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ORIGINAL ARTICLE

Retrospective Cohort Study

Gastric intestinal metaplasia is associated with gastric dysplasia but is inversely correlated with esophageal dysplasia

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Abstract

AIM

To determine which clinical factors might be associated with gastric intestinal metaplasia (IM) in a North American population.

METHODS

Pathology and endoscopy databases at an academic

medical center were reviewed to identify patients with and without gastric IM on biopsies for a retrospective cohort study. Patient demographics, insurance status, and other clinical factors were reviewed.

RESULTS

Four hundred and sixty-eight patients with gastric IM (mean age: 61.0 years ± 14.4 years, 55.5% female) and 171 without gastric IM (mean age: 48.8 years ± 20.8 years, 55.0% female) were compared. The endoscopic appearance of atrophic gastritis correlated with finding gastric IM on histopathology (OR = 2.05, P = 0.051). Gastric IM was associated with histologic findings of chronic gastritis (OR = 2.56, P < 0.001), gastric ulcer (OR = 6.97, P = 0.015), gastric dysplasia (OR = 6.11, P = 0.038), and gastric cancer (OR = 6.53, P = 0.027). Histologic findings of Barrett's esophagus (OR = 0.28, P = 0.003) and esophageal dysplasia (OR = 0.11, P = 0.014) were inversely associated with gastric IM. Tobacco use (OR = 1.73, P = 0.005) was associated with gastric IM.

CONCLUSION

Patients who smoke or have the endoscopic finding of atrophic gastritis are more likely to have gastric IM and should have screening gastric biopsies during esophagogastroduodenoscopy (EGD). Patients with gastric IM are at increased risk for having gastric dysplasia and cancer, and surveillance EGD with gastric biopsies in these patients might be reasonable.

Key words: Gastric; Intestinal metaplasia; Atrophic gastritis; Biopsies; Esophagogastroduodenoscopy

Core tip: Gastric intestinal metaplasia (IM) is a precursor to gastric adenocarcinoma. There are no North American consensus recommendations as to which patients might benefit from esophagogastroduodenoscopy (EGD) with biopsy for screening or surveillance for gastric IM. Patients who smoke or have the endoscopic finding of atrophic gastritis are more likely to have gastric IM and should have screening gastric biopsies during EGD. Patients with gastric IM are at increased risk for developing gastric dysplasia and cancer, and surveillance EGD with gastric biopsies in these patients might be reasonable.

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INTRODUCTION

Gastric cancer is the fifth leading type of cancer worldwide, with 952000 new cases diagnosed in 2012. With 723000 reported deaths in 2012, gastric cancer is the third most common cause of cancer-related mortality[1,2]. The annual incidence of gastric cancer in 2013 based upon the SEER database was 7.5 per 100000 persons with an annual death rate of 3.5 cases per 100000 in the United States population[3]. The lower prevalence of gastric cancer in Western countries is also associated with the diagnosis of gastric cancer at a later stage, which results in a poor 5-year survival of 20% within the United States[4]. Patients diagnosed with early stage gastric carcinoma have a significantly better prognosis with 5-year survival rates approaching 90%[5,6].

The mechanisms responsible for gastric carcinogenesis are not completely known. However, gastric cancer is thought to arise from a premalignant cascade potentially initiated by *Helicobacter pylori* (*H. pylori*) infection[7-9]. In 1988, Correa[10] first described a pathway through which premalignant lesions could become gastric cancer. This cascade progresses from non-atrophic gastritis to atrophic gastritis, gastric intestinal metaplasia (IM), gastric dysplasia, and ultimately gastric carcinoma. Gastric IM has since become well established as a premalignant lesion that is associated with an increased risk of gastric carcinoma[11-13]. The largest observational study of patients with precancerous gastric lesions in the Western world included 61707 individuals with gastric IM and found an annual incidence of progression to gastric cancer of 0.25%[14].

