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Helicobacter pylori Presence in Laryngeal Fold Pathologies and the Importance of Localization on Fold

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ABSTRACT

Objective: *Helicobacter pylori* (HP) is a gram-negative, microaerophilic, spiral bacterium that resides in the stomach and duodenum. The association of HP with gastric cancer has been classified as a group 1 carcinogen. It can have similar effects in other tissues, such as the larynx, as it does in the gastric mucosa. *Helicobacter pylori* can be detected in the normal larynx and benign, premalignant, and malignant laryngeal lesions. We aimed to investigate whether HP was a risk factor for carcinoma and its incidence according to the laryngeal region.

Material and Methods: One hundred six patients who underwent laryngeal suspension microlaryngoscopy in Adana City Training and Research Hospital ENT clinic between 2020 and 2022 were included in the study. The patients were divided into three groups according to the pathology results. Group 1 was defined as benign lesions (laryngeal polyp, cyst, nodule, Reinke's edema), group 2 as precancerous (dysplasia, Ca-in-situ), and group 3 as T1 glottic laryngeal carcinoma. Tissue sections were evaluated for HP with a light microscope.

Results: The rate of HP observed in the larynx tissue detected histopathologically was 2.8% in the benign group, 6.3% in the premalignant group, and 1.9% in the malignant group (p= 0.648). No significant difference was observed in the incidence of *Helicobacter pylori* when evaluated according to the laryngeal regions, such as anterior, middle, posterior, or along the entire cord (p= 0.404).

Conclusion: *Helicobacter pylori* can infect the laryngeal mucosa but is not a risk factor for laryngeal cancer. The location of the laryngeal lesion on the vocal fold has no effect on HP positivity.

Keywords: Laryngeal carcinoma, precancerous, benign lesions, *Helicobacter pylori*, location

ÖZ

Vokal Kord Lezyonlarında Helikobakter Pilori Varlığı ve Lezyonun Korddaki Yerinin Önemi

Giriş: Helikobakter pilori mide ve duodenumda bulunan, gram-negatif, mikroaerofilik, spiral bir bakteridir. Gastrik kanser için grup 1 karsinojen olarak kabul edilmektedir. Gastrik mukozada yaptığı lezyonları laringeal mukozada da yapabilir. Normal larinks mukozasında, benign, premalign ve malign laringeal lezyonlarda rastlanabilir. Bu lezyonlardaki HP varlığını, larinks kanseri ile ilişkisini ve lezyonun vokal korddaki yerine göre bulunma olasılığını incelemeyi amaçladık.

Gereç ve Yöntemler: 2020-2022 yılları arasında Adana Şehir Eğitim ve Araştırma Hastanesi KBB kliniğinde larinks süspansiyon mikrolaringoskopi yapılan 106 hasta çalışmaya alındı. Hastalar patoloji sonucuna göre üç gruba ayrıldı. Grup 1 benign (vokal nodül, polip, kist, reinke ödemi), grup 2 premalign (displazi, karsinoma in situ), grup 3 T1 glottik larinks kanserinden oluştu. Doku kesitlerinde HP varlığı ışık mikroskobu ile değerlendirildi.

Bulgular: Benign grupta HP görülme oranı %2,8, premalign grupta %6,3, malign grupta %1,9 idi (p= 0,648). Vokal kord ön, orta, arka ve tüm vokal kord olarak bölgelere ayrıldığında HP görülme oranında anlamlı değişiklik izlenmedi (p= 0,404).

Sonuç: *Helicobacter pylori* laringeal mukozayı enfekte etmekte ancak laringeal karsinom için risk faktörü oluşturmamaktadır. Laringeal lezyonların vokal kordda tuttuğu alanlarda HP pozitifliği açısından fark yoktur.

