

The phenotype of gastric mucosa coexisting with Barrett's oesophagus

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Abstract

Background/Aims—Barrett's oesophagus complicates the gastro-oesophageal acid reflux. *Helicobacter pylori* infection, particularly with cagA positive strains, induces inflammatory/atrophic lesions of the gastric mucosa, which may impair acid output. No systematic study has investigated the phenotype of the gastric mucosa coexisting with Barrett's oesophagus. This study was designed to identify the phenotype of gastric mucosa associated with Barrett's oesophagus.

Methods—In this retrospective case control study, the phenotype of the gastric mucosa was histologically characterised in 53 consecutive patients with Barrett's oesophagus and in 53 (sex and age matched) non-ulcer dyspeptic controls. Both patients and controls underwent extensive sampling of the gastric mucosa (two antral, one incisural, and two oxyntic biopsies). Intestinal metaplasia (IM) was categorised (type I, complete IM; types II and III, incomplete IM) by the high iron diamine stain; cagA status was ascertained by genotyping.

Results—*Helicobacter pylori* was present in 19 of the 53 patients with Barrett's oesophagus and in 30 of the 53 controls ($p < 0.02$); eight of the 19 patients with Barrett's oesophagus and 28 of the 35 controls harboured cagA positive *H pylori* ($p < 0.03$). The histological severity of non-atrophic gastritis detected in the controls was significantly higher than that detected in the patients with Barrett's oesophagus ($p < 0.0001$). Multifocal atrophic gastritis was present in 4% of the patients with Barrett's oesophagus and in 23% of controls ($p < 0.01$). The odds ratio for the association between multifocal atrophic gastritis and Barrett's oesophagus was 0.20 (95% confidence interval, 0.006 to 0.60). Gastric IM was detected in 13.2% of the patients with Barrett's oesophagus and in 30.1% of the controls ($p < 0.03$). Type III IM at the gastric mucosa was only detected among controls.

Conclusions—Barrett's oesophagus is associated with a low prevalence of *H pylori* cagA positive infection and multifocal atrophic gastritis. This pathobiological pattern is considered to be associated with a low risk of distal gastric cancer.

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Keywords: Barrett's oesophagus; gastritis in Barrett's oesophagus; Barrett's oesophagus and gastric precancerous lesions

Barrett's oesophagus has been recognised as the major risk factor for oesophageal adenocarcinoma.¹⁻³ The presence of metaplastic columnar epithelium in the oesophagus has been causally related to the development of 64-86% of all oesophageal non-squamous cancers.⁴⁻⁸ Based on this association and other pathogenetic considerations, most authors prefer to restrict the definition of Barrett's oesophagus to the presence of intestinalised columnar epithelium (Barrett's specialised epithelium) cephalad to the gastro-oesophageal junction.⁴⁻¹¹

Helicobacter pylori is the major aetiological agent of chronic gastritis.¹²⁻¹⁴ The cagA gene is part of the cag pathogenicity island of the *H pylori* genome. Strains harbouring the cagA gene are associated both with high grade gastritis and precancerous atrophic/metaplastic lesions, which may result in stomach cancer.¹⁵⁻¹⁷ Recent reports suggest that infection with cagA positive strains may confer a decreased risk for both proximal gastric cancer and Barrett's oesophagus.^{18 19}

Because Barrett's oesophagus develops as a consequence of acid reflux, it is self evident that patients with this condition should have a normal (or increased) acid production.^{20 21} *Helicobacter pylori* infection, particularly with cagA positive strains, is associated with both severe inflammation and multifocal atrophic gastritis; both of these conditions may result in decreased acid production.²² Thus, the hypothesis of an inverse relation between *H pylori* (particularly cagA positive) infection and the development of Barrett's mucosa has a plausible explanation.^{19 23-26}

Our study was performed to characterise the phenotype of gastritis associated with Barrett's oesophagus. We also explored the association between the patterns of gastro-oesophageal lesions, *H pylori* infection, and the cag genotype of *H pylori* strains infecting these patients.

