Primary mucosal melanoma

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Primary mucosal melanomas are rare, biologically aggressive neoplasms. The distribution of head and neck, female genital tract, anal/rectal, and urinary tract sites is 55.4%, 18.0%, 23.8%, and 2.8%, respectively. The median age at presentation is the seventh decade, and women are given the diagnosis more frequently than men. Unfortunately, most afflicted individuals harbor micrometastatic disease and experience a course characterized by multiple local recurrences before the clinical development of distant disease. Approximately a third of patients have nodal involvement at presentation, and the overall 5-year survival is only 25%. Despite aggressive surgical resection and a multitude of adjuvant treatments, the prognosis remains grave. Early detection, which is difficult because of the occult anatomic locations in which these tumors occur, allows the best hope for cure. (J Am Acad Dermatol 2007;56:828-34.)

Primary mucosal melanoma is an exceedingly rare neoplasm. As a result, there is a paucity of data elucidating its etiopathogenesis and predictive factors. Overall, primary mucosal melanomas behave more aggressively and have a poorer prognosis than their cutaneous counterparts. Because of the unusual anatomic locations in which they occur and the lack of early presenting signs and symptoms, mucosal melanomas are virtually always diagnosed at advanced stages.

This article will detail the key pathogenic and diagnostic features of this vexing disease. Special emphasis will be placed on the presentation, diagnosis, and treatment of tumors from the head and neck, female genital tract, and anorectum.

EPIDEMIOLOGY

Mucosal melanoma remains a rare disease, accounting for 0.03% of all new cancer diagnoses. According to the National Cancer Data Base Report on Cutaneous and Noncutaneous Melanoma, cutaneous melanoma comprises 91.2% of all melanoma, whereas ocular, mucosal, and unknown primaries account for 5.2%, 1.3%, and 2.2% of cases, respectively. Mucosal melanoma is most common in the head and neck (55.4% of cases), with female genital tract, anal/rectal, and urinary tract sites responsible for 18.0%, 23.8%, and 2.8% of cases, respectively.¹

Unlike the dramatically increasing incidence of cutaneous melanoma, the incidence of mucosal melanoma has remained relatively stable.² Because of lesions arising in the female genital tract, it is found more frequently in women (65%). However, a slight male predominance exists among oral cavity and sinonasal lesions. The peak age for diagnosis of mucosal melanoma is between 70 and 79 years, on average one to two decades later than cutaneous melanoma. Overall, the incidence of mucosal melanoma is similar among African Americans, Asians, and Caucasians.¹ Reports of skewing toward African Americans and Asians are most likely secondary to the markedly lower incidence of cutaneous melanoma in these racial groups.

PATHOGENESIS

The etiopathogenesis of mucosal melanomas is not yet fully elucidated. As neuroectodermal derivatives, melanocytes are known to migrate to the skin, retina, uveal tract, and other ectodermally derived mucosa. Melanocytes migrate much less frequently to endodermally derived mucosa, such as the nasopharynx, larynx, tracheobronchial tree, and esophagus.³ This explains the lower frequency of melanoma in these locations.

Although their function is not fully understood, the presence of melanocytes in the mucous membranes is well established. Several investigators have quantified the density of melanocytes specific to certain mucosal epithelia. For example, the density of melanocytes in the nasal and oral mucosa is 1500/mm² (compared with 800/mm² on the abdomen and 2380/mm² on the skin of the penis).⁴,⁵
Furthermore, there is a marked variation in the numbers of dopa-positive melanocytes on the gingival epithelia in adults. Melanocytes have also been documented in the deep stroma of the nasal cavity (including the nasal septum and middle and lower turbinates), respiratory mucosa, mucous glands, esophagus, small bowel, and urogenital tract.

Because mucosal melanomas are frequently found at mucocutaneous junctions, they were once believed to arise only as extensions of melanocytic hyperplasia from adjacent skin. Indeed, some mucosal melanomas do evolve in this manner. However, there are now several cases describing primary melanocytic junctional activity solely within the mucosal epithelium.

