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SPECIALIZED INTESTINAL METAPLASIA IN PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX DISEASE

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Barrett's metaplasia is commonly a long-term sequel of reflux oesophagitis. It is a recognised risk factor for developing adenocarcinoma. There is compelling evidence linking specialized intestinal metaplasia (SIM) in Barrett's oesophagus (BE) with adenocarcinoma of the lower oesophagus. The prevalence of SIM was studied in 839 patients with symptoms of gastro-oesophageal reflux and endoscopically confirmed reflux oesophagitis and/or BE. The association of SIM with age, symptoms, smoking, non-steroidal anti-inflammatory drugs (NSAIDs), endoscopic and histopathological findings was investigated. Patients were divided into three groups: (1)those with SIM, (2)those with gastric-type columnar lined oesophagus (G-CLO), and (3)those with oesophagitis only. SIM was histologically detected in 119(14.18%) patients, G-CLO in 75(8.94%) and oesophagitis (endoscopically and/or histologically) in 645(76.88%). Patients with SIM or G-CLO were significantly older. Patients with grade III and IV oesophagitis were also significantly older. No statistically significant correlation with symptoms, smoking, the use of NSAIDs, hiatus hernia and Helicobacter pylori infection was found between the three groups. Also, no statistical correlation was found between SIM and the length of the BE or oesophagitis.
In conclusion, the presence of SIM and G-CLO is associated with older age. Grade III and IV oesophagitis are also associated with older age. SIM does not correlate with symptoms, smoking, NSAIDs, oesophagitis, hiatus hernia, Helicobacter pylori infection or the length of the BE.

Key words: Barrett's oesophagus, specialized intestinal metaplasia, gastro-oesophageal reflux disease

INTRODUCTION

Barrett's oesophagus (BE) is characterised by replacement of the lower oesophageal squamous mucosa by specialized intestinal type of epithelium containing goblet cells as a result of gastro-oesophageal reflux disease.[1] The prevalence of the disease has increased dramatically in western communities[2] Patients with specialized intestinal metaplasia (SIM) are at increased risk of developing high-grade dysplasia and invasive adenocarcinoma. [3, 4]

The purpose of the study was to estimate the prevalence of SIM in a cohort of patients who had gastro-oesophageal reflux-related lesions diagnosed after upper digestive endoscopy. The association of SIM with age, symptoms, smoking, non-steroidal anti-inflammatory drugs (NSAIDs), endoscopic and histopathological findings was investigated.

PATIENTS AND METHODS

Patients:

The endoscopic reports of all new patients with gastro-oesophageal reflux-related lesions attending for an elective endoscopic examination of the upper gastrointestinal tract over a four years period (1998-2001) were reviewed. There were 839 patients who met these criteria. The clinical notes of these patients were studied for the symptoms of gastro-oesophageal reflux, smoking and the use of non-steroidal anti-inflammatory drugs (NSAIDs). The Histopathology reports of the endoscopic biopsies of these patients were then reviewed. Patients were divided to three groups:[1]

those with SIM,[2] those with gastric-type columnar lined oesophagus (G-CLO), and [3] those with oesophagitis only.

Endoscopy:

At the time of the endoscopy the levels of the squamocolumnar and oesophagogastric junctions were measured in centimetres from the incisor teeth or gums. The oesophagogastric junction was identified as the proximal margin of the gastric folds. The macroscopic appearance of the oesophagus was described as either Barrett's (3 cm or more of columnar epithelium extending above the oesophagogastric junction) or short-segment Barrett's (less than 3 cm of columnar epithelium). Macroscopic oesophagitis was graded according to the Hertzel [5] grading system as follows: grade 0, normal appearing mucosa; grade 1, mucosal oedema, hyperaemia and/or friability of mucosa; grade 2, superficial erosions involving less than 10% of the mucosal surface of the distal 5 cm of oesophageal squamous mucosa; grade 3, superficial erosions or ulcerations involving 10-50% of the distal oesophagus; and grade 4, deep ulceration anywhere in the oesophagus or confluent erosions of more than 50% of the distal oesophageal squamous mucosa. Other endoscopic pathological conditions were recorded. If Barrett epithelium was identified, biopsies were taken from the Z-line in addition to four-quadrant biopsies at 2-cm intervals along the Barrett's epithelium. In patients with oesophagitis random oesophageal biopsies were taken. In all patients a biopsy was taken from the gastric antrum.

