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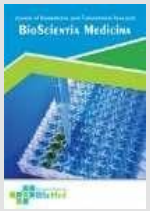

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Primary Malignant Melanoma of the Hard Palate: A Rare Case Report

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A B S T R A C T

Background: Primary malignant melanoma of the oral cavity is an uncommon and aggressive malignancy with a poor prognosis. The hard palate is a rare site for primary melanoma, and early diagnosis is often challenging due to its asymptomatic nature in the initial stages. **Case presentation:** We present the case of a 58-year-old female who presented with a pigmented lesion on the right hard palate and a neck mass. The lesion had been present for a year and had gradually increased in size. The neck mass had appeared three months prior and was associated with pain. Imaging and biopsy confirmed the diagnosis of malignant melanoma with cervical lymph node metastasis. The patient underwent wide excision with right hemimaxillectomy and modified radical neck dissection type II, followed by planned postoperative radiation therapy. **Conclusion:** This case highlights the importance of considering melanoma in the differential diagnosis of pigmented oral lesions. Early diagnosis and aggressive treatment are crucial for improving outcomes in this rare but aggressive malignancy. The use of adjuvant therapies, such as radiation and targeted therapy, may be beneficial in select cases.

1. Introduction

Malignant melanoma, a formidable adversary in the realm of oncology, is primarily recognized for its cutaneous manifestations. However, its insidious presence can extend beyond the skin, infiltrating the mucosal surfaces of the oral cavity. Primary malignant melanoma of the oral cavity, though an infrequent occurrence, represents a diagnostic and therapeutic challenge that demands unwavering attention from clinicians and researchers alike. The hard palate, a relatively uncommon site for primary melanoma, further amplifies the complexity of this clinical entity. Primary malignant melanoma of the oral cavity constitutes a mere fraction of all melanoma cases, accounting for approximately 0.2-8.0%, and an even smaller proportion of oral malignancies, at around 0.5%.[1] The hard palate, while not the most frequent site of oral melanoma, presents a unique set of challenges due to its anatomical location and the potential for delayed diagnosis. The insidious nature of this malignancy, often asymptomatic in its early stages, can lead to significant delays in seeking medical attention, thereby allowing the tumor to progress unabated. The consequences of delayed diagnosis are profound. Oral melanoma is notorious for its aggressive behavior and propensity for early metastasis. The 5-year survival rate for oral melanoma, ranging from 5-20%, underscores the gravity of this disease.[2] The elusive etiology of oral melanoma further complicates its management. While

chronic irritation, tobacco exposure, alcohol consumption, and formaldehyde exposure have been implicated as potential risk factors, the precise mechanisms underlying its development remain shrouded in uncertainty.[3]

The clinical presentation of oral melanoma is a kaleidoscope of possibilities, ranging from macules and patches to nodules, and exhibiting a spectrum of colors, including brown, black, gray, red, purple, and even depigmentation.[4] The lesions are characteristically asymmetrical, with irregular borders, and may be multiple in number.[5] Amelanotic melanoma, devoid of pigmentation, poses a particularly formidable diagnostic challenge, often masquerading as benign tumors or squamous cell carcinoma.[6] The absence of definitive diagnostic criteria for early-stage oral melanoma further compounds the difficulty in its timely identification. While dermoscopy can aid in clinical evaluation, the intricate anatomy and irregular surface of the oral mucosa present technical hurdles that limit its utility.[7] Biopsy, the gold standard for diagnosis, necessitates a high index of suspicion and a proactive approach to pigmented oral lesions. The cornerstone of treatment for oral melanoma is surgical intervention, with the overarching goal of achieving complete resection with tumor-free margins.[8] The anatomical constraints of the oral cavity, particularly the hard palate, often necessitate extensive surgical procedures, such as hemimaxillectomy, which can have significant functional and cosmetic implications for the patient. Adjuvant therapies, including radiation therapy, chemotherapy, and immunotherapy, may be employed in select cases to enhance local control and improve survival outcomes.[9] Although melanoma is traditionally considered radioresistant, emerging evidence suggests a potential role for radiation therapy in improving local control and overall survival in oral melanoma.[10] Targeted therapies, such as imatinib for metastatic melanoma harboring c-kit mutations and dabrafenib or vemurafenib for BRAF-positive melanoma, offer a glimmer of hope for patients with advanced disease.[11]

The prognosis for oral melanoma remains guarded, with a 5-year survival rate of approximately 25.5% for mucosal melanoma of the head and neck.[12] The presence of lymph node metastasis at the time of diagnosis portends a particularly dismal outlook.[13] Several molecular markers, including bcl-2, p53, and p16, have been investigated for their prognostic significance in oral melanoma, but their clinical utility remains to be fully elucidated.[14] The rarity and aggressive nature of primary malignant melanoma of the hard palate necessitate a heightened level of vigilance among clinicians. A proactive approach to pigmented oral lesions, coupled with a low threshold for biopsy, is paramount in ensuring timely diagnosis and optimizing treatment outcomes. The ongoing quest for novel diagnostic and therapeutic modalities holds the promise of improving the prognosis for patients afflicted with this formidable foe.

