CASE REPORT
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A rare case of primary mucosal melanoma involving the oropharynx

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ABSTRACT

Melanomas are malignant tumors arising from melanocytes. A vast majority of melanomas occur on cutaneous surfaces. Rarely, melanomas can also be found in various extracutaneous sites where melanocytes are scarcely present. Here, we present a 58-year-old Caucasian man who was referred to the ENT department of the Antwerp University Hospital with the complaint of a mass in the left oropharynx and a palpable cervical lymph node. Fiberoptic endoscopy showed a black mass arising from the left pharyngeal wall at the superior border of the oropharynx. Fluorodeoxyglucose positron emission tomography computed tomography (FDG-PET-CT) and magnetic resonance imaging (MRI) of the liver revealed liver metastases and lymph node metastases along the coeliac trunk branches and in the left neck. A transoral biopsy confirmed the diagnosis of primary mucosal melanoma, and the tumor was staged as pT4aN2M1. A full-body inspection by the dermatology department did not reveal any suspected skin lesions. Immunotherapy with nivolumab and ipilimumab was started.

To conclude, mucosal melanomas are rare, yet very aggressive and have a dismal prognosis. The epidemiologic, genetic, and biologic differences between mucosal and cutaneous melanomas have adverse implications for both treatment and prognosis of mucosal melanoma. Imaging, including PET scan, is of great importance in evaluating the extent of the lesion and distant metastases.

Keywords: Mucosal melanoma, oropharynx, immunotherapy

Introduction

Melanomas are malignant tumors arising from melanocytes, the pigment-producing cells of our body that protect us against the harmful effects of the sun. A vast majority of melanomas occur on cutaneous surfaces and are associated with exposure to ultraviolet light. Rarely, melanomas can also be found in various extracutaneous sites where melanocytes are scarcely present. We report a rare case of primary mucosal melanoma (MM) of the oropharynx.

Case presentation

A 58-year-old Caucasian man was referred to the ENT department of the Antwerp University Hospital with the complaint of a mass in his left oropharynx. Three weeks before, he had noticed a left-sided neck mass, which reduced in size after taking amoxicillin-clavulanic acid 1 g twice a day for one week. However, he had complaints of a sore throat, dysphagia, left-sided ear pain, and bloody, purulent oral discharge for the past few days. This patient had a history of depression, alcoholic liver cirrhosis with esophageal varices, cholecystolithiasis, mitral insufficiency, and type 2 diabetes mellitus with polyneuropathy. He overcame his alcohol addiction 20 years ago, but did not quit smoking (40-pack years). According to the patient's family history, there was no prevalence of cancer in first- and second-degree relatives.

On clinical examination, a firm cervical lymph node of 4–5 cm in diameter was palpable on the left side in area II. Oral inspection revealed a black mass at the level of the left tonsil, which started bleeding with the slightest manipulation. Fiberoptic endoscopy showed a black mass arising from the left pharyngeal wall at the superior border of the oropharynx with a projection into the nasopharynx (Figure 1).

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A fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET-CT) scan was performed (General Electric Discovery MI digital PET/CT with CT parameters: tube voltage = 120 kV, tube current = 80–200 mA [Smart mA], and slice thickness = 1.25 mm) and confirmed a hypermetabolic oropharyngeal mass measuring 31 × 18 × 27 mm in size with a cranial projection (Figures 2a and 2b). Furthermore, the scan revealed increased metabolic activity of both the palpable cervical lymph node and the liver, requiring further investigation (Figure 3a). Magnetic resonance investigation (MRI) of the liver confirmed diffuse metastases and suspicious lymph nodes along the coeliac trunk branches. The ultrasound of the neck was suggestive of a malignant necrotic lymph node, although fine needle aspiration cytology was inconclusive.