**DIAGNOSIS**

Differentiating a primary mucosal melanoma from a metastasis of an unknown or regressed cutaneous tumor can be diagnostically challenging. Reliable clinical findings include the presence of a precursor lesion such as melanoma in situ in the mucosa. Unfortunately, these features are typically absent, given the delayed diagnosis and presence of secondary changes such as ulceration. When biopsying these lesions for pathologic diagnosis, it is imperative to include a rim of normal-appearing tissue, which may harbor the precursor lesion. Contributing to the diagnostic dilemma is the frequent lack of melanin pigmentation in these tumors (amelanotic melanoma), which clinically may resemble lymphoma or angiosarcoma.

Histologically, primary lesions are characterized by nested and single growth of atypical melanocytes in the surrounding mucosa. Similar to the methods used for cutaneous melanoma, immunohistochemical stains, such as S-100, HMB-45, Melan-A, and Mart-1, can aid in the diagnosis of these tumors. Other histopathologic features of mucosal melanomas include frequent angioinvasion and multicentricity. These findings are important factors in the aggressive behavior, early metastatic spread, and local control failure characteristic of mucosal melanoma.

In a recent study by Curtin et al using DNA for comparative genomic hybridization, distinct sets of genetic alterations were identified in different subtypes of melanoma. Whereas melanomas arising on skin without chronic sun damage had frequent mutations in BRAF, those mutations were much less common in melanomas occurring on acral skin, mucosal surfaces, and chronically sun-damaged skin. These findings suggest differing routes by which these tumors develop, which may ultimately impact response to treatment.

**STAGING**

In general, the growth of mucosal melanoma closely resembles the nodular pattern of its cutaneous counterpart. This characteristic, in part, explains the poor prognosis of these lesions, and several studies have corroborating data that link survival most closely with tumor thickness. Patients with lesions less than 2-mm thick have a significant survival advantage over those with lesions greater than 2 mm. Because of the typical delay in diagnosis, the vast majority of mucosal melanomas present to clinicians as large, polypoid tumors with nodal involvement. Because of this advanced presentation, Breslow depth alone is of little use in the staging of the majority of primary mucosal melanomas. With this in mind, most authors advocate continued use of the clinical staging system developed for cutaneous melanoma, where stage I is clinically localized disease, stage II is regional lymph node disease, and stage III is disseminated disease.

Most patients with mucosal melanomas present with clinically localized disease. However, despite garnering local control surgically, 5-year survivors are rare. The rich vascular and lymphatic submucosal network contributes greatly to the early development of metastases in mucosal melanomas. As such, local recurrence usually does not occur in isolation, but rather represents a marker for distant disease. A more thorough understanding of the prognostic factors involved is needed so that a comprehensive, uniform staging system can be developed.

**DIAGNOSTIC WORKUP**

When a mucosal melanoma is diagnosed, there is frequently debate among clinicians concerning the extent of workup necessary to exclude metastatic melanoma, either as the source of the mucosal lesion or from the mucosal primary itself. Certainly, when a mucosal melanoma is detected, a total body skin examination is paramount to rule out a primary cutaneous melanoma that has metastasized. To evaluate the primary site, a computed axial tomography scan or magnetic resonance image may help determine the extent of involvement around various anatomic structures. Given the propensity for mucosal melanoma to disseminate and to exclude metastatic melanoma from a cutaneous primary, a basic metastatic workup should be considered. This workup includes serum lactate dehydrogenase, chest radiograph, and combined positron emission tomography/computed tomography scanning of the chest, abdomen, and pelvis.
SUBTYPES OF MUCOSAL MELANOMA

Head and neck

Primary mucosal melanomas of the head and neck comprise 55% of all mucosal melanomas. These tumors arise most frequently in the nasal cavity (55% of reported cases), followed by the oral cavity (40%). As with most mucosal melanomas, those in the sinonasal region typically affect the elderly, with a mean age of onset of 70 years. Oral melanomas, on the other hand, tend to occur at a younger age than their sinonasal counterparts, with most afflicted individuals younger than 40 years. The youngest case reported to date involved an 8-month-old African American girl with sinonasal melanoma. A slight male preponderance exists in both oral cavity and sinonasal mucosal melanomas.