2. Case Presentation

The patient in this case report is a 58-year-old female who presented to the clinic with a chief complaint of a dark-pigmented lesion on the right side of her hard palate. The lesion had been insidiously growing over the past year, starting as a small, inconspicuous spot roughly the size of a mung bean and gradually expanding to reach the diameter of a 500 rupiah coin. The patient denied any associated symptoms such as bleeding or ulceration from the palatal lesion. Furthermore, she reported no similar pigmented lesions elsewhere in her oral cavity or on her skin. Three months prior to her presentation at our clinic, the patient noticed the emergence of a lump on the right side of her neck, approximately at the level of her collarbone. This lump, initially solitary and about the size of a marble, progressively increased in number over time, forming a cluster of palpable masses along the right side of her neck. The patient also reported experiencing pain associated with these neck lumps. Seeking medical attention for her concerns, the patient visited Dr. Hasan Sadikin General Hospital. There, she underwent biopsies of both the palatal lesion and the neck masses. The

biopsy results revealed a grim diagnosis: malignant melanoma with metastasis to the right cervical lymph nodes. The patient's medical history was otherwise unremarkable, with no history of tobacco or alcohol use, which are known risk factors for certain head and neck cancers.

Table 1. Patient demographics and initial presentation.

Characteristic	Description
Age	58 years
Gender	Female
Chief complaint	Dark pigmented lesion on the right hard palate
Duration of palatal lesion	1 year
Initial size of palatal lesion	Mung bean-sized
Current size of palatal lesion	500 rupiah coin-sized
Associated symptoms (palatal lesion)	None
Neck mass duration	3 months
Initial size of neck mass	Marble-sized
Current presentation of neck mass	Multiple palpable masses
Associated symptoms (neck mass)	Pain
Previous medical evaluation	Biopsy at Dr. Hasan Sadikin General Hospital
Diagnosis	Malignant melanoma with metastasis to right cervical lymph nodes
History of tobacco use	No
History of alcohol use	No

The patient's overall condition was assessed as moderately ill, suggesting a degree of systemic impact from her underlying malignancy. Her vital signs, including blood pressure, heart rate, respiratory rate, and temperature, were all within normal ranges, indicating stable cardiorespiratory and thermoregulatory function. A thorough examination of the patient's oral cavity revealed a striking finding on the right side of her hard palate: a dark, pigmented macule measuring 2.5 cm by 2.5 cm. The lesion's borders were irregular, extending past the midline of the palate, and it appeared to be firmly attached to the underlying hard palate structure. Additionally, multiple smaller, dark-pigmented macules, ranging in size from 0.3 to 0.5 mm, were observed scattered around the main lesion. Palpation of the patient's neck revealed the presence of multiple enlarged lymph nodes located in levels II and III on the right side. These lymph nodes formed a conglomerate mass, and a scar from the previous biopsy was also noted in the area. Importantly, the skin overlying the enlarged lymph nodes appeared normal, with no discoloration or other visible abnormalities.

Computed tomography (CT) scan of the head: A CT scan of the patient's head provided detailed visualization of the palatal and neck masses. The scan revealed a 3.62 x 3.18 x 0.68 cm solid mass originating from the right hard palate, with evidence of destruction of the palatine process of the maxilla. This mass exhibited heterogeneous density and irregular borders, further raising suspicion of malignancy. Additionally, the CT scan confirmed the presence of multiple enlarged lymph nodes in level IIa of the right neck, consistent with the clinical examination findings. Importantly, there was no evidence of intracranial metastasis, suggesting that the disease had not yet spread to the brain. Chest X-ray: A chest X-ray was performed to assess for potential lung metastasis. The X-ray showed no signs of metastatic disease in the lungs, indicating that the melanoma

had not spread to this vital organ system. Biopsy of Palatal Lesion: Microscopic examination of the biopsy specimen taken from the palatal lesion revealed the characteristic features of malignant melanoma. The tumor cells were arranged in nests and sheets, exhibiting marked pleomorphism (variation in size and shape) and hyperchromatism (increased nuclear staining). The presence of melanin pigment within the cytoplasm of some tumor cells further supported the diagnosis of melanoma. Biopsy of Neck Mass: The biopsy of the neck mass showed similar histopathological features to the palatal lesion, confirming the presence of metastatic melanoma in the cervical lymph nodes. Based on the clinical, imaging, and histopathological findings, the patient was diagnosed with primary malignant melanoma of the hard palate with metastasis to the right cervical lymph nodes. The tumor was staged according to the American Joint Committee on Cancer (AJCC) staging system for melanoma. The final stage was determined to be stage IV, indicating advanced disease with distant metastasis.

Table 2. Clinical and diagnostic findings.

