Digestive Diseases and Sciences, Vol. 50, No. 5 (May 2005), pp. 824–832 (© 2005)
DOI: 10.1007/s10620-005-2647-0

The Role of (Duodeno)gastroesophagopharyngeal Reflux in Unexplained Excessive Throat Phlegm

J. POELMANS, MD, PhD,* L. FEENSTRA, MD, PhD,* and J. TACK, MD, PhD†

Gastroesophageal reflux (GER), through the occurrence of gastroesophagopharyngeal reflux (GEPR), is an established cause of several otorhinolaryngological (ORL) manifestations. It has been suggested that unexplained excessive throat phlegm might also be a manifestation of GER, but formal evidence is lacking. The aim of the present study was to investigate the prevalence of GER as well as duodenogastroesophageal reflux (DGER) in consecutive patients with chronic complaints of excessive throat phlegm. Fifty-nine consecutive patients with chronic unexplained excessive throat phlegm, transparent in 33 patients (TTP) and yellow in 26 patients (YTP), underwent gastrointestinal endoscopy, 24-hr dual esophageal pH monitoring, and fiberoptic DGER monitoring. Proximal esophageal DGER monitoring was performed in seven YTP patients and analysis of bile acids in throat phlegm was performed on 16 samples. The effect of high-dose acid suppressive therapy was evaluated at 2-week intervals. Endoscopy and pH monitoring established a diagnosis of pathological GER in 75% of the patients. Pathological DGER was present in 56% of the patients and this was associated with YTP. Proximal DGER exposure was high in all investigated subjects and chemical analysis revealed a median bile acid concentration of 0.184 μM in nine YTP samples and no detectable bile acids in seven TTP samples. After a median of 4 weeks of acid suppressive therapy, most patients improved and 61% became asymptomatic. YTP patients were more likely to require maintenance acid suppressive therapy than TTP patients. Unexplained excessive throat phlegm is a sign suggestive of GER and GEPR, and unexplained yellow throat phlegm a sign suggestive of duodenogastroesophagopharyngeal reflux (DGEPR).

KEY WORDS: gastroesophageal reflux disease; bile reflux; throat phlegm; pH monitoring; Bilitec monitoring; proton pump inhibitor.

Gastroesophageal reflux disease (GERD), defined by the presence of symptoms or lesions that can be attributed to the reflux of gastric contents into the esophagus, is one of the most common disorders affecting the gastrointestinal tract. Heartburn and acid regurgitation are the classical GERD symptoms and reflux esophagitis is the most important lesion (1). However, reflux or its effects may extend beyond the esophagus, thereby potentially causing or contributing to a variety of supraesophageal manifestations through gastroesophagopharyngeal reflux (GEPR) or through reflexes, elicited by gastroesophageal reflux (GER) (1, 2). Over the last decade, GER and GEPR have been identified as important factors in the pathogenesis of several common chronic pediatric and adult supraesophageal inflammatory disorders, including posterior laryngitis, pharyngitis, otitis media, sinusitis, asthma, and bronchitis (3–16). In addition, GER and GEPR have been implicated in the pathophysiology of many commonly occurring

Manuscript received July 29, 2004; accepted October 5, 2004.
From the *Department of Otorhinolaryngology–Head and Neck Surgery and †Department of Medecine, Division of Gastroenterology, University Hospitals, Leuven, Belgium.
Address for reprint requests: Jan Tack, MD, PhD, Center for Gastroenterological Research, Catholic University of Leuven, Herestraat 49, B-3000 Leuven, Belgium; Jan.Tack@med.kuleuven.ac.be.

supraesophageal symptoms including sore throat, dysphonia, nonproductive cough, globus pharyngeus, halitosis, nasal congestion, and chronic ear complaints (1, 3, 5, 7, 15, 17–19). Using combined esophago-pharyngeal pH monitoring, acid GEPR has been demonstrated in patients with suspected reflux-related supraesophageal manifestations (5–7, 20). Results of combined esophago-oropharyngeal, esophagonasopharyngeal, and esophagotracheal pH monitoring have shown that acid GEPR may extend into the oropharynx, the nasopharynx, and the trachea (11, 20, 21). The recent finding of high concentrations of pepsin/pepsinogen in middle ear effusion samples from children with otitis media with effusion (OME) led the authors to conclude that gastric juice refluxes from the nasopharynx, through the eustachian tube, into the middle ear and may be the primary factor in the initiation of OME (9).

Chronic throat clearing, excessive throat phlegm, and feelings of postnasal drip are reported to be almost invariably present in patients with suspected supraesophageal reflux (3, 7, 22, 23). It has been suggested that, whether transparent, white, yellow, or green, the coloration of excessive throat phlegm and postnasal drip represents the gastric content in many cases (22, 23). However, formal evidence for this is lacking to date.

Duodenogastroesophageal reflux (DGER) refers to the reflux of duodenal contents. Esophageal exposure to both acid and DGER is the most prevalent reflux pattern, and both acid and DGER show a graded increase in severity from controls to esophagitis patients, with the highest values observed in patients with Barrett's esophagus (24). Whether, similar to GER, DGER may also extend into the proximal esophagus and whether, similar to gastric contents, bile may actually reach the pharynx remain to be established.

