An Update on Mucosal Melanoma: Future Directions

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Abstract
By definition, mucosal melanomas are malignant primary tumors originating from melanocytes located in the mucosal membranes of the nasal cavity and accessory sinuses, oral cavity, lips, and pharynx, and vulvar, vaginal, or anorectal, or basically any other part of the mucosal surface lining. These malignant melanomas usually occur in occult sites, which in combination with the lack of early specific signs contribute to the delay in diagnosis and poor prognosis of the disease. Given the rarity of mucosal melanomas, knowledge about their pathogenesis and risk factors is insufficient and when compared with cutaneous melanoma, they have the lowest five-year survival rate. Surgical resection is frequently the first approach to primary tumors, even though the utility of lymph node surgery and radiation therapy is not well established. Novel molecular techniques such as whole exome sequencing have become routine in order to aid patient care. They show great promise in the treatment of rare and usually fatal diseases such as mucosal melanomas. Target therapy against c-KIT activating mutations, frequently seen in mucosal melanomas, and the immunotherapy have emerged as a promising treatment modality for these aggressive tumors.

Key Words: mucosal melanoma, melanoma epidemiology, mucosal melanoma management

Introduction
Mucosal melanoma (MM) is a rare form of malignant melanoma, representing 1% of melanoma cases (1), with a five-year survival rate of 25% as opposed to approximately 80% in cutaneous melanomas (1,2). This variant of malignant melanoma mainly affects the head and neck, followed by anorectal and vulvo-vaginal mucosa, in order of prevalence (1-3). Some authors are extremely adamant that in MM, such as oral MMs, the disease outcome is invariably fatal despite any treatment (4). On the other hand, other researchers claim that a host of new treatment options has been developed for patients with melanoma. Despite the lower rates of 5-year survival of MM, compared with cutaneous and ocular melanoma, the recent findings with regards to the molecular changes that underlie the development of MMs have offered new hope for the development of more effective systemic therapy (5).
EPIDEMIOLOGY

Incidence of MM is higher in women than in men, mostly due to female genital tract melanomas. The incidence increases with age, with more than 2/3 of patients being older than 60 years of age. The disease is more frequent among whites than blacks (2). A large recent analysis comprising almost five hundred patients from 15 skin cancer centers in Germany with histologically confirmed diagnosis reported that the most common site of MM was the head and neck region, in agreement with the literature (1-5), followed by the female genital tract and anorectal region (7). Conversely, in Asia with up to 25% incidence MM represents the second most common subtype of melanoma, after acral melanoma; gastrointestinal melanomas, specifically at the lower tract, represent almost 26% of cases of MM (8).

ETIOPATHOGENESIS

Unlike cutaneous melanomas, MM is not associated with ultraviolet radiation exposure, and the fact that genetic mutations are variable among different types of MM suggests that melanoma subtypes differ not only clinically but also biologically (1). MM originates from melanocytes that have migrated from the neural crest, although it is becoming clear that melanoma is not just a single disease, but rather a family of diseases characterized by particular molecular abnormalities. In that context, MM represents a unique subgroup in this emerging molecular classification system, which has tremendous implications for the development of new and effective therapies for patients with MM and will be addressed in detail below (9).

DIAGNOSIS

It is of paramount importance to exclude the possibility of metastatic lesions from primary cutaneous melanoma, especially on sites where they rarely present as a primary MM (2). Due to the highly variable clinical presentation of MM and areas of occurrence that are difficult to access during physical examination, it is frequently confused with other conditions, leading to disease progression being at an advanced stage by the time diagnosis is confirmed by biopsy (1). MMs of the head and neck are usually flat, but may be elevated when present in the oral cavity, although they are usually polypoid or seen as poorly defined masses when detected in the sinonasal area. Vulvovaginal MM are also usually polypoid but nevertheless may present as satellite lesions or nevi (3). When a diagnosis of mucosal melanoma is confirmed, it is essential to exclude the regression of a previous melanoma and cutaneous or eye melanoma metastasis, reinforcing the importance of dermatologic and ophthalmologic follow-up of these patients even with no previous history of the disease (1).

Staging

According to the literature, a specific TNM classification is available only for skin and ocular lesions, and there is a simple system for HNMM is based on 3 stages, namely stage I: MM limited to primary site; stage II: MM with neck lymph node metastasis; and stage III: MM with distant metastasis (5). Nevertheless, the new TNM classification includes malignant melanomas of upper aerodigestive tract. This classification applies only to HNMM. However, Ballester Sánchez et al. consider the Ballantyne simplified staging system applicable to all MM, only extending stage II to regional lymph node involvement instead of the neck lymph nodes (1).