Patients and methods

PATIENTS

Barrett's oesophagus was defined as the presence of histologically confirmed specialised columnar (intestinalised) epithelium not less than 3 cm above the oesophagogastric junction. Columnar mucosa less than 3 cm from the Z line (so called short/ultrashort Barrett's oesophagus) was excluded from our study. Other exclusion criteria were a past history of foregut surgery, malignant diseases, and previous anti-*H pylori* treatment.

The test group of patients with Barrett's oesophagus comprised 53 patients (34 men: mean age, 64 years; range, 41-89; and 19

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women: mean age, 63 years; range, 24–85). In all cases, multiple oesophageal (two to five) and two antral, one incisural, and two oxyntic mucosal samples were available. None of the patients had an active or healed peptic ulcer or focal mucosal lesions.

A control population of 53 consecutive sex and age matched subjects (34 men: mean age, 64 years; range, 41–89; and 19 women: mean age, 63 years; range, 24–85) was retrospectively selected from patients recorded in the electronic archives of the same institution from which the patients with Barrett's oesophagus were recruited. In selecting the control group, the exclusion criteria were: (1) clinical symptoms other than dyspepsia; (2) endoscopy features suggesting reflux oesophagitis and/or active or healed peptic ulcer and/or gastro-oesophageal focal lesions; (3) previous anti-*H pylori* treatment, (4) treatment with proton pump inhibitors and/or H₂ receptors antagonists within the two weeks before endoscopy, and (5) fewer than five (two antral, one incisural, and two oxyntic mucosa) gastric biopsy specimens taken during the endoscopy.

HISTOPATHOLOGICAL EVALUATION OF OESOPHAGEAL AND GASTRIC BIOPSY SPECIMENS

Serial sections (5 µm thick) prepared from formalin fixed, paraffin wax embedded biopsy samples were stained with haematoxylin and eosin and with modified Giemsa for the detection of *H pylori*. In both gastric and/or oesophageal samples, when goblet cells were detected, additional sections were prepared and stained with the high iron diamine (HID) reaction to determine the phenotype of the intestinal metaplasia (IM).²⁷ When different subtypes of IM coexisted, type III was considered dominant to type II, and type II dominant to type I.

Gastritis was classified as non-atrophic, atrophic autoimmune, and multifocal atrophic gastritis (MAG).¹² MAG was defined as the presence of unequivocal glandular loss and/or IM in two or more gastric samples, irrespective of their provenance. Cases in which atrophic/metaplastic lesions were detected in only one of the gastric samples were classified as focal atrophy.¹⁴ In four patients (all from the control group), non-metaplastic borderline glandular loss was detected in one of the antral specimens only; because of the absence of definite atrophy and IM, these cases were categorised as non-atrophic gastritis. After the intensity of the mucosal inflammatory infiltrate was scored separately in each gastric biopsy, a combined grade (low *v* high) was generated for each of the gastric regions (antrum, incisura angularis, and corpus). Inflammation was graded as: (1) absent, when no inflammatory infiltration or only sparse mononuclear cells were detected throughout the lamina propria; (2) low grade, when an easily detectable infiltrate, most frequently restricted to the interfoveolar area, was present; and (3) high grade, when the infiltrate was extensive and/or diffuse throughout the whole thickness of the lamina propria, mostly associated with lymphoid follicular structures. Among the non-atrophic gastritis

cases, the above reported scoring system allowed us to distinguish the prevalent location of the inflammatory lesions (antrum + angularis incisura *v* oxyntic mucosa).

All histological evaluations were performed by two of the authors (VR and MR) who, unaware of the clinical information, examined simultaneously each slide and reached a consensus on each score.