Gastric IM is characterized by a change from the normal glandular epithelium found in the stomach to a small-intestinal phenotype. The pathogenesis of gastric IM remains unclear but is thought to involve environmental stimuli that lead to differentiation of the gastric stem cells towards an intestinal phenotype[15-17]. Pathologically, gastric IM can be recognized by the presence of a simple columnar epithelium containing Paneth cells, absorptive cells, and goblet cells[15]. Additionally, gastric IM may be classified further based on histologic appearance into complete (type Ⅰ) and incomplete (type Ⅱ or Ⅲ). Complete (type Ⅰ) gastric IM is recognized by the presence of a small intestinal mucosal phenotype with goblet cells containing sialomucins interspersed between absorptive cells and a well-defined brush border. Incomplete (type Ⅱ or Ⅲ) gastric IM is characterized by a colonic mucosal phenotype with tortuous crypts lined by tall columnar cells containing sulfomucins[18]. The incomplete pattern of gastric IM is associated with the greatest risk of progression to gastric cancer[19-25]. A study completed in Spain found that the incidence of gastric cancer in patients with incomplete IM was 16 (18.2%) out of 88 patients and 1 (0.96%) out of 104 patients with complete IM when followed for a mean of 12.8 years[26]. However, in practice pathologists, even

at most academic institutions, do not typically make the distinction between different types of gastric IM. The two types of incomplete IM are based on sulfomucin content, which cannot be determined by hematoxylin and eosin (H and E) staining alone. Pathologically, this distinction may be difficult to make as incomplete and complete gastric IM can coexist, and the finding of gastric IM can be very focal even on a small biopsy specimen.

The prevalence of gastric IM in the general population is difficult to assess due to the fact that it is an asymptomatic lesion that can only be found on histologic evaluation of gastric tissue, typically obtained by esophagogastroduodenoscopy (EGD). In 2010, Sonnenberg *et al*[27] published the results from a retrospective study of 78985 patients undergoing EGD and gastric biopsy in the United States and found that the prevalence of gastric IM was 7%. Within this patient population there was a continuous age-dependent rise in finding gastric IM from age 0 to 90 years. Furthermore, the frequency of gastric IM is geographically variable, as shown by a Chinese study that found gastric IM in 29.3% of 1630 consecutive patients with *H. pylori* infection presenting for a screening EGD[28,29].

Guidelines put forth by the European Society of Gastrointestinal Endoscopy (ESGE) in 2012 recommended that at least two biopsies from the antrum (greater and lesser curvature) and two biopsies from the corpus (greater and lesser curvature) be taken for adequate assessment of premalignant gastric conditions. These guidelines recommended that patients with extensive atrophic gastritis or gastric IM should be offered surveillance endoscopy every 3 years. They also recommended that if *H. pylori* infection is diagnosed, then eradication should be offered to decrease the progression to dysplasia and carcinoma[30]. Despite strong epidemiologic and molecular data linking gastric IM and gastric carcinoma, there are currently no North American consensus guidelines as to which patients might benefit from EGD with biopsy for screening or surveillance endoscopy[22]. The aim of this study was to determine what clinical factors might be associated with gastric IM in a United States population so as to identify potential indications for screening and/or surveillance by using EGD with gastric biopsies.

MATERIALS AND METHODS

This study was conducted at University of Virginia Medical Center, a single tertiary-care hospital that performs both outpatient and inpatient endoscopic procedures for patients from a wide geographic area (including significant portions of Virginia, West Virginia, and Tennessee). This study was approved by our institutional review board.

Pathology and endoscopy databases were reviewed to identify patients with and without gastric IM. Patients who had pathology-confirmed gastric IM from 2005-2011 were extracted from a dedicated pathology database. Using an endoscopic billing database, a control group of patients was established by reviewing 300 consecutive patients who had undergone EGD with biopsies (186 patients had gastric biopsies) from March to June 2011, from which 171 patients were identified who had gastric biopsies without gastric IM. The rate of gastric IM in this control group of patients was 5%, which we have previously reported[31]. All upper endoscopies were performed by experienced gastrointestinal endoscopists, and all pathological diagnoses included in this study were made by academic pathologists at our institution. Diagnosis of gastric IM was made histologically on H and E-stained slides. Diagnosis of *H. pylori* infection was made histologically using immunohistochemical stains.

