# Mucocutaneous Melanoma – A Diagnostic and Therapeutic Problem

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Received: January 1, 2022
Accepted: April 19, 2022

**ABSTRACT** Mucosal melanoma, or so-called mucosal-oral melanoma is a rare but serious diagnostic and therapeutic problem. The "primary mixed" mucocutaneous forms of melanoma, which affect both the mucosa and the adjacent skin, are also particularly problematic and rare. Given that the staging, diagnosis, and treatment of mucosal (oral) melanoma differs from that of cutaneous melanoma, staging in mixed melanoma (primary mucocutaneous melanoma) as well as decisions for each subsequent diagnostic and therapeutic step should be individualized and modified according to the recommendations of the respective two classifications (for cutaneous but also mucosal melanomas), while at the same time or at least to a large extent overlapping with them. In practice, the following paradoxes occur during staging – there are melanomas with the same tumor thickness, but in different stages, which should be treated in a different, consensus-based way. At the same time, it would be appropriate for the surgical interventions to be in accordance with the patient's wishes for minimal trauma/reduced risk of developing facial disproportion. We present the case of a 69-year-old patient with a newly-developed lesion in the area of the mucosa of the upper lip and adjacent skin, which was identified as a primary mucocutaneous form of melanoma after surgical removal. The complex pathogenesis of the disease is discussed herein, emphasizing the role of UV radiation, iatrogenic immunosuppression with mycophenolate mofetil, tacrolimus, and prednisolone (due to severe glomerulonephritis leading to kidney transplantation), as well as the potential possible but speculative pathogenetic role of acetyl salicylic acid, etc. Primary mucosal and mucocutaneous forms of melanoma remain a challenge for clinicians, and steps for their diagnosis and treatment should be an expression of multidisciplinary, consensual solutions.

**KEY WORDS:** mucosal melanoma, oral melanoma, upper lip melanoma, advancement flap, rotation flap, dermatologic surgery

## INTRODUCTION

Terms such as oral melanoma or oral mucosal melanoma are often used interchangeably, especially when referring to pigmented malignant lesions (melanomas) affecting or localized primarily in the area of the lips (1).

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2022;30(2):82-88

Mucosal melanomas account for no more than 1% of the total number of melanomas (2). Oral mucosal melanoma, in turn, accounts for about 25% of mucosal melanomas that affect the head and neck (3). Primary mucosal melanomas are extremely rare and can occur not only in the oral cavity and lips, but also in the esophagus, nasopharynx, larynx, and anogenital area (1). The most common site of oral mucosal melanoma is the hard palate and the maxillary part of the gingiva (4). Areas such as the buccal mucosa, the mandibular gingiva, the floor of the oral cavity, the lips, and the tongue remain less frequently affected (5).

Melanoma of the lips is considered to be part of mucosal/oral melanoma (1). We present a patient with a borderline localized *de novo* pigmented lesion/borderline lesion (subsequently identified as nodular and superficial melanoma of the transitional mucosa – mucosal melanoma) in the upper lip, but also affecting the skin in the immediate vicinity (mucocutaneous form of oral melanoma). Important pathogenetic, clinico-pathological, diagnostic, and therapeutic aspects of this type of mixed oral mucosal-cutaneous melanoma or so-called "mucocutaneous melanoma" are yet to be elucidated.

## CASE REPORT

We present the case of a 69-year-old patient who was admitted for the first time to the Department of Dermatology, Venereology and Dermatologic Surgery due to the appearance of a nodule about a centimeter in diameter, with relatively clear boundaries, brownish-blue in color, and located on a pale brown macula in the upper lip and its border with the skin (Figure 1a). Clinical and dermatoscopic data indicated mucosal melanoma, with possible differential diagnosis in favour pigmented basal cell carcinoma, glomangioma, and mucosal melanotic macula with nodular vascular prominence of the transitional mucosa (Figure 1a). The lesion was about three years old, and, according to anamnestic data, it initially affected the upper lip and subsequently the adjacent skin.

