Case Series

# A nuanced exploration delving into malignant melanomas occurring in unexpected and less common anatomical locations

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## Abstract

Malignant melanoma originates from melanoma cells, which derive from the neuroectoderm of the ectodermal mucosa. The chameleonic presentation of malignant melanoma, its often asymptomatic nature, the rarity of the lesion, the grim prognosis, and the imperative for highly specialized treatment are critical factors that merit careful consideration. Herein, we report a compilation of five cases of malignant melanomas occurring at unusual anatomical locations, which were initially misdiagnosed, which on careful analysis with the use of immuno-histochemical stains were correctly diagnosed as malignant melanoma.

**Keywords:** Anal, malignant, melanoma, mucosa, nasal

## Introduction

Malignant melanomas, originating primarily from melanocytes, are tumors primarily associated with the skin, stemming from the embryological neural crest during fetal development. These cells disperse to various sites in the body, including both cutaneous and mucosal regions. Although primary extracutaneous malignant melanomas are infrequent, they may present in distinct locations such as the rectum, mucosa, eyes, conjunctiva, nose, urogenital tract, esophagus, and meninges. Malignant transformation of melanocytes can occur upon exposure to ultraviolet (UVB) light, a recognized carcinogenic stimulus. It is noteworthy, however, that this correlation is not evident in mucosal melanoma, a type characterized by heightened malignancy attributed to its rapid growth and early metastasis.[1]

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## Case 1

A 16-year-old female presented with a sizable soft tissue swelling over the scalp region, measuring 6 × 5 × 3 cm, persisting for the past 2 years [Figure 1a]. Initially, the swelling was pea-sized and progressively enlarged over time. Repeated attempts at fine needle aspiration cytology (FNAC) yielded a hemorrhagic sample, initially diagnosed as hemangioma at a local hospital. The latest FNAC revealed occasional atypical cells, exhibiting bizarre and plasmacytoid morphology, with some displaying conspicuous nucleoli [Figure 1b]. The melanin pigment was observed in occasional cells. Cytological findings suggested a malignant lesion likely to be a malignant melanoma. Subsequent resection and histopathological examination, along with immuno-histochemistry (IHC), confirmed the diagnosis of malignant melanoma. The cells



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were present in sheets and dispersed singly; the cells were very pleomorphic and showed conspicous nucleoli [Figure 1c]. Occasional cells showed the presence of the melanin pigment. Positive staining for HMB45 and S-100 supported the conclusive diagnosis [Figure 1d and e]. The patient is presently doing well in a 1-year follow-up.

## Case 2

A 49-year-old man reported difficulty in breathing, unilateral nasal obstruction, and recurring episodes of epistaxis. Imaging revealed a polypoidal, homogeneously enhancing vascular soft tissue mass measuring 3.5 × 2.3 × 0.9 cm in the left nasal cavity, predominantly in the anterior region, affecting the anterior septum and lateral nasal wall. On gross examination, the polypoidal mass was largely cystic, and the inner lining showed multiple hyper-pigmented areas [Figure 2a]. Histopathological examination showed sheets of malignant cells exhibiting moderate to marked pleomorphism and conspicous nucleoli with occasional cells showing the presence of the melanin pigment [Figure 2b]. Masson Fontana stain for melanin was positive in the cytoplasm of cells [Figure 2c]. This led to the diagnosis of malignant melanoma, a conclusion further affirmed by IHC, which demonstrated positivity for HMB45 and S-100, while testing negative for CK and CD45.

## Case 3

A 55-year-old man presented with symptoms of rectal bleeding and a persistent non-healing ulcer in the anal region over a period of 3 months. Magnetic resonance imaging (MRI) revealed a well-defined lobulated mass, measuring 11 × 6 × 5 cm, affecting the terminal rectum and anal canal. This mass led to luminal constriction with dilation of the rectosigmoid colon, involving the mesorectal soft tissue along with multiple enlarged lymph nodes, the largest measuring 2.5 × 1.9 cm. Histopathological examination showed the presence of malignant cells in sheets [Figure 3a]. The cells were large, showing moderate to marked pleomorphism, with a few of them being plasmacytoid in appearance [Figure 3b]. No melanin pigment was seen in the cells. Based on the morphology, the tumor appeared to be a poorly differentiated malignant neoplasm. The tumor cells exhibited positivity for S-100 and Melan-A, while they were negative for CK and CD45 [Figure 3c and d]. Based on morphology, the initial possibility of non-Hodgkin's lymphoma was given. However, IHC confirmed the diagnosis as malignant amelanotic melanoma. The patient succumbed to illness due to widespread metastasis in a 2-year follow-up period.

