Zapleti gastroezofagealne refluksne bolezni, 10-letne izkušnje

Complications of gastroesophageal reflux disease: 10-year experience

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Izvleček

Namen: *Gastro-ezofagealna refluksna bolezen (GERB) je pogosta bolezen sodobnega časa, ki nastane zaradi kroničnega zatekanja želodčne vsebine v požiralnik. Vzrok sta neravnovesje med škodljivimi in varovalnimi dejavniki sluznice požiralnika in motnja v delovanju spodnjega požiralnikovega sfinktra (LES). Prehodna sprostitev LES, ki se pojavlja pogosteje in traja dlje kot je fiziološko normalno, je glavni vzrok za nastanek GERB-a. Škodljive učinke refluksa poslabšata motena peristaltika požiralnika, ki ne zmore sproti čistiti požiralnika pri motilitetnih motnjah požiralnika in moteno praznjenje želodca pri velikih hiatalnih kilah ali peptičnih ulkusih. Tipični simptomi GERB-a so pekoč občutek ali bolečina za prsnico, vračanje grenke ali kisle želodčne vsebine v žrelo, redkeje odinofagija in ekstraezofagealni znaki, kot so nekardiogena prsna bolečina, kronični kašelj in hripavost.*

Abstract

Purpose: *Gastroesophageal reflux disease (GERD) is a common condition of modern times resulting from chronic reflux of gastric contents into the esophagus. The cause underlying GERD involves an imbalance between noxious and protective factors of the esophageal mucosa and a functional disorder of the lower esophageal sphincter (LES). The transitional release of the LES appearing more frequently and longer than physiologically normal is the main cause for the development of GERD. The negative effects of reflux can increase by disturbed esophageal motility, which is unable to regularly clear the esophagus in esophageal motility disorders and disturbed gastric emptying in large hiatal hernias and peptic ulcers. Typical GERD symptoms include a burning sensation or pain behind the sternum, return of bitter or acidic gastric content into the esophagus, rare odynophagia*

Metode: *Pregled literature in kliničnih primerov v 10-letnem obdobju na Oddelku za torakalno kirurgijo UKC Maribor.*

Rezultati: *V članku predstavljamo 10-letne izkušnje s kirurškim zdravljenjem GERB-a in njegovih zapletov. Zdravljenje refluksnega ezofagitisa in z GERB-om pogojene astme, ni v domeni kirurga. Kirurško zdravljenje je indicirano pri pasažnih ovirah in v primerih, ko GERB-a ni mogoče obvladovati z medikamentozno terapijo. V desetih letih (2006 – 2015) smo opravili 928 posegov za odpravljanje in preprečevanje zapletov GERB-a.*

Zaključek: *Znani so številni možni zapleti GERB-a, med katerimi sta posebej nevarna razvoj Barrettovega požiralnika kot prekancerogenega stanja sluznice požiralnika in razvoj žleznega karcinoma distalnega dela požiralnika. Ob zdravljenju osnovne bolezni je potrebna natančna diagnostična obdelava obolelih, saj je klinična slika GERB-a velikokrat podobna težavam povezanih z drugo torakalno patologijo.*

and extraesophageal signs, such as non-cardiac chest pain, chronic cough, and hoarseness.

Methods: *A literature revue and a review of clinical cases over a 10-year span in the Department for Thoracic Surgery University Medical Centre Maribor.*

Results: *The study was also drawn from 10 years of experience with surgical treatment of GERD and its complications. The treatment of reflux esophagitis and asthma as a GERD complication is not the domain of a surgeon. Surgical treatment is indicated in passage-blocking conditions and in cases in which GERD cannot be managed with medical therapy. In the period from 2006–2015 we performed 928 surgeries to remove and prevent GERD complications.*

Conclusion: *Several possible complications of GERD are known, among which the development of Barret's esophagus as a pre-malignant condition of the esophageal mucosa and the development of glandular carcinoma of distal esophagus are especially dangerous. Therefore, a precise diagnostic treatment is necessary when treating the underlying disease of patients as the clinical picture of GERD often resembles problems related to other thoracic pathologies.*