Histology:

The specimens were fixed in 10% formalin and embedded in wax. Serial sections were cut and stained with haematoxylin and eosin and Alcian blue. The sections were assessed for the presence of SIM, gastric type mucosa and Helicobacter pylori (H.pylori). SIM was strictly defined by the presence of goblet cells on haematoxylin and eosin staining, and intense blue staining of acid mucin in goblet cells by Alcian blue. Dysplasia and malignancy were recorded. H.pylori in antral biopsies was identified.

Statistical analysis:

Differences in clinical variables between groups (non-parametric data) were analysed by Fisher's exact test and chi-squared test.

RESULTS

Prevalence:

A total of 839 patients were included in this study. SIM was histologically detected in 119(14.18%) patients, G-CLO in 75(8.94%) and oesophagitis only (endoscopically and/or histologically) in 645(76.88%). There were 486 men (57.93%) and 353 (42.07%) women. The median age of patients in the three groups was 63, 63 and 56 years respectively. Patients with SIM or G-CLO were significantly older in comparison to those with oesophagitis only (p-value of 0.003 and 0.01 respectively), Table I. Table II shows patients' age in the three groups in relation to length of the metaplastic segment and grade of oesophagitis. In both SIM and G-CLO groups, the difference in age between patients with long segment of metaplastic epithelium and those with short segment was statistically not significant (p-values of 0.78 and 0.79 respectively). In oesophagitis only group, patients with grade III and IV oesophagitis were significantly older (grade I vs III gave a p-value of 0.002 and grade I vs IV gave a p-value of 0.005).

Symptoms

The three groups were compared to each other for the main symptoms of gastro-oesophageal reflux including heartburn, regurgitation and dysphagia (Table I). There was no significant difference between groups in these clinical parameters.

Association with tobacco and non-steroidal anti-inflammatory drugs :

There was no association between the presence of SIM and smoking or the use of non-steroidal anti-inflammatory drugs (Table I).

Endoscopic and histological analysis:

Endoscopic oesophagitis with various grades was found in 645 patients. The diagnosis was confirmed histologically in 605 (93.8%) patients with negative results in the remaining patients (6.2%) (Table III).

In 27 patients where endoscopy showed only oesophagitis, histological examination revealed the presence of metaplastic epithelium in addition to oesophagitis. Twelve of these patients had grade I oesophagitis, 8 had grade II, 6 had grade III and one had grade IV. Hiatus hernia was reported in 8 of them. The histology revealed SIM in 21 patients and G-CLO in six. Further endoscopic evaluation of the metaplastic segment with oesophageal biopsies according to Barrett's protocol was done after a period of treatment with proton pump inhibitors. Twenty patients had a metaplastic segment of <3 cm (14 with SIM and 6 with G-CLO) and 7 patients had a metaplastic segment =/>3 cm, all of them had SIM.

The three groups were compared for the presence of hiatus hernia and H. pylori colonization (Table III). There was no significant difference between the three groups.

Short metaplastic segment (<3 cm) was detected in 128 patients, 81 (63%) with SIM and 47 (37%) with G-CLO, while long metaplastic segment (3 cm or>) was found in 66

patients, 38 (57.6%) with SIM and 28 (42.4%) with G-CLO. The SIM and G-CLO groups were compared for endoscopic oesophagitis and the length of the metaplastic segment. SIM did not statistically correlate with the presence of oesophagitis or the length of metaplastic segment (Table III).

Invasive adenocarcinoma was detected in 2 patients (0.24% of all patients) and low-grade dysplasia in 2 patients (0.24% of all patients). All lesions were associated with a long Barrett's segment.