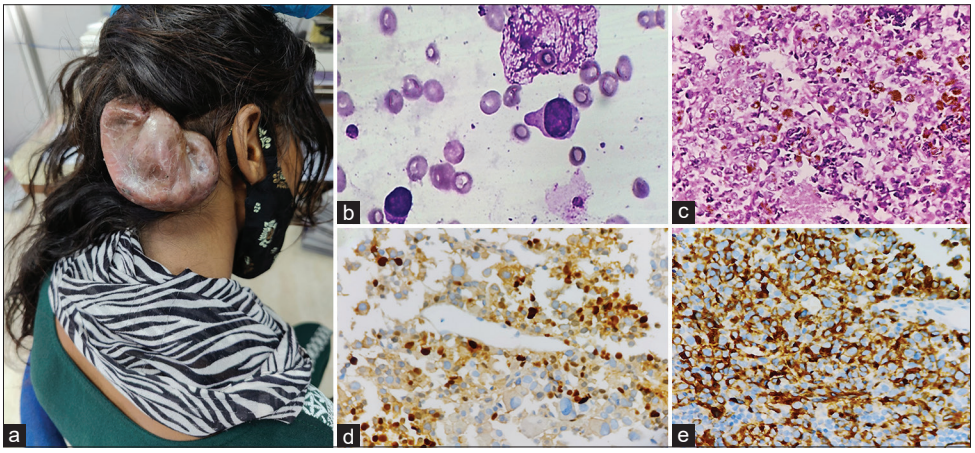


**Figure 1:** (a) Clinical image showing a large soft tissue swelling over the scalp region; (b) cytology revealed occasional atypical cells, exhibiting bizarre and plasmacytoid morphology, with some displaying conspicuous nucleoli (MGG 400x); (c) histopathological image showing malignant cells present in sheets and dispersed singly and cells showing marked pleomorphism with the presence of melanin pigment in a few cells (HE 400x); (d) S-100: Positive (400x); (e) HMB45: Positive (400x)

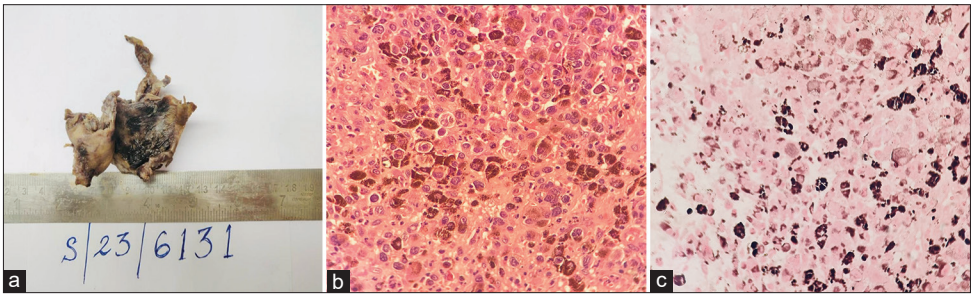


**Figure 2:** (a) Gross image of the opened-up polypoidal cystic mass, the inner lining showing multiple hyper-pigmented areas; (b) high-power view showing sheets of malignant cells with the presence of the melanin pigment in a few of the cells (HE 400x); (c) Masson Fontana stain demonstrating the melanin pigment in the cytoplasm of malignant cells (400x)

