VIA MEDICA

CASE REPORT

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Mucosal melanoma — clinical presentation and treatment based on a case series

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ABSTRACT

Melanoma is malignant disease originating from melanocytes (pigment cells that occur mainly in the skin and constitute a type of defence from ultraviolet radiation). Melanocytes also occur outside of the skin (among others — in the eyeball, the mucosal lining of the digestive tract from the oral cavity to the anus, the nasal cavity and the paranasal sinuses, and the urinary and reproductive tracts). Many known cases of melanoma in the aforementioned locations exist.

The main factor responsible for the development of skin melanoma is ultraviolet radiation. In the case of mucosal melanoma, aetiological factors are still unknown. Mucosal melanoma most often develops in places that are hidden and not accessible through standard testing. Therefore, the disease develops without any signs for a long period of time before the proper diagnosis is established (usually at a disseminated stage, at a point where no successful localised treatment can be applied), which, in combination with a more aggressive course in comparison to more typical locations (the skin, the eyeball), a different sensitivity to systemic treatment (usually the lack of a mutation in the *BRAF* gene), and the lack of a separate standardised treatment procedure, is the cause of worse outcomes and poor prognosis.

Mucosal melanomas occur very rarely (about 1.5 % of all melanomas); however, the knowledge that a melanoma may also develop in locations that are often omitted during routine examination (the anus, the oral cavity, the urogenital region), may increase the chances of early diagnosis and attaining better treatment results.

In this paper, a brief description of the characteristics of mucosal melanoma is presented, along with a presentation of the most common locations, symptoms, diagnostic possibilities, and available treatment (including immunotherapy). Based on the available literature and personal experience, several cases of patients treated in the Institute of Oncology are described.

Key words: mucosal melanoma, mucosal melanoma treatment, nivolumab, pembrolizumab, ipilimumab

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Introduction

Melanocytes — cells that produce melanin — occur in the basal layer of the skin, the uvea, the arachnoid mater, and pia mater, but can also be found in the mucosal lining of the airways, digestive and urogenital tracts. Due to the presence of melanocytes mucosal melanoma may develop in all of the aforementioned locations. Mucosal melanoma is very rare, constituting only 0.03% of all neoplasms, and about 1.5% of all cases of melanoma [1–3]. While melanoma can develop on the surface of all mucosa, the majority occur in the mucosa of the head and neck (31–55%), the anus and rectum (17–24%), and the vulva and vagina (18–40%); the less common locations are the mucosal lining of the pharynx, larynx, urinary tract, uterine cervix, oesophagus, and gallbladder [3, 4]. It is noted, however, that a certain fraction of mucosal melanoma patients may be the ones who could

not have a primary lesion identified, and individuals with a skin melanoma that has undergone regression.

The incidence of skin melanoma has been rising — also in Poland — in the past two decades, while remaining stable in the case of mucosal melanoma [5, 6]. The risk of developing mucosal melanoma rises with age, and most of the patients are over 60 years of age (median age of diagnosis is 70 years). The incidence of mucosal melanoma is only twice as high in Caucasian individuals as in the African American population, while in the case of skin melanoma, this ratio is 16 to 1 [7]. Skin melanoma occurs more often in men than it does in women, and the frequency of occurrence of mucosal melanoma is 87% higher in women than it is in men, which is probably related to a greater percentage of melanoma of the reproductive organs in women [3].

Melanomas of the mucosa are characterised by a more aggressive course, and patients have a worse prognosis when compared to other types of melanoma (skin and ocular melanoma). The overall five-year survival rate for skin melanoma amounts to 80%, while for mucosal melanoma it only reaches 25%. The poorer treatment outcomes and shorter survival rate may be related to a generally more advanced disease upon diagnosis, anatomical factors that hinder complete resection and ample lymphatic drainage from the surfaces of mucosa, and other genetic and biological factors. The lack of early symptoms, and a sneaky evolution in locations that are typically inaccessible to examination, cause mucosal melanomas to be diagnosed late, at a time when the disease is very advanced. Amelanotic forms, which are not rare in the case of mucosal melanomas, additionally make the diagnosis more difficult. What is interesting, besides a lower survival rate since diagnosis, mucosal melanoma patients also have lower survival rates regardless of the stage of the disease, which especially pertains to people with metastases (M1 parameter) [3].