In the oral cavity, the hard palate and maxillary alveolus are the predominant sites of involvement. Patients may have a friable pigmented lesion, ill-fitting dentures, ulceration, or bleeding. In addition, many of these lesions are incidentally discovered during routine oral or dental examinations. Unfortunately, the vast majority of patients lack early symptoms, and the average time from the appearance of symptoms to evaluation by a healthcare professional is 9 months. Contributing to this delay in diagnosis, approximately a third of oral melanomas are amelanotic. As a direct result of these obstacles, most mucosal melanomas of the oral cavity are diagnosed at an advanced stage, with a Breslow depth greater than 4 mm on presentation. There appears to be a racial discrepancy in the incidence of oral melanomas. Among the Japanese, oral mucosal melanoma accounts for 7.5% of all melanomas, versus less than 1% for Caucasians. This difference has led many investigators to speculate the role of hereditary or environmental influences. Given the disproportionately low incidence of cutaneous melanomas among African Americans and Asians, the data pertaining to the incidence of oral melanomas in these groups are difficult to interpret. A study involving Ugandan Africans revealed a disproportionately high incidence of oral mucosal melanomas, whereas similar reports of African Americans and Asians showed an incidence comparable with that of Caucasians.

Several case series have demonstrated that up to a third of oral melanomas are preceded by melanosis, which is postulated to represent the radial growth phase occurring before the development of vertical growth. Whether a survival advantage exists in cases with preceding melanosis is debatable, and numerous studies have had conflicting outcomes.

The exact origin of sinonasal melanomas is often difficult to determine because of anatomic limitations and locally advanced presenting stage. Approximately 80% of cases occur in the nasal cavity and 20% in the sinuses. Within the nasal cavity, the lateral wall and turbinates are most frequently involved. Among the paranasal sinuses, the maxillary sinus is the most common site, followed by the ethmoid, frontal, and sphenoid sinuses. Most patients present with epistaxis or unilateral obstruction. More advanced presentations may include pain and facial distortion. Unlike oral lesions, sinonasal melanomas are only rarely diagnosed incidentally during routine examinations, such as flexible endoscopy. Because the role of melanocytes in the sinonasal region is thought to be detoxification by metabolizing polycyclic aromatic hydrocarbons, some investigators have speculated a possible link between environmental and immune factors and the pathogenesis of these melanomas.

Sinonasal mucosal melanomas have a slightly better prognosis than those in the oral cavity. Nonetheless, the mean 5-year survival for head and neck lesions is only 10% to 25% (reported range; 0%-48%), regardless of the primary site. As with all mucosal melanomas, the most frequent scenario is local recurrence followed by metastatic disease. Reinforcing the observation that local recurrence is rarely an isolated phenomenon, a study conducted at M.D. Anderson Cancer Center (Houston, Tex) revealed that 90% of metastatic disease was associated with local recurrence. Once a lesion recurs, metastases are usually discovered within 3 months. The development of nodal disease appears to have a direct negative effect on prognosis. Because of the virtually universal advanced stage at presentation, the significance of Breslow depth is undetermined.

Treatment modalities for head and neck mucosal melanomas have yielded disappointing results. The general consensus is to attempt complete surgical excision of the primary site, followed by postoperative radiation therapy for microscopic or macroscopic residual disease or nodal involvement. Unfortunately, complete resection is frequently compromised by critical anatomic structures. Further, because melanoma has a high capacity for sublethal damage repair, these tumors are unresponsive to conventional radiation therapy. Newer methods, such as hypofractionation and neutron beam therapy, may play an adjunctive role in the future. Adjuvant chemotherapy using dacarbazine alone or in combination with other agents has not affected survival outcome. Prophylactic lymph node dissection also does not impact the outcome and is
reserved for patients with clinically evident nodal involvement. There are no case series reporting the use of a polyvalent melanoma vaccine in patients with mucosal melanomas.

