CLINICAL STUDY

THE RELATIONSHIP BETWEEN LARYNGOPHARENGEAL REFLUX AND HISTOLOGIC TYPE OF INLET PATCH MUCOSA AND PRESENCE OF HELICOBACTER PYLORY IN INLET PATCH

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SUMMARY

Aim: Our study investigates the relations between the histological type of the "inlet patch" mucosa and the presence of helicobacter pylori (H. pylori) in these lesions, and the symptoms and findings of Laryngopharyngeal reflux (LPR) in patients with LPR and "inlet patch" [heterotopic gastric mucosa of the cervical esophagus (HGM)].

Material and Methods: A total of 21 patients, 17 female (81%) and 4 male (19%), with LPR who had "inlet patches" as seen in the upper gastrointestinal system endoscopy without gastroesophageal reflux findings and who did not have lower esophageal sphincter failure as shown by the esophagus manometry were covered by the study. The type of the heterotopic gastric mucosa and the presence of Helicobacter pylori were investigated by taking histopathological samples in order to verify the diagnosis of the patients detected to have "inlet patch" in their upper gastrointestinal system endoscopy examination.

Results: 14 patients (66.7%) had antral type, while 7 (33.3%) had fundal type gastric mucosa epithelia. The histopathological examination revealed that 5 of the patients (23.8%) had Helicobacter pylori while 16 patients (76.2%) did not. The statistical analysis demonstrated that there was no difference between the type of the "inlet patch" mucosa and the signs and symptoms of LPR ($p>0.05$) but there was a statistically significant increase in such symptoms as postnasal drip ($p=0.003$) and globus sensation in the throat ($p=0.023$) in patients with Helicobacter pylori. Further, the mean value of the reflux symptom index of the patients included in the study was 25.57 ± 3.53, while the mean value of the Reflux Finding Score was 15.14 ± 3.42.

Discussion: The results of the study revealed that there was no relation between the "inlet patch" mucosa type and the presence of H. pylori in this mucosa, and the level of LPR disease.

Keywords: Laryngopharyngeal Reflux, inlet patch, helicobacter pylori

SERVİKAL ÖZOFAGUS YERLEŞİMLİ HETEROTROPİK GASTRİK MUKOZA TİPİ VE HELİKOBAKTER PİLORİ VARLIĞI İLE LARENGOFARENGEAL REFLÜ İLİŞKİSİ

ÖZET

Amaç: Çalışmamızda larengofarengeal reflü (LFR) hastalığı olan ve 'inlet patch' [servikal özofagus yerleşimli heterotopik gastric mukoza (HGM)] bulunan hastalarda, 'inlet patch' mukozasının histolojik tipinin ve bu lezyonlarda helikobakter pylori (H.p.) varlığının LFR semptom ve bulguları ile ilişkisi araştırılmıştır.

Yöntem ve Gereçler: Çalışmaya LFR hastalığı olan, üst gastrointestinal sistem endoskopisinde (ÜGSE) 'inlet patch' saptanıp gastroözofegeal reflü bulguları olmayan ve yapılan özofagus manometre incelemesinde alt özofageal sfinkter (AÖS) yetmezliği bulunmayan toplam 21; 17'si kadın (% 81), 4'ü erkek (% 19) hasta dahil edildi. ÜGSE muayenesinde 'inlet patch' tespit edilen hastalarda tanıyı kesinleştirmek için histopatolojik örnekler alınarak heterotopik mide mukozasının tipi ve Helicobacter pylori (H.p.) varlığı araştırıldı.