In mucosal melanoma patients, metastases are most often observed in the lungs (54%), liver (35%), and bones (25%) — the arrangement of metastasis locations differs from the case of skin melanoma, where metastases are found mainly in the skin (13–38%), lungs (18–36%), and lymph nodes (5–34%) [8].

Currently, there are no known risk factors for the development of mucosal melanoma. No relationship with ultraviolet radiation has been proven, and viral aetiology has also been excluded (within it — a relationship with SMV, EBV, HPV, or HSV) [9–11]. However, a greater percentage of individuals with history of formaldehyde exposure develop mucosal melanoma, as well as those who smoke tobacco (melanoma of the oral cavity), which may indicate the mutagenic effect of these two factors as well as an influence on the development of the illness [3, 7, 12, 13].

The types of molecular disorders responsible for the development of skin and mucosal melanoma differ from each other. In the case of skin melanoma, mutations in the *BRAF* gene occur in about half of the patients, while in the case of mucosal melanoma this mutation was identified in only a small number of patients (3–11% mucosal melanomas have the *BRAF* gene mutation, and another 5–14% have a mutation in the *NRAS* gene). However, the percentage of mutations occurring in the gene responsible for coding the receptor for tyrosine kinase (*KIT*) is greater. This mutation was identified in around 39% of mucosal melanoma patients, and 20% of rectal melanomas have deactivating mutations in the *NF1* gene [14–16]. Mucosal melanomas contain an average of 8193 point mutations per tumour, which is over 10 times fewer mutations than skin melanoma (86,495 changes). While gene amplifications are rare in skin melanoma, they are present in about 85% of mucosal melanomas. Furthermore, the mucosal melanoma has an average of 3.7 more structural variants when compared to the skin melanoma, and the cause of this increased chromosomal instability has not yet been explained [3].

Due to the rarity of its occurrence, the mucosal melanoma's aetiopathogenesis and clinical course are poorly known, and there is a lack of separate, specific recommendations pertaining to treatment, although the ESMO (European Society of Medical Oncology) and NCCN (National Comprehensive Cancer Network) recommendations point out the importance of radiotherapy in this group of patients [17].

In the process of diagnosing mucosal melanomas, it is crucial to rule out metastatic disease from a different location (primary lesion in the skin or eyeball), which means a thorough examination of the entire skin and mucosa, including a dental, ophthalmological, rectal, and gynaecological examination.

The main treatment method for patients who develop mucosal melanoma is surgical treatment. Unfortunately, due to its sneaky evolution and late diagnosis at a usually advanced stage, the results of surgical treatment are not satisfactory. A further limit to the precision of a resection is the location, which significantly defines the attainable surgical margin (the maxillary sinus, the rectal canal). In the treatment of mucosal melanomas, a relatively wide scope of resections was applied (i.e. abdominoperineal rectal resection in the case of anal cancer); however, long-term analyses show that long-term effects are not better when compared to a local excision with a wide margin, while the quality of life of the former patients is incomparably worse. Because of this, a wide local excision of the primary lesion is currently recommended, regardless of location, instead of a more extensive and debilitating operation. Radiotherapy improves localised control of the lesion

but does not affect the improvement of overall survival (OS). Currently there is no effective systemic treatment for this group of patients, and the results of treatment for mucosal melanoma in comparison with skin melanoma are clearly worse [18], which justifies the search for new methods.

Case reports

Case 1

A 56-year-old female came to the regional centre in May of 2017 due to swelling of the right side of her face. The patient was hospitalised in August 2017 in the department of otorhinolaryngology (ORL) in a voivodeship-level hospital for diagnostic purposes pertaining a tumour of the right nasal cavity — a biopsy was taken from the right maxillary sinus, and a partial resection of the lesion (R1) was performed; the pathology result established a diagnosis of melanoma. During another hospitalisation in a regional ORL department, a computed tomography (CT) imaging of the sinuses was performed, and showed an abnormal mass within the entire right maxillary and frontal sinuses, the right ethmoid sinus, and the right chamber of the sphenoid sinus, with an occlusion of the outflow tracts. The masses filled the nasal cavity on the right, with an infiltration of the right levator anguli oris, and a partial destruction of the cavity's medial wall the ethmoid bone. After several weeks, the patient underwent her first consultation at Centrum Onkologii — Instytut (COI) in Warsaw, and during the diagnostic process no mutation in the V600 codon of the *BRAF* gene was detected.

