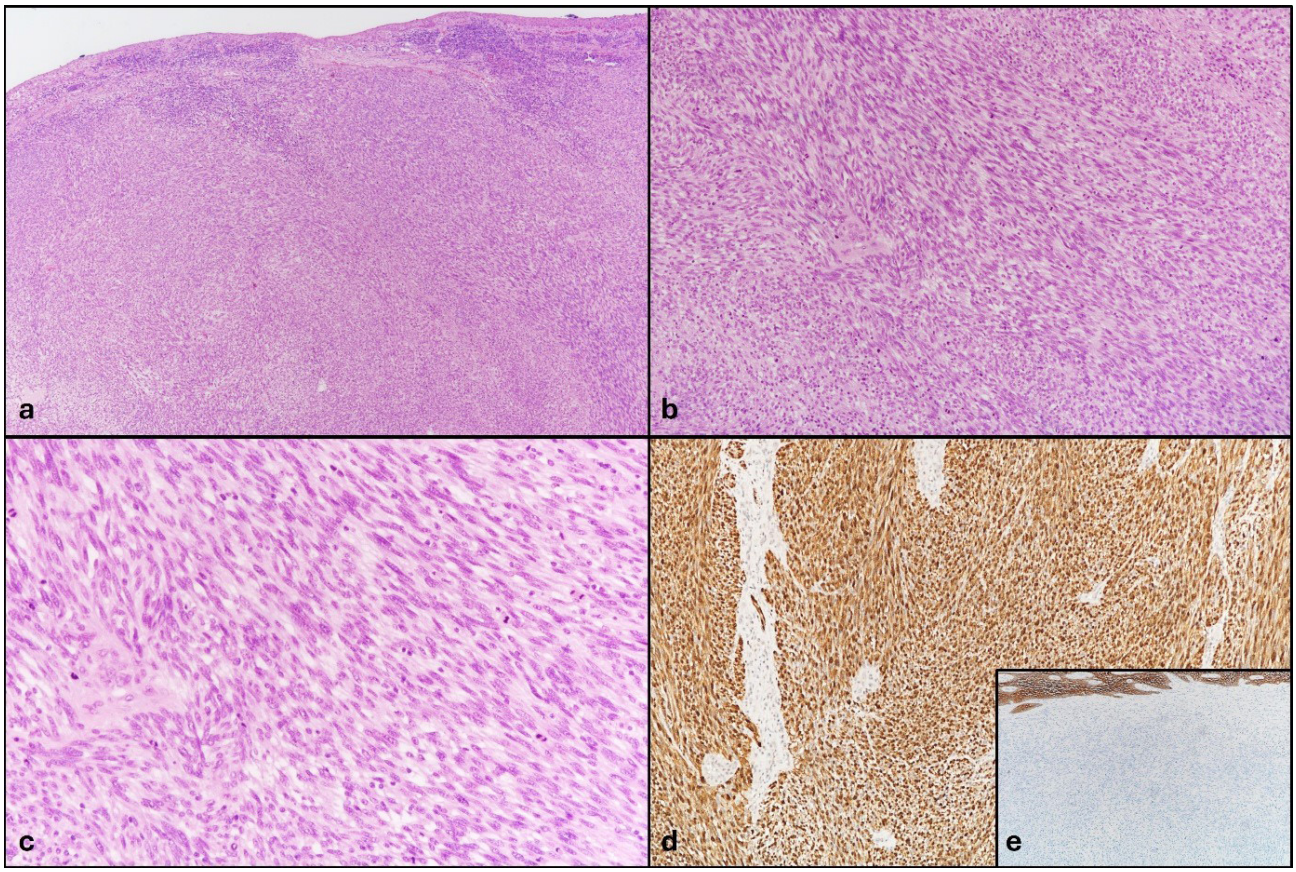

Figure 2: a-b-c: Malignant tumor infiltration composed of spindle cells beneath the epithelium, showing atypia and high mitotic activity (H&E x40, x100, x200); d: Diffuse S-100 positivity in the tumor (x100); e: Negative staining for cytokeratin (x40).