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a collection of symptoms resulting from chronic return of gastric content into the esophagus (heartburn, regurgitation, painful swallowing, chronic cough and hoarseness). The cause lies in the imbalance between noxious and protective factors of esophageal mucosa and a functional disorder of the lower esophageal sphincter (LES). A transitional release of LES and lowered basal LES pressure are the main causes underlying the development of GERD. Negative effects of reflux can increase by disturbed esophageal motility, which is unable to regularly clear the esophagus (esophageal motility disorders and scleroderma) and disturbed gastric emptying (large hiatal hernia, peptic ulcer, and diabetic gastropathy). The development of GERD is also conditioned by other factors, such as obesity, inappropriate nutrition, consumption of coffee, alcohol, specific drugs, and smoking. The disease is chronic and requires continued treatment. GERD appears in 7%-10% of adults every day, in 14% once a week, and in 44% once a month. Diagnostic procedures for GERD include the following: proton pump inhibitor (PPI) test; endoscopic examinations; contrast-enhanced X-ray examinations; 24-hour pH testing; manometry; and esophageal impedance. Quality of life is strongly affected due to the disease. Late complications of GERD are particularly unfavorable as the complications place the patient's life at risk on account of a possible malignant alteration of esophageal mucosa.

Possible complications of GERD are reflux esophagitis, asthma, peptic stricture, short esophagus, Barrett esophagus, and esophageal adenocarcinoma (1).

Diagnostic procedures

This clinical diversity dictates the use of different diagnostic endoscopic, imaging, and functional tests (2):

- *Endoscopy* is required to describe the presence of inflammation, stenosis, the position of the esophagogastric (EG) junction for assessment of the esophageal length, and size of the hiatal hernia (the distance between the EG junction and hiatal borderlines). An integral part of the otorhinolaryngologic examination is panendoscopy defining the pharyngolaryngeal status.
- *The barium esophagram* shows the location, length, and nature of the strictures, which are not endoscopically passable. The barium esophagram demonstrates shortening of the esophagus and the presence of a hiatal hernia, as well as gastric acid reflux.
- *Manometry* measures the tone of the lower esophageal sphincter and detects disturbed esophageal motility; both have important prognostic value.
- *24-hour pH testing* for detecting the presence and extent of reflux, the results of which are quantified using the DeMeester scoring system. The score considers the total number of reflux episodes, percentage of time when the pH value in the esophagus is < 4 in a standing and lying position, the duration of the longest reflux episode, and the number of reflux episodes lasting > 5 min.
- *Esophageal impedance* is the latest examination measuring electrical impedance in the esophageal lumen.

Treatment of GERD

Treatment of GERD focuses on the elimination of reflux and all accompanying complications. The initial treatment usually focuses on preventing the reflux, as follows: avoiding fatty foods, coffee, and chocolate; having meals at least 2 hours before sleep; limiting or avoiding use of alcohol and cigarettes; and reducing the body weight. Persistent

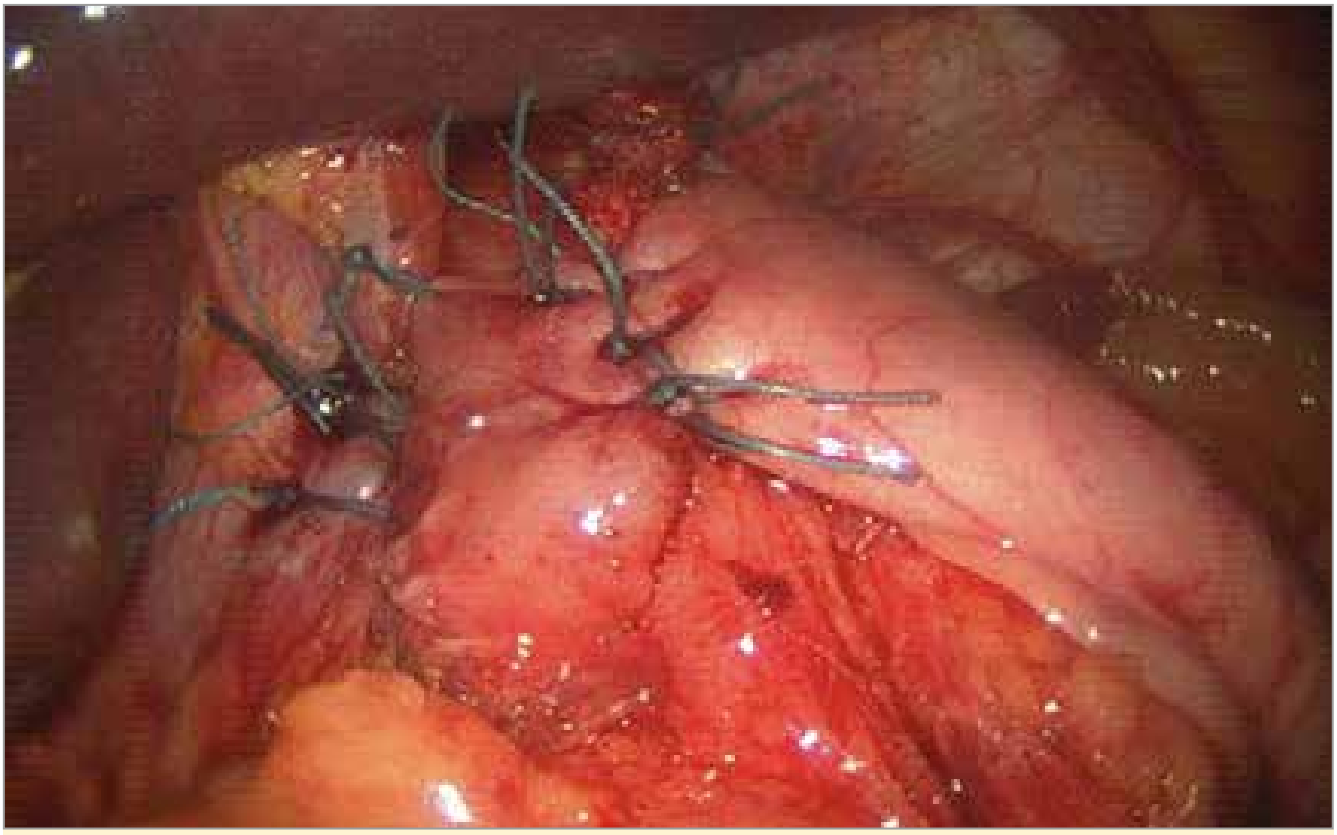

Figure 1: *Laparoscopic demonstration of Nissen fundoplication.*

symptoms of esophagitis are treated with antacids and proton pump inhibitors (PPIs). The standard dose of a PPI (20 mg a day) for 4-8 weeks eliminates the problems of > 90% of patients with reflux esophagitis. Grades C and D reflux esophagitis require higher doses of a PPI and recovery is rare [80%] (3). Reflux esophagitis may re-appear in approximately 80% of patients 30 weeks after discontinuing PPI therapy (1). Relapse is more frequent in patients with hiatal hernias or weakened clearing of acid from the esophagus. In fact, these patients require continuous therapy.

Although PPIs are highly effective drugs in nevtralizing gastric acid, they are not effective in patients with decreased or low basal LES pressure, disturbed esophageal motility, hiatal hernia, prolonged clearing of the esophagus, and the presence of individual complications. Gastric acid, pepsin, bile acids, pancreatic enzymes, and lecithin give rise to acidic or alkaline gastric and duodenal liquid mixed with food that continues to be present in the esophagus. More aggressive treatment approaches, such as surgical intervention, are reasonable.

Anti-reflux surgeries

Surgical treatment is curative and mostly more effective long-term compared to therapy with medications. The main indications for surgical treatment are as follows:

- unsuccessful treatment with medications;
- irreducible, large axial and paraesophageal hiatal hernia;
- LES pressure < 10 mm Hg;
- severe esophagitis (C or D by Los Angeles (LA_ classification), bleeding, strictures, and ulcers;
- Barret's esophagus; and
- non-typical symptoms, including chronic cough, difficult breathing, aspirations, hoarseness, chronic pharyngitis, and enamel damages.

The objective of the surgical procedure is to have at least 2 cm of distal esophagus inside the abdomen and a LES pressure at least three times higher than the pressure inside the abdomen. Two surgical methods are possible (always laparoscopic), as follows: Nissen fundoplication (Figure 1); and Toupet fundoplication, which is a complete or partial 270° wrap of the esophagus. In patients with a short esophagus we perform the esophageal lengthening procedure (Collis gastroplasty) and then anti-reflux surgery. It has been shown that approximately 90% of patients experience no problems with GERD 18 months after anti-reflux surgery (4).

Dilatation of the esophageal strictures

Dilatation of the stricture is the method of choice for relieving the symptoms of dysphagia (5). The condition resolves when the stricture is extended to 14 mm. A general recommendation for performing dilation is to choose a dilatator 1 mm wider than the diameter of the stricture and dilates gradually to the desired width (Figure 2). Repeated strictures are common.

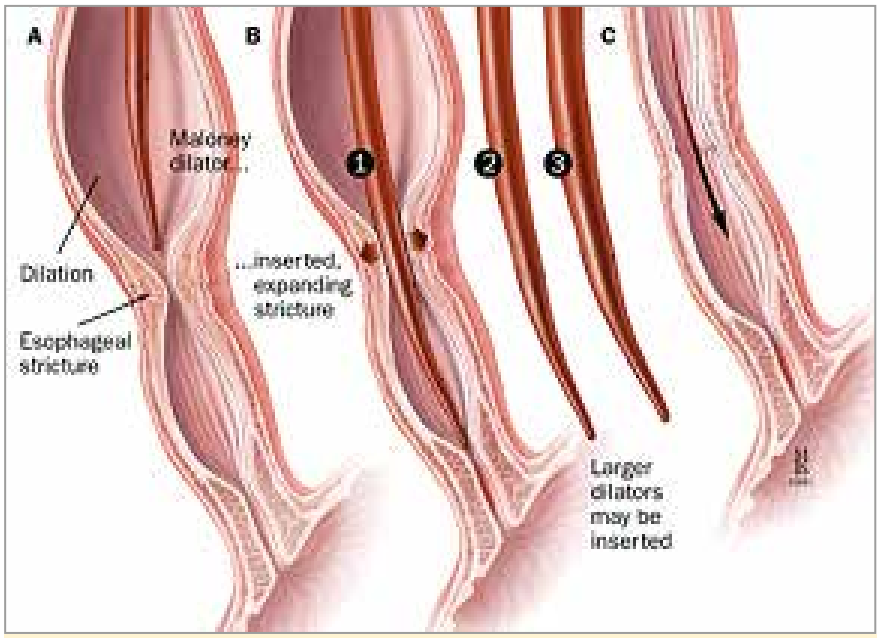

Figure 2: *Gradual widening of esophageal stricture with rubber dilators (bougies).*

Table 1: *Main complications listed by year and gender and treated in the period from 2006-2015 in the Department of Thoracic Surgery of the University Medical Centre Maribor*

Year	ESOPHAGEAL CARCINOMA	REFLUX DISEASE	STRICTURES & SHORT ESOPHAGUS
2006	29	52	2
2007	29	38	4
2008	35	50	1
2009	30	52	2
2010	35	47	3
2011	47	51	1
2012	39	39	4
2013	48	62	2
2014	52	61	3
2015	49	59	4
Total	393	511	24
m	351	195	10
f	42	316	14

Table 2: *LA classification system*

Grade A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involve less than 75% of the circumference
Grade D	One (or more) mucosal break which involves at least 75% of the esophageal circumference

Esophageal resection

Esophageal resections are rarely indicated in patients with GERD. In patients in whom dilatation of strictures or ensuring a proper intra-abdominal esophageal length is not possible, and patients in whom anti-reflux procedures did not achieve the desired therapeutic effect are exceptions (1). A special group is represented by patients who consequently developed glandular carcinoma and require radical esophageal resection and additional oncologic therapy. The most common approach is the formation of a gastric tube (conduit) and its trans-hiatal elevation upwards, forming a cervical or intra-thoracic EG anastomosis (Figure 3).

MATERIALS AND METHODS

Ten-year follow-up on clinical cases at the Department of Thoracic Surgery of UMC Maribor

In Slovenia the treatment of esophageal conditions is within the domain of thoracic surgeons. Treatment of GERD complications account for a significant share of this pathology. Surgeries mainly cover the EG junction. Surgeries are indicated in passage-blocking conditions (strictures, fibrotic processes, and short esophagus) and tumors. The reflux cannot be managed by introducing PPIs or other therapies. This condition can only be treated with a surgical anti-reflux procedure.

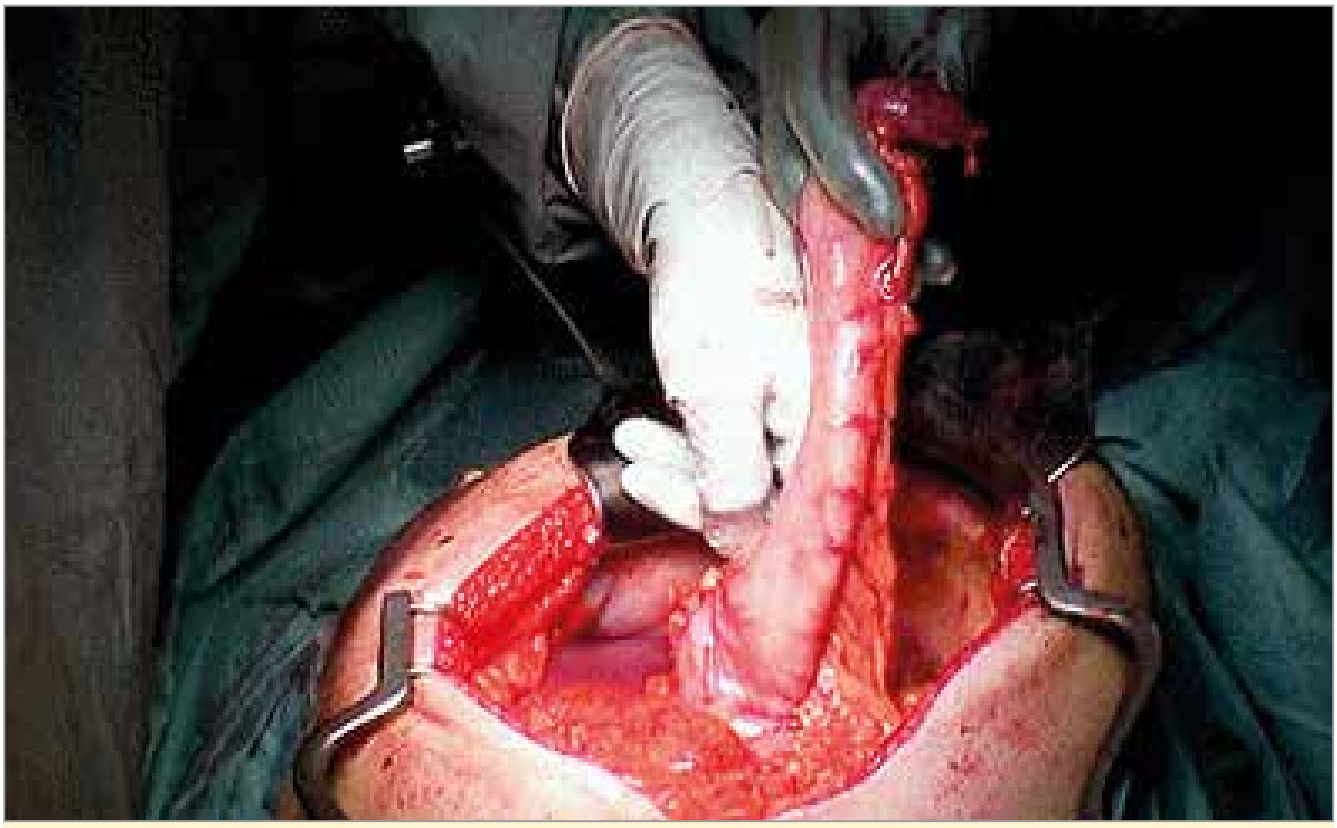

Figure 3: *Formed gastric tube for trans-hiatal elevation into the right pleural space.*

From 2006 to 2015 we performed 928 surgeries to remove and prevent GERD (Table 1 and Figure 4). During this period of time we treated 393 esophageal carcinomas (351 males and 42 females). To cure these patients, 82 underwent a resection. Other patients received palliative treatment by introducing esophageal stents or gastrostomas.

In the same period, we surgically treated 511 patients with severe reflux diseases (316 females and 195 males). The number of these patients did not change dramatically. In most cases, we performed laparoscopic Nissen fundoplications. Esophageal scarring in the absence of confirmed malignant pathology and with a stricture and/or short esophagus syndrome are very rare. Only 24 patients with a female preva-

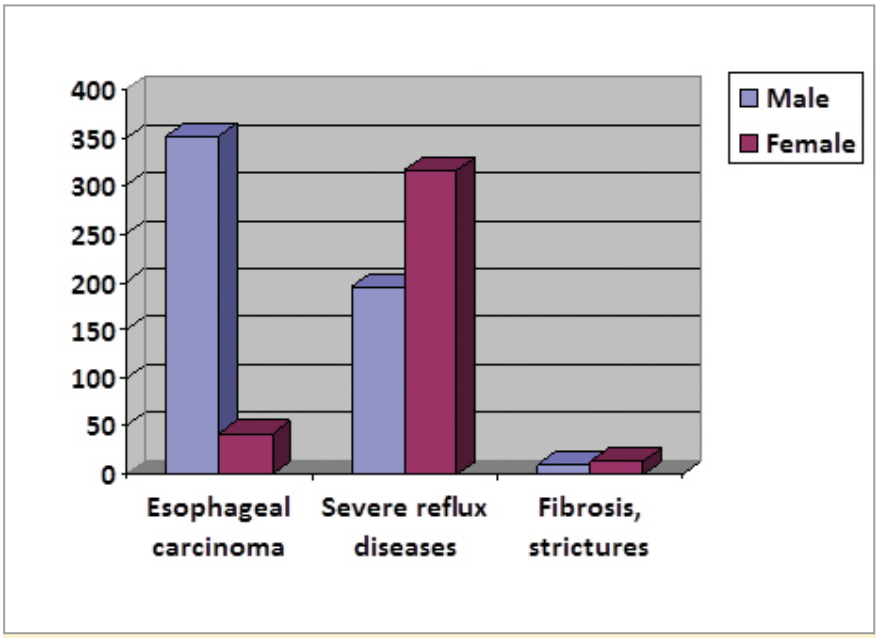

Figure 4: *Treated GERD complications (divided into main pathology and gender).*

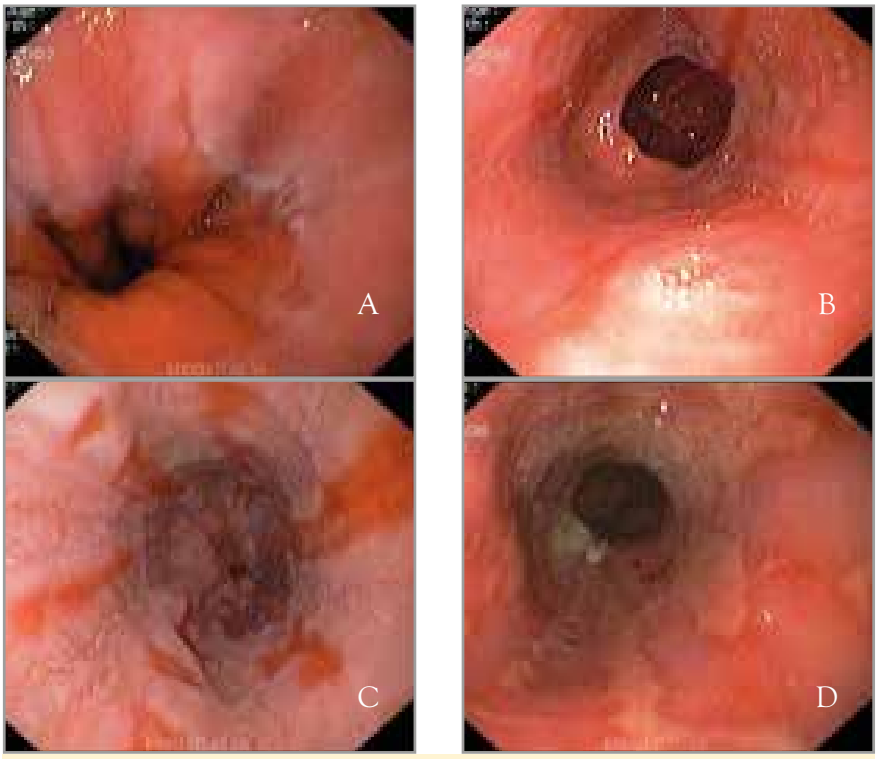

Figure 5: *Grade of esophagitis A-D (endoscopic demonstration of altered esophageal mucosa).*

lence were treated at our institution. Dilatation of the stricture was the method of choice for relieving the symptoms of dysphagia

DISCUSSION

GERD is a common disease. Symptoms of GERD are chronic and significantly lower the quality of life. In most patients, the symptoms of GERD can be eliminated or at least relieved with a special diet and proper medication. In patients in whom conservative treatment did not achieve the desired therapeutic effect and the condition led to GERD complications, the patients were candidates for a more aggressive approach to treatment and surgical therapy. Laparoscopic fundoplication is the gold standard for the surgical treatment of severe forms of GERD; esophageal resection remains the surgical method of choice in cases of glandular esophageal carcinoma.

Good knowledge of the clinical picture is the basis for all further diagnostic and therapeutic procedures.

Possible GERD complications: Reflux esophagitis

Reflux esophagitis is a general term to describe erosions and sores on the esophageal mucosa due to exposure to gastric contents (6). Reflux esophagitis is classified according to the extent of erosions according to the so called LA classification system [Table 2 and Figure 5] (1). Macroscopic esophagitis (Grade A) is present in 44% of patients reporting of chronic problems with heartburn. Reflux esophagitis increases the prevalence of peptic strictures to 10-20 and the prevalence of Barrett's esophagus to 8%–20% (7). The key role in the development has the extended or weakened clearing of acid from the esophagus. Multilayer, non-squamous cell epithelium eventually enables invasion of ions into the deeper layers of the esophageal wall. Typical endoscopic changes in early reflux esophagitis include hypertrophy of the basal zone and extension of papillae. In advanced stages, numerous intra-epithelial polymorphonuclear cells (inflammatory cells) are found (7).

Asthma as a GERD complication

Regurgitation and/or aspiration of gastric juice is a potential trigger for severe asthma (8,9). Respiratory symptoms associated with asthma (e.g., cough, wheeze, and dyspnea) are increased among patients with GERD (10,11). There are three potential mechanisms for asthma as a GERD complication: increased vagal tone; heightened bronchial reactivity to other stimuli; and micro-aspiration of refluxed material into the tracheobronchial tree. Acidification of the distal part of the esophagus results in vagal stimulation and consequent esophago–tracheo–bronchial reflex which leads to clinical

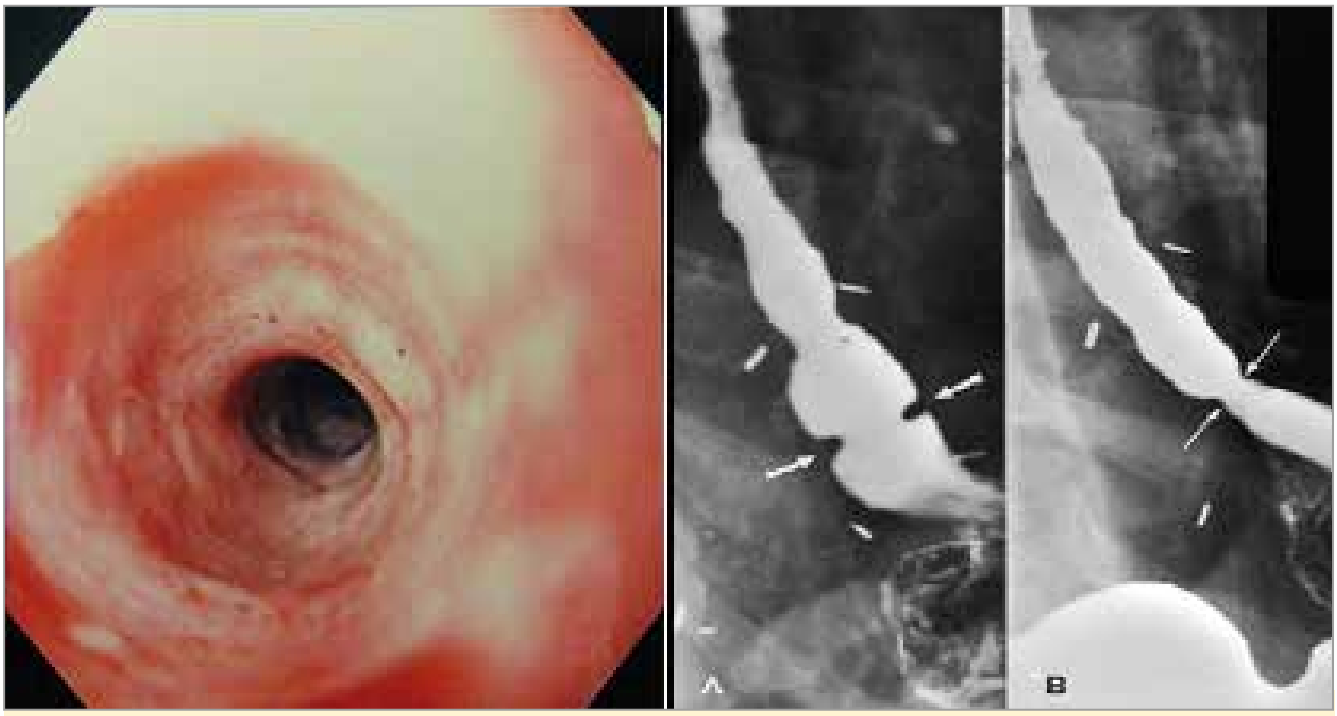

Figure 6: *Endoscopic demonstration of peptic stenosis (left) and contrast-enhanced X-ray image of esophageal stenosis (right A-B).*

manifestations of respiratory obstruction (12). If micro-aspiration is present, the response is further augmented. There is evidence that GERD treatment improves asthma symptoms, but with variable objective outcome (13–17).