Bulgular: Hastaların 14'ünde(% 66,7) antral tip , 7'sinde (% 33,3) ise fundal tip gastrik mukoza epiteli saptandı. Yapılan histopatalojik değerlendirmede hastaların 5'inde (% 23,8) H.p. tespit edilirken, 16'sında (% 76,2) tespit edilmedi. Yapılan istatistiksel analizde 'inlet patch' mukozasının tipi ile LFR semptomları ve bulguları arasında fark bulunmazken ($p > 0,05$), H.p. tespit edilen hastalarda semptomlardan postnazal akıntı ($p = 0,003$) ve boğazda takılma hissinde ($p=0,023$) istatistiksel olarak anlamlı artış olduğu görüldü. Ayrıca çalışmaya dahil edilen hastalarda reflü semptom indeksi ortalaması $25,57 \pm 3,53$ iken, Reflü Bulgu Skor ortalaması $15,14 \pm 3,42$ olarak tespit edildi.

Tartışma: Elde edilen sonuçlara göre 'inlet patch' mukoza tipi ve bu mukozada H.p. varlığı ile LFR hastalığının şiddeti arasında ilişki bulunmadığı tespit edildi.

Anahtar Sözcükler: Larengofarengeal reflü, servikal özofagus yerleşimli heterotopik gastrik mukoza, helikobakter pilori

INTRODUCTION

LPR is the flow back of the stomach contents without gagging or vomiting at a force to reach over the upper esophageal sphincter[1].

The contact of the acids and pepsins in the stomach contents with the laryngeal mucosa may cause non-specific irritation symptoms and mucosa lesions in the respiratory system.

"Inlet patch" [heterotopic gastric mucosa of the cervical esophagus (HGM)] is the name given to the islands of the gastric epithelia that are located at the 1/3 of the upper esophagus (generally 15-20 cm

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to the proximal of the gastroesophageal intersection) having a slightly bulgy presence than the esophageal mucosa with fine borders and red-orange color and are found in single, paired or tripartite groups. It was first described by Schmidt in 1805[2]. The detection frequency of this lesion during the upper gastrointestinal system endoscopy varies between 0.29% and 10% depending on its recognition by the endoscopist[3,4]. The major factor that underlies the symptoms, clinical findings and complications seen in patients with "inlet patch" like dry cough, pachydermia, stenosis, esophagotracheal fistula, hemorrhage, perforation, and even malign transformation is the heterotopic secretion of acids[5].

Helicobacter pylori is a gastrotopic bacterium. It can colonize in only gastric type epithelia, especially in the acidic gastric site, of the stomach like heterotopic gastric mucosa and the gastric metaplasis sites in the duodenum[6]. An ample number of neutrophiles and lymphocytes meet in the infected site and initiate mucosal inflammation also by the effect of chemotactic proteins secreted by the bacterium following colonization with Helicobacter pylori[7].

Inlet patch's containing of acid secreting gastric mucosa cells, its proximity to the larynx in its location and Helicobacter pylori's chronic inflammatory effects in the entire gastroduedonal system are known. Our study is based on the idea that these two factors might be playing a role in the etiology of LPR disease.

The purpose of this study is to clarify whether there is a relation between the symptoms and findings of LPR disease and the size of the detected lesion, the lesion's distance to the incisors, the type of the gastric mucosa in the lesion, and the presence of Helicobacter Pylori in patients with LPR and inlet patch.

MATERIAL and METHODS

954 patiens who undergo upper gastrointestinal system endoscopy were detected prospectively for inlet patch. A total of 21 patients, 17 female (81%) and 4 male (19%), with LPR who had inlet patches as seen in the without gastroesophageal reflux findings and who did not have lower esophageal sphincter failure as shown by the esophagus manometry were covered by the study.

The patients, who had gastroesophageal reflux findings as seen in the upper gastrointestinal system endoscopy and lower esophageal sphincter failure as detected by the esophageal manometry, were excluded from the study as they were suggested to have gastroesophageal reflux. The patients covered by the study were selected among those who did not have any systemic diseases (diabetes mellitus, hypertension, asthma), who did not have acute or chronic infective inflammatory diseases, and who did not have a history of continuous drug use (teophylline, nitrate, anticholinergics, calcium channel blockers, oral contraceptives). Patients suspected to have malignities were not included in the study either.

An informed consent form was taken from each patient at the Türkiye Yüksek İhtisas Education and Training Hospital for the study.

