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Primary Mucosal Melanoma: Uncommonly Described Entity

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Abstract

Because of rarity and clinical challenges arising from different anatomic location, our understanding of optimal management of mucosal melanoma remains limited. The most common sites for primary mucosal melanoma are head and neck followed by anorectal, and vulvovaginal regions. Data are limited but improved understanding has led to change in management from more radical excision to conservative surgery with negative margins. We try to summarize available evidences for management this uncommonly described entity.

Keywords: Primary mucosal melanoma; Head and neck malignant melanoma; Anorectal malignant melanoma; Vulvovaginal malignant melanoma; Malignant melanoma of mucosa

Background

Malignant melanoma arises by malignant transformation of the normal melanocytes. Distribution of malignant melanoma includes cutaneous (91.2%), ocular (5.3%), mucosal (1.3%), and unknown primary site (2.2%) [1]. Because of rarity and clinical challenges arising from different anatomic location, our understanding for the optimal management of mucosal melanoma remains limited. Malignant melanoma can arise from the mucosal epithelium of respiratory, alimentary, and genitourinary tracts, all of which contain melanocytes. The most common sites for primary mucosal melanoma include head and neck followed by anorectal, and vulvovaginal regions (55, 24, and 18%, respectively). Rarer sites are urinary tract, gallbladder, and small intestine.

Although melanocytes share same embryologic origin, mucosal melanomas behave more aggressively and have many different characteristics compared to cutaneous melanomas. Mucosal melanomas are multifocal in 20% cases, while cutaneous melanomas are multifocal in 5% [2,3]. 40% of mucosal melanomas are amelanotic, while <10% of cutaneous melanomas [3]. In the following section we described this uncommonly presented entity. 5 year survival for mucosal melanoma is 25%, while that for cutaneous melanoma it is 80.8% [1].

Etiopathogenesis

Mucosal melanoma arises in non-sun exposed parts of the body and risk factors are not properly defined. Incidence increases with age and > 65% of patients are older than 60 years [4]. The difference between white and black population is less pronounced compared to cutaneous melanoma and mucosal melanomas are approximately twice higher among whites compared to blacks [5]. The higher incidence in females compared to males is because of the predominance of genital tract melanomas in females, which account for 56.5% of mucosal melanomas among them [5]. There is no difference in rates between genders for extragenital mucosal melanomas.

For oral mucosal melanoma cigarette smoking has been suggested as a risk factor [6]. Formaldehyde has been implicated in sinonasal mucosal melanoma [7]. Genetic studies identified increased prevalence of c-KIT mutation and lower expression BRAF and NRAS oncogene mutation in mucosal melanoma compared with cutaneous melanoma [8,9].

Diagnosis and Staging

Whole body skin examination and ophthalmic examination are important to exclude possibility of metastatic lesion from primary cutaneous or ocular melanoma and it is more important when diagnosing melanoma in sites, where it occurs uncommonly. To distinguish primary lesions from metastases Allen and Spitz identified junctional or in situ melanoma component with intact epithelium overlaying invasive melanoma as main diagnostic criteria for primary melanoma [10]. As diagnosis of mucosal melanomas is usually delayed and many lesions are ulcerated, this criterion is not easy to assess.

There is no uniformly accepted staging system for mucosal melanoma and varies depending on the primary site. A simplified staging system originally developed for head and neck melanoma can be applied to all cases of mucosal melanoma [11] (Table I).

Mucosal Melanoma of the Head and Neck

Presentation

Commonly occur in the nasal cavity (most commonly involving the turbinates and nasal wall) 55%, paranasal sinuses (most commonly maxillary and ethmoid sinuses) 15%, oral cavity (most commonly involving the hard palate and upper alveolus) 25% [12]. Uncommonly, it arises in pharynx, larynx, or esophagus [13-15]. Sinonasal mucosal melanomas present with nasal obstruction, epistaxis, or loss of smell [16]. Mucosal melanoma of the oral cavity presents as painless bleeding mass, an ulcerated area, mucosal discoloration, or ill-fitting dentures [17]. Regional lymph node involvement has been estimated to be present in 25% of oral cavity lesions and 6% sinonasal mucosal melanoma. Any suspicious lesion should undergo biopsy.

Staging

Workup includes clinical examination with endoscopic inspection for paranasal disease, CT and/or MRI of the primary site and CT and/or PET imaging to assess for lymph node involvement or distant metastases.

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The American Joint Committee on Cancer (AJCC) staging system for head and neck is used for this subset of disease and staging starts at stage III reflecting poor prognosis (Table II) [18].

