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Reference

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Prevalence and Predictive Factors of Histopathological Complications in Children with Esophageal Atresia

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Abstract

Objectives  Endoscopic follow-up after esophageal atresia (EA) tracheoesophageal fistula (TEF) repair is recommended to detect esophageal histopathological complications. We investigated the prevalence of histopathologically proven esophageal complications (peptic esophagitis, gastric metaplasia, and eosinophilic esophagitis) and assessed the predictors of these complications in children with EA-TEF.

Methods  This is a prospective longitudinal cohort study performed between September 2005 and December 2014 comprising 77 children with EA-TEF followed-up until February 2017. Univariate analysis was performed using the Wilcoxon's rank-sum test for continuous variables and the Pearson's chi-square test for categorical variables. Multivariable analysis was performed using a Cox regression hazard model. The association between clinical factors and histopathologically proven complications was estimated using a Cox regression hazard model with time until the appearance of complications as the time scale.

Results  All 77 children received proton pump inhibitors (PPIs) \( n = 73 \) or H2 receptor antagonists (H2RA). A total of 252 endoscopies were performed in 73 children (median 2.6/child, range: 1–29). Median age at study completion was 4.9 years (range: 2.3–11.5 years). Histopathologically proven complications occurred in 38 children (52%): peptic esophagitis \( n = 32, 44\% \), eosinophilic esophagitis \( n = 15, 21\% \), and gastric metaplasia \( n = 9, 12\% \). A total of 82% patients were on PPI or H2RA at the time of diagnosis of histological complication. Multivariable Cox regression analysis showed that patients with recurrent anastomotic strictures (>3 dilations) had a higher risk of occurrence of histopathologically proven complications over time (hazard ratio: 3.11, 95% confidence interval [CI]: 1.53–6.34). On univariate analysis, the result of the first endoscopy was not associated with the occurrence of histopathologically proven complications (odds ratio: 0.8, 95% CI: 0.16–3.95).

Conclusion  Histopathologically proven complications with potential long-term consequences occurred in approximately 50% of children after EA-TEF repair. A history of recurrent anastomotic strictures (>3 dilations) had a higher risk of occurrence of histopathologically proven complications over time. Children with EA-TEF warrant close and systematic long-term follow-up at specialized multidisciplinary clinics with endoscopic evaluation.

Keywords  ► esophageal atresia  ► esophagitis  ► eosinophilic esophagitis  ► acid reflux  ► endoscopy

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Prevalence and Predictive Factors of Histopathological Complications in Children with EA

Introduction

Esophageal atresia (EA) with or without associated tracheoesophageal fistula (TEF) is a common congenital malformation, which prognosis has drastically changed over the past three decades.1 The clinical course of EA-TEF is usually complicated by gastroesophageal reflux disease (GERD) and previous retrospective studies have shown that endoscopic surveillance in EA-TEF patients provides a high yield of detection of gastroesophageal reflux (GER)-related histopathologically proven complications in childhood and adolescence.2–7 Reportedly, peptic esophagitis was observed in 34 to 75% of the children2–7 and eosinophilic esophagitis (EoE) in 10 to 18%;6,8 Considering the potential long-term complications such as gastric2–7,9 and/or intestinal metaplasia,10 the recent European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition guidelines recommend the need for systematic surveillance in this population11 because studies have shown that patients’ symptoms do not correlate with histopathological complications precluding any symptom-based surveillance in this population.5,7

Since September 2005, all children diagnosed with EA-TEF are included at birth in the EA-TEF clinic at our hospital where they undergo systematic follow-up and endoscopic surveillance. All children receive proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RA) for at least a year after birth. We aimed to investigate the prevalence and the predictors of histopathologically proven esophageal complications, which may have significantly influenced the long-term outcome in our cohort comprising children diagnosed with EA-TEF who were followed-up over an 11-year period.

Methods

Patients

Children born with EA-TEF between September 2005 and December 2014 who were followed-up at the EA-TEF clinic of the Sainte-Justine University Hospital Centre, Montreal, were prospectively included in this longitudinal cohort study. Final evaluation was performed upon completion of the study in February 2017.

All children were treated with oral PPIs (lansoprazole 1–2 mg/kg) or H2RA, which was initiated when the child was able to tolerate oral/enteral feeding. Upper endoscopic examination was performed in all children after discontinuation of PPI or H2RA or when indicated by clinical symptoms at any time during follow-up (excessive regurgitation suggestive of anastomotic stricture, dysphagia, food impaction, and hematemesis).

The study was approved by the ethical committee of CHU Sainte-Justine (CHUS: #2751). All parents/guardians signed the informed consent form for inclusion of their children in the database and for subsequent studies.

Clinical Data

Clinical data were prospectively collected and included: (1) baseline characteristics (sex, prematurity, birth weight, type of atresia, and other associated anomalies), (2) surgery-related variables (“long gap” was defined as a gap measuring ≥3 cm in length or ≥ the height of two vertebral bodies, and/or anastomosis under tension, type of surgery), (3) postoperative complications (anastomotic leak, need for esophageal resurgery, fundoplication), (4) anastomotic stricture and/or recurrent anastomotic stricture defined as ≥3 dilations needed to treat the stricture,11 and (5) antacid treatment (nature, date of first and last prescription).

Endoscopy

One or more biopsies were obtained above the proximal gastric folds, at least 1 cm away from the gastroesophageal junction. Barrett’s esophagus was macroscopically defined as a velvety red tongue-like structure extending upward into the esophagus from the proximal gastric folds at the gastroesophageal junction. This entity was differentiated from hiatal hernia or gastric pull-up after carefully delineating the gastroesophageal junction, which was identified at the proximal margin of the gastric folds. When Barrett’s esophagus was identified macroscopically, at least one additional biopsy was obtained from the affected segment. Such caution was needed primarily in children who presented with long-gap atresia, wherein gastric pull-up was commonly noticed.

EoE was defined as >15 eosinophils/high-power field (×400 magnification), and peptic esophagitis and gastric metaplasia were defined as previously described.7 The number and results of esophagoscopy(ies) and the results of histopathological analysis of esophageal biopsies were recorded.

Statistical Analyses

All analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC). Descriptive data are presented as medians (interquartile ranges: q1 and q3) for continuous variables and as frequencies (%) for categorical variables. Univariate analysis was performed using the Wilcoxon’s rank-sum test for continuous variables and the Pearson’s chi-square test for categorical variables. Patients with histopathologically proven complications observed during follow-up were compared with patients without histopathological complications. Odds ratio (OR) with 95% confidence interval (CI) were indicated whenever available.

Kaplan–Meier’s survival curve was plotted to show the overall probability of appearance of histopathologically proven complications during follow-up. In children showing multiple histopathologically proven complications, only the first event was recorded. If no histological complication appeared during follow-up, censoring was stated at the time of last follow-up or study end.

The association between clinical factors and histopathologically proven complication (peptic esophagitis, EoE, gastric metaplasia) was estimated using a multivariable Cox regression model with time to event (age at the appearance of complication) or to censoring date (age at the time of censoring) as time scale. Variables that were clinically
relevant or turned out to be significant on univariate analysis at a level of \( p < 0.25 \) were put in the Cox regression model using a stepwise selection with an entry level set at 0.25. The hazard ratio (HR) and 95% CI were calculated.

The Cox regression model was tested for potential multicollinearity issues by respecting a variance inflation factor < 5 and was tested for proportional hazards assumption. The limitation of 1 variable out of 10 included subjects was respected. The best-fitted model based on the Akaike’s information criterion value was used as the final model. Anastomotic strictures and recurrent strictures, long-gap EA, anastomotic leak post-EA repair, and length of hospitalization > 30 days were subjected to this model. Long-gap EA was a variable that was removed from the final analysis due to the absence of effect. Furthermore, children with long-gap EA invariably required hospitalization for > 30 days and were therefore included in the variable “length of hospitalization.”

A sensitivity analysis of children with histopathologically proven complications was performed for peptic esophagitis using the same Cox regression model.

A two-sided \( p \)-value < 0.05 was considered statistically significant.

**Results**

A total of 85 children were initially included. Eight patients died during early follow-up secondary to associated cardiac malformations and were excluded. Seventy-seven children (44 males, 57%) were finally included in the analysis. Median time of follow-up at study completion was 4.9 years (3.6, 8.0). All children received a PPI \((n = 73)\) or a H2RA \((n = 4)\) from the moment when the child was able to tolerate oral/enteral feeding. Patients’ characteristics and postoperative complications are listed in Table 1.

We performed 252 endoscopies in 73 children (median 2.6 endoscopies/child, range: 1–29). The first endoscopy was performed at a median age of 1 year (1, 3). We observed that 42 children (55%) underwent at least two endoscopic examinations during their follow-up (median age at the second endoscopic examination was 2 years (1, 3). An anastomotic stricture was diagnosed in 33 children at a median age of 2.7 years (1, 6.6). A recurrent anastomotic stricture (requiring > 3 dilations) was noted in 17 children.

**Histological Complications**

Histopathologically proven complications occurred in 38 children (52%). At the median time of follow-up of 4.9 years, 50% remained at risk of development of histopathologically proven complications, as demonstrated by the Kaplan–Meier’s survival curve (► Fig. 1).

Peptic esophagitis was demonstrated in 32 patients (44%, 28 on PPI or H2RA), EoE in 15 (21%, 13 on PPI or H2RA), and gastric metaplasia in 9 (12%, 8 on PPI or H2RA). EoE improved with PPI treatment in seven children and required withdrawal of food allergens (cow milk, soya, eggs, peanuts, and fish) in eight children. In 9 out of 14 patients who had an antireflux procedure, histological complications were present during follow-up (esophagitis \( n = 9 \), EoE \( n = 2 \), and gastric metaplasia \( n = 3 \)). PPIs were discontinued in five of them during follow-up with re-prescription in one.

**Risk Factors Associated with the Development of Histopathologically Proven Complications**

**Peptic Esophagitis**

On univariate analysis, the type of atresia, birth weight, prematurity, length of initial hospitalization, type of surgery, or anastomotic stricture requiring < 3 dilations did not significantly differ between children with and without esophagitis. However, the presence of peptic esophagitis was associated with a history of anastomotic leak (OR: 7.2, 95% CI: 2.07–25, \( p < 0.001 \)) and with recurrent anastomotic strictures (OR: 43, 95% CI: 13.3–140, \( p = 0.01 \)).
Multivariable Cox regression analysis showed that an anastomotic leak was significantly associated with a higher risk of development of peptic esophagitis over time (HR: 3.18, 95% CI: 1.56–6.49, \( p = 0.0008 \)).

**Gastric Metaplasia**
The type of atresia, birth weight, prematurity, length of initial hospitalization, type of surgery, or anastomotic leak did not significantly differ on univariate analysis between children with and without gastric metaplasia. However, gastric metaplasia was associated with recurrent anastomotic stricture (OR: 5.4, 95% CI: 1.26–23.2, \( p = 0.01 \)). Multivariable Cox regression models were not interpretable secondary to a small number of children studied.

**Eosinophilic Esophagitis**
The type of atresia, birth weight, prematurity, length of initial hospitalization, type of surgery, the presence of the long-gap deformity, anastomotic leak, anastomotic stricture, or recurrent anastomotic stricture did not significantly differ between children with and without esophagitis. On univariate analysis, the presence of EoE was significantly associated with peptic esophagitis (OR: 4.8, 95% CI: 1.37–17.1, \( p = 0.01 \)) and gastric metaplasia (OR: 12.2, 95% CI: 2.6–57, \( p = 0.003 \)). Multivariable Cox regression models were not interpretable secondary to a small number of children studied.

**Any Histological Complication**
Table 2 shows the results of comparison between children with any histopathologically proven complication observed during follow-up and those without any histopathologically proven complication. On univariate analysis, no significant intergroup differences were observed in terms of type of atresia, birth weight, prematurity, length of initial hospitalization, or type of surgery performed. However, long-gap atresia (\( p = 0.03 \)), anastomotic leak (\( p = 0.002 \)), and the presence of anastomotic stricture (\( p = 0.02 \)) or recurrent anastomotic stricture (\( p = 0.0004 \)) were more commonly observed in the group with histopathologically proven complications.

Multivariable Cox regression analysis showed that only children with recurrent anastomotic strictures (those requiring \( > 3 \) dilations) demonstrated a significantly higher risk of development of any histopathologically proven complication (HR: 3.11, 95% CI: 1.53–6.34, \( p = 0.0002 \)).

Among the 42 children who underwent at least two endoscopic examinations (median age at first endoscopy 12 months [12, 36] and median age at last endoscopic examination 36 months [24, 60]), we attempted to determine whether a first normal endoscopic examination without any histopathologically proven complication would predict the absence of complications during follow-up. No significant association was observed between the result of the first endoscopic examination and the occurrence of histopathologically proven complications on univariate analysis (OR: 0.8, 95% CI: 0.16–3.96, \( p = 1.0 \)).

**Discussion**
In the present study, we reported that in a study population comprising children diagnosed with EA-TEF who received treatment with PPI or H2RA and who were prospectively...
followed-up over 11 years, histopathologically proven complications occurred in 52% of the children. We also showed that during follow-up, long-gap EA, anastomotic leak, and the presence of anastomotic stricture or recurrent anastomotic stricture were significantly more common in the group showing histopathologically proven complications on univariate analysis. Multivariable regression analysis revealed that only the presence of recurrent anastomotic strictures was significantly associated with the occurrence of any histopathologically proven complication.

During follow-up, peptic esophagitis was detected in 32 of 73 children (44%) and gastric metaplasia (a consequence of peptic esophagitis) in 9 (12%). Previous retrospective case series have reported histopathologically proven peptic esophagitis in 34 to 75% of children with EA and gastric metaplasia in 2 to 17% of children. These results were observed to be in agreement with our findings. 2–7 Koivusalo et al reported the larger pediatric case series comprising 209 patients followed-up over 15 years. They showed that grade 1 esophagitis was present in 36%, grade 2 esophagitis in 16%, and gastric metaplasia in 17% of the studied patients. 5 In the present study, peptic esophagitis and/or gastric metaplasia were observed to be significantly associated with a history of anastomotic leak and/or recurrent anastomotic strictures. This suggests that children demonstrating such postoperative complications warrant close endoscopic surveillance.

EoE was present in 15 of 73 children (21%)—a finding in agreement with previous studies that have reported a prevalence of 10 to 18%. 6,8 This number is higher than the prevalence of approximately 1 in 10,000 reported in the general population. 12 We cannot rule out the possibility that the high prevalence of EoE reported in children with EA-TEF may be related to the close endoscopic and histopathological surveillance performed even in asymptomatic children, thereby increasing the yield of detection of anomalies. Whether EoE occurring in those with EA-TEF is related to GERD, to PPI-responsive EoE, or to allergy remains unclear. We observed that approximately 50% of the children showed an improvement in EoE with PPI treatment, as reported in non-EA patients by a recent meta-analysis. 13 Although we did not observe any association with surgery-related factors, we noted that EoE was significantly associated with the presence of peptic esophagitis and gastric metaplasia.

### Table 2: Univariate analysis for intergroup comparison during follow-up between patients with and without any histopathological complications

<table>
<thead>
<tr>
<th></th>
<th>Histological complications, n = 38</th>
<th>No histological complications, n = 35</th>
<th>p-Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>15 (39.5)</td>
<td>17 (48.6)</td>
<td>0.43</td>
<td>0.69 (0.27–1.75)</td>
</tr>
<tr>
<td>Males</td>
<td>23 (60.5)</td>
<td>18 (51.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of atresia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>4 (10.5)</td>
<td>2 (5.7)</td>
<td>0.64</td>
<td>4.3 (1.1–17.2)</td>
</tr>
<tr>
<td>C</td>
<td>32 (84.2)</td>
<td>32 (91.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>2 (5.3)</td>
<td>1 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-gap EA</td>
<td>11 (29)</td>
<td>3 (8.6)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight &lt;2.5 kg</strong></td>
<td>19 (50)</td>
<td>18 (52.9)</td>
<td>0.8</td>
<td>0.89 (0.35–2.24)</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>27 (71.1)</td>
<td>31 (88.6)</td>
<td>0.06</td>
<td>0.32 (0.09–1.11)</td>
</tr>
<tr>
<td>Thorascopy</td>
<td>11 (28.9)</td>
<td>4 (11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization of &gt; 30 days</td>
<td>21 (58.8)</td>
<td>12 (36.4)</td>
<td>0.09</td>
<td>2.3 (0.88–6.01)</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>31 (16, 116)</td>
<td>21 (15, 32)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td><strong>Complications after surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>15 (39.5)</td>
<td>3 (8.6)</td>
<td>0.002</td>
<td>6.96 (1.8–26.85)</td>
</tr>
<tr>
<td>Need for esophageal resurgery</td>
<td>6 (15.8)</td>
<td>5 (14.3)</td>
<td>0.86</td>
<td>1.13 (0.31–4.08)</td>
</tr>
<tr>
<td>Fundoplication</td>
<td>9 (23)</td>
<td>5 (14)</td>
<td>0.14</td>
<td>1.86 (0.55–6.22)</td>
</tr>
<tr>
<td><strong>Anastomotic stricture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>22 (57.9)</td>
<td>11 (31.4)</td>
<td>0.02</td>
<td>3.0 (1.15–7.84)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>14 (36.8)</td>
<td>3 (8.6)</td>
<td>0.004</td>
<td>6.22 (1.61–24.1)</td>
</tr>
</tbody>
</table>

**Abbreviations**: CI, confidence interval; EA, esophageal atresia; OR, odds ratio.  
**Note**: Data presented as n (%) for qualitative variables and as median (interquartiles) for continuous variables.
suggesting that EoE could be a consequence of GER in patients with EA, although the contributory role of an allergic factor cannot be ruled out.

Multivariable Cox regression analysis demonstrated that the occurrence of recurrent anastomotic strictures (anastomotic strictures requiring >3 dilations as opposed to those responding to ≤3 dilations) was associated with the presence of histopathologically proven complications, suggesting that GER may facilitate the persistence of strictures.

We did not observe any statistically significant association between the absence of histopathologically proven complications at the time of the first endoscopic examination and the occurrence of complications during subsequent follow-up. Schalamon et al reported that complications appear in the first 3 years during the evolution of EA-TEF in children. However, we showed here that the result of the first endoscopic examination did not predict the long-term outcome. Therefore, endoscopic surveillance must be continued even if the first endoscopic examination shows unremarkable findings. Interestingly, we found that neither a systematic antacid treatment nor antireflux surgery was able to completely prevent the occurrence of esophageal histopathological complications in this population. This could be related to a poor compliance to medical treatment, or to a severe form of acid reflux not responding to treatment. The presence of a partial gastric pull-up which secretes acid above the wrap is also a possible explanation in patients who underwent an antireflux procedure.

There are several strengths of this study. The prospective study design with the study period extending over 11 years without any child lost to follow-up. A close and careful follow-up with good adherence to work up over the study period in all children allows a comprehensive data record regarding the endoscopic and histopathological findings for the entire cohort. The population characteristics, the survival rate, the causes of mortality, and the incidence of complications were observed to be in agreement with previous reports from other hospitals suggesting the generalizability and applicability of our data to other centers. One limitation of this study is the limited number of biopsies obtained for a diagnosis of Barrett’s esophagus. We therefore acknowledge that in a few children, the findings of gastric or even intestinal metaplasia may have been missed and that our results are likely to represent an underestimation of the true histopathological complications. Also, the small number of children included in the study precluded multivariate regression analysis for gastric metaplasia and EoE separately.

In conclusion, histological complications with potential long-term consequences were observed in approximately 50% of children diagnosed with EA-TEF even after treatment with PPI or H2RA following initial surgery. A history of anastomotic leak and/or recurrent anastomotic strictures is associated with the occurrence of these complications. This highlights the importance of close and aggressive long-term follow-up in vulnerable/high-risk children at specialized multidisciplinary clinics with careful endoscopic and biopsy evaluation.

Conflict of Interest
None declared.

References