Electronic medical records, including pathology and endoscopy reports, were reviewed and information about patient demographics, insurance status, and possible risk factors for the development of gastric IM and gastric dysplasia was collected. Potential risk factors of interest included a first-degree family history of gastric cancer, presence of *H. pylori* infection on gastric biopsy, and certain clinical indications for endoscopy. Additional patient characteristics of interest included social factors such as lifetime history of tobacco use, alcohol use (if reported within the past year), and acid suppression therapy with proton-pump inhibitors or H_2-receptor antagonists. Unfortunately, ethnic background was not available for analysis, as data from earlier patients were derived from a different electronic medical record system that did not reliably capture this information.

Frequency data were summarized as percentages and analyzed by exact logistic regression. Continuous variables were summarized by the median and range of distribution. Univariate and age-adjusted multivariate analyses were conduct by way of exact logistic regression to compare patient outcomes between those with and without gastric IM. A two-sided $P \leqslant 0.05$ decision rule was established a priori as the null hypothesis rejection criterion, and 95%CI construction for the OR was based on the Mid-P method[32]. The exact statement of the SAS version 9.2 LOGISTIC procedure was utilized to conduct the exact logistic regression analyses (SAS Institute Inc., Cary, NC).

RESULTS

Patients and demographics

Four hundred and sixty-eight patients (mean age: 61.0 years ± 14.4 years, 55.5% female) with gastric IM diagnosed on gastric histopathology and 171 patients (mean age: 48.8 years ± 20.8 years, 55.0% female) without gastric IM on gastric biopsies were included in this study. Refer Table 1 for patient characteristics.

Patients with pathologically-diagnosed gastric IM were statistically more likely to be older ($P < 0.001$). When insurance status was evaluated, patients with Medicare were significantly more likely to have gastric IM [OR 1.94 (1.20, 3.17), $P = 0.007$], whereas patients with private insurance were less likely to have gastric IM [OR 0.66 (0.44, 0.99), $P = 0.047$]. We did not detect

Table 1 Patient characteristics and their associations with gastric intestinal metaplasia

	Gastric IM (+) *n* = 468	Gastric IM (-) *n* = 171	Univariate analysis	Multivariate analysis [OR (95%CI)]
Age (mean/median, yr)	61.0/64.0	48.8/53.0	$P < 0.001$	--
Male sex	208 (44.4%)	77 (45.0%)	$P = 0.928$	--
Family history of gastric cancer	23 (5.7%)[1]	5 (2.9%)	$P = 0.557$	1.38 (0.52, 4.25), $P = 0.555$
Tobacco use	214 (48.6%)[2]	61 (36.5%)[3]	$P = 0.007$	1.73 (1.18, 2.55), $P = 0.005$
Alcohol use	100 (22.7%)[2]	46 (26.9%)	$P = 0.219$	0.76 (0.50, 1.16), $P = 0.199$
H2-blocker use	21 (5.1%)[4]	13 (7.6%)	$P = 0.251$	0.74 (0.35, 1.59), $P = 0.426$
PPI use	258 (62.6%)[4]	94 (55.6%)	$P = 0.088$	1.23 (0.84, 1.79), $P = 0.282$
Medicare	245 (52.4%)	46 (26.9%)	$P < 0.001$	1.94 (1.20, 3.17), $P = 0.007$
Medicaid	24 (5.1%)	27 (15.8%)	$P = 0.003$	0.57 (0.30, 1.09), $P = 0.090$
Private insurance	118 (25.2%)	72 (42.1%)	$P < 0.001$	0.66 (0.44, 0.99), $P = 0.047$
Uninsured	68 (14.5%)	32 (18.7%)	$P = 0.885$	1.04 (0.64, 1.71), $P = 0.885$

[1]Information about family history was missing from 65 patients who had gastric intestinal metaplasia; [2]Information about social history was missing from 28 patients who had gastric intestinal metaplasia; [3]Information about tobacco use was missing from 4 patients who did not have gastric intestinal metaplasia; [4]Information about H2-blocker and/or PPI use was missing from 56 patients who had gastric intestinal metaplasia. IM: Intestinal metaplasia; PPI: Proton-pump inhibitor.