Treatment

Wide local excision is the treatment of choice if R0 resection can be achieved. The surgical approach is same as for other common malignancies of that particular site. Local resection is followed by appropriate reconstruction. Therapeutic neck dissection is indicated in the presence of lymph node metastasis. Elective neck dissection in the presence of local disease only is not indicated. Sentinel node biopsy doesn't have an established role in the management of head and neck mucosal melanoma. Local recurrence occurs in 29-79% of cases even after despite aggressive surgical treatment [19-22].

Malignant melanoma are relatively radioresistant, but some studies have shown benefit [20,21].Temam et al found local control rates of 26% with surgery alone and 62% with postoperative radiation therapy in 69 patients with mucosal melanoma [22]. Several series have reported improvement in local recurrence with adjuvant RT but no improvement in survival [23]. Role of RT has not been established in trails. Postoperative RT is usually indicated for positive surgical margins or narrow surgical margins and recurrent disease. Some centres routinely use postoperative RT if palpable lymph nodes or extracapsular extension present. RT is not used if lesions are close to the eye or central nervous system. Primary RT is applied to patients who are not candidates for resection and when adequate resection margin is not possible.

Prognosis of the head and neck mucosal melanoma is usually poor with 5 year survival rate of 12-30%. 10% have distant metastasis at presentation. Local recurrence occurs in 40% of nasal cavity lesions, 25% of oral cavity lesions, and 32% of pharyngeal tumours. Overall local recurrence occurs in 55% -66% and nodal recurrence in 16%-35%. Most of the recurrences occur within first 3 years [24]. Nodal involvement reduces median survival time of 18 months and multiple local recurrences are the most common cause of treatment failure. As per Memorial Sloan-Kettering Cancer Centre study independent prognostic predictors include stage at presentation, tumor thickness >5mm, vascular invasion, and distant failure are the only independent predictors of outcome of mucosal melanoma of the head and neck [18]. In localized lymph node negative primary mucosal melanoma microstaging according to invasion into tissue compartments are found to be a significant and independent predictor of poor survival (Table III).

Anorectal Malignant Melanoma

Presentation

Anorectal mucosal melanoma accounts for < 3% of all malignant melanomas and 0.05% of colorectal malignancies and <1% of all anal canal cancers [25,26]. Though risk factors are not identified, indirect evidence implicates human immunodeficiency virus infection as a risk factor [25]. Majority arises from mucocutaneous junction, but it can also arise from anal verge skin or rectal and anal mucosa. Lesions at or proximal to the dentate line present with more advanced disease due to delay in diagnosis, while lesions distal to the dentate line more commonly recurs within lymph nodes, which may represent differences in nodal drainage. Irrespective of location, the long-term prognosis remains poor in all cases of anorectal melanoma [26].

Anorectal melanoma present with bleeding, mass, change in bowel habits and occasionally as an incidental finding on pathologic evaluation of hemorrhoidectomy or anal polyp specimen. Regional lymph nodes are involved in 60% of patients at presentation, and distant metastases are present in 30% [27,28].

Staging

Work-up include rectal examination, rectal ultrasound, and CT and/or PET imaging to assess for distant metastases. AJCC doesn't include any specified staging system for anorectal melanoma, but a simplified system as described can be applied (Table I).

Treatment

Primary goal is to perform a sphincter preserving negative resection margin (R0) excision. Ross et al reviewed 32 patients with melanoma treated with either APR or local resection and concluded that local recurrence was lower in the APR group compared to local excision (29% vs 58%), however there was no difference in overall survival (19.5 months vs 18.9 months) [27]. Retrospective studies also confirmed comparable overall survival between APR and local excision [29,30]. Resection status and tumor stage were significantly associated with prognosis, but the type of resection (abdominoperineal resection or local excision) was not significant. Patients with positive surgical margins suffer inferior survival. Abdominoperineal resection is reserved for patients with bulky local disease, involved anal sphincter, anal incompetence and for selected patients with local recurrence. Inguinal lymphadenectomy is performed for clinically apparent disease in inguinal lymph nodes. Adjuvant RT has not shown improvement in overall survival. 5-year survival for R0 resection is 19% and for cases with involved margins is 5%. Factors adversely affecting prognosis in localized disease include perineural invasion, tumor size and thickness, and the presence of amelanotic melanoma.

