Review Article

Capsula Eburnea

MALIGNANT MUCOSAL MELANOMA OF THE HEAD AND NECK: A RARE ENTITY

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SUMMARY

While mucosal-based melanomas of the head and neck region are uncommon lesions, when they do arise, they usually exhibit a highly aggressive clinical course. Experience with these tumors is, limited; as such, well worked out treatment protocols for the treatment of such lesions are in short supply. It appears as though mucosal melanomas (MuMs) develop more frequently in the nasal cavity and paranasal sinus region, and less often in the oral cavity. The incidence of nodal metastasis seems to be significantly lower in sinonasal MuMs than it is in MuMs of the oral cavity; this observation may be useful in evaluating whether a neck dissection is necessary to determine the location of the primary MuM.

Introduction

Mucosal melanoma (MuM) of the head and neck is an uncommon occurence [1–4]; of all types of melanomas originating in the head and neck area, mucosal-based tumors have the poorest prognosis [1]. In a National Cancer Database report which included 84,836 cases of cutaneous and non-cutaneous melanomas from the entire body, only 1.3% of the malignancies were showed to be mucosal in origin; most of these (55%) were located in the head and neck region [5]. The nose and paranasal sinuses are the most common sites of origin, followed by the oral cavity [6]. In general, MuMs are more common in men and occur most frequently between the 6th and 8th decades of life [7,8]; however, there are rare reports of MuMs developing even in early childhood. Melanoma may arise from pre-existing mucosal nevi, which occur in 0.1% of the population [6], but no risk factors associated with an increased likelihood of developing a Mum have been identified to date. From a clinical point of view, any MuM of the oral cavity needs to be differentiated through physical examination from pigmented mucosa or melanosis commonly seen in black patients. The survival of patients with MuMs of the head and neck is exceedingly poor; with the ideal treatment approach for these lesions remaining a controversial topic. Surgery, when feasible, currently representes the mainstay of treatment. The efficacy of postoperative radiation, as well as the optimal management strategy for the regional nodes, remains unclear-due, in large part, to the rarity of this disease and the lack of extensive prospective studies.

Sites of tumor origin

1. Nose and paranasal sinuses

MuMs occur most frequently in the nasal cavity, with the anterior portion of the nasal septum (33%) and the lateral nasal wall (28%) being the most common sites of tumor origin, followed by the middle and inferior turbinates (15%), and the nasal vestibule (10%)

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[9,10,12]. In the paranasal sinuses, the most common site of origin is the maxillary sinus, followed by the ethmoid (6%), frontal, and sphenoid sinuses (1%) [10,11]. Patients with sinonasal melanomas commonly present with epistaxis and nasal obstruction [9] as well as unilateral polyposis with or without pigmentation. While the majority of patients (75%) with melanomas of the nasal cavity is diagnosed with clinically localized disease [12], melanomas of the paranasal sinuses are usually diagnosed at a more advanced stage. Presumably, this explains why patients with nasal melanoma have a more favorable outcome compared to those with melanomas of the paranasal sinuses [13]. Concurrent nasal and paranasal lesions are infrequent. Nasal cavity MuMs are generally characterized by multicentric clinical presentation, and the exact extent of the disease may be very difficult to evaluate. In contrast with squamous cell carcinoma, MuMs of the nasal cavity and paranasal sinuses are less likely to metastasizes to retropharyngeal and submandibular nodes than to lungs and brain [14]. Lymph node metastases are found at the time of initial presentation in only 5.7% of the cases reported [2].

2. Oral cavity

Approximately 40% of all MuMs of the head and neck ragion originate in the oral cavity, with the majority (70%) occurring in the mucosa of the upper alveolus and the hard palate [9]. A pigmented lesion, sometimes found casually during an oral examination, is the presenting symptom in many patients. Other symptoms include illfitting dentures and mucosal ulceration [9]. The lesion may be flat or may be a nodular polypoid mass. Occasionally, it is non-pigmented. Most melanomas of the oral cavity are diagnosed at an early stage, but in contrast with sinonasal melanomas, 25% of patients with oral cavity melanomas presented with lymph node metastases as per a recent report from the Memorial Sloan-Kettering Cancer Center [9]. In a study by Chaudhry and colleagues [15], more than 50% of 93 patients with melanoma of the oral cavity had clinical evidence of nodal involvement, and 20% demonstrated clinical or radiographic evidence of generalized dissemination. The likelihood of cervical lymph node metastasis increases when the tumor thickness is more than 5 mm [16].