Table 2 Association among indications and gastric intestinal metaplasia

	Frequency in patients with gastric IM[1]	Frequency in patients without gastric IM[1]	Univariate analysis	Multivariate analysis [OR (95%CI)]
Abdominal pain	188 (41.7%)	93 (54.4%)	$P = 0.005$	0.81 (0.55, 1.18), $P = 0.267$
Weight loss	63 (13.5%)	21 (7.4%)	$P = 0.014$	1.81 (0.95, 3.66), $P = 0.073$
GI bleed	38 (8.4%)	13 (7.6%)	$P = 0.755$	1.23 (0.63, 2.52), $P = 0.558$
Nausea	60 (13.3%)	27 (15.8%)	$P = 0.426$	0.97 (0.58, 1.65), $P = 0.903$
Dysphagia	59 (13.1%)	26 (15.2%)	$P = 0.490$	0.74 (0.44, 1.26), $P = 0.259$
Barrett's esophagus	10 (2.2%)	8 (4.7%)	$P = 0.123$	0.32 (0.12, 0.92), $P = 0.034$

[1]The denominator (n) used to calculate the percentage of patients by indication (in each row) may vary depending on what was available from the clinical records. IM: Intestinal metaplasia; GI: Gastrointestinal.

a statistically significant association between a positive family history of gastric cancer and gastric IM. A history of recent alcohol abuse was not associated with gastric IM; whereas, a lifetime history of tobacco abuse was significantly associated with gastric IM [OR 1.73 (1.18, 2.55), $P = 0.005$].

Indication for endoscopy

Four hundred and eighteen patients with pathology-proven gastric IM and all 171 controls without gastric IM underwent EGD with gastric biopsies. Among indications for procedures (Table 2), Barrett's esophagus [OR 0.32 (0.12, 0.92), $P < 0.034$] was associated with an inverse association with gastric IM on multivariate analysis. Whereas, weight loss correlated with a trend towards increased frequency of gastric IM [OR 1.81 (0.95, 3.66), $P = 0.073$].

Endoscopic findings

The two most frequent endoscopic findings (Table 3) on EGD (prior to any pathologic confirmation) in this patient population were gastritis (137/589, 23.3% for all patients) and gastric mucosal nodularity (104/589, 17.7%).

Endoscopic findings of a gastric mass [OR 8.84 (1.88, ∞), $P = 0.005$] and atrophic gastritis [OR 2.05 (1.00, 4.58), $P = 0.051$] were significantly associated with finding gastric IM on histopathology by multivariate analysis. The endoscopic appearance of duodenal polyps [OR 4.21 (0.81, ∞), $P = 0.081$] trended towards an increased association with finding gastric IM on biopsies. On multivariate analysis, the esophageal abnormalities of an esophageal mass [OR 0.04 (0.01, 0.16), $P < 0.001$], esophagitis [OR 0.49 (0.26, 0.91), $P = 0.023$], and Barrett's esophagus [OR 0.56 (0.26, 1.21), $P = 0.134$] were found to inversely correlate with finding gastric IM on histopathology.

Histopathological diagnoses

When all patients with and without gastric IM were considered, the most frequent histologic diagnoses encountered were chronic gastritis (305/639, 47.7%) and gastric polyps (46/639, 7.2%). Histologic diagnoses and associations for patients with and without gastric IM found on surgical pathology are shown in Table 4.

On univariate and multivariate analyses, patients with biopsy-proven gastric IM were found to have an increased association with the following gastric histopathological diagnoses (multivariate odds ratios are reported): Chronic gastritis [OR 2.56 (1.75, 3.76), $P < 0.001$], gastric ulcer [OR 6.94 (1.47, ∞), $P = 0.015$], gastric dysplasia [OR 6.11 (1.07, 131.57), $P = 0.038$], gastric cancer [OR 6.53 (1.17, 139.41), $P = 0.027$], and autoimmune metaplastic atrophic gastritis [OR 5.64

