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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Podoplanin and ABCG2: Malignant Transformation Risk Markers for Oral Lichen Planus

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Abstract

Background: Oral lichen planus (OLP) is a potentially malignant disorder associated with an increased risk for oral cancer. The purpose of this study was to determine protein expression of podoplanin and ATP-binding cassette, G2 subfamily (ABCG2) in patients with OLP and evaluate their use as biomarkers for OLP malignant transformation risk.

Methods: Podoplanin and ABCG2 expressions were determined in samples from 110 patients with untransformed OLP and 9 patients with malignant transformed OLP (mean follow-up of 5.1 years). We compared podoplanin expression, ABCG2 expression, and clinicopathologic parameters between the two groups.

Results: Podoplanin expression was observed in 48 of 110 (43.6%) cases of untransformed OLP and in 8 of 9 (88.9%) cases of transformed OLP. ABCG2 expression was found in 23 of 110 (20.9%) cases of untransformed OLP and in 6 of 9 (66.7%) cases of transformed OLP. Multivariate regression analysis revealed that podoplanin or ABCG2 expression was associated with 17.13-fold [95% confidence interval (95% CI), 1.71-171.22; $P = 0.016$] or 6.04-fold (95% CI, 1.20-30.36; $P = 0.029$) increased risk of malignant transformation, respectively. The risk of OLP malignant transformation was considerably higher with coexpression of podoplanin and ABCG2 than without coexpression of podoplanin and ABCG2 (odds ratio, 25.24; 95% CI, 4.48-142.27; $P < 0.001$).

Conclusions: The expressions of podoplanin and ABCG2 in OLP were significantly associated with malignant transformation risk.

Impact: Our data suggested that podoplanin and ABCG2 may be used as biomarkers for risk assessment of oral malignant transformation in patients with OLP. *Cancer Epidemiol Biomarkers Prev; 19(3); 844–9. ©2010 AACR.*

Introduction

Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease of unknown cause. It has a prolonged clinical course that can persist for many years despite various treatments (1, 2). Patients with OLP carry an increased risk of developing oral squamous cell carcinomas (OSCC), which led the WHO to classify OLP as a potentially malignant disorder (3). In several well-conducted studies, the malignant transformation rates of OLP ranged from 0.4% to 5.3%, with median follow-up of >5 years (4-7). Malignant transformation may occur in all clinical types of OLP (7, 8). At present, histologic assessment of epithelial dysplasia is the gold standard for determining the malignant transformation risk of OLP; however, substantial interobserver and intraobserver variation is a problem in the histopathologic assessment of epithelial dysplasia presence and severity (9, 10). Therefore, objective biomarkers are needed that evaluate and clarify the risk of OLP malignant transformation and do not require the ability to recognize morphologic changes.

Podoplanin, a mucin-type transmembrane glycoprotein, is one of the most highly expressed lymphatic-specific genes in cultured human lymphatic endothelial cells (11, 12). Podoplanin deficiency in mice results in congenital lymphedema (13), and podoplanin expression has been reported in squamous cell carcinomas of esophagus, lung, skin, and oral cavity (14-18). Podoplanin is also expressed in hyperplastic and dysplastic areas adjacent to the primary tumors (17, 18), indicating that its abnormal expression occurs early in oral tumorigenesis. Kawaguchi et al. (19) reported high expression of podoplanin in oral leukoplakia and suggested the use of podoplanin as a biomarker for oral cancer risk in patients with oral premalignancy.

The ATP-binding cassette, G2 subfamily (ABCG2) is a member of ATP-binding cassette transporter protein superfamily that produces multidrug-resistant cancer. It is also known as a molecular determinant of the side population phenotype in stem cells (20). This phenotype has been found in several types of carcinoma cell lines,

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including esophagus, nasopharynx, and oral cavity (21-23). Furthermore, ABCG2 expression has been found in solid tumors of retinoblastoma and hepatocellular, esophageal, and head and neck squamous carcinomas (24-27). ABCG2 is increasingly thought to be one of stem cells markers and/or play a central role in tumorigenesis (24-26).