**DIFFERENTIAL DIAGNOSIS OF PIGMENTED ORAL LESIONS**

Mucosal melanomas in the oral cavity can be confused with several benign lesions. Melanosis is an extremely common benign pigmentation of the attached gingiva, especially among African Americans. Based on its location, bilaterality, and symmetry, melanosis may be differentiated clinically from malignancy. Oral nevi are only present in 0.1% of the general population. Intramucosal nevi account for 55%, blue nevi for 36%, and junctional nevi for 3%. Because some investigators have suggested that repeated mechanical trauma may lead to malignant transformation, prophylactic excision is recommended. Patients with Peutz-Jeghers syndrome have pigmented lesions of the oral mucosa with intestinal polyposis, and a family history can typically be elucidated. Mucosal lentigines may also be found in patients with LAMB syndrome or LEOPARD syndrome. The characteristic systemic features of these syndromes allow for a clinical diagnosis. The clinical spectrum of Addison’s disease typically includes diffuse pigmentation of mucosal surfaces, in particular the buccal mucosa, gingiva, and tongue. Dental amalgam, a mercury-containing alloy for dental fillings, represents the most common source for oral pigmentation. Obtaining a dental history may aid the diagnosis. Melanotic macules are common benign pigmented lesions most commonly found on the vermilion border of the lip and gingival and buccal mucosa. Characterized histologically by a normal number of basal melanocytes with increased basal melanin deposition, these macules have no malignant potential. Macular pigmentation of Laugier and Hunziker is an uncommon disorder that may present with pigmented macules on the lips, oral cavity, fingernails, and toenails. Melanocytic nevi, or moles, are usually present at birth and can be found in any location on the body. They are usually benign but can rarely develop into melanoma. Angiomas and other vascular lesions may resemble amelanotic mucosal melanomas. Erythroplakia and oral squamous cell carcinoma most commonly occur on the lateral and ventral surfaces of the tongue and the floor of the mouth. Granular cell tumors occur more commonly in women and darkly pigmented races and have a predilection for the tongue.

In general, one should have a low threshold for performing a biopsy of a suggestive oral lesion. Any change in color or texture of the oral mucosa, especially fixed, solitary lesions, must be definitively explained. Though mucosal melanomas are rare, their overall poor prognosis warrants prudent investigation in the hope of an earlier diagnosis.

**LARYNX/PHARYNX**

Primary mucosal melanoma of the larynx and pharynx is exceedingly rare. Only 10 cases of laryngeal melanomas have been reported. Most laryngeal melanomas occur in the supraglottic region. The 5-year survival for patients with pharyngeal melanoma is only 13%. As the majority of patients present with disseminated disease, radical resections with nodal dissections have not improved the average survival time of 7.5 months.4,10

**ESOPHAGUS**

Approximately 200 cases of esophageal mucosal melanoma have been described. Dysphagia, weight loss, and hematemesis are common presenting symptoms. The origin of these tumors is thought to be related to the embryologic migration of melanocytes down the upper two thirds of the esophagus. As the majority of patients present with disseminated disease, radical resections with nodal dissections have not improved the average survival time of 7.5 months.16,20

**FEMALE GENITAL TRACT**

Primary mucosal melanomas of the female genital tract account for 18% of all mucosal melanomas and 3% of melanomas diagnosed in women.1 Usually affecting postmenopausal women between 60 and 70 years of age, approximately 500 cases have been reported to date. Vulvar melanomas, which are the second most common vulvar malignancy, greatly outnumber vaginal melanomas. Primary cervical and uterine melanomas are much more rare, with only 15 case reports in the literature. Presenting symptoms are similar to other tumors and include abnormal discharge, bleeding, pruritus, and the presence of a polypoid mass. Most of these lesions are black or gray-black in color, whereas only 6% are amelanotic. In an excellent review by Wechter et al, 15% of patients with vulvar melanoma reported a family history of cutaneous melanoma, and one patient was found to have a germline mutation in the melanocortin type 1 receptor.

Although case series have reported conflicting frequencies regarding exact anatomic sites, most vulvar melanomas appear to be located on the mucosa of the labia minora, followed by the labia majora and clitoris. Obscuring this distribution is the
observation that many of these lesions extend to the mucocutaneous border of the vagina, where melanocytes are most concentrated.16 Most vaginal melanomas arise in the lower vagina. Postulated to represent precursor cells, melanoblasts within the vaginal epithelium are present in approximately 3% of women.34 Although 70% of patients present with clinically localized disease, the overall prognosis is dismal.34,35 For vulvar melanomas, which had a mean Breslow depth of 2.8 mm in one series33 (Fig 1), the 5-year survival is 15% (with nodal metastases) to 54% (without nodal metastases).1,34-36 Even more grim, the 5-year survival for vaginal melanomas is less than 10%.37,38 Unfortunately, most series have shown that only a small minority of these melanomas have a tumor thickness less than 2 mm.13 The overall 5-year survival is only 6%, and the mean survival time is 25 months.39

Treatment strategies have yielded conflicting results. In a series presented by Memorial Sloan Kettering (New York, NY), the only patient to survive 5 years underwent radical abdominoperitoneal resection.42 However, other studies have yielded contradictory data, reporting favorable survival outcome from local excision alone.13 Before definitive conclusions can be made, large matched groups of patients comparing these modalities is needed. The role for adjuvant chemotherapy and radiotherapy is still debatable, but experience with cisplatin and interferon has not been promising.19 The benefit of lymphadenectomy is unknown, and prophylactic dissection has not increased survival.