The aim of this study was to prospectively investigate the role of GER and DGER in consecutive patients with chronic excessive throat phlegm. We used upper gastrointestinal (GI) endoscopy and pH monitoring to study the prevalence of GERD and we used fiberoptic bilirubin monitoring to study the prevalence of DGER. Furthermore, as throat phlegm may have a spectrum of colours of which the pathophysiological significance is unknown, we investigated a putative role for supraesophageal reflux of duodenal contents by studying the correlation of the colour spectrum of throat phlegm with the presence of acid GER and DGER, by investigating the presence of DGER in the proximal esophagus and by analysing throat phlegm composition. Finally, we assessed the response of excessive throat phlegm to antireflux therapy.

MATERIALS AND METHODS

Patient Selection. Consecutive adult patients with chronic refractory unexplained complaints of excessive throat phlegm, seen at the ORL outpatient clinic, were referred to the Department of Gastroenterology. We refer to these patients as throat phlegm patients. All patients had chronic complaints of excessive throat phlegm for at least 3 months (median, 3 years; IQR, 6 months–7.5 years). Before referral, other apparent causes of their symptoms (i.e., allergy, upper airway infection, abscess, tumour, anatomical obstructive intranasal abnormalities) had been ruled out. None of the patients had a history of bronchopulmonary, neurological, cardiovascular, or systemic disease, and all patients had normal plasma bilirubin levels. Even though these patients had not been treated for GERD, they are called "refractory" from an ORL point of view, as previous "conventional" medical therapies (mucolytics, antihistamines, antibiotics, and corticoids) and/or surgical treatments, including nasal and sinus surgery, had only led to incomplete or no improvement. None of the patients were on acid-suppressive medication for at least 6 months.

Throat Phlegm Symptoms. The patients reported that troublesome throat phlegm could be felt adherent to the pharyngeal wall or to the laryngopharynx, oropharynx, and/or nasopharynx. Feelings of phlegm adherence to the nasopharyngeal wall were frequently interpreted as postnasal drip.

All patients reported the evacuation of transparent throat phlegm several times daily, thereby obtaining some temporary relief. Some patients reported the evacuation of exclusively transparant throat phlegm; these patients are referred to as transparant throat phlegm (TTP) patients. In addition, some patients also reported the evacuation of yellow stained throat phlegm with a frequency varying from at least once a week to several times daily. We refer to these patients as yellow throat phlegm (YTP) patients.

ORL and GERD Examinations. All patients were seen by one of the authors (J.P.) and underwent careful history taking, completed with an extensive symptom questionnaire covering the frequency and severity of classical and atypical reflux symptoms and suspected reflux-related supraesophageal symptoms, as reported previously (25). They also underwent an extensive standardized ORL examination including a magnifying 90° telescopic laryngoscopy.

In order to establish a diagnosis of GERD, all patients subsequently underwent upper GI endoscopy, followed by esophageal manometry and 24-hr ambulatory dual-channel esophageal pH monitoring on one of the next 4 days. In order to quantify DGER, all patients also underwent 24-hr ambulatory Bilitec monitoring. During the recording time, only liquid meals (Nutridrink; 1.5 kcal/ml—13% proteins, 48% carbohydrates, 39% lipids, Nutricia, Bornem, Belgium), not interfering with Bilitec monitoring were used (31). Patients were asked preferably to drink water and to avoid coffee, tea, and fruit juices during the recording. Subsequently, regardless of the outcome of investigations, all patients received standard antireflux therapy consisting of proton pump inhibitor (PPI) intake and lifestyle measures.

Endoscopy. During endoscopy, the presence of erosive esophagitis was noted and its degree was scored (1 to 4) according to the classification of Savary-Miller, which served as a basis for reimbursement in Belgium (26). A hiatal hernia was diagnosed if >2 cm of gastric mucosa appeared above the

diaphragm during endoscopy. In addition, the presence of peptic ulcers in the stomach or duodenum was noted.

Ambulatory pH and DGER Monitoring. Ambulatory esophageal pH monitoring was performed using dual-channel antimony pH electrodes located 5 and 20 cm above the upper level of the lower esophageal sphincter (LES) (Synectics Medical, Stockholm, Sweden). A fiberoptic spectrophotometer Bilitec 2000 (Synectics Medical) was used to quantify DGER 5 cm above the upper level of the LES. The system consists of a miniaturized probe of 2.5-mm diameter that carries light signals into the esophagus and back via a plastic fiber optic bundle. Before each study, the pH probe was calibrated in buffer solutions of pH 7 and 1 and the Bilitec probe was calibrated in water.

An episode of acid reflux was defined as a decrease in esophageal pH <4 during more than 10 sec (27). A diagnosis of GERD was based on the presence of esophagitis and/or a distal esophageal pH <4 for a duration exceeding 4% of the time (29, 31). Proximal acid exposure time was judged abnormal when it exceeded 0.8% (29). An episode of DGER is defined as an increase in esophageal bilirubin absorbance >0.14 during more than 10 sec (31). Pathological DGER is present when intra-esophageal bilirubin absorbance is above 0.14 for more than 4.6% of the time (31).

In seven patients, in addition to a distal bile reflux monitoring probe 5 cm above the LES, a second probe was placed in the proximal esophagus 20 cm above the LES.