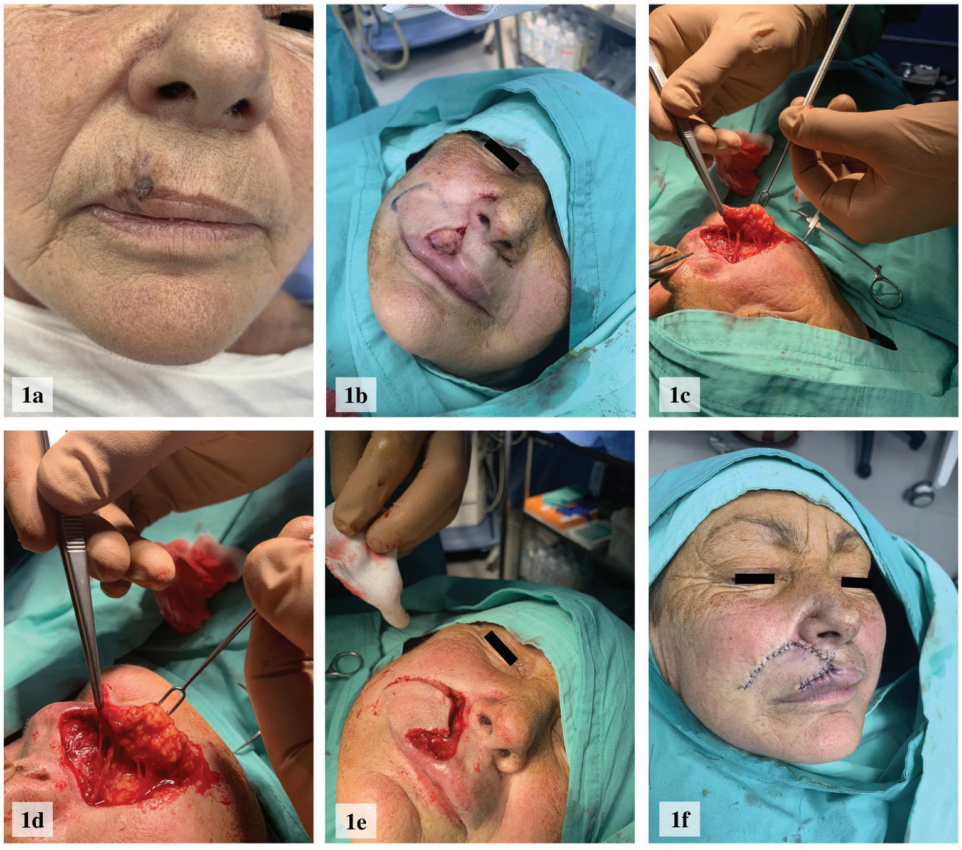


**Figure 1a.** A patient with a pigmented nodular lesion located on the border of the upper lip and the adjacent skin. Notably, the perilesional macular part of the lesion extends more than an inch onto the skin and mucous membranes.
**Figure 1b.** Surgical removal of the entire lesion in the form of a triangle with a surgical safety field of 0.2 cm in all directions.
**Figure 1c/1d.** Rotation advancement plastic surgery, with the incision crossing the nasolabial fold near the right nostril, then descending parallel to it and perpendicularly to the mandibular bone. The intact branches of the facial artery can be seen, which have not been interrupted and provide better future vitality of the rotated skin segment.
**Figure 1f.** Direct postoperative results immediately after adaptation of the wound edges.

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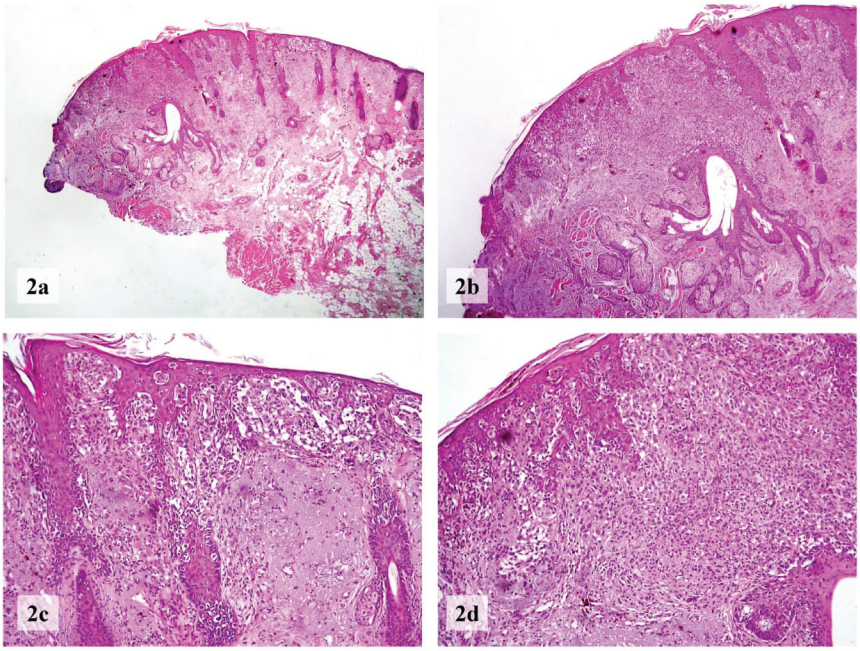


**Figure 2.** A thin epidermis with numerous follicular units of the sebaceous follicle type and marked solar elastosis (a and b). Extensive proliferation of variably pigmented, atypical melanocytes, singly dispersed and nested, is seen within the epidermis, both at the junctional zone and in a pagetoid distribution. Extensive involvement of follicular units can also be observed (c). Dermal invasion is apparent (d).