Peptic stricture

A stricture is a narrowing of the esophagus measuring < 13 mm in diameter and causes dysphagia (15). Peptic esophageal stricture results from chronic esophagitis leading to fibrosis (1). Long-term exposure of the esophageal mucosa to gastric acid, pepsin, bile, and pancreatic enzymes causes inflammation, which is replaced in the reparation phase with fibrotic tissue (4). The process is gradual and begins with mucosal edema and infiltration of inflammatory cells into the lamina propria. Chronic esophagitis progresses transmurally, even into peri-esophageal tissues, with subsequent fibrosis and scarring (Figure 6). Peptic strictures usually occur at the EG junction and measure 1–4 cm in length; the prevalence of peptic strictures among non-treated reflux patients is 8%–25% (5).

Short esophagus

The term short esophagus indicates the intra-abdominal length of the esophagus measuring < 2.5 cm (18). The prevalence of short esophagus among non-treated reflux patients is 1%–5% (1). The process is identical to the process of peptic strictures, whereby the scarring in short esophagus is longitudinal. Short esophagus is often associated with hiatal hernia. Short esophagus is treated surgically; a transabdominal Collis gastroplasty is performed.

Barrett's esophagus

The Barrett's esophagus is a condition of altered distal esophageal mucosa first described by Barrett in 1950 (19). Barrett's metaplasia is the result of chronic esophageal reflux caused by gastroesophageal reflux of gastric acid, bile, and other noxious substances. In most patients, reflux-induced mucosal damage is repaired by the regeneration of squamous cell epithelium, and in some for reasons that are not clear, through columnar metaplasia (20,21). Barrett's syndrome is usually diagnosed during an endoscopic examination in middle-aged

patients with an average age of 55 years who complain of GERD (20). Two criteria need to be met for diagnosing the Barrett's syndrome, as follows: the endoscopist is required to record the presence of cylindrical epithelium in the distal esophagus; and the histologic findings of samples obtained from the biopsy of the cylindrical epithelium needs to indicate intestinal metaplasia. Individual studies show that the presence of gastric cardiac epithelium in the esophagus is a pre-disposition for the development of esophageal carcinoma (30 times higher than the healthy population). This type of change is classified under Barrett's esophagus (19).

The basic principle of treatment is the elimination of gastroesophageal reflux. Regular endoscopic examinations are important in patients with GERD for identifying Barrett's esophagus (2,20). Opinions regarding esophageal resection are divided and a less aggressive endoscopic mucosal reception is performed more and more frequently (19,22).

Esophageal adenocarcinoma

The incidence of squamous cell esophageal carcinoma has decreased in recent years, but the incidence of adenocarcinoma is increasing (23). Esophageal adenocarcinoma develops in the region of Barrett's metaplasia (24). Carcinogenesis in metaplastic cells begins with a genetic change; proto-oncogenes are activated and/or tumor suppressor genes are disabled (25,26). The incidence of esophageal adenocarcinoma is 4.87 per 100,000 white males and 0.68 in 100,000 in white females (27). Unlike squamous cell esophageal carcinoma, which is most often located in the middle one-third of the esophagus, esophageal carcinoma is most often located in the distal one-third of the esophagus. Metastases to neighboring and regional lymph nodes appear early (28). Locally advanced esophageal adenocarcinoma is clinically manifested as an esophageal obstruction. Locally advanced esophageal adenocarcinoma causes advanced dysphagia for solid food and is also often accompanied by weight loss. An accurate diagnosis is followed by a multidisciplinary treatment. The disease has a poor diagnosis [5-year survival, 8%–12%] (26).

CONCLUSION

The number of patients with GERD complications is on the rise. Based on our experience, surgery can significantly improve the course of the disease and the quality of life in select cases. Several possible complications of GERD are known, among which the development of Barrett's esophagus is a pre-malignant condition of esophageal mucosa and the development of glandular carcinoma of distal esophagus is especially dangerous. Therefore, a precise diagnostic treatment is necessary when treating the underlying disease of patients as the clinical picture of GERD often resembles problems related to other thoracic pathology.

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