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DISEASES OF THE ESOPHAGUS

Original article

Detailed esophageal function and morphological analysis shows high prevalence of gastroesophageal reflux disease and Barrett's esophagus in patients with cervical inlet patch

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SUMMARY. **Although the pathogenesis of cervical inlet patch (CIP) is not fully understood, most authors consider it as a congenital abnormality, whereas others surmise it to be related to gastroesophageal reflux disease (GERD). We aimed to evaluate esophageal function and the prevalence of GERD and Barrett's esophagus in patients with CIP. GERD is defined by the presence of erosive esophagitis or an abnormal pH monitoring. Seventy-one consecutive patients with endoscopic and histological evidence of CIP were prospectively evaluated. Esophageal symptom analysis, 24-hour simultaneous biliary reflux and double-channel pH-monitoring, and esophageal manometry were carried out in 65/71 (92%) patients and in 25 matched controls. Six patients were not suitable for testing and were, therefore, excluded. The histological evaluation of the heterotopic islands showed cardia and/or oxyntic mucosa in 64/65 (98%) patients and specialized intestinal metaplasia (SIM) in one patient (2%). The cardia and/or oxyntic mucosa was accompanied by focally appearing pancreatic acinar metaplasia and pancreatic ductal metaplasia in 7/64 (11%) and in 1/64 (2%), superficial mucous glands in 6/64 (9%), and SIM in 2/64 (3%) cases. In total, SIM was present in three patients (5%), and one of them had low-grade dysplasia. At the gastroesophageal junction, 28 (43%) patients had columnar metaplasia, including nine (14%) patients with SIM. Erosive esophagitis was present in 37 (57%) cases. Thirty-two patients (49%) had abnormal acid reflux in the distal and 25 (38%) in the proximal esophagus. Abnormal biliary reflux was present in 25 (38%) cases. On the basis of endoscopic and pH studies, GERD was established in 44/65 (68%) patients. Typical reflux symptoms were common (33/65, 51%). The combined 24-hour biliary and double-channel pH-monitoring detected significantly more significant acidic reflux at both measurement points and significantly longer bile exposure time in the distal esophagus in patients with CIP. Acid secretion in the CIP was detected in three (5%) cases. Esophageal manometry revealed decreased LES pressure and prolonged relaxation with decreased peristaltic wave amplitude, and an increased number of simultaneous contractions in the esophageal body. The detailed evaluation of the esophageal morphology and function in subjects with CIP showed a high prevalence of GERD and Barrett's esophagus. Further studies are needed to evaluate whether combined acidic and biliary reflux is able to promote similar histomorphological changes in the CIP, as it is shown distally in patients with Barrett's esophagus.**

KEY WORDS: **Barrett's esophagus, cervical inlet patch, gastroesophageal reflux disease.**

INTRODUCTION

A cervical inlet patch (CIP) is a heterotopic columnar mucosal island in the cervical esophagus. Currently, most authors consider it a congenital abnormality; however, others suspect that it has a common pathogenesis with Barrett's esophagus and it is related to gastroesophageal reflux disease (GERD).[1] Recently, Meining and Bajbouj published a new theory according to which a CIP may develop from mucus gland cysts of the cervical esophagus after eruption.[2] The detection of CIP is difficult and highly dependent on the endoscopist.[3] Consequently, its prevalence varies between 0.1 and 10% in the literature.[4–6] The clinical significance of CIP is still largely unknown because

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most studies evaluated a small series of patients and the available data are almost exclusively restricted to the endoscopic and histological description of this entity.

Therefore, in the present study, we set out to evaluate the esophageal function in patients with a CIP and to investigate its relationship to GERD and Barrett's esophagus.

PATIENTS AND METHODS

In January 2006, we launched a prospective study to evaluate the esophageal function in patients with CIP. Until June 2009, 11,700 consecutive patients with various gastrointestinal symptoms underwent upper gastrointestinal endoscopy at the endoscopy unit of our institution. Endoscopists were aware of the study but were not instructed to pay a special attention in looking for CIP. Seventy-one (0.6%) of these patients (41 males, 30 females, mean age: 49 [23–77] years, mean body mass index [BMI] 26.1 [17.0–46.2]) had histologically confirmed endoscopic evidence of CIP. In 65 of these patients, esophageal function tests (esophageal manometry and 24-hour double-channel pH-metry combined with biliary reflux monitoring) and esophageal symptom screening were carried out. Six patients (four males, two females) were not suitable for the evaluation of esophageal function and were, therefore, excluded from further studies: two patients with Los Angeles grade D (LA-D) esophagitis had severe peptic esophageal stricture, one with LA-A esophagitis had a large Zenker's diverticulum, one had previous corrosive injury (lye ingestion in childhood) and subsequent multiple stricture formation, one had advanced lung cancer, and one had advanced pancreatic cancer. These patients had cardia/oxyntic type metaplasia in the CIP without other metaplasia or dysplasia. Five had single and one double patch. The size of the patch was <10 mm in three, 10–20 mm in two, and >20 mm in one patient.

An age-, sex-, and BMI-matched group of 25 subjects without CIP and without any other esophageal disease or symptom were evaluated as controls (males: 14, females: 11, mean age: 48 [25–71] years, BMI: 25.8 [18.9–36.0]). During the course of esophageal function testing, all conflicting drugs were stopped appropriately. Proton pump inhibitors were stopped 7 days before testing, whereas other drugs affecting gastrointestinal motility, acid secretion, or visceral sensitivity were suspended 72 hours before evaluation. The study protocol was approved by the Medical Ethics Committee of the University of Szeged.

Esophageal symptom analysis

Patients were asked to complete a standardized questionnaire[7] regarding their symptoms related to GERD, such as heartburn, chest pain, gastroesophageal acid regurgitation, dysphagia, globus sensation, coughing, and wheezing. Smoking habits and alcohol and coffee consumption were also recorded.

Upper gastrointestinal endoscopy and histological evaluation

The presence and the severity of esophagitis were assessed by upper gastrointestinal endoscopy (Olympus Q130, Q160, GIF-FQ 260Z) on the basis of the LA classification.[8] The histological evaluation consisted of standard hematoxylin-eosin, Giemsa, and periodic acid Schiff-Alcian blue (pH = 2.5) stainings. The counterparts of columnar metaplasia were divided into cardiac, fundus (oxyntic), oxyntocardiac, and specialized intestinal ones. Furthermore, other associated columnar mucosa was also noted as pancreatic acinar metaplasia (PAM) and pancreatic ductal cell metaplasia (PDM), together with superficial mucous glands within the metaplastic area. Histologically, superficial mucous glands are located beneath the foveolar epithelium. Although they may resemble to cardiac glands, their cytoplasm contains more translucent, mainly neutral mucin reminiscent of ulcer-associated cell lineage, or of 'pseudopyloric' metaplasia. Moreover, superficial mucous glands are arranged in a typical back-to-back architecture in the lamina propria, and they never reach the luminal surface. If dysplasia was suspected further, immunohistochemical investigation was performed using p53 (clone Do7, Labvision Corporation, Fremont, CA, USA) and Ki67 (clone B56, Histopathology Ltd., Budapest, Hungary) antibodies to minimize the interobserver variation.

24-hour double-channel intraesophageal pH-monitoring with simultaneous biliary reflux monitoring

The 24-hour intraesophageal pH-monitoring studies was carried out on an inpatient basis using the classical DeMeester criteria.[9,10] Both biliary reflux values and proximal pH results were considered abnormal in accordance with Cool's criteria.[11] After an overnight fasting period, a double-channel, nasoesophageal, antimony pH-probe (Synectics Medical, Stockholm, Sweden) was positioned. The pH sensors were located at 5 and 20 cm above the LES and were connected to a portable data logger (Digitrapper pH, Synectics Medical). A computer-assisted data analysis was carried out with the Polygram for Windows 98 software supplied by Synectics Medical. The following parameters such as the number of pH < 4 episodes, the percentage of the time below pH 4, the number of pH < 4 episodes longer than 5 minutes, and the longest pH < 4 episode were recorded during the full length of the study and were evaluated separately in

the upright, supine, and postprandial (120 minutes) periods. The DeMeester score was also calculated. For the biliary reflux monitoring, a fiber-optic probe was positioned 5 cm above the LES and was connected to a portable data logger (Bilitec 2000, Synectics Medical). Optical density (OD) was measured at 540 nm wavelength. Parameters such as the number of OD > 0.14 episodes, the percentage of the time above OD 0.14, the number of OD > 0.14 episodes longer than 5 minutes, and the longest OD > 0.14 episode were recorded during the full length of the study and were evaluated separately in the upright, supine, and postprandial (120 minutes) periods. During pH and biliary reflux monitoring, patients were on a standard diet. To rule out food-induced artifacts during biliary reflux monitoring, all reflux episodes that started during meals were excluded, and foods that may cause color interference were not allowed.

Esophageal manometry

Esophageal motility was studied by standard water-perfused stationary manometry (Polygraph HR, Synectics Medical) with computer-assisted analysis of the tracings (Polygram 5.06C2, Synectics Medical) according to our previously published protocol. Briefly, after an overnight fasting period, a nasoesophageal probe was introduced. The station pull-through technique was applied, and measurements were made at the levels of the LES, the esophageal body, the upper esophageal sphincter, and the pharynx on the basis of Castell's criteria.[12,13]

Statistical analysis

For statistical analysis, the GraphPad Prism 4.0 software (GraphPad, La Jolla, CA, USA) was used. Group means were compared by Student's unpaired *t*-test, with the Welch's correction if the variances were different. The level of significance was set at $P < 0.05$.

RESULTS

The morphological evaluation of the heterotopic mucosal islands showed that 47 (72%) patients had single, 14 (22%) had double, and 4 (6%) had triple mucosal patches. The size of the patches varied between 2 mm and 30 mm: <10 mm: 22/65 (31%), 10–20 mm: 37/65 (57%), >20 mm: 6/65 (9%). The dominant histological structure was cardia and/or oxyntic type mucosa (COM) in 64/65 (98%) patients, whereas one (2%) patient had specialized intestinal metaplasia (SIM). This latter patient had long-segment Barrett's esophagus as well in the distal part of the esophagus. In patients with COM-type patches, the dominant histological pattern was accompanied by focally appearing PAM and PDM metaplasia in 7/64 (11%) and in 1/64 (2%), superficial mucous glands in 6/64 (9%), and SIM in 2/64 (3%) cases. In total, SIM was present in 3/65 patients (5%), and one of them had low-grade dysplasia. High-grade dysplasia or invasive adenocarcinoma was not observed in the heterotopic mucosal patches of our patients.

Upper gastrointestinal endoscopy showed erosive esophagitis in the distal esophagus in 37/65 (57%) cases (LA-A: 14/65 [21%], LA-B: 12/65 [18%], LA-C: 8/65 [12%], LA-D: 3/65 [5%]), whereas the mucosa was macroscopically intact in 28/65 (43%) subjects. Axial hiatal hernia was seen in 29/65 (45%) patients, with a size range of 2–7 cm.

In the distal esophagus, 28/65 (43%) patients had columnar metaplasia. Sixteen of them (16/65, 25%) had COM alone, and 4/65 (6%) had SIM alone. The remaining 8/65 (12%) patients had predominantly COM in the distal esophagus with focally present SIM in five, PAM in four, superficial mucous glands in three cases, and PDM in one patient. Low-grade dysplasia was observed in three of the nine (33%) patients with SIM and in none of the patients without SIM. Neither high-grade dysplasia nor invasive adenocarcinoma was observed in the metaplastic mucosa of the distal esophagus. The mean length of columnar metaplasia in the distal esophagus was 1.0 (0.5–1.5) cm in patients with COM and 5.5 (0.5–17.0) cm in patients with SIM.

Clinical symptom analysis was carried out in 65 patients who underwent the esophageal function tests. Twenty-five of them (25/65, 38%) were either completely free of the evaluated esophageal and extra-esophageal symptoms (10/65, 15%) or had such symptoms less than once a week (15/65, 23%). Forty patients (40/65, 62%) had symptoms occurring at least once a week. These were predominantly heartburn and/or acid regurgitation reported by 33/65 (51%) patients, whereas other symptoms such as chest pain, chronic cough, asthmatic wheezing, dysphagia, or globus sensation were less frequently observed (Table 1). The number of abstinent patients (smoking, and alcohol and coffee consumption) was 47/65 (72%), 37/65 (57%), and 29/65 (45%), respectively.

Table 1 Prevalence of esophageal and extraesophageal symptoms occurring at least once a week in patients with cervical inlet patch

Symptom	Prevalence
Heartburn	22/65 (31%)
Acid regurgitation	22/65 (31%)
Heartburn or acid regurgitation	33/65 (51%)
Chest pain	16/65 (25%)
Cough	9/65 (14%)
Asthma/wheezing	6/65 (9%)
Dysphagia	11/65 (17%)
Globus sensation	4/54 (6%)

The manometry of the LES showed significantly decreased pressure, length, and abdominal length in patients with CIP, whereas the relaxation time was significantly longer compared with controls. In the esophageal body, the amplitudes of peristaltic waves were decreased, and the number of simultaneous contractions was increased compared with controls. The duration, the propagation velocity of the esophageal body contractions, and the studied parameters of the upper esophageal sphincter region were similar (Table 2).

The 24-hour combined biliary reflux and double-channel pH-monitoring revealed that patients with CIP had significantly more distal and proximal acidic reflux than controls. During biliary reflux monitoring, the number of reflux episodes was similar, but patients with CIP had significantly longer bile exposure time in the esophagus (Table 3). According to the internationally accepted normal values, abnormal acidic reflux was observed in the distal esophagus in 32/65 (49%) patients. Abnormal proximal acidic reflux was detected in 25/65 (38%) cases. Abnormal biliary reflux was found in 25/65 (38%) cases. Combined abnormal biliary and acidic reflux was observed in 16/65 (25%) patients. On the other hand, 14/65 (21%) patients had no proximal reflux at all. Ten of them had normal distal pH profiles as well, with the highest DeMeester score of 6.5. Furthermore, 9 of these 10 patients had normal parameters on biliary reflux monitoring as well.

When combining the results of endoscopy and pH-monitoring, abnormal acid exposure was found in the distal esophagus in 6/28 (21%) patients without esophagitis, whereas it was 7/14 (50%), 8/12 (75%), 8/8 (100%), and 3/3 (100%) in patients with LA-A, LA-B, LA-C, and LA-D esophagitis, respectively. Eleven of the 33 patients (33%) with normal pH-monitoring had erosions in the distal esophagus: 7/11 LA-A, 4/11 LA-B. However, 44/65 (68%) patients had GERD, based on the abnormal results of endoscopy or pH-monitoring.

Temporary acid secretion of the heterotopic mucosa was proved only in 3/65 (5%) cases.

Gastrointestinal diseases other than GERD and Barrett's esophagus were infrequent in our patients with CIP. *Helicobacter pylori*-positive gastritis was found in 11/65 (15%); none of them had colonization of the bacterium in the heterotopic mucosa. We also diagnosed celiac disease in two patients and Crohn's disease in one.

DISCUSSION

Although, recently, a number of papers were published on the clinical significance of CIPs, a detailed prospective analysis of the esophageal function of such patients has not been carried out yet. Moreover, most studies evaluated a relatively low number of patients. To our knowledge, our study is the largest in

Table 2 Manometric assessment of the esophageal function in patients with cervical inlet patch (mean ± SEM)

Patient group	CIP (n = 65)		Controls (n = 25)		P	
LES						
Pressure (mmHg)†	14.1 ± 0.9		26.8 ± 1.7		<0.001	
Relaxation time (second)	10.9 ± 0.3		8.7 ± 0.3		<0.001	
Length (cm)	3.2 ± 0.1		4.8 ± 0.2		<0.001	
Abdominal length (cm)	1.4 ± 0.2		3.3 ± 0.2		<0.001	
	DS	WS	DS	WS	DS	WS
EB peristaltic wave						
Amplitude at						
3 cm	56 ± 5	84 ± 5	83 ± 8	116 ± 6	<0.01	<0.001
8 cm	46 ± 3	78 ± 5	68 ± 8	101 ± 6	<0.02	<0.01
13 cm	34 ± 3	50 ± 5	51 ± 5	69 ± 6	<0.01	<0.02
18 cm	32 ± 4	44 ± 4	50 ± 9	57 ± 7	=0.06	=0.07
Above the LES (mmHg)						
Duration at						
3 cm	3.6 ± 0.1	3.6 ± 0.1	3.7 ± 0.2	3.8 ± 0.2	ns	ns
8 cm	3.2 ± 0.1	3.5 ± 0.1	3.4 ± 0.2	3.5 ± 0.2	ns	ns
13 cm	3.0 ± 0.1	3.0 ± 0.1	3.3 ± 0.2	3.1 ± 0.1	ns	ns
18 cm	2.7 ± 0.1	2.6 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	ns	ns
Above the LES (second)						
Propagation velocity (cm/s)	3.6 ± 0.1	3.2 ± 0.2	3.9 ± 0.2	3.3 ± 0.1	ns	ns
Simultaneous contractions (%)	10 ± 2	4 ± 1	3 ± 2	1 ± 1	<0.05	<0.05
UES						
Pressure (mmHg)†	63 ± 3		71 ± 6		ns	
Relaxation time (second)	1.1 ± 0.1		1.2 ± 0. 1		ns	
PHX						
Contraction amplitude (mmHg)	38 ± 15		39 ± 16		ns	

†Mean pressure at the high pressure zone of the sphincter. CIP, cervical inlet patch; DS, dry swallow; EB, esophageal body; ns, not significant; PHX, pharynx; UES, upper esophageal sphincter; WS, wet swallow.

Table 3 Results of simultaneous biliary reflux and double-channel esophageal pH-monitoring in patients with cervical inlet patch (mean ± SEM)

Patient group	CIP ($n = 65$)	Control ($n = 25$)	P
pH – 20 cm above the LES			
Number of pH < 4 episodes, 24 hours	14 ± 3	4 ± 1	<0.01
Upright	12 ± 2	4 ± 1	<0.01
Supine	1.3 ± 0.6	0.1 ± 0.1	<0.05
Postprandial	9 ± 2	3 ± 1	<0.01
>5 minutes, 24 hours	0.33 ± 0.15	0.04 ± 0.04	<0.05
Longest episode (minutes)	2.2 ± 0.5	0.6 ± 0.2	<0.01
Fraction time pH < 4, 24 hours (%)	0.5 ± 0.1	0.1 ± 0.1	<0.01
Upright (%)	0.8 ± 0.2	0.3 ± 0.1	<0.01
Supine (%)	0.12 ± 0.06	0.01 ± 0.01	<0.05
Postprandial (%)	1.3 ± 0.3	0.5 ± 0.2	<0.05
pH – 5 cm above the LES			
Number of pH < 4 episodes, 24 hours	79 ± 8	38 ± 7	<0.01
Upright	65 ± 7	32 ± 6	<0.01
Supine	13.4 ± 2.7	5.2 ± 1.5	<0.01
Postprandial	46 ± 5	22 ± 5	<0.01
>5 minutes, 24 hours	2.33 ± 0.57	0.60 ± 0.26	<0.01
Longest episode (minutes)	13.8 ± 4.6	4.2 ± 1.0	<0.05
Fraction time pH < 4, 24 hours (%)	5.3 ± 1.1	1.7 ± 0.4	<0.01
Upright (%)	6.7 ± 1.1	2.4 ± 0.6	<0.01
Supine (%)	3.61 ± 1.22	0.63 ± 0.27	<0.02
Postprandial (%)	11.2 ± 1.9	4.7 ± 1.3	<0.01
DeMeester score	20.5 ± 3.4	7.5 ± 1.4	<0.01
Bile – 5 cm above the LES			
Number of OD > 0.14 episodes, 24 hours	13 ± 3	9 ± 2	ns
Upright	10 ± 2	7 ± 2	ns
Supine	3.2 ± 1.0	1.6 ± 0.5	ns
Postprandial	5 ± 1	3 ± 1	ns
>5 minutes, 24 hours	2.70 ± 0.54	1.40 ± 0.29	<0.05
Longest episode (minutes)	58.2 ± 18.1	18.8 ± 4.3	<0.05
Fraction time OD > 0.14, 24 hours (%)	8.4 ± 2.4	2.4 ± 0.5	<0.02
Upright (%)	7.1 ± 1.8	3.2 ± 0.8	<0.05
Supine (%)	10.03 ± 3.63	1.21 ± 0.63	<0.02
Postprandial (%)	7.0 ± 2.1	3.1 ± 1.2	ns

CIP, cervical inlet patch; ns, not significant.

the literature. Studies evaluating the prevalence of CIP[4–6] reported a large variance (<0.1–10%). This is generally explained by the difficulty of endoscopic detection. Because the heterotopic columnar mucosal patch is usually located immediately below the upper esophageal sphincter, it is easily overlooked by the endoscopist if the withdrawal of the endoscope is not careful enough.[3] The primary purpose of the present study was not to collect epidemiological data on the prevalence of CIP in the population; accordingly, the endoscopists were not called upon or instructed to search for CIP during routine endoscopies. This may contribute to the relatively low prevalence rate observed in this study. Although the value of new endoscopic techniques[14] such as narrow band imaging has not been tested yet for the detection of CIP, to our knowledge, our unpublished initial experience with these endoscopic modalities indicate that such contrast enhancement techniques can facilitate the recognition of these lesions. Consequently these techniques may help to provide more precise patient selection for studies carried out in patients with CIP and a better estimation of its prevalence. The histological structure of these mucosal patches is usually oxyntic mucosa. There are only few reports available on other glandular structures, such as intestinal metaplasia.[15–17] In our series, we found two cases with SIM and one with low-grade dysplasia. Furthermore, we observed other metaplastic tissues, such as PAM and PDM, and superficial mucous glands in our patients. The latter can be differentiated from cardiac glands by its histomorphology, and it has not been reported yet in this location by other authors. *Helicobacter pylori* colonization in the heterotopic mucosa is mainly considered as part of *Helicobacter*-positive gastritis; however, its prevalence is different in the conducted studies.[18–20] We observed a relatively low prevalence of *Helicobacter*-positive gastritis, and none of the patients had *Helicobacter* colonization in the heterotopic mucosa.

Regarding the clinical symptom spectrum, dysphagia and globus sensation are considered as major symptoms associated with CIP.[21–25] Others reported significant respiratory symptoms as well.[26,27] These symptoms were commonly observed in our patients but were less frequent than typical symptoms of GERD, such as heartburn and acid regurgitation. Similarly to the observation of Baudet *et al.*,[21] such symptoms were present at least weekly only in one-fourth of our patients. Furthermore, the prevalence

of heartburn was also similar to their value (28%). On the other hand, acid regurgitation was common; hence, 50% of our patients had at least weekly occurring symptoms typical of GERD. Although there are data suggesting that the eradication of the CIP may improve symptoms located at the level of the throat, the pharynx, or the proximal esophagus,[23] we are of the opinion that further prospective studies with longer follow-up periods are needed to rule out the role of GERD or functional diseases in the generation of such symptoms.

The relationship between CIP and GERD or Barrett's esophagus is controversial in the literature. On the basis of case reports – as adenocarcinoma may develop from the heterotopic columnar mucosa – some authors suspect the role of proximal gastroesophageal reflux in the pathogenesis of this lesion. However, it should be noted that still less than 30 cases of proximal esophageal adenocarcinoma have been reported in the literature.[28] The similarities between cytokeratin and mucin core protein expression in patients with CIP and Barrett's esophagus established by Lauwers *et al*.[29] may support the possibility of 'de novo' development of heterotopic columnar mucosal patches in the cervical esophagus. The other theory considers CIP as a congenital lesion – similarly to other heterotopic gastric mucosal patches[30] – and says that such patients have a higher risk of developing GERD and Barrett's esophagus. Avidan *et al*.[31] conducted an epidemiological study and found an increased prevalence of GERD and Barrett's esophagus in patients with CIP. Although our results may not end this debate, the prevalence of GERD symptoms was higher compared with the data obtained in the general population.[32,33] Hiatal hernia and endoscopic signs of GERD such as erosive esophagitis were common, similar to the observation of Baudet *et al*.[21] Furthermore, the prevalence of columnar metaplasia in the distal esophagus was also high (13% SIM, 27% other). Esophageal function analysis proved a significantly higher acidic and biliary exposure of the esophagus in patients with CIP compared with age-, sex-, and BMI-matched controls. Manometric evaluation showed alterations of the LES and esophageal body function, which may predispose the patients to gastroesophageal reflux. On the other hand, pathological proximal reflux was not frequent enough to be a real cause of the development of CIP. Only 38% of the cases had abnormal acid exposure in the proximal esophagus, and the majority of them only slightly exceeded the upper limit of the internationally accepted normal values. Although it is not known how much acidic (and/or biliary) reflux would be necessary to induce metaplastic transformation in the mucosa of the proximal esophagus, patients with Barrett's esophagus, where a real metaplastic process is suspected, generally have more severe acidic and biliary reflux.[34,35] On the basis of these findings, it would be interesting to examine what other abnormalities may be related to this small congenital lesion during the ontogenesis of the esophagus that may consequently predispose these patients to GERD.

The need for follow-up in patients with CIP is also questionable. It is known that the lesion is generally benign, as only a small number of malignant transformations have been reported in the literature, and to date, there has only been one patient with SIM and high-grade dysplasia in the CIP.[17] In contrast, we do not know what degree of acid and/or bile exposure may induce inflammation and cell proliferation at the esophageal inlet and what factors can promote or inhibit this process.

Besides these theories, an interesting new pathophysiological hypothesis was published by Meining and Bajbouj recently.[2] According to their concept, the variability in the macroscopic appearance of the patches and in the onset of clinical symptoms may not be explained by the embryological origin of this lesion. They proposed that CIPs are erupted cysts developing from occluded proximal esophageal glands. Our results failed to provide a good support for this new hypothesis, because our patients were commonly free of symptoms related to the throat, the pharynx, or the proximal esophagus. This may indicate that if they ever had a cyst, it was also asymptomatic. Despite these results, we agree that further studies are needed to test this theory.

Acid secretion in the heterotopic glandular mucosa is another interesting question. Although some authors highlight on this,[21,36] we found only three cases (5%) in whom the proximal pH drop was not preceded by a distal reflux episode. Taking into account that pH probes can not always be positioned accurately at the level of the heterotopic islands – especially if they are smaller than 1 cm and the proximal pH sensor is fixed at 15 cm above the distal one – it is not surprising that we found such a low prevalence of this. Furthermore, the acid production of these patches compared with the volume of saliva swallowed is probably not enough to produce a significant drop in the pH (to pH < 4).

Regarding gastrointestinal comorbidities, the observed disorders were all infrequent and probably accidental.

CONCLUSIONS

The detailed evaluation of the esophageal morphology and function in subjects with CIP showed a high prevalence of GERD and Barrett's esophagus. Further studies are needed to evaluate whether combined acidic and biliary reflux is able to promote similar histomorphological changes in the CIP, as it is shown distally in patients with Barrett's esophagus.

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