

The Presence of Gastric Intestinal Metaplasia in Patients Undergoing EGD with Biopsy is Associated with a Family History of Gastric Cancer in the United States

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regarding the screening and surveillance of premalignant gastric lesions emerge, attention should be paid to patients with a family history of gastric cancer, and possibly those with lower socioeconomic status who might be at increased risk for gastric IM.

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Key words: Gastric intestinal metaplasia; Gastritis; EGD; Biopsy; Gastric cancer; Insurance

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ABSTRACT

AIM: Gastric intestinal metaplasia (IM) is a pre-malignant lesion that can develop into adenocarcinoma through a sequential cascade involving non-atrophic gastritis, atrophic gastritis, IM, gastric dysplasia, and ultimately carcinoma. To estimate the prevalence of gastric IM in patients undergoing EGD with biopsy at an academic medical center; and determine what clinical factors might be associated with gastric IM.

METHODS: Three hundred consecutive patients presenting for EGD with biopsy at a tertiary-care medical center were enrolled in a retrospective single-center cohort study.

RESULTS: Gastric biopsies found *H. pylori* infection in 2% ($n=6$), chronic gastritis in 20% ($n=61$), and gastric IM in 5% ($n=15$) of patients. A first-degree family history of gastric cancer was a risk factor for having gastric IM (OR 8.51, 95% CI: 1.52-40.22, $P=0.018$) on age-adjusted multivariate analysis. Uninsured patients (OR 5.1, 95% CI: 2.4-11.2, $P<0.001$) and those with Medicaid (OR 3.6, 95% CI: 1.3-9.7, $P=0.014$) were more likely to have chronic gastritis as compared to those with private insurance on age-adjusted multivariate analysis.

CONCLUSION: A family history of gastric cancer significantly increased the odds of having gastric IM. Uninsured patients and those with Medicaid were at increased risk of having chronic gastritis and trended towards having IM on gastric biopsies. As guidelines

INTRODUCTION

Gastric intestinal metaplasia (IM) is defined by the replacement of the normal gastric glandular epithelium by intestinal epithelium, which is recognized by the presence of goblet cells, Paneth cells, and absorptive cells. The pathogenesis of gastric IM is believed to include differentiation of gastric stem cells towards a small intestinal epithelial phenotype, potentially as an adaptive response to adverse environmental factors^[1-3]. Several subgroups of gastric IM are currently recognized including complete (Type 1) and incomplete (Type II, III) based on the classification system described by Filepe *et al*^[4]. Based on retrospective data, type I gastric IM is associated with a relatively low risk of gastric cancer, whereas type III has a stronger association with gastric cancer^[4-8]. Gastric IM is more prevalent among men than women, and shows a continuous age-dependent rise^[9]. Finally, gastric IM is considered a pre-malignant lesion that can develop into gastric adenocarcinoma through a sequential cascade initially described by Correa *et al*^[10] involving non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, gastric dysplasia, and ultimately carcinoma.

H. pylori (HP) is a gram-negative, spiral, urease-producing organism that is associated with gastric and duodenal ulcers, chronic gastritis, and mucosa-associated lymphoid tissue (MALT) lymphoma. Chronic infection with HP is known to play a role in the

development of atrophic gastritis and gastric IM^[9,11]. Prospective studies in populations with a high prevalence of HP have shown a 10-fold increased risk of gastric cancer among patients with chronic HP infection^[12,13]. As a result the World Health Organization classified HP as a class 1 or definite human carcinogen in 1994.

Gastric cancer is the fourth most common cause of cancer worldwide with 974000 new cases diagnosed in 2002 (8.6% of all newly diagnosed cancers), and it is the second leading cause of cancer-related death with 700000 deaths related to gastric cancer in 2002^[14,15]. The early stages of gastric cancer are typically asymptomatic, and the diagnosis is typically made at an advanced stage. In Western countries with a lower incidence of gastric IM, the 5-year survival rate for gastric cancer is less than 20%^[16]. The incidence of gastric cancer has declined over the past several decades partially due to the recognition of certain risk factors including HP infection. Despite the epidemiologic link between gastric IM and adenocarcinoma, there are no clear guidelines regarding who to screen; at what interval; and if screening identifies gastric IM, whether or not gastric surveillance should be pursued. The role of screening and/or surveillance for gastric IM is particularly unclear in the United States, where gastric adenocarcinoma is uncommon^[5]. As such, our aims were (1) to determine the frequency of gastric IM in patients undergoing EGD with biopsy at a tertiary academic medical center that included both insured and uninsured patients; and (2) to determine what clinical factors might be associated with gastric IM.

