Results of Esophageal Biopsies Performed During Triple Endoscopy in the Pediatric Patient

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Background: Endoscopic examination (direct laryngoscopy and bronchoscopy) is the method of choice for diagnosis of respiratory symptoms of unknown cause in children. However, gastroesophageal reflux is being recognized increasingly often as a cause of pediatric respiratory symptoms and is difficult to diagnose on the basis of findings from direct laryngoscopy and bronchoscopy. In cases in which gastroesophageal reflux was included in the differential diagnosis, we additionally performed esophagoscopy with esophageal mucosal biopsies.

Objectives: To determine the feasibility, safety, and efficacy of routinely performing esophageal biopsies during triple endoscopy in children.

Methods: Twenty-four children ranging in age from 2 weeks to 10 years were referred for airway evaluation. Under general anesthesia, children underwent direct laryngoscopy and bronchoscopy and esophagoscopy with mucosal biopsy.

Results: Esophageal mucosa biopsy specimens were quickly and safely obtained during endoscopic evaluation. There were no complications. Reflux esophagitis was present in 54% of biopsy specimens, as suggested by basal cell hyperplasia, papillary elongation, and/or inflammatory cell infiltrates.

Conclusion: Gastroesophageal reflux is often difficult to diagnose in the pediatric population. When direct laryngoscopy and bronchoscopy is performed during examination of the child with airway symptoms, the addition of esophagoscopy with mucosal biopsies will safely and quickly provide data regarding the potential contribution of gastroesophageal reflux.


Gastroesophageal reflux (GER) commonly occurs in infants and children. Physiologic GER is characterized by the effortless passage of gastric contents into the esophagus without evidence of clinical symptoms or disease. Pathologic GER, referred to as GER disease (GERD), is the state in which reflux of gastric contents into the esophagus is severe enough to cause clinical symptoms or tissue injury. Substantial morbidity may be associated with GERD, with a mortality rate as high as 15% if it goes untreated.

The symptoms of GERD in infants and children are often quite different from those experienced by adults. In as many as 30% of cases, GERD may manifest as respiratory symptoms in infants and children. Many of these children have “silent” GERD, in which respiratory symptoms are the only indication of pathologic reflux. Respiratory symptoms caused by aspiration of gastric contents include chronic cough, chronic bronchitis, recurrent pneumonia, and bronchopulmonary dysplasia. Furthermore, reflux and aspiration may elicit reflex-mediated laryngospasm (a form of central apnea), and respiratory symptoms have been shown to occur without aspiration. Irritation of distal esophageal afferents resulting in a vagally mediated reflex bronchospasm has been shown to be a cause of reactive airway disease in some children. A reflex resulting from vagal stimulation has also been shown to cause laryngospasm, which may manifest as either obstructive apnea or stridor.

Otolaryngologists are often called on to examine infants and young children with chronic respiratory problems. In many of these cases, GERD should be included in the differential diagnosis for causes of airway distress. In many of these cases, GERD has been considered as the primary cause of the respiratory compromise, but no formal diagnostic testing has been undertaken to confirm the presence of GERD. The otolaryngologist will perform direct laryngoscopy and bronchoscopy (DLB) in infants and children with substantial airway distress; this is an opportune time to evaluate the esophagus as well. An esophageal biopsy is one technique to assess for the pathologic changes associated with GER.

The goals of the present study were to evaluate rigid esophagoscopy with
PATIENTS AND METHODS

Patients were examined prospectively between December 1, 1997, and April 4, 1997. The patient cohort included 24 infants and children who were referred to a university hospital for evaluation of airway compromise where GERD was considered as one possible cause of airway symptoms. The patients' ages ranged from 2 weeks to 10 years (average, 20 months). The study group consisted of 17 boys and 7 girls.