3. Other sites

The most common of these rarer sites of tumor origin are the nasopharynx and the larynx. The presenting symptoms of nasopharyngeal melanomas are similar to those of sinonasal melanomas, i.e., epistaxis, nasal obstruction, and Eustachian tube obstruction with serous otitis. Laryngeal melanomas occur almost exclusively in patients of Caucasian origin and may present with hoarseness, dysphagia, soreness, sensation of a lump in the throat, or a neck mass [7]. The majority of laryngeal melanomas occur in the supraglottic larynx and their diagnosis is usually delayed. Rarely, MuMs caused by iatrogenic deposit of dental amalgam may be found in the pharyngeal wall and in the mouth. Most frequently, these are located in the gingival and alveolar mucosae and should be recognized as distinct entities for which no further action is required.

Tumor staging

There is no universally accepted system within the TNM Staging System of the American Joint Committee on Cancer (AJCC) or the Union Internationale Contre Le Cancer (UICC) for the staging of MuM of the head and neck, with the exception of melanomas of the conjunctiva. A simplistic system used by most clinicians recognizes three stages: Stage I for localized disease, Stage II where nodal metastases are present, and Stage III where distant metastases are present. While this system is straight forward, it does not take into account the extent of the primary tumor and places too much emphasis on lymph node metastases, which are uncommon in MuM and may not have the same impact on prognosis as they do in cutaneous melanoma [9]. Alternatively, MuMs can be staged according to the AJCC staging criteria for the site of origin (tongue, maxillary sinus, and so forth), which places proper emphasis on the extent of the primary tumor as a predictor of outcome. In a retrospective study of 28 patients with MuM of the head and neck that were staged in this manner, Loree et al. [17] found that the five-year survival rate in patients with T1 and T2 tumors was 32% and in patients with T3 and T4 tumors, 0% (P 1/4 0.05). Even though the application of PET scan in the diagnosis of MuMs remains in its infancy, this approach appears to be quite useful in screening for distant metastases. Routely performing a PET scan may not be essential; however, in patients requiring radical surgical resection, especially

orbital exenteration or craniofacial resection, one may consider a PET scan to rule out obvious distant metastases.

1. Lymphatic metastases

Overall, in 18.7% of patients with malignant mucosal melanoma of the head and neck, lymphatic metastases were evident on presentation, whereas in 16.4% of patients (90 of 550 evaluable cases), these developed after treatment. The total number of patients with lymphatic metastases before and after treatment was 33.4% (240 of 610 evaluable cases). The five-year survival rate of patients with lymphatic metastases was 21.4% (14 of 66 evaluable cases) versus 30% for patients without lymphatic metastases (42 of 141 evaluable cases) [18-41]. Shah and colleagues concluded that lymphatic metastases do not affect survival rate of patients with this type of malignancy. In their study, the five-year survival rate was 27% for lymph node negative patients and 19% for lymph node positive patients. In contrast, cutaneous melanoma patients with positive lymph nodes had a 39% survival rate, compared to an 80% survival rate for patients without lymphatic metastases at five years [25]. It is likely that the severity of this disease depending on the characteristics to the primary lesion is such that lymphatic metastases do not alter its course.

2. Local treatment failure

Treatment failure at the primary site is a significant problem with this malignancy. Many authors have commented on the importance of this issue. The propensity of malignant mucosal melanoma to fail at the primary site has dire consequences for the survival of the patient [31]. Stern and Guillamondegui obseved that 9 out of 10 surviving patients did not relapse [30]. In another article, Andersen and colleagues noted a discrepancy between recurrence free and crude survival at five years [27]. Out of 484 patients in 14 series in which specific information about local control was provided, 258 patients (53.3%) failed locally. Pooled data from nine studies (on 196 patients) provided information about the salvage rate in local failure. For 49 of these 196 patients, salvage therapy was successful after two or more attempts to control the disease surgically, for a mean salvage rate of 25% and a range of 0-75% [22,24,25,27,29-34,36,37,39].