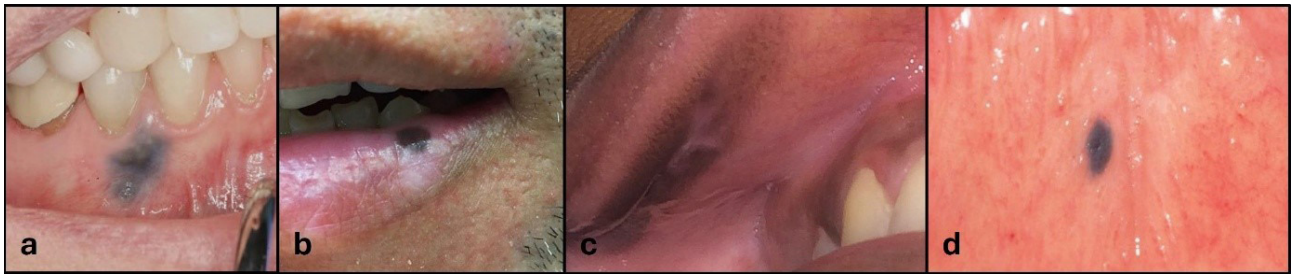

Figure 3. Lesions recommended for evaluation in the differential diagnosis of malignant melanoma.[3,9] **a**- Amalgam tattoo (gingiva); **b**- Melanotic macule (lower lip); **c**- Melanoacanthoma (upper labial mucosa); **d**- Melanocytic nevus (palate).

Case 2

A 58-year-old male patient presented to the outpatient clinic with a complaint of pigmentation on his hard palate. Although the patient had been aware of the pigmentation for the past three years, he did not feel the need to visit a dentist due to the asymptomatic nature of the pathology until the prolonged persistence of the condition urged him to consult for thorough evaluation, diagnosis, and treatment. The patient's medical history revealed that he has been under medication for chronic eosinophilic leukemia since 2007. Apart from this, his medical history was non-contributory. On intraoral examination, symmetrical bluish-purple pigmentation was observed on both the right and left sides of the midline of the hard palate (Figure 4a). No other areas of pigmentation were recorded on the oral mucosa, skin, or fingernails.

After an incisional biopsy, histopathological examination revealed numerous siderophages in the tunica propria, within vascularity and mild fibrosis (Figure 5).

The patient declared he has been under imatinib therapy for his chronic eosinophilic leukemia for 17 years which initially started at 400 mg, and continued at a dose of 200 mg for the past two months prior to presentation. A detailed literature review revealed that intraoral mucosal pigmentation may be observed as a sporadic side effect of imatinib therapy, and the intraoral pigmentation detected on the patient's hard palate is a rare case of imatinib-induced pigmentation. Considering the drug-induced pigmentations are benign and innocuous and do not require active treatment, routine follow-up was recommended for the patient. One year follow-up examination showed no significant changes of the lesion (Figure 4b).

Drug-induced oral melanosis accounts for an estimated 10–20% of acquired oral pigmentation attributed to certain medications[2,13], encompassing antimalarials, including chloroquine, hydroxychloroquine, and quinacrinen.[2] Other medications involved are antipsychotics like chlorpromazine, chemotherapeutics such as bleomycin, imatinib, busulfan, and fluorouracil, antifungals like ketoconazole, antimicrobials such as tetracycline and minocycline, and antiretrovirals like zidovudine.[2]

