

# Reflux Esophagitis in Three Cats Associated With Metaplastic Columnar Esophageal Epithelium

Gastroesophageal reflux is a relatively common condition in dogs and cats and may lead to secondary reflux esophagitis. A consequence of chronic gastroesophageal reflux that is well described in humans is Barrett's esophagus, which is the replacement of the normal squamous epithelium of the distal esophagus with metaplastic columnar epithelium. Three cats with clinical and endoscopic signs of chronic esophagitis had metaplastic columnar epithelium on biopsy of the distal esophageal mucosa. Suspected underlying causes were cardiac incompetence and sliding hiatal hernia. Two cats had complete resolution of the clinical signs after treatment. One cat was euthanized. *J Am Anim Hosp Assoc* 2006;42:65-70.

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## Introduction

Gastroesophageal reflux is the passage of gastric juice from the stomach into the esophagus, a condition that may cause reflux esophagitis in people and in animals.<sup>1,2</sup> Gastroesophageal reflux is usually secondary to alterations of the lower esophageal sphincter or the diaphragmatic esophageal hiatus.<sup>3-9</sup> Factors that are associated with altered function of these structures are general anesthesia, hiatal hernia (sliding and para-esophageal), cardiac incompetence, chronic vomiting, positioning of the animal during surgery (Trendelenburg position), delayed gastric emptying, and rhinogastric or pharyngostomy tubes that bypass the esophageal sphincter.<sup>5-15</sup>

Reflux is not invariably a cause of esophagitis, as a certain degree of reflux is physiological in animals and in people.<sup>16,17</sup> In humans, factors that affect the occurrence of reflux esophagitis include the nature of the refluxate, esophageal clearance, volume and frequency of the reflux, duration of the refluxate in the esophagus, and esophageal mucosal integrity.<sup>18</sup> The resulting lesions may be limited to the mucosa in mild cases or may involve the muscular layer and lead to stricture, ulceration, and perforation of the esophagus in severe cases.<sup>17,19</sup> Severe complications such as stricture and ulceration of the esophageal wall are common with chronic gastroesophageal reflux.<sup>12,20,21</sup>

A complication not reported in animals but well described in humans is the replacement of normal squamous epithelium in the distal esophagus with metaplastic columnar epithelium.<sup>17,22,23</sup> This lesion is known as Barrett's esophagus.<sup>17,22,23</sup> The purpose of this paper is to describe three cats with gastroesophageal reflux that had metaplastic columnar esophageal epithelium demonstrated on histopathology, similar to Barrett's esophagus.

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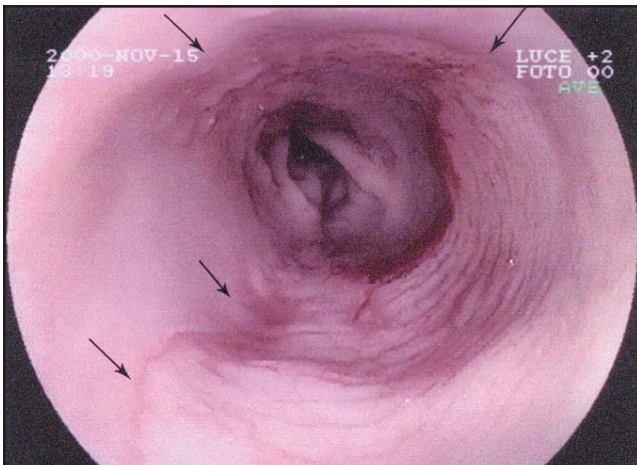
## Case Reports