Diagnosis of LPR: The presence of LPR symptoms and findings in the patients was investigated by using the Reflux Symptom Index (RSI) and the Reflux Finding Score (RFS)[8,9]. Each patient filled in the nine-item RSI questionnaire which ranks the complaints of the patients from zero to five (0: none, 1: slight, 2: mild, 3: moderate, 4: severe, 5: very severe) (Table 1). Indirect laryngoscopy images were recorded using a 90º 5.8 mm Hopkins Telescope (German) in order to calculate the Larynx Finding Score. The same physician performed the indirect laryngoscopy in order to enable standardization. An otorhinolaryngologist evaluated the indirect laryngoscopy images without knowing in which group the patients were who was also blind to the diagnoses and the endoscopic findings were scored. The patients were evaluated by using the RFS questionnaire taking pseudosulcus vocalis, ventricular obliteration, erythema, laryngeal edema, edema of the vocal cord, diffuse laryngeal edema, hyperthropy in the interaritenoid area, granulation, and the presence of a thick endolaryngeal mucus into consideration. Patients with scores over 13 for RSI and 7 for RFS were considered to have the LPR disease.

Upper Gastrointestinal System Endoscopic Examination: The upper gastrointestinal system endoscopy was performed on all the patients by using an Olympus GIF XQ (Tokyo, Japan) endoscope. The largest size of the detected lesions and their distance to the incisors were set.

Esophagus Manometry: An MMS (Medical Measurement Systems) brand (ver. 8.4i Beta) manometry system with water perfusion was used in the examination of the patients' esophagus body and lower esophageal sphincter evaluation. Following calibration, the lower esophageal sphincter was found and the patients had wet swallowing, and pressure

analysis for the esophageal body and lower esophageal sphincter were done. The patients with lower esophageal sphincter pressure values lower than 10 mmHg were considered to have LES failure and were not included in the study.

Histopathological Examination: For the histopathological evaluation punch biopsies were taken from the lesions during the upper gastrointestinal system endoscopy in order to verify the diagnosis of inlet patch. Following the excision of 5 micrometers of paraffin sections from the samples, the type of the gastric mucosa was investigated by Hemotoxylin Eosine staining while the presence of Helicobacter Pylori was investigated by staining with Giemsa's stain.

Statistical Analysis: All the data obtained were transmitted to the PASW (Predictive Analytics Software) Statistics 18.0 program. The Kolmogorov-Smirnov Normality Test revealed that the data had no normal distribution. While the Mann-Whitney Test was used to pinpoint the differences between the groups in order to compare the data that included two groups, the Kruskal-Wallis H Test was used for the data that covered more than two groups. The Spearman Correlation Test was used to determine the level of intergroup and intragroup relations.

Table 1. The Reflux Symptom Index (RSI).

Within the last month, how did the following problems affect you?	0: No problem; 5: Severe problem.					
Hoarseness or a problem with your voice	0	1	2	3	4	5
The need to clear your throat	0	1	2	3	4	5
Excess throat mucus or postnasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
Coughing after you ate or after lying down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensations of something sticking in your throat or a lump in your throat or globus sentation in throat	0	1	2	3	4	5
Heartburn, chest pain, or stomach acid coming up	0	1	2	3	4	5

RESULTS

A total of 21 patients were included in the study and out of these 14 patients (66.7%) had antral type, while 7 (33.3%) had fundal type inlet patch mucosa. The size of the largest of the mucosal islets detected during upper gastrointestinal system endoscopy was 12 mm, while the smallest was 3 mm (mean: 7.62 ± 2.34). While the furthest distance of these lesions to the upper incisors was 23 cm, the closest was 14 cm (mean: 19.14 ± 2.33). There was no relation between the size of the HGM islets and their distance to the incisors, and all the other parameters.

