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ORIGINAL ARTICLE

Vocal Cord Leukoplakia: Characteristics and Pathological Significance

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ABSTRACT

Leukoplakia is a nonspecific clinical term used to describe a mucosal white patch or plaque that cannot be easily scraped off. Leukoplakia of vocal cord represents a chronic inflammation or exposure to irritants which can also stimulate development of precancerous conditions or cancer. This study aimed to determine clinical and histopathological characteristics of vocal cord leukoplakia. A total of 66 patients were included. All patients with a clinical diagnosis of vocal cord leukoplakia who had undergone direct laryngoscopic examination and biopsy were analyzed retrospectively. The most common pathological finding was mild dysplasia (25.8%). Cancer was detected in 18.2% of cases. Malignancy was more frequent in cases with unilateral vocal cord involvement (23.4%) when compared with bilateral cases (5.2%) and in patients with localized lesions (19.3%) when compared with lesions involving whole cord (11.1%), but the differences were not statistically significant ($p > 0.05$). Smoking history was found to be related with cancer diagnosis ($p < 0.001$). In the presence of a serious smoking history, there is high-risk for malignancy and leukoplakia should be sampled immediately for histopathological examination. Although statistically not proven, cancer rates are higher in more localized and unilateral lesions.

Keywords: Vocal cords, Leukoplakia, Larynx, Laryngeal epithelium, Preneoplastic condition.

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INTRODUCTION

Leukoplakia can be described as a mucosal white patch or plaque that cannot be easily scraped off.[1] It is a clinical term and does not have a special pathological equivalent.[1] Although the term, leukoplakia, is generally used for oral and laryngeal lesions, it can be used to describe other white patches seen in gastrointestinal and genitourinary tract. Since, it is a nonspecific clinical term, leukoplakia is widely used in otolaryngology without consideration of etiology and histological features. Sometimes, terms of histopathological diagnosis, such as keratosis, hyperkeratosis and dysplasia are used instead of leukoplakia and terminological confusion arises.[1] In otolaryngological practice, leukoplakia of vocal cords is a remarkable and significant clinical finding. More or less, leukoplakia of vocal cord represents a chronic inflammation or exsposure to irritants which can also stimulate development of precancerous conditions or cancer. Smoking and other inhaled irritants, alcohol consumption, laryngopharyngeal reflux and infectious conditions are among common causes.

Histopathological diagnosis of a cancer or a premalignant condition in patients with vocal cord leukoplakia is crucial for prevention or early diagnosis of laryngeal squamous cell carcinoma (SCC). The survival rate of patients with laryngeal SCC has not significantly improved over the last decades despite advances in medical technologies and oncology.[2] For cancer of the larynx, early recognition is still the key to success. In this study, we aim to describe clinical characteristics and histopathological examination results of vocal cord leukoplakias.

MATERIALS AND METHODS

Subjects and Inclusion Criteria

The medical records of the patients who had surgery for vocal cord leukoplakia between January 2000 and March 2011 at our institution were retrospectively reviewed after Institutional Ethical Board approval. Our policy for vocal cord leukoplakia sampling is total cold knife excision of the lesion for histopathological examination. Initially, 94 patients were identified, but only 66 of these patients fulfilled the study inclusion criteria. Inclusion criteria were:

a. Persistent leukoplakia of true vocal cords at least for 2 months
b. Absence of erythroplakia
c. Absence of an obvious mass lesion or exophytic lesion of vocal cords
d. Absence of previous head and neck malignancy
e. Absence of previous endolaryngeal surgery
f. Absence of history of radiation therapy to head and neck region
g. Normal bilateral vocal fold mobility
h. Absence of any other synchronous undefined laryngeal lesions.

Review Process

Demographic features, symptoms, localization and extension of leukoplakia according to laryngoscopic examination, smoking habits and pathological examination results were reviewed. For definition of lesion extention,

each vocal cord was divided into three equal segments: Anterior, middle and posterior. Frequencies of involvement of totally six parts on the two vocal cords were determined for each patient. Involvement of all three segments on the same vocal cord was defined as total involvement. Relation between total involvement of vocal cord(s) by leukoplakia and cancer detection rate was statistically analyzed. Cancer detection rates among cases with unilateral and bilateral involvement of the cords were also compared.

Histopathological examination results were classified according to the most severe form of the lesion for each patient. The histopathological findings were graded from mild to severe as inflammatory changes, hyperkeratosis, squamous hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma *in situ*, microinvasive SCC and invasive SCC. These findings were classified in four groups: inflammatory changes, hyperkeratosis, squamous hyperplasia in mild changes group (group 1); mild dysplasia and moderate dysplasia in early precancerosis group (group 2); severe dysplasia and carcinoma *in situ* in advanced preinvasive lesions group (group 3) and microinvasive SCC and invasive SCC in cancer group (group 4).