Imatinib mesylate is a tyrosine kinase inhibitor targeting the Bcr-Abl protein, c-Kit, and platelet-derived growth factor receptor.[14] Imatinib treatment is generally well tolerated, with a low prevalence of severe side effects.[14] While hypopigmentation is a common side effect of imatinib therapy, intraoral hyperpigmentation has been observed seldom and its' exact mechanism is still unclear.[14] Although pigmentation of the oral cavity associated with imatinib therapy is a rare phenomenon, it is increasingly recognized in clinical practice and may be underreported. It is essential for medical and dental professionals to remain vigilant about the potential for mucosal pigmentation in patients undergoing imatinib treatment. Accurate diagnosis of imatinib-induced pigmentation necessitates a thorough medical history and careful evaluation of characteristic clinical features since growing body of literature presents imatinib as a drug associated with characteristic blue-gray discolorations primarily affecting the palatal mucosa.[13] When the clinical diagnosis remains uncertain, biopsy is a valuable tool. It helps differentiate drug-related mucosal pigmentation from other conditions, such as melanoacanthoma, oral mucosal melanoma, oral melanocytic nevi, or systemic diseases.[13,14] (Figure 6)

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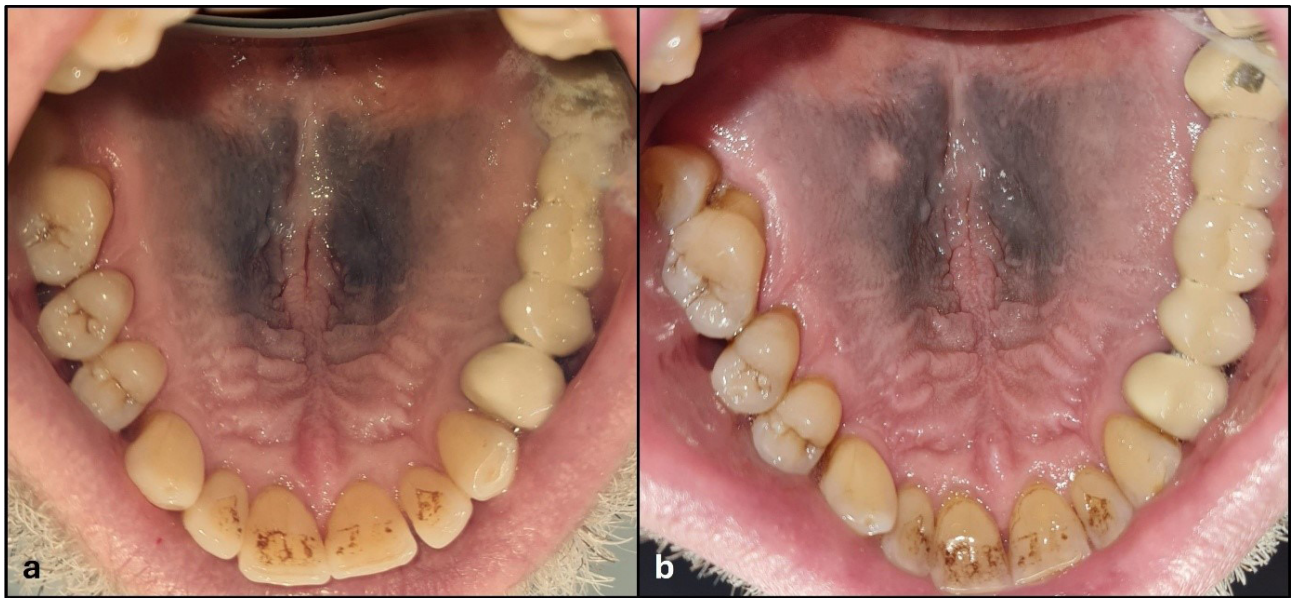

Figure 4: a -A symmetric, homogeneous bluish-purple discoloration of the hard palate; **b**-The follow-up imaging of the patient one year later.

