Classification of vocal fold leukoplakia by clinical scoring

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ABSTRACT: *Background.* Vocal cord leukoplakia comprises a variety of lesions. The purpose of this study was to stratify vocal leukoplakias before surgery.

Methods. Patients with an initial diagnosis of vocal leukoplakia who underwent surgical excision at a tertiary referral center in Taiwan were recruited for this study. Their clinical records, including age, sex, preoperative laryngoscopic images in the office setting, and final pathology reports were collected and analyzed.

Results. Patient age ($p = .010$), nonhomogenous lesion texture ($p = .001$), and existence of hyperemia ($p = .014$) were identified as independent factors predicting malignancy. A predictive formula was established accordingly. The model showed an excellent discrimination role by receiver operating characteristic curve analysis (area under the curve = 0.86; $p < .001$).

Conclusion. This study confirmed the value of a scoring system based on laryngoscopic characteristics and patient age for predicting the histologic results in vocal leukoplakia. It is helpful for classifying vocal leukoplakia and pretreatment planning. © 2016 Wiley Periodicals, Inc. *Head Neck* **38**: E1998–E2003, 2016

KEY WORDS: laryngoscopy, scoring, vocal leukoplakia, larynx, dysphonia

INTRODUCTION

Leukoplakia refers to whitish patches associated with a spectrum of histological diagnoses ranging from benign to malignant lesions.[1–4] Patients with vocal leukoplakia, similar to other vocal fold mucosal lesions, usually suffer from hoarseness and expect to regain their voice after adequate therapy. There is still no consensus on the ideal treatment of vocal fold premalignant lesions. Stripping of mucosa, CO2 laser excision, or ablation, or even radiation has been suggested as an option. From a study reviewing 56 cases by Schweinfurth et al,[5] most of the cases of vocal fold leukoplakia reduction in histologic aggressiveness occur after serial universe microflap excision but there were still few that progressed. Thus, vocal leukoplakia should be managed individually based on its benign or malignant possibilities of the lesion.[6–8] In suspected benign lesions, observation or superficial excision to preserve as much subepithelial tissue as possible is preferred, whereas deeper excision is adequate in cases with malignant potential.

Although clinical classification and staging procedures exist for leukoplakia in other sites,[4,9] to our knowledge, there has been no report in English about the classification of the vocal fold leukoplakia before surgery, and the management thus varies among surgeons.

The appearance of vocal leukoplakia varies among individuals and is closely related to histologic findings.[10,11] Advances in high-quality digital imaging systems and distal chip fiber-optic laryngoscopy have made it possible to distinguish between benign and malignant vocal cord mucosal disorders (Figure 1). As reported previously,[10] laryngoscopic characteristics can be determined using a laryngoscopic imaging recording system, with adequate interobserver reliability. The purpose of the present study was to establish a scoring system by combining clinical demographic and laryngoscopic characteristics in order to improve the management of vocal leukoplakia.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Chang Gung Memorial Hospital before conducting the study. Patients diagnosed with vocal leukoplakia between January 2010 and April 2014 were enrolled. Clinical records, including information on age, sex, smoking habit, medical history, preoperative laryngoscopic images in the office setting, and final pathology reports were collected.