Examination	**Findings**
General appearance	Moderately ill
Vital signs	Within normal limits
Oral cavity examination	2.5 x 2.5 cm dark, pigmented macule on right hard palate; irregular borders; fixed to palate; multiple smaller pigmented macules scattered around
Neck examination	Multiple enlarged lymph nodes in levels II and III on the right side; conglomerate mass; biopsy scar present; normal overlying skin
CT scan of the head	3.62 x 3.18 x 0.68 cm solid mass on right hard palate; destruction of palatine process of maxilla; heterogeneous density; irregular borders; multiple enlarged lymph nodes in right level IIa; no intracranial metastasis
Chest X-ray	No evidence of intrapulmonary metastasis
Biopsy of palatal lesion	Malignant melanoma
Biopsy of neck mass	Metastatic melanoma
Final diagnosis	Primary malignant melanoma of the hard palate with metastasis to right cervical lymph nodes (Stage IV)

Given the advanced stage of the disease, the patient was deemed a candidate for surgical intervention with the aim of achieving local control and improving quality of life. The surgical plan involved a wide excision of the palatal tumor, encompassing a right hemimaxillectomy to ensure adequate margins. Additionally, a modified radical neck dissection type II was planned to address the metastatic lymph nodes in the neck. During the surgical procedure, the extent of the tumor invasion was confirmed. The blackish macule on the hard palate measured 3 cm by 2.5 cm and had infiltrated the underlying bone. Multiple lymph nodes, ranging in size from 2 to 3 cm, were identified in the right neck, extending from levels I to IV along the sternocleidomastoid muscle. No enlarged lymph nodes were found in level V. Following the surgical resection, the patient's postoperative course was closely monitored. She was planned to receive adjuvant radiation therapy to further reduce the risk of local recurrence. Despite the aggressive surgical intervention, the patient's prognosis remained guarded due to the advanced stage of the disease at presentation. The presence of lymph node metastasis and bone invasion indicated a high risk of distant

recurrence and decreased overall survival. The patient was counseled regarding the potential benefits and risks of adjuvant therapies and the importance of close follow-up for early detection of any recurrence.

3. Discussion

The precise etiology behind the development of oral melanoma, encompassing those that originate in the hard palate, continues to be an enigma in the field of oncology. In stark contrast to cutaneous melanoma, where the detrimental effects of ultraviolet radiation exposure are well-established, the causative factors driving the emergence of oral melanoma remain poorly understood. The current landscape of research presents several hypotheses, including the potential roles of genetic predisposition, chronic irritation, and exposure to environmental carcinogens. The complex interplay of these factors, and possibly others yet to be discovered, contributes to the elusive nature of oral melanoma's origin. The notion that genetic susceptibility plays a role in the development of oral melanoma is supported by several lines of evidence. The observation of familial clustering, where multiple members of a family are affected by the disease, suggests an inherited predisposition. Additionally, researchers have identified specific genetic mutations associated with an increased risk of melanoma development, both in the skin and mucosal surfaces. Mutations in tumor suppressor genes, such as CDKN2A, which encodes the p16 protein that regulates cell cycle progression, have been implicated in both cutaneous and mucosal melanomas. Similarly, mutations in CDK4, a gene involved in cell cycle control, and BAP1, a tumor suppressor gene with diverse functions, have also been linked to an increased risk of melanoma. These findings suggest a shared genetic basis for melanomas arising in different anatomical locations, highlighting the importance of genetic predisposition in the pathogenesis of this malignancy.[11,12]

However, the specific genetic landscape of hard palate melanoma and its potential distinction from melanomas arising in other oral subsites remain areas of active investigation. The hard palate, with its unique anatomical and functional characteristics, may harbor distinct genetic alterations that contribute to the development of melanoma in this location. Further research is needed to elucidate the precise genetic mutations and their functional consequences in hard palate melanoma, which could potentially lead to the development of targeted therapies and improved prognostication. The hard palate, being an integral part of the oral cavity, is constantly exposed to a barrage of mechanical and thermal stressors during the process of mastication. The consumption of hot food and beverages, coupled with the potential exposure to irritants such as tobacco smoke and alcohol, creates a chronic inflammatory milieu in the oral mucosa. This persistent inflammation has been hypothesized to play a role in the development of oral melanoma by inducing DNA damage and creating a microenvironment conducive to tumorigenesis. The inflammatory response, while essential for wound healing and defense against pathogens, can also have detrimental effects when it becomes chronic and dysregulated. The release of reactive oxygen species and other inflammatory mediators can cause DNA damage, leading to mutations that drive the malignant transformation of melanocytes. Additionally, chronic inflammation can promote the proliferation and survival of transformed cells, suppress the immune response, and stimulate angiogenesis, all of which contribute to tumor growth and progression. The patient in the presented case had no history of tobacco or alcohol use, which are known risk factors for oral cancer. This suggests that other sources of chronic irritation, such as ill-fitting dentures, chronic infections, or even the repeated trauma of mastication itself, may have contributed to the development of her hard palate melanoma. Further research is needed to elucidate the specific mechanisms by which chronic irritation promotes oral melanoma development and to identify potential preventive strategies.[13,14]