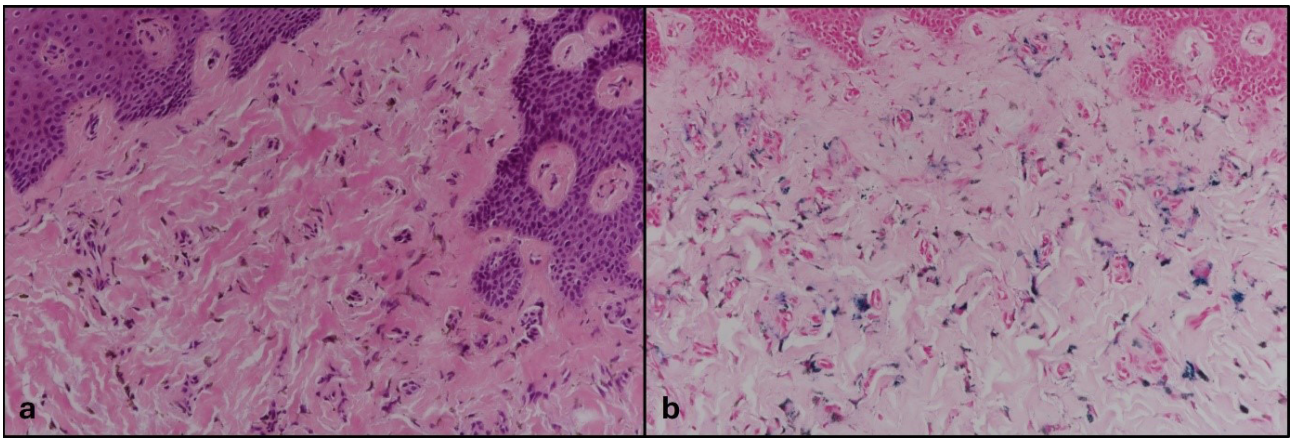

Figure 5. Hemosiderin accumulation characterized by dermal dendritic cells and siderophages in the tunica propria (**a**-H&E, x100; **b**- Iron stain, x100).

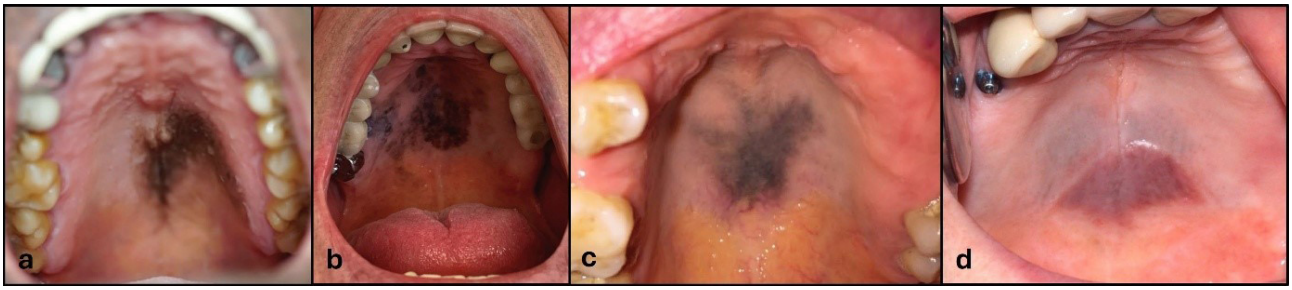

Figure 6. Lesions recommended for evaluation in the differential diagnosis of drug-related pigmentation.[2,4,8,11] **a**- Melanoacanthoma; **b**- Oral mucosal melanoma; **c**- Melanocytic nevus; **d**- Beta thalassemia.

Case 3

During the intraoral examination of a 27-year-old female patient who presented to our clinic for a routine annual dental control, a well-defined, solitary, dark blackish elevated patch was detected on the attached lingual gingiva of the patient's mandibular right posterior area. (Figure 7a) The patient was unaware of the lesion since the lesion was asymptomatic, and her medical history was non-contributory. The patient's panoramic radiograph revealed no signs of pathology. (Figure 7b) The clinical preliminary diagnosis included oral melanocytic nevus or melanoma, and the patient was