Table (1): ***Demographics, symptoms and risk factors***

	SIM n=119	*G-CLO n=75*	*Oesophagitis n=645*	*p-value*
Age Median (years)	63	63	56	0.001✷
Sex Ratio (M:F)	81:38	46:28	359:286	0.67
Symptoms				
Heart burn	97 (81.51)	61 (81.3)	512 (79.38)	0.87
Regurgitation	60 (50.42)	36 (48)	312 (48.37)	0.43
Dysphagia	18 (15.12)	10 (13.33)	98 (15.19)	0.97
Risk factors				
Smoking	39 (32.77)	27 (36)	225 (34.89)	0.88
NSAIDs	15 (12.61)	9 (12)	60 (9.3)	0.43

Values in parentheses are percentages. SIM, specialised intestinal metaplasia; G-CLO, columnar lined oesophagus; NSAIDs, non-steroidal anti-inflammatory drugs. ✷ significant value.

Table (2) : ***Frequency of patients and Age in relation to length of the Barrett's segment and grade of oesophagitis***

		Number	*Median age (Years)*
SIM			
	Barrett's segment (< 3 cm)	38 (31.93%)	67
	Barrett's segment (3 cm or >)	81 (68.07%)	61
	Total	119 (100%)	63
G-CLO			
	Metaplastic segment (< 3 cm)	28 (37.33%)	66
	Metaplastic segment (3 cm or >)	47 (62.67%)	62
	Total	75 (100%)	63
Oesophagitis			
	Grade I	394 (61.09%)	53
	Grade II	164 (25.43%)	59
	Grade III	67 (10.39%)	63
	Grade IV	20 (3.1%)	64
	Total	645 (100%)	56

SIM, specialised intestinal metaplasia; G-CLO, columnar lined oesophagus.

Table (3): ***Endoscopic and histopathological findings***

	SIM n=119	*G-CLO n=75*	*Oesophagitis n=645*	*p-value*
Endoscopic oesophagitis	24 (20.17%)	15 (20%)	645 (100%)	0.57★
Histologic oesophagitis	24 (20.17%)	15 (20%)	605 (93.8%)	
Hiatus hernia	46 (38.66%)	29 (38.67%)	211 (32.71%)	0.34
Helicobacter pylori	42 (35.29%)	30 (40%)	260 (40.3%)	0.6
Metaplastic segment (< 3 cm)	81 (68.07%)	47 (62.67%)		0.44★
Metaplastic segment (3 cm or >)	38 (31.93%)	28 (37.33%)		
Dysplasia	2 (1.7%)	0	0	
Cancer	2 (1.7%)	0	0	

[H] χ^2 test between SIM and G-CLO groups. SIM, specialised intestinal metaplasia; G-CLO, columnar lined oesophagus.

DISCUSSION

There is compelling evidence linking specialized intestinal metaplasia with adenocarcinoma of the lower oesophagus, oesophagogastric junction and gastric cardia. [6, 7] The prevalence of SIM varies considerably in the reported series between 9% and 36%. [8-10] It is 14.18% in this study. The increased recognition of the presence of a short Barrett's segment and its link with SIM, routine biopsy of cases with oesophagitis and the addition of Alcian blue staining increased the sensitivity of capture of cases of metaplasia in recent studies.

In this study patients with SIM were significantly older than patients with only oesophagitis, however patients with G-CLO showed the same correlation. These findings suggest that some patients might develop SIM at an older age and/or after long periods of gastro-oesophageal reflux, a finding that is in keeping with data reported by Aste et al. [11] This can also be supported by the fact highlighted by this study and others [8, 11] that severe oesophagitis is associated with older age. Although some investigators reported an association between older age and long segment of BE with SIM, [11] this study could not find this correlation significantly in patients with metaplastic epithelium with or without SIM.

There was no clear association between SIM and reflux symptoms, tobacco consumption and NSAIDs which is in keeping with all other investigators, [8, 9, 12, 13] except one, [10] who found a significant correlation between SIM and the severity of reflux symptoms.

