Diagnosis of Vocal Cord Leukoplakia: The Role of a Novel Narrow Band Imaging Endoscopic Classification

Xiao-Guang Ni, MD, PhD; Ji-Qing Zhu, MD; Qing-Qing Zhang, MD; Bao-Gen Zhang, MD; Gui-Qi Wang, MD, PhD

Objectives: The purpose of this study was to introduce a new narrow band imaging (NBI) endoscopic classification for the diagnosis of vocal cord leukoplakia.

Study Design: Case series.

Methods: From January 2010 to February 2018, a total of 120 cases of vocal cord leukoplakia were enrolled in this study. The NBI endoscopic system was used to examine the vocal cords. Each lesion was observed by NBI endoscopy and evaluated according to the detailed morphologic findings of intraepithelial papillary capillary loop (IPCL). The superficial IPCL patterns were classified into six types (types I–VI). The differential diagnosis abilities of NBI classification for benign and malignant leukoplakia were investigated.

Results: Out of the 120 cases of vocal cord leukoplakia, 81% (97 of 120) related to benign lesions (including inflammation, epithelial proliferation, hyperkeratosis, dyskeratosis, mild dysplasia, and moderate dysplasia); the remaining 19% (23 of 120) consisted of malignant lesions (including severe dysplasia, carcinoma in situ, and invasive carcinoma). The accuracy of differential diagnosis for vocal cord leukoplakia using NBI endoscopy was up to 90.8% (109 of 120), significantly higher than that of white light imaging (70.0%, 84 of 120) ($\chi^2 = 16.536, P = 0.000$). The sensitivity, specificity, and positive and negative predictive values of the diagnosis for malignant vocal cord leukoplakia under the NBI endoscope were 82.6%, 92.8%, 73.1%, and 95.7%, respectively. There is relatively good consistency between the NBI endoscopic diagnosis and pathological diagnosis (kappa = 0.718, P = 0.000).

Conclusion: The new NBI endoscopic classification of vocal cord leukoplakia can improve the accuracy of distinguishing benign and malignant leukoplakia.

Key Words: Laryngoscopy, narrow band imaging, vocal cord, leukoplakia, diagnosis.

Level of Evidence: 4

INTRODUCTION

Vocal cord leukoplakia is a common cause of hoarseness. It can be seen that the surface of vocal cord is covered by white plaque under laryngoscopy, and the white plaque is difficult to remove. Pathologically, vocal cord leukoplakia can be stratified according to the thickness of the keratin layer of the squamous epithelium, which can be classified as parakeratosis and hyperkeratosis. The disease may be accompanied by simple hyperplasia, dysplasia, and even carcinoma; thus, it is regarded to be precancerous laryngeal lesions. The appearances of vocal cord leukoplakia are largely identical in the macroscopic examination even though the pathological character may differ. This makes it difficult for physicians to evaluate the extent of dysplasia of vocal cord leukoplakia and detect the occurrence of canceration using the conventional laryngoscopy, which might result in overtreatment or undertreatment of vocal cord leukoplakia in different patients. Therefore, an accurate preoperative assessment of the pathological character of vocal cord leukoplakia shows clinical significance in the selection of an appropriate treatment plan and the prediction of prognosis of a patient. Recent studies have found that narrow band imaging (NBI) endoscopy can facilitate the early and differential diagnosis of head and neck cancers by observing the intraepithelial papillary capillary loop (IPCL) patterns at the mucosal surfaces, and the examination has come to be widely used in the diagnosis of laryngeal cancer. We were the first to put forward the NBI endoscopy-based diagnostic classification of laryngeal lesions in 2011, and vocal cord leukoplakia was then defined as a type III lesion. Recently, the diagnostic classification using NBI endoscopy has been applied to identify benign and malignant leukoplakia, but the results from different scholars are quite different. To resolve the inconsistency, a study focusing on vocal cord leukoplakia was carried out, and a new NBI classification of vocal cord leukoplakia was introduced by reclassifying the previous system in a more accurate and delicate manner and discussing the clinical value of the
MATERIALS AND METHODS