Evaluation proceeded as follows: first, the child's airway was evaluated. With the use of direct laryngoscopy, the supraglottic and glottic airway was examined with the patient under general anesthesia. Next, rigid bronchoscopy was performed to assess the subglottic area as well as the main bronchi. The presence of any congenital anomalies, structural defects, or lesions was noted. Next, the rigid bronchoscope was withdrawn from the trachea and introduced into the esophagus. Esophagoscopy was performed to the level of the gastroesophageal junction, and the esophagus was evaluated for anatomical defects or signs of reflux, including erythema, ulcers, or erosions. Finally, biopsy specimens were taken from the esophageal mucosa approximately 3 cm proximal to, and at the level of, the gastroesophageal junction by means of 1.8-mm radial jaw serrated biopsy forceps (Microvasive, Watertown, Mass).

Biopsy specimens were then evaluated by permanent histopathologic examination. On the basis of recent studies, the following criteria were used to determine the presence of esophagitis: (1) intraepithelial lymphocytes, neutrophils, and/or eosinophils; (2) basal hyperplasia 25% of the thickness of the epithelium; and (3) elongation of the papillae 50% of the thickness of the epithelium. Basal hyperplasia and elongation of the papillae were considered present only in biopsy specimens whose orientation was unequivocal. Esophagitis was considered severe if there were 20 inflammatory cells per high-power field. All other cases with positive findings were considered mild.

RESULTS

Thirteen (54%) of the 24 children had histological features suggestive of esophagitis (Table). Specimens from 4 of these children met the criteria for severe esophagitis. The other 9 cases of esophagitis were classified as mild. Basal hyperplasia was found in 11 (85%), papillary elongation in 9 (69%), and inflammatory cells in 9 (69%).

Of the specimens taken from 24 children, 5 (21%) were considered poorly oriented and therefore were not included in our evaluation for the presence of basal hyperplasia or papillary elongation (cases 2, 9, 13, 22, and 23). Furthermore, none of the specimens from these 5 cases was found to exhibit inflammatory cells, and therefore these patients were not considered to have esophagitis by any criteria.

Initial airway symptoms in the cohort of 24 children included stridor (12 patients), apnea (10 patients), wheezing (1 patient), and chronic cough (2 patients) (Table). Sixteen children (67%) were found to have upper-airway anomalies during endoscopy: 2 children exhibited vascular compression of the distal trachea, 2 children had tracheal stenosis associated with cystic hygroma, 3 patients had severe laryngomalacia, 1 child had right membranous choanal atresia and left nasal stenosis without atresia, 2 children had posterior laryngeal clefts (type 1), 5 children had subglottic stenosis, and 1 child had a bifid epiglottis (Table). Five of these 16 children also met histological criteria for esophagitis.

Eight children (33%) exhibited visible endoscopic evidence of an inflammatory airway process, including edema, erythema ("red streaks"), or subglottic stenosis (cases 1-6, 15, and 22). Five of these children exhibited stridor alone, 1 had stridor and apnea, 1 had apnea alone, and 1 had chronic cough. Five of these 8 children met histological criteria for esophagitis.

Four (17%) of our 24 children were found to have no anatomical anomalies or airway endoscopic findings suggestive of reflux-induced injury (cases 7, 18, 19, and 23). All 4 of these children had histories of apnea, and 1 also had stridor. Only 1 of these 4 patients met strict histological criteria for esophagitis.

As described in the literature, we found that changes in esophageal mucosa indicative of esophagitis fell into 2 categories: reactive epithelial changes and inflammatory reactions. Reactive epithelial changes, including basal hyperplasia and papillary elongation, mark the proliferative response of the epithelium to injury (Figure 1). Inflammatory cells are also used in the diagnosis of esophagitis. In addition to neutrophils and lymphocytes, eosinophils are markers for reflux esophagitis in the pediatric population (Figure 2).

In addition to the above absolute histological criteria for reflux esophagitis, some authors have reported that early indicators of esophagitis include balloononing of cells (Figure 3) and dilation of mucosal capillaries with resultant hemorrhage (vascular lakes) (Figure 4). Balloon cells and vascular lakes were present in esophageal biopsy specimens of 8 (33%) and 3 (13%), respectively, of the 24 children we examined. However, because these features are not yet widely recognized diagnostic criteria for reflux esophagitis, we did not use these in our strict criteria for esophagitis. Had we included these criteria for esophagitis, an additional 4 patients would have been considered to have mild esophagitis, bringing the total to 17 (71%) of 24 children with esophagitis.