Patients were also grouped according to smoking history. Four groups consisted of patients with more than 40 pack-year smoking history, between 20 and 40 pack-year smoking history, less than 20 pack-year smoking history and without a smoking history.

Statistical Analysis

In statistical analysis, Fisher's exact test was used for categorical variables, and Mann-Whitney test was used for continuous variables since the data was not normally distributed. The p-values of ≤ 0.05 were considered to be statistically significant.

RESULTS

Totally, 66 patients (61 male and 5 female) met the inclusion criteria for analysis. Mean age of the patients was 54.8 years (ranged between 35 and 76 years, SD, 10.1). Most common presenting symptom was hoarseness in 59 (89.4%) patients and globus sensation was encountered in seven patients (10.6%). Nineteen patients (28.8%) had reflux symptoms besides voice change.

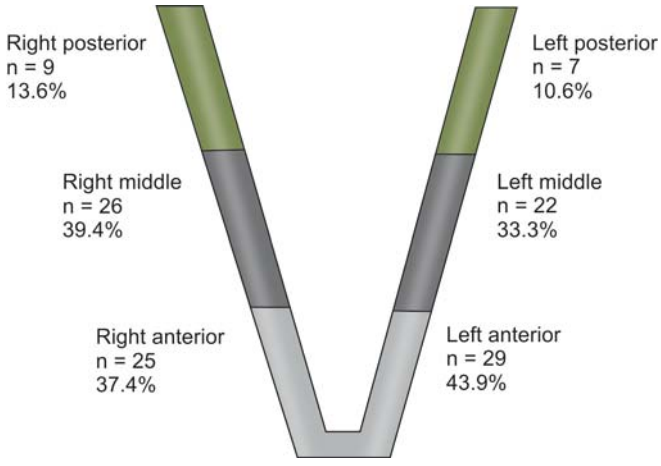

Fig. 1: Localization of leukoplakia on vocal cords

Most common site of involvement was left anterior (43.9%; Fig. 1). Posterior segment involvement was rare and posterior of the right cord and the left cord were involved in 13.6 and 10.6% of the cases respectively. The most common histopathological finding was mild dysplasia found in 17 patients (25.8%; Table 1). Microinvasive SCC was reported in four patients (6.1%) and invasive SCC in eight patients (12.1%).

In 19 patients (28.8%), vocal cords were involved bilaterally. Cancer development was reported in one (5.2%) of 19 patients with bilateral involvement and 11 (23.4%) of 47 patients with unilateral involvement. The difference between the two groups was not statistically significant (Fisher's exact test $\chi^2 = 2.99$, $p = 0.156$).

Total involvement of vocal cord was detected unilaterally in five patients (7.6%) and bilaterally in four patients (6.1%). Cancer (microinvasive or invasive SCC)

Table 1: Histopathological examination results (SCC: Squamous cell carcinoma)

Pathological results	*n*	*%*	*Groups*	*n*	*%*
Inflammatory changes	10	15.1	Group I (mild changes group)	22	33.3
Hyperkeratosis	4	6.1			
Squamous hyperplasia	8	12.1			
Mild dysplasia	17	25.8	Group II (early precancerosis group)	26	39.4
Moderate dysplasia	9	13.6			
Severe dysplasia	5	7.6	Group III (advanced preinvasive lesions group)	6	9.1
Carcinoma *in situ*	1	1.5			
Microinvasive SCC	4	6.1	Group IV (cancer group)	12	18.2
Invasive SCC	8	12.1			
Total	66	100.0		66	100.0

Table 2: Comparison of histopathological examination results with smoking history

Smoking history	*Group I (%)*	*Group II (%)*	*Group III (%)*	*Group IV (%)*	*Total*
Heavy smoker (> 40 pack-year)	1 (7.1)	4 (28.6)	1 (7.1)	8 (57.2)	14 (100.0)
Moderate smoker (20-40 pack-year)	5 (33.3)	6 (40.0)	1 (6.7)	3 (20.0)	15 (100.0)
Light smoker (< 20 pack-year)	9 (40.9)	12 (54.5)	0	1 (4.6)	22 (100.0)
No smoking history	7 (46.7)	5 (33.3)	3 (20.0)	0	15 (100.0)

was present in 11 (19.3%) of 57 patients with partial vocal cord involvement and in one (11.1%) of nine patients with total vocal cord involvement. The difference between the two groups was not statistically significant (Fisher's exact test $\chi^2 = 0.35$, $p = 1.0$).