The purpose of this study was to determine podoplanin and ABCG2 protein expression in OLP with or without malignant transformation and determine their usefulness as biomarkers for risk assessment of OLP malignant transformation.

Materials and Methods

Patients and Tissue Specimens

All patients with the clinical and pathologic diagnosis of OLP in the Department of Oral Mucosal Diseases, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine from 1978 to 2007 were included (untransformed OLP, n = 110; malignant transformed OLP, n = 9). The mean follow-up period was 5.1 y (range, 1.33-19.25 y), excluding two patients who received the diagnosis of OLP with malignant transformation at the first visit. Biopsy specimens were obtained and subsequently formalin fixed and paraffin embedded. Paired paraffin blocks from premalignant and postmalignant transformation were kept for two patients. This study was approved by the institutional review board.

Histologic Examination

H&E-stained slides (5 μm thick) were cut for routine diagnostics. Reexamination of the slides confirmed the diagnosis of OLP in all cases. The WHO criteria (28) for OLP and epithelial dysplasia were used when reexamining the histopathology of the sections. The presence of dysplasia was graded as mild, moderate, or severe. Dysplasia was mild when dysplastic changes were present in lower third of the epithelia, moderate when two thirds of the epithelia were affected, and severe when the whole thickness of epithelia was involved.

Table 1. Patient baseline characteristics

	Untransformed OLP (n = 110)	Malignant transformed OLP (n = 9)	P
Age (y)			0.036
Mean (SD)	45.3 (12.3)	54.2 (8.9)	
Range	9-74	41-70	
Sex, n (%)			0.682
Female	84 (76.4)	8 (88.9)	
Male	26 (23.6)	1 (11.1)	
Diet, n (%)			1.00
Bland	49 (44.5)	5 (55.6)	
Spicy	26 (23.6)	2 (22.2)	
Missing	35 (—)	2 (—)	
Smoking, n (%)			0.536
Never	76 (69.1)	7 (77.8)	
Past and present	7 (6.4)	1 (11.1)	
Missing	27 (—)	1 (—)	
Ethanol intake, n (%)			1.00
Never	74 (67.3)	7 (77.8)	
Past and present	9 (8.2)	1 (11.1)	
Missing	27 (—)	1 (—)	
Follow-up (y)			0.943
Mean	4.76	4.61	
Range	1.33-14.5	0.03-18.3	
Epithelial dysplasia, n (%)			
Nondysplasia	99 (90.0)		
Dysplasia	11 (10.0)		
Tumor stage, n (%)			
Early		9 (100.0)	
Advanced		0 (0.0)	

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Tissue Processing and Immunohistochemistry

Serial tissue sections (5 μm thick) from formalin-fixed, paraffin-embedded tissue blocks of OLP were mounted on positively charged glass slides. Immunohistochemical staining was done using the streptavidin-peroxidase method. Briefly, slides were deparaffinized through a series of xylene baths and rehydrated with graded concentrations of ethanol. Then, endogenous peroxidase was inactivated by treatment with 3% hydrogen peroxide for 10 min. To restore antigenicity, tissue sections were incubated with 0.1% trypsinase for 30 min at 37°C followed by incubation with 10% goat serum for 30 min at room temperature. The slides were then incubated with D2-40 monoclonal antibody (anti-podoplanin; 1:150 dilution; Zeta Corp.) overnight at 4°C followed by incubation with goat anti-mouse antibody (Dako Corp.) for 30 min at 37°C. A 3,3′-diaminobenzidine detection kit (Dako) was applied until desired staining intensity was achieved. Finally, the sections were counterstained with hematoxylin and then dehydrated and mounted under a coverslip. Another continuous tissue section was stained with BXP-21 monoclonal antibody (anti-BCRP/ABCG2; 1:40 dilution; Abcam Corp.) using the same method.

Cytoplasm and/or membrane immunoreactivity was considered to indicate podoplanin or ABCG2 expression. Podoplanin and ABCG2 expression was classified as 0 (if no expression was observed in any part of the epithelium or tumor) or 1 (if expression was observed in any part of the epithelium or tumor).