The esophagus manometry evaluation revealed that the antral type mucosa group's mean lower esophageal sphincter pressure value was 26.28 ± 7.17 mmHg (max: 38, min: 12) while the fundal type mucosa group's value was 21.42 ± 4.89 mmHg (max: 29, min: 16) ($p > 0.05$). 5 of the patients (23.8%) had positive Helicobacter, whereas 16 of them (76.2%) had negative results. When the groups were evaluated separately, it was seen that 4 of the patients with antral type mucosa (29%) were Helicobacter positive, while only 1 patient (14%) among those who had fundal type mucosa was positive ($p > 0.05$).

The patients' mean score for "Reflux Symptom Index" (RSI) and "Reflux Finding Score" (RFS) was RSI: 25± 4.08, RFS: 15.36 ± 3.08 for those with antral type mucosa; and RSI: 26.71 ± 1.80, RFS: 14.71± 4.28 for those with fundal type mucosa. When the RSI and RFS scores were evaluated separately, it was seen that there was no statistically significant difference between the two groups ($p>0.05$) (Table 2). Further, when the symptoms and findings were separately analyzed, it was seen that dry irritating cough ($\rho= 0.83$) among the symptoms and pseudosulcus vocalis ($\rho= 0.75$) among the findings had a statistically significant correlation with RSI and RFS respectively ($p < 0.01$). There was also a statistically significant increase in symptoms like postnasal dripping and globus sensation in the throat in patients with Helicobacter pylori in the inlet patch ($p=0.003$, $p=0.023$ respectively) (Table 3).

Table 2. Mean Score of RSI and RFS and ratio of H. Pylori positivity in two patient groups.

	Patients with antral type mucosa	Patients with fundal type mucosa	p value
Mean Score of RSI ± Standart Deviation	25± 4.08	26.71 ± 1.80	NS
Mean Score of RFS ± Standart Deviation	15.36 ± 3.08	14.71± 4.28	NS
Ratio of H. pylori positivity	29	14	NS

Table 3. Difference of Mean Score of postnasal dripping and globus sensation in patients with and without H. Pylori positivity.

	Patients with H. pylori in inlet patch mucosa	Patients without H. pylori in inlet patch mucosa	p value
Mean Score of postnasal dripping symptom ± Standart Deviation	1,81 ± 0,66	0,8 ± 0,45	0.003
Mean Score of globus sensation in the throat symptom ± Standart Deviation	3,13 ± 0,62	4 ± 0,71	0.023

DISCUSSION

The inlet patch is seen during the endoscopy with a slightly bulgy presence than the esophageal mucosa with fine borders and red-orange colored lesions. The sizes of the lesions might vary between a few millimeters and a few centimeters[10]. In our study, the largest of the mucosal islets had a size of 12 mm, while the smallest one had a size of 3 mm (mean: 7.62 ± 2.34) and the furthest distance between these lesions and the upper incisors was 23 cm, while the closest distance was 14 cm (mean: 19.14 ± 2.33). In line with other studies, we did not find a correlation between the sizes of the islets and their distance to the upper incisors, and the patients' LPR symptoms and findings[11].

A definitive diagnosis for the inlet patch can be obtained through histopathological evaluation. The co-existence of the muscular structure of the esophagus wall, the esophageal mucosa, and the gastric mucosal islets is typical in the histology of this lesion. The gastric mucosa can be seen in antral, fundic, or transitional types[12]. In our study 14 (66.7%) of the patients with inlet patch had antral type, 7 had (33.3%) fundic type epithelium, while there was no incidence of transitional type epithelia.

Studies conducted on the subject stated that the inlet patch might have been especially related to LPR symptoms like burning sensation in the throat, dry and long cough, and the constant need to clear the throat[12,13]. The tissue's acid production in the site was considered to be responsible for the major factor in the pathophysiology of the symptomatic inlet patch[14]. In line with other studies, we found Laryngopharyngeal reflux symptoms too in patients with inlet patches.

