Failed Nissen Fundoplication in Two Patients Who Had Persistent Vomiting and Eosinophilic Esophagitis

By Chris A. Liacouras
Philadelphia, Pennsylvania

The following report describes two patients who had chronic symptoms of gastroesophageal reflux and persistent histological esophagitis, despite aggressive medical antireflux therapy, who continued to have esophagitis and remained symptomatic post antireflux surgery (Nissen fundoplication). Both patients demonstrated a severe eosinophilic esophagitis with normal gastric and duodenal histology before and after surgery. Postoperatively, each received the diagnosis of allergic enteritis and both responded clinically and histologically to oral corticosteroids and an elemental diet.

INDEX WORDS: Fundoplication, gastroesophageal reflux, eosinophilic esophagitis.

G ASTROESOPHAGEAL reflux disease (GERD) is one of the most common upper gastrointestinal disorders in children.1,2,3 Typically, symptoms such as vomiting, regurgitation, heartburn, globus, epigastric pain, and nausea improve with medical therapy consisting of acid blockade and prokinetic agents. Children who have persistent, severe esophagitis who remain symptomatic despite medical treatment are often referred for an antireflux procedure. The following report describes two patients who had symptoms of chronic GER and persistent esophageal eosinophilia, despite medical therapy, who underwent a Nissen fundoplication. One year post-surgery both remained symptomatic and continued to have a severe eosinophilic esophagitis. Further evaluation showed that both patients had an allergic enteritis, and both patients responded to oral steroids. The second patient’s symptoms recurred after a steroid taper and subsequently improved after administration of an elemental diet followed by the slow reintroduction of food.

CASE REPORTS

Patient 1

A 6-year-old boy was referred with a history of chronic abdominal pain, nausea, regurgitation, and a 5-year history of intermittent vomiting. At ½ years of age, gastrointestinal evaluation included an anatomically normal upper gastrointestinal series and an upper endoscopy, results of which showed histological esophagitis (eosinophils). The patient was initially started on ranitidine and metoclopramide with minimal symptomatic benefit. At 4 years of age, after a repeat upper endoscopy, he continued to demonstrate esophagitis (normal gastric and duodenal histology), and the patient’s medications were changed to omeprazole and cisapride. At 5 years of age, a pH probe was performed (off acid blocking medications) results of which showed a reflux index of 9.3% (normal 0%-5%). Because of ongoing symptoms and severe esophagitis the patient underwent a Nissen fundoplication.

The patient had no post surgical complications but remained symptomatic, complaining of persistent nausea and epigastric pain. Ranitidine and cisapride were restarted without change in symptoms. An upper endoscopy performed 8 months after surgery continued to show persistent esophagitis (eosinophils and a hypertrophied basal zone layer, Fig 1). Review of symptoms included a history of asthma and eczema. There was no history of weight loss, diarrhea, occult bleeding, mouth sores, joint pain, or fever.

The examination at time of referral was only remarkable for a child who had allergic shiners under his eyes. His weight was 21 kg (50th percentile) and his height 118 cm (50th percentile). Complete blood count showed a hemoglobin level of 13.1 g/dL and a white blood cell count of 9,200/mL with 13% eosinophils. The total peripheral eosinophil count was 1,196 cm3 (normal, 100 to 300) and the quantitative IgE level was 312 IU/mL (normal, 0 to 90).

Oral methylprednisolone (1.5 mg/kg/d) was begun Ten days after beginning steroid therapy, the patient became asymptomatic. After 4 weeks of therapy, an upper endoscopy demonstrated normal esophageal histology. Steroid therapy was weaned over 6 weeks. Follow-up showed no recurrence of symptoms 12 months after steroid therapy.

Patient 2

A 16-year-old girl who had a chronic history of vomiting, heartburn, and epigastric pain, status post Nissen fundoplication, was referred for continued regurgitation and substernal burning. Past medical history was remarkable for a 8-year history of regurgitation and heartburn. At 12 years of age, she started taking ranitidine. Two years later, because of persistent symptoms, upper endoscopy was performed, which revealed severe esophagitis (eosinophils). The patient’s medications were changed to omeprazole and cisapride. After 6 months, the patient complained of worsening epigastric and chest pain. Results of an upper gastrointestinal series demonstrated normal anatomy; 24-hour pH probe showed a reflux index of 7.5%, and upper endoscopy findings continued to show a severe esophagitis with eosinophilic infiltration. Nissen fundoplication was performed without complication.

Postoperatively, the patient again began to complain of water brash, heartburn, and epigastric pain, and omeprazole and cisapride were restarted. Results of upper gastrointestinal series 1 year after surgery demonstrated an intact Nissen wrap. A repeat upper endoscopy showed
Fig 1. Esophageal biopsy specimen (patient 1) taken 8 months after Nissen fundoplication. Severe esophagitis is characterized by collections of numerous eosinophils, which are readily identified by their characteristic cytoplasmic granules (arrows) and marked hyperplasia of the basal cell layer (line), which comprises almost the entire thickness of the squamous epithelium (H&E, original magnification x60.)

severe eosinophilic esophagitis. Family history was unremarkable; review of systems was positive for asthma and a weight loss of 10 pounds over 3 months.