Anahtar Kelimeler: Larinks kanseri, prekanseröz, benign lezyonlar, helikobakter pilori, yer

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INTRODUCTION

Benign, precursor and malignant lesions are frequently found in the endoscopic examinations performed on patients who present to ear, nose, and throat (ENT) clinics with hoarseness. Although some benign lesions are followed through non-operative treatments such as voice therapy; the majority of benign and premalignant lesions, and if the patient accepts surgery, most malignant lesions undergo surgery. Larynx cancer is the second most common tumor among head and neck cancers (1). Other than smoking and alcohol use, human papillomavirus (HPV), chemical carcinogens, positive family history, previous radiotherapy (RT), and history of head and neck cancers play a role in etiology. Acid-pepsin diseases, such as laryngopharyngeal and gastroesophageal reflux, are considered risk factors, although their association cannot be definitively proven solely by providing an acidic environment. In the pathophysiology, there is a transformation from normal epithelium to squamous intraepithelial lesions and then carcinoma (Ca), and this transformation is affected by many factors. The carcinogenic effect of HPV, one of the viral agents, has been well-defined in the tonsil, oropharynx, and larynx, bringing a different dimension to staging and treatment in recent years. It exerts this effect by proliferating in epithelial cells (2).

Helicobacter pylori is a gram-negative, microaerophilic, spiral bacterium that resides in the stomach and duodenum. Its helical structure, motility facilitated by flagella, and urease-positive nature contribute to its protection from acid. Urease tests, smears, culture, and polymerase chain reaction (PCR) are used for diagnosis, but culture and PCR are the most sensitive (3). Gastric cancer can occur indirectly with inflammation or directly with protein modulation and genetic mutation. The association of HP with gastric cancer was accepted as a group 1 carcinogen (International Agency for Research on Cancer) in 1994 (4).

Helicobacter pylori has been detected in the middle ear, paranasal sinuses, oral cavity, and laryngeal mucosa in many studies; however, these studies mentioned temporary colonization of the epithelium with this bacterium. Even if there is no gastric involvement, HP may be in these regions (5). It can have similar effects in other tissues, such as the larynx. *Helicobacter pylori* can be detected in the normal larynx and benign, premalignant, and malignant laryngeal lesions. Burduk et al. on the other hand, defined HP as a laryngeal carcinogen or co-carcinogen, reporting that it triggered tumorigenesis (6). Jacob et al. found that HP could cause cancer by proliferation in laryngeal epithelial cells (2). In addition, there is a substantial number of studies showing that it does not cause laryngeal cancer.

We could not find any study in the literature regarding the location of laryngeal lesions in the anteroposterior axis of the vocal fold and the relationship with HP. Only the study by Islam et al. investigated *Helicobacter pylori* in the interarytenoid region (7). In our study, we categorized all benign, premalignant, and malignant lesions in the larynx into three regions in the anteroposterior direction and examined them for HP. We aimed to investigate whether the presence of *Helicobacter pylori* in laryngeal benign, premalignant, and malignant lesions is a risk factor for carcinoma and its incidence according to the laryngeal region.

MATERIALS and METHODS

Subjects and Study Design

One hundred six patients who underwent laryngeal suspension microlaryngoscopy in our hospital, in the ENT clinic between 2020 and 2022, were included in the study. Ethics committee approval was obtained from our hospital (90/1585). Patients aged over 18 years and those who were willing to participate in the study were included. The age and sex information of the patients was recorded. Patients with a history of reflux, chronic gastritis, peptic ulcer, and gastric resection, those who were treated for HP, and patients who used antibiotics in the last one month were excluded from the study.

Suspension laryngoscopy was performed under general endotracheal anesthesia. The location of the laryngeal lesion was recorded as anterior, middle, and posterior one-third by dividing the entire cord or the larynx into three equal parts in the anteroposterior direction (Figure 1). Punch biopsies taken were sent to pathology. The patients were divided into three groups according to the pathology results. Group 1 was defined as benign lesions (laryngeal polyp, cyst, nodule,

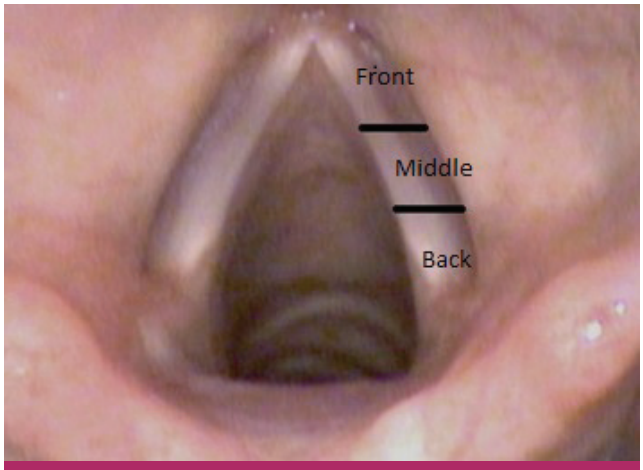

Figure 1. Location of the laryngeal lesion in the anteroposterior direction (1/3 front,1/3 middle,1/3 back of the vocal fold).