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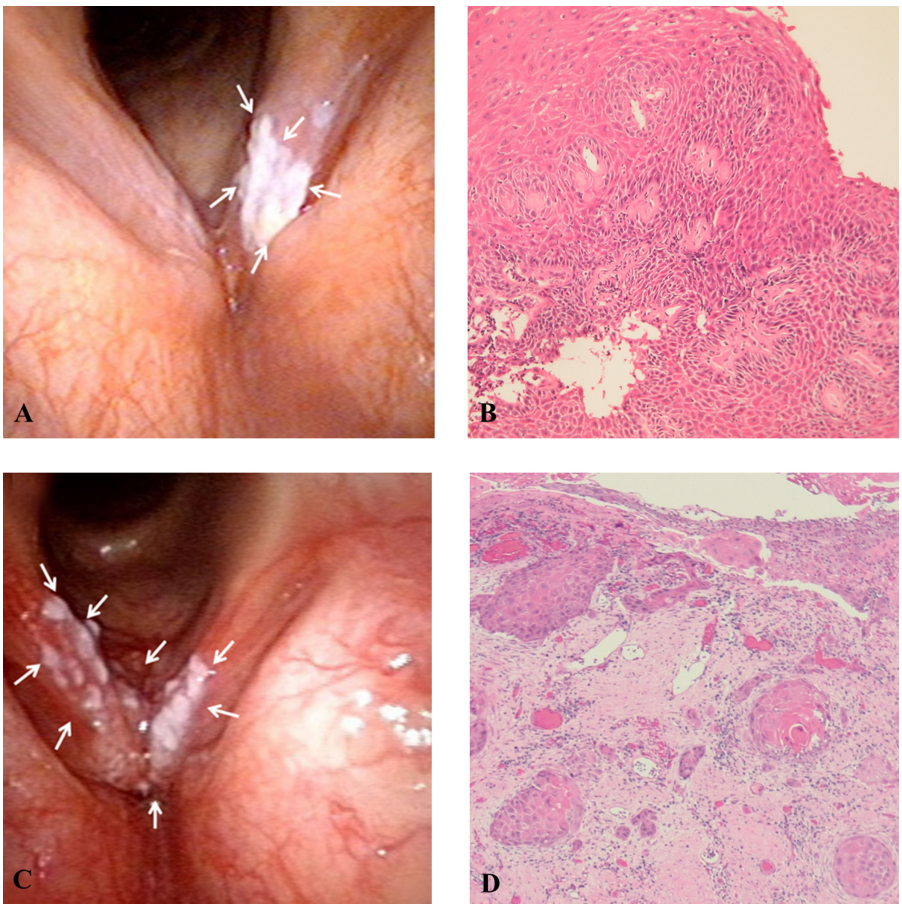

FIGURE 1. A 69-year-old man presented with left vocal leukoplakia. The laryngoscopy demonstrated regular surface in texture and absence of hyperemia (arrowhead) (A); the final pathology showed squamous hyperplasia (hematoxylin-eosin staining, original magnification ×100) (B). A 77-year-old man presented with bilateral anterior vocal leukoplakia. The laryngoscopy showed irregularity in texture and presence of hyperemia (arrowhead) (C); the final pathology was squamous cell carcinoma (hematoxylin-eosin staining, original magnification ×100) (D).

Treatment

Patients presenting with vocal leukoplakia underwent microdirected excisional biopsy by CO_2 laser. After multisectional histologic examination, pathologists made a histologic diagnosis according to the World Health Organization classification.[12] Patients with a final diagnosis of severe dysplasia, carcinoma in situ, or invasive squamous cell carcinoma were scheduled for surgical reexamination within 4 weeks, with the possibility of further excision at the same time. Those patients were followed up at 1 to 3-month intervals for the first 6 months, and 2- to 4-month intervals for the following 6 months. Patients with a diagnosis of no, mild, or moderate dysplasia were followed up at 3 to 6-month intervals in the first year. Patients without local recurrence after 1 year of follow-up were asked to come back for examination every 6 to 12 months, or whenever they felt a significant and persistent change in vocal quality and/or effort.

Laryngoscopic examination

All patients underwent in-office fiber-optic laryngoscopy before excisional biopsy. Images of the vocal cord mucosa were captured by a high-quality, digital, distal-chip laryngoscope connected to a white light source imaging system (Laryngoscope: ENF Type VT; Platform: EVIS Exera II; Olympus Optical Co., Tokyo, Japan) and were stored in the picture archiving and communication system. The laryngoscopic characteristics recorded included color, texture, size, hyperemia, and thickness and symmetry, which were previously shown to be consistent between observers.[10] The laryngoscopic characteristics were rated by the senior author (T.J.F.). The definitions of the characteristics, such as homogeneity of color and regularity of texture, are listed in Table 1. The laryngoscopic features proved to have independent predictive values from multivariate analysis were re-evaluated by another senior laryngologist (W.N.L.).

Statistical analysis

Descriptive statistics were calculated for baseline subject characteristics and the results are reported as mean ± SD. Univariate analysis was performed using chi-square or Fisher's exact tests to compare categorical variables and Student's *t* tests for continuous variables. Multivariate analysis of glottic malignancies was conducted using a stepwise logistic regression model fitted using a backward selection

TABLE 1. Laryngoscopy characteristics of vocal leukoplakia.