Table 3 Associations among endoscopic findings (prior to or without histopathology) and gastric intestinal metaplasia

	Frequency in patients with gastric IM, *n* = 418	Frequency in patients without gastric IM, *n* = 171	Univariate analysis	Multivariate analysis (OR, 95%CI)
Gastritis	100 (23.9%)	37 (21.6%)	$P = 0.557$	1.34 (0.84, 2.08), $P = 0.223$
Atrophic gastritis	55 (13.2%)	9 (5.3%)	$P = 0.004$	2.05 (1.00, 4.58), $P = 0.051$
Gastric mass	20 (4.8%)	0 (0%)	$P = 0.001$	8.84 (1.88, ∞), $P = 0.005$
Gastric ulcer	42 (10.0%)	11 (6.4%)	$P = 0.163$	1.42 (0.71, 3.01), $P = 0.339$
Gastric nodularity	71 (17.0%)	33 (19.3%)	$P = 0.503$	0.74 (0.46, 1.20), $P = 0.213$
Linitis plastica	1 (0.2%)	0 (0%)	$P = 0.710$	0.27 (0.01, ∞), $P = 0.788$
Esophagitis	28 (6.7%)	23 (13.4%)	$P = 0.011$	0.49 (0.26, 0.91), $P = 0.023$
Esophageal mass	2 (0.5%)	13 (7.6%)	$P < 0.001$	0.04 (0.01-0.16), $P < 0.001$
Barrett's esophagus	21 (5.0%)	13 (7.6%)	$P = 0.235$	0.56 (0.26, 1.21), $P = 0.134$
Duodenitis	17 (4.1%)	11 (6.4%)	$P = 0.234$	0.69 (0.30, 1.60), $P = 0.337$
Duodenal polyp	8 (1.9%)	0 (0%)	$P = 0.063$	4.21 (0.81, ∞), $P = 0.081$
Duodenal mass	4 (1.0%)	0 (0%)	$P = 0.253$	1.58 (0.26, ∞), $P = 0.353$
Duodenal ulcer	2 (0.5%)	2 (1.2%)	$P = 0.407$	0.21 (0.02, 2.20), $P = 0.179$

IM: Intestinal metaplasia.

Table 4 Association among histopathological biopsy results and gastric intestinal metaplasia

	Frequency in patients with gastric IM, *n* = 468	Frequency in patients without gastric IM, *n* = 171	Univariate analysis	Multivariate analysis (OR)
Chronic gastritis	265 (56.6%)	55 (32.2%)	$P < 0.001$	2.56 (1.75, 3.76), $P < 0.001$
Gastric polyp	35 (7.5%)	11 (6.4%)	$P = 0.669$	1.07 (0.53, 2.31), $P = 0.861$
MALT lymphoma	5 (1.1%)	0 (0.0%)	$P = 0.209$	1.48 (0.26, ∞), $P = 0.372$
Erosive gastritis	1 (0.2%)	6 (3.5%)	$P = 0.002$	0.06 (0.0, 0.43), $P = 0.003$
H. pylori infection	46 (9.8%)	6 (3.5%)	$P = 0.007$	3.07 (1.33, 8.20), $P = 0.007$
Gastric ulcer	18 (3.8%)	0 (0%)	$P = 0.003$	6.97 (1.47, ∞), $P = 0.015$
Gastric dysplasia	19 (4.1%)	1 (0.6%)	$P = 0.017$	6.11 (1.07, 131.57), $P = 0.038$
Gastric cancer	21 (4.5%)	1 (0.6%)	$P = 0.010$	6.53 (1.17, 139.41), $P = 0.027$
Autoimmune metaplastic atrophic gastritis	12 (2.6%)	0 (0%)	$P = 0.023$	5.64 (1.36, ∞), $P = 0.035$
Esophagitis	5 (1.1%)	5 (2.9%)	$P = 0.125$	0.36 (0.09, 1.41), $P = 0.138$
Barrett's esophagus	14 (3.0%)	13 (7.6%)	$P = 0.016$	0.28 (0.12, 0.63), $P = 0.003$
Esophageal dysplasia	2 (0.4%)	4 (2.3%)	$P = 0.053$	0.11 (0.01, 0.64), $P = 0.014$
Esophageal cancer	1 (0.2%)	1 (0.6%)	$P = 0.535$	0.13 (0.01, 9.88), $P = 0.402$
Eosinophilic esophagitis	1 (0.2%)	6 (3.5%)	$P = 0.002$	0.10 (0.00, 0.74), $P = 0.020$
Carcinoid tumor	10 (2.1%)	0 (0%)	$P = 0.043$	5.13 (1.02, ∞), $P = 0.047$
Duodenitis	2 (0.4%)	6 (3.5%)	$P = 0.006$	0.13 (0.02, 0.65), $P = 0.012$
Duodenal polyp	5 (1.1%)	1 (0.6%)	$P = 0.645$	1.2 (0.16, 29.49), $P = 0.944$
Duodenal ulcer	2 (0.4%)	0 (0%)	$P = 0.536$	0.63 (0.07, ∞), $P = 0.628$