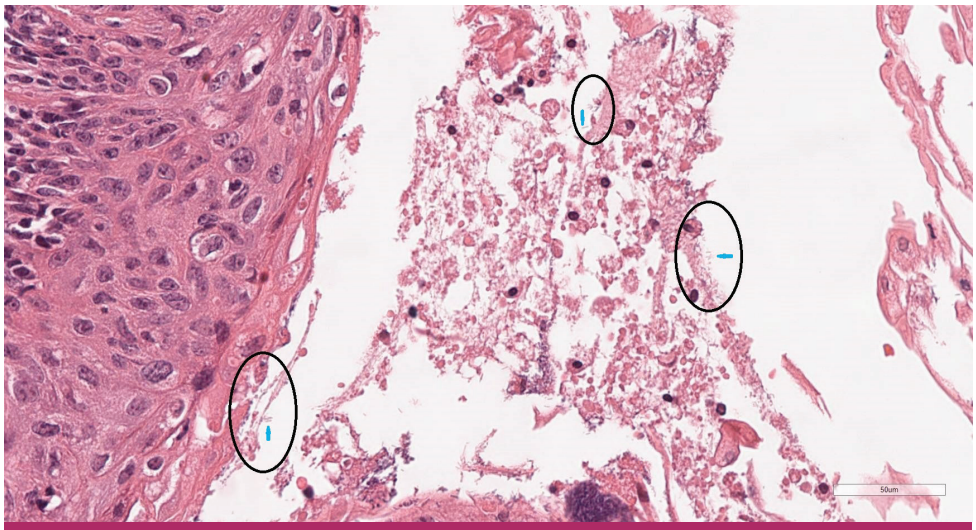

Figure 2. Larynx squamous cell carcinoma, hematoxylin-eosin staining, 400x.

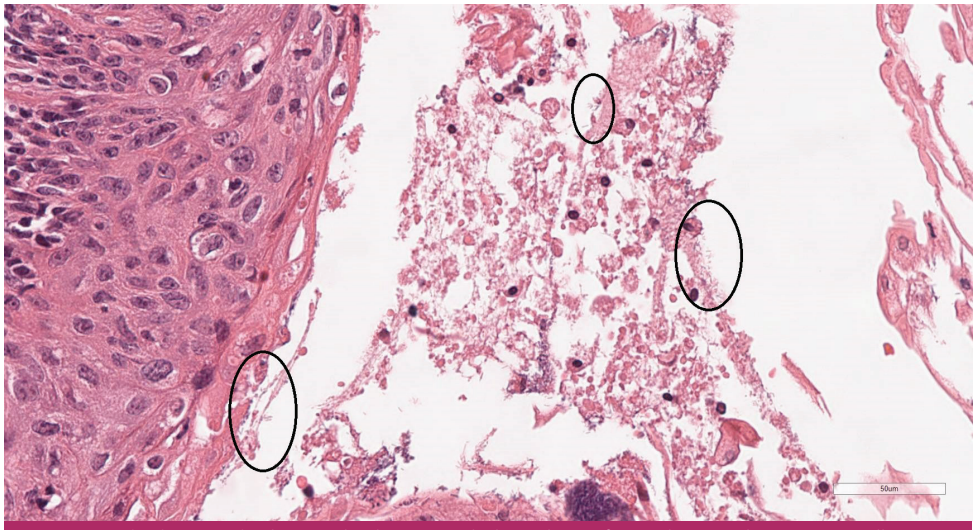

Figure 3. *Helicobacter pylori* bacterial colonies (circled) on the surface in laryngeal squamous cell carcinoma, hematoxylin-eosin staining, 400x.

Reinke's edema), group 2 as precancerous (dysplasia, Ca-in-situ), and group 3 as T1 glottic laryngeal carcinoma. Pathologic evaluations were performed by a single experienced pathologist. Benign and malignant tissue sections were fixed with 10% formalin and embedded in paraffin blocks. Sections with a thickness of four microns were stained with hematoxylin and eosin and evaluated for HP with a light microscope at 400x high magnification (Figure 2,3).

