Diagnosis and consequences of gastroesophageal reflux in otolaryngology
Smit, C.F.G.M.

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Chapter 4

Gastropharyngeal and Gastroesophageal Reflux in Patients with Head and Neck Cancer

M.P. Copper
C.F. Smit
L.D. Stanojcic
P.P. Devriese
P.F. Schouwenburg
L.M.H. Mathus-Vliegen

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ABSTRACT

Gastropharyngeal reflux may play a role in the etiology of squamous cell cancer of the head and neck and contribute to complications in head and neck cancer patients after surgery or during radiotherapy.

To investigate the prevalence of gastropharyngeal and gastroesophageal reflux in patients with head and neck cancer, ambulatory 24-hour double-probe pH monitoring was performed in 24 untreated patients with laryngeal or pharyngeal squamous cell carcinoma. In addition, 10 patients who had been irradiated in the head and neck area were analyzed for reflux to study the effect of radiotherapy on reflux.

Only 4 of the 24 head and neck cancer patients (17%) had neither pathologic gastropharyngeal nor gastroesophageal reflux. Esophageal acid exposure was abnormal in 5 patients and acid exposure at the level of the upper esophageal sphincter was abnormal in 4 patients. Eleven patients had pathological reflux in both areas. Irradiated patients did not differ from the untreated patients considering the prevalence of pathologic gastropharyngeal or gastroesophageal reflux.

The data obtained in this study indicate that reflux is a common event in head and neck cancer patients.
INTRODUCTION

Squamous cell cancer originating in the mucous membranes of the upper aerodigestive tract accounts for more than 95% of all malignant tumors of the head and neck, and is worldwide one of the major malignancies. Several factors are known to increase the risk of developing squamous cell cancer in the head and neck. The major risk factors are lifestyle factors such as smoking and alcohol consumption. Alcohol potentiates tobacco-related carcinogenesis but is also an independent risk factor. The relation between the development of squamous cell cancer and other factors such as genetic predisposition, dietary deficiencies, occupational factors, and viral infections was recognized in the past two decades. Gastroesophageal reflux appears to be associated with various otolaryngological disorders such as globus pharyngeus, dysphonia, dysphagia, chronic throat-clearing, posterior laryngitis, laryngeal granulomas and subglottic stenosis. Reflux may play a role in the pathogenesis of carcinomas of the upper aerodigestive tract as well, since reflux has frequently been described as a possible etiologic factor or co-factor for head and neck cancer. If so, acid gastric juice has to traverse the upper esophageal sphincter and reach the larynx and pharynx to induce lesions leading to carcinoma. In 1976 Glanz and Kleinsasser described 35 cases of chronic hypertrophic laryngitis that developed into laryngeal carcinomas. Ward and Hanson studied 19 non-smokers with laryngeal carcinoma. In all patients a positive history of gastroesophageal reflux was noted. Morrison described a series of nonsmoking patients with T1 cancer of the vocal cord. In these patients strong indications were present that reflux could have been a major factor in the development of their disease. Koufman studied a group of patients with laryngeal carcinoma. In 26 patients he performed a double-probe pH-measurement with the proximal probe placed 2 cm above the upper esophageal sphincter. In 58% of cases he found a pathologic gastropharyngeal reflux. Freije et al. evaluated 23 nonsmokers with laryngeal carcinoma for gastroesophageal reflux. Nine patients had some indication of reflux, although this was only evaluated by radiographic examination. In the other 14 patients there was at least a history of symptoms of reflux or treatment of reflux. Biacabe et al. found evidence for silent gastroesophageal reflux in 37% of 72 patients treated for laryngopharyngeal cancer. To investigate the prevalence of gastroesophageal and gastropharyngeal reflux in patients with laryngeal or pharyngeal carcinoma we performed ambulatory 24-hour double-probe pH monitoring in 24 untreated head and neck cancer patients. In addition, in 10 patients irradiated for cancer in the head and neck the effects of radiotherapy on reflux in the head and neck area were studied.
Table 1: Gastropharyngeal reflux (GPR) and gastroesophageal reflux (GER) in 24 patients with laryngeal or pharyngeal carcinoma.

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92% + 58% ++/++ 33% + 62% + 67% - (15/24) (16/24)

*Alcohol consumption: + = 1-3 consumptions per day, ++ = more than 3 consumptions per day
†complaints of reflux = heartburn more than once a week
‡GPR, GER + = pathologic reflux
GLc = Glottic laryngeal carcinoma; HPc = Hypopharyngeal carcinoma; Opc = Oropharyngeal carcinoma; SLc = Supraglottic laryngeal carcinoma. TNM: UICC TNM classification.
Patients and Methods

Patients:
The study population comprised 24 patients with histologically confirmed squamous cell carcinoma or carcinoma in situ of the larynx or pharynx. These patients did not yet receive treatment for their cancer. The characteristics of the patients are listed in Table 1. In addition, ten patients were studied after radiotherapy for laryngeal or pharyngeal cancer. Four of these 10 patients were also measured before radiotherapy and were then part of the group of the 24 patients mentioned above as well (patients 2, 3, 7 and 14). The characteristics of the irradiated patients are listed in Table II.