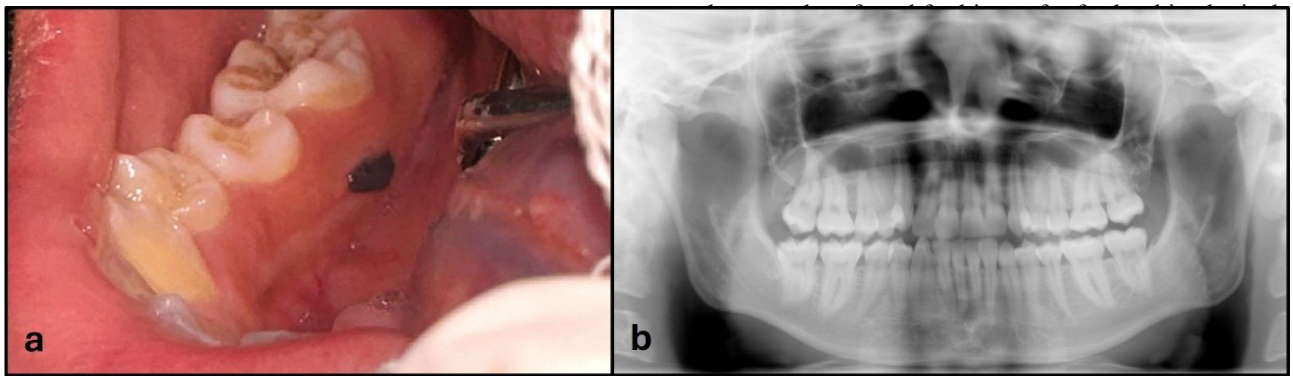

Figure 7: a-A well-demarcated, solitary, elevated lesion with a dark blackish-red coloration that was located on the attached lingual gingiva of mandibular right posterior teeth; **b-** The patient's panoramic radiograph revealed no signs of pathology.

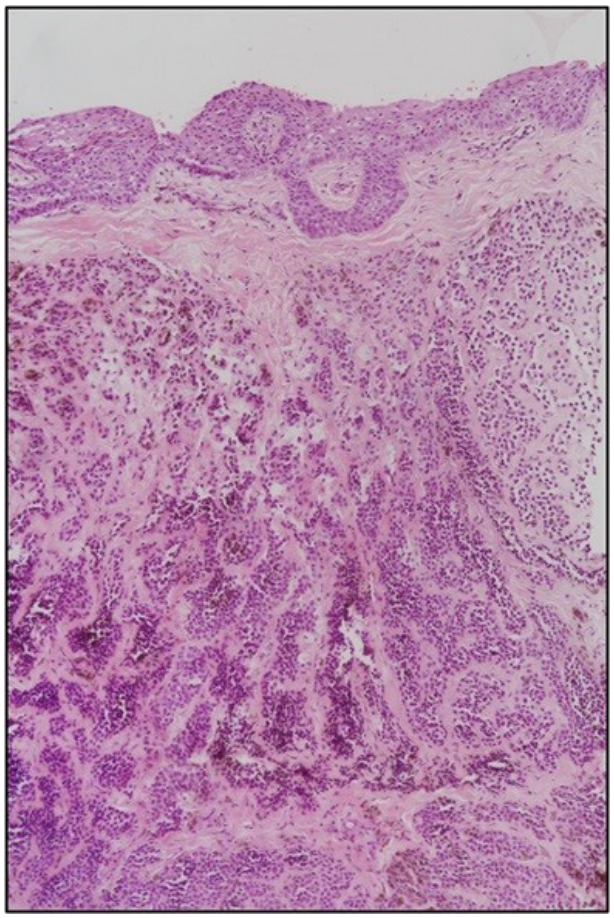

Figure 8. Intradermal nevus characterized by nests of melanocytic nevus cells exhibiting typical tunica propria localization (H&E, x100).

evaluation. The result of the incisional biopsy was identified as melanocytic intradermal nevus. (Figure 8)

Oral melanocytic nevi are rarely found within the oral cavity compared to the skin,[1,15] with the hard palate being the most frequently affected site.[15,16] Similar to the present case, most lesions are asymptomatic and are typically identified during routine dental examinations.[5,17] Clinically, the common melanocytic nevus typically appears as a solitary, smooth, well-defined papule that is either flat or elevated, generally measuring less than 10 mm in diameter, although larger lesions have also been documented.[16,17] Due to its rarity, clinicians and dentists may encounter difficulties in recognizing this condition. The clinical presentation of oral melanocytic nevus is not definitive for diagnosis; therefore, a biopsy is typically necessary to distinguish them from other pigmented lesions, such as melanocytic macules, Smoker's melanosis or amalgam tattoos and more critically, to rule out early-stage malignant melanoma.[1,5,15,16] (Figure 9) The preferred treatment is surgical excision, which is associated with a favorable prognosis and a low likelihood of recurrence.[5]