Known concomitant diseases in the patient included arterial hypertension, hypercholesterolemia, and kidney transplantation due to CKD due to glomerulonephritis in 2017. Systemic medication intake included: mycophenolate mofetil 1000mg (1-0-1), tacrolimus 1.5 mg (1-0-1), prednisolone 5 mg (1-0-0), amlodipine 5 mg (1-0-1), bisoprolol 5 mg (1-0-0), acetyl salicylic acid 100 mg (0-0-1), and fenofibrate 160 mg (0-0-1). Family history was negative for skin cancer. The patient was adequate and afebrile. Diagnostic and paraclinical procedures found no data indicating any clinically relevant changes with the exception of: total cholesterol – 6.94 mmol/L; HDL – 2.01 mmol/L; LDL – 4.67 mmol/L.

Surgical treatment was planned under local anesthesia, with the lesion being initially removed with a 0.2 cm surgical safety field in all directions in the form of a triangle, followed by rotation advancement plastic surgery to cover the defect (Figure 1a-f). The surgical defect was closed with single intermittent sutures.

The postoperative period went smoothly, with only slight swelling in the area of the lip. Therapy with Enoxaparin Na 0.4 mL s.c. was started once daily

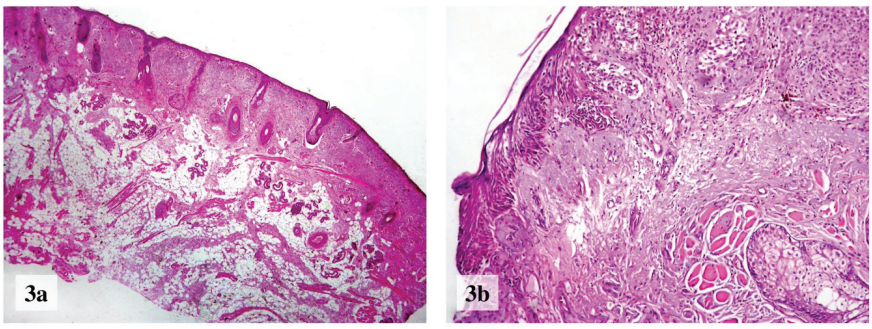


**Figure 3.** The right side of Figure 3 (a) shows a drop-off of hair follicles, though solar elastosis is still present. Figure 3 (b) shows epidermal involvement with an absence of hair follicles (one stray sebaceous lobule is seen in the deeper tissue), prominence of vessels, and skeletal muscle, with some solar elastosis. This represents a vermilion border, indicating a partial mucosal melanoma.

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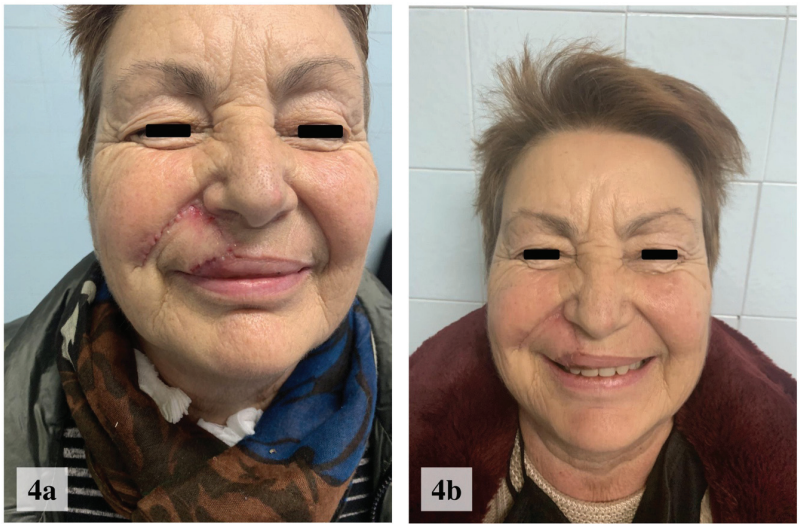