METHODS

Consecutive patients who underwent EGD with biopsies, from March to June 2011, at the University of Virginia, were identified by reviewing a billing database. Patients' electronic medical records were subsequently reviewed to attain demographics, insurance status, and other potential risk factors that might be associated with gastric IM. Risk factors of interest included family history of gastric dysplasia or gastric cancer among first-degree relatives, presence of HP infection on gastric biopsy, and the clinical indications for endoscopy. Additional patient characteristics of interest included a history of alcohol or tobacco abuse, and whether patients were taking a proton-pump inhibitor or H2-blocker therapy. The endoscopic diagnoses made visually at time of EGD were compared to the histopathologic diagnoses found on gastric biopsies. High-definition gastroscopes (GIF-H180, Olympus America, Center Valley, PA) were used for nearly all cases. All pathological diagnoses included in this study were made by academic pathologists at the University of Virginia. This study was approved by our IRB.

Frequency data were summarized as percentages and analyzed by Fisher's exact tests and exact logistic regression. Continuous variables were summarized by the median and the range of the measurement distribution. Age-adjusted multivariate analyses were performed by way of exact logistic regression to examine the association between pathological diagnosis and type of health care coverage. The statistical software package; SAS version 9.2 (SAS Institute Inc., Cary NC), was used to conduct the statistical analyses.

RESULTS

Three hundred patients who underwent EGD and biopsy were included in the study, 54.3% ($n=163$) of patients were female, and the median age was 53.0 years (range: 1 to 91 years). Types of health care coverage included private insurance for 44% ($n=132$), Medicare for 29% ($n=87$), Medicaid for 9.7% ($n=29$), and uninsured for 15.3% ($n=52$) of patients.

Pathological diagnoses from gastric biopsies

Histopathological analysis of gastric biopsies found the following diagnoses: HP infection in 2% ($n=6$), chronic gastritis in 20% ($n=61$), gastric IM in 5% ($n=15$), gastric dysplasia in 0.7% ($n=2$), and gastric cancer in 0.03% ($n=1$) of patients. The pathological diagnoses found on gastric biopsies are listed in table 1.

Table 1 Frequency of pathologic diagnoses among patients undergoing EGD with biopsy

<i>H. Pylori</i> infection	Chronic gastritis	Gastric IM	Gastric dysplasia	Gastric cancer
6 (2%)	61 (20.3%)	15 (5%)	2 (0.7%)	1 (0.03%)

Demographic associations with gastric IM

A family history of a first-degree relative with gastric cancer was associated with a significantly increased risk of having gastric IM on univariate ($P<0.01$) and multivariate analysis (OR 8.51, 95% CI: 1.52-40.22, $P=0.018$). Neither tobacco use nor alcohol use were associated with gastric IM on univariate analysis. Furthermore, neither proton-pump inhibitors nor H2-blockers were associated with finding gastric intestinal metaplasia on gastric biopsies on univariate analysis (Table 2).

Table 2 Possible risk factors associated with the development of gastric intestinal metaplasia.

Risk factor	Frequency of patients with gastric IM	Frequency of patients without gastric IM	Association with gastric IM	
			Univariate analysis	Multivariate analysis
Family history of gastric cancer	3/15 (20%)	6/285 (2.1%)	$P<0.01$	OR 8.51 95% CI:1.52-40.22 $P=0.018$
PPI	3/15 (2%)	159/411 (38.7%)	$P=0.44$	$P=0.595$
H2 blockers	0/15 (0%)	21/285 (7%)	$P=0.61$	$P=0.403$
Alcohol use	5/15 (33.3%)	100/280 (35.7%) ²	$P=1.00$	$P=0.592$
Cigarette use	7/14 (50%) ¹	119/280 (42.5%) ²	$P=0.59$	$P=0.845$

¹ 1 patient with gastric intestinal metaplasia had unknown cigarette use history; ² 5 patients without gastric intestinal metaplasia had unknown alcohol and cigarette use history.