When patients were classified according to smoking history, most common histological diagnosis was either microinvasive SCC or invasive SCC in heavy smokers whereas either group I or group II pathologies were more common in less smokers (Table 2). Difference in cancer frequency between nonsmokers (group IV) and with smoking history (groups I, II, III) was statistically significant (Mann-Whitney test, $u = 74.0$, $p < 0.001$).

DISCUSSION

Leukoplakia can be a clinical representation of a benign pathological situation, such as inflammation, any level in carcinogenic transformation or a cancer. For determining accurate histological diagnosis of leukoplakia, light microscopic examination still remains the most common and reliable method. Histopathological grading of leukoplakia is not uniform but it is mainly related to the potential for malignant transformation. There are more than 20 classifications of laryngeal epithelial lesions worldwide but two of them are more commonly used: WHO dysplasia grading system and Ljubljana classification.[1,3] In WHO dysplasia classification system, categories are hyperplasia with increased number of cells; mild, moderate and severe dysplasia; and carcinoma *in situ*. Ljubljana classification includes mainly three groups: lesions with minimal risk of progression to invasive carcinoma, including squamous and basal-parabasal cell hyperplasia; potentially malignant group (atypical hyperplasia or risky epithelium); and carcinoma *in situ*. Whatever, the system used in histological evaluation and classification, severity of changes in laryngeal epithelium can be put into a scale from mildest to most severe according to potential biological behavior. In the present study, we put the histological findings into an order according to malign transformation potential and degree of changes in normal epithelial architecture. Only the most severe change was taken into account. The first three degrees were inflammation, keratosis and epithelial hyperplasia without atypia. These 3° constituted the mild changes group with no or minimal risk of malignant transformation. We separated severe dysplasia from the mild and the moderate forms and evaluated with carcinoma *in situ* in advanced preinvasive lesions group. The mild and the moderate degrees of dysplasia were grouped as early precancerosis group. The rationale for this grouping is difficulty of distinguishing between severe dysplasia and carcinoma *in situ* histopathologically and common coexistence of these two histopathological diagnoses in the same pathological specimen. Cancer group was consisted of microinvasive and invasive forms of SCC.

Recently, noninvasive and convenient diagnostic methods for detection of laryngeal dysplasia and cancer development are evolving. These include touch smear cytology, optical coherence tomography, narrow band imaging, fluorescence laryngoscopy and contact endoscopy.[4-9] However, none of these are in common clinical use so biopsy and histopathological examination are still the mainstay of the diagnostic management process.

When a vocal cord leukoplakia accompanies an irregular mass lesion on the vocal cords, high clinical suspicion for laryngeal cancer arises. In that case management strategy is not so debatable. However, if a vocal cord leukoplakia only appearing like a patch or simple whitening of mucosa, there are different management strategies including follow-up without any medication and cessation of carcinogens, such as tobacco and alcohol; treatment with retinyl palmitate, proton pump inhibitors; direct laringoscopy and biopsy for histological diagnosis; excisional biopsy; ablation with laser and stripping.[10-14] Among these, follow-up with cessation of possible carcinogens, such as tobacco and alcohol together with treating irritating acid reflux is a common strategy. However, clinical characteristics of the disease should be well known not to lose time in case of a cancer or a high-risk lesion of cancer development. Head and neck cancers are more frequent among people with low socioeconomic status and it is not infrequent to see non compliant patients who do not attend follow-up visits regularly and do not change smoking and drinking habits. So that, we planned this study to determine clinical characteristics of vocal cord leukoplakia which may harbor a cancer or carry a high-risk for cancer development.

In English literature, studies regarding vocal cord leukoplakias are scarce. Many of the studies are about vocal cord dysplasias and malignant transformation rates of dysplastic lesions of vocal cords in time. Localization of the vocal cord leukoplakia is also rarely studied to date. Superior surface and anterior parts of vocal cords reported to be more involved by glottic dysplasia but the data regarding common localizations of vocal cord leukoplakia is not present according to our knowledge.[15,16] In the present study, we have found that, like leukoplakias are commonly located on anterior and medial parts of the cords and posterior involvement was rare. A comprehensive review of laryngeal leukoplakia by Isenberg et al was published in 2008.[17] According to this review, mild/moderate dysplasia and severe dysplasia were found in 33.5 and 15.2% of the laryngeal leukoplakia biopsy specimens respectively. The overall malignant transformation rate reported was 8.2% in vocal cord dysplasias. Malignant transformation rates during follow-up were 3.7, 10.1 and 18.1% in patients with no dysplasia, with mild and moderate dysplasia and with severe dysplasia respectively. In this review, the authors did not report the rate of cancer at initial biopsy. Total frequency of dysplasias and carcinoma *in situ* in our study is 48.5% and consistent with the rates reported in this review. In our study, cancer was detected in 18.2 % of the patients with vocal cord leukoplakia and it is relatively high.