**ANAL/RECTAL**

Primary mucosal melanomas of the anorectum account for 24% of all mucosal melanomas and less than 1% of malignant tumors of this site.1 Presenting symptoms include pain, rectal bleeding, and the presence of a large ulcerated, polypoid mass. Up to 30% of lesions may be amelanotic and, thus, unrecognized until an advanced mass develops.20 Most anorectal mucosal melanomas are believed to arise from the transitional zone of the anal canal, where melanocytes are present in the highest numbers.20

Approximately 80% of patients present with stage I disease (local disease), 10% with stage II (palpable nodes), and 10% with stage III (distant metastases).12 Unfortunately, most series have shown that only a small minority of these melanomas have a tumor thickness less than 2 mm.13 The overall 5-year survival is only 6%, and the mean survival time is 25 months.13

**URINARY TRACT**

Accounting for only 3% of all mucosal melanomas, melanomas of the urethral mucosa are an extremely rare entity. To date, 25 cases in male patients and 40 cases in female patients have been reported.44 Of all genitourinary sites, the penis is most commonly affected, but the vast majority of these cases are cutaneous.

Among male patients, the most common presenting symptoms include hematuria, dysuria, and the presence of a black lesion. The distal urethra is the most frequent site, followed by the meatus. However, melanomas involving more proximal locations along the urethra have been reported.16 For the more common distal lesions, treatment options include partial penectomy or urethrectomy with or withoutinguinal node dissection. Radical cystoprostatectomy with pelvic node dissection is advocated for proximal lesions. Unfortunately, no survival benefit has been obtained with either approach.16,20

Most female patients with primary urethral mucosal melanoma present with similar symptoms of
urinary frequency, dysuria, hematuria, and hesitancy. A black necrotic mass is frequently evident, which may resemble a urethral polyp, prolapse, or carbuncle. Various treatment strategies, including local excision, radiotherapy, cryosurgery, and anterior exenteration, have been disappointing. Of the 40 reported cases, only two survived for 5 years.

Only 3 cases of primary mucosal melanoma of the urinary bladder have been reported. The 3 patients presented with clinically localized disease but died of distant metastases less than 3 years after radical operation.

CONCLUSION

Primary mucosal melanomas are exceedingly rare and biologically aggressive malignancies. Unlike cutaneous melanomas, the occult locations in which mucosal melanomas occur preclude sun exposure as a predisposing risk factor. The relatively inaccessible and various locations in which these tumors arise also make consistent early screening difficult. Although the majority of patients present with clinically localized disease, the thickness and growth pattern of the primary tumors at diagnosis causes them to behave in a manner similar to thick, ulcerated nodular cutaneous melanomas. As such, most patients harbor micrometastatic disease at presentation and experience a course characterized by multiple local recurrences before the clinical development of distant disease and eventual death.

A multitude of adjuvant treatments, including various chemotherapy regimens and radiotherapy, have been unsuccessful in improving the dismal prognosis, and aggressive surgical resection remains the primary modality of choice. Regardless of the therapy used, the prognosis is grave. Approximately a third of patients have nodal involvement at presentation, and the overall 5-year survival is only 25%. Because of the rarity of this disease, there are no randomized clinical trials comparing the efficacy of various treatment modalities, which, in turn, hinders significant therapeutic advancements. As experience with the polyvalent melanoma vaccine continues to grow, perhaps it will prove beneficial in the treatment of this ominous disease.

As with all melanomas, early detection allows the best hope for cure. Therefore, we believe that educating our primary care, gynecology, otolaryngology, and dental colleagues concerning the presenting characteristics of this disease is of paramount importance. Practitioners in these fields must maintain a low threshold for performing biopsies of suggestive lesions in these occult anatomic locations.

REFERENCES