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CASE STUDY

The Esophageal Cascade: Reflux, Inflammation, Metaplasia, Dysplasia, and Neoplasia

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The case presented here illustrates the possible complications of gastroesophageal reflux disease (GERD). In its simple form, GERD poses no expectation of extra mortality. However, certain histopathologic complications of GERD predispose to the development of esophageal adenocarcinoma. The clinical course, diagnosis, treatment, prognosis, and preventive surveillance of GERD and Barrett metaplasia are discussed.

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In August 1998, a 51-year-old white male veterinarian applied for term insurance in the amount of $350,000. On the application, he admitted to a 15- to 20-year history of heartburn and "acid belching." Over the years, he had treated himself with antacids, with partial relief of symptoms. About 5 years before his application, his personal physician advised him that he was suffering from "girt" and instructed him to continue taking the antacids, avoid caffeine and alcohol, and elevate the head of his bed. His symptoms improved, but his sleep became disturbed, because his body tended to slide toward the foot of the bed.

The proposed insured's distress continued to wax and wane until 2 years before he applied for insurance. At that point, his symptoms became more continuous, and he began to experience painful swallowing and hoarseness. He was then referred to a gastroenterologist, who performed esophagogastroduodenoscopy. Quoting his specialist, the proposed insured reported that "my gut was in my gullet." He was then placed on ranitidine with some improvement of symptoms. Two to three months later, the ranitidine was replaced with omeprazole. Since that time, he had been alternating between ranitidine and omeprazole, reserving the omeprazole for rare flare-ups, and had remained largely free of symptoms (including his dysphagia and hoarseness).

His medical history was otherwise unre-

markable. The proposed insured was a current smoker (1.5 packs per day for 30 years). His father died of colon cancer at the age of 55 years.

To obtain information about the endoscopic and (if done) biopsy findings and the intended follow-up, an attending physician's statement was requested and received from the gastroenterologist in the form of copies of his 2 letters to the referring physician.

The pertinent information in those letters included (1) an endoscopic appearance of erosive esophagitis with subtle narrowing of the lumen just above the esophagogastric junction, (2) "rosy red, gastric-appearing mucosa" extending 7.5 cm above the esophagogastric junction, consistent with Barrett's esophagus, (3) a pathologic description of biopsied tissue from the distal esophagus indicating "specialized intestinal-type metaplasia" with a small area of "possible low-grade dysplasia," (4) the gastroenterologist's recommendation that the patient be maintained on ranitidine with use of omeprazole instead of ranitidine for exacerbations of his symptoms, and (5) a request that the patient return in 6 months for follow-up endoscopy. (That recommendation was made 22 months before the proposed insured's application for insurance.)

DISCUSSION

Gastroesophageal Reflux Disease

The proposed insured experienced heartburn and regurgitant symptoms typical of gastroesophageal reflux disease (GERD), defined as "the sequelae, both clinical and histopathologic, of the movement of gastroduodenal contents into the esophagus."[1] Minor gastroesophageal reflux with fleeting symptoms is extremely common, falling short of what reasonable clinicians would label as "disease" (ie, "GER without D"). It is estimated that about 25% of the general population experience this physiologic form of reflux at least once monthly.[2]

The stratified squamous epithelium of the esophagus, unprotected by the sophisticated defense mechanisms of the stomach and duodenum, is highly vulnerable to peptic injury. Acting upon this fragile substrate, multiple factors may play a role in the development of GERD. These interdependent factors include gastric acid production, impaired function of the lower esophageal sphincter (LES), delayed gastric emptying, individual variations in esophageal mucosal resistance, gravity, and impaired esophageal acid clearance.[3] An abnormally low LES pressure is perhaps the most common dysfunction in GERD, and this may be adversely affected by certain foods (eg, fats, chocolate, carminatives, xanthines, and alcohol) and agents (eg, cigarette smoking, calcium channel blockers, anticholinergics, and prostaglandins). The 2 steps in esophageal acid clearance are (1) swallow-induced esophageal peristalsis and (2) secretion of saliva (which has an alkaline pH).