Given that MM are aggressive tumors, T1 and T2 are omitted and the primary tumor classification skips from T0, where there is no evidence of primary tumor, to a mucosal disease (T3) with the tumor limited to the epithelium and/or submucosa, followed by T4 when moderately advanced or very advanced disease is present. T4a indicates moderately advanced disease with tumor involving deep soft tissue, cartilage bone or overlying skin; T4b indicates very advance disease, with the tumor involving the brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, or mediastinal structures (10). Implementation of appropriate staging systems for other locations of MM is required to provide not only adequate staging, but also treatment planning and prognostication for patients (2). Further data regarding melanoma staging was published by the AJCC (11), even though MM is not specifically mentioned (12).

Mucosal melanoma of the head and neck

HNMM are uncommon malignancies that arise mainly in the nasal cavity and paranasal sinuses, followed by the oral cavity (9). The incidence of OMM is higher in Japanese than in Caucasians patients, with Japanese patients representing up to 8% of all malignant melanomas. Upper gingival and palatal mucosas are the most commonly affected sites (13). Immunohistochemical staining PD-L1 in MM was not correlated with age, sex, or anatomical localization of the tumor. Interestingly, patients with PD-L1-positive HNMM had a significantly longer recurrence-free survival (P=0.026). In contrast to cutaneous melanoma and some other malignancies, a relevant PD-L1
overexpression in MM of the head and neck could not be confirmed (14).

Due to the rarity of sinonasal mucosal melanoma (SMM), prospective studies are not available in the literature. SMM show poor prognosis due to high metastatic potential requiring wide resection as main treatment modality, with adjuvant radiotherapy to improve local control (15). Incidence of SMM in the nasal cavity is increasing, especially in Caucasian women in the USA, and retrospective studies reveal a poor prognosis (15,16).

**Mucosal melanoma of the anorectal area**

Anorectal mucosal melanomas have been associated with the poorest prognosis of all mucosal melanomas sub-regions and could benefit strongly from screening efforts in order to establish an earlier diagnosis and improve survival rates after treatment (7).

**Mucosal melanoma of the vulvovaginal area**

Mucosal melanoma of the vulva and vagina are normally diagnosed at the labia, vagina, urethra, or cervix and present as aggressive tumors with the clinical aspect of a mass, normally accompanied by pain, bleeding, or itching, and less commonly dysuria or ulceration (3).

**Mucosal melanoma in unusual locations**

In theory, MM can occur in any mucosal lining of the human body. A small amount of MM cases have been described in less common sites, such as the male urethra, the bladder, the esophagus, and other parts of the intestine (1).

**MUCOSAL MELANOMA TREATMENT**

Free margin resection of the tumors is generally difficult due to the complicated location of the lesions and the multifocal nature of the disease (1). Surgical resection is frequently the first approach to primary tumors, even though the utility of lymph node surgery and radiation therapy is not well established (3). Nevertheless, radiotherapy may be used as an adjuvant treatment; in cases where lesions are unresectable, definitive radiotherapy could be considered. Despite aggressive locoregional management, recurrent disease is common and treatment remains challenging (17). Novel molecular techniques such as whole exome sequencing have become routine in order to aid patient care and show great promise in treatment of rare and usually fatal diseases such as mucosal melanomas.

A systematic review with meta-analyses of upper airways tract MM treatment revealed that surgical resection with postoperative radiotherapy remains the gold standard for locoregional control. No studies investigated quality of life, treatment-related mortality, or morbidity. Furthermore, their results indicated that the addition of radiotherapy to surgery reduces the rate of locoregional recurrence (HR, 0.50; 95% CI, 0.42-0.87). Since there was no statistically significant difference in overall survival (HR, 1.16; 95% CI, 0.98-1.37), more robust studies are needed to determine the usefulness of target therapy (after proper validation) in improving overall survival (18).