<table>
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<tr>
<th>Patient No.</th>
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20% + 40% + 50% + 60% + 70% +

pH measurement:
Double-probe pH monitoring was performed by using two monocristalline antimony pH sensors positioned along a single Digitrapper Mark III catheter with a diameter of 2.1 mm. (Medtronic, Skovlunde, Denmark). The distance between both sensors was 15 to 20 cm and a silver-silver chloride cutaneous electrode was placed as reference on the skin. Both probes (pH sensors) were calibrated simultaneously in buffer solutions of pH 7 and pH 1 before monitoring. A flexible laryngoscope was introduced transnasally until a good view of the hypopharynx was obtained. Under endoscopic view the proximal probe was placed in the upper esophageal sphincter so...
that the proximal probe was just surrounded by esophageal mucosa. A recent study showed that this endoscopical placement of the proximal probe in the upper esophageal sphincter without manometry is an accurate method. Accordingly, the distal probe was positioned 15 to 20 cm distally of the proximal probe depending on the height of the patient. The distance from the tip of the nose to the lower esophageal sphincter was determined using the pH transition point (withdrawal technique). The patients were encouraged to eat their regular meals without restrictions and to continue their normal daily and nocturnal routines. In a diary, the patients reported body position, meals, and drinks.

**Data analysis:**

The criteria of Richter et al. were used for the distal probe to distinguish between physiologic and pathologic reflux. The authors defined as normal: pH below 4 less than 5.5% of the total time, less than 8.2% of the time in upright position and less than 3.0% of the time in supine position. For the proximal probe, situated in the upper esophageal sphincter, our criteria for the normal values for gastroesophageal reflux were used. Gastropharyngeal reflux was defined as pathological if the percentage of time of pH below 4 was more than 0.1% of the total time, and/or more than 0.2% of the time in the upright position, and/or more than 0.0% of the time in the supine position. Patients who had more than three reflux episodes (pH below 4) during 24 hours were considered to have pathologic gastroesophageal reflux as well.

**RESULTS**

Sixteen of 24 head and neck cancer patients (67%) had a pathologic gastroesophageal reflux (table 1). Seven of these patients had gastroesophageal reflux in the upright and in supine positions, seven patients only in upright position, and the other two only in the supine position. Fifteen of 24 patients (62%) had a pathologic gastropharyngeal reflux. Three of these 15 patients had pathologic gastropharyngeal reflux in upright and in supine position, and 12 patients only in the upright position. Eleven patients had combined gastroesophageal and gastropharyngeal reflux. In five patients with gastroesophageal reflux there were no signs of gastropharyngeal reflux and in four patients with pathologic values at the level of the upper esophageal reflux pathologic gastroesophageal reflux could not be detected. Only four of the 24 patients (17%) had no gastroesophageal or gastropharyngeal reflux at all. A minority (40%) of the 20 patients who had pathologic reflux values had complaints related to reflux such as heartburn.

The two patients in the group of untreated head and neck cancer patients who were nonsmokers (patients 15 and 18) had respectively 45 and 318 episodes of
gastropharyngeal reflux during 24-hour monitoring. The percentage of time with a pH under 4.0 in these two patients was 1.2 and 12.6 respectively. The other 22 patients, all smokers, had a median value of 6 episodes of reflux, and a median value of 0.1% fraction time below pH 4.0 during 24 hours. In the group of 10 irradiated patients, 6 had pathologic gastropharyngeal reflux (60%) and 7 patients had pathologic gastroesophageal reflux (70%). In one patient no pathologic reflux at all was detected, and 4 patients showed combined pathologic gastroesophageal and gastropharyngeal reflux (table II). Four patients were analyzed both before and after radiotherapy. Two of these patients developed pathologic gastropharyngeal reflux after radiotherapy that did not exist before treatment. Fifty percent of the irradiated patients had complaints of heartburn.

**DISCUSSION**

Animal studies have shown that gastric fluids may cause severe damage to the upper airway mucosa. There is strong suspicion that the acid character of gastric juice is not the only important factor in the etiology of chronic irritation of mucosa in patients with gastroesophageal reflux disease, because substances such as bile and pepsin may play an important causative role as well. In humans gastropharyngeal reflux is a well-known etiological factor in the development of chronic laryngitis. Jacob et al. found a significant increase of proximal acid exposure in patients with laryngitis using dual-site ambulatory pH recording. Shaker et al. performed an ambulatory 24-hour simultaneous three-site pharyngoesophageal pH monitoring in a group of 14 patients with laryngeal symptoms and objective findings of posterior laryngitis. They found a prevalence of gastroesophagopharyngeal reflux of 86% in this group. A pathological study of laryngopharyngoesophagectomy specimens in patients undergoing surgery, most of them because of stage IV hypopharyngeal cancer, showed esophageal disease in 54% of the patients. Thirty-three percent of the patients had esophageal pathology directly related to reflux, such as Barrett’s esophagus and esophagitis. Wilson et al. compared ambulatory 23-hour pH monitoring with a biopsy of the posterior larynx and proximal esophagus in 97 patients. They found a much weaker relation between reflux and laryngitis than other researchers have. As stated before, chronic irritation of the larynx leading to laryngitis eventually may develop into squamous cell carcinoma.