### Case No. 1

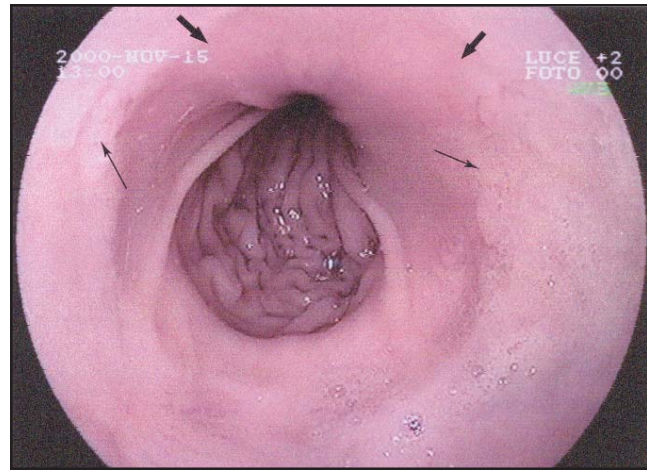
An 18-month-old, male domestic shorthair cat was presented to the Department of Veterinary Clinical Science at the University of Milan. The cat had a history of vomiting after food intake since the age of 3 months. Vomiting occurred initially 2 to 3 times weekly but then increased to an episode 2 hours after every meal. Eructation and vocalization were often observed after vomiting.

Upon physical examination, the cat was thin, emaciated, and mildly dehydrated. No changes were detected on routine laboratory tests (i.e., complete blood count [CBC], serum biochemical profile). Direct and positive-contrast upper gastrointestinal (GI) radiographic studies with barium sulphate were unremarkable. Upper GI endoscopy<sup>a</sup> revealed a severe, localized, chronic esophagitis on the right ventrolateral wall of the middle-to-distal third of the esophagus. The lesion was characterized by a white, irregular, raised mucosa that easily bled during passage of the endoscope. Margins of the lesion were well demarcated from the surrounding normal mucosa [Figure 1]. Close to the cardia, a localized proliferation of the esophageal mucosa assumed a nodular form. The lower esophageal sphincter was wide open so that the gastric cavity could be observed from the distal esophagus. The mucosa surrounding the sphincter was very hyperemic [Figure 2]. The circumferential plication of the distal esophageal mucosa was absent. No resistance was encountered when removing the bent tip of the endoscope from the stomach back into the esophagus. From the clinical and endoscopic findings, severe reflux esophagitis from cardiac incompetence was diagnosed. With standard endoscopic biopsy forceps, multiple biopsies were taken of the macroscopically involved mucosa, including an area 2 cm from the cardia.

Histopathology of the affected mucosa showed a severe esophagitis characterized by hyperplasia of the epithelial



**Figure 1**—Esophagoscopy of an 18-month-old, male domestic shorthair cat (case no. 1) revealing chronic esophagitis (arrows). The esophagitis is characterized by a white, irregular, raised mucosa that bled easily.



**Figure 2**—Esophagoscopy of case no. 1, showing that the lower esophageal sphincter is wide open and the gastric cavity can be observed from the distal esophagus. The mucosa surrounding the sphincter is very hyperemic (thick arrows). Close to the cardia, a nodular proliferation of the mucosa (thin arrows) is present.

basal layer. As a result of the hyperplasia, the deeper and thicker papillae occupied more than two-thirds of the mucosal layer. Some of the squamous epithelium was replaced by metaplastic epithelium of goblet columnar cells that were periodic acid-Schiff (PAS)-positive, and columnar cells with a brush border and few cytoplasmic vacuoli similar to small intestinal epithelium. These cells were organized in rough, villous structures lacking absorptive capacity (i.e., prismatic absorptive cells were absent, indicative of incomplete intestinal metaplasia), and they contained areas of cardiac gastric epithelium characterized by atrophic mucous glands. A moderate inflammatory infiltrate of lymphocytes, plasma cells, and rare neutrophils was observed in the mucosa, sometimes penetrating among pavement cells. Rare fundic glands with parietal cells were also seen [Figures 3, 4].

An antireflux cardioplasty was recommended for this cat after 3 weeks of conservative treatment of the esophageal lesion with ranitidine<sup>b</sup> (2 mg/kg per os [PO] *q* 12 hours), metoclopramide<sup>c</sup> (0.2 mg/kg PO *q* 12 hours), and a commercial low-fat diet.<sup>d</sup> Following persistent clinical signs, the owner presented the cat for surgery 1 year later. Endoscopy revealed worsening of the lesions previously observed, with numerous, deep, round, 3- to 4-mm mucosal ulcers [Figure 5]. The lower esophageal sphincter was open, and a normal gastric mucosa could be observed.

Because of the cat's poor condition, it was euthanized. Histopathology of the second endoscopic biopsies and of necropsy specimens revealed that the distal esophagus had areas of hyperplastic squamous epithelium with deep and irregular papillae. The intestinal metaplasia was more extensive and was characterized by columnar goblet cells with a brush border that were PAS-positive. A number of inflammatory cells (i.e., neutrophils, lymphocytes, plasma cells) were present among the epithelial cells. An intense inflammatory

infiltrate of lymphocytes, plasma cells, and rare macrophages was present in the underlying stroma. Close to the cardia, the large ulcerative lesion of the esophagus was infiltrated with lymphocytes and monocytes. No dysplastic epithelial elements were present in the intestinal mucosa.

### Case No. 2

A 3.5-year-old, female domestic shorthair cat was presented for mild dyspnea, stertorous respiratory sounds, and vomiting twice weekly since the age of 4 months. The physical examination did not reveal any abnormalities, but survey lateral and ventrodorsal thoracic radiographs showed a soft-tissue mass in the dorsocaudal thoracic cavity. A positive-contrast esophagram with barium sulphate revealed cranial displacement of the esophagogastric junction and most of the stomach through the diaphragm (i.e., hiatal hernia). Routine laboratory tests (i.e., CBC, serum biochemical profile) were normal.

A retrograde rhinoscopy showed a large, pedunculated polyp occupying two-thirds of the nasopharynx. On esophagoscopy, the mucosa of the distal third of the esophagus was diffusely hyperemic along a 5-cm tract proximal to the cardia. The cardia was open and lax, which allowed the bent tip of the endoscope to be pulled back into the esophagus, suggesting the presence of a sliding hiatal hernia and a mild degree of cardiac incompetence [Figure 6].

After excision of the nasopharyngeal lesion, conservative treatment for reflux esophagitis was initiated with ranitidine (2 mg/kg PO *q* 12 hours), metoclopramide (0.2 mg/kg PO *q* 12 hours, for 15 days), and a commercial, highly digestible diet.<sup>d</sup>

Histopathology of the esophageal biopsy showed an intestinal villous epithelium with mucous and goblet cells that were PAS-positive and numerous glandular crypts. The latter appeared short, irregular, and tortuous. A moderate lymphocytic, plasmacytic, inflammatory infiltrate was present diffusely in the lamina propria and infiltrated the epithelial cells.

The cat had complete resolution of both the respiratory and gastroesophageal clinical signs within a few days after surgery and starting medical treatment. Follow-up endoscopy was done 6 months after surgery and showed a less extensive lesion in the distal esophagus. Repeat biopsies confirmed the presence of persistent intestinal metaplasia.

Clinical follow-ups were done every 3 months for 1 year, and the cat remained asymptomatic.

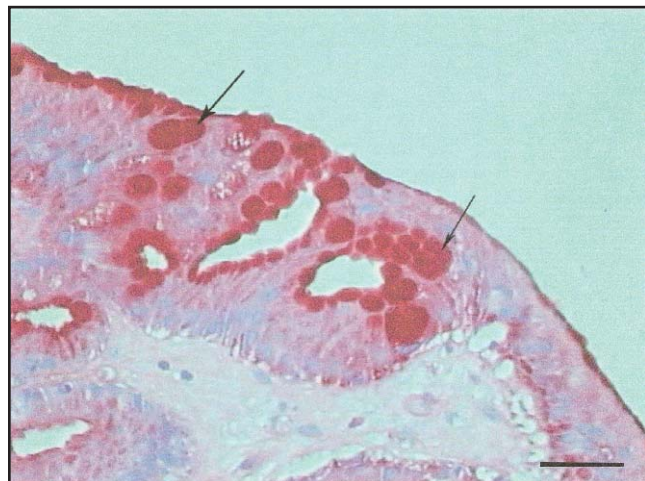
### Case No. 3

A 2-year-old, male domestic shorthair cat was presented with a 4-month history of vomiting that occurred 4 to 5 hours after eating. At presentation, physical examination and laboratory findings (i.e., CBC, serum biochemical profile) were normal. Survey thoracic and abdominal radiographs revealed an air-filled mass in the caudodorsal thoracic region from herniation of the stomach cranially through the diaphragm.

An upper GI endoscopy revealed foamy material in the distal esophagus. Gastroesophageal reflux was seen, and the

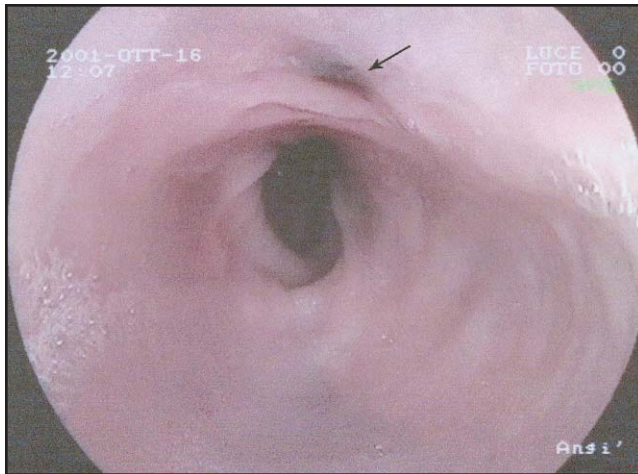


**Figure 3**—Histopathology of hyperplastic esophageal epithelium of case no. 1, showing an island of incomplete intestinal metaplasia (thin arrows). Mucous goblet cells with a brush border characteristic of intestinal cells are also seen (thick arrow). Chronic inflammation with a moderate lymphomonocytic infiltrate is present in the esophageal connective tissue stroma (short arrow centrally) (Hematoxylin and eosin stain, 10X; bar=40  $\mu$ ).

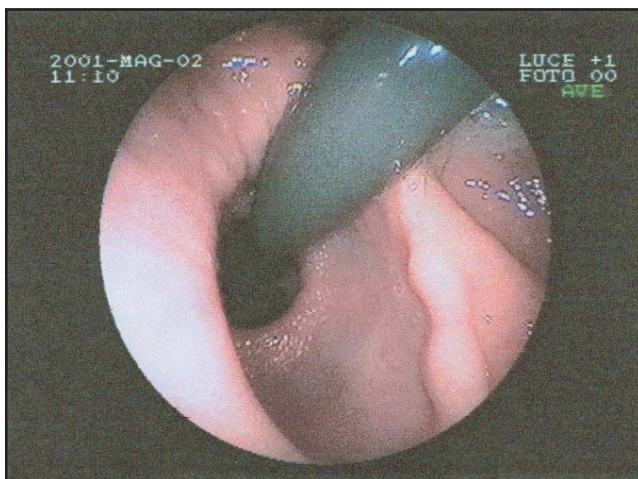


**Figure 4**—Histopathology of esophageal epithelium of case no. 1, taken at the same time as Figure 3. The mucins in the goblet cells (arrows) of the metaplastic epithelium stain positive with PAS stain, indicating the presence of acidic mucins (Periodic acid-Schiff stain [PAS], 40X; bar=20  $\mu$ ).

mucosa of the distal third of the esophagus appeared edematous and moderately hyperemic. The cardia was open, and the bent endoscope could be pulled back into the esophagus easily. A diagnosis of cardiac incompetence associated with hiatal hernia was made, and biopsies were taken from both the esophagus and the stomach. Conservative treatment was initiated with clebopride<sup>e</sup> (15  $\mu$ g/kg PO *q* 12 hours, 30 minutes before meals, for 20 days) and ranitidine (2 mg/kg PO *q* 12 hours for 20 days). The cat improved for 1 week; then the vomiting recurred.



**Figure 5**—Esophagoscopy of case no. 1, performed 1 year after the initial endoscopy. The mucosal lesions are more severe, and a deep, round, mucosal ulceration about 3 to 4 mm in diameter is present (arrow).



**Figure 6**—Endoscopic view of the cardia of a 3.5-year-old, female domestic shorthair cat (case no. 2) from within the stomach. The open cardia allowed the bent tip of the endoscope to be pulled back into the esophagus, suggesting cardiac incompetence.