3. Distant metastases

Pooled data from 11 series showed the average distant metastatic rate at presentation to be 10% (44 of 437 patients). In 12 studies, data were available for metastases after treatment; with average being 51.5% (171 of 332 patients). Furthermore, in four series, information was available regarding local failure and distant metastasis. 90 of 123 patients (73.1%), who failed their initial treatment and had local recurrence developed distant metastases. These data showed local failure to be a harbinger of distant metastasis [20-22,24,-27,29-34,36,37].

4. Survival

In 21 series of malignant mucosal melanoma (962 patients), mean survival rate at three years was 39.2%; the range was 7-65% (93 of 237 patients). At five years, mean survival rate was 17.1%, with a range of 0-48% (161 of 937 patients). At 10 years, mean survival rate was 4.8%, with a range of 0.5-26% (22 of 453 patients). In three studies including data from a follow-up period of more than 10 years, the survival rate was 1.2% (1 of 82 patients) [19-22,24,26,27,29-33,36—41]. Eneroth and Lundberg reported this single survivor at 20 years in their series of 41 patients[39]. Survival rates were correlated with the originating site of the tumor. Patients with nasal melanoma fared better than those with either oral cavity or pharyngeal melanoma. In pooled data from five studies (203 patients), five-year survival rate for patients with nasal melanoma was 30.9% (30 of 97); for those with sinus melanoma, it was 0% (0 of 27 patients). For patients with oral cavity melanoma, five-year survival rate was 12.3% (8 of 65 patients); while for those with pharyngeal melanoma, it was 13.3% (2 of 15 patients) [20,25,29,31,33].

Treatment of the primary melanoma

The key factor in determining outcome in patients with MuMs is the extent of the primary tumor (i.e., formal clinical/pathologic staging) [9,17]. Unfortunately, many of these patients are diagnosed at a late stage; thus their chance for survival is lower than that of patients with cutaneous melanoma, the majority of whom are currently diagnosed at an early stage of the disease. In addition to clinical stage, tumor thickness greater than 5 mm, vascular invasion observed by light microscopy, and the develop-ment of distant metastases were found to be independent predictors of outcome in a cohort of 59 patients with MuM

of the head and neck in a study by Patel and colleagues [9].

1. Surgery

Surgery currently offers the best prospect for cure and local control of malignant mucosal melanoma of the head and neck. Radiation therapy and chemotherapy have been used alone or in combination with surgery. Treatment results with these approaches have been consistently disappointing. Although many patients eventually die of this disease, some can survive for prolonged periods of time with local and even metastatic disease in a relatively indolent state [33]. The aim of local surgical intervention in these patients is to decrease the tumor burden in order to ease symptoms. Lee et al., in their study of 35 patients with MuMs of the head and neck region, compared the most common treatment modalities [32]. Local disease control was achieved in six out of 15 patients treated with radical surgery, versus one out of 11 patients treated with local resection and zero out of eight patients treated with radio or chemotherapy, or a combination of the two. Similarly, another study with 42 patients showed that patients treated with surgery have a significantly better outcome [30]. In the series of Andersen and colleagues, all survivors were treated with surgery. Six patients treated with single modality radiation had either no response (four patients) or a short-lived response (two patients). Further six patients treated with chemotherapy also had no response. None of the six patients treated with adjuvant chemotherapy had a complete response; all progressed rapidly to death due to uncontrollable disease [27]. In another European study by Guzzo and colleagues, out of five patients treated with chemotherapy, immunotherapy, and radiation became disease free; all progressed to death rapidly. However, 42 of 43 patients treated with surgery achieved a disease free status for variable periods of time, although only five of these patients did not relapse and the four-year survival rate in this study was a dismal 7% for those who were treated with surgery [38]. Of the 21 patients of Panje and Moran, the only three survivors were treated with surgery alone, while three patients treated with chemotherapy died without response to the therapy [31]. At the Memorial Sloan-Kettering Cancer Center, radiation was used as a stand-alone palliative measure [25]. Harrison did not use radiation to treat any