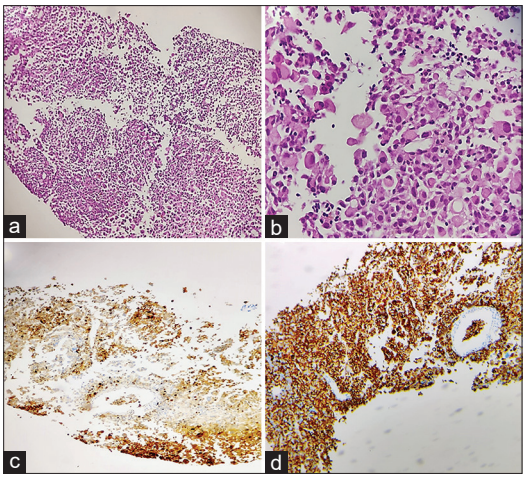


**Figure 3:** (a and b) Histopathological image showing the presence of malignant cells in sheets and cells showing moderate to marked pleomorphism, a few of them appearing plasmacytoid in appearance (HE 40x, 400x); (c) S-100: Positive (40x); (d) Melan-A: Positive (40x)

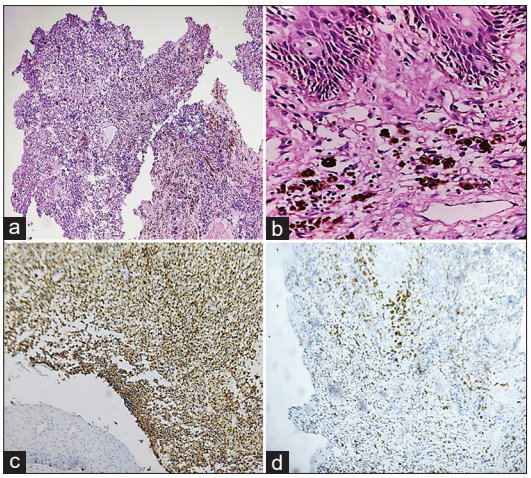


**Figure 4:** (a and b) Histopathological examination showing a poorly differentiated neoplasm arranged as sheets, cells showing marked pleomorphism, and inconspicuous nucleoli. Focal areas showing the presence of the melanin pigment (HE 40x, 400x); (c) HMB45: Positive (40x); (d) MITF: Positive (40x)

## Case 4

A 22-year-old man reported a 1-month history of an ulcerative lesion in the buccal mucosa. Examination revealed a pigmented ulcero-proliferative growth measuring 1.5 × 1 cm in the right lower jaw, extending to the right buccal mucosa. An incisional biopsy was performed, and histopathological examination indicated a poorly differentiated malignant neoplasm. IHC revealed positivity for Melan-A and HMB45 and negativity for CK and CD45. Thus, a final diagnosis of malignant melanoma was established.

## Case 5

A 47-year-old woman presented with a 4 × 3 cm ulcero-proliferative lesion on the right upper alveolus persisting for 1 month, following a history of tooth extraction on the same side. A PET scan revealed an active hypermetabolic lesion in the right upper gingivo-buccal sulcus, premolar region, with associated bone destruction (tumor size: 2.7 × 1.8 cm, SUV max = 7.35). Additionally, an active hypermetabolic intra-pulmonary nodule was identified in the upper lobe of the left lung, measuring 0.7 × 0. 5 cm (SUV max = 2.4). Histopathological examination initially suggested a poorly differentiated neoplasm resembling non-Hodgkin's lymphoma as the cells were arranged as sheets [Figure 4a]. The cells showed marked pleomorphism and had inconspicuous nucleoli. Focal areas showed the presence of the melanin pigment in cells [Figure 4b]. The IHC panel revealed positivity for HMB45 and MITF, while testing negative for CD20, p63, CD138, and SMA, with a Ki67 proliferation index of 60% [Figure 4c and d]. A final diagnosis of malignant melanoma was proffered. The patient was lost to follow-up.