Esophageal Manometry. Esophageal manometry was performed using an eight-lumen manometric assembly incorporating a sleeve sensor, as previously reported (25). With the sleeve adequately positioned across the gastroesophageal junction, 10 wet swallows (5 ml water) were administered at 30-sec intervals.

Bile Acid Dosage in Throat Phlegm. From throat phlegm patients, one or more morning, fasted, samples of throat phlegm were collected and were subsequently analyzed for the presence of bile acids using the 3-α-hydroxysteroid dehydrogenase enzymatic assay (28).

Antireflux Therapy. Regardless of endoscopic, pH-metric, and Bilitec monitoring findings, to which the prescribing physician was blinded, all patients received antireflux therapy consisting of omeprazole, 20 mg b.i.d., or lansoprazole, 30 mg once daily. In addition, they were instructed to apply antireflux lifestyle measures. All patients were followed at 2-week intervals until their complaints of excessive throat phlegm had resolved or were markedly improved. The PPI therapy was gradually decreased if the patient was asymptomatic for at least 4 weeks on a given dose. This allowed determination of the lowest effective maintenance dose, if any. Subsequently, most patients entered long-term follow up.

Statistical Analysis. All results are expressed as median and interquartile ranges (IQR) and compared by. *t*-test or chi-square testing wherever appropriate. *P* values were considered to be significant at <0.05. Bonferoni's correction for multiple testing was applied.

RESULTS

Patient Characteristics. The study recruited 32 men and 27 women (mean age, 46 years; range 14–78 years). Eleven (19%) patients were smokers and 19 (32%) drank alcohol daily. There were 33 (56%) TTP patients and 26 (44%) YTP patients. Demographic characteristics did not differ between TTP and YTP patients. Smoking (31 vs. 9%; $P = 0.03$) and daily alcohol use (46 vs. 21%; $P = 0.04$) were more prevalent in YTP patients. Eleven patients (17%) had a history of sinus surgery, which tended to be more prevalent in YTP patients (27 vs. 9%; $P = 0.07$).

Symptom Pattern and Clinical Signs. Other potentially reflux-related chronic symptoms such as frequent throat clearing (80%), sore throat (68%), nasal congestion (53%), feelings of postnasal drip (49%), dysphonia (49%), cough (44%), halitosis (41%), and globus pharyngeus (36%) were also frequently found in throat phlegm patients. In contrast, classical reflux symptoms of heartburn or regurgitation were experienced on a weekly basis by only 20 (34%) patients and were never a predominant symptom. Feelings of postnasal drip (73 vs. 30%; $P = 0.001$) and nasal congestion (69 vs. 39%; $P = 0.02$) were more prevalent in YTP patients. Sore throat was less prevalent in YTP patients (46 vs. 85%; $P = 0.002$), but this was no longer significant when all patients who smoked or drank alcohol daily were excluded from the analysis.

On clinical ORL examination, yellow-stained or transparent phlegm clumps, strains, or fragments adherent to the larynx and/or the pharyngeal wall could be seen in several throat phlegm patients. Reflux-related ORL signs were edema and erythema of the posterior larynx (posterior laryngitis) in 31 (53%) patients and erythema of the pharynx in 27 (46%) patients. There were no significant differences in the prevalence of posterior laryngitis and pharyngeal erythema between YTP and TTP patients.

Classical GERD Investigation. Erosive esophagitis according to the Savary-Miller classification was found in 33 (56%) patients: 14 grade 1, 11 grade 2, 2 grade 3, and 6 grade 4 (1 esophageal ulcer, 3 Barrett's esophagus, and 2 Barret's esophagus with ulcer). A hiatal hernia was present in 23 patients (39%). Peptic ulcers were found in four patients (7%; two gastric and two duodenal), of which two had *Helicobacter pylori* (Hp) on gastric biopsies and one reported regular use of NSAID's. In three patients, peptic ulcers occurred in the presence of esophagitis or Barrett's esophagus.

Table 1 summarizes endoscopic findings in TTP patients and YTP patients. The prevalence of esophagitis did not differ significantly between the groups, but a hiatal hernia was found more frequently in YTP patients. The prevalence of "severe" lesions on upper GI endoscopy (esophagitis grades 3–4, Barrett's, peptic ulcer) was not significantly different between the patient groups (6/26 vs. 4/33; NS).

TABLE 1. RESULTS OF ESOPHAGEAL INVESTIGATIONS IN TRANSPARENT THROAT PHLEGM (TTP) PATIENTS AND YELLOW THROAT PHLEGM (YTP) PATIENTS

	TTP (n = *33*)	*YTP* (n = *26*)	P *value*
Presence of esophagitis, *n* (%)	17 (52%)	16 (62%)	NS
Presence of hiatal hernia, *n* (%)	7 (21%)	16 (62%)	0.002
Distal acid exposure, % of time (IQR)	2.6% (0.7; 6.5)	5.4% (3.5; 11.6)	NS
Proximal acid exposure, % of time (IQR)	0.1% (0.0; 0.3)	1.3% (0.3; 2.5)	0.02
Pathological distal acid exposure, *n* (%)	13 (39%)	19 (73%)	0.01
Pathological proximal acid exposure, *n* (%)	4 (12%)	13 (54%)	<0.001
Prevalence of LES pressure, 10 mm Hg, *n* (%)	2 (8%)	5 (16%)	NS
Prevalence of peristaltic amplitude 30 mm Hg, *n* (%)	9 (27%)	5 (19%)	NS
Distal esophageal DGER exposure, % of time (IQR)	2.2% (0.3; 6.9)	18.6% (13.0; 25.8)	<0.001
Pathological distal esophageal DGER exposure, *n* (%)	9 (27%)	23 (92%)	<0.001