Exposure to environmental carcinogens, particularly those found in tobacco smoke and certain occupational settings, has been strongly linked to an

increased risk of various cancers, including oral melanoma. Polycyclic aromatic hydrocarbons (PAHs), a class of potent carcinogens generated during the incomplete combustion of organic matter, are abundant in tobacco smoke and have been shown to induce DNA damage and promote tumorigenesis in various tissues. Occupational exposure to certain chemicals, such as formaldehyde, has also been associated with an increased risk of oral melanoma. Formaldehyde is a widely used industrial chemical with known carcinogenic properties. Studies have shown that workers exposed to formaldehyde have a higher risk of developing various cancers, including oral melanoma. The potential role of human papillomavirus (HPV) infection in the pathogenesis of oral melanoma has also been investigated, but the evidence remains inconclusive. While HPV infection is a well-established risk factor for cervical and other anogenital cancers, its association with oral melanoma is less clear. Some studies have reported the presence of HPV DNA in oral melanoma tissues, but others have failed to find a consistent association. Further research is needed to clarify the potential role of HPV in oral melanoma development. The development of oral melanoma, including those arising in the hard palate, is likely a multifactorial process involving the interplay of genetic predisposition, chronic irritation, and exposure to environmental carcinogens. The relative contribution of each factor may vary among individuals, and the complex interactions between these factors remain to be fully elucidated. The absence of a clear and identifiable single causative agent poses a challenge for the prevention and early detection of oral melanoma. However, understanding the potential risk factors and their underlying mechanisms can help identify individuals at increased risk and guide the development of targeted preventive and therapeutic strategies. The quest to unravel the precise etiology of oral melanoma continues, driven by the urgent need to improve the prevention, early detection, and treatment of this devastating disease. Advances in genomic technologies, such as next-generation sequencing, are providing unprecedented insights into the genetic landscape of oral melanoma, revealing potential therapeutic targets and prognostic markers. Furthermore, the investigation of the tumor microenvironment and its role in oral melanoma progression is opening new avenues for therapeutic intervention. Targeting the complex interactions between tumor cells and their surrounding stroma may offer novel strategies to inhibit tumor growth, invasion, and metastasis.[15,16]

The development of effective preventive measures for oral melanoma remains a challenge due to the lack of a clearly defined etiology. However, promoting healthy lifestyle choices, such as smoking cessation and limiting alcohol consumption, can reduce the risk of oral cancer in general. Additionally, raising awareness among healthcare providers and the general public about the signs and symptoms of oral melanoma can facilitate early detection and improve outcomes. In conclusion, the genesis of oral melanoma, particularly those originating in the hard palate, remains an area of active investigation. The complex interplay of genetic, environmental, and possibly immunological factors contributes to the elusive nature of this malignancy's origin. Further research is needed to elucidate the precise mechanisms underlying oral melanoma development, which will ultimately lead to improved preventive, diagnostic, and therapeutic strategies for this challenging disease. The molecular underpinnings of oral melanoma are an intricate tapestry of genetic and epigenetic alterations that orchestrate the transformation of normal melanocytes into malignant entities. The acquisition of these alterations disrupts the delicate balance of cellular signaling pathways, leading to uncontrolled proliferation, invasion, and metastasis. The following discussion explores the key molecular players and pathways involved in the pathogenesis of oral melanoma, with a particular focus on their relevance to the presented case of hard palate melanoma. The development of oral melanoma is driven by the activation of oncogenes and the inactivation of tumor suppressor genes. Oncogenes are genes that promote cell growth and proliferation,

while tumor suppressor genes act as brakes, preventing uncontrolled cell division and maintaining genomic stability. The delicate balance between these two opposing forces is crucial for normal cellular homeostasis, and its disruption can lead to the initiation and progression of cancer.[16,17]

The BRAF gene encodes a serine/threonine kinase that plays a critical role in the MAPK signaling pathway, which regulates cell growth, differentiation, and survival. Activating mutations in BRAF, most commonly the V600E mutation, are frequently observed in cutaneous melanoma and, to a lesser extent, in oral melanoma. These mutations lead to constitutive activation of the MAPK pathway, driving uncontrolled cell proliferation and promoting tumorigenesis. The presence of BRAF mutations in oral melanoma has been associated with a more aggressive clinical course and a poorer prognosis. The NRAS gene encodes a small GTPase that also functions within the MAPK signaling pathway. Activating mutations in NRAS, although less common than BRAF mutations, have been identified in a subset of oral melanomas. These mutations similarly lead to constitutive activation of the MAPK pathway and contribute to tumor development and progression. The KIT gene encodes a receptor tyrosine kinase that plays a role in various cellular processes, including cell growth, differentiation, and survival. Gain-of-function mutations in KIT have been identified in a subset of mucosal melanomas, including those arising in the oral cavity. These mutations lead to constitutive activation of the KIT receptor, promoting tumor growth and survival. The presence of KIT mutations in oral melanoma has been associated with a distinct clinical and pathological phenotype, often characterized by amelanotic presentation and a predilection for mucosal sites. The TP53 gene encodes the p53 protein, a critical tumor suppressor that functions as a guardian of the genome. p53 plays a pivotal role in maintaining genomic stability by inducing cell cycle arrest, DNA repair, or apoptosis in response to DNA damage or other cellular stresses. Inactivating mutations in TP53 are frequently observed in various cancers, including oral melanoma. The loss of p53 function allows cells with damaged DNA to survive and proliferate, contributing to tumorigenesis and progression.[17,18]