Statistics

The presence of HP according to the groups was analyzed with the Chi-square test. Analyzes were made using the IBM SPSS 21 software. The statistical significance level was set at 0.05.

RESULTS

There were 36 patients (13 women, 23 men) in the benign group, 16 patients (two women, 14 men) in the precancerous group, and 54 patients (one woman, 53 men) in the malignant group. The mean age was 56.28 ± 13.46 (range, 24-90) in the benign group, 66.25 ± 8.19 (range, 54-83) in the premalignant group, and 66.54 ± 10.06 (range, 42-89) in the malignant group. Nodules were the most common pathology in the benign group (36.1%).

The rate of HP observed in the larynx tissue detected histopathologically was 2.8% in the benign group, 6.3% in the premalignant group, and 1.9% in the malignant group (p= 0.648) (Table 1).

Table 1. Laryngeal HP rate by pathological diagnosis

	H. pylori (+)	*H. pylori* (-)	Total	
	n (%)	n (%)	n (%)	p
Benign	1 (2.8)	35 (97.2)	36 (34.0)	0.648
Precancerous	1 (6.3)	15 (93.8)	16 (15.1)	
Malignant	1 (1.9)	53 (98.1)	54 (50.9)	

Table 2. Ratio of laryngeal HP by location

	H. pylori (+)	*H. pylori* (-)	Total	
Location	n (%)	n (%)	n (%)	p
Front	1 (2.0)	50 (98.0)	51 (48.1)	0.404
Middle	0 (0.0)	17 (100.0)	17 (16.0)	
Back	1 (11.1)	8 (88.9)	9 (8.5)	
All	1 (3.4)	28 (96.6)	29 (27.9)	

There was no significant difference in the incidence of *Helicobacter pylori* when evaluated according to the laryngeal regions, including the anterior, middle, posterior, or along the entire cord (p= 0.404) (Table 2).

DISCUSSION

Laryngeal HP infection is rarely observed. In our study, the rate of HP observed in benign, premalignant, and malignant laryngeal lesions did not differ. Additionally, the incidence of HP did not differ according to the lower laryngeal region.

The development of laryngeal malignancy is a long and extensive process that is affected by many factors. With chronic inflammation, apoptosis is suppressed and cell proliferation increases. De Martel et al. reported that 16% of cancers were due to infections (8). Lopez described oncogenic pathogens as HPV, Epstein-Barr virus (EBV), and HP (9). It has been proven and predicted that laryngeal cancers may also be affected by these infections. In our study, the presence of the carcinogenic effect of HP was investigated and contrary to many studies, no effect was observed.

The larynx is part of the upper aerodigestive tract. It is natural for the esophagus and stomach pathologies to affect this voice box. It has been determined that HP can be transmitted from the stomach to the oral cavity or from the oral cavity to the stomach. Therefore, HP can be found in the larynx, even if it is not in the stomach. Reflux symptoms are seen in 40-60% of patients with dysphonia, and esophagitis is observed in 63% of patients with laryngitis (10,11). Using rapid urease tests, the authors determined that the presence of antral HP predisposed to laryngeal cancer by increasing gastric acid and acid reflux, while HP located in the stomach body prevented laryngeal cancer by decreasing gastric acid. If HP settles in the lower esophageal sphincter, it increases gastroesophageal reflux, thereby enhancing susceptibility to laryngeal cancer (12). Contrary opinions are also present in the literature. In our study, we found that HP was located at a very low rate in patients with laryngeal cancer (1.9%). In one meta-analysis, HP was associated with a 2.03-fold increase in laryngeal cancer risk (13).

Laryngeal benign lesions are also frequently observed in the larynx, especially in the vocal cords. Microlaryngoscopic surgeries performed on polyps, papillomas, and nodules that do not respond to voice therapy have aroused curiosity in terms of the presence of HP. In Fang's study, HP was found in 40% of polyps using rapid urease tests, but not in nodules (14). In another study, HP positivity was found with the same test on polyps at a rate of 32%, laryngitis at 45%, cancer at 46%, and in controls at 9% (15). In our study, although the rates were lower than in other studies, benign lesions were more common than malignant lesions (2.8% benign vs. 1.9% malignant). In a study, *Helicobacter pylori* was detected in five out of 55 benign lesions using PCR, with three being polyps, one a nodule, and one a papilloma (5). There are also studies in which benign lesions were never found positive. In our study, no positive lesions were found in benign lesions either. In the study conducted by Tiba, HP was positive in urease tests in 57% of benign laryngeal lesions and this rate increased to 71% with PCR analysis (16). We believe that these variations in positivity rates may be attributed to differences in diagnostic methods. Serology, rapid urease tests (RUT), *Campylobacter*-like organism (CLO) tests, PCR, and reverse transcriptase (RT)-PCR methods are used for diagnosis. The most sensitive method in tissue is RT-PCR (17). With the RUT, Borkowski detected that six out of 35 patients (17.1%) had chronic laryngitis, and it was reported that other bacteria such as *Streptococcus salivarius* could settle in the larynx and contribute to a positive status (18). As in our