At time of referral, the patient’s weight was 50 kg (25th percentile) and height was 167 cm (75th percentile). Her physical examination findings were normal. Laboratory investigation included a complete blood count with a hemoglobin level of 14.8 g/dL and a white blood cell count of 8,500 µL with 15% eosinophils; 24 hour pH probe findings showed a reflex index of 6.5% with normal esophageal acid clearance and no reflux episodes more than 10 minutes in duration.

Oral methylprednisolone (24 mg twice daily) was begun. Within 4 days, the patient’s symptoms improved. Four weeks after beginning therapy, repeat upper endoscopy demonstrated normal esophageal histology. However, upon tapering the steroids, the patient’s symptoms returned. The patient began taking elemental formula (Vivonex) with their characteristic cytoplasmic granules (arrows) and marked hyperplasia of the basal cell layer (line), which comprises almost the entire thickness of the squamous epithelium (H&E, original magnification x60.)

DISCUSSION
Gastroesophageal reflux is one of the most common disorders diagnosed in pediatric gastroenterology. In the majority of patients, symptomatic and histological improvement can be achieved with a combination of acid blocking and prokinetic medications. In a minority of cases, GERD cannot be controlled with medication, and surgery may be required. Indications for antireflux surgery include anatomic defects (esophageal stricture, hiatal hernia, Barrett’s esophagus), aspiration or recurrent pneumonia, persistently abnormal 24-hour pH probe findings, and chronic esophagitis associated with symptoms of heartburn, vomiting, dysphagia and regurgitation despite the use of medical therapy.4-5 Our report depicts two patients who had chronic esophagitis (primarily eosinophils) and symptoms consistent with GER, unresponsive to aggressive antireflux medical therapy, who were presumed to have reflux-induced esophagitis and underwent fundoplication. Postoperatively, both patients remained symptomatic and subsequently allergic esophagitis was diagnosed.

For the past 15 years, the esophageal eosinophil has been considered to be the primary marker for reflux esophagitis in children. In 1982, Winter et al6 correlated the observation of esophageal eosinophils to abnormal esophageal acid clearance in pediatric patients. Although he linked the presence of esophageal eosinophils to abnormal esophageal acid clearance, none of the 46 patients studied had more than three eosinophils per high-power field (HPF). Since that time, several reports have identified adult patients who had severe eosinophilic esophagitis and symptoms of GER unresponsive to aggressive antireflux medical therapy. Lee7 reported on a series of 11 patients with greater than 10 esophageal eosinophils per HPF who had dysphagia, heartburn, vomiting, and esophageal strictures (3 of 11). He theorized that reflux was the cause of the strictures; however, reflux was not documented in any patient by 24-hour pH probe. Attwood et al8 described 12 patients presenting with dysphagia who had more than 20 esophageal eosinophils per HPF (mean, 56/HPF). Normal pH monitoring was noted in 97%. Finally, Vitellas et al9 reported on 13 boys who presented with dysphagia (12 of 13), allergic manifestations (10 of 13), peripheral eosinophilia (12 of 13), and proximal esophageal strictures (10 of 13) who failed medical antireflux therapy. None had reflux seen during barium study; 85% improved with steroid therapy.

In 1995, Kelly et al10 described a series of children who had chronic esophagitis (esophageal eosinophilia) with severe symptoms who did not respond to antireflux therapy but instead responded to an amino acid-based formula. Only one patient underwent a 24-hour probe, results of which showed no evidence of reflux. The patients were placed solely on an amino acid based formula for a median of 17 weeks. Symptomatic improvement was seen within an average of 3 weeks; subsequently, regular foods were slowly reintroduced. He suggested an immunologic basis secondary to either a delayed hypersensitivity or a cell-mediated hypersensitivity response.

Although the majority of pediatric patients who have GER respond to medical antireflux therapy, it may be difficult to distinguish the child with chronic reflux symptoms and esophagitis who has GERD from those who have primary allergic eosinophilic esophagitis. Patients who have GERD typically have a markedly abnormal 24-hour pH probe finding (reflux index >10%; prolonged episodes lasting more than 15 minutes) and
few eosinophils seen on esophageal biopsy (<5/HPF). In contrast, the above two cases demonstrate that patients who have an allergic primary eosinophilic esophagitis have a greater degree of esophageal eosinophilia (>15/HPF) and only a mildly abnormal 24-hour pH probe finding (reflux index <10%). They also had an allergic history (eczema, asthma, rhinitis) and a history of a peripheral serum eosinophilia. Concerns should be raised in any patient who has chronic symptoms of GER and a persistent, severe eosinophilic esophagitis if only mild reflux is demonstrated by pH probe or if a peripheral eosinophilia is present. These patients should undergo evaluation for allergic or eosinophilic enteritis before surgery is undertaken.

REFERENCES