When GERD symptoms are typical (as was the presentation of the proposed insured), the diagnosis may be assumed without testing. On the other hand, endoscopy is indicated to investigate atypical symptoms (eg, chest pain, dysphagia, sore throat, hoarseness, gingivitis, and asthma), which may occur as consequences of complications of GERD, either esophageal or extraesophageal. Esophageal complications include (1) peptic ulcer of the esophagus, with the risk of perforation, bleeding, and fistula formation (tracheoesophageal or pleuroesophageal); (2) stricture, affecting 10% of GERD patients seeking attention[4]; and (3) Barrett's esophagus (discussed below). The proposed insured may have developed an early stricture, based on the endoscopic findings, but the gastroenterologist made no further mention of this. There appeared to be no indication for esophageal dilation.

Extraesophageal complications of GERD result from gastric fluid crossing an incompetent upper esophageal sphincter and entering the mouth during sleep. Consequences of this include dental erosion, sore throat, globus sensation, and airway involvement due to subtle aspiration (laryngitis, subglottic ste-

nosis, chronic bronchitis, and asthma).[2] The proposed insured's hoarseness most likely resulted from this form of laryngitis, but this apparently was resolved after effective treatment.

In this case, the proposed insured became refractory to lifestyle changes and antacid treatment and, as already noted, eventually developed symptoms suggesting complication of GERD by a mild stricture (dysphagia) and laryngitis (hoarseness). Under these circumstances, it became necessary to perform a diagnostic investigation in the form of esophagoscopy. Although this procedure revealed distal esophagitis in this case, it has been observed that approximately 30% of GERD patients have normal-appearing esophageal mucosa on endoscopy. Because of this, it has been suggested that the definitive diagnosis of GERD be established through computed ambulatory 24-hour esophageal pH monitoring,[5] with the diagnostic criterion defined as the percentage of total test time during which a pH of less than 4 prevails.[6] In practice, however, this technique is seldom used.

The initial medical management of mild to moderate GERD consists of eliminating those foods and agents that decrease LES pressure, a liquid antacid (particularly a preparation containing alginic acid [eg, Gaviscon], which forms a foamy barrier at the gastroesophageal junction),[7] weight reduction, avoidance of tight-fitting garments, fasting for 2–3 hours before bedtime, and nocturnal postural drainage (using 15-cm blocks under the head posts of the bed). In the present case, the proposed insured was partially responsive to some of these measures but eventually became refractory to treatment and was referred to a gastroenterologist.

After endoscopic and histologic identification of the proposed insured's esophagitis with early stricture and Barrett metaplasia (discussed below), the second level of medical treatment was instituted, namely one of the antisecretory of drugs known as histamine H_2-receptor antagonists, specifically rantidine. This approach has been demonstrated to heal mild to moderate esophagitis in 60–70% of patients.[8] However, the proposed insured in this case experienced only partial relief, prompting institution of the third level of medical treatment, a proton pump inhibitor (PPI), omeprazole, during symptomatic exacerbations. This approach was largely successful in controlling the reflux symptoms, in keeping with findings gleaned from the current medical literature. An 8- to 12-week course of PPIs (very potent suppressors of gastric acid secretion) for severe esophagitis has been shown to produce healing in approximately 90% of cases.[9] The safety of long-term PPI use has been questioned, largely because omeprazole has been shown to induce hypergastrinemia and gastric carcinoid in rats.[10] However, the increase in plasma gastrin levels is considerably less in humans. Additional study is needed to elucidate the risk of long-term PPI therapy.

Another form of medical treatment of difficult cases of GERD involves use of prokinetic agents. These drugs, exemplified by cisapride, increase both LES pressure and gastric emptying (thereby producing a mechanical defense against reflux). Prokinetic agents may be used singly or in conjunction with one of the H_2-receptor antagonists.[11]

Surgical treatment of GERD is indicated in many patients who either (1) exhibit a poor response to all medical measures, (2) have 1 or more of the extraesophageal manifestations of GERD, or (3) develop Barrett metaplasia (see below).[10] This treatment option should also be considered for young people who otherwise might be subjected to the inconvenience and risks of lifetime PPI therapy. The technique used is fundoplication, which creates a valvelike mechanism by wrapping a gastric pouch around the distal esophagus. Laparoscopic fundoplication produces results equal or superior to those obtained with the open technique, eliminating reflux in 90–95% of patients.[12]

Barrett's Esophagus

The case history described here is most noteworthy for the endoscopic and histopath-

ologic detection of columnar metaplasia of the distal esophageal epithelium and an equivocating pathologic suspicion of low-grade dysplasia within the metaplasia. Over the years, the medical community has progressed through an evolution of various misconceptions and disagreements concerning the exact nature of Barrett's esophagus. Because of this controversy, 2 definitions are in order.

Metaplasia

Metaplasia is the replacement of one type of adult cell by another, most commonly encountered in lining epithelia. The pathogenesis of metaplasia is unclear in most cases. However, in many instances it appears to be an adaptation to abnormal environmental alterations, particularly chronic irritation.[13]

Dysplasia

Dysplasia is a nonneoplastic, disorganized cell growth that is not an adaptive change, usually involving epithelial tissues subjected to chronic irritation and characterized by pleomorphism, large dark nuclei (increased DNA content), and an increase in normal mitotic activity. Dysplasia is always considered premalignant but is capable of reverting to normal differentiation upon removal of the causative irritant (paraphrased from Golden et al[14]).

Controversy over exactly what constitutes Barrett's esophagus has loomed for at least 4 decades. Earlier criteria for the diagnosis of Barrett's esophagus referred merely to replacement of the native stratified squamous cell epithelium with columnar epithelium or, more specifically, gastric-like epithelium, extending some arbitrary distance (eg, 2–5 cm) above the gastroesophageal junction.[4] The prevailing modern definition identifies the replacement epithelium as "specialized intestinal (goblet cell-containing) metaplasia" (SIM), the only mucosal tissue that poses the risk of adenocarcinoma of the esophagus (discussed below).[3,15] Hence, the attending physician's whimsical reference to "gut in . . . gullet" in his explanation to the proposed insured in the case presented above.

Although not the first to describe a columnar epithelial lining of the esophagus, Barrett published a treatise in 1950[16] that would later form the basis for applying his name to the condition we now recognize as esophageal epithelial metaplasia. However, in that report, Barrett proposed that this condition occurred not as metaplasia of the esophagus but as normal gastric columnar mucosa in a segment of the gastric cardia that had become mediastinalized as the result of a congenetically short esophagus. Seven years later, Barrett acknowledged that the organ in question was, in fact, esophagus lined by columnar epithelium.[17] However, he still failed to recognize the distinctive characteristic of the columnar epithelium to be given the Barrett name, namely, that it occurs as intestinal-like epithelium.

Part of the debate over what is and is not Barrett's esophagus ensues from the natural occurrence in some individuals of normal gastric mucosa within the distal 3 cm of the esophagus.[18] This nonmetaplastic, ectopic gastric epithelium has been mistakenly labeled as Barrett's esophagus but is generally considered to have no clinical significance. Although this confusion has been largely eliminated, pathologic reports should be scrutinized carefully before accepting the histologic diagnosis of "Barrett's esophagus."

Clinically, Barrett's esophagus is characterized by those symptoms of the underlying GERD, which is undeniably the major cause of the metaplasia. The risk of developing Barrett's esophagus increases with increasing severity of GERD. The diagnosis of Barrett's esophagus may be suspected in any case of severe, long-standing GERD, particularly in the presence of other complications. However, support for the diagnosis relies on the endoscopic finding of the characteristic rosy, velvety mucosal lining extending upward from the esophagogastric junction for various lengths. A biopsy of this tissue is necessary to confirm the diagnosis. Among patients

having endoscopy for symptoms of GERD, 10–15% are found to have Barrett's esophagus.[19]

The major purpose of esophageal biopsy (and collection of endoscopically directed brush cytology specimens) in the setting of Barrett metaplasia is the detection and grading of any regions of dysplasia within the metaplastic tissue. Treatment and surveillance options (discussed below) are strongly influenced by the presence or absence of dysplasia and, if present, the distinction between high- and low-grade dysplasia, as determined by the degree of alteration of nuclear morphologic and glandular structure.

