Low prevalence of Barrett’s esophagus in a risk area for esophageal cancer in South of Brazil

Diego Michelon DE CARLI¹, Amanda Faria de ARAUJO² and Renato Borges FAGUNDES¹,²,³,⁴

ABSTRACT – Background – Barrett’s esophagus is a complication of gastroesophageal reflux disease (GERD) that is a precursor of esophageal adenocarcinoma. The incidence of esophageal adenocarcinoma has been increasing in most Western countries. Rio Grande do Sul (RS), the Southernmost state of Brazil has the highest rates of esophageal cancer with low prevalence of esophageal adenocarcinoma. Objective – To investigate the prevalence of Barrett’s esophagus among patients underwent to upper gastrointestinal endoscopy in the last 5 years. Methods – The records of patients underwent upper gastrointestinal endoscopy between 2011 and 2015 were analyzed. Demographic data, GERD symptoms, endoscopic findings, extension and histological diagnosis of columnar epithelium of the esophagus were recorded. Significance among the variables was accessed by chi-square test and Fisher’s exact test with 95% CI. Results – A total of 5996 patients underwent to upper gastrointestinal endoscopy in the period were included. A total of 1769 (30%) patients with GERD symptoms or esophagitis and 107 (1.8%) with columnar lined esophagus were identified. Except for eight patients, the others with columnar lined esophagus had GERD symptoms or esophagitis. Barrett’s esophagus defined by the presence of intestinal metaplasia occurred in 47 patients; 20 (43%) with segments over 3 cm and 27 (57%) with segments shorter than 3 cm. The global prevalence of Barrett’s esophagus was 0.7% and in GERD patients 2.7%. The odds ratio for the occurrence of columnar lined esophagus in patients with GERD was 30 (95%CI=15.37-63.34). The odds ratio for the presence of intestinal metaplasia in long segments was 8 (95%CI=2.83-23.21). Conclusion – GERD patients had a risk 30-folds greater to present columnar lined esophagus than patients without GERD symptoms. Long segments of columnar lined esophagus, had a risk eight-folds higher to have Barrett’s esophagus than short segments. Barrett’s esophagus overall prevalence was 0.7%. In GERD patients, the prevalence was 2.7%. Long Barrett’s esophagus represented globally 0.3% and 1.1% in GERD patients.


INTRODUCTION

Barrett’s esophagus (BE) is a complication of gastroesophageal reflux disease (GERD) characterized by the replacement of squamous epithelium of the distal esophagus with columnar epithelium¹,². Diagnostic criteria for BE all over the world, except in the Great Britain and Japan, include the presence of intestinal metaplasia with goblet cells³,⁴. Barrett’s esophagus is considered a precursor of esophageal adenocarcinoma which incidence has been increasing in the last years, mainly in the USA, Europe, and Asia⁵,⁶,⁷,⁸,¹⁰,¹¹,¹². Rio Grande do Sul (RS), the Southernmost state of Brazil has the highest rates of esophageal cancer in the country. Squamous cell carcinoma is the main histological type, while adenocarcinoma prevalence is low⁶. On the other hand, despite RS shows a high prevalence of GERD symptoms⁵,¹³, data on the occurrence of BE is scarce. There is only one study that identified intestinal metaplasia in the distal esophagus in 29% of the patients underwent upper gastrointestinal (GI) endoscopy⁴.

The aim of this study was to investigate the prevalence of columnar-lined esophagus (CLE) among patients who underwent to upper GI endoscopy in a reference center of the central region of RS in the last five years and estimate the prevalence of BE (columnar epithelium with intestinal metaplasia) in this area.

METHODS

The records of patients who underwent upper GI endoscopy between January 2011 to December 2015 at Hospital Universitário de Santa Maria (HUSM) were analyzed. HUSM is a reference center for the central region of RS State, covering 45 cities and approximately 1.2 million people. Gender, age, and clinical symptoms of GERD (heartburn and acid regurgitation) were computed. In the endoscopy records, a search for the diagnosis of hiatal hernia, esophagitis, and columnar-appearing esophagus was made. For the esophagus columnar-appearing, the extension and the histological diagnosis was registered. Incomplete or duplicate records were excluded. The records of patients submitted to an endoscopy for upper GI bleeding or endoscopic procedures like percutaneous endoscopic gastrostomy, endoscopic treatment of esophageal varices, esophageal strictures or achalasia dilatations were excluded too. The data was analyzed with SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp). Qualitative variables using absolute and relative frequencies and the mean and standard deviation to report quantitative variables were described. The significance between variables using qui-square or Fisher exact test when appropriate, at a significance level of P<0.05 was made. All procedures were made according to the ethical standards specified in Helsinki declaration. The Institutional Review Board approved the study protocol.

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RESULTS

A total of 5996 patients were eligible for the study. Among them, were found 112 patients with the endoscopic diagnosis of a columnar-appearing esophagus. In five of these patients the histological diagnosis showed squamous epithelium, thus they were excluded from the analysis. Table 1 displays the histological diagnosis related to the extension of CLE of the remaining 107 (1.8%) patients. A total of 1769 (30%) patients with GERD symptoms or esophagitis were identified. Among patients with CLE, only eight did not present GERD symptoms or esophagitis. The mean age of GERD patients was 56.35 (±15.22) years, and 59% were female. Non-GERD patients had a mean age of 47.62 (±10.21) years, 50% female. The extension of CLE ranged from 0.5 to 14 cm. The frequency of CLE in patients without GERD was 0.13%, and it occurred in segments less than 1.0 cm. BE occurred in 47 patients who represented 44% of the patients with CLE. The global prevalence of CLE was 1.7%, and its prevalence in GERD patients was 5.6%. The overall prevalence of BE was 0.7% whereas in GERD patients it was 2.7%. The odds ratio for the occurrence of CLE in patients with GERD was 30 (CI95%=15.37-63.34). The odds ratio for the presence of BE in long segments was 8 (CI95%=2.83-23.21). Patients with long BE represented 0.3% overall and 1.1% of GERD patients. A significant association of CLE with GERD symptoms (P=0.04) was identified in contrast with no association with age (P=0.18), genre (P=0.77), esophagitis (P=0.50) or hiatal hernia (P=0.1).

TABLE 1. Histological findings in the patients with columnar lined esophagus by the extent of the CLE (n=107)

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Extension of CLE</th>
</tr>
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<tbody>
<tr>
<td>Fundic epithelium</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Cardiac epithelium</td>
<td>54 (42%)</td>
</tr>
<tr>
<td>Columnar epithelium without IM</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>Columnar epithelium with intestinal metaplasia (BE)</td>
<td>27 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>82 (77%)</td>
</tr>
</tbody>
</table>

CLE: columnar-lined esophagus; IM: intestinal metaplasia; BE: Barrett’s esophagus.

DISCUSSION

In a five-years period, the records of inhabitants of a risk area for esophageal cancer, who underwent upper GI endoscopy were analyzed. CLE was identified in 1.7% of the population sample. The frequency of CLE in GERD patients was 5.6% and in patients without GERD was 0.13%. BE occurred in less than half of patients with CLE, presenting an overall prevalence of 0.7% and 2.7% in GERD patients.

These findings disagree with the previous report in the same area that identified 29% of patients underwent upper GI endoscopy presenting intestinal metaplasia in the distal esophagus. The differences between these studies can be explained by their small sample (97 patients) and the finding of only short segments with less than three centimeters. They also did not find differences between patients with or without GERD symptoms. Probably the results of this larger sample reflect with more accuracy what happen in this population. On the other hand, these results are in parallel with others developed in Brazilian states even with smaller samples.

They are also comparable with the rates reported from other countries including those countries where adenocarcinoma is the predominant histological type of esophageal cancer.

CLE is considered a marker for GERD. The distance between the most proximal and most distal esophageal biopsies positive for CLE define the length of the esophageal segment injured by reflux leading us to the concept of the squamous-oxyntic gap. The probability of the occurrence of intestinal metaplasia has been reported to be directly proportional to the length of the squamous-oxyntic gap. Our findings comply with these statements. GERD patients presented a risk 30-folds greater to have CLE than patients without GERD. Furthermore, segments with three centimeters or more showed eight more chances to have intestinal metaplasia, i.e. Barrett’s esophagus.

The diagnosis of BE is still a conundrum once there are controversies on its proper definition and diagnostic criteria. CLE can present three types of epithelium: cardiac, oxyntic-cardiac and intestinal metaplasia. There is a general agreement among GI societies all over the world that is essential the endoscopic identification of CLE for the diagnosis of BE. The main differences are related to the requirement for the presence of intestinal metaplasia with goblet cells in biopsies from CLE. The American Gastroenterology Association (AGA) states that only intestinal metaplasia (with goblet cells) represents BE and predisposes to adenocarcinoma. In contrast, the British Society of Gastroenterology defines BE as any metaplastic columnar epithelium identified by endoscopy and confirmed by histology above the gastroesophageal junction, equal or greater than 1 cm. In both recommendations, to obtain biopsies is essential for the diagnosis but biopsy sampling has some flaws, mainly in the short segments, as we could see in some patients with suspected short segments who presented squamous epithelium in the histopathological exam. Otherwise, a biopsy from the vicinity of the esophagogastric junction with intestinal metaplasia could either represent BE or intestinal metaplasia of the proximal gastric mucosa. Due to this uncertainty and to the retrospective nature of this study it is not possible affirm if some intestinal metaplasia founded in short segments were targeted appropriately and therefore, they could be from the stomach.

Patients with CLE without intestinal metaplasia seems to have a lower risk for cancer progression than patients with intestinal metaplasia, but their risk is greater than the general population. Furthermore, the risk of cancer among the patients with a short-segment is lesser than for patients with long-segment. Our findings show that fundic epithelium, oxyntic-cardiac epithelium and columnar epithelium without goblet cells were much more frequent in short-segment than in long-segment. Whether the biopsies came from the esophagus, they represent a very low risk for cancerization, but it could also be possible that some of those samples could come from the stomach, as it was demonstrated elsewhere. In this last case, their meaning does not represent any risk. This point reinforces AGA position of not recommending the term Barrett’s Esophagus for patients with CLE with no intestinal metaplasia.

This study has some limitation as for its retrospective design, which could introduce some bias in the data. Another potential bias, already mentioned, is the probability of error sampling for biopsies, mainly in short segments. It is possible that some biopsies came from gastric mucosa and not from the esophagus. The highlight of this study is its large sample and the survey period. To the best of our knowledge, it’s the larger sample which accessed the prevalence of CLE and BE in Brazil.
In conclusion, this study demonstrated the global frequency of CLE was 1.7%, and when the approach is narrowed to patients with GERD, it turns out to be 5.6%. BE defined by the presence of intestinal metaplasia with goblet cell presented an overall prevalence of 0.7% and 2.7% in patients with GERD. GERD patients were identified with a risk 30-folds greater to present CLE than patients without GERD. Patients with a long segment of CLE had an increased risk of eight folds to have BE. Long BE counted for 0.3% of the population sample and 1.1% of GERD patients. Screening for BE in the general population in a region where the prevalence of adenocarcinoma of the esophagus is a rare event could be not worthwhile. The follow-up of these patients with long-segment of BE will reveal if the surveillance is cost-effective. Moreover, more research needed to understand the pathogenesis of CLE and elucidate the progression from gastric metaplasia to intestinal phenotype – Barrett's esophagus – associated with cancer.

Authors' contributions
Fagundes RB and De Carli DM designed the research protocol. Araujo AF conducted the process for IRB permission and collected the data. Fagundes RB, analyzed the data and wrote the manuscript. All authors read and approved the manuscript final version.


RESUMO – Contexto – Esôfago de Barrett, complicação da doença do refluxo gastroesofágico (DRGE), é lesão precursora do adenocarcinoma esofágico. O adenocarcinoma esofágico apresenta incidência crescente principalmente no ocidente. O estado do Rio Grande do Sul apresenta taxas mais altas de câncer esofágico no Brasil, porém com baixa prevalência de adenocarcinoma. Objetivo – Investigar a prevalência de esôfago de Barrett em pacientes submetidos a endoscopia digestiva alta nos últimos 5 anos. Métodos – Revisão de prontuários dos pacientes submetidos a endoscopia digestiva alta entre 2011 e 2015. Registrados dados demográficos, sintomas de DRGE, achados endoscópicos, extensão e diagnóstico histológico de epitelização colunar do esôfago. A significância entre as variáveis foi acessada pelos testes do qui-quadrado e exato de Fisher com IC95%. Resultados – Foram incluídos 5996 pacientes. Identificamos 1769 (30%) com sintomas de DRGE ou esofagite e 107 (1,8%) com epitelização colunar. A exceção de oito pacientes com epitelização colunar, os demais apresentavam sintomas de DRGE ou esofagite. Esôfago de Barrett definido pela presença de metaplasia intestinal ocorreu em 47 pacientes; 20 (43%) com segmentos acima de 3 cm e em 27 (57%) com segmentos menores. A prevalência global de esôfago de Barrett foi 0,7% e em pacientes com DRGE foi 2,7%. A razão de chances para a ocorrência de epitelização colunar em pacientes com DRGE foi 30 (IC95%=15,37-63,34) e para a ocorrência de metaplasia intestinal em segmentos longos foi 8 (IC95%=2,83-23,21). Conclusão – Pacientes com DRGE apresentaram risco 30 vezes maior que pacientes sem DRGE para a ocorrência de epitelização colunar. O risco de ocorrência de esôfago de Barrett em segmentos longos foi oito vezes maior. A prevalência global de esôfago de Barrett foi 0,7%. Em pacientes com DRGE a prevalência foi 2,7%. Segmentos longos de esôfago de Barrett representaram globalmente 0,3% e em pacientes com DRGE 1,1%.


REFERENCES