Intestinal Metaplasia of the Esophagus in Children With Esophageal Atresia

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Objectives: Patients with esophageal atresia/tracheoesophageal fistula (EA-TEF) can develop Barrett esophagus as a long-term consequence of their condition. Intestinal metaplasia (IM), a risk factor for developing adenocarcinoma of the esophagus, has not been well-characterized in the pediatric population.

Methods: Retrospective review of patients with EA-TEF followed at 3 academic pediatric centers between the years 1997 and 2014.

Results: Among 542 children and adolescents, 1.3% (7 patients, 5 girls) were diagnosed with IM based on endoscopy and pathology. Six of the patients had EA-TEF type C, whereas the last patient had a “long gap” type A atresia. Patients were diagnosed with gastric metaplasia either before the IM diagnosis in 4 patients or concomitantly in 3. The median (range) age of diagnosis for gastric metaplasia was 7.9 (range 2–17.2) and for IM 10.9 (2–17.2) years. Gastroesophageal reflux (GER) symptoms were nonspecific. Five patients were on proton pump inhibitor therapy for symptomatic GER at the time of diagnosis of IM. 2 of the 7 patients had previously undergone Nissen fundoplication. One patient, who had undergone a Nissen fundoplication, was restarted on proton pump inhibitor once the diagnosis of IM was made. All patients had repeated endoscopy and dysplasia was not observed with a median follow-up of 1.7 (range 1–4.9) years.

Conclusions: IM occurs in patients with EA-TEF, some as young as 2 years. Therefore, early endoscopic surveillance should be considered in this GER-prone population.

Key Words: esophageal atresia, esophagitis, gastric metaplasia, gastroesophageal reflux, intestinal metaplasia

What is Known
- In adults operated on for esophageal atresia-tracheoesophageal fistula the incidence of Barrett esophagus with intestinal metaplasia, a condition known as a risk factor for developing adenocarcinoma of the esophagus, is high.
- The natural history of this intestinal metaplasia is unknown.
- Intestinal metaplasia has not been well-characterized in the pediatric population.

What is New
- We show that intestinal metaplasia has an incidence of at least 1.3% in the esophageal atresia-tracheoesophageal fistula pediatric population compared to 0.12% in the general pediatric population.
- Gastric metaplasia (median age of diagnosis for gastric metaplasia of 7.9 years) appears to occur before intestinal metaplasia (median age of diagnosis for intestinal metaplasia of 10.9 years) in children with esophageal atresia-tracheoesophageal fistula.
- Reflux symptomatology does not reflect histopathology of patients’ esophagus.

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GM, which is hypothesized to be a precursor lesion for IM, has been reported to occur in 8% to 36% (mean age 7.3–10.3 years) of children with EA-TEF (10,12,13). Therefore, one can hypothesize that IM has been so far underreported in children with EA-TEF. Because IM may have serious long-term consequences for these patients and since specific treatment and surveillance protocols are available and recommended for this lesion, we decided to examine the incidence and characteristics of patients with IM in a multicenter cohort of children operated for EA-TEF.

METHODS

Patients

Patients followed in the EA-TEF Clinics of 3 pediatric academic institutions (Centre Hospitalier Universitaire Ste-Justine [Montreal, Canada], Sydney Children’s Hospital [Sydney, Australia], CHU de Lille [Lille, France]) were identified as having IM. In these 3 centers all patients with EA are followed in a specialized multidisciplinary EA clinic wherein patients are carefully and systematically screened for esophageal complications of GERD.

The diagnosis included endoscopic and pathologic results. Consent for participation in a multicenter database of patient data was obtained from each child’s parents or primary caregiver.

A retrospective chart review was performed and the following data were collected and analyzed: demographics (sex, term, date of birth), medical history (type of EA-TEF, associated malformations), esophageal reflux history and treatment (pH-metry/impedance, medications, and surgery), esophagogastroduodenoscopy history (results, pathology).

The patients have signed a consent form for inclusion in the database and subsequent retrospective studies. CHUSJ: 2751 (Approved [renewal] 2015-12-19); Lille: 910270 (November 26, 2009); Sydney: NLR/14/SCHN/514 (December 18, 2014).

Endoscopic Data

Endoscopic results were drawn from reports within the chart. Methods used to analyze BE endoscopically have been described elsewhere (13). In brief, the BE macroscopic aspect was defined as velvety-red tongue extending up the esophagus from the proximal gastric folds at the gastroesophageal junction (Fig. 1). BE endoscopic aspect was differentiated from hiatal hernia or gastric pull-up by carefully locating the proximal margin of the gastric folds (Fig. 2). If macroscopic BE aspect was seen multiple biopsies (at least 2) were systematically taken of the lesion. Biopsies were also taken from esophagus proximal and distal to the lesion.

A diagnosis of BE required endoscopic diagnosis and confirmation on histopathology.

Pathology Data

Esophagitis was defined as the elongation of papillae and basal hyperplasia.

When biopsies from endoscopically suspected metaplasia showed a columnar epithelium, they were considered as BE. As proposed by the Montreal definition and classification of gastroesophageal reflux (14), endoscopically suspected esophageal metaplasia, both cardiac- and intestinal-type metaplasia, are included in the definition of BE (14,15). Metaplasia type was defined as GM or IM (Fig. 3). In biopsies in which metaplasia was suspected, Alcian Blue was used to highlight goblet cells and readily distinguish IM.
Endoscopic surveillance after diagnosis of GM and IM varied among the centers, with endoscopies every 6 to 36 months. Dysplasia was not observed with a median follow-up of 1.7 (range 1–4.9) years.