Discussion

The diagnosis and management of pigmented oral lesions present considerable challenges due to their diverse

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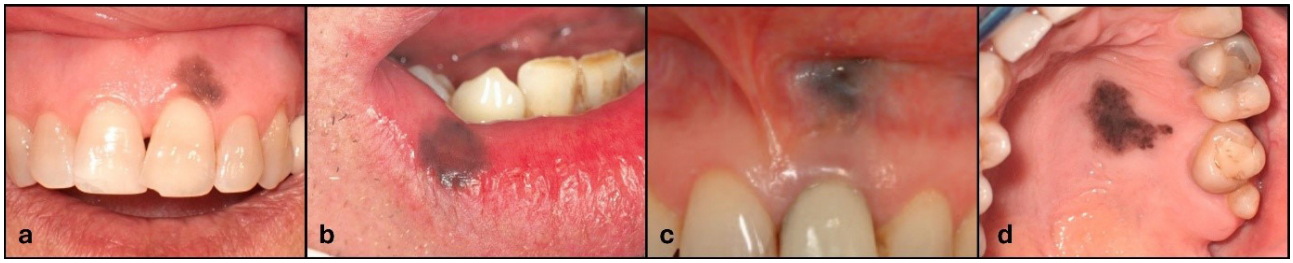

Figure 9: Lesions recommended for evaluation in the differential diagnosis of oral melanocytic nevus.[2,9,15] **a**- Oral melanotic macule; **b**- Smoker's melanosis; **c**- Amalgam Tattoo; **d**- Oral mucosal melanoma.

etiologies, ranging from benign conditions to potentially life-threatening pathologies. In all three presented cases, early and accurate diagnosis was achieved through comprehensive clinical examination complemented by histopathological assessment, underscoring the essential role of these diagnostic modalities in clinical decision-making. Each case highlights a distinct diagnostic consideration: the malignant potential inherent to oral mucosal melanoma, the underrecognized mucosal pigmentation associated with long-term imatinib therapy, and the rarity of oral melanocytic nevi as differential diagnostic entities.

The literature highlights the pivotal role of dental care providers including dental hygienists and medical/dental general practitioners as primary points of contact, enabling the early identification and referral of pigmented lesions for specialized care. Although physiological pigmentations are commonly encountered, focal pigmentations including amalgam tattoos, melanocytic nevi, and melanotic macules require attention due to their less frequent occurrence and potential implications.[18] Recent studies[3,19] emphasize the increasing clinical recognition of these entities and the need for improved awareness among dental professionals.

In order to provide effective management, recognition of clinical features and acquisition of a detailed patient history that includes familial, social, and occupational factors are vital.[19] Particularly for lesions exhibiting features such as asymmetry, variegated coloration, rapid growth, or ulceration, biopsy and subsequent histopathological assessment remain indispensable. Because of the broad variability in presentation, pigmentation patterns, and underlying causes, the differential diagnosis of pigmented oral lesions is inherently complex. The solitary lesions can often be definitively diagnosed with biopsy, but diffuse pigmentations require a comprehensive evaluation involving detailed history-taking and laboratory investigations to detect underlying medical conditions.

In conclusion, this case-based report underscores the importance of employing a systematic diagnostic framework for distinguishing among rare oral pigmented lesions. The observations highlight the critical role of interdisciplinary collaboration among dental, medical, and pathology specialists in facilitating early detection and improving patient outcomes. Moreover, the findings emphasize the ongoing need for continuous professional development and the regular refinement of diagnostic algorithms to ensure precise identification and effective management of these uncommon lesions.

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