COMMENT

Physiologic GER is common in infants. Fortunately, reflux in this population is largely self-limited; approximately 50% of 2-month-old infants regurgitate at least 2 times a day, with only approximately 1% continuing to have reflux at 12 months of age. In contrast, pathologic
Reflux in the pediatric population (GERD) is often not self-limiting. It is estimated that 8% of infants and young children have GERD, with the potential for developing severe complications. The natural course of GERD without active treatment was documented in 1959; today such a study would be considered unethical, given the high incidence of morbidity and mortality. In 1959, results showed that 60% of infants with untreated GERD had persistent symptoms at 2 years of age, and 30% still exhibited symptoms at 4 years of age. Of the children with persistent symptoms at 4 years of age, half eventually formed strictures; the remainder died secondary to malnutrition. Thus, the prevailing consensus is that early detection and treatment are important goals.

### Initial Symptoms and Biopsy Results

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Initial Examination</th>
<th>Initial Symptoms</th>
<th>Biopsy Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4½ mo</td>
<td>Stertor and stridor</td>
<td>Severe esophagitis–basal hyperplasia and papillary elongation, marked intraepidermal neutrophilic and eosinophilic inflammatory infiltrate (≥20 inflammatory cells/high-power field)</td>
<td>Severe laryngeal edema and subglottic stenosis</td>
</tr>
<tr>
<td>2</td>
<td>3 mo</td>
<td>Stridor</td>
<td>Severe stridor necessitating frequent intubations, Basal hyperplasia, papillary elongation, lymphocytic infiltrate</td>
<td>Mild subglottic stenosis</td>
</tr>
<tr>
<td>3</td>
<td>16 mo</td>
<td>Severe stridor necessitating frequent intubations, Basal hyperplasia, papillary elongation, lymphocytic infiltrate</td>
<td>Moderate laryngeal edema and subglottic stenosis</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12 mo</td>
<td>Intermittent stridor, stertor, apnea, Basal hyperplasia, papillary elongation, intraperidermal lymphocytic and eosinophilic infiltrate</td>
<td>Mild edema and erythema of vocal cords, edema of the right mainstem bronchus</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6½ y</td>
<td>Chronic cough</td>
<td>Basal hyperplasia and papillary elongation</td>
<td>Moderate edema and edema of carina</td>
</tr>
<tr>
<td>6</td>
<td>2 wk</td>
<td>Intermittent stridor</td>
<td>Basal hyperplasia, balloon cells, vascular lakes</td>
<td>Mild subglottic stenosis</td>
</tr>
<tr>
<td>7</td>
<td>8 y</td>
<td>Recurrent apnea</td>
<td>Balloon cells, papillary elongation, basal hyperplasia</td>
<td>Normal airways</td>
</tr>
<tr>
<td>8</td>
<td>2 mo</td>
<td>Intermittent stridor associated with feedings</td>
<td>Basal hyperplasia, papillary elongation, intraepithelial eosinophilic infiltrate</td>
<td>Laryngomalacia</td>
</tr>
<tr>
<td>9</td>
<td>1½ mo</td>
<td>Intermittent stridor</td>
<td>Poorly oriented, balloon cells, vascular lakes</td>
<td>Laryngomalacia, mild edema and bogginess of distal esophageal mucosa</td>
</tr>
<tr>
<td>10</td>
<td>2 y</td>
<td>Apnea, recurrent otitis media</td>
<td>Severe esophagitis–basal hyperplasia and papillary elongation, neutrophilic and eosinophilic inflammatory infiltrate (≥20 inflammatory cells/high-power field)</td>
<td>Tonsillar and adenoid hypertrophy with nasopharyngeal obstruction, mild edema at gastroesophageal junction</td>
</tr>
<tr>
<td>11</td>
<td>17 mo</td>
<td>Aspiration, cough</td>
<td>Basal hyperplasia, balloon cells, vascular lakes</td>
<td>Posterior glottic cleft</td>
</tr>
<tr>