Clinical Materials

The patients who complained of hoarseness were recruited to receive endoscopic examination of the larynx with a video endoscope enabling NBI observation at the Department of Endoscopy of Cancer Hospital, Chinese Academy of Medical Science, Beijing, China, from January 2010 to February 2018. Patients who had white plaque at the surfaces of the vocal cords were included in the study. All patients had a definite pathological diagnosis. Exclusion criteria consisted of the following: 1) obvious benign or malignant lesions on the vocal cords, for example, cauliflower-like or ulcerative tumor, polyp, cyst, Reinke's edema, and papilloma; 2) definite pathological diagnosis; and 3) allergy to lidocaine, hemorrhagic disease, and inability to understand and sign an informed consent form. The study was approved by the medical ethics committee of the above hospital, and informed consent was obtained from each patient prior to inclusion.

Examination of Vocal Cord Leukoplakia

Examination of the vocal cord leukoplakia was performed using an Olympus Evis Lucera 260 system incorporating a BF-260 video-bronchoscope (Olympus Medical Systems, Tokyo, Japan). The examinations of all patients were performed by one experienced endoscopist. Patients were placed in a horizontal, supine position. Prior to endoscopic examination, the surface of the nasal cavity was anesthetized and lubricated with 2% lidocaine hydrochloride gel. The instrument was introduced through the nasal passage to observe, in sequence, the nasopharynx, oropharynx, hypopharynx, and larynx. The larynx was first observed in the white light image (WLI) mode and then examined under NBI mode. Representative images were collected before direct vision biopsy of the vocal cord leukoplakia. The biopsy specimens were preserved in 10% formalin and submitted to pathological examination.

Classification of Vocal Cord Leukoplakia According to IPCLs at Mucosal Surfaces Under NBI Endoscope

The followings are the six types of vocal cord leukoplakia classified according to the morphologic characteristics of the IPCLs at the mucosal surfaces through NBI endoscopy (Fig. 1):

Type I: There are no IPCLs, but white plaque can be observed on the vocal cord, with obliquely running vessels and branching vessels indistinctly present under the white plaque.

Type II: There are white patches on the vocal cord, but neither IPCLs nor obliquely running vessels or branching vessels can be found.

Type III: IPCLs can be seen at the surface of the vocal cord mucosa where the epithelium is not covered by the leukoplakia, showing small brown spots with a relatively regular arrangement and without clear boundaries. No obliquely running vessels or branching vessel can be observed.

Type IV: IPCLs can be observed on the vocal cord, showing large brown spots and embedded at the surface of white plaque.

Type V: IPCLs on the vocal cord can be seen, showing large brown spots, which appear at the surface of the vocal cord mucosa outside the leukoplakia with obvious boundaries.

Type VI: IPCLs are visible at the surface of the vocal cord, characterized by large brown spots or twisted earthworm-like vessels distributed at the surface of the leukoplakia and also at the surface of the vocal cord epithelium outside the leukoplakia.

Fig. 1. Narrow band imaging classification of vocal cord leukoplakia according to IPCL patterns. (A1–3) type I IPCL pattern; (B1–3) type II IPCL pattern; (C1–3) type III IPCL pattern; (D1–3) type IV IPCL pattern; (E1–3) type V IPCL pattern; (F1–3) type VI IPCL pattern. IPCL = intraepithelial papillary capillary loop. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
practiced NBI endoscopic examination for over 3 years) using the conventional WLI and NBI endoscopy, respectively. They were not informed of the leukoplakia pathological diagnosis before evaluation. The two endoscopists consensus evaluations were accepted as final classification and diagnosis results. Under the WLI mode, the vocal cord leukoplakia was roughly divided into two subtypes: 1) malignant leukoplakia: appeared as thick white plaque, a rough surface, and congestive vocal cord mucosa; and 2) benign leukoplakia: appeared as thin white plaque in a uniform color and a flat surface. Under the NBI endoscope, the vocal cord leukoplakia was classified as 1) malignant leukoplakia: types IV, V, and VI; and 2) benign leukoplakia: types I, II, and III. The pathological results were regarded as the gold standard for definitive diagnosis of vocal cord leukoplakia. Histopathologically, the vocal cord leukoplakia can be divided into two types: 1) malignant leukoplakia: severe dysplasia, carcinoma in situ, and invasive carcinoma; and 2) benign leukoplakia: inflammation, simple hyperplasia, mild and moderate dysplasia.