Barrett's esophagus in the form of SIM is the major risk factor for adenocarcinoma of the esophagus, and among such patients, the annual incidence of this cancer is about 1%.[20] The incidence of adenocarcinoma among patients with high-grade dysplasia is unknown, but the risk of this malignancy in Barrett patients is 30–40 times that encountered in the general population.[21] In the Netherlands, a retrospective case-control study of 96 patients with Barrett's esophagus, with and without adenocarcinoma, revealed an increased cancer risk in the presence of longer metaplastic segments, smoking, and (possibly) male sex[22]; the proposed insured in the present case had all 3 of these risk factors. This malignancy mainly affects middle-aged and older adults and has a predilection for white men, occurring uncommonly in blacks and Asians.[23]

For unknown reasons, the incidence of esophageal adenocarcinoma has been rapidly rising during the past 3 decades. A large study analyzing cancer incidence data from 9 areas in the United States during 1976–87 revealed increases in the rates of adenocarcinoma of the esophagus in men ranging from 4% to 10% per year (the most rapid rise in incidence of any malignancy during that time period).[24] Twenty years ago, squamous carcinoma (which has no association with Barrett's esophagus) made up about 95% of esophageal cancers; currently in the United States and Europe, adenocarcinoma and squamous carcinoma occur with nearly equal frequency, such that esophageal adenocarcinoma (once a rare tumor) now ranks as one of the 15 most common cancers in white men.[25]

The management of Barrett's esophagus without dysplasia consists of measures indicated for GERD plus endoscopic surveillance (see below). PPIs are usually needed. However, although PPIs will usually eliminate the acid component of the refluxate, bile reflux may continue, and this significantly promotes Barrett metaplasia.[26] Additionally, because 40% of patients with Barrett's esophagus are asymptomatic, assessing the response to drug treatment may be difficult.[27] No form of medical or surgical treatment has been reliably shown to completely reverse the metaplasia of Barrett's esophagus. Ablation of Barrett metaplasia with laser or photodynamic therapy has been studied and has shown some promise, but additional investigation of this approach is needed.[28] Antireflux surgery (fundoplication) has been favored by some experts, calling attention to the relative risk of progression of Barrett metaplasia to dysplasia (22% with medical treatment; 3% with surgery).[29]

In the presence of low-grade dysplasia, medical management is acceptable, but antisecretory measures should be maximized, and surveillance must be assiduous (see below). Both high-grade dysplasia and cancer demand resection.

Surveillance of Barrett's esophagus, as with any premalignant condition, is a serious undertaking. Recommendations by the 1990 Barrett's Esophagus Working Party of the World Congresses of Gastroenterology are precise on this subject. The degree to which these recently modified recommendations[30] are followed will strongly influence the assessment of future mortality (Table 1).

RISK ASSESSMENT

Uncomplicated GERD with mild to moderate symptoms and an acceptable response to medical management poses no significant expectation of extra mortality. Severely symp-

Table 1. Management of Barrett's Esophagus (Recommendations of World Congresses of Gastroenterology)*

Condition	Management
Gastroesophageal reflux disease	Antireflux therapy (medical, surgical).
Specialized intestinal metaplasia	Endoscopy, biopsy, brush cytology (every 2 years).
Low-grade dysplasia	Intensive antireflux therapy for 8–12 weeks. Repeat biopsy, cytology. If improved, repeat examination every 6 months until 2 consecutive examinations reveal no dysplasia. If persistent, continue intensive therapy and examine patient every 6 months.
High-grade dysplasia	Resection all columnar-lined esophagus; if risk of operation is prohibitive, use ablation.

* Abridged from Dent et al.[30]

tomatic GERD and/or an inordinate therapeutic requirement might portend a minor or modest mortality risk. In some cases, the risk classifier may be justified in requiring endoscopy before any offer of insurance.