In addition to genetic mutations, epigenetic modifications, such as DNA methylation and histone acetylation, play a crucial role in the pathogenesis of oral melanoma. These modifications can alter gene expression without changing the underlying DNA sequence, leading to the activation of oncogenes and the silencing of tumor suppressor genes. DNA methylation involves the addition of a methyl group to the cytosine base within CpG dinucleotides, typically located in gene promoter regions. Hypermethylation of CpG islands in the promoter regions of tumor suppressor genes can lead to their transcriptional silencing, effectively inactivating their tumor-suppressive functions. In oral melanoma, hypermethylation of genes such as CDKN2A, RASSF1A, and MGMT has been reported, contributing to tumor development and progression. Histones are proteins around which DNA is wrapped to form chromatin. The addition or removal of chemical groups, such as acetyl groups, to histone tails can alter the accessibility of DNA to the transcriptional machinery, thereby influencing gene expression. In oral melanoma, aberrant histone modifications, such as global histone hypoacetylation and specific histone methylation patterns, have been observed, leading to the dysregulation of gene expression and promoting tumorigenesis. The tumor microenvironment (TME) encompasses the complex network of cellular and non-cellular components surrounding the tumor, including immune cells, fibroblasts, endothelial cells, extracellular matrix (ECM) components, and soluble factors. The TME plays a critical role in the growth, invasion, and metastasis of oral melanoma, and its dynamic interplay with tumor cells influences the clinical behavior and response to therapy. The immune system plays a crucial role in recognizing and eliminating cancer cells. However, oral melanoma cells can employ various strategies to evade immune surveillance, allowing them to escape detection and

destruction by the host immune system. These strategies include downregulation of MHC class I molecules, which are responsible for presenting tumor antigens to cytotoxic T cells, and expression of immune checkpoint ligands, such as PD-L1, which inhibit T cell activation. Additionally, tumor cells can secrete immunosuppressive cytokines, such as TGF-β and IL-10, that create an immunosuppressive microenvironment within the TME, further hindering the anti-tumor immune response. The formation of new blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis) is essential for tumor growth and metastasis. Oral melanoma cells can secrete pro-angiogenic and pro-lymphangiogenic factors, such as VEGF, FGF, and PDGF, that stimulate the growth of new vessels, providing the tumor with nutrients, oxygen, and a route for dissemination to regional lymph nodes and distant organs. Targeting angiogenesis and lymphangiogenesis represents a promising therapeutic strategy for oral melanoma, and several anti-angiogenic agents are currently under investigation in clinical trials. The ECM provides structural support and regulates various cellular processes, including cell adhesion, migration, and differentiation. Oral melanoma cells can remodel the ECM by secreting matrix metalloproteinases (MMPs) and other proteolytic enzymes, which degrade ECM components and facilitate tumor invasion and metastasis. The balance between ECM deposition and degradation is critical for maintaining tissue homeostasis, and its disruption in the TME can contribute to the aggressive behavior of oral melanoma.[17,19]

The epithelial-mesenchymal transition (EMT) is a complex cellular program that enables epithelial cells to acquire mesenchymal characteristics, such as increased motility and invasiveness. EMT plays a crucial role in embryonic development, wound healing, and tissue regeneration, but it can also be hijacked by cancer cells to promote invasion and metastasis. In oral melanoma, EMT has been implicated in the acquisition of metastatic potential. Tumor cells undergoing EMT lose their epithelial cell-cell adhesion and polarity, and acquire a spindle-shaped morphology and increased migratory capacity. This allows them to detach from the primary tumor, invade the surrounding stroma, and intravasate into blood or lymphatic vessels, ultimately leading to the establishment of distant metastases. Several signaling pathways and transcription factors have been implicated in the regulation of EMT in oral melanoma, including TGF-β, Wnt/β-catenin, Snail, Slug, and Twist. Targeting these pathways and factors may offer novel therapeutic strategies to inhibit EMT and prevent metastasis in oral melanoma. Cancer stem cells (CSCs) are a small subpopulation of tumor cells that possess the ability to self-renew and differentiate into diverse cell types, thereby driving tumor growth and recurrence. CSCs have been identified in various cancers, including oral melanoma, and their presence has been associated with a more aggressive clinical course and resistance to therapy. The identification and characterization of CSCs in oral melanoma have been challenging due to the lack of specific markers and the heterogeneity of the tumor. However, recent studies have identified several potential markers, such as CD133, ALDH1, and ABCG2, that may be useful for isolating and targeting CSCs in oral melanoma. The development of therapies that specifically target CSCs represents a promising approach to improve the treatment of oral melanoma and reduce the risk of recurrence. The molecular landscape of oral melanoma is a complex and dynamic network of interconnected pathways and processes that drive the initiation, progression, and metastasis of this malignancy. The identification of key molecular players and their functional roles has provided valuable insights into the pathogenesis of oral melanoma and opened new avenues for therapeutic intervention. Further research is needed to fully elucidate the molecular mechanisms underlying oral melanoma development and to identify novel therapeutic targets and prognostic markers. The development of personalized medicine approaches, based on the individual molecular profile of each patient's tumor, holds great promise for improving the

treatment and outcomes of this challenging disease.[14,17]