Blind and Pathologic Review of Specimens

The immunohistochemical staining was evaluated by two investigators (W-W.J. and W.L.). If the opinions of the two investigators differed, agreement was reached by careful discussion. The statistical analysis was done independently by one statistician (Q-B.H.). The pathologic diagnosis of sample was determined by an oral pathologist on duty from the Department of Oral Pathology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. The confirmation diagnosis was done by another oral pathologist (J.L.) when serial sections were taken.

Statistical Analysis

The main statistical analysis was the comparison of podoplanin and ABCG2 expression between untransformed OLP and malignant transformed OLP by χ^2 test or Fisher's exact test. The effects of sex, diet, smoking, and ethanol intake on OLP transformation were also determined. The effect of age was determined by Student's *t* test. Logistic regression was applied to evaluate hazard ratios for the malignant transformed OLP. Odds ratios (OR) with 95% confidence interval (95% CI) and *P* values were reported. All tests were two-sided, and *P* values of <0.05 were considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of study participants are presented in Table 1. The mean age of patients with

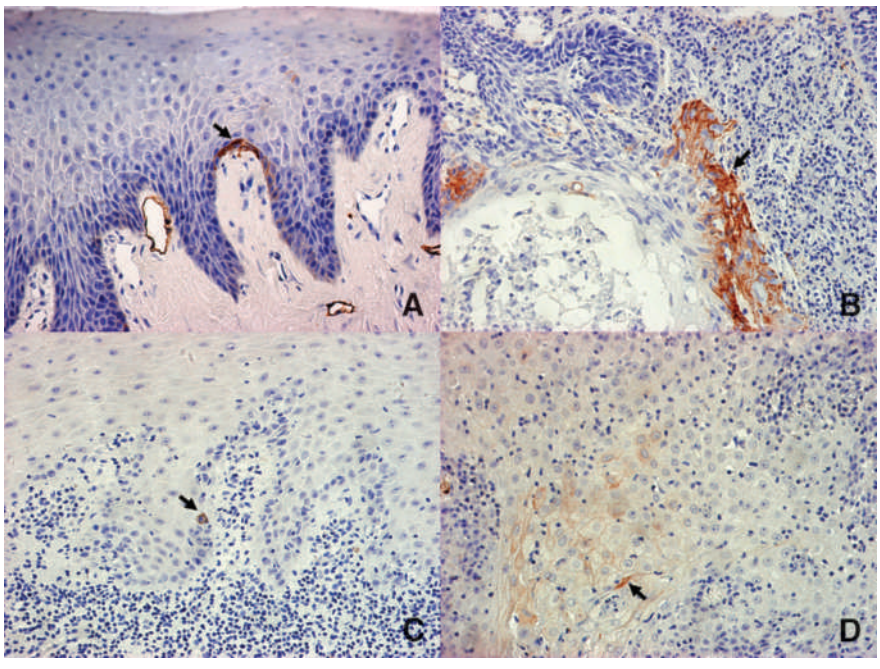

Figure 1. Immunohistochemical staining of podoplanin- and ABCG2-positive cells. A, podoplanin expression in untransformed OLP. B, podoplanin expression in transformed OLP. C, ABCG2 expression in untransformed OLP. D, ABCG2 expression in transformed OLP. Magnification, ×200.

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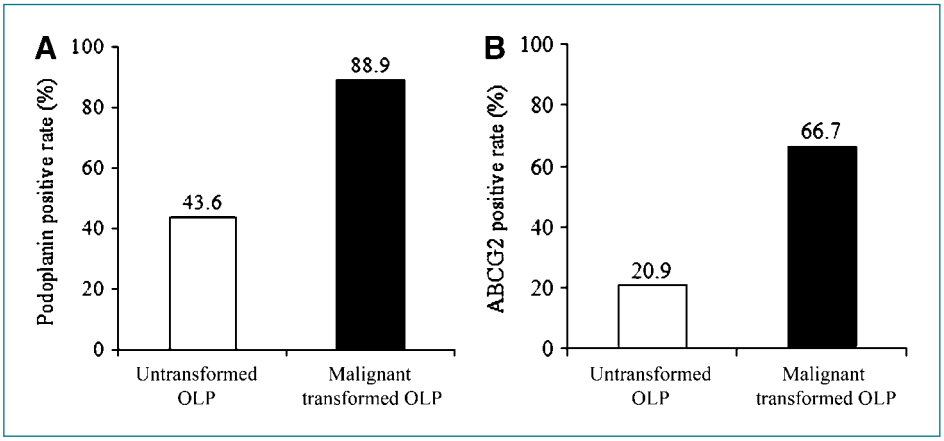