Vulvovaginal Melanoma

Presentation

It occurs primarily in vulva (95%) and vagina (3%). Urinary bladder, urethra, or cervix is rare sites. Although vulvar melanoma is <1% of all melanomas, they represent 10% of all malignant tumors of the vulva [31].Chronic inflammatory disease, viral infections, chemical irritants, and genetic factors have been implicated as risk factors [32]. Vulvovaginal melanoma commonly presents with pruritus, vaginal bleeding, a vaginal discharge, dyspareunia, or a mass.

Staging

Work-up includes clinical assessment with a pelvic examination, CT and/or MRI of the primary site and CT and/or PET imaging for distant metastasis. Vulvar melanoma is staged according to AJCC TNM classification for cutaneous melanoma [33]. No staging system has demonstrated prognostic accuracy for vaginal melanoma. Previously described simplified clinical staging system can be used for the purposes of standardization (Table II); however its prognostic utility is limited.

Treatment

Vulvar Melanoma: Wide local excision with negative margins is the adequate treatment and it has replaced the more radical surgeries. Melanomas <1 mm thick should be treated with at least 1 cm skin margins and for thicker melanomamargins can be extended up to 2 cm [34]. The excision should incorporate all layers of skin and subcutaneous tissues and extends upto muscular fascia below. Radical vulvectomy is reserved for large tumors and inguinal lymphadenectomy is done in the presence of nodal disease. Even after extensive surgery prognosis is poor in advanced cases.

Vaginal Melanoma: achieving wide local excision with negative margins can be difficult without pelvic exentration because of multifocality and anatomical constrain. Whenever possible, wide excision with negative margins is adequate. There may be a role of adjuvant RT in selected cases.

Patients with vulvar melanoma have 5-year survival rates of 24-

Table I: Staging System Mucosal Melanoma.

Stage I	Clinically localized disease
Stage II	Regional nodal involvement
Stage III	Distant metastatic involvement

Table II: AJCC Staging Primary Mucosal Malignant Melanoma-Head and Neck.

T3	Mucosal disease
T4a	Moderately advanced disease Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metástases
N1	Regional lymph node metastasespresent
M0	No distantmetastasis
M1	Distantmetastasispresent
Stage Grouping	
Stage III	T3, N0, M0
Stage IVA	T4a, N0, M0, T3–T4a, N1, M0
Stage IVB	T4b, Any N, M0
Stage IVC	Any T, Any N M1

Table III: Microstaging in Lymph Node Negative Primary Mucosal Malignant Melanoma.

Level 1	Melanoma in situ
Level 2	Invasion in the lamina propria only
Level 3	Invasion into deep tissue

77% and those with vaginal melanoma have 5-year survival rates of 5-25% [35].

Other rare sites have also been reported for primary mucosal melanoma. These include esophagus, stomach, small and large bowel and lungs. Surgery with negative margins remains adequate treatment, but prognosis is poor.

Role of Systemic Therapy

Data are limited on the role of adjuvant systemic therapy in mucosal melanoma. High dose interferon (HDI) alpha has been approved for treatment of stage III cutaneous melanoma. Only data on the efficacy of adjuvant systemic therapy for mucosal melanoma are from a Chinese phase II randomized trial of interferon versus chemotherapy. In this study both temozolomide based chemotherapy and HDI were effective and safe as adjuvant therapies for the resected mucosal melanoma as compared with observation alone. However, relapse free survival was better with temozolomide-based chemotherapy compared to HDI. These results should be replicated in a larger population study before general recommendation [36].

The anti-CTLA4 monoclonal antibody ipilimumab has been shown to significantly prolong survival in some patients with cutaneous melanoma, but there are no randomized trials in mucosal melanoma. Targeted treatment against BRAF and KIT mutation may provide addiction treatment options in some cases, but data are limited [37].

Conclusion

Wide local excision with negative margins is the standard of treatment for mucosa malignant melanoma and gives best chance of cure. Mucosal melanoma of head and neck are approached in the same way as head and neck squamous cell carcinoma. Wide local excision with negative margins has replaced more radical pelvic exentration for vulvvaginal melanoma and abdominoperineal resection for anorectal melanoma. Regional lymphadenectomy is indicated in presence of clinical evidence of disease in lymph nodes. There is role of sentinel lymph node biopsy in vulvar malignant melanoma. Adjuvant RT may offer improved local control in selected patients with margin positive or recurrent disease, but improved overall survival has not been demonstrated. KIT inhibitors may have potential role as targeted therapy in future. Distant metastases are managed in the same way as cutaneous malignant melanoma.

Conflict of interests

Authors have no conflict of interests to declare

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