Distal acid exposure was pathological in 32 patients (54%), while proximal acid exposure was pathological in 17 patients (30%). In three patients, proximal pH monitoring data were not available due to technical failure. Table 1 summarizes the data on acid exposure and on esophageal manometry in TTP and YTP patients. Proximal esophageal acid exposure and the prevalence of distal and proximal pathological acid exposure were significantly higher in YTP patients. According to the prevalence of esophagitis or of pathological distal acid exposure, a diagnosis of GERD was established in 44 patients (75%), and significantly more YTP patients (24/26; 92%) than TTP patients (20/33; 61%) were diagnosed with GERD ($P = 0.01$). Abnormalities on esophageal manometry were found in 11 TTP patients (33%) and 7 YTP patients (27%).

DGER Investigation. Due to technical failure, DGER results were not available for one patient. DGER exposure was pathological in 32 patients (55%). YTP patients had significantly higher distal esophageal DGER exposure and a higher prevalence of pathological DGER exposure (Figure 1 and Table 1).

All seven YTP patients who underwent double-probe esophageal DGER monitoring had elevated DGER, not only in the distal esophagus (median, 13%; IQR, 9.5–19.6%) but also in the proximal esophagus (median, 7.4%; IQR, 1.8–20.8%) (Figure 2).

In nine samples, obtained from eight patients, consisting of predominantly yellow-stained throat phlegm or containing clearly visible yellow-stained phlegm within a rather watery solution, the presence of bile acids was demonstrated (total bile acid concentration median, 0.184 μM; interquartile range, 0.025–0.231 μM). In seven other samples, obtained from six patients, containing no clearly visible yellow-stained phlegm, no bile acids were detected (below threshold for detection).

Response to Antireflux Therapy. On antireflux therapy with omeprazole, 20 mg b.i.d., or lansoprazole, 30 mg once daily, the evacuation of TTP ceased in most (61%) throat phlegm patients and was reduced, no longer being troublesome, in the others. The evacuation of YTP ceased in all YTP patients. Additional reflux-related symptoms, if present, also responded to therapy. The sensation of postnasal drip disappeared in most (69%) and improved in the other throat phlegm patients. Nasal congestion ceased in a majority (77%) of throat phlegm patients and improved (13%) or remained unchanged in the others (10%). There were no significant differences in the response of these symptoms to antireflux therapy between YTP and TTP patients. The time needed to become asymptomatic was on average 4 weeks (lQR, 2–16 weeks). The patients with Hp-positive ulcers received standard eradication therapy.

Fifty-one (86%) patients entered long term follow up (median, 10 months; range, 3–36 months). At the end of follow up, more YTP patients (21/23; 91%) than TTP-patients (19/28; 68%) required PPI maintenance therapy to remain asymptomatic ($P = 0.04$). In addition, of those in need of a PPI maintenance dose, more YTP patients (15/21; 71%) than TTP patients (7/19; 37%) ($P = 0.03$) required a full PPI maintenance dose. In 11 patients (19%), PPI therapy could be stopped while maintaining lifestyle measures, without recurrence of excessive throat phlegm or other reflux-related symptoms. The follow-up ORL examination revealed that the erythema of the posterior larynx and pharynx and, to a lesser degree, also the edema of the posterior larynx were reduced or disappeared in most patients; throat phlegm clumps, strains, or fragments were no longer observed.

DISCUSSION

Excessive throat phlegm is a common symptom and unexplained excessive throat phlegm is a frequently occurring clinical condition. Although it has been suggested that excessive throat phlegm and postnasal drip may represent supraesophageal reflux of gastric content in many cases (22, 23), this has not been formally proven. In

