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Reflux Laryngitis in a Patient with Zollinger Ellison Syndrome and the Role of Epidermal Growth Factor

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Keywords

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Zollinger Ellison syndrome (ZES) results in gastric acid hypersecretion caused by a gastrin-secreting tumor. It is estimated to occur in approximately one patient per million in the United States. It is thought to be responsible for 0.1 to 1% of all duodenal ulcers and 1 in 50 patients with ulcers requiring surgery (1, 2). The three most common symptoms are abdominal pain, diarrhea, and heartburn, with less prevalent complaints of weight loss, gastrointestinal bleeding, nausea, and vomiting (3). Clinically the most common manifestation of ZES is peptic ulcer disease, which has been reported to occur in 71–93% of patients (1, 3). Due to frequent misdiagnosis and likely temporizing effects of current antireflux therapy, the diagnosis of ZES is often delayed for approximately 4 to 6 years. Signs and symptoms of gastroesophageal reflux, which were previously underestimated, are now regarded as common manifestations of ZES (3). Recently GERD symptoms have been shown to occur in up to one-third of ZES patients, with 43–60% having GERD-related endoscopic abnormalities of the esophagus (2, 4, 5). To date the development of reflux laryngitis occurring in the setting of reflux disease in ZES has not been appreciated. This case report represents the first such report of reflux laryngitis, which occurred in a 42-year-old man with ZES.

CASE REPORT

A 42-year-old white male was originally diagnosed with metastatic gastrinoma in 1995. Prior to diagnosis the patient complained of 11 years of gastric bloating and heartburn and 3 years of frequent nausea, vomiting, and diarrhea. Definitive diagnosis was made after EGD demonstrated severe esophagitis and severe duodenal ulcerations with a subsequent fasting serum gastrin level of 298 pg/ml and a positive secretin stimulation test. Abdominal CT scan

and biopsy verified metastatic gastrinoma. EUS and MRI suggested that the primary tumor may be in the head of the pancreas but no definitive localization was established.

In December 1999, the patient enrolled in the research study, titled “A Safety and Efficacy Study of Long-Term Oral Administration of Pantoprazole in Patients with Zollinger Ellison Syndrome or Other Hypersecretory Conditions.” The study was approved by the UCLA Institutional Review Board and was conducted at the UCLA Medical Procedures Unit. The patient had a baseline acid output (AO) of 10.0 mEq/h and was started on pantoprazole, 40 mg b.i.d. This dose was increased to pantoprazole, 80 mg b.i.d., 7 days later when the protocol-required AO measurement was 26 mEq/h. The patient responded well to increased doses of 80 mg b.i.d. pantoprazole, with a reduction in the AO to 0.88 mEq/h and corresponding serum gastrin levels ranging from 157 to 622 pg/ml. AO was 1.4 mEq/h at the 6-month assessment. The patient’s compliance was ensured by careful questioning and pill counting. Over this time period, the patient had occasional flares of his hypergastrinemic state, which was manifested by mild stomach pain and intractable nausea, vomiting, and diarrhea.

In December 2001, the patient was admitted to the emergency department due to severe stomach pain, nausea, and vomiting. He also described an acid or sour taste in his mouth that was present during the nocturnal hours. This symptom started in the early morning hours and lasted for several hours. During the subsequent follow-up, EGD demonstrated esophagitis, large gastric folds, and a normal larynx, with an appropriately controlled AO of 2.73 mEq/h and a serum gastrin of 622 pg/ml. Although two-channel 24-h esophageal pH monitoring was negative for acid breakthrough, the pantoprazole dose was increased empirically up to 120 mg p.o. b.i.d. to control the presumed acid breakthrough. Over the next several months the patient reported throat soreness, throat clearing, and a foreign-body sensation in the throat but denied abdominal pain, weight loss, or shortness of breath. In June 2002, studies demonstrated an AO of 0.86 mEq/h and gastrin of 495 pg/ml. During the same visit, EGD showed large gastric folds without any evidence of peptic or duodenal ulceration. On examination of the larynx, the vocal cords were mobile, however, moderate posterior laryngeal inflammation overlying the right and left vocal cords consistent with reflux laryngitis was diagnosed at the time of endoscopy (Figure 1). Examination by an otolaryngologist confirmed the diagnosis of reflux laryngitis with +3 posterior commissure hypertrophy consistent with acid reflux. As a result, the pantoprazole dose was changed to 80 mg p.o. t.i.d. for better reflux control. After this dosage change two-channel probe pH monitoring indicated less than 6% reflux within 24 h, which was within the normal range, and less erythema of the vocal cords was noted 3 months later during follow-up upper endoscopy (Figure 2).