A transoral biopsy was taken under general anesthesia. Histopathological examination revealed a solid malignant tumor composed of large epithelioid and spindle-shaped melanocytes, containing abundant melanin pigment. There was an *in situ* component with nested and pagetoid spread of single and multiple melanoma cells in the surface epithelium, indicating primary malignant melanoma of the tonsil. The malignant cells were markedly atypical with pleomorphic nuclei and prominent nucleoli. There were numerous mitotic figures. The tumor invaded deeply within the submucosa, with invasion of the underlying striated muscle and seromucous glands. The invasion

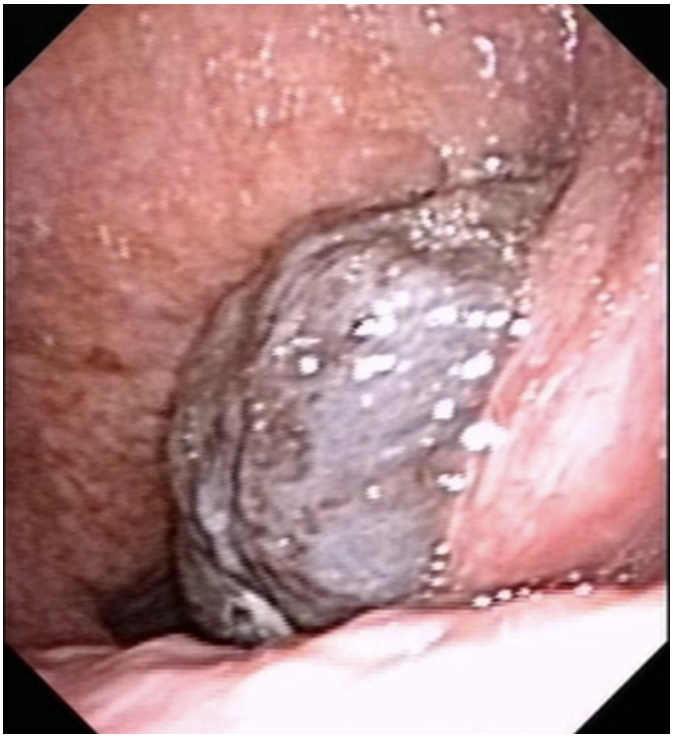

Figure 1. Fiberoptic endoscopy revealing a mass arising from the left pharyngeal wall at the superior border of the oropharyn

Main Points:

- Mucosal melanomas are rare, and therefore, metastases from a primary cutaneous melanoma should always be excluded.
- More than half of all mucosal melanomas are located in the head and neck area, mainly involving the sinonasal and oral cavity.
- In advanced mucosal melanoma tumors, a combination of anti-PD-1 and anti-CTLA-4 treatment should be considered.
- Despite aggressive treatment, mucosal melanoma has a poor prognosis with a five-year overall survival rate of < 30%.