IM: Intestinal metaplasia; *H. pylori*: *Helicobacter pylori*; MALT: Mucosa-associated lymphoid tissue.

(1.36, ∞), $P = 0.035$]. Patients with *H. pylori* infection on gastric pathology also had a significant association with gastric IM [OR 3.07 (1.33, 8.20), $P = 0.007$].

Patients with gastric IM were found to have an inverse association with pathology-proven duodenitis [OR 0.13 (0.02, 0.65), $P = 0.012$]. Furthermore, gastric IM was inversely associated with several esophageal histopathological diagnoses including Barrett's esophagus [OR 0.28 (0.12, 0.63), $P = 0.003$], esophageal dysplasia [OR 0.11 (0.01, 0.64), $P = 0.014$], and eosinophilic esophagitis [OR 0.1 (0.0, 0.74), $P = 0.02$].

DISCUSSION

Although the incidence of gastric cancer is relatively low within the United States, the 5-year survival for this disease remains poor. In large part, this is because gastric neoplasia is frequently diagnosed at an advanced stage when endoscopic and surgical therapies are less effective. There is a relative paucity of data concerning the frequency and significance of premalignant gastric lesions within the United States population. Best estimates of the prevalence of gastric IM in patients undergoing EGD with biopsy is probably between 5%-7%[27,31]. With an estimated 7 million EGDs done each year in the United States[33], this represents at least 350000 patients with gastric IM who could be diagnosed by the addition of a just a few gastric biopsies to these routine procedures.

Gastric IM is widely accepted as a premalignant lesion that can lead to gastric carcinoma[10]. Uemura *et al*[34] followed 1246 patients with *H. pylori* and gastric IM over a mean of 7.8 years and found that gastric cancer developed in 36 patients with a relative risk of 6.4 (2.6, 16.1), $P < 0.001$. In the present study, gastric IM was similarly associated with a six-fold increased odds ratio of finding gastric cancer [OR 6.53 (1.17, 139.41), $P =$

0.027].

H. pylori infection is recognized as one of the primary risk factors leading to the development of atrophic gastritis and gastric IM[8,9,23], which is probably a consequence of having a long-term chronic inflammatory state. Our study demonstrated a statistically significant association between gastric IM and *H. pylori* infection [OR 3.07 (1.33, 8.19), $P = 0.007$], as might be expected. Several prior studies have attempted to induce regression of gastric IM through treatment of *H. pylori* infection with varying results. A recent metaanalysis by Wang *et al*[35] included 12 studies and a total of 2658 patients with atrophic gastritis and gastric IM. They found that atrophic gastritis in the antrum can be reduced through treatment of *H. pylori* infection; however, atrophic gastritis in the corpus or gastric IM regardless of location in the stomach failed to regress with eradication of *H. pylori*. This observation that once gastric IM develops that subsequent *H. pylori* treatment might be ineffective supports the hypothesis that gastric IM is likely a breakpoint in the carcinogenic pathway leading to gastric cancer.