**Statistical Analysis**

The statistical analysis software SPSS 20.0 (IBM Corp., Armonk, NY) was used in this study. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the diagnosis of vocal cord leukoplakia comprising malignancies in the WLI and NBI modes were calculated. The chi-squared test was applied to the analysis of intergroup differences, with $P < 0.05$ being considered statistically significant. The kappa statistic was used to measure the agreement between the WLI and NBI endoscopic diagnoses and the pathological ones. This study characterized kappa over 0.7 as excellent, 0.4 to 0.7 as fair to good, and below 0.4 as poor.

### RESULTS

#### Clinical and Pathological Characteristics

A total of 100 patients were enrolled in this study, including 96 males and four females, with a median age of 56 years (age 26–86 years). These patients were involved in 80 cases of unilateral vocal cord and 20 cases of bilateral ones. In other words, this study analyzed a total of 120 cases of vocal cord leukoplakia, among which 14.2% (17 of 120) related to chronic inflammation, 25.0% (30 of 120) to epithelial proliferation/hyperkeratosis/dyskeratosis, 27.5% (33 of 120) to mild dysplasia, 14.2% (17 of 120) to moderate dysplasia, 13.3% (16 of 120) to dysplasia/carcinoma in situ, and 5.8% (7 of 120) to invasive carcinoma. See Table I.

#### Comparison of WLI and NBI in Diagnosis of Vocal Cord Leukoplakia

A total of 84 cases of vocal cord leukoplakia (14 malignant and 70 benign) were accurately diagnosed by means of the conventional WLI endoscopy, representing a diagnostic accuracy of 70.0% (84 of 120), whereas accurate diagnosis of 109 cases of vocal cord leukoplakia (19 malignant and 90 benign) was achieved by means of NBI endoscopy, with the diagnostic accuracy of 90.8% (109 of 120). The difference between the two methods was statistically significant ($\chi^2 = 16.536, P = 0.000$). The sensitivity, specificity, PPV, and NPV of the diagnosis of malignant vocal cord leukoplakia under the conventional WLI endoscopy were 60.8%, 72.2%, 34.1%, and 88.6%, respectively. The sensitivity, specificity, PPV, and NPV of the diagnosis of malignant vocal cord leukoplakia under the NBI endoscopy were 82.6%, 92.8%, 73.1% and 95.7%, respectively. In comparison with the conventional WLI, the NBI endoscopic diagnosis of malignant leukoplakia had a higher specificity ($\chi^2 = 14.265, P = 0.000$) and a greater PPV ($\chi^2 = 9.648, P = 0.002$). In addition, there was no statistically significant difference between the two methods in sensitivity ($\chi^2 = 2.681, P = 0.189$) and NPV ($\chi^2 = 3.146, P = 0.089$). See Table II. The consistency test showed that the degree of consistency between WLI and pathological diagnosis was poor (kappa = 0.254, $P = 0.003$), and the degree of consistency between NBI and pathological diagnosis was excellent (kappa = 0.718, $P = 0.000$).