The inherent aggressiveness and the proclivity for early metastasis are hallmarks of oral melanoma, distinguishing it from its cutaneous counterpart and underscoring the gravity of this malignancy. The rich vascular and lymphatic network that permeates the oral mucosa creates an ideal conduit for the dissemination of tumor cells, facilitating their spread to regional lymph nodes and distant organs, including the lungs, liver, and brain. The unfortunate reality of this aggressive behavior is poignantly illustrated in the presented case, where the patient already exhibited cervical lymph node metastasis at the time of diagnosis, highlighting the insidious nature of this disease. The depth to which the primary tumor invades the surrounding tissues serves as a critical prognostic indicator in oral melanoma. Deeper invasion correlates with a heightened risk of both lymph node metastasis and distant spread, casting a shadow of a worse prognosis. The intricate anatomy of the oral cavity, with its close proximity of vital structures and abundant vascular and lymphatic channels, further amplifies the significance of invasion depth. In the context of the presented case, the tumor's infiltration into the underlying bone of the hard palate is particularly concerning. This signifies a substantial depth of invasion, breaching the natural barrier posed by the bony structure and gaining access to the rich vascular and lymphatic network within. The presence of bone invasion serves as an ominous sign, indicating a high likelihood of metastatic disease and underscoring the need for aggressive therapeutic intervention. The assessment of invasion depth in oral melanoma relies on a combination of clinical examination, imaging studies, and histopathological evaluation. While clinical examination can provide an initial estimate of tumor thickness, imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) offer a more precise assessment of the extent of invasion, particularly in relation to critical anatomical structures. Ultimately, the definitive evaluation of invasion depth is achieved through histopathological examination of the resected specimen, where meticulous measurement and microscopic assessment are performed to determine the Breslow thickness, a key prognostic factor in melanoma.[13,14]

The presence of lymph node metastasis represents a significant turning point in the course of oral melanoma, marking the transition from localized to systemic disease. The lymph nodes, acting as filters for the lymphatic system, are often the first site of distant spread for tumor cells that have escaped the primary tumor. The involvement of lymph nodes not only portends a worse prognosis but also necessitates a more extensive treatment approach, often involving neck dissection and adjuvant therapies. In oral melanoma, the sentinel lymph node biopsy (SLNB) technique, which has proven valuable in the staging and management of cutaneous melanoma, faces limitations due to the complex and variable lymphatic drainage patterns of the oral cavity. The intricate network of lymphatic vessels and the potential for multiple drainage pathways make the identification of a single sentinel lymph node challenging. Consequently, elective neck dissection, which involves the removal of lymph nodes in specific levels of the neck, is often recommended for patients with clinically or radiologically suspicious lymph nodes, even in the absence of a positive SLNB. The presented case exemplifies the importance of lymph node assessment in oral melanoma. The patient's presentation with palpable cervical lymph nodes prompted further investigation, leading to the diagnosis of metastatic disease. The presence of lymph node metastasis not only influenced the staging and prognosis but also guided the surgical management, necessitating a modified radical neck dissection to address the involved lymph nodes. The occurrence of distant metastasis, primarily to the lungs, liver, and brain, represents the most devastating complication of oral melanoma. Once the tumor cells have breached the confines of the regional lymph nodes and gained access to the systemic circulation, they can seed distant organs, leading to the establishment of

metastatic lesions. The presence of distant metastasis is associated with a dismal prognosis, with a 5-year survival rate of less than 20%. The lungs, being the most common site of distant metastasis in melanoma, are particularly vulnerable due to their rich blood supply and extensive capillary network. Metastatic lesions in the lungs can manifest as solitary or multiple nodules, often leading to respiratory symptoms such as cough, shortness of breath, and chest pain. The liver, another frequent site of metastasis, can be affected through hematogenous spread via the portal vein or hepatic artery. Metastatic lesions in the liver can impair liver function, leading to jaundice, abdominal pain, and ascites. Brain metastasis, although less common than lung or liver metastasis, carries a particularly grave prognosis. The blood-brain barrier, a protective mechanism that restricts the passage of substances from the bloodstream into the brain, poses a challenge for the delivery of systemic therapies. Metastatic lesions in the brain can cause a range of neurological symptoms, including headaches, seizures, focal neurological deficits, and cognitive impairment. The management of distant metastasis in oral melanoma remains a formidable challenge. Systemic therapies, such as immunotherapy and targeted therapy, have shown some promise in improving survival in select cases, but their overall efficacy remains limited. The development of novel therapeutic strategies that can effectively target and eradicate metastatic lesions is an area of active research, fueled by the urgent need to improve outcomes for patients with advanced oral melanoma.[15,16]