Today the best method to demonstrate gastroesophageal reflux is ambulatory 24-hour pH monitoring. Dual-probe pH monitoring with positioning of the proximal probe close to the larynx and pharynx may be of special interest for the otolaryngologist because minute amounts of acid are already capable of inducing significant injury to laryngeal structures. However, a great drawback of most
studies investigating the relationship between reflux and head and neck cancer is that the majority of these studies found only historical evidence for a link between reflux and cancer, but that prospective studies are lacking. Another drawback of many studies is that only gastroesophageal reflux and not gastropharyngeal reflux is investigated. We found a very high percentage of pathologic gastropharyngeal or gastroesophageal reflux of 62% and 67% respectively in patients with head and neck cancer. These data indicate that it is important to be aware of the fact that reflux is a common phenomenon in these patients. Series reporting pH monitoring data for patients with biopsy proven erosive esophagitis have found that up to 23% of such patients do not demonstrate pathologic levels of esophageal acidification on 24 hour pH monitoring. This known relative lack of sensitivity presumably affects upper probe data as well as single probe data, indicating that the prevalence of gastropharyngeal reflux in head and neck cancer is probably even higher than 62%.

Our series of 24 untreated head and neck cancer patients included only two nonsmokers. However, both patients had a very high number of gastropharyngeal reflux episodes and a high percentage of fraction time with a pH below 4.0. These data support the statement of Freij et al. and Ward and Hanson that reflux might be a major etiological factor in head and neck cancer in the nonsmoking population. More research is necessary to confirm this observation in larger groups.

Normal healthy individuals have multiple barriers against reflux and the resulting mucosal damage. The most important barriers are the lower and upper esophageal sphincter tone, esophageal epithelial resistance and esophageal acid clearance. Esophageal clearance is an important defense against the development of reflux esophagitis and normally occurs in two sequential steps. One or two peristaltic sequences empty virtually all acid from the esophagus, leaving a minimal residual that sustains a low pH, which is neutralized by swallowing saliva. The ability of saliva to neutralize acid is primarily due to bicarbonate. Radiotherapy for head and neck malignancies influences salivary secretion thereby compromising one of the defense mechanisms against reflux esophagitis. After radiotherapy of the mucous membranes in the head and neck, the production of mucous is notably reduced, resulting in xerostomia. This is not only a result of a failure of the major salivary glands to excrete saliva, but is also caused by a decreased trapping ability and a loss of the secretory functions as well. These theoretical data suggest reflux could have more devastating effects in irradiated patients compared with nonirradiated patients. If irradiated patients had a higher incidence of pathologic reflux, as suggested by others, the mucosal damage would even be higher. We did not observe different percentages of patients with pathologic gastroesophageal or gastropharyngeal reflux in both groups.

As far as we know, 24-hour double-probe pH measurements have never been
investigated prospectively in head and neck cancer patients, except in one study of Koufman.\textsuperscript{12} The proximal pH probe is usually positioned 2 cm above the lower esophageal sphincter to assess gastroesophageal reflux.\textsuperscript{12,31} However, it is our personal experience that the proximal probe should be placed in the upper esophageal sphincter. A probe placed above the sphincter can produce high numbers of artifacts, also called pseudo-reflux episodes, because of loss of mucosal contact.\textsuperscript{15,22,26} Additionally, one could conceivably miss episodes of acid reflux because of the presence of upper airway mucus and the relatively large space within the hypopharynx.\textsuperscript{34}

**CONCLUSION**

These new data indicate that pathologic gastroesophageal and gastroesophageal reflux are common events in head and neck cancer patients. During work-up of the patients it is important to rule out esophagitis or a Barrett's esophagus possibly giving rise to a second primary tumor in the esophagus. A relation between reflux and postoperative complications such as pharyngocutaneous fistula and pulmonary distress has already been described.\textsuperscript{14,30} Reflux also may contribute to extensive mucositis during irradiation in the head and neck area.\textsuperscript{14} To reduce the amount of complications in patients undergoing extensive surgery or high-dose external-beam radiotherapy, it is advisable to investigate the presence of gastroesophageal and gastroesophageal reflux. In the presence of pathologic findings, patients should be given antireflux therapy perioperatively or during radiotherapy.
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