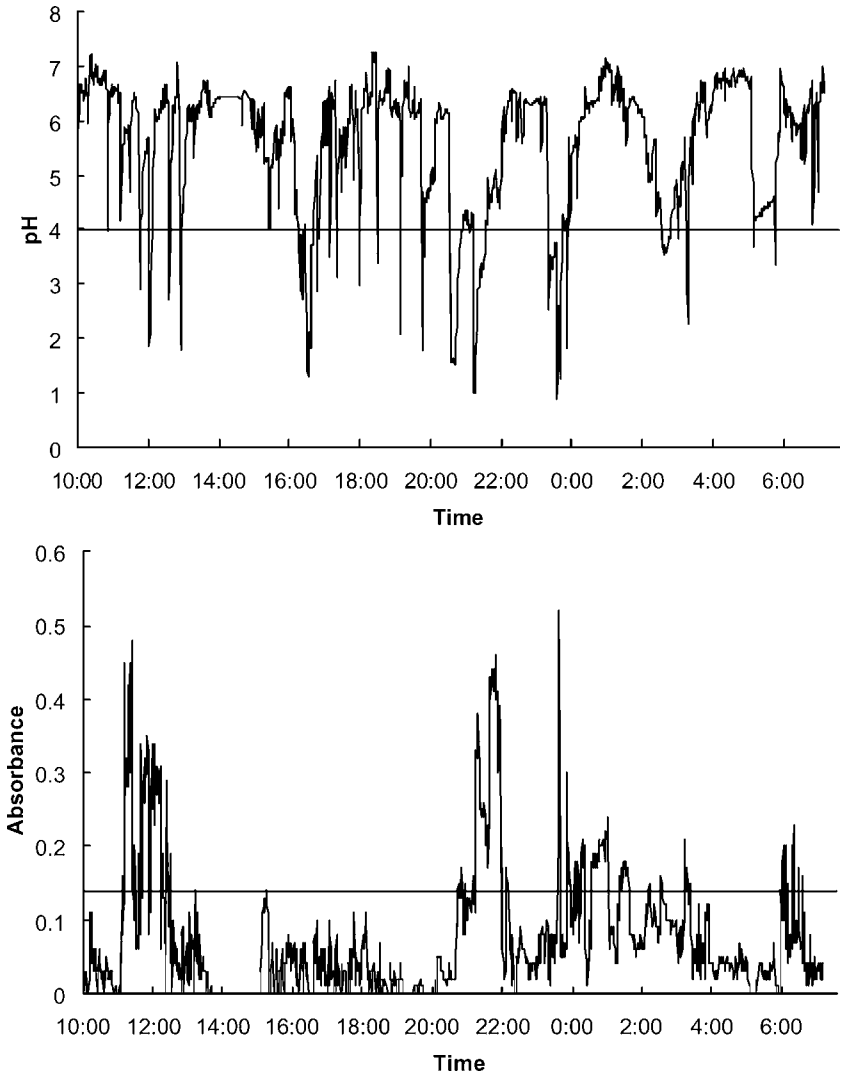

Fig 1. Representative tracing of combined pathological pH and Bilitec monitoring in a patient with chronic unexplained excessive throat phlegm. The *X* axis depicts time. The *Y* axis in the upper panel depicts intraesophageal pH, and the *Y* axis in the lower panel depicts bilirubin absorbance. Cutoffs of normal ranges are indicated (pH <4 and absorbance >0.14). Increases in bilirubin absorbance generally did not correspond to meal times.

the present study, we investigated the association of unexplained excessive throat phlegm and GER, and using endoscopy and pH monitoring, we could demonstrate pathological GER in the vast majority of patients. In keeping with the hypothesis that supraesophageal reflux is involved in the pathogenesis of unexplained excessive throat phlegm, the majority of patients became asymptomatic during treatment with standard PPI therapy.

Studies in esophageal manifestations of reflux disease have established that DGER, assessed by fiberoptic bilirubin monitoring, is an important cofactor related to the extent of the reflux, the presence of lesions, and the response to PPI therapy in GERD (27, 29–31). In the present study, approximately half of the patients also had pathological DGER.

Given the high prevalence of GERD and the excellent response to PPI therapy, we might hypothesize that GER plays an important role in the origin of these chronic complaints. Theoretically, the origin of excessive throat phlegm may involve different etiological mechanisms, including direct supraesophageal reflux of gastric contents, altered biophysical properties of pharyngeal mucus, and altered mucus clearance mechanisms. It is conceivable, and in our opinion even likely, that mucus as well as other