Mortality concerns apply mainly to the most serious complication of GERD, Barrett's esophagus. If this diagnosis has been established, the underwriting process should attempt to assign the proposed insured to 1 of various risk subsets on the basis of such variables as metaplastic segment length, the presence or absence of intestinal-like epithelium, the presence or absence of dysplasia, and the adequacy of surveillance.

In the process of mortality subset identification, the risk assessor should benefit from a logical classification of Barrett metaplasia. Such a classification was proposed by Spechler and Goyal[15] in a 1996 report in which they decried the prevailing clinical infatuation with the term "Barrett's esophagus," declaring that "we have reached the point where the persistent use of this artificial and variably defined term may hamper our understanding of the condition to which it is applied." In the interest of correlating the histopathologic findings of esophageal metaplasia with (1) the presence of GERD, (2) the risk of adenocarcinoma, and (3) the implications for surveillance, they proposed a new classification. This classification (Table 2) relies on (1) detection of columnar epithelium, (2) determination of whether that columnar epithelium exists as short segment involvement at the esophagogastric junction or as long segment involvement of the esophagus, and, most importantly, (3) classification of the columnar epithelium on the basis of whether it contains SIM. This approach best addresses the risk of future mortality. Therefore, medical directors and underwriters should consider this classification and exercise special effort to demand completely informative endoscopy and pathology reports.

Many pathology reports will specify "Barrett's esophagus" or "columnar metaplasia" without qualifying the histologic diagnosis as to whether the epithelium exists as SIM (ie, the type of columnar metaplasia that predisposes to adenocarcinoma). Unless this can be clarified, it must be assumed for mortality risk assessment that the tissue is, in fact, SIM.

Low-grade dysplasia will identify a substantial risk of future mortality, and individuals with high-grade dysplasia will be uninsurable before surgery. Risk assessment after resection for dysplasia or cancer will be determined by existing underwriting guidelines. In any case of Barrett's esophagus, with or without dysplasia, in which surveillance fails to meet the World Congresses of Gastroenterology recommendations (Table 1), sound underwriting judgment may require postponement of the application. Accordingly, underwriting action on the case considered here (Barrett's esophagus with questionable dysplasia and no follow-up since first detected

Table 2. Classification of Esophageal Metaplasia

Classification	Association With GERD	Associations With Adenocarcinoma	Endoscopic Surveillance Recommended
Columnar epithelium with SIM	Variable	Yes	Yes
Columnar epithelium without SIM	Variable	Unlikely	Probably not
Esophagogastric junctional SIM	Unclear	Probable	Unclear

* GERD indicates gastroesophageal reflux disease; SIM, specialized intestinal metaplasia. Adapted from Spechler and Goyal.[15]

22 months before application for insurance) was deferred pending verification of appropriate surveillance. Unfortunately, no such evidence has been presented.

CONCLUSION

Simple gastroesophageal reflux is a ubiquitous condition that is unworthy of adverse underwriting action. When this condition becomes severe enough to require medical attention, it achieves the status of disease—GERD, which is still usually a standard mortality risk. However, when certain complications arise, extra mortality becomes a realistic expectation. This is especially true when the native esophageal stratified squamous epithelium is partially replaced by metaplastic columnar epithelium, particularly when the replacement epithelium is in the form of SIM. This has come to be known as Barrett's esophagus, although Barrett himself didn't recognize this specific type of metaplasia.

Because of the increased incidence of adenocarcinoma in the presence of Barrett's esophagus, specific guidelines for the surveillance of Barrett's esophagus have been developed. The risk classifier must be assured that these guidelines are followed. If proper surveillance is lacking, a standard offer of insurance would usually be imprudent. In the presence of vigilant surveillance, the underwriting decision will usually be a choice between a standard or modestly substandard offer. The occurrence of dysplasia in Barrett's esophagus requires intense surveillance, and high-grade dysplasia must be underwritten in the same manner as carcinoma in situ.

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