Studies demonstrated that the inlet patch was able to produce acid and this characteristics point out to the possibility that it might be an ideal site for Helicobacter pylori colonization with ratio of 73 %[4,15]. In another study the rate of Helicobacter pylori colonization in the inlet patch mucosa was reported to be 5.3%[16]. A study conducted in Turkey argued that this rate was 25% and this situation was stated to be related to the relatively high incidence of Helicobacter pylori infection in Turkey[17]. In our study, while 5 of the inlet patch patients were Helicobacter pylori positive (23.8%), 16 patients were Helicobacter pylori negative (76.2%). Further, in line with the results of the study which stated that all the patients with Helicobacter pylori in the inlet patch mucosa also showed the symptom of globus sensation in the throat, the results of our study revealed that there was a statistically significant elevation in the globus sensation and postnasal dripping symptoms in patients with Helicobacter pylori than the patients without Helicobacter pylori ($p< 0.05$)[18].

Laryngopharyngeal reflux (LPR) disease is caused by the contact of the gastric content with the larynx, pharynx, trachea, and oral mucosa by passing over the upper esophageal sphincter. Both LPR and gastroeusophageal reflux are brought about the damage caused by the contact of the mucosa with acids and pepsins but LPR has some physiopathological differences than gastroeusophageal reflux. It has protective mechanisms like mucosal bicarbonate production and primary peristaltism that prevent acid damage in the esophagus as different from the larynx and the pharynx[19]. Moreover, in the gastroeusophageal reflux disease the reason why the acidic gastric content has a retrograde flow to the esophagus is the formation of a common cavity (Common Cavity Phenomenon) because of the similar pressures of the esophagus and the gastric lumens which in turn were formed as a result of the esophageal sphincter failure that is the most significant anti-reflux barrier. This, however, is not seen in LPR. The main factor in LPR is the mucosal inflammation formed by the contact of the acids with the laryngeal mucosa and the upper esophageal sphincter and the upper esophageal sphincter spasm as a reflex[20]. Therefore, we have included isolated LPR patients without upper esophageal sphincter failure into our study. Dry chronic cough dry irritating cough, sensation of an obstruction in the throat (globus sensation), the constant need to clear the throat, vocal defects, and difficulty swallowing are among the symptoms of LPR, formed secondarily to mucosal damage and reflex spasm, and its laryngeal findings include pseudosulcus vocalis, diffuse laryngeal edema, interarytenoid hyperemia, granulation, and thick endolaryngeal mucus[21].

The dependability and utility of the method of scoring these symptoms and findings in LPR diagnosis have been proven by studies. In a study by Belafsky et al., 25 LPR patients' RSI scores of 21.2 were decreased to 12.8 following a 6-month treatment. The same study found that the mean RSI score of asymptomatic individuals taken into the study as the control group was 11.6. According to these results, individuals with RSI scores above 13 were considered to be abnormal[8]. In another study by Belafsky et al., the mean RFS score was found to be

11.5 for 40 patients diagnosed with LPR through 24-hour double probe pH monitoring. The mean score for the control group with 40 patients was found to be 5.2 (95%). Based on these results, if RFS > 7 with 95% accuracy, the patient was considered to have LPR[9]. We also used these scoring methods in order to evaluate the patients regarding LPR. The mean RSI and RFS scores of the patients covered by our study were 25.57 ± 3.53 and 15.14 ± 3.42 respectively. While these mean scores were RSI: 25± 4.08; RFS: 15.36 ± 3.08 for patients with antral type mucosa, they were RSI: 26.71 ± 1.80; RFS: 14.71± 4.28 for patients with fundal type mucosa.

CONCLUSION

These results may point out to the high probability that patients with inlet patch also have the LPR disease. Moreover, it may be suggested that even a little amount of acid produced from the antral cells will be sufficient enough to cause laryngeal mucosa damage and this may be the reason why the mucosa type does not bring about a difference between the severity of the symptoms and findings. The presence of Helicobacter pylori in these lesions may elevate the severity of the symptoms and findings but new studies with wider patient populations should be conducted in order to shed more light on the issue.

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