Intestinal metaplasia at the gastro-oesophageal junction: *Helicobacter pylori* gastritis or gastro-oesophageal reflux disease?

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Abstract

***Background*—Intestinal metaplasia, whether in the cardia or the distal oesophagus, has been uniformly defined as specialised columnar epithelium, suggesting a relation with Barrett's oesophagus. It is, however, not clear whether the risk factors associated with intestinal metaplasia are identical at both sites.**

***Aims*—To investigate biopsy specimens obtained below the squamocolumnar junction (SCJ) in relation to endoscopic aspect, gastric histology, and clinical presentation.**

***Patients and methods*—In 423 patients investigated the endoscopic aspect of the SCJ was classified as unremarkable (group I, n=315) or suggestive of Barrett's oesophagus (group II, n=108). Standardised biopsy specimens from the antrum, corpus, and directly below the SCJ were investigated.**

***Results*—Intestinal metaplasia was detected at the SCJ in 13.4% of group I patients, where it was significantly associated with gastric intestinal metaplasia (odds ratio (OR) 6.96; confidence interval (CI) 2.48 to 19.54) and *H pylori* (OR 7.85; CI 2.82 to 21.85), and in 34.3% of group II patients where it was significantly associated with reflux symptoms (OR 19.98; CI 6.12 to 65.19), erosive oesophagitis (OR 12.16; CI 3.86 to 38.24), and male sex (OR 6.25, CI 2.16 to 18.14), but not with *H pylori* or gastric intestinal metaplasia.**

***Conclusion*—This study suggests that the pathogenesis of intestinal metaplasia at the SCJ is not uniform: at an endoscopically unremarkable SCJ it is a sequela of *H pylori* gastritis, but coexisting with endoscopic features of Barrett's oesophagus it is associated with male sex and gastro-oesophageal reflux disease.**

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Keywords: intestinal metaplasia; Barrett's oesophagus; gastric cardia; *Helicobacter pylori* gastritis; gastro-oesophageal reflux disease

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The incidence of adenocarcinoma at the gastro-oesophageal junction is on the increase.[1 2] These carcinomas differ from those in the rest of the stomach.[3] They share epidemiological characteristics with, and often originate from, segments of Barrett's oesophagus, expressing a metaplasia–dysplasia–carcinoma sequence.[4 5] Traditionally Barrett's oesophagus is defined as a circumferential segment of columnar lined epithelium of, arbitrarily, 2 or 3 cm in length in the lower oesophagus.[6 7] Recently, however, this macroscopic definition has been questioned,[8] as it excludes shorter segments and "tongues" of columnar lined epithelium, which are frequently found in the distal oesophagus, and endoscopic measurements may be imprecise.[9] Only the specialised columnar epithelium defined by intestinal type goblet cells—one of the three typical forms of mucosa found in Barrett's oesophagus[10]—carries an inherent risk of malignancy.[11 12] It has therefore been proposed that the diagnosis of Barrett's oesophagus be reserved for patients with intestinal metaplasia detected in biopsy specimens from the distal oesophagus.[12]

In several studies involving the screening of consecutive endoscopy patients for intestinal metaplasia at the gastro-oesophageal junction biopsy specimens obtained immediately below the squamocolumnar junction (SCJ) revealed intestinal metaplasia in between 9.4% and 30% of patients without traditional Barrett's oesophagus.[13–16] The well known association of traditional Barrett's oesophagus with symptoms and endoscopic features of gastro-oesophageal reflux disease (GORD) was, however, not confirmed in these studies,[13 15 16] nor was the usual preponderance of male sex.[14 16] The results of these studies seem to indicate that an asymptomatic, possibly premalignant, lesion is present in many individuals, the prevalence of which might match that of traditional Barrett's oesophagus in an autopsy series, which was 20 times higher than the clinical prevalence.[17]

Nevertheless, a number of questions remain to be answered. Biopsy specimens obtained directly below the SCJ will probably contain gastric cardia mucosa if the endoscopic aspect of a normally positioned SCJ is unremarkable. If endoscopy is suggestive of even very short "tongues" of Barrett's oesophagus, biopsy material may contain metaplastic epithelium originating in oesophageal mucosa. Screening consecutive patients may thus be expected to reveal intestinal metaplasia in both metaplastic oesophageal, and in gastric cardia mucosa. It has been suggested that such a differentiation is not critical, as specialised columnar epithelium indicates an increased risk of cancer regardless of its precise localisation within the gastro-oesophageal junction.[12] It is, however, not

Table 1 Endoscopic classification of the squamocolumnar junction (SCJ)

Group	*Location of SCJ*	*Appearance of SCJ*
I	Within 2 cm above gastro-oesophageal junction	Unremarkable, (i.e. relatively straight on insufflation of air)
II (eccentric SCJ)	As above	Eccentric, irregularly serrated on insufflation of air
II (tongues of Barrett's oesophagus)	As above	"Tongue(s)" and/or islands of columnar epithelium extending into the distal oesophagus
II (segments of Barrett's oesophagus)	Shifted >2 cm above gastro-oesophageal junction (i.e. circumferential segment of columnar mucosa)	Any, mostly irregular with additional tongues

known whether intestinal metaplasia of the cardia and that originating from oesophageal mucosa have a common pathogenesis and identical associated risk factors. In a previous study on *H pylori* gastritis of the cardia region, which excluded patients with Barrett's oesophagus and non-infected patients, we found intestinal metaplasia of the gastric cardia in 20.7% of 135 patients.[18] The present study was performed to investigate whether different subsets of patients with intestinal metaplasia at the SCJ are identifiable on the basis of the endoscopic aspect of the SCJ, clinical presentation, and *H pylori* infection of the gastric mucosa.

Methods

SUBJECTS

In the first part of the study (June 1995 to end of February 1996) 379 consecutive patients undergoing elective upper gastrointestinal endoscopy were investigated. The endoscopic aspect of the SCJ was normal in 336 and suggestive of Barrett's oesophagus in 43 patients. In the second part of the study (March 1996 to end of May 1997) only selected patients with endoscopic features suggestive of Barrett's oesophagus (n=78) were enrolled. Patients with gastric or oesophageal carcinoma, prior gastric resection, previously known and histology proved Barrett's oesophagus, coagulation defects, or varices were excluded. Eligible patients were admitted to this study after giving their informed consent to the extended biopsy protocol, which had been approved by the local hospital ethics committee. The clinical indications for endoscopy and the presence of reflux symptoms were recorded.

ENDOSCOPY

Endoscopy was performed in a standardised manner by experienced endoscopists. The appearance of the SCJ was carefully studied in the prograde view after insufflation of air and after retroversion in the stomach. Erosive oesophagitis was defined as an unequivocal defect in the squamous mucosa and graded. For the purpose of this study however it was only reported as absent or present. The proximal margin of the gastric mucosal folds was taken as a landmark of the normal gastro-oesophageal junction.[6] The SCJ was classified on the basis of its endoscopic appearance and location as unremarkable (group I) or suggestive or typical of Barrett's oesophagus to a variable extent (group II). Group II was further subdivided into three subgroups as defined in table 1.

Mucosal biopsy specimens were obtained with a standard forceps in accordance with the following protocol: three antral biopsy specimens about 2 cm from the pylorus, and three corpus specimens from the mid-region of the greater curvature. Patients from group I had two biopsy specimens taken from columnar mucosa immediately below the SCJ. In patients with endoscopic suspicion of Barrett's oesophagus (group II), four quadrant oriented biopsy specimens were obtained immediately below the SCJ, including the most cranially sited parts of the "tongues". Patients with segments of Barrett's oesophagus had further biopsy specimens taken (up to 12) in order to map the whole columnar lined area in the oesophagus for dysplasia.

HISTOLOGY

Two biopsy specimens from both the antrum and corpus and all the biopsy specimens obtained from the SCJ were immediately fixed with 4% neutral formalin. Sections (4 μm) were cut and stained with haematoxylin and eosin for gastritis grading in accordance with the Sydney system,[19] and for the detection of intestinal metaplasia in antral and/or corpus mucosa. For evaluation in this study intestinal metaplasia was not graded but merely noted as present or absent. In antral and corpus biopsy specimens a modified Giemsa stain was used to detect *H pylori*. Additional Alcian blue (pH 2.5) staining was performed on all SCJ biopsy specimens to detect intestinal metaplasia defined by goblet cells.[20 21] Non-goblet Alcian blue positive columnar cells alone were not sufficient for the diagnosis of intestinal metaplasia.[22 23] All histological sections were evaluated by a single pathologist blinded to the individual patient's clinical condition (TG).

H PYLORI STATUS

In addition to histology we used a previously validated rapid urease test (HUT-test, Astra GmbH, Wedel, Germany) for the enzymatic detection of *H pylori* in one antral and one corpus biopsy specimen.[24] *H pylori* infection was assumed when active gastritis with bacteria of typical shape was found histologically and/or the rapid urease test was positive.

STATISTICAL ANALYSIS

Multiple logistic regression was used to assess the factors with basic influence on intestinal metaplasia in SCJ biopsy specimens. Further calculations compared patients from group I with those from group II. Between group differences for clinical and demographic variables were compared by the χ^2 and t tests and the odds ratios (OR) were calculated at $p<0.05$ (SPSS package).

Table 2 Classification of the squamocolumnar junction (SCJ), demographic data, Helicoabcter pylori status, and prevalence of intestinal metaplasia at the SCJ

	Group I (n = 315)	*Group II (eccentric SCJ) (n = 60)*	*Group II (tongues of Barrett's oesophagus) (n = 32)*	*Group II (segments of Barrett's oesophagus) (n = 16)*	*p Value (χ^2)*
Age (y)	52.2 (16.2)	54.8 (14.8)	59.1 (14.1)	62.6 (9.4)	0.005
No of men	148 (47)	35 (58.3)	24 (75)	13 (81.3)	0.0004
H pylori positive	156 (49.5)	22 (36.7)	15 (46.9)	6 (37.5)	NS
Intestinal metaplasia*	42 (13.4)	9 (15)	14 (43.8)	14 (87.5)	<0.0001

Values are expressed as number (%) except for age which is expressed as mean (SD).
*Intestinal metaplasia found in biopsy specimens from the SCJ.
p values are for comparison of patients from group I with those from group II as a whole.

Results

Of the 457 patients enrolled, SCJ biopsy specimens from 16 patients revealed squamous epithelium with no or minimal amounts of columnar mucosa and these patients were excluded. A further 18 patients were excluded because of recent proton pump inhibitor treatment, or the use of antibiotics in the four weeks preceding endoscopy, leaving 423 patients for final evaluation.

Multiple regression analysis for the entire study population revealed two independent basic factors associated with intestinal metaplasia in biopsy specimens from the SCJ: an appearance of the SCJ suggestive or typical of Barrett's oesophagus—that is, group II ($p<0.0001$), and the presence of gastric intestinal metaplasia—that is, in antral and/or corpus mucosa ($p<0.0001$).

Table 2 shows the endoscopic classification of the SCJ for the overall population evaluated, together with demographic data, *H pylori* status, and the prevalence of intestinal metaplasia detected in biopsy specimens at the SCJ. Patients with an unremarkable SCJ (group I) are compared with those whose SCJ was suggestive or typical of Barrett's oesophagus (group II). The latter patients were older and men predominated. The prevalence of *H pylori* gastritis was slightly higher in group I ($p=0.0814$). The prevalence of intestinal metaplasia detected at the SCJ increased stepwise from group I (13.4%) to the subgroups of group II: from an eccentric SCJ (15%) to "tongues" of Barrett's oesophagus (43.8%) and segments of Barrett's oesophagus (87.5%), resulting in a 34.3% overall prevalence in group II.

Table 3 compares patients from group I with intestinal metaplasia detected at the SCJ with those without intestinal metaplasia. Those harbouring intestinal metaplasia were older, and more frequently had *H pylori* gastritis and/or gastric intestinal metaplasia. Further analysis of the eight uninfected patients with intestinal metaplasia detected at the SCJ in group I revealed coexistent gastric intestinal metaplasia in four, two of whom had antral atrophy, suggesting multifocal atrophic ex-*H pylori* gastritis. No patient had dysplasia associated with intestinal metaplasia at the SCJ.

When group II patients (those with endoscopic features of Barrett's oesophagus) with and without intestinal metaplasia at the SCJ were compared, the only significant finding was male sex: 31/37 patients (83.8%) with intestinal metaplasia were males compared with 41/71 (57.7%) without intestinal metaplasia ($p=0.0067$). Low grade dysplasia associated with intestinal metaplasia at the SCJ was found in one patient with a segment of Barrett's oesophagus, and high grade dysplasia and subsequently a small unsuspected oesophageal adenocarcinoma was found in another. Further analysis identified two patients with intestinal metaplasia in biopsy specimens taken from below an eccentric SCJ (group II-E): neither patient had GORD or active *H pylori* gastritis, but both had gastric intestinal metaplasia and mucosal atrophy, suggesting multifocal atrophic ex-*H pylori* gastritis.

Table 4 compares the data of all patients from groups I and II who had intestinal metaplasia at the SCJ. Although their mean age was similar, two different subsets of patients can be identified on the basis of the endoscopic appearance of the SCJ: although the sex distribution was about equal in group I, most patients from group II were males (OR 6.25; confidence interval (CI) 2.16 to 18.14). Intestinal metaplasia at the SCJ detected in group I was often associated with *H pylori* infection (OR 7.85; CI 2.82 to 21.85) and gastric intestinal metaplasia (OR 6.96; CI 2.48 to 19.54). Patients with an SCJ suggestive or typical of Barrett's oesophagus (group II) did not share these features, but showed a highly significant association with reflux symptoms (OR 19.98; CI 6.12 to 65.19) and erosive oesophagitis (OR 12.16; CI 3.86 to 38.24) that was not seen in group I patients.

Table 3 Comparison of group I patients with intestinal metaplasia at the squamocolumnar junction (SCJ) with those without intestinal metaplasia

	With intestinal metaplasia (n = 42/315 (13.4%))	*Without intestinal metaplasia (n = 273/315 (86.6%))*	*p Value (χ^2)*
No of men	19/42 (45.2)	129/273 (47.3)	NS
Age (y)	60.1 (13.2)	51.0 (16.4)	0.001
H pylori positive	34/42 (81.0)	122/273 (44.7)	<0.0001
Gastric intestinal metaplasia	26/42 (61.9)	38/273 (13.9)	<0.0001
Reflux symptoms	5/42 (11.9)	37/273 (13.6)	NS
Erosive oesophagitis	5/42 (11.9)	42/273 (15.4)	NS

Values are expressed as number (%) except for age which is expressed as mean (SD).

Table 4 Data of all patients with intestinal metaplasia at the squamocolumnar junction (SCJ)

	Group I (n = 42)	*Group II (eccentric SCJ) (n = 9)*	*Group II (tongues of Barrett's oesophagus) (n = 14)*	*Group II (segments of Barrett's oesophagus) (n = 14)*	*p Value (χ^2)*
Age (y)	60.1 (13.2)	52.5 (14.1)	57.7 (14.5)	62.9 (13.9)	NS
Males	19 (45.2)	7 (77.8)	12 (85.7)	11 (78.6)	0.0004
H pylori positive	34 (81)	2 (22.2)	6 (42.9)	5 (37.5)	<0.0001
Gastric intestinal metaplasia	26 (61.9)	2 (22.2)	2 (14.3)	3 (21.4)	0.0001
Reflux symptoms	5 (11.9)	7 (77.8)	8 (57.1)	12 (85.7)	<0.0001
Erosive oesophagitis	5 (11.9)	4 (44.4)	7 (50)	12 (85.7)	<0.0001

Values are expressed as number (%) except for age which is expressed as mean (SD).
p values are for comparison of patients from group I with those from group II as a whole.

Discussion

This study shows that intestinal metaplasia in biopsy specimens from the SCJ is not always indicative of Barrett's oesophagus, suggesting that its pathogenesis is not uniform. Of our patients with an unremarkable SCJ, 13.4% had intestinal metaplasia of the cardia, significantly associated with older age, *H pylori* gastritis, and gastric intestinal metaplasia. Of patients with endoscopic features suggestive or typical of Barrett's oesophagus, 34.3% had intestinal metaplasia at the SCJ which was associated with male sex, oesophagitis, and reflux symptoms, but not with *H pylori* or gastric intestinal metaplasia.

Antral intestinal metaplasia is common in long standing *H pylori* gastritis.[25–27] Given the histoanatomical and functional similiarity of the mucosa in the antrum and cardia[28] and their similar inflammatory responses to *H pylori* infection,[18 29] the development of intestinal metaplasia of the cardia would seem to be a logical consequence of *H pylori* carditis.[18 30] The significant association of cardia intestinal metaplasia and gastric intestinal metaplasia suggests the former is often a part of widespread metaplastic changes in the stomach, a view supported by a recent preliminary report.[31] As Barrett's oesophagus may go unrecognised during life in some subjects we cannot completely exclude silent and non-erosive GORD as a cause of intestinal metaplasia at an unremarkable SCJ. The frequent association with gastric intestinal metaplasia would, however, not support this pathogenetic model.

Several studies have screened for intestinal metaplasia at the SCJ in patients without traditional Barrett's oesophagus. In two, the data indicate a 7% rate of cardia intestinal metaplasia (in patients without short segment Barrett's oesophagus).[13 14] Another study investigating a 95% male veterans population without Barrett's oesophagus, in which five SCJ biopsy specimens were obtained, revealed a 23% rate of cardia intestinal metaplasia.[15] As intestinal metaplasia is often patchy its prevalence may rise with increasing numbers of biopsy specimens. As in our study, no dysplasia or association with GORD, but a significant association with *H pylori* gastritis was found.[15] The latter was however not confirmed by a recent Australian study of 158 patients (mean age 50.8 years) without traditional Barrett's oesophagus.[16] With only two SCJ biopsy specimens obtained, a 30% prevalence of intestinal metaplasia but no association with reflux symptoms or endoscopic oesophagitis was found. The authors claim that all these patients had short segment Barrett's oesophagus, but as the endoscopic aspect of the SCJ was not reported, the number of patients actually having intestinal metaplasia of the cardia cannot be assessed. Neither distal gastric biopsy specimens, urease testing, nor non-invasive tests were performed to detect *H pylori* gastritis. As intestinal metaplasia itself may be hostile to *H pylori* colonisation,[32] the true prevalence of *H pylori* may have been underestimated.

Despite the frequent occurrence of cardia intestinal metaplasia, its association with *H pylori* gastritis and multifocal gastric intestinal metaplasia, there is still no evidence that this finding indicates an increased risk of malignancy in the cardia. Several studies have established *H pylori* gastritis as a risk factor for the development of distal gastric cancer of the diffuse or intestinal type, but not for cancer of the gastric cardia.[33 34]

In an attempt to detect even minor endoscopic signs suggestive of Barrett's oesophagus we evaluated a subgroup of patients with an eccentric SCJ. Endoscopic differentiation between unremarkable and eccentric was sometimes difficult, and this subgroup may well have some bias in terms of interobserver variation. When present, the area of columnar lined oesophageal mucosa in such patients was small and the prevalence of intestinal metaplasia at the SCJ in this subgroup was low (15%), close to the 13.4% in patients with cardia intestinal metaplasia. Some patients with intestinal metaplasia at an eccentric SCJ were males and had GORD, suggesting an "ultrashort" segment Barrett's oesophagus, but as others with no GORD had multifocal intestinal metaplasia, "intestinal metaplasia of the cardia" may be the correct diagnosis here. Obviously, an eccentric SCJ is neither predictive of intestinal metaplasia, nor will it distinguish Barrett's oesophagus patients from those with cardia intestinal metaplasia. If "tongues" of Barrett's oesophagus are visible the probability that biopsy specimens will contain one of the three types[10] of metaplastic oesophageal mucosa is clearly higher. The prevalence of specialised columnar epithelium in 32 patients with such tongues was 43.8%, and none of these had associated dysplasia. This result accords with the 37–48% rate of specialised intestinal metaplasia without dysplasia reported in two studies on short segment Barrett's oesophagus.[35 36] Similarly to the latter study 57% of our patients with tongues of Barrett's oesophagus presented with GORD symptoms and 50% had erosive oesophagitis.

This shows that specialised columnar epithelium may develop silently in some patients and will only be detected by meticulous endoscopy and biopsy of even short tongues of columnar lined lower oesophagus. Although rarely reported, dysplasia and malignancy may exist or develop in short segment Barrett's oesophagus.[4 5 37 38]

In conclusion, our study indicates that intestinal metaplasia of the cardia is relatively common and occurs mainly in elderly *H pylori* infected patients with multifocal gastric intestinal metaplasia. To date there is no evidence that cardia intestinal metaplasia is a premalignant condition, thus—except in scientific studies—follow up endoscopy examinations are unnecessary. Specialised columnar epithelium apparently occurs only in metaplastic oesophageal mucosa and differs pathogenetically from cardia intestinal metaplasia. Our data confirm that men with reflux symptoms and/or endoscopic oesophagitis are at risk. Unlike other authors[13 16] we believe the terms "specialised columnar epithelium" and "short segment Barrett's oesophagus" should be restricted to patients with endoscopic features of Barrett's oesophagus and intestinal metaplasia on histology.

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