**Figure 4a.** Clinical picture at day 13. **Figure 4b.** Clinical picture at day 26.

for a period of 3 days, and good therapeutic results were observed. Histopathological findings indicated a superficial spreading malignant melanoma, featuring numerous atypical melanocytes both as solitary units and in nests, distributed along the junctional zone and extending into the epidermis in a pagetoid configuration (Figure 2a-d). Similar involvement of hair follicles was also noted (Figure 2c). Atypical melanocytes also extended into and filled the papillary dermis, representing a Clark's level III lesion with a Breslow thickness of 2.0 mm (Figure 2d). Mucosal involvement – specifically, of the vermilion of the lip – was also noted (Figure 3a, right side of the figure, and Figure 3b). Mitotic activity was readily identified, without evidence of ulceration or regressive changes. Clear resection margins were found (lateral margins – 3 mm, deep margin – 5 mm (Figure 2a-e). Good aesthetic results were achieved (Figure 4a and Figure 4b). No data on systematization of the disease were found during the screening. As a result, malignant melanoma of the transitional mucosa (cutaneous/mucosal form) was diagnosed as T2aN0M0, stage 1B, and another staging for pure mucosal melanomas was discussed: stage III (T3N0M0). MRT for the head and neck was performed, with no data for locoregional progression.

Subsequent follow-up found no evidence of progression of the underlying disease, and re-excision was recommended in order to achieve a total resection field of 1 cm in all directions, followed by radiotherapy. Due the patient's refusal to undergo re-excision (due to risk of unsatisfactory final cosmetic

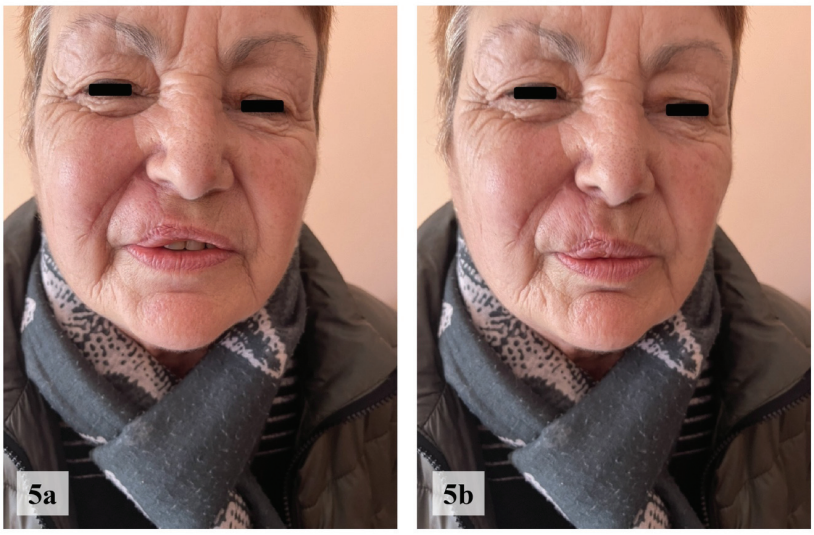


**Figure 5.** Excellent clinical outcome 6 months later, with no clinical and apparent signs of melanoma progression.

effect), a general compromise was reached to continue the therapy – radiotherapy and close monitoring – and if necessary to respond situationally. A 6-month follow up showed no signs of tumor progression and excellent overall aesthetic results (Figure 5a-b).

## DISCUSSION

The pathogenetic background of mucosal oral melanomas has in practice proven difficult to decode, as it can be extremely heterogeneous and not always understandable in terms of possible pathogenetic sequences or their grading. Within this multifactorial background, it often remains unclear what is the leading reason for its occurrence, and hence how it should be approached most adequately and/or optimally in favor of the patient. This is especially challenging when it comes to the so-called primary "mixed" or mucocutaneous forms of melanoma on the head and neck, because unlike cutaneous melanoma they show significant differences in both pathogenetic and diagnostic/therapeutic responses.

The "right decisions" in these cases are individual and often made as a result of in-depth discussions with the relevant tumor commission/tumor board. The key factors in case described herein are 1) solar radiation in the photo-exposed area of the upper lip, as well as 2) immunosuppression due to the available kidney transplant due to glomerulonephritis. The combination of these two factors is likely to lead to a mutation pattern that could not be eliminated/controlled by cell cycle regulators and/or the immune system, which would be a good explanation for the late onset of the tumor (6).