A large Dutch study by de Vries *et al*[36] of 61707 patients with gastric IM found that 874 patients developed a new diagnosis gastric cancer when followed over 10 years. The annual incidence of gastric cancer among patients with gastric IM in this study was 0.25%. Although these patients were followed for a total of 10 years, the median interval between diagnosis of gastric IM and gastric cancer was only 0.9 years. These data take on new meaning when compared to the annual incidence of Barrett's esophagus progressing to adenocarcinoma, which is estimated to range between 0.12% and 0.5%[37]. Paradoxically, in the West, screening and surveillance guidelines for Barrett's esophagus have been in place for over a decade, and they are widely practiced; whereas multi-society or multi-national consensus on the screening and surveillance for gastric IM is lacking in Western nations. In 2002, Whiting *et al*[38] published a study conducted in the United Kingdom that examined if annual endoscopic surveillance could detect new cases of gastric cancer at an earlier and possibly curative stage. The study followed 1753 patients over 10 years, and 14 new cases of gastric cancer were diagnosed at earlier stages (67% were stage Ⅰ and Ⅱ *vs* 23% stage Ⅲ or Ⅳ; $P < 0.05$).

Part of the difficulty in reaching North American guidelines is the lack of consensus among practicing gastroenterologists in the United States regarding the management of gastric IM. Our group, in conjunction with University of Virginia Center for Survey Research, conducted a survey of American Society for Gastrointestinal Endoscopy (ASGE) members that resulted in 162 responding endoscopists (85% gastroenterologists, 82% men, from 32 states, 53% in private practice). This survey uncovered that while 56% of these physicians considered gastric IM to be a premalignant lesion, only 26% screen for gastric IM, but 42% survey for gastric IM (at a time interval anywhere between 6 mo and 5 years). Importantly, 97% of respondents felt that societal guidelines for management of premalignant gastric lesions would be beneficial to clinical practice[39]. These results were further supported by a study by Vance *et al*[40] that showed "variability in the knowledge and practice patterns of United States endoscopists related to surveillance of gastric intestinal metaplasia".

In the 2006 ASGE guideline, "the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract", it was stated that "endoscopic surveillance for gastric IM has not been extensively studied in the United States and therefore cannot be uniformly recommended". However, those guidelines did recommend that "patients at increased risk for gastric cancer due to ethnic background or family history may benefit from surveillance"[22]. In this present study, family history of gastric cancer had an increased odd of being associated with the presence of gastric IM, but this finding was not significant, which could be due to a lack of power. European/ESGE guidelines published in 2012 recommended surveillance endoscopy for patients with extensive atrophic gastritis or gastric IM based on evidence from strong systematic reviews and large cohort studies. They did, however, note that future prospective studies were required to assess the cost-effectiveness of surveillance endoscopy in this patient population[30]. In 2014, Areia *et al*[41] conducted a cost-utility economic analysis from a societal perspective in Portugal using a Markov model and found that endoscopic surveillance every 3 years for patients with premalignant gastric conditions such as extensive atrophy or IM was cost-effective. Recently, Kim *et al*[42] have advocated that "Gastric cancer screening with endoscopy should be considered in individuals who are immigrants from regions associated with a high risk of gastric cancer (East Asia, Russia, or South America) or who have a family history of gastric cancer. Those with findings of atrophic gastritis or intestinal metaplasia on screening endoscopy should undergo surveillance endoscopy every 1 to 2 years".

Limitations of this present study include that it was a retrospective study conducted at a single academic medical center and that we did not have complete data on patient ethnicity to review. Data from 2010 from the United States Census Bureau about Albemarle County, Virginia (which is where the University of Virginia is located) reports the following ethnic demographics for its residents: 63.7% are White, 16.3% are Hispanic or Latino, 12.6% are Black or African American, 4.8% are Asian, 0.9% are American Indian or Alaska Native, and 0.2% are Native Hawaiian or other Pacific Islander. As such, the vast majority of patients in our study were White, Hispanic, or Black. Despite including a large number of patients with gastric IM, which remains a somewhat uncommon finding in the United States, our study could still be limited by a lack of statistical power.