Figure 2. Frequency of podoplanin and ABCG2 expression. A, the frequency of podoplanin expression is 43.6% in untransformed OLP and 88.9% in transformed OLP. *, $P = 0.012$, χ^2 test. B, the frequency of ABCG2 expression is 20.9% in untransformed OLP and 66.7% in transformed OLP. **, $P = 0.006$, χ^2 test.

transformed OLP was 54.2 years compared with 45.3 years for patients with untransformed OLP ($P = 0.036$, Student's t test); however, differences in sex, diet, smoking, and ethanol intake or follow-up period were not observed between the two groups.

Podoplanin Expression in Untransformed and Transformed OLP

Podoplanin expression was found in the cytoplasm and/or membrane of epithelial cells of untransformed (Fig. 1A) and transformed (Fig. 1B) OLP. We observed podoplanin expression in 48 of 110 (43.6%) cases of untransformed OLP and in 8 of 9 (88.9%) cases of transformed OLP ($P = 0.012$, χ^2 test; Fig. 2A). In addition, podoplanin expression was consistently detected in the endothelial cells of lymphatic vessels in both untransformed and transformed OLP.

ABCG2 Expression in Untransformed and Transformed OLP

ABCG2 expression also showed a mixed pattern of membranous and cytoplasmic staining in the untransformed (Fig. 1C) and transformed (Fig. 1D) OLP. We observed ABCG2 protein expression in 23 of 100 cases (20.9%) of untransformed OLP and in 6 of 9 (66.7%) cases of transformed OLP ($P = 0.006$, χ^2 test; Fig. 2B).

Coexpression of Podoplanin and ABCG2 in Untransformed and Transformed OLP

We observed coexpression of podoplanin and ABCG2 in 12 of 110 (10.9%) cases of untransformed OLP and in 6 of 9 (66.7%) cases of transformed OLP ($P < 0.001$, χ^2 test). Furthermore, 59 of 110 (53.6%) samples of untransformed OLP and 8 of 9 (88.9%) samples of transformed OLP expressed at least one of two proteins ($P = 0.076$, χ^2

Table 2. Logistic regression analysis of factors in OLP transformation

Characteristic	OR (95% CI)	*P*
Univariate analysis		
Age	1.07 (1.00-1.13)	0.042
Sex	0.40 (0.05-3.38)	0.403
Diet habit	0.75 (0.14-4.16)	0.746
Smoking	1.55 (0.17-14.48)	0.700
Ethanol intake	1.18 (0.13-10.67)	0.886
Podoplanin	10.33 (1.25-85.47)	0.030
ABCG2	7.57 (1.76-32.58)	0.007
Multivariate analysis		
Age	1.10 (1.02-1.19)	0.016
Podoplanin	17.13 (1.71-171.22)	0.016
ABCG2	6.04 (1.20-30.36)	0.029
Multivariate analysis		
Age	1.09 (1.01-1.18)	0.021
Coexpression ofpodoplanin/ABCG2	25.24 (4.48-142.27)	<0.001

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test). Interestingly, we detected coexpression of podoplanin and ABCG2 in both patients for which paired pretransformation and posttransformation OLP samples were available.