Association between insurance status and chronic gastritis and gastric IM

Table 3 shows the frequencies of several pathologic diagnoses by type of insurance/payer. More uninsured patients and those with Medicaid had chronic gastritis and gastric IM as compared to patients with private insurance. Table 4 highlights that uninsured patients (OR 5.1, 95% CI: 2.4-11.2, $P<0.001$) and those with Medicaid (OR 3.6, 95% CI: 1.3-9.7, $P=0.014$) were significantly more likely to have chronic gastritis as compared to those with private insurance on age-adjusted multivariate analysis. Uninsured patients ($P=0.15$) and those with Medicaid ($P=0.15$) trended towards an increased frequency of gastric IM, but this did not reach statistical significance on univariate analysis.

Table 3 Frequency of pathologic diagnoses by type of insurance/payer.

Pathologic diagnosis	Uninsured	Private insurance	Medicaid	Medicare
Frequency of chronic gastritis	42.3% ($n=22$)	16% ($n=16$)	31% ($n=9$)	16.1% ($n=14$)
Frequency of gastric IM	7.7% ($n=4$)	2.3% ($n=3$)	6.9% ($n=2$)	6.9% ($n=2$)
Gastric dysplasia	0% ($n=0$)	0% ($n=0$)	0% ($n=0$)	2.3% ($n=2$)
Gastric cancer	0% ($n=0$)	0% ($n=0$)	0% ($n=0$)	1.1% ($n=1$)

Table 4 Univariate and multivariate analyses to evaluate for associations among pathological diagnoses and type of health insurance/payer status.

Pathologic diagnosis	Medicaid vs. private payer		Uninsured vs. private payer	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Chronic gastritis	$P=0.020$	OR 3.59 95% CI: 1.30-9.72 $P=0.014$	$P<0.001$	OR 5.11 95% CI: 2.39-11.15 $P<0.001$
Gastric IM	$P=0.220$	$P=0.155$	$P=0.101$	$P=0.152$

DISCUSSION

It has been theorized since the late 1980s that gastric IM is part of a pathway leading to gastric carcinogenesis^[10]. A cohort study performed by Filipe *et al*^[4] followed patients with gastric IM over 10 years and found a 10-fold increased risk of developing gastric cancer. Subsequently, a Japanese study published in 2001 by Uemura *et al*^[17] found a 6.4-fold increased risk of progression to gastric cancer in HP-positive patients who had a previous diagnosis of gastric IM. There is currently little data regarding the prevalence of gastric IM in U.S. academic medical centers. Sonnenberg *et al* conducted a large retrospective cohort study that found the prevalence of gastric IM in a geographically diverse population of 78985 patients to be 7%, and there was a continuous age-dependent rise from age 0 to 90 years. However, as these investigators studied biopsy samples obtained by private gastroenterologists that were sent to a for-profit laboratory for pathological analysis, patients of lower socio-economic class were under-represented, with Medicaid being the primary insurer in only 3% of the study population^[9]. In this present study, we found that 5% of the patients undergoing EGD with biopsy for various indications had gastric IM. Our results might be more generalizable as the gastric biopsies were obtained at an academic medical center that cares for both insured and uninsured patients from Virginia and several surrounding states (including West Virginia and Tennessee).