Factors	Score	Definitions
Color		
Homogenous	0	The color of vocal cord leukoplakia is distributed evenly
Heterogeneous	1	The color of vocal cord leukoplakia is not distributed evenly
Texture		
Regular	0	The surface of vocal cord leukoplakia is smooth and flat
Irregular	1	The surface of vocal cord leukoplakia showed granular appearance
Size		
Small	0	The sum of all vocal cord leukoplakia is less than half length of 1 true vocal cord
Large	1	The sum of all vocal cord leukoplakia exceeds the half length of 1 true vocal cord
Hyperemia		
Absence	0	The vocal cord leukoplakia is associated without peripheral erythema or increased vascularity
Presence	1	The vocal cord leukoplakia is associated with peripheral erythema or increased vascularity
Thickness		
Thin	0	The lesion is thin and blood vessels beneath the lesion are visible
Thick	1	The lesion is thick and blood vessels beneath the lesion are invisible
Symmetry		
Symmetric	0	Lesions are distributed at similar sites of the bilateral cords
Asymmetric	1	Lesions are located at one or unopposed sites

procedure, including variables with p values $< .05$ in univariate analysis. The independent laryngoscopic features were calculated with the Kappa coefficient test for paired proportions to determine consistency among the raters. A predictive laryngoscopic-score model was devised based on the preoperative morphological parameters identified as significant for glottic malignancy by multivariate logistic regression analysis. The power of discriminating values for morphological parameters in predicting glottic malignancies were identified using receiver operating characteristic (ROC) curve analysis. True-positive rates (sensitivity) were plotted against false-positive rates (1-specificity) for all classification points. All calculations were performed using SPSS software version 17.0 (SPSS, Chicago, IL). Two-sided p values $< .05$ were considered statistically significant.

RESULTS

There were 243 patients diagnosed with vocal leukoplakia in the study interval. Patients without clear in-office preoperative laryngoscopy images, complete resection of lesions, or histology reports were excluded. A total of 112 patients with a clinical indication of vocal leukoplakia were enrolled in this study, including 109 men and 3 women. The age of the study cohort ranged from 31 to 88 years (mean, 58 years). The pathologic diagnosis of vocal leukoplakia is listed in Table 2. A total of 42.0% of cases were noted as malignant (from severe dysplasia to invasive carcinoma). The demographic data and laryngoscopic characteristics were compared between the benign and malignant groups (Table 3). Univariate analysis identified significant differences in patient age and laryngoscopic characteristics, including color, texture, size, hyperemia, and symmetry of lesions between malignant and benign lesions.

TABLE 2. Histologic diagnosis of vocal leukoplakia in study cohort.

Diagnosis	No. of patients ($n = 112$)	%
Nondysplasia	50	44.6
Mild squamous dysplasia	9	8.0
Moderate squamous dysplasia	6	5.4
Severe squamous dysplasia	1	0.9
Carcinoma in situ	15	13.4
Squamous cell carcinoma	31	27.7

The parameters with significant predictive values in univariate analysis were incorporated into multivariate logistic regression analysis. Age, texture, and hyperemia were identified as independent factors associated with malignant disease after stepwise multivariate logistic regression analysis (Table 4). The interrater reliability test generated from the correlation of different raters showed substantial and almost perfect agreement in hyperemia (87%; $\kappa = 0.72$; $p < 0.001$) and texture (93%; $\kappa = 0.81$; $p < .001$).The Hosmer–Lemeshow goodness-of-fit test demonstrated no evidence of lack-of-fit in the selected model ($p = .644$). We proposed the following formula based on a combination of the significant parameters and their regression coefficients:

$$\text{Score} = 0.060\ (\text{age}) + 2.609\ (\text{texture}) + 1.307\ (\text{hyperemia})$$

ROC curves of the predictive scoring model showed that it has an excellent discrimination power for histology

TABLE 3. Comparison of factors between benign and malignant vocal cord leukoplakia.

Variables	Benignity ($n = 65$)	Malignancy* ($n = 47$)	p value
Age, y	55.12 ± 11.10	62.11 ± 9.15	.001
Sex, Male	63	46	.145
Smoker	56	42	.405
Color (homogenous)	51	13	.000
Texture (regular)	39	4	.000
Size (small)	35	13	.007
Hyperemia (absent)	39	7	.000
Thickness (thin)	22	17	.735
Symmetry (symmetric)	32	14	.048

TABLE 4. Multivariate logistic regression analysis and prediction scoring model for vocal leukoplakia.