#### Association Between NBI Endoscopic Classifications of Vocal Cord Leukoplakia and Pathological Findings

In the NBI mode, vocal cord leukoplakia with benign lesions was mainly classified as type II, accounting for 63.8% (60 of 94) of all benign cases according to the NBI endoscopic classification. The diagnostic accuracy of benignity among the type II cases was 64.2%, with the sensitivity, specificity, PPV, and NPV of 58.8%, 87.0%, 95.0%, and 33.3%, respectively. In the cases of...
malignancy, the vocal cord mucosa not covered by white plaque was observed carefully because there was usually abnormal vessel dilatation (type V and VI), which occurred in 69.2% of all malignant cases. The diagnostic accuracy of malignancy among the type V and VI cases was 85.8%, with the respective sensitivity, specificity, PPV, and NPV of 52.2%, 93.8%, 66.7%, and 89.2% (see Table III).

DISCUSSION
Vocal cord leukoplakia is considered to be precancerous lesions closely relating to the incidence of laryngeal cancer.8,9 Benign leukoplakia has a certain degree of self-restriction and reversibility, which can be observed or superficial excision. For malignancies, treatment should be administered as early as possible, and deeper excision should be performed to prevent recurrence and deterioration.10,11 Laryngoscopy is the most important examination for the diagnosis of vocal cord leukoplakia. The relationship between leukoplakia and atypical hyperplasia is determined mainly by observing the color of leukoplakia, surface texture, size, hyperemia, thickness, edema, symmetry, and so on.12 Particularly, nonhomogeneous lesion texture and existence of hyperemia are independent factors for predicting the risk of malignancy under the laryngoscope.13 However, the preoperative evaluation and examination using the conventional video laryngoscopy are unlikely to fully agree with the postoperative pathological finding, which often leads to overtreatment or undertreatment.

NBI is a novel imaging technique for endoscopic diagnosis, which has gained rapid development in recent years. It was first applied to the examination of early gastrointestinal cancer.14 Over the past few years, this new image-enhanced technology already has proven effective in the early diagnosis of head-and-neck squamous cell carcinoma, including laryngeal, hypopharyngeal, oropharyngeal, nasopharyngeal, and oral cancers, as well as for unknown primary cervical lymph node metastasis.15–17 Unlike the common endoscopes with a white light source having red, green, and blue wavelengths, the NBI endoscope uses the light of specific blue and green wavelengths (blue at 415 nm and green at 540 nm) and eliminates the longest red ones with an RGB (red, green, and blue) filter so that the light can only reach the surface layer of the tissue and enhance the details of certain structure of the surface of the mucosa, especially the IPCL patterns at the mucosal surfaces. This is regarded as a convenient approach to the early identification of malignant tumors under the endoscope.18,19 The NBI endoscope is mainly used to evaluate the character of lesions by observing the changes of the IPCL patterns at the mucosal surfaces.20 Based on the dynamic changes of the IPCL patterns at the mucosal surfaces as the larynx undergoes the pathological changes from a normal state to dysplasia and then to carcinoma, we first proposed the classification of five IPCL pattern types of laryngeal lesions.7 The classification reported an accuracy of 90.4% in relation to the diagnosis of laryngeal lesions, significantly higher than that of the conventional WLI (76.9%). According to the classification, IPCL type V suggests a relatively high possibility of malignancy, among which type Va is characteristic of large irregular brown spots, solid or hollow with clear outlines, and corresponds to severe dysplasia and carcinoma in situ. The present diagnosis and classification using the NBI laryngoscope worldwide basically depends on the Ni classification. Meta-analysis showed that the overall sensitivity of the laryngeal cancer diagnosis based on type V was 0.82 (95% confidence interval [CI]: 0.75–0.87) and the specificity was 0.93 (95% CI: 0.82–0.97).21

<table>
<thead>
<tr>
<th>NBI Patterns</th>
<th>n</th>
<th>Chronic Inflammation</th>
<th>Epithelial Proliferation/ Hyperkeratosis/Dyskeratosis</th>
<th>Mild Dysplasia</th>
<th>Moderate Dysplasia</th>
<th>Severe Dysplasia/ Carcinoma in Situ</th>
<th>Invasive Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>60</td>
<td>9</td>
<td>18</td>
<td>18</td>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>21</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>V</td>
<td>13</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>VI</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>17</td>
<td>30</td>
<td>33</td>
<td>17</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