Logistic Regression Analysis of Malignant Transformation Risk in OLP

To evaluate the risk of OLP malignant transformation, clinicopathologic parameters and podoplanin and ABCG2 expression were analyzed by logistic regression. In the univariate regression analysis, podoplanin and ABCG2 expression was associated with 10.33-fold (95% CI, 1.25-85.47; $P = 0.030$) or 7.57-fold (95% CI, 1.76-32.58; $P = 0.007$) increased risk of malignant transformation, respectively (Table 2). Patient age was also a significant factor in the univariate model; however, the OR was only 1.07 (95% CI, 1.00-1.13; $P = 0.042$). To further assess the influence of each factor, we then did multivariate regression. All three factors retained statistical significance. The OR for transformation was 17.13 for podoplanin (95% CI, 1.71-171.22; $P = 0.016$) and 6.04 for ABCG2 (95% CI, 1.20-30.36; $P = 0.029$; Table 2). Interestingly, when age and coexpression of podoplanin and ABCG2 were considered as cofactors, the risk of OLP malignant transformation was considerably higher compared with OLP without coexpression of podoplanin and ABCG2 (OR, 25.24; 95% CI, 4.48-142.27; $P < 0.001$; Table 2)

Discussion

In the present study, we evaluated the risk of OLP malignant transformation during a relatively long follow-up period. Age was found to be a significant clinicopathologic predictor for OLP malignant transformation (Table 2), but sex, diet, smoking, and ethanol intake were not predictors, which was consistent with previous reports (4, 7, 8).

Podoplanin has been used as a specific marker for lymphatic vessels, and its upregulation has been observed in several cancers (14-18). It has been reported that podoplanin is expressed in ~90% of OSCCs and is restricted to the invasive front of squamous cell carcinoma (16-18). In oral potentially malignant disorders, Kawaguchi et al. (19) classified 37% of oral leukoplakia patients positive for podoplanin expression. It was also reported that podoplanin was highly expressed in the basal cell layers in some of the hyperplastic and dysplastic areas adjacent to the squamous cell carcinoma (18). In the present study, we found that 43.6% of the untransformed OLP samples showed podoplanin expression, whereas 88.9% of the malignant transformed OLP samples expressed podoplanin; these expression patterns were similar to those found in primary OSCC (18). The malignant transformation risk was much greater in patients with podoplanin expression. Taken together, these data not only support the potential importance of podoplanin in early oral tumorigenesis but also suggest that podoplanin may be used as a biomarker for evaluating malignant transformation risk in patients with oral potentially malignant disorders.

Podoplanin expression alone may be too weak to elaborate carcinogenesis (19). Podoplanin-positive cells in the epithelial layers may represent upward clonal expansion of stem cells during carcinogenesis, and oral potentially malignant disorders with such clonal expansion may imply significantly higher risk of malignant transformation. ABCG2 has been used as a multidrug resistance marker for cancer as well as side population cell marker through the ability to exclude Hoechst dye 33342 in a side population of stem cells. It has also been used in several tumors to sort out presumptive stem cells (20-23). In addition, side population cells have been reported to possess cancer stem cell–like properties (29-31). Recent study suggested that side population cells may play an important role in oral tumorigenesis (23). Therefore, we did immunohistochemical staining of both ABCG2 and podoplanin in the present study. We found that 66.7% of malignant OLP samples expressed ABCG2; patients with ABCG2 expression had a 6.04-fold increased risk of transformation compared with those without ABCG2 expression. Although additional experiments are needed to determine whether ABCG2-positive cells are cancer stem cells in oral potentially malignant disorders, ABCG2 has already revealed the potential as an early detection biomarker in OLP malignant transformation.

Although dysplasia has been used as the gold standard for evaluating the risk of oral cancer development, there is a substantial interobserver and intraobserver variation when evaluating the presence and severity of epithelial dysplasia (9, 10). Moreover, 11 of 110 OLP samples showed mild dysplasia in our study, but all 11 patients did not develop OSCC during the follow-up period. Therefore, immunohistochemical staining of podoplanin and ABCG2 may be better for evaluating malignant transformation risk in OLP compared with histopathologic assessment of epithelial dysplasia; however, it was still limited by the overall numbers of converted patients. Further studies need to be done by a large cohort to draw a strong conclusion.

In summary, podoplanin and ABCG2 in OLP were significantly associated with malignant transformation risk. Our data suggested that podoplanin and ABCG2 may be useful as biomarkers for risk assessment of oral malignant transformation in patients with OLP.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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