Histopathology of esophageal biopsies showed a severely hyperplastic epithelium with an increased basal layer and increased thickness of the papillae. Rare intraepithelial neutrophils were seen. One biopsy showed an island of gastric-like epithelium with metaplastic, PAS-positive goblet cells [Figure 7]. The mucosa was edematous, hyperemic, and infiltrated with lymphocytes and plasma cells. A Barrett-like esophagus secondary to gastroesophageal reflux was diagnosed. A cardioplasty followed by esophagopexy and a left-sided, incisional fundic gastropexy were performed.<sup>9</sup> Postoperative treatment included ranitidine (2 mg/kg PO *q* 12 hours for 20 days), metoclopramide (0.2 mg/kg PO *q* 12 hours for 20 days), and a commercial, highly digestible



**Figure 7**—Biopsy of esophageal mucosa of a 2-year-old, male domestic shorthair cat (case no. 3), showing nonkeratinized, hyperplastic squamous epithelium of the esophagus and a metaplastic epithelium composed of goblet cells that are PAS-positive for mucins. An island of gastric-like epithelium that is clearly metaplastic is also seen (arrows) (PAS stain, 2.5X; bar=200  $\mu$ ).

diet.<sup>d</sup> The clinical signs resolved within a few days after surgery, and the cat did well throughout a clinical follow-up time of 1 year.

## Discussion

Clinical signs of gastroesophageal reflux and esophagitis are similar and may include anorexia, dysphagia, pain at swallowing, hypersalivation, and regurgitation of whitish, thick saliva.<sup>10</sup> The major causes of gastroesophageal reflux in dogs and cats are hiatal disease, chronic vomiting, an anesthesia-induced reduction in lower esophageal sphincter pressure, and cardiac incompetence.<sup>3-11</sup> In most cases, gastroesophageal reflux results in esophagitis, which is demonstrated by gross endoscopic lesions and/or histopathological changes in the esophageal mucosa. Esophagitis can be present despite a grossly normal-appearing mucosa; therefore, an esophageal biopsy is indicated whenever esophagitis is suspected.<sup>3,4,22</sup> The incidence of reflux esophagitis in the cat is thought to be low, but the disease may occur more often than documented.<sup>2,3</sup>

In humans, gastroesophageal reflux disease (GERD) is one of the most prevalent clinical conditions afflicting the GI tract.<sup>17</sup> Gastroesophageal reflux disease is defined as any symptomatic clinical condition or histopathological alteration resulting from episodes of gastroesophageal reflux.<sup>17</sup> Some people with GERD experience reflux esophagitis, a condition where histopathological changes occur in the esophageal mucosa.<sup>17</sup> A severe histological consequence of chronic gastroesophageal reflux in humans is Barrett's esophagus.<sup>17,23</sup> Although its pathogenesis is unclear, in Barrett's esophagus, metaplastic columnar epithelium replaces the normal squamous epithelium to provide greater resistance to the effects of gastroesophageal reflux.<sup>17</sup> A wide variety of cell types and histopathological features are

encountered in Barrett's mucosa, including gastric, small intestinal, or colonic epithelial cells.<sup>17</sup> One hypothesis to explain these findings is that esophagitis with destruction and ulceration of squamous epithelium from gastroesophageal reflux is followed by re-epithelization by pluripotential, undifferentiated stem cells that can differentiate into a variety of cell types.<sup>24</sup> The most frequently observed histopathological change in adult humans is a distinctive, specialized columnar epithelium characterized by goblet cells that are PAS-positive and Alcian blue-positive and assume a villous structure.<sup>24</sup> These cells indicate incomplete intestinal metaplasia.<sup>24</sup> An association has also been established between Barrett's esophagus and adenocarcinoma of the esophagus, causing Barrett's esophagus to be considered a premalignant condition.<sup>24</sup> Studies that have addressed medical treatment of Barrett's esophagus have not documented resolution of the mucosal changes after such treatment, and data on the regression of Barrett's esophagus after antireflux surgery are conflicting.<sup>17,20,23</sup>

The study reported here documents Barrett's-like esophagus in three cats. One case was affected by cardiac incompetence (case no. 1), one case had a sliding hiatal hernia (case no. 2), and one case had both cardiac incompetence and a hiatal hernia (case no. 3). In case no. 2, the hernia may have occurred secondary to a reduction in normal cardiac pressure from increased inspiratory effort associated with a large, inflammatory, rhinopharyngeal polyp.<sup>25</sup> Clinical signs exhibited by the three cats were those of esophagitis. On esophagoscopy, gross findings were indistinguishable from esophagitis.