In this study, we observed that localized and unilateral lesions are more related with cancer development however, this relation could not be proved statistically. Future studies may show possible relationship between localized lesions with increased cancer development risk. Strong relationship of severe smoking history with high cancer development rate within the vocal cord leukoplakia was documented in our study, so that a high-risk group is well-defined. Although the difference was not statistically significant, we recommend biopsy of a localized and unilateral leukoplakia immediately when smoking history is present.

REFERENCES

1. Gale N, Zidar N. Benign and potentially malignant lesions of the squamous epithelium and squamous cell carcinoma. In: Cardesa A, Slootweg PJ (Eds). Pathology of the Head and Neck. Springer, Berlin-Heidelberg 2006;1-29.
2. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: A site-specific analysis of the SEER database. Int J Cancer 2005;114:806-16.
3. Hellquist H, Cardesa A, Gale N, Kambic V, Michaels L. Criteria for grading in the Ljubljana classification of epithelial hyperplastic laryngeal lesions. A study by members of the Working Group on Epithelial Hyperplastic Laryngeal Lesions of the European Society of Pathology. Histopathology 1999;34: 226-33.
4. Ustundag E, Kaur AC, Boyaci Z, Keskin G, Aydin O. Combined use of histopathology with touch smear cytology in biopsies of the larynx. Eur Arch Otorhinolaryngol 2006;263: 866-71.
5. Kraft M, Glanz H, von Gerlach S, Wisweh H, Lubatschowski H, Arens C. Clinical value of optical coherence tomography in laryngology. Head Neck 2008;30:1628-35.
6. Watanabe A, Taniguchi M, Tsujie H, Hosokawa M, Fujita M, Sasaki S. The value of narrow band imaging for early detection of laryngeal cancer. Eur Arch Otorhinolaryngol 2009;266: 1017-23.
7. Arens C, Reussner D, Woenkhaus J, Leunig A, Betz CS, Glanz H. Indirect fluorescence laryngoscopy in the diagnosis of precancerous and cancerous laryngeal lesions. Eur Arch Otorhinolaryngol 2007;264:621-26.
8. Warnecke A, Averbeck T, Leinung M, Soudah B, Wenzel GI, Kreipe HH, Lenarz T, Stöver T. Contact endoscopy for the evaluation of the pharyngeal and laryngeal mucosa. Laryngoscope 2010;120:253-58.
9. Malzahn K, Dreyer T, Glanz H, Arens C. Autofluorescence endoscopy in the diagnosis of early laryngeal cancer and its precursor lesions. Laryngoscope 2002;112:488-93.
10. Issing WJ, Struck R, Naumann A. Long-term follow-up of larynx leukoplakia under treatment with retinyl palmitate. Head Neck 1996;18:560-65.
11. Simpson CB, Archilla AS, Velázquez RA, McGuff HS. Resolution of vocal fold leukoplakia with proton-pump inhibitor therapy. Ear Nose Throat J 2006;85:362-64.
12. Minni A, Barbaro M, Rispoli G, Diaferia F, Bernardeschi D, Filipo R. Treatment with laser CO_2 cordectomy and clinical implications in management of mild and moderate laryngeal precancerosis. Eur Arch Otorhinolaryngol 2008;265:189-93.
13. Gallo A, de Vincentiis M, Della Rocca C, Moi R, Simonelli M, Minni A, Shaha AR. Evolution of precancerous laryngeal lesions: A clinicopathologic study with long-term follow-up on 259 patients. Head Neck 2001;23:42-47.
14. Sadri M, McMahon J, Parker A. Management of laryngeal dysplasia: A review. Eur Arch Otorhinolaryngol 2006;263: 843-52.
15. Lahav Y, Burns JA, Feinberg S, Heaton JT, Zeitels SM. Initial anatomic geographic presentation of glottal dysplasia. Ann Otol Rhinol Laryngol 2009;118:321-25.
16. Zeitels SM. Premalignant epithelium and microinvasive cancer of the vocal fold: The evolution of phonomicrosurgical management. Laryngoscope 1995;105(S1):1-44.
17. Isenberg JS, Crozier DL, Dailey SH. Institutional and comprehensive review of laryngeal leukoplakia. Ann Otol Rhinol Laryngol 2008;117:74-79.

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