Prevalence of Barrett Esophagus in Adolescents and Young Adults With Esophageal Atresia

Anne Schneider, MD,† *Frédéric Gottrand, MD, PhD,** *Marc Bellaiche, MD,*‡ *François Becmeur, MD, PhD,*† *Alain Lachaux, MD, PhD,*§ *Laure Bridoux-Henno, MD,*¶ *Jean-Luc Michel, MD, PhD,*|| *Christophe Faure, MD, PhD,*** *Paul Philippe, MD,*†† *Yvan Vandenplas, MD, PhD,*‡‡ *Claire Dupont, MD,*§§ *Anne Breton, MD,*¶¶ *Jean Gaudin, MD,*|||| *Thierry Lamireau, MD, PhD,**** *Laurence Muyshont, MD,*††† *Guillaume Podevin, MD, PhD,*‡‡‡ *Sheila Viola, MD,*§§§ *Valérie Bertrand, MD,*¶¶¶ *Dominique Caldari, MD,*|||||| *Stéphanie Colinet, MD,***** *Catherine Wanty, MD,*†††† *Erik Sauleau, MD, PhD,*‡‡‡‡ *Emmanuelle Leteurtre, MD, PhD,*§§§§ *and Laurent Michaud, MD**

Objective: To study the prevalence of Barrett esophagus (BE) (gastric and/or intestinal metaplasia) in adolescents treated for esophageal atresia (EA).

Summary of Background Data: EA patients are at high risk of BE.

Methods: This multicenter prospective study included EA patients aged 15 to 19 years. All eligible patients were proposed an upper endoscopy with multistaged esophageal biopsies under general anesthesia. Histological suspicion of metaplasia was confirmed centrally.

Results: One hundred twenty patients [mean age, 16.5 years (±1.4)] were included; 70% had been treated for gastroesophageal reflux disease (GERD) during infancy. At evaluation, 8% were undernourished, 41% had received antireflux surgery, and 41% presented with GERD symptoms, although only 28% were receiving medical treatment. Esophagitis was found at endoscopy in 34% and confirmed at histology in 67%. BE was suspected after endoscopy in 37% and was confirmed by histology for 43% of patients (50 gastric and 1 intestinal metaplasia). No endoscopic or histological anomalies were found at the anastomosis site. BE was not significantly related to clinical symptoms. In multivariate analysis, BE was associated with EA without fistula ($P = 0.03$), previous multiple antireflux surgery ($P = 0.04$), esophageal dilation ($P = 0.04$), suspicion of BE at endoscopy ($P < 0.001$), and histological esophagitis ($P = 0.02$).

Conclusions: Patients with EA are at high risk of persistent GERD and BE. The development of BE is related to GERD history. Long-term systematic follow-up of the esophageal mucosa including multistaged biopsies is required, even in asymptomatic patients. (NCT02495051).

Keywords: Barrett metaplasia, esophageal atresia, esophageal carcinoma, esophagitis, gastroesophageal reflux

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The frequency of Barrett esophagus (BE) has increased in adults in the last decades because of increasing prevalence of gastroesophageal reflux disease (GERD) and obesity, and decreasing prevalence of *Helicobacter pylori* infection.[1] BE is rare in children, and the prevalence of intestinal metaplasia was recently estimated to be 0.12% in a population of non-GERD-predisposed children (without neurodevelopmental or tracheoesophageal abnormalities).[2] A meta-analysis of 4 cohort studies showed a prevalence of BE of 0.3% to 4.8% in a pediatric population with GERD.[3]

Esophageal atresia (EA), the most common congenital anomaly affecting the esophagus, predisposes the patient to severe and prolonged GERD, and the prevalence of mucosal esophagitis is as high as 90% in some series.[4] Because GERD plays a major role in the development of BE by causing repeated mucosal damage, development of BE is a concern even in children and young adults in this specific population. However, information about the prevalence of BE in the EA population is limited because few studies have been published. The few published studies have included limited numbers of patients and have not always included protocol biopsies, which has resulted in wide range of prevalence (5%–36%).[1]

The aim of our study was to assess the prevalence of BE (gastric and/or intestinal metaplasia) in a population of adolescents/young adults who had been treated for EA in early infancy. The secondary objectives were to study esophagitis and histological anomalies at the esophageal anastomosis level and the factors associated with BE in this patient group.