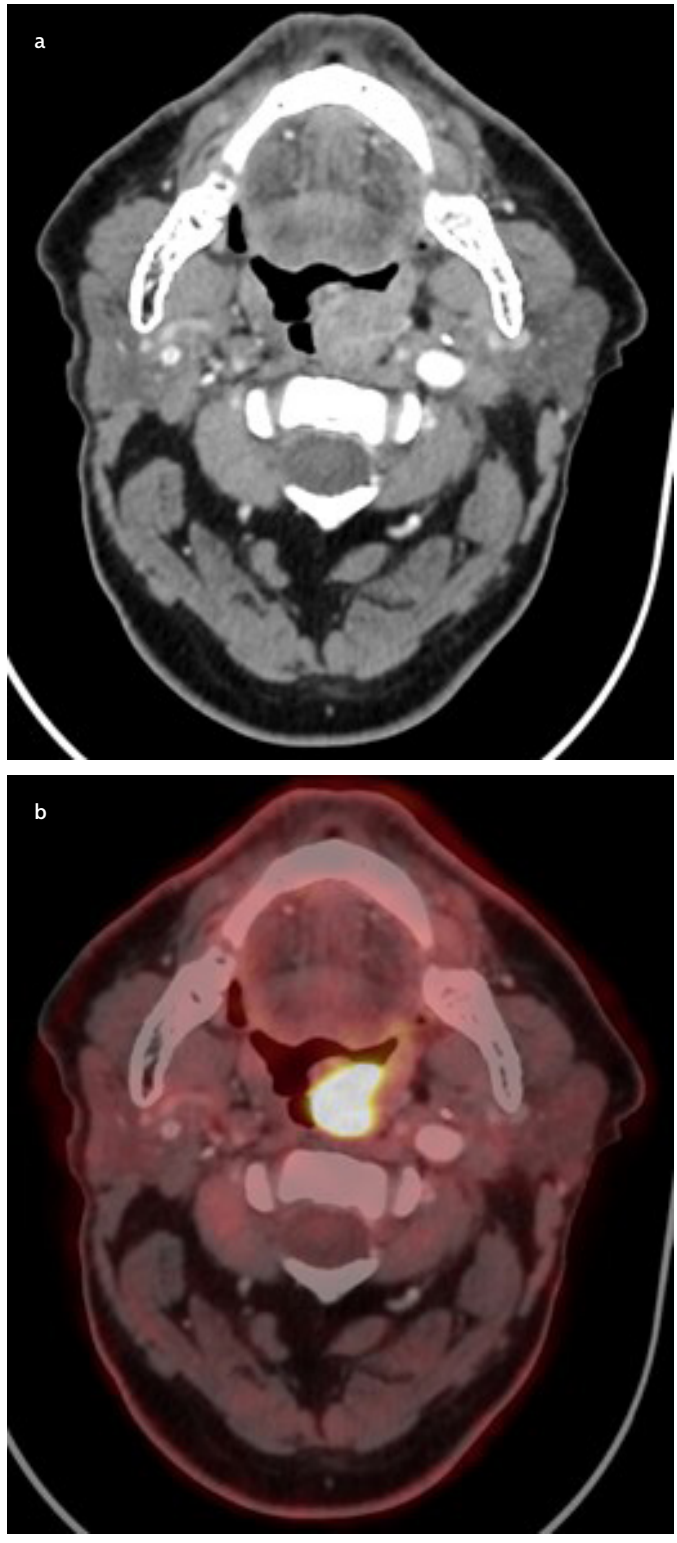

Figure 2. a,b. (a) Contrast-enhanced computed tomography (CT) image, axial plane, showing an oropharyngeal mass measuring 31 × 18 × 27 mm, (b) Axial fused dedicated head and neck fluorodeoxyglucose positron emission tomography CT image showing high FDG uptake (SUVmax 26) in the oropharyngeal mass

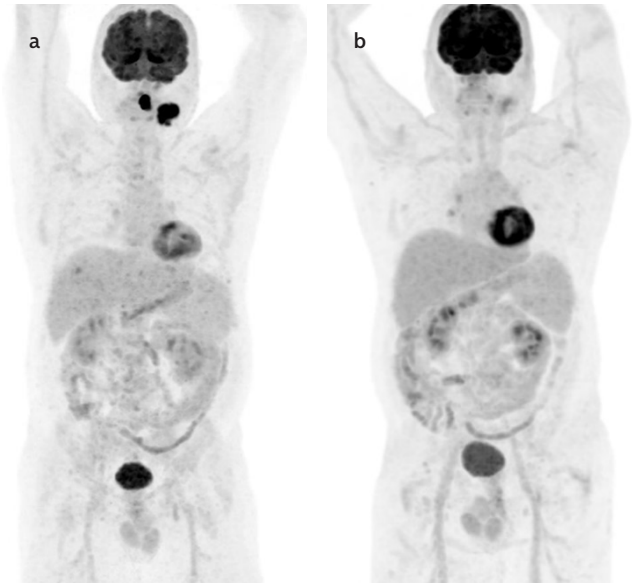

Figure 3. a,b. Whole-body fluorodeoxyglucose positron emission tomography computed tomography scan, (a) Before treatment, showing an FDG-avid oropharyngeal mass, cervical lymph nodes on the left side and a small focus of increased FDG uptake in the liver, (b) Five months after the start of the treatment, showing a complete metabolic remission of the oropharyngeal mass and partial metabolic remission of the cervical lymph nodes. The liver metastases are too small for PET detection