**Targeted therapy for mucosal melanoma**

In a recent study, SMM showed high expression of HER4 (70.3%), a member of EGFR family, which also was correlated to a high CD44 immunopositivity (65.6%) and suggests that molecular target therapy for HER4 in SMM might be beneficial. Indeed, HER4 and CD44 expression indicate that HER4 positivity might be an important factor in valuing the prognosis of patients with the disease (19), even though further molecular studies are required to clarify the tumor profile, its microenvironment, and immune compartment.

c-KIT aberrations are relatively common in MM, potentially leading to an eminent role of c-KIT inhibitors such as imatinib, sunitinib, dasatinib, nilotinib, and masitinib. Nilotinib (NCT01099514) and masitinib (NCT01280565) are in clinical trials for patients with advanced melanomas who have c-KIT mutations. A single-arm, phase II Tasigna® Efficacy in Advanced Melanoma (TEAM) trial evaluated the KIT-selective tyrosine kinase inhibitor in patients without prior KIT inhibitor treatment. Ten of the eleven responding patients had exon 11 mutation, suggesting that nilotinib may be an effective treatment option for patients with specific KIT mutations (20). The combination of dabrafenib and trametinib or vemurafenib with cobimetinib are FDA approved for primary and metastatic melanomas harboring specific activating mutations in the BRAF kinase domain. Nevertheless, the low prevalence of BRAF mutations in mucosal melanomas reduces the utility of these new treatments, which is likely to be limited to a small subset of patients (3).

NRAS gain was recently evaluated in acral, mucosal, chronic sun-induced damage (CSD), and non-CSD melanomas in China, with an overall incidence of 14%. Surprisingly, MMs presented a 15.8% incidence (6). NRAS mutations are not usually reported in MMs, even though Heppt et al. found a similar incidence...
of NRAS mutations (13.8%) in Germany, and the affected patients can benefit from target therapy with binimetinib, pending clinical trial validation (7).

Heppt et al. demonstrated that NRAS (13.8%), KIT (8.6%), and BRAF (6.4%) mutations were evenly distributed amongst 444 tumors within all MM groups (7). NRAS mutations in esophageal melanomas, a very unusual site even for MM, were detected at a higher percentage than in cutaneous melanomas (21). Even though the case series only included 16 melanomas of the esophagus, this result reinforces the importance of approaching the tumors in an individual basis, in the context of personalized medicine.

Employing an immunotherapy approach, such as involving anti-PD-1 agents, is supported by scientific evidence, not only in mucosal but also in acral melanomas. Recently, response rates to PD-1 blockade in patients with acral and MMs were slightly lower but comparable to response rates in cutaneous melanomas and support the routine use of anti-PD-1 agents for MM (22).

Prognostic factors and treatment outcomes

Several independent risk factors for disease progression have to be considered, such as male gender (P = 0.047), advanced tumor stage (P = 0.001), nodal disease (P = 0.001), and incomplete resection status (P = 0.001). Female genital tract MMs present the highest overall survival (P = 0.030), along with patients without ulceration (P = 0.004). Multivariate risk factors for overall survival are metastasis stage at diagnosis (P = 0.002) and incomplete resection of the primary tumor (P = 0.001). As previously mentioned, anorectal melanomas are associated with the poorest prognosis among all MM (7). Screening for NRAS, KIT, and BRAF mutations in MM might prove beneficial in the near future, although solid evidence regarding their potential as well as new targeted therapies in cutaneous melanomas are lacking (15).

The future in mucosal melanoma research and treatment

Next generation sequencing is a bioinformatics tool that is becoming highly integrated in cancer research. Sequencing data is becoming widely available, and the further efforts in analysis should focus on individual mutations or structural variants when the main driver mutations or structural variants are absent in the melanoma sample. Single-cell RNA sequencing could also be applied to longitudinal melanoma samples under therapy. Analysis of these samples would simultaneously reveal the phenotypic expression changes from the therapy in both the microenvironment and immune compartment, apart from the tumor itself. These data would be useful for discovering cell autonomous resistance mechanisms and non-cell autonomous resistance mechanisms from the same sample.

The advent of bioinformatics analysis provides relevant information that can be used for treatment in a personalized medicine setting. As sequencing costs decrease and algorithms become better at predicting epitope binding and T-cell receptor recognition, it could become possible to provide many melanoma patients with a personalized immunization therapy for their tumor. Interdisciplinary teams of cancer biologists, immunologists, bioinformaticians, and clinicians will have to work together to drive melanoma research and treatment forward (23).

CONCLUSION

This review pinpointed several burdens related to malignant MM epidemiology, ranging from difficulties in treatment to late diagnosis of the disease. Residual primary lesions, positive cervical lymph nodes, and c-Kit mutations act as adverse prognostic factors for metastatic OMMs. The kit inhibitor imatinib could benefit metastatic patients presenting c-Kit mutations (24,25). Scientific evidence for treatment choice in other types of MMs is poor, and immunotherapy has emerged as a promising treatment modality for these aggressive tumors.

References: