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Prognostic factors in head and neck mucosal malignant melanoma

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ABSTRACT

Objective: Primary mucosal malignant melanoma of the head and neck (HN-PMMM) is an aggressive and uncommon neoplasm. Herein, we present a series of 33 patients and the results of treatment, and aimed to determine prognostic factors in HN-PMMM.
Methods: Patients who were diagnosed as having HN-PMMM in our reference hospital, between 2005 and 2014 were evaluated. Thirty-three of these patients who had follow-up data were included. Surgical margin status was extracted from the original pathology reports. Archived materials were retrieved for the histopathologic findings: ulceration, necrosis, lymphovascular invasion, perineural invasion, pigmentation, and presence of an in situ component. Mitotic activity was evaluated using phosphohistone H3 (PHH3) immunohistochemical staining.
Results: We found an association of PHH3 mitotic activity with overall survival in a univariate analysis and to our knowledge, this is the first report among the available case series of HN-PMMM to evaluate mitotic activity using immunohistochemical staining. We also investigated the relationship between multicentricity and locoregional recurrence, which the authors believe is also a first.
Conclusion: PHH3 mitotic activity can be used a prognostic factor for head and neck mucosal malignant melanoma.

1. Introduction

Melanoma is a malignant tumor of melanocytes. Although the lineage of this tumor is known to be the same as cutaneous melanoma, primary mucosal malignant melanoma (PMMM) is a distinct entity with completely different clinical, embryologic, genetic, and prognostic features [1]. Primary mucosal malignant melanomas of the head and neck (HN-PMMM) are rare and aggressive neoplasms that comprise 0.7–3.8% of all head and neck tumors. The upper aero-digestive tract, especially sinonasal area and oral cavity, is the most common location for HN-PMMM [2,3].

Designation of prognostic factors and staging are problematic in HN-PMMM. Well known histopathologic prognosticators of cutaneous melanomas, such as Breslow thickness and Clark index, are of no value for mucosal melanomas [4,5]. The impact of mitotic activity on prognosis of HN-PMMM is controversial [6–9]. It is well-known that there are some challenges in determination of mitotic count such as distinguishing mitotic figures from apoptotic cells, suboptimal sections due to technical artefacts, failure of identification of

Abbreviations: PMMM, primary mucosal malignant melanoma; HNPMMM, primary mucosal malignant melanoma of the head and neck; H3, PHH3phospho-histone; MI, mitotic index; AJCC, American Joint Committee on Cancer; OSR, overall-survival rate; SEER, Surveillance, Epidemiology, and End Results.

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hot spots on hematoxylin and eosin stains and interobserver variability. Aforementioned challenges could be overcome by the use of phospho-histone H3 (PHH3) antibody [1,10–12]. Prognostic value of the mitotic count by PHH3 has been shown in cutaneous melanoma but has not been studied in HN-PMMM [13].

There is a need for better understanding of the clinical and pathologic factors that impact on prognosis. Rarity and imponderable course of the disease make it difficult to get enough data to determine predictive factors in terms of prognosis. The determination of prognostic and predictive factors is of essential importance.

In the current study, we aimed to investigate various clinical and pathologic parameters that may have an impact on the prognosis of 33 HN-PMMM patients. We also evaluated mitotic index (MI) by the aid of PHH3 antibody and investigated whether the use of an immunhistochemical marker could reveal the possible prognostic impact of MI in HN-PMMM.

2. Materials and methods

The study was approved by the local ethics committee of Istanbul University, Faculty of Medicine. Patients who were diagnosed as HN-PMMM between 2005 and 2014 were searched for in the computer system of Pathology Department of Istanbul University, Istanbul Faculty of Medicine. The search yielded 46 patients. Thirteen patients without adequate follow-up data were excluded. Adequate follow-up examination was defined as follows: post-treatment follow-up examinations once a month in the first year. In the second post-treatment year frequency of follow-up examinations altered to once in three months. Patients were followed once in six months in the third post-treatment year and after third year follow-up examinations performed annually. Clinical and endoscopic evaluation performed in every visit besides radiologic evaluation (MRI) in the sixth month post-treatment. Total body positron-emission tomography/computed tomography (PET/CT) once a year for evaluation of distant metastasis or locoregional recurrence.

2.1. Pathologic review

Macroscopic data, which included surgical margin status, were extracted from the original pathology reports. Archived hematoxylin and eosin slides were retrieved for the histopathologic findings: ulceration, necrosis, lymphovascular invasion, perineural invasion, and presence of an in situ component and pigmentation. Mitotic activity was evaluated using PHH3 immunohistochemical staining. Surgery specimens for surgical treatment group and pretreatment biopsies for primary radiotherapy group were used for the aforementioned analysis.

2.2. Immunohistochemical examination

The immunohistochemical examination was undertaken using 3 micron-thick sections of formalin-fixed, paraffin-embedded tissues. PHH3 immunohistochemistry (polyclonal antibody, 1/400; Cell Marque, Rocklin CA; antigen retrieval EDTA Ph8.0) was performed using a Ventana Benchmark XT system (Arizona, USA). Signal was visualized with a 3.3′ diaminobenzidine detection kit (Fig. 1). Tonsil tissue was used as the positive control. For each case, the whole slide was scanned under 100× magnification for the designation of hot spots. Mitotic cells highlighted by PHH3 immunohistochemistry were counted in the hot spots under 400× magnification and expressed as the number of mitotic cells per mm^2.

2.3. Statistical analysis

The primary end point of our study was overall survival (OS). OS was defined as the time from initial treatment to death of any cause. OS was calculated using the Kaplan–Meier method and univariate analyses of multicentricity, and for vascular invasion, perineural invasion, necrosis, and PHH3-MI. Between group comparisons were performed using Cox regression analysis with a backward Cox regression model (vascular invasion, perineural invasion, necrosis, multicentricity and PHH3-MI). A p value of 0.05 or less was considered significant. Statistical analyses were performed using SPSS version 21 (IBM Corp, Armonk, NY).

3. Results

3.1. Patient demographics &clinical properties

In this study, we investigated 33 patients with HN-PMMM. The mean age of patients in the study was 62 years (range, 28–87 years; SD 13.8). There were 14 men and 19 women in the cohort, with a slight female predominance (57%) (Table 1). Ten (30%) patients presented with lesions in the oral cavity (5 hard palate, 3 gingiva, 2 mucosa of lip), 21 (64%) patients presented

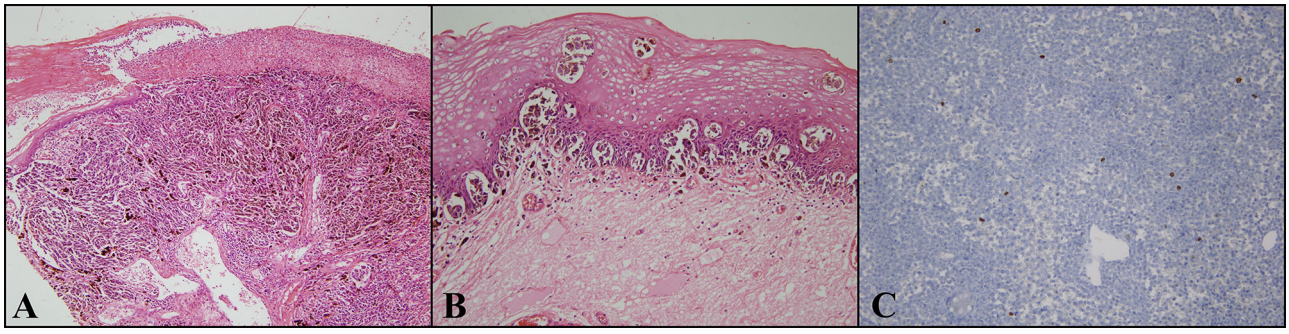

Fig. 1. (A) Malignant melanoma comprised of spindle cells with heavy pigmentation, invading surface epithelium (left) and inducing ulceration (right) (HE × 100). (B) In situ component (HE × 200). (C) Mitotic figures highlighted by PHH3 immunohistochemistry (PHH3 × 200).

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