<td>12</td>
<td>2½ mo</td>
<td>Failure to thrive, wheezing and tachypnea associated with feedings</td>
<td>Papillary elongation, balloon cells, vascular lakes</td>
<td>Bifid epiglottis with narrowed trachea</td>
</tr>
<tr>
<td>13</td>
<td>2 y</td>
<td>Stridor and sleep apnea</td>
<td>Poorly oriented, balloon cells, vascular lakes</td>
<td>Significant collapse of epiglottis and supraglottic tissues secondary to cystic hygroma</td>
</tr>
<tr>
<td>14</td>
<td>5 mo</td>
<td>Stridor</td>
<td>Mild basal hyperplasia, intraepidermal lymphocytic infiltrate, balloon cells</td>
<td>Narrowing of glottic inlet secondary to cystic hygroma, mild distal esophageal stricture with moderate edema</td>
</tr>
<tr>
<td>15</td>
<td>8 mo</td>
<td>Apnea</td>
<td>Normal</td>
<td>Mild subglottic stenosis, mild edema at gastroesophageal junction</td>
</tr>
<tr>
<td>16</td>
<td>7½ mo</td>
<td>Stridor</td>
<td>Normal</td>
<td>Vascular anomaly with distant tracheal compression</td>
</tr>
<tr>
<td>17</td>
<td>9 mo</td>
<td>Intermittent stridor and emesis with feedings</td>
<td>Normal</td>
<td>Laryngomalacia</td>
</tr>
<tr>
<td>18</td>
<td>6 mo</td>
<td>Apnea</td>
<td>Normal</td>
<td>Normal airway</td>
</tr>
<tr>
<td>19</td>
<td>3½ mo</td>
<td>Intermittent stridor, apnea</td>
<td>Normal</td>
<td>Normal airway</td>
</tr>
<tr>
<td>20</td>
<td>1 mo</td>
<td>Stridor, failure to thrive</td>
<td>Normal</td>
<td>Right membranous choanal atresia and left-sided stenosis without atresia</td>
</tr>
<tr>
<td>21</td>
<td>2 y</td>
<td>Chronic cough</td>
<td>Severe esophagitis–basal hyperplasia, papillary elongation, eosinophilic inflammatory infiltrate (≥20 inflammatory cells/high-power field)</td>
<td>Innominate artery compression</td>
</tr>
<tr>
<td>22</td>
<td>10 y</td>
<td>Stridor</td>
<td>Poorly oriented</td>
<td>Subglottic stenosis</td>
</tr>
<tr>
<td>23</td>
<td>2½ mo</td>
<td>Apnea</td>
<td>Poorly oriented, balloon cells</td>
<td>Normal airway</td>
</tr>
<tr>
<td>24</td>
<td>2 y</td>
<td>Aspiration, cough</td>
<td>Severe esophagitis–basal hyperplasia, papillary elongation, eosinophilic inflammatory infiltrate (≥20 inflammatory cells/high-power field)</td>
<td>Posterior glottic cleft</td>
</tr>
</tbody>
</table>
like adults, up to 30% of infants and children with GERD have respiratory symptoms. Similarly, it has been reported that in children with chronic pulmonary disease, treatment for reflux improved pulmonary symptoms in 85%. The authors concluded that GERD is a causative factor in pediatric chronic pulmonary disease.

In general, studies have shown that symptoms associated with GERD correlate poorly with severity and are not useful in the diagnosis or treatment of GERD. Therefore, a variety of diagnostic studies are used to confirm the presence and assess the severity of GERD. These include esophageal pH monitoring (EpHM), esophagoscopy with or without biopsy, technetium scintigraphy, barium esophagography with video swallow, esophageal manometry, and the Bernstein esophageal acidification test.

Esophageal pH monitoring is still considered the procedure of choice for diagnosing GERD in both children and adults. This is an additional procedure that at many institutions requires radiological placement and an additional hospital stay. Although EpHM is helpful in documenting the presence and severity of GER, recent studies have concluded that it may not be as sensitive as esophagoscopy with biopsy when used to evaluate the presence and severity of esophagitis in infants and young children. Regardless, the early recognition of esophagitis is clinically significant, as this may be an important determinant of prognosis and necessity of surgical intervention.