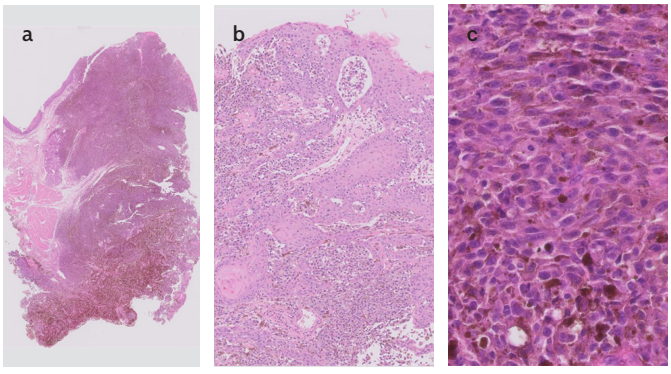

Figure 4. a-c. Hematoxylin and eosin staining. (a) Melanoma invading deep into the tonsillar tissue, original magnification × 50, (b) Intraepithelial melanocytic proliferation with pagetoid spread and nesting, original magnification × 200, (c) Atypical pleomorphic melanoma cells containing melanin pigment, original magnification × 400

depth was 5.5 mm. No lymphovascular invasion nor perineural invasion were observed. Next-generation sequencing analysis was performed, however, was not informative owing to interfering melanin pigment in the cells. Additional polymerase chain reaction analysis did not detect a BRAF mutation.

The diagnosis of a nodular MM was established, which was staged as pT4aN2M1 (American Joint Committee on Cancer eighth edition 2017 classification). A full-body inspection by the dermatology department did not reveal any suspected skin lesions. The patient was treated with immunotherapy consisting of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg for four three-weekly cycles followed by nivolumab monotherapy, initially at a dose of 240 mg every two weeks, and subsequently, after five administrations, at a dose of 480 mg every four weeks until March 2020. Overall, the treatment was well tolerated with only limited rash and hypothyroidism (FT4 = 1.7 pmol/L with normal range = 11.5–22.7 pmol/L, TSH = 115.94 mU/L with normal range = 0.55–4.78 mU/L) requiring substitution. An FDG-PET-CT scan five months after the start of treatment revealed a complete metabolic remission of the oropharyngeal mass and a partial metabolic remission of the cervical lymph nodes (Figure 3B). The MRI of the liver six months after the start of treatment showed an increased number of diffuse liver metastases and new metastatic involvement of the gallbladder. Nevertheless, nivolumab treatment was continued, and the MRI after nine months showed no further evidence of tumor progression. Nivolumab treatment is ongoing.

Discussion

Primary MM represents 1%–2% of all melanomas (1, 2). More than half of all MMs are located in the head and neck area, mainly involving the sinonasal and oral cavity (2). Other common extracutaneous sites involve the eye, anorectum, and the genitourinary tract. Only 16 cases of oropharyngeal MM have been described in the literature (Table 1) (3-14). Owing to the low incidence, mucosal metastases from primary cutaneous melanoma should always be excluded, and a full-body inspection is recommended. MM occurs later in life than its cutaneous counterparts, with a median age of diagnosis of 70 and 55 years, respectively (15). Although the incidence rates of cutaneous melanoma are increasing worldwide, the incidence rates of MM remain stable (2).

The etiology, risk factors, and pathogenesis of MM remain unclear (16). Although alcohol and tobacco use are the known risk factors for head and neck squamous cell carcinoma, no similar evidence exists for MM. Tobacco use is known to cause mucosal melanin hyperpigmentation and could therefore contribute to the pathogenesis of head and neck MM (17). Three cases have been published on sinonasal MM after occupational exposure to formaldehyde for a long time, suggesting a causal relationship (2). Oral MM may be associated with pre-existing melanosis and is seen in about one-third of patients.1 In addition, no association with viruses could be determined (10). Although the incidence of cutaneous melanoma is twice as high in the Caucasian than in black population, MM has no preference for a particular race or geographical area (1). In contrast to cutaneous melanoma, exposure to ultraviolet radiation is unlikely to be implicated. This raises the question of why melanocytes are present in mucosal sites. It is believed that they produce a variety of cytokines and neurotransmitters, thereby modulating immune responses and contributing to tissue homeostasis (18).

The presenting symptoms of MM are similar to those of other tumors arising from the same site. Endoscopy reveals that MM may have different degrees of pigmentation, ranging from a full black mass to a translucent mass seen in the case of amelanotic melanoma. Lesions may either have a macular or a nodular appearance, and satellite lesions are often present. At the time of diagnosis, the prevalence of metastases in head and neck MM is 10%–25% and rises to 60%–65% in laryngeal/pharyngeal MM (2).

Table 1. Overview of previously reported patients with oropharyngeal mucosal melanoma

AUTHOR/ YEAR	AGE SEX	RISK FACTORS	PRESENTING SYMPTOMS	INTERVENTIONS	PRIMARY TUMOUR	METASTASES	PRIMARY TREATMENT	DISEASE COURSE	OUTCOME
OSORIO M ET AL./2017	62/F	None	Bleeding from a left tonsillar lesion while brushing teeth	MRI scan head/neck, PET/CT scan, biopsy	Left tonsillar mass extending to the soft palate	No evidence of metastases on imaging. Regional nodes confirmed after left level I–V SND	Partial pharyngectomy (R0 resection), left level I–V SND, reconstruction with free radial forearm flap and a pharyngeal constrictor advancement. pharyngoplasty; adjuvant radiotherapy (30 Gy); adjuvant immunotherapy	NA	Free of disease 11 months after treatment
JENA A ET AL./2016	58/M	Smoker	Dysphagia and swelling in the mouth for 2 years	CT scan head/neck/ chest, biopsy	Left posterior tonsillar pillar	No evidence of metastases on imaging	Surgical resection; adjuvant chemotherapy (5 cycles of Dacarbazine)	At 2 years follow-up, patient developed pulmonary metastases and local recurrence, requiring palliative treatment	NA
MILOJEVIĆ M ET AL./2015	71/M	Smoker	Sensation of foreign body in the throat, dysphagia, odynophagia and right cervical lumb	CT head/neck, MRI chest/abdomen, full-body inspection by dermatologist, biopsy (tonsillectomy)	Right tonsil	Regional nodes confirmed on imaging	Tonsillectomy, SND was declined by patient, chemotherapy (tamoxifen) and radiotherapy	NA	At 7 months follow-up, the patient is doing well and with no signs of local recurrence and stable lymph nodes
BADERCA F ET AL./2014	53/M	Smoker	Bleeding, odynophagia, jaundice and melena	Gastroscopy, unspecified radiological examination, biopsy (tonsillectomy)	Right tonsil	Regional, gastric and ileal metastases	Tonsillectomy, further treatment was NA	NA	NA
BADRUDDOZA S ET AL./2009	48/M	NA	Sore throat, dysphagia, hemoptysis	NA	Left tonsil	NA	Tonsillectomy	NA	NA
STÁREK I ET AL./2006	35/M	NA	NA	MRI scan head/neck, PET/CT scan, biopsy	Right tonsillar fossa	No evidence of metastases on imaging nor right level II-IV SND	Surgical resection (mandibulotomy approach), right level II-IV SND	NA	Free of disease 18 months after treatment

Table 1. Overview of previously reported patients with oropharyngeal mucosal melanoma (continued)

AUTHOR/ YEAR	AGE SEX	RISK FACTORS	PRESENTING SYMPTOMS	INTERVENTIONS	PRIMARY TUMOUR	METASTASES	PRIMARY TREATMENT	DISEASE COURSE	OUTCOME
OZTÜRK O ET AL./2001	38/F	Smoker (10 pack-years)	Dysphagia and a black lump in throat	MRI scan head/ neck, unspecified radiological examination, biopsy	Right hypopharyngeal/ oropharyngeal wall	No evidence of metastases on imaging	Neoadjuvant chemotherapy and immunotherapy (4 cycles of interleukine-2, interferon-alpha, cisplatin and dacarbazine), surgical excision (R0 resection), adjuvant chemotherapy and immunotherapy (3 more cycles); adjuvant radiotherapy (66 Gy)	At 12 months follow-up, patient developed cranial and lung metastases	NA
	66/M	NA	Dysphagia and left cervical lump	MRI scan head/ neck, unspecified radiological examination, biopsy	Left tonsil	Regional nodes confirmed on imaging	Tonsillectomy (R0 resection) and left radical neck dissection, adjuvant immunotherapy (interferon-alpha), radiotherapy (70 Gy)	At 3 months follow-up, patient developed bone metastases (right iliac bone)	Succumbed 6 months after treatment
	46/M	NA	Enlargement of a black mass on tongue for 1 year	Unspecified radiological examination, biopsy	Two black nodular masses at the tongue base	Regional nodes confirmed on imaging	Surgical excision (mandibulotomy approach), left radical neck dissection, adjuvant chemotherapy and immunotherapy (5 courses of interleukin-2, interferon-alpha, dacarbazine, vincristine and cisplatin)	At 3 months follow-up, patient developed multiple pulmonary metastases	Succumbed 1 year after treatment
GORSKY M ET AL./1998	86/M	NA	Sore throat for 6 months	NA	Tonsillar area	NA	Radiotherapy	NA	Succumbed 7 months after treatment
	59/M	NA	NA	NA	Tonsillar area	NA	NA	NA	Succumbed 5 years after treatment

Table 1. Overview of previously reported patients with oropharyngeal mucosal melanoma (continued)

AUTHOR/ YEAR	AGE SEX	RISK FACTORS	PRESENTING SYMPTOMS	INTERVENTIONS	PRIMARY TUMOUR	METASTASES	PRIMARY TREATMENT	DISEASE COURSE	OUTCOME
XAVIER R ET AL./1996	75/F	NA	Odynophagia, dysphagia, sialorrhea, right cervical lumb	CT head/neck, bone scan, abdominal ultrasound, chest x-ray, full-body inspection by dermatologist, biopsy (tonsillectomy)	Right tonsil	Regional nodes confirmed on imaging	Tonsillectomy, lymph node resection was declined by patient, radiotherapy and chemotherapy (tamoxifen)	NA	At 6 months follow-up, the patient is doing well with no signs of local recurrence and stable lymph nodes
JOHNSON I ET AL./1994	57/M	Lifelong smoker	Sore throat, odynophagia, blood-stained saliva for 2 months	CT whole body, biopsy	Lesion in the oropharynx, extending distally 4 cm from the base of the left tonsil	No evidence of metastases on imaging	Wide resection	At 2 months follow-up, patient developed local recurrence and re-resection was performed	NA
SVANE-KNUDSEN V/1957	48/F	NA	Left-sided neck pain	Full-body inspection by dermatologist, biopsy	Left tonsil	No metastases on clinical examination	Neoadjuvant radiotherapy, radical tonsillectomy, adjuvante radiotherapy	NA	At 23 months follow-up, the patient is doing well with no clinical signs of local recurrence nor metastases
MESARA, BW ET AL./1968	52/M	NA	Enlargement of left tonsil for 6 months	Unspecified radiological examination, biopsy	Left tonsil	Regional and lung metastases	Chemotherapy (phenylalamine perfusion)	Progressive growth	Succumbed 6 months after treatment
	40/M	NA	Sore throat for 3 months, cervical lump	Unspecified radiological examination, biopsy	Left pharyngeal wall	Regional nodes	Radiotherapy (cobalt)	Progressive growth	Succumbed 4 months after treatment

SND: Selective neck dissection, CT: Computed tompgraphy, MRI: Magnetic resonance imaging, NA: Not available; R0: Microscopically margin-negative resection, Gy: Gray, M: male, F: Female