of his 40 patients and reported a 27.5% five-year survival rate [22]. Freedman et al. found no advantage at three years and five years (60.7% and 34.2% survival rates, respectively) for patients treated with combined surgery and radiation versus those treated with surgery alone (75% and 61.3%, respectively). Of the 18 patients who were treated with radiation alone, none survived for five years [33]. In contrast, Holdcroft and Gallagher, in their review of the AFIP series, showed that patients treated with surgery alone survived an average of 31 months, versus 43 months for those treated with surgery and radiation [21]. The finding of Conley support extended local resection over local resection alone. It is noteworthy that he reported a case of recovery with radiation treatment only, as well as a case with distant metastases and spontaneous regression [23,24]. More recent studies have reported a better five-year survival rate, and attributed this to advancements in surgical techniques and to intraoperative and postoperative patient care that allow for more radical procedures [32].

2. Radiation therapy

Several authors have reported on their experience using radiation therapy as the primary treatment modality. Steward's research group noted only a transient response in three out of 15 patients treated with radium implants or external beam radiation [42]. In 1991, Gilligan and Slevin reported a crude survival of 17.9% in 28 cases of sinonasal melanomas. Local control was achieved in 61% of their patients [35]. However, their article lacked immuno-histochemical evidence; in addition, 20 cases were excluded due to advanced local or metastatic disease. In the four most recent series in which radiation was used as the primary treatment modality, local control rates ranged from 44% to 61% [43]. The authors of these studies encouraged broader use of hypofractionation in the treatment of this disease. Ample clinical and basic scientific evidence support the theory that melanoma has a high sublethal damage repair capacity, making it resistant to conventional fractionation schemes [44,45]. More recently, cutaneous malignant melanoma has been treated with neutron beam radiotherapy with good results in local disease control in patients with Stage III melanoma [46,47]. Although it remains to be seen whether these results can be extrapolated to the mucosal counterpart of

this disease these finding can certainly provide clues for newer treatment approaches.

3. Chemotherapy

The results of chemotherapy treatment in mucosal melanoma of the head and neck are difficult to evaluate objectively. There have been no reports on chemotherapy as the only treatment approach. In several studies, chemotherapy has been utilized in a noncontrolled fashion as an adjuvant therapy, with consistently disappointing results. At best, the occasional patient receiving chemotherapy has shown a transient, short-lived response. A variety of agents have been used alone and in combination with each other. Andersen et al. treated six patients with adjuvant chemotherapy, with no observed response; similarly, Guzzo and colleagues treated five patients with no response; finally, three patients treated with chemotherapy also showed no response to the treatment in a study by Panje and Moran [27,31,38,48].

4. Interferon Alpha Therapy

Intereferons (IFNs) are a family of glycoproteins with a broad spectrum of action including antiviral, immunomodulatory and antiproliferative effects, as well as prodifferentiating and antiangiogenic ones [49-53]. IFN alpha possesses antitumoral qualities due to a combination of its direct activities and indirect immune-mediated effects [51]. IFN alpha is associated with significant side effects that have an important impact on the patient's quality of life and the physician's choice of adjuvant postsurgical treatment [54,55]. Several trials have examined the role of IFN alpha in the adjuvant treatment of melanoma patients at a hight risk of relapse, including patients with deep primary lesions and those with lymph node involvement.

5. Immunotherapy

Immunotherapy has been used in the form of the Bacillus Calmette-Guérin vaccine for treatment of mucosal melanoma, but only as adjunctive treatment in isolated cases. As such, its effectiveness is difficult to evaluate. More recently, improved survival rates have been reported in patients with metastatic cutaneous melanoma treated with a polyvalent melanoma vaccine, compared with a historic group of patients a similar stage disease [49,50]. Others have reported mixed results with such treatments. There have been no reports of similar studies with mucosal melanoma patients.