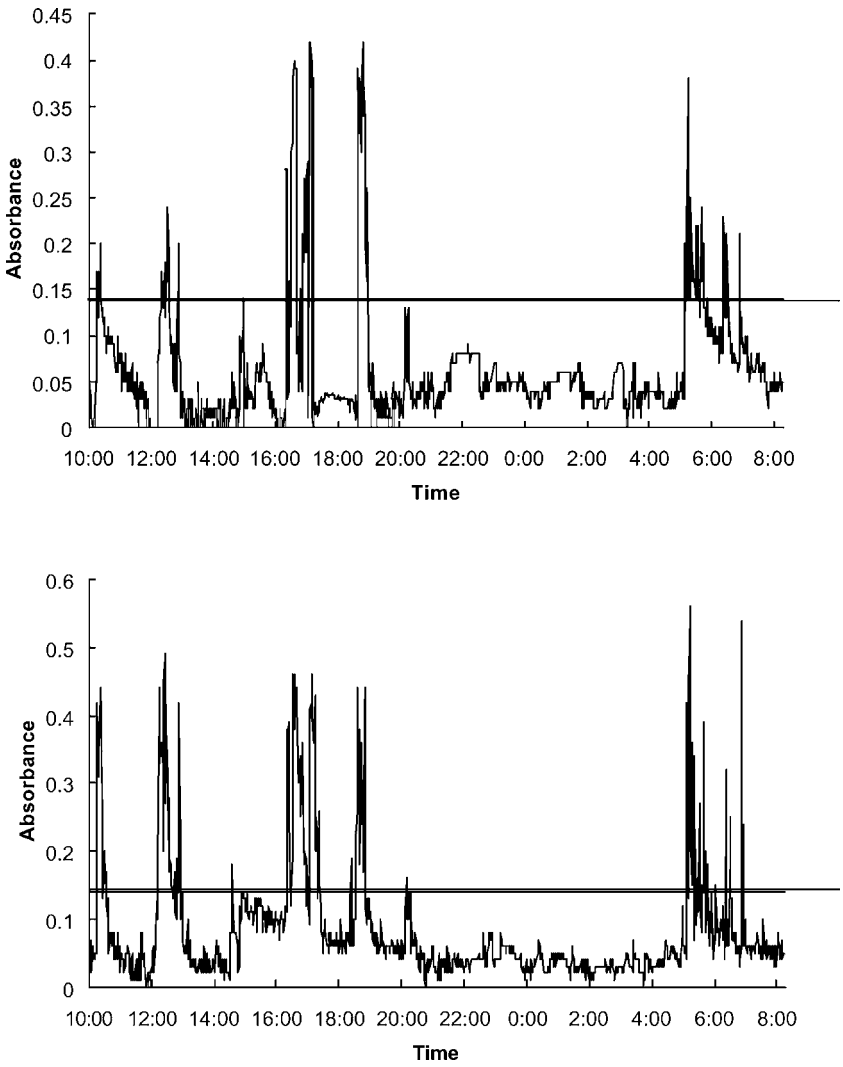

Fig 2. Representative tracing of dual Bilitec monitoring in a patient with unexplained excessive yellow-stained throat phlegm. The *X* axis depicts time; the *Y* axis depicts bilirubin absorbance. The upper panel shows Bilitec monitoring 20 cm proximal to the lower esophageal sphincter. The lower panel shows pathological Bilitec monitoring 5 cm proximal to the lower esophageal sphincter. Cutoffs of normal ranges are indicated (absorbance >0.14).

constituents of gastric origin, may reflux into the esophagus and subsequently into the pharynx. Alternatively, throat phlegm may originate from the mucous blanket that under physiological conditions covers the surface of the pharyngeal wall and mainly consists of salivary mucoproteins, repleted with mucoproteins secreted by airway mucosa that are continuously drained toward the pharynx through the mucociliary clearance process. This mucous blanket moves aborally from the pharynx toward the esophagus and the stomach by regular swallowing acts. Under pathological conditions, the pharyngeal mucus might become more abundant and/or more viscous, thereby changing this normally unperceived process to one inducing a sensation of excessive and/or more difficult to clear throat phlegm. Similar to pH-related changes in rheological properties of gastric, biliary, and respiratory mucus (32–34), we can postulate a potential for refluxed acid to increase the viscosity of pharyngeal mucus. When a drop in pharyngeal pH due to acid reflux spreads from the pharynx to the larynx and into the trachea, this only may not increase the viscosity of local mucus but also may slow or even impede airway mucociliary clearance, resulting in stasis of secretions. Brief (60-sec) exposure of the rabbit trachea to HCl and pepsin at different pH levels has a direct inhibitory effect on mucociliary flow (35). In addition, the enzymatic activity of pepsin may

directly affect the underlying cilia (35). Similar effects on viscosity of surface mucus and on mucociliary clearance may occur in the middle ear (36) and potentially also in the nasosinusal complex when acid reflux extends into the nasopharynx to reach the eustachian tube and the posterior nose (9). Impaired pharyngoesophageal clearance mechanisms including pharyngeal hypocontractility and esophageal motility disorders may play an additional role in some patients with symptoms of excessive throat phlegm. Finally, as animal experiments have shown that gastric juice causes mucosal injury and induces inflammation in the larynx and trachea (37, 38), changes in secretion and/or in the physical properties of airway mucus may occur secondarily to inflammation. Antireflux therapy with PPI eliminates or reduces GER and GEPR and may, by acting directly or indirectly on the pathophysiological mechanisms described above, eliminate or reduce excessive throat phlegm and, if present, also other associated reflux-related symptoms and signs.

All patients reported the evacuation of throat phlegm several times daily, and this could be transparent or yellow colored. When subdividing patients according to whether or not they reported evacuation of yellow throat phlegm, we found that YTP patients had a higher prevalence of GERD and of hiatus hernia. Moreover, YTP patients had more severe proximal acid exposure, more severe DGER exposure, and a higher prevalence of pathological distal acid exposure, proximal acid exposure, and DGER exposure. As throat phlegm occurs within or extends into the nasopharynx, this may be perceived as postnasal drip. Initially, prior to medical antireflux therapy, YTP patients had a higher prevalence of associated feelings of postnasal drip and nasal congestion. These findings may reflect a different DGEPR distribution pattern in YTP patients compared to TTP patients indicating reflux which is more severe, is of a higher volume, and possibly extends more frequently into the nasopharynx (29, 39). The observation that more YTP patients were in need of PPI maintenance therapy to remain asymptomatic is also compatible with more severe reflux, which could be related to the nature and/or the volume of the refluxate. Most studies have shown that acid and DGER episodes occur together and that exposures to both components of the refluxate are well correlated (24, 27, 30, 31, 40). On the other hand, during combined Bilitec and pH studies, individual patients may have more pronounced exposure to one of both components (24, 27, 29, 31), and bile reflux episodes last significantly longer than acid reflux episodes, suggesting different contributing reflux and clearance mechanisms (41). Finally, mixing of bile with acid may partly neutralize the acidity of the refluxate and contribute to underestimation on pH monitoring with a pH <4 cutoff. These considerations may help to explain why the difference in DGER exposure between YTP and TTP was more pronounced than the difference in distal esophageal acid exposure. Although studies have shown that DGER responds to PPI therapy, presumably indirectly through a decrease in intragastric fluid volume, the effect of acid suppression on DGER is less complete compared to the effect on acid reflux (30, 31, 40). Smoking and daily alcohol intake were more prevalent in YTP patients than in TTP patients. It is well known that smoking cigarettes and regular alcohol intake enhance GER. Whether these habits also stimulate DGER is actually uinknown and requires further investigation. Nevertheless, these lifestyle features are unlikely to be the primary cause, as most patients did not use alcohol or tobacco regularly.