Although pigmented mucosal lesions can occur throughout the head and neck regions, they are especially common in the oral cavity. The differential diagnosis includes melanosis, melanotic macula, nevi, racial pigmentation, smoking-associated melanosis, postinflammatory pigmentation, amalgam tattoo, medication melanosis, melanoacanthoma, Peutz-Jeghers syndrome, Addison's disease, Kaposi's sarcoma, hemangioma, vascular malformations, and MM (19).If the pigmented lesion is suspicious, a biopsy should be performed. In the case of amelanotic MM, it is important to distinguish between squamous cell carcinoma and other types of cancer. Regarding our case report, according to the imaging (PET-CT) and without taking into account the clinical aspects, the most obvious diagnosis would be either oropharyngeal squamous cell carcinoma or tonsillar lymphoma.

The histopathological diagnosis is straightforward in up to 90% of the patients when the tumor is melanin rich.[16] MM is characterized by the proliferation of neoplastic melanocytes with variable phenotypes: polyhedral, round, fusiform, epithelioid, spindle, pleomorphic, microcytic, or a mixture of them. Vascular invasion, necrosis, and mixed phenotype are associated with worse prognosis (2, 16). Unfortunately, some lesions contain less or no melanin (amelanotic melanoma). Therefore, immunohistochemical analysis is often required and remains the diagnostic gold standard (1, 2). Useful markers include S-100 protein, MART-1/Melan-A, tyrosinase, HMB-45, and microphthalmia-associated transcription factor (20).

Depending on the stage, various therapeutic options have been used in treating MM, largely on the basis of the treatment of cutaneous melanomas. Complete surgical resection with clear margins is the first line of treatment in patients with limited disease (10). However, local recurrences are common. Some authors recommend prophylactic neck dissection, although there is no additional benefit on the the five-year overall survival rate (OSR) (20). As with cutaneous melanomas, sentinel lymph node biopsy is sometimes performed but has no established role in the treatment of MM. Adjuvant radiotherapy should improve locoregional control but has no proven effect on the five-year OSR (21). Primary radiotherapy is used as an alternative treatment for inoperable patients or when an adequate resection margin cannot be achieved.

In cases of advanced disease, systemic therapy is used, including chemotherapy, targeted therapy, or immunotherapy (22). Studies of standard chemotherapy regimens have shown similar response rates in patients with MM and cutaneous melanoma. Recently, molecular profiling of melanomas has identified driver mutations (BRAF, N-RAS, KIT, NF1), which can be used for more targeted therapy (2, 23). However, the prevalence of BRAF and N-RAS mutations is much lower in MM than in cutaneous melanomas. Further research is needed to determine the role of this therapy in the treatment of MM. Immunotherapy has been shown to significantly prolong survival in patients with cutaneous melanoma. However, randomized trials in MM are still missing. The combination of anti-PD-1 (nivolumab) and anti-CTLA4 therapy (ipilimumab) has shown a significantly improved efficacy compared with monotherapy, with a twice as good objective response rate for patients with MM of 37.1% versus 60.4% for patients with cutaneous melanoma (24). The median progression-free survival was 5.9 months and 11.7 months, respectively. Data on systemic therapy in the adjuvant setting are scarce; therefore, no conclusions can be drawn.

As mentioned earlier, MMs are genetically distinct from their cutaneous counterparts, have anatomical constraints, tend to develop later in life, are more often diagnosed at an advanced stage, and have a higher recurrence rate. Therefore, despite aggressive treatment, MM have a poor prognosis with a five-year OSR of <30%, whereas cutaneous melanomas have a five-year OSR of 80% (2).

In conclusion, MMs are rare, yet very aggressive and have a dismal prognosis. Because of the low incidence, metastases from a primary cutaneous melanoma should always be excluded. The epidemiologic, genetic, and biologic differences between mucosal and cutaneous melanomas have adverse implications for both treatment and prognosis of MM. Imaging, including PET scan, is of great importance to evaluate the extent of the lesion and distant metastases. In cases of limited disease, resection is recommended. In cases of advanced MM, the combination of anti-PD-1 and anti-CTLA-4 treatment should be considered.

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