6. Systemic therapy

MuM of the head and neck is a highly malignant tumor [12]. Although local and regional control is possible, many patients succumb to distant metastases. Therefore, it seems reasonable to add appropriate systemic therapy to the treatment protocol of patients with advanced MuMs once the risk/benefit ratio has been evaluated. Due to the scarcity of clinical trials using systemic immunotherapy or chemotherapy in patients with MuMs, treatment regimens should be similar to those used in the clinical management of cutaneous melanoma. Chemotherapy is mainly used in the treatment of disseminated disease and for palliative care. However, drugs such as taxols currently show promise for adjuvant use in the future [18]. MuMs of the head and neck continue to pose a parti-cularly difficult treatment challenge for clinicians, as the overall outcome and long-term survival rate of affected patients are very poor. Due to the rarity of this neoplasm, individual experience is quite limited and as a consequence most of the information accrued regarding MuMs derives from collective retrospective reports in the peer-reviewed literature. MuM continues to be a disease with unpredictable behavior. Decisions regarding a radical surgical approach need to be critically contemplated in view of the rate of local failure and functional outcome; however, the approach with the best prospect for long-term survival remains surgical resection, with or without radiotherapy. The presence of regional disease is uncommon and may not influence the therapeutic outcome as significantly as in cutaneous melanomas. Distant metastasis, either at presentation or developing during treatment, represents an ominous finding not compatible with prolonged survival. Alternative therapy directed at systemic disease remains an important objective for future investigations. Because of the rarity of the disease, random prospective trials may be difficult to establish; however, such trials may be possible if several institutions with sizable regional referral bases of melanoma patients are able to collaborate and pool their collective experiences.

Conclusions

Mucosal melanoma of the head and neck is a highly malignant tumor. Few patients survive for prolonged periods of time. Some claim that curing of this disease is not pos-

sible; indeed, long term survival statistics seem to substantiate this claim. Among the categories of mucosal melanomas of the head and neck region, the ones originating in the sinuses are the most lethal, followed by tumors originating in the oral, pharyngeal and nasal cavities. Local failure is a significant problem for most treated patients, and evaluating the adequacy of excision margins in this anatomic area. The question of whether any affiliation exists between the adequacy of resection and the incidence of diffuse melanomatosis has not yet been elucidated. Most patients with local treatment failure can be successfully treated with curative intent if they do not present concurrent distant metastases. In more recent studies, in which surgical treatment has been aggressive and prompt due to early detection, salvage rates have been acceptable. In addition, patients with local failure can be treated multiple times, resulting in prolongation of disease free survival.

It is unclear whether modern surgical techniques, with advances in patient care that hallow to perform more radical surgery, have impacted the survival or local control rates in these patients. The problem is compounded by not only the nonuniform standards of distinguishing between radical surgery and local resection in scientific articles, but also by the small number of patients affected by this disease. Due to the rarity of this condition, many studies include data on patients acquired over several decades, during which time surgical approach may have changed. The risk of distant metastases exists in patients with local failure, especially when repeated. Distant metastases should be thoroughly investigated with state-of-the-art radiographic methods. Whole body positron emission tomography approach may emerge as a novel modality of choice for the screening of metastatic melanoma. Regional metastases in this disease do not affect survival. This has been demonstrated by several authors in extensive studies and contrasts sharply with the behavior of cutaneous melanoma of the head and neck. However, this conclusion may have been reached due to the very poor overall survival rates in patients with MuMs of the head and neck region. Distant metastases continue to be synonymous with a rapid clinical deterioration and short survival period after their detection. No available conventional approach has resulted in improved survival in this situation. In few select cases, surgical or radiotherapeutic intervention for local symptomatic control may be indicated. Scattered reports in the literature indicate that occasional longer survival with stable distant metastases is possible. Clinical features of distant metastatic disease in mucosal melanoma of the head and neck should be further investigated for obtaining newer therapies. Chemotherapy should not be administered unless under a protocol study. The role of Immunotherapy in the management of MuMs should be further addressed in future studies. Radiation therapy may play an increasing role in the treatment of MuMs in the future. As the radiobiology of this malignancy is being elucidated, newer methods, such as hypofractionation, neutron beam therapy, and implants, may be employed in combined approach treatment protocols. Undoubtedly, obtaining accurate data on the efficacy of these treatments is imperative for reaching a better understanding of the optimal treatment course to adopt in the treatment of MuMs of the head and neck region.

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