



Expression of S100, HMB45 and Melan A in Oral Mucosal Melanoma

**Nikhil I. Malgaonkar^{1*}, Noura Turki Alotaibi¹, Noura Mohammed Alharbi¹
and Reema Faleh Alsawat¹**

¹*Department of Oral Medicine and Diagnostic Sciences, AL Farabi College of Dentistry and Nursing, Ishbilya, Riyadh, KSA.*

Authors' contributions

This work was carried out in collaboration among all authors. Author NIM designed the study and did the statistical analysis. Author NTA did the data retrieval and literature review. Author NMA wrote the first draft of the manuscript. Author RFA did the final manuscript preparation, bibliography and the proof reading. All authors read and approved the final manuscript.

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ABSTRACT

Background: Malignant melanomas of the oral cavity are rare tumours. The diagnosis of mucosal melanoma can be difficult especially when it presents itself in its amelanotic form.

Methodology: An electronic search was carried out on Pubmed and Medline database to find studies addressing this question published between Jan 2001 and April 2020. Multiple studies are done to determine the staining and positivity of the above mentioned three markers were found. A total of 4 studies were finally selected for this review which tried to determine the efficiency of these three markers in the diagnosis of oral mucosal melanomas.

Results: The patient's data that stained positive S100, HMB45 and Melan A from 4 studies were selected.

Conclusion: S100 continues to remain the most sensitive marker for melanoma with its promising ability in diagnosing the desmoplastic variant. The lack of specificity is still a drawback of S100.

Keywords: S100; HMB45; Melan A; oral mucosal melanoma.

*Corresponding author: E-mail: nikhil.malgaonkar@gmail.com

1. INTRODUCTION

Malignant melanomas of the oral cavity are rare (0.2-8%) tumours. The diagnosis of mucosal melanoma can be difficult especially when it presents itself in its amelanotic form [1]. Such malignancies mimic various other soft tissue tumours leading to further confusion rendering regular light microscopy inadequate for diagnosis. The immunohistochemical analysis becomes extremely necessary in such cases to arrive at a definitive diagnosis. HMB45, S100 and Melan A are the most frequently used markers directed against melanocytic differentiation antigens that can help in the diagnosis of melanomas [2]. Although these markers have been used frequently and extensively for the diagnosis of cutaneous melanomas, the use of these markers in melanomas of oral mucosa is relatively new and infrequent. Oral mucosal melanomas differ from cutaneous melanomas with respect to incidence, clinical features and growth patterns [3-10]. Hence the study of these markers in melanomas of the oral cavity deserve special attention. The present systematic review is aimed at compiling the data and results of studies that have analysed and determined the extent and magnitude of positivity of S100, HMB45 and Melan A in oral melanomas and to determine the overall efficacy of these three immunohistochemical markers in the diagnosis oral mucosal melanomas [11,12-17].

2. MATERIALS AND METHODS

An electronic search was carried out on Pubmed and Medline database to find studies addressing this question published between Jan 2001 and April 2020. Multiple studies are done to determine the staining and positivity of the above mentioned three markers were found. Certain criteria were followed to further select studies and filter out studies that did not fit the inclusion criteria. A total of 4 studies were finally selected for this review which tried to determine the

efficiency of these three markers in the diagnosis of oral mucosal melanomas.

The data from all 4 studies were combined. The total number of cases from each study were added and the total cases that stained positive for each marker were added and the mean percentage was calculated with the help of simple arithmetic calculations. Since the studies included did not include a control group, a comparison of each marker with the control group was not possible. Meta-analysis with the present data was not possible since the studies included did not statistically compare the expression of the three markers among each other.

3. RESULTS

The patient's data that stained positive S100, HMB45 and Melan A from 4 studies were selected. Since the authors of these studies did not use a statistical test to compare the markers in pairs and since these three markers are known to show positivity with melanomas, the meta-analysis of this data in paired form could not be done.

4. DISCUSSION

Mucosal melanomas differ from cutaneous melanomas in various aspects. Risk factors, as well as prognostic factors for oral melanomas, differ from those for cutaneous ones. Results of cutaneous melanomas cannot be blindly applied to oral melanomas as they deserve special attention and separate mention [1]. Human melanocytes may be heterogenous /site-specific because the melanocytes are also regulated and maintained by site-specific HOX genes. The melanocytes could be affected by local factors like secretions of the surrounding cells [4]. The significance of immunohistochemistry in the diagnosis of oral mucosal melanomas, especially in the case of an amelanotic variant as well as a desmoplastic variant, cannot be overemphasized.

Table 1. The results of the selected 4 studies with percentages

Author	S100	HMB45	Melan A
Molly Smith et al	18/20	21/22	14/14
Bruno Andrade et al	22/22	22/22	19/22
Chuan Hang Yu et al	15/17	16/17	12/17
Manju Prasad et al	34/35	25/35	30/35

Based on the results of selected studies, it was evident that S100 is the marker with the highest expression among all three markers. The interpretation of these results is not as simple and straightforward as it may seem because of the wide range of cells that stain positively with S100, to begin with. Also, the results of the included studies and the results of our study need to be discussed in the light of histopathological variations of oral mucosal melanomas and the specificity and sensitivity of each marker with respect to staining melanocytes.

