Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 505–509

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Podoplanin expression in oral leukoplakia—a prospective study

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ARTICLE INFO

Article history:
Paper received 13 September 2018
Accepted 6 December 2018
Available online 13 December 2018

Keywords:
Leukoplakia
Podoplanin
SIN grading
Preneoplasia
Precancer
Epithelial dysplasia

ABSTRACT

Purpose: The aim of this prospective work was to examine oral leukoplakia for their podoplanin expression to determine whether podoplanin expression is associated with the degree of dysplasia.
Materials and methods: We took biopsy samples from 50 patients with oral leukoplakia in 2013. The preparations studied by immunohistochemistry were analyzed in correlation with the degree of dysplasia and other clinicopathological variables.
Results: The Chi-square test showed a significant correlation between podoplanin expression and the degree of dysplasia according to the squamous intraepithelial neoplasia (SIN) classification ($p = 0.033$). Also, a significant association between age grouping and podoplanin expression was found. We were able to show that the distribution is the same for both age groups in relation to the score of podoplanin expression ($p = 0.003$).
Conclusion: In a comparable retrospective work of our working group, it could be shown that podoplanin is a reliable predictive marker for the assessment of the risk of malignant transformation. The present work was able to substantiate the assumption that podoplanin not only plays an important role in the context of malignant degeneration but also exerts a major influence in advance.

1. Introduction

Oral cancer is the sixth most common cancer worldwide (Amagasa et al., 2006), with an annual incidence of 500,000 (Vormittag et al., 2009). The incidence of oral cancer varies between 0.1% and 40% and shows significant geographic variations (Nahum et al., 1961). Despite intensive therapy and ongoing improvement of diagnostic techniques, the prognosis of oral squamous cell carcinoma continues to be poor (Safi et al., 2015, 2017a, 2017b). Irrespective of the stage of cancer, the majority of studies report 5-year survival rates between 45% and 63% (Cooper et al., 2004; Eich et al., 2008; Rutkowski et al., 2010; Kreppel et al., 2011; Siegel et al., 2017). In 2013 an international multicenter study showed a significant improvement in the 5-year-survival rate of patients with oral squamous cell carcinoma within the last two decades, although the patients were older, the cancer was more advanced, and there was a higher rate of distant metastases (Amit et al., 2013). The results suggest that the prognosis for patients with oral squamous cell carcinoma has improved over time, presumably due to the remarkable advances in medical imaging and therapy. Nevertheless, better early detection methods of potentially malignant changes in the oral mucosa are necessary to counteract the trend of advanced disease with increased distant metastases (Amit et al., 2013).

Oral leukoplakia are considered to be important premalignant lesions in the development of oral cancer. Oral leukoplakia are a detectable risk factor for oral squamous cell carcinoma with a malignant transformation rate of 0.1%–18% (Pindborg et al., 1968; Silverman et al., 1984; Reibel, 2003). They are described as a "predominant white lesion of the oral mucosa, which cannot be defined as any other known lesion (van der Waal and Axell, 2002; Warnakulasuriya et al., 2007)."

Dysplastic changes within oral leukoplakia are considered to be associated with greater risk of malignant transformation. However, the majority of oral squamous cell carcinoma develops from lesions that lack dysplastic changes, thus making the predictive value of

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https://doi.org/10.1016/j.jcms.2018.12.005
1010-5182/

dysplasia insufficient (Tabor et al., 2003; Amagasa et al., 2006; Kujan et al., 2006, 2007; Kreppel et al., 2012).

By identifying parameters that allow an adequate and early assessment of potential malignant transformation, the survival of patients might be ameliorated. Early diagnosis of high-risk, potentially malignant lesions may lead to a significant reduction in the overall transformation rate, which is reported between 17% and 24%, and therefore may enable a compelling prognostic improvement (Schepman et al., 1998; Holmstrup et al., 2006; Kreppel et al., 2012). Depending on this, treatment decision making for oral leukoplakia might be improved. In other cancers, molecular biomarkers have already been developed as risk indicators for malignant transformation (Safi et al., 2015).