NBI = narrow band imaging.
Recently, there have been numerous reports on the Ni classification-based differential diagnosis of vocal cord leukoplakia under the NBI endoscope aiming to improve the accuracy of preoperative differential diagnosis. However, the findings of these studies on the NBI endoscopic diagnosis of vocal cord leukoplakia show a poor consistency. Staníková et al. reported that the sensitivity of the diagnosis of malignant lesions in patients with vocal cord leukoplakia under the NBI endoscope was 88.0% and specificity was 89.5%.22 Yang et al. carried out a differential diagnosis of suspicious malignant vocal cord lesions (including vocal cord leukoplakia) using the NBI endoscopy, according to which the sensitivity, specificity, PPV, NPV, and accuracy were 66.7%, 72.5%, 60.9%, 78.0%, and 70.6%, respectively.23 Shoffel-Havakuk et al., in order to avoid interrater differences, invited six experienced laryngoscopists to evaluate the NBI endoscopic images independently and summarized the evaluation results, from which they found that the respective sensitivity, specificity, PPV, and NPV of laryngeal cancer diagnosis under the NBI endoscope were 58.6%, 61.2%, 56.7%, and 63.1%, respectively.24 The reasons for this inconsistency are mainly because the surface of the vocal cords is covered with white patches, which affects the exposure of IPCL at the surface of the mucous membrane, namely the umbrella effect,25 which leads to the difference between the emphases and perspectives of the different scholars at the time of observation. In order to improve the accuracy and consistency of the Ni classification-based differential diagnosis of vocal cord leukoplakia under the NBI endoscope, we further divided the vocal cord leukoplakia into several subtypes according to the appearances of different lesions under the NBI endoscope and put forward a new NBI classification focusing on the vocal cord leukoplakia. The new method was designed to solve the problems brought by the above umbrella effect and improve the consistency between NBI endoscopic diagnosis and pathological diagnosis. It is a crucial procedure to differentiate benign and malignant lesions of vocal cord leukoplakia. If carcinoma is detected, in most cases it indicates laryngeal cancer in the early stage. Therefore, physicians should focus on searching for evidently large brown spots on the vocal cords, that is, the existence of type Va specified in the Ni classification, when using the NBI endoscopy to diagnose vocal cord leukoplakia. To facilitate the observation under the NBI laryngoscope, the locations and sizes of spots corresponding to different types of vocal cord leukoplakia have been presented and distinguished in the new classification. In addition to observing the surface of the leukoplakia, the entire vocal cord should be observed closely, especially to observe the surface not covered by the leukoplakia, and the information about whether leukoplakia is malignant may probably appear here. For the new NBI classification of vocal cord leukoplakia, types I to III indicate benign leukoplakia and types IV to VI suggest malignancies. The classification is highly consistent with the pathological diagnosis of vocal cord leukoplakia. The accuracy of this classification in judging the pathological nature of vocal cord leukoplakia was 90.8%, which is significantly better than that of the conventional WLI endoscopy (70.0%).

CONCLUSION

The differential diagnosis of vocal cord leukoplakia remains the focus and challenge in the field of laryngoscopic examination. The NBI endoscope is useful for the early diagnosis of laryngeal cancer because NBI endoscopy shows a relatively high accuracy according to the abnormal IPCL patterns at the mucosal surfaces. However, if the IPCLs are covered by the white plaque on the vocal folds, it will lead to reduced sensitivity to the diagnosis. In order to overcome this effect, this study subdivided the original NBI endoscopic diagnostic classification and proposed a new diagnostic classification of vocal cords leukoplakia. The new NBI endoscopic classification of vocal cord leukoplakia can improve the accuracy of distinguishing benign and malignant leukoplakia. Whether the NBI classification can improve the diagnostic accuracy of leukoplakia and the consistency between the different observers still needs further confirmation by multicenter clinical trials.

BIBLIOGRAPHY