The aggressive nature and metastatic potential of oral melanoma, as exemplified in the presented case, underscore the critical importance of early detection and prompt intervention. The insidious onset and often asymptomatic nature of this malignancy necessitate a high index of suspicion among healthcare providers and the general public. Any suspicious pigmented lesion in the oral cavity should be thoroughly evaluated, and biopsy should be considered to rule out malignancy. Furthermore, the management of oral melanoma requires a multidisciplinary approach involving close collaboration between oncologists, surgeons, radiation oncologists, and pathologists. The complex interplay of genetic, environmental, and immunological factors in the pathogenesis of this disease necessitates a comprehensive treatment strategy that addresses both the primary tumor and the risk of regional and distant metastasis. The ongoing research into the molecular mechanisms underlying oral melanoma progression and the development of novel therapeutic targets offer hope for improved outcomes in the future. Until then, vigilance, early detection, and aggressive multidisciplinary management remain the cornerstones of combating this formidable foe. The tumor microenvironment (TME) is a complex and dynamic ecosystem that surrounds and interacts with the tumor, playing a pivotal role in its growth, invasion, and metastasis. The TME comprises a diverse array of cellular and non-cellular components, including immune cells, fibroblasts, endothelial cells, extracellular matrix (ECM) components, and soluble factors. The intricate interplay between these components and the tumor cells creates a network of signals and interactions that can either promote or inhibit tumor progression. In the context of oral melanoma, understanding the role of the TME is crucial for developing novel therapeutic strategies that target not only the tumor cells themselves but also the surrounding microenvironment that supports their growth and spread. The immune system, with its sophisticated network of surveillance and effector mechanisms, is constantly on the lookout for aberrant cells, including cancer cells.[16,17]

However, tumor cells, including those of oral melanoma, have evolved various strategies to evade immune recognition and destruction, allowing them to thrive and disseminate. This process of immune evasion involves a complex interplay between tumor cells and immune cells within the TME, and its understanding is crucial for developing immunotherapeutic approaches that can overcome these barriers and unleash the full potential of the

immune system against cancer. One of the key mechanisms by which oral melanoma cells evade immune surveillance is through the downregulation of major histocompatibility complex (MHC) class I molecules. These molecules are responsible for presenting tumor-specific antigens to cytotoxic T cells, which can then recognize and destroy the cancer cells. By reducing the expression of MHC class I molecules, tumor cells effectively cloak themselves from the immune system, rendering them invisible to cytotoxic T cells. Another strategy employed by oral melanoma cells is the expression of immune checkpoint ligands, such as programmed death-ligand 1 (PD-L1). These ligands bind to their corresponding receptors on T cells, such as programmed cell death protein 1 (PD-1), delivering inhibitory signals that dampen the T cell response. This immune checkpoint pathway, while essential for preventing autoimmunity, can be exploited by tumor cells to suppress the anti-tumor immune response. The development of immune checkpoint inhibitors, such as antibodies targeting PD-1 or PD-L1, has revolutionized the treatment of various cancers, including melanoma, by unleashing the immune system against the tumor. In addition to these cell-surface mechanisms, oral melanoma cells can also secrete immunosuppressive cytokines, such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), into the TME. These cytokines create an immunosuppressive milieu that inhibits the activation and function of various immune cells, including T cells, natural killer (NK) cells, and dendritic cells. This immunosuppressive microenvironment further protects the tumor from immune attack and facilitates its growth and spread.[17,18]

The formation of new blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis) is essential for tumor growth and metastasis. Tumors, including oral melanoma, require a constant supply of nutrients and oxygen to sustain their rapid growth and proliferation. Angiogenesis, the process of new blood vessel formation from pre-existing vessels, provides the tumor with these vital resources, enabling it to expand beyond the diffusion limits of oxygen and nutrients. Similarly, lymphangiogenesis, the formation of new lymphatic vessels, provides a conduit for the dissemination of tumor cells to regional lymph nodes and distant organs. The lymphatic system, with its extensive network of vessels and lymph nodes, plays a crucial role in immune surveillance and fluid homeostasis. However, tumor cells can hijack this system to their advantage, using the lymphatic vessels as a highway for metastasis. Oral melanoma cells can actively promote angiogenesis and lymphangiogenesis by secreting various pro-angiogenic and pro-lymphangiogenic factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). These factors stimulate the proliferation and migration of endothelial cells, the building blocks of blood and lymphatic vessels, leading to the formation of new vessels that support tumor growth and spread. Targeting angiogenesis and lymphangiogenesis represents a promising therapeutic strategy for oral melanoma. Several anti-angiogenic agents, such as bevacizumab (a monoclonal antibody targeting VEGF) and sunitinib (a multi-targeted tyrosine kinase inhibitor), have shown efficacy in various cancers, and their potential role in the treatment of oral melanoma is currently under investigation. The extracellular matrix (ECM) is a complex network of proteins and polysaccharides that provides structural support and regulates various cellular processes, including cell adhesion, migration, and differentiation. The ECM also plays a crucial role in maintaining tissue homeostasis and preventing the invasion and metastasis of cancer cells. In oral melanoma, the TME undergoes extensive remodeling, characterized by the degradation and deposition of ECM components. Tumor cells secrete various proteolytic enzymes, such as matrix metalloproteinases (MMPs) and serine proteases, that degrade the ECM, creating pathways for tumor cell invasion and migration. Additionally, tumor cells can stimulate the production of ECM components, such as collagen and fibronectin, by fibroblasts within the TME, leading to the formation of

a dense and supportive stroma that further promotes tumor growth and invasion. The balance between ECM degradation and deposition is critical for maintaining tissue integrity and preventing tumor invasion. Disruption of this balance in the TME, as observed in oral melanoma, can lead to the breakdown of tissue barriers and facilitate the spread of tumor cells to adjacent and distant sites. Targeting ECM remodeling represents another potential therapeutic strategy for oral melanoma, and several inhibitors of MMPs and other proteolytic enzymes are currently under development.[17,18]