The invariable association of YTP with DGER as well as the almost-invariable association of YTP with pathological DGER, together with the disappearance of YTP in all patients following medical antireflux therapy, indicates that YTP was the result of DGER and probably subsequent duodenogastroesophagopharyngeal reflux (DGEPR). This is further supported by the observation that all YTP patients who underwent double-probe esophageal DGER monitoring had high DGER exposure both in the distal and in the proximal esophagus. Distal DGER was pathological in all, and although no established normal values are available for proximal DGER exposure, the median value of proximal DGER exposure was higher than the upper limit of normal for distal DGER exposure, making it very likely that these values reflect abnormal proximal DGER exposure.

The finding of a proximal extent of DGER implicates the potential of subsequent DGEPR, especially when pressure in the upper esophageal sphincter (UES) is low, as during sleep or UES relaxation (42). As Bilitec monitoring in the pharynx is technically not feasible, we used an enzymatic assay to investigate the presence of bile acids in nine yellow-stained and in seven transparent throat phlegm samples. The invariable presence of bile acids in YTP samples at concentrations comparable to those found in esophageal and gastric aspirates of GERD patients (43) further supports the conclusion that YTP in these patients resulted from DGEPR.

In summary, we have demonstrated a high prevalence of GERD and a favorable response to antireflux therapy in patients with chronic excessive throat phlegm. Furthermore, we have shown that DGER may extend into the proximal esophagus and the pharynx. As this is associated with YTP, DGER and supraesophageal bile reflux are contributing factors to reflux-related supraesophageal symptoms and clinical signs in ORL patients. In light of the findings of this study we might consider unexplained excessive throat phlegm a sign suggestive of GER and

GEPR and unexplained YTP a sign suggestive of proximal esophageal and supraesophageal DGER.