Variables	Regression coefficient	95% CI	*p* value
Age, y	.060	0.016–0.127	.010
Texture (regular vs irregular)	2.609	1.576–21.107	.001
Hyperemia (absence vs presence)	1.307	0.176–2.767	.014

Abbreviation: 95% CI, 95% confidence interval.
Score = 0.060* age + 2.609* texture + 1.307* hyperemia.

grading (area under the curve = 0.86; 95% confidence interval [CI] = 0.79–0.93; $p < .001$; Figure 2). A cutoff of 4.17 was chosen to increase the specificity (100%), whereas 6.60 corresponded to a sensitivity of 80.4% and specificity of 81.5%.

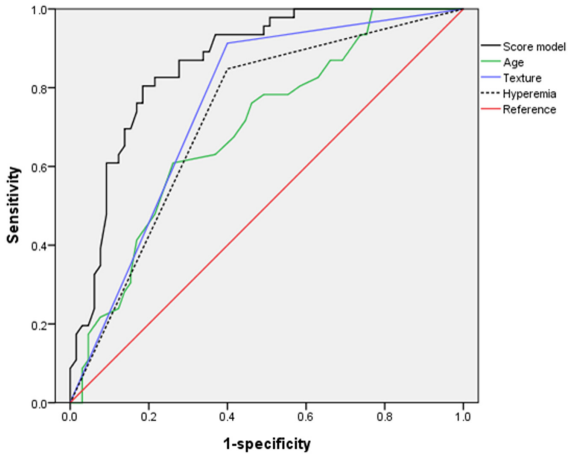

FIGURE 2. Receiver operating characteristic (ROC) analysis of the score model and various independent predictors for determining histology grading. The area under the ROC curves for the score model, age, texture, and hyperemia were 0.86 (95% confidence interval [CI] = 0.79–0.93; $p < .001$), 0.70 (95% CI = 0.60–0.79; $p < .01$), 0.76 (95% CI = 0.67–0.85; $p < .01$), and 0.72 (95% CI = 0.63–0.82; $p < .01$), respectively.

DISCUSSION

Laryngeal intraepithelial lesions can be classified on the basis of their histologic findings as vocal nodules, polyps, or cysts. Vocal leukoplakia is defined according to its appearance as a whitish patch on the vocal folds. However, vocal leukoplakia can indicate a variety of histologic diagnoses, including benign, premalignant, and malignant lesions.[13]

The transition from a normal epithelium to squamous cell carcinoma of the larynx is a lengthy process, and individual vocal leukoplakia can be recognized at some point during the process of transformation.[2,6,14] Cigarette smoking and alcohol consumption are generally recognized as major risk factors for vocal leukoplakia, similar to the situation for laryngeal cancer. In the present cohort, 87.5% of patients were regular smokers. Patients with vocal leukoplakia and high tobacco consumption are suggested to have a high incidence of malignancies,[15] with cigarette smoking suggested to be a good predictor. However, the incidences of smoking were similar in both groups in the current study. This may be because of the high overall smoking rate in the study populations, therefore, we suggested the scoring system is more helpful in smokers with vocal leukoplakia.

A long-term follow-up study demonstrated that the capability of lesions to evolve into invasive carcinoma was significantly correlated with the grade of dysplastic change of clinical vocal leukoplakia.[2,7] The grade of dysplasia is thus useful for predicting the incidence of malignant progression.[7,13,16] However, a histologic classification can only be made after excision of the lesions, and severe hoarseness may occur after inadequate excision without proper evaluation in advance (Figure 3). Therefore, it is important to identify preoperative factors and classify lesions before excision and thus the incidence of such complications can be decreased.

In the present study, laryngoscopic characteristics and patient age at presentation were identified as useful factors for differentiating between benign and malignant lesions. Application of the novel scoring system would thus help to ensure adequate removal of the leukoplakia lesion with preservation of healthy tissue.

Mucosal appearance of vocal leukoplakia has been suggested to be unreliable in predicting the histology findings.[17] However, the development of the distal-chip laryngoscope and high-quality digital imaging system has made it easier to record images of vocal fold lesions. In our previous report, we identified 6 laryngoscopic parameters that demonstrated good interobserver reliability. Four of these characteristics (color, texture, size, and hyperemia) were closely correlated with histologic findings.[10] However, these 4 variables may also interact with each other.