MOLECULAR ASSESSMENT OF *H PYLORI* cagA STATUS

All cases showing bacteria with morphology consistent with *H pylori* were investigated for the presence of cagA positive strains by means of a molecular genetic method. To obtain template DNA, not less than five sections, 5 µm thick and obtained from each of the six gastric samples taken from the same patient, were pooled together and combined in a 1.5 ml microcentrifuge tube for dewaxing and proteinase K digestion, as described previously.²⁸ The extracted DNA was purified by the phenol/chloroform method according to a standardised protocol.²⁹ As a positive DNA control, bacterial DNA was extracted and purified from suspensions of cultured *H pylori* colonies known to be cagA positive or cagA negative (10⁵ cells/ml), which had previously been formalin fixed and embedded in paraffin wax. A negative control, consisting of all reagents but no tissue section, was carried out for each DNA extraction.

Amplification was performed in a final volume of 50 µl of polymerase chain reaction (PCR) mixture containing 0.8 µM of each primer, 0.2 mM of each deoxynucleotide (dATP, dGTP, dTTP, and dCTP), 75 mM Tris base (pH 9.0), 20 mM ammonium sulphate, 0.01% Tween 20, 3.0 mM MgCl₂, 1 U thermostable DNA polymerase (Advanced Biotechnologies, Surrey, UK), and 50–100 ng of DNA template. The reaction was carried out in a Perkin Elmer-Cetus thermocycler (Foster City, California, USA). Negative and positive controls (see above) were run in parallel for each amplification. cagA gene amplification was carried out using the following set of primers (5'-ATAATGCTAAATTAGACAACCTTGAGCGA-3' and 5'-AGAAACAAAAGCAATACGATCATTC-3').

Briefly, DNA amplification by the PCR was carried out as follows: denaturation at 94°C for five minutes in the first cycle, followed by annealing for 30 seconds at 55°C, extension for two minutes at 72°C, and denaturation for 30 seconds at 94°C, for a total of 40 PCR cycles. The extension of the last cycle was increased to five minutes to ensure complete extension of the amplified fragment. The PCR products were resolved by 2% agarose or 12% polyacrylamide gel electrophoresis and were visualised after ethidium bromide (0.5 µg/ml) or silver staining (Bio-Rad, Richmond, California, USA).

The sensitivity of the reaction was investigated by performing the PCR on serial 10-fold dilutions of DNA extracted from a known number of *H pylori* cells. The minimum number of bacteria detectable by PCR ranged from 50 to 100.

Table 1 Phenotype of gastric mucosa in patients with Barrett's oesophagus and in non-ulcer dyspeptic controls

Gastric phenotype		Number (%)	Gastric intestinal metaplasia (high iron diamine)			<i>H pylori</i> negative	<i>H pylori</i> positive	
			Type I	Type II	Type III		<i>cagA</i> positive	<i>cagA</i> negative
Normal mucosa	Patients	6 (11.3)	–	–	–	6	–	–
	Controls	4 (7.50)	–	–	–	4	–	–
Non-atrophic antral predominant gastritis	Patients	40 (75.5)	–	–	–	24	6	10
	Controls	31 (58.5)	–	–	–	8	18	5
Focal atrophy	Patients	5 (9.40)	2	3	0	3	1	1
	Controls	5 (9.40)	3	2	0	1	4	0
Autoimmune (corpus restricted) gastritis	Patients	0	–	–	–	0	–	–
	Controls	1 (1.8)	–	–	–	1	0	0
MAG	Patients	2 (3.80)	2	0	0	1	1	0
	Controls	12 (22.6)	7	2	3	3	6	3

MAG, multifocal atrophic gastritis.

STATISTICAL METHODS

Statistical analysis was based on the likelihood ratio χ^2 test (χ^2_{LR}) for frequency tables. *p* Values < 0.05 were considered significant. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by Peto's formula.

Results

PHENOTYPE OF THE BARRETT'S MUCOSA

The histochemical phenotype (HID) of the intestinalised oesophageal epithelium was type I in nine of the 53 patients with Barrett's mucosa, type II in 16, and type III in the remaining 28.