REFERENCES

1. Richter JE: Typical and atypical presentations of gastroesophageal reflux disease. Gastroenterol Clin North Am 25:75–102, 1996
2. El-Serag HB, Sonnenberg A: Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology 113:755–760, 1997
3. Hanson DG, Kamel PL, Kahrilas PJ: Outcomes of antireflux therapy for the treatment of chronic laryngitis. Ann Otol Rhinol Laryngol 104:550–555, 1995
4. Sataloff RT, Castell DO, Katz PO, Sataloff DM: Reflux Laryngitis and Related Disorders. Albany, NY, Delmar Thomson Learning, 2003
5. Koufman JA: The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation on the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 101:Suppl 53, 1991
6. Shaker R, Millbrath M, Ren J, Toohill R, Hogan WJ, Li Q, Hofman CL: Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. Gastroenterology 109:1575–1582, 1995
7. Noordzij JP, Khidr AK, Desper E, Meek RB, Reibel JF, Levine PA: Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. Laryngoscope 112:2192–2195, 2002
8. Ward PH, Bercy G: Observations on the pathogenesis of chronic nonspecific pharyngitis and laryngitis. Laryngoscope 92:1377–1382, 1982
9. Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall JP, Pearson JP: Is gastric reflux a cause of otitis media with effusion in children? Laryngoscope 112:1930–1934, 2002
10. Poelmans J, Tack J, Feenstra L: Chronic middle ear disease and gastroesophageal reflux disease: A causal relation? Oto Neurotol 22:447–450, 2001
11. Phipps CD, Wood WE, Gibson WS, Cochran WJ: Gastroesophageal reflux contributing to chronic sinus disease in children. A prospective analysis. Arch Otolaryngol Head Neck Surg 126:831–836, 2000
12. Ulualp SO, Toohill RJ, Hoffman R, Shaker R: Possible relationship of gastroesophagopharyngeal reflux with pathogenesis of chronic sinusitis. Am J Rhinol 13:197–202, 1999
13. DiBaise JK, Olusola BF, Huerter JV, Quigley EMM: Role of GERD in chronic resistant sinusitis: a prospective open label, pilot trial. Am J Gastroenterol 97:843–850, 2002
14. Sontag S, O'Conell S, Khandelwall S, Miller T, Nemchausky B, Schnell TG, Serlovski R: Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 99:613–620, 1990
15. Harding SM, Richter JE: The role of gastroesophageal reflux in chronic cough and asthma. Chest 111:1389–1402, 1997
16. Ducolone A, Vandevenne A, Jouin H, Grob JC, Coumaros D, Meyer C, Burghard G, Methlin G, Hollender L: Gastroesophageal reflux in patients with asthma and chronic bronchitis. Am Rev Respir Dis 135: 327–332, 1987
17. Ossakow SJ, Elta G, Bogdasarian R, Colturi T, Nostrant TT: Esophageal reflux and dysmotility as the basis of persistent cervical symptoms. Ann Otol Rhinol Laryngol 96:387–392, 1987
18. Loehrl TA, Smith TL, Darling RJ, Torrico L, Prieto TE, Shaker R, Toohill RJ, Jaradeh SS: Autonomic dysfunction, vasomotor rhinitis, and extraesophageal manifestations of gastroesophageal reflux. Otolaryngol Head Neck Surg 126:382–387, 2002
19. Poelmans J, Tack J, Feenstra L: Prospective study on the incidence of chronic ear complaints related to gastroesophageal reflux and on the outcome of antireflux therapy. Ann Otol Rhinol Laryngol 111:933–938, 2002
20. Shaker R, Bardan E, Gu C, Kern M, Torrico L, Toohill R: Intrapharyngeal distribution of gastric acid refluxate. Laryngoscope 113:1182–1191, 2003
21. Jack CIA, Calverly PMA, Donnelly RJ, Tran J, Russell G, Hind CR, Evans CC: Simultaneous tracheal and esophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. Thorax 50:201–204, 1995
22. Toohill RJ, Kuhn JC: Role of refluxed acid in pathogenesis of laryngeal disorders. Am J Med. 103 (5A):100S–106S, 1997
23. Olson NR: Laryngopharyngeal manifestations of gastroesophageal reflux disease. Otolaryngol Clin North Am 24:1201–1213, 1991
24. Vaezi MF, Richter JE: Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. Gastroenterology 111:1192–1199, 1996
25. Poelmans J, Feenstra L, Demedts I, Rutgeerts P, Tack J: The yield of upper gastrointestinal endoscopy in patients with suspected reflux-related chronic ear, nose and throat symptoms. Am J Gastroenterol 99:1419–1426, 2004
26. Ollyo JB, Lang F, Fontolliet C, Monnier P: Savary-Miller's new endoscopic grading of reflux-esophagitis: a simple, reproducible, logical, complete and useful classification. Gastroenterology 98:A100, 1990
27. Tack J, Bisschops R, Koek GH, Sifrim D, Lerut T, Janssens J: Dietary restrictions during ambulatory monitoring of duodeno-gastroesophageal reflux. Dig Dis Sci 48:1213–1220, 2003
28. Turley SD, Dietschy JM: Re-evaluation of the 3 alpha-hydroxysteroid dehydrogenase assay for total bile acids in bile. J Lipid Res 19:924–928, 1978
29. Cool M, Poelmans J, Koek G, Sifrim, D, Feenstra L, Janssens J, Tack J: Characteristics and clinical relevance of proximal esophageal pH monitoring. Am J Gastroenterol 99:2317–2323, 2004
30. Vaezi MF, Richter JE: Duodenogastroesophageal reflux and methods to monitor nonacidic reflux. Am J Med 111 (Suppl 8A):160S–168S, 2001
31. Tack J, Koek G, Demedts I, Sifrim D, Janssens J: Gastro-esophageal reflux disease poorly responsive to proton pump inhibitors: acid reflux, bile reflux or both? Am J Gastroenterol 99:981–988, 2004
32. Johnson LR: Gastric secretion. In: Johnson LR, (ed). Gastrointestinal Physiology. 5th ed. St. Louis, MO, Mosby, 1997:82
33. Nakayama F: Pathogenesis of gallstones. In: Nakayama F (ed). Cholelithiasis: Causes and Treatment. Tokyo–New York, Igaku-Shoin, 82, 1997
34. Holma B, Hegg PO: pH and protein-dependent buffer capacity and viscosity of respiratory mucus. Their interrelationship and influence on health. Sci Total Environ 84:71–82, 1989
35. Gaynor BE: Gastroesophageal reflux as an etiologic factor in laryngeal complications of intubation. Laryngoscope 98:972–979, 1988
36. White DR, Heavner B, Hardy SM, Prazma J: Gastroesophageal reflux and eustachian tube dysfunction in an animal model. Laryngoscope 112:955–961, 2002
37. Delahunty JE, Cherry J: Experimentally produced vocal cord granulomas. Laryngoscope 78:1941–1947, 1996
38. Wynne JW, Ramphal R, Hood CI: Tracheal mucosa damage after aspiration. Am Rev Respir Dis 124:728–732, 1981
39. Sifrim D, Holloway R, Silny J, *et al.*: Non-acid gastroesophageal reflux Gastroenterology 120(5):2161, 2001

40. Champion G, Richter JE, Vaezi MF, Singh S, Alexander R: Duodenogastroesophageal reflux: relationship to pH and importance in Barrett's esophagus. Gastroenterology 107:747–754, 1994
41. Koek GH, Vos R, Flamen P, Sifrim D, Lammert F, Vanbilloen B, Janssens J, Tack J: Oesophageal clearance of acid and bile: a combined radionuclide, pH and Bilitec study. Gut 53:21–26, 2004
42. Kahrilas PJ, Dodds WJ, Dent J, Haeberle B, Hogan WJ, Arndorfer RC: Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. Gastroenterology 92:466–471, 1987
43. Vaezi MF: Duodenogastroesophageal reflux. In: Castell DO, Richter JE (eds). The Esophagus. 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 1999, pp 424–426