On the other hand, the anamnestic data provided by the patient indicate high daily sun exposure for the last 7-8 years (villa, flowers and garden in a suburban area). The fact that immunosuppression is generally associated with a 2- to 4-fold increased risk of developing various forms of cancer (including melanoma) in both men and women should not be overlooked (7). Solar radiation has been known for decades as the single key factor in the emergence of genetic instability through the generation of diverse types of mutations in both melanoma and non-melanocytic skin tumors (8,9). Despite being largely speculative according to a number of authors, the idea of acetyl salicylic acid-induced melanoma has been repeatedly mentioned and discussed as a possibility in the medical literature (10-12).

Intake of 100 mg acetylsalicylic acid daily in our patient dates back to 2017 (after a kidney transplant), as the first anamnestic and photographic data on changes in the upper lip started one year later, namely in 2018. The mutational pattern of mucosal melanomas differs from that of cutaneous melanomas (1). BRAF/NRAS mutations in mucosal melanoma are lower in frequency (12,13), while c-Kit mutations are significantly more common in mucosal melanomas (12).

The danger in the event of the possible development of progression is that mucosal melanomas on the neck and head are characterized by a significantly lower frequency of c-Kit mutations compared with mucosal melanomas in the anogenital area (13,14). In practice, this limits the possibilities for therapeutic response in the event of locoregional/distant recurrences, in contrast to mucosal melanomas in the anogenital area and cutaneous melanomas with variable localization, e.g. where the mutational pattern is different or far more „saturated with mutations" (1).

The lack of dissemination of the process at the time of hospitalization was the reason for not performing a mutational analysis of the tumor, as this remains an option in the future or in the event of the development of possible progression. Surgical treatment of primary mucosal melanomas is similar to that of cutaneous melanomas and is performed in a similar way, with the aim of achieving a total resection field of 1 to 2 cm depending on the tumor thickness determined by the first excision (12).

Unlike cutaneous melanomas, the need for a sentinel biopsy for moderately thick mucosal melanomas (TD between 1.00-4.00 mm in the second excision) is not fully understood and is subject to future analysis and detailed discussion before application (15,16). The localization of melanoma in the area of the face and especially the lip could also pose a serious therapeutic challenge particularly due to the fact that surgical treatment in 2 surgical sessions (according to the AJCC guidelines) may cause excess tissue removal leading to significant postoperative facial disproportion (17). The final aesthetic result could be a serious reason for a number of patients to cancel the second surgical session (as in the patient we described) or to request a different resection field in a single surgical excision. This problem in our patient was further complicated by the mixed nature of the tumor that affected both the skin and the mucosa (Figure 1a). When using the AJCC skin melanoma staging system (17), the melanoma was practically in stage IB (T2aN0M0), but when applying the classification for staging of mucosal melanomas the stage changed to a significantly less favorable one: stage III (T3N0M0). This paradox stems from the fact that melanoma with the same tumor thickness can be staged differently depending on its location. Localization, in

turn, can be decisive for applying a different stereotype of clinical behavior. The compromise solution in our patient was to avoid sentinel biopsy (lack of preoperative scatter data), but recommend mandatory re-excision with an additional field of surgical safety of 0.7 cm on the sides and 0.5 cm in depth to comply with the minimum recommendations (total resection field between 1-2 cm) for surgical treatment of cutaneous but also mucosal moderately thick (1.00-4.00 mm) melanomas, according to the guidelines of AJCC (1,17). The risks for patients become even more serious when re-excision and re-plastic surgery in the area of the upper lip are refused for example for cosmetic reasons as in our patient.

Therefore, the clinical decisions and approach in these patients must remain focused on active monitoring and possibly a rapid follow-up response if necessary. To what extent the reduction in the number of surgical sessions or the personalization of melanoma surgery to a single surgical session (OSMS/one step melanoma surgery) would help solve this problem is still unclear (18), but there is still some hope that such an approach is beneficial (19).

## CONCLUSION

We presented the case of a patient with a rare form of "mixed type", where a newly-emerged mucocutaneous melanoma involving primarily the mucosa of the upper lip and subsequent immediately localized adjacent skin was treated surgically by rotation advancement plastic adjacency. We have discussed the complex nature of the factors that are likely to play a key role in the development of aggressive neoplasms, namely: 1) iatrogenic immunosuppression with three potent drugs, 2) possible aspirin/blockade of inflammatory cascade, and 3) UV radiation as an inducer of mutations and a powerful additional immunosuppressant.

The problem areas we focused on were the familiar diagnostic and therapeutic options, which still do not offer a definitive solution and are instead the result of individual, consensual solutions. Understanding, diagnosing, and treating this form of melanoma remains a major challenge for multidisciplinary teams.

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