HELICOBACTER PYLORI INFECTION

Helicobacter pylori infection was present in 19 of the 53 patients with Barrett's oesophagus and in 36 of the 53 controls (*p* < 0.02). *Helicobacter pylori cagA* positive strains were detected in eight of the 19 *H pylori* positive patients with Barrett's oesophagus and in 28 of 36 *H pylori* infected controls (table 1). The OR for the coexistence of Barrett's oesophagus and *H pylori cagA* positive infection was 0.28 (95% CI, 0.13 to 0.61).

GASTRIC PHENOTYPE (PATIENTS WITH BARRETT'S OESOPHAGUS V CONTROL GROUP)

Six of the 53 patients with Barrett's oesophagus and four of the 53 control subjects (none of whom were infected with *H pylori*) had a histologically normal stomach mucosa (table 1).

Non-atrophic gastritis was present in 40 of the 53 patients with Barrett's oesophagus and in 31 of the 53 controls (*p* > 0.05; table 1). In both patients and controls, the grade of inflammation detected in antral/incisural specimens was more severe than that assessed in the oxyntic samples (that is antral predominant, non-atrophic gastritis). High grade inflammation was significantly higher in the control group (*p* < 0.0001; table 2). Sixteen of the 40 patients with Barrett's oesophagus and 23 of the 31 control subjects who had non-atrophic gastritis were infected with *H pylori* (*p* < 0.009). *cagA* positive strains were detected in the 18 of the 31 controls and six of the 40 patients with Barrett's oesophagus (*p* < 0.03; table 1).

Table 2 Non-atrophic antral predominant gastritis: grade of inflammatory lesions in patients with Barrett's oesophagus and controls

	Low grade	High grade
Patients (40/53)	33	7
Controls (31/53)	13	18

One control patient had a morphological pattern consistent with atrophic (non-metaplastic) corpus predominant gastritis. On the basis of this pathological pattern, a possible autoimmune aetiology was suggested and later confirmed by appropriate serological tests. On these bases this case was excluded from further analysis.

Focal atrophic gastritis (associated with metaplastic changes) was detected in an equal number of patients and controls (five cases each) (table 1). Table 1 reports the *H pylori* status and the prevalence of *cagA* positive infection. Type I IM was present in two patients with Barrett's oesophagus and type II was found in three patients. Among the five control subjects showing focal atrophic/metaplastic changes, type I IM was present in three patients and type II in two.

Among both the patients and the controls, MAG featured loss of glands, always coexisting with IM. MAG was diagnosed in two patients with Barrett's oesophagus (table 1). In both these patients atrophic/metaplastic lesions (exclusively located in the antral and/or angular samples) featured type I IM (table 1). The only patient infected with *H pylori* had a *cagA* positive strain. Twelve control subjects had MAG (table 1) (prevalence of multifocal atrophic gastritis in patients with Barrett's oesophagus v controls, *p* < 0.01). The OR for the coexistence of MAG and Barrett's oesophagus was 0.20 (95% CI, 0.06 to 0.60). The histochemical phenotype of gastric IM among the controls was: type I in seven subjects, type II in two, and type III in the remaining three (table 1). In this group of controls, nine subjects were infected with *H pylori*, six of whom had a *cagA* positive strain.

Discussion

In the past decades, a dramatic decline in the incidence of distal gastric cancer has occurred in many populations of the industrialised

world,³⁰ whereas in these same populations the incidence of adenocarcinoma of the gastro-oesophageal junction (distal oesophagus and cardia) has increased substantially.^{31 32} Adenocarcinomas of the junction may arise from either Barrett's mucosa in the distal oesophagus or from the gastric mucosa of the cardia. The simultaneous increase of these two conditions is, however, difficult to explain because they appear to result from contrasting pathophysiological settings. Barrett's oesophagus, a consequence of gastro-oesophageal reflux disease (GERD), requires a normal (or increased) acid output. In contrast, the development of intestinal metaplasia in the cardia is mostly related to *H pylori* infection and is most often associated with decreased acid secretion.^{25 33-36} Thus, the increasing incidence of oesophageal and proximal gastric adenocarcinoma might be related to different pathobiological conditions, each with its own natural history.