DISCUSSION

Proton pump inhibitors (PPIs) are the drugs of choice for acid suppression in ZES. With close monitoring, PPIs have been proven to be extremely safe and effective in controlling gastric AO (1, 6-8). The goals of acid suppression therapy in ZES are to maintain a basal AO of < 10 mEq/h in patients with sporadic ZES and <5 mEq/h for ZES MEN-1, GERD, or prior gastric surgery (6-9). This AO target was achieved for this patient with pantoprazole,

but nonetheless, empiric upward titration was necessary due to clinical signs and symptoms. Since ZES may continue to worsen over time if the tumor is not excised, it is not surprising that over a period of 2 years, acid secretion for this patient required upward titration of the dosage.

GERD is thought to be associated with a number of laryngeal disorders, with reflux laryngitis being the most common. Although controversial, the likely mechanism of reflux laryngitis is thought to be secondary to (a) direct acid and pepsin contact, (b) chronic throat clearing and cough, which lead to vocal cord irritation and damage, or (c) a combination of both (10). Common symptoms associated with reflux laryngitis include hoarseness, vocal fatigue, chronic throat clearing, chronic cough, excessive throat mucus, dysphagia, and globus sensation. The patient described in this report had experienced each of these symptoms. The term esophagopharyngeal reflux (EPR) is used to describe esophageal acid reflux into the laryngeal and pharyngeal areas. Confirmation of suspected EPR by 24-h pH monitoring has been documented to occur in 17.5–70% of suspected cases. Since GERD and EPR are intermittent events, the use of pH monitoring may not be reliable in suspected reflux laryngitis (11). Treatment of patients with suspected reflux laryngitis with antireflux medications has been shown to be effective (10, 13), especially short-term treatment with a PPI (12).

The case reported here is the first reported incident of reflux laryngitis in a patient with ZES. Nearly all patients with ZES have gastric acid hypersecretion and a third of these patients experience reflux esophagitis, so it is surprising that reflux laryngitis has not been reported in other patients with ZES. The paucity of reported reflux-associated laryngitis in ZES patients is similar to the unexpected lack of endoscopic or histological evidence of mucosal damage. Further, the rate of Barrett's esophagus is similar to that in the general population (14). This phenomenon may be explained by the accumulating evidence that gastric epidermal growth factor (EGF) plays a key physiologic role in the protective mechanisms and functional integrity of the esophageal mucosa (14–16). The role of salivary EGF in esophageal and gastric mucosal maintenance in an animal model has been well established. Rats deprived of EGF by sialoadenectomy were shown to have a 31–36% decrease in mucosal coat thickness and a 38–41% decrease in adherent mucin content (17). Sarosiek *et al.* demonstrated that EGF is pivotal in maintaining esophageal mucosa's ability to counteract the high luminal hydrogen concentration (16). Patients with esophagitis have been found to have a lower luminal release of EGF, suggesting that decreased esophageal EGF may either decrease the healing rate or facilitate the development of tissue breakdown (18). Along with this growing evidence that EGF plays a protective role, EGF has also been shown to be just as effective as cimetidine in preventing and healing gastric and duodenal ulcers in rats (14, 15). Although this Case Report did not focus on identifying the mechanisms responsible for protection of the esophagogastric mucosa in patients with ZES, recent evidence reported by Sarosiek *et al.* has shown that EGF production is elevated in ZES patients and may be the primary reason why the prevalence of esophagitis is much lower than would be expected (14). If this hypothesis is correct, the increased EGF levels may also provide added protection to the laryngeal mucosa in ZES patients. These patients could potentially benefit from stimulation of salivary secretion and thus its EGF protective

component by chewing gum before and after each meal as was used as a therapeutic approach to the treatment of patients with GERD (19).

CONCLUSION

There is growing evidence that EGF may play a role in protecting the esophageal mucosa from acid reflux. EGF may also aid in preventing reflux laryngitis in ZES patients and in non-ZES patients, however, further studies will be needed to validate this hypothesis.

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Lower Esophagus

Vocal Cords

Fig 1.
Esophagitis and reflux laryngitis.

Lower Esophagus

Vocal Cords

Fig 2.

Resolution of esophagitis and reflux laryngitis with increased frequency of PPI.