The prevalence of H. pylori infection did not differ between groups. This may not be surprising since epidemiological studies failed to show an association between tumours of the oesophagus or cardia and H. pylori. [14] This finding is in agreement with other investigators. [8, 15] However, it contradicts the observation made by Morales et al, [13] who identified SIM in 24 of 104 patients undergoing endoscopy with a strong association with H. pylori infection. Similarly, there was no link between SIM and oesophagitis, either endoscopic or histologic. The association between endoscopic and histological evidence of oesophagitis is variable in published series. Many investigators could not find any correlation with endoscopic oesophagitis, [8-10, 12, 13] but some found a significant link with histological oesophagitis [8, 12] or carditis. [13, 16]

It is well known that hiatus hernia is associated with reflux oesophagitis and Barrett's oesophagus as the relaxed lower oesophageal sphincter in such patients predisposes to frequent and longer reflux episodes.[17, 18] Although the prevalence of hiatus hernia in both SIM and G-CLO groups (38%) was higher than in the oesophagitis only group (32%), the difference was not statistically significant. This was in agreement with Carton et al, [19] who reported hiatus hernia in 17% of patients with SIM, however this contradicts the observation made by Aste et al, [11] who significantly related SIM to the presence of hiatus hernia with an exceptionally high prevalence (48.2%) of hiatus hernia in their patients. Avidan et al, [20, 21] reported an increased risk of high-grade dysplasia and adenocarcinoma of the oesophagus in patients with hiatus hernia as they

had more severe acid reflux than patients with other forms of gastro-oesophageal reflux disease.

SIM was diagnosed in 21 patients in whom endoscopy only revealed various grades of oesophagitis. In 14 of them further endoscopy revealed the presence of short segment (<3 cm) of BE. All these patients had histologically proven oesophagitis and 8 of them had hiatus hernia. The endoscopic diagnosis of BE especially with short segment is difficult in some patients because of uncertain anatomic landmarks, severe oesophageal inflammation, or hiatus hernia; the endoscopist's skill play an additional important role. Moreover, short segments of BE often do not involve the entire circumference of the oesophagus, but appear as fingers of red mucosa above the squamo-columnar junction. [22].

SIM was found to be independently associated with long segments of metaplastic epithelium by Aste et al [11] and Spechler et al. [12] They suggested that during mapping of the metaplastic area more biopsies were taken from longer segments, resulting in greater odds of identifying this specific epithelium. In this study however, no correlation was found between SIM and the length of the BE probably because of the high prevalence of SIM in patients with short metaplastic segment, 81 (63%) out 128 patients, in comparison to 15% and 18% respectively in their studies.

Although the occurrence of dysplasia and adenocarcinoma in short segments of BE is documented,[6, 7] none of them was found in such lesions in this study. However, the frequency and inherent risk of malignancy in short segments of BE are still unknown. The prevalence of dysplasia in SIM varies in literature from 0 to 12% [12, 13, 23], being 1.7 % in this study.

In conclusion, gastro-oesophageal reflux disease could induce either oesophagitis or epithelial metaplasia of the lower oesophagus. Oesophagitis increased in severity in older patients. Also patients with metaplastic epithelium, with or without SIM, were older. This observation could prompt the hypothesis that younger patients (aged under 50) with gastric-type columnar-lined oesophagus might not need endoscopic follow-up because of the low risk of adenocarcinoma. Nevertheless, accurate mapping of the metaplastic epithelium after the age of 50 in order to assess whether they maintain the low-risk histological profile is advisable. SIM is prevalent in patients undergoing upper gastrointestinal endoscopy for symptoms of gastro-oesophageal reflux disease, either in short or long segments of BE. SIM does not correlate with symptoms, smoking, NSAIDs, oesophagitis, hiatus hernia, Helicobacter pylori infection or the length of the Barrett's segment. Small areas of metaplasia could be masked by severe inflammation, and patients with endoscopic signs of distal oesophagitis should be carefully re-examined after an adequate medical treatment. This approach could lead to the identification of areas of metaplastic epithelium. The histological diagnosis of SIM could eventually shift these patients into surveillance programs.

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