The epithelial-mesenchymal transition (EMT) is a complex cellular program that enables epithelial cells, which are normally tightly bound together and exhibit apical-basal polarity, to acquire mesenchymal characteristics, such as increased motility and invasiveness. EMT plays a crucial role in various physiological processes, including embryonic development, wound healing, and tissue regeneration. However, this process can also be hijacked by cancer cells to promote invasion and metastasis. In oral melanoma, EMT has been implicated in the acquisition of metastatic potential. Tumor cells undergoing EMT lose their epithelial cell-cell adhesion and polarity, and acquire a spindle-shaped morphology and increased migratory capacity. This allows them to detach from the primary tumor, invade the surrounding stroma, and intravasate into blood or lymphatic vessels, ultimately leading to the establishment of distant metastases. The EMT process is orchestrated by a complex network of signaling pathways and transcription factors. Transforming growth factor-beta (TGF-β), a multifunctional cytokine with diverse roles in development and disease, is a key inducer of EMT in various cancers, including oral melanoma. TGF-β signaling activates a cascade of intracellular events that lead to the downregulation of epithelial markers, such as E-cadherin, and the upregulation of mesenchymal markers, such as N-cadherin and vimentin. Other signaling pathways, such as Wnt/β-catenin, Notch, and Hedgehog, have also been implicated in the regulation of EMT in oral melanoma. These pathways converge on a set of transcription factors, including Snail, Slug, Twist, and Zeb, which orchestrate the transcriptional reprogramming associated with EMT. Targeting these pathways and transcription factors may offer novel therapeutic strategies to inhibit EMT and prevent metastasis in oral melanoma.[19,20]

4. Conclusion

Primary malignant melanoma of the hard palate is a rare and aggressive malignancy with a poor prognosis. Early diagnosis and aggressive treatment are crucial for improving outcomes. This case highlights the importance of considering melanoma in the differential diagnosis of pigmented oral lesions and the potential benefits of adjuvant therapies in select cases.

5. References

1. Tchernev G, Lotti T, Wollina U. Palatal melanoma: "The Silent Killer". Open Access Maced J Med Sci. 2018; 6(3): 552-5.
2. Bondi S. Mucosal melanoma of the hard palate: surgical treatment and reconstruction. Int J Environ Res Public Health. 2021; 18(6): 3042.
3. Cooper H, Farsi M, Miller R. A rare case of oral mucosal amelanotic melanoma in a 77-year-old Immunocompromised Man. J Clin Aesthet Dermatol. 2021;14(1):27-29.
4. Zito PM, Brizuela M, Mazzoni T. Oral Melanoma. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2024.
5. Meleti M. Primary mucosal melanoma of the head and neck: a retrospective analysis of 103 cases. Oral Oncol. 2015; 51(6): 548-54.
6. Longo F. Melanoma of the oral cavity: a review of the literature. Anticancer Res. 2018; 38(6): 3245-53
7. Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol. 2009; 27(2): 135-45.

8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1): 7-30
9. American Joint Committee on Cancer. Melanoma of the skin. In: AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017; 581-94
10. Lallas A, Apalla Z, Lazaridou E, Ioannides D. Oral malignant melanoma: Epidemiology, clinical presentation, diagnosis and staging. J BUON. 2019; 24(2): 451-6.
11. Mendenhall WM, Amdur RJ, Morris CG, Werning JW. Melanoma of the head and neck. Am J Clin Oncol. 2014; 37(4): 380-4
12. Scoggins CR, Reintgen DS, Ross MI, Urist MM, McCarthy KS, Bartolucci AA. Intermediate-thickness melanomas of the extremity. A decision analysis comparing the techniques of elective lymph node dissection and lymphatic mapping with sentinel lymphadenectomy. Cancer. 2001; 91(7): 1275-84.
13. Morton DL, Thompson JF, Cochran AJ. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014; 370(14): 1323-32.
14. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet. 2014; 383(9915): 816-27.
15. Luke JJ, Flaherty KT, Ribas A, Long GV. Targeted agents and immunotherapies: optimizing outcomes in melanoma. Nat Rev Clin Oncol. 2017; 14(8): 463-82.
16. Robert C, Schachter J, Long GV. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015; 372(26): 2521-32.
17. Hodi FS, O'Day SJ, McDermott DF. Improved survival with Ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363(8): 711-23.
18. Chapman PB, Hauschild A, Robert C. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011; 364(26): 2507-16.
19. Hauschild A, Grob JJ, Demidov LV. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012; 380(9845): 358-65.
20. Long GV, Stroyakovskiy D, Gogas H. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014; 371(21): 1877-88.