In a recent report on the use of EpHM, Colletti et al suggested that if esophageal biopsy specimens demonstrate the presence of esophagitis, EpHM is considered redundant and unnecessary as a further diagnostic tool. However, the authors also posed a number of guidelines for appropriate use of EpHM in the examination of an infant or child with suspected GERD. First, if there is still a question, after esophagoscopy and biopsy, as to whether a child’s respiratory disease is related to GERD, EpHM may be used to assess whether a temporal relationship exists between the respiratory symptoms and episodes of reflux. Second, if esophagoscopy with biopsies fails to demonstrate gross or histological evidence of GERD, EpHM may still be used as a further diagnostic tool to document pathologic GER. Third, in children who are under medical treatment for GERD, EpHM can be used...
to determine whether treatment is effective or if surgical intervention seems warranted.

Recently the European Society of Pediatric Gastroenterology and Nutrition proposed that infants and young children with suspected GERD be examined by esophagoscopy with biopsies to assess for any gross lesions and/or histological evidence of reflux esophagitis, and others have advocated the use of esophagoscopy with biopsies as the first line of diagnostic testing. Esophagoscopy with biopsies allows the otolaryngologist the advantage of visualizing lesions or anatomical anomalies. Furthermore, it is suggested that esophagoscopy with biopsies is more sensitive than EpHM when evaluating for the presence of esophagitis in the pediatric population in particular.

The aim of the present study was to maximize our detection of esophagitis in a population of infants and children referred for airway evaluation. We therefore limited our biopsies to relatively distal sites in the esophagus. In retrospect, it is unclear whether obtaining biopsy specimens from more proximal, cephalic areas of the esophagus would be more indicative of reflux that is injurious to the airway. However, the presence of any reflux esophagitis may result in vagally mediated reflex bronchospasm or laryngospasm, with resulting stridor or apnea. Therefore, treatment of esophagitis diagnosed on the basis of distal biopsy specimens is still indicated for these children. We have modified our protocol to include both proximal and distal esophageal biopsies.

Some authors have proposed that epithelial damage indicative of early esophagitis includes balloon cells and vascular lakes. Balloon cells have often been overlooked as markers for esophagitis because normal variants of esophageal mucosa including glycogenic acanthosis, and glycogen-filled cells may be mistaken for balloon cells. Vascular lakes have been shown to be early markers of reflux esophagitis. Vascular lakes are the histological counterpart of the mucosal red streaks visualized during esophagoscopy. Evaluating the sensitivity of these histological features as criteria for reflux esophagitis is beyond the scope of the present study, but further investigation of early esophageal changes of reflux esophagitis seems warranted, especially in the pediatric population, with the goal of early detection and the potential for improving the prognosis. Early in our study, consistency of histopathological readings was a weak point. However, with time, we, and our pathologists, have become more proficient and consistent in detecting the subtle changes associated with reflux esophagitis.

For several reasons, we conclude that infants and children who undergo DLB as part of the evaluation of airway distress should undergo triple endoscopy, including esophagoscopy with biopsies at that time. First, the additional procedure adds little time to the overall operative time. Second, esophagoscopy may disclose the presence of anatomical anomalies that may not be apparent by DLB alone. Third, if esophagoscopy with biopsies is performed at the time of DLB, additional diagnostic testing may be avoided. Fourth, because the presence of esophagitis is an important determinant of outcome, the histological diagnosis provided by biopsies may provide valuable guidance for intervention. Finally, in the present study, rigid esophagoscopy with biopsies was safely performed in infants as young as 2 weeks. Flexible esophagoscopy would be adequate for this purpose and may have a lower risk of complications. Regardless, we conclude that when DLB is performed during examination of the child with airway distress, the addition of esophagoscopy with mucosal biopsies will provide data regarding the potential contribution of GER. Our routine evaluation is now triple endoscopy, including esophageal biopsies.

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REFERENCES