## Discussion

Cutaneous melanomas are the most common manifestation of the disease, making up over 90% of all melanomas. Among the less common forms (less than 10%) of melanoma, ocular melanoma constitutes 5%, melanoma of unknown origin accounts for 2%, and mucosal melanoma makes up 1%.[2] Non-cutaneous melanomas typically originate most frequently from the mucous membranes that line the respiratory, digestive, and genitourinary tracts as well as from the eyes and cerebral meninges. Mucosal melanomas can exhibit substantial heterogeneity in morphological characteristics, developmental processes, and biological behavior, posing challenges for accurate clinical diagnosis. The maxillary gingiva is the predominant site of occurrence, followed by the palate and mandibular gingiva, in cases of oral mucosal melanoma.[3] Incidences have also been documented on the tongue, lip, and buccal mucosa. It is noteworthy that the prevalence of melanomas in the head and neck region, particularly in the palate, may be attributed in part to the developmental and anatomical proximity of the palate to the nasal cavity.[4] The prognostic utility of the Clark and Breslow classifications in oral melanoma remains unvalidated, primarily attributed to architectural distinctions between the oral mucosa and skin. Notably, the oral mucosa, being thinner than the skin, lacks analogous histological reference points such as the papillary and reticular dermis. Broadly, the growth pattern of oral mucosal melanoma closely mirrors the nodular pattern observed in its cutaneous counterpart. This resemblance contributes to the generally poor prognosis associated with these lesions. Patients with lesions measuring less than 2 mm in thickness demonstrate a significant survival advantage compared to those with thicker lesions exceeding 2 mm.[5] Despite the absence of published guidelines from the American Joint Committee on Cancer for the staging of oral mucosal melanomas, a simplified Tumor, Node, Metastasis (TNM) classification within the clinical staging system recognizes three stages and has demonstrated a prognostic value.

Malignant melanoma affecting the nose and paranasal sinus is a rare and severe condition, with the incidence of intranasal malignant melanomas ranging from 0.6% to 3.8%.[6] Patients commonly exhibit sinonasal congestion and epistaxis upon presentation. The malignancy is characterized by high aggressiveness attributed to

its abundant vascularity, leading to a propensity for metastasis. Diagnosis poses challenges, with approximately 20% of cases being multi-focal and around 40% exhibiting amelanotic characteristics.[7] Malignant melanoma originating in the rectum is a rare and highly aggressive tumor within the rectal region. Frequently misdiagnosed as benign hemorrhoids or polyps, these lesions often escape early detection. In the rectum, melanocytes predominantly reside in the ano-squamous transition zone. The majority of anorectal melanomas emerge from the dentate line, with 65% localized within the anal canal or at the anal verge.[8] Lymphatic dissemination commonly extends to the inguinal or inferior mesenteric nodal basins. The primary sites for metastases include inguinal lymph nodes, followed by mesenteric, hypogastric, and para-aortic lymph nodes, as well as the liver, lung, skin, and brain. Initial presentation often reveals locoregional lymph node metastases in nearly 60% of cases. Furthermore, upon diagnosis, distant metastases are discerned in 26–38% of patients.[9]

IHC utilizing HMB-45, S-100, and Melan-A proves to be more sensitive in distinguishing this tumor from other neoplasms. The incorporation of MITF in conjunction with the aforementioned markers is employed for the diagnosis of melanoma due to its elevated sensitivity and specificity for melanomas. Extensive local invasion, tumor recurrence, and distant metastasis contribute to an unfavorable prognosis, with a mean survival time of 3.5 years. At the time of diagnosis, approximately 80% of patients present with melanoma localized to the skin, 15% with regionally advanced disease, and 5% with disseminated cancer.[10] Primary intervention entails the surgical excision of the primary lesion with an oncologically adequate margin, incorporating lymphadenectomy for confirmed lymph node metastasis. Radiotherapy is employed as a palliative strategy in specific regions, such as the head and neck, to mitigate hemorrhagic complications and neurologic symptoms. Although radiotherapy and chemotherapy lack efficacy when used in isolation, occasional consideration is given in elderly or medically compromised patients. Post-operatively, in cases where surgical margins are unattainable, their application aims to bolster local control and diminish metastatic potential.

## Conclusion

The scarcity of occurrences at such unusual locations, coupled with the limited instances of patients presenting at early stages, has posed a challenge in conducting definitive trials to ascertain the most effective treatment for melanoma that is amenable to cure. The curative potential of surgical excision applies primarily to patients with localized malignant melanoma. In cases of disseminated disease, the treatment goal shifts to prolonging survival and enhancing quality of life. Given the diverse presentation of malignant melanoma in uncommon locations, it is crucial to consider it as a potential differential diagnosis when reporting poorly differentiated malignant lesions based on morphology. Consequently, early diagnosis and confirmation through IHC have become paramount for initiating prompt treatment in the localized phase of the disease.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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