PATIENTS AND METHODS

This study was a noninterventional, multicenter, international (France, Belgium, Canada, and Luxembourg) prospective study running over a 3-year period. Patients were recruited in 20 centers that participated in the French-speaking Group of Gastroenterology, Hepatology, and Nutrition (GFHGNP) and/or were members of the

From the *Reference Center for Congenital and Malformative Esophageal Disorders, Hôpital Jeanne de Flandre, Lille; †Department of Pediatric Surgery, CHU, Strasbourg, France; ‡Department of Pediatric Gastroenterology, Hôpital Robert Debré, Paris, France; §Department of Pediatric Gastroenterology, HFME, Lyon, France; ¶Department of Pediatric Gastroenterology, CHU, Rennes, France; ||Department of Pediatric Surgery, CH Départemental Félix Guyon, Saint Denis-La Réunion, France; **Department of Pediatric Gastroenterology, Hôpital Mère-Enfants Ste Justine, Montréal, Canada; ††Pediatric Surgical Service, Centre Hospitalier de Luxembourg, Luxembourg, Grand-Duché du Luxembourg; ‡‡Department of Pediatric Gastroenterology, AZ VUB, Bruxelles, Belgium; §§Department of Pediatric Gastroenterology, CHU, Caen, France; ¶¶Department of Pediatric Gastroenterology, Hôpital des Enfants, Toulouse, France; ||||Department of Pediatric Surgery, CHU, Poitiers, France; ***Department of Pediatric Gastroenterology, Hôpital des Enfants, Bordeaux, France; †††Department of Pediatric Gastroenterology, HUDERF, Bruxelles, Belgium; ‡‡‡Department of Pediatric Surgery, CHU, Angers, France; §§§Department of Pediatric Gastroenterology, Hôpital Trousseau, Paris, France; ¶¶¶Department of Pediatrics, CH, Le Havre, France; ||||||Department of Pediatric Gastroenterology, HME CHU, Nantes, France; ****Department of Gastroenterology CHC, Liège, Belgium; ††††Department of Pediatric Gastroenterology and Hepatology, UCL, Cliniques Universitaires St Luc, Bruxelles, Belgium; ‡‡‡‡Public Health, Methods in Clinical Research Team, CHU, Strasbourg, France; and §§§§Centre Biologie Pathologie, Lille, France.

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Reprints: Anne Schneider, Reference Center for Congenital and Malformative Esophageal Disorders, Pediatric Gastroenterology Hepatology and Nutrition Unit, Jeanne de Flandre University Hospital, Faculty of Medicine, University Lille 2, Avenue Eugène Avinée, 59037 Lille Cedex, France. E-mail: schneider.an@orange.fr.

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EA national registry.[5] This study was approved by the regional ethical committee (CPP Nord Ouest) and declared to the National Informatics and Privacy Committee (CNIL) and the French Consultative Committee for Treatment of Information in Biomedical Research (CCTIRS). All patients and their parents signed an informed consent form.

The inclusion criteria were patients aged 15 to 19 years with medical history of EA except for those treated with esophageal replacement (eg, coloplasty, gastric transposition). Patients were selected from files of each participating center among all the EA pediatric population, even if they were asymptomatic. EA was classified according to Ladd classification.[6] All eligible patients received upper gastrointestinal endoscopy under general anesthesia with standardized esophageal staged biopsies. Following the French Society of Digestive Endoscopy guidelines, at least 12 biopsies were obtained as 4 quadrant biopsy specimens every 2 cm starting 1 cm from the Z-line, and 4 quadrant biopsy specimens at the anastomotic level[7]; biopsies were also obtained for any macroscopic lesions (Fig. 1). Depending on the equipment available at each center, endoscopic biopsies were guided using acetic acid staining (22% of patients) or electronic chromoendoscopy (25% of patients; 2/3 Narrow Band Imaging). Histological studies were performed at each participating center, and all cases of suspected metaplasia were confirmed centrally by the same expert gastrointestinal pathologist (Pr. E Leteurtre, Centre Biologie Pathologie, Lille, France).

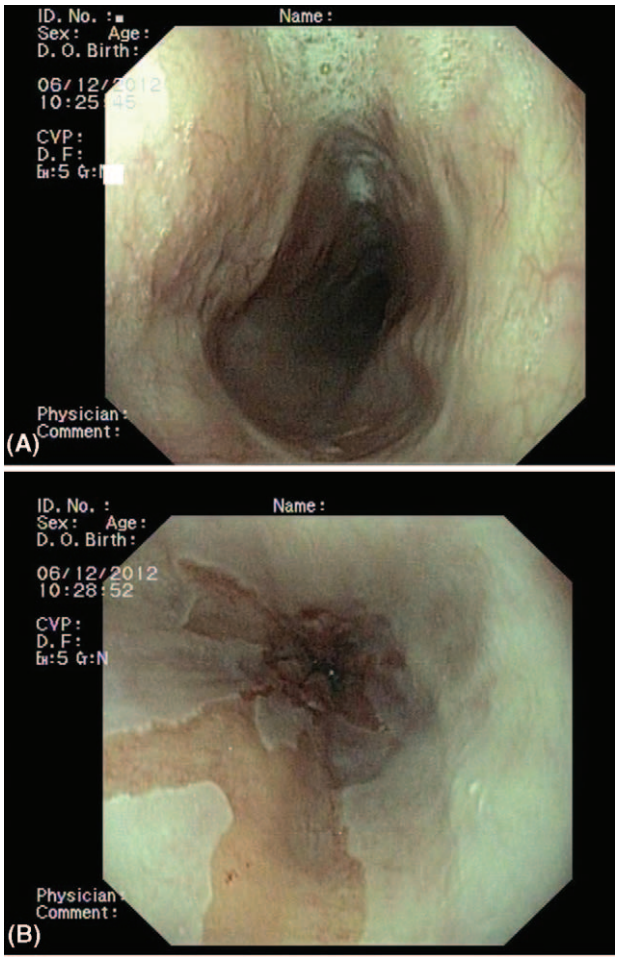

FIGURE 1. Endoscopic view of a normal anastomosis (A) and suspicion of esophageal metaplasia (acetic acid staining) (B), with gastric metaplasia confirmed by histology.

Standardized questionnaires were used to collect information about each patient's medical history, actual symptomatology, and the results of endoscopic studies and histological examination. A history of GERD was defined as the presence of symptoms of GERD (vomiting/regurgitation or extradigestive symptoms) and/or pH-metry-confirmed or endoscopically confirmed GERD in early infancy. Persistent GERD was defined as GERD that remained obvious after the age of 2 years. Systematic treatment of GERD was defined as treatment with a systematic proton pump inhibitor (PPI) after the initial surgery to prevent GERD until at least the age of 1 year.

Nutritional status was evaluated by the Z-score for weight/height. Undernutrition was defined as a Z-score for weight/height ≤ -2.0 standard deviations. At inclusion, the following symptoms were recorded: GERD symptoms (pyrosis and/or retrosternal pain); dysphagia (difficulties in swallowing, esophageal obstruction) with mild dysphagia as symptoms of dysphagia occurring <1/week; adaptive behaviors while eating (need to drink fluids during eating, avoidance of some types of food or eating slowly)[8]; and regular coughing.

Endoscopic esophagitis was defined using the Hetzel-Dent classification,[9] suspicion of BE was defined using the Prague classification,[10] and a long BE was defined as an extension of BE ≥ 3 cm above the Z-line.[7] Microscopic esophagitis was identified by neutrophil/eosinophil infiltration, basal cell hyperplasia, elongation of papillae, dilation of intercellular spaces, and necrosis/erosion.[11] Mild esophagitis was defined as esophagitis without necrosis or erosion. Suspicion of BE was defined endoscopically as pink mucosa >1 cm above the Z-line. BE was confirmed histologically as columnar epithelium of 3 types: cardiac-type mucosa, fundic-type mucosa, or intestinal metaplasia (with the presence of goblet cells).[11,12]

Statistical Analysis

Description of variables included the frequency of each variable for qualitative variables and the mean $\pm$ standard error for quantitative variables. Univariate statistical analyses were performed to compare 2 qualitative variables using Pearson χ^2 test after checking that the expected counts were large enough. Backward logistic regression was used for multivariate analysis and included all covariates significant at the 20% level in the chi-square analysis. The type I error was set at 5%.

RESULTS

One hundred twenty patients with a mean age of 16.5 years ($\pm$1.4) were included, 54% were males. EA types according to Ladd classification were distributed as 90% type III, 5% type I, and 5% type IV (Table 1).[6] The mean weight/height Z-score at the time of evaluation was 0.5 ($\pm$1.9), and 8% of patients were undernourished. A gastrostomy tube was required in 23% of the patients, and 2% of the total group still received complementary enteral nutrition at the time of inclusion.

The patients' medical histories revealed that 90% had had GERD during early infancy, although only 70% of the total group had been treated systematically with PPIs, and 71% had persistent GERD (Table 1). At inclusion, 41% of the patients complained of GERD symptoms, whereas only 28% of the total population was receiving PPI treatment. Antireflux surgery had been performed in 41% of the patients at a mean age of 2.7 years ($\pm$3.2); 80% had received a Nissen fundoplication, and 13% had repeated surgery. Esophageal dilation for esophageal stenosis had been performed in 46% of the patients. A mean of 4.2 dilations was performed per

TABLE 1. Characteristics of the Population Studied and Comparison Between Patients Presenting With and Without Histological Barrett Esophagus

	Total Population (n = 120)	BE^+ (n = 51)	BE^- (n = 69)	*P*	Multivariate Analysis
Sex male/female (%)	54/46	51/33	49/67	0.05	NS
EA type I/III (%)	5/90	83/41	17/59	0.05	OR 4.8 [95% CI: 1.2–20.2] $P = 0.03$
Initial GERD (%)	90	46	54	0.08	NS
Persistent GERD (%)	71	52	48	0.001	NS
Systematic GERD treatment (%)	70	45	55	0.04	NS
Actual GERD treatment (%)	28	70	30	<0.001	NS
Unique antireflux surgery (%)	35	55	45	0.001	OR 3.3 [95% CI: 1.1–10.1] $P = 0.04$
Repeat antireflux surgery (%)	5	100	0		
Esophageal dilation (%)	46	54	46	0.02	OR 4.4 [95% CI: 1.1–17.6] $P = 0.04$
Suspected endoscopic BE (%)	37	82	18	<0.001	OR 24.7 [95% CI: 5.5–111.0] $P < 0.001$
Long BE (%)	17	91	9	<0.001	NS
Histological esophagitis (%)	43	54	46	<0.001	OR 6.1 [95% CI: 1.4–26.8] $P = 0.02$

BE indicates Barrett esophagus; BE^-, patients presenting without histological BE; BE^+, patients presenting with histological BE; CI, confidence interval; EA, esophageal atresia; GERD, gastroesophageal reflux disease; NS, not significant; OR, odds ratio.

patient; 35% had a single dilation. The mean age at the first dilation was 4.7 years (±5.8). Only 3% had received mitomycin application for recurrent esophageal stenosis, and none had received a stent or local corticosteroid injection.

At inclusion, 58% of the patients complained of dysphagia, which was rated as mild for half of the patients. Fifty-two percent used adaptive behaviors while eating, and 40% complained of cough (half of them for >2 months/year). Twelve percent of this young adult population reported smoking.

All patients except 6 had received a minimum of 12 biopsies; for the 6 exceptions, no biopsies had been taken from the anastomosis. The mean number of biopsies per patient for the entire group was 11.8 biopsies. Endoscopic examination revealed esophagitis in 34% of patients, hiatal hernia in 8%, anastomotic stenosis in 3%, and suspected BE in 37%. Twenty patients (17%) had a long BE.

Histological analysis revealed that 67% of patients had esophagitis, which was mild in 89% of these patients. Histological analysis also confirmed BE in 43% of patients; there were 50 cases of gastric metaplasia, and 1 of intestinal metaplasia (Fig. 2). The distribution of histological types of metaplasia is reported in Figure 3. No histological anomalies were found at the esophageal anastomosis level.

A comparison of the characteristics of the patients having histological BE (n = 51) with those not having histological BE (n = 69) is summarized in Table 1. Significant independent factors associated with histological BE were EA without fistula, previous multiple antireflux surgery, esophageal dilation, histological esophagitis, and BE suspected after endoscopy. Surprisingly, no associations were found between BE and any clinical symptom.