**DISCUSSION**

We describe here 7 patients (5 girls) with IM of the esophagus, with a median age of 10.9 years, the youngest being 2 years, observed in 3 pediatric multidisciplinary EA-TEF clinics. This results in a prevalence of at least 1.3% (95% confidence interval 0.34–2.24), which is similar to the prevalence observed in adolescents and young adults (9) and 10-fold higher than the prevalence reported in a population of children not prone to GERD (11).

There are only 5 other pediatric IM cases in patients with EA-TEF described in the literature (4,16). Pedersen et al (16) reported one 6-year-old child with IM and Koivusalo et al (4) have recently reported that the IM developed before GM in 3 of their 4 IM patients and Pedersen et al (16) observed GM and IM in the single patient seen in their series.

Whether GM is a precursor lesion for IM and could be considered as a risk factor for esophageal cancer is still controversial (5). It has, however, been shown that immunophenotypic changes may be present in GM without specialized epithelium (17) and genetic markers associated with adenocarcinoma development are present in children with GM (18). Our results suggest that GM could be used to direct the evaluation, treatment, and follow-up for GERD in EA-TEF patients and, if present, should prompt careful endoscopic follow-up and screening for IM. We suggest that the presence of GM should lead to aggressive GERD therapy even if long-term PPI therapy does not preclude GM to progress toward IM. It has been well accepted and recommended that acid suppression be used to prevent adenocarcinoma in adult patients with IM (19).

As previously reported in patients with EA-TEF (13), clinical symptoms do not correlate with the severity of the GERD. We did not find any specific symptom, which could have predicted the presence of IM in the patients. This highlights the importance of systematic endoscopic follow-up in this population, even in patients operated for their GERD, since 2 out of 7 patients who had previously undergone Nissen fundoplication developed GM and IM. Likewise, long-term PPI treatment of children with GM did not preclude the evolution toward IM in the present series suggesting that other factors may drive the evolution of epithelial metaplasia.

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**TABLE 1. Patient characteristics, pathology and symptomatology**

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Sex</th>
<th>EA-TEF type</th>
<th>Associated malformations</th>
<th>GM Dx, y</th>
<th>IM Dx, y</th>
<th>Nissen?</th>
<th>Dysphagia</th>
<th>Impaction</th>
<th>Coughing</th>
<th>Regurgitation</th>
<th>Odynophagia</th>
<th>Other a</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>A</td>
<td>4.9</td>
<td>4.9</td>
<td>No</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td>Choking, gagging, wheezing</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>C</td>
<td>17.2</td>
<td>17.2</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>C</td>
<td>8.3</td>
<td>13.6</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>C</td>
<td>Cardiac</td>
<td>6</td>
<td>10.9</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>C</td>
<td>Cardiac</td>
<td>14.9</td>
<td>16.2</td>
<td>No</td>
<td>Y</td>
<td>—</td>
<td>Y</td>
<td>—</td>
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</tr>
<tr>
<td>6</td>
<td>F</td>
<td>C</td>
<td>2</td>
<td>2</td>
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<td>Y</td>
<td>Y</td>
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<td>—</td>
<td>—</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td></td>
</tr>
</tbody>
</table>

Dx = diagnosis; GM = gastric metaplasia; IM = intestinal metaplasia; VACTER = vertebral, anus, cardiac, tracheoesophageal fistula, renal.

a No patients experienced pyrosis.
Several groups have identified that long-gap atresia, esophageal dysmotility, anastomotic complications, esophagitis, and need for antireflux surgery as risk factors for the development of BE (2,4,9). In the present study, the majority (6/7) of the patients had a type C EA-TEF with an uneventful postoperative history. Some authors have reported that severe esophageal dysmotility is associated with esophagitis and severe GERD (2,20,21). Whether patients who develop IM have more severe esophageal dysmotility is unknown and further research with high-resolution esophageal manometry study needed. Whether a genetic factor may also be involved in this population is unknown (22).

To our knowledge, there is no previous report of the high prevalence of females with IM. The low number of patients with IM, however, reported here precludes any definitive association between female sex with IM.

The strengths of the present study are its multicenter design from 3 large specialized EA clinics across 3 continents. The careful endoscopic follow-up of the patients in the 3 centers allowed a high detection rate of IM in a large cohort of patients, which allows us calculate IM prevalence in patients with EA-TEF.

There are also some limitations related to the retrospective design of the study. Endoscopic techniques may have varied across the different centers/endoscopists, making possible that some gastric or IM may have been missed. Another pitfall of the present study is the total number of biopsies taken as it does not strictly follow the guidelines for Barrett surveillance (23). We therefore acknowledge that some gastric or IM may have been missed and that our results are most likely an underestimation.

Although the incidence of esophageal adenocarcinoma in BE is estimated to be 0.1% to 2.9% (5), the severity and consequences of this disease requires vigilance as suggested in recent recommendations for long-term surveillance of adult patients operated on for EA-TEF (24). Pediatric endoscopists should be aware of diagnosis and surveillance of BE and 4 quadrants biopsies should be obtained in areas of suspected BE and IM.

REFERENCES