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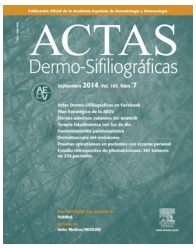

REVIEW

Mucosal Melanoma: An Update☆

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KEYWORDS
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Abstract Mucosal melanoma is a rare melanoma subtype that differs from the cutaneous form of the tumor in its biology, clinical manifestations, and management. Diagnosis is usually late due to a lack of early or specific signs and the location of lesions in areas that are difficult to access on physical examination. Surgical excision is the treatment of choice for localized disease. The value of sentinel lymph node biopsy and lymphadenectomy is still unclear. Radiotherapy can be used as adjuvant therapy for the control of local disease. *KIT* mutations are more common than in other types of melanoma and this has led to significant advances in the use of imatinib for the treatment of metastatic mucosal melanoma.

PALABRAS CLAVE
Melanoma mucoso;
KIT;
Imatinib;
Melanoma de cabeza y cuello;
Melanoma ano-rectal;
Melanoma vulvo-vaginal

Actualización en melanoma mucoso

Resumen El melanoma mucoso es un subtipo infrecuente de melanoma que difiere del melanoma cutáneo en su biología, clínica y manejo. El diagnóstico suele realizarse de forma tardía debido a su localización en zonas de difícil acceso a la exploración física y a la falta de signos específicos y tempranos. La cirugía es el tratamiento de elección en caso de enfermedad localizada. El papel de la biopsia selectiva de ganglio centinela y de la linfadenectomía permanece todavía incierta. La radioterapia se puede emplear como tratamiento adyuvante con el fin de controlar localmente la enfermedad. Existe un mayor porcentaje de mutaciones en *KIT* que en otros tipos de melanoma, lo que ha llevado a avances significativos en el tratamiento de la enfermedad metastásica con imatinib.

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Introduction

Mucosal melanoma arises from melanocytes in the mucosal membranes. Melanocytes are found on all mucosal surfaces, where rather than protect against sun damage, they have immunological, antibacterial, and phagocytic functions and participate in antigen presentation and cytokine production.[1] While all melanocytes have the same embryonic origin, the microenvironment to which they are exposed varies according to their final destination. Depending on their location, they will be found in different types of tissues, surrounded by different cells, and as a result, their growth and maintenance—and consequently the development of melanoma—will be affected by different adhesion molecules and signaling pathways.[2]

Because mucosal melanoma is rare, there are no specific staging or treatment protocols, and much remains to be learnt about the pathogenesis of this disease.

Epidemiology

Mucosal melanoma accounts for 1% of all melanomas, but in contrast to cutaneous melanoma, whose incidence is rising, the incidence of mucosal melanoma has remained stable.[3–5] This subtype of malignant melanoma affects first and foremost the head and neck, followed by the anorectum and the vulva and vagina.

Mucosal melanoma has a later onset than the cutaneous form. The mean age at diagnosis is 70 years,[6] although melanoma of the oral cavity develops sooner.[7] Unlike cutaneous melanoma, mucosal melanoma is more common in women, with a male to female ratio of 1.85:1.[3] This higher frequency in women can be explained by the relatively high frequency of melanoma of the female genital tract, which is the most common type of melanoma in women.[8] The head and neck is the most common site of mucosal melanoma in men.

Blacks, Asians, and Hispanics have a higher proportion of mucosal melanoma than other types of melanoma.[9] Up to 9% of all melanomas diagnosed in blacks and Asians are mucosal, compared with 1% in whites.[8] The absolute incidence of mucosal melanoma, however, is higher in whites.

Etiology and Pathogenesis

Because mucosal melanoma is a rare condition, little is known about its pathogenesis, and no risk factors have been identified to date. Unlike cutaneous melanoma, mucosal melanoma is not associated with UV radiation exposure. Furthermore, no associations have been observed with human papillomavirus, herpesvirus, or polyomavirus.[2] Formaldehyde has been postulated as a risk factor for sinonasal melanoma,[10,11] and melanoma of the oral cavity may be preceded by oral melanosis.[12] While tobacco can induce pigmented lesions on the oral mucosa, there is insufficient evidence to conclude that this substance is carcinogenic in mucosal melanoma.

Different types of melanoma are associated with different mutations. *BRAF* mutations, for instance, are common in cutaneous melanoma but rare in mucosal melanoma.[13] A higher proportion of mutations and multiple copies in the receptor tyrosine kinase gene *KIT* have been found in mucosal melanoma, with figures ranging from 15.6% to 39%, depending on the series.[14,15] Beadling et al.[15] detected *KIT* mutations in 15.6% of mucosal melanomas and increased *KIT* copy number in 26.3%. The authors also reported that these percentages varied according to the site of the melanoma, with higher rates observed for tumors in the vulvar and vaginal regions (44.4%) than in the head and neck (8.3%). In a similar study, *KIT* mutations were detected in 35% of vulvar melanomas, 9% of anorectal melanomas, 7% of nasal cavity melanomas, 20% of penile melanomas, and 0% of vaginal melanomas.[16] *NRAS* mutations were also detected in 10% of the mucosal melanomas analyzed and *BRAF* mutations in 6%. One European study reported *KIT* mutations in 30% of genital melanomas, but did not detect similar mutations in sinonasal or anal lesions.[17] Other genetic alterations described for mucosal melanoma are a higher frequency of focal amplifications of *CDK4* and loss of *CDKN2A* locus, as well as chromosomal aberrations distinct to those seen in melanomas arising in skin with chronic sun damage.[18] The studies published to date have analyzed few cases, and larger studies are therefore needed to determine whether the tendencies described above are significant. That said, the fact that genetic mutations vary among different types of melanoma suggests that melanoma subtypes differ not only clinically but also biologically.

Clinical Characteristics and Diagnosis

Mucosal melanoma is difficult to diagnose because of its highly variable clinical presentation and its location in areas that are difficult to access during physical examination (Figs. 1 and 2). It is frequently confused with other conditions for a long time, and is often at an advanced stage by the time diagnosis is confirmed by biopsy.

Approximately 20% of mucosal melanomas are believed to be multifocal[19] and 40% amelanotic,[20] compared with just 5% and 10% for cutaneous melanomas, respectively (Table 1).

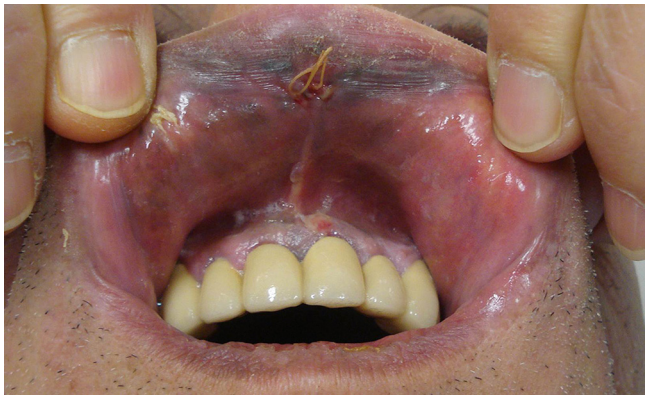

Figure 1 Oral mucosal melanoma.