In December of 2017, immunotherapy (nivolumab — drug program) was initiated. As a continuation of local treatment, due to persistent bleeding from the lesion, the right external carotid artery was ligated, and a total maxillectomy with orbital exenteration was performed (R1 resection — February 2018). After surgery, the patient underwent adjuvant radiotherapy (May 2018) on the postoperative site up to a total dose of 5500 cGy/t. Immunotherapy was continued. In a control CT scan in September 2018, a suspicious lesion in the postoperative area was described, as well as lesions in the bronchi. The small tumour in the vicinity of the zygomatic bone in the postoperative lesions had a diameter of approximately 11 mm (previously 19 × 14 mm) and was not enhanced by contrast. The patient had a thin-needle biopsy of the lesion performed three times; no malignant cells were discovered. A 15 × 9 mm focal lesion on the right side of the trachea appeared, as well as a 6 mm lesion in the proximal section of the left bronchus, and an 11 mm lesion in the lower right lobar bronchus.

In March of 2018 the patient had a bronchoscopy with tissue sampling for the purpose of pathological testing — melanoma cells were detected in the sample tissue. The patient was referred to radiation oncologist to be qualified for brachytherapy. The patient remains in an overall adequate state. Due to the extensive surgery in the maxillofacial region, she has problems with speech. Laboratory tests show no significant abnormalities besides normocytic anaemia. The patient continues immunotherapy with no significant toxicity and no further disease progression.

Case 2

A 66-year-old male presented to the regional centre complaining of abnormal defecation pattern. Magnetic resonance imaging (MRI) of the pelvis performed in October 2017 described a cauliflower-like tumour mass in the lesser pelvic cavity sized 85 × 100 mm infiltrating subcutaneous tissue of the coccygeal region. A cutting needle biopsy (CNB) of the anal tumour was performed, showing a melanoma (*melanoma malignum* Melan A+, S-100 –/+). During the diagnostic process at COI, no distant metastases were described in the imaging, and a lack of the *BRAF B600* mutation was confirmed. Immunotherapy (pembrolizumab) was given within a drug program. In February 2018 the patient underwent radiotherapy of the rectum and lymph nodes with a dose up to 2500 cGy. In the most recent control CT (March of 2018), a tumourous mass was apparent, encompassing the anus and prostate, with stable dimensions and constant, transverse infiltration with dimensions of 61 × 43 mm, as well as lymph nodes of stable dimensions (a 12 mm lymph node by the right external iliac vessels, a 14 mm node by the right internal iliac vessels, and a node by the left external iliac vessels with 10 mm in the short axis). No metastases have been found so far. The patient remains in good general condition, with pain well controlled with analgesics. The disease has been stable for a year, and the immunotherapy has had the side effect of joint pain and skin pruritus assessed as level 1.

Case 3

A 65-year-old female presented to her regional gynaecology clinic due to vaginal bleeding. History included hypertension, asthma, and 20 years of cigarette smoking. In July 2018 an in-hospital biopsy of a vaginal lump was performed, and an initial diagnosis of a vaginal polyp was made. However, the results of pathology testing contained the diagnosis of a non-pigmented mucosal melanoma [CK(–), S100(+), HMB45(+)]. In a CT scan of the thorax, abdomen, and pelvis performed in 2018 no metastases were found (including any metastases to the lesser pelvis). In September 2018,

the patient underwent her first consultation at COI. Gynaecological examination showed an abnormal lesion about 2 cm in diameter in the vaginal wall, near the urethral opening, with a suspicion of infiltration of its distal part. In a CT of the thorax, abdomen, and pelvis performed in September 2018, the uterine body was smooth, free, ante-flexed, and with no pathological mass within the projection of the adnexa. Additionally, clinical examination revealed enlarged right inguinal lymph nodes.

Then, in October 2018, the patient underwent an excision of the exophytic lesion along with the distal part of the urethra (about 1 cm). Pathology results revealed infiltration of the mucosa and muscle layer of the urethra. The melanoma was 20% necrotic, and its greatest dimension was about 1.4 cm. The infiltration encompassed the mucosa and muscle layer of an ulcerated urethral wall. Neoplastic invasion of vessels was noted. No neoplastic invasion of the nerve fibres was revealed. Malignant infiltration was present in the front margin (R1), while other margins were free. The patient was referred for qualification for immunotherapy with immune checkpoint inhibitors and is currently being qualified for a clinical study.

Discussion

Mucosal melanoma immunotherapy

Current data on the effectiveness of checkpoint inhibitors is limited in the case of patients with mucosal melanoma. Several institutions have published analyses of patients with the diagnosis of mucosal melanoma, who were undergoing immunotherapy. The percentage of objective responses was, however, low (11.8%), although permanent responses were noted (including a permanent response to ipilimumab used as first-line treatment, and pembrolizumab as the second line). With a median observation time of 10.1 months, the median progression-free survival (PFS) and overall survival (OS) were 3.1 and 8.8 months, respectively. Nevertheless, amongst the scant number of patients who achieved objective responses, survival exceeding 56 months was observed [19]. In a comparative analysis of anti-PD-1 and anti-CTLA-4 treatment, a higher effectiveness of anti-PD-1 drugs was shown. In a French analysis, a total of 110 patients were included in the study. The median PFS was somewhat better in the group that received anti-PD1 drugs, when compared to the anti-CTLA4 group (3.9 months, compared with 2.9 months, P = 0.025) [20]. Single series of cases from other institutions revealed a complete lack of objective responses to anti-PD-1 treatment [21], although in other reports, the objective responses were seen in 23% of patients suffering from mucosal melanoma (median PFS — 3.9 months) [22].

The results of immune checkpoint inhibitor-based immunotherapy as monotherapy in patients with mucosal melanoma seem to be only somewhat better than known outcomes of chemotherapy. In the largest analysis of 95 patients undergoing chemotherapy due to mucosal melanomas, the median OS amounted to 12.1 months with the response rate of 26.3%. The results of this analysis were comparable to historical case series, and no statistical difference was revealed in the scope of responses between skin melanoma and mucosal melanoma (30% and 20%, P = 0.206); similarly, no difference was shown between patients of Caucasian and African origin (20% and 36%, respectively), and the median PFS in subsequent patient series amounted to 3 to 10 months [23].

The earliest results of immunotherapy are those from ipilimumab treatment (an anti-CTLA-4 drug). A retrospective analysis of 33 patients, most of whom were treated earlier at least once, showed a complete response in one patient, a partial response also in one patient, and six patients with stable disease according to the iRECIST immunological response criteria. The median OS from the time of the first dose of ipilimumab was 6.4 months (range: 1.8–26.7 months) [24].

Another analysis of 71 patients with metastatic mucosal melanoma treated with ipilimumab in an expanded access program in Italy showed an objective responses in 12% of patients, and a disease control rate of 36%, with a median observation time of 21.8 months. The average PFS in this patient group was 4.3 months, and the median OS reached 6.4 months [25].

In another study, which included patients with mucosal melanoma, seven patients were assessed, of whom only four completed the induction phase of four cycles of ipilimumab. One-year OS in this study was 14% and all patients with mucosal melanoma died within 24 months after receiving the first dose of ipilimumab. Of the patients studied, one achieved partial response, and two achieved stabilisation of disease [26]. The median OS, which amounted to 10.1 and 11.2 months, achieved by patients in the drug registration studies for ipilimumab, seems to be longer in comparison with the median OS found in smaller studies (6.4, 6.7, and 5.8 months, respectively) [24, 25, 27]. Ipilimumab treatment in conjunction with radiotherapy was also used in neoadjuvant treatment at the Memorial Sloan Kettering Cancer Centre. After applying such treatment, an R0 resection proved to be possible, as well as a single pathological response [28].

It has been shown that monoclonal antibodies aimed at PD-1 or PD-L1 are more effective, when compared with ipilimumab, in the treatment of melanoma patients, which suggested greater effectiveness in the treatment of

mucosal melanoma. The effectiveness of anti-PD1 antibodies in mucosal melanoma patients has so far been fairly well documented. The effectiveness of pembrolizumab treatment was tested based on data from registration studies. Of the patients treated in the studies of KEYNOTE-001 (NCT01295827), -002 (NCT01704287), and -006 (NCT01866319), 84 (5%) were treated for a diagnosis of mucosal melanoma. Fifty-one of 84 patients did not receive earlier ipilimumab immunotherapy. In patients with a diagnosis of mucosal melanoma, the objective response rate was 19%, and the median response duration was 27.6 months. Responses were achieved in 22% of patients not treated with ipilimumab, and in 15% of those who were treated with this drug as the first line of treatment. The average PFS amounted to 2.8 months, and the median OS reached 11.3 months [29].

The first interesting case of response to nivolumab immunotherapy in a patient with mucosal melanoma was reported in the CheckMate 066 study. A case of a patient with an untreated metastatic mucosal melanoma was described, with high initial lactate dehydrogenase (LDH) activity (seven-times the upper reference limit). The patient was included into a clinical trial, achieving partial response and subsequently permanent total response. LDH activity decreased significantly within two months of the beginning of treatment (at which time the patient achieved partial response) and was maintained at a low level throughout the observation period. The patient suffered only mild side effects (levels 1–2: vitiligo and skin rash).

The research team suggested that nivolumab treatment may be considered in mucosal melanoma patients with high LDH activity [30]. In order to evaluate the effectiveness of nivolumab in patients with a diagnosis of mucosal melanoma, a phase III study analysis was conducted. In 86 patients with mucosal melanoma, who were treated in clinical trials, the percentage of objective responses amounted to 23.3% for nivolumab as monotherapy, and 37.1% in the group treated with nivolumab combined with ipilimumab. The average PFS was 3.0 months for patients treated with nivolumab monotherapy, and 5.9 months for those receiving nivolumab plus ipilimumab, which suggests that nivolumab in combination with ipilimumab has greater effectiveness than any one of these drugs given as monotherapy [31]. An interesting fact is that the expression of PD-L1 in skin and mucosal melanoma patients was different; fewer patients with mucosal melanoma were PD-L1 positive (17.4% and 28.6% with a 5% PD-L1 expression in the group receiving nivolumab monotherapy and the group receiving combination therapy, respectively). In skin melanoma patients, this percentage was 34.3% and 36.8%, with 5% having PD-L1 expression in monotherapy and combined therapy. The rates of treatment response were higher in the group of mucosal melanoma patients with a greater than 5% PD-L1 expression, although responses were still observed in the < 5% PD-L1 expression group, both in those receiving monotherapy as well as nivolumab with ipilimumab [31].

Sequential treatment in mucosal melanoma patients was evaluated in Japanese institutions. Out of 60 patients, only 38% finished treatment with four doses of ipilimumab. Objective response was achieved in the second-line of immunotherapy in 3.6% of patients. Side effects associated with immunotherapy occurred in 78% of the patients, and 70% of them had level 3 and 4 side effects, where 31% of patients had two or more side effects. A time less than 28 days between the first- and second-lines of treatment correlated with the development of immunological complications [32].

New treatment methods for mucosal melanoma include combinations of immunotherapies, or immunotherapies and local therapies. Single examples of effective peritumoral injections with β-interferon (IFN-β) and interleukin 2 (IL-2) in combination with nivolumab have been reported [33, 34]. Targeted treatment, including that with the use of BRAF/MEK or KIT inhibitors (imatinib), may be considered in the carriers of adequate mutations [35].

Mucosal melanoma of the oral cavity

The diagnostic criteria for primary oral cavity mucosal melanoma include the appearance of a clinical and microscopic presentation of a neoplasm in the mucosa of the oral cavity, the presence of melanocytic proliferative nests in the mucosa of the oral cavity, and failure to establish a different primary location [36, 37]. Considering the fact that 1/3 of oral mucosal melanoma cases develop from previously existing melanotic lesions, every abnormalities in the area are worth assessing, and an excisional biopsy should be performed in doubtful situations. Excision still remains the main treatment method, which is combined with adjuvant radiotherapy, and immuno/chemotherapy. These melanomas are characterised by several features:

— they usually develop de novo; however, in 1/3 of cases they develop from a previous melanotic lesion [38, 39];
— initially the tumour is usually symptom-less, with the appearance of a flat mark or slightly raised, irregular melanotic lesion [40, 41];
— at a later stage of the disease, swelling, ulceration, bleeding, and pain appear, with the possibility of dental mobility, and the primary lesion becomes raised and lumpy
— the primary lesion may develop satellite lesions [42];
— amelanotic types of melanoma in the oral cavity are not rare, they usually delay diagnosis and treatment, and consequently have a worse prognosis [43];

— in about 25% of patients, metastases to the regional lymph nodes are present at the time of diagnosis [40, 41];
— 5-year survival rate is poor, at 12.3–16.6%, with a median survival of 2 years [38, 44].

Melanoma of the colon and anal mucosa

Melanoma of the anorectal region is often initially misdiagnosed as haemorrhoids, which significantly delays the proper diagnosis, and worsens patient prognosis. Most melanomas in this area are localised within the reach of the *per rectum* examination, which, in most cases, enables them to recognise any abnormalities. Unfortunately, even 1/3 of anorectal melanomas are amelanotic, and a biopsy of the lesion is key in the diagnosis of a suspicious lesion. The Miles operation (an abdominoperineal resection in anorectal melanoma) was considered the standard treatment for melanoma in this location. Currently, it seems that wide local excision will take its place. While a less invasive treatment, it gives similar long-term results. A wide local excision provides more local remissions, but does not affect the OS rate, and adjuvant radiotherapy improves local maintenance but does not affect survival [45–48]. The five-year survival rate for locally advanced disease is 26.7%, and 9.8% for disease with metastases to lymph nodes, with a median OS of 24 months and 17 months, respectively. In patients with metastases to the lymph nodes, a selective lymphadenectomy is recommended [49]. Additionally, the melanoma in this particular area:
— is the most common primary site of melanoma of the digestive tract mucosa [50];
— is the third most common location after skin and ocular melanoma [50];
— melanoma of the ano-rectal region occurs most often in patients 65–70 years of age, with women in the lead [45, 49];
— the primal lesion may occur in the anal canal, the rectum, or in both of these places;
— in most cases it occurs within 6 cm of the anal verge [51];
— the most common symptoms are: anal bleeding, pain and discomfort in the anal region, as well as anal prolapse of the tumour [2];
— amelanotic tumours constitute about 30% of cases [2];
— non-specific symptomatology, polymorphism of the primary site often influence a wrong primary diagnosis — this pertains to about 2/3 of patients (most often diagnosed as haemorrhoids, adenocarcinoma, polyps, rectal cancer) [46, 51];
— at time of diagnosis, 30% of patients already has metastases (regional or distant) [45, 52];
— overall survival remains poor (20% after 5 years with median survival of 14–20 months) [18, 51, 53].

Melanoma of the genitourinary system

Genito-urinary melanomas are rare and can develop from the mucosa of any part of the genitourinary tract (the vulva, vagina, cervix, urethra, bladder). Women are affected more often. Following features are characteristic of these melanomas:
— melanoma developing from the female genital tract constitutes 18% of all cases of mucosal melanoma and most often pertains to the vulva (76.7%) and vagina (19.8%) [2, 39];
— vulvar melanoma usually affects women around 68 years of age, mainly Caucasian (90%), and develops around the clitoris and labia majora [54];
— the main symptoms of vulvar melanoma include: bleeding, lumpy lesions or a thickening on the vulva, pruritus, pain, inflammation, pain during urination, discharge [55, 56];
— the main treatment method for vulvar melanoma is surgical excision, and, similarly to the previously described forms of mucosal melanoma, a more conserving surgery is recommended due to a lack of difference in survival [57].

Melanoma of the airways

Melanomas of the airway mucosa are most often located in the nasal cavity and the paranasal sinuses, and the tumour can also be amelanotic. They are characterised with the following features:
— the most common symptoms include: unilateral obstruction of the nasal cavity, pathological tissue mass, nasal bleeding [58];
— at a more advances stage: pain, facial deformation, less often exophthalmos double vision;
— macroscopically the tumour has the appearance of a multi-shaped brown or black mass, often ulcerated;
— 5-year survival rate for melanoma of the nasal cavity is 31%, and 0% for melanoma of the maxillary sinus [44].

Summary

Awareness of the possibility for melanoma occuring in places that are available for examination (i.e. the oral cavity, urogenital region, anal canal) allows for a diagnosis of the disease at an early stage, which gives an opportunity for better treatment outcomes. A diagnosis of the disease at a point of dissemination, which is unfortunately when mucosal melanoma is most frequently diagnosed, is still predictive of a very unfavourable outcome, and the results of systemic treatment are poor. The presented cases show that immunotherapy can be an effective method of treatment for patients

with metastatic mucosal melanoma, although generally mucosal melanomas have poorer outcomes when compared with skin melanoma (shorter PFS and OS) when it comes to treatment with nivolumab, or pembrolizumab in monotherapy. Some patients may benefit significantly from immunotherapy, especially combination of anti-PD-1 with anti-CTLA-4, but currently we have no legitimate predictive biomarkers for patient selection. Despite many effective treatment options for skin melanoma, data on the treatment of melanomas in other locations are limited, and clinical decisions are often made based on retrospective data and reports from other institutions, including case series analyses.

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