In case no. 1, the affected area was mainly localized to the ventrolateral aspect of the distal esophageal mucosa, which may have occurred from the curled position (that cats assume during rest) facilitating contact of the refluxate with this area. In humans and in animals, gastroesophageal reflux is enhanced when the head rests lower than the stomach.<sup>14,17</sup> In case nos. 2 and 3, the lesion involved the diffuse distal third of the esophageal mucosa. Biopsies were taken at least 2 cm proximal to the cardia to avoid biopsying the physiological gastric mucosa that may be present at the normal esophagogastric junction.

Unlike normal esophageal mucosa, the metaplastic mucosa yielded specimens similar to gastric and intestinal endoscopic biopsies. Histopathologically, the metaplastic lesions observed in these three cats were markedly similar to Barrett's esophageal lesions in humans. The metaplasia was always of the intestinal type and tended to have a zonal distribution centered on the distal third of the esophageal mucosa. Unlike in human lesions, eosinophils were not frequently observed.<sup>23,24</sup>

The presence of metaplastic gastric epithelium in the distal esophagus has been observed with chronic reflux esophagitis in small animals and may be a defense mechanism against the repeated insults of the gastric juice.<sup>3</sup> Positive staining of histological samples with PAS is important to identify the presence of metaplastic goblet cells. These cells may be few in number, as observed in case no.

3, where only a small island of gastric-like epithelium with intestinal metaplasia was seen. The metaplastic epithelium should not be confused with biopsy of normal cardiac mucosa or of herniated gastric mucosa secondary to a hiatal hernia. A detailed description of the exact biopsy site by the endoscopist can help avoid this problem.

Squamous dysplasia has been described in one cat with esophagitis secondary to gastroesophageal reflux, and speculation was made about the possible significance of this condition as a precursor to squamous cell carcinoma.<sup>3</sup> Other histopathological findings in clinical and experimental esophagitis in cats have included squamous cell hyperplasia or dysplasia, mucosal erosions and ulcers, and lymphocytic/plasmacytic inflammatory infiltrates.<sup>3,22,26</sup>

Case no. 3, which was treated with cardioplasty, esophagopexy, and gastropexy, had complete resolution of clinical signs after surgery. Case no. 2 was followed by endoscopy, and the intestinal metaplasia was still present 6 months after surgery, although clinical signs resolved. Further investigations are required in cats to determine whether these mucosal lesions are a direct result of gastroesophageal reflux or may arise for other reasons.<sup>24</sup> The premalignant potential of Barrett's lesion in cats is unknown and suggests that animals affected by this lesion should undergo repeated clinical and endoscopic examinations.

## Conclusion

Intestinal metaplasia of the esophageal mucosa associated with chronic gastroesophageal reflux, similar to Barrett's esophagus in humans, was documented in three cats. The clinical and endoscopic aspects of this condition were similar to that of simple, chronic esophagitis. Cardiac incompetence or hiatal hernia may be associated with the lesion. On histopathology, the lesion was characterized by intestinal epithelial metaplasia of the distal third of the esophageal mucosa. The stratified squamous epithelium normally lining the esophagus was replaced by metaplastic, intestinal-type, columnar epithelium, defined by the presence of PAS-positive goblet and columnar cells. Rare, fundic, gastric glands were also present.

<sup>a</sup> Fujinon EG-201FP video-gastroscope; Fujinon Corporation, 324

Uetake, Kita-Ku, Saitama city, Saitama 331-9624, Japan

<sup>b</sup> Ranidil; Menarini Ind Farm Riunite, 50131 Firenze, Italy

<sup>c</sup> Plasil; Gruppo Lepetit S.p.A., 20020 Lainate, MI, Italy

<sup>d</sup> Hill's A/D; Hill's Pet Nutrition, Topeka, KS 66601

<sup>e</sup> Motilex; Laboratori Guidotti S.p.A., 56010 Pisa, Italy

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