The results of the present study showed that 2 of these features, texture and hyperemia, had independent predictive values for the grade of differentiation in vocal leukoplakia. The appearance of oral leukoplakia and its relationship with malignancy has been reported for decades.[18,19] Inhomogeneous oral leukoplakia with erythromatous component was known as erythroleukoplakia or erythroplakia that had 4-fold higher risk in malignant transformation than those homogenous leukoplakia.[18] Around 91% of specimens of oral erythroplakia showed severe dysplasia to invasive carcinoma in histologic examinations.[19] However, the correlation of the irregular surface and redness with malignancy in vocal leukoplakia has not been well studied. The derived formula based on patient age, lesion texture, and hyperemia showed excellent discrimination for histologic diagnoses. For example, an older patient diagnosed with vocal leukoplakia with an irregular surface and hyperemia on laryngoscopic examination would be considered to be at high risk of malignancy, and their management should thus be more aggressive. In contrast, a relatively young adult with smooth vocal leukoplakia and lack of hyperemia would be more likely to benefit from conservative management (eg, proton-pump inhibitor and cessation of tobacco use) and close follow-up. Vocal leukoplakia can thus be stratified into high-risk and low-risk groups for malignancy

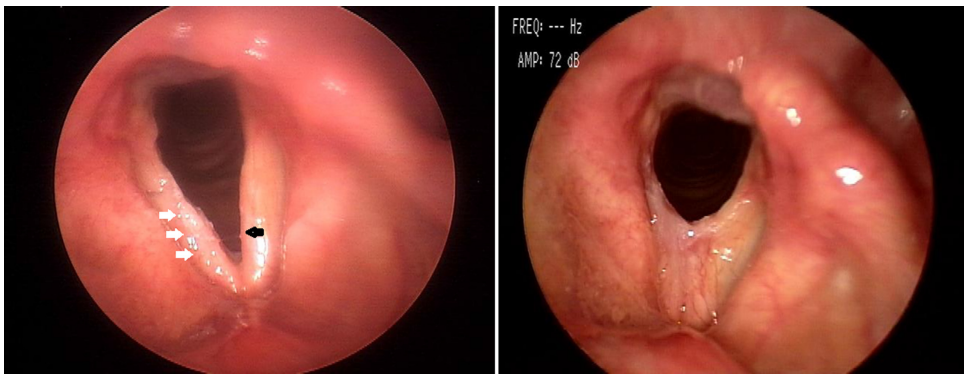

FIGURE 3. A case of a 68-year-old man with bilateral vocal leukoplakia. The laryngoscopy demonstrated regular surface in texture and absence of hyperemia on the right side (white arrow) and a tiny lesion on the left side (black arrow) (A); inadequate deep excision of bilateral cords resulted in an anterior laryngeal web. (B).

using the scoring system. Inexperienced staff can also be trained to interpret the laryngoscopic characteristics from existing photographs, thus reducing the incidence of misinterpretation. Not only the scoring model but also these laryngoscopic features are worth extensive study to search for connections between macroscopic and microscopic findings.

Although some reports have used novel equipment with a different light source for the clinical classification of vocal leukoplakia,[20,21] the present scoring system has the advantage of using a bright white light endoscope, which is commonly used in practice.

Despite the encouraging results of this study, the role of excisional biopsy for vocal leukoplakia still remained. For instance, in a case of low score vocal leukoplakia, after an interval of follow-up, direct laryngoscopy intervention would still be necessary whenever the lesions progressed. However, an optimal cutoff can be determined by individual institution for achieving the specific purpose of the scoring model. In those who used it to maximize its screening value, a practical lower reference cutoff score could be chosen to increase the specificity, whereas a higher cutoff would increase the sensitivity. Thus, the incidence of misinterpretation may decrease when the surgeon can weigh the risk before surgery.

There were still several limitations of this study. Although there was no literature in English with a larger series in measuring the preoperative risk factors of vocal leukoplakia, the limited case number of the present study still showed the boundary of the conclusions. The weakness of its retrospective design and high exclusion rate also may confound the study. However, the result from multivariate analysis convinced us that the above factors showed a positive predictive role even with such limitation. Vocal leukoplakia with the appearance of irregular surface and redness are suggested to be managed more aggressively than those without the features.

More clinical factors may show significant impaction when the cohort grows and increases the sensitivity and specificity by modifying the current scoring system. A prospective cohort study with a larger sample size is needed to validate the use of the novel scoring system and to confirm the optimal cutoff point.

CONCLUSION

The laryngoscopic characteristics showed a good inter-rater consistency and were related to the histologic results. The vocal leukoplakia can be categorized by the laryngoscopic characteristics and patients' age at presentation before surgery. The scoring model by combining these factors is helpful in guiding the decision on management.

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