In this study, we demonstrated that patients with biopsy-proven gastric IM were significantly more likely to be cigarette smokers and to have endoscopic findings

of gastric atrophy, which should prompt at least gastric biopsies (preferably *via* systematic endoscopy for gastric mapping[43] and with multiple biopsies taken from the antrum, incisura, lesser curve, and gastric body) during EGD to histopathologically confirm atrophic gastritis and also to screen for gastric IM. When multifocal, extensive, or incomplete gastric IM are found, we believe that surveillance endoscopy is reasonable, which we and others[20] conduct at 3-year intervals in the absence of any dysplasia. If focal areas of dysplasia or early gastric cancers are found, then we offer endoscopic mucosal resection or endoscopic submucosal dissection[44,45], when appropriate[46], in addition to more frequent endoscopic surveillance. Again, in this context, our data demonstrated that the presence of gastric IM is clinically significant, as this condition was associated with the pathologic findings of gastric dysplasia and cancer.

Interestingly, our study showed that gastric IM appears to confer a protective effect against the development of esophageal pathology including esophagitis, Barrett's esophagus, and esophageal dysplasia. The most likely etiology for this inverse relationship among gastric IM and these esophageal pathologies is the reduction in gastric acid secretion found in patients with atrophic gastritis and gastric IM.

In summary, we hope that the data presented in this study might be of use as guidelines and recommendations concerning the screening and surveillance of gastric IM and other premalignant gastric lesions in a United States patient population are developed. Patients who smoke or have the endoscopic finding of atrophic gastritis are significantly more likely to also have gastric IM, and these risk factors should prompt screening gastric biopsies during EGD. Patients with gastric IM are at increased risk for developing gastric dysplasia and cancer, and a program of surveillance biopsies in these patients might be reasonable. Conversely, patients with gastric IM appear significantly less likely to be diagnosed with Barrett's esophagus and esophageal dysplasia.

COMMENTS

Background

Gastric intestinal metaplasia (IM) is a precursor to gastric adenocarcinoma. However, there are no North American consensus recommendations as to which patients might benefit from esophagogastroduodenoscopy (EGD) with biopsy for screening or surveillance for gastric IM.

Research frontiers

Endoscopic technology has advanced significantly in the past two decades, and high-definition white-light endoscopy and advanced optical imaging techniques now allow accurate real-time diagnosis of luminal gastrointestinal disorders, which formerly required formal histopathologic review of biopsy specimens. Careful endoscopic examination remains critical to the correct diagnosis of conditions such as atrophic gastritis, gastric intestinal metaplasia, and early gastric cancers.

Innovations and breakthroughs

In Western nations and populations, the epidemiological risk of gastric IM has been largely ignored given the lower prevalence of gastric cancer, as compared to Asian, South American, and Eastern European populations. However, data are re-emerging that demonstrate that gastric IM can be an important problem in Western populations. In the present study, gastric IM was associated with a statistically significant six-fold increased odds ratio of finding gastric cancer. Being mindful of clinical demographic factors and findings on endoscopic evaluation of the stomach can assist in determining which patients might benefit from screening gastric biopsies. Proper diagnosis of gastric IM might also identify a patient population that might benefit from surveillance endoscopy.

Applications

Patients who smoke or have the endoscopic finding of atrophic gastritis are more likely to have gastric IM and should have screening gastric biopsies during EGD. Patients with gastric IM are at increased risk for having gastric dysplasia and cancer, and surveillance EGD with gastric biopsies in these patients might be reasonable.

Terminology

Gastric intestinal metaplasia is characterized by the replacement of the normal gastric glandular epithelium by a small-intestinal phenotype, and it often accompanies or follows chronic *Helicobacter pylori* infection of the stomach. Dysplasia is an abnormal change to tissue (in this case the gastric epithelium) that is considered premalignant. EGD is a procedure performed using a flexible endoscope whereby endoscopic views of the upper gastrointestinal tract (esophagus, stomach and duodenum) are obtained. EGD can also enable sampling of the mucosa of the upper gastrointestinal tract, often by using cold biopsy forceps.

Peer-review

This is a valuable attempt to analyze IM with the development of gastric cancer. It is a well conducted and well written study.

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