study, histopathologic methods are also frequently preferred. According to Pajice, this bacterium is absent in the normal laryngeal flora (19).

The significance of HPV-dependent pathways in laryngeal precancerous lesions is well-known and has gained even more prominence in recent years. However, studies on the contribution of HP to premalignant lesions are newly emerging. Chen stated that HP was located in the laryngeal mucosa and was associated with leukoplakia (20). Rubin reported that *Helicobacter pylori* was significantly higher in serology in precancerous lesions (dysplasia and frank carcinoma) (21). It remains a mystery at what stage *Helicobacter pylori* makes this contribution and at what rate it has effects at the cellular level, apart from lesion size, pathologic type, and coexistence with reflux, protein modulation, and genetic mutation.

Some authors did not detect *Helicobacter pylori* in similar numbers of malignant and benign laryngeal lesions using histopathology, immunohistochemistry, and/or rapid urease tests (RUTs). It was concluded that the larynx was not a reservoir (12,22,23). In addition to studies that found no effect of HP on cancer (24), some studies reported HP was an independent risk factor for laryngeal cancer (25,26). Yen-ting demonstrated an association between laryngeal and hypopharyngeal cancers in patients with peptic ulcers (27). All these studies indicated that *Helicobacter pylori* was a co-factor capable of contributing to the development of laryngeal cancer. Yılmaz found that only one patient tested positive using PCR among 74 cases of laryngeal squamous cell carcinoma (SCC), and this presence was not detected in histopathology and immunohistochemistry. There is no connection between *Helicobacter pylori* and upper respiratory tract disorders (3). The rate of positive patients in our study was very low in all groups and was insignificant among the groups. Some authors found *Helicobacter pylori* in more than one-third of the lesions. Titiz found it in 80.9% of cancers with PCR, and no positives were found in benign ones (28). In a study that emphasized localization, HP positivity did not change according to the location of the lesion, such as the supraglottic, glottic, and subglottic regions. It was observed that the supraglottic region colonized HP more but it wasn't significant (25). The present study, which points to location as an anteroposterior direction, found no significant difference.

In patients with positive rapid urease test (RUT) and serology, PCR was performed on both vocal cord pathology and the interarytenoid region. PCR results were negative in all regions, including the interarytenoid region (7). The vocal cord was not analyzed by dividing it into regions, as done in our study. We investigated the vocal cords in the anteroposterior direction, dividing them into three, and we found no significant difference in terms of HP colonization. Anticipating that reflux mostly affects the posterior commissure area, we planned this study to evaluate both benign lesions and laryngeal cancer. We included T1 laryngeal carcinoma in the study to predict the area where cancer developed and to clarify the region. Using PCR instead of histopathology for HP testing could have increased the number of positive cases, providing a more accurate assessment.

CONCLUSION

Helicobacter pylori can infect the laryngeal mucosa but is not considered a risk factor for laryngeal cancer. Evidence for an active role in otorhinolaryngologic diseases is insufficient due to significant and wide differences between studies. There was no difference in the anteroposterior location of the laryngeal lesion in terms of HP positivity.

Ethics Committee Approval: This study wass approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (Decision no: 1585, Date: 14.10.2021).

Author Contributions: Concept/Design: ZAE, SOE, AK, ÖK; Analysis/Interpretation: AK, ZAE, SOE, ÖK; Data Acquisition: ÖK, SOE, NYE, İY; Writing: SOE, ZAE, AK; Critical Revision: NYE, SOE, İY; Final Approval: İY, NYE, SOE.

Conflict of Interest: All authors declare that they have no conflict of interest.

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