S100 has been proved to be the most sensitive marker based on our cumulative findings but out of the 4 studies included for this review, S100 was the most sensitive marker in only two studies when seen individually. S100B variety of S100 protein is highly expressed in melanomas and high levels of expression of S100 in cutaneous melanomas corresponds to poor prognosis and lower expression corresponds to better prognosis [5]. Among the studies included in this review, the study done by Manju Prasad et al found positivity with S100 for 97 % of their melanomas. A majority of their cases showed strong staining with S100. Although being highly sensitive, S100 does stain other cells like histiocytes, myoepithelial cells and other cells of neural crest origin¹. A study done by Molly Smith et al found S100 to be the least sensitive marker among all three markers [6]. Bruno Augusto Andrade et al in their research found all cases positively stained with S100. The significant finding of this study was that S100 staining was seen in the cytoplasm as well as in the nuclear region unlike the other 2 markers [7]. Similarly, Chuan Hang Yu found S100 positivity with only 88% of their cases and the HMB45 was found to be more sensitive (with 94% cases) than S100 [2]. A striking finding from the study by Manju et al was their study sample contained five desmoplastic variants of oral melanomas which stained positively only with S100. HMB45 staining was not observed with any of the desmoplastic variants while only one out of five was stained with Melan A [1]. A similar finding was observed by Seung Ki Min who treated 12 oral melanoma tissue samples with S100 and HMB45 and found that S100 was positive with all 12 cases while HMB45 failed to stain 7 out of 12 cases [8]. The role of S100 in the diagnosis of this rare variant is extremely encouraging where HMB45 fails [9]. The low specificity of S100 can be compensated by not using S100 alone but using it in combination with other melanoma

markers. Melan A is also known as melanoma antigen is a melanocyte differentiation antigen found in healthy melanocytes, melanoma cells and retinal pigmented epithelium [9]. Melan A has been shown to stain adrenal cortices, Leydig and theca cells from the ovary and the neoplasms originating from these cells. A study done by Molly Smith et al found Melan A to be the most sensitive of all the markers used in their study. Most of the cases in their study presented with epithelioid and spindle cell pattern which suggests an encouraging role of Melan A in the diagnosis of such variants unlike the desmoplastic variant [6]. The inspiring role of Melan A in differentiating spindle-shaped presentation of melanoma from other spindle cell entities and its role in the detection of microscopic metastasis in sentinel lymph nodes has been accentuated by the study by Manju Prasad et al. [1]. A study done by Bruno Augusto Andrade consisted of 22 cases of oral melanomas, the majority of which presented with epithelioid and spindle-shaped patterns with no desmoplastic variant, but Melan A turned out to be the least sensitive of the three markers. Oral melanomas being rare, it is too early and difficult to comment with any conviction regarding the role of Melan A in the diagnosis of each of the individual histologic variants [7].

HMB45 recognizes a glycoprotein known as Pmel and the staining appears to be proportional to pigment content within the lesion and less or no pigment in the lesion leading to no staining [9]. Although the sensitivity of this marker is low, the very fact that this antibody does not appear to react with any nonmelanocytic tissues suggests a good specificity for this marker [10]. Among the studies included in our review, a study done by Chuan-Hang Yu suggested HMB45 to be a less sensitive marker than S100 but the staining intensity of HMB45 to be higher than that of S100 and Melan A [2,8-13]. The role of S100 in diagnosing metastatic melanomas was suggested to be more significant than that of HMB45 and Melan A [2]. The expression of HMB45 in spindle cell and round cell oral melanomas has not been explored enough to arrive at a concrete conclusion but a study done by D Gazit et al found S100 to be a more sensitive marker in such lesions compared to HMB45 [11,18-23]. Since the staining intensity of this marker directly correlates with Pmel, the diagnostic value of HMB45 in amelanotic melanomas also needs to be explored [12,24,25].

5. CONCLUSION

Oral melanomas are extremely rare entities and form 0.2-0.8% of the total melanomas. The extreme rarity of this lesion makes it infeasible to conduct frequent immunohistochemical studies and with a larger sample size. The present review with the help of limited available studies has tried to throw light on the efficiency and diagnostic values of S100, HMB45 and Melan A in oral melanomas, markers which are frequently used in cutaneous melanomas. S100 continues to remain the most sensitive marker for melanoma with its promising ability in diagnosing the desmoplastic variant. The lack of specificity is still a drawback of S100. Melan A and HMB45 being more specific, can be of significance but their role in the diagnosis of spindle cell and desmoplastic variants need to be explored further. Regarding the role of these markers as well as new emerging markers need more studies in future.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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