In our patient population, private insurance and Medicare covered 73% of the study population, and 27% were uninsured or had Medicaid. Patients who were covered by Medicaid or had no insurance were at increased risk of having chronic gastritis and possibly intestinal metaplasia when compared to patients with private insurance. These findings are similar to those found by Sonnenberg *et al*^[9] who showed that when compared to other insurance types, Medicaid coverage was more common in patients with HP, chronic gastritis and gastric IM. The most recent U.S. Census Bureau from 2010 found the following distribution of insurance types: private insurance 64%, Medicare 14.5%, Medicaid 15.9%, and uninsured 16.3%. The U.S. Census Bureau data for Virginia in 2010 showed the following distribution of insurance types: private insurance 70.6%, Medicare 14.5%, Medicaid 8.3%, uninsured 14.1%. In comparison, our study population, which included 9.7% Medicaid and 15.3% uninsured patients, was similar to both the state and national insurance population statistics, and as such our results are possibly representative of the larger national population. Assuming that insurance status and the type of health care coverage correspond to socio-economic status, our data suggests that those with a lower socio-economic status (i.e., those with Medicaid or uninsured) had an increased odds of having chronic gastritis on gastric biopsies.

An important finding in this study was that a family history of gastric cancer was associated with significantly increased odds of finding gastric IM on gastric biopsies. These results correspond with those published in a 2010 meta-analysis by Rokkas *et al*^[3] that included 11 retrospective studies and 1500 patients who had first-degree relatives with gastric cancer as compared to 2638 controls. The results showed that a first-degree family history of gastric cancer was associated with increased prevalence of HP infection, gastric atrophy, and gastric cancer with odds ratios of 1.9, 2.2, and 2.0, respectively. Our data were also interesting as they uncovered a large population of patients who had chronic gastritis (20%) but were largely HP-negative (only 2% HP-positivity), which supports other observations in the era of active HP eradication^[18].

ASGE guidelines published in 2006 stated that endoscopic surveillance for gastric IM has not been extensively studied in the

U.S. and therefore cannot be uniformly recommended. However, patients at increased risk of gastric cancer due to ethnic background or family history may benefit from surveillance^[5]. Whiting *et al* performed a study in the U.K. examining whether annual endoscopic surveillance could detect new gastric cancers at an earlier stage. The study examined 1753 patients and diagnosed 14 new cases of gastric cancer over 10 years. At the time of diagnosis, the cancers were at an earlier stage (67% were stage I and II vs. 23% of later stages; $P < 0.05$), and the 5-year survival of patients with gastric cancers detected by surveillance endoscopy was significantly higher than for those who had cancers detected by open-access endoscopy^[19]. Furthermore, de Vries *et al*^[20] conducted a nationwide cohort study in the Netherlands that identified 61707 patients with gastric IM and followed them up to 14 years found a 0.25% annual incidence (over 5 years) of developing gastric cancer. These authors concluded that development of clinical guidelines on endoscopic surveillance or treatment of premalignant gastric lesions is strongly indicated, and that surveillance for gastric IM should be considered. These recommendations seem very reasonable, as screening and surveillance for Barrett's esophagus is well accepted and as recent data show the absolute annual risk (or incidence) of progression from Barrett's IM to esophageal adenocarcinoma is only about 0.12%^[21], which is less than half that described above for progression of gastric IM to gastric adenocarcinoma. In fact, these studies and others formed the basis of recently published joint European societal guidelines for the "Management of precancerous conditions and lesions in the stomach"^[22].

A limitation of this study is its retrospective design. Furthermore, these results could be prone to selection bias, as this study was conducted at an academic referral center. Due to the retrospective design, there may be unmeasured or unknown variables that were not studied or controlled for. However, retrospective studies have value in particular as they raise questions worthy of studying in larger cohort studies and in a prospective manner.

In this study, we demonstrated that a positive family history of gastric cancer was associated with a nine-fold increased odds of gastric IM, which is a known premalignant lesion. Furthermore, we demonstrated in a U.S. population that uninsured patients and those with Medicaid may be more likely to have gastric IM, and on multivariate analysis these patients with presumed lower socioeconomic status had a four-to-five-fold increased odds of having chronic gastritis. As societal guidelines regarding the screening and surveillance of premalignant gastric lesions are developed in the U.S. and other Western nations, patients with these characteristics should be paid special attention as they are at risk for gastric IM and might benefit from endoscopic screening and/or surveillance.

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