DISCUSSION

In the present study, we defined BE as replacement of the squamous epithelium by columnar epithelium that is intestinal metaplasia positive or negative in the distal esophagus.[13] This definition is still controversial because some authors believe that gastric metaplasia is also a risk factor for carcinogenesis,[14–16] whereas others do not.[17] Using a combined immunohistochemical/histochemical method, Cabibi et al[18] showed that some immunophenotypic changes can be present despite the absence of goblet cells. A recent study of pediatric BE showed genetic markers in half of the 10 patients, and these markers were also identified in adult patients with Barrett adenocarcinoma.[19] EA patients are particularly at risk of long-term acid exposure, and the histological modifications of intestinal metaplasia are progressive.[20,21] Thus, we considered a columnar-lined esophagus without intestinal metaplasia as part of the BE definition.

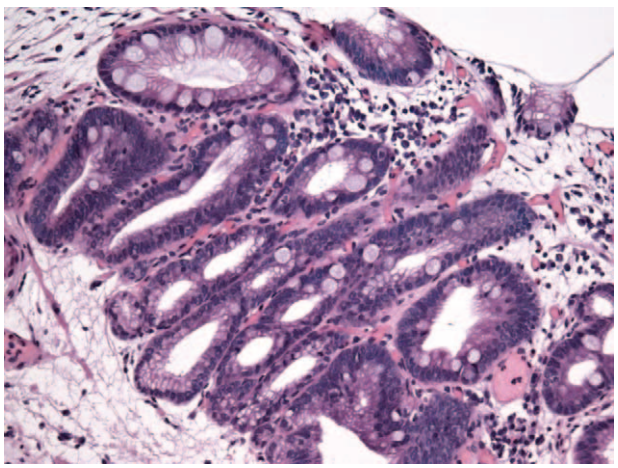

FIGURE 2. Histological aspects of intestinal metaplasia, characterized by goblet cells in a 17-year-old esophageal atresia patient (hematoxylin–eosin staining) (Pr. Leteurtre, Centre Biologie Pathologie, Lille, France).

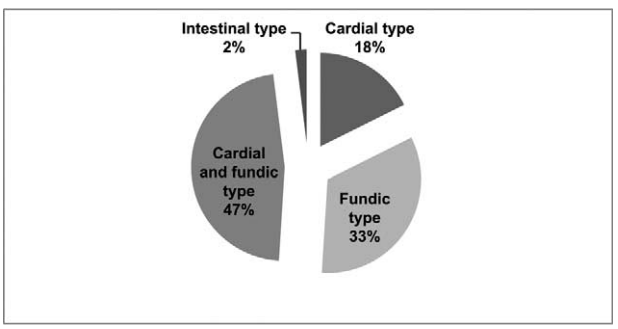

FIGURE 3. Histological types of Barrett esophagus in this esophageal atresia population.

TABLE 2. Prevalence of Barrett Esophagus in Esophageal Atresia Populations

Authors	Study Design	Patients Biopsied	Age at Biopsy (Years)	No. Biopsies/ Patient	Esophagitis	Metaplasia	Type of Metaplasia
Lindahl, 1993[14]	Prospective	37	7.6 (2–11)	MI	65%	3 (8%)	Gastric
Somppi, 1998[16]	Prospective	35	12.6 (3–30)	MI	57%	2 (6%)	Gastric
Krug, 1999[22]	Prospective	17	>18	MI	MI	2 (12%)	Intestinal
Deurloo, 2003[4]	Prospective	21	>25	MI	90%	1 (5%)	Intestinal
Deurloo, 2005[17]	Prospective	40	17 (10–26)	MI	75%	3 (8%)	Gastric
Taylor, 2007[25]	Retro/prospective	MI	33 (20–48)	MI	MI	7 (11%)	Intestinal
Castilloux, 2010[20]	Prospective	45	7.3 (0.4–17)	≥1	31%	16 (36%)	Gastric
Sistonen, 2010[23]	Prospective	101	36 (21–57)	MI	25%	21 (21%)	Gastric and intestinal (n = 6)
Burjonrappa, 2011[24]	Retrospective	38	6.6 (0.6–19)	MI	16%	12 (32%)	Gastric and intestinal (n = 1)
Maynard, 2013[8]	MI	41	18–44	MI	MI	15%	Intestinal

MI indicates missing information.