In this study, we selected podoplanin, which is a 38-kd mucin-type transmembrane glycoprotein. It is specifically expressed on lymphatic endothelial cells. Several reports indicated that a high expression of podoplanin is associated with poor survival, a low response to neoadjuvant radiochemotherapy, and lymph node metastasis (Yuan et al., 2006; Kreppel et al., 2010, 2012, 2013). In squamous cell carcinomas, podoplanin is restricted to the invasive front. By the switch of cadherin podoplanin expressing cells, migratory properties are acquired. Furthermore podoplanin plays an important role in cell migration and invasiveness during carcinoma progression (Martin-Villar et al., 2005; Wicki et al., 2006; de Vicente et al., 2013). In 2012 we could show, in a retrospective study, that there is a strong statistical association between podoplanin expression and squamous intraepithelial neoplasia (SIN) grading of the oral leukoplakia ($p = 0.009$) (Kreppel et al., 2012).

2. Materials and methods

2.1. Patients

The prospective study included 50 consecutive treatment-naive patients with oral leukoplakia at the Department of Oral and Maxillofacial Surgery at the University of Cologne between 2012 and 2013. The biopsy specimens were histologically graded according to the squamous intraepithelial neoplasia (SIN) classification of the World Health Organization in 2005. Oral leukoplakia was defined as a predominant white lesion of the oral mucosa, which cannot be defined as any other known lesion (van der Waal and Axell, 2002; Warnakulasuriya et al., 2007). Both homogeneous and non-homogeneous leukoplakia were included in this study. From the medical charts, clinicopathological parameters were obtained.

The study was designed in accordance with the Declaration of Helsinki of 2002 and was approved by the institutional ethical committee (Study-No. 12-035). Informed consent was obtained from all patients.

2.2. Tissue processing and immunohistochemical analysis

Formalin-fixed, paraffin-embedded specimens were obtained from the operation theater and handled in the Department of Pathology at the University of Cologne for further processing. Representative areas of the lesions and normal-appearing tissue were included. An excision biopsy was performed in smaller lesions with a 2- to 3-mm perimeter of the normal-appearing mucosa.

Immunohistochemistry was performed using the avidin-biotin peroxidase complex (ABC) technique (Yuan et al., 2006; Kawaguchi et al., 2008; Kreppel et al., 2010). We used monoclonal antibody D2-40 diluted 1: 100 (Vector Laboratories, Burlingame, CA, USA). The expression of podoplanin in lymphatic endothelial cells in the stroma served as a positive internal control. For each case, only one slide was analyzed. We used a scheme previously published by Kawaguchi et al. (2008), to compare our results with those in the literature (Kawaguchi et al., 2008). Score 0 was assigned when no podoplanin expression was detectable in the area of the lesion. Score 1 was defined as podoplanin expression restricted to the basal layer. When podoplanin expression was detectable in the basal layer and suprabasal region, this was rated as Score 2. Expression of podoplanin in 2–3 supra-basal areas was considered as Score 3. When podoplanin expression was observed in more than three areas in the suprabasal layer, Score 4 was assigned. The entire section of the biopsy was examined under the consensus of an experienced pathologist (U.D.) who was blinded with respect to clinical data.

2.3. Statistical analysis

Associations between podoplanin expression and clinicopathological variables were assessed using the Wilcoxon rank-sum test for continuously distributed variables and the chi-square test for categorical variables. The Fisher exact test was used instead of the chi-square test if the expected frequency was <5. All statistical analyses was were carried out with IBM SPSS Statistics 21 (Armonk, NY, USA).

3. Results

The study included 50 patients, comprising 28 men and 22 women (mean age 61.4 ± 11.19 years). The leukoplakic mucosal lesions were most commonly detected in the mandibular mucosa (24%) and in the area of the planum buccale (24%). In 20% of the subjects, a leukoplakia was found in the tongue area. Leukoplakic changes of the floor of the mouth were found in 16% of cases, in five patients were these changes were found in the hard palate (10%), and in three patients such changes were found in the soft palate area (6%) (Table 1).

No podoplanin expression was observed in 24% of the patients, whereas podoplanin expression extending to the suprabasal layers was observed in 54% of the patients.

The associations between podoplanin expression and clinicopathological parameters are shown in Table 2. Podoplanin expression was significantly associated with SIN classification ($p = 0.033$) and the age of the patients ($p = 0.003$).

4. Discussion

To analyze the degree of dysplasia within this prospective study, we chose the squamous intraepithelial classification (SIN) for oral leukoplakia. This classification differentiates low-grade intraepithelial neoplasia (SIN I), moderate intraepithelial neoplasia (SIN II), and high-grade intraepithelial neoplasia (SIN III). SIN III is analogous to a carcinoma in situ. The advantage of this is the avoidance of histopathologically difficult differentiation between high-grade intraepithelial neoplasia (SIN III) and carcinoma in situ (Driemel et al., 2006). Several studies have also shown that a classification according to the World Health Organization Classification of 2005 brings no advantage in terms of the assessment of a malignant transformation of the oral mucosa change. The fewer the categories chosen for the classification of changes in the oral mucosa, as in the SIN classification, the higher the predictive value for the malignant transformation, primarily due to comparability (Gale et al., 2014).

Based on multiple studies, it has been reported that podoplanin is a marker of malignant transformation in oral leukoplakia and other oral precursor lesions such as lichen planus (Yuan et al., 2006; Kawaguchi et al., 2008; Funayama et al., 2011). We confirmed the observation of Funayama et al., who observed that podoplanin

Table 1
Patient characteristics.

Characteristic	n (%)
Patients	50
Men	28 (56%)
Women	22 (44%)
Age (years)	
Mean ± SD	61.4 ± 11.19
Median	61.0
Site	
Floor of mouth	8 (16%)
Tongue	10 (20%)
Lower jaw	12 (24%)
Hard palate	5 (10%)
Soft palate	3 (6%)
Cheek	12 (24%)
Podoplanin expression	
No podoplanin	12 (24%)
Podoplanin expression at the basal layer	11 (22%)
Podoplanin expression at the suprabasal layer extending to 1 area	9 (18%)
Podoplanin expression at the suprabasal layer extending to 2–3 area	11 (22%)
Podoplanin expression at the suprabasal layer extending to >3 areas	7 (14%)

Table 2
Presents associations between podoplanin expression and clinicopathological parameters.

Parameter	No podoplanin	Expression in the basal layer	Suprabasal expression at 1 area	Suprabasal expression at 2–3 areas	Suprabasal expression at >3 areas	*p* Value
Age (%)						**0.003**
≤60 years	5 (20%)	1 (4%)	9 (36%)	4 (16%)	6 (24%)	
≥61 years	5 (20%)	10 (40%)	2 (%)	7 (28%)	1 (4%)	
Gender (%)						0.056
Men	10 (36%)	8 (27%)	4 (14%)	4 (14%)	2 (7%)	
Women	2 (9%)	3 (14%)	5 (23%)	7 (32%)	5 (23%)	
Location (%)						0.070
Floor of mouth	2 (25%)	1 (13%)	3 (38%)	2 (25%)	0 (0%)	
Tongue	1 (10%)	3 (30%)	1 (10%)	3 (30%)	2 (20%)	
Lower jaw	1 (8%)	2 (17%)	5 (42%)	0 (0%)	4 (33%)	
Hard palate	1 (20%)	2 (40%)	0 (0%)	2 (40%)	0 (0%)	
Soft palate	0 (0%)	2 (67%)	0 (0%)	0 (0%)	1 (33%)	
Cheek	5 (42%)	1 (8%)	2 (17%)	4 (33%)	0 (0%)	
SIN classification (%)						**0.033**
Epithelial hyperplasia	12 (40%)	6 (20%)	6 (20%)	5 (17%)	1 (3%)	
SIN I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
SIN II	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	
SIN III	0 (0%)	4 (21%)	3 (16%)	6 (32%)	6 (32%)	

Significant *p* values of <0.05 are shown in boldface type.

expression in oral leukoplakia is strongly associated with the SIN classification stage (Funayama et al., 2011). Our study results showed that suprabasal podoplanin expression was present in more than three areas of leukoplakia with SIN III. In all SIN III leukoplakia, podoplanin expression was observed at least in the basal cell layer. These results are in contrast to study findings by Gissi et al., who recently showed that podoplanin expression was found in two or more areas in 87.5% of cases in leukoplakia with dysplasia. However, their study cohort was relatively small, as they included only 8 patients (Gissi et al., 2018). In our study, 20 patients with dysplastic leukoplakia were included. Of these dysplasias, 60% showed podoplanin expression in two or more suprabasal areas. A total of 40% of the leukoplakias classified as dysplastic according to the SIN classification showed a podoplanin only in the area of the basal membrane or in a suprabasal area. Also with regard to leukoplakia without dysplasia, we found results other than those of Gissi et al. In our study, 20% of biopsy samples with epithelial hyperplasia had a podoplanin expression in two or more suprabasal areas; Gissi et al. found only in 9.8% of cases that podoplanin expression in more than two suprabasal parts (Gissi et al., 2018).

Furthermore, our group demonstrated that podoplanin expression is significantly related to the degree of tissue dysplasia (Kreppel et al., 2012). The present work supports the assumption that podoplanin can be used as a predictive marker for assessing the dysplasia status of leukoplakia. Podoplanin is not only crucial for malignant transformation, but it can even be assumed that podoplanin has a decisive influence on tissue transformation and therefore is relevant at the beginning of the disease.

Moreover, there is a significant association between the expression of podoplanin and the age of the patients ($p = 0.003$). In the younger half of the patients, 30.0% had a podoplanin score of 3 or 4, and in the older half 32.0%. These results show that age does not affect podoplanin expression. Kreppel et al. and Inoue et al., for example, could find no significant relationship between the age of the patients and the expression of podoplanin (Inoue et al., 2012; Kreppel et al., 2012). One possible reason for this could be the retrospective study design, which was chosen by both Kreppel et al. and Inou et al. Kawaguchi et al. also showed a significant association between patient age and podoplanin expression in their prospective study (Kawaguchi et al., 2008).

A major advantage of the present study was the prospective study design, which prevented a selection bias in the data collection. A retrospective study with a similar hypothesis was carried out in 2012 by our research group. It has been shown that podoplanin is a reliable predictive marker for the assessment of the risk of malignant transformation (Kreppel et al., 2012). In addition, in this study, we found a significant relationship between localization and podoplanin expression, which Kreppel et al. and Inoue et al. in their retrospective studies so far could not find (Inoue et al., 2012; Kreppel et al., 2012).

Gissi et al. showed a sensitivity of 87.5% and a specificity of 96.87% for the expression of podoplanin in dysplastic and non-dysplastic leukoplakia. In addition, Gissi et al. showed that the sensitivity and specificity of podoplanin in the tongue area are reduced to only 75% (Gissi et al., 2018). Further studies have already shown that there is a significant correlation between podoplanin expression and oral cancer–free survival (Kawaguchi et al., 2008; Saintigny et al., 2009; Shi et al., 2010; Kreppel et al., 2012). For this reason, podoplanin represents a pioneering marker for the early detection of leukoplakic oral mucosal lesions and is associated with a higher malignant transformation rate.

In the future, it may be of interest to correlate podoplanin expression with other clinical instrumental techniques, such as brush border biopsy or VELscope (Vision Enhanced Lesion Scope) or other immunohistochemical markers. In their review, Retzbach et al. indicated the future use of podoplanin as a target for targeted chemotherapy. Basic research shows promising initial results in the use of antibodies against podoplanin. Especially *Maackia amurensis* seed lectin (MASL), used as an oral medication, could provide favorable conditions for treat oral leukoplakias with medication. This could potentially avoid major resections of the precancerous lesions and the resulting patient disability (Retzbach et al., 2018).

5. Conclusion

The present prospective study shows that podoplanin expression in oral leukoplakia is significantly associated with degree of dysplasia. The high sensitivity and specificity of podoplanin in dysplastic altered oral leukoplakia has previously been demonstrated. In the future, podoplanin may serve as a target for chemotherapeutic treatment of oral leukoplakia.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

There are no conflicts of interest in the materials or subject matter dealt with in the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2018.12.005.

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