Characterising the different phenotypes of the gastric mucosa is a crucial step in our quest to detect the different conditions that underlie the development of one or the other type of cancer.³⁷⁻³⁹ No systematic study has investigated the phenotype of the gastric mucosa coexisting with Barrett's oesophagus. In our present study, we have combined the histological and histochemical characterisation of the Barrett's mucosa with an extensive gastric biopsy sampling protocol and the molecular genotyping of *H pylori*.

Helicobacter pylori infection was found in a third of the patients with Barrett's oesophagus and in almost two thirds of the control patients with non-ulcer dyspepsia. This low prevalence of *H pylori* contrasts with the data available from a similar northern Italian population, in which the rate of infection was histologically documented to range from 65% (dyspeptic non-ulcer patients) to 84% (patients with gastric dysplasia).⁴⁰⁻⁴² A low prevalence of *H pylori* infection in patients with Barrett's oesophagus has been reported in other studies, which also detected a low prevalence of cagA positive strains among the infected patients.^{18 21 23} In our study, only 12 of 53 patients with Barrett's mucosa were infected with cagA positive strains. This prevalence is significantly lower than that documented in our control group (28 of 53), and that recently ascertained in the same geographical area.⁴² The significance of the inverse relation between cagA positive infection and Barrett's oesophagus (OR, 0.28; 95% CI, 0.13 to 0.61) supports the hypothesis of a mutual exclusion between Barrett's oesophagus and cagA positive *H pylori* infection.

The phenotype of the gastric mucosa in patients with Barrett's oesophagus (low grade or no inflammation and virtual absence of atrophy) is compatible with high or normal acid output, a requirement for the development of GERD.^{17 43 44} It is conceivable that the higher grade of inflammatory/atrophic mucosal lesions found in the controls results in an impairment of the acid output that (perhaps in association with other factors) prevents (or at

least does not promote) acid reflux and, therefore, does not lead to the development of Barrett's mucosa. Only two of 53 patients with Barrett's oesophagus had multifocal atrophic gastritis and none had type III gastric IM, which is known to be associated with the highest risk of stomach cancer. In contrast, multifocal atrophic gastritis was detected in 12 of the 53 control patients, three of whom had type III IM. In biological terms, the inverse relation (OR, 0.20) between Barrett's oesophagus and multifocal atrophic gastritis (a major precursor of distal gastric cancer) suggests a mutual exclusion of these two pathological conditions.

Types II and III intestinal metaplasia have long been considered to be a greater risk factor for the development of gastric adenocarcinoma than the other non-sulphated type.^{45 46} The finding that type III IM is highly prevalent in the specialised Barrett's mucosa (a site at high risk for the development of adenocarcinoma) further supports this concept.^{5 6}

A possible limitation of our study is the lack of information on the possible coexistence of IM in the cardia.^{37 47 48} Divergent data have been reported concerning the relations between *H pylori* infection and cardia intestinalisation. Data from Finland excluded a major role for the bacterium in the aetiology of the IM located at the squamocolumnar junction.³⁹ Other reports significantly associate cardia intestinalisation and *H pylori* infection, and show an inverse relation with the presence of Barrett's mucosa.^{47 49 50} The existence of two aetiological types of IM at the oesophagogastric junction has been reported recently; one being associated with *H pylori* infection and the other not associated with infection.^{37 38 51} Our data support the hypothesis that adenocarcinomas arising from Barrett's mucosa and those originating from the proximal (juxtacardial) stomach have a different morphogenesis.

In conclusion, our study showed that patients with Barrett's oesophagus are mostly affected by mild, non-atrophic, antral predominant gastritis. In these patients, the rates of *H pylori* infection (particularly with cagA positive strains) and multifocal atrophic gastritis are lower than would be expected in the same epidemiological context. The low prevalence of gastric atrophic/metaplastic lesions makes patients with Barrett's oesophagus at low risk of (distal) intestinal-type cancer development. Conversely, the high prevalence of the sulphomucin positive type III IM in the Barrett's mucosa is consistent with the high risk of oesophageal adenocarcinoma.

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