The prevalence of BE in EA populations varies widely and depends on several factors,[1] such as the number of esophageal biopsies, the characteristics of the population studied, and the definition of BE. The prevalence of BE has been reported to range from 5% to 36% (Table 2) and the prevalence of intestinal metaplasia as 0% to 3% in children and 5% to 15% in adults.[4,8,14,16,17,20,22–25] Sistonen et al[23] reported a 4-fold higher prevalence of BE among the adult population with a repaired EA compared with the general population. Our study found prevalence rates of 42% for gastric metaplasia and 1% for intestinal metaplasia in adolescents and young adults with a repaired EA. Ours is the largest series published, and it has several strengths. This was a prospective multicenter study designed to determine the prevalence of BE. More importantly, we used a standardized protocol of multistaged esophageal biopsies under general anesthesia, with exact descriptions of the landmarks, and we obtained at least 8 biopsies from each patient. Another strength is the centralized confirmation by an expert gastrointestinal pathologist for all metaplasia cases. To our knowledge, no other series used general anesthesia. Only 4 studies followed a biopsy protocol and only 1 included a minimum of 1 systematic biopsy[20]; the other studies did not report the precise number of biopsies.[17,23,24] It is recognized that the diagnosis of BE increases with the number of biopsies performed;[14,25] this may explain the higher frequency of BE diagnosed in our series than in previous studies.

EA is a risk factor for the development of BE.[1] GERD, which occurs frequently and may be prolonged in EA patients, probably plays a major role in the development of BE by causing repeated mucosal damage. Our study confirms the key role of GERD in BE in EA because all of the significant independent factors associated with histological BE are related to GERD: peptic esophagitis; previous multiple antireflux surgery, which probably reflects more aggressive and resistant GERD; type I EA, which is associated with a higher frequency of GERD and aggressive than in type III; and esophageal dilation, which is also associated with GERD.[26] As described previously in an adult population with severe GERD, Nissen fundoplication is not beneficial and should not be considered for the treatment of BE or for the prevention of dysplasia progression.[27,28] Our study is the first to show that Nissen fundoplication does not prevent BE in EA patients.

Progression to esophageal adenocarcinoma has been reported rarely in association with BE in patients with EA, and only 3 clinical cases have been reported.[29–31] Our results showing a high frequency of BE in this young population must be considered. The first successful operation for EA was reported in the late 1950s. Because of the marked improvements in the prognosis for EA (<5% mortality),[6] most patients with EA now reach adulthood and are thought to have a long life expectancy. It is expected that the population of adults with EA will increase markedly in the coming years. Clinicians should consider the fact that the risk of Barrett adenocarcinoma increases with age and that there is a high mortality associated with esophageal cancer (13% 5-year survival rate).[1]

The choice of endoscopy protocol is critical for the proper diagnosis of BE. We found in the present study that suspicion of esophageal metaplasia after endoscopy is a strong predictor of histological BE (25-fold higher risk) if the protocol is standardized using specific criteria,[10] using staining (eg, acetic acid) and/or magnification endoscopy (eg, color enhancement, zoom, chromoendoscopy), and under specific conditions (eg, general anesthesia).

Another important finding from our study is that no specific symptoms were associated with BE, as has been shown in adult populations without EA.[13,14,17,20] This is particularly true for EA patients because they have had abnormal esophageal function since birth and, therefore, probably do not recognize symptoms[8] and develop adaptive feeding behaviors with time. Because of the patchy presentation of BE, multistaged biopsies (≥8) should be taken at 4 quadrants every 2 cm above the gastroesophageal junction. In 2007, Taylor et al[25] proposed recommendations for the long-term follow-up of EA patients; these included a clinical assessment between the ages of 15 and 25 years with upper endoscopy only if reflux symptoms or dysphagia occured. The results of our study contradict this recommendation and strongly support the idea that systematic upper GI endoscopy and multistaged biopsies should be performed before the transition to adulthood in all patients with EA, even if asymptomatic. If no BE is found, endoscopy should be repeated every 5 to 10 years through adulthood. If BE is present, endoscopy surveillance should be repeated every 3 years if no dysplasia is found but twice a year in patients with dysplasia, after the recommendation for BE in adult patients.[1]

Finally, to our knowledge, this is the first study to report on the histological changes at the site of the esophageal anastomosis. Although 6 cases of epidermoid carcinoma have been reported in 45-year-old patients with EA,[32–34] none